



# Modeling and Simulation in Evo-Devo

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## Contents

Introduction .....	2
Modeling as a Distinctive Strategy .....	2
The Aims of the Modeler .....	4
Two Kinds of Progress in Modeling .....	5
Trade-Offs and Model-Model Relationships .....	6
Exploring and Contrasting Possibilities in Evo-Devo .....	7
Summary .....	8
Cross-References .....	9
References .....	9

## Abstract

Modeling and simulation are increasingly important as tools in many scientific disciplines. Our aim in this chapter is to outline some key aspects of modeling, illustrating our discussion with examples from evo-devo and emphasizing features of particular relevance to the discipline. We begin by characterizing modeling as a distinctive two-step theoretical strategy in science. Then we highlight the role of the modeler's aims in assessing a model, distinguish two types of progress in a modeling tradition, and outline the influential idea of trade-offs in modeling. Last, we focus on modeling as a way to clarify the link between evolution and development.

## Keywords

Modeling · Simulation · Scientific strategies

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## Introduction

In this chapter, we sketch some key aspects of modeling, illustrating them with examples from evo-devo and connecting them to central aims in the field, such as the explaining the generation of variation. We begin by circumscribing the kinds of “models” of interest in the chapter, for the terms “model” and “modeling” are used broadly. In some uses, all theoretical activity in science is a kind of modeling; in others, the notion of a model encompasses diagrams or applies to “model” organisms. For this chapter, however, the models we focus upon are those that demand specialized technical skills to construct; skills particular to building and analyzing models, rather than any particular scientific discipline. Thus, the examples we use are mathematical models, such as sets of coupled differential equations, or computer simulations written in a programming language such as C or Python or R.

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## Modeling as a Distinctive Strategy

We view modeling as a distinctive two-step strategy for investigating and understanding a complex natural phenomenon:

- Step 1: the modeler(s) construct and study a simplified analogue of the phenomenon. This is the model.
- Step 2: insights drawn from investigating the model are used to say something about the original phenomenon (the target).

These two steps provide a framework that helps organize the topics we cover below and can be illustrated with a concrete example. Consider one modeling approach used in evo-devo where Boolean equations capture gene regulatory interactions and their changes over time (see the chapter “Modeling Evolution of Developmental Gene Regulatory Networks”). In these models, gene expression is either on or off, and controlled by a Boolean function that responds to whether other genes are on or off (Kauffman 1969). Typically, time is divided into discrete steps, so gene **A** might be switched on at time  $t+1$  when gene **B** is on and gene **C** is off at the previous time-step,  $t$ . In this case, **B** is an excitatory regulatory connection and **C** is inhibitory. This modeling approach allows networks of gene regulation to be represented with sets of interrelated Boolean equations. Incremental changes to these equations, such as changing the logic functions or the genes referenced in the equations, capture the evolution of the regulatory networks.

In step 1, the role of simplification is crucial. Models are inevitably partial (or abstract) representations of the target: they include a selection of the target’s features and rarely aim for completeness. And models are often highly idealized, making assumptions that are known not to hold of the target. Thus, modeling simplifies the target, often replacing it with something that is false. This may make the model more readily comprehensible, easier to analyze, or simply render the problem tractable, given mathematical or computational constraints. The Boolean

models mentioned above are abstract: focusing on gene regulation clearly omits many other features of regulation and development process. The Boolean models also are idealized: we know that genes are not simply on or off, but can be transcribed at a variety of different rates. Yet such assumptions clearly make building, analyzing, and exploring the model far more tractable. We will come back to this important issue in the sections about “aims” and “trade-offs.”

Importantly, in Step 1, the model has a standing of its own – it can be, and often is, studied independently of its bearing on the target. This might require some formal analytic proofs if the model is a set of equations, or perhaps the statistical analysis of data produced by many runs of a simulation. This first step typically represents a significant proportion of what we consider “modeling”. For example, Boolean Networks are often studied with little mention of actual biology; instead, the goal has been to more deeply understand the model itself (see, e.g., Aracena et al. 2009). We return to this issue in the section about “progress” in modeling.

In Step 2, we tie the insights drawn from the model back to the *target(s)* – one or more systems in the natural world that the model represents and that we aim to understand with the model’s aid. Targets can range from specific events and processes with known empirical significance to far more general phenomena with less direct connections to familiar empirical cases. For example, Peter et al. (2012) construct a Boolean gene regulatory model with over 50 genes based on years of meticulous studies of the initial stages of sea urchin development. They use the model to explore the outcome of manipulating particular genes and compare these outcomes to experimental manipulations. The target in this case is highly specific: the regulatory system of a particular animal. In contrast, Payne and Wagner (2015) construct a Boolean model of gene regulation that contains only three genes. They use it to “systematically explore the relationship between circuit form and function” by generating nearly 17 million distinct three-gene circuits with different Boolean equations. In cases such as this, the models are not tracking a particular target, but are being used to explore the consequences of certain assumptions in a more generic domain (see Wimsatt 1987; Kokko 2007 for interesting general discussions). We return to this idea in the section on “exploring possibilities.”

Above we described this two-step approach as “distinctive.” By this we mean that the explicit focus on the model and its analysis contrasts with approaches to theorizing where scientists construct theories about the natural world with no intermediate analysis of a model. Classic examples of *direct* analysis are Darwin’s theory of evolution by natural selection or Mendeleev’s periodic table (see Godfrey-Smith 2007; Weisberg 2007). Neither used mathematical models in their theorizing. In contrast, the strategy of modeling operates *indirectly*. By this, we mean that we can break it into two steps outlined above. These steps need not be distinct, but it is helpful to think of them as separate steps for analytical purposes.

We can find both direct and indirect approaches in evo-devo. Consider two books: Kirschner and Gerhart’s *Plausibility of Life*, a book-length treatment of their theory of facilitated variation (Kirschner and Gerhart 2006) and Andreas Wagner’s *The Origins of Evolutionary Innovations* (Wagner 2011). Both books pursue the same central question: how is new variation generated? This topic falls under the rubric of

*evolvability* – a central theme in evo-devo (Hendrikse et al. 2007; see the chapter “► [Evolvability](#)”). Yet the way the authors address this question is different in each book. Kirschner and Gerhart lay out several general principles such as “weak signaling” and “exploratory processes” that capture aspects of developmental systems affecting their ability to produce new variation. These principles are distilled from a careful analysis of actual examples and supported by arguments that draw specific causal details of developmental systems. Wagner’s book also contains a good deal of detail about developmental systems. But for theorizing, Wagner derives his key results from highly idealized mathematical models and simulations of these systems. Wagner’s approach is indirect as his work relies on studying and theorizing about the models themselves. This does not mean that Kirschner and Gerhart’s ideas cannot serve as inspiration for constructing formal models (see Parter et al. 2008). Rather, it shows that their own approach to theorizing does not revolve around the use of formal models as an intermediary step.

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## The Aims of the Modeler

We characterized modeling as a two-step process. A modeler constructs and explores a model and then makes claims about the target based on properties of the model. What licenses this inference from model to target? This question has generated much discussion in philosophy (see Weisberg 2013 for an overview), but a key idea is that models must resemble their targets in some key respects.

The mere claim that a model resembles its target is not enough, however. Since a model omits, abstracts, and idealizes, we need to know which kinds of model-world resemblances matter and to what extent: they may be alike in terms of input-output profile and/or in dynamics and/or in qualitative versus quantitative details, and in various other respects. It is tempting to think we can answer this question by looking at the model and the target and judging the objective similarities and differences between them: treating genes as Boolean switches is a good approximation, or it is not. But this is too simple. The merits of a model are context-sensitive, and they depend on the aims of those using it. Ronald Giere captures this point by characterizing modeling in the following generic way:

*Scientists (S) use a model (X) to represent some aspect of the world (W), for specific purpose (P). (Giere 2004)*

Thus, what makes the resemblance between a model and target sufficiently good depends (at least partially) on what the modeler’s goals are when constructing and using it. For instance, a model might supply accurate predictions while not capturing important causal factors. If the modeler’s goal was understanding the causal structure of the target, then such a model may count as a failure, its predictive prowess notwithstanding.

Attending to the modeler’s goals is important because one’s goals may vary (and there may be more than one goal) even when similar abstractions are made in the

model. The contrasting uses of Boolean models above by Peter et al. and Payne and Wagner supply one example of this. Both models use a simple Boolean representation of gene expression and regulation, but their aims are very different. Peter et al. use their model to predict outcomes in one particular system, while Payne and Wagner use their model to make a very general point about the relationship between regulatory architecture and its function.

These goals can vary even when scientists use the same model. Consider a sophisticated model of the evolution of tooth development built by Salazar-Ciudad and Jernvall (2002). The model has several layers: it captures the interaction of gene products and their regulation, the physical forces governing cell growth and division, and the diffusion of signaling molecules between cells. It can produce a wide variety of three-dimensional shapes comparable to actual tooth shape by comparing the number and location of cusps: the pointy outcrops on a tooth's surface. This model figures in several papers; here, we contrast just two of them (see also the chapter “► [Computational Modeling at the Cell and Tissue Level in Evo-Devo](#)”). The first, “A computational model of teeth and the developmental origins of morphological variation” (Salazar-Ciudad and Jernvall 2010), focuses directly on the evolution of tooth morphology, showing that by “systematically tinkering” with their model, it could produce a wide variation of shapes, comparable to those found in an actual population of seals. The second paper, “Adaptive dynamics under development-based genotype–phenotype maps” (Salazar-Ciudad and Marín-Riera 2013), uses the same model but, as its title suggests, the focus is on something far more general. Here, the model is used to obtain generic insights into the interaction between natural selection and development. These two papers have different aims, and thus we need to test the adequacy of the model with different criteria in each case. For example, the more general claims made in the second paper rely on a key assumption: that the tooth model represents development in general. The aims of the modeler thus form an important part of any modeling endeavor, and of evaluating its success (see Wimsatt 1987 for examples of the rich diversity of aims).

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## Two Kinds of Progress in Modeling

Like the living world, modeling projects change, diversify, and often go extinct over time. Paying attention to the trajectory of a modeling project is informative because it highlights a common worry regarding models: they oversimplify the empirical realities of the systems under study. When we look at a productive modeling project over time, we can often see two types of progress, each related to one of the two steps of modeling described above (Levy 2011).

*Internal progress* occurs when improvements are made to the model itself – a more elegant, tractable mode of representation is discovered, complexities and details get added, a new analytical technique provides deeper or more widely applicable insight. (whether and to what extent this will count as progress will also depend on the inquiry's goals). In contrast, *external progress* involves improvements regarding how well the model captures real-world phenomena, increasing one's

understanding or predictive capacity regarding the target. This mode of progress requires validation of results vis-à-vis the world, and a closer tracking of targets.

Both modes of progress can be important and valuable – internal progress increases one’s understanding of the model, perhaps allowing one to explore more possibilities or provide additional confidence in the results. External progress, in contrast, enhances one’s understanding *of the world* through the model. However, it is important not to confuse the two modes, and some criticisms of modeling projects (such as their degree of realism, or concerns about the legitimacy of idealizations) can be seen as making such a charge.

Consider, for example, reaction-diffusion models originating with Turing (1952). These models portray basic pattern generation processes via a simplified scenario in which a pair of diffusing morphogens interact with each other and with embryonic cells. (Interestingly, Turing was entirely self-conscious of his modelling approach, noting early in his paper that “this model will be a simplification and an idealization, and consequently a falsification” (p. 37).) Subsequent work saw a steady course of development of these models for the next 40 or 50 years (Kondo and Miura 2010). It would have been easy to view this as progress in explaining actual pattern formation. But, in fact, only more recently have we seen empirical, external progress (Vanag and Epstein 2009). It now appears somewhat more reasonable to conclude that reaction-diffusion models have advanced our understanding of *actual* pattern formation processes. We have made external progress regarding pattern formation.

This example illustrates several points concerning the practice of modeling. First, the two-step process has definite utility, as it can free the modeler from the need to keep close tabs on the empirical applicability of her work, thus allowing her to make headway on more in-principle aspects. At the same time, it is important not to confuse this kind of internal progress – primarily at the mathematical level alone and involving an increased understanding of the model itself – with progress on understanding the model’s target.

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## Trade-Offs and Model-Model Relationships

Following a seminal paper by ecologist Richard Levins (1966), many see modeling as a balancing act in which one is attempting to satisfy multiple, partly conflicting goals. Levins highlighted three such goals: generality, precision and realism. His principal idea was that these three desiderata often trade off against each other: to be realistic, a model has to either sacrifice generality, applying faithfully to a small set of targets and/or sacrifice precision, because a complex realistic model is often not amenable to exact analysis. Likewise, if one aims for generality – especially if one also aims to attain exact results in one’s modeling – this requires idealization and approximation, thus resulting in an unrealistic model. Other potential trade-offs also exist, such as between explanatory power and predictive accuracy. The extent to which a given accuracy or insight counts toward a model’s success will depend on the goals with which it is put forward. Sometimes a qualitative, yet explanatorily valuable model is preferable to an accurate yet less explanatory one (or vice versa).

This conflict between different modeling goals is relevant in evo-devo models as these trade-offs must be made regarding both evolution and development – processes that operate across very different timescales. In most traditional evolutionary models, the representation of the relationship between genotype and phenotype (or fitness) is highly simplified. Yet this is often coupled with a model of evolutionary change that is meant to accurately track information about changes in genetic variation. In contrast, a model that incorporates phenotypic or developmental detail might adopt a very simple view of evolutionary change. Niklas (1994), for example, explores the rise of disparity in plant shape using a model of plants that combines facts about their development, morphology, and fitness. But the same model tracks evolution using a simple hill-climbing adaptive walk, thus ignoring many important details about evolution change, such as mutation rates. Our point is that it is possible to make different trade-offs regarding different parts of models, so a model may be realistic with respect to development, but highly abstract where evolution is concerned.

We can address the conflict between these desiderata in various ways. Levins himself suggests building multiple models of the same phenomenon, each embodying a different trade-off, to give it a more complete treatment. Another approach is to clarify the limitations of one's assumptions and methods. Developing this understanding is itself a modeling endeavor, typically proceeding by contrasting different modeling approaches. For example, Jong and Ropers (2006) compare several qualitative approaches to gene regulation including the Boolean regulatory models mentioned above. They conclude that understanding the connectivity of interactions in networks, rather than tracking the precise details with high accuracy, may explain how a network behaves. Depending on the aims of the modeler, analyses like this may justify when and why certain trade-offs can be made.

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## Exploring and Contrasting Possibilities in Evo-Devo

We have described models as standalone systems, one step removed from the real world. Most times, such systems do not represent any actual phenomenon in the world. Seen in this light, models are an excellent arena in which to explore a space of possibilities: How could a particular trait evolve? What would occur if such-and-such a constraint were present? How would an organism of *this* sort respond to *that* kind of selection pressure?

One modeling approach used to explore possibilities relevant to evo-devo is the construction of a *developmental morphospace* (see the chapter “► [Mechanisms of Pattern Formation, Morphogenesis, and Evolution](#)”). This is a multidimensional space where each of the dimensions captures some aspect controlling the generation of a particular morphology. Raup's shell morphospace (Raup 1966) is a well-known example. Raup used a mathematical model with just four parameters to generate a huge variety of different shell shapes. Many of the resulting regions of the resulting four-dimensional morphospace held shell shapes that could be categorized into taxonomic groups. But there were also shapes that no shell has ever taken. It was

these unrealized possibilities that many found interesting. Were these shapes absent because they were selected against or was there some developmental constraint preventing them from being generated at all? Reflecting on this model played a central role in one early cross-disciplinary effort to link evolution and development using *developmental constraints* (Smith et al. 1985; see the chapter “A Macroevolutionary Perspective on Developmental Constraints in Animals”).

Using models to generate and explore these possibilities provides a rigorous approach to thinking about what kinds of phenotypic variations are possible and the connections between them. A morphospace is not the only example – above we referenced a model that generated a space of gene regulatory circuits. Such modeling endeavors are not without problems, however. Because they are highly abstract and idealized, they often draw on subtle assumptions about the way a model represents the world. For example, visualizing a morphospace often prompts ideas that draw on the distance between different shell shapes or the relative size of regions of shell shapes. But distance and volume in morphospace may reflect the model’s mathematical assumptions more than reality (see Mitteroecker and Huttegger 2009). Again, this highlights the two steps in modeling: regardless of how rigorous the model itself is, we must be careful when interpreting how models map to the world.

Importantly, this ability to contrast different possible scenarios places modelers in an ideal position to pursue a central aim of evo-devo: to clarify when and how development makes a difference to evolution. One way to do this is by contrasting the performance of several related models, and then identifying what factor *makes the difference* between them. For example, Jiménez et al. (2015) explore six different regulatory mechanisms that can produce the same patterning in multicellular development. They show that, despite producing the same pattern, these mechanisms vary in their propensity to generate new patterns under mutational changes. The difference-maker, in this case, is the developmental mechanism generating the particular pattern. By showing the contrasting evolutionary effects produced by the different possible mechanisms, such modeling demonstrates why development is essential to understanding the trajectory of evolutionary change.

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## Summary

Modeling is a particular scientific strategy, with distinctive advantages and pitfalls. In this chapter we highlighted some core features of this strategy, including the role of idealization and abstraction, its “two-step” structure, and the importance of the goals of a modeler. We also exposed some possible problems associated with modeling, such as confusing internal and external progress. Last, we emphasized the importance of modeling for evo-devo, of how it can highlight the role that developmental processes play in understanding evolutionary change.



## Cross-References

- ▶ [A Macroevolutionary Perspective on Developmental Constraints in Animals](#)
- ▶ [Computational Modeling at the Cell and Tissue Level in Evo-Devo](#)
- ▶ [Evolvability](#)
- ▶ [Mechanisms of Pattern Formation, Morphogenesis, and Evolution](#)
- ▶ [Modeling Evolution of Developmental Gene Regulatory Networks](#)

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