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Trumping the Trumps: addressing complexities through BioLogical rationality

De Trumps van deze wereld aftroeven: pak complexe problemen aan met, door de SysteemBioLogie ontwikkelde, complexe redelijkheid.

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VU VRIJE UNIVERSITEIT AMSTERDAM

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A mere progress report on 20 years of Li(v)(f)e science?

It is a little bit over twenty years ago that, in the very same auditorium I told some of you and many others about my plans, as fairly recently appointed Professor of Molecular Cell Physiology. The lecture was entitled '*Leven()de wetenschap*', with both meanings intended: I aimed for a new science that should be very much alive, and I hailed science itself. In this presentation, you will find that that has not changed much. Contrary to Rosanne Hertzberger whom some of you may have heard at our symposium today, I think that science of many types holds enormous promise for us and Society. This promise does not only reside in its underpinning of new technologies and therapies, but also in what is forgotten most, in stabilizing Society by underpinning our moral values and their evolution. Systems Biology definitely is such a science that deals with dynamics and diversity, as you will see below and in a few minutes.

Just a few years later, when I accepted also my Chair of Systems Biology at the University of Manchester to become an even closer colleague to my friend Douglas Kell (also present here), my inauguration lecture was entitled 'Dancing the molecules' ('*Laat de moleculen dansen'*). I then talked about my intention to move the molecules in the living cell, for instance by increasing their numbers and to do this both in experiments and in computations. In this way I thought I should be able to elucidate how living cells work through their dynamic molecular networkings, and how cells at other times might fail to work, such as in disease. In the latter context I was aiming for an accelerated development of better medicines, e.g. together with Adriano Henney at AstraZeneca, then at Alderley Park near Manchester.

In both auditoria my lectures were received with enthusiasm. Now, in England this often comes from innate politeness (Yes they have it, they have it, except perhaps in the House of Commons), but at our Calvinist VU, such enthusiasm is not easily obtained; so it may actually have meant something. We will see more of this today…

But most colleagues in biochemistry and molecular cell biology, or for that matter in mathematics or physics, thought nothing of it: 'Pff, equations in molecular biology: ridiculous'. Peter Ruhdal Jensen would testify to this. Or: 'Wet-lab experiments in mathematics, come on, biology is a soft quasi-science'. My students here find such times hard to imagine, but I remember how Douglas, Steve Oliver, John McCarthy and I needed to work on field and funders to make both aware of the scientific bonanza that lay ahead in systems biology. But this did result in six research centers on systems biology being funded in the UK. And with Karl Kuchler, Adriano Henney and later Roel van Driel and others, we did the same for German systems biology and its subsequent funder, and with success: an extensive research program emerged on the systems biology of the liver. In neither Germany nor the UK, it is now frowned upon if wet-lab data are interpreted mathematically in the same lecture or paper, as they are presented. Systems biology has become mainstream.

In The Netherlands most new developments usually emerge 25 years later. But particularly Roel van Driel has been successful in much accelerating this. And, by now, even papers in EMBO Journal and Cell routinely involve mathematical equations.

So, a year ago, I thought I owed you an update on *my* systems biology, 20 years after my inaugural lecture. Preparing for the update lecture, I began to realize that 'we' had pretty much done what we promised: 'We' had made a dynamic model of yeast glycolysis in terms of its components, sorted out how regulation could be quantified, identified cancer as a systems disease, found a network target for drugs against sleeping sickness, projected the yeast and human genome sequence in terms of a metabolic map, developed systems immunology and pharmacology, pinpointed the importance of individualized network-based medicine, showed that phosphatases should be equally or even more important as/than kinases in signaling, etcetera, etcetera. For the non-systems biologists, I should clarify that most of 'we' is in fact 'they': in systems biology we collaborate with our students and colleagues so intensely and we exchange our most recent methodologies so quickly, that one should see the progress more as produced by a field of

people than by many independent individuals. Not that I would wish to deny the enormous importance of my immediate coworkers to the developments; I am merely grateful that they pulled me along.

As are biochemistry and molecular biology, systems biology is here now, and it is here to stay. And now that its first missions have been completed, network-directed individualized medicine can be developed in full, with all due subtleties and caution.

The thrill in science lies much more in discovering than in the reporting thereof. So, a progress report did not seem to be maximally exciting to me. You can read the progress in our publications and in the publications of many others, including the speakers at today's symposium. Or, as the funders tend to do, you can count their citations, or the number of citations of the word systems biology and you will find a quasi-exponential growth, well exceeding 'molecular biology'. Or, much better, I could discuss one of the profound discoveries we contributed. But then my lecture would become highly technical, hard perhaps for some of the audience and boring for me, because I had already heard the same story many times at conferences. So, I decided to present to you some brand-new work, inclusive of my own new systems biology computations. This work is based on our work of the immediate past and therewith includes a progress report. What follows should then bring you, my audience, and me on a par, by talking about important issues outside systems biology that I hardly had a better understanding of than you, before I implemented the systems biology approach.

What made me change my mind

Systems Biology: a new rationality for complex systems

First: the conventional rationality

Rationality refers to employing logical consistency only, when deriving conclusions from existing knowledge and acceptable assumptions. Rationalism, developed by Descartes and Spinoza, refers to the

corresponding philosophical position that truth is to be established by intellectual deduction. Experimental testing with the resulting information being used as validation or falsification, was then seen as less important. Empiricism holds the opposite view that knowledge comes only or primarily from sensory experience. Empiricism appears to dominate in biochemistry and molecular biology in the sense that all hypotheses need to be validated experimentally. In computational physics on the other hand, results of often lengthy computations based on established principles, are accepted as 'evidence'. The latter is the deductive basis of new knowledge. And of course we molecular biologists also use the deductive mode: If we sequence a genome and find a stretch of DNA with extensive homology to a gene of known function in a different organism, we attribute that same function to that stretch; we rarely bother testing this. And of course, physics was not quite happy with the exclusively deductive evidence for Higgs' boson and went for empirical evidence and ultimately found it. Therefore present-day sciences use a combination of deductive and empirical streams of evidence. I refer to this combination of deduction and experimental testing of hypotheses as, by now, 'conventional rationalism', and to the corresponding attitude as 'conventional rationality'.

This conventional scientific rationality does not suffice for complex biology however. The number of recognized underlying principles is too small to deduce the organization and behavior of living organisms from them; one cannot compute the molecular state of a living cell by an extensive energy minimization calculation. For functional reasons, the cell is 'caught' in a local minimum, which is strategically not even close to equilibrium. And the number of truly different experiments that can or have been carried out on a particular cell is far smaller than the possible number of binary interactions of 25 000 components, i.e. 0.6 billion. So there is no way in which we can understand living organisms by conventional rationality.

Since the original rationalism was defined and developed only a few miles away from this auditorium, and because Baruch Spinoza associated himself with, then radical, Christians, I am tempted to update its definition in this temple of Abraham Kuyper, after all called the *vrije Universiteit*. So we

should speak freely. Above, I claimed that systems biology has developed methodologies that enable us to understand life at least partially. What then is the quintessence of this new reasoning in systems biology, and thereby of its new rationality fit to address systems of high complexity? I will now discuss how the complex rationality of systems biology came about and what it entails.

Simple solutions impossible, the complex solutions incomprehensible

William of Occam (1285 - 1349) is well known for his *adagio* that explanations should be as simple as possible (*Pluralitas non est ponenda sine necessitate*), which is all too often simplified to 'explanations must be simple to be valid'. We shall refer to the latter as 'Occam's razor'. For sure, a single step, such as transcription or terminal respiration, that is both rate limiting and the prime regulator for all processes of life, would have been the simplest option. There is however no such simplicity in living cells.

Even the simplest organisms that we know of have a genome with well over 300 genes, understandably so in view of the complexity that minimal Life requires for fitness. In view of evolutionary selection and optimization, it then is likely that all these 300 genes exercise some control on fitness, at least under some circumstances that are relevant for the survival of the species. For the human case (each of us has 25 000 different genes) this implies that thousands of molecular processes together may control any of our important functions. The observation that there are not 25 000 but 'only' some 200 oncogenes and tumor suppressor genes, was perhaps foreseen by Orwell: Almost all genes may exercise some control over almost any human function, but the extent of this control varies widely between them. Throughout the latest 20 years my teams have been finding the control of functions of living cells and organisms to be following this 'law of Orwell' (*All animals are equal but some are more equal than others*).

All too often it takes a while before I realize the full implications of experimental findings. So it was not in 1983 but only a decennium ago that I did. The implication is that explanations of biological phenomena should

have a complexity in excess of 300 (degrees of mutually cross-talking degrees of freedom). This is dramatic for two reasons: It constitutes the end to Occam's razor for life sciences. And, it means that Biology cannot be understood by the human mind (alone). For, our brain can at most operate two tasks at the same time, not 25 000.

Light at the end of the tunnel: new systems-biology methods

As to the first issue, we - six centuries after William of Occam, yes we were late - formulated the opposite principle (*Pluralitas non est eliminanda sine necessitate*): in explanations of a human function one should start with explanations of a complexity of twenty-five thousand and only reduce that complexity when one finds good reasons to do so.

With respect to the second issue, I started wondering how existing life sciences are managing to deal with objects of study that are too complex to understand. The answer is that there is more to sciences than 'understanding' in the cause-effect sense that I was thinking of. One may also determine the sequence of events, even if this is not necessarily a causal chain. Or, one may make an inventory, such as determine a genome sequence, or make a metabolomics footprint of an organism. Indeed, such big-data science is fascinating and important, although not necessarily leading to understanding. If fortified with pattern analysis, it may even lead to discoveries that are not limited by pre-formulated hypotheses and my dear colleague Douglas Kell has become keen on this. So indeed, most cell biology publications in well-quoted journals are data driven now. Hypotheses, their testing and discussion are considered 'not done', unless such considerations lead to a simple explanation obeying Occam's razor principles.

Even though molecular cell biology was dealing with a subject that was too complex to ever understand in terms of Occam's razor criteria, the topic was thriving and the corresponding number of publications increasing exponentially. But for people like me who are keen on causal explanations, there was a reason to worry: the way it was going cell biology would hardly

ever lead to true understanding and to robust interventions by new therapeutic drugs against cancer, diabetes or Parkinson's disease.

Rather than adapting to the science around us, we therefore continued to *dance the molecules* and *liven up the life sciences* by cause-effect, say bottom-up, systems biology. We developed and implemented systems biology methods that could deal with the complexity. We did this by making mathematical models of pathways, such as glycolysis, in various living organisms, thereby working our way up, we thought, towards the complexity of the whole. Some said that such working up should be impossible. But when there are problems that are theoretically too difficult to solve, one should turn to engineers such as Jens Nielsen, Sef Heijnen (present today) and Bernhard Palsson. Bernhard's team was the first to add biochemical information to the genome that had been sequenced now 20 years ago, and then made a map of the biochemistry of that genome. This map thereby included all the *chemical* complexity. As more often, the engineers were kind enough to involve other systems biologists, including Douglas Kell (also present here), Jens, and myself. Hence I found myself on prime-time Dutch television explaining what this meant and what the implications of knowing the biochemical whole of an individual on the basis of her DNA sequence, could be for disease diagnosis and therapy. Of course, we should recognize that this constitutes merely a plane through the iceberg, and not even its tip: there is also transcription, translation, epigenetics, dynamics, *etcetera,* and it will take a while before we have made the corresponding static maps, and then the dynamic versions thereof. It is no surprise therefore that so many of my PhD students and postdocs here look so pale: they are hard working to get us those maps, whilst I am touring the planet to learn from my other colleagues.

With this I learned that we now do have ways to understand systems of this tremendous complexity. Robbert Dijkgraaf (last Saturday's NRC-Handelsblad) is no longer completely right with his: '*Evenmin als wij intuïtie hebben voor elementaire deeltjes of zwarte gaten, snappen we verbanden van triljoenen actoren.*' Just as little as we have intuition for elementary particles and back holes, we do not understand networks of trillions of

actors]. We do understand some aspects of these networks, such as how we can predict and detect inborn errors of metabolism. As I am speaking, colleagues all around the world are practicing systems biology using the new methods. They come to new understanding of networks in living cells. They are also discovering principles of operation of these networks, an area where my teams have made exciting discoveries. My colleagues and coworkers have revolutionized the life sciences by enabling for the first time, *true* understanding of their networking-based functions in terms of molecular interaction properties.

~omics and completeness

Induction, i.e. the inference of the cause from an observed effect, is a logically feebler methodology than deduction: a single conclusion can often be deduced from more than one set of premises, many of which may be unknown. Thereby conventionally, induction does extend beyond the formulation of hypotheses, predictions of which can then be tested subsequently. In conventional scientific rationality one then accepts the hypothesis that has survived all attempts of falsification as the one that is likely to be right. The attempts to falsify should include both falsification by deduction from underlying principles and by predicting new behavior that is subsequently not reproduced in targeted experiments. But in the highly complex biology there too many alternative hypotheses and too few deductive and experimental tests are possible. Up to recently, if a hypothesis failed a test, one could always invoke a yet unknown gene that added an interaction responsible for the experimental observations, and this on top of and saving the hypothesis being tested. This was a state of affairs that Occam was precisely warning against. Systems Biology ended this predicament, by using genomics to establish the *complete* catalogue of genes and corresponding metabolic activities, eliminating the option of invoking yet another, unknown protein to rescue a hypothesis.

Multiple parallel explanations

Knowing what all the options are does not lead one to the single right option. Applying Occam's razor might seem to do so, but we have just seen that Occam's razor is unlikely to lead to the truth as the truth needs to be complex not simple. In addition it is accepted that parameter values and observations come with errors in them. Therefore the future is not one of a single 'best' concept of how a living system works, but one of a number of concepts for all of which the systems biologist then established a probability of being correct. Thanks to the increase in computer power, systems biology has been able to develop the strategy of working with all options that meet a number of restrictions, at the same time (such as in massive parallel modeling and flux variability analysis. My colleagues Kaz Maeda and Fred Boogerd, from Tokyo and Amsterdam have developed and implemented an amazing methodology to do this; I call this the rubber band method.

Multiple causation and pleiotropic interventions

Above I already mentioned that in biological systems, functions tend to be controlled by multiple active components at the same time but to different extents. This requires an extension to the conventional rationality that tries to find the single cause for each phenomenon. (Metabolic) control analysis (MCA) is a way to deal with such multiple causation and its causes. MCA has further shown that Biology is subject to fundamental principles, such as one that relates the relative strengths of causation of a certain concentration at steady state, to the more dynamic causation of reaction rates by metabolite concentrations. This is my favorite concentration control-connectivity theorem. I call these MCA principles 'laws' because they have a foundation that is as generic as that of the second law of thermodynamics, i.e. deduction from generally accepted underlying assumptions. The multiple causation principle has the further corollary that multiple intervention can well be more effective than single intervention.

Biology has more such scientific laws. Some of these are more empirical, such as the one purporting that all life on Earth contains DNA with the four

bases deoxy A, T, G and C. In a fascinating training course at the University of Amsterdam, called 'How to build an alien', astrophysicists, astrochemists and systems biologists stimulate students to think what other life-forms might be possible on other planets, but also on Earth.

Data integration

Conventional rationality was usually applied to issues of rather limited complexity, nothing like that of a network of 25 thousand independent genes that only together determine health and disease. Such vast networks require very large numbers of experimental tests. Traditionally such tests were executed under different experimental conditions and even with different living cells. Systems Biology has progressed to standardization. Data deriving from a multitude of experiments, carried out in many different laboratories and reported on precisely, are then collected by proper bioinformatics. The systems biologist then tries to find which mathematical model of reality is able to integrate all data consistently. That model should be mechanistic, i.e. realistic in terms of already existing principles of operation of biological matter.

Circular causality

In our systems biology analyses of living cells, we often found circular causality, i.e. where A caused an effect B, which itself was a cause of an effect C, which was again itself a cause, … of A. An increase in A may then reverberate through this network such that an increase in any of the three components is preceded ('caused'?) by an increase in either other component. Conventional rationality would refuse to deal with such a system, deeming it too complex or vague. Even worse: In biological reality the arrows between the components are often reversible, such as in A←→ B, such that not only A causes B but also B causes A.

Systems Biology deals with circular and reversible causality in three steps, i.e. by first eliminating the circularity of the network by fixing one component and determining the remaining causality, by then repeating this by fixing a

different component, and by then using computation to reconstruct what should happen when the two subnetworks constitute the original total network. My colleagues Van der Weijden, Snoep, Jensen and others completed such a task already at the beginning of the two decennia I am here reporting on. They produced an integral understanding of how DNA supercoiling affected gene expression of topoisomerases and how the expression of the topoisomerases affected DNA supercoiling: a complete picture of the circular causality around DNA structure.

Causality and Bayesian statistics

Statistics refuses to deal with causality; it only wishes to deal with correlations. In their *Book of Why*, Pearl and Mackenzie describe how Pearl grew up in the field of statistics but then noted that for complex networks statistics became useless. The incidence of lung cancer in females in the USA rose during the last part of the previous century, whilst that in men decreased. At the same time the number of women smoking increased whilst the number of men smoking, decreased. Scientific statistics would conclude that lung cancer correlates with smoking, but would then declare any discussion of whether lung cancer causes people to smoke, or smoking causes lung cancer, 'unscientific'. In bioinformatics Bayesian networks have become highly popular. The famous theorem of Bayes, applied to the above example, would read:

$$P(smoking|lung\ cancer) = P(lung\ cancer|smoking) \cdot P(smoking)/\ P(lung\ cancer)$$

i.e. If 8 % of the smokers contract lung cancer, and 20% of the population is smoking, whilst the overall probability of contracting lung cancer is 2%, then the probability of a lung cancer patient to have been a smoker should be 80%. It is important now that the symbol | should not be interpreted as the causal arrow $\Leftarrow$, because then the theorem would read:

$$P(lung\ cancer \Rightarrow smoking) = P(smoking \Rightarrow lung\ cancer) \cdot P(smoking)/\ P(lung\ cancer)$$

And one might then infer that the chance is 80% that lung cancer causes smoking. This illustrates that a Bayesian probability of co-occurrence (correlation) does not correspond to the probability that a certain cause has

a certain effect. The Bayesian probabilities are ones of correlation rather than cause effect relations. They are thereby uninformative per se if one wishes to understand what causes lung cancer, as would be similar probabilities referring to correlations of the application of medicinal drugs with percentages of remission. In their book Pearl and Mackenzie argue that their idea of adding their 'do-calculus' is the discovery of the century to resolve this stalemate. In my mind they merely reinvent mechanistic systems biology. Bayesian statistics is for statisticians and not for those seriously interested in improving the functioning of complex systems.

The teleological cause

In everyday practice, explanations often break with conventional causality and its rationality. Being asked why I ride my bicycle, I might explain: "because I go to the VU Amsterdam". However, 'going to the VU Amsterdam' is not *really* the cause of riding the bicycle. This is an example of a teleological explanation, an explanation in terms of an aim. Such explanations are and should be banned from physics and chemistry. An electron does not circle the proton because it wants to form a hydrogen atom (teleological explanation), but because that configuration is the minimal possible energy (causal explanation). But in Biology teleological explanations are useful if and because they relate to evolutionary fitness: we should only find networks in living cells that lead to maximum evolutionary fitness. Systems biology has made great progress in enabling the use of teleological causality, such as in using objective functions in flux balance analysis. My colleagues Molenaar, Bruggeman, Teusink, Nielsen, and Palsson have contributed greatly to our understanding of apparently inefficient behavior of living cells.

The systems biology developments: a new 'complex rationality'

Summarizing, systems biology has been developing a new way of robust reasoning; a way that is able to deal with the behavior of systems as complex as having hundreds of degrees of freedom coupled nonlinearly. This 'complex rationality' combines all the above and some more methodologies,

i.e. it (i) uses the completeness of genomics inclusive of proteomics and metabolomics, etcetera, (ii) accepts that phenomena are caused by multiple actors and uses MCA-like methodologies to deal with this multiple causation, (iii) comes with pleiotropic intervention strategies for biotechnology and therapy, (iv) integrates all relevant experimental data into single mechanistic models of reality, (v) accepts multiple parallel explanations with explicit likelihood factors, (vi) refrains from the use of Bayesian statistics alone, (vii) enables explanation in terms of aims such as fitness. Complex rationality adds these methodologies to the tenets of conventional rationality, i.e. that the truth must not be falsified, neither by deductions from well accepted underlying principles, nor by critical experiments, and that there should be maximum attempts at such falsifications.

I conclude that systems biology has come up with a new rationality, a better way of robust reasoning about complex systems than conventional rationality was.

Society: Populism replacing rationality

The re-emergence of populism

Whilst running the rat race of front level science, I would still now and then glance at Newspapers and Talk-Shows. Thereby I witnessed a surge in brief and overly clear statements, such as: 'Would you want more or fewer Amsterdammers' (but then a different equivalent). 'Fewer, OK, I shall take care of this'. Or, 'If you do not like it here, then leave the country, just leave! That is a choice you have, don't you?'. But even worse, I then witnessed that these people and the political parties they belonged to, would not lose but win subsequent elections. I witnessed endless emphasis on the increasing average age of our population and on the young no longer being able to pay for the old, whilst the most robust source of rejuvenation of the population, i.e. immigration, was suppressed illegally. I heard a presidential candidate deeply insult at least 51% of the population of his country, and still being voted into office whilst running against a candidate who is part of that fraction. A politician in a beloved, though often aberrant, country was

voted back in with two charges of corruption on his name. Much worse of course, another 'president' was butchering his population with support from a re-elected president, the EU only being concerned about the resulting immigration. When my colleague chemist said: 'Wir schaffen das', she was ridiculed by the Dutch press, which must have been oblivious of the 1938 scandals at the Dutch-German border.

Rather verbosely, I here tried to illustrate how I, looking from the side of the conventional rationality of science, was surprised at the apparent dismissal of rationality in important areas of society such as politics, health management, and economics. This conventional rationality favors decision making on the basis of logical deduction or the results of targeted experiments with clear Yes/No answers. In present-day politics, I more and more witness that decisions are based on opinions in political parties that happen to be in government rather than on the basis of scientific evidence that exists or can be obtained.

With respect to global warming some politicians argue that not all scientists have come to the same answer ('STOP it') and that therefore there is no reason for scrapping the destruction of forest for the construction of more oil pipelines. This reminded me of the phenomenon that one of our most important findings was also considered vague initially. This was the result that control of a disease was not residing in a single molecule, but was distributed over many. Had control resulted in a single process, this would have indeed appeared to be clearer, but reality was more complex than that.

I remember being asked at the end of one of my lectures, which molecular conformation should then be held responsible for the type of cancer I had been discussing. When I answered: 'Not any one in particular; we found that many are responsible, or rather their networking is', I saw despair and commiseration appearing on the face.

It is actually hard for the human mind to comprehend fully that important processes can be limited not by one but by many processes at the same time; intuition has it that processes are always determined by a single step, which tends to be the first irreversible step in the pathway. My chemistry

colleagues would understand this intuition, as for chemical-reaction pathways this tends to be true. Not so my biochemistry colleagues Bert Groen, Roelof van der Meer, and Ron Wanders, of course. They were clever enough to just design and do the experiment and then found control to be distributed, and this for one of the most important processes of life, i.e. ATP ('energy package') synthesis. My teams, have since extended this to the control of DNA structure, proton energy, ammonia assimilation, drug pharmacokinetics, cancers, and perhaps Parkinson's disease (see below).

What is this populism?

What is this populism? Only somewhat deviant from the definitions by Adam Taylor (Washington Post) and Cas Mudde (University of Georgia), I turn to the definition by Juvenal (100 C.E.) who referred to 'bread and circuses: "to generate public approval, not by excellence … or by satisfying the most immediate or base requirements of a populace —but by offering a palliative: for example food (bread) or entertainment (circuses)". I cannot help being reminded of this when watching programs on Dutch public television, which now alternate between political news about how North Korea may send nuclear missiles into Tokyo, and sports news about Excelsior playing soccer against Feyenoord.

Populism: a network issue itself

It is not just Donald Trump: many politicians make ostensibly simplistic or even stupid, policy assertions or insult the majority of their voters. These are not the dictators that can take their power for granted, but elected politicians that continue to be voted into office or parliament well after publishing their one-liners.

Is it then the voters that are at fault? Well, maybe Yes, or maybe No. I am a voter, and I am confused when it is election time and I am supposed to read hundreds of pages of programs of political parties and to watch debates managed by 'journalists' who think in terms of a person's leadership winning

a debate rather than her arguments. Also for those journalists it must be impossible to force the politicians to deal with all those complex issues that the journalists cannot fully understand either. Political scientists, sociologists and economists write PhD theses on many of those issues.

I think neither politicians, nor voters nor journalists alone are responsible for populism. It is another case of 'Orwell's law': The whole is a network and all actors are guilty although some are more guilty than others. Control is distributed but not evenly.

If populism is a disease of the network of politics, what then may be done against it?

Systems immunology: an inspiration

The idea that systems biology may help in cases of war and peace, emerged when I was studying innate immunity in terms of computational systems biology. We modelled the extent of inflammation that would occur upon injection (by a mosquito or a nurse) of an amount of infective material into a tissue. We found that for a small amount the inflammation would be limited and the injected material would be dealt with effectively. When injecting more material this would not change much. However when injecting more material than a certain threshold, the inflammation would jump up to a much higher intensity, similar to an allergic response. Subsequently, reducing the amount of injected material to levels well below the threshold did not remove the highly inflamed state. Only when the injected material was reduced to virtually zero, the inflammation subsided. When we then increased the injected material again, to levels still well-below the original threshold, the tissue *immediately* jumped back to the highly inflamed state: we had modelled in terms of cells and molecules, the emergence of a chronic inflammation, similar to that of rheumatoid arthritis.

The systems biology model enabled us to determine what the cause was in the immunology case. For sure Orwell's law applied: it was not a single molecule or cell in the network. Most of the molecules and cells exercised

some control on the balance between acute and chronic inflammation, and the balance was controlled by a positive-feedback subnetwork. Our model also showed why a certain drug molecule that interfered with the positive feedback loop failed to return the network definitively from the chronic to the acute inflammation state: at least one additional action having to do with stem- cell activation or fibroblast infiltration, was needed to make the cure persist.

The analogy with war and peace is strong, for instance in comparison with the political situation around the start of the First World War: countries engage in political provocations with consequences that subside subsequently. But once a provocation exceeds a threshold, a full blown war may break out, which will not subside even after the initial provocations have subsided: the political arena has been sensitized too much. Populists stirring up society on irrational grounds would be harmless at low dosage, but could flip-flop society at high dosages, and once such a society had flipped, it would be difficult to return it to a well-balanced state. The pogroms in Eastern Europe may well have been one example, the ethnic troubles in the Democratic Republic of Congo another. Also the provocations by Kim Jong-un and Donald Trump, may be harmless, but only up to a certain intensity. Thereafter, the situation may turn into an irreversible mess. All too often the victims will not be the causers but by-standers such as those on board the MH17 or PS752.

These similarities between what we were finding in systems immunology and what seemed to happen in politics, gave me hope: If we are able to deal with the analogy of populism and its effects in immunology, we should be able to understand and begin to deal with the network problem populism in Society.

How systems biology may help trump the Trumps of this world

The tenet of systems biology

The similarity of the war-peace system and inflammation, is a further validation of the tenet of systems biology, i.e. that both the function and the

malfunctioning of complex systems are determined more by how they are networked than by the inherent properties of their components. With inherent properties I refer to interesting properties of proteins such as their 3D structure, or of human individuals, such as the color of their eyes (I like green). These are irrelevant for the functioning of the living cell or Society, other than that they effect the properties of individuals that *are* relevant, i.e. the rates at which they interact with other individuals.

A responsibility: furnish the new methodologies

By now you may have thought 'Cobbler, please stick to your last', or 'why should a simple biochemist like Westerhoff tell us about populism and Trump'? Well, because human Society is complex in ways that may be similar to the complexity of the living cell, systems biologists avail of methodologies that may help improve the way Society is handled by politicians, voters, and journalists. And, as responsible members of Society and because their research was paid for by Society, the systems biologists may have the duty to do so. To be clear: I am not referring to duty to rule Society such as in a technocracy, but the duty to furnish tools to enable the voters and politicians better to steer Society towards what is best for all rather than towards the re-election of some.

I would like us to assume this unique responsibility rather than the simpler option of sticking to my original last (and to the originally intended Progress Report). After all, complex networks are my expertise, as are methods to analyze and even to steer them towards optimality. And, I'd rather be an Albert Einstein or Rita Levi-Montalcini than a Wernher von Braun. Dr Levi-Montalcini was a victim of triple discrimination: she was told at first by her father not to go to university but to rather prepare for a more traditional future, she was denied a University position when Mussolini instated laws in violation of the international laws of justice, and she had to hide when Hitler invaded Italy. She built a laboratory in her bedroom instead and was subsequently welcome in the United states where she then discovered that human cells talk to each other, e.g. through Nerve Growth Factor (NGF). Not surprisingly she promoted Italian Systems Biology, for instance by assisting at the 2005 systems biology meeting in Milano, organized by Lilia Alberghina,

also present here. But, equally important for now, like Einstein she drew the conclusions that she should be active politically and became a Senator, who was loathed by Italian populists because of her insistence on the benefit for all. You may be stimulated to follow her footsteps, as she lived to the age of 103, celebrating her 100th birthday in the Town hall of Rome. Lilia still has to tell me how swinging that party was …. I was not invited.

The inspiration goes even further: in 1980 she was elected to the Italian Academy of Sciences-of the forty, with illustrious international members such as Albert Einstein, Erwin Schrödinger, Louis Pasteur, Hendrik Lorentz, and Bruce Alberts. Illustrious national members include ones some of us know, such as Andrea Melandri, Cecilia Saccone and our very own Lilia Alberghina.

The idea: help complex Society, by building on its analogies with living organisms

Society is complex, much like biology. One could draw analogies such as between metabolites and goods, between enzymes and workers, between signal transduction proteins and managers, between mRNA and professors, between DNA and the Constitution, between cells and towns, between tissues and states, and between the body (or an ecosystem) and the European Union. In 2020, the State of the Art in cell systems biology is that we can (and are allowed to) (i) identify all its components with their interaction properties, (ii) test our models by precise intervention experiments using the CRISPR-Cas methodologies explained earlier today by John van der Oost, (iii) observe multiple components at fast time scales and in parallel, (iv) model all processes simultaneously in their dynamic interactions. In Society, (i) it is unethical and hopefully soon forbidden to define completely who the individuals are and how they are interacting, (ii) it is forbidden to do causal analyses by intervention experiments, (iii) many processes take years to complete, making scientific analyses too slow. This would seem to pre-empt ambitions to understand Society effectively and indeed we have not seen much success of economic or political modelling in the prevention of financial crises, new arms races, or crashes of civilian airliners in war zones.

However, the fact that both systems can be modelled mathematically may enable a transdisciplinary approach, i.e. one in which societal disciplines such as economics and political sciences on the one hand, collaborate with systems biology on the other. In such an approach one could see if in biology there are issues that mimic important issues in economics or politics. For both types of issues, models might then be made using congruent modelling methodologies. Those models could then be used to (i) translate societal problems into systems biology problems,(ii) discover possible solutions to those problems by systems-biology modelling, (iii) validate those solutions experimentally in (synthetic) biology systems, and (iv) then use the two models to back-translate the successful solutions to society.

Members of parliament, voters, and journalists could then use the resulting models of Society to test out their ideas or the ideas proposed by political parties on how to improve Society by taking subtle measures, by voting for a particular political party or by asking corresponding questions to politicians.

In this way we may well trump the Trumps of this world, including the Murdochs, the Andrews, the Poetins and the Baudets.

Proofs of principle

Am I again bluffing my way into a new field, as a member of the audience (Hans van Beek) might again say? In a sense I am indeed. But this is often necessary to propel important issues. But let me now provide some proofs of principle in which I show that with systems biology tools one can indeed understand features of Society, in economics as well as politics.

Economics with fixed supply and demand

The first is simple economics with a supply-demand system with two components: a soap producer, say Unilever or Procter & Gamble, and soap consumers, say, you and me. In between them is the number of soap bars, which we can translate to the price of soap by taking its inverse; if there are 5 soap bars then their price is 20 eurocents a piece. The biological equivalent most familiar to me is that of mitochondrial oxidative phosphorylation. Mitochondria are the power houses of our cells making

quanta of useful ('Gibbs') energy in the form of the molecule ATP. The quanta can then be used for the many essential life processes that require such energy, such as protein synthesis, signal transduction, contraction, anabolism, and transport.

Systems biology has used precise experimentation (as shown today by Guy Brown and yesterday by Annamaria Colangelo), as well as mathematical modelling by software such as our Jacky Snoep's JWS Online, Pedro Mendes' and Ursula Kummer's Copasi, or Guido van Rossum's Python. For this presentation I will limit myself to Copasi.

I first consider the impression one might get when looking at many biology textbooks, including the fantastic one by Bruce Alberts and colleagues. In the diagrams it seems that each molecule knows precisely what to do. So I modelled the case where Unilever precisely produces 100 soap bars per day and we have 200 consumers that each use one soap bar per day. I began with 250 soap bars. Not surprisingly, my model shows that in 2.5 days the soap runs out. What should surprise you is that I have been able to model this economic problem by simply using standard systems biology methodologies. This is the main point I am going to make here: using systems biology methodologies we can model economics. But of course, this first example has nowhere near the complexity that we would consider useful.

I will therefore model a solution one may propose for the economic problem: I rule that Unilever should precisely produce not 100 but 200 bars of soap per day. Sure enough putting that into the model, I get a stable level of soap bars at 250, and a stable price. So that reads swell, does it not?

Well, systems biology offers criteria and methods to analyze the robustness of systems. In the mitochondrial case we would ask what would happen if the number of ATP consumers would increase a bit. I translated this into an economy model in which the number of soap consumers increased and found that the system ran out of soap before the end of the month, the soap price then increasing enormously. If conversely Unilever's machines would begin to work harder because of less breakdown and repair issues, the

number of soap bars would increase until the warehouses would crash under their weight: My systems-biology models show that a precise plan economy such as the ones in the communist countries in the eighties, may not work. They come with sudden and unpredictable shortages in some commodities, and expensive surpluses in others. And indeed, this was a major factor leading to the dismantling of the Soviet Union.

Learning from mitochondrial bioenergetics: a flexible economy

Our mitochondria however, appear to be a robust source of ATP for our vital processes. What would we learn from them?

Well, processes in the cell that consume ATP are elastic in the sense that they consume less if there is less of it, either by gear shifting (i.e. by using less ATP for each job, as my students Yanfei Zhang and Thierry Mondeel are making me discover) or by just reducing their activity. In the economy model, this would mean that the consumers would use less soap when its price increases. Adding this aspect of consumer elasticity to the model, led to a situation that *was* stable to fluctuations in number of consumers or activity of producers.

Consumers using less soap per person might be a smelly solution however. Again inspired by the mitochondrial case, I also modelled the possibility that Unilever would respond to a price hike by producing more soap. This led to a situation where consumers would only consume a little less soap per person, and Unilever directors and shareholders enjoyed their increased profit: everybody happy.

The overarching conclusion is that both in cell biology and in society, it is more important for stability and robustness that processes are elastic (flexible) than that they precisely do what might have been predicted to be optimal. This is also what I aim for in my teaching: graduates that are able to respond to intellectual challenges.

A lesson learnt from asocial (cancer) cells: a government needed with the vision of the best for all

This then seems to have become a plea for a free market economy, à la what the European Commission and Neelie Kroes and the more recent Dutch finance ministers have tried to achieve: unlimited competition. But, I haven't finished yet!

Chiara Damiani and colleagues have thought about the issue that the cells in our body undergo somatic mutations. Pernette Verschure and Marianne Rots would add multiple epigenetic changes to this. As a consequence the individual cells of any of our tissues differ somewhat from each other. Systems Biology had already made the genome-wide metabolic map of the human and Chiara and Lilia had made a sub-version thereof focusing on carbon, nitrogen and energy metabolism. To this map Chiara then applied mutagenesis *in silico*, asking which up-mutations would produce a robust steady state with increased flux through the mutated step. She found many cases where this would happen and, because we thought that this might reflect the many different cells of our tissues, she categorized them. And now for the bottom-line: She found that a significant proportion of the somatic mutants was 'asocial': they were not efficient; they did not produce 36 ATP per molecule of the sugar they ate, but only 4. Yes, they still needed lots of ATP to thrive and grow but they solved this issue not by being efficient, but by consuming much more sugar. This should be detrimental to the other, not-mutated cells, which normally and socially took the more efficient option of respiring the sugar to carbon dioxide and producing the 36 ATP per sugar molecule (glucose).

Remembering this, I first made a model of a collection of social cells, i.e. of the way we used to think about our tissues. These cells made ATP, but not only to sustain their selves, but also to ensure that the intestines would take up enough precursors and the lungs enough oxygen. Sure enough this then led to a stable and robust system with cells as happy as they can be (I guess). I then added that one of the cells underwent a somatic mutation such that it expended all its resources on itself rather than on uptake of common resources. The resulting model showed, dramatically, how not initially but some-time later, this cell and its progeny, compromised the growth of all the other, social cells and lead to their extinction. More

paradoxically perhaps, although the mutant cells thrived at first, they would ultimately also stop growing and begin to die due to lack of substrate for growth: by fencing for themselves, the asocial cells would ultimately NOT fence for themselves at all. To counter Richard Dawkins two times over: The selectable unit is neither the selfish gene nor the selfish genome: it is the selfish physiology, which in our case involves the entire human body. And this selfish physiology requires social cells as well as social genes.

I translated these findings to the market economy and found the analogy: a few asocial consumers (or producers) would ultimately crash the economy for all.

How to prevent this from happening? One might surmise that one should stimulate the producers of the consumable (e.g. soap), i.e. Unilever, something the Dutch government would definitely consider. My modelling showed however that it is a bad idea: this would be a waste of money as it would have no effect at all: the soap price would drop immediately and Unilever (or rather the model thereof) would take the money, perhaps say thank you, and produce less rather than more soap.

I then simulated a government that would observe where changes in commodities occurred and then stimulate processes that control those commodities. This did stabilize the system and allowed both social and asocial consumers to persist.

I conclude that both living cells and Societies' economies need governments observing where there are shortages and surpluses, and stimulating and inhibiting where needed to even those out. This then is a lesson to European governments that refuse to do this. The Dutch government refuses to lend support to countries in the South of the EU, although it did so in the past to the South of The Netherlands, with good results. In my analysis, Draghi understood this and enforced such North-South support in an indirect way, thereby keeping the EU economy from crashing.

Hard nuts to crack: the time warps of global warming and aging

Frans Timmermans and Frau Doctor von der Leyen also have a different nut to crack, i.e. to make economically-rich countries engage in measures to abate *global* warming, whilst the richest country refuses to do so. The same model as before would show that refusing to take its part in investment towards global warming, would make the USA outgrow the countries that do invest, but would also ultimately disenfranchise the USA themselves.

Another aspect of the nut is also hard to crack: how can we understand how modulation of processes of a characteristic time of minutes or days (such as eating our steak, or flying to Bangkok) may effect processes that only after a century may lead to a sudden catastrophe such as the flooding of Amsterdam. This is what I call 'the time-warp problem'. We encountered it when engaging in the systems biology of ageing and Parkinson's disease, at the level of mitochondria, their production of reactive oxygen species (ROS) and the mitochondrial suicide (mitoptosis) that both Vladimir Skulachev and we proposed some 20 years ago. Here life proceeds normally until around the age of 80 a fairly sudden deterioration occurs in many body functions. We made the systems biology model of the mitochondrial processes that were all happening at a time scale of seconds to hours. And to my surprise, we did observe that everything functioned well, except for a sudden deterioration around 100 years of age: the time warp, counter intuitive to me, came out automatically! We also found that many processes exercised control on the time at which the time warp occurred, suggesting multiple 'elixirs' (coffee being one of them; good news for me and some of you!).

Should we put in the uncertainties in the parameters values of the model, we would see that, should they be 20% off, the time of the time warp might readily come 20 years earlier or later, but the time warp itself would persist. Transposing this to the case of global warming, it becomes clearer that Trumps, extrapolating from their today's experience in the White House or a Coral Gables golf course, may not be aware of any catastrophe ahead. And indeed they will be able to find that there is no scientific certainty about the precise timing of the catastrophe. But, we should now act on the basis of

the most probable models, which suggest that there is most probably something wrong in the State of planet Earth.

A systems biology model of populism

Returning to the European economy: Why doesn't the Dutch government support it as much as the president of the European bank did and will do? I guess that that was because of a different network structure around them. Draghi needed not to be voted in again by 'ordinary people', whilst the Dutch government worries about its own persistence often more, than about the wellbeing of the country. The Dutch politicians have to deal with the populism of their opposition.

I thus modelled populism by adding two types of seat in parliament to the network (i.e. 'Populist' and 'Balanced'), with asocial consumers voting for the former because they proposed to spend all resources on their wellbeing ('lower the taxes and give them 1000 euro') and social consumers voting for the latter because they proposed also to spend resources on the country's import of raw material. Sure enough, the model of that situation crashed again taking with it both the social and the asocial consumers.

What then? Using MCA, Systems Biology can calculate which processes should be stimulated to have a desired effect. One may also do this after adding various processes that had not yet been included in the model. One of these could be the conversion of asocial consumers into social consumers by education in values such as paying taxes (to be used for the building of the port of Rotterdam to import goods). My modelling showed that this would stabilize the country and allow all to thrive and largely behave socially.

Diversity and a multicultural society

Earlier on I alluded to the important role Amsterdam has played in the development of rationalism. Only to a limited extent however, this was the role of native Amsterdammers. Neither Descartes nor Spinoza was born here. They came here because it was then easy to immigrate and because they could here retain the values they preferred. In fact, they did change

their moral and philosophical positions, but this was perhaps precisely because they were not forced to do so. Looking at this city's history, I would guess that its growth and persistence has much come from the very fact that its population has been diverse. What I have not emphasized before is that in systems biology neither molecules nor cells know precisely what to do. They move and behave erratically, as observed already by Antonie van Leeuwenhoek.

My group has analyzed this in terms of average performance and found that a typically diverse system might easily perform six times better than a corresponding homogeneous system, when growing to outbalance a persistent challenge. We are applying this to the evolution of cancer cells in the presence of anti-cancer drugs, explaining why certain tumors may escape destruction by drugs against those tumors. By characterizing the tumor heterogeneity, we aim not only to catch the average cell, but also the cells that are resistant against the drug. For society the message is that heterogeneity and diversity is good for Society to profit from new opportunities. It also means that when taking measures to abate asocial individuals, the heterogeneity presents an additional problem that should be identified and addressed by individualized measures.

Conclusions

The lessons learnt from my systems biology analyses of Societal issues include:

- De-escalation requires multiple intervention
- Elastic →more robust
- Governance with social vision is needed (to support social behaviour)
- Government needs to observe and act accordingly at multiple sites
- Fundamental values + training are required to disarm populism
- The time warps of ageing / global warming can be understood
- Diversity is a plus

The fact that these conclusions make sense, constitute the proof of principle of my proposal: it will be worth our while, if not our responsibility as scientists, to offer the rationality we developed for understanding the complex system of the living cell, to Society. This should enable again proper decision making vis-à-vis the complex problems that surface in the equally complex Society. Where conventional rationality, which was optimal for simple systems, became powerless for complex Societal problems, and where it was then all too often replaced by populism, this should constitute a much needed improvement: the complex Societal problems at hand are threatening the 'Life' of the civilized Societies on this planet.

This message should be met with approval by Minerva, goddess of wisdom. Wisdom had to come a long way, from the relative simplicity of Athens' wisdom through the conventional rationality of Descartes, Spinoza and Hume, to the wisdom of the complex rationality developed by systems biology. The latter is far from the wisdom of swords and should be able to trump the Trumps, i.e. the populists, of this world. It is much closer to the wisdom and laws (Logos) of Life itself (Bios).

Summary

- Our democratic systems come from Athens and were designed to deal with a society of 10 000 at most.
- They are based on rational discussions
- We are now witnessing (see House of Commons, Senate, *Tweede kamer*) that our best systems are networks that may not quite be up to dealing with today's complex societies and are bullied by populism.
- We need a new rationality that can deal with the network complexity of present-day Society
- I have shown how systems biology methodologies and principles:
    - help understand complex systems in terms of networking of their components
    - help predict the effects of therapeutic interventions

    - constitute a modern type of rationality, optimal for complex systems
- This complex, Systems Biology rationality is characterized by decision making on the basis of:
    - Precise experiments
    - Deduction
    - Complex (modelling-based) induction
    - In a large but determined network
- I propose that:
    - the same rationality be applied to the complex problems of our society, such as discrimination, immigration, and, finance.
    - voters and politicians are provided with systems biology tools to be able to deal with the complexity of Society appropriately
- I call upon my fellow scientists and students not to just stick to their last, but to assume their societal responsibilities and offer the new rationality to Society.

Acknowledgements

Already after my PhD defense, there were too many people for me to be able to acknowledge their contributions, direct or indirect. In a sense this has become easier now with the recognition of the importance of networks: I acknowledge the dominant help I received from my networks, both academic and personal. Looking into the audience, I can see that they are vast.

I wish to remind everyone that the functioning of the network does not much depend on its components but much more on its networking. So please, rest assured that systems biology will continue to thrive, even when I may now venture into other fields.

My gratitude includes my beloved PhD students and postdocs, who I have seen grow younger and younger; now some are 40 years younger than me. I recognize young kids that I perhaps attracted to systems biology grow grey hair and wear University gowns. But grey hair and university gowns remain signs of wisdom, in this case including signs of wisdom with respect to life-science complexity. And I can already see that other young kids will follow.

I also acknowledge my Universities, i.e. my *alma mater*, the University of Amsterdam, the university where I have been even more active (the Vrije Universiteit Amsterdam), as well as the University of Manchester, which allowed us (with the UK-funder BBRSC doing even more so) to develop systems biology most rapidly in the new Manchester Centre for Integrative Systems Biology and the corresponding doctoral training center.

And then Anneke, I do not like thanking you merely as a partner for assuming the many responsibilities that I failed to assume. I prefer to compliment you: You have developed a fascinating career of your own from the molecular biology of H5, through the nuclear pore complex *avant la lettre*, all the way to systems forensics. And similarly, Emilia, you have developed a creativity of your own that I admire. We have witnessed some of this today.

And, finally:

That was it.

Ik heb gezegd; ik heb geschreven.