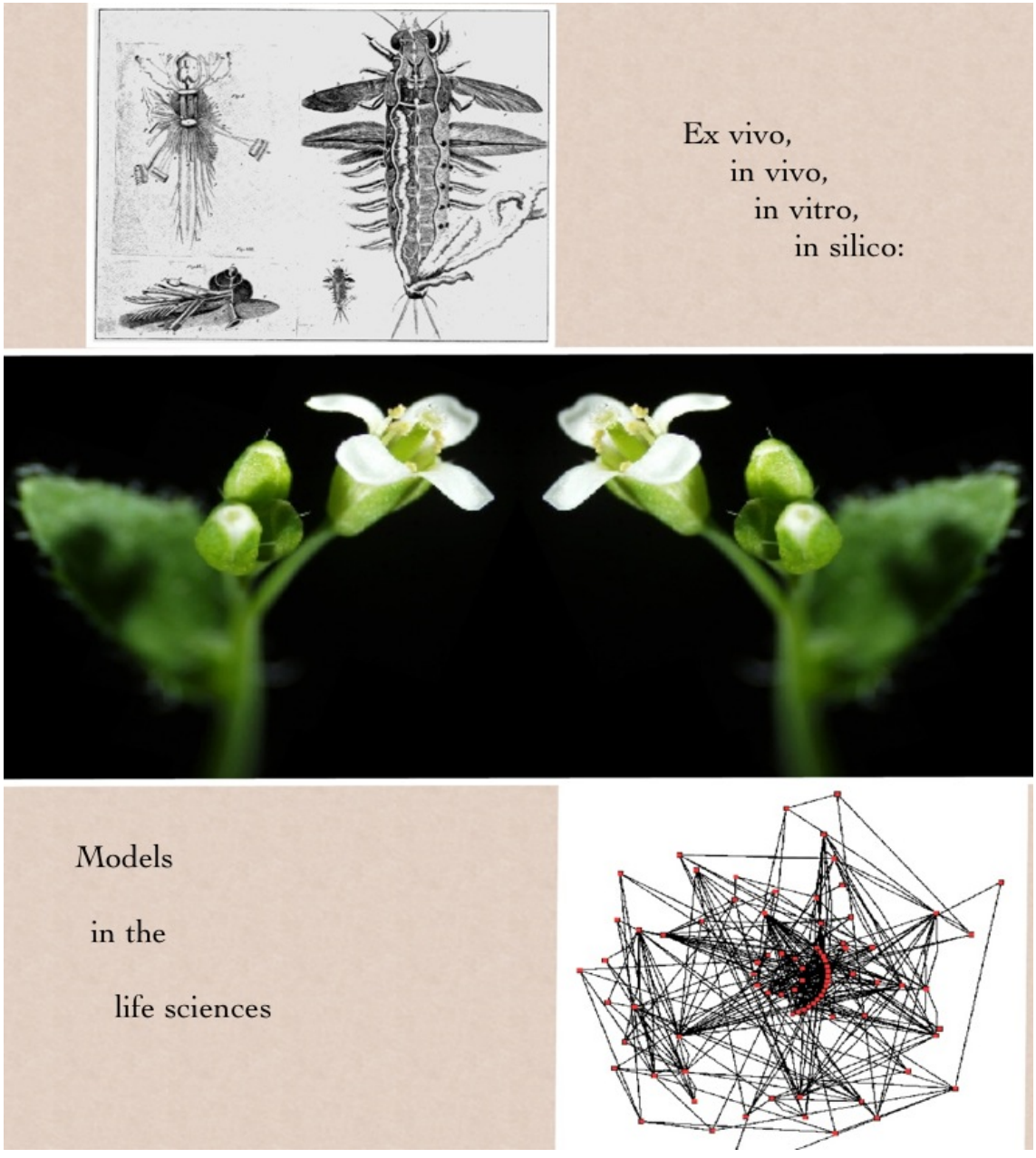
Second European Advanced Seminar in the Philosophy of the Life Sciences



PROGRAM and ABSTRACTS

Hosted by the Brocher Foundation

Hermance (Geneva), Switzerland, September 10-14, 2012

Monday, September 10

11:00 Welcome reception: *Presentation of the EASPLS*

12:00 Lunch

14:00 **Marcel WEBER** (Geneva)

Experimental Modelling: Exemplification and Representation as Theorizing Strategies.

Nina ATANASOVA (Cincinnati), *Comment – Discussion*

15:00 **Jean GAYON** (Paris)

Model Organisms in Biology and Medicine.

Tarquin HOLMES (Exeter), *Comment – Discussion*

16:00 Break

16:15 **Alessandro MINELLI** (Padua)

Model Organisms in Evo-Devo. Promises and Pitfalls of the Comparative Approach.

Jan BAEDKE (Bochum), *Comment – Discussion*

Tuesday, September 11

09:00 **Josephine DONAGHY** (Exeter)

Models and Theory in Metabolic Control Analysis.

Andrea ESANU (Bucharest)

Modeling Open-ended Evolution.

Sebastien DUTREUIL (Paris)

How/Why Should One Model the Organisms/Environment Interactions?

10:30 Break

11:00 **Marie KAISER** (Geneva), *Comment – Discussion*

12:00 Lunch

14:00 **Giovanni BONIOLO** (Milan)

Modeling Molecular Biology Complexity.

Dan NICHOLSON (Vienna), *Comment – Discussion*

15:00 **Philippe HUNEMAN** (Paris)

Computer Simulations in Evolutionary Theory.

Fridolin GROSS (Milan), *Comment – Discussion*

16:00 Break

16:15 **Silvia DE MONTE** (Paris)

Differential Attachment and the Evolution of Social Groups.

Maximilian HUBER (Geneva), *Comment – Discussion*

Wednesday, September 12

09:00 **Rebecca MERTENS** (Bielefeld)

Flexible Tools: The Lock and Key Model Across Biochemical Boundaries.

Tudor BAETU (Vienna)

Quantitative Mechanistic Explanations.

Ann-Sophie BARWICH (Exeter)

Making Sense of Smell: Models in Olfaction Theory.

10:00 **Pierre-Olivier MÉTHOT** (Geneva), *Comment – Discussion*

10:30 Break

11:00 **Adam TOON** (Bielefeld)

Molecular Models in Vitro and in Historico.

Guillaume SCHLAEPFER (Geneva), *Comment – Discussion*

12:00 Lunch

14:00 **Daniel BROOKS** (Bielefeld)

Problem Agendas in Neuroscience.

Arnon LEVY (Jarusalem)

Model Organisms Aren't Models.

15:00 **Pierre-Alain BRAILLARD** (Paris), *Comment – Discussion*

15 :30 Break

16 :00 **Michael DIETRICH** (Dartmouth)

Model Choice and Method Selection in Molecular Evolution.

Jean HARRINGTON (Exeter), *Comment – Discussion*

Thursday, September 13

09:00 **Amir TEICHER** (Tel-Aviv)

"In Stemma": Mendel's Model and Human Heredity in Germany, 1900-1933.

Cecilia NARDINI (Milan)

Generalizing Randomized Control Trials.

Pierre-Luc GERMAIN (Milan)

Disease Models Between Replica and Instruments.

10:30 Break

11:00 **Thomas REYDON** (Hannover), *Comment – Discussion*

12:00 Lunch

14:00 **Sabina LEONELLI** (Exeter)

Model Organisms in Vivo and in Silico: Data, Speciments and Models.

Gladys KOSTYRKA (Paris), *Comment – Discussion*

15:00 **Werner CALLEBAUT** (Vienna)

Multiscale Modeling.

Stephan KOPSIEKER (Bielefeld), *Comment – Discussion*

Friday, September 14

10:00 Closing Lecture

Bruno STRASSER (Geneva)

The End of Model Organism?.

11:30 Closing discussion

12:30 Lunch

ABSTRACTS

Marcel WEBER (Geneva)

Experimental Modelling: Exemplification and Representation as Theorizing Strategies.

Abstract models have been at the center of the philosophy of science for several decades now. Their epistemic function is widely thought to provide representations of the world, representations, which may reflect the theoretical as well as practical concerns of the modelers (much like maps). Abstract models are as important in biology as in other sciences, however, there are also distinct kind of models, namely model organisms and a third kind, which we refer to as experimental models (biologists also use the term "model system"). In experimental models, some biological process or interaction is artificially recreated, sometimes using living organisms, sometimes computer simulation. Such models are concrete, not abstract; however, concrete entities are often used for representation purposes (e.g., maps again). I argue in this paper that experimental models may serve two epistemic functions that are akin to theorizing: (1) *exemplification* of some theoretical kind, (2) *representation* of natural processes. Concerning (1), when a model is used for exemplification, the question is not whether it correctly represents the world, but whether it has instances in nature that are of the same theoretical kind. But irrespectively of whether it has such instances in nature, experimental models allow biologists to study the properties of significant theoretical kinds. An example are the experimental models used to study competition, which are designed to exemplify Gause's competitive exclusion principle and the theory of the niche based on this principle. Such models have been used to study adaptive radiation, thus in a sense they study the evolutionary implications of competition *theory*. As regards (2), there exist model systems where some biological process is used to *stand in* for another one, e.g., growth stimulation and inhibition by toxins and antidotes in bacteria is used to model trophic interactions. This is relevantly similar to computer-based simulation models where the dynamics of some system is represented by an algorithm. As in (1), biologists use experimental models to study the properties of a *theory*. I contrast this use of experimental models with certain uses of model organisms in molecular biology, where the goal is normally to identify the *function* of some entities, not to better understand the implications of a theory.

Jean GAYON (Paris)

Model Organisms in Biology and Medicine.

Alessandro MINELLI (Padua)

Model Organisms in Evo-Devo. Promises and Pitfalls of the Comparative Approach.

There is a very long tradition in the use of model organisms (e.g., chick, mice and a few sea urchin species) in developmental biology, and evolutionary biology has similarly relied on the study of model species like *Drosophila melanogaster* and *Escherichia coli*. With the advent of evolutionary developmental biology (evo-devo), number and diversity of model species have been rapidly and steadily increasing, eventually becoming the object of targeted conceptual problems focussing on the foundation of their heuristic function and the possible criteria to be adopted for their selection. The starting point for such a critical analysis is, to answer the question, models of what these models are assumed to be. On the one hand, experimental data obtained on model organisms are generalized to more or less inclusive higher taxa to which they belong (for example, *Drosophila melanogaster* is used as a model for all *Drosophila* species, or for the whole of flies (Diptera) or the whole of insects, or even the whole of bilaterian animals); on the other hand, evidence from one or more models is extrapolated to a different species, which for ethical or practical reasons cannot be used as the direct target of investigation. In the latter sense, several organisms (*Escherichia coli*, *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, *Drosophila melanogaster* and *Mus musculus*) were introduced in the '90s as nonhuman models to accompany the development of the Human Genome Project. Precisely in this context it was affirmed that "because all organisms are related through a common evolutionary tree, the study of one organism can provide valuable information about others (Collins et al., 1998). This seemed to gain eventually support from the first genomes to be sequenced, when ca. 25% of the genes in the yeast were found to have a homologue in *C. elegans*. However, there are two major problems with this assumption. One problem is of metaphysical nature, as taking one species as representative of another goes against the increasingly accepted view of species (and higher taxa) as individuals, rather than classes. The other problem, of empirical nature but with profound consequences on our understanding of living beings, is the complexity of the genotype→phenotype map, whose popularly accepted linearity is denied by phenomena such as (i) the far-reaching consequences of the fine regulatory control of gene expression, (ii) pleiotropy, and (iii) polyphenism, that is, the frequent occurrence of alternative normal phenotypes in the absence of any genetic difference. Selection of model species can have far-reaching consequences on our understanding of major biological processes or mechanisms. Cell-lineage studies in *C. elegans* have provided a long-lasting skewed appreciation of embryonic development and cell differentiation in nematodes and in animals at large; this has been recently mitigated by the discovery of a radically different behaviour in other nematode species, whose cell-lineage is much closer to what was expected to be found in *C. elegans*, but actually was not found there. Phylogeny is increasingly used as a reference against which to select model species, but this is often contradictory, unless one accepts that the choice must be guided by previous knowledge (or best guess) on the phylogenetic distribution of characters or phenomena on which a research project is specifically targeted. As a consequence, there are problems where the close relatives of a target species (for example, apes in respect to humans, in the domain of neurosciences) are best candidates to become model species. In many contexts, however, research has been targeted towards "basal" representatives of a smaller or larger branch of the tree of life, in the expectation that a 'basal' branch would be a reasonable proxy for the unknowable common ancestor of a lineage. There are problems, however, both with

fixing a notion of 'basal branch' unambiguously, and especially with taking representatives of a 'basal' branch as repositories of primitive characters. A final point to be discussed, regarding the role of model species in evo-devo research, is the tension (Love, 2010) between the need to keep individual variation in model organisms to a minimum (a condition obviously favouring repeatability of results) and the need to study variation as the material basis of evolvability and, thus, of evolution.

Josephine DONAGHY (Exeter)

Models and Theory in Metabolic Control Analysis.

Metabolic control analysis (MCA) was developed in the early 1970's in order to bring theoretical and experimental work on control of metabolism into a more responsive relationship with each other. Its construction was not preceded by a positive theoretical conception of the control of metabolism or the existence of a relevant data set. Therese archers developing it regarded it as a quantitative systemic perspective on metabolism which should replace the dominant theory of the rate limiting step. The mathematical model in this instance could be interpreted to at first be an instrument with which to construct a theory and then to become the theory. I am going to argue that even in this case of theory construction the model and theory remain distinct aspects of scientific practice. The model does not go on to become the theory: it retains a 'life of its own'.

According to Morgan and Morrison(1999) the autonomy of models from theory and data reveals itself through their function as instruments where they take on a 'life of their own'. One sense in which this phrase has been developed by Galison (1997) in relation to material instruments is to point out that the initial research context of the instrument is indeterminate of the future trajectory of that instrument. The theory, instruments and experiments involved in research can have their own modalities of change and the instruments can become associated with new contexts and uses. I argue that this is also true of mathematical models as non-material instruments. Once the development of MCA has facilitated the construction of a theory of metabolic control its life does not become that theory. Its associated theory of metabolic control initial undergoes a period of relative stasis where as the model is modified in several directions in order to ease its utilisation. Additionally, the model becomes used in adifferent context, theoretical perspectives on the dominance and genetic mutations.

Galison, P. 1997. *Image and logic: A material culture of microphysics*, University of ChicagoPress.

Morrison, M. & Morgan, M. S. 1999. "Models as mediating instruments." In: Morrison, M.& Morgan, M. S. (eds.*) Models as Mediators*. Cambridge University press.

Andrea ESANU (Bucharest)

Modeling Open-ended Evolution.

Darwinian evolution by natural selection bears a manifold of abstract models in evolutionary biology and some of them accommodate more empirical content than strictly-computational or equation-based models. There is a class of models that have a good deal in common with the idea of "historical narratives" of evolution. These are artificial ecosystems that seek to implement, yet not very successfully, "open-ended" evolution.

The issue of open-ended evolution can be summed up by asking under what Modeling conditions will an evolutionary system continue to produce novel forms, because evolution does not seem to be just a matter of historical contingency, but also a matter of *evolvability* – a characteristic that biological systems might possess intrinsically. However, Artificial Life systems such as TIERRA and AVIDA produce a rich diversity of organisms initially, but ultimately peter out. One hypothesis is that evolvability might be connected with what some evolutionary biologists call "facilitated variation", and Artificial Life systems fail to display evolvability because they fail to give an proper account of variation.

Recent advances in cellular biology shed light on a number of mechanisms for generating evolved features in biological systems. While the concept and mechanism of natural selection is well understood, the variation component of the theory of evolution remains under-developed. The theory of facilitated variation (FV) seeks to prove that complex biological systems can arise with a limited number of variation mechanisms. The key observation in FV theory is that organisms are designed such that random genetic changes are channelled in phenotypic directions that are potentially useful. Research on logic circuits and RNA secondary structure (Parter, Kashtan & Alon, 2008) found, for instance, that facilitated variation is actually enhanced in environments that change from time to time in a systematic way: varying environments are generated from the same set of sub-goals but in different combinations. Organisms that evolve under such varying goals not only remember their history but also generalize to future environments, exhibiting high adaptability to novel goals. Rapid adaptation is exhibited by goals composed of the same sub-goals in novel combinations, and by goals where one of the sub-goals was never seen in the history of the organism. It seems that organisms store information in their genomes about their past environments. Elements of facilitated variation theory, such as weak regulatory linkage, modularity, and reduced pleiotropy of mutations, develop spontaneously in these environments. Such environments seem to promote facilitated variation and allow evolution to generalize to novel conditions, i.e., they make room for evolvability.

There are also indirect arguments in favor of a model with FV, coming from the analysis of older models based on cellular automata. For instance: von Neumamn cellular automata are brittle (T. S. Ray, 1994). Overcoming this brittleness and discovering how to make self-replicating patterns more robust so that they evolve to increasingly more complex states might be an important problem in the study of artificial evolution. Von Neumann cellular automana do not display genotype-phenotype decoupling, and this might explain why the organic diversity in these models ultimately peters out (K. Ruiz-Mirazo, J. Umerez, A. Moreno, 2008).

In the light of the information regarding the mechanisms of variation and the property of evolvability, I hold that an open-ended model of evolution should be designed as to *promote* facilitated variation (it might be easily simulated top-dow, but this is not the point).

I see several advantages to such an approach:

i) A model (cellular automaton) that promotes FV would allow us to structure a concept of *evolvability* that might be extended to biological systems. The constraints on the model might be strong (due to restricted variation), but, as I predict, the tests will show that, without such constraints, evolution in the model would appear highly improbable, irrespective of the histories/scenarios chosen.

ii) It cannot be the aim of such a model to predict future ecosystems in detail. This would be as nonsensical as to predict trajectories of gas particles in statistical physics

(Thurner, 2011). However, the model should be able to settle, *via* sets of simulations, a series of *systematic* facts about organisms and how they evolve (for instance, how organization interferes with adaptation).

iii) There should be also some *analytical* (global) constraints in the model and it would be interesting to compare them to the analytical constraints characteristic for the standard models in evolutionary biology. One important observation to stress would be that such an open-ended model would not embed optimality principles, like strictly numerical or equation-based models.

The basic insight is that, although we can give a mathematical expression to the ratio between variation and diversity in an open-ended model of evolution, as we can give a computational expression to the idea of small evolutionary steps, the important virtue of the model, if successful, would not rest on the mathematical aspects themselves, but on a plausible representation of evolution as a historical process, yet significantly controlled by a set of general conditions of variation and selection.

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T. S. Ray (1994): "An Evolutionary Approach to Synthetic Biology: Zen and the Art of Creating Life", *Artificial Life* 1(1/2): 195–226. MIT Press.

K. Ruiz-Mirazo, J. Umerez, A. Moreno (2008): "Enabling Conditions for 'Open-Ended Evolution'", *Biol Philos* 23: 67–85, doi 10.1007/s10539-007-9076-8.

S. Thurner (2011): "A Simple General Model of Evolutionary Dynamics", in Hildegard Meyer- Ortmanns & Stefan Thurner (eds.), *Principles of Evolution*, Springer.

Sebastien DUTREUIL (Paris)

How/Why Should One Model the Organisms/Environment Interactions?

Proposed in 1982 (Lovelock and Watson), "Daisyworld" was the first model to show that the regulation of a planetary variable (temperature) could emerge from feedback between life and its environment, partially answering the critique of teleology initially addressed to the Gaïa hypothesis (GH). Since then, Daisyworld literature has developed during the 80's and 90's and was convoked, with other elements (empirical discoveries, theoretical arguments), in the debate on GH that flourished during the same period. This simple model was based on general properties assigned to living beings and the environment, pursuing generality rather than description of actual cases. In part for this reason, it is often presented as an element that does not "prove" an important statement of the early GH – "by its influence on its environment life may have contributed to maintain the Earth habitable" -, but at least give a plausible mechanism by which this maintenance of habitability could be achieved. Presented as part of GH's *explanans*, I would argue that this model may also have contributed to a shift of the *explanandum* : from the habitability of the Earth to the stability of the conditions that prevail on Earth.

A systematic bias in Daisyworld models was early detected and criticized - daisies alter the same environmental variable in the same direction at the local level and the global level. This lead, along with the abstract nature of the model, some authors to claim that in order to better understand the interactions between life and its environment one shall not only move from abstract and simple models to more complex and realistic ones but shall also abandon GH (Kirchner, 2003). Such complex and realistic models representing the interactions between life and its

environment flourished in the past decades both in ecology and in Earth sciences, detached from the direct literature on GH. In spite of this, discussions on Gaïa were not abandoned and neither were daisyworld models. Furthermore, a new generation of abstract models started to grow – e.g. (Downing and Zvirinsky 1999, Williams and Lenton 2008) – and was convoked in the gaïan literature.

The aim of this paper is twofold: (i) to evaluate the role of *in silico* models – from Daisyworld to more recent ones - within GH, (ii) to understand the influence of these models on the ecological and geological literature.

Downing, K., Zvirinsky, P., 1999, The simulated evolution of biochemical guilds: reconciling Gaia theory and natural selection. *Artificial life, 5(4):291-318.*

Kirchner, J., 2003, The Gaïa hypothesis: conjectures and refuations, *Climatic Change* 58: 21– 45.

Lovelock, J.E. and Watson, A.J. 1982. The regulation of carbon dioxide and climate: Gaia or geochemistry. *Planet. Space Sci.*, 30, No. 8, 795-802.

Williams, H.T.P. and Lenton, T. M. 2008, Environmental regulation in a network of simulated microbial ecosystems, *PNAS*, 105, 30.

Giovanni BONIOLO (Milan)

Modelling Molecular Biology Complexity.

Over the last decades there has been a decrease of skepticism, even among the philosophers, towards the use of mathematical tools in biology and biomedicine. Nevertheless there are still those who affirm that biology, and life in general, is too complex to be formally grasped. I do not want to contend such a claim but just to underline that it is extremely difficult to deny that mathematical approaches adopting differential equations, calculus of probability and statistics, knots theory and graph are extensively used. Certainly, mathematical representations do not mirror real biological and biomedical entities and processes, but not even the physical representations mirror physical entities and processes. Nevertheless, in both cases, they offer good models allowing the understanding of what is occurring and, sometimes, also the predictions of what will occur. Summing up, it seems difficult to object the usefulness of the mathematics within the life sciences.

In spite of this situation, there is a certain diffuse reluctance to give the right cognitive value to a particular mathematical tool: logic.

Many times and for many scholars, speaking of logic means speaking of axiomatization and they object that life cannot be axiomatized. We could agree with them, but logic does not mean axiomatization. Logic means a set of rules that correctly allow moving from a formula (whatever it could be or represent) to another formula. Objecting that logic does not help in any way biological and biomedical sciences is tantamount to neglect that differential equations, calculus of probability and statistics, knots theory and graphs have a logical structure. Moreover, and less trivially, it means also ignoring that computer programs, including those that everyday are used in system biology and in computational biology, are isomorphic to proofs in a well-defined range of logical systems *via* the so-called Curry-Howard correspondence. That is, actually there is more logic in biology and biomedicine then that it appears. Certainly, it is hidden and in order to draw it out we have to think the matter in a more philosophically exhaustive way. But there is.

Over these last years we are developing a new formal language for molecular biology that we have called *Zsyntax*. It is based on the very simple, but surprisingly effective, idea that a biochemical process, occurring infra- or inter cells, can be written as a theorem (with all the computational and representational benefits that this

formalization allows).
In the talk, after a brief presentation of *Zsyntax*, I present two issues on which we are working: 1) how *Zsyntax* could modellize the molecular control mechanisms by means of a context-sensitive approach; 2) how the molecular biology complexity grasped *via* (scale-free and non-scale-free) networks could be "simplified" to Zsyntax, and thus modellized.

Philippe HUNEMAN (Paris)

Computer Simulations in Evolutionary Theory.

Here I will investigate the relations between biological evolution and computer simulations of evolving entities through natural selection. I argue that what is proper to algorithmic evolution is that the selective dynamics of one modeled entity - for ex. genes, or species – is happening in the simulation with no immediate entangling with other levels of a hierarchy, unlike in biological evolution, where all the levels of the biological hierarchies are present together and their selective dynamics are entangled. The object of simulation is called thereby a "pure possible process". This amounts computer simulation to propose "pure possible processes" of evolution, processes in which we know what kind and level of selection is at work. Algorithmic investigation therefore suggests processes as *candidate explanations for the patterns* of evolution we see out there. First, this fact allows one to solve issues which have been recently raised about the validation problem for simulation; second, in those conditions computer science is also likely to suggest new kinds of evolutionary processes whose outcomes would be *discontinuous* patterns of evolution. Drawing on recent work by Richard Watson, I finally consider how the longstanding issue of gradualism vs. discontinuities in evolutionary theory can be reassessed on the grounds of new insights provided by simulations like genetic algorithms. In conclusion I qualify the strong AL thesis according to which evolution by natural selection can be conceived of as an algorithm, and evolutionary biology as a branch of a general science of such alorithms.

Silvia DE MONTE (Paris)

Differential Attachment and the Evolution of Social Groups.

The emergence and persistence of social ventures, where individuals concur in the sustainment of a community at the cost of a personal investment, has been largely addressed in a game-theoretical framework. The evolution of costly cooperation has been first formalized in the context of dyadic interactions, where the formation of pairs and the accomplishment of the game are concomitant. When individuals play in couple, several mechanisms have been shown to effectively promote cooperation even for a Prisoner's Dilemma type of interactions, where it is always in one own's interest to defect in a single round of the game. Cooperation may be maintained if individuals are genetically related or if a sufficient assortment between cooperators is ensured, for instance via the knowledge of the co-player's past behavior or reputation, or via the population structure.
Those results have then been extended to games involving a number N of players, where the Public Goods Game plays the same prototypical role as the Prisoner's Dilemma. The PGG formalizes the so-called tragedy of the commons, whereby cheaters who do not contribute to the public goods are always better off, in a one-shot game, than cooperators that pay a cost to sustain the collective enterprise.

Sociality, however, relates not only to the act of helping others, but also to the context where social games are played, among which the way groups are formed in the first place. In extending the framework from two players to N-players games, the processes that lead to group formation have often been overlooked in holding the group size constant. This assumption of social interaction in groups of fixed size has been recently relaxed in different ways: group size can vary in response to an external forcing that periodically increases the variance among groups (Chuang et al., 2009 ; Hauert et al., 2002; Hauert et al., 2006 ; Peña 011) or can coevolve with cooperation (Pfeiffer & Bonhoeffer 2003, Aviles 2002, Van Veelen et al. 2010, Powers at al. 2011).

I will discuss the case where group formation is underpinned by 'social' mechanisms that also affect group performance (for instance, stickiness can concur both to the individuals' aggregation and to group cohesiveness), with the aim of explaining the evolutionary emergence and maintenance of temporary aggregates in social microbes (Shimkets 19 86 , Smukalla et al. 2008, Nanjundiah 2011).

By means of a mathematical model I will show that when group formation is taken into account, sociality can evolve under minimal hypothesis concerning reciprocal recognition and assortment. Namely, sociality can thrive by generating a different group size distributions for social or asocial individuals, even under blind random interaction and in the absence of within-group assortment. This point of view will be explained by means of a toy model of group formation by differential attachment and applied to more realistic numerical simulations where group formation is addressed by spatially explicit of interacting self-propelled particles.

Finally, I will discuss the relevance of different theoretical approaches and conceptual tools to the evolution of cooperation in social microbes and argue that more mechanistically based models are needed in order to formulate quantitative predictions about the social behaviour of unicellular organisms.

Rebecca MERTENS (Bielefeld)

Flexible Tools: The Lock and Key Model Across Biochemical Boundaries.

The instrumental turn led to a fundamental shift in model theory: The importance of models was no longer limited to their adequate representation of phenomena or theories; instead they have been regarded as instruments of scientific investigation (Morgan and Morrison 1999). According to this view “models do more than simply ‘stand for’ something else” (Griesemer 2004, p. 435); they serve as powerful tools for different kinds of scientific practices and are highly flexible in use (Fox-Keller 2000). In this presentation I will focus on the flexibility of conceptual models and especially on their usage in cross-disciplinary contexts. Using the example of the lock and key model in 20th century biochemistry, I will specify how models influence the development of research programs and provide the necessarily openness for knowledge generation across disciplinary boundaries.

References:

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Tudor BAETU (Vienna)

Quantitative Mechanistic Explanations.

Mathematical models of molecular networks integrate substantial knowledge of molecular mechanisms with the application of laws, modeling and analysis strategies borrowed from chemistry, engineering, cybernetics and systems theory in order to yield quantitative mechanistic explanations. The view defended in this paper is that mathematical models play an explanatory role, although this role is not directly concerned with the identification of relevant mechanistic components and features, but rather with an attempt to answer the question "Can the proposed mechanism generate the target phenomenon in all its minute quantitative/dynamic details?" On one hand, mathematical models of molecular mechanisms do not fully satisfy manipulationist and mechanist criteria for complete explanations, and in this sense they cannot replace mechanistic explanations. On the other hand, however, there is a clear sense in which they cover explanatory ground beyond the reach of mechanistic explanations, most notably by accounting for quantitative-dynamic aspects of the phenomena under investigation. Even though a qualitatively complete description of a mechanism demonstrates the causal contribution of the mechanism to the generation of its target phenomenon, such a description usually fails to explain minute quantitative-dynamic aspects of the phenomenon in question. A closely related problem is that we cannot always rely on commonsense mechanistic intuitions in order to understand how a mechanism produces a phenomenon. Some phenomena are produced by stochastic mechanisms, while others are the result of complex interactions between partially overlapping mechanisms. In such cases, our intuitions are unreliable; complete mechanisms may appear as containing gaps, while seemingly complete mechanisms may in fact fail to generate their target phenomena. Only precise numerical computations can determine whether the mechanism can or cannot generate its target phenomenon in all its minute quantitative-dynamic details. Thus, mathematical models of molecular mechanisms allow for 'proof of principle' explanations demonstrating that the proposed mechanisms can generate their target phenomena down to minute quantitative-dynamic details. Conversely, mathematical models may also reveal unsuspected 'black boxes' in current mechanistic explanations and prompt their revision. In addition, as shown by the examples discussed in this paper, they can provide unexpected explanations for novel phenomena, as well as reveal unusual properties of mechanisms, thus generating new insights about the causal- mechanistic structure of the world.

Ann-Sophie BARWICH (Exeter)

Making Sense of Smell: Models in Olfaction Theory.

Smell or olfaction is one of our two chemical senses, the other being taste. Unlike shape or composition, the odour of a molecule is not an intrinsic property but it is linked to a particular mechanism of perception. It is a sensory response that occurs when particular molecules stimulate the appropriate receptors in the nasal epithelium. The identification of these receptors and their particular character is thus the essential condition for the construction of any hypothesis about the olfactory recognition mechanism involved. Understanding this mechanism and determining what feature of the molecule causes the perception of its particular odour is likewise essential for the classification of odours by virtue of the relevant molecular properties. In light of this, the aim of this paper is to explore a contemporary controversy in olfaction theory,

which concerns the interdependence between, on the one hand, the causal mechanism of primary smell reception and, on the other, structural classifications of odours.

Until recently, biologists were unable to identify the specific processes of odour recognition, because the odorant receptors (ORs) in our noses were unknown. In 1991 Buck and Axel discovered a multigene family encoding ORs in the mammalian genome, identifying them as G-protein-coupled receptors. This discovery had important implications for further olfactory research, because it identified smell receptors as a class of G-proteins, strongly suggesting that molecules cause a particular odour by docking on a specific primary receptor according to a shape-sensitive "lock and key" mechanism. Orthodox opinion about primary smell recognition therefore takes shape to be the key feature underlying molecular recognition. However, this account faces several severe experimental problems and still lacks conclusive demonstration. An alternative account (Turin 1996), referring instead to molecular vibration in the infra-red range as the key feature of olfactory molecular recognition, has been widely disregarded, though it has not been rejected on experimental grounds.

By contrasting the two accounts this paper reconstructs the different strategies of conducting and interpreting experiments implicit in the competing theories. The central topic of this analysis is the mechanism of primary odour recognition. Most of the difficulties that surround the reconstruction of this mechanism concern the insufficiently explored nature of the ORs. Since methods for the stabilisation and purification of ORs are still in an early stage, the interpretation of ‘in vitro’ experiments, simulating an odourant reaction at an isolated receptor protein, remain speculative to a certain degree. Olfactory receptors are, in fact, highly unstable and olfactory research therefore extrapolates results from other research areas involving G-coupled proteins. Moreover, with respect to the overall complexity of smell perception, involving individual genetic variations in the olfactory receptor expression, ‘in vitro’ results are difficult to extrapolate back into ‘in vivo’ studies. The paper thus outlines the competing epistemological strategies and arguments designed to establish the validity of an experimental result or observation in favour of a particular model of primary odour recognition. This comparison will then be used to explore the extent to which experimental practice must be bound to existing epistemic assumptions in order to be accepted as ‘evidential’.

Adam TOON (Bielefeld)

Molecular Models in Vitro and in Historico.

Recent philosophy of science has seen considerable interest in the question of what scientific models are and how they represent the world. In earlier work, I have suggested that we may answer these questions by understanding models as props in games of make-believe, like children’s dolls or toy trucks. As well as helping us to solve these philosophical problems, however, any account of models should also provide a convincing analysis of the practice of modelling. In this talk, I will assess the make-believe view through a contemporary, empirical study of molecular modelling (‘in vitro’), as well as a historical case study (‘in historico’). My empirical study will examine the use of three-dimensional, physical models of molecules, as well as a computer modelling program. I will suggest that the make-believe view gains support when we look at the way that molecular models are used and the attitude that users take towards them. In addition, I shall argue, this approach points towards a new account of how models are used to learn about the world, through what I call *imagined experiments*. My historical study will focus on the cardboard cut-out

models created by the founder of stereochemistry, J. H. Van't Hoff (1852-1911). Drawing on recent work by historians of chemistry, such as Christoph Meinel, Peter Ramberg, and Alan Rocke, I will suggest that the make-believe view offers a framework with which to make sense of these early molecular models and the important role that they played in the development of stereochemistry.

Daniel BROOKS (Bielefeld)

Problem Agendas in Neuroscience.

The complexity of biological phenomena presents many challenges to the work of philosophers and scientists alike. Not least of which is coming to grips with the plurality of disciplines and their epistemic resources such as the research interests or goals, experimental methods, and models that are deployed to explain such phenomena. This issue is of especial relevance in the philosophy of the neurosciences, where researchers are faced with integrating these often incompatible elements of scientific practice into a singular explanation.

In this presentation I will argue that while most accounts by philosophers of neuroscience focus on the products of integration, i.e. ideally complete explanations (cf. Craver 2007, Bechtel 2008), the integration of epistemic resources is better regarded as a process by which collaborative *problem agendas* are constructed for the disciplinary perspectives in question. The term problem agenda (Love, 2008) designates a set of problems that motivate interdisciplinary collaboration for investigating complex phenomena that cannot be explained by any one of the involved disciplines alone. Typical "problems" here include articulating criteria for explanatory adequacy, constructing a shared theoretical vocabulary or at least mutual awareness of differences in vocabulary, division of explanatory labor, and characterizing the phenomenon or phenomena to be explained. Focusing on integration as a process rather than product of interdisciplinary collaboration emphasizes the fact that the problems associated with interdisciplinary collaboration are subject to constant modification, based on both the emergence of new experimental results and ongoing conceptual negotiations between researchers of different disciplinary approaches. It is then unsurprising that models play an essential role in this endeavor, both as representations of explanandum phenomena localized to particular disciplinary perspectives, and as loci for promoting interdisciplinary dialogue (whether critical or constructive). Either way, models offer important insights for interdisciplinary integration because they are often the starting point, and the target for, cross-disciplinary interaction. To this end I will highlight some of these insights as they impact the construction of problem agendas, focusing specifically on the role of the Reichardt Detector Model in the neuroscience of motion vision on reconceptualizing the complex phenomenon of motion adaptation.

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Arnon LEVY (Jarusalem)

Model Organisms Aren’t Models.

Much biology studies a small class of species known as “model organisms”, such as E. coli, yeast and mice. I will argue that despite the epithet, model organisms are not models. In making this claim, I presuppose an understanding of models as vehicles for surrogative (or indirect) representation and reasoning: understanding one object by reasoning about a distinct object. Model organisms play a more empirical role. They are specimens that serve as bases for extrapolation. I will tackle two lines of thought that might lead one to think that model organisms are (surrogative) models. First, it may be supposed that assessments of model-target similarity play a key role in model organism based inferences. But I argue that the similarity in question is akin to statistical representativeness, and not to a comparison between two objects. Second, model organisms are seen as constructs, suggesting that they are somehow abstract or idealized. I will argue that though construction does exist in both kinds of models, the difference in degree is too great to support appeals to idealization and abstraction in the case of model organisms.

Michael DIETRICH (Dartmouth)

Model Choice and Method Selection in Molecular Evolution.

With the rise of sequence databases and the proliferation of programs to analyze those sequences, biology in general, and molecular evolution in particular, have experienced a control revolution. As researchers have worked to manage this flood of sequence information, computers have become an inescapable part of any sequence analysis. This presentation explores the impact of computer automation on research in molecular evolution through the problem of modeling nucleotide sequence evolution.
This presentation will consider how what at first seemed to be a simple comparison between sequences became increasingly mired in empirical and methodological challenges of managing and making both models and methods. I will outline how models of nucleotide substitution proliferated creating a problem of model choice that was then embedded in a computer program aimed at automating that choice. By analyzing how this model choice program was used, I will argue that computer automation allowed most biologists todisregard the significant limitations of the automated method, despite explicit disclaimers made by the program’s creators and some more methodologically sophisticated users. This disengagement from computerized methods has important implications for the creation of new constitutive standards within science.

Amir TEICHER (Tel-Aviv)

“In Stemma”: Mendel’s Model and Human Heredity in Germany, 1900-1933.

Following the re-discovery of Mendel’s laws of heredity and the subsequent successful implementation of these laws in Botany and Zoology, scientists dealing with human traits (mainly psychiatrists and racial/physical anthropologists) attempted to implement the Mendelian model in their own fields of expertise. A transition to the

human sphere, however, required certain conceptual shifts: for example, tracking human lineages was to substitute the unfeasible manipulation of breeding processes ('crossing experiments'). The Mendelian model, in addition to a particular implicit experimental design, was propagated using a certain graphic format and a specific denotation method. Based on an exploration of scientific publications published during the first third of the twentieh century, my presentation will deal with various aspects of the propagation of the Mendelian model among German genealogists, psychiatrists and anthropologists. First, I will give a concise historical account of the ways in which the scientists themselves reflected on the complexities of using the Mendelian model in their own fields. Then, I will exemplify some unexpected (and less-known) 'side-effects' of the inference habits induced by the Mendelian model, and point out to the ways in which a model, in and by itself, may have characteristics which can affect areas of thought not necessarily related to its original target. Special attention will be given to elements of visualization, on the one hand, and mathematical formulations, on the other hand, which the model promoted. Finally, I will examine the ways in which new insights into the nature and function of models are pertinent to my account and can enrich our understanding of the occurences in the scientific fields depicted above.

Cecilia NARDINI (Milan)

Generalizing Randomized Control Trials.

Despite the large development of *in vitro* models and animal models of disease in the past years, clinical trials on a population of patients remain indispensible for testing new proposed remedies before they are allowed access to the market. Randomized controlled trials (RCT), where patients are randomly assigned to receive the experimental treatment or a comparison standard which may even be a placebo, do often raise ethical concerns. Nonetheless, they are at present the only tool for assessing with conclusiveness a new treatment's safety and efficacy in human use.

The concern that results from RCTs may not be readily generalizable to the target population of patients has become a major issue nowadays, due to recent controversies. This concern is often motivated through the consideration that the patient sample which is subjected to the trial is constituted by highly selected population and for this reason particular groups of patients, such as for instance patients with co-morbidities, are systematically underrepresented in trial results. Developing trials that fit patients seen in practice–so called pragmatic design for trials–has been proposed as a possible solution to the problem.

Comparatively little attention has been paid instead to the statistical method that is used for designing and analysing the trial, and the impact it might have on the generalizability of trial results. In my paper I start from the consideration that restricting attention to the composition of the sample alone can be misleading, and I analyse the problem of generalizability from the point of view of philosophy of statistics by comparing the two main statistical schools, the frequentist and the Bayesian. I identify some elements in the statistical methodology that bear relevance to the possibility to extrapolate results to the full population of patients, and I investigate whether one school of statistics is endowed with better tools to tackle this problem.

Pierre-Luc GERMAIN (Milan)

Disease Models Between Replica and Instruments.

Being highly standardized and increasingly crafted, model organisms are oftedepicted as *instruments*. The metaphor has proved to be highly adequate for the historical and sociological studies of models organisms, but it is still unclear to what extent it is useful in the understanding of the epistemological problems they encounter. I propose to address this question using three examples from molecular medicine, which bridge *in vitro* and *in vivo* disease models: cancer iPSC lines, tumour xenograft models, and genetically engineered disease models.

I argue that to fully understand some disease models, it is necessary to view them as observational instruments: they are primarily means of making visible differences that were undetectable. I contrast this conception of disease models from another, inspired from physiology: that of the model as *replica*. I argue that no line can be drawn between the two, and that they are rather the two extremes of a continuum. The position of disease models on this continuum is largely determined by the magnitude of the informational input into the model. As a consequence, the actiity of disease modelling in contemporary biomedical research is not essentially different from the more general activity of experimentation – and must be evaluated as such.

If disease models are often best characterized as observational instruments, it follows that the question of "the best disease model" is in general ill-founded. Models are very often complementary, and cannot be evaluated in isolation. It is only in a set of tools and practices that they can be appropriately understood and evaluated. The point is made even stronger by the fact that biomedical research changed dramatically since the classical drug screening programme of the NCI: in modern biomedical research, information does not flow in a linear and unidirectional way from bench to bedside. The success of a model cannot simply be measured by the attrition rates at the next step, but must take into account the capacity of the model to incorporate feedback from other models, including human models.

Sabina LEONELLI (Exeter)

Model Organisms in Vivo and in Silico: Data, Speciments and Models.

This talk will pick up on my previous work, jointly with Rachel Ankeny, on the history and epistemology of model organisms, the specific features of these organisms in comparison to other organisms used for experimental research in biology and biomedicine, and the current efforts to organise, disseminate and analyse data obtained on model organisms through digital databases. I will look at the problems arising out of current attempts to 'digitise organisms' and what this means in terms of philosophical understandings of experimentation and modelling both in silico and in vivo.

Werner CALLEBAUT (Vienna)

Multiscale Modeling.

Bruno STRASSER (Geneva)

The End of Model Organisms?

The rise of the experimental life sciences in the twentieth century has crucially depended on its reliance on a few model organisms. Unlike naturalists who examined a broad range of species and adopted a comparative perspective, experimentalists generalized their findings from a small number of "exemplary" cases. After more than a century of successes, this approach seems to be coming to an end. An analysis of the published literature shows that there has been a recent explosion in the number of species used in experimental research and a return to comparative perspectives. This result brings us to revisit our standard narratives about the development of the life sciences and the relations between natural history and experimentalism.

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