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Crossing Boundaries in Science:
Modelling Nature and Society – Can We Control the World?

Johannes Fritsch, Yvonne Borchert and Jörg Hacker (Eds.)

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NOVA ACTA LEOPOLDINA

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Crossing Boundaries in Science:
Modelling Nature and Society – Can We Control the World?

Documentation of the Workshop of the German National Academy of Sciences Leopoldina

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Die Vorträge und Diskussionen wurden zur besseren Lesbarkeit redaktionell bearbeitet und zusammengefasst (FRITSCH und BORCHERT). Sie erscheinen daher nicht in wörtlicher Rede.

Preface of the publishers:

The presentations and discussions were edited for readability and summarised (FRITSCH and BORCHERT). They therefore do not appear in direct speech.

Nova Acta Leopoldina NF Nr. *419*, 7–9 (2017)

Introduction and Short Summary of the Workshop

Johannes Fritsch (Berlin)*

A History of Free Enquiry

In 1652, four physicians established the Academia Naturae Curiosorum in the Free Imperial City of Schweinfurt. It is now the oldest continuously existing academy of medicine and the natural sciences in the world. The four physicians invited leading scholars of their day to join them in 'exploring nature […] for the glory of God and the good of mankind'. The motto they selected for this ambitious objective was Nunquam otiosus ('never idle').

The members realised that in order to draft a proposed encyclopaedia they would have to gather existing knowledge and subject it to discussion. To this end, in 1670 Sachs Lewenhaimb, a physician in Breslau (Wrocław), initiated the world's first journal of natural science and medicine, *Miscellanea Curiosa Medico-Physica Academiae Naturae Curiosorum*, which is still in print today.

Soon after it was established, the Academy started to seek public recognition. It gained this in August 1677, when it was granted official approval by Emperor Leopold I. Ten years later, Leopold I awarded the Academy special privileges, guaranteeing its independence from the various ruling dynasties in the region and providing complete freedom from censorship for all its publications. Since then, the Academy has been called *Sacri Romani Imperii Academia Caesareo-Leopoldina Naturae Curiosorum* – or the Leopoldina for short.

A Workshop for Leopoldina's Mission

The members of Leopoldina still come together in regular meetings to share and discuss their work. In 2008, the Leopoldina was appointed as the German National Academy of Sciences, taking on the responsibility to disseminate the newest scientific information not only among scientists but also to the public and politicians. As an expression of this commitment, the Academy initiated a new format of workshops under the theme *Crossing Boundaries in Science*. These workshops are meant to stimulate discussions between areas of research that are particularly dependent on new forms of interdisciplinary cooperation and method transfer.

In this publication, we present the talks given at the first workshop of this series, entitled "Modelling Nature and Society – Can We Control the World?" The workshop took place in the city of Weimar from 30 June to 2 July 2016. Its objective was to provide an overview of

* Nationale Akademie der Wissenschaften Leopoldina.

current attempts to understand and control complex systems in nature and society. We asked 13 researchers from different fields of scientific research to answer four principal questions:

– Can your complex system of interest be reduced to a small number of predictive variables and which attributes of the system do these variables describe?
– What are the trade-offs when employing rich statistical models, based on large amounts of data ('big data'), instead of simple reductionist models?
– Does your model have sufficient predictive power to allow for target-oriented strategic interventions?
– Natural complex systems tend to self-organise. Can you harvest the power of naturally occurring self-organisation to create more fault-tolerant information processing systems?

The answers to these questions are, naturally, as diverse as the fields of study represented at this workshop. To give a short overview:

Peter Schuster (Professor Emeritus, Institute for Theoretical Chemistry, University of Vienna, Austria) identifies a number of sources of complexity in natural systems focusing on biochemical pathways: the lack of knowledge about these systems, the lack of technology to record their behaviour accurately enough, the combinatorial explosion of possible pathways in strongly interacting systems, and the tinkering hand of evolution.

Christiane Nüsslein-Volhard (Max Planck Institute for Developmental Biology, Tübingen) describes the long path toward understanding one of the complex outcomes of evolutionary tinkering: the process of morphogenesis, i.e. the development of a single fertilised egg to a complex organism consisting of billions of differentiated and organised cells. She emphasises the importance of conceptual insights in reducing the complex interplay of genes and environment in a developing embryo to a number of key growth factors. Identifying those factors, namely gradients of molecules called 'morphogens', earned Nüsslein-Volhard the 1995 Nobel Prize in Physiology or Medicine.

Marc Thilo Figge (Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute, Jena) introduces the power of computational modelling for studies on pathogen-host interactions, particularly the conditions under which pathogenic fungi can cause life-threatening infections of the lung and in blood. Using data from infected patients, he creates 'virtual patients', a promising candidate model for patient-dependent interventions.

Wolf Singer (Max Planck Institute for Brain Research, Frankfurt am Main) illustrates the surprising robustness of the most complex biological system known to mankind: the mammalian cortex. Despite its unrivalled complexity, the cortex can still compensate for regional damage. Singer proposes that some of the brain's architectural principles could serve as a blueprint for more robust artificial systems, namely: distributedness, a flat hierarchy, and adaptivity combined with a central evaluation system.

Wolfram Burgard (Albert Ludwigs University, Freiburg) turns the attention to those systems that may benefit from complexity-based robustness, namely autonomous learning machines such as self-driving cars. He describes recent solutions to the problem of building intelligent agents with a focus on probabilistic and numeric models in concert with big data.

Eran Elinav (Weizmann Institute of Science, Rehovot, Israel) also exploits the use of big data; specifically, for the prediction host-microbiome interaction in the human gut. By feeding machine learning algorithms with large amounts of data, including gut microbiome DNA, meal features, logged activity and aspects of personal life, his models manage to devise personalised predictions of how particular foods will affect blood sugar levels in healthy and

diabetic subjects, resulting in highly personalised diets that may reduce the risk for developing obesity and diabetes significantly.

Thorsten Wiegand (Helmholtz Centre for Environmental Research, Leipzig) walks the audience through the types of models that are used in ecology in the attempt to predict the behaviour of ecosystems. His presentations follow a path from analytical and numerical equation models through agent-based and individual-based models to his own pattern-oriented approach to modelling ecosystems.

Iain Couzain (Max Planck Institute for Ornithology, Constance) reports on the groundbreaking advances his group has made in modelling the collective movement behaviour of schools of fish as well as the implications of their models for other social species. His agent-based models identify and incorporate the perceptual information used by the individual members to predict phase transitions and global states of the whole group.

Rudolf Stichweh (University of Bonn) introduces the surprisingly diverse definitions one can give to the concept of a 'society'. How can we differentiate between hunter-gatherer societies, states, civilisations and a world society? Stichweh proposes that the level of differentiation and socio-cultural evolution are the main dimensions along which these social systems differ and develop.

Thomas Lengauer (Max Planck Institute for Informatics, Saarbrücken) demonstrates the inner workings of his computational drug resistance model for viral pathogens such as HIV. Tapping into a growing database on viral resistance, his team developed a model to predict promising drug combinations for a given patient. Today, these statistical models can surpass the performance of rules-based expert systems. However, Lengauer emphasises that prediction of outcome for a complex system is not the same as understanding that system's underlying mechanism.

Dirk Brockmann (Humboldt University of Berlin) explores a different aspect of pathogen-host interaction: the complex dynamics of global disease spread depending on social interactions and travel. By combining transmission dynamics within populations with a novel measure of distance for the global transport network (effective distance), his models manage to predict global disease spread with significantly increased accuracy compared to previous attempts.

Alan Kirman (CAMS, Ecole des Hautes Etudes en Sciences Sociales and Aix Marseille University, France) discusses a novel approach at modelling the dynamics of the global economy. He argues for a paradigm shift away from classic economic models based on the rational individuals seeking efficient outcomes towards modelling the adaptive behaviour of systems of individuals, each of whom follows rather simple rules.

Dirk Helbing (Swiss Federal Institute of Technology, Zürich, Swiss) concludes the workshop by arguing the case for his social force model, a model inspired by physics but adapted to social behaviour. He describes this model as being able to explain phenomena as diverse as traffic jams, crowd dynamics or industrial flows. Even more, he expects the social force model to accurately describe the dynamics in social economic systems, citing the vision of creating an operating system for society.

We hope that this collection of talks will stir your interest in the most recent advancements in our understanding of the complexity of nature and society. 365 years after the founding of Leopoldina, this workshop shows once more that our members are guided by the academy's original spirit: to explore nature, for the good of humanity.

Evening Lecture / Abendvortrag

Eröffnung des Abendvortrags

Jörg Hacker ML (Halle/Saale)
Präsident der Nationalen Akademie der Wissenschaften Leopoldina

Der mehrtägige Workshop „Modelling Nature and Society – Can We Control the World?“ ist der Auftakt zur neuen Veranstaltungsreihe „Crossing Boundaries in Science“ und wird großzügig vom Bundesministerium für Bildung und Forschung (BMBF) gefördert, dem mein herzlicher Dank gilt. Besonders Professor Dr. Frank Laplace möchte ich dafür danken, dass er diese Idee mit entwickelt und vorangetrieben hat. Diese Tagungsserie knüpft an die vom *Frege Centre for Structural Sciences* der Friedrich-Schiller-Universität in Jena organisierte und ebenfalls vom BMBF unterstützte Veranstaltungsreihe „Jena Life Science Forum“ (JLSF) an. Das JLSF fand in den Jahren 2009 und 2010 zum Thema „The Molecular Language of Life“ sowie mit Unterstützung der Leopoldina zum Thema „Designing Living Matter. Can We Do Better than Evolution?“ im Jahre 2012 statt.

Zu den zentralen Aufgaben der Leopoldina als Nationaler Akademie der Wissenschaften gehört es, Politik und Öffentlichkeit zu gesellschaftlich herausfordernden Fragen zu beraten und enge Bezüge zwischen Wissenschaft, Forschung, Politik und Gesellschaft zu etablieren. Das Ziel dieser Veranstaltungsreihe soll es daher sein, frühzeitig Forschungsgebiete zu identifizieren, deren zukünftige Entwicklung und gesellschaftliche Anwendung möglicherweise in besonderem Maße zur interdisziplinären Zusammenarbeit anregen. Umgekehrt dient Interdisziplinarität vielleicht sogar als Grundlage für solche Forschungsergebnisse. Die Veranstaltungen sollen deshalb Erfolg versprechende Wissenstransfers intensiv debattieren – von konzeptuellen Anregungen über Methodenimporte bis zu Anwendungen neuer Technologien.

Bei der diesjährigen Veranstaltung in Weimar werden wir uns mit der wissenschaftlichen Modellbildung komplexer biologischer und sozialer Netzwerke sowie mit zielgerichteten und strategischen Eingriffen in diese Systeme befassen. Dabei stehen mikroskopisch kleine Systeme im Mittelpunkt, wie beispielsweise Gen-Netzwerke und das Immunsystem, aber auch globale Fragen, etwa aus dem Finanzsektor und aus den Verkehrssystemen. Alle diese Systeme haben eine Eigenschaft gemeinsam: Sie sind komplex. Für das Individuum ist ihre Komplexität kaum greifbar. Sie sind wenig vorhersagbar und meist nicht zu kontrollieren. Denken wir etwa an die globalen Finanzströme, an die Neuverschuldung von Staaten und – ein aktuelles Thema – den Austritt Großbritanniens aus der Europäischen Union; keine konstruierte Parallele, sondern tatsächlich ein komplexes Geschehen. Der einführende Vortrag von Professor Dr. Peter Schuster im Goethe-Nationalmuseum trägt daher auch den provokanten Titel: „Vom Modell zur Steuerung – Sind wir überfordert von der Komplexität der Welt?“

Mithilfe unseres thematisch weitgefächerten Workshops zur Modellierung komplexer Systeme möchten wir zudem herausfinden, was unterschiedliche Fachdisziplinen voneinander lernen können. Gibt es analoge konzeptuelle und methodische Grundlagen, um z. B.

sowohl ökologische, molekulare und gesellschaftliche Netzwerke zu modellieren? Welche und wie viele Variablen sind relevant und überhaupt sinnvoll für das angemessene Modellieren und für das Verständnis unterschiedlicher komplexer Systeme? Welche Prinzipien der natürlichen Selbstorganisation können angewendet werden, um belastbare, fehlertolerante Infrastrukturen in unserer Gesellschaft zu schaffen? Diese und andere Fragen sollen im Fokus dieses Workshops stehen.

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Vom Modell zur Steuerung – Sind wir überfordert von der Komplexität der Welt?

Peter Schuster ML (Wien, Österreich)[1]

Abstract

"Everything that is not simple is complex" – this is how a mathematical purist might define the aspect of complexity. However, what are the factors that determine whether a system is complex or not? As it turns out, complexity can be attributed to several causes: inadequate insight and knowledge, lack of technology, and untamable diversity. Consider, for instance, the movements of the planets in the geocentric worldview of Ptolemy. The complexity of precisely predicting planetary motion, eccentricities and equants only disappeared when a new insight took hold: Newton's laws of gravity. However, a full understanding of nonlinear systems was not possible until analytical mathematics and large numerical calculations could be simulated on computers. Even with these modern technologies, we can only mimic the complexity of nature in very simple cases. The evolutionary search for biomolecules is one example. Yet, the ultimate challenge of complexity research still resides in the enormous diversity of solutions that either emerge in nature or are created by humans. We find this diversity everywhere in biology, sociology, economics, and other disciplines. Here, we will provide an overview of the enormous complexity that awaits the researcher who seeks to model, predict, and control genuine systems in nature and human society.

1. Was versteht man unter Komplexität?

Komplexität ist zwar leicht zu erkennen, aber nur schwer, präzise zu definieren. Anders als einfache, reagieren komplexe Systeme auf Veränderungen auf nicht vorhersehbare Weise. Solche Strukturen sind oft Netzwerke von Wechselwirkungen, in denen kompensatorische Schwächung und Verstärkung von überlagerten Signalen es erschweren oder unmöglich machen, kausale Abläufe nachzuvollziehen.

Um Komplexität zu fassen, kann man aber prinzipiell so vorgehen, wie beim verwandten Problem der „Nichtlinearität". Statt eine Definition zu geben, charakterisiert man über das Gegenteil: Nichtlinear ist alles, was nicht linear ist. Für die Komplexität hieße dies: Komplex ist alles, was nicht einfach ist. Allerdings gibt es daneben noch eine dritte Möglichkeit, die „Kompliziertheit": etwas, was weder einfach noch komplex ist. Einfach zu modellieren wäre etwa die Kausalkette: A→B→C. Kompliziert dagegen wäre schon eine nicht verzweigte Kette mit einer Million Einzelschritten: A→B→C→…→Z. Komplex ist sie aber noch nicht. Denn die Vorhersage, dass man bei Z landen wird, ist sicher, auch wenn der zeitliche Ablauf schwer zu ermitteln ist. Ein anschauliches Beispiel für den Unterschied zwischen einem einfachen und einem komplexen System bieten die Glykolyse und die alkoholische Gärung im zellfreien Milieu und in der Zelle (siehe Abb. 1).

1 Exzerpiert und vereinfacht nach dem Vortragsmanuskript von Peter Schuster, Universität Wien, Österreich.

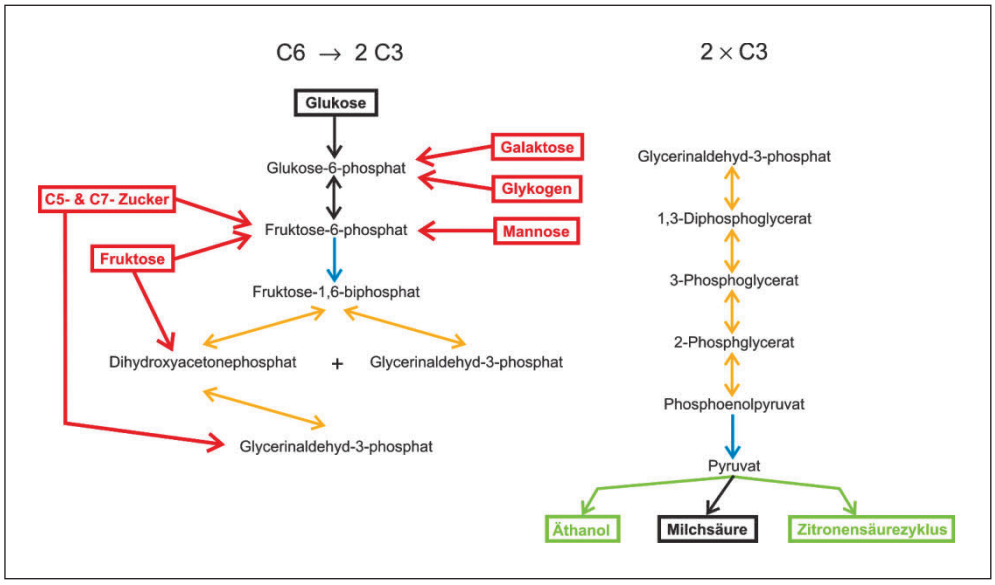

Abb. 1 Ein Ablaufdiagramm der Glykolyse. Glukose mit sechs Kohlenstoffatomen wird in sechs Reaktionsschritten in zwei Moleküle Glycerinaldehyd mit je drei Kohlenstoffatomen zerlegt. Glycerinaldehyd wird in einer Folge von weiteren sechs Reaktionen in Milchsäure oder Äthanol umgewandelt oder als Pyruvat in den Zitronensäurezyklus eingespeist. Damit ist die Glykolyse *in vitro* im Wesentlichen eine eindimensionale Kette biochemischer Reaktionen (schwarze und gelbe Pfeile). Allerdings dienen zwei irreversible Reaktionsschritte (blaue Pfeile) der Regulation. In den komplexen Mechanismus einer Zelle eingebettet, wird an dieser Stelle, durch die Einspeisungen anderer Zucker (rot), aus der einfachen Kette ein Reaktionsnetzwerk mit Verzweigungen.

Glykolyse *in vitro* ist eine Kette von zehn oder elf Reaktionen, bei denen ein Molekül Glucose in zwei Moleküle Brenztraubensäure umgewandelt wird und zwei Moleküle des chemischen Energieträgers ATP sowie zwei Moleküle NADH erzeugt werden. Je nach der Art des Gärungsprozesses wird mit NADH Brenztraubensäure (Pyruvat) zu Milchsäure reduziert (Milchsäuregärung) oder Acetaldehyd zu Ethanol (alkoholische Gärung).

Unter physiologischen Bedingungen fungieren drei der Reaktionsschritte auch als Regulatoren: (*i*) die Phosphorylierung der Glucose, (*ii*) die Phosphorylierung von Fructose-6-phosphat und (*iii*) die Dephosphorylierung von Phosphoenolpyruvat in Pyruvat. Schritt (*i*) wird durch die Konzentration der Reaktionsprodukte reguliert: Ist sie zu hoch, kommt die Reaktion zum Stillstand. Die beiden Schritte (*ii*) und (*iii*) regulieren die gesamte Reaktionskette und arbeiten dabei wie Schalter, die bei bestimmten Substratkonzentrationen umgelegt werden. Die Schalterfunktion selbst basiert auf der Geschwindigkeit der Reaktion, die wiederum von der Substratkonzentration abhängt. Diese Nichtlinearität entsteht durch Wechselwirkungen zwischen den Untereinheiten des jeweiligen Enzyms, das die Reaktion katalysiert. Aber selbst bei einer Kette mit Tausenden von Reaktionen würden solche Regulationsmechanismen die Berechnungen der Produkt- und Substrat-Konzentrationen zwar kompliziert und langwierig machen, aber nicht komplex.

Komplex wird die Glykolyse erst, wenn sie als Teil des zellulären Metabolismus abläuft. Dann wird aus der Reaktionskette ein ganzes Reaktionsnetzwerk. Man braucht der Glykolyse nur die anderen, in der Natur häufig vorkommenden Monosaccharide als Substrate anzubie-

ten, und schon entstehen etliche Verzweigungen, die von den einzelnen Reaktionen abgehen. Richtig komplex wird das Netzwerk, wenn wir die Glykolyse als Teil des gesamten metabolischen Reaktionsnetzwerks betrachten, dessen zahlreiche Verzweigungen alle Vorhersagen schwierig machen.

Warum ist das Verhalten stark verzweigter, rückgekoppelter Systeme wie der Glykolyse so schwer vorherzusagen? Wie sich zeigt, speist sich Komplexität unter anderem aus drei wesentlichen Quellen.

2. Komplexität als Resultat mangelnden Wissens

Im geozentrischen Weltbild von Pythagoras von Samos (ca. 570–510 v. Chr.) sind die Himmelskörper auf durchsichtigen Hohlkugeln befestigt, den Sphären, die sich gleichförmig um die im Mittelpunkt stehende Erde drehen. Die beobachtbaren Bewegungen der Fixsterne, der Sonne und des Mondes waren mit der Vorstellung von solchen Sphären leicht in Einklang zu bringen. Bei den Planetenbewegungen aber ergaben sich gewaltige Unstimmigkeiten, die erst Claudius Ptolemäus (ca. 100–160 n. Chr.) mit eleganten, aber ziemlich komplexen Berechnungen zu beheben vermochte. Um die beobachteten Planetenbahnen durch eine Überlagerung gleichförmiger Kreisbewegungen zu erklären, benötigte er drei virtuelle Mittelpunkte der Himmelsmechanik sowie zwei zusätzliche hypothetische Sphären (siehe Abb. 2).

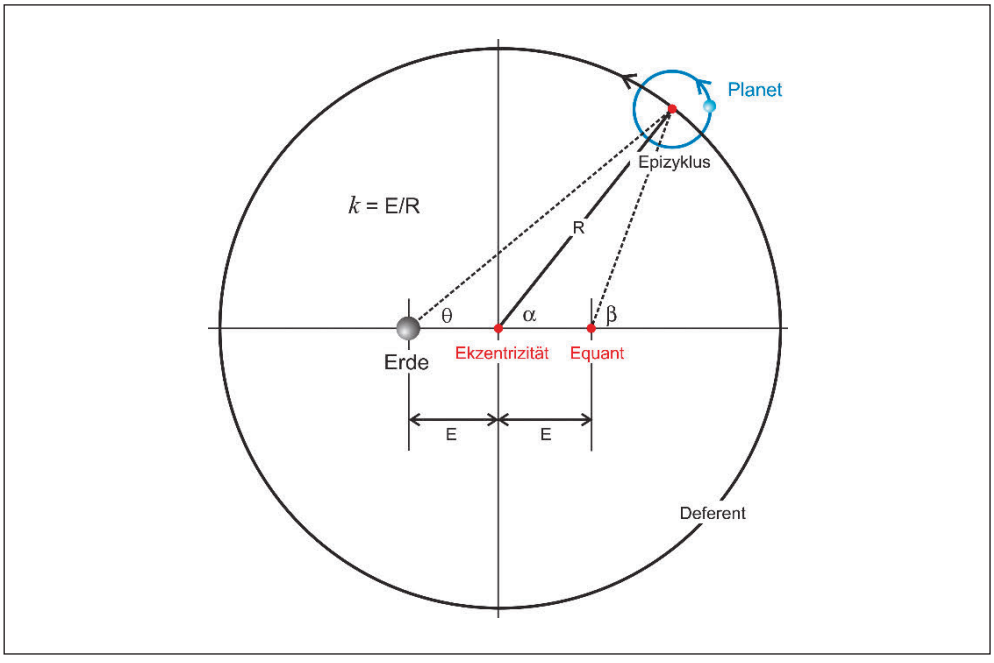

Abb. 2 Ein Diagramm zur Berechnung der von der Erde aus beobachteten Planetenbewegungen im ptolemäischen Weltbild. Ptolemäus führte zur Berechnung der Planetenbahnen Epizyklen ein, Bahnen, auf denen sich die Planeten um die Hauptbahn (Deferent) herumbewegen. Zur Berechnung benötigt man noch zwei weitere Werte: die Exzentrizität und den Equant.

Erst Johannes Kepler (1571–1630) überwand die dogmatischen Vorgaben eines geozentrischen Weltenmodells mit Kreisbahnen und konstanten Winkelgeschwindigkeiten. Er beschrieb die Umlaufbahnen der Planeten um die Sonne ohne zusätzliche virtuelle Punkte. Endgültig „dekomplexifiziert" aber wurde das Verständnis der Himmelsmechanik erst mit Newtons Bewegungs- und Gravitationsgesetzen. Mit Ausnahme von Korrekturen, die durch Einsteins Relativitätstheorie notwendig werden, können seither die Bewegungen aller Himmelskörper erklärt werden.

Neues Wissen, das verschiedene Beobachtungen auf gemeinsame Prinzipien zurückführt, kann also den Anschein der Komplexität überwinden.

3. Komplexität aus Mangel an methodisch-technischen Möglichkeiten

3.1 Abhängigkeit von Anfangsbedingungen

Im Jahr 1899 schrieb Henri Poincaré (1854–1912) eine Arbeit zur Lösung einer Preisaufgabe, die der schwedische König Oscar II. (1829–1907) gestellt hatte. Deren Ziel war es, die mechanische Stabilität des Sonnensystems zu beweisen. Das Dreikörperproblem Sonne – Planet – Erde hat auch instabile Lösungen und insbesondere komplexe, in hohem Maße irreguläre Bahnen. Poincaré schrieb über die Empfindlichkeit der Lösungen gegenüber Parametern und Anfangsbedingungen:

„Eine sehr kleine Ursache, die wir nicht bemerken, bewirkt einen beachtlichen Effekt, den wir nicht übersehen können, und dann sagen wir, der Effekt sei zufällig. Wenn die Naturgesetze und der Zustand des Universums zum Anfangszeitpunkt exakt bekannt wären, könnten wir den Zustand dieses Universums zu einem späteren Moment exakt bestimmen. Aber selbst wenn es kein Geheimnis in den Naturgesetzen mehr gäbe, so könnten wir die Anfangsbedingungen doch nur annähernd bestimmen. Wenn uns dies ermöglichen würde, die spätere Situation in der gleichen Näherung vorherzusagen – und dies ist alles, was wir verlangen – so würden wir sagen, dass das Phänomen vorhergesagt worden ist, und dass es Gesetzmäßigkeiten folgt. Aber es ist nicht immer so; es kann vorkommen, dass kleine Abweichungen in den Anfangsbedingungen schließlich große Unterschiede in den Phänomenen erzeugen. Ein kleiner Fehler zu Anfang wird später einen großen Fehler zur Folge haben. Vorhersagen werden unmöglich, und wir haben ein zufälliges Ergebnis."[2]

Diese visionäre Aussage aus Poincarés Arbeit ist eine bedeutende Pionierleistung und wird oft als der Beginn der Chaostheorie angesehen.

Ebenfalls um die Wende vom 19. zum 20. Jahrhundert fanden einige Chemiker – allen voran der aus Lettland stammende deutsche Physikochemiker Wilhelm Ostwald (1853–1932) – Hinweise für das Auftreten komplexer Dynamik und spontaner Musterbildung bei chemischen Reaktionen. Der Computerwissenschaftler Alan Turing (1912–1954) veröffentlichte im Jahr 1952 ein auf chemischer Reaktionskinetik basierendes mathematisches Modell der Musterbildung, das er als eine Erklärung der embryologischen Morphogenese vorschlug. Diesen Pionierleistungen fehlten, anders als Kopernikus mit seinem Weltenmodell, keine unentdeckten Naturgesetze. Was Ostwald und Turing fehlte, war eine Methodik, mit der komplexe Systeme untersucht werden konnten. Erst ab der zweiten Hälfte des 20. Jahrhunderts standen die nötigen mathematisch-analytischen und numerischen Methoden zur Verfügung, um komplexe Systeme zu untersuchen und zu modellieren.

2 Frei übersetzt nach Oestreicher 2007. Die ursprüngliche französische Version findet sich in Poincaré 1892.

3.2 Deterministisches Chaos

Den Durchbruch schaffte im Jahre 1963 der Atmosphärenphysiker und Meteorologe Edward Norton Lorenz (1917–2008).[3] Am Computer integrierte er das relativ einfache Differentialgleichungssystem

$$\frac{dx}{dt} = \alpha\,(y - x), \quad \frac{dy}{dt} = x\,(\beta - z) - y, \quad \text{und} \quad \frac{dz}{dt} = x\,y - \gamma\,z \qquad [1]$$

und entdeckte, dass unregelmäßig oszillierende Lösungskurven entstehen, wenn die Parameter α, β und γ aus bestimmten Wertebereichen gewählt werden. Wie von Henri Poincaré vorausgesagt, hing die Lösung des Gleichungssystems sehr stark von den Parameterwerten und den Anfangswerten ab. Für sehr nahe beisammen liegende Parameterwerte bleiben die Lösungskurven ein Zeitintervall lang fast ununterscheidbar. Danach aber weichen sie immer stärker voneinander ab, sodass nur kurzzeitige Vorhersagen korrekt sind.

Das empfindliche Verhalten der Lösungskurven gegenüber den Anfangsbedingungen bezeichnet man heute als deterministisches Chaos. Nicht zufällig stammen die lorenzschen Differentialgleichungen aus einer vereinfachten Beschreibung atmosphärischer Luftströmungen; die in ihnen beschriebene chaotische Dynamik ist eine wesentliche Ursache dafür, wie schwierig es ist, das Wetter langfristig vorherzusagen. Kurz- und mittelfristige Prognosen haben sich über Jahrzehnte hinweg zwar immer weiter verbessert; diese Fortschritte gehen aber in erster Linie auf die Vervielfältigung der Messdaten zurück, die wir heute von Wettersatelliten, Wetterflügen und anderen Messungen bis hinauf in die Stratosphäre erhalten.

Das Beispiel der Strömungsphysik von Gasen ist sehr illustrativ: In der Luftfahrttechnik erlaubt sie die Vorhersage der aerodynamischen Eigenschaften unterschiedlicher Profile mit höchster Genauigkeit, und es werden kaum mehr Experimente im Windkanal ohne vorherige Berechnung durchgeführt. Demgegenüber steht der tägliche Wetterbericht. Was macht hier den Unterschied? Die Antwort ist dieselbe wie im einleitenden Beispiel der Glykolyse: Der Windkanal bietet eine einfache und (abgesehen von kontrolliert variierten Versuchsparametern) konstante Umgebung. Dagegen besitzt die Erdoberfläche mit ihren Flachländern, Gebirgen, Wasser- und Eismassen sowie starken vertikalen und horizontalen Temperaturunterschieden höchst heterogene Randbedingungen für den atmosphärischen Fluss. Neben der Komplexität, die Gasströmungen an sich innewohnt, ist es die Einbettung in eine komplexe Umwelt, die die Dynamik der Atmosphäre in der Natur so schwer vorhersagbar macht.

Der Vergleich zeigt, dass die Ergebnisse stark von verfügbaren technischen und methodischen Möglichkeiten abhängen. So führen korrekte wissenschaftliche Modelle – je nach der Natur des Problems – zu Ergebnissen von sehr unterschiedlicher Verlässlichkeit.

4. Komplexität durch Vielfalt

In der Mathematik gibt es eine unschlagbare Methode zur Erzeugung von Vielfalt: die Kombinatorik. Setzt man eine Kette aus zehn Gliedern zusammen, von denen jedes aus zehn Typen beliebig ausgewählt werden kann, dann beträgt die Zahl der möglichen verschiedenen Ketten 10^{10} oder 10 Milliarden. Die Vielfalt der Kombinatorik ist auch das Erfolgsrezept der

3 Siehe Lorenz 1963.

Biologie. Durch die Kombination von Bausteinen zu eindimensionalen Ketten wird die Zahl möglicher Sequenzen von Nukleinsäuren oder Proteinen gewaltig: Für Ribonukleinsäuren (RNA) von der Länge einer typischen transfer-RNA gibt es etwa 10^{45} verschiedene Nukleotidsequenzen, für ein kleines Protein hingegen, das etwa so groß wie Lysozym aus Hühnereiklar ist, 10^{168} verschiedene Aminosäuresequenzen. Die Evolution kann daher immer nur in einem winzig kleinen Ausschnitt des riesigen Raumes aller möglichen Sequenzen stattfinden.

Allerdings reicht eine große Zahl verschiedener Ketten nicht aus, um echte Vielfalt zu schaffen. Ein Beispiel, an dem man dies gut sehen kann, ist heteropolymeres Plastik. Solche Materialien bestehen aus extrem vielen verschiedenen Sequenzen. Jedoch haben praktisch alle von ihnen die gleichen Eigenschaften, sodass das Endprodukt weitgehend einheitlich bleibt. Wodurch kommt nun die augenscheinliche Vielfalt in der Biologie zustande? Biopolymersequenzen falten sich unter gleichen Umgebungsbedingungen auf eindeutige Weise. Es ist diese dreidimensionale Struktur, die letztlich die molekularen Eigenschaften eines Biomoleküls bestimmt. Die Beziehung zwischen Strukturen und Eigenschaften kann als mathematische Abbildung verstanden werden, aus dem Raum der Strukturen in einen Raum jener Parameter, die die Eigenschaften des Biomoleküls quantifizieren. In der Abbildung 3 ist diese Beziehung zwischen Bausteinsequenzen und Eigenschaften als Folge von zwei Abbildungen skizziert, die den Vorstellungen der Strukturbiologie entsprechen.

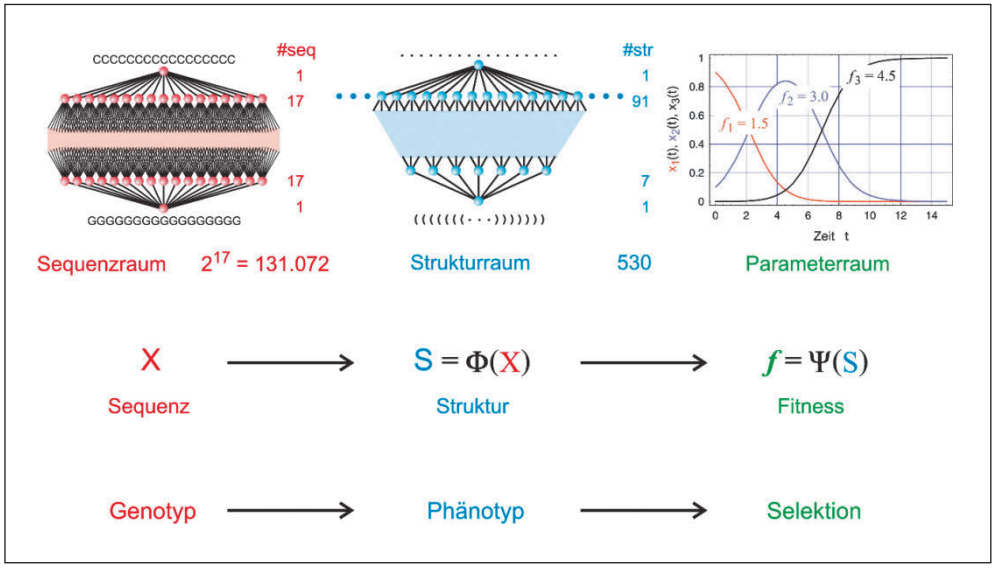

Abb. 3 Das Paradigma der Strukturbiologie. Die Beziehung zwischen Sequenzen, Strukturen und Fitness ist anhand eines einfachen Beispiels, einer kleinen binären Sequenz mit der Länge 17, als eine Folge von zwei (mathematischen) Abbildungen (Pfeile) skizziert. Statt der vier Basen des Erbguts verwendet dieses Beispiel zwei Werte (C, G), um einen Sequenzraum zu illustrieren.[4] Er besteht aus 131 072 Sequenzen. Diese werden auf 530 mögliche räumliche Strukturen abgebildet.[5] Die Strukturen wiederum entsprechen Phänotypen, deren Fitness als eine zweite Abbildung aus dem Strukturraum auf Fitnesswerte verstanden wird.

4 Siehe Reader und Joyce 2002.
5 Siehe Schuster 2006.

Die Vielfalt der Eigenschaften von Biopolymeren entsteht dort, wo eine kleine Veränderung der Sequenz, etwa der Austausch eines einzigen Nukleotidbuchstaben (eine Punktmutation), eine Änderung der molekularen Struktur zur Folge hat. Dies ist nicht immer der Fall – es gibt auch strukturneutrale Mutationen. Verändert die Sequenzänderung aber die Struktur, so kann das die molekularen Eigenschaften des Biopolymers stark beeinflussen. Eine solche strukturverändernde Mutation kann die Fitness des Organismus, also die Anzahl der Nachkommen, erhöhen, verringern oder unberührt lassen. Die Abbildungen 4 und 5 illustrieren diese Vorgänge am Beispiel eines RNA-Moleküls.

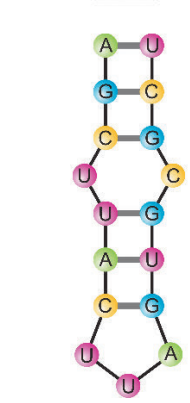

Abb. 4 Die Sekundärstruktur eines kleinen RNA-Moleküls. Die Abbildung zeigt einen einfachen „Hairpin Loop", der aus den vier Basen der RNA (A, C, G, U) aufgebaut ist. Die Nukleotid-Kette (oben) nimmt die Sekundärstruktur leicht ein, denn sie hat die geringste freie Energie. Das Prinzip der Strukturbildung lässt sich mithilfe der Basenpaare veranschaulichen: A paart mit U und G paart mit C. Gelegentlich kommen auch GU-Paarungen vor. Unter der Sequenz am oberen Rand des Bildes ist eine schematische Darstellung von Sekundärstrukturen in einem Alphabet mit drei Symbolen gezeigt. Klammern kennzeichnen Basenpaare, einzelne Punkte stehen für ungepaarte Nukleotidreste.

Zusammengefasst können wir sagen, dass kombinatorische Komplexität bei Biomolekülen aus zwei unabhängigen Quellen entsteht: aus der Diversität durch kombinatorische Vielzahl von Sequenzen und durch die komplexe Beziehung zwischen Sequenzen, Strukturen und biochemischen Eigenschaften. Sind beide Kriterien erfüllt, dann resultiert eine unerschöpfliche Vielfalt von molekularen Strukturen mit einem ungeheuer breiten Spektrum von Eigenschaften.

5. Komplexität durch Evolutionäres Basteln

Neben der Diversität der Biomoleküle birgt die Evolution noch eine weitere Quelle der Komplexität: die sogenannte evolutionäre Bricolage, zu Deutsch das evolutionäre Basteln mit dem bereits vorhandenen molekularen Baukasten. Der Begriff geht auf den Franzosen François Jacob (1920–2013) zurück. Im Jahr 1977 führte er in seinem Artikel *Evolution and tinkering* (1977)[6] aus, dass die Evolution kein grundlegendes Neudesign hervorbringt, sondern stets aus dem bereits Vorhandenen schöpfen muss. Dabei würden Teile einer Gesamtstruktur so umfunktioniert, dass sie in Aufgaben zum Einsatz kommen, für die sie

6 Siehe Laubichler 2007.

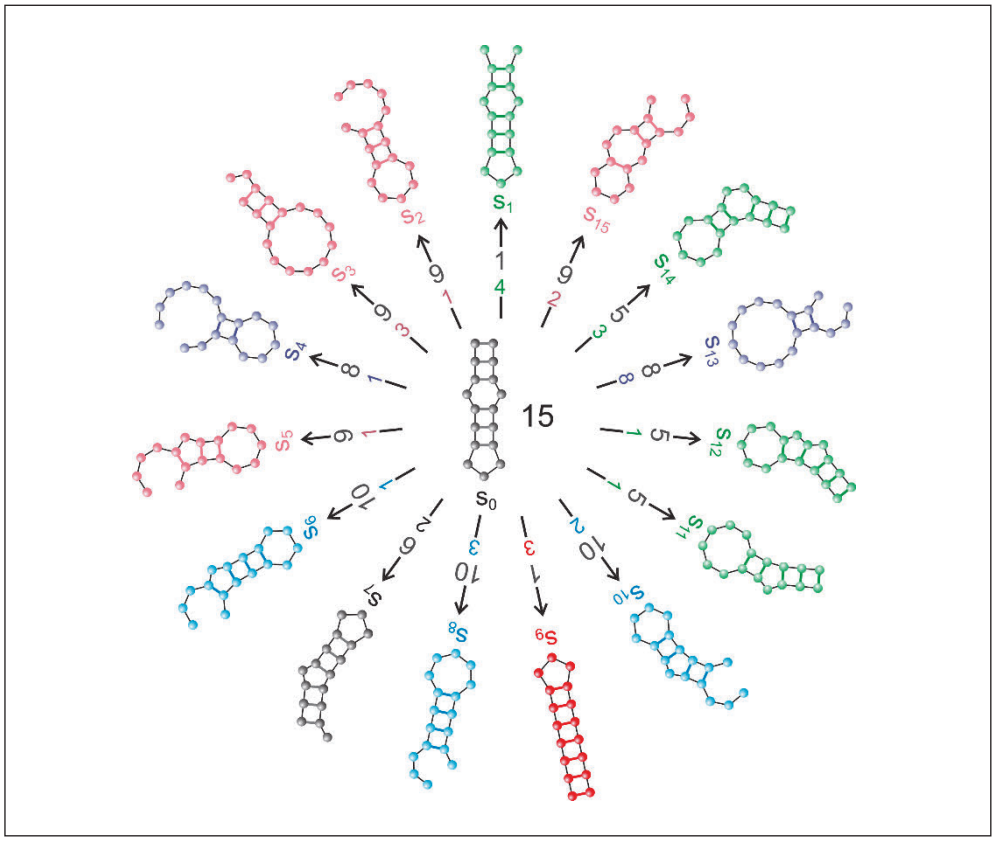

Abb. 5 Die Strukturen aller Einfehler-Mutanten einer kleinen RNA. Die Abbildung zeigt die Sekundär-Strukturen aller 51 Einfachpunktmutationen der Sequenz X0 aus Abbildung 4. Einige Mutationen bringen dieselbe Struktur hervor. Die häufigste ist die Struktur in der Mitte; sie kommt insgesamt 15-mal vor. Die Häufigkeiten der anderen Strukturen (farbige kleine Zahlen) sind im inneren Kreis angegeben. Die großen grauen Zahlen geben ein Maß für die Unähnlichkeit von zwei Strukturen (die Basenpaardistanz) an. Beispielsweise sind S1 und S9 der dominierenden Struktur S0 am ähnlichsten, oder am wenigsten unähnlich.

ursprünglich nicht gedacht waren. Jacob verglich die Natur mit einem Bastler (franz.: *le bricoleur*), der nicht neu designen kann, sondern seine „Konstruktionen" aus vorhandenen Stücken zusammenbauen muss.

Seit Jacobs Arbeit sind zahllose Beispiele von evolutionärer *Bricolage* aus vielen Bereichen der Biologie bekannt geworden.[7] Besonders eindrucksvoll sind Ergebnisse der Kombination von Entwicklungsbiologie und Molekulargenetik,[8] die gezeigt haben, dass vom Ursprung her gleiche (homologe) Gene[9] in verschiedenen Arten unterschiedliche Regulationsfunktionen ausüben. Die aus diesen homologen Genen produzierten, evolutionär konservierten Proteine erfüllen also unterschiedliche Aufgaben in verschiedenen Arten.

7 Siehe Duboule und Wilkins 1998.
8 Siehe Carroll 2008.
9 Als homolog werden Gene genannt, die phylogenetisch von einem gemeinsamen Vorfahren abstammen.

Fortlaufendes Basteln führt zu überaus komplexen Formen der Wechselwirkung durch Akkumulation zufälliger Funktionszuordnungen, sodass die Bestandsaufnahme und Analyse biologischer Regelkreise noch erschwert ist. Es ist daher naheliegend, auch das evolutionäre Basteln als eine Quelle von Komplexität in der Biologie anzusehen.

6. Künstliche Evolution umschifft das Problem der Komplexität

6.1 Wie schafft es die Natur, aus der ungeheuren Vielfalt möglicher Lösungen die brauchbaren herauszufinden?

Ein Erfolgsrezept hat Charles Darwin (1809–1882) entdeckt und korrekt gedeutet.[10] Die darwinsche Evolution findet in Populationen statt und benötigt drei voneinander unabhängige Systemeigenschaften.

- Die Individuen der Population müssen sich vermehren können.
- Neben perfekten Kopien bringt diese Reproduktion auch fehlerbehaftete Kopien (Mutationen) hervor, die zur Variation der Eigenschaften von Individuen führen. Neben der Mutation entspringt die genetische Vielfalt bei höheren Organismen außerdem der Rekombination: Bei der sexuellen Reproduktion werden die Genome der beiden Paarungspartner in Pakete zerlegt und in den Nachkommen neu kombiniert. Dadurch entstehen Genome mit neuen Genkombinationen, ohne dass durch Mutation neue Gene auftreten.
- Infolge eines Wettbewerbs um endliche Ressourcen kommt es zur Selektion jener Mutationen, die die höchste Fitness erzeugen.

Das Selektionsprinzip an sich ist einfach. Komplex wird die Biologie, wenn man danach fragt, welche Eigenschaften eines Organismus seine Fitness bestimmen und wie sie dies tun. In der Realität ist die Befähigung zur Reproduktion die wichtigste der drei Eigenschaften darwinscher Evolution, denn die anderen beiden ergeben sich zwangsläufig: Kein natürlicher Prozess tritt mit vollkommener Genauigkeit ein – schon allein aufgrund der thermischen Bewegung der Moleküle sind Fehler unvermeidbar. Und dass die Ressourcen in einer endlichen Welt endlich sind, ist eine Trivialität.

Von allen bekannten Biomolekülen haben nur die Nukleinsäuren, RNA und DNA, die Fähigkeit, als obligate Vorlagen für eine Reproduktion dienen zu können. Das Eigenschaftswort obligat bedeutet, dass jede Sequenz repliziert werden kann. Nukleinsäuren sind daher gute Kandidaten für das Studium von darwinscher Evolution in einfachen chemischen Systemen.

6.2 Probieren statt studieren: Künstliche Evolution als methodischer Ausweg?

Wie können wir als Forscher evolutionäre Prozesse experimentell untersuchen, ohne an der Komplexität natürlicher Systeme zu scheitern? In den 1960er Jahren wurden die ersten erfolgreichen Evolutionsexperimente im Reagenzglas durchgeführt.[11] Zur Reproduktion von RNA-Molekülen diente ein einfaches Enzym, Qβ-Replikase, welches aus *Escherichia-coli*-Bakterien isoliert wurde, die mit Qβ-Bakteriophagen infiziert waren. Einige Zeit nachdem

10 Siehe Darwin 1859.
11 Siehe Spiegelman 1971.

Sol Spiegelman (1914–1983) und Mitarbeiter die ersten erfolgreichen Evolutionsexperimente durchgeführt hatten, gelang Christof K. Biebricher (1941–2009) im Laboratorium von Manfred Eigen die erste vollständige molekularkinetische Analyse dieser künstlichen Evolution.[12] Sehr bald wurde erkannt, dass die evolutionäre Optimierung *in vitro* auch zur Herstellung von vermehrungsfähigen Molekülen mit vorbestimmten Funktionen eingesetzt werden kann. Dabei wird die natürliche Auslese durch künstliche Selektion nach den Vorgaben des Experimentators ersetzt. Die im Laborbetrieb am meisten verwendete evolutionäre Methode wird SELEX (*systematic evolution of ligands by exponential enrichment*) genannt. Bei dieser Methode erfolgt die künstliche Selektion mithilfe einer Chromatographiesäule, an welche die Zielmoleküle gebunden sind, für die optimale Bindemoleküle „gezüchtet" werden sollen. Die Verbesserung der gewünschten Eigenschaften erfolgt in Selektionszyklen, die so oft wiederholt werden, bis ein zufriedenstellendes Ergebnis erzielt wurde.

Bei der Optimierung durch eine solche künstliche Evolution ist eine Kenntnis der funktionellen Strukturen nicht notwendig. Damit wird die größte Komplexitätsklippe der Strukturbiologie umschifft, die, wie wir vorhin beschrieben, in den ungeheuer verwickelten Beziehungen zwischen Sequenzen und Strukturen besteht. Die Steuerung der Synthese von Molekülen mit vorbestimmbaren Eigenschaften wird von unserem Wissen über die Biomoleküle auf den Evolutionsprozess übertragen. Dementsprechend wurde das komplexe Problem der Sequenz-Struktur-Eigenschaft-Beziehung auf das einfache Problem des evolutionären Designs übertragen.

Eine Redewendung in den Vereinigten Staaten lautet: „There is no free lunch", und dies gilt in vollem Umfang auch hier. Bei den evolutionären Methoden müssen sehr viele Moleküle synthetisiert und ausprobiert werden, wogegen das rationale Design, wie man die nicht evolutionäre direkte Methode nennt, mit der einfachen Synthese der optimalen Verbindung auskommt. Mangel an Wissen wird in der evolutionären Biotechnologie mit dem Aufwand einer gewaltigen Materialschlacht bezahlt.

7. Komplexität ohne Ende – ein Ausblick

Zum Schluss betrachten wir noch die Entwicklung von Komplexität in der biologischen Evolution als Ganzes. Die Komplexität von Individuen nimmt ebenso zu wie jene der biologischen Welt als Ganzes. Obwohl es schwer fällt, einen Mechanismus für die Komplexitätszunahme anzugeben, ist es nicht schwer, Beispiele zu finden, die zeigen, dass die genetische Information eines Organismus im Laufe der darwinschen Evolution nicht systematisch zunimmt.[13] John Maynard Smith und Eörs Szathmáry ordnen in ihrer Monografie die Komplexitätszunahmen der Biosphäre in Phasen, sogenannten *major transitions*.[14] Solche Hauptübergänge führen von Einzelmolekülen zu Genomen, von einer RNA-Welt zu einer DNA-RNA-Proteinwelt, von Prokaryoten zu Eukaryoten, von Einzellern zu Vielzellern, von solitären Individuen zu Tiergesellschaften, von Primatengesellschaften zu menschlichen Gesellschaften. Und diese wiederum haben von der Steinzeit bis heute in mehreren Übergängen stark an Komplexität zugenommen.

12 Biebricher et al. 1983, Biebricher 1983.
13 Siehe Schuster 2016.
14 Siehe Maynard Smith und Szathmàry 1995.

Wer diese Komplexität in Natur und Gesellschaft verstehen und meistern will, kommt um die richtige Kombination rigoroser mathematischer Analyse großer Mengen sorgfältig ausgewählter Daten und umfangreicher Computersimulationen nicht herum. Noch steckt unser Verständnis der komplexen Lebensvorgänge in den Kinderschuhen. Dennoch gelingt es an einigen Stellen bereits, die metabolischen Prozesse zu modellieren und zu steuern, so etwa im Fall von Viren und Bakterien. Und ich bin überzeugt, dass wir auf diesem Gebiet rasant dazulernen werden. Alle zwei bis drei Jahre gibt es eine umwälzende Neuerung – die CRISPR-Cas9-Technologie war die jüngste und sicher nicht die letzte. Zugleich behalten grundlegende Erkenntnisse, wie die mendelschen Gesetze der Vererbung ihre Gültigkeit. Das Wissen um Epigenetik hat die biologischen Erkenntnisse entscheidend erweitert,[15] auch wenn Tier- und Pflanzenzüchter heute wie damals ihre Samen und Tiere für die Kreuzungen nach denselben auf Mendel zurückgehenden Kriterien aussuchen. Auch die aus der Molekularbiologie abgeleiteten Grundeinsichten, wie das Dogma „DNA macht RNA macht Proteine“ (Crick), werden entlang neuer Erkenntnisse modifiziert, ergänzt und erweitert, während ihre prinzipielle Gültigkeit bestehen bleibt.

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15 Siehe Jablonka und Lamb 2005.

Diskussion

Gast: Sie haben bei den chemischen oder biochemischen Wegen von Schaltern gesprochen. Ich habe dies so früher auch gelernt. In der Biologie gibt es jedoch keine digitalen Schalter, mit denen man an- und ausschalten kann, sondern die Komplexität entsteht dadurch, dass analog gearbeitet wird. Die Steuerung von Genexpression, bei der kein Gen an- oder ausgeschaltet wird, ist ein sehr analoger Prozess, der von vielen Dingen beeinflusst wird, zum Beispiel davon, wie viel exprimiert wird.

SCHUSTER: Ich glaube, dass die Daten von der Phospho-Fructokinase zeigen, dass die Phosphorylierung keinen solchen Schalter hat. Aber die einzelnen Enzyme arbeiten an dieser Stelle genau so, dass sie den Rest der Reaktionskette anschalten und abschalten. Wir verwenden An- und Abschalten eher als Analogie.

SINGER: Herr SCHUSTER, Sie haben, abweichend von Ihrem Titel, einen recht optimistischen Ausblick gegeben. Wenn wir nur genügend Daten – gute Daten – haben, genügend Rechenkapazität und genügend intellektuelle Kapazität, um analytische Rechnungen anzustellen, dann werden wir mit diesen Systemen zurechtkommen. Das alles ändert aber doch nichts daran, dass die Dynamik dieser Systeme prinzipiell fast nicht voraussagbar ist – auch, wenn wir die Randbedingungen gut kennen. Und, abgesehen davon, dass wir sie nicht kennen, bedeutet das ja aber auch, dass die Steuerbarkeit dieser Systeme außerordentlich problematisch ist. Ich hätte gern Ihren Kommentar dazu, wie wir das, was wir täglich lesen, verstehen sollen. Nämlich, dass Eingriffe zum Beispiel in die Finanzmärkte oder Wirtschaftssysteme durch Besteuerungen bestimmte Effekte nach Ende der Wahlperiode haben werden. Wie wahrscheinlich ist es, dass es sich dabei um Wunschträume handelt und überhaupt keine wissenschaftliche Basis dafür existiert, solche Prognosen zu machen? Und wie verhält es sich dann mit dem Eingreifen? Sollte man nicht lieber evolutionäre Algorithmen anwenden, um herauszufinden, wie sich komplexe Systeme stabilisieren lassen, anstatt dirigistisch einzugreifen.

SCHUSTER: Ich glaube nicht, dass man eine pessimistische Perspektive haben muss. Aber man benötigt eine rigorose mathematische Beschreibung des Problems, egal ob Finanzmarkt oder Biosphäre. Ein Beispiel wäre der Windkanal und der Wetterbericht. Bei beiden gibt es Luftströmungen, und um diese zu beschreiben, werden dieselben Gleichungen verwendet. Der Windkanal ist sehr einfach und ohne Profil angelegt, sodass er eine perfekte laminare Strömung erzeugt, mit der man gut modellieren kann. Im anderen Fall haben wir dieselben Gleichungen, dieselben Strömungen, aber eine heterogene Oberfläche, nämlich die Erdoberfläche. Dies erzeugt Turbulenzen auf allen Skalen. Dann komme ich eigentlich nur weiter, wenn ich mit vielen Messstationen arbeite, also mit Big Data. Langfristige Vorhersagen werden dann allerdings sehr ungenau oder falsch. Ich brauche also ein ordentliches mathematisches Modell, die richtigen Daten und dann entsprechende Computersimulationen. Ohne die geht es nicht.

Gast: Sie sagen, man brauche exakte mathematische Beschreibungen für ein Problem. Ich persönlich sehe das nicht, vor allem nicht bei Big Data. Es gibt dabei ja eigentlich keine exakte mathematische Beschreibung. Mit Big Data können wir nichts vorhersagen, sondern wir können nur retrospektiv erkennen, dass es vielleicht Korrelationen gibt.

Schuster: Aber ich muss die Big Data ja irgendwo eingeben. Denken wir an den Wetterbericht. Die Daten kommen in ganz einfache Wettermodelle hinein. Mit Big Data meine ich eine große Zahl, aber nicht wahlloses Sammeln in der Hoffnung, dass irgendwann einmal jemand kommen und die richtigen Schlussfolgerungen ziehen wird. Ich meine große Mengen der richtigen Daten, muss aber auch mit der entsprechenden Computerunterstützung arbeiten können.

Lengauer: Aus meiner Sicht schließen sich die mathematische Theorie und Big Data nicht aus, sondern können sich in der besten aller Welten ergänzen. Das beste Beispiel, das wir jüngst gesehen haben, sind die Gravitationswellen, die sicher eine Big-Data-Komponente haben. Daten, die dabei gesammelt werden, sind umfangreich und zunächst unstrukturiert und von Hand nicht zu durchsuchen. Wir haben jedoch auch eine unglaublich starke Theorie, die uns in die Lage versetzt, diese Daten zu interpretieren. Und so eine Theorie hätte ich in der Biologie liebend gern auch; eine kleine Portion davon wäre uns schon sehr lieb. Diese gibt es heute noch nicht, und die Frage ist, ob es sie je geben wird.

Friedrich: Herr Schuster, Sie haben gezeigt, wie komplex das Ökosystem ist. Ist es denkbar zu modellieren, wie sich ein Ökosystem verhält, wenn man einen genetisch modifizierten Organismus darin freisetzt? Wir Wissenschaftler werden ja dazu aufgefordert, uns zu den möglichen Risiken zu äußern.

Schuster: Meiner Meinung nach wissen wir über modifizierte Organismen noch zu wenig. Aber, wenn ich einen solchen Organismus freisetze, dann ist die sichere Prognose, dass dieser keine drei Generationen überlebt, da er ganz einfach weit weg ist vom Optimum der natürlichen Organismen. Eingriffe in das Ökosystem unternimmt der Mensch ja sowieso schon seit jeher. Ein Beispiel sind die Kaninchen in Australien. Das war kein gentechnischer Versuch, aber er hatte katastrophale Folgen. Das kann man auch sehr schön bei uns beobachten: Wir haben Tiere, die es vorher hier nie gab und die alle durch den Menschen hereingebracht worden sind. Beispielsweise die Waschbären: In der Nähe von Göttingen auf Schloss Berlepsch gab es einen alten Grafen, der Waschbären mochte, sich welche hat kommen lassen und diese dann dort in einem Käfig gehalten hat. Sein Sohn fand jedoch: „Die armen Waschbären im Käfig, die lassen wir jetzt mal frei!“ Und dann haben sie begonnen – das war ungefähr 1920 – sich munter zu vermehren und nach Süden zu wandern. Nach dem Zweiten Weltkrieg waren sie in Salzburg, und jetzt sind sie schon in Kärnten. Ich sehe nicht, dass durch die Gentechnik, wie etwa CRISPR, etwas völlig anderes geschieht.

Hacker: Über den Brenner werden sie es wohl auch noch schaffen. Herr Schuster, herzlichen Dank für Ihren Vortrag und für die Diskussion.

Opening Remarks

Bärbel Friedrich ML (Berlin)[1]

On behalf of the German National Academy of Sciences Leopoldina and as a member of the Scientific Board of this conference, it is my great pleasure to welcome you to the workshop "Crossing Boundaries in Science". This workshop is devoted to the topic of Modelling Nature and Society and thus addresses the question 'Can We Control the World?'. I am delighted that so many guests accepted our invitation to participate in this scientific event that is taking place at one of the most splendid cultural sites in Germany, the city of Weimar.

The German National Academy of Sciences Leopoldina, which has organised this workshop, is one of the oldest academies of sciences worldwide. It was established in 1652. 25 years later, it was officially endorsed by the German Emperor Leopold I. Today, the Leopoldina counts more than 1,500 members who are outstanding scientists from all disciplines and more than 30 countries. Among them are 32 Nobel laureates, and we are particularly honoured to welcome one of them, Professor Christiane Nüsslein-Volhard, who will give the first presentation in this session. In addition to acting as a scholarly society, the Leopoldina has adopted two major mandates since it was appointed the German National Academy of Sciences in 2008: to provide advice to policy makers and to civil society, and to represent the German scientific community on the international level. The Leopoldina is dedicated to identifying major scientific developments that may have a societal impact in the future, including topics such as climate change, energy supply, the sustainable use of natural resources, demographic change, and new technologies for human healthcare – all of which are going to be discussed during the next two days.

About the Workshop

The Crossing Boundaries in Science workshop follows in the footsteps of the Jena Life Science Forum conference series organised by the Friedrich Schiller University in Jena. We are grateful for the valuable advice we received from two colleagues who were involved in the preceding conferences, Olaf Küppers and Frank Laplace, and for the financial support from the Federal Ministry of Education and Research.

Crossing Boundaries in Science aims to stimulate the open discussion of scientific fields involving new forms of interdisciplinary cooperation and translational science. We hope that the selection of presentations will shine light on anticipated or emerging social transformations arising from scientific developments as well as on their potential ethical implications.

1 German National Academy of Sciences Leopoldina, Halle/Saale, Berlin.

This first workshop is entitled "Modelling Nature and Society – Can We Control the World?" and focusses on the scientific modelling of complex biological and social networks. The conclusions derived from such models for targeted and strategic interventions will be discussed. Topics such as molecular gene networks, the immune system, epidemiological phenomena, traffic dynamics, financial systems and man-made climate change will be addressed. The complexity of these systems is barely comprehensible to the individual. And scientists are well aware of the limitations in modelling sophisticated, complex systems, since the results of strategic interventions into complex systems do not often meet the expected predictions.

Crossing Boundaries in Science will approach these challenges during what I hope will be lively discussions at the end of each session, raising questions such as:

– Are there analogous conceptual bases for the analysis of different complex networks?
– How many variables are required or useful for appropriate modelling?
– Are there advantages in using simplified versus comprehensive models based on big data?
– Can science contribute to targeted strategic interventions into complex cross-linked systems?

The excellent opening lecture by Peter Schuster last night already gave us some clues about the challenges and pitfalls of scientific models and their application to the management of complex systems.

Final Remarks

Finally, I would like to express my gratitude to the members of the Scientific Board for drafting the concept and programme of the workshop on Modelling Nature and Society. I would also like to extend my thanks to the speakers for their upcoming contributions. Last but not least, I would like to acknowledge those behind the scenes who organised and coordinated this meeting, in particular Yvonne Borchert, Johannes Fritsch, and Stefan Artmann.

Session 1

Chair: Jörg HACKER ML (Halle/Saale)

Nova Acta Leopoldina NF Nr. *419*, 33 – 44 (2017)

Gradient Models in Developmental Biology: A Historical Perspective

Christiane Nüsslein-Volhard ML (Tübingen)[1]

Abstract

The problem of complexity formation in the development of organisms has fascinated biologists for centuries. The contribution provides a historical perspective on research work in this field of developmental biology, starting at the beginning of the 20th century, when Theodor Boveri suggested that cell fates may depend on a graded distribution of some substance in the egg. In the 1920s, Hans Spemann discovered an organiser region in the newt embryo. In 1952, Alan Turing proposed a mathematical model to explain self-organisation from initially homogeneous states based on chemical interactions. In 1969, Lewis Wolpert coined the term 'positional information' and proposed a model of a gradient of a morphogen that elicits different responses depending on its concentration. In 1972, Gierer and Meinhardt formulated their gradient theory of local activation and lateral inhibition based on non-linear kinetics. This view was supported by mutant phenotypes in *Drosophila*. Systematic mutant screens in *Drosophila* and subsequent cloning of the genes have led to the identification of a large number of morphogenetic proteins.

1. Introduction: Theodor Boveri

The problem of how complexity arises in the development of every single organism has fascinated biologists for centuries. By the beginning of the twentieth century, it had been recognised that the final pattern of cell differentiation in the embryo is established through a gradual process during which initially simple patterns are elaborated to achieve increasingly greater complexity. The morphological steps that produce this complexity are reproducible from one embryo to the next. However, the underlying mechanisms were unknown. Based on the observable polarity in sea urchin and nematode eggs, the German zoologist Theodor Boveri suggested that initial cell decisions might depend on a graded distribution of some substance in the egg, such that different amounts of that substance would be included in the different cells formed through cleavage (Boveri 1901). The central ideas that emerge from Boveri's view of development are that spatial patterns are present as polar distributions of morphogenetic substances from the earliest stages, that these patterns are simple, and that the subsequent influence of genes on chromosomes builds the ultimate functional patterns in the final organism.

In Boveri's days, genes were still to be discovered, genetics had not yet been developed, and the biochemical means of isolating and identifying molecular components were very limited. Despite these limitations, Hans Spemann, one of Boveri's students, took the next big step when he discovered a specific region of the gastrulating newt embryo (*obere Urmundlippe*) which, when transplanted into the opposite side of a host embryo, would in-

1 Max Planck Institute for Developmental Biology, Tübingen.

duce the formation of a new body axis in the surrounding tissue. This organiser experiment was very famous at the time (and led to the 1935 Nobel Prize) and many researchers tried to isolate the inducing 'factor' from that organiser region (Spemann 1935). But these attempts failed. The molecular nature of the organiser was revealed only recently, after molecular genetics had been introduced to the analysis of embryology.

2. Turing: Reaction-Diffusion

In 1952, Alan Turing, the famous mathematician and code breaker, published the paper *The Chemical Basis of Morphogenesis*, in which he described a mathematical theory according to which patterns arise from uniformity by self-organisation triggered by chemical interactions. In simulations on his early computers, Turing described the emergence of patterns from the interaction of two substances which he called morphogens if the two morphogens diffuse at different rates. These types of models with two interacting diffusing morphogens were later coined reaction-diffusion (RD) models.

At the time, Turing's paper made little impact. Many biologists dismissed it because it was mathematically too complicated; further, it failed to explain that biological specimen scaled, i.e. adjusted to size variations which Turing's model could not explain. In addition, the discovery of the double helix in 1953 diverted the attention of biologists toward the study of molecular biology in prokaryotes and embryology became increasingly unpopular.

Nevertheless, in the early 1970s, a number of molecular biologists who had contributed to the elucidation of the genetic code, protein synthesis, and DNA replication turned to developmental biology with the aim of understanding the molecular basis for the increased complexity arising during development from the near homogenous egg cell. Several model systems were established, with research focussing on gene regulation and pattern formation in eukaryotes. Sydney Brenner introduced the nematode (roundworm) *Caenorhabditis*

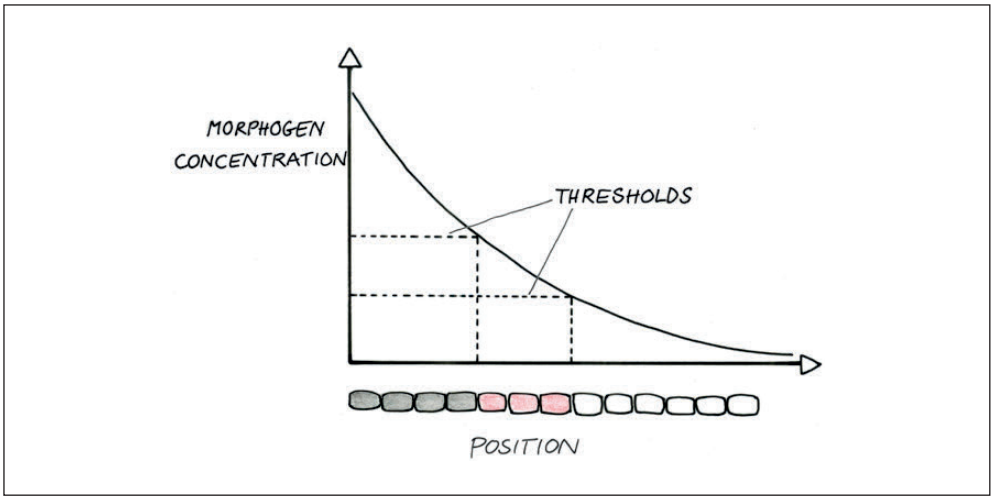

Fig. 1 Wolpert's concept of positional information: a morphogen elicits different responses at different concentrations. Thresholds of responses lead to a subdivision of the field.

elegans as a genetic model system, Alan Garen and Seymor Benzer turned to *Drosophila melanogaster*, François Jacob started to work on mouse embryos, and George Streisinger selected the zebrafish *Danio rerio* as a vertebrate in which genetic approaches were feasible. The laboratories of the theoretical biologists Lewis Wolpert and Alfred Gierer investigated the striking regenerative capacities of the polyp *Hydra attenuata*.

Lewis Wolpert introduced the concept of *positional information*: the position of a cell within a developing field could be defined by the local concentration of a morphogenetic substance distributed in a concentration gradient. Complexity could arise from morphogens eliciting different responses with different thresholds above which a specific response would occur. Different concentration ranges must somehow translate into different cell states (Fig. 1) (Wolpert 1969).

Wolpert realised that early morphogenesis generally takes place when embryos are still very small, in areas comprised of 50 or 100 cells at most, and Francis Crick calculated that for such a small space, diffusion from a local source and decay in a 'sink' could result in a linear gradient (Crick 1970). Crick's simple calculations, however, only showed that gradient formation by simple diffusion in embryos was plausible, not that gradients actually do exist.

3. Gierer and Meinhardt: Autocatalysis and Lateral Inhibition

Based on regeneration experiments in hydra, Alfred Gierer and Hans Meinhardt in Tübingen proposed a more versatile mathematical theory of biological pattern formation (Gierer und Meinhardt 1972). Their model incorporates two features frequently observed in biological systems: autocatalysis and lateral inhibition. Like Turing's model, it is based on the different diffusibility of two components: a short-range activator with strong self-enhancing capabilities coupled to an inhibitor of longer range that suppresses the activator in the surrounding areas. The Gierer-Meinhardt equations were formulated in terms of non-linear reaction-diffusion kinetics, although the underlying concepts were not motivated by biochemistry, and both Gierer and Meinhardt always pointed out that there might be many different realisations of their theory. The diffusion and degradation of molecules was the simplest way to implement short-range activation and long-range inhibition in the models, but apart from inhibition Gierer and Meinhardt also considered other mechanisms for transporting and depleting a substrate (Fig. 2).

Although the theory was driven by the experimental work on hydra, it also provided an important general recipe for self-organisation using realistic boundary conditions and plausible parameters. By introducing source densities in addition to the activator-inhibitor system, scaling could be explained, making Gierer and Meinhardt's theory immediately attractive to developmental biologists. Strikingly, even in the absence of specific molecular data, these models correctly predicted the behaviour of several biological systems. With the inherent property of self-regulation, the final pattern is largely independent of the starting conditions. Based on these concepts, Meinhardt performed computer simulations of patterns that could be observed during development, such as embryonic polarity, segmentation, formation of spacing patterns, the positioning of stomata in plants or bristles in the epidermis of insects, the generation of net-like and branched structures like venation patterns in leaves, arborisations of trachea and blood vessels, and the chemotactic behaviour of eukaryotic cells.[2]

2 Meinhardt 1982; summarised in Roth 2011.

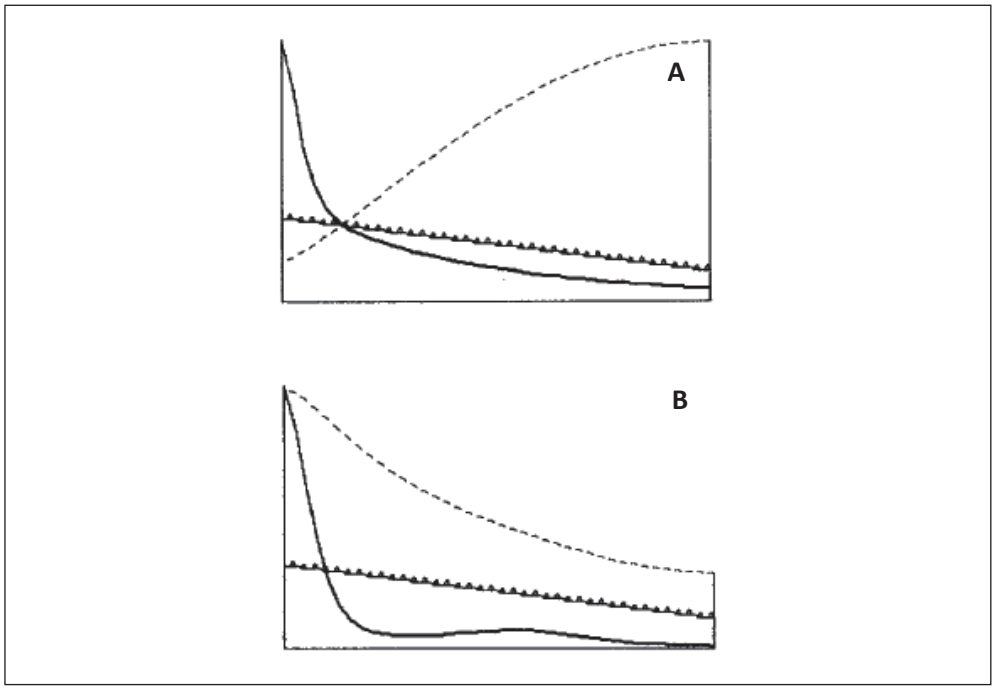

Fig. 2 Gierer-Meinhardt Model: Simulations of gradient formation by autocatalysis and lateral inhibition. (*A*) Depletion model, (*B*) Diffusion model. Solid line: Activator. Dashed line: Inhibitor. Triangles: Source density. From Gierer and Meinhardt 1972.

4. Morphogens

At the time, the concept of gradients was not widely accepted, although the famous mirror image duplications obtained after experimental manipulations of the insect eggs had pointed to the existence of gradients as determinants of the patterning of the egg axes (Sander 1960). Morphogens had not yet been identified and were thought to be elusive substances present at very low concentrations. There were plenty of reasons why it was so difficult to isolate morphogens, or indeed any factor that would instruct embryonic tissue to develop a particular structure. In the assays that were attempted, extracts to be tested for their biological activity were added to fragments of embryos (or stumps of the body column in the case of hydra) that were deprived of the hypothetical factor. One problem with such an assay seemed to be that the factor may never have been completely absent from the embryo fragment, but upon operation may even redistribute or regenerate and thus cause erratic results. Furthermore, the coarse experimental interferences upset delicate balances within the developing embryo, causing artefacts that were difficult to distinguish from real effects.

When Gierer and Meinhardt published their theory, I was a graduate student in Tübingen working on transcription of bacteriophage DNA. I cannot pretend that I fully grasped their model, but, in a mysterious way, the problem of pattern formation and morphogens fascinated me. At the time, Friedrich Bonhoeffer's group worked on DNA replication in

Tübingen. John Cairns had found that the enzyme thought to perform the replication, the Kornberg-polymerase, was not the right one, because, strikingly, a mutant lacking this enzyme was able to replicate normally (Lucia and Cairns 1969). Bonhoeffer performed systematic screens for temperature-sensitive mutations of DNA replication and identified the gene that encoded the replicating enzyme as well as other essential components of DNA replication. This work demonstrated how a mutation could cleanly and specifically eliminate one protein without affecting anything else. The missing factor could be isolated using an *in vitro* complementation assay. This convinced me of the power of a genetic approach to identify and isolate morphogens. I consulted the literature about combining embryology with genetics and soon found *Drosophila*.

At that time, *Drosophila* genetics largely dealt with mutants affected in the structures of the adult fly. Only a small number of embryonic mutants had been collected by scientists from the lab of Donald Poulson at Yale (Wright 1970). In the early seventies, some promising papers on *Drosophila* embryonic development were published. In a famous experiment, IIImensee and Mahowald (1974) demonstrated a transplantable activity localised at the posterior pole that could induce pole cell formation at the anterior. Even a mutant – *grandchildless* – was described that lacked pole plasm and pole cells, albeit in another *Drosophila* species. It seemed feasible to identify more genes encoding such factors by screening for maternal mutations that affected the informational content of the egg. A mutant embryo lacking a morphogenetic factor might be rescued by the injection of extracts from wild-type embryos and thus provide an assay for the isolation of the factor, which would be much more specific than was possible with operations on normal embryos. Most excitingly, Garen and Gehring (1972) reported a rescue of a maternal mutant, deep orange, by cytoplasmic transplantation. I joined the lab of Walter Gehring at the Biozentrum in Basel in 1975 with the long-term goal to isolate morphogens in *Drosophila*.

5. Morphogenetic Mutants

To test the feasibility of using genetics to identify such genes, I first studied mutants that were available at the time. A fascinating maternal mutation, *bicaudal*, caused the formation of larvae with two rear ends in mirror-image symmetry, albeit with erratic and low penetrance (Nüsslein-Volhard 1979). In a pilot screen, I isolated a new maternal mutant, *dorsal*, with a very specific loss of ventral pattern elements, such that the entire embryo appears dorsalised. The mutant *dorsal* has a clean, penetrant, and non-variable phenotype that is also dosage dependent. The phenotypic series suggested the existence of a gradient with a maximum at the ventral side of the egg determining the dorso-ventral axis. Taken together with the *bicaudal* phenotype, this implied that the anteroposterior and dorso-ventral axes were set up independently by two gradients positioned at right angles to each other (Nüsslein-Volhard 1979).

In collaboration with Eric Wieschaus, with whom I shared a lab for three years at the European Molecular Biology Laboratories (EMBL) in Heidelberg, we set out to study the genetics of *Drosophila* development, with the aim to identify most, if not all, of the genes that are involved in patterning the *Drosophila* larva along the dorso-ventral and anteroposterior axes. Two sets of genes are required for larval patterning. Maternal genes such as *bicaudal* and *dorsal* would be expressed in the female during oogenesis and would provide components required for embryonic development already in the egg. Zygotic genes would

supply components via transcription in the embryo and affect later patterning events. Mutations in both classes would cause lethality in the embryo and display a phenotype visible in the larval structures. Screens for maternal mutants are very tedious because they require two generations of inbreeding until homozygous females that can be tested for the production of abnormally patterned embryos can be obtained. We decided to first do large-scale screens for zygotic mutants because they were easier than maternal screens and extremely rewarding. Indeed, these projects resulted in a large and very exciting collection of patterning mutants, many of which turned out to encode morphogens.[3]

The screen for embryonic patterning mutants required the establishment of inbred families of flies derived from individual males arising from mutagen-treated sperm and scoring eggs from brother-sister matings carrying the same putative mutation. We tested about 20,000 inbred families in the generation that produces homozygous embryos and identified mutations in 40 genes affecting the anteroposterior pattern and about the same number affecting the dorsal-ventral pattern (Fig. 3).

Mutations affecting segment number and polarity were particularly fascinating because of the strange and unexpected pattern defects displayed in the mutant larvae. Three classes of such mutations could be distinguished (Nüsslein-Volhard and Wieschaus 1980). First, there were five gap gene mutants that displayed large deletions in unique embryonic regions in a gene-specific manner. Mutants of the eight pair-rule genes showed pattern deletions in every other segment with different frames of deletions for each gene. The third class of mutants, segment polarity mutants, displayed deletions associated with duplications in each segment. The possibility of grouping genes into classes suggested to us – who were unaware of their molecular function – that the segmented pattern was sequentially established. Initially, large unique regions were specified that guided the establishment of a first periodic pattern with double-segment periodicity. This pattern in turn was subdivided into fields of individual segments, each with its own pattern and polarity. Hans Meinhardt tried to incorporate the mutant phenotypes into a model assuming an activator peak at the posterior pole, based on the hierarchical induction of cell states, but this model did not fit the data very well – the understanding of the molecular interactions of the gene products had to wait for the molecular cloning of the genes.

6. Maternal Gradients

At the Friedrich Miescher Laboratory in Tübingen, my research group turned to mutations in those genes that affect the informational content of the egg. In parallel, similar screens for maternal mutants were performed in Princeton in the lab of Eric Wieschaus. Altogether, mutants in a total of about 40 maternal genes that cause pattern defects in the embryo have been identified. The mutant phenotypes affect either the anteroposterior or dorso-ventral pattern, supporting the notion of their independent establishment. Strikingly, three classes of mutants sharing the same or similar phenotype in each class were identified to affect the pattern along the anteroposterior axis. Some displayed anterior defects (prototype *bicoid*), others lacked the abdomen with head and tail present (prototype *oskar*), and still others lacked only the terminal regions with the middle intact (prototype *torso*). Eleven genes shared the dorsalised phenotype

3 Nüsslein-Volhard and Wieschaus 1980; reviewed in Wieschaus and Nüsslein-Volhard 2016.

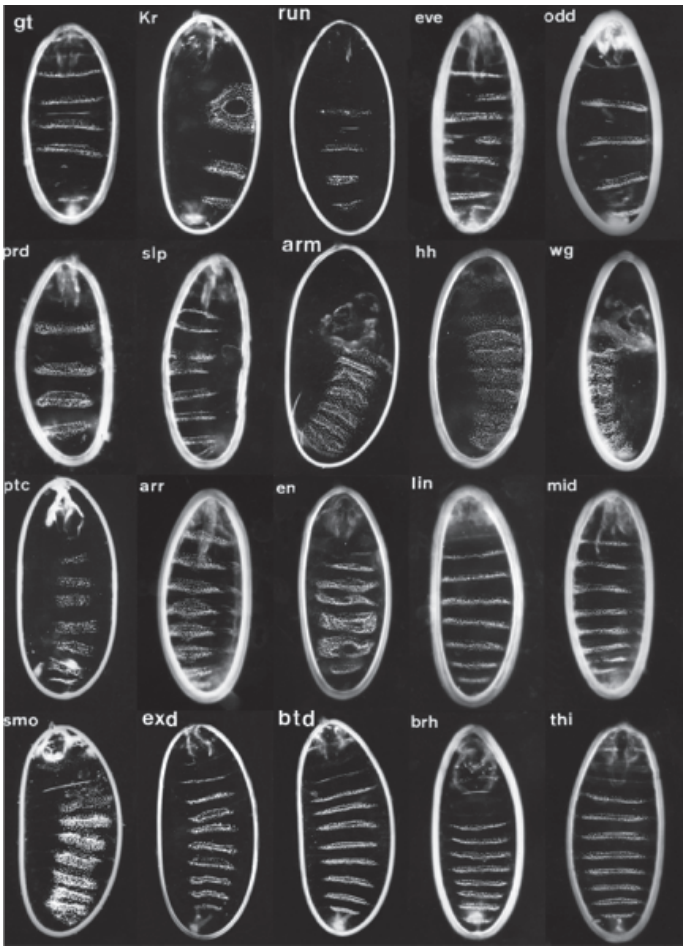

Fig. 3 Zygotic mutants affecting the *Drosophila* larval pattern along the anteroposterior axis. The figure shows the phenotypes of 20 of the 40 genes identified. For further explanations: Wieschaus and Nüsslein-Volhard 2016.

with *dorsal*, whereas mutants in the genes *Toll* and *cactus* displayed ventralisation, which suggests that they interacted to establish a gradient along the dorso-ventral axis (Fig. 4).[4]

To elucidate the functions and characteristics of each of the maternal genes, we performed cytoplasmic transplantations. These revealed that, in several instances, the phenotype could be rescued by the transplantation of cytoplasm from wild type embryos. Mutants in the gene *bicoid* were particularly fascinating; embryos produced from mutant females lacked the head and thorax entirely while the abdomen was still present (Fig. 4*b*). Hans-Georg Frohnhöfer, a graduate student in my lab, performed transplantation experiments and noted that the ante-

4 Reviewed in Johnston and Nüsslein-Volhard 1992.

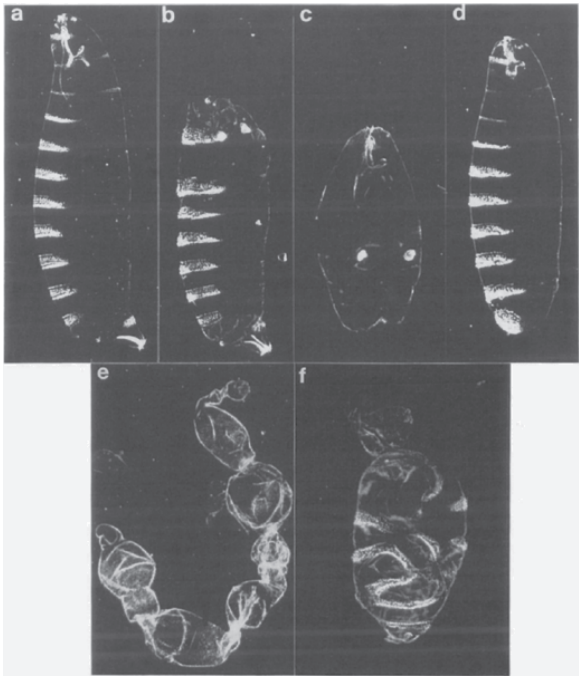

Fig. 4 Maternal mutants affecting the *Drosophila* larval pattern: (*a*) wild type, (*b*) *bicoid*, (*c*) *oskar*, (*d*) *torso*, (*e*) *dorsal*, (*f*) *cactus*. For further explanations: Nüsslein-Volhard 1991.

rior tip of embryos contained an activity that, when transplanted into *bicoid* mutant embryos, would rescue the phenotype. Following the transplantation of anterior cytoplasm to the middle or posterior egg positions, anterior structures developed in these regions. These experiments demonstrated the existence of a localised organising activity with a long-range effect on the embryonic pattern (Frohnhöfer and Nüsslein-Volhard 1986). The molecular cloning of the *bicoid* gene revealed that the *bicoid* mRNA is localised at the anterior pole of the egg and comprises the transplantable activity (Fig. 5). *bicoid* encodes a transcription factor. Wolfgang Driever showed that the Bicoid protein is distributed in an exponential gradient with a high point at the anterior tip and detectable levels well into the posterior region of the embryo.

This strongly suggests that the mRNA provides the source of the protein gradient spreading by diffusion from the anterior pole (Driever and Nüsslein-Volhard 1988a). A target gene, the gap gene *hunchback*, is expressed at concentration levels above those reached at about 50 % egg length. Remarkably, changing the source density by varying the number of gene copies of *bicoid* demonstrated a dependence of the *hunchback*-expression domain on the Bicoid protein concentration (Driever and Nüsslein-Volhard 1988b). Bicoid works by controlling the transcription of several gap genes in a concentration-dependent manner. It is the first described morphogen and still provides an intensely studied paradigm of morphogen action, since, to this date, the molecular mechanisms of its production and function are still not completely understood (Wieschaus 2016).

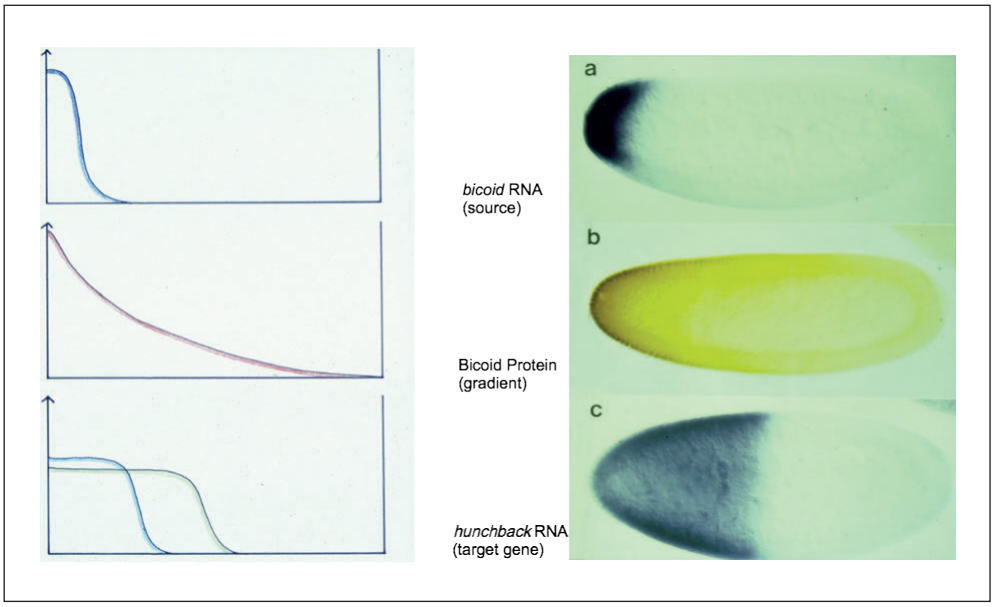

Fig. 5 Spatial distribution of *bicoid* mRNA, bicoid protein and *hunchback* mRNA. The left panel includes a hypothetical second target gene expression with a threshhold more anteriorly.

The investigation of the genes of the four classes revealed that, in each case, gradients of transcription factors are produced from localised signals. However, in each case, the mechanisms of gradient formation and establishment of polarity are widely different.[5] In two cases, the gradient source is a localised RNA, while in the other two cases it is an extracellular signal. In the case of the dorso-ventral pattern, for example, the *dorsal* gene, already identified in 1979, produces a transcription factor that is evenly distributed along the dorso-ventral axis in the freshly fertilised egg. The Dorsal protein is taken up into the cleavage nuclei at the ventral side but remains in the cytoplasm at the dorsal side, resulting in a gradient of nuclear localisation of the morphogen Dorsal. The polarity arises from a signal outside the egg cell emanating from the follicle cells that surround the growing egg cell during oogenesis. The signal, the product of the *spätzle* gene, activates the membrane-bound receptor Toll at the ventral side, releasing an inhibition by the Cactus protein of the nuclear uptake of the Dorsal protein (Roth et al. 1989).

In summary, the spatial pattern of the *Drosophila* embryo along the anteroposterior axis is established by two gradients emanating from the localised RNA sources at the anterior and posterior poles. Additionally, two short-range gradients specify the head and tail end independently. One gradient determines the dorso-ventral axis with a high point at the ventral midline of the egg. In each of these systems, a cascade of interactions of several morphogenetic proteins are involved in the establishment of the gradients; however, the type of interactions formulated in the reaction-diffusion models do not seem to play a role in any of them. In particular, there is no evidence for lateral inhibition. These early morphogens are transcription

5 Reviewed in Johnston and Nüsslein-Volhard 1992.

factors that control the activity of several target genes in a concentration-dependent manner. Further subdivisions occur through a cascade of activation and repression involving combinatorial transcriptional control and concentration dependence.

This mechanism is possible because, in the early *Drosophila* embryo, the spreading of proteins is not impaired by cell membranes. In later stages, however, when the subdivision into the repeated pattern of about 14 segments occurs, cell-cell interactions via signalling systems are involved. In these cases, a secreted ligand spreads throughout the tissue and is taken up by a receptor in the neighboring cells to activate the transcription of target genes. This mechanism also works in other contexts, such as organ formation and patterning of the adult structures in the imaginal discs. There is a limited number of conserved signalling pathways, including Notch, Hedgehog, Wnt, EGF, and BMP. Most of the genes encoding these ligands and receptors were first identified in the *Drosophila* screens of zygotic patterning mutants.[6]

In cellular systems, it is difficult to measure the parameters of diffusion and stability. Therefore, the sole fact that models can simulate the outcomes of experimental manipulations is not proof of the underlying mechanism. Nevertheless, gradient systems based on reaction-diffusion kinetics, in which proteins with different diffusibility interact with each other, have recently been proven plausible based on measurements of the physical parameters of the interacting molecules in the eggs of frogs, ascidians, and zebrafish. As a more general concept, it seems that, in many systems, gradients emanating from opposite poles establish the initial conditions that polarise the tissue. They trigger transcriptional networks of activators and repressors, resulting in the correct positioning of boundaries defining distinct cell states.[7] Whether the morphogens in cellular systems spread by diffusion in the extracellular space are transmitted via a relay system or distributed along thin cellular protrusions called cytonemes is still a matter of controversy.

7. Summary and Conclusions

At the beginning of the 20th century, Boveri suggested that cell fates may depend on a graded distribution of some substance in the egg. In the 1920s, Spemann discovered an organiser region in the newt embryo that could influence its surroundings, whereby the distance from the organiser determined the fate of the cells. In 1952, Turing proposed a mathematical model to explain self-organisation from initially homogeneous states based on chemical interactions. This famous reaction-diffusion (RD) model involves a slowly diffusing 'morphogen' interacting with an inhibitor molecule that easily diffuses. In 1969, Wolpert coined the term 'positional information' and proposed a model of a gradient of a morphogen that elicits different responses depending on its concentration. Crick (1970) calculated that a simple source-and-sink model could work to establish linear gradients of morphogens inside an embryo. In 1972, Gierer and Meinhardt proposed their gradient theory of local activation and lateral inhibition based on non-linear kinetics. Their model can explain many biological patterns. In insect eggs, mirror image duplications obtained after experimental manipulations point to the existence of gradients as determinants of the patterning of the long and short axes of the egg (Sander 1960). This view was supported by mutant phenotypes in *Drosophila* (Nüsslein-

6 Reviewed in Wieschaus and Nüsslein-Volhard 2016.

7 Reviewed in Briscoe and Small 2015.

Volhard 1979). Systematic mutant screens in *Drosophila* and subsequent cloning of the genes have led to the identification of a large number of morphogenetic proteins.[8]

The gradient models of Meinhardt failed to explain the development of the early *Drosophila* embryo because genetic analysis revealed a strong influence of localised maternal determinants rather than self-organisation. The first morphogen discovered was the product of the *bicoid* gene, a transcription factor produced by a RNA source localised at the anterior pole of the *Drosophila* egg. It spreads towards the posterior and activates target genes in a concentration-dependent manner (Driever and Nüsslein-Volhard 1988b, 1989). In cellular systems, pattern formation depends on cellular interactions involving several conserved signalling systems in which ligands spread in the extracellular space and activate membrane-bound receptors in target cells in a concentration-dependent manner. There is a limited set of such signalling systems that are highly conserved and operate in many tissues and, at several times, in the development of all metazoans.

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Nova Acta Leopoldina NF Nr. *419*, 45–51 (2017)

Systems Biology of Infection

Marc Thilo Figge (Jena)[1]

Abstract

Infectious diseases are unique in their potential for explosive global outbreaks as well as for chronic impact on their human targets. Fungal infection rates have risen dramatically over recent years and are a cause of increased morbidity and mortality, especially in patients with weakened immune systems. The excessive use of antibiotics contributes to the increased susceptibility of humans to pathogenic fungi, of which the ubiquitous fungus *Aspergillus fumigatus* and the opportunistic yeast *Candida albicans* are the most common types. Combining experimental and theoretical studies, systems biology of infection represents an interdisciplinary approach to describing and predicting in a quantitative manner the dynamic immune response to invading pathogens.

My talk is about modelling infections that may be life-threatening for people – people like the biblical figure Job, who had painful sores or boils from the soles of his feet to the crown of his head. He took a piece of broken pottery and scraped himself with it. Even today, we do not know exactly what disease he suffered from. Still, today we know of a condition called Job's syndrome that is associated with a mutation in an important gene that is involved in lymphocyte differentiation and in the neutrophil chemotactic activity. Patients with a defect in that gene develop recurrent skin and respiratory tract infections involving not only bacteria, but also fungi. And it is such fungi that we are particularly interested in at the Hans Knöll Institute in Jena.

There are millions of fungal species, but only a couple of hundred are pathogenic for humans. And even these pathogens are mainly dangerous for immunocompromised patients. However, modern medicine is, in a sense, responsible for a growing number of immunocompromised patients due to interventions in the immune system associated with certain types of surgery – transplants for instance – or during cancer treatment. Under these conditions, infections can more easily take hold. Over the past two decades, the number of sepsis cases has increased significantly, and 5 % of all cases are caused by fungal pathogens. This may seem like an insignificant number, but these fungal infections are associated with a high rate of mortality due to limited means of diagnosis and therapy.

1. Two Prominent Fungi

The two most important human-pathogenic fungi are *Aspergillus fumigatus* and *Candida albicans*. *A. fumigatus* is the most ubiquitous airborne fungus. It lives in your garden, where

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it produces small spores of two to three micrometres in size. These are the so-called conidia that, when inhaled, reach the alveoli of the lung. Each day, you inhale between hundreds and thousands of these conidia, depending on how often you are in your garden. Once in the lung, the conidia are confronted with the innate immune response and are usually promptly removed. If they are not, they will swell, germinate and can cause invasive pulmonary aspergillosis. These infections are associated with a high mortality rate that is often due to late diagnosis.

The other widespread fungus is *C. albicans*. It is very likely that everybody in the audience carries this commensal that lives on human mucosal surfaces. It has a small diameter of three to four micrometres, but it can change its morphology. As a yeast, it is usually harmless unless it develops pathogenic hyphae that can penetrate the skin, which can cause superficial infections that are experienced by many people. Massive invasions are associated with a disintegration of the tissue. In the worst case, it can cause bloodstream infections and sepsis.

To study infections by *C. albicans*, whole blood infection models are used in which human blood is infected with *C. albicans*. Flow cytometry or killing assays show us that the number of free *Candida* cells strongly decreases after the initial infection. Certain immune cells in the blood called monocytes associate with *Candida*, for example by phagocytosis. But this effect appears to be quite small. In contrast, neutrophils, another type of white blood cell, will phagocytose *Candida* cells in increasing amounts. Figure 1 shows an example of this process of phagocytosis.

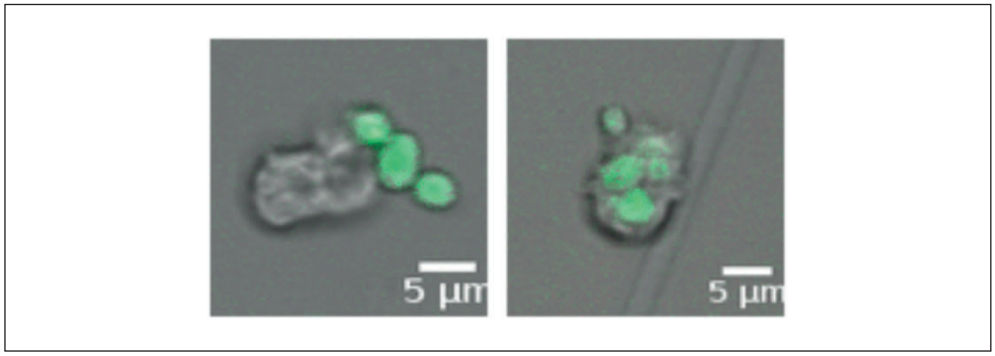

Fig. 1 *Candida glabrata* cells (*green*) and neutrophils (*grey*) in a confrontation assay before (*left*) and after (*right*) phagocytosis.

2. The Purpose of Infection Modelling

Our central aim is to quantify mechanisms contributing to the killing of *Candida* cells in human whole blood. To do this, we create models for this assay and study 'virtual patients' in order to generate predictions for various manipulations of the conditions in that system. The strength of mathematical modelling for these kinds of problems is simplification, i.e. the reduction of complexity. What I consider to be the art of mathematical modelling is to find a model that is rich or complex enough to describe phenomena you are interested in while remaining simple enough to not become a one-to-one map of reality itself. In other words,

finding the mathematical approach in which your model incorporates all existing experimental data that can still be predictive. And then, perhaps after new experiments have been completed, you can extend the model with a kind of bottom-up approach.

3. A State-Based Model for the *Candida*-Neutrophil-Monocyte System in Human Whole-Blood

From experiments, we know that *Candida* cells can be phagocytosed (swallowed) by immune cells. Once a neutrophil swallows a *Candida* cell, it becomes more likely to begin swallowing them even more often. Neutrophils can kill by phagocytosis or by releasing antimicrobial peptides that kill the *Candida* cells extracellularly. *Candida* cells, in turn, can escape the immune response and become 'resistant' to killing and phagocytosis. A whole network of interactions develops over time that includes the direct and indirect killing of *Candida* cells by neutrophils. In addition, monocytes can engage in phagocytosis of *Candida* cells in the blood. Thus, there are many states that the cells can exist in.

Consequently, we use a state-based model to describe this system. Transitions from one state to the next are described by rates, but we do not know the actual rate values. Therefore, we need to set up an algorithm that initialises the model with arbitrary parameters over and over again and then select those parameters that best describe the observed data. Figure 2 shows a scheme simulated by a Monte Carlo model, an approach very well known in theoretical physics, that returns the values for all rates with low standard deviation. If you then fit these curves to the development of the actual number of *Candida* cells present in the blood, you see that they fit the experimental data nicely.

In addition, we can find out which intracellular and extracellular contributions of neutrophils and monocytes produce the observed numbers of killed *Candida* cells as a function of

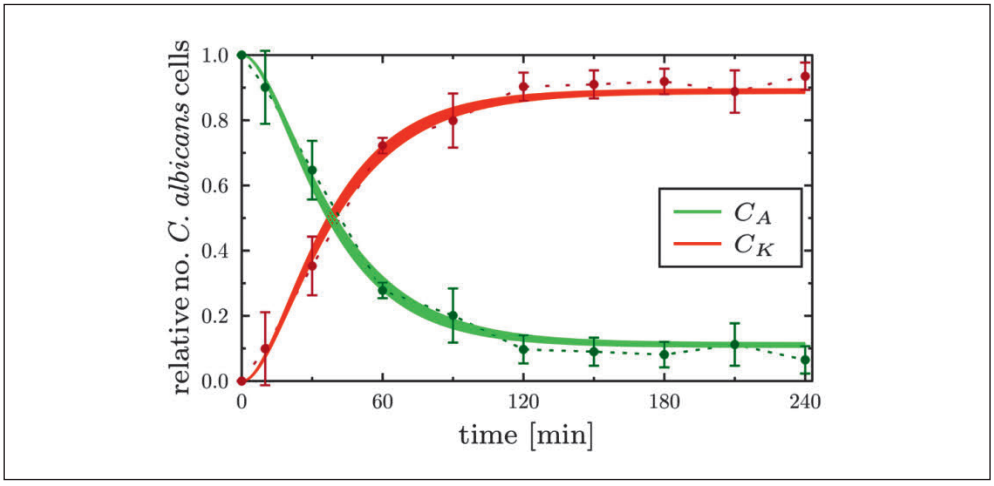

Fig. 2 The number of killed (C_K: red) and alive (C_A: green) *Candida albicans* cells for the human whole-blood assay. The width of this curve is a variation that you get within the standard deviation for the values of the estimated model parameters. This variation is small compared to the standard deviations of experimental measurements.

time. This is information about the cell populations that are not directly accessible in the experiment. As it turns out, the immune response mainly originates from the neutrophils when it comes to *C. albicans* infection. 67 % of *Candida* cells are killed intracellularly by neutrophils, 30 % are killed extracellularly by antimicrobial peptides (a large number that was a surprise), and only 3 % are killed by the monocytes in human whole-blood.

4. Creating a Virtual Patient

Now that our model fits the existing data, we can start generating virtual patient data. Such data would be very hard to collect from real patients. The model correctly predicts that if a patient has neutropenia (lack of neutrophils in the blood), the number of killed *Candida* cells is reduced by 50 % and the number of *Candida* cells that are associated with neutrophils is strongly reduced, too. These are the typical signs in neutropenic patients who are experiencing sepsis due to *C. albicans* infections. In contrast, in monocytopenia (lack of monocytes in the blood), the immune response stays strong, predicting that its response is not predominantly based on monocytes in the case of infections by *C. albicans*.

5. From States to Agents: Bottom-Up Modelling

One limitation of state-based model is that it neglects all spatial aspects. However, cells must meet in space and time before they can interact, and the diffusion of cells in blood is an important parameter for their activity. At this point, we can start building our model from the bottom up: We extend the state-based model to an agent-based model. This new model incorporates the transition rates derived from the state-based model. The agent-based model has migration parameters that are associated with the diffusion constants of monocytes and neutrophils. Now, cells really are objects that are moving in time and space. Figure 3 shows a typical simulation of one microliter of blood.

Again, we repeat these simulations many times over and over again to estimate the diffusion constants that fit the data best. Interestingly, when estimating the diffusion constants for neutrophils and monocytes (Fig. 3), we find an optimal region that is elongated along the dimension for the monocytes. This illustrates how monocyte diffusion constants do not matter much for the outcome of *C. albicans* infections in whole blood. In addition, the diffusion constants of neutrophils must stay inside a small interval in order to fit the data. Thus, the agent-based model fits the same experimental data as the state-based model but includes the whole spatio-temporal complexity.

Keeping neutrophil diffusion constant while changing monocyte diffusion does not significantly change the outcome. However, keeping monocyte diffusion constant and changing the neutrophil diffusion generates a condition resembling neutropenia, at about one fourth of the normal diffusion constant value, even though the patient has a completely normal total number of neutrophils. Still, this immune paralysis resembles the condition of neutropenia. We can now apply this knowledge to the treatment of patients with neutropenia. A virtual patient with a 75 % decrease of neutrophils is in light neutropenia. From our predictions, we get an idea of how the diffusion constant of the patient's reduced number of neutrophils should be increased in order to get him into a safe regime where he can still cope with the infection.

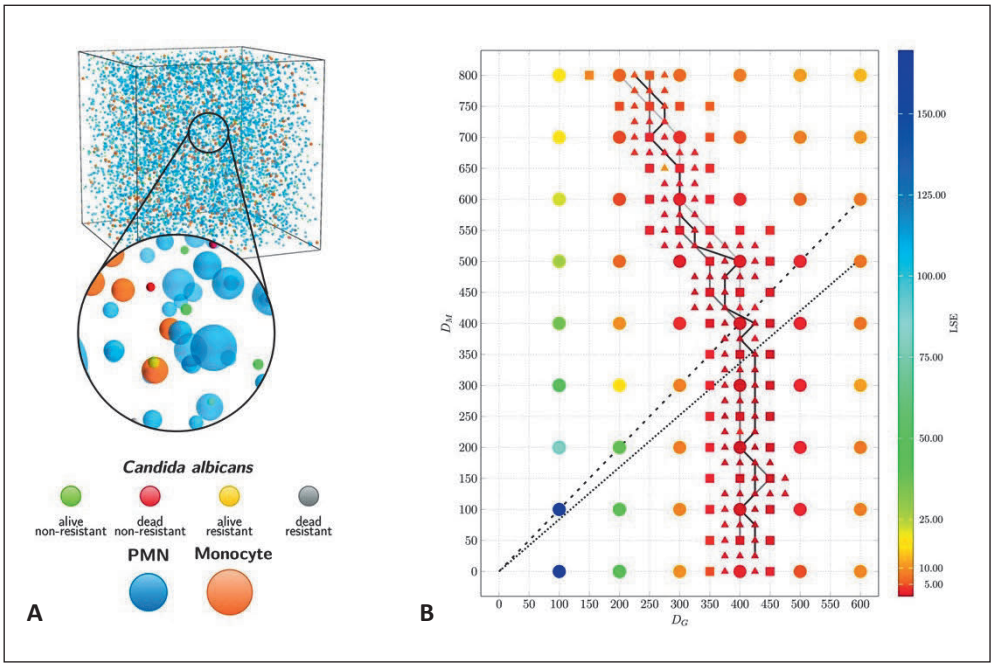

Fig. 3 (*A*): Neutrophils (blue), monocytes (orange) and *Candida* cells in different colours (green: alive non-resistant, red: dead non-resistant, yellow: alive resistant, grey: dead resistant). Red blood cells have been removed for visibility reasons. (*B*): Estimation of diffusion constants for monocytes and neutrophils by a grid search algorithm with automatic refinement.

6. A Hybrid Agent-Based Model

Next, we could build up our model even further by incorporating a multi-scale approach, where the diffusion of molecules is modelled at the molecular level of cytokines. The resulting model is called a hybrid agent-based model. We have done this in the context of a different fungal infection.

Remember *A. fumigatus*: when its conidia reach the lung, they appear in the alveoli, where they are confronted with macrophages. We built a computer simulation of an alveolus that is equivalent to a real alveolus, i.e. this is a to-scale model. Based on this simulation, we can make predictions by performing numerical experiments that could never be done in the lung under physiological conditions.

In this model, we can let macrophages randomly search for conidia. The result is that on average, even after about one day, the macrophages will not find the conidia. This is a condition that cannot be very healthy, because after only six hours the conidia swell and start to germinate. With many simulations and different parameter sets we have shown that in 70 % of the cases the macrophages will not find the conidia in time.

Why is this so? In short, for the macrophages it is like finding a needle in a hay stack. The solution is not to search at random. Our model shows that with a chemotactic signal guiding alveolar macrophages to the site of the conidium, the macrophage finds its way and at some point will locate the target. This can happen very fast indeed. How fast depends on the

properties of the chemokine. Thus, our hybrid agent-based model predicts the presence of a chemokine that is as of yet unknown.

Our simulations also can be used to screen several scales or several orders of magnitudes for the diffusion constant of chemokines and their secretion rate. They show that a low ratio of diffusion constant over secretion rate is required to ensure that the conidia are found in time. We would, of course, be interested in looking at not only one alveolus, but at an entire alveolar sac, because these are the more or less independent building blocks of the lung. Today, however, this cannot be realised by agent-based models and requires a different modelling approach in order to cope with the increasing number of model parameters.

7. An Internal Conflict: Inflammation versus Infection

In reality, conidia are confronted by different levels of the immune system. For instance, apart from phagocytic cells there is also the complement system, which helps the innate immune response in recognising pathogens. Together, these parts of the immune system are always set up to counteract an increasing infection with increased inflammation. However, for obvious reasons, it is always preferable to stay at the lowest possible level of inflammation. There is a conflict in the current literature concerning the role of macrophages with respect to this goal of keeping inflammation at bay. On the one hand, it is said that the impairment of macrophages is a risk factor for invasive mycosis. On the other hand, it is stated that they are actually not important.

We wanted to figure out whether our models could provide us with information with regard to this conflict. As it turns out, if the conidia are not in the resting state, they can be more easily recognised by the complement system. From this perspective, it would be better for the conidia to stay in the resting state. On the other hand, after the macrophages come in after an hour or so, they cannot deal so well with hyphae. So, from this point of view, it would be better to already be in the hyphal state at this stage. Because macrophages will phagocyte conidia when they are in the resting state, it would be an advantage to quickly change into the hyphal form. Neutrophils can deal with both forms, conidia and hyphae. At the same time, however, when they are recruited to the lung in large numbers they can easily harm the lung tissue itself.

Agent-based models for this problem would contain so many model parameters that we would not be able to identify their values in a responsible way. That is why we applied evolutionary game theory. Game theory deals with decisions and choices of strategies in order to counteract some action. In evolutionary game theory, we only deal with relative statements like ‘this morphotype can be easier phagocytosed than the other morphotype’. In this manner, the number of parameters is strongly reduced, allowing us to derive some statements that are difficult to make by other means. The general outcome is this: The model appears to show that there actually is an important role for macrophages. They remain involved in phagocytosis as long as the infection dose is low. An everyday infection may not lead to the recruitment of a lot of neutrophils. However, if the infection dose is very high, for example ten, a hundred or a thousand times higher than the daily inhalation dose, then the response of the macrophages leans toward calling help for the neutrophils. Again, this neutrophil recruitment should by all means be avoided because ultimately, a sepsis patient may be suffering not as much from a pathogen anymore but from his own immune system going berserk.

8. Short Summary

In summary, in systems biology we use mathematical modelling and computer simulation in combination with experiments. We can provide insights that are not accessible in lab experiments. We can direct future research by generating hypotheses that can be tested. We can turn biomedical research into quantitative science. And we can, I believe, simplify real world complexity by taking bottom-up modelling approaches.

We investigated bloodstream infections by the pathogenic fungus *C. albicans* in human whole-blood and interpreted the data in a virtual infection model, quantifying the relative impact of immune cells during infection clearance. The virtual infection model was initially formulated as a state-based model (Hünniger et al. 2014) and was then extended to an agent-based model by applying a bottom-up approach (Lehnert et al. 2015). This approach enables self-consistent modelling in which predictions are grounded on a comprehensive description of all available experimental data. In the context of an *A. fumigatus* infection, the strength of computational biology was demonstrated in a simulation of infection scenarios that are not accessible in wet-lab experiments today. We applied hybrid agent-based modelling to predict the migration strategy of macrophages in human lung alveoli (Pollmächer and Figge 2015) as well as evolutionary game theory on graphs to reconcile contradictory views on the role of these phagocytes depending on the infection dose (Pollmächer et al. 2016).

Despite all the achievements in systems biology of infection, it seems to be highly questionable that we can 'control the world by modelling', even when limiting this claim to 'the world of a single infection patient'. Turning once again to Job, it becomes clear that, as a patient in his day and age and in his specific family situation, being infected by pathogens alone was only one of his troubles.

Acknowledgements

The modelling was done by Sandra Timme, Johannes Pollmächer and Theresa Lehnert; Stefanie Dietrich and Susanne Brandes performed the image analysis. We have been working with the following collaborators: Axel Brakhage, Oliver Kurzai and Peter Zipfel from the HKI as well as Stefan Schuster from the Friedrich Schiller University in Jena. Financial support was provided by the *Sonderforschungsbereich FungiNet* (Project B4) that is funded by the German Research Foundation (DFG) and the Centre for Sepsis Control and Care funded by the Federal Ministry of Education and Research (BMBF) at the University Hospital in Jena.

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Session 2

Chair: Angela D. Friederici ML (Leipzig)

Nova Acta Leopoldina NF Nr. *419*, 55 – 61 (2017)

Real Neuronal Networks: Resilience Despite or Because of Complexity?

Wolf Singer ML (Frankfurt/Main)[1]

Abstract

Both man-made systems and biological organisms resist challenges that endanger their structural and functional integrity. In technical systems, error tolerance is usually enhanced by increasing redundancy: critical functions are implemented in multiple subsystems that operate in parallel. In living systems, resilience has been optimised by evolutionary selection. As a complementary strategy, organisms exploit the capacity of complex dynamic systems to self-organise. At first sight, it appears counterintuitive that increasing the complexity of a system would enhance its robustness. The brain serves as an example of principles that render an extremely complex system astoundingly robust, error-tolerant and resilient. The stability of other complex systems, such as economic, social, and political systems, may benefit from implementing the self-organising principles that evolutionary selection has identified as efficient.

Evolution has very consequently led to systems of ever-increasing complexity. The question is: why? Increasing one's complexity may increase one's autonomy: improving cognitive systems helps to upgrade internal models of the world and thus the coping strategies for difficult situations. Or, complexity may by itself increase the resilience of a system. Or, maybe, both answers could be true?

If the aim is to enhance the robustness of a system, there are two principal strategies. One is to increase redundancy – just to double or multiply critical components – which is a widely used strategy for technical systems, in airplanes for example. But recently, and in aviation as well, there is a trend to increase the complexity of control systems. Today, networks of microprocessors are implemented that organise control of functions in a distributed way. As it turns out, this strategy is more robust than simply doubling the computers with each being devoted to all functions. The reason for this increase in robustness is the ability of complex systems to self-organise. If a processor drops out, the network reorganises and either fully compensates or shows 'graceful degradation' rather than an abrupt loss of function.

1. From Feed-Forward Networks to Reciprocally Coupled Modules

Over the course of evolution, we have seen a dramatic increase of complexity of the nervous system, in large part simply due to the increasing number of components. The human brain consists of up to 100 billion neurons. Its extreme complexity arises from the network of connections between these cells. A basic architectural principle that these networks adhere to is

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distribution: functions are distributed across many centres and are interlinked. Most interactions are reciprocal. This is a big challenge for model makers, because reciprocally coupled networks easily run away or die out.

It is important that these systems all have a flat hierarchy. The evolution of nervous systems started with linear and strictly feed-forward networks that generate predictable responses: the sensory layer transduces inputs from the environment, then a couple of intermediate neurons combine these inputs and feed them to the output level that generates a behavioural response. In a strictly feed-forward system, different functional states cannot superimpose and must be implemented in a serial manner. Also, due to the lack of memory, they cannot handle sequences very well. And due to the lack of reciprocal connection, they cannot self-organise.

Over the course of evolution and especially with the development of the mammalian cortex, a completely new architectural principle emerged: the cortical module. The six-layer cortex consists of modules with a size of about one by one millimetre by two millimetres (in depth) each. These modules are repeated all over the cortex. Their coupling strategies are rather homogeneous. Their internal circuits are both feed-forward and reciprocal. Modules are coupled through reciprocal connections and constantly influence each other. One cubic millimetre of cortex contains about six kilometres of cable (axons). Each neuron, such as the pyramidal cell in Figure 1, communicates with up to 20,000 others and receives inputs from as many other neurons that can be immediate neighbours or live in far-off cortical and subcortical regions.

2. Evolution Sticks to Successful Principles

Evolution is extremely conservative. From neuronal ganglia in snails to the human cortex, the properties of nerve cells are conserved and are based on the exact same biophysical principles. Evolution has also been extremely conservative with respect to the invention of new structures. Since the emergence of the cerebral cortex in lower vertebrates, no fundamentally new brain structure has emerged. Evolution has mainly scaled up the volume of the cortex and of the support structures that this computational system needs to function. So, more of the same makes all the difference, which is a characteristic of complex systems: new properties can emerge from increases in complexity.

In less complex animals, the path from sensory areas in the cortex to the executive centres is fairly short. As evolution proceeded, more and more modules were added, and new cortex areas were formed that were no longer directly connected to the outer world through the sensory or effectors channels and were instead connected to the already existing areas. The neurons in these new cortical areas mainly talk to other cortical neurons. It is a self-referential system with a huge number of re-entry loops, and the environment is only coupled into the system very loosely. One current idea is that this system is a hypothesis-generating system that contains an internal model of the outer world and uses this model for the interpretation of sensory signals and the programming of adapted responses.

The main difference between our next cousins, the great apes, and us is that our brains contain more neo-cortex. We know that the cortex is subdivided into many functional subdomains. However, their internal computational processes are likely to be similar, irrespective of whether they are devoted to seeing, hearing, touching, or abstract coding. What differs is the structure of their respective input data.

Fig. 1 A pyramidal cell (red) in the cerebral cortex

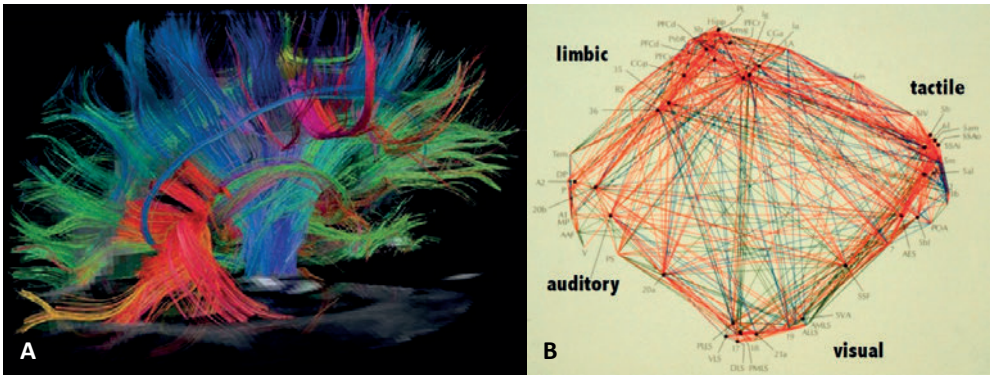

Fig. 2 (*A*): Fiber pathways in the human brain. (*B*): Representations of polymodal objects. Non-local vectors of spatio-temporal relations between distributed responses. *Black dots*: Cortical areas processing tactile, auditory and visual information. The areas belonging to the limbic system attribute emotional connotations to the contents of the cognitive processes in such a system.

The distribution of cortical functions is reflected by the density of reciprocal connections. A staggering 70 % of all possible connections between the nodes of this network are realised. Neurons can send information to any other neuron via only a few intervening nodes, allowing for a mindboggling complexity of interactions. Figure 2 shows the result of tracing the connections in a living human brain with diffusion tensor imaging and a graph of the connections between sensory areas of the cat cerebral cortex.

3. Representing the World in a Distributed Network

Consider a system that looks exactly the same but is several orders of magnitude more complex, such as the brain of a primate. If a human stands in front of a barking dog and touches its fur, myriads of neurons will be active in the visual system, representing different visual aspects of this dog. The same will be true for neurons in the tactile system, where specific activity patterns arise as one touches the fur. At the same time, the auditory cortex will analyse the incoming sound waves of the dog bark. And the limbic system will attribute an emotional connotation: Is it a dangerous dog, is it a peaceful dog, do I have to run away or not? This is what is meant by distributed coding.

4. The Binding Problem

Where in this system is the dog represented? The answer is that there is no local representation. The representation of the dog is distributed as a very complex cloud of spatiotemporal activity patterns. This is not what our intuition suggests. Such coding strategies are very versatile and economical but pose problems. One of them is the 'binding problem': If there was not only a dog out there, but also a cat, there would be two interpenetrating clouds of activity in this network. At any moment in time, some neurons will code for aspects of both the cat and the dog. So which neuronal response is bound to which cloud needs to be well-defined. Three decades ago, we obtained first evidence that the semantic relations between the neuronal responses signalling the various features of the dog are recoded in temporal relations between the respective responses. Responses of neurons whose activity represents aspects of the same object are made coherent.

So apparently, the brain uses the option to align signals in time in order to bind together what belongs together. There is evidence that in certain diseases, like schizophrenia and autism, this ability to bind distributed activity is disturbed. These patients bind contents that should be kept separate and *vice versa*.

5. Assuming Linearity in a Non-Linear World

We can, of course, only perceive, imagine, and comprehend what our brains allow us to perceive, imagine, and comprehend. The brain is as much the product of evolutionary adaptation as any other organ in our body. The macroscopic world in which life has evolved is a very narrow slice of the world. Our sense organs only select information from the environment that is relevant to our survival. Accordingly, the heuristics our brain uses to understand the environment and the responses it generates are adapted to ensure survival and reproduction, not to discover an absolute truth.

Consequently, our cognition is most likely extremely restricted. We know that both our perceptions and probably also our inferred models of the world are limited by our cognitive constraints because our perceptions depend on prior knowledge stored in the brain and *a priori* expectations.

With this restricted cognitive tool set, our brain aims to predict the next state of our environment and the consequences of our interference with it. Assuming the dynamics of the world to

be highly non-linear would not allow us to derive any prediction about our environment. That is why our predictions are mostly based on the assumption of linear world dynamics. For the same reason, we assume that we can control the world. Indeed, our everyday experience seems to support this notion. Many processes in the world in which we evolved exhibit dynamics that have a low dimensionality and can be approximated with linear functions.

One consequence of this linear-mindedness is our poor intuition for complex non-linear systems. The design of artificial intelligent systems reflects our linearity-based approach: most of them have a serial feed-forward architecture. Even the very complex deep learning architectures follow this principle. This, however, is not the way nature has designed intelligent systems! We also tend to construct social and economic systems based on the assumption that they should be hierarchical, exhibit linear dynamics and be controllable. Most business structures have a CEO at the top, and even our democratic governmental systems have prime ministers. We assume that these 'deciders' are endowed with a kind of meta-intelligence that allows them to control the hierarchy below them.

However, our confidence in top-down control is only partly warranted. Many systems we create in the world have exactly the same graph structure as the networks in the brain: they are highly reciprocally coupled, they have very high dimensional non-linear dynamics, and the predictability of the developmental trajectories of such systems is extremely limited. Since we have little intuitive insight into complex self-organising systems, we overestimate their predictability. Fortunately, however, complex self-organising systems are robust, and their exceptional resilience allows us to survive in them even if we do not comprehend their dynamics. So the question is: Can we learn from evolution how to enhance the resilience of our man-made complex systems? Are there general design principles that support robustness, error-tolerance, and stability?

6. Learning from Evolution to Trust Complex Systems

All living systems are complex. They are self-organising and exhibit non-linear dynamics. All of these systems are robust and fault-tolerant; that is how they have survived. The brain is the prime example because it is the most complex organ that we encounter in the living world, and it is amazingly robust and error-tolerant. Most of the time, its sophisticated structure develops without major errors and minor lesions can be compensated.

7. Potential Design Principles for Robust Complex Systems

The brain's connectome, which can be described as a comprehensive map of neural connections, resembles a rich club architecture, and this architecture is adapted to real-world conditions by an experience-dependent developmental process. The connectome is shaped by epigenetic influences: connections are stabilised or destroyed depending on their functional validation. This process is complemented by adult learning. In this case, however, inappropriate connections are no longer physically removed, but the existing connectome is modified functionally by learning and by modifying the efficiency of synaptic contacts.

This ability to constantly adapt to a changing environment is only possible because brains have something that many other man-made systems do not: central evaluation systems. These

systems reside deep inside the brain, supervise the global states of the brain and are able to distinguish between consistent and inappropriate states.

8. Stabilising Complex Architectures with Control Systems

These evaluative systems are phylogenetically old. And, as far as we can tell, all complex brains have such systems. They evaluate the consistency and the validity of activity patterns generated in the rest of the brain and they reinforce useful and consistent activity patterns with reward signals so that the likelihood of them reoccurring is increased. They do not have to know the semantic content of the details that are processed in the rest of the brain. All they should know is whether an activity pattern makes sense internally, whether it gives coherent solutions, and whether the behaviour that results from it is beneficial or harmful. The result of this evaluation is expressed by the release of neurotransmitters that permit subsequent adaptive changes of the connectome. Thus, they enable adaptive changes to the environment and make it possible for the self-organising brain to behave in a goal-directed manner. Without this control system, the brain would not know in which direction to evolve its functional architecture.

Evolution follows the same principle: complex organisms have behavioural dispositions that have been optimised due to natural selection. However, in this case the reward is not instantaneous but provided by survival and successful reproduction. Those who did not do it well simply died out.

9. Suggestions for Managing Complex Systems

Based on these observations in the nervous system of higher animals, how should we optimise the management of complex systems? *First*, we should create an architecture that supports self-organisation, including reciprocal coupling, distributedness, flat hierarchy and adaptivity, an important principle that is rarely implemented. *Second*, we should implement mechanisms for evaluation of global states to allow for the supervised adaptation and self-optimisation of interaction architectures. *Third*, communication systems need to be implemented that assure the reliable transmission of undistorted information among large numbers of nodes.

10. The Emergence of New Qualities

The trend towards more and more complexity has an interesting spin-off. Rendering the interaction architecture more complicated leads to the emergence of new qualities. It certainly looks like the brain has managed, by increasing its complexity especially in the cortex, to construct a high-dimensional dynamic state space for the storage of information, encoding, and fast retrieval of information. This has apparently led to the emergence of novel cognitive functions such as abstract thought, the generation of symbolic codes and language, the development of a theory of mind, and ultimately self-awareness. Agents endowed with these cognitive capacities are in turn able to engage in the development of socio-cultural networks that led to the emergence of the immaterial social realities as John Searle called them ‘belief systems’, ‘attributions of mental and spiritual dimensions’, and ‘value systems’.

In conclusion, whatever the reasons for the continuous increase of the complexity of the interaction networks of our biosphere, we certainly owe our existence to the resilience of complex self-organising systems. Applying the principles that underlie this counterintuitive resilience may well help us understand and manage complex systems of our own making. Finally, understanding the ability of complex systems to generate new qualities that are ontologically different from the building blocks may even help to explain, within a naturalistic framework, the emergence of particularly human phenomena such as our spiritual dimension.

Nova Acta Leopoldina NF Nr. *419*, 63 – 67 (2017)

Autonomous Intelligent Systems in Robotics

Wolfram Burgard ML (Freiburg)[1]

Abstract

During recent years, artificial intelligence, machine learning, and robotics have become key technologies for various applications including logistics, service robots, and self-driving cars. The fundamental techniques employed in the most successful applications rely on numerical approaches, which rely heavily on probabilistic or numeric representations and utilise large amounts of data to optimise their parameters. I will discuss recent solutions provided by the above-mentioned fields for building intelligent agents that, in certain cases, are even outperforming humans. I will argue that the sheer amount of available data combined with the appropriate algorithms means that we are now within reach of applications with great potential for assisting humans in their everyday life. Furthermore, I will discuss aspects of the ongoing digital revolution based on novel machine learning algorithms.

We are mostly interested in building systems that perceive their environment, create internal models (like our brain does), and generate goals and actions to achieve them. That is the basic definition of an intelligent agent. A robot is a physical agent, or a computational model that can live in the physical world. This type of agent could help us in our everyday life, assisting us with various tasks and duties. Realising a robotic assistant requires some form of artificial intelligence; these agents would first have to understand their environment in order to figure out what they should best do next.

1. What Is Artificial Intelligence?

Defining 'intelligence' is particularly difficult, and it is even harder to define what 'artificial intelligence' (AI) means. Today, the discipline of AI mainly focuses on rational thinking and rational acting. The research in the context of agents that think rationally is driven by the idea that agents who think rationally will also behave rationally. However, there are computational models that have no direct symbolic (i.e. rational) meaning but are rather sub-symbolic, such as several probabilistic representations of neural networks, which do not have interpretations that allow us to understand how the system reaches its decisions.

In AI research, most researchers are interested in building agents that act rationally, thereby freeing them from computational architectures that can easily be interpreted by humans. Usually, these agents have some sort of performance measure they are trying to maximise, which would be equivalent to minimising error or failure. If the agent behaves optimally, AI researchers call it intelligent.

Whoever has a cell phone in his or her pocket carries around at least one AI. They come with speech recognition assistants we can talk to. Also, the key algorithm in navigation sys-

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tems was developed in the field of AI. Optical character recognition heavily relies on AI methods, such as pattern recognition and face classification. Sorting photo albums, ranking websites, and recommendation systems along the lines of 'other people who bought this also bought that' all involve an AI component at their core.

The reason for the current omnipresence of AI is its enormous success over the past couple of years. And it is becoming more and more successful. Not only software agents, like the ones in our cell phones, but also physical agents like robots are now beginning to enter many areas of our daily lives. Other popular applications of AI are computer games and strategy (e.g. chess, checkers) or combat games. Combat games in particular make heavy use of AI-based technology: If the agent needs to get from A to B, they apply the very same algorithm that is running in the navigation system of your car to find the best path. Indeed, some AI systems now outperform humans. A few years ago, for instance, the expert system IBM Watson won the game show Jeopardy. Watson can store and analyse about 2×10^8 pages of text from the internet. It is a bit like the *Drosophila* of AI as it evolves in the direction of human intelligence.

2. The Deep Learning Revolution

Today, the major conferences in artificial intelligence, machine learning, and pattern recognition are dominated by deep learning and deep networks. This combination of big data and highly parallel computing architectures has rendered decision making or segmentation for image analysis by neural networks much more powerful than any previous technology. The methods of deep learning, implemented in deep neural networks, have become enormously powerful. Last year, an event took place that left me stunned: The AI 'Alpha-Go' played against a human world champion in Go and won. Alpha-Go is mostly based on big data and deep learning, implemented in large artificial feed-forward neural network. So how do these networks operate?

The lowest layers of multi-layer deep networks learn relatively simple features of input data, such as black-white transitions, corners, or edges in the case of images. The higher you go in these networks, the more invariant the responses of the nodes will be: for instance, the nodes in higher layers of a deep neural network trained on facial recognition will start responding to images of different faces from different angles as a form of image compression. In some cases, we can visualise what a network has learned. If you run a network on YouTube cat videos, what you might get are 'cat neurons' that best respond to the most representative cat face in the videos (see Fig. 1).

3. Robotics

One of the most intensively discussed aspects in robotics these days is autonomous cars. In this realm of robotics, virtually every aspect is 'AI complete', meaning that in order to solve a particular problem, the system needs to understand how the world around it works. For this very reason, robotics is an extremely complex science that faces enormously hard challenges. Even vacuum cleaners, like those you can buy in a home supply store, are running AI algorithms (apart from the simplest models that just move randomly). The better models employ dedicated algorithms to systematically clean the floor. Some use AI-based algorithms that are also used to develop self-driving cars, such as Google's car.

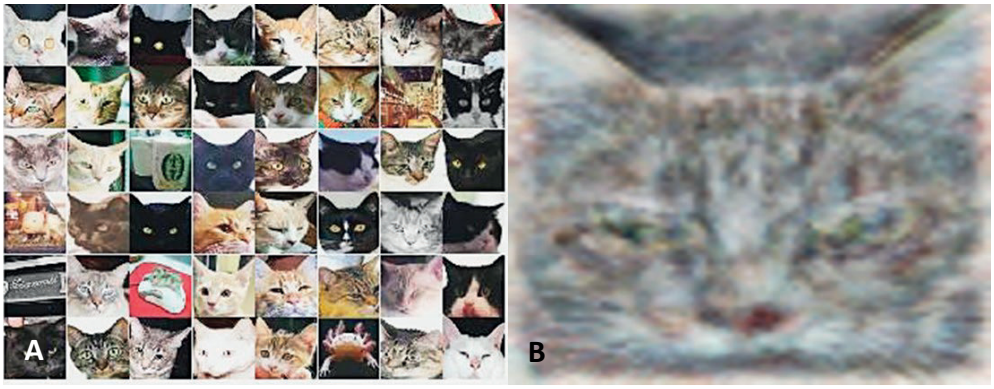

Fig. 1 Visualising what a network has learned. (*A*): Top stimuli of the test set. (*B*): optimal stimulus ('cat neuron'). (https://googleblog.blogspot.de/2012/06/using-large-scale-brain-simulations-for.html)

You may wonder why the Google car does not simply use GPS to figure out its position. One of the major challenges of autonomous driving is to be sufficiently accurate; for example, to remain in a specific lane. GPS is typically not accurate enough for this. Therefore, the Google car, for example, uses range scanners installed on the roof of the car to localise the vehicle.

4. State Estimation

Based on the incoming data, Google's car employs state estimation and utility maximisation algorithms, methods that are at the heart of all of robotics. The so-called particle filter is a highly parallel algorithm that generates a hundred thousand hypotheses as to where the vehicle might be located and then uses a 'survival of the fittest' mechanism to figure out the most likely hypothesis.

Once the particle-filter algorithm has gathered enough information to resolve the ambiguities, it provides a highly accurate estimate about where the Google car (or any other robot that implements it) is located with respect to its immediate environment. The same algorithm can also be used for accurately localising robots designed to navigate with very high accuracy on factory floors. Please note that this algorithm can also deal robustly with ambiguities. It can directly represent them and support decision making in cases of uncertainty. Even in highly ambiguous situations, the robots can still make rational decisions about where and how to move, which is particularly hard for humans.

5. On-the-Fly Map Generation with Particle-Filter Algorithms

The robotic systems described above all employ some kind of map. One of the major challenges in robot navigation is how to build such maps. The robot must know what the environment looks like and where it is in this map. This can be a problem the robot needs to solve when it enters an environment for the first time or when the environment has changed.

Luckily, in order to generate a new map, you can feed this data into the same state estimation algorithm as the one used for localisation with about 10,000 hypotheses. With this

approach, a robot can maintain a probability distribution about where it is in its environment and what this environment looks like. This approach has turned out to be enormously robust in allowing robots build maps of large-scale environments and even very complex settings.

6. Optimisation

Recently, mapping has also been achieved with optimisation-based approaches, which have turned out to be a powerful alternative concept in AI and robotics. In an optimisation-based mapping problem, one tries to find the most likely map of the distribution out of all potential maps of the environment. The key idea is to think about the problem as a kind of a mass-spring system that converges to a minimum energy configuration after a certain time. This technique is applied to generate the maps that can be accessed with smartphones and computers today.

When applying the optimisation-based mapping algorithm to large parking structures, we can get a certain map and think about interesting alternative applications like autonomous parking. These methods of autonomous positioning and mapping are not only relevant for autonomous cars, but also in logistic processes. One application is the production process for the Boeing 777 fuselage.

7. Maps *versus* Features

In summary, on the one hand we have seen huge successes by deep neural networks in figuring out high-level features with very variable input data. On the other hand, there are state estimation algorithms for autonomous navigation. It is an interesting and still open question as to whether robots need highly accurate maps in order to perform accurate navigation tasks or whether a neural network could learn features to take over that task as well.

Two weeks ago, one of my students demonstrated a robot with a deep neural network that learns how to navigate. She trained the network to generate the next action out of the ten most recently perceived observations. For each target location, we calculated the optimal path towards it, let the robot run along that path, and trained the deep neural network to process the incoming sensory data. Our hope was that by doing this repeatedly, the robot would learn to navigate all target locations without explicit internal representations.

Our network can learn the optimal path from the current location to the target, but it can do even more. The robot with a larger window and the same neural network implicitly learned how to navigate around in our building. This can also be done based on laser range scans, like those performed by the device on the roof of Google's car. Our hope is that we can ultimately free autonomous navigation systems from requiring a map and allow them to arrive at completely sub-symbolic representations.

8. Applications for Representation-Free AI Systems

Another recent trend is to directly connect robotic devices to the human brain. For example, in the Cluster of Excellence BrainLinks-BrainTools, we are building brain-controlled robots, i.e., robots that can be controlled by thoughts, for example as an aid for paralysed people (Fig.

2). Here, we also use neural networks to classify brain signals and apply such techniques to identify imagined arm movements. These signals can then be used as go-signals, for instance in a feeding task. In addition, and this idea may sound pretty scary, one can also think of robot-controlled brains, i.e. robots that send signals to your brain. In fact, people from the 'Life Hand Project' have already built a prosthesis that communicates with the nervous system in the arm, which in turn sends signals to the brain to re-establish the sense of touch.

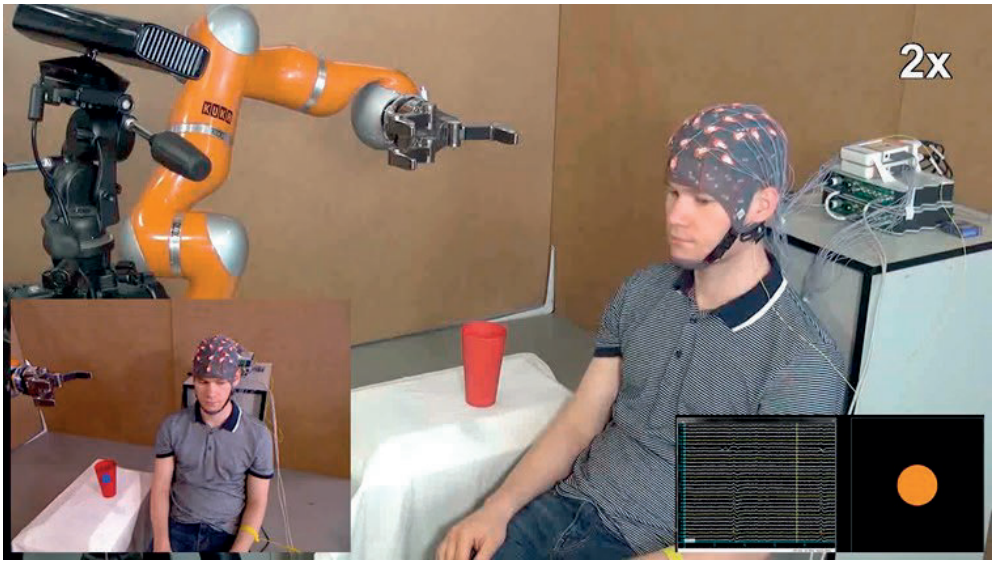

Fig. 2 By using neural networks to classify brain signals (lower right window) and applying such techniques to identify imagined arm movements, one can use these identified brain patterns as go-signals to a brain-controlled robot.

9. Big Data

Very often, people are concerned about big data and how their data is being used by companies that provide services to us. The typical situation is that these services are helpful to us and at the same time profitable for the companies. One example is called crowd sourcing. In the context of navigation systems, the companies track all the positions of all cars and all their velocities. Based on the velocities, a centralised system can estimate the time we need in order to reach our destination and re-route us in a potentially better fashion. Applications like these only work if people are willing to share their data. And it is a decision that we as a society have to make as to whether we want such benefits by providing the corresponding information.

In summary, AI and robotics have changed a lot in recent years and they will keep changing. Big data and computational architectures in combination will provide us with new solutions and features that we can use to make our everyday lives better.

Discussion of Session 2

Guest: Professor Singer, you described 'moving from simple to complex' as an evolutionary principle. While this may be true for the brain and many organisms, I wondered whether this is true for nature in general, because there are also organisms that simplify, like parasites. Obviously, there must be a boundary beyond which no further simplification is possible. Could you comment, please?

Singer: I am unfortunately not an evolutionary biologist, so I lack examples, but I would imagine this: what looks like simplification, is increased specialisation. However, I am not educated enough in this domain to give a definitive answer.

Guest: I think that from a scientific and technological point of view, these robots are fascinating. But I like driving! I do not know if I want to live in a world where robots are working in my place and are walking through the streets. What would be left for us to do if robots were taking over everything?

Burgard: They are already taking over certain aspects today. Think about airplanes: nowadays they are basically robots. I like the saying: 'The best you can do, when you enter an airplane is to ask the pilot to get off'. Because when you look at it, most of the recent accidents were due to pilot error. And there is only around one single case where the pilot rescued the plane. A member of the team that is building the self-driving car at Google once said: 'The most unreliable aspect of a car nowadays is the driver'. So the idea is to make our world a better and a safer place.

Guest: Wouldn't an increased presence of robots cause more problems, like people not talking to each other anymore?

Burgard: Why would that be the case? If you sit in the car that drives for you, you can talk to your fellow passenger and maybe to other people on the phone.

Guest: Yes, but if a robot brings me all my stuff, I cannot talk to him. If a person brings me my stuff, we can have a chat.

Burgard: I, for instance, have Amazon Echo at home and from time to time I talk to it – she is always friendly, by the way – which does not say anything about my wife. She is also always friendly.

Singer: Are these systems truly autonomous or do you have to have a huge computer somewhere and a wireless connection in order to do all this programming and deep learning? Because if that is the case, which I think it still is, then you are in trouble: you cannot afford a transitory disconnection. So, unless you achieve intelligent systems that are portable and energy efficient, like the brain, for example, things will become difficult.

Burgard: Yes, autonomous cars have computers installed that do the computations offline. In the very beginning, those were entire computer racks. Today, they are the size of a pizza box. However, most of the learning still happens offline, and improved classifiers are uploaded to the cars remotely. Like on your smartphone – you get an update for your car.

Friederici: So we can observe outcomes of a system like robot drivers. But this does not tell us anything about the underlying algorithms. I was wondering whether anyone in robotics would take up the idea of learning from the biological system, or is this so far off that you would rather say: 'We do our own thing'?

Burgard: Right now, people are returning to architectures that you find in biology. Deep networks in particular are a rough approximation of the brain's architecture and they are computationally very, very powerful. These architectures are also found in biological systems. Deep neural networks were already being explored some 20 years ago. The major change is that today we have an enormous amount of labelled training data. We would love to have computational architectures that are more like the brain. Maybe we could connect neurons in the very same way, but we do not yet have algorithms for training networks of that kind.

Singer: Yes, training algorithms exist that are physiologically plausible. But there has not yet been hardware implementation of a use-dependent plastic synapse.

Burgard: Also, microscopic aspects of brain, such as synapses, cannot be modelled accurately. What we are using are all very rough approximations.

Guest: I think that, with your talks, we are moving towards the interdisciplinary part of the workshop. Also, this was the first time that I really saw a transition to social science questions. Mr. Singer, I was wondering whether you are also working on literature from organisational theory and sociology, particularly about flat hierarchies and resilient systems. These principles are now being applied in building organisations. Google, for instance, hires very highly trained people who self-organise all the way. There is not that much hierarchical structure anymore. Do you see more of those developments and do you interact with sociology and social sciences in that regard?

Singer: Only very loosely. Every now and then when I give talks, I discuss these questions. I realise that the confidence in flat hierarchies increases because of the failures of top-down control. When I talk to business advisers who make a huge amount of money by shaking the structure of an organisation, I realise that their concepts are pretty loose most of the time. And when I ask them: 'What are you doing that justifies your high salaries? What is the point of it?' they say: 'It is not that we have a recipe of how to produce a stable situation, or a resilient system, but it is just shaking it, like introducing a mutation and then leaving it to a Darwinistic process to select the good parts. But this shaking process requires enormous efforts due to the inertia of established routines'.

Guest: My second question is about autonomous driving. We live in a society, and one basic principle of how we interact is responsibility: We are being held responsible for our actions. So, who is responsible when an algorithm drives the car? The algorithm? Or is it the human being who programmed the algorithm? Algorithms have busted a lot of money in the financial markets. I think that is a question where the social sciences and the natural sciences meet. Can you please comment on that?

Burgard: Yesterday, I had a discussion with law scholars, and one of them had the opinion that someone always needs to be held responsible. Currently, the responsibility stays with the driver at all times. That, however, would not change the reality of driving; we would be constantly anxious about the car making mistakes. Of course, if there were no cars, car accidents would not happen, and we would save many lives. So, as a society, again and again we transform the tools we use and the risks we are willing to take. One solution to the problem is not to impose responsibility on the driver unless he makes a mistake. Think

about it: by using autonomous cars, we could reduce the number of fatalities by 50 %. Is that something we want? If the answer is yes, we could, for example, leave the responsibility with society itself. This is happening. For example, my university is not allowed to buy insurance. So whatever damage the university causes is paid for by the state. This could be a solution to solving this problem.

Guest: What I found quite interesting was the supervision or evaluation system. You explicitly said that it does not take any kind of external factors into account, so it evaluates the internal consistency. And I just wondered, is there some internal logic that, if violated, this system would report? If so, what does that logic look like?

Singer: The brain, of course, needs to know when it has reached a solution. And it needs to distinguish the solution from the computational history. It can only learn if it has a consistent solution state. There must exist some measure of consistency in the brain. We do not yet know what the signature of a result is.

Still, the evaluation systems must be able to read this signature. They must recognise that the brain is now in a state that is equivalent to a solution. Now you can print and now you can change the synaptic weights. It is likely that a reward is associated with this signal. If it happens, you feel good; if it doesn't happen, you know there is still a conflict between competing drives and you feel uneasy.

This internal consistency test is one aspect of the evaluation system. But there are subsystems that compute prediction errors. They know from experience and from past heuristics what is supposed to happen if you do this or that. If you do something and the reward is lower or higher than expected, this system comes into the play. It will then change the state of the system by modifying the synaptic weights. So it does not have to know about what the reward was for. All it needs to know is whether the prediction is confirmed by what happens. And it favours states that converge towards those predicted states that are associated with the highest rewards.

Lengauer: Now I am a bit confused, because on the one hand, you very convincingly said that the brain does not have a central organiser, but this evaluation system sounds very much like a central organiser.

Singer: No, it is not. Because it has no knowledge about detailed processes. It never decides anything. It does not know whether a consistent brain state has been achieved because you made an elegant arithmetic calculus or because you happened to do a consistent motor act, like skiing. It is blind to the contents. It only evaluates states. So it is not like a chancellor or a CEO who would have to know this: I do X in order to achieve Y. No, it finds out *post festum* whether what has happened is consistent or not.

Lengauer: So it only observes.

Singer: Yes. It doesn't need to be very clever. It needs to be able to evaluate states.

Friederici: I found the aspect of the brain being so tolerant to damage very interesting. I was wondering how robots would achieve this. During learning, are they error-tolerant? Or later on?

Burgard: You can gain robustness against failure by redundancy. We are not talking about three copies like with airplanes, but maybe 10,000 or 100,000 copies instead. But then, these architectures for learning have a well-known theory behind them. So we can evaluate how robust they are and how we can increase their robustness. For example, cross-validation is a technique where you evaluate how robust a classifier is relative to unseen examples.

Friederici: When we look at the development of the human being, what we see is that, very early on during development, the system is more tolerant of errors than it is later on. Do you have an explanation for this?

Singer: Well, embryos and newborns are extremely tolerant of oxygen deficiency because the system is tuned to resist that risk during birth. Later, they have a lot of degrees of freedom in order to compensate. We investigated a young girl that came to us when she was 14 years old. To our great surprise, we found that she was lacking an entire cerebral hemisphere. The thalamus, the striatum, everything was lost on one side. Just the brain stem and one hemisphere were left. The girl had a nearly normal visual field. She must have lost the Anlage for the second hemisphere at the embryonic stage of about three months. This caused the optic nerves to re-route when they grew into the brain, to map into the one hemisphere left. So, new maps formed in that hemisphere. She was also perfectly fine with respect to motor abilities. She could roller skate, she could bicycle, she had a normal IQ. She was a little bit clumsy with the fine control of the hand contralateral to the missing hemisphere. She was unaware of this malformation, and she probably still does not know about her 'problem'. Her example shows how efficient these self-organising error-correcting forces are during development in biological systems.

Session 3

Chair: Carmen BUCHRIESER ML (Paris)

Nova Acta Leopoldina NF Nr. *419*, 75 – 82 (2017)

Host Microbiome Interactions in Health and Disease

Eran Elinav (Rehovot, Israel)[1]

Abstract

The mammalian intestine contains trillions of microbes, a community that is dominated by members of the Bacteria domain but also includes members of Archaea, Eukarya, and viruses. The vast repertoire of this microbiome functions in ways that benefit the host. The mucosal immune system co-evolves with the microbiota beginning at birth, acquiring the capacity to tolerate components of the community while maintaining the capacity to respond to invading pathogens. The gut microbiome is shaped and regulated by multiple factors, including our genomic composition, the local intestinal niche, and multiple environmental factors including our nutrition and bio-geographical location. Moreover, it has recently been highlighted that dysregulation of these genetic or environmental factors leads to aberrant host-microbiome interactions, ultimately predisposing hosts to pathologies ranging from chronic inflammation, obesity, the metabolic syndrome and even cancer. We have identified various possible mechanisms participating in the reciprocal regulation between the host and the intestinal microbial ecosystem and demonstrate that the disruption of these factors in mice and humans leads to dysbiosis (microbial imbalance) and susceptibility to common multifactorial diseases. Understanding the molecular basis of host-microbiome interactions may lead to development of new microbiome-targeted treatments.

1. Studying the Microbiome

This talk is entitled ‘Host Microbiome Interactions’ because 2016 is an era in which, for the first time, we can accurately measure the biggest set of variables that determine our individualised response to food, including genetics of the host. Our individual genetics and lifestyle have an important effect on our glycemic responses, which is the effect that food has on blood sugar (glucose) levels after consumption. But the most interesting and poorly understood factor of all is the composition and function of our gut microbiome.

The microbiome is a huge and complex, but poorly understood microbial ecosystem that resides within every one of us from the moment we are born to the moment we die. This microbial ecosystem consists not only of trillions of bacteria and thousands of different microbial families, but also of hundreds of types of viruses, fungi, and parasites. They basically form a world within a world inside each one of us. During the last eight years, this very young field of research has demonstrated that the microbiome has a fundamental impact on almost every aspect of our physiology.

A scanning electron microscope photo (Fig. 1) taken from a normal small intestine with a 160,000-fold magnification shows heels or bumps lining epithelial cells of our gastrointestinal tract, the home of the densest and most diverse microbiome we host. On top of the epithelial cells lining the intestine sit bacteria that look like a carpet of shoe laces, composing the healthy microbiome environment.

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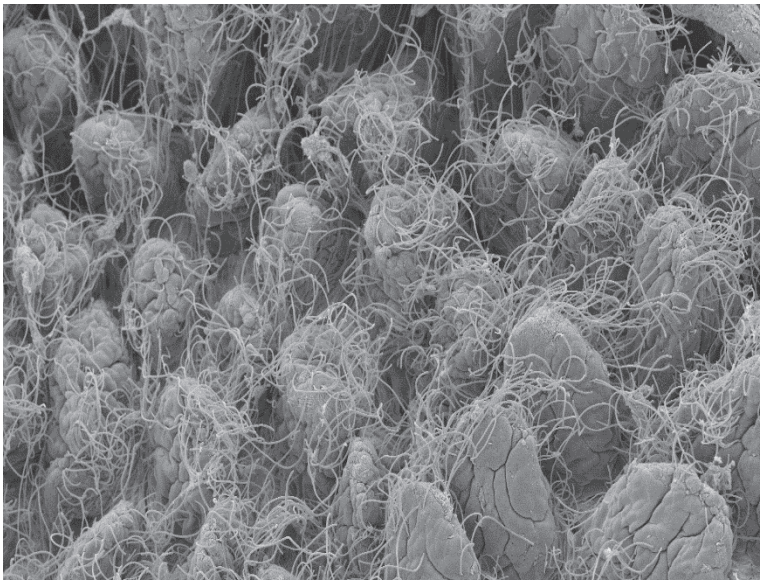

Fig. 1 Microscope photo taken from a normal small intestine with a 160,000-fold magnification.

One of the themes of this meeting is complexity. In fact, the microbiome – especially the gut microbiome – is one of the most complex biological systems, and we are just starting to comprehend it. Until eight years ago, science knew that many bacteria live inside our body, but we had no way of studying them because most of these bacteria cannot be cultured under normal conditions. One of the consequences of the Human Genome Project, finalised in 2001, were technological breakthroughs that finally allowed us to sequence huge chunks of genomic data. Using these approaches, called next generation sequencing, we were able to study the microbiome for the first time and start understanding what it does and what is so important about it. We were quite shocked to see that there about as many microbial cells in our body as we have own body cells and that we carry about 150 times more microbial genes than human genes within our body. While we know a lot about the 20,000 genes that compose our eukaryotic body, we know almost nothing about the three million microbial genes that are part of us and greatly impact us.

2. The Microbiome: A Physiological Layer of Great Complexity

You can imagine the microbiome as a 'neglected organ'. It is a signalling hub that integrates many signals originating in various parts of the organism. Some of these signals come from the eukaryotic part; for example, our individual genetics and immune system have a great effect on the microbiome. Also, almost any environmental factor that surrounds us affects the composition and function of the gut microbiome. The microbiome integrates and processes

all these signals, interacting with the host – and it's these interactions which researchers now believe are important in determining our state of health and our risk of developing common multifactorial disease.

Looking into the leading scientific journals of the last couple of years, you will see that alterations in the composition of the microbiome have been linked to almost any common multifactorial human disease. It is the biggest challenge for us to investigate the mechanisms underlying these perturbations. This will take a lot of effort, and I will give you one example of one of our very recent projects illustrating how we can harness the huge amount of big data that we take from our microbiome in order to determine its impact on common diseases.

3. The Obesity-Diabetes Epidemic and Our Dieting Failure

The disease that I am mostly going to talk about is obesity, one of the worst epidemics in human history that affects billions of people worldwide. During the last 20 to 30 years, there was a huge increase in the prevalence of obesity in the United States, Europe and in East Asia, especially in China. The rapid pace of the epidemic implies that environmental factors are the major driving force. At the same time, there has been a rise in closely related diseases such as diabetes, estimated to affect half a billion people worldwide today. The predisposing disease called pre-diabetes even impacts up to 40 % of the adult American population and over 50 % of the adult Chinese population. 50 years ago, this disease did not exist in China.

Nutrition affects the gut microbiome within our gastrointestinal tract, the first stage to interact with our diet. This interaction affects metabolism in health and disease. I will show you how we can harness big data-driven approaches to decode this highly complex biological system in order to develop rational interventions in common multifactorial diseases such as obesity. Many people attempt to change their metabolism by intervening in their nutrition. When you look at the overwhelming data regarding different diets, you can see that they work in the short term. In the long run, however, the vast majority of people regain their weight and often even more weight than what they started with.

So, we asked: 'Why, despite all the effort and the huge amount of money that our society invests in our dietary attempts for the last 30 or 40 years do we fail so miserably?' The basis for what we address in nutrition today is rather boring nutritional studies from the 1970s and 1980s which resulted in giving food a grade or a score. Based on these grading systems we, physicians, dieticians, or the books at the airport basically try to build diets that are supposed to be good for us. The calories are one grading system which gives a number to any food on earth. So, we use combinations of foods based on this grading system to build a diet.

A more commonly used grading system than calories in the nutritional world is called the glycaemic index, which assigns gives grades to foods based on how much they raise our blood sugar levels. The glycaemic index is based on a very small number of studies from the 1970s in which ten to 20 human individuals were given identical food and then their blood sugar levels were monitored for a two-hour period. For example, if these ten people were given an identical piece of celery, their average blood sugar levels rose about 40 % within 15 minutes and went back to normal within two hours, resulting in a glycaemic index of about ten. Now if the same group of people were given an identical piece of chocolate cake, the average rise of their blood sugar levels was much higher, like 90 %, resulting in a glycaemic index of about 60. There are many, many charts on the internet with glycaemic index scores for any food on

earth. When you go to your dietician or your family physician or if you buy a book, there is a very high chance that your new diet will be based on these sets of glycaemic indices.

4. Individual Responses to the Same Food

When you do this study not on ten but on 1,000 people – like we have done – you will see that individual differences in the glycaemic responses can be huge. For example, when we gave an identical amount of glucose or bread to 1,000 people, the average was exactly the well-known glycaemic response of glucose or bread. However, while some people eat sugar and their blood sugar levels do not spike at all, they rise to diabetic levels in others.

Therefore, the average response to certain kinds of food does not predict the individual response. This variability, which we have seen in several different kinds of food, really limits the applicability of the glycaemic index as an average. This tells us that the concept of following a one-size-fits-all diet cannot be effective. So, our goal is to develop a personalised approach to dieting.

In contrast to classic diets, such as those mentioned above, our approach could lead to tailor-made diets that actually work. The basis is a large-scale study which we performed as a strategic collaboration with my friend and colleague Eran Segal, a mathematician heading a large group at the Weizmann Institute, which we started around four years ago. For this study, we recruited participants online. Even though we never publicised it, by the end of the study close to 20,000 people were on the waiting list. Once a candidate was admitted to participate, we asked them to let us perform tests on them for a week. First, they filled out a large body of questionnaires on their medical backgrounds, their family history, their dietary preferences and so forth. We analysed their host genetics and performed an array of blood tests. And, of course, we took stool samples that were deeply analysed (in-action sequencing) for composition and function of the participants' gut microbiomes. Finally, we connected each participant to a glucose monitor that sits on the skin and takes samples of blood sugar levels every five minutes.

During this test week and the following week, the 'follow-up week', the monitor would collect a total of 2,000 blood sugar measurements. In addition, we gave each participant a smartphone app specifically designed for this project. They used it to tell us everything they did during the follow-up week: what they were eating, how much of it, when they were waking up, when they were going to sleep – as much information as possible.

After the conclusion of the follow-up week, we created a 'mirror image' for each participant, an overview of their habits based on their smartphone diary entries. We also gave people a very detailed analysis of their gut microbial frames. Most participants were really surprised by their own mirror image, a testament to the fact that we experience our own bodies very differently compared to external observers. And we were pleasantly surprised to see how quickly people got emotionally attached to their gut microbes.

Most importantly, a couple of weeks after the completion of the blood sugar measurements and app reports, a large, talented, and smart group of computational biologists – students and post-docs in both of our groups – took this unprecedented amount of big data and devised a machine learning algorithm that trained itself to predict the participants' individual physiological responses to any of the foods they had been exposed to. So far, we have profiled over 1,000 people, studied individual responses to over 50,000 meals and analysed over

two million blood glucose samples. In addition, we sequenced over ten billion meta-genome reads. This is the largest study of its kind to ever have been performed.

If we look at the statistics of this one cohort – the Israeli cohort – we see how their profile resembles what we find in populations of developed countries all over world: 50 % of the people are overweight, 20 % are obese, and 25 % are pre-diabetic. Pre-diabetic individuals form a very important sub-set of society: they already feature disturbances in their blood sugar maintenance but they are not yet diabetic. However, they have a 70 % chance of developing frank diabetes within ten years of the diagnosis. We really have no way of controlling the progression of this condition. From my previous experience as a physician, I can tell you that when these people come to our practice, we basically have nothing to offer them. We tell them to exercise and to lose weight, but they never do it.

The microbiome was a central part of the analysis of the Israeli cohort. Figure 2 shows the results of a comparison of the microbiome in people from different parts of the developed word.

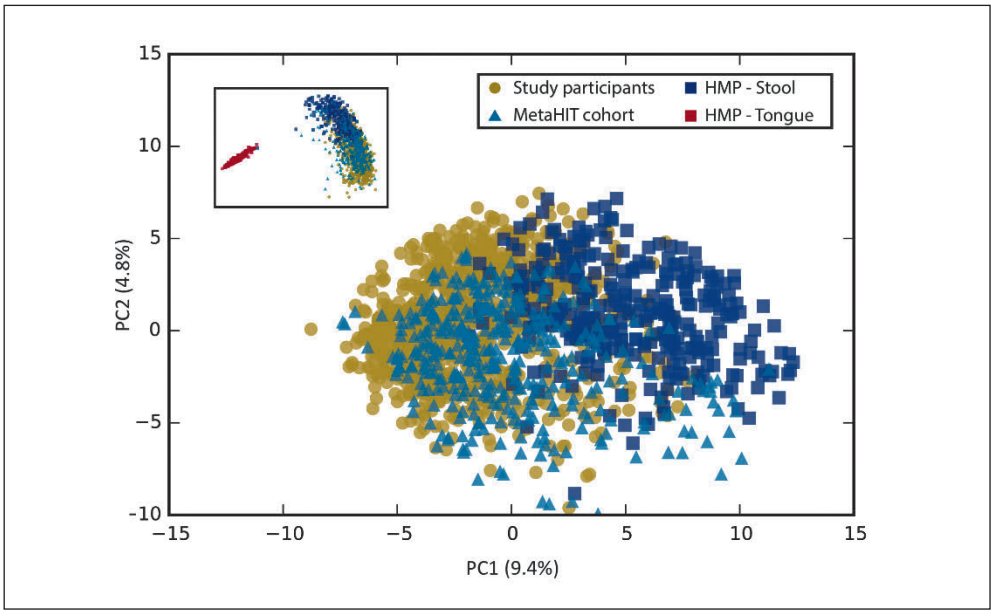

Fig. 2 Principal components analyses of microbiome distribution. Each dot here represents one person. Colours and symbols represent different cohorts. Dots that are very close to each other represent individuals with a very similar microbiome. Dots that are very far away from each other represent individuals with very distinct microbiomes. The result of the analysis represents each person's microbiome (one dimension per component) in a diagramme with only two dimensions. It shows that the composition of the microbiomes collected in the Israeli cohort overlaps greatly with microbiomes collected in studies in the US or in Europe.

We tested whether the other information that we collected from our cohort, i.e. the interaction of glycaemic response and body mass index, corresponds to well-known results from other studies.

We expected from those studies that the more obese people were, the higher their overall glycaemic response to foods would be. And that is exactly what we found in our cohort. The

same direct correlation was also found with the haemoglobin A1c, wake up glucose and age – the older you are the higher your average glycaemic response. We also found an inverse correlation with the 'good' cholesterol (HDL). All these were checks aimed at ensuring that our participants were not altogether different from participants in previous studies.

In this study, we performed only a single intervention: we asked each individual to eat a breakfast that we gave them after a night-time fast each morning of the seven days of follow-up period. This allowed us to give an identical breakfast that would allow us to directly compare the entire 1,000-person cohort. The breakfast included identical pieces of white bread in two of the days, bread plus butter on two other days, sugar on two other days, and fructose on one day. The average glycaemic response to any of these test foods was exactly the glycaemic index of that food, but the variability in the response across participants was huge. Figure 3 shows on its left that the average response is the glycaemic index but the variability is massive.

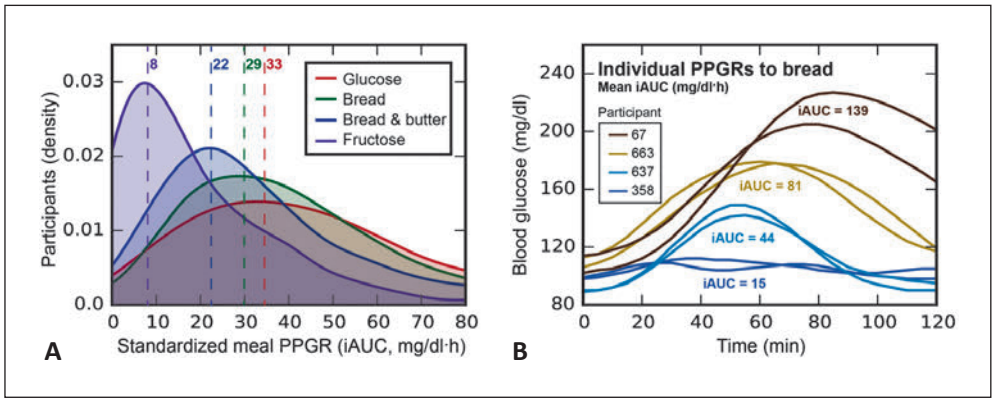

Fig. 3 Testing the cohort response for standardised meals. (*A*): glycaemic responses and indices; (*B*): individual responses.

If we look at how a certain person responds to a certain food on two different days, we can see that the response is very uniform (Fig. 3*B*). The variability between people is high, but low for any individual from day to day. And it looks like there is a certain rule for everyone that is deeply rooted within their physiology. No one knows yet what that rule is and how it comes about.

We collected a huge amount of data that will keep us busy for the next ten or 15 years. But we are already beginning to see clues about factors that may be part of the individual response rules. Of course, the more diabetic you are and the more obese you are, the more radical your response would be to whatever food you eat. So this was well expected. But we started to see novel things, for instance that responses to fructose are associated with the emergence of certain bacteria.

Sure, these were responses to test foods, but participants also reported their real-life behaviour. So we also have a huge amount of food-related data and the variability in the response to them is huge, just like for the test foods. There are very interesting counterintuitive examples: people who eat a bowl of rice versus people who eat a bowl of ice cream. You may expect – I did – that all people have a huge glycaemic response to ice cream and a smaller one to rice. But there are individuals who showed exactly the opposite: they did not spike on

ice cream but did greatly spike on rice. Actually, when we tested the entire cohort, we found that 70 % of the individuals do not spike on ice cream – which may be a good inspiration for many of us ice cream lovers.

5. A Predictive Algorithm

The major aim of this study was to develop a predictive algorithm for the individual glycaemic response. Some predictions look quite obvious: if we eat a diet with more carbohydrates, on average we will spike. But when we measured the predictability of this 'gold standard' of the field of nutrition science, the predictability was very low at only 0.37, meaning that 63 % of the glycaemic response was unexplained by carbohydrates.

In contrast, we used machine learning algorithms that used the big data of 900 of the individuals as input and trained itself to develop an individualised algorithm for each of these individuals. Then we took the data of the remaining 100 individuals that did serve as training data and asked the trained algorithm to predict their individual responses.

When we start adding other features into the personalised algorithm, such as other meal features, the logged activity, the microbiome features or personal aspects, its predictive power greatly improves to 0.67. So by applying a machine learning approach to big data, you can actually develop an approach that predicts physiological response without even understanding the responsible physiological mechanisms. The microbiome is the single most robust and important set of parameters that has achieved this predictability power. When we applied the algorithm to the 100 remaining individuals, its predictive power even rose to 0.7, showing that the training induced a reproducible response.

6. Validating the Algorithm

Now it was time to see whether this approach works in real life. As a validation study, we took a group of individuals, most of whom were pre-diabetic. This big sub-set of individuals already feature changes in their blood sugar responses, indicating that about 70 % of them will become diabetic in ten years. Remember, there is no real solution for this huge sub-set of individuals. Actually, when we put the one-size-fits-all recommended diet – the American Heart Association Diet – into our algorithm, more than half of these individuals on this diet would progress faster to diabetes.

We put these pre-diabetic individuals through the exactly same weekly process and then we asked the algorithm to devise a set of good diets and a set of bad diets for each of these individuals. All diets were isocaloric so there would be no caloric differences that could have affected the results. But between individuals these diets were very different; some components of one's good diet would appear as somebody else's bad diet and *vice versa*. We then asked the individuals to eat only their personalised good diet for a week followed by their personalised bad diet for a week while we extensively measured and monitored them.

Figure 4 shows one of our participants. She was given a set of good diets tailored to her and a set of bad diets tailored to her. You probably would not be able to do tell which of the diets was the 'good' one or the 'bad' one, because when we tried this on our students that were involved in the study we got a 50 % success rate. For example, the good diet included ice

cream, but also hummus and eggs and the bad diet included sushi and, for some reason, corn. It is really counter-intuitive. But when we measured her glucose levels, the difference became very clear (see Fig. 4): during the week of bad diet – the one with the sushi and the corn – her blood sugar level spiked many, many times to almost diabetic levels. In contrast, when she ate the good diet she normalised her blood sugar levels.

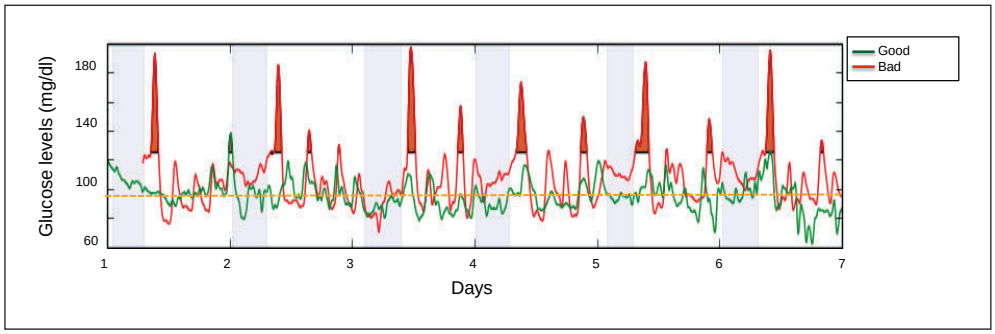

Fig. 4 Example of blood glucose response to algorithm-tailored diets. Good diet: red. Bad diet: green.

The statistical significance of the difference between the diets was huge. For a different individual, the good diet included croissants, halva, and hummus and the bad diet for some reason included peaches and grapes. But again: when that individual was given his individual bad diet, he spiked to very high levels and when he was given his individual good diet he normalised his blood sugar levels.

All but one of our participants achieved a significant improvement during the good week and deterioration during the bad week. In this validation cohort, our predictability reached 0.8, which is close to what we think we can achieve based on the existence of some intra-individual variability. We actually profiled the gut microbiome every day of the good week and every day of the bad week because this gave us an opportunity to really study in detail what the microbiome is doing. We found out that when these individuals improved during the good week or deteriorated during the bad week, we could identify a signature of bacteria which in all of them changed to the same direction, even though each individual started with a unique microbiome and we gave a different intervention to each individual.

In summary, these results show that an extensive big data analysis – even without understanding any mechanism – can identify putative drivers of disease. In this way, we identified microbes as potential drivers and effectors of the glycaemic response that could not be identified in any other way. What was really reassuring was that some of these bacteria had been described before in studies looking at diabetic individuals. Many of the others are new bacteria that nobody has seen before.

In the physiological and pathophysiological context, we always encounter a high degree of variability and complexity, which is the theme of this meeting. Often, we are afraid of that complexity: we try to reduce it, we try to ignore it, or we look at averages and not at variants. However, now, technologies are available that enable us to start exploiting and understanding how variability manifests in risk for common diseases. And you can apply the same set of rules to look at any disease state using big data and smart computation analysis tools.

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Modelling Ecosystems – From Plant to Animal Communities

Thorsten Wiegand (Leipzig)[1]

Abstract

There is now a broader public awareness that ecosystems are under increasing pressure due to climate change, habitat loss and fragmentation, extinctions of species, and biological invasions. This raises concerns about their future ability to provide the ecosystem services required for human well-being. Designing target-oriented strategic interventions requires a general understanding of the underlying mechanisms that drive ecosystem dynamics as well as detailed case-specific data-driven analyses. Modelling ecosystems is crucial to this endeavour. However, ecosystems are inherently difficult to study: they are subject to internal and external stochasticity, and the scales with which data are collected are not necessarily the scales relevant for their dynamics. Moreover, different species present specific challenges to modelling attempts due to their particular natural history. So, ecological research is often case-driven with limited powers of generalisation. As a consequence, no general theories akin to those in physics exist. There is an ongoing discussion regarding the appropriate level of detail required for modelling and understanding ecological systems. Simpler conceptual models and more detailed data-driven models possess their own advantages and disadvantages. As I will discuss, new technological developments and the increasing availability of detailed remote sensing data provide exciting opportunities to reach levels of understanding that were unthinkable just a few years ago. It is hoped that these advances will allow ecologists to keep up with the increasing challenges that ecosystems are facing today.

1. Modelling in Ecology

Ecosystems are hierarchically structured and involve genes, individuals, populations, and communities of plants and animals co-existing together in a given landscape. Beyond that, their dynamics influence and are influenced by feedbacks on a larger scale, such as global climate or the global carbon cycle. Moreover, ecosystems are driven by abiotic factors such as topography or soil, stochasticity introduced by the climate, and disturbance events such as floods or fires. And, of course, we humans also drive ecosystems.

Given this complexity, it is not surprising that ecology has subdivided into many different sub-disciplines which investigate different aspects of ecosystems. For example, population ecology investigates patterns and dynamics at the population level. When many different populations interact in the same area, we are talking about the community level driven mostly by competition or predator-prey interactions, in short: factors that regulate the growth of populations. One more level up, ecosystem ecology studies the biotic (living) and the abiotic (non-living) components of ecosystems and their interactions, i.e. the flow of energy and matter through ecosystems.

All these disciplines were developed to better understand how ecosystems work. This is an important endeavour because when ecosystems are under pressure, it ultimately becomes

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a problem for us humans. The Millennium Ecosystem Assessment outlined four different groups of services that ecosystems provide to us: provisioning, regulating, supporting, and cultural. The pressures that ecosystems are facing today include climate change, habitat loss and fragmentation, species extinction, and invasion of alien species. To mitigate these effects, we must develop an understanding of the underlying interactions between organisms and their environment. Accurate theories and predictive models are indispensable in this effort.

Wikipedia defines a theory as 'a well substantiated explanation of some aspects of the natural world that is acquired through the scientific method and repeatedly tested and confirmed through observation experimentation'. In contrast, a model is defined as 'a purposeful and simplified representation of the reality that makes a particular feature of the world easier to understand, to define, to quantify, visualise or to simulate'. A model assembles current knowledge that is regarded as important for the question on hand into a logical framework and explores the consequences of that knowledge. In doing so, there are always trade-offs among realism (how well the model structure mimics the real world), generality (the range of situations where the model applies) and precision (the accuracy of the model predictions). For example, a realistic model in general does not have great generality because it needs to include case-specific details.

Usually one model cannot fulfil all these wishes at the same time. Each model type has its own domain and comes with different trade-offs. The appropriate model type must be selected based on the scientific question and the data on hand. We can divide models in ecology roughly into four categories: statistical and phenomenological models, analytical equation models, numerical equation models and rule-based simulation models, including agent-based models or cellular-automata models.

2. Statistical and Phenomenological Models

Statistical and phenomenological models search for patterns in the data and extrapolate them. For instance, classic regression models are based on correlations in the data. This type of modelling has recently been extended to incorporate non-linear relationships, Bayesian approaches, and more realistic mechanistic components. Machine learning approaches make predictions based on properties of training data and are particularly related to big data. Finally, null model approaches are used to detect patterns in the data. This is done by randomising certain aspects of the data and leaving others intact to find out which components in the data cannot be explained by random fluctuations alone.

While these models can show high levels of precision, they have a number of shortcomings and problems. Often, they cannot be transferred to new situations, so they are not general. And, in many cases, they cannot be used to describe dynamic behaviour. Ecologists, however, want to understand the mechanism and processes driving the dynamics of their ecosystems.

3. Analytical Equation Models

Analytical equation models have a long tradition in physics and were among the first models applied in ecology to describe the dynamics of populations and communities. The simplest analytical models are differential equations, such as the logistic growth model shown in Figure 1.

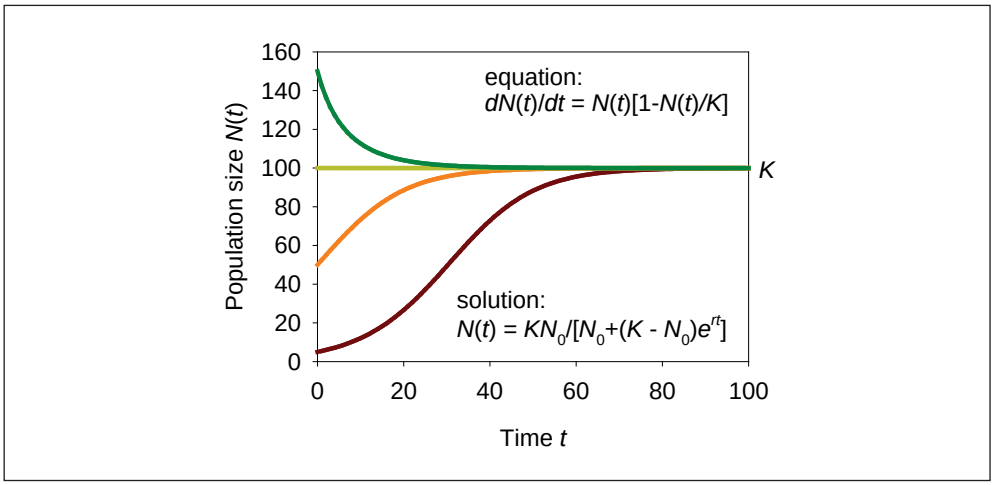

Fig. 1 A logistic growth model, an analytical equation model. This model describes exponential population growth with per capita rate r if the population is small, but resource limitations will lower reproduction and/or survival with increasing population size $N(t)$ and cause it to stabilise around a carrying capacity K.

An advantage of this type of model is that analytical solutions can often been found, e.g. by the rules of calculus. This allows to directly study the impact of model parameters, such as the growth rate r or the capacity K in the logistic growth model (Fig. 1). Analytical equation models are used to describe the dynamics of single populations, of interacting populations such as predator-prey systems, or of entire food webs and communities. They can also be extended to incorporate random variables. Such stochastic differential equations have gained particularly importance in ecology, especially for the study of population extinction and neutral theory.

Analytical equation models have a number of shortcomings and problems, however. The 'fear' of biologists to collaborate with modellers appears to be rooted in this type of model: they are formulated in an abstract mathematical way and their parameters often have no direct correspondence to measurements taken in the field. And, because of the mathematical formalism, they are extremely difficult to communicate and become a type of 'black box' for ecologists who are not familiar with equation models.

When I was a tutor in mathematics classes for biologists, many of the students studied biology exactly because they never wanted to be bothered with mathematics again. That may be part of the reason why there is still a certain resistance against modelling and theory within the ecological community.

One limitation of analytical equation models is that their equations can often only be solved for idealised situations and not for more realistic field conditions. But ecologists need solutions for real systems. This is especially true if spatially explicit processes play a role.

4. Numerical Equation Models

Numerical equation models can be seen as an extension of analytical equation models. They are basically numerical iterations of equation models and can overcome several of the aforemen-

tioned shortcomings. Most importantly, they can describe more realistic field situations. Metapopulation models, for instance, are spatially explicit and assume a stochastic balance between extinction and recolonisation of small local populations inhabiting patches of suitable habitat. Forest gap models include mechanistic representations of processes such as the carbon balance of trees and competition for light that drives growth and survival. On the other side of the continuum are complex ecosystem models that emerged in the 1960s and 1970s under the label 'big biology'. They describe the flow of matter and energy in a system and could often only represented by flow charts with many boxes and many arrows, so they were complicated to assess.

However, just like any other type of model, numerical equation models have their own particular shortcomings and problems: they can become too complex very quickly, especially if the model is supposed to include everything that is known about a system. This renders them at times intractable, making model analysis and parameterisation very complicated.

One relatively simple and still tractable example of this class of models is FORMIND (Fischer et al. 2016), a forest simulation model developed by my colleague Andreas Huth. Here, the forest is conceptualised by gaps; when a big tree dies and falls, it creates a gap. FORMIND follows the fate of those gaps, where trees compete for light and space. The carbon balance of each tree is modelled based on photosynthesis and respiration. Relationships of the diameter of a tree to its height and the shape of its canopy determine the model trees' carbon content. And finally, mortality and recruitment are represented by stochastic components. Figure 2 shows what this type of simulation can look like.

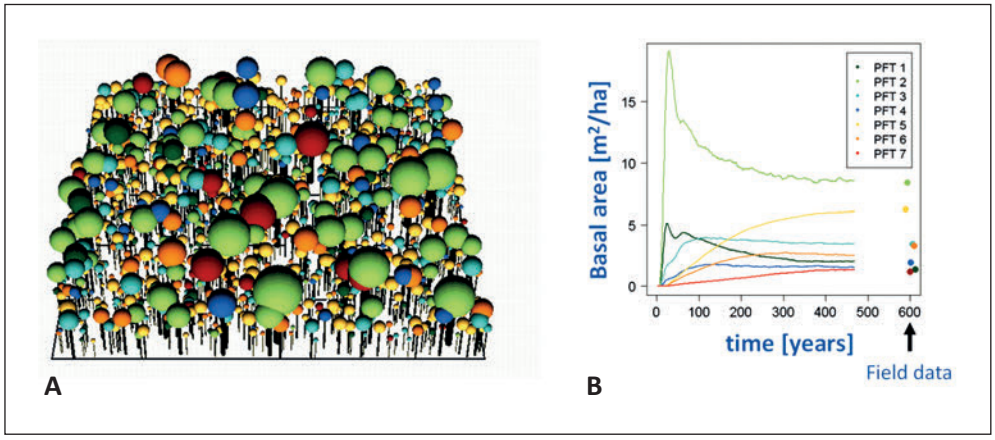

Fig. 2 In the example, the FORMIND forest simulation model describes a forest succession in a 100 m × 100 m plot based on seven different plant functional types (PFT). (*A*): The graph shows a snapshot of the locations and sizes of the trees; and (*B*): the graph shows the time series of the total basal area of the different plant functional types.

Typically, four, five, or six functional simulation types are used, i.e. different strategies of trees (e.g. pioneer or climax species). They are required to represent reasonable dynamics with pioneer species that are then replaced by other species later in the succession. Due to the long tradition in forest research, forest modellers are in the lucky position that sufficient data is often available to find the right parameters for these models, or, in scientific jargon, to 'parameterise' these models.

Based on all these building blocks, numerical equation models can predict realistic dynamics of forests. The FORMIND model has been applied to forest management in many tropical areas of the world.

5. Agent-Based and Individual-Based Models

Finally, there are agent-based and individual-based models (Grimm and Railsback 2005). They are completely different from the models discussed above. Emerging in the 1990s, they came with a characteristic novelty: they did not always require (differential) equations! This is sometimes very difficult to communicate to mathematicians, but these models can be directly based on simple computer code, simple 'rules'. You may say 'rules are equations, too', but in these models there is still no equation to interrogate.

The individual is the unit of the model. This can be a plant, an animal, a blood cell, or whatever is of interest. The fate of each individual is simulated in a stochastic manner, based on its interactions with other individuals and the environment. All population or community level properties emerge as a consequence of those local interactions. Thus, the spatial dynamics can become very realistic. Individual-based models are structurally realistic because the unit of the model is also the unit of the observation. This has the enormous advantage that now the abundant knowledge of ecologists and biologists about the behaviour of individuals can be directly incorporated in the model. And, of course, they are easy to communicate to ecologists.

But again, one should not forget the shortcomings we touched upon before: very specific methods are required to cope with the complexity of these models. Often, the model design is quite *ad hoc* and not tied to theory, so generality is sometimes lost.

6. General Problems with Modelling in Ecology

To summarise this part, here are some general problems of the models in ecology. The first problem is uncertainty. Measurements and parameter values are uncertain. The representation of processes is uncertain: It is often not exactly known how the system works, so our assumptions are usually simplifications. Additionally, ecosystems may possess very strong inherent stochasticity: for example, when an individual moves its movements can be close to random – so it is uncertain where the individual will end up exactly. Ultimately, the environment itself is very uncertain and stochastic: climate and other sources constantly disturb ecosystem dynamics. In the end, the output of all these models will be a distribution of probable outcomes and not a nicely defined deterministic value.

Additionally, data in ecology is always sparse. There is almost never sufficient data to determine the values of model parameters directly. Consequently, small errors in the input can propagate into big errors in the predictions. Additionally, data collection usually lasts only two to four years, the typical period for a doctorate degree, but data on a large spatial and temporal scale are usually missing. However, many ecological phenomena unfold on larger scales, causing the up-scaling problem: how to extrapolate data from small scales to describe the phenomena of interest on large scales. Finally, natural history is often idiosyncratic: each system may have specific features that drive its dynamics.

7. Potential Solutions for the Limitations in Ecosystem Modelling

Figure 3 shows a graph that describes the relationship between model complexity and the payoff of the model. So we may have a trade-off between realism and tractability of a model.

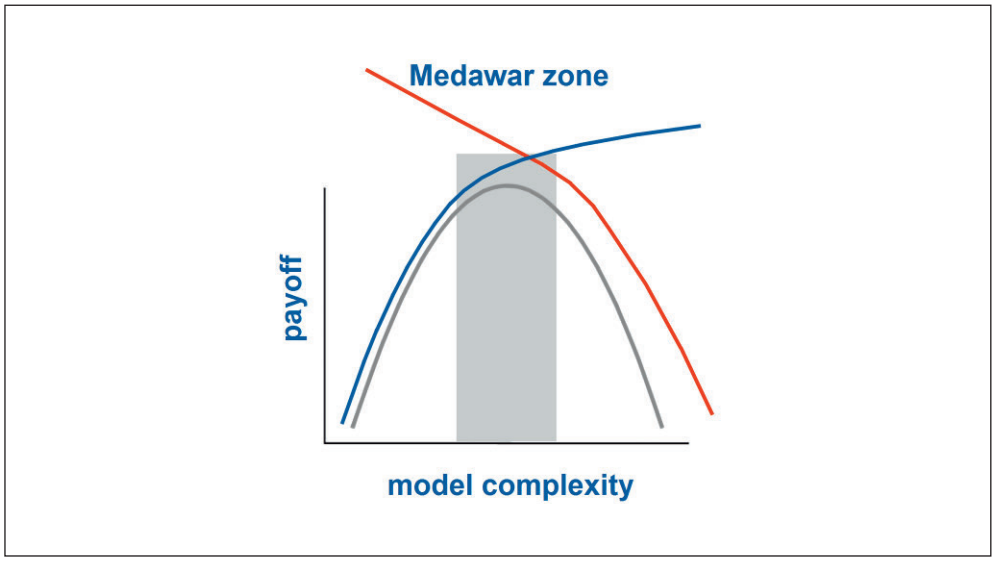

Fig. 3 The Medawar Zone: Trade-off between realism and tractability of a model versus its complexity. Usually there is a zone of intermediate complexity where the payoff is high. (Modified after Grimm et al. 2005.)

Structural realism is the ability of a model to produce independent predictions that match observations. It increases with model complexity. However, at the same time the increased complexity makes the model analysis more complicated. Additionally, if more and more parameters need to be determined with the same amount of data, the parameter and prediction uncertainties increase. Thus, there is a zone of intermediate complexity that is balanced between structural realism and intractability, where the payoff is maximised. This area is called the Medawar Zone.

8. Finding the Medawar Zone

It is difficult to find the Medawar zone without a systematic modelling strategy. One solution was developed in ecology at the end of the 1990s, when Hilborn and Mangel published the book *The Ecological Detective* (1997). Its central tenet was confronting models with data. Their strategy was to use numerical equation models and apply methods of statistical inference to determine the appropriate level of model complexity. They emphasised the principles of parsimony and asked: 'Can the data justify the amount of detail in the model (i.e. its complexity)?' Their methods were based on likelihood functions and information theoretical approaches, like the Akaike Information Criterion (AIC). The methods of Hilborn and Man-

GEL revealed that the additional biological detail in many models was often not justified and that, in fact, the data was not sufficient to trade for complexity. Nowadays, extensions of this approach, including Bayesian inference, have broad applications in ecology.

9. Pattern-Oriented Modelling

At the end of the 1980s, when the first individual-based or agent-based models appeared, scientists were very excited about the promise of such computer simulation models to unify ecological theory. However, the initial enthusiasm quickly dissipated due to a number of problems, including a lack of methods to cope with the issues of model complexity and error propagation, and the models were often designed *ad hoc*, not tied to theory, and lacking generality. To be fair, one could not expect full solutions to these problems within the 10 or 20 years these models would be around; analytical equation models had some 200 years to find them.

Together with my colleague Volker GRIMM and others (GRIMM et al. 2005), we developed pattern-oriented modelling as a strategy to find the Medawar zone for individual-based simulation models. We explicitly followed the basic research programme of science: the explanation of observed patterns. Patterns are characteristic structures that contain information on the internal organisation of a system. In practice, we compare the ability of alternative models with different levels of complexity to reproduce several patterns at the same time. The focus on multiple patterns is important because it is well known that substantially different models can reproduce the same pattern. However, two or more patterns that describe different characteristics of the system are not that easily to reproduce at the same time by different models.

I will now illustrate this modelling strategy with an example of my own work conducted under a European Research Council (ERC) advanced grant. A big question in ecology is to explain the high species richness of tropical forests. Traditionally, ecologists assume that each species in a given ecosystem is different and occupies its own ecological niche, thereby limiting the interactions with others required for its persistence. However, around 2001 the publication of a book by tropical ecologist Stephen HUBBELL called *The Unified Neutral Theory of Biodiversity and Biogeography* caused a big 'scandal' that shook the fundamentals of ecology. What upset many ecologists about this book was that HUBBELL claimed that neutral models, a class of analytical models that assumed that all species are identical (and have no niches), could explain important properties (patterns) of species rich communities. For example, these models can predict the distributions of rare and abundant species in tropical forests or coral reefs. Clearly, neutral models were not really welcome because all the work ecologists had done for so long on species differences and niches suddenly seemed irrelevant.

Ecologists before HUBBELL usually focussed on differences among species and started with the most complex situation, whereas HUBBELL used the simplest case as a starting point. He tested how far he could go with his radical assumptions to find out how much detail must be added to a neutral model to explain important properties of species in rich communities.

My strategy was to combine the strengths of different models. We used the analytical predictions of neutral theory as point of reference and started with a spatially explicit and individual-based version of a neutral model. This allowed us to compare the model output with many more patterns extracted from inventory maps of tropical forests (Fig. 4) that were possible with the analytical neutral theory. We used also null model approaches to identify spatial patterns in the

distribution maps of trees (Wiegand and Moloney 2014). Finally, we developed alternative model versions that included the simplest neutral models and also models where species were different and tested their ability to reproduce the patterns observed in the forest inventories.

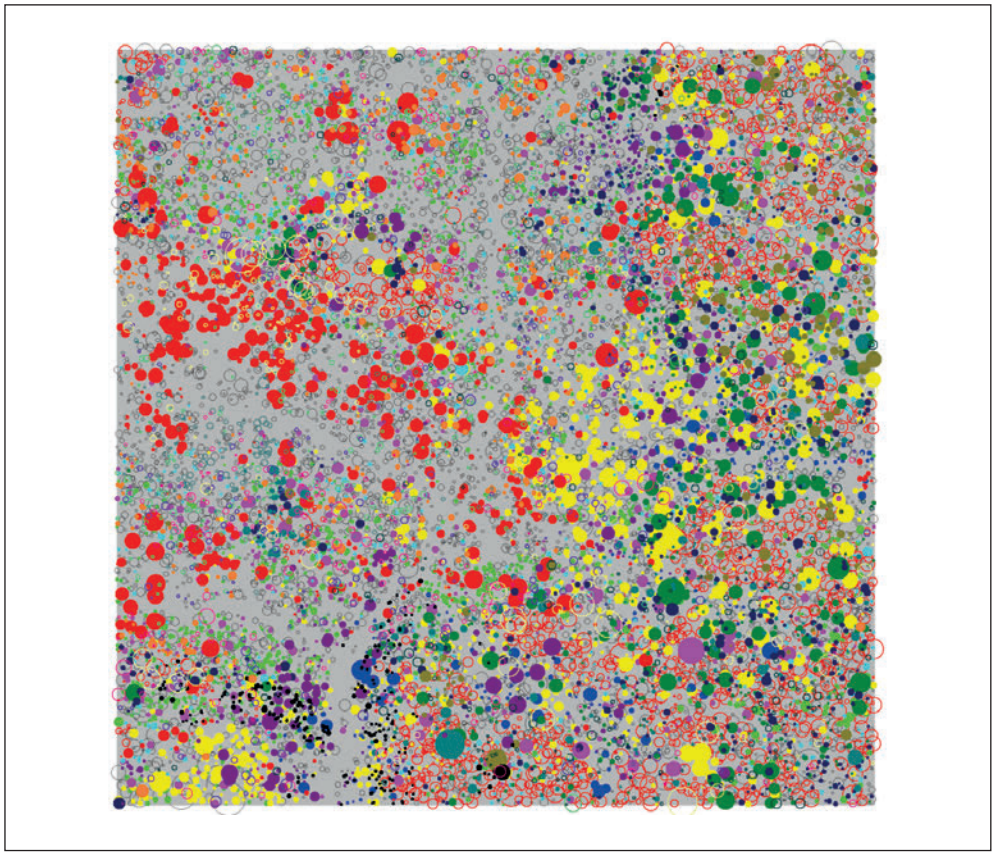

Fig. 4 Spatial inventory data of the Sinharaja tropical forest in Sri Lanka and patterns that can be extracted from such data. The size and status of every tree is measured every five years. This allows extraction of data on survival and growth of trees used to parameterise the models. Additionally, it includes the size distribution patterns of individual species, information on the spatial aggregation pattern of individual species and co-occurrence patterns of different species that live close to one another. We can also determine how many species can be found on average in an area of a given size and how the local species composition changes in space. Finally, the inventory data contain information on the ecological similarity of neighboured individuals and how strongly they compete.

One challenge with this pattern-oriented approach was to parameterise 200 or 300 species to describe the interactions of a total of 20,000 to 200,000 individuals. We were very lucky to get access to the data of the CTFS-ForestGEO network of the Centre of Tropical Forest Science (CTFS), one of the largest data enterprises in ecology. Today, that network comprises 63 field sites all over the world that all follow the exact same protocol. They comprise completely mapped inventory plots of tropical, subtropical and temperate forest of up to 50 hectares, recording and mapping every tree bigger than one centimetre in diameter, and then monitor-

ing the development of each tree every five years. This has generated a huge amount of data. Figure 4 shows as an example a representation of the larger trees in one forest in Sri Lanka.

We used individual-based dynamic biodiversity models with different complexities to find out how complex our model must be to recreate forests with observed spatial structures as those shown in Figure 4. Our hypothesis was that the neutral models are oversimplified and would completely fail to capture any of the complex spatial structures in species diversity.

To meet the technical challenges of the pattern comparisons, we developed new methods of stochastic inference that allowed us to use well-established optimisation tools to fit the model to the observed summary statistics. We also made no attempt to parameterise individual species. That would have been impossible as there were 200 species, many of them so rare that little to nothing was known about them. So we used distributions for their parameters. If the variance of the distribution was zero, we obtained a neutral model, because then this property was the same for all species. Increasing the variance yielded more and more variability in the properties of the different species.

The surprising and unexpected result was that the simple neutral model already provides a very good approximation of the complex spatial structures of species in rich tropical forests (May et al. 2015). The model was able to fit all individual patterns with very high precision and to fit several patterns together with sufficient precision (but not all). So, it looks that Hubbell was right, after all. Our structurally realistic model failed in an especially informative way. This allowed us to test specific hypotheses on the relative importance of species differences and niches in explaining additional properties (patterns) of species-rich communities.

In summary, to cope with complexity, one should try to combine the strengths of the different types of models, employ analytical models and predictions from ecological theory as starting points, then access new data sources by using statistical and phenomenological models to identify patterns in the data, and strive to explain these patterns rather than modelling a complete system. To do this, one can take advantage of newer methods of statistical inference for model selection that can actually tell us how much complexity is needed. As always, one must apply Occam's razor: keep models as simple as possible but as complex as necessary.

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Discussion of Session 3

Lengauer: Dr. Elinav, you showed us a regression model that takes personalised features as input and regresses the glycaemic response. How did you formalise the glycaemic response? I assume it is a scalar number. What is that scalar? Also, you said that the most informative set of features were the features characterising the microbiome. What kind of features are these, and how many dimensions did you need to characterise the microbiome?

Elinav: To your first question, it is not a one-point-one-time feature. We took advantage of the fact that during the monitoring week we had many, many points of measurement, and therefore we measured areas under the curve.

Concerning your second question, we are talking about hundreds of features of the microbiome. We are continuing to dig deep into the data and to add more and more features. There is no single feature that makes a high contribution, but many, many features, each adding a small contribution. You would never be able to do this without an unbiased machine learning approach. The overall aim would be to dig more into the microbiome to enable a good prediction by only using the microbiome and perhaps a set of easily obtainable clinical features. We are actually very close to achieving this. In this study, we did not know what would work and what would not, so we recorded everything we could. But now, since we see that the microbiome has a relative heavy contribution, we are trying to find out whether we can get to a point where only the microbiome plus some clinical metadata can achieve a decent, if not identical, predictability without the need for all of the rest.

Lengauer: Are the genetic features metabolic features?

Elinav: When you focus on the microbiome, these include two basic sets of next-generation sequencing data. First, there is the 16S ribosomal DNA data set, which gives you the relative abundance with its many associated features. The more important and the much more informative set is the short metagenomic sequence, which gives us gene abundance, pathway abundance, and modular abundance.

Guest: Dr. Elinav, you showed us some special individualised diets. For some people, chocolate is good; for others, red wine is good. Did you check whether that is congruent with the individuals' personal preferences? Some people like red wine, some people like chocolate, and some like chips.

Elinav: That is a question that I am often asked. I will divide my answer into two parts: On a very general level, we are aware that people judge some foods as good for them and some foods as bad. However, nobody has ever measured that feeling of something that makes sense. We intuitively connect to what people think or feel. This is why we had a very high level of compliance in this study as compared to any clinical trials that have been done in the last 15 years. On a more specific level, however, we did not measure or ask people to

tell us what they think would be a good or bad diet for them. Therefore, I cannot answer your question in a scientific way. But if I may speculate, I guess people would not be able to intuitively say what is good or bad for them.

Guest: I have a question for both speakers about validation of these models. Specifically, for Dr. Wiegand: Is there a way to apply your model to a different patch of forest? Or do you somehow have control over all these parameters that you have included in your model?
A similar, slightly more specific question for Dr. Elinav: You mentioned you have trained individual decision trees for every person and then you took 900 of these and validated them on 100 other persons. Are you combining the predictions of these different individual models for new members of society? Or are you validating these predictions of the individual models on new data per person?

Wiegand: We developed two different strategies for model validation. The first is that the models have a structured realism: one can test many additional structures in the data that were not used for model parameterisation. We attempt to test as many of such secondary predictions as possible. If the model predictions don't match these additional patterns, we probably have a problem with our model. The second strategy is to use independent data from different areas. So, for example, the forest model, or FORMIND model, I have presented is based on more general functional types instead of individual species and therefore also applies to similar forests. This allows us to use the model for the management of tree logging with different scenarios.

Elinav: I will add that the biggest risk we face is overfitting. Basically, we take 900 individuals and build this decision-tree-based analytical model, which is the same for each participant. We have tens of thousands of these decision points. But everyone goes through the same process. So, the results are different but the process is the same process. The danger here is that you are building a model that fits the 900 people almost perfectly, but will not fit any other population. So, with the group of 10, we corroborated the population-based decision tree. While we have seen quite decent results, we have not yet reached saturation. So, the more people we add, the better the results will be.

Friedrich: Are there any approaches to combining these microbiome studies with genetic data directly, since many metabolic diseases are caused by genetic modifications?

Elinav: As I mentioned in the beginning of my talk, we also performed quite an extensive host-genetic analysis by doing a million deep analyses on each one of these 1,000 individuals. Actually, the data that I presented here did not include these host genetics simply because it takes more time. We have now completed this huge genetic database. With it, we have a unique opportunity to do something that has never been done before: a head-to-head comparison of the contribution of host genetics versus the microbiome with respect to a particular predictive model or a particular clinically relevant question, in this case glycaemic management. This is work in progress. The results have not yet been finalised. As we expected, so far, the microbiome data may be as predictive or even more predictive than genetic data for glycaemic responses.

Guest: I am interested in the dynamics of the microbiota, such as daily fluctuations. Do you see or have to control for such dynamics?

Elinav: The dynamics of the microbiome is an additional factor. What I have shown you is a snapshot microbiome analysis. It tells you nothing about the dynamics of the microbiome. Still, this is a critical question when looking at the long-term effects of a dietary intervention. For example, one really important question is: if we intervene in a personalised diet

for a long period of time in a certain individual, would the microbiome drastically change in response? What we are checking for now is whether we would have to revisit that person's data in order to tweak the personalised predictions based on an altered microbiome. In the interventional part, we measured the microbiome every single day. We have done this in other studies as well. The simplest answer I can give you is that if there is one environmental factor that affects the microbiome in a drastic and reproducible manner, it is the diet. Within two to three days of a drastic change in diet, you see very reproducible changes in both the composition and the function of some of the members of this ecosystem.

Buchrieser: You gave us a wonderful example of how important the microbiome is in our hands. It is conceivable that diet and microbiome go together. But in the last years, the microbiome seems to have become responsible for everything: for gut and brain, for autism, for asthma – what do you think about this?

Elinav: We must be very careful and very responsible. The microbiome like CRISPR-Cas is a very sexy scientific subject at the moment. We are very happy about that, but the microbiome is often being oversold. It is certainly not responsible for everything. In many cases, it is not even the main driver. So, it is important to stay very cool and to follow the data rather than our megalomaniac dreams. The hype is helping and harming the field at the same time. The way out is to follow the data.

Friedrich: For modelling your forest ecosystem, is it also important to include the soil ecosystem with all the species?

Wiegand: In some aspects, it can become important. Trees in certain types of habitats associate with the soil in a particular manner. There has been a lot of work done on these plots where they take soil samples and relate the spatial distribution of the species to soil nutrients or mycorrhiza which are very important for the growth of certain species. Pathogens, herbivores, and small insects are relevant factors, too. For instance, the Janzen-Connell hypothesis poses that in big patches of trees of one species, species-specific pest pathogens and herbivores can accumulate and affect only conspecific individuals. In this way, they regulate the growth of abundant populations. This is a big theme in tropical forest ecology. But one also needs to be a bit careful not to include everything, because then the model becomes intractable.

Session 4

Chair: Axel Brakhage ML (Jena)

Nova Acta Leopoldina NF Nr. *419*, 97–107 (2017)

Modelling Biodiversity and Collective Behaviour

Iain Couzin (Constance)[1]

Abstract

Understanding how social influence shapes biological processes is a central challenge in contemporary science and is essential for achieving progress in a variety of fields ranging from the organisation and evolution of coordinated collective action among cells, or animals, to the dynamics of information exchange in human societies. Using an integrated experimental and theoretical approach, I will address how and why animals exhibit highly coordinated collective behaviour. I will demonstrate new imaging technology that allows us to reconstruct (automatically) the dynamic, time-varying networks that correspond to the visual cues employed by organisms when making movement decisions. Sensory networks have been shown to provide a much more accurate representation of how social influence propagates in groups and their analysis allows us to identify, for any instant in time, the most socially influential individuals within groups and to predict the magnitude of complex behavioural cascades before they occur. I will also investigate the coupling between spatial and information dynamics in groups and reveal that emergent problem solving is the predominant mechanism by which mobile groups sense and respond to complex environmental gradients. Evolutionary modelling demonstrates that such 'physical computation' readily evolves within populations of selfish organisms, allowing individuals to collectively compute the spatial distribution of resources and to allocate themselves effectively among distinct and distant resource patches without requiring information about the number, location, or size of the patches. Finally, I will reveal the critical role uninformed, or unbiased, individuals play in effecting fast and democratic consensus decision-making in collectives and will test these predictions with experiments involving schooling fish and wild baboons.

When I was a kid and I saw footage on the BBC in natural history programmes, I was fascinated. Ever since, I have wondered how and why groups of animals form and coordinate their behaviour. Now, as a scientist, I am even more fascinated because I now know that animals in flocks or schools are unrelated individuals. We have got very little understanding from an evolutionary perspective as to why unrelated organisms, in contrast to, say, the social insects, form these beautiful patterns.

We cannot use a verbal argument to understand how these interactions scale to collective properties. So it has become essential for us to use modelling techniques, mathematical models, and agent-based models to get inside the head of the individual animal to understand what makes it tick and why it behaves the way it does. When I started this research, there was no available experimental data at all. So, I speculated about the types of interactions that individuals may exhibit, as did some other researchers in physics and some biologists. For example, individuals may tend to match their behaviour with the behaviour of near neighbours.

One underlying assumption of such models is that individuals exist at certain positions. In these physical systems, the organisms themselves provide the energy, so they are far from equilibrium. Individuals also interact with the other individuals. If birds in flight get too close and collide, it can be fatal, so they exhibit a tendency to avoid collisions. On the other hand,

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if individuals become isolated from groups, they can lose the benefits of living in a group. And the costs of being isolated can be massive: being eaten by predators, for instance. There is a tendency for individuals to be attracted to others and perhaps also to align their path with that of near neighbours.

1. States of Living Matter

One could use continuous functions, step functions, or a variety of ways to model these tendencies. These models have one thing in common: they all predict that large groups of individuals take one of a number of fundamental states similar to the macroscopic states of matter:

– a swarm-like state that has statistical properties very similar to a mosquito swarm;
– a parallel fluid-like state that we typically think of when we see these types of groups and
– a rotating state in which the individuals are perpetually rotating around an empty core.

Another prediction of these models is that groups of animals exhibit strong forms of collective memory. For example, if you keep all interactions identical and just increase the preferred speed of all individuals, the system will spontaneously go from a swarm-like state into a rotating state. Increasing the speed even further will move the system into a parallel state.

Interestingly, when we slow the individuals down again, the system remains in the parallel state up to certain point and then it flips back directly into its original swarm-like state, skipping the rotation state altogether. So the system can occupy two completely different collective states under identical individual behaviours (preferred speeds).

This demonstrates that emerging patterns strongly depend on previous patterns, even though none of the individuals in the group has any memory of that history. Indeed, there appears to exist an inherent underlying low-dimensional dynamic that is reminiscent of purely physical systems. For instance, if you cool pure water down to slightly below the freezing point, it will stay liquid. But if you now introduce a tiny perturbation, the water will quickly transition to its solid state, or ice. So water, too, can exist in two different states, liquid and solid, under the same condition (the same temperature). Physical examples like these turn out to be informative about information transfer within groups of animals.

2. Telepathy or Something Else?

It is understandable that in the 1950s, the 1960s, and even into the 1970s, people believed there must be some kind of telepathy at work to give rise to the remarkably synchrony seen in swarms of animals. However, one feature that differentiates groups of animals from physical systems is, of course, that they evolve. The rules that govern their interactions are subject to strong natural selection. And as we have seen in Professor Singer's talk, natural selection can produce systems with long-range synchrony emerging from local interactions.

Now, if we add a predator to the same model and a common sense rule for individuals like 'move away from the predator should it come too close', we get some complex dynamics, such as individuals being able to detect and respond to the predator – not by seeing it but by responding to the wave of escape behaviour that propagates very quickly across the group. Of course, if a model has many parameters, it is sometimes unclear whether it actually captures

reality or just produces patterns that look like reality without revealing anything about the underlying mechanics.

3. Fish Tracking

When I set up my own lab for the first time, we planned to work on schooling fish. In the United States, wild fish are bred for the fishing industry to use as live bait. So you can buy a thousand of them for 70 dollars and they are delivered to your doorstep. Given that my lab employees are mostly physicists, this turned out to be a much more practical approach than trying to catch our own fish. The fish we ordered are so-called surface feeders; they swim near the surface, regardless of how deep the water is. Figure 1 shows how the fish transition between collective states in one of our water tanks. They produce a rich dynamical system and we aimed at interrogating this system with the same level of detail that previously was only possible for theoretical models.

In collaboration with Hai Shan Wu from China, we developed a software (it took about seven or eight years to develop) that could track the motions of all the individuals in our schools of fish (Strandburg-Peshkin et al. 2013). It does not lose track of them even when they cross each other's paths, which is an extremely difficult challenge in computer vision. By tracking our fish over hundreds of hours, we managed to collect high quality data, including their polarisation (how well aligned they are) and their rotation. In our data, we only ever see the three fundamental states that we predicted, regardless of the group size. This means that the three states are indeed attractors in this low-dimensional space. In its transitional regime, the system is unstable and will flip back and forth.

So, what are driving transitions in these collective dynamics? One hypothesis from our model was that changes of individual behaviour, like a change in speed, might drive changes in collective behaviour. But remember, there are two different metastable collective behaviours for the exact same individual behaviour. Another hypothesis from our model was that stochastic perturbations cause transitions. It turns out that both processes are important. The transition from a locally and globally disordered state to the two locally ordered states is driven by a change in individual behaviour, or by a change in speed. But the transition between two ordered states, such as the polarised and the rotating state, is driven by random fluctuations that can cause the whole group to flip from one attractor to the other, i.e. the system is in a metastable regime.

Microscopically, the polarised state and the rotating state look very different. There is no evidence, however, that fish know what group size they are in or whether they are in the rotating state or in the polarised state. Regardless of group size, as you increase speed, you increase the local polarisation in the local neighbourhoods of all the fish. We even tried to train the fish to recognise what state they are in, but they simply cannot do it.

4. The Wisdom of the Fish Crowd?

We often think about computation taking place in computers or in the brain. But computation can also happen in real social networks while the individuals are not aware of the computation at all. Our fish, like many other fish, live in dappled streams where light is variable and they prefer to be in the dark regions, a characteristic most fish share. Therefore, we used a projector

to simulate various lighting conditions. The computational challenge to the whole group of fish is to find a group behaviour that avoids the light areas and finds the darkest regions.

With this experimental setting, we were able to find the first experimental evidence that the individuals become much better at solving the problem when the group size increases. Was this a kind of 'wisdom of the crowds'? The term goes back to Sir Francis Galton, a cousin of Charles Darwin. At a livestock fair, there was a competition to guess the weight of an ox. Galton took part, but his guess was far off the ox's true weight. But when he took the average of the guesses of the eight hundred villagers, who had also guessed the ox's weight, the result was only one pound away from the true weight. He concluded that rough estimates of many individuals, if combined, could lead to great accuracy. Perhaps our own experiment was a little bit like Galton's: each individual fish takes a local noisy guess at the solution to the problem of avoiding light. Of course, fish cannot perform explicit mathematical calculations like Galton did. But perhaps, through their social interactions averaging all their motions, they are effectively averaging their imperfect individual guesses.

However, our data showed that individual fish are not capable of estimating the light gradient at all, regardless of group size (Berdahl et al. 2013). Which leads us to a conundrum: if the individuals are not utilising the local light gradient, how on earth is the group so good at responding to and tracking these light gradients? Of course, natural selection has come up with a beautiful and simple solution. The fish simply move faster in the brighter regions and slow down in darker regions. For a single individual, it would be a very poor strategy to try and stay inside a dark region. But fish in large groups, when combining this strategy with social interactions, are suddenly able to detect and sense light gradients.

The question is: how do they do it? When individuals in the dark region slow down, that leads to disorder. Meanwhile, individuals on the bright side are moving fast. This situation behaves as if there were a sort of spring-like potential between the two areas, where the spring gets tighter and tighter and exerts a centrifugal force towards the dark region. Additionally, in the dark regions the fish become more densely packed, which means the attraction is stronger towards them. Both factors are important.

Astoundingly, schools of fish can spontaneously grow by taking in more fish from the outside, to match the length scale of the environment that is important to them, even though they do not know what a length scale is. Natural selection has found this beautiful emergent property that allows them to spontaneously grow until they match the length scale. If they grow too large, this creates shear forces in the group and they will split up and then regrow to find the optimal length scale for their environment.

We have been able to exploit this very simple rule ('move faster in the light') for tracking light gradients with micro-robots. It is also being used in autonomous underwater vehicles to track phytoplankton plumes, oil spills, and so on. Yes, fish are selfish actors, but a type of physical computation evolves very readily among genetically completely selfish agents. They are just trying to optimise conditions for themselves, at the cost of others if need to be, for the benefit of the whole group.

5. Evolution toward Phase Transition

If we model this system and take it to the hydro-dynamic limit, there is a phase transition: the environment causes the system to fluctuate between a solid-like state and fluid-like state. Part

of the system can solidify while other parts remain fluid. By evolving to allow the environment to flip across that phase-like transition, groups of individuals could compute how to optimise their collective behaviour among different patches of the environment, even if they are not aware of how many patches there are. We looked at up to fifty patches and found that groups of individuals can perform a kind of physical computation that complements energetically expensive types of cognition such as brain activity (Hein et al. 2015).

6. Through the Eyes of Schooling Fish

We also developed software that tracks the individuals, maps their body posture over time, calculates where the eyes are and then reconstructs the pathways of photons onto the retina of each individual hundreds of times per second with graphic process units, allowing us to reconstruct the visual field of any individual in the group (see Fig. 1).

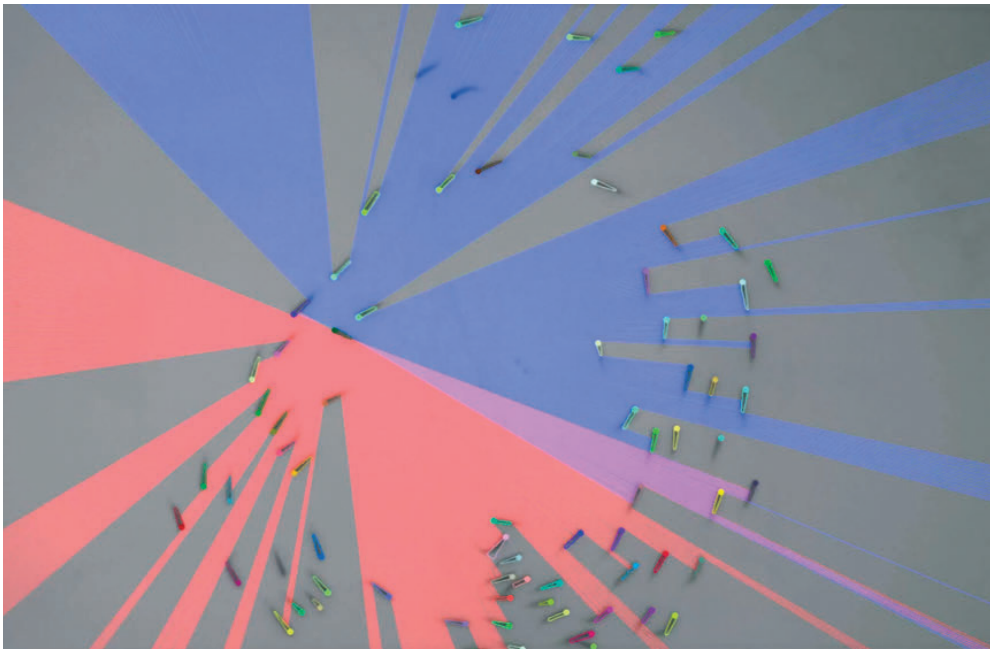

Fig. 1 The visual fields of a schooling fish. *Red*: left visual field, *blue*: right visual field.

Our schooling fish do not use the lateral line organ for social behaviour, they use vision. If you turn the lights off, they cannot school at all. They use their lateral lane to respond to the environment, but not for the social environment. We were able to show that a network of fish visual fields is much better than previously used models at explaining how behavioural changes spread through groups. Individuals are not simply interacting with a fixed number of neighbours within a local radius. But no one had tested how they interact with their visual neighbourhoods.

7. Tickling a Fish to Provoke Waves of Escape

To really get at the heart of this problem, we looked at a hallmark of collective behaviour: the rapid spread of behavioural change in the response to a predator. We conducted experiments in which we had a little fibre that came up from below and tickled any of the fish that we wanted to startle. This kind of mechano-sensory stimulus always causes what is called a C-start in the fish, an emergency evasion behaviour. So, we could tell with certainty which fish initiated a social wave. If we missed the fish just by a millimetre, there was no influence on the group at all. We conducted 205 sessions and for each one we knew exactly who was the initiator of a tickle-provoked social cascade.

Sometimes you get large scale cascades. But most of the time nothing happens; no one responds, or only one or two individuals respond. So, *a priori* it is very difficult to understand if one animal's C-start will cause a cascade across the group or not. To reach an understanding, we had to establish a functional mapping between the visual input the fish get and their motor output, which is a very difficult task.

Each sensory modality, including but not limited to vision, receives high-dimensional sensory input. The organism then must translate that input (potentially in combination with knowledge of its past behaviour) into a low-dimensional behavioural output. Locomotion in fish is controlled by a relatively small number of neurons in the hindbrain. Even physiologically, this is inherently a dimensionality reduction problem.

Using a computational visual field reconstruction, body posture mapping, and machine learning techniques, we could reveal which visual features our species pay attention to. Interestingly, they use two of the simplest possible visual features, the area subtended on the retina by others and the logarithm of the metric distance to others. It really amazed me at first, but we think it is because this is a very robust strategy, even if the water gets murky. Based on this understanding, we were able to construct a network of influence.

8. Revealing a Behavioural Network

We revealed a hidden network of communication much like neurobiologists attempt to do. Since the inception of neuroscience, people have been trying to unravel the structure of the circuits that give rise to individual brain dynamics. Here, we are looking at the structure of a social circuit that gives rise to collective behaviour. And we would not have been able to do this without understanding the mapping of visual input to motor output. Even though these fish use the simplest visual feature, the network itself is complex, directed, and weighted.

9. Fish Social Networks Have High Cliquishness

These networks are not of a classic type such as small world or scale free networks; they are in a completely different regime. Rather, they have a somewhat grid-like nature. We believe that these evolved networks share some very interesting properties that could someday benefit us. But first we need to understand how social influence relates to network structure. If you go to the literature on this topic, you will frequently see assumptions such as: the most socially influential individuals are those with lots of neighbours, especially when the neighbours

have what is called a low cliquishness, i.e. a low propensity for clustering with others. These assumptions come from epidemiology, where they are valid. They are based on the notion that collective behavioural changes behave like diseases spreading through a group. Intuitively, this assumption makes sense: if I had a disease, the longer you and I were to stay in close proximity to you, the higher the probability would be that I infect you, too. But if you only interact with your tight little clique of friends and you do not have any friends outside that group, the best I could do is to infect this little clique and the infection is not going to spread. So, from the point of view of a virus, a high number of neighbours and low cliquishness are desirable conditions.

Our experiment explicitly tested, based on the actual propagation of behavioural change, whether this assumption is true for fish schools. As it turns out, the most socially influential, so-called super-spreaders of behavioural contagions are those with a low number of neighbours, especially if their neighbours have a high cliquishness: exactly the opposite of what previous models would have predicted!

10. Simple versus Complex Contagions

Why is this the case? It is largely because social contagion is a so-called complex contagion, whereas diseases are so-called simple contagions, to use terms from the network literature. Let us assume that, instead of a disease, I have a certain political view, and I try to convince my colleague to agree with that view. I could try all day, but maybe we do not have this relationship in which constantly trying to convince another individual of something can truly influence them. I may influence a person slightly, but he may not be convinced. Yet I could also influence a different colleague who later interacts with the first person and conveys the same information and convinces them. This means that individuals can be influenced both directly and indirectly through these loops. And it is these loops that are extremely important in terms of how behaviours spread through groups.

By understanding the relationships in a particular network, we can predict on a case-by-case basis how an individual group will behave. In the fish tank, we know which individual we are going to stimulate. We can reconstruct the network dynamics from fragments of time and then predict very precisely not just how far a behaviour is going to spread, but exactly who is going to be changing behaviour and when (Rosenthal et al. 2015). Thus, the very complex, dynamical stochastic system of a school of fish becomes surprisingly predictable, but only because we are able to map the visual features they are actually using.

11. Informed Consensus Decisions in Groups

Fish have brilliant memories. After just six trials, they can remember different targets for several months. However, we got no evidence that fish recognise who has that information. A simple individual-based model in which we assume that individuals exhibit the so-called schooling tendency can reconcile group behaviour with individual goal-oriented behaviour. If an individual is not very hungry, their goal-oriented tendency will be weak and that individual will not risk leaving the group. However, if the individual is hungry, then their goal-oriented tendency to find or move toward food may be very strong and they may leave the group.

It turns out that one individual in a group of one hundred cannot convey information about a potential food source to all the others. But five informed individuals can, if they make it to the front of the group, which will then tend to move in their direction. And with ten informed individuals, suddenly and spontaneously the group moves in the correct direction. So, as the proportion of informed individuals increases, the accuracy of information transfer increases for all group sizes. For instance, 85 % accuracy in a small group of ten requires around half the individuals to have the information. But larger groups, like the group of two hundred in this example, require less than 5 % of the individuals to actually know where they are going. Yet, to an observer, it looks like all individuals know exactly where to go. We simulated migrating animal groups and cell sheets. In these large groups, a microscopic proportion of individuals that actually know where to go can inform the whole field of individuals or cells where to move.

Our real fish demonstrate very similar relationships of accuracy versus number of informed individuals. But again, fish are selfish individuals. What if there is a conflict with respect to where to go? Can they resolve this conflict, i.e. can they also make collective consensus decisions?

Two factors turn out to be very important: the number of individuals that want to go in each direction and the geometry, i.e. the angle at which they disagree. Let us consider a group of one hundred individuals in which five prefer to go one way and five prefer to go another way. Our simulations show that at a particular angular difference there is a sudden transition: up to a critical difference of opinion, the individuals split the difference and they will tend to move at the average angular difference, but at the critical angle one group wins over the other and the whole group follow either one or the other preferred directions of travel. Figure 2 shows this graphically.

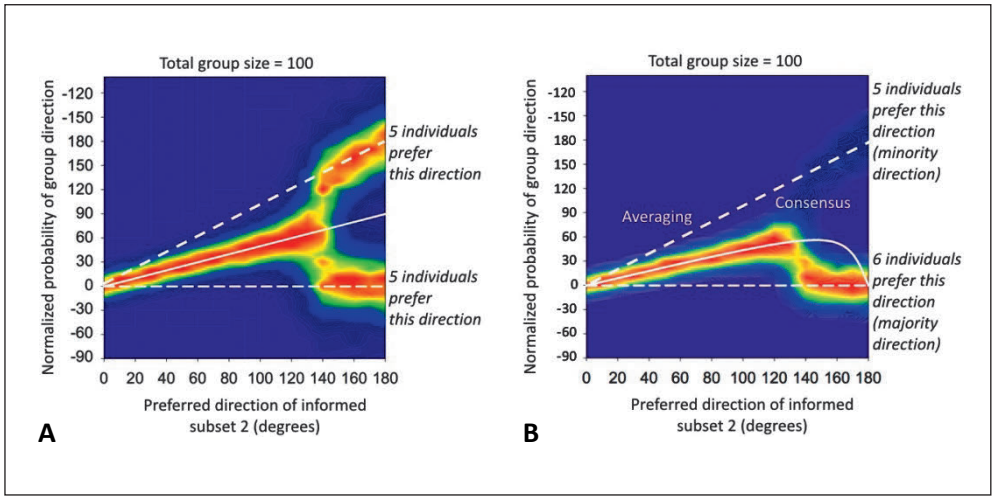

Fig. 2 (*A*): Equal number of individuals with opposing preferences. As long as the angle is below a critical bifurcation the groups remain in averaging phase. Above the angle of a pitch ball bifurcation they end up randomly choosing one way over the other. (*B*): Unequal number of individuals with opposing preferences. The consensus selected by the group is the direction preferred by the majority of individuals with a certain preference.

What if, instead of five versus five in our group of 100, we have six versus five? Now, we find that, as before, below a critical angular difference the group moves in the average of the preferred directions, but above that difference, the fish go from averaging to consensus, and the consensus selected is almost always the direction preferred by the majority (Fig. 3*B*). No individual is calculating; the group is collectively computing a new majority direction. Imagine that they are actually moving towards physical targets. As they get closer and closer, the angle is going to grow and grow. They will always reach the critical angle and choose the majority-preferred direction.

12. Uninformed Individuals Can Break the Spell of an Opinionated Minority of Fish

What happens if a minority becomes strongly opinionated and unwilling to give up on their preferred direction? Will that allow them to always get their way? Our simulations (Couzin et al. 2005, 2011) tell us that if there is a majority of six versus a minority of five with a preference of 0.3 for both groups, the majority will win almost 100 % of the time. But if the minority becomes only slightly more opinionated, they can begin to influence the group dynamic. At 0.5, the minority is winning half of the time. So, if the minority becomes sufficiently strongly opinionated, they completely dominate the dynamics, and the group goes wherever the minority wants to go. However, this is only the case when all individuals have a preference. If there are individuals who are either uninformed or do not care where they are going, that changes everything.

With no uninformed individuals, the majority is still winning 60 % of the time. If the whole group is uninformed, they cannot come to consensus. But if only ten or twelve uninformed individuals are added to the group, that pushes control back to the majority. If the minority preference is set higher still, they will begin to control the dynamics and achieve their goal up to 98 % of the time. But again, if additional ten or twelve uninformed individuals are added, this pushes the control back to the majority. Therefore, a few uninformed individuals can democratise the decision making of a large group.

We think this effect is a general principle. We find it in models of collective behaviour, in models of coupled oscillators and neurodynamics, and, most recently, in classic physical spin systems. A small proportion of unbiased individuals increases the probability of reaching a consensus. It prevents the group from fragmenting and acts as a form of social glue. It increases the speed of reaching consensus. And it makes the decision-making process more sensitive. Individuals can be noisy as long as there is a small proportion of completely untuned individuals; they can make the system extremely effective.

This theoretical study makes the verifiable prediction that uninformed individuals should inhibit the influence of a strongly opinionated minority. We can train our schooling fish to have preferences for a blue target or a yellow target. We can change the strength of their preferences with respect to those colours, and of course we can add in individuals that are untrained. As it turns out, a very small absolute number of uninformed individuals exert a very strong influence on the collective dynamics. A strongly opinionated minority of real fish can win initially, but if we add in five or ten untrained and uninformed fish, control returns to the majority, just as we predicted. In summary, the diversity of opinion strengths and particularly low opinion strength are not just adding noise, they are fundamentally changing the collective dynamics.

13. From Fish to Baboons

Very recently, we turned to what biologists would consider one of the most hierarchically organised societies on the planet, that of olive baboons (Strandburg-Peshkin et al. 2015). We put collars on almost all adults within a whole troop of baboons so that we could monitor where each individual is at any moment in time within sixty centimetres of accuracy.

There are many examples of why some individuals tend to go one way while other individuals tend to go another way, but just like in our models, these baboons would almost always come to a consensus. This is surprising to primatologists and the public because they often think that a dominant individual dictates where the group is going. But that turns out not to be the case. Dominant males and subordinate females both win half of the time. What matters is the number of individuals who care one way or another. Thus, we can replicate the bifurcation diagrammes in primates. This is why a general theoretical framework can be so useful.

14. Adding Context to Group Dynamics

What we were missing, however, was the environmental context. So, this year we went to Kenya. Using the latest drone technologies, we mapped the physical structure of the environment through which baboons are moving with an accuracy of around five centimetres in full 3D plus a vegetation index. This had never been done before. No one had even considered the complexity of the environment. We developed a formal information theoretic approach that incorporates all the features that we found to be important, such as visible neighbours and different habitat features that individuals are experiencing as they move.

What we discovered was that social behaviour does not manifest itself exactly as we had predicted in our model. Baboons in the wild tend not to only consider the current location of others. Instead, they interact strongly with the paths that the others have previously taken through the environment. By combining all these features, we could show that by adding the habitat to the social information we get a much higher power to predict where every individual is going to move next over a range of different spatial and temporal scales.

Humans are arguably the most complex primates that we have studied. There are many aspects of human creativity, consciousness, and decision making that are very complex. But in large crowds we are actually following autopilot-like rules by using the subconscious mimicry of those around us. Actors can subtly manipulate where pedestrians are looking and how they draw their attention. We can learn a lot about these different systems.

In conclusion, it is time for our field to move beyond thinking about individuals as interacting particles and to think of them as probabilistic decision-making entities that base movement decisions explicitly on sensory information. Just over a year ago, I moved from Princeton to Constance to set up a new department at the Max Planck Institute. We actually only received money for a new building. This is pertinent because many people were saying: ‘How do you bring physicists, computer scientists, mathematicians, biologists together?’ Well, we got 32 million euros for a building where we are all going to meet together. We are going to be working together, we are going to be mixed on different floors, and we are going to have superb experimental facilities, including a 15 by 15 by eight metre room for 3D imaging and closely watching reality environments. I think this is the way that science must go to really integrate modelling and experimental work.

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Evolution and Control of Society

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Abstract

The history of human social systems illustrates that societies can be small or large social systems, from hunter-gatherer societies to states, civilisations and, finally, to contemporary world society. However, they all share common defining features such as self-sufficiency and self-reproductive closure. In sociology, descriptions and analyses of society are primarily based on two analytics: different forms of differentiation of society and different modes of sociocultural evolution. The interplay of differentiation and evolution in the history of human society shows that there are also different types of societal control: control by structures/memories resulting from evolution, control by goals, and control by normative and cognitive expectations. Society obviously consists of billions of control projects which reciprocally limit their probabilities of success. Therefore, it is much more probable that actors are controlled by society than that some individual or collective actor may be able to control society. Sociology is a historical science, like evolutionary biology, and as such is not about anticipatory control but explaining how and why things happen.

1. What is Society?

For sociologists, society is a very important concept. In the last 2,500 years, from Aristotle to Niklas Luhmann, there has been a remarkable consensus on the principal characteristics of societies. Of course, words change; during the antiquity the word 'society' did not yet exist. Instead, *koinonia politike* was the term used. Aristotle characterised society as self-sufficient, meaning that to exist, a society does not require any external input, such as resources or information. This is probably the most traditional definition of society. In our days, sociologists and social theorists characterise society as a system of self-reproductive closure: whatever societal structures and processes exist, they are produced not from outside but always from within society.

What is happening in a conference room is clearly a social system. But nobody would call it a society. The city of Weimar, where this conference is held, is also a social system, but again, Weimar is not and never was a society. Society always seems to be the most encompassing social system, comprising all the other social systems.[2] Furthermore, a society always has a spatial dimension; we understand society as the spatially most extensive social system.

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2 Cf. the first edition of the *Encyclopaedia Britannica*: Art. Society, Vol. III, p. 614: "The social principle in man is of such an expansive nature, that it cannot be confined within the circuit of a family, of friends, of a neighbourhood: it spreads into wider systems, and draws men into larger communities and commonwealths; since it is in these only, that the more sublime powers of our nature attain the highest improvement and perfection of which they are capable."

2. Types of Societies

There are four major types of society in the history of human social systems:

– Hunter-gatherer societies,
– States,
– Empires and civilisations,
– World society.

Human societies can be very small indeed and can consist of only a few dozen individuals. These small societies often live in self-sufficient ways, self-reproducing all the constitutive social structures and processes. Tens of thousands of years ago, hunter-gatherer societies were the only type of society, with thousands of small bands distributed over the earth. They were self-sufficient and did not have intensive contact with others. For this reason, it is adequate to call them societies.

Then, eight to ten thousand years ago, the second autonomous type of society arose. Anthropologists call them states. This anthropological concept of 'state' differs significantly from the way historians conceive states. For most historians, states are the territorial, mostly monarchical states of medieval and early modern Europe, and this implies the later global diffusion of this form. For anthropologists, though, states are coupled to the rise of agriculture and to political and religious role structures arising in agricultural societies.

Over the last four to six thousand years, two new kinds of society arose, called empires and civilisations. Empires integrate numerous other societies (states and hunter-gatherer societies) based on political and military means and empires are often of short duration as wars are going on in them all the time. Civilisations are primarily defined by cultural boundaries. China is a remarkable example of a civilisation existing for at least 2,500 years. And Europe became a civilisation around 800 A. D. in defining itself as *res publica christiana* in contrast to the Islamic world and adding ever new social and cultural structures in the following centuries.

Today, sociologists advocate the hypothesis that the societies of the world have merged into one large world society, consisting of 7.5 billion human individuals and billions of social systems (families, interactions, networks, organisations, function systems) in which these individuals participate by being partially included in them. If the hypothesis of world society is correct, then there is no sociality and no socially relevant information outside of this one system. In some respects, one could say that this world society obviously is a very risky social structure, because if something goes wrong in this large social system (climate problems, nuclear war), it cannot be corrected by other societies evading these problems and finding better solutions. In any case, the idea of world society appears to be the most promising hypothesis for describing the present-day social world (Stichweh 2000, 2007).

3. Describing Human Societies by their Structures of Differentiation

In sociology, social theory, anthropology, and history, there are many theories and methods for describing and analysing social systems. In the cognitive traditions of sociology as a discipline, there are two major approaches for the description and analysis of (whole) societies: differentiation theory and the theory of sociocultural evolution.

Looking at the forms and processes of internal differentiation of society (= building of systems internal to systems) has functioned for 150 years now as one of the most prominent strains of social theorising Luhmann (1982). There are different forms of differentiation of society. The earliest and most elementary form of differentiation is segmentation. At the end of the 19th century, Herbert Spencer and Émile Durkheim agreed that segmentation is the form of differentiation of hunter-gatherer societies. On the one hand, there are loose associations of several very similar segments (similar role-sets with a small number of different roles) forming one society. But, with circumstances and ecological conditions changing, segments can be separated again and one segment is then able to exist as one autonomous, self-sufficient society.

The second form of differentiation is called stratification, a social form characteristic of states, empires and civilisations. It is one of the major principles in the history of human social systems. Stratification means that the whole population is divided hierarchically into large collectivities. Such collectivities can be estates, classes and castes. Inequalities among these collectivities are the most important feature of social structure. For individual members of society, these collectivities are total systems encompassing all aspects of their way of life in the respective collectivity.

In India, for instance, there are still castes based on lineage, creating a very complex stratified society which, besides hundreds of castes, consists of hundreds of tribes. It is still customary to marry into your caste or your tribe. But India erected a super-structure that contains the system of castes and tribes, a democracy which in its strategic roles in politics and administration is based on selective participation of members of castes and tribes. In this respect, India seems to be unique among the world's countries. In Europe there never were castes, but instead estates, or what is in French états or in German *Stände*. Whereas castes are based in ethnicity and regional origins, estates combine hierarchical rank with societal functions. There are the clergy, the aristocracy bound to military and political functions, the bourgeoisie and finally the agrarian groups in society. This is the typical set of estates in early modern Europe.

The third type of differentiation in the history of society is a centre-periphery structure, which is complementary to stratification. You can find it all over the world. There are centres of social life, which function as centres in the emergence of societal systems. With growing spatial distance from the centre, the degree of integration into society decreases. For example, if you look at 16th-century Russia, it was not really an empire yet. There, the state was built around one major city, Moscow, and the laws of Russia were primarily meant for and sanctioned in Moscow. The peripheries were very weakly integrated into this early modern Russian society. Only from the 17th century on were the peripheries slowly integrated into the emerging Russian empire (Raeff 1983).

In present-day world society, we live in neither a segmentary system nor in a stratified society nor in a centre/periphery structure, although all these differentiation forms exist as secondary structures in the present-day world. India is a good example for the continuities of stratification; families and states illustrate the continuity of segmentation as a principle; and there are centre/periphery-relations to be observed as internal differentiations of the economy and of other function systems of world society. But all the mentioned cases of differentiation are not the first order, dominant structures of contemporary society.

For the first time in the history of human social systems, we live in world society as an everyday, non-negotiable reality. World society is characterised by something which sociolo-

gists call functional differentiation.[3] It consists neither of strata nor of social collectivities, but of communication systems to which individuals contribute but do not belong: communication systems such as the economy, the polity, science, education, religion, law, and art, to name just a few. The economy is a function system that comprises all communications which are related to prizes, payments and other structural components. The polity is a wholly different system comprising states, elections, referenda, and in democracies the universal inclusion of everyone as voter and in some respects even as a potential political actor in a responsible position (Stichweh 2016). Science is yet another function system which is completely different from the polity and the economy. Functional differentiation is the primary form of differentiation of world society. All the function systems are clearly world systems.

4. Describing Human Social Systems as Being Based in Sociocultural Evolution

Describing a society by its structure of differentiation seems somewhat static. Indeed, looking at structures of differentiation means looking at stabilised results of sociocultural evolution. Therefore, social differentiation is only a part of a more encompassing social process which we call sociocultural evolution. Sociocultural evolution must be distinguished from biological evolution. Biological evolution is responsible for the diversity of plant and animal life on earth and this includes the emergence of hominids and finally *Homo sapiens* and insofar the anthropological preconditions of human social systems. Darwinian biological evolution may in some very limited form still be relevant for a few aspects of behaviour in contemporary society. But at some point in history, some ten thousand years ago, sociocultural evolution took over, realising a completely new type of information transfer that transformed the history of human social systems.

Looking at (transgenerational) information transfer or information inheritance, we speak with regard to the distinction of biological evolution and sociocultural evolution from a duality of inheritance theories (Boyd and Richerson 1985, Richerson and Boyd 2005). Both theories are about transferring and storing information. But the mechanisms of transferral and storage are radically different in the two cases. In sociocultural evolution, transfer is always based on communication, and there are many forms of communication, all of which are relevant, for example teaching and learning, persuasion, and the more indirect forms of communication and observation, which then induce imitation in others. Sociocultural information is stored in expectations, rules, institutions, and other kinds of social memories. All of these storage mechanisms are somehow sets of condensed information and in sociocultural evolution they take the place which is claimed by the (human, animal) genome in biological evolution.

In looking at structures and transformations of sociocultural evolution, learning and education are especially interesting institutions. Simple and complex forms of learning function as memories in sociocultural evolution. And education specialises on the transfer of this stored information. This happens in everyday living in the educational practices in families, but it is intensified in the educational activities of schools and universities. And when schools and even universities in the last 250 years became near universal institutions that included everyone, this established a more extended availability of plural forms of sociocultural memory.

3 On different theories of functional differentiation: Stichweh 2013, Thomas 2013.

But the near universal replication of the 'same' memories doesn't function as a safeguard against changes in these memory elements. Instead, it makes it much more probable that in these processes of transfer changes of variations occur and some of these variations are positively selected and institutionalised.

There is an obvious coupling of sociocultural evolution and differentiation. Differentiated social systems are the most stable forms of storage of sociocultural information. In segmentary systems, the whole society as a relatively undifferentiated unit functions as the storage of the information structures from which these societies are built. In stratified societies, there are very different cultures of information which distinguish the strata from one another. And, of course, in stratified societies, there must exist some semantics, institutions (e.g. property and forms of servitude), personal mobility and interactional practices which guarantee that the strata are still part of the same society.

In functionally differentiated societies, there is again a need for societal semantics which integrate society and for techniques and institutions which are orthogonal to functional differentiation. Nonetheless, most relevant sociocultural information is built into the structures of highly autonomous and highly complex function systems. And, in some respects, the autonomy of function systems is so advanced that it becomes realistic to postulate evolutionary processes of their own for many of the function systems of contemporary world society. We can observe economic evolution (Nelson and Winter 1982), the evolution of science (Campbell 1988), legal evolution (Stein 2009) and the evolution of art (Luhmann 1995). These autonomous evolutionary processes bring about their own mechanisms of variation and their own selection environments, all of them internal to the respective function systems.

5. Modes of Control of Society

Is it possible to control society – a society described on the basis of structures of differentiation and processes of sociocultural evolution? First of all, we have to know what the concept of control means. If you look at an organisation, you may have a controlling interest in this organisation. This will normally mean that if in a conflict situation in this organisation a vote on a certain decision should become necessary, you will be in a position to enforce your will. However, this may be true in an organisation but would be an unrealistic understanding for a society or a functional subsystem of a society where no actor will ever have a controlling interest. Therefore, we need a more modest concept of control in looking at society. We could speak of limitations of possibility and of a space of alternative courses for a system which is definitely limited by control positions in society.[4]

In this understanding, all structures of a system and all selective features of internal and external environments have a somehow controlling influence on society. It is never about determination which looks only at one solution and enforces this one solution, but only about a selectivity which limits the space of possibilities.

4 The most systematic concept of control in sociology has been formulated by Talcott Parsons. He works with a binary distinction of 'information' and 'energy' (which he took from Norbert Wiener) and understands control as the use of information for controlling energetic aspects of the realities of systems. This understanding is well compatible with our understanding here, to look at control as something which resides in structures and memories (=stabilised information); Parsons 1977.

Under these premises, there are many modes of control. One can try to control a system with goals and then one will select actions and strategies of which one believes that they allow approximations to these goals. It is, again, not direct determination but a selection among alternative options. And one can try to control society by expectations. There are normative expectations and cognitive expectations. In the case of normative expectations, one will normally announce these normative expectations and will threaten some sanctions which one will use if these expectations are not met. Regarding cognitive expectations, somehow it is the other way around. Cognitive expectations regard states of the world and formulate how one expects these states of the world to be. But in formulating them one makes clear that one will change cognitive expectations if the respective states of the world prove to be otherwise. Therefore, cognitive expectations are no way to control society. It is exactly the other way around. By formulating cognitive expectations, one makes clear that one is willing to be controlled by society and one will change one's own state depending on the changes of state occurring in society.

To be controlled by society is nearly always much more realistic than to hypothesise that one can somehow control society. And there is one last remark which should be made. There are always control projects which accept the limitations and fulfil the conditions stipulated in these few remarks. But there are always many of them instituted by many individual and collective actors. And in this plurality of control projects lies at the same time their most important limitation. What none of these individual and collective actors can anticipate are the many other control projects which are instituted concurrently. And this is the point where sociocultural evolution takes over once more and is selective and determinative in shaping the conditions of success for these competing projects in a way that no one can anticipate. Therefore, in the end, sociocultural evolution is the force which brings about results which nobody anticipates or predicts and which can only be understood when they are realised and cognitive expectations are restructured. Sociology as the science of sociocultural evolution then becomes – like evolutionary biology (Mayr 2004) – a historical science which does not know how to control society but mainly has to wait until something has come about and then – retrospectively – often is able to explain why it happened. And historical explanation does not mean explanation by one reason or cause, but explanation by a long and useful list of conditions (Diamond 2017) which participated in bringing about something relevant.

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Discussion of Session 4

Kirman: Dr. Couzin, you said in passing that it is very bad to be isolated because you know you are likely to get picked out by a predator. But there is a lot of literature on war regarding the question of whether it is better for ships to sail in convoys or scattered around. It is not so obvious to me mathematically that an isolated individual floating out there is going to attract more attention from some predator than a group. And my second question is: You said that, in some animals, intention is obvious. But bees, for example, vigorously indicate whether they think they have found an advantage for their hive. So, is there more to it?

Couzin: In relation to the first question, there is a lot of work in progress, but it has really been quite difficult to address this issue. So, we have done two things. One is that we looked at controlling one side of this equation: we had real predators, real fish predators, hunting and exerting a selection pressure on a virtual prey population. Nothing in the rules I set made the members of this virtual prey population evolve to isolate themselves individually. They evolved to group together and to move together.

This relates to existing theories. For example, if a predator is at a certain distance from which it can detect your group, if you move close to another individual, you are a little more easy to see, but you have also divided your risk by two. We have shown in the real world that predators really struggle above a certain group size. The per capita probability to become their meal is very low. But if we slice up these groups to make them into smaller entities, the risk shoots up. For single individuals, the risk is around 98 %. This goes back to old studies in Russia. If you put a single fish in a tank, it will be caught within nine to ten seconds, but if you put in twenty fish, an hour later the predator still has not caught anything.

Now, in relation to what you said about the bees, this is a very different scenario. Bees have evolved to work together for the benefit of their colony and have developed specific signalling mechanisms to communicate with each other. You can think of a bee colony almost as a distributed brain. The organisms that I study are selfish. We have investigated for a long time whether they can indicate their confidence, for example. We have a paper showing that they can actually do this. Their directedness is correlated with how strongly they influence others, even though the others are not aware of it. But they are not identifying it like the bees are. Remember, in conflict situations, when there is a small proportion of uninformed individuals, the strength of preferences plays no longer a role. That is not because their confidence has changed. It is because the dynamics of the system have changed. So, there are lots of non-trivial non-linearities when you start dealing with these collective systems. Hence, modelling has been very important. Turning to things like physical spin systems which have been studied for a very long time has provided us with insights that other types of models have never provided before.

KIRMAN: Professor STICHWEH, one would have thought that what structured societies, certainly early on, was to a large extent geography: being concentrated around rivers or being blocked into certain areas. But you never mentioned somewhat basic geographical considerations.

STICHWEH: The physical features of the earth are external to society. As environmental conditions, they are nonetheless relevant for the evolution of society. On the other hand, it is remarkable that human social systems have established themselves under all ecological conditions.

KIRMAN: But today, resources are still geographically located – minerals, oil, and so on.

STICHWEH: Yes, of course. But, you know, it is also true that there is a new type of economy arising that surfaces in our information economy. Resources are still important, but not as important as they were for many earlier societies. You cannot explain the economic structures of Switzerland or Israel by pointing to external resources.

LENGAUER: Dr. COUZIN, it seems to me that you based much of what you said on simulation. But some of these things look to me like they may invite closed-form solutions. For instance, are there closed-form analyses of the bifurcation states?

COUZIN: I mostly base my knowledge on experiments. But you are right. The models that I showed you here were simulations due to time constraints. If, for example, you look at this story with the uninformed individuals and the role they play in terms of these bifurcations, in the paper, there is also an analytic model. So, we have used moment expansion and moment closure to find an analytic solution. We think this is a general principle because these analytic models give us a solution to the bifurcations.

NÜSSLEIN-VOLHARD: You said that for motion, the lateral line does not play a role. So, what do they see in the other fish? Did you conduct experiments where your fish have different sizes or different colours, species, or speeds of swimming? I mean, they must be very similar if they respond properly according to this model.

COUZIN: It is a very interesting question, this issue of what the fish are paying attention to. There are two aspects. They are paying attention to things like the angle subtended on the retina of other individuals. The angle is subtended, not the orientation. They have no idea of the orientation. Christoph KOCH showed earlier that there is a very simple neural model that allows you to do this very quick ranking of objects of different size.

Now, that is not suggesting that this is universal. This fits for escape behaviour. One thing we have done is map the three-dimensional structure of the retina of zebrafish. They have a high-resolution region around 62 degrees coming up. We are beginning to map which areas of the retina are sensitive to temporal changes and which areas are sensitive to other features. So, we trying to get at it from the physiological angle.

We have developed a close-looped virtual reality environment whereby we reconstruct the world at 120 Hertz from the perspective of the eyes of a focal individual, much like the Oculus Rift virtual reality headset. So, now we can have virtual photorealistic fish with motion-captured data or simulated data. It is unbelievable – we can simulate physical objects in the water and you cannot distinguish between them. You can have the virtual fish, virtual food particles, and virtual predators. I think that is going to be one of the technologies that is really going to allow us to represent the exact same stimuli on exactly the same part of the retina repeatedly for different individuals in order to really get the mapping from vision to motor response.

Session 5

Chair: Bärbel Friedrich ML (Berlin)

Nova Acta Leopoldina NF Nr. *419*, 121–128 (2017)

Modelling Viral Infections and the Development of Drug Resistance

Thomas Lengauer ML (Saarbrücken)[1]

Abstract

Evolution lies at the centre of several widespread diseases. In infectious diseases, a foreign pathogen invades a human host and exploits him or her to reproduce. In turn the infected host stages an immune response targeted at exterminating the pathogen. In medical care, this process is supported by drug therapy (antibiotics or antiviral drugs). In response to treatment, the pathogen itself evolves into forms that evade the immune system and are resistant to the drugs administered. Once resistance to a treatment arises, the treatment regime has to be changed to be effective against the newly evolved pathogenic strain. For some viruses, antiviral drugs are routinely combined to most effectively curb viral replication. The selection of a suitable drug combination rests on the analysis of the resistance profile of the current viral strain, is patient-specific, and is so complex that it requires computer support. Over the past 15 years, bioinformatics has advanced to aid in the selection of drug therapies in this setting. Bioinformatics-assisted therapy selection for HIV infections is now clinical routine. Here, we report on the state of the art in the field of bioinformatics-supported resistance analysis and give perspectives on further developments.

1. The Chain of Knowledge Acquisition

Johannes Kepler (1571–1630) wanted to understand the paths of the planets in the heavens. He was an assistant to Tycho Brahe (1546–1601), who at the time was working as imperial astronomer for the Bohemian King Rudolf II (1552–1612) in Prague. During his days in Copenhagen, Brahe had collected vast amounts of observational data. Kepler analysed the data and published a compendium of 350 pages called *Tabulae Rudolfinae*. Kepler basically performed what today would be called data mining – inspecting data by hand and then coming up with laws. Importantly, Kepler's laws were purely descriptive; he found formulas that fit the data very nicely, but they could not really explain why the planets move as they do. The causal basis was missing. Still, Kepler's laws predicted the heavenly motions much better than all previous models.

Even without an understanding of why his formulas worked, Kepler's discovery was a leap forward. About a generation later, Isaac Newton (1643–1727) came up with what is considered the foundation of celestial mechanics: the universal law of gravity. Newton's laws offered a more general view of the heavens and celestial mechanics, and they had more general applications than Kepler's laws. Kepler's laws can be derived from them mathematically.

So the path of knowledge acquisition went from data collection (Brahe's observations) to identifying highly predictive patterns (Kepler's laws) that helped select the most plausible

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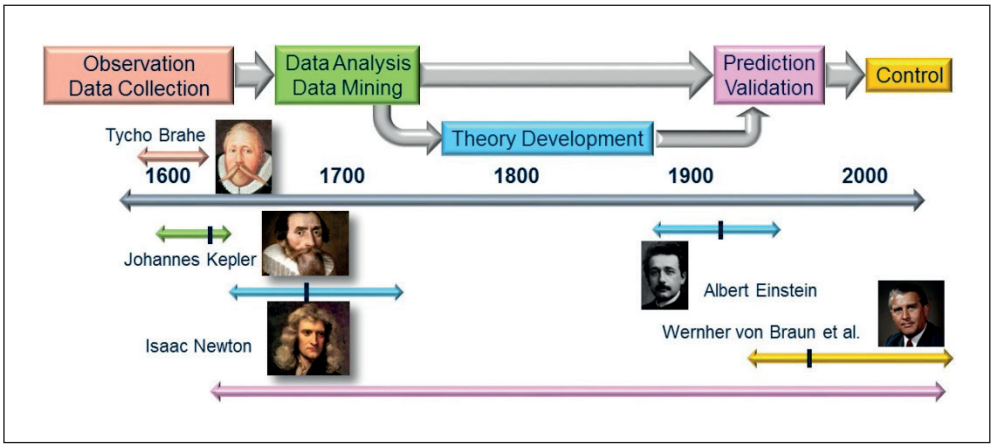

Fig. 1 The chain of knowledge acquisition illustrated on the example of celestial mechanics.

hypothesis (Newton's laws). Finally, at the beginning of the 20th century, Albert Einstein (1879–1955) incorporated Newton's laws into an even broader theory: his theory of general relativity. And again, predictive power increased and the application scenario widened (to larger speeds and stronger gravity).

All along, there had been no way to try and control a celestial body. Then, in the mid 1930s, Wernher von Braun (1912–1977), among others, started applying this predictive power to navigating the heavens, developing the first rockets that could reach the earth's orbit. Now, more than 350 years after Brahe's first glance through a quadrant, the chain of knowledge acquisition had come to a robust plateau. Unifying the laws of the cosmos with those of the micro-cosmos has not yet been achieved, however.

2. From Celestial Bodies to Viral Infections

Today, the problem of viral replication is as mind-boggling as the heavenly motions must have been in Kepler's days. The human immunodeficiency virus (HIV) is arguably the most intensively studied virus of all. Just like Tycho Brahe, we have a lot of data at our disposal. We have cohort studies of patients. We have worldwide data collection. We have voluminous data bases of genetic sequences. We have epidemiological data. And we have data on *in vitro* experiments with viruses.

But the interactions of HIV with its host are not yet sufficiently understood. New drugs are being continually developed in order to find new approaches to suppressing the virus; eradication of the virus seems impossible, in principle. But the virus usually finds escape routes by repeatedly developing resistance. So today, prevention is still the most successful measure in handling the HIV challenge.

In a way, we are standing in Kepler's shoes: we look at the available data and try to learn patterns. There are global patterns in evolution as the virus adapts to human immune systems. There are patterns of geographic distribution, of temporal distribution and of the way epidemics develop. There are patterns of viral resistance to both changing characteris-

tics of the immune systems of the hosts and changing drug therapies. And there are patterns of developing viral resistance to drugs which, in contrast, are observed inside the individual patient.

3. Trying to Predict Resistance to Drugs

We already have predictive statistical models for viral resistance to drug therapies. But what is largely missing is a general theory to afford an understanding of the underlying molecular causes. To arrive at such a theory, we require a deeper understanding of how HIV interacts with the host. Ideally, we would come up with a quantitative mechanistic molecular model of the action of the virus inside a host cell, in different tissues, and in the body as a whole. But our field is still far from providing a unified or integrated theory.

Compared to EINSTEIN's theory, a powerful prior that was recently used to deduce from a few measured gravitational wave forms the size and the rotation speed of black holes merging 1.4 billion years ago – compared to this predictive power and generality, biology is still in a state akin to alchemy.

4. The Molecular Basis of Viral Drug Resistance

Just one example of ongoing research will illustrate the complexity of the virus-host interaction of HIV. HIV protease is a protein that cleaves other viral proteins, a key component of viral replication. Some HIV drugs block the active site of HIV protease, the place where the protein catalyses the cleavage reaction, thereby prohibiting the cleavage process.

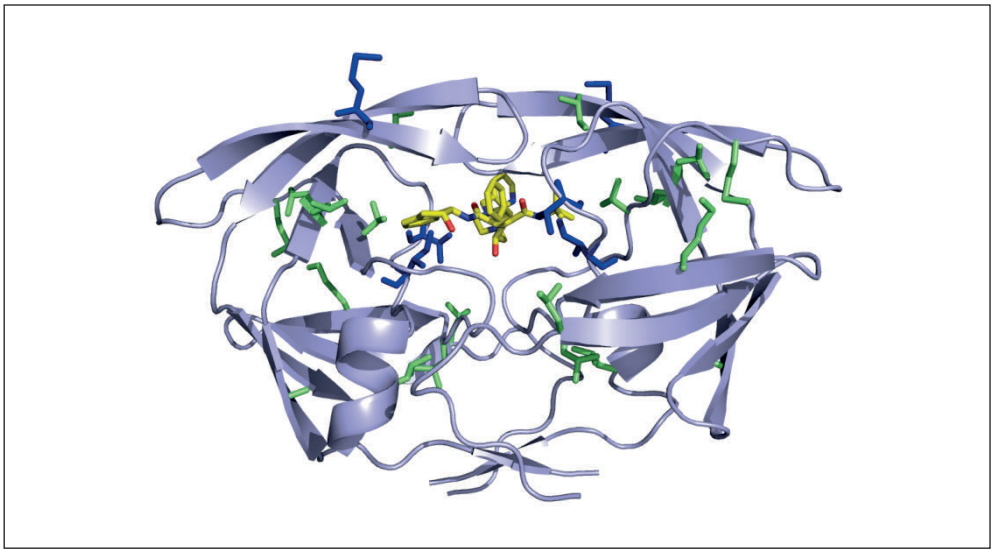

Fig. 2 Space-filling representation of HIV protease. Certain amino-acid residues relevant to drug resistance are represented as green and blue sticks.

But as the genome of the virus changes from generation to generation, the structure of HIV protease changes in very subtle ways. Some of viral descendants produce a structure for HIV protease that rejects previously effective drugs but can still perform its cleavage function on viral substrates. Resistance mutations like these can appear not only around the active site but all over the protein (see Fig. 1). To this day, nobody understands how these very subtle changes can leave the protein intact while rendering drugs ineffective – not because of a lack of data, but because the energetics of the molecular processes of drug binding and cleavage are not properly understood.

Mazen Ahmad, a very talented computational biophysicist in my lab, investigated the energetic balance of HIV protease and found that, as the protein binds a substrate, its free energy changes only minutely. In contrast, its enthalpy and entropy, which add up to yield the free energy, both oscillate wildly. He found a new way of decomposing the free energy into terms which facilitate a more specific energetic analysis of the processes that underlie resistance development. We are currently applying these findings to data on drug resistance of the HIV protease. In this way, we hope to finally understand the molecular basis of the development of drug resistance.

5. Estimating Viral Drug Resistance with the Computer

HIV is extremely dynamic. It exists in myriads of variants that can be quite different from each other. Different viral strains can differ in up to 20 % of their genome – an enormous fraction – while still performing all of HIV's functions. The virus evolves very quickly inside patients. It is the most dynamic virus we know, much more dynamic than the influenza virus, for instance.

Each patient harbours a diverse population of viral strains. A single drug can only suppress a fraction of these strains and, therefore, is normally not sufficient for successful treatment. Thus, the goal of treatment is to administer a suitable combination out of an arsenal of currently over two dozen drugs. Each population of HIV inside a patient has its own molecular fingerprint and no two patients carry the same one. And that fingerprint changes with time. Our job is to infer viral drug resistance from these fingerprints and suggest promising drug combinations.

We do this by data mining. Our database comprises over 150,000 therapy changes throughout Europe, collected by the EuResist Consortium of which the Arevir database is the German part. The current drug arsenal affords over 1000 viable treatment options from which we select the most effective ones, a combinatorial problem that we attack with statistical learning techniques (see Fig. 3).

In vitro assays for measuring viral drug resistance are not feasible in clinical routine. Lab tests are expensive, take between 10 and 20 days, and can only be done in a few high-safety labs. So instead of performing a resistance test on the individual patient in the lab, we use the available data on resistance and treatments to build statistical models that can suggest viable treatments for patients based on the knowledge of the viral genomes they harbour. This *in silico* resistance test takes less than a day and entails only the moderate cost of viral genome sequencing.

6. Rules-Based Systems for Resistance Prediction

There are two ways of finding specific treatments for a specific viral fingerprint: expert rules and statistical models. Expert rules have been used since the beginning of the millennium and

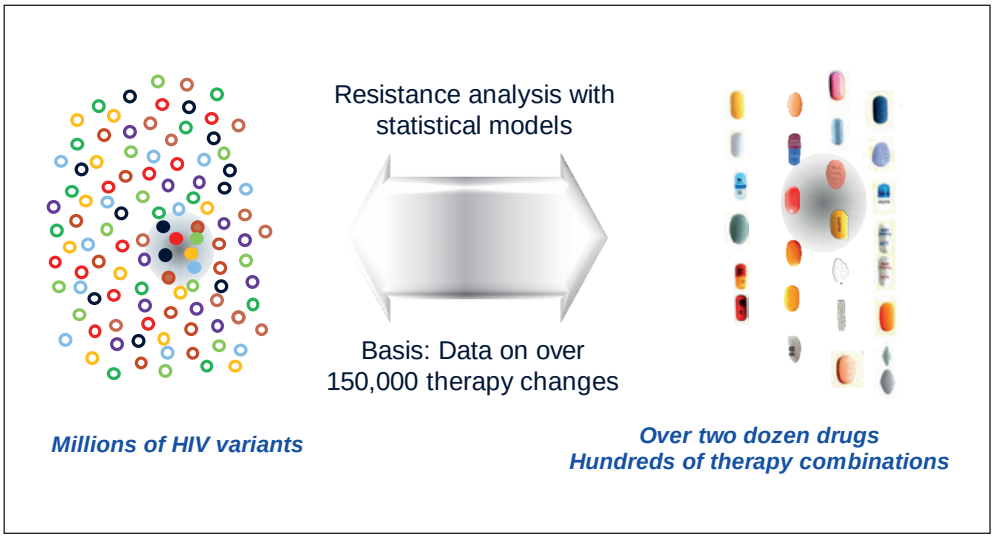

Fig. 3 The challenge of finding the most effective drug combination for individual HIV sub-sets.

have definite advantages and disadvantages. The idea is that experts regularly use the results of *in vitro* resistance tests, knowledge from the field literature, and their clinical experience to craft rules such as: 'If there is a mutation in position X of the target protein of the virus then do not give drug Y'. Rules of this kind were formulated for each of the available drugs. Expert rules are hand-crafted by committees and modified regularly. Currently, there are about 400 expert rules for HIV. One advantage of expert rules is their immediate availability. Furthermore, they are expressive and easy to understand. And they are convincing because they come with a seal of authority.

But expert rules also have clear disadvantages. They have the bias inherent to committee decisions. Simple rules do not apply in complex situations. If a patient harbours a virus with many mutations, the typical answer is: 'You can't do anything for that patient anymore. His virus has too many mutations'. However, this answer is not always all there is to it.

7. Statistical Models Outperform Rules-Based Systems in Difficult Situations

Our statistical models are created in an entirely different manner. The only manual process is managing and creating the database of 150,000 therapy exchanges. All other steps are algorithmic. The idea here is to let the data speak for themselves, to let the data identify the resistance mutation. Statistical models tend to be more discriminatory than expert rules; after all, they analyse a high-dimensional space (comprising dozens of drugs and potentially millions of genetic variants). In this symposium, several presenters mentioned that humans cannot cognitively deal well with high-dimensional spaces. Algorithms, in contrast, can be applied to highly complex situations. Algorithms are free of bias although the underlying databases are not. However, there are mathematical approaches for de-biasing databases, as well.

Here is how data-driven resistance analysis works: our geno2pheno[2] server, which is openly available over the internet and can be queried without cost, receives the sequence representing the viruses harboured by a patient as input. This sequence is then compared to the wild-type reference sequence to identify the mutations of the patient-specific viral population. Up until the beginning of the millennium, such servers were purely rules-based and, for highly therapy-experienced patients, the rules frequently said: 'No therapy option remaining'.

The geno2pheno server has a statistical prediction model that is trained on the large EuResist Database. This model estimates the resistance level for each drug. If the resistance level stays below a certain threshold, then the drug is still somewhat effective against HIV and may become part of the patient's individualised combination treatment. Moreover, our model also identifies mutations responsible for reducing resistance, something that is very difficult to do with rules-based systems. It turns out that our model can find a drug combination even in cases in which rules would have produced a negative result.

On the geno2pheno server, we offer several resistance analyses, some of which have been subjected to numerous retrospective validation studies. The server is widely used in clinical routines and recommended by the German-Austrian and European therapy guidelines. Meanwhile, the success rate of HIV therapy has risen dramatically. Between 1992 and 2000, the failure rate for HIV treatments was about one third (see Fig. 3). Between 2008 and 2010, it had declined to one tenth. This was not only due to computer-based resistance analysis, but also to the invention of new drugs. HIV is among the very few scenarios where computer-assisted selection of drugs combinations has become clinical routine.

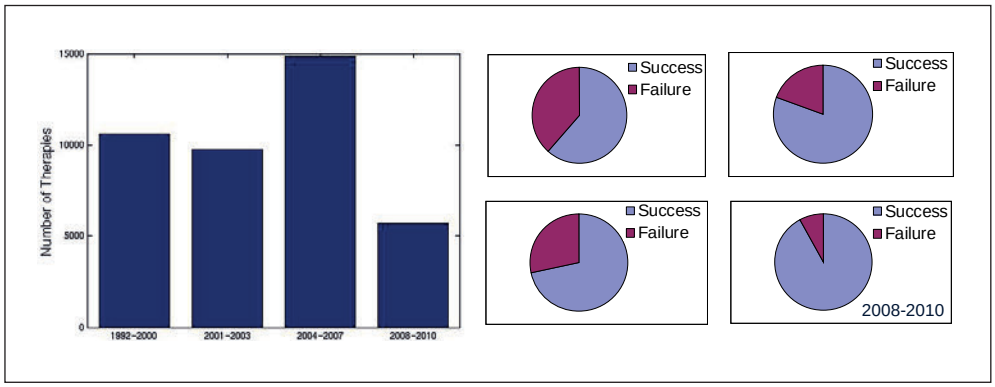

Fig. 4 Increase in HIV therapy success rate. Data taken from the EuResist Database.

Of course, statistical models have their own limitations: a lot of data is required for them to generate reliable results. Typically, when a new drug arrives on the market, there is not yet sufficient resistance data to incorporate it into our model. For Hepatitis B and Hepatitis C, for instance, our server still only works with rules, not with statistics.

And rules are still a very strong competitor. Doctors love rules. Rules are non-mathematical; they speak the language of people. For HIV, there are several rules-based servers that are

2 For further information see: www.geno2pheno.org (last accessed: 10. May 2017).

widely used. But for certain resistance phenotypes, there are no rules. And for these phenotypes, the statistical model is really without competition.

But the largest obstacle for bringing data-driven prediction engines to clinical practice is the lacking interpretability of their predictions. The more 'intelligent' an engine is the harder it is to bring it to be used routinely on patients. In fact, to our knowledge, no engine that predicts not only the resistance level of the virus to individual drugs but suggests whole drug combinations has made that step yet. This includes an engine that we have been offering for over ten years. The reason is that therapy prediction engines do not justify their therapy proposals in terms understandable to a medical practitioner. The only argument they can give is of the character: 'a support vector machine in a space with many thousand dimensions found that this therapy is far away from the decision boundary on the side indicating effectiveness of the therapy' – which is entirely unhelpful to a physician.

8. From Prediction to Understanding

The methods I discussed are applicable, in principle, to all diseases that

- have an evolutionary character involving resistance development,
- are sufficiently long-term for the cycle of resistance development and treatment change to be iterated multiply, and
- afford a sufficiently large arsenal of drugs.

This applies to infectious diseases such as Hepatitis B, Hepatitis C, and tuberculosis – a bacterial disease. However, the most wide-ranging future perspective is in cancer. Tumour cells have an evolving parasitic genome that can be considered the pathogen in this case. But the tumour genome is much more complex than the viral genome. For a malignant cell, there is a large number of paths to resistance to chemotherapy, too many for a purely data-driven approach.

For curbing viral resistance, we are more at Kepler's level of understanding than at Newton's or Einstein's. We do not have a general theory, so our predictions have limited reliability. Our success rate is still substantially lower than we want. How can we increase it? One answer to that question that is frequently heard is: 'More data!' I do not subscribe to this view. With blind data analysis alone, we will not get much further. What we need is a biomechanistic model, a model based on actual molecular understanding of resistance pathways. This will require a global research effort, but I believe that there is going to be much progress within the next decade.

In summary, in the absence of causal knowledge, a data-driven approach can pave the way to predictive success. However, we cannot predict things with certainty without understanding them. There are many people who think, 'Since you have that much data and you can predict – what else do you need?' But data-driven approaches deliver unreliable results, leading to both patients who are denied therapies due to false calls of viral resistance and others who receive ineffective therapies due to undetected resistance. No HIV patient wants to belong to either category.

Even though data analysis cannot bring forth causal knowledge on its own, it can still help tremendously in gaining such knowledge. In the old days, it took a genius like Newton to figure out which hypothesis to test. Today, an introductory data analysis can act as a filter that reduces an initially overwhelming number of testable hypotheses to a manageable set

of hypotheses that is enriched with promising hypotheses. Subsequently, this subset can be analysed with other means, e.g. lab tests, in order to afford causal understanding.

In the HIV scenario, data analysis can point to promising drug combination treatments. But the availability of data should never create the illusion of safety or immobilise us with respect to basic research. Data analysis and theory are not opponents. They can both work in concert, with data analysis being the first step and theory building being the second step in the chain of knowledge acquisition.

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Global Connectivity and the Spread of Infectious Diseases

Dirk Brockmann (Berlin)[1]

Abstract

The spread of infectious diseases has become a global concern. In light of the recent outbreaks of Zika in South America and MERS in the Middle East as well as the 2013 Ebola crisis, researchers are developing a range of methods and strategies to mitigate disease spread. One of the key challenges is to understand the key features that shape patterns of global disease spread. The complexity and redundancy of global transport networks suggests that the systematic identification of hidden patterns in spatially incoherent disease dynamics is next to impossible. Here, we will discuss how the concept of effective distance, as a replacement for conventional geographical distance, helps us understand global disease dynamics and how it can be employed as a new technique for developing predictive tools and means for testing effective containment strategies.

1. Tools for Predicting the Dynamics of Human Infectious Disease

'Can we control the world?' is not a humble question. Any person with common sense would immediately answer with a 'no'. Being humble is undoubtedly quite important when talking about infectious diseases and about trying to tackle or understand their spread. On the one hand, infectious diseases are natural phenomena. But especially human infectious diseases are also social phenomena. And the way we move across the globe plays an important role in the spread of these diseases.

In 2009, an outbreak of the influence virus H1N1 started in Mexico and then spread across the world. There was the MERS coronavirus in Saudi Arabia and, of course, the Ebola crisis. And now there is Zika. The gut feeling of most people is that these outbreaks are happening at an increased rate. This is also reflected by the fact that Hollywood is producing more movies about the spread of diseases, blockbusters such as *Outbreak* or *Contagion*. Their plot: there is a huge pandemic and everyone panics, and finally a hero saves the world or fails to do so. The real story is more complex and more interesting.

2. The True Story of Infectious Disease Spread

The human population is increasing and half of mankind now lives in urban areas. At the same time, global mobility is at an all-time high. Together, these developments are bad for humans and good for pathogens. Then again, there is a kind of revolution happening in epidemiology. As Dr. Lengauer showed us, a lot of data is available today, data we can use to

1 Humboldt University of Berlin; Robert Koch Institute.

investigate the properties of infectious diseases. Beyond that, a global network of molecular surveillance is now at our disposal; viral or bacterial genomes are routinely sequenced and this micro-evolutionary information is used to model transmission pathways.

3. Networks of Epidemiology

One type of data that is pivotal in reconstructing and predicting pathways of transmission are host mobility networks. Figure 1 depicts a global host mobility network, the worldwide air transportation network. Each node represents a location (airport) in space. Links between these nodes are connections between these airports. In contact pattern networks, nodes are individuals and links are contacts and thus potential transmission pathways between individuals, quantifying, for instance, how much time infected people spend together.

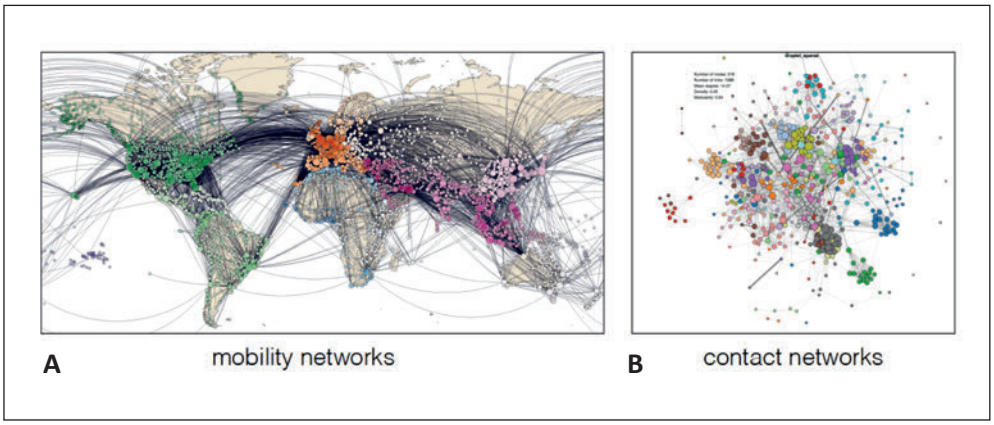

Fig. 1 (*A*): The worldwide air transportation network. This network has approx. 4,000 airports and 25,000 direction connections. More than three billion passengers travel on this network each year. Every day, all passengers travel more than 15 billion km in total; that is three times the radius of our solar system. (*B*): A contact pattern network between 1,000 students. Contacts are reconstructed by measuring individuals' proximity to each other using cell-phone Bluetooth information. Strong links reflect pairs of individuals that spend a lot of time together.

Mobility networks like the worldwide air transportation network are very important in studying global disease dynamics. Contact pattern networks exist on a much finer scale and help us understand transmission dynamics in groups of individuals.

A few decades ago, researchers had to make a lot of assumptions about the rate at which individuals interact. Quantitative experiments had not yet been conducted. Today, however, we have means of reconstructing individual face-to-face interactions. For example, a few years ago, a colleague of mine, Sune Lehmann of the Technical University of Denmark (DTU), purchased 1,000 cell phones and distributed them among a random group of DTU students. This was the deal: the students got a free cell phone and in return the cell phones monitored everything the students did with high temporal resolution over the course of months or years. The phones provided information about how the students moved around in Copenhagen and how much they interacted physically and on social media through texting,

etc. With this data, the researchers could investigate whether social media interactions were predictive for real world interactions. I started a collaboration with Lehmann on a particular aspect of their data: the amount of time any two students spent together over the course of a longer period, say three months.

Some students spent a lot of time in a group of people, while others spent a lot of time with only one other person: they were dating, so they spent most of the nights together, which is a substantial fraction of a 24-hour cycle. The data set revealed other interesting phenomena, like strong links breaking or strong links forming. There even were some triplets in the data! We can use this kind of technology to quantify important factors of disease transmission: for instance, how much time any two people spend together on average. For the DTU students, it was about 3.6 minutes on average. But the distribution is very broad: some people spent ten hours a day together and others only seconds.

4. Digital Epidemiology

Experiments like the Danish cell phone study and similar projects kicked off a whole new field called digital epidemiology. Today, more and more of this data is collected on the web. Statistical models use these growing big data sets to extract information about the dynamics of human infectious diseases. In addition to mobility and contact patterns, we have genetic information. Powerful algorithms can exploit this data to derive statistical inferences about the near future, similar to what is happening in meteorology.

This approach is very powerful, but it is also risky, especially because large datasets, powerful computers, and sophisticated statistical methods invite researchers to treat data as a black box. Different, parameter-rich methods applied to the same data can yield contradictory results. Recently, an interesting paper was published in which researchers gave a data set to different teams of scientists, 29 teams in total. They were given a data set on soccer referee decisions and were asked to determine whether the referees were more likely to hand red cards to players with dark skin than to those with light skin. Twenty teams – 69 % – found a statistically significant positive effect and nine teams – 31 % – observed a non-significant effect.

In addition, correlation is not causation. Just because observation A in a data set correlates strongly with observation B does not mean that A causes B, nor that B causes A, nor that both are caused by a third effect. The book *Spurious Correlations*, published by Harvard student Tyler Vigen, beautifully illustrates this limitation of retrospective, big-data-driven research. For example, there is a very strong correlation between the number of sociology doctorates in the US and worldwide non-commercial space launches. The human brain spots correlations all the time. It is a powerful tool for finding patterns in data, but we often cannot know if these patterns are meaningful if we do not understand the underlying mechanism, as Dr. Lengauer pointed out earlier.

5. Mobility and its Effect on Disease Spread

So, in trying to understand global disease dynamics, we try to keep our questions simple. For instance, we would like to know where a pathogen came from and when and where it will likely appear next after an outbreak. In an ideal situation, a disease spreads like a wave at a

constant speed, making a calculation of subsequently affected areas easy. During the bubonic plague, this assumption of constant speed actually corresponded to reality because most people did not travel very far. But today, that is no longer the case, as illustrated in Figure 1 on the left. Each day, humans are travelling about 14 billion kilometres on planes alone, three times the radius of our solar system. In just a day, you can go from anywhere on the globe to anywhere else. What does this long range mobility mean for spreading phenomena? Computer simulations show that today, because of long-range traffic, an initial outbreak can yield new secondary outbreaks far away. Geographic distance to the original outbreak location correlates no longer well with arrival time, and the spatial pattern of disease spread is spatially incoherent. Regular wave patterns no longer exist. Educated guesses about when the disease is going to hit a particular location become next to impossible. We can actually see this in real data: Figure 2 shows a simulation of outbreaks based on today's mobility network and two real recent events, H1N1 in 2009 and SARS in 2003.

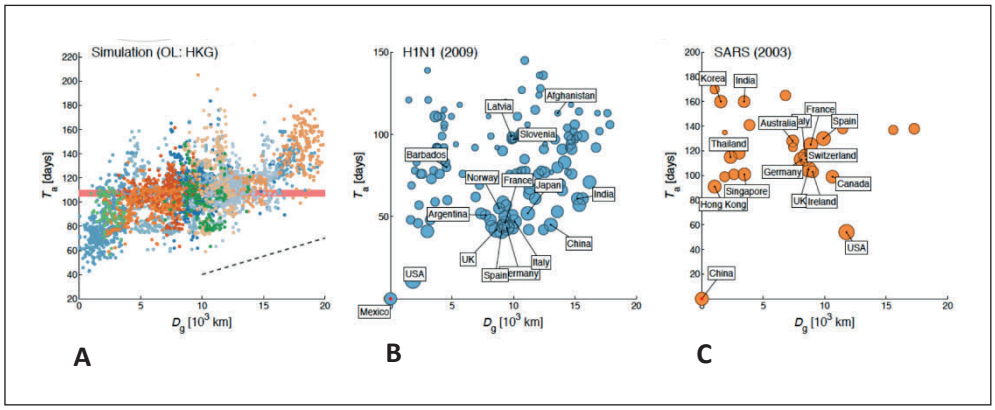

Fig. 2 (*A*): A computer simulation for a virus like H1N1 with a hypothetical outbreak in Hong Kong. (*B*): Actual data from the 2009 H1N1 outbreak. (*C*): Actual data from the 2003 SARS outbreak. D_g: distance of a particular location to the origin of the outbreak, T_a: time of arrival at that particular location.

The simulation still shows a correlation of distance and speed of disease spread of about 250 to 400 kilometres per day. This is about 100 times faster than the Black Death in the 14th century. However, both in the simulation and during the actual events, mere geographic distance is not a predictor of arrival time. That is why we have to develop mechanistic mathematical models and algorithms that take into account global connectivity and have to rely on computer simulations to make predictions on the spatio-temporal pattern of modern, global disease dynamics.

6. Mobility-Based Models of Disease Spread

Computational, predictive models for global disease dynamics are similar to weather forecast systems. Researchers are putting a lot of effort into making them more precise and reliable. There is even a tool for making global disease dynamics predictions, called "GLEaM", the

Global Epidemic and Mobility Simulation Tool. It is very sophisticated and integrates a lot of information and data. You can choose from thousands of origins, specify the number of available hospital beds in that location, the global mobility, the commuter traffic, and much more. The hope with models like these is that the more data they are fed, the more precise their predictions will get. This is a major direction of research in this area. And even though they have become quite good at making short term predictions, there are several issues with these mechanistic models, and I remain sceptical for many reasons that an emphasis on computational detail is by itself a promising path to take. One of them is that dynamical systems at the core of computer simulations require the correct set of parameters (including their values) and initial conditions. But in situations like the Ebola, Chikungunya, MERS or other emer-

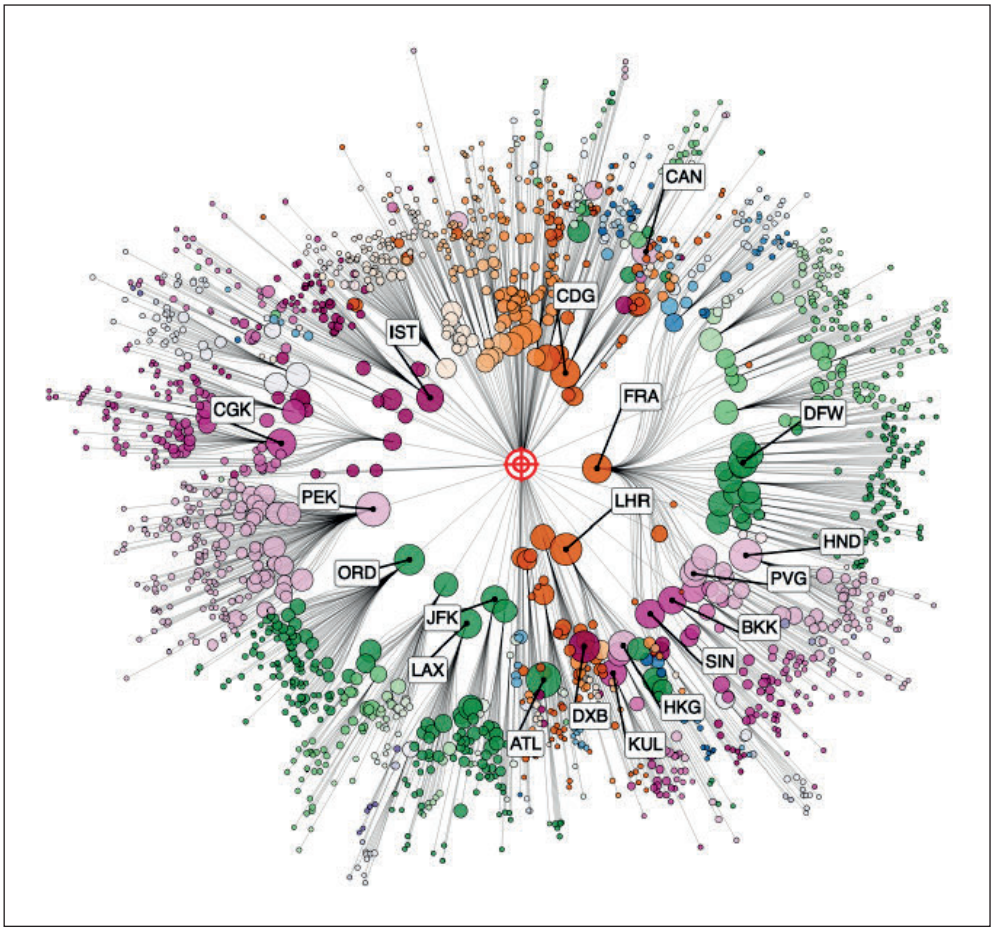

Fig. 3 The network depicts the perspective of the Berlin airport Tegel (TXL, central red node) using the concept of effective distance. All airports of the worldwide air transportation network are arranged in a circle, the distance to the centre is the effective distance from TXL to the respective airport. The tree represents the most probable spreading route from a hypothetical outbreak in Berlin. A number of airports that may be geographically distant, for example Beijing (PEK), are effectively close to TXL and a gateway to many other airports.

gent epidemics, the initial conditions and the disease parameters are exactly the unknown factors. So, in situations where we actually need these models, we cannot use them reliably.

7. Redefining Distance

Recently, we started playing with one of the parameters of our statistical models: distance. Looking at the worldwide air transportation network, we realised that from the point of view of a pathogen, cities like London or Frankfurt are much closer to New York than many small American towns, simply because there is more traffic connecting both places. You can redefine distance in this manner for any two locations on the planet to restructure the air traffic map. We developed a mathematical theory that accounts for this fact and introduced a new distance measure that is small between places that are strongly connected by traffic and large for places that are connected by small passenger flux. When this theory is applied and visualised, radial distances become what we call effective distances (see Fig. 3). Now you can look at places that are relevant for disease dynamics, like Freetown in Sierra Leone, where the Ebola outbreak happened. London Heathrow, for instance, is very close to Freetown effectively. Beijing is not far from Sierra Leone either, as connections go through Heathrow. This way, we can find the most effective spreading routes and identify the nodes in the network that are most effective for spreading diseases.

Effective distance maps are more than just an illustration of how the world looks from a different angle. Figure 2 shows the result of a computer simulation for the two pandemics already (SARS and H1N1) discussed above.

In Figure 4*B*, the spread creates a concentric pattern on the world map of effective distance. Now we can measure the speed of the disease wave and predict when the epidemic is going to hit other locations. This way, we get a much higher predictive power.

8. Understanding Disease Transmission

The speed at which diseases travel through populations depends not only on effective distance between locations, but also on the way the disease is transmitted between individuals in those locations. Traditional epidemiology usually tries to extract some limited information about transmission dynamics from data recorded during recurrent epidemics or endemic diseases. In contrast, it would be helpful if one could inject a pathogen into the population, record how it spreads, and then repeat that experiment 1,000 times in order to develop a correct theory – but of course we cannot do that. Nevertheless, with good contact pattern data we can approximate this experimental scenario.

Vaccination is a very powerful weapon against some infectious diseases. Today, a number of eradication programmes are in place, for instance against polio and measles. A very simple question in this context is: what fraction of the population must be vaccinated in order to eradicate a disease? It has to be a number between zero and 100 %. What that number is depends on the properties of the disease itself. Another number is crucial in finding the critical vaccination threshold for eradication. It is called the basic reproduction number or R_0. It is the average number of secondary infections caused by an infected individual and describes at which exponential rate a disease can spread through a susceptible population. For influenza

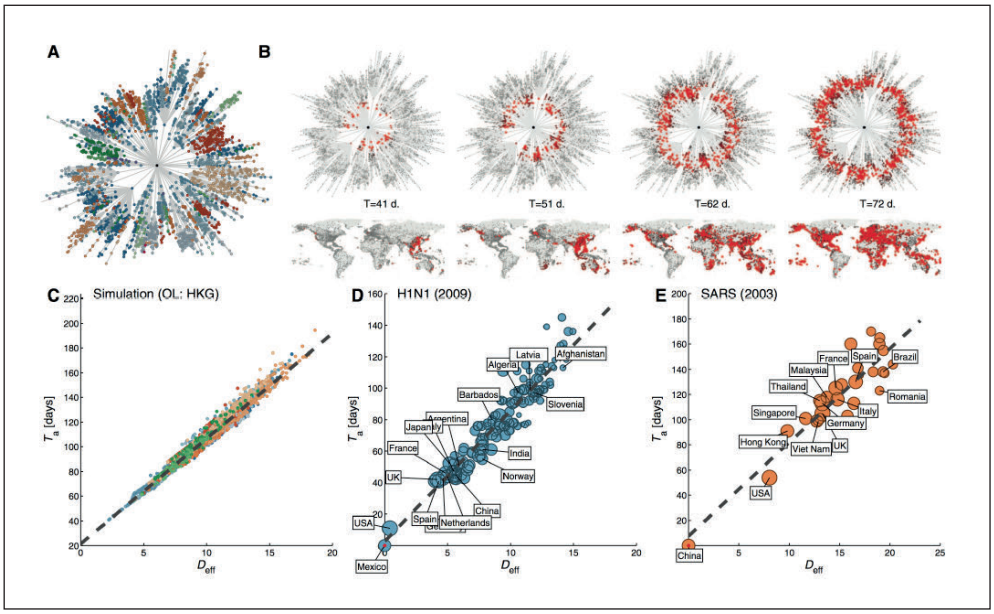

Fig. 4 An illustration of the usefulness of effective distance in a hypothetical outbreak scenario, the same as in Figure 2 with an initial outbreak location in Hong Kong. (*A*): Depicts the effective distance perspective of Hong Kong onto the rest of the world. (*B*): A computer-simulated pandemic in the effective distance representation compared to the traditional visualisation. With the effective distance approach, complex spatio-temporal patterns are mapped onto generic concentric wave fronts that are much easier to quantify, understand, and employ in pattern based predictions. Panels (*C*), (*D*) and (*E*) depict the same information as Fig. 2, the only difference is that geographic distance is replaced by effective distance, which is a much better predictor for epidemic arrival times.

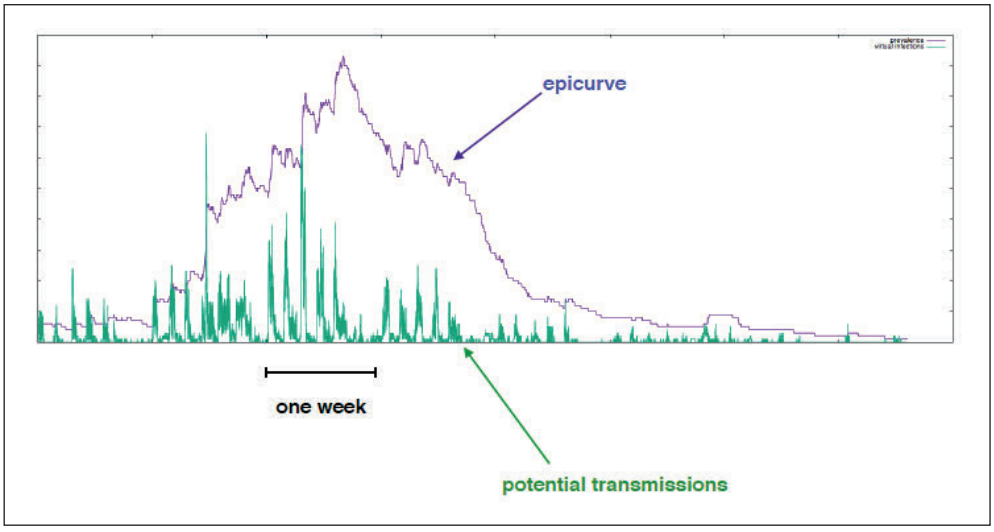

Fig. 5 A simulated epidemic on student interaction data. *Violet*: Prevalence data from classical infection models based on basic reproduction values. *Green*: Actual contact data.

it is maybe 1.4 to four. For measles, the basic reproduction number is very high: 12 to 18. In a susceptible population, measles will explode. Epidemiologists have been using an equation to estimate from R_0 the critical vaccination threshold: $1 - 1/R_0$. For instance, if R_0=2, 50 % would have to be vaccinated. For measles, you get a number between 91 and 96 % because its R_0 is so large.

The equation for the critical vaccination threshold comes from a very simple mechanistic model that rests on a couple of very crude assumptions: all individuals behave the same way and are identical, any pair of individuals is as likely to interact as any other pair, fluctuations do not matter, and the system is in equilibrium. However real contact patterns between people are more diverse: they show strong temporal modulations, such a circadian or weekly rhythms. Groups form and individuals may leave a group and join another. In a nutshell, everyone does not interact with everyone else in the same way.

So instead of using a crude theory to derive critical vaccination thresholds, we ran virtual Bluetooth epidemics on the Copenhagen student interaction data. Figure 5 shows an epicurve that epidemiologists usually look at and the actual transmission rates in the Copenhagen mobile phone epidemic.

The actual contact patterns are very jagged. And it is these contacts during which infected individuals and susceptible ones meet. Usually, this kind of data is not accessible in traditional epidemiology. Instead, prevalence models are relatively smooth curves. However, critical vaccination thresholds depend on the particular patterns of interaction.

9. Virtual Vaccination Programmes Find Real Critical Vaccination Thresholds

We ran thousands of these virtual epidemics and virtually vaccinated individuals, measured the critical vaccination threshold in the population as a function of disease parameters, and found that not only R_0 matters, but also the infectious period. The simulations show that hypothetical critical vaccination thresholds overestimate those actually required for disease eradication – at least in a population of Danish students. As a next step, we aim to find more representative populations to apply this novel method to more realistic scenarios.

In summary, the spread of infectious diseases around the globe depends on both global mobility and the transmission dynamics within populations. We could show that using effective distance as a model parameter instead of geographic distance increases predictive power considerably. Novel experimental methods, such as mobile phone interactions, now provide a type of data previously inaccessible, allowing a more accurate estimation of host-to-host interaction. Together, these novel approaches can increase the ability of data-based statistical modelling to predict the most likely paths of disease spread in our highly interconnected world.

Discussion of Session 5

Helbing: Was your result on the critical vaccination thresholds bad news for pharma companies?

Brockmann: The system predicts that we do not have to vaccinate as much. But, despite this, there still was a big measles outbreak in Berlin last year. The reason cannot be a self-sustained measles epidemic. Instead, there were local outbreaks. So even if we are actually above this critical vaccination threshold, we may still have local outbreaks due to the 'injection' of the disease at certain places.

Friedrich: If I understand correctly, HIV treatment is a fantastic example for a successful individualised approach or individualised medicine. But you still ask for a theory, since the data are not sufficient. Do you have a strategy? For instance, you showed us the studies of HIV protease – would it help to develop a theory?

Lengauer: It wouldn't help our patients in the short term, I think. But, for the first time, we would be able to speculate about mutations that we have not seen before. We could develop new drugs with the added knowledge of what resistance mutations they might evoke. This knowledge could lead to better drugs, which would help patients in the long run. What would help patients more immediately is a reliable mechanistic model of virus-host interaction. We are happy that, with blind data analysis in this system, we already achieve high predictiveness of drug resistance. But this is not true for all systems. For instance, it is unlikely to be the case in cancer. And it is difficult to recognise in advance whether a system submits to pure data analysis without mechanistic knowledge or not.

Guest: You both commented on the importance of the quality of data. More data may not be providing all the solutions, as Dr. Lengauer said. Dr. Brockmann just added that the data can be biased and that there are mathematical methods to de-bias them. Could you comment on the importance of the quality of the data? In particular, what are the ways to de-bias data?

Lengauer: One approach in personalised medicine is to train models only on data from controlled studies. That is the approach we are using. Controlled studies are naturally limited in scope with, say, a few hundred highly controlled patients. Still, we have collected 150,000 therapy exchanges based on such data. Our geno2pheno server is receiving queries involving new data daily. But we do not store this data, and we do not use it for training because it does not come from a controlled setting and because the users would not appreciate that.

The other approach is the one Google Flu uses, namely to take data from everywhere and basically monitor every sneeze in the world. They have to take into account the risk of people unintentionally corrupting or even intentionally faking that data. I don't believe that just increasing the volume of data without worrying about its quality is going to be the solution, so we are sticking to the first route.

De-biasing always means removing biases. But biases can only be defined in terms of reference. And this reference is subjective. In HIV therapy, for instance, the Italian reference is different from the German reference. Italians rule out different drug combinations compared to Germans. So, the de-biasing issue is a very difficult one. The only thing I can say at this point is that absolute objectivity does not exist. When you de-bias something, you de-bias it with reference to your own view of the world. We can only offer the methods for doing this. The view of the world is inherently subjective and should be supplied by the respective medical community.

Brockmann: The word 'data' is so very broad that it may be helpful to differentiate what we mean by it. Some data comes out of controlled experiments. That data can be huge, too, like the data that came out of the machinery that measured gravitational waves. Then there is genetic information like meta-genomic data. This is clean data.

In contrast, Google Flu Trend data or the data that is scraped off the internet is not clean. It has biases that you do not even know about. You just look at something and then you scrape it off and then you see signals in it. But you cannot repeat this. You cannot test it in any way by generating a new data set. I find that very problematic, although I do it myself. But you should be very careful, and there are many people who are not.

Guest: Is data about individual genome profiles included in your models? Or, what happens if it is included?

Lengauer: We are only working with the viral genome. The viral genome has 10,000 bases. It is not large at all. We have also been looking at the relevant region in the patient genome, the HLA genes, which is also comparatively limited. We have conducted initial studies, but it looks like it is not worth the trouble of including this region in the analysis. Otherwise, we would have to change clinical procedures and patients would have to be genotyped. All of this is difficult. People in clinical routines usually resist it unless it is necessary. And, so far, it has not seemed to be pressing enough.

Guest: There is also the problem of some treatments that are very complicated and depend a lot on the way in which they are taken. And that, of course, would depend on the population of patients and whether or not they are actually going to respect those rules. So is there a sort of second qualification?

Lengauer: Yes. That the computer suggests the ideal treatment is definitely an overstatement. What we do is provide an interpretation of the viral genome. The doctor takes this interpretation and crafts his or her own therapy. They do not automatically take up what the report says. And that is due to all the things we do not consider, for instance, whether the patient can tolerate a drug or how committed the patient is to taking the drugs. Of course, sometimes patients do not take the drugs and they claim to have taken them. But this is a quite difficult area. Sometimes, the genomic fingerprint of the virus is indicative of the patient's compliance. But the patients cannot be expected to tell the truth in this respect.

Session 6

Chair: Thomas LENGAUER ML (Saarbrücken)

Nova Acta Leopoldina NF Nr. *419*, 141–148 (2017)

Modelling the Economy as a Complex Interactive System: Unintended Consequences

Alan Kirman (Paris, France)[1]

Abstract

Economic theory has developed in such a way as to be consistent with the socio-political liberalism which became dominant after the Enlightenment. The doctrine of *laissez faire* and the argument that leaving people as much as possible to their own devices would lead to a socially desirable state was based on the belief that an 'Invisible hand' would lead society to such a state. As economic theory developed, it was never able to give a formal justification for this assertion. The discipline was confined to the study of the welfare properties of equilibrium states without explaining how they were attained. Thus, crises were said to be generated by exogenous shocks and not to come from within the system. Changing our two-hundred-year old paradigm to thinking of the economy as a complex adaptive system allows us to consider economies out of equilibrium and the fact that they may self-organise into states which are far from optimal. Such systems with their feedbacks are unpredictable and policy measures can generate unexpected consequences. Accepting this idea may lead to more realistic and more modest economic theory.

Over the last two centuries, there has been a growing acceptance of social and political liberalism as the desirable basis for societal organisation. Indeed, this is the basic paradigm on which modern economic theory and our standard economic models are based. It was Adam Smith (1723–1790) who in 1776 first suggested that when individuals are left to their own devices, the economy will self-organise into a state which has satisfactory welfare properties.

This paradigm, however, is at odds with what has been happening in many other disciplines. In fields such as statistical physics, ecology, and social psychology, it is now widely accepted that systems of interacting individuals will not have the sort of behaviour that corresponds to that of the average or typical particle or individual. In economics, however, this realisation has not had much effect. While other disciplines moved on to study the emergence of non-linear dynamics as a result of the complex interaction between individuals, economists relentlessly insisted on basing their analysis on the concept of rational optimising individuals, acting as though they were isolated particles.

Yet, this paradigm is neither validated by empirical evidence nor does it rest on sound theoretical foundations. It has become an assumption. It has been the corner stone of economic theory despite the fact that the persistent arrival of major economic crises suggested that the analysis was flawed. Experience suggests that amnesia is prevalent among economists and that, while each crisis provokes a demand for new approaches to economics (witness the birth of George Soros' Institute for New Economic Thinking), in the end, inertia prevails and economics returns to the path it had been following all along.

1 CAMS, École des Hautes Études en Sciences Sociales and Aix-Marseille University.

1. Confidence in Our Theory

There has been a remarkable tendency to use a period of relative calm to declare victory over the enemy. Recall the declaration of Robert E. Lucas Jr. (*1937), Nobel Prize winner and President of the American Economic Association in his presidential address in 2003, in which he said: "Macroeconomics in this original sense has succeeded: its central problem of depression prevention has been solved, for all practical purposes, and has in fact been solved for many decades".

In 2004, Ben Bernanke (*1953), later to become chairman of the Federal Reserve Board and to face one of the two greatest crises of the twentieth and twenty-first centuries, celebrated the 'Great Moderation' in economic performance over the previous two decades, which he attributed in part to improved economic policy making. He was referring to the fact that the evolution of the macro-economy had become much less volatile.

Both economists and policy makers had been lulled into a sense of false security during this brief period of calm. Whilst our models worked well during this period, one is tempted to ask: Would not any model have done so? Learning to sail when there is no wind does not equip one to face storms. What we need are models to help us understand and deal with crises rather than clinging to models which are acceptable in calm periods but must be abandoned in times of crisis.

2. The Crisis since 2008

Then came 2008, and, as always in times of crisis, commentators and policy makers started to ask why economists had not anticipated the onset and severity of the crisis. Even Her Majesty the Queen of the United Kingdom was moved to ask 'her economists' what had gone wrong. She received the following reply from the British Academy: "So in summary, Your Majesty, the failure to foresee the timing, extent and severity of the crisis […] was principally the failure of the collective imagination of many bright people […] to understand the risks to the systems as a whole".

This was not very reassuring, as those same bright people had previously portrayed themselves as 'scientific advisers'. The *Economist* had on its cover an ice cream labelled 'Modern economic theory' which was melting, with the title, 'Where it went wrong and how the crisis is changing it'. But little change has really happened. Jean Trichet (*1942), the Governor of the European Central Bank, made an appeal for economists to rethink the very foundations of economic theory. Adair Turner (*1955), the head of the Financial Services Authority in the U. K., went even further and held economists responsible for the crisis. He said: "But there is also a strong belief, which I share, that bad or rather over-simplistic and overconfident economics helped create the crisis. There was a dominant conventional wisdom that markets were always rational and self-equilibrating, that market completion by itself could ensure economic efficiency and stability, and that financial innovation and increased trading activity were therefore axiomatically beneficial".

These statements are witness to the dissatisfaction on the part of policy makers shared by a number of economists. Both Trichet and Turner put their finger on the essential problem with modern economic theory: the idea that the economy would automatically self-organise into a satisfactory state. As unfounded as the idea was, it fit so well with the predominant

social and political philosophy that it has been perpetuated. Indeed, the only way to answer the criticisms expressed by these policy makers after 2008 is to abandon the central tenet of economic theory, namely that the economy will self-organise into a state which is 'optimal' or 'efficient'. The current paradigm based on 'methodological individualism' does not capture the way in which the economy functions, and pushes to one side many of the most important aspects of the economic system.

Why then, was it – and is it still – so difficult to change this paradigm? The answer would seem to be that economists and those they advise have become so wedded to their models that they no longer look at what Herb Simon (*1934) described as 'inconvenient reality'. Consider the following statement by Mario Draghi (*1947), the Governor of the European Central Bank: "And the first thing that came to mind was something that people said many years ago and then stopped saying it: the euro is like a bumblebee. This is a mystery of nature because it shouldn't fly but it does. So the euro was a bumblebee that flew very well for several years. And now – and I think people ask 'how come?' – probably there was something in the atmosphere, in the air, that made the bumblebee fly. Now something must have changed in the air, and we know what after the financial crisis. The bumblebee would have to graduate to a real bee. And that's what it's doing".[2]

To the man in the street this makes no sense. Bumblebees do fly, and if we have models which say that they cannot, then it is the model and not the bumblebee that has to be changed. We have moved away from what constitutes a true science, trying to explain observed phenomena to the point that, when the evidence contradicts our theory, we have doubts about the evidence rather than the theory.

We are told that economies in equilibrium have nice properties, particularly that nobody can be made better off without making somebody worse off. But how does this happen? What is the nature of the 'invisible hand' that leads the economy into a desirable state? This is the problem that economists have never been able to solve. The basic idea is that the markets will somehow modify prices until an equilibrium is reached. Our history is redolent with various verbal explanations as to how prices will rise in times of excess demand or fall as excess supply emerges and that in this way the invisible hand will do its work. Yet, with no formal argument to justify this, the only way out was to simply assume that the economy was in equilibrium and that if it was ever knocked off course it would rapidly return. Anything that knocked it off course was exogenous and not part of the normal functioning of the system.

What we should recognise instead is that the economy, like an eco-system, is capable of going through internal crises. Understanding and analysing this process is more important than studying economies in some sort of 'steady state'. This vision is difficult to reconcile with modern economic analysis. Until the 1950s, economists and particularly macroeconomists had a rather pragmatic view as to how the economy functioned, but with the advent of Gérard Debreu (1921–2004), economics moved from a discipline using physics as its basic model to one using axiomatic mathematics. This led us deeper into difficulty. We put more and more stringent and unrealistic restrictions on the assumptions about the rationality of individuals and moved further away from man as a reasonable but not ultrarational individual.

2 Speech by Mario Draghi, President of the European Central Bank, at the Global Investment Conference in London, 26 July 2012.

All of this should, one might think, have caused a change of mind-set with those in authority, but consider the statement by Alan Greenspan (*1926)[3] in 2011 some three years after the onset of the crisis: "With notably rare exceptions (2008, for example), the global 'invisible hand' has created relatively stable exchange rates, interest rates, prices and wage rates."

But it seemed that the economic theory ship simply sailed on, unperturbed by the upheavals in the economy. Yet there are many who were dissatisfied with this and explicitly asked for alternatives. I will now suggest the route I believe we should follow.

3. An Alternative Vision

We should treat the economy as a complex adaptive system, using computational models that generate large sudden endogenous changes such as those which we observe in real economies. Therefore, we should focus on the direct interactions between individuals, who are not omniscient but follow simple rules of behaviour. These interactions are central to the understanding of aggregate behaviour. Consider the two approaches – the standard one and that which thinks of the economy as a complex interactive system.

The Standard Approach

- Our models must be built on sound micro-foundations.
- As Lucas has argued, one should only make assumptions about individual characteristics.
- Individuals should satisfy economists' axioms of rationality.
- They should optimise in isolation.
- They understand the economy they function in.
- Aggregate behaviour is like that of a rational 'representative agent'.
- The focus is on efficient outcomes.

The Economy as a Complex Adaptive System

- Aggregate behaviour emerges from the interaction between individuals.
- Individuals follow simple rules.
- They adapt to their environment.
- They are not irrational and do not act against their own interest but are not optimisers.
- They have limited and largely local information.
- Coordination, not efficiency, is the main problem.

4. Which of These Two Approaches Should We Choose?

Taking the second position undermines the faith in the stable self-organisation of our economies, which has always been the cornerstone of our faith in economic liberalism. Focusing our attention on the results of the interaction between economic agents rather than on the 'optimising' behaviour of the individuals would represent a paradigm shift in economics. Instead of trying to explain the elaborate structure of an ant hill by the behaviour of the 'representa-

3 Alan Greenspan is Former Chairman of the Federal Reserve Bank.

tive ant', we would recognise that this structure emerges from the interaction between many simple individuals with extremely local and limited knowledge.

We are not like ants, but we are perhaps closer to ants than to *homo economicus*. The complex system approach is nicely summarised by Robert J. Shiller (*1946), a recent winner of the Nobel Memorial Prize in economics, as he says: "An economy is a remarkably complex structure. The analogy between the brain and the computer is familiar but one can make the same analogy between the computer and the economy".

The brain is, indeed, a remarkably complex structure, and I remember my father telling me when I was small that if the structure of our brain were simple enough for us to understand it, we would not be able to understand it. The lesson for us is that we are faced with a complex system over which we have little direct control. Just like climatologists, who even though their understanding of the system improves over time still cannot make precise forecasts beyond a very short horizon. Economists should be more modest and admit the limitations to our capacity to predict what the evolution of the economy will be and what the consequences of any policy measure will be.

5. Financial Economics

An objection that will immediately be raised is that the financial sector of the economy is somehow different, that we have results showing that markets are efficient, and that liberalising these markets leads to the best possible allocation of resources. The number of ex-mathematicians and physicists engaged by financial institutions suggests that there is a level of technical competence in this field which exceeds that in other parts of economics. Unfortunately, the foundations of financial economics are as weak as those of economic theory in general.

The basic idea of the theory is simple: Individuals receive private information and then act independently upon it by buying or selling assets. Their transactions modify asset prices and thus reveal their information to all the participants in the market. But when Louis Bachelier (1870–1946) introduced this idea in his thesis in 1900, the mathematician Henri Poincaré (1854–1912) immediately pointed out the essential weakness in this approach. People, he said, do not observe their own information independently and then act upon it. They tend to watch other people and follow what they do. They act like sheep. This simple observation is at the heart of the explanations of financial bubbles and crashes. Yet despite many objections from Poincaré, John Maynard Keynes (1883–1946), Benoît Mandelbrot (1924–2010), and others, Bachelier's 'random walk' hypothesis for the evolution of stock prices has become the basis for modern financial analysis.

Few would argue that bubbles in the financial sector were not heavily involved, if not responsible, for the 2008 crisis. Bubbles are a recurring phenomenon, even if they are in contradiction with modern macro and financial theory. The growth in size and importance of the derivatives market rather than stabilising the economy has had the opposite effect. According to Bachelier, financial market prices convey all the necessary information to investors but derivatives. In fact, they diminish this transmission. If you buy a mortgage-backed security which is, in effect, a share in many underlying mortgages, checking on the health of those assets becomes a difficult and expensive task. So, as the market expanded, rather than checking, the actors in the market bought and sold these assets and even though

more and more mortgages were becoming delinquent their price did not fall. However, at one point the information that the situation was worsening caused some market participants to check on the underlying assets and this revealed the toxicity of the latter. At that point, others started to check and the market collapsed. This was not only catastrophic for financial markets but had severe consequences for the real economy, recalling the warning of Warren Buffet (*1930), who already said this in 2002: "In my view, derivatives are financial weapons of mass destruction, carrying dangers that, while now latent, are potentially lethal". But it is still not clear if either the warnings or our experience will lead to any significant changes in financial economics.

6. Income and Wealth Inequality

One of the primary concerns in our economies in recent times has been with the growing wealth and income inequality. Indeed, the popular success of Thomas Piketty's (*1971) recent book *Capital in the Twenty First Century* (2014) suggests that there is a growing resentment at the concentration of wealth in so few hands. Initially, even Adam Smith argued that the invisible hand would tend to equalise incomes and wealth. Yet nothing in the theoretical literature since then has suggested what automatic mechanisms would achieve this. To avoid the difficulties with interpersonal comparisons of utility, Pareto produced the idea of a ranking which only ranks a state of the economy above another if in the preferred state nobody is worse off and somebody is better off. This, of course, has nothing to say about the distribution of wealth or income in the two states. Economists have come to accept Pareto's criterion which simply does not involve the distribution of income or wealth. But why would people object to a distribution that results from the self-organising of the economy? The answer is that for most people there is a threshold above which inequality becomes socially unacceptable.

This is reflected in the number of protests associated with the Occupy Wall Street movement in the U. S. and similar movements in European countries. The evolution of real wages for individuals in different parts of the income distribution has destroyed much of the faith in the argument that the path to wealth was one which was open to all. The idea that the economy self-organises to enrich not only those at the top of the income distribution but all those below has little support today.

7. Incentives

The last feature of the invisible hand I want to mention is that of incentives. It has long been argued that *laissez faire*, the very basis of economic liberalism, provides the right incentives for people to do what turns out to be in the common interest. Yet, a little reflection leads one to doubt this simple assertion. The classic example is the Tragedy of the Commons, in which each individual has an incentive to overgraze the land, but collectively this leads to disaster.

Economists observe that this is a problem of 'externalities'. One person's action has a direct and, in this case, detrimental effect on the welfare of others. This is considered to be the cause of a 'market failure', but in our increasingly interdependent world it is worth reflecting on the fact that such externalities are omnipresent and central to the functioning of the economy. They are not just inconvenient frictions.

Furthermore, in the sort of system where people react to or anticipate the actions of others, taking a course of action may produce unforeseen consequences. A well-known and rather simple example is that which has been termed the 'Cobra Effect'. The British administration in India was concerned about the number of venomous cobras in Delhi. A bounty was therefore offered for every dead cobra. Initially, this was a successful strategy as large numbers of snakes were killed for the reward. However, enterprising people began to breed cobras for the income. When the government found out about this, it cancelled the bounty and the cobra breeders set the now-worthless snakes free. As a result, the wild cobra population actually increased. The measure had exactly the opposite of the intended effect.

Most people remember the paradox of blood donation. As soon as a fee is paid by the authorities to encourage more giving of blood, the amount diminishes. People do not want to be seen as involved in doing something for a monetary reward. Another example is that of the Haifa creche or kindergarten. When fines are imposed for being late, people come even later. The problem changed from being an ethical or moral one to a calculation as to whether the new price was worth paying.

This is directly relevant to the financial sector since very large fines have been imposed on banks which have violated various rules. The most recent examples are the manipulation of the forex markets and the LIBOR declarations together with banks taking positions against their own clients. The banks, in some cases, openly admitted that they had simply factored into their calculations potential fines for wrongdoing.

We have moved far from markets which were based on trust and integrity to ones in which manipulation of the rules is predominant. New and more complicated regulations, though they may be needed now, are not enough to solve this problem.

The lesson from all of this is that individuals will adapt to whatever rules are put in place and new norms, whether bad or good, will emerge. History is full of examples of taxes that have produced perverse results. It is very difficult to predict what the effect of a policy will be in a system as complex as the economy, but within the standard modelling framework there is no place for unexpected consequences.

8. Conclusion

I have dealt at some length with the nature of, and reasons for, the failure of the Invisible hand to deliver the expected results which would justify *laissez faire* or economic liberalism. I have also suggested that we need to radically rethink our vision of the economy and to recognise that it is a complex adaptive system which we cannot fully control, and in which we can, at best, see patterns in the evolution of the system and react to them. This will mean being much more modest, but perhaps more realistic in our attempts to implement policy measures and not spend our time arguing that simply liberalising markets will solve all our economic problems. I will conclude by citing Mervyn A. King (*1948), the ex-Governor of the Bank of England, when discussing the work of Friedrich August von Hayek (1899–1992): "The message from Hayek is that we should avoid the hubris of thinking that we understand how the economy works, just as we should avoid the hubris of thinking that leaving markets to their own devices will lead to nirvana".[4]

4 Mervyn A. King, April 2013.

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The Dream of Controlling the World – And Why It Is Failing

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Abstract

If we just had enough data, could we optimise the world and run it like a 'benevolent dictator'? The answer is no. The attempt to build a digital crystal ball to predict our future and a digital scepter to control it is destined to fail, no matter how powerful the information systems we build are. Even though we have moved from a time when there was too little data for evidence-based decisions to a time in which one can make data-driven decisions, there is still a gap between the complexity of the world and the data we have on it. And this gap is rapidly broadening. Though our computational powers are exponentially increasing, they cannot keep up with the increase in complexity! I call this problem the 'complexity time bomb'. Fighting complexity is a lost battle if we do not learn how to use complexity to our advantage by turning from centralised to distributed control and from a top-down to a bottom-up approach that supports self-organisation and self-governance.

In his 2008 essay *The End of Theory*, *WIRED* author Chris Anderson[2] formulated a dream: the truth, he argued, would reveal itself if we just had enough data. Then, the right course of action to improve the world would directly follow from the data. Therefore, governments and companies have recently collected huge piles of data. Secret services are monitoring every citizen in increasing detail, and a number of companies are doing this too. So, are we beginning to see Chris Anderson's dream come true? Can big data yield the best possible decisions? Does it allow to rule the world like a 'wise king' or 'benevolent dictator'?

Every day, companies such as Google and Facebook conduct millions of behavioural experiments on us to figure out how we can be nudged to click a certain link or buy certain products. Increasingly, we are becoming remotely controlled beings, and this novel approach to governance is becoming more and more interesting for politics, too (Thaler 2009, Sunstein 2016). It turns out that nudging can change our behaviour, but it has failed to make us healthy and slim and nice to our environment. So, today's nudging is not as efficient as its inventors would like it to be. But stronger reinforcement mechanisms such as personalised pricing are constantly being developed.

China is even testing a citizen score, a personal number that represents your obedience; if you do something desirable, you will get plus points, but if you deviate from the expectations of those who rule, you will get minus points.[3] A similar secret service programme called 'Karma Police' is run in Great Britain. In conclusion, today basically everything you do is

1 Swiss Federal Institute of Technology, Zurich, Switzerland.
2 See Anderson 2008.
3 See Stanley 2015, *Big Data* 2016.

being tracked: the links you click,[4] what your political opinion is and whether it supports that of the government, whether you pay your loan on time, or whom you interact with. All that data is being evaluated and can determine what kind of job you get, what interest rate you receive, and also what countries you are allowed to travel to – that is the plan, at least in China.

This is Orwell's 1984 combined with Huxley's *Brave New World*. Certainly, top-down systems like these can force people to do certain things. Maybe one could even make entire societies behave in certain ways, if people are likely to oppose the intended changes were to be removed using a 'predictive policing' approach. This is being discussed, too, and algorithms to determine who might do something wrong or might disturb the public order have already been developed. So we are pretty close to a totalitarian society in which you do not need to violate a law to be put to prison – the likelihood or the possibility that you might disturb the plan of the government might be enough. These algorithms also take into account your social contacts, your friends, and your neighbours. Even if your behaviour is perfectly okay, the behaviour of your friends or neighbours could mess up your entire life. I do not think this is the kind of society we would like to live in.

The technological revolution has brought our society to a crossroads, where we need to make up our minds and decide what our digital future should look like (Helbing 2016a, 2015c). Data-driven versions of various historical forms of government can now be built: fascism 2.0 (a totalitarian 'Big Brother' society and 'brave new world'), communism 2.0 (a state that believes it knows what is best for us and would impose it on us – the 'Big Mother' society), feudalism 2.0 (the 'Big Other' society [Zuboff 2015], also known as 'surveillance capitalism' run by global IT corporations). Of course, we could also build a democracy 2.0 – a participatory society that empowers people and fosters collective intelligence.

If we do not pay attention now, we could lose freedom and self-determination, human dignity, assumed innocence, fairness and justice, pluralism, democracy, participation, and most likely peace and many of our jobs. This is not just a theoretical threat. We have seen how easily democracies can be turned into other forms of government. It happened in Hungary. It is happening in Turkey, in Poland, and in France. Democracy has become pretty unstable, so it is time to speak up and defend it. Because I still believe it is the best system if we just upgrade it with digital means.

Privacy, human rights, and the division of power are important to sustain peace. Self-determination promotes creativity and innovation. Pluralism and diversity are the basis of societal resilience (Helbing 2015a, b) (the ability to deal with shocks and other unexpected developments), for high innovation rates, and collective intelligence (Page 2007). I am convinced that co-creation, co-evolution, collective intelligence, self-organisation, and self-governance, considering externalities (i.e. external effects of our actions), will be the success principles of the future.

1. Upgrading Democracy with Technology

I am not against the use of technology such as Big Data and Artificial Intelligence – on the contrary. However, I am arguing for a different use of technology – a way of use that is

4 Revealed by Beall 2016, Martin 2016, Fox-Brewster 2017.

now called 'values by design' or 'ethically aligned design'. IEEE (Institute of Electrical and Electronics Engineers) has recently drafted guidelines in this direction (*IEEE* 2016), and Elon Musk shares this perspective too. He has invested one billion US dollars into the OpenAI initiative to make artificial intelligence an instrument for everyone (Mack 2015). In the meantime, Amazon, Apple, Facebook, IBM, and Microsoft have decided as well to work on the development of moral artificial intelligence (Hern 2016). Even Pope Francis has spoken up. He demands a Europe 2.0, a new European humanism, and asks: "What has happened to you, the Europe of humanism, the champion of human rights, democracy and freedom?"

It is a wrong understanding of society to believe that the truth will emerge from big data and a benevolent dictator approach will produce the best results. Even though the economic development of Hungary is strongly data-driven, and Viktor Orbán seems to consider himself a benevolent dictator, Hungary has fallen back economically. It started off as the leading eastern European country and ended up last in the rankings. Since Turkey is governed in an autocratic way, its economic situation has been deteriorating too. A world-wide data-driven analysis by Heinrich Nax and Anke Schorr confirms that democratic forms of governance create economic benefits (Nax and Schorr 2015).

Now, why is today's data-driven control not working so well? It sounds so intuitive: more data yields more knowledge, and more knowledge implies more power and success. However, optimisation creates in fact a decelerating growth curve. At some point in time the optimal state is reached and you cannot get beyond it. It is the wrong paradigm for society. The right kind of paradigm would be based on creativity, co-creation, and co-evolution, which is expected to produce an accelerating, exponential growth curve because it is not restricted to innovating within the current system (as the optimisation approach is), but it innovates the system too (i.e. it also comes up with totally new, 'disruptive' solutions which are outside of today's system).[5] Figure 1 shows the development of the world economy since 1991. It is really saturated as you would expect for an optimisation approach. This is the problem and we need to pursue a totally different approach now – based on an open and participatory information and innovation ecosystem.

It turns out that even though the information technology sector has exploded, it has not created the overall macro-economic growth that was expected. The current approach has also not solved our biggest problems yet, which are climate change, the financial, economic and public spending crisis, conflicts and wars, mass migration and terrorism, which may all result from today's lack of sustainability. That means likely future resource shortages if we do not change the current economic system from a consumption-oriented system based on linear supply chains towards a circular and sharing economy, which would be able to provide a high quality of life for more people with less resources.

So, something is wrong with today's top-down control approach, which is dominated by a few IT monopolies. This approach works like a data-driven version of the command economy – something that obviously has not worked very well in the past due to the lack of flexibility and creative freedoms. Interestingly, if you look at the top ten list of the most liveable cities in the world, for many years, none of the big IT-nations has been represented

5 The Limit to Growth study, Global 2000, and other studies trying to anticipate our future have concluded that, in a world of limited resources, an economic and population collapse would occur, no matter how the simulation parameters are chosen. This means that the system of equations must itself be changed, meaning that we need to innovate and change the system.

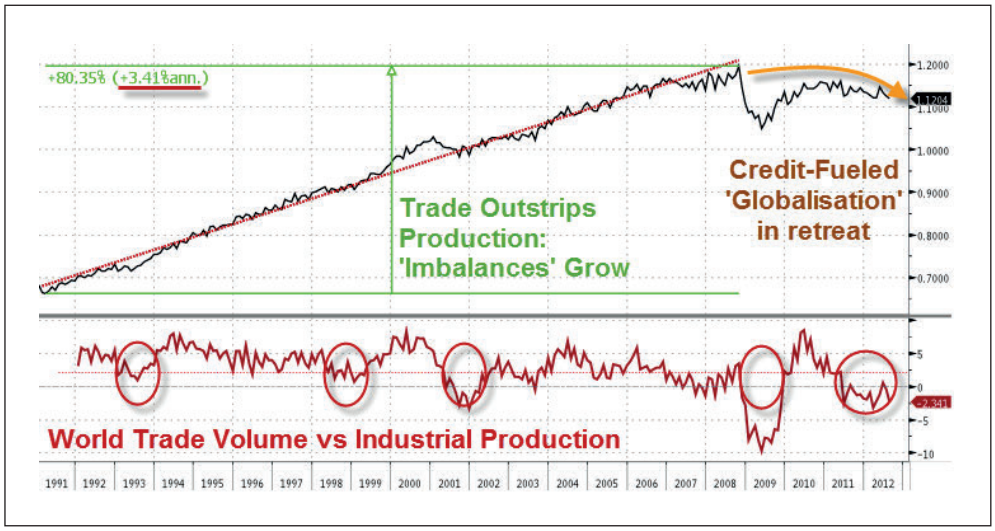

Fig. 1 The volume of world trade has reached saturation in the past decade (Source: Long 2012).

on it. It is therefore no surprise that a recent event on 'disrupting cities through technology', which included all relevant stakeholders, concluded that the concept of smart cities as fully automated, data-driven structures has failed (*Wilton Park* 2017a, b). Society is not a machine (Helbing 2017). Therefore, I advise that we use big data, but use it in a different way – not in the sense of a 'black box society' (Pasquale 2016), but in favour of an open and participatory information ecosystem (Helbing 2015d). The idea of a much more participatory and inclusive approach is now spreading in many countries, including the United States, as the 'Open Letter on the Digital Economy' shows.[6]

Even though we have an exponentially increasing processing power – doubling approximately every 18 months according to Moore's law[7] – the overall data volume is increasing even faster. It is currently doubling every twelve months (Schilling 2014). This means that, within just one year, we produce as much data as in all the years before, in the entire history of humankind. As a consequence, the gap between the data we produce and the data one can process is opening up more and more. Therefore, there is a kind of 'dark data' that can never be evaluated, which means that we need science to decide what data to process and how. So science is back, in contrast to what Chris Anderson and his followers have claimed.

Another important point is the quickly increasing connectivity of our world. Basically, we are connecting companies and people more and more, creating a combinatorial explosion of complexity (see red factorial curve in Fig. 2). It overtakes the data volume, which means that top-down control will work decreasingly well as time goes on. In fact, if you have listened to the talks of the last World Economic Forums, the conclusion is basically this: "We have

6 Open Letter on the Digital Economy. Available at: http://openletteronthedigitaleconomy.org (last accessed: 10. May 2017).

7 Moore's law. In: Wikipedia. Available at: https://en.wikipedia.org/wiki/Moore's_law (last accessed: 10. May 2017).

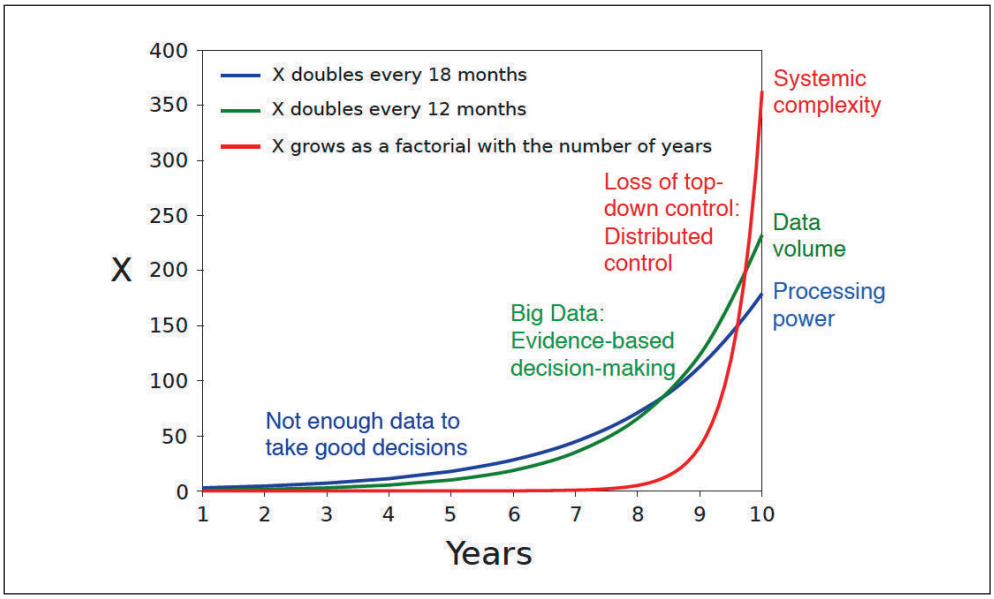

Fig. 2 Two exponential curves and a factorial curve, schematically illustrating the increase in computational processing power, overall data volume, and systemic complexity (Helbing et al. 2015b).

lost control of the world". Therefore, we need a new control paradigm – one that is based on distributed control and the subsidiarity principle (which implies significant levels of self-organisation and self-regulation).

We really need to understand complex systems much better, and we need digital platforms to support a self-organised coordination in a highly complex and diverse world. Society cannot be steered like a car. It is not a mechanical system. It is an evolutionary system in which the behaviour of its parts is adapting and changing, interactions matter a lot (or even dominate the system behaviour), and noise is important (Helbing 2008, 2012). In complex systems, interactions can produce unexpected outcomes and emergent phenomena such as 'phantom traffic jams' or stop-and-go waves (Helbing 1998). Even if you had a perfect mass surveillance system and could read the minds of all people, you could not prevent the traffic jam. You would just see it happen. However, we have mathematical formulas that allow us to understand these stop-and-go waves and how they come about.

Surprisingly, perhaps, there is no need to know much about psychology, and we do not need to read minds. The only thing that matters is the interactions between cars. These imply that, above a certain density threshold, small variations in speeds will be amplified, which creates a domino effect that causes a situation nobody wants (Helbing 2001). Note that the drivers in this experiment are all people who use modern technology and have all the data that seems to be necessary to accomplish the task. They are also well educated – they have driver's licenses and they want to avoid traffic jams. Nevertheless, traffic jams are still happening. This traffic flow problem is a prime example for systems that are unstable – there are many of them. When confronted with such systemic instabilities, things can go totally wrong, even if you have the very best intentions (Helbing 2013). The occurrence of cascading effects is

a typical reason for the loss of control. Another example is the financial crisis, where a good performance of the individual actors could not avoid a global meltdown (*British Academy* 2009). When Lehman Brothers went bankrupt, this created a cascade of bankruptcies all over the United States. Hundreds of banks failed, causing losses of hundreds of billions of dollars.

Let me give a further example. We recently did a decision experiment in the lab, where we could predict an incredible 96 % of all decisions (Maes and Helbing 2016). That is unheard-of accuracy in social experiments. Still the deterministic model that produced these accurate predictions was unable to predict the aggregate, macroscopic outcome well. That means the overall results were quite different. The next surprise was that when we added some noise to the deterministic model, making the microscopic model predictions of individual behaviours less accurate, the macroscopic outcome was much better.

The reason why adding noise can produce more accurate macro-predictions is that small deviations from deterministic behaviour can trigger cascading effects that cause completely different kinds of outcomes. Consequently, to get a good aggregate picture, we do not need to know every individual behaviour. We do not need mass surveillance, as the aggregate picture is the only thing that a policy maker needs to care about.

With Albert Einstein, I would like to say: "We cannot solve our problems with the same kind of thinking that created them". Most of the big unsolved problems of the globe are those related to systemic instability. This ranges from unstable supply chains to economic booms and recessions and breakdowns of cooperation to tragedies of the commons, from electrical blackouts to financial crises, and from crime to war.[8] To improve the state of the world, we need explanatory models. In many cases, complexity science, based on non-linear interactions between a complex system's components (such as individuals and companies), has delivered a new understanding of these problems, where the conventional 'linear thinking' fails to work.

In fact, it is possible to explain even counter-intuitive macro-phenomena from 'micro-level' interactions, as is common in physics. Moreover, by changing the interactions, many problems occurring in complex systems can be solved. There are numerous nice success stories in complexity science for this. In the following, I will discuss some of my own work.

My research started with pedestrian and crowd dynamics (Helbing and Johansson 2010). In pedestrian flows, as people interact with each other, they create self-organised macro-phenomena such as lanes of uniform walking direction where different directions of motions are separated from each other. This can be simulated in a computer. It takes just the higher relative velocity between people moving in opposite directions to produce the lane formation phenomenon. Traffic signs, police men, or laws are not required for this. But lane formation is not the only self-organisation phenomenon we found. We also discovered oscillatory flows at bottlenecks, stripe formation in two crossing flows, and clogging phenomena at bottlenecks, when fleeing crowds try to evacuate themselves (Helbing et al. 2000).

Besides pedestrian models, models for traffic flows, logistics, and supply networks, disaster spreading and response, social coordination and cooperation, opinion formation, the emergence of social norms and social preferences, as well as models for the spreading of crime, conflict, diseases, knowledge, and culture have been developed.[9]

8 For further information see: www.coss.ethz.ch/publications.html and https://scholar.google.de/citations?user=ebrNfPAAAAAJandhl=enandoi=ao (last accessed: 10. May 2017).

9 Brockmann and Helbing 2013, Schich et al. 2014; for further information see: www.coss.ethz.ch/publications.html (last accessed: 10. May 2017).

Some of this work has also been applied in practical contexts. The following provides an incomplete list:

– A pedestrian software for crowd and evacuation simulations was developed based on the social force model of pedestrian motion discussed below. The software is now commercially available and internationally distributed. It has, in the meantime, supported the planning of the Formula One Grand Prix in Abu Dhabi, the North Melbourne Station, and various arenas and mass events all over the world.
– Based on an application of the 'slower-is-faster effect' observed in pedestrian crowds, certain steps in the semiconductor production of Infineon Technologies could be improved, which has increased the throughput by 30 % (Helbing et al. 2006).
– The observation of self-organised oscillations of pedestrian flows at bottlenecks inspired a new traffic light control approach based on concepts of emergent coordination and self-control, which is patented (Lämmer and Helbing 2008, Helbing and Lämmer 2012). The practical performance of this approach has been successfully tested in the city of Dresden.

2. The Social Force Model

In the following, I will discuss just one kind of model which has helped to understand and solve complex real-world problems (Helbing et al. 2015a): the social force model. Different kinds of models – from agent-based, to cellular automata, to gas-kinetic, fluid-dynamic, and stochastic – have been developed for various other kinds of problems.[10] The social force model can explain all the above-mentioned observations (lane formation, oscillations at bottlenecks, stripe formation, and the clogging phenomenon of escaping crowds at bottlenecks). The model has been inspired by physics but adapted to social behaviour. It is based on an equation of motion and an acceleration equation. The latter contains several different force terms that represent different motivations of a pedestrian, for example to adjust their speed, to walk into a certain desired direction of motion, or to keep some distance to other people, as reflected by repulsive forces.

The social force model not only reproduces the observed self-organisation phenomena in a qualitative way. It also passes empirical and experimental tests. For example, we have compared the model with empirical pedestrian trajectories (Johansson et al. 2007) and performed a series of lab experiments (Moussaid et al. 2011, 2009). The obtained knowledge was also applied to study practical problems such as crowd disasters. In the past, for example, several crowd disasters have occurred during the Hajj, the Muslim pilgrimage. For this reason, the Saudi Arabian government asked me and other experts for an analysis of the problem (Haase et al. 2016). During the Hajj, an estimated 1.5 to 3 million people walk from the Holy Mosque in Mecca to Mina, where they perform the 'stoning the devil' ritual. On the Jamarat Bridge in Mina, the temptation by the devil is represented by several pillars. The pilgrims are supposed to demonstrate their resistance to these temptations by throwing little stones ('pebbles') against the pillars. This has caused extremely crowded situations on the Jamarat Bridge in the past, such that crowd disasters happened on average every two to three years. In 2006, a crowd disaster occurred on the open plaza in front of the entrance to the Jamarat

10 For further information see: www.coss.ethz.ch (last accessed: 10. May 2017).

Bridge which happened to be recorded. Our video analysis revealed that there was first a transition from smooth pilgrim flows to stop-and-go-flows, which may be seen as an advance warning signal of potential trouble to come (Johansson et al. 2008).

After this, there occurred a second unexpected transition to crowd turbulence, when the density was so high that pilgrims were erratically pushed around by others in the crowd, probably without intent. There is a transfer of forces from one body to the next, and the forces add up with unpredictable sizes and directions such that the situation becomes uncontrollable, even by many soldiers. Later, we found out that the same mechanism was also the cause of the Love Parade disaster (Helbing and Mukerji 2012). Movies taken by participants of the event showed turbulent waves, as we had expected. These made people stumble and fall on top of each other.

As the occurrence of such deadly crowd disasters is not acceptable, the Saudi Arabian government has built a new Jamarat Bridge in the past years.[11] A five-level-structure with more capacity replaced the old Jamarat Bridge and different ramps leading to the different levels made sure to separate different pilgrim flows. They also put together a team of international experts to help come up with suggestions. A Saudi Arabian expert team responsible for the implementation selected several of them for realisation. One of the suggestions made was to avoid crossing and counter-flows, meaning to implement a unidirectional flow organisation. This has worked safely for many years. The government was very happy with the results and the work received high international recognition. In the following years, I was no longer involved in expert workshops or otherwise. Then, in 2015, a crowd disaster happened, most likely due to the occurrence of crossing flows (Haase 2017).

3. Optimisation Itself Does Not Necessarily Prevent Turbulent Flow in Crowds

In that year, another team was apparently trying to maximise flow and comfort by minimising travel times. This may have led to stronger variations in the density and flow than in previous years and to crossing flows. Despite the optimisation and at least five thousand CCTV cameras, the crowd disaster could not be prevented. So optimisation and surveillance are no guarantee for functionality and safety, as I said before.

One of the neglected problems of optimisation is the right choice of the goal function. In the above case, it seems that travel times were chosen rather than safety (which was optimised in previous years). In the case of our economy, gross domestic product was maximised rather than sustainability. Unfortunately, in many cases one only finds out too late that another goal function should have been chosen.

What is possible, however, is to model the complexity of pedestrian flows with reasonably simple models and to explain what is going on, under what conditions, and why. By now, we can also understand many other troubling self-organisation phenomena. For example, we can predict various kinds of traffic congestion and the travel times associated with them (Helbing et al. 2009). However, we cannot predict the moment when congestion sets in, because this may depend on a random event, such as the overtaking manoeuvre of a truck. Despite this complication, we have been able to develop an analytical theory of vehicle flows that can help to overcome traffic congestion.

11 For further information see: http://web.archive.org/web/20140816222258/ and www.trafficforum.org/crowdturbulence (last accessed: 10. May 2017).

The right approach for this is 'mechanism design', or in this case an adaptive cruise control (ACC) system that is changing the interactions between successive cars (Kesting et al. 2008). In such a way, it is possible to get rid of congestion, even if not every car is equipped with an ACC system. As stop-and-go waves show, self-organisation in complex systems does not necessarily produce desirable outcomes, but we can generate favourable outcomes by changing the interactions. This approach can also be applied to urban traffic. In our self-organised traffic light control, traffic flows control the traffic lights in a bottom-up way rather than the other way around, as it is common today. This approach makes traffic flow much more efficiently than the state-of-the-art control systems, attempting to optimise the flow by a traffic control centre.[12]

We propose to apply a similar approach to social and economic systems. Mechanism design (Maskin 2008) can improve the outcome of social and economic interactions, for example in markets (whose performance depends on the respectively applied auctioning mechanism) (Ferscha et al. 2012). What we need for this is knowledge from game theory, complexity science, or computational social science. In fact, Noble Prize winner Elinor Ostrom has proven with empirical observations that self-governance can be efficient if the institutional design is well-chosen (Ostrom 2015). Therefore, I propose to use personal digital assistants to help us take better decisions (Helbing 2015e). Information systems that support our creativity, innovation, and coordination will also benefit the economy and society altogether. They will improve business models, products and services, cities, and the world. Reputation systems, for example, can influence social interactions in a way that promotes responsible behaviour, cooperation and quality (Diekmann et al. 2014).

Such digital assistants working for us can now be built. We just need to create a suitable institutional framework. 'Digital democracy' is such a framework that allows the knowledge and ideas of many minds to come together and create 'collective intelligence' (Helbing und Pournaras 2015). Massive open online deliberation platforms (MOODs) can support this (Helbing and Klauser 2016).

It turns out that diversity is highly important to come up with good solutions that work for many people (Page 2007, Woolley et al. 2010, Hidalgo et al. 2007). So it is very important to promote value pluralism and to reach a balance of interests ('social forces'), in order to produce solutions that do not just improve a system for a single group. To enable combinatorial innovation and a flourishing, thriving economy, solutions should benefit many groups of companies and people.

In order to support this, my team and I have recently started to work on a digital platform called Nervousnet.[13] It aims to measure the externalities between people and companies and the environment. We can use smartphones and the Internet of Things to do these measurements collectively in a crowd-sourced way. We could then give undesired effects such as noise, pollution, or rubbish a price and desirable things such as cooperation, education, or the reuse of resources a value. With such a system, people could actually earn money for producing data and sharing them with others, as well as for producing positive externalities. This could be the basis of the participatory digital economy that I imagine for the future.

12 For further information see: www.stefanlaemmer.de and www.stefanlaemmer.de/#Literatur (last accessed: 10. May 2017)

13 For further information see: www.nervousnet.info (last accessed: 10. May 2017).

The approach would create multidimensional incentive systems or, if you want, multi-dimensional financial markets, which would help to manage complex systems in a differentiated, multi-factorial way and even to build self-organising or self-regulating systems (Helbing 2016b). Such a multi-dimensional financial system can now be created using blockchain technology. In other words, 300 years after the inception of the concept of the 'invisible hand' presented in the previous talk by Alan Kirman, we can finally make it work by combining the Internet of Things with blockchain technology and complexity science.

Such a system could establish new kinds of incentives which would boost a circular and sharing economy. Thereby, we could mitigate or even overcome the resource crises expected for the future. Rather than implementing a circular and sharing economy by regulations and laws, this approach would create new market forces promoting a more responsible and efficient use of resources and recycling (Helbing 2014, 2016c). In a similar way, one could produce incentives supporting social coordination, cooperation, and peace.

In summary, my vision of the digital economy and society of the future is that of a networked, well-coordinated, distributed system of largely autonomous (sub-)systems. I do believe we should use Big Data, but it should be used in an open, participatory, fair and democratic way. We should also use Artificial Intelligence, but in a symbiotic and ethical way. We should further use incentive systems, but in a multidimensional way. It is also fine to create an operating system for society, but it should provide everyone opportunities for creativity and innovation, for bottom-up participation and co-creation. We need a new societal framework, a finance system 4.0 and socio-ecological capitalism to solve the problems of the future. According to my vision, this digitally upgraded capitalism would also be democratic, so smart technologies alone will not create smart cities and smart nations. It is the combination of smart technologies and smart citizens which creates smarter societies. Let us now build this together!

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Discussion of Session 6

Lengauer: That sounds like a nice conclusion, but we still want to allow for questions. Maybe I can start with the first question. There is quite an apparent inconsistency between the two of you, if I may polarise a little. Alan, you claim that there is no invisible hand. Dirk, you claim that there is one if we look for it. So, can I just confront you with each other?

Kirman: I think it is not really an inconsistency. The invisible hand as envisaged by economists has basically been a market system which somehow gathers the information and then sends it back to everybody. And what Dirk has in mind is quite a different sort of invisible hand, I think, with which this information is going back and forth. One thing that worries me about Dirk's vision of things is that he wants the invisible hand to reach down from the government to tell people how to act. But there is a lot of work going on to suggest that, in fact, governments themselves do a lot of innovation. And that bothers people because it is in contrast to what, I think, Dirk has in mind and the general idea of *laissez faire*.

Helbing: First of all, I want to clarify that a government telling people how to act is not what I wanted to suggest. Coming back to the question, I also do not think we have inconsistent positions. We have just looked at the problem from different perspectives. My point of view is that, without doing anything, the invisible hand sometimes works, but often fails because self-organisation may have desirable or undesirable outcomes. Traffic congestion, financial crises, and crowd disasters may happen if the right kinds of interaction mechanisms and institutions are not put in place. The important point is that digital technologies, namely the combination of the Internet of Things with blockchain technology, can now put the right interactions in place to get the desired outcomes. It is the challenge of complexity science to identify those institutions and interaction mechanisms that create desirable outcomes. I have nothing to say against governments as coordinating and enabling institutions.

I think, basically, there will be a combination of top-down and bottom-up forms of organisation in the future, pretty much as the subsidiarity principle demands. If you have problems that are not computationally difficult and for which you don't need to innovate, then optimisation is fine, of course. You can solve these problems in a top-down way. There are many other problems, however, where creativity and innovation are needed or the optimisation problem is so computationally difficult that it cannot be solved in real time. Innovation happens mostly on the bottom. So, it is really important that we have this combination of top-down and bottom-up. What we now need to do is to strengthen the bottom-up part with the new digital technologies that are now becoming available (the Internet of Things, blockchain technologies, DAOs etc.). I am not arguing against the use of digital technologies, I am just saying we should use them in a smarter way that produces desirable outcomes while being compatible with our fundamental values.

Guest: As economists, we usually try to learn from the hard sciences. Is there something that the hard sciences can learn from economists? And, to Professor Helbing, I also really like the idea of distributed control, but the problem is: whose control? Consider digitalised platforms. Should we have public control of platforms that then allow people to have the crowd sourcing of ideas, collaboration, interaction, and so on and so forth?

Kirman: My objection to the standard approach in economics is that we have learned from classical mechanics that we could understand high-level behaviour by making general assumptions about how the individuals in a system behave in isolation. When we observe them, they do not seem to behave according to our assumptions. But sometimes, when we put them all together, the whole system does seem to behave as if the assumptions were true. With all due respect to Ian, that is what I think. If you want to understand how the structure of an ant colony develops, you would not look at a 'representative' ant. That is my only point, that we should stop making strong assumptions about individuals. We should worry much more about collective behaviour. From this point of view, we have little to teach the 'hard sciences'.

Helbing: I think it is important to take heterogeneity into account. People are different, and it's also important to consider that many people have social preferences. This is not built into the conventional paradigm of the 'homo economicus'. I think considering this allows you to understand a lot more things. And if you go away from the representative agent approach, then you can understand many of the emergent phenomena that happen only if there are sufficiently many people or companies interacting with each other. These 'meso-level' phenomena may not happen if an infinite number of people or companies are interacting. I predict a similar development in economics as that which we experienced in physics, when we went from mechanics to quantum mechanics or to the theory of relativity. So, there will be a paradigm shift, I think, and it is already on its way.

Regarding the question to me: yes, these platforms should be publicly managed. The World Wide Web, Wikipedia, and OpenStreetMap may serve as examples of how such management could look like. However, I expect that the governance concept will further develop in a way that supports collective intelligence.

Closing Remarks

Thomas Lengauer ML (Saarbrücken)[1]

Many presentations in this symposium have made the salient point that nature is complex and that modelling nature poses a great challenge. At the same time, our workshop has demonstrated that we are becoming increasingly ambitious with our models. Three levels of understanding were outlined by our speakers.

The least ambitious level is to understand why something has happened in the past. For instance, today, based on many historical analyses, a picture of the causative origins of the First World War is emerging. However, no one could have predicted that war at the time. Prediction without explanation is second most ambitious level. Here, data analysis plays the leading role. But the ultimate ambition of a scientist is to understand the world and find causal explanations in unified theories. The issues on this highest level of ambition have not been eased significantly by the availability of data or novel data analysis methods. Reaching understanding seems to be as difficult as ever.

But the symposium has also shown us that control does not always require understanding. By predicting their behaviour accurately, we can already influence systems positively without really understanding how they work. Still, for many systems, accurate prediction remains a great challenge. In the end, we all need to be modest. We tend to overestimate our abilities and to underestimate the complexity of natural systems. All of us are working hard to increase the little control we have over the diverse complex dynamics of our world, to alleviate suffering, and to understand our universe.

So, can we control the world? I believe we can answer that question with a resounding: Not yet!

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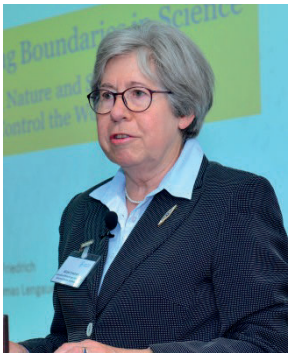

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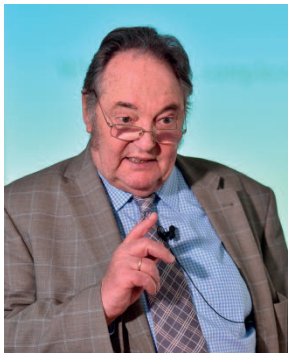

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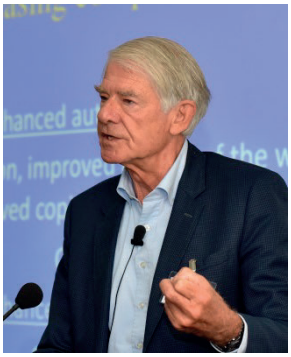

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