Andreas Wagner

Models in the Biological Sciences

ABSTRACT: *An attempt is made for a crude classification of important types of models used in the biological sciences. This classification comprises model organisms, iconographic models, mathematical models, and computational models. The notion of a model organism is discussed further with respect to the problem of biological homology among genes and gene products. The notion of a mathematical model is further subdivided into statistical, functional, phenomenological, causal, analogical, and idiosyncratic models, classes of models that are not to be seen as mutually exclusive. Further, reasons are given why the category of computational models deserves a status separate from that of mathematical models. Finally, it is proposed that all the model categories discussed, as diverse as they may be, share an important feature.*

Different areas in science use the notion of a model with very different meanings and connotations. These differences are not likely to facilitate a universal definition of the term, and such a definition is made even more difficult by the closely related notion of a theory. What is considered a theory and what a model may depend on the field of research. What is a model in economics, for example, would be considered a theory in physics, and vice versa. In biology, the distinction between theory and model is blurry, and does not go far beyond the vague notion that a theory applies to a larger range of phenomena than a model. Therefore, the distinction will not be emphasized here. Instead, examples for the most important classes of models in biology are given. They are followed by a brief discussion of what might be a unifying theme among them.

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1. The model organism

This notion of a model is probably unique to biology, although it bears some resemblance to that of a model system in other areas. It does not refer to a conceptual model, i.e., to a mental construct, but to an organism whose biology may be informative with respect to biological processes in other organisms. However, a series of assumptions, derived from a conceptual model (or theory) of biological evolution stand behind this very material notion of a model.

The vast and growing field of molecular biology has lead to spectacular insights into the mechanistic basis of a multitude of biological processes, such as the regulation of cell division, embryonic development, genetic and epigenetic inheritance, and many more. However, there may be of the order of 10^7 species on earth, many of them still unknown. Given finite resources, we will only be able to study a small fraction of these species. Moreover, the exploration of biological processes at the submicroscopic and molecular level is a difficult, time consuming, and expensive endeavor. In order to gain a deep understanding of the molecular mechanisms governing living beings, it is therefore advisable to study a select few organisms in depth, and to hope that they provide useful information that can be generalized to others. Examples of such model organisms include *Escherichia coli* as a member of the bacteria, *Caenorhabditis elegans* as a member of nematode worms, and *Drosophila melanogaster* as a member of the insect order diptera, and, more general, of arthropods. They all are studied as members of a larger class of organisms, and biologists hope to learn something about the other organisms in that class by studying one member. This notion of a model organism also extends to medical genetics, an area whose progress is hampered by the fact that its main subject, humans, can not be subjected to genetic experiments. If a particular disease is to be studied, an animal model for the disease is often used, i.e., a species in which a similar disease occurs and which is as closely related to humans as possible. In addition to relatedness, several other considerations enter the choice of the model system. These include the availability of mutants in disease causing genes, or the availability of techniques to carry out a particular line of experimentation in the chosen species.

The assumption behind such a research strategy is that biological taxonomy reflects evolutionary relatedness of organisms, and that similar biological processes are at work in related organisms. Although ques-

tions regarding the origins of observed biological similarities harbor deep conceptual problems for evolutionary biology in general, the strategy has overall been very successful. Especially if the relevant organisms are not separated by enormous time intervals (on an evolutionary scale), the approach is likely to produce fruitful results. Investigations of the immune system of mice contribute in important ways to an understanding of its human counterpart, results from research on limb development of chickens is likely to be applicable to most, if not all vertebrates, and insights into Drosophila eye development are relevant to the development of facet eyes in general. In addition to its "local" success, this research approach has also shown that some biological processes share important properties even in very different species. On the far end of the spectrum of possibilities are cellular processes that may be similar in most eucaryotic organisms. For example, proteins regulating the onset of cell division are thought to function in similar ways in yeast and in humans (Nurse 1990), and therefore probably also in most other eucaryotes. As a general rule, however, it can be observed that problems regarding the evolutionary origin of observed similarities arise, as the evolutionary distance between taxa increases. This is best illustrated through the example of a common line of experimental analysis used to establish functional similarities between genes in different species.

Genes acting in a particular biochemical pathway of distantly related species often show striking similarity in their DNA sequence. This similarity, along with further phylogenetic and biochemical evidence is often taken to support the hypothesis that the two genes derive from an ancestral gene in a species that existed before the two lineages split. The two genes are then said to be homologous (more specifically, orthologous). In some organisms, techniques are available to replace one gene by another gene, and to assay the effects that such a replacement has on the organism. In some such experiments, it is found that a homologous gene from a very distantly related species can substitute for the function of the "native" gene in the context of a particular experiment. From the point of view of the experimenter, the two genes have identical functions. In some cases such functional similarity can be quite surprising, because hundreds of millions of years may have passed since the lineages leading to the two species split. To give an example, the cell cycle regulatory gene *CDC2* of humans has a homologous counterpart in the *yeast Schizosaccharomyces pombe*, the gene *cdc2*$^+$. *CDC2* can completely substitute for the function of the yeast gene *cdc2*$^+$ (Nurse 1990).

An example illustrating the potential problems that may arise in interpreting the results of such experiments is given by the mouse gene *Hoxb-6* which is part of a regulatory gene network implicated in mouse development. It has a homologue in the *Drosophila* gene *Antennapedia*, which plays an important role in establishing the identity of individual body segments in the body plan of *Drosophila*. When expressed (i.e., "turned on") during development in body regions outside its normal range of activity, a striking change in the phenotype of the adult fly occurs, namely the transformation of legs into antennae. When the mouse gene is expressed in a similar fashion in *Drosophila*, the same transformation of legs to antennae is observed (Malicki et al. 1990). This example points towards a potential difficulty in determining on what level the similarity resides in this example. Clearly, vertebrate and segmented insect bodies are two very different structures, where "different" is to be understood in terms of the concept of homology. Two structures in two related organisms are called homologous in the historical sense if they are derived from the same structure in the common ancestor, i.e., if they are identical by descent. There are many "similar" structures in two organisms for which it is not clear whether they are derived from one structure in the common ancestor. However, there are also many cases where non-homology is established beyond reasonable doubt, the example given here being one of them. Thus, the mouse gene *Hoxb-6* that may be able to substitute for the function of *Antennapedia* in *Drosophila* does so in an entirely different functional context. Is it possible to identify some sense in which the respective biological processes in both organisms are similar, solely based on the fact that some of their components are similar in DNA sequence and that they can functionally substitute for each other in the context of a given experiment? The question is likely to have a straightforward answer in this particular example which is benign compared to others. This is because a large body of independent evidence suggests that the two genes are embedded in a network of interacting genes, and features of the whole network may be conserved between flies and vertebrates. It is likely that a transfer of function of the entire network has taken place during evolution. While the network is embedded in the process of body segmentation of the fly, it is used to pattern non-homologous structures, such as the limb or the hindbrain of mice (McGinnis and Krumlauf 1992). How such transfers of function take place is not understood, since it is hard to envision functional intermediates in other organisms. However, it can be said that the appro-

priate level of similarity or representation is the organization of a system of interacting developmental genes. As evolutionary distances increase, the perceived similarities among biochemical processes may comprise smaller and smaller parts of these processes, until they do not extend much beyond the level of individual molecular components. Indeed, there are many examples of individual molecules that seem to be used as building blocks of entirely different biochemical processes in different organisms. A prominent one is that of ras proteins which are ubiquitous in eucaryotes, and have an important role in many signal transduction processes. They are involved in the nutrient driven control of the cell cycle in the yeast *Saccharomyces cerevisiae*, as well as in the development of the genitals of the nematode worm *Caenorhabditis elegans*, and in the development of photoreceptor cells in *Drosophila* (Greenwald and Broach 1990; Rubin 1991). While their biochemical functions and amino acid sequence are similar in all these cases, the biochemical pathways in which they are embedded may be entirely different. Many of the components with which they interact need not even be the same in two organisms. In this and similar examples, it is often not clear in which sense an observed functional or sequence similarity implies that one process can be used as a model for another one in a different organism. Not even the organization, but only individual building blocks of a biochemical pathway may be similar among different organisms. As in many other cases, there is a large grey zone between dissimilarity and similarity of biochemical processes, and only the two extremes of the spectrum are clearly defined.

2. Iconographic Models

This class of models consists in pictorial or qualitative descriptions of a system's parts or of a system's behavior. It is often used to merely illustrate properties of a system that are already represented in a mathematical model. Whereas in this role a pictorial presentation might not be viewed as a model in its own right (because the mathematical representation is the operationally useful model), there are cases where pictorial representations do clearly serve as models. These are situations where no mathematical model may exist, and where spatial relations among a system's parts are important. Especially molecular biology and biochemistry are rife with examples for such models. This is because in these ar-

eas frequently qualitative rather than quantitative (kinetic) features of interactions among molecules are studied. To give an example, an iconographic model might consist in a representation of how exactly a DNA-binding protein binds to DNA, i.e., what the general shape of the protein is, which parts of it make contact with DNA, and which amino acid residues contact DNA. Another example is the model of the ribosome, the cell's protein synthesis machinery. Here, issues of concern are the interaction of the ribosome with RNA, the access of aminoacyl-tRNA molecules to the site of translation, the location of the catalytic site generating peptide bonds, etc. As is evident from these examples, such models are usually not a wild guess, but often emerge from experimental evidence accumulated over years or even decades of research. Often, they can be used to guide further experiments or even predict the results of such experiments. For example, in a DNA-binding protein changes of amino acid residues that are in contact with DNA are likely to cause more profound changes in its biological activity than changes in other residues.

3. Mathematical Models

In this area the activity of modeling is most similar to modeling in the physical sciences. The literature is vast, and it comprises modeling efforts at all levels of biological organization, from the regulation of gene activity to models of cultural evolution. Any attempt to give a comprehensive overview would be futile. Here, only a crude classification along a few general diagnostic axes shall be given.

3.1 Statistical and functional models

A statistical model represents relations among random variates that correspond to empirically measurable quantities. A simple statistical model is the linear relation $Y=aX$ among two random variates, X and Y. To give an example, X might be blood pressure in humans and Y the temperature of the environment. The model $Y=aX$ is a hypothesis regarding the statistical relation between these random variates. It states that they are linearly related via a proportionality constant a.hether this hypothesis for

a particular value of a is supported by a data set can be established by statistical methods, in this case linear regression analysis.

Functional models, on the other hand, are models that pertain to functional interactions among a systems parts, or among a set of state variables used to characterize a system. A possible example is enzyme kinetics. Many enzymes show an almost linear dependency of reaction velocity on substrate concentration for low substrate concentrations. Velocity then levels off at a maximum value towards very high substrate concentrations. This observation is predicted by the Michaelis-Menten model of enzyme kinetics, which has at its core some basic assumptions about how enzymes interact with their substrates (e.g., Murray,1989). In the kinetic equations derived from this model, the relevant state variables are concentrations of enzyme, substrate, and reaction product, as well as other quantities derived from these, e.g., velocity as the change in substrate concentration. The physicalistic assumptions of Michaelis-Menten kinetics translate into certain functional relations among the state variables in the kinetic equations.

Statistical models about relations of observable quantities often follow from functional models. For example, in the case of enzyme kinetics, one might observe that the statistical relation among substrate concentration and velocity is approximately linear for intermediate substrate concentration, but that there is no such relation at high substrate concentrations. Therefore, statistical models can be considered "weaker" than functional models, because a statistical model does not imply a functional relation among its constituent variables. Moreover, the reverse statement, that statistical relations will follow from functional relations, is often true. Statistical models are nevertheless important tools in the validation of functional models. They can often be used to validate parameters or even assumed functional relations among state variables embedded in the functional model. Furthermore, in cases where there is no functional model available, statistical models may be the only tool to make predictions regarding a system's behavior.

3.2 Causal and phenomenological models

In a causal model a biological process is represented through the interaction of well-specified variables at a lower level of biological organization. For example, in reaction-diffusion models of embryonic pattern

formation, the interaction of specified substances (activators and inhibitors) produce stable patterns of concentrations that influence the development of body structures. In phenomenological models, on the other hand, it is only the organization of the system that is known, and one may be quite ignorant of the system's constituents. A potential example are biological clock models. Here, the molecular oscillators that underlie biological rhythms are in most cases unknown. All that one may have at hand is some quantifiable oscillating variable (the "phenomenon"), such as activity patterns of an organism, physiological parameters, or biochemical markers (without knowledge of whether these parameters are causal to the oscillation, or just associated with it). In these cases, one may nevertheless be able to make some profound statements about the nature of the oscillators. This is because different types of oscillators behave quite differently when perturbed. Whatever the oscillating variables are, an undamped harmonic oscillator will react quite differently from a nonlinear limit cycle oscillator to moderate perturbations. The latter will assume its original oscillation with a phase shift depending on the magnitude and time of the perturbation, whereas the former is likely to oscillate at a different amplitude after the perturbations. Biological clocks can often be ubjected to experimental perturbations (e.g., light pulses during periods of low light for a circadian rhythm), and through the effect of such perturbations, one can infer the type of oscillation at hand. In order to do that, little information about the variables causing the oscillation may be necessary. In other words, one could say that causal models account for both the organization and the nature of the state variables that underly a biological process. Phenomenological models account only for the organization among the variables. The distinction is not clear cut, since one can easily envision systems that are a mixture of both types. For example, some state variables may be known whereas others are not.

3.3 Analogical and idiosyncratic models

By an analogical model I mean a mathematical model of a biological process which resembles a process in some other area, e.g., classical mechanics. This resemblance is usually found in models involving differential or difference equations. In these cases, it is also straightforward to pinpoint the origin of the resemblance, which lies within the functional

relations of the state variables used to characterize a system. The state variables themselves may have completely different interpretations in the two models. Two examples shall illustrate the nature of analogical models.

The first example is an analogy between chemical kinetics and ecology. It is taken from community ecology, an area in which theoretical work is dominated by the Lotka-Volterra equations (Murray 1989; Rosen 1970). In these equations, the individual state variables are population densities, x_i, of individual species i. The structure of the equations is given by

$$dx_i/dt = x_i\,(a_i + \sum_j b_{ij}x_j)\;\; 1 \le i \le n$$

The coefficients b_{ij} denote interactions among the species, where $b_{ij}>0$ implies that species j enhances the growth of species i (e.g., it might be a food source for species i), and $b_{ij}<0$ implies that species j inhibits the growth of species i. The parameters $a_i>0$ reflect the intrinsic growth rates of species i. These equations are analogous to a system of chemical reactions involving a set of reactants whose concentrations are denoted by the state variables x_i. The parameters b_{ij} correspond to reaction rates of the bimolecular reactions between i and j. The a_i's correspond to autocatalysis of reactant i. Thus, formally Lotka Volterra equations correspond to chemical reaction networks, although for any given Lotka-Volterra system, the corresponding chemical network need not be known or even exist.

The second example is taken from solid state physics and neurobiology. One of the tasks of solid state physics is to explain the behavior of various magnetic materials under different assumptions about the interaction of the atoms within these materials, and under different external conditions, such as varying temperature or external magnetic fields. In this area, the Ising model, a mathematical model representing the magnetic moments of individual atoms as spins S_i with values ± 1 has proven enormously successful (Binder and Young 1986). A sizable industry devoted to the exploration of this and related models exists in physics. A simple version of the model is given by the dynamical system

$$S_i(t+1) = \sigma\,[\sum_{i,j=1}^{n} w_{ij}\,S_j\,(t) + h]$$

Here, h corresponds to a constant external magnetic field, and w_{ij} to the influence that the magnetic moment of atom j has on that of atom i. These coefficients will depend on factors such as the distance of two atoms within the material. Various extensions of the model are possible, such as stochastic or asynchronous dynamics, or continuous state variables. This class of models has found important applications in neuroscience as the Hopfield model of associative memory (Amit 1989). The task of an associative memory lies in "recalling" a stored pattern (e.g., an image) after being presented with a similar (incomplete, distorted etc.) pattern. In the Hopfield model, whose formal structure is identical to that of the Ising model, the state variables now represent the activity states of individual neurons (a value of (+1) implying that a neuron fires at time t). The interactions of individual neurons are not mediated by a magnetic field. Instead, the coefficients w_{ij} correspond to the influence that neuron j exerts on neuron i through the axon that connects the two neurons. The summation of individual influences corresponds to the integration of the inputs of all neurons at the cell body of neuron j, and h corresponds to a firing threshold, a level of activation that has to be reached in order for a neuron to fire. As with any analogy, the correspondence between features of one model and the other is limited, and features unique to each modeled system enter both models. Here, such assumptions regard mostly the nature of the connectivity coefficients w_{ij}. For example, in the magnetic case a fundamental symmetry, $w_{ij}=w_{ji}$ holds. This symmetry is violated in the neural case. If neuron i is connected to neuron j via an axon, the reverse connection need not even exist, let alone be of equal strength.

Analogical models in the spirit of these examples are ubiquituous, so ubiquituous in fact that it may be difficult to find models whose structure bears little resemblance to models in other areas. Possible cases for such "idiosyncratic" models are to be found where a model was designed to fit a particular experimental phenomenon with great accuracy or detail. One example is the Hodgkin-Huxley model of nerve membranes (e.g., Murray 1989). It was designed to represent the propagation of electric signals along the nerve axon of the giant squid. Because its structure closely adheres to the studied system, it is capable of making very specific predictions about the system. This entails that the model structure is complicated, involving numerous parameters and state variables specific to the axon. Because it is tailored to a very specific prob-

lem, with as little abstraction as possible, analogies to models in other areas are not likely to be extensive.

The three axes of model classification suggested here, statistical-functional, causal-phenomenological, and analogical-generic are neither intended to be comprehensive, nor are they to be seen as orthogonal. For example, a causal model is usually also a functional model. In the remainder of this section, the relation of biological models to observational or experimental data is briefly discussed.

3.4 Mathematical models and data

Similar to mathematical models in other areas, biological models interact with data to varying degrees. A crude classification in this regard might take into account the extent to which a model was initially designed to solve a concrete experimental problem. There are models, one might call them conceptual models, that may never have been intended to explain a particular experimental result. Instead, they provide a new perspective on large classes of evidence, evidence that might be only qualitative. Connectionist models of parallely distributed neural processes are a potential example (e.g., Rumelhart and McClelland 1986). Their commonalities with neural networks may not go much beyond the fact that a large number of simple computational units are connected in a network-like fashion. Individual units may function substantially different from real neurons, and also the connectivity architecture of the entire system may be quite unrealistic. Nevertheless, such models have provided researchers with an intuition for high level cognitive processes, including associative memory, generalization, and abstraction. They may not accurately reflect the structure of any biological network, but their value lies in providing a new perspective on previously poorly understood phenomena. Also, such conceptual models may provide a general framework, within which it may be possible to design realistic models explaining a particular experimental phenomenon. They may thus serve the function of a paradigm, providing a particular perspective on a large body of data.

Contrary to originally conceptual models, most mathematical models in biology are likely to have originated from an attempt to explain a particular set of experimental or observational data. Take the example of Lotka-Volterra equations in ecology. They were originally designed to

explain an aspect of the population dynamics of predatory fish in the Adriatic after the First World War. Such models may retain their initially close interaction to an underlying body of data. However, in many areas one observes a tendency towards abstraction and generalization, which is not always motivated by experimental evidence. A sizable industry may develop which explores properties of the model from a mathematical rather than a biological point of view. Lotka-Volterra equations again serve as an example. Their mathematical structure can be expanded to cover very general scenarios of species interactions, and a sizable industry has developed in this area. Often, a specific scenario of species interaction is postulated either in terms of plausibility, or in terms of a more or less vague reference to empirical evidence. Then, an equation describing the scenario is established and a detailed analysis of the equation is carried out, usually without further reference to biological evidence. The resulting body of work may be one of the reasons why many experimentally oriented biologists do not hold mathematical work in their area in high esteem. It is often perceived as irrelevant to biological problems, as inaccessible to experimental tests, or even as intrinsically unfalsifiable. This perception is due to a fundamental difference of what a mathematical model is to an applied mathematician and to a biologist.

4. Computer models

Computer power has increased exponentially over the last decades, and a concomitant increase in the importance of computers in biological modeling can be observed. Two basic uses can be distinguished, only one of which is sufficiently self-contained to be called a computer model in its own right.

Many mathematical models of biological processes are so complex that they can not be solved analytically. If this is the case researchers often resort to numerical solutions of the equations representing the biological process, solutions that are obtained either through deterministic or stochastic (Monte-Carlo) methods. The computer is then only a tool to obtain the solution of a mathematical problem which is the actual representation of the biological problem. However, computers serve more and more often as stand-alone devices in determining a solution to a biological problem. For example, population genetic models of evolutionary processes involving many genes are almost always analytically

intractable. In some cases it may be possible to write down a differential or difference equation describing the evolution of some variable of interest. However, this equation may be very difficult to solve numerically. Also, crucial simplifying assumptions may be hidden in the equation. In these cases, a simulation approach is often the method of choice. For example in the case of population genetics, a simulation usually involves a representation of individuals (through their genome) and of populations of individuals in the computer. The simulated individuals undergo processes thought to be of importance in the evolutionary scenario under consideration, e.g., simulated mating and recombination, (implemented by swapping of genes between the simulated genomes of two stochastically chosen individuals), or selection (implemented by stochastic choice of individuals for survival into the next generation according to some fitness criterion). While there are usually aspects of the simulation that are analytical, e.g., the calculation of fitness from given values of genetic variables according to some algorithm, it is the simulation itself that is the representation of the biological process. No all-encompassing mathematical framework need exist in which the simulation is embedded. Even if such a framework exists, however, the simulation can often be used to validate whether assumptions of that framework can be violated without affecting the results. Because the simulation is in this case used to validate or refute assumptions of a mathematical model, it merits the status of a representation of a biological process independent of that model.

Taken to its extreme, this approach of individual based modeling harbors considerable dangers. Because of ever increasing computing power, one can simulate the behavior of systems with more and more complex interactions among their parts. If no intuition is available independently of the simulation on what the essential features of the modeled system are, one may arrive at results that do not yield any insight regarding these features, and how they govern the behavior of the system. As the complexity of the model approaches that of the modeled system, one may lose predictive and/or explanatory power.

5. Conclusions

The examples for biological models given here show that there are not only considerable differences in the usage of the term between fields, its meanings vary also widely within biology. Because of this heterogeneity of meanings, the question "what is a model?" may be ill-posed. However, to just leave things at that is not very satisfactory. Although any very general characterization of models is likely to be vacuous, a practitioner, i.e., in this case a biologist, would probably argue that models do share a basic property. They are epresentations of something else, of a process or of a structure. In this sense, one might be tempted to say that a model is a sign in the semiotic sense, but this is not a sufficient criterion. All models can be viewed as signs, because they are used to communicate something (an aspect of a system's dynamics or structure). However, not all signs are models. This is because, from a practical point of view, a model has to capture some aspect of the modeled entity, an aspect that one might be interested in. In order to be useful, the model must possess some internal structure that resembles the structure of the modeled entity.

If one is willing to accept a model as being some sort of a representation, it becomes evident that one can not easily refine the notion of a model via a certain relation to reality that it might have. Since our perception is also a representation of reality constructed by our mind or our brain, one can only meaningfully speak of relations among models. Falsification then consists in a certain type of mismatch between the structure of two models, one of which we feel is closer to reality. Whether it is possible or necessary to refine the distinction between sign and model will be left open. As a weak substitute for such clarification, it is noted that the classes of biological models listed here adhere to the admittedly vague characterization given. They are all representations of a biological process or structure, and their goal is to convey information about the internal workings of the entity they represent.

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Herausgegeben von
Brigitte Falkenburg
und Susanne Hauser

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