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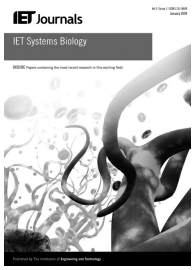

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Pushing limits by embracing complexity

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Abstract: In this essay, celebrating the tenth anniversary of this journal, the author describes his journey, from being an engineering student to being a researcher in the biomolecular and biomedical sciences. Along the way, he is going to explain how he learned that handling the complexity of biological systems and cellular processes can provide guidance in situation we all face in our everyday life. In particular, he has in mind the decisions one faces in choosing the topic for a University degree and how to deal with the uncertainty when it comes to career decisions. Looking back at a decade of mathematical modelling in the biological and biomedical sciences, he is going to consider the role mathematical abstraction has played in systems biology and the role theory should play in systems medicine. By describing his own journey, he hopes to encourage young engineers and scientists to follow an interdisciplinary path.

1 Setting out

Reaching my final year as a student of control engineering in Hamburg, life seemed complex and uncertain. I had no clue to what could happen and what I would be able to do. Fortunately, I saw one day on the University's notice board a poster about an exchange programme. Not knowing what this could bring, I signed up for a year at the University of Portsmouth, on the south coast of England.

I enjoyed a walk along the seafront in Portsmouth, watching the ferries coming in and leaving the harbour, when on the 10 October 1993, I received a phone call that changed my life. My father was on the phone and he told me that he has an incurable disease that slowly destroys his lungs. Nothing could be done. What can you do about things that are beyond comprehension?

About to finish my engineering degree, we were told that we are now experts in solving complex problems, in getting things done. And now this, everyone – the doctors, my father and certainly me: clueless. I obviously could not do anything. So what I did right after hearing the news about my father, is that I went straight to the bookstore.

There were only a few books on offer but one small book on genetic engineering had a brief introduction to molecular biology. Comparing engineered systems with living systems that consist of genes, proteins and cells, I realised that the systems we deal with in engineering can be 'complicated' but the word 'complex' should really be reserved for what we see in nature. Within one hour of reading, it became clear to me that my future should not be in engineering but in bio-medicine. With no prior experience in molecular biology, I pursued my new passion, learning biology, in the quite rooms of the University library, where I could be on my own but was not alone.

What I would like to share with you, is the story how over the following years, I made a discovery that profoundly changed both, my work and the way in which I conduct my life. At the end of this journey, you will understand how 'By embracing complexity, trying the seemingly impossible, we can eventually push the limits what is practically possible'.

2 To become an academic

While the books that founded control engineering in the 1960s, gathered dust on the library shelves, the books in the biology section were mostly brand new, shiny, heavy and full of colourful diagrams and images. The first thing that struck me while browsing these books is the complexity of living systems. The beauty we observe in nature is the result of non-linear spatio–temporal interactions, across multiple levels of structural and functional organisation. Our body consists of organs, which are composed of tissues and tissues are built from cells. Cells, only a few micrometres in size, are constructed from molecules and their behaviour, their functioning, is determined by signals, communicated through molecules. A living system is thus the result of interactions across a huge range of temporal and spatial scales. While molecules are on the nanometre scale and their interactions can take place in fractions of a second, the consequences of these interactions are determining the functioning of your body, including, for example, the intestinal system, which is several metres long and ensures that the food you eat, keeps you alive for many years. Our body is an incredibly complex system, unlike anything humankind has ever been able to construct. Engineers are rightly proud of what they manage to build.

However, looking at the functioning of a single cell, it is mind blowing; it appears to be beyond comprehension. I was immediately fascinated by the complexity and beauty that emerges from natural systems.

I finished my engineering degree, and applied for PhD programmes. In the process, I was very lucky to meet Peter Wellstead, who was then the head of the Control Systems Centre at UMIST in Manchester, up in the north of England. Peter, and my supervisor John Edmunds allowed me to do my PhD in control engineering but they also encouraged me when I came up my own project idea.

With all the determination you may have, you will not get anywhere without the help of a boss who allows you to be a mentor and friend. Again and again, I was lucky to meet such wonderful people, who taught me not only a thing about work but also demonstrated the human dimension of academia. My PhD project was subsequently the first chance to sneak in something from my secret passion. I asked whether it is possible to improve inferences about complex systems, by accounting for uncertainty in observations? The answer I found was positive. Accounting for the uncertainty may not make your predictions more certain but at least the predictions are more truthful, more honest. That can already be progress. I completed my PhD in control engineering in 1997, trained to understand complex non-linear dynamical systems with the help of mathematical modelling. And for sure: I continued my secret passion for reading books outside my area of work.

During my evening sessions at the University library, I discovered an interesting connection between cellular systems and what I had learned in control engineering: The functioning of cells is determined by temporal changes in the concentrations of molecules. The behaviour of cells, especially cell division, cell differentiation and cell death, is best described in terms of dynamical systems! The biology books were full of interaction maps that listed molecules and had arrows between them to define interactions. Surprisingly, these diagrams were not the starting point to understand the behaviour of cells, they were often the endpoint of studies.

I was however convinced that in order to infer cellular function from molecular reaction networks, there is no alternative to using dynamical systems theory because changes over time matter to what is happening with the cell. Only a few people were studying cell functions as dynamical systems at the time and this was good news for me: I found a research gap, I had an agenda!

Soon after my first appointment as a lecturer in control engineering, I was invited to spend a year as a research fellow at the Technical University Delft. The colleagues who invited me to the Netherlands had no idea that I would not work on engineering problems. Instead, I enjoyed their beautiful library to prepare the next step in my quest. In 1999, I decided to no longer make a secret out of my desire to work in the life sciences and returning to Manchester a year later, I spoke to senior colleagues about the idea. No, they did not consider it a good idea and argued that my career path would become uncertain. They were my friends, and while I took the advice of my mentors serious, the discussions actually assured me to follow my instincts.

I had no plan, so the first thing I did, was to write emails to biologists, enquiring whether there is an interest in mathematical modelling of cellular systems, pointing out the obvious relevance of this. The response was disappointing: Most colleagues did not even bother to reply, they were too busy measuring things, with too little time to think about what the data meant for the functioning of cells. The response, or lack of it, did not bother me much. It was too late, I had made my mind up, I will not give up … new paths are created by walking them.

As the biologists in my university were not really interested in what we now refer to as 'systems biology', I decided to become one of them, at least in a small way: I applied to become a member of their department. I visited their building and 'wet labs', their 'offices' full of instruments, washing basins and flasks. And they were wearing white coats. There was a notable absence of computers that littered the desks of our offices in the engineering department. I was excited to see on the benches of the labs those flasks with small amount of liquids, whose analysis would lead to the statements I read about during my library sessions. My excitement about working near these labs was, however, short lived and by now you will be able to guess how the Department of Biomolecular Sciences initially responded to my application.

In your work, or in your life, if things seem easy, then you are probably not making much progress. Therefore, by accepting the complications as inevitable, by persisting, I eventually found my way into the Department of Biomolecular Sciences. They no longer had to reply to emails from me – I started chatting to them during the departmental coffee breaks!

3 The emergence and acceptance of systems biology approaches

When I started off with the study of disease related processes, I was motivated by technological advances that allowed increasingly accurate and seemingly more comprehensive measurements of cellular processes, allowing us to 'zoom in' to molecular details. This technology-driven zooming-in on details, has however negative side effects [1]. For example, from where I am today, it seems quite obvious to me that we cannot understand tissue organisation by studying cells in isolation of their environment, and yet this is, to this day, what most people do: seeking explanations for complex diseases at tissue and organ level, in terms of cells, single pathways involving a relatively small number of molecular components. However, before we discuss the limitations of what we have been doing, we should celebrate the rethinking systems biology has brought about.

Back in 1993 very few people tried to understand cellular behaviour using methodologies from systems theory. Large scale sequencing projects required computational and statistical tools, which made bioinformatics an accepted and soon integral part of the biological sciences. Around the year 2000 it became increasingly clear that the engineering and physical sciences, with their expertise in modelling dynamical systems, could play a role in understanding cell functions. Peter Wellstead, with his outstanding reputation in control engineering, approached the Institute of Electrical Engineers in London with the idea of a new journal that could promote the development and application of engineering concepts in the biological sciences. It was quite clear that initiatives were required to promote systems biology approaches and to explain the difference to what was known as bioinformatics. Tools for statistical analyses, machine learning, clustering, pattern recognition not only require different training, compared to the modelling and simulation of dynamical systems. If we accept that apoptosis is an inherently dynamic phenomena, in which

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the temporal evolution of molecular concentrations plays a role in determining the behaviour of the cell, then bioinformatics approaches will simply not give you the required understanding. It was thus important to emphasise the differences between bioinformatics and systems biology approaches, and to promote a dynamical systems perspective of cell functions.

Creating a journal is one mechanism by which one can support this process. On the other hand, I was always interested in bridging different areas, not trying to separate things. I consider systems biology an approach to the study of cellular systems, not a discipline. I was thus hesitant to get involved in a journal but was strongly motivated by Kwang-Hyun Cho, a Korean electrical engineer who visited me during his sabbatical leave in 2002 and 2003. Kwang-Hyun used his time with me in Manchester to prepare a transition in his career, focussing on biological systems. With his relentless energy as a driving force, we founded in 2004 the first international journal dedicated to systems biology. Kwang-Hyun is now a professor at the Korea Advanced Institute of Sciences and Technology (KAIST) and is also to this day editor in chief of the journal.

Fortunately, the use of mathematical modelling in cell biology is now widely accepted and I have enjoyed fruitful years during which we established close collaborations with experimental laboratories. The importance of this shift in thinking that systems biology brought about – away from cataloguing components towards an understanding of functional activity – should not be underestimated. If we agree that the dynamics of a system matter, this implies that we have to change the way we think about cellular systems; and we have to change the way we conduct our experiments. While in 1993 this was not sufficiently appreciated, most experimentalists now accept that generating data with state-of-the-art hardware also requires additional brainware to make sense of the data. This expertise comes from statistics, machine learning and, of course, the theory of dynamical systems [2].

Over the last ten years, the thing we now call 'systems biology' has been established as an interdisciplinary approach, using the theory of dynamic systems to study the behaviour of cellular systems. Despite of its success, the experiments that are required to construct mathematical models, are time consuming and expensive. To make matters worse, our work also demonstrates that things are far more complex than what the leading experts have suggested over the last twenty years.

4 Food processing as a truly complex system

To give you an idea of the complexity and uncertainty that biomedical research faces, I want to give you a concrete example. The intestinal system digests your food, extracts water and the nutrients that keep you going. The over 6 m long digestive system is a truly complex multilevel system: The colon's inner lining of epithelial cells is organised into more than 10 000 crypts per square centimetre, each build from around few thousand cells. At the bottom of the crypts is a niche, housing only a hand full microscopically small stem cells. The function of these stem cells is to divide, translocate and then differentiate into cells that take up a role in the intestinal system.

Once the water is absorbed from your food, life gets rough for epithelial cells. There is tremendous chemotoxic and mechanical stress on the tissue. As a consequence, cells in our body die and are replaced a trillion times every day. Because of the stress the tissue receives, the intestinal epithelium is completely renewed every week. If you could be an epithelial cell in your colon, for one day only, your eating habits are likely to change … I suppose 'smoothies' would literally be everyone's favourite diet. The intestinal system demonstrates biological complexity: in living systems, everything is changing, all the time, across multiple levels of structural organisation (from molecules to organs) and across multiple levels of functional organisation (from molecular reactions to the organ's physiology). Fig. 1 illustrates multilevelness as a key characteristic of biological complexity, using the intestinal system as an example.

There are complex mechanisms in place to avoid any malfunctioning of tissues in the human body and we are making tremendous advances in measuring these molecular processes … and yet devastating diseases like cancers occur. One important scientific quest is to explain the transition of a benign unproblematic excessive cell growth into a malignant tumour. My father was an old man when he died on 30 October in 2011 but why are young people, or even small children dying of diseases, like brain tumours?

I moved to the University of Rostock in 2003, where over the coming years we have developed mathematical models of molecular networks through which cells process information from the outside and in response decide to divide, differentiate or to undergo cell death. For most projects, we focus on a single small network, typically centred around one receptor molecule that receives the signal and a few molecules in the cell that interact and transfer the information to the nucleus where the expression of genes is altered in response to environmental signal the cell received. We now appreciate that that the progression of neoplasms into a malignant tumour and the spread of cancer cells from one tissue into another, is however, a process that involves a heterogeneous population of cells, coordinated across multiple levels of functional and structural organisation. We are therefore facing a new challenge: We accept that we are dealing with non-linear dynamics in cellular systems but we now also realise that

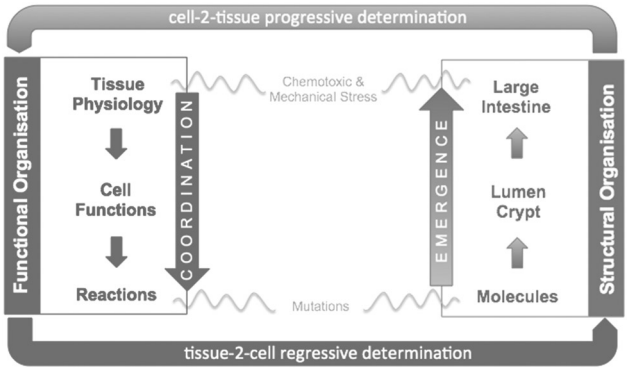

Fig. 1 *Intestinal system as an example for multilevelness*

Key characteristics of biological complexity are non-linear interactions taking place across multiple levels of structural and functional organisation. The function of the organ or tissue (here nutrient absorption) emerges from cellular interactions. The need to repair and maintain the tissue, on the other hand, coordinates the functioning of the stem cells in the intestinal crypt. In this reciprocal and simultaneous determination between tissue and cells, levels are interdependent but not necessarily causally linked. Multilevelness creates a significant practical and conceptual challenge because common reductionist approaches by which we study a whole in terms of its parts, are bound to fail: the whole and its parts determine the functioning of each other and can therefore not be looked at in isolation

existing methods fail to capture the multilevel nature of tissues. Let me explain this. In a tissue, every cell owes its presence to the agency of all the remaining cells, and also exists for the sake of the others. The whole (tissue) and its parts (cells) reciprocally produce each other; determine the functioning of each other. In other words, a tissue is self-organised and because of that, we cannot study subsystems in isolation: To understand tissues as a whole, we need to study the system as a whole.

Biological systems are complex, not only as a consequence of non-linear dynamics, but also as a consequence of multilevelness: the functioning of tissues is determined by interactions taking place across multiple levels of structural and functional organisation. In relation to cancer research, this means that the origins of a cancer may not be exclusively linked to mutations but instead they are a problem of tissue organisation as well. If you believe that mutations matter most, you are likely to buy the latest technology to 'zoom in' on molecular details, but if you consider tissue organisation important, you actually need to 'zoom out'. The current practice is largely determined by a culture of technology-driven reductionism. For decades, molecular biology has been pre-occupied with 'zooming in' on molecular details, when in fact we also require methodologies that help us to 'zoom out', to integrate the information about molecular mechanisms into an understanding of tissue organisation.

5 Next generation complexification

What I argued in relation to the example of the intestine is that the behaviour of cells is largely determined by their function in the system as a whole. As a consequence, the 'microscopes' of experimentalists, allowing us to study single cells and molecular processes, have to be complemented with 'macroscopes' that allow us to integrate our knowledge across multiple levels of structural and functional organisation. The big open question is what these methodologies, enabling cross-level inferences, could look like? Let me tell you about my first explorations into this direction.

Systems theory is the study of organisation, using mathematical modelling to reduce a complex reality into another abstract representation. For systems biology approaches, dynamical systems theory has been the conceptual framework of choice. Molecular interaction maps are interpreted as biochemical reaction networks, with differential equations being the dominant formalism to encode biochemical interactions. The structure of interaction maps encodes feedback mechanisms that, through modelling, help explain biological phenomena in terms of the system's robustness, sensitivity and behaviour. So far, so good.

Encoding mathematical equations by giving them a biological interpretation, linking a semantic to syntax, is at the heart of modelling. The *art* of modelling is to make appropriate assumptions in the process, finding the right balance between parsimony and detail of a model. So far the wisdom.

In trying to convince biologists of modelling, the assumptions required in modelling are frequently swept under the carpet. The focus is usually put on the predictions derived from the model. The 'realism' of the model is implied by making references to (bio)chemical or physical principles, when in fact the biochemical reality of the cell is usually far more complicated than what the equations allow for. If one is honest about the uncertainty and assumptions in constructing a model, it turns out that most models of cellular processes are phenomenological representations. 'Phenomenology' has, however, no good reputation, giving the impression of arbitrariness. To refer to 'a principle of mass action' and suggesting a heritage of these ideas from physics has been a common strategy to assure biologists that the model is 'realistic' … whatever that would really mean. Frankly speaking, we have not been honest enough about the assumptions on which the models rest. A discussion of the semantic frameworks that are used to construct models in biology will be important and valuable and should occur in the coming years. What we can observe is not nature itself, but nature exposed to our method of questioning. Models are never accurate descriptions of nature; they are no more but also no less than, accurate descriptions of our limited ability to understand complex systems [3].

What is actually going on in cells is far too complicated to build models that are realistic in terms of the chemistry and physics of molecular interactions. Therefore, *en route* to multiscale models that connect molecular interactions in cells with tissue-level physiology, we should not only strive for biochemical or biophysical representations but something else, something that is not yet really there. Differential equation models are suitable for the description of causal mechanisms in cells but fail when it comes to cross-level relationships. This is because the relationship between a tissue and its cells is one of 'interdependence not one of 'causal determination': the tissue coordinates the functioning of cells but cells have a degree of autonomy by which they interpret the environment … that they themselves create (Fig. 1). I cannot see how conventional approaches could account for this self-referential whole-part relationship that is underlying the self-organisation or self-fabrication we see in living systems.

What we therefore have to realise is the following: As the complexity of a system increases, our ability to make precise and yet significant statements about its behaviour with conventional methods diminishes until a threshold is reached beyond which precision and significance (or relevance) become almost exclusive characteristics. Because of this, our challenge is now a search for new concepts that can represent causal intralevel processes as well as interlevel relations (constituent interdependence). Seeking an understanding of the behaviour of a system as a whole, we should seek simplicity in complexity. In other words, we require new methodologies that can generalise cellular mechanisms into principles of tissue organisation. I do not know how this is best achieved but from my experience in systems theory, I know that generalisation can be achieved through abstraction.

We have arrived in the year 2011, when this realisation motivated me to engage in discussions with philosophers of science. Philosophers are experts for the slogan that 'there is nothing new under the sun' and because of that they can help you taking a birds-eye perspective. The study of philosophy helped me to put things into perspective: To know what we know about cells is great, but to know what we do not know, is equally important. We should not make things appear simpler than they are. When it is appreciated, complexity can be a great motivation.

Looking across the field of cancer systems biology, we notice that most projects make inferences that go far beyond the given context. For example, it is common practice to

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choose an *in vitro* experimental model to investigate an *in vivo* phenomenon and many projects will choose to focus on either a metabolic network, gene regulatory network or a particular signalling pathway, which is believed to be of relevance to some cell function or higher tissue-level physiological process. The assumption is that even though the evidence is strongly dependent on the experimental context, one would still be able to gain insights beyond that context.

In research publications, the authors present the results, generated within the given and narrow experimental context, in the main part of their paper but in the discussion, they usually speculate how their piece of evidence fits into the larger picture. Review articles play an enormously important role in cancer research because they focus on just that: the integration and generalisation of highly contextual evidence at the cellular level, to explain tissue level phenomena. The articles I found most exciting, present a 'theory' or 'hypothesis'. For example, scanning the literature on epithelial cell renewal, one reads about the 'unitarian hypothesis', the 'single stem cell hypothesis', compared to the 'niche hypothesis', a discussion about the 'hierarchical model' against the stochastic model, the development of a 'tissue field organisation theory' as a response to the prevalent 'somatic mutation theory' and so forth. I believe that the development and discussion of such explanatory models, which requires us to 'zoom out' integrate, generalise and abstract, should receive more attention. What I set out to do over the last couple of years, is to search for a formal framework that can help formulating and validating such explanatory models and inferences. This is probably when I stopped doing what can be done and started with what cannot not be done. However, as my friend Mike Mesarovic told me: 'It is less frustrating not to catch a big fish, than it is not to catch a small fish. So you might as well go for the big questions'.

6 Coming of age

Dynamical systems theory is an ideal tool to support highly focused studies of cellular mechanisms. My search therefore concentrates on a mathematical framework that in a similar way can support the search for principles of tissue organisation. The way I proceed is what modellers typically do: I graphically sketch the system and then translate this diagram into a formal mathematical setting, where I have tools available to explore the model (Fig. 2).

As described above, in the self-fabricating, self-organised epithelial tissue with two cross-level processes going on simultaneously: The tissue with its physiological function, emerging from stem cells and in the other direction, the tissue coordinates the behaviour of stem cells according to the demand for maintenance and repair. The emergence of the tissue and its functioning is a consequence of progressive cell-to-tissue determination, while the coordination of cell behaviour can be referred to as regressive tissue-to-cell determination.

Capturing this in an arrow diagram, the duality between emergence and coordination is realised by reversing the arrows. This observation gives us a hint where to find a suitable mathematical representation. Category theory is making use of such diagrams and the notion of duality is a central element of the theory. If we draw two triangular diagrams, one for cell-to-tissue and the other for tissue-to-cell determination, once the objects of the diagram are defined, the theory will complement the triangle into a commutative square. What we require specifically for our representation of tissue organisation is however not two triangles that complement each other in a square, but two triangles that can be fused in one corner where the state of the tissue and cell-driven changes in the extracellular environment, the tissue field, are related. For tissue-2-cell coordination, the pair of tissue field and tissue state determines cell's internal recognition of the environment, while in case of cell-2-tissue determination the pair determines the cell's intracellular action (Fig. 2).

From 2003, I no longer visited university libraries but conducted my travels through biology and mathematics in the Internet, where I discovered David Ellermann's theory of adjoint functors [4]. While Ellerman's theory and examples have different semantics in mind, I believe that

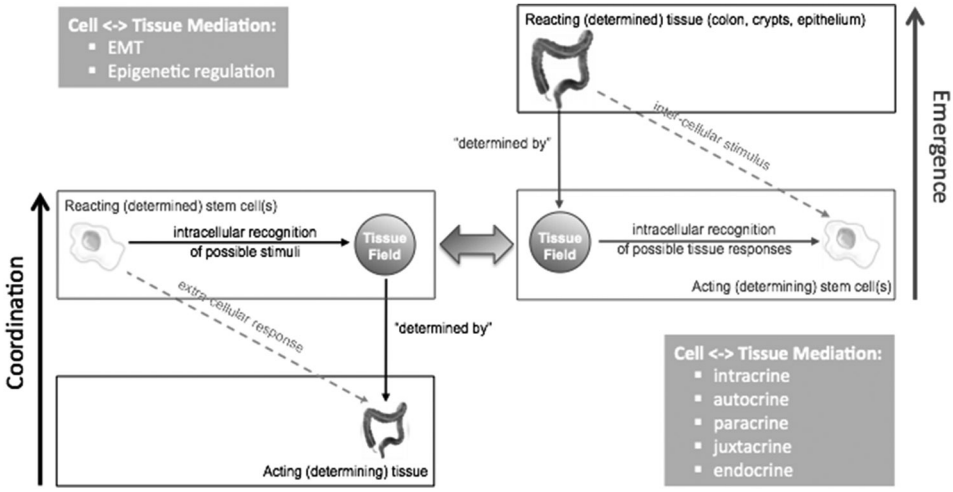

Fig. 2 *Diagrammatic model of tissue organisation*

The cell and tissue levels are interdependent but not necessarily causally linked: molecular reactions, driving the functioning of the cell, are causal intralevel relations, while there are also interlevel relations, or constituent interdependence. The structure of the tissue emerges from the stem cells but the tissue, as a whole, with its physiology also coordinates the functioning of the cells. The cell has however some degree of autonomy; the cell is not simply instructed but interprets its environment. This self-referential process in which cells react to the environment, which they also themselves build, is likely to play a crucial role for understanding of tissue malfunctioning, leading to adenoma-carcinoma tumours. Model above suggests that carcinogenesis is a process akin to organogenesis [5]. A consequence of this view is that to understand cancer we should not try to seek causes in cells but in tissue organisation. This in turn means that we require novel approaches to study multilevel systems.

his theory might be useful to model tissue organisation. However, before I can test my framework, one important ingredient is missing – dynamics.

At this point, another hero of mine enters the scene. Mike Mesarovic is a truly remarkable person and an inspiration. He is not only one of the founders of general systems theory, he is also the author of the second report from the club of Rome, and he was the first person to introduce the idea of systems biology – in 1968, when I was only two years old! He has been ahead of his time in many ways and it was a great honour when in 2004, he invited me to become an adjunct professor at Case Western Reserve University. Although I could appreciate the beauty of his abstract systems descriptions, it took me several years before I realised that his book on *Mathematical General Systems Theory* from 1975 contains a theory that could be applied to the study of tissue organisation.

The theory starts off with the most abstract and hence the most general definition of a system as a set of related objects. What follows in this wonderful book, is a step-by-step narrowing down of context, until we reach those state-space representations we are familiar with from dynamical systems theory. Going now the other direction, from specific towards general representations, the process of abstraction should enable us to generalise from causal mechanisms to law-like principles of tissue organisation. I hope.

Assembling all elements together, I have now come up with a first draft of a category-theoretic representation of a tissue organisation (Fig. 3). This is to provide everyone who is brave enough to take up the challenge, with a conceptual framework in which to formulate hypotheses about tissue organisation. For example, one should now cast questions regarding the progression of a neoplasm into a (adeno) carcinoma in this framework. We have only just begun with this research and I have no idea where this is going to lead us.

In the tissue functor model, theorem proving will be used to validate principles of tissue organisation, similar to how numerical simulations are used to validate molecular and cellular mechanisms. For mechanistic models the emphasis lies more on discussing predictions arising from the model (assuming that the assumptions to create the model were valid). For the tissue functor representation, the focus is on the discussion of assumptions. Once these are accepted, if only in a defined context, then the conclusions of the analysis must be accepted as a logical consequence. The tissue functor model is thus meant to clarify and expose our assumptions and hypotheses and to suggest experiments that could unravel cellular mechanisms that in turn provide evidence for, or against, a postulated tissue organising principle. The underlying assumption of my optimism for the value of this research is the idea that at tissue level there might be simple explanations, despite of the complexity of the underlying cellular mechanisms. The search for organising principles is a search for simplicity in complexity. Yes, I have no idea where this work is going to lead, whether it will turn out to be useful, or not, but this is also why I enjoy being a scientist.

7 From road trips to roadmaps

The representation of tissue organisation, that I just described, is what I am currently working on. Rather being the end of a story, it is a beginning. We have nevertheless now come to the end of the road trip through my life and work. Having experienced blind alleys, beautiful intellectual landscapes and having met wonderful people along the journey, it is time to sum it all up in a roadmap.

I am excited about the things to come; like an explorer, who has now available the equipment to start an expedition into a new world, searching for principles of tissue organisation. This trip will not be easy though. To start with, there are many cellular mechanisms but only a few law-like

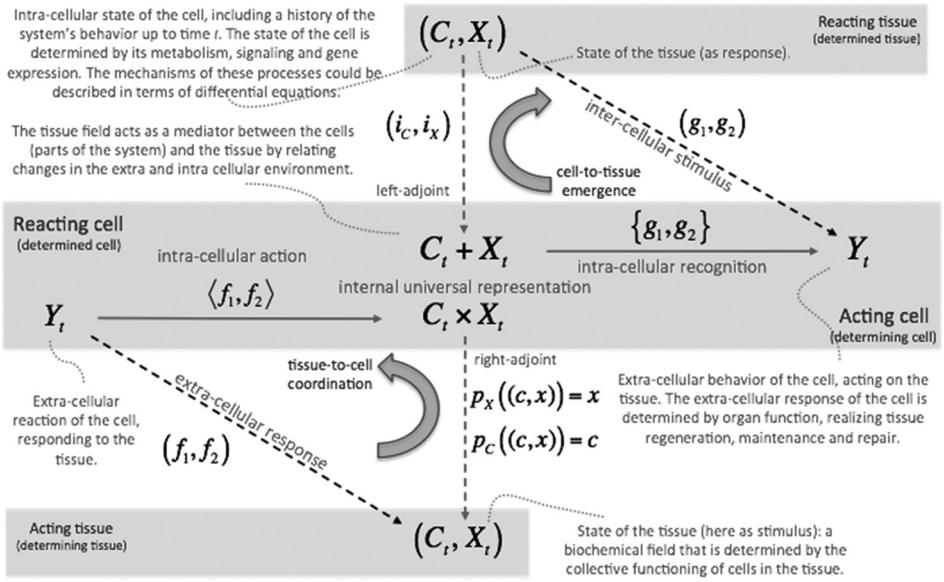

Fig. 3 *Tissue functor model*

Mathematical translation of the conceptual model in Fig. 2, where each element in this diagram has a clearly defined mathematical interpretation, using concepts from Ellerman's theory of adjoint functors as well as Mesarovic's and Takahara's Mathematical General Systems Theory. Intracellular processes, typically modelled using differential equations, are generalised in this representation. While models of intracellular processes would be used to describe and understand mechanisms underlying cell functions, the goal for the tissue functor model is to identify principles of tissue organisation. While numerical simulations, sensitivity and stability analysis are typical tools that one would use to study mechanisms, the search for organising principles relies on theorem proving [6].

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principles to be discovered. Secondly, I cannot do this on my own. I am not a proper mathematician and neither do I have medical training. I have, however, always enjoyed working in interdisciplinary teams and I am therefore looking forward to this joint (ad)venture.

While the illness of my father sparked my interest, I do not study cellular systems because it is useful; I study nature's complexity because it is beautiful. If living systems were not complex, it would not be worth trying to understand them. Following the phone call on the 10 October 1993, it was clear that nothing could be done about the lung emphysema my father had. I accompanied him during the final days, hours and the very moment his body gave up on 30 October 2011. The feeling of helplessness you experience with these diseases is terrible. Like the difficult questions we face in our private life, complex scientific problems, provide a source of uncertainty and frustration. However, there is another perspective I leave you with. This is what I have found: When I was told that nothing could be done about my father's disease, I went into the bookstore. There was indeed nothing that could be done, except studying the problem. By embracing complexity, taking the uncertain route, we can experience great joy and take part in a collaborative effort that will eventually push the limits of what is possible.

All I could hope for during the last 21 years, was to be a contributor of tiny pieces to an enormously large puzzle that is the emergence of diseases from tissue malfunctioning. My dream is now to witness how someone, hopefully someone who reads this, sees a picture emerging from that puzzle to which thousands of scientists contribute every day with their work. Such a picture could sketch a principle of tissue organisation. Our greatest hope for better treatments of diseases, like cancer, therefore lies therefore in a new generation of scientists. This new generation should not only pin their hopes on new technologies. The future of medicine does not lie in a new generation of technologies: If we only pursue a technology-driven agenda, we will eventually recognise, that it is not only a lack of technologies that hinders progress, but more importantly a lack of *ideas* that limits us.

Not only technologies but new ideas, novel methodologies, are thus the future of medical research [7]. To embrace the complexity living systems, requires us to appreciate the value of theory for medical research: What we observe with technologies is not nature itself, but nature exposed to our method of questioning. This is why there is nothing more practical than a good theory! New paths in this direction are created by walking them, so that interesting advances often come about when people are prepared to diverge from established routes. Regardless of what you study, or what your area of expertise is, at some point you should try to use your experience in another context and you may be surprised where this takes you. It therefore also does not matter too much what you do to begin with, what counts is the readiness and curiosity for new routes at a later stage. Twenty-one years ago, I was an engineer with no idea about what lies ahead but what I know now is, that your dreams really can come true. What I discovered over the years is that the complexity of my personal life, the uncertainty and fear you encounter in making decisions about your life and career but also the challenges we face in academic research, can be approached in the same way.

If failure seems inevitable, you might as well fail at something you love, rather than as something you feel you have to do. Whatever you do, failure is no problem, not trying is. For all the complex problems we have to comprehend before we can do something about them, we comprehend them by doing something about them. By embracing complexity and trying the seemingly impossible, you eventually push the limits of the practically possible, in your life and with your work.

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