INTERVIEW WITH PROF. OLAF WOLKENHAUER

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Editorial (Lorenzo Casini)

It is a great pleasure for me to act, once again, as guest editor of an issue of *The Reasoner*. This time I take advantage of this possibility to talk about an emerging discipline to which I have lately turned my attention, viz. systems biology.

Systems biology - I quote an authoritative source of common knowledge, viz. Wikipedia - is

> a term used to describe a number of trends in bioscience research, and a movement which draws on those trends. Proponents describe systems biology as a biology-based inter-disciplinary study field that focuses on complex interactions in biological systems, claiming that it uses a new perspective (holism instead of reduction). (...) An often stated ambition of systems biology is the modeling and discovery of emergent properties, properties of a system whose theoretical description is only possible using techniques which fall under the remit of systems biology.

This is all very intriguing, as it seems that systems biology offers a new, unconventional way to reason about biological systems. Yet, the above characterisation is also rather vague. The identity criterion of the discipline depends - I keep paraphrasing Wikipedia---on one or more of the following features:

- systems biology's own subject matter, viz. complex biological systems and interactions---but hasn't this been the subject matter of biology *simpliciter* all along?

- the peculiar, holistic rather than reductionist paradigm that systems biology advocates---but hadn't this idea already been advocated by the general systems theorists of the 1960s?

- the use of new “operational protocols” for performing research, where hypotheses formulation and laboratory experiments are complemented with mathematical modelling and computation - OK, this is an original element, but there are analogous applications of the same tools to disciplines as diverse as physics (e.g., phase transition phenomena), epidemiology (e.g., pandemic diffusion) and finance (e.g., asset pricing); what's so special about biology?

- the application of dynamical systems theory to molecular biology - again, true, and yet there must be something more to systems biology, since dynamical systems theory has been applied to many other disciplines (see above), so what is special with biology?

- a “socioscientific phenomenon”, having to do with integration of data, interdisciplinary tools and personnel---true, but such a socioscientific phenomenon is nowadays common to all academic research, with fewer and fewer researchers operating in isolation, whether in the sciences or in the humanities, so why erect this fact as distinctive feature of the systems biology community?

Perhaps the truth is a mix of all this. Still, I'm left somehow dissatisfied and with many unanswered questions which make my head spin. What *is* systems biology? What theoretical and practical changes is it responsible for? And what can philosophers do to clarify the conceptual foundations of systems biology, investigate its methodology and the nature of its subject matter? Luckily, I have the chance to ask these questions to a first-class systems biologist, Prof Olaf Wolkenhauer - and perhaps make his head spin as well!? So, here we go, let the interview begin.

Interview with Olaf Wolkenhauer

Olaf Wolkenhauer heads the Department of Systems Biology and Bioinformatics at the University of Rostock, Germany (www.sbi.uni-rostock.de). Among other things, he holds an adjunct position in the Department of Electrical Engineering and Computer Science at Case Western Reserve University, is co-founder of the first international journal for *Systems Biology*, and a fellow of the Stellenbosch Institute for Advanced Study (STIAS).

Lorenzo Casini: Hi Olaf, and thank you for accepting to be interviewed for The Reasoner.

Olaf Wolkenhauer: Thank you!

LC: You have a background in control engineering, you held a position in a department for biomolecular sciences, and you have a variety of interests, ranging from maths to philosophy of science. What, if at all, holds together all these subjects? Perhaps some skill that a good system biologist should possess?

OW: The glue between my interests is *systems theory,* with the goal to provide both a conceptual basis and a working method for the scientific explanation of biological phenomena. A good system biologist should possess a fascination for biology and, above all, (s)he requires persistence. A systems biology approach is an interdisciplinary approach - a collaboration of (at least) two experts from different fields of specialisation. Ideally, the collaborators work, with equal interest, together on *one and the same* research question – where either of them would have small or no chance to succeed separately. This is a crucial point – a blessing and a curse at the same time.

LC: There are plenty of projects out there that claim to apply a systems biology methodology. How would you define systems biology?

OW: My definition of systems biology is pretty much identical to a definition agreed upon by a large number of funding bodies across Europe (cf. www.erasysbio.net). Systems biology aims at understanding the dynamic interactions between components of a living system, between living systems and their interaction with the environment. Biological questions are addressed through integrating experiments in iterative cycles with mathematical modeling, simulation, and theory. A difference is that I consider it an *approach*, not a discipline. Once systems theoretic approaches and mathematical modeling are widely accepted in the life sciences, I would not mind if the notion of "systems biology" disappears.

LC: What is the background and methodology of a system biologist? One could (provocatively) argue that systems biology is more a by-product of developments germane to other disciplines (e.g. dynamical systems theory, evolutionary computation)* as-applied-to *biology, rather than a development of biology proper. To what extent are systems biologists* biologists *rather than applied mathematicians or versatile computer scientists, physicists or engineers?

OW: You are right; to a large extent the current practice is to apply existing mathematical tools in a biological context. I do however believe that this is changing. Mike Mesarović described already in 1968 the situation that still exists: Theoreticians have to take a stronger interest in biological questions and biologists have to start asking questions that are based on systems-theoretic concepts. Once this happens, things will change.

Take for example cancer research, which could provide the stimulus for the development of new theory. Cancer is a process that involves individual cells whose behavior however is largely influenced by their environment. For problems of this kind, covering multiple scales (from cells to tissues) and multiple levels of functioning (from cell division to tissue physiology), we need new conceptual tools. Conventional mechanistic bottom-up modeling and numerical simulations won't take us far. The top level of complex biological systems is not only an emergent property of the lower levels but because there exists causation in both directions, one cannot study some lower-level subsystem in isolation from its environment and higher (spatio-temporal) levels. The theory of multilevel systems that exists needs further development, but what is already there is also not fully appreciated, yet.

Because, in my view, systems biology is not a discipline as such, there is also not really something like a 'systems biologist'. Systems biology is an interdisciplinary approach to answer biological questions. A range of expertise is required, designing experiments, analyzing data, building mathematical models, realizing computer simulations and developing theoretical concepts and computational tools. The common ground is, or should be a biological research problem.

LC: What is systems theory, exactly, and why is it needed in biology?

To me, systems theory is foremost a way of thinking and, rather than obtaining new facts, I consider it more interesting to discover new ways of thinking about them. Technological advances have been a driving force for the life sciences but we ought to realize that many barriers to progress have to do with the way we approach biological questions. Just as we need new devices for better measurements, we also need new methodologies to change the way we think about or understand biological complexity. For example, in my view the process of modeling is as important, if not more important, than a model itself. In modeling we need to identify observables, characterize system variables and speculate about how these could interact or interrelate. The difficulties of this process, and the apparent "failure" of models in this process, are in fact the real basis for a better understanding.

The purpose of a model is therefore not so much to fit the data, but to sharpen our questions. Like a good novel, it is the entire story that matters, not just the ending.

LC: What do you consider the main stumbling blocks for the application of systems theory, or a better understanding of biological systems in general? How do you try to address these difficulties?

Biological complexity is the main hurdle for a better understanding of biological systems and hence the main reason why molecular and cell biology has to change. A living system is complex, not so much due to a large number and variety of components, but because (i) every aspect and component of a living system is subject to constant change and transformation (evolution being the underlying organizing principle); (ii) there are counterintuitive nonlinear relationships between variables interacting in space and time (counterintuitive phenomena that are also limiting the effectiveness of analytical and computational tools); and finally, which brings us to Immanuel Kant, (iii) living systems consist of multiple levels of organization, manifesting both regressive and progressive causality (underlying which is the principle of self-organization). Reciprocal interactions are particularly problematic because of their circular, self-referential character: In living systems, the whole is the product of the parts, but the parts in turn depend upon the whole for their own proper functioning and existence.

For example, 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 and the whole (that is an organ). In a self-organizing system, such as an organ, the whole (tissue) and its parts (cells) reciprocally produce each other; they determine the behavior and functioning of each other. This provides a challenge not only for experimentalists but also for modelers, who quickly find Dynamical Systems Theory being rather limited when it comes to nonlinear, spatial processes to describe multiscale systems.

I am looking into Mathematical General Systems Theory, developed by Mesarović and Takahara in the 1970s, to provide both a conceptual basis and a working method for the study of multilevel systems. My goal is to identify cross-level relationships and ultimately organizing principles (which to me are the biological equivalents to a laws of physics). This is may appear more abstract to begin with, but I am convinced that at the end there is nothing more practical than a good theory.

LC: You collaborate, among other people, with Mihajlo Mesarović, who contributed to the development of systems theory. What does systems biology inherit from him?

OW: I am very lucky to have worked with Mike. Right now we are in frequent Email contact, discussing the role of theorems in the search for organizing principles in biology. He wrote in 1968 (!) an article entitled “Systems Theory and Biology” which not only referred to the notion of “systems biology” for the first time, but also contains a number of observations and recommendations that remain true to this day! He was and is right that we need to think beyond pathway-centric, mechanistic, quantitative modeling and dynamical systems theory.

Together with Yasuhiko Takahara, he has produced the most comprehensive formal theory of systems. The success of differential equations in the physical and engineering sciences has meant that people consider such state-space approaches “the” way to model reality, when in fact this is only a special case of more general time systems. Reading their 1972 book in which they formulate their mathematical theory of general systems, I was shocked to find out that the notion of a state-space is only a secondary concept that derives from a much more general formulation. The principle limitation of conventional mechanistic modeling and numerical simulations within dynamical systems theory is that as the complexity of a system increases, our ability to make precise and yet general statements diminishes. This is particularly apparent in the current efforts in multiscale modeling. As an engineer, I was myself so firmly stuck in conventional dynamical systems theory, that for a long time I did not fully appreciate Mesarović’s call for a different, non-numerical language of complexity.

Mike wrote, in 1968, “In spite of the considerable interest and efforts, the application of systems theory in biology has not quite lived up to expectations.” We should worry whether this could not apply to systems biology in 2020 as well. The need to rethink biological complexity is obvious, to this day. This includes the fact that theory and applications are intimately related and none can make significant progress without the other.

LC: Among your sources of inspiration is also Robert Rosen. His idea that living systems are self-referential and closed to efficient causation as well as his `proof' that living systems must have non-computable models have been quoted and discussed. Still, there seems to be more to Rosen's intuitions than we have so far appreciated. What have you inherited from him?

OW: I am fond of Rosen's critique that biological systems are simply a special case of physical systems. He has developed various ideas to demonstrate the complexity of biological systems and what make them special. Similar to Mesarović's work, I think Rosen's ideas deserve more attention. The big difference between the two is, however, that Mesarović has developed a comprehensive mathematical framework that enables a step-by-step analysis, while it is more difficult to follow some of Rosen's arguments using mathematics. I subsequently gave up trying to understand "what Rosen really meant".

Mike Mesarović demonstrated the constructive origin of a state space by developing a more general framework in which state-based models are only a special case. Rosen also realized the limitations that arise if one assumes a state-space (e.g. smooth manifolds), *a priori*. He suggested an alternative relational approach, in which there is some set of abstract states. The starting point for modeling is then a representation of the measurement process through observables. The state space is replaced by a set of mappings: instead of starting with a smooth manifold and then defining an algebra, one starts with an algebra of maps. Relational biology in the sense of Rosen thus describes entailment without states. In other words, rather than making assumptions about what the system under study is, in itself, one starts with a description of what can observe.

Rosen also demonstrated that closure to efficient causation is a defining characteristic of living systems and showed how the complexity of self-organizing or self-referential systems challenges us. Rather than trying to sell nature as being simpler than it is, promising unrealistic progress, I believe we should embrace biological complexity, accept it and find a language to describe it. Biological complexity is the source of the variety and beauty we find in nature. This should motivate us to invest more time and effort in understanding understanding.

LC: Certain philosophers complain that the special sciences lack proper laws-Mendel's laws perhaps being a notable exception. It looks to me that systems biologists aim to abstract robust generalisations, if not laws, from phenomena. Do you believe that systems biology will ever lead to the formulation of laws whose scope and strength are analogous to the laws of physics?

OW: Yes, I am convinced that we will be able to formulate these "abstract robust generalizations" or 'organizing principles' as I prefer to call them. Organizing principles provide a deeper understanding of the behavior of a system – why it behaves the way it does in reality, independent from a particular manifestation of the system in the real world.

One problem is that we do not really look for organizing principles. We are so preoccupied with and drowning in molecular details that we miss the wood for the trees. The beauty of organizing principles is that if you're familiar with a principle you don't have to be familiar with all of its applications. This, however, requires methodologies to study categories of systems rather than particular exemplifications.

The search for organizing principles requires approaches different to what we have today – more abstract ones. In systems biology, we would have to break out of the current pathway-centric framework and mechanistic modeling that dominates systems biology to this day. The role of theorem proving is an example. Theorems play an important role in conventional systems theory (e.g. in stability analysis) but only “behind the scenes”. For the formulation of organizing principles, however, we need non-numerical approaches, like theorem proving to become accepted as a scientific explanation in the life sciences.

Finding organizing principles is an order of magnitude more challenging than mechanistic modeling because they are rare and more difficult to justify. But as Mike Mesarović once told me, “It is less frustrating not to catch a big fish than it is not to catch a small fish. We might as well ask the big questions.”

LC: The nature of the projects that nowadays aim to pass as systems biology is rather heterogeneous. This can clearly affect the public's perception of this new field of research. How would you warn against the confusion engendered by the ubiquitous reference to systems biology in all these projects?

OW: I am not sure what the public’s perception of the field is but I worry that even in the (life) sciences the understanding of why we need systems biology is equally as poor as it may be in the public. A key point is that a systems approach, using systems theory to give an explanation of biological phenomena, is first of all a different way of thinking about the organization and behavior of biological systems. It is for this reason that the impact of systems biology approaches is also more difficult to measure. With new buzzwords coming and going, I am indeed worried that the need for a change in the way we tackle biological complexity is not sufficiently appreciated.

Not only do we have to convince the biological community to accept systems-theoretic explanations, we also have to convince the modelers that systems theory is not restricted to mechanistic modeling and dynamical systems theory. There is thus lots of scope to change the way people think about their research problems.

It is disappointing to see researchers relabeling their work as systems biology, without changing anything in how they work.

LC: People tend to have an idealised picture of science as a fast and reliable results-generating enterprise, and ignore that good quality research can be slow, and need not necessarily involve large-scale and expensive projects. What do you regard as exemplars of the accomplishments of interdisciplinary research and what lesson should science policy makers draw from such exemplars?

OW: To do mathematical modeling at the life sciences interface is to engage in an act of discovery and conjecture, intuition and inspiration. However, to paraphrase Winston Churchill, in systems biology, success is going from failure to failure without loss of enthusiasm. Discovery (of truly exciting results) is hard to accomplish and failure is frequent.

Surely, good research can come from small projects and the development of mathematical tools is certainly inexpensive compared to experimental research. Still, I would disagree with you. Achieving progress, say in understanding the cellular origins of a disease, requires the collaboration of many specialists from a range of disciplines spread across several locations. I don’t think the life sciences can offer much in terms of success stories here.

The life sciences are a long way off from what physics achieved in terms of large-scale projects. The Large Hadron Collider (LHC) required decades of work, involves a very large number of scientists and institutes and cost billions. Compare this effort and investment to figure out whether the Higgs boson exists with the question of how cancer develops in a human body. The fact is that the largest possible project for cancer research in Europe will provide you with about 12 million Euros, for about three to five years … . When they tried to launch the LHC, it broke down, the repair costing about 16 million Euros, more than what you can get to generate a breakthrough in treating some disease. Is there anyone who would argue that cancer is a simpler problem than the Higgs boson? Physicists have developed a culture in which large teams collaborate on a joint project. They don't do this because it is more fun than lonely brooding over a problem in the office, but because they won't be able to solve the problem otherwise. Pick a disease and you will find a need for similar efforts. The fact is, however, that there is neither the funding for such large scale efforts, nor is there any long term strategy to realize a truly comprehensive project to address any disease. The truth is that in collaborative life science projects most experimentalists do not dare to make themselves too dependent on other labs – the risk of failure (in terms of receiving further funding and generating publications) is considered too high.

A massive change in research culture is required to make real progress. Policy makers need to steer this process, otherwise necessary changes will not happen. Interdisciplinary research requires an extra effort on behalf of all sides, including strategic consideration for targeted research programmes and support for the initiation of cross-disciplinary collaborations.

LC: On a different note, what do Kant or Schopenhauer have to do with systems biology? I'm intrigued by the reasons that drive a* scientist *towards philosophy. At what stage of their professional growth and for what reason do working scientists like you feel the need to interrogate philosophy to understand science, that is, their own domain of expertise? What kind of answer, if at all, can they find in philosophy?

OW: For a start, I am grateful to Schopenhauer for pointing out that there exist explanations; that knowledge based on reason is possible and that science therefore does make sense. We can establish truth, in the world of experience – hurray! His *principle of sufficient reason* is naturally the basis for the sanity and salary of scientists.

If you agree that what we can observe is not nature itself, but nature exposed to our method of questioning, then it makes sense not only to build models but to try to understand how we do this.

My interest in the philosophy of science and epistemology stems from the fact that scientific explanation in biology is hampered by complexity and uncertainty. Despite the immense technological advances, we are still very limited to what we can measure and what we can handle mathematically, say, in the theory of nonlinear dynamical systems. There are thus practical, if not in-principle, limitations to what we can know. What we observe in biological experiments is not nature itself, but nature exposed to our method of questioning. *Data do not speak for themselves*, and it is not possible to conduct experiments without any implicit hypothesis or preconceived idea. For this reason it is worthwhile thinking about the way we think, perceive data, conceive ideas, understand and generate knowledge. Philosophers can help us with this.

LC: Why your interest in Schopenhauer in particular, and how do these ideas relate to systems theory, maybe Mesarovic and Rosen as well?

The common ground for my interest in Schopenhauer, Mesarovic and Rosen is their ‘relational perspective’. The aim of systems biology is not things (molecules, cells etc.) in themselves but the interactions and inter*relations* between things. For example, life is a relationship among molecules and not a property of any molecule (Linus Pauling) - there are living systems, there is no living matter (Jacob Monod). A consequence of this view is to give objects and relations between objects the same identical ontological status.

For living systems, the most interesting relations are whole-part relationships. In living systems, the properties and behavior of every part of a system are largely determined by their function in the system as a whole. In a natural system this goes under the notion of ‘self-organization’ and when described formally, leads us to self-referential systems in mathematics. Biology, mathematics and philosophy meet at this point.

Schopenhauer’s *principium individuationis* tells us that in the world of experience any object always and everywhere exists purely by virtue of another object. Schopenhauer distinguishes different principles of explanation, related to the class of objects one is dealing with. The definition that a system is (or reflects the existence of) a relationship between objects follows naturally. Mesarović starts with such a general definition, but considered as a formal relation on families of sets. A complex system is then a relation on systems. My interest in mathematics is thus its very definition as a study of sets and relationships, including transformations between sets and their elements.

For Schopenhauer causation is the *principle of explanation of change*; it is a relationship, not between things, but between changes of states of things … does this not fit perfectly with a systems-theoretic approach?

According to Schopenhauer understanding, through inference, is the subjective correlate of matter or causal entailment (which he considers one and the same). Understanding causal relationships is then the sole function of the understanding and its only power. Conversely, all causality and consequently the whole of reality, is only for the understanding, through the understanding, in the understanding. In systems theory understanding arises from transforming, abstracting one reality into another – through modeling. For complexity, then, it is simplicity that is most interesting. With regard to modeling, simplicity is therefore ultimate perfection.

LC: Thank you for answering my philosophical questions, Olaf. And thank you for practicing philosophical reflection yourself, which has made this interview all the more interesting and my job a lot easier!

OW: Thank you. I hope my answers clarify my interest in philosophical questions and why a philosophy of systems biology actually could benefit from such discourse. I would urge philosophers of science not to wait until we have died, to only then analyze the work done and where we got it wrong.