

ESF WORKSHOP ON PHILOSOPHY OF SYSTEMS BIOLOGY

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ABSTRACTS

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William BECHTEL: *From Molecules to Environments: Chronobiology as Integrative Pursuit*

Across the life sciences researchers working on closely related phenomena (if not the same phenomenon) are often segregated into different fields or disciplines, publish in different journals and attend different conferences, and may be either unaware or incapable of relating to each other's work. Chronobiology, and especially the study of circadian rhythms, is a clear exception. Researchers from molecular biology to behavioral biology and psychology, from basic science departments to clinical specialties, are professionally engaged with each other and make productive connections to each other's work. In part this is due to historical and sociological factors; chronobiology is a small field initiated by a handful of prominent pioneer investigators. My contention, though, is that this integration is maintained by the fact that the researchers working on various aspects of circadian rhythms all connect in relevant ways to the project of understanding clock mechanisms. The idea of mechanism is often associated with reductionism, which is misunderstood as entailing that higher-level inquiries, such as studying behavior, is just in the service of testing lower-level explanatory accounts and that clinical studies are just applications of these lower-level accounts. Correctly understood, however, mechanistic explanations embrace both reductionism and systems approaches. A powerful strategy for understanding a mechanism is to decompose it into its parts and operations. But these parts and operations only produce the phenomenon of interest when they are organized and their behavior appropriately orchestrated. This requires mechanistic researchers also to recompose mechanisms both conceptually in diagrams and, increasingly, in computational models. As a whole, a mechanism interacts with its environment, which may itself exhibit the systemic organization of a mechanism. These higher-level relations between a mechanism and its environment are parts of the explanation of the mechanism's behavior, not just consequences of it. As I will illustrate, accounts of

circadian phenomena are multi-level, relating intracellular molecular components, intercellular and inter-organ coordination within an organism, and behaviors within social organizations on a planet that has a particular day-night cycle.

Manfred DRACK: *Advents of Systems Biology – Elements of Early Biological System Approaches*

System approaches in biology have a long history and there are many precursors of systems biology. The focus in this talk will be on the thinking of Paul A. Weiss and Ludwig von Bertalanffy. Some important aspects or elements of their contributions towards making the system concept operable in biology will be discussed. To them, considering whole living systems, which includes their organisation, is equally important as the dynamics within systems and the interplay between different levels from molecules over cells to organisms. Facts from developmental biology have been an important impulse to develop an organismic biology. Compared with today's systems biology, which is often a bottom-up approach from molecular dynamics to cellular behaviour, the early thinkers had a different agenda. For them, it was also important to consider the influences of the whole on the parts and the organisation of the parts to make the whole perform properly. Bringing together the early heuristics with recent formalisms and novel experimental set-ups can lead to fruitful results and understanding. This talk is based on an article by Drack and Wolkenhauer.

Melinda FAGAN: *Experimenting communities in stem cell biology: exemplars and interdisciplinarity*

This paper examines how 'experimenting communities' produce reliable knowledge about stem cells. Knowledge-producing practices in stem cell research are organized around exemplary methods, which furnish standards for a broader constellation of experiments. Comparisons within such a network establish robust results. Reliable knowledge about stem cells thus depends on both exemplary standards and robustness across a range of experimental systems. This paper focuses on three exemplary methods from different periods of stem cell research: (1) the spleen colony assay (1960s), (2) creation of embryonic stem cell lines (1980s), and (3) single-cell gene expression studies (2000s). Each method depends on interdisciplinary collaboration, for establishment as a source of reliable data and as a standard for a broader network of experimental systems. Interdisciplinarity is thus at the core of experimental methods in stem cell research. Some consequences of this social epistemic organization, relevant to science policy and clinical translation, are also discussed.

Gabriele GRAMELSBERGER: *The Simulation Approach in Biology*

Cell biology is a scientific discipline, which is widely based on wet lab experiments and 'thing knowledge'. But during the past years computer based simulations have extensively entered the scene. Most important, they have influenced the experimental style of cell biology by introducing a more process orientated knowledge into biology. For instance, experiments have turned from start/end experiments into time resolved experiments. The reason therefore is to gain increasing knowledge about time based processes and developments, which are required for running and evaluating computer based simulations. The paper will explore the 'process knowledge' in biology, which increasingly allows merging simulation and experimentation. Furthermore, it will argue that-introducing a process resp. simulation approach-introduces the 'engineering paradigm' into biology. As the term 'engineering' is often interlinked with practices and 'thing knowledge', the paper will instead discuss Gaston Bachelard's theory-orientated concept of 'technical realism' in order to show that the process resp. simulation approach interfere even in the run-up of wet lab experiments, turning cell biology necessarily into synthetic biology.

Sara GREEN: *Models and Embodiment*

In recent years there has been an increasing interest in how we learn with and from models. This paper is a short presentation of a part of my PhD project that focuses on how new epistemic entities can be established in science through an oscillation between different experimental setups or models. Different models are used to achieve different epistemic goals. While some models open new research fields and may take the role as research attractors through an embodiment of questions, other models are more stabilized and serve as vehicles for generating answers about other research objects. Likewise, while some models provide the empirical import to an explanation, other models can create explanatory connections or open up new possibilities of functions and mechanisms in a role as idealized fictions. I will draw on a case study within systems biology to exemplify how models can come together to create and stabilize new epistemic entities.

Michael JOFFE: *Causal links, chains, networks and cycles in biology*

This paper sets out to explore the various meanings of causal system in biology, and how they relate to one another. “System” here indicates the different ways in which causal relationships can combine, for example in chains, webs/networks and cycles/loops. In doing this, it also hopes to shed light on the topic of emergence. The discussion focuses on four major branches of biology, including both “organised” and “non-organised” systems, but excluding animal behaviour.

Biologists have a clear implicit concept of causation. It embraces both mechanism and difference-making, and can be expressed as “a causal relationship is one that has a mechanism that by its operation makes a difference”. Biological processes involve a mechanism and an input; in some cases the mechanism transforms the input, in others the input damages the mechanism. With different processes, either the input or the mechanism may be seen as “the cause”.

Chains consist of flow diagrams or causal influence chains. They have some general properties: rate-limiting steps in the former and possible non-transmissibility in the latter. Webs/networks differ from chains by their branching property: multiple consequences and/or inputs. The latter involves multiple causation, each input being a tendency, which can be analysed statistically. Inputs can be additive or involve effect modification, a concept that requires more work; it can be approached from the mechanistic or the difference-making viewpoint.

Cycles/loops can involve feedback, either balancing (negative) or reinforcing (positive) – concepts with a long history in biology. Evolved systems mainly have balancing feedback. Systems with feedback tend to have characteristic endogenous causal processes, and emergent properties. Systems Biology seeks an understanding of emergence, to explain phenomena where the traditional reductionist approach is inadequate, by integrating disparate technologies/methods. It focuses on causal interactions, as well as feedback. Life itself can be seen as a series of self-perpetuating cycles.

Tarja KNUUTTILA & Andrea LOETTIGERS: *Varieties of Noise: Analogical Reasoning in Synthetic Biology*

In philosophical discussion models have typically been located between theories and experiments. Although the relationship between models and theories may seem closer than the one between models and experiments, there is a growing body of literature that focuses on the similarities and differences between modeling and experimentation (e.g. Morgan 2002, Mäki 2005, Lenhard 2007, Winsberg 2009, Parker 2009, Barberousse et al. 2009, Peschard forthcoming). The issue of materiality has gained a central position in this discussion: the question has been whether the kind of material used, the different or the “same stuff” (Morgan 2003), licenses us to distinguish models from experiments. In our presentation we study the various standpoints taken in this discussion through the practice of synthetic modeling. Synthetic

models amalgamate features of both model organisms and theoretical models: On the one hand they are constructed from the “same stuff”, i.e. from biological material such as genes and proteins, as their real target systems. On the other hand mathematical models are used as blueprints for their construction. We will study in particular a synthetic model called the Repressilator (Elowitz and Leibler 2000) and its place in the modeling practice of synthetic biology. We will argue that the respective constraints of the modeling approach and the experimental approach gave rise synthetic models such as the Repressilator. We will also discuss the epistemic role the “same” materiality plays in synthetic modeling.

Ulrich KROHS: *Convenience Experimentation*

Systems biology aims at explaining life processes by means of detailed models of molecular networks, mainly on the whole-cell scale. The whole cell perspective distinguishes the new field of systems biology from earlier approaches within molecular cell biology. The shift was made possible by the high throughput methods that were developed for gathering ‘omic’ (genomic, proteomic, etc.) data. These new techniques are made commercially available as semi-automatic analytic equipment, ready-made analytic kits and probe arrays. There is a whole industry of supplies for what may be called *convenience experimentation*. My paper inquires some epistemic consequences of strong reliance on convenience experimentation in systems biology. In times when experimentation was automated to a lesser degree, modeling and in part even experimentation could be understood fairly well as either being driven by hypotheses, and thus proceed by the testing of hypothesis, or as being performed in an exploratory mode, intended to sharpen concepts or initially vague phenomena. In systems biology, the situation is dramatically different. Data collection became so easy (though not cheap) that experimentation is, to a high degree, driven by convenience equipment, and model building is driven by the vast amount of data that is produced by convenience experimentation. This results in a shift in the mode of science. The paper shows that convenience driven science is not primarily hypothesis-testing, nor is it in an exploratory mode. It rather proceeds in a gathering mode. This shift demands another shift in the mode of evaluation, which now becomes an exploratory endeavor, in response to the superabundance of gathered data.

Marco NATHAN: *Causal interactions in complex biological systems*

The goal of this talk is to investigate the nature of causal interactions in complex biological systems. More specifically, in the first part of the talk, I introduce the concept of causation by concentration, a particular form of causation—widespread in biology and, more generally, in science—where an effect is triggered by a concentration of entities. By focusing on the causal role played by concentrations, I argue against the claim that all causal relations in a system can be reduced to actual physical interactions between components of the system; robust causal explanations must also encompass potential ‘redundant’ causes. In the second part of the talk, I discuss some applications of causation by concentration to more complex biological systems (both at the micro- and macro-level), which require further refinements. I conclude by pointing out some general implications for systems biology. In particular, I emphasize that the presence and importance of these irreducible causal relations does not entail a radical emergentist approach, according to which the behavior of the system as a whole cannot be reduced to the behavior of its component parts.

Nancy J. NERSESIAN: *Models of Interdisciplinarity in Systems Biology*

Although there is a tendency, especially among policy makers, to treat interdisciplinarity as all fitting into one box, investigations in science studies have shown the need to understand interdisciplinarity in a more nuanced way. Our research on interdisciplinarity in the bio-engineering sciences had led us to consider three main varieties: multidiscipline, interdiscipline, transdiscipline. In this presentation I will discuss our on-going 4-year ethnographic (this study involves collecting and analyzing observational, interview, and

historical data) research study into two laboratories in the emerging transdisciplinary field of integrative systems biology. The aspiration of this field, as recounted by our respondents, is to create emergent "trans" space that is created by this research and allows for multiple kinds of adaptations and agents. One lab does only computational modeling in collaboration with bio-scientists in academia and industry; the other does both modeling and the experimentation. Both labs are largely populated by graduate students with engineering backgrounds. The directors of these labs have quite different perspectives on how training should proceed for researchers in this field. In the talk I will focus on how researchers position themselves and other given their developing identification with specific epistemic values.

Gry OFTEDAL & Anders STRAND: *Causality in Biological Systems*

Investigations of causal relations in biological systems provide interesting input to the philosophy of causation. Likewise, a philosophical understanding of causation in complex systems is relevant for scientific inquiry in systems biology and other biological research areas. We use the phenomena of genetic redundancy and distributed robustness in biological systems, as revealed in gene knockout and gene knockdown experiments, as an entry into discussing how a counterfactual approach to causation may handle complex biological cases. In many experiments, when a gene is knocked out or down, there is not a detrimental effect on the functionality of the system, as the system is robust in the sense that other genes or a systemic change compensate for the dysfunctional gene. In such cases there seems to be no counterfactual dependence between the knocked out gene and the phenotype in question, although we would want to argue that this gene is causally relevant. We suggest that cases of robustness can be understood using a counterfactual approach by way of decreasing or increasing the resolution of the relevant causal representation. When decreasing the resolution of our causal model we represent as cause a higher-level variable or entity such as a gene cluster or an organism, and relevant counterfactual dependencies might obtain at this level. By increasing the resolution one might be able to represent causal pathways involving stepwise causal dependence under different counterfactual scenarios, and thereby establish causal relevance in the absence of direct counterfactual dependence.

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Matti SINTONEN: *Advents of Systems Biology – Elements of Early Biological System Approaches*

Systems biology still is in the process of becoming. With roots in molecular biology and genomics, it employs researchers with widely varying disciplinary backgrounds.

This paper deals with the disciplinary profile of systems biology. Starting with an account of what a discipline is I shall ask, following Renaissance logician Giacomo Zabarella, if its research object, *res considerata*, research method, *res considerandi*, research goals or aims, *finis*, are distinct enough justify calling it a discipline. An interim conclusion at least is that the *res considerata* of synthetic biology, entire living organisms and their functional properties and behaviour, is not unique to the study fields (or discipline, if it is one). However, its *res considerandi*, the holistic methodological approach and way of studying how systems level properties arise from the interaction of its parts does speak in favour of a distinct research profile. I shall employ what I call the interrogative approach to illustrate how the very questions of systems biology differ from those of molecular biology. The attractions of the approach can be appreciated through a previous example. Ernst Mayr has argued that a seemingly innocent explanation-seeking why-question, say, "Why does organism O exhibit a pattern of behaviour B" takes different kinds of answers in evolutionary and functional biology. In the same way, systems biological examples demonstrate that there is a divide within functional biology, since its questions seem to lead to different kinds of patterns of explanation than those in molecular biology.

I shall use this interrogative approach also to illustrate how the *finis*, the goals or aims of systems biology, support of unique disciplinary profile. One aspect of this is that it is both basic and applied inquiry – and

that in fact it is hard to separate the two aspects since they are so closely intertwined in actual research. The profile of systems biology is more complicated still if it is seen as the crucial step towards synthetic biology since, from this perspective, technology in its many guises is in the picture from the start. The interrogative approach also throws light on one of the most salient (and somewhat paradoxical) features of systems biology, viz., interdisciplinarity. Systems biology is an interdisciplinary (and integrative) discipline.

Olaf WOLKENHAUER: *The Epistemology of Systems Approaches in the Life Sciences*

Systems biology is an approach by which biological questions are addressed through theory and iterative cycles of *data-driven modelling* and *model-driven experimentation*. The two central questions of systems biology are: (i) How do the components within a cell interact, so as to bring about its structure and realise its functioning? (ii) How do cells interact, so as to develop and maintain higher levels of structural and functional organisation (e.g. tissue)? To this day, most models in systems biology are *mechanistic models*, describing (sub)cellular reaction networks. These models are developed within Dynamical Systems Theory (DST). In DST, *causation is the principle of explanation of change*; a relation, not between things, but between changes of states of things. The prevalent practice in systems biology is *pathway-centric*, that is, a “bottom-up” approach that starts from experimental data at the molecular and cell level, followed by inferences about the consequences processes at the molecular level have at higher-levels of organization (e.g. the tissue or organ level). The pre-occupation with molecular details lets us forget that the ultimate goal is to identify fundamental laws of (human) biology! We therefore offer a new perspective using Mathematical General Systems Theory (MGST). We believe that MGST has the potential to successfully shift the focus of research - from the molecular/cell level to the tissue level, from network models to multilevel systems, from studying mechanisms to identifying organizing principles. We explain the value, rationale of abstraction and provide an overview of routes in the search for organizing principles. We show that modeling and theorem proving are distinct while playing mutually supporting roles in understanding cellular phenomena.