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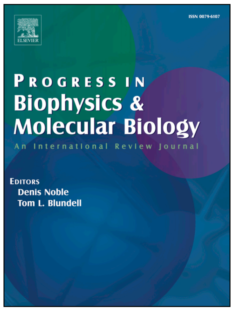

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ACHILLES AND THE TORTOISE

Some Caveats to Mathematical Modeling in Biology

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Abstract

Mathematical modeling has recently become a much-lauded enterprise, and many funding agencies seek to prioritize this endeavor. However, there are certain dangers associated with mathematical modeling, and knowledge of these pitfalls should also be part of a biologist's training in this set of techniques. (1) Mathematical models are limited by known science; (2) Mathematical models can tell what *can* happen, but not what *did* happen; (3) A model does not have to conform to reality, even if it is logically consistent; (4) Models abstract from reality, and sometimes what they eliminate is critically important; (5) Mathematics can present a Platonic ideal to which biologically organized matter strives, rather than a trial-and-error bumbling through evolutionary processes. This "Unity of Science" approach, which sees biology as the lowest physical science and mathematics as the highest science, is part of a Western belief system, often called the Great Chain of Being (or *Scala Natura*), that sees knowledge emerge as one passes from biology to chemistry to physics to mathematics, in an ascending progression of reason being purification from matter. This is also an informal model for the emergence of new life. There are now other informal models for integrating development and evolution, but each has its limitations.

Keywords: Mathematical modeling; evolution; development; epigenetic landscape; dialectics

1. Introduction

While I enjoy mathematical models, I am deeply suspicious of them. So, I thank the organizers for their tolerance in inviting me to a symposium celebrating the centenary of D'Arcy Thompson's magisterial book *On Growth and Form.* I tend to agree with Thompson's contemporary, Alfred North Whitehead, on many things, including his dictum (Whitehead 1919) that the motto of every scientist should be "Seek simplicity and distrust it." Mathematics abstracts complex biological phenomena and simplifies them. I tend to distrust such simplifications in biology.

Models come in several major forms (Gunawardena 2014a). There are *mathematical* models (often called "formal models") such as the laws of gravitation and thermodynamics. But this is not the only type of model. There are *intellectual* models (sometimes called "informal models" in contradistinction to the mathematical ones) such as evolution, which are frameworks in which to place new data. And there are "physical models" such as the DNA double helix or the planetary atom, which similarly abstract information, decide what is important, and represent it physically. In biology, there are also "model organisms," such as *E. coli* and *Drosophila melanogaster*, which purport to be relatively accessible species where the information acquired in studying them can be extrapolated into numerous other species. The major part of this article will concern mathematical modelling, while the second half will concern some intellectual models.

2 Critiques of mathematical modeling in developmental and evolutionary biology

Since I am not a practitioner or theorist of computer modeling, I will be discussing (a) critiques of mathematical modeling, *i.e*, why I think mathematical modeling is powerful, and as with any powerful entity, it must be powerfully regulated, (b) the *model of science* that celebrates mathematical modeling as the best way to do science, and (c) other non-mathematical models of evolutionary developmental biology**.** In this regard, I follow a liberal arts tradition, attributed to

Carnap (1937), “Anything you can do I can do meta.” By model, I am using Ian Barbour’s (1974) definition that “a model is a symbolic representation of selected aspects of behavior of a complex system for particular purposes. It is an imaginative tool for ordering experience, rather than a description of the world.”

This last point is critical—a model is *not* representing reality. It is abstracting some processes from reality so they can be logically ordered. Models are abstractions, tools, and are not descriptions. As Latour and Hermant (1998) and Gerard de Vries (2016) have concluded, the models, the pictures in our mind, do not correspond to reality, but with other pictures in our mind.

2.1. Critique 1: Mathematical models are limited by the science known at the time.

Since models are not descriptions of reality, but tools that allow coherence with other models, they can be deleterious to other scientific programs that may be better at depicting reality. To use an evolutionary phrase, they may form a peak of local fitness that prevents one from getting to a peak of even higher fitness. My first critique of models is that models are limited by the scientific paradigms of their times.

The chief exemplar of a model being constrained by the science of its times is Sir William Thomson’s (Lord Kelvin’s) disproof of Darwin’s theory of evolution (Thomson 1862; Livio 2013). Darwin went to his grave worrying about Lord Kelvin’s “odious” critique of his evolutionary theory. Since physics has models wherein every piece of macroscopic matter in the universe—whether an apple or a planet—is subject to pre-existing mathematical law, it has enormous power. Which is why William Thomson could confidently declare that the sun could not be more than 100 million years old, far younger than Darwin needed for his theory. (Turtles, for instance, are thought to have originated some 260 million years ago; insects probably arose 400 million years ago.)

On the basis of the sun’s being a molten ball that could not regenerate the heat it lost from conduction and radiation into space, the laws of thermodynamics predicted its having a rather short span of activity. Lord Kelvin did not know that solar energy came from nuclear fusion and not combustion. (Kelvin did believe in some sort of Theistic evolution; but time was too short for Darwin’s natural selection.) Thus, Lord Kelvin’s mathematics were good, but they could only conform to the non-applicable science. Thomas Huxley (1869), Darwin’s champion and President of the Geological Society of London, could not let Thompson’s challenge go unanswered. “I desire to point out,” he declared, “that this seems to be one of the many cases in which the admitted accuracy of mathematical processes is allowed to throw a wholly inadmissible appearance of authority over the results obtained by them. Mathematics may be compared to a mill of exquisite workmanship, which grinds you stuff of any degree of fineness; but, nevertheless, what you get out depends on what you put in” (Huxley, 1869; Gould 2002). So here we have the GIGO (Garbage In/Garbage Out) principle of computer science, expressed politely and explicitly by Dr. Huxley.

Many other intellectual models have also suffered from this fallacy. The original model of DNA synthesis was based on crystal replication. (No enzyme known at that time took instructions from its substrate. DNA polymerase was the first such protein known wherein the substrate—in this case, the sequence of nucleotides--determined the product.) Similarly, Darwin’s model of hereditary transmission was based, like Lamarck’s, on the known physiology of use and disuse. So, the first caveat I wish to make about mathematical models is that they are limited by the scientific paradigms of their times.

2.2. Critique 2: Mathematics can tell us what can happen, not what does or did happen.

J. B. S. Haldane is reputed to have said (Maynard Smith 1965) that “an ounce of algebra is worth a ton of verbal argument.” However, a set of molecular interactions can be worth more than any equation. I pursued my PhD in a laboratory focusing on the human X chromosome. As such a student, I learned the Bayesian statistics to counsel pregnant women whose families had an X-linked disease. Depending on how many male relatives did not have the disease, one could ascertain the prior, conditional, and joint probabilities for that woman carrying an affected fetus. However, once PCR and SNPs were identified for X-linked genes whose mutations caused hemophilia and Duchenne muscular dystrophy, that mathematical knowledge became about as useful as my slide rule[1]. You no longer quote a probability; you show a Southern blot. You can find out if a fetus has the disease-causing allele.

Simply put, a mathematical model tells us that a phenomenon CAN happen that way. Molecular biology tells us a phenomenon most likely DOES happen this way. Mathematics is a half-way house. This is certainly how I see QTLs. QTLs don't identify a gene. They give a probability that a gene involved in producing a particular phenotype is within a particular domain of the chromosome. This "half-way house" status is also the case for reaction-diffusion mechanisms. These models cannot distinguish an activator of an activator from the repressor of a repressor.

Thus, mathematical and logical models can tell what might have happened; but they cannot tell what actually did or does happen. The danger is that these models form a local fitness peak from which it is difficult to migrate[2]. However, this ability to tell what might have happened highlights the importance of mathematical and logical models in those areas where events are not able to be repeated or when the actual molecules are not important. For instance, the models recently proposed by Montevil and Mossio (2015) for the origin and maintenance of biological organization frees one to think in a new way and are not dependent on particular molecules. Similarly, in one of the pioneering applications of mathematical modeling to developmental biology, Jonathan Bard (1977) demonstrated how the timing of neural crest differentiation can generate all the known striping patterns in extant zebra species.

This ability to mix experimentation and modeling is also why the research of some of the scientists at this conference (Fred Nijhout, Stuart Newman, and Jukka Jernvall, for instance) is so critical. Stuart Newman and Jukka Jernvall are combining reaction-diffusion models with experimentation to find the actual molecules used to make organs such as limbs and teeth, respectively (*e.g.* Glimm et al 2014; Harjunmaa et al 2014); and Fred Nijhout has been able to model the non-linear one-carbon metabolism for wild-type and mutant human phenotypes

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[1] A portable non-electronic calculator that somehow got us to the moon and solved the structure of DNA (Smithsonian 1984; Chadarevian 2003).

[2] A similar analysis concerning the ability of mathematical analysis to provide only "can happen" rather than "did happen" explanations has been proposed independently by Alan Love (2017).

(including those with cryptic genetic variation), because such metabolic networks “are among the few systems in which the structure of the entire system and the kinetics of the components are well enough understood to be able to develop accurate mathematical models” (Nijhout and Reed, 2014). In addition, the recent work of Arkhat Abzhanov (2017) has shown the molecular correlates of those scale and shear factors that could cause the skull shape differences diagrammed in Thompson’s “theory of transformations.” Unlike Thompson, though, Abzhanov’s work is underlain by data from the experimental analysis of development.

It should be noted that this interpenetration of mathematical modeling and experimentation to study development and evolution is not new. It can be seen as the regeneration of Hans Przibram’s biological research program that had been truncated by the Austrian Nazis in 1938. In 1902, Przibram had helped establish the Biologische Versuchsanstalt “to enable a quantitative treatment of biological problems.” Concentrating on the relationship of animal and plant development to evolutionary biology, it sought to “make biology an exact science” with “a mathematical theory of organic life, based on quantitative measurement and linked with geometry, physics, and chemistry” (Przibram 1913; Müller 2017). Both Paul Weiss and Ludwig von Bertalanfy would base their versions of systems theory of Przibram’s work. Przibram knew Thompson, and Thompson sent graduate students Dorothy Wrinch and Joseph Woodger to work with Przibram in Vienna. Thompson and Przibram grew apart, however, as Przibram felt that Thompson de-emphasized evolution, and Thompson felt that Przibram’s zealousness for experimentation was misplaced (Müller 2017). As Seneschal claims, the two were allies in the nascent campaign to infuse biology with physics and chemistry, but “where D’Arcy Thompson saw analogies, the Przibram brothers did experiments” (Senechal 2012). Müller (2017) sees Hans Przibram as forerunner not only to Thompson, but also as the person whose integration of modeling and experimentation helped initiate and fuse together evolutionary developmental biology and theoretical biology. Such integration of experiment and modeling is paramount for evolutionary developmental biology.

2.3. Critique 3. Real-world models can provide a better explanation than the mathematical model.

Kepler’s mathematical laws of planetary motion work, and Newton figured out a gravitational explanation for them. But the mathematical and physical explanations do not explain why the actual planets have such nearly circular orbits. Other orbits are mathematically possible. Planets whose orbits are circle-like ellipses survive because if the orbits were more elliptical, shear forces would rip the planets apart when they reached the periapsis of the orbit. There appears to be natural selection of those orbits favoring circle-like ellipses (Harris and Ward 1982). There are real world limits to what reason can solve.

The “models” for this type of error are Zeno’s paradoxes, where Zeno claimed to have disproved the concept of motion. For instance, the logical paradox of Achilles and the tortoise, “proves” logically that the tortoise, if given any head start, cannot be caught by the logically minded Achilles (Dowden 2009). Diogenes the Cynic is supposed to have walked out of Zeno’s lecture, saying that his physical action refutes Zeno’s mathematical logic.

When I was a newly minted assistant professor, a model emerged that promised to revolutionize developmental biology. This was Stuart Kaufmann’s (1981) binary code model that progressively partitioned the *Drosophila* embryo into 14 distinct regions. The model was simple, it was elegant, and it explained so much of the data. And when the first RNA localization studies on *Drosophila* embryos were published, the location of critical developmental gene transcripts followed exactly the partitions predicted by the model. Unfortunately, as the details of the transcription activators became known, the origins of this order were found to have little to do with the beautiful mathematics. Rather than a utilizing a unified global ordering system, the transcription was performed “inelegantly” by local contractors (Akam 1989). Like much of biology, it was dirty and contingent, not lawful and spare[3].

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[3] This does not mean that such global generic mechanisms weren’t present in earlier organisms to initiate these patterns (Nanjundiah 2005; see Newman and Forgacs 2006; Newman 2016), that a pre-pattern might originate in the surrounding cells (see González-Reyes and St. Johnston 1998), or that other species may use such generic mechanisms. However, such global systems have not been found in contemporary *Drosophila*. The importance of experiments for rejecting models and suggesting other alternatives is a critical part of normative science (see Bard and French 1984).

So, my third criticism is that mathematics can give a model that explains the phenomenon, but which does not work as nature actually does.

2.4. Fourth critique: in abstracting reality, the things left behind can be very important.

The best example of abstracting out important things is probably in evolutionary theory. The mathematics of population genetics is based on a notion of fitness where there is a single genome in each animal, the genes determine the phenotype as a direct readout, and the environment selects those genetic combinations that best fit into the environment. This means that symbiosis (multiple genomes functioning in an organism) is a rarity, important only in lichens and such; that developmental plasticity (where the environments help instruct the phenotype of an organism) can be ignored as marginal; and that the environment is a preformed entity that selects the phenotype that can best fit the pre-existing conditions.

We now know that these assumptions are not correct (Gilbert and Epel 2015; Sultan 2015), and their corrections have become the basis of the "Extended Evolutionary Synthesis" (Laland et al 2015). We know that the origin of species may not always, or even usually, come from the slow accumulations of structural gene mutations. First, evolutionary developmental biology has shown that mutations of regulatory genes can produce relatively rapid anatomical changes (Carroll 2006). Second, symbiosis is critical for development in many, if not all, species, and it provides selectable genetic variation (Gilbert et al 2015; Brooks et al 2016; Roughgarden et al 2017). There is more than one functional genome per individual, and variation from symbionts can be inherited in several ways. Third, plasticity is the norm, and animals have evolved to be able to recognize and process signals from the environment to generate the best phenotype it has in its repertoire (Pigliucci 2001; West-Eberhard 2003; Gilbert et al 2015). Moreover, the developing embryo can also alter the environment. This is the idea of niche construction (Odling-Smee et al 2003; Laland et al 2008). The modern synthesis is, at best, a first approximation of evolution, because it abstracted away these four critical features, thinking that they were marginal.

Developmental biology has also been prone to such abstractions. "The mammalian placenta" does not exist. There are many types of placentas, each having different modes of blood flow.

Similarly, developmental biologists will talk about “amphibian gastrulation,” even though the modes of gastrulation differ enormously from one group of amphibians to another. These abstractions have often been based on our having a model organism that “represents” the others of its clade—the mouse *Mus musculus* as representative mammal, the frog *Xenopus leavis* as model amphibian; *Drosophila melanogaster* as model insect. Thus, both evolution and development have restricted themselves by having models that abstract the physical reality way from organisms.

2.5. The fifth critique. Mathematical models can be Platonic rather than evolutionary. This critique, which pertains to the models of D’Arcy Thompson, is that such models can become Platonic archetypes to which matter strives, a telos. According to Thompson (1917; p. 1097), “Not only the movements of the heavenly bodies must be determined by observations and elucidated by mathematics, but whatsoever else can be expressed by number and defined by natural law. This is the teaching of Plato and Pythagoras, and the message of Greek wisdom to mankind.”

Here, modeling looks at biology as something Platonic rather than something evolutionary. As Evelyn Hutchinson (1948) and Stephen J. Gould (1971) point out, Thompson’s 1917 opus is a theory of the production of form through geometric changes. It provides a perfect mathematical goal to which organisms may be seen to be striving. Thompson maintains that the deviations from the mathematical are unimportant. But one must remember (as Haldane did), that mathematics can only model regularities, and that evolution has a large component of contingencies (see Rao and Nanjundiah 2017). Evolutionary changes are what economic modelers aptly call “black swans.”

There is a danger that, rather than modeling evolution or development through evolutionary selection, the models become ideas, and evolution becomes merely the trajectories toward a pre-existing endpoint. Thus, once you can place the phenotype into an equation, you have “solved” the problem. The equations are pre-existing attractors[4].

In our research (Moustakas-Verho et al 2014), modeler Rolf Zimm found that turtles can form their scutes using two sequential reaction-diffusion systems. This was exciting because the properties of this model could also explain why turtle scute patterns are nearly identical in all species. But this may not be the optimal evolutionary situation, a pre-destined mathematically determined goal. The turtle was "locked" into having that pattern of scutes if it had scutes at all. This is not a pre-defined endpoint. Indeed, when softshell turtles modified this pattern, they became scuteless.

3. The model of science that claims models are the goal of science

3.1. The Great Chain of Being

So why do we give priority and even hegemony to mathematical models? Our structuring of science is often organized by a model that originated in ancient Greece, dominated Medieval and Renaissance Europe, and which still pervades our education system: ¨The Great Chain of Being." *This is the model of science that says that science should strive towards mathematical models*. The Great Chain of Being (sometimes called the *Scala Natura*) has been the predominant mode of ordering the universe from ancient Greeks through the present. Supposedly destroyed by the branched tree of Darwinism, and supposedly destroyed by the inversion of priorities that was Romanticism, it continues to dominate the way we order nature. Indeed, if we want to see how models influence us, one might not find a better example.

Basically, the Scala Natura is ordering of entities from pure matter to pure idea. At its base are rocks and dirt. Then comes minerals, then plants, then animals, and then humans. After humans came the orders of angels, and thereafter, there has been debate as to whether God is the highest entity in the chain, or that which is outside it (Lovejoy 1933). During the formation of science as a discipline, the Great Chain of Being reigned supreme. As Arthur Lovejoy noted, "Next to the word 'Nature', 'the Great Chain of Being' was the sacred word of the eighteenth

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[4] Toulman (1990) and Latour (2017, pp. 185-190) speculate that the "real" scientific revolution, that of Erasmus and Montaigne (stressing doubt and uncertainty), was hijacked and re-directed by the mathematically inclined natural theologians, who desired certainty and obedience to divinely ordained laws.

century, playing a part somewhat analogous to that of the blessed word 'evolution' in the late nineteenth."

The Scala Natura was the basis of Lamarckianism, which was basically turning the Great Chain into a Great Escalator. It is the basis of the "missing link," which was a link in the Great Chain (Gould, 1977). It is very much with us today in written and graphic depictions of "evolution" (Rigato and Minelli 2013). Indeed, when many people think about evolution, what they think about is not a branched tree, but a great chain. The chain was seen (and still sometimes is still seen) as being totally complete, where there are transitions from one group to another. Polyps, for instance, were either the highest plant or lowest animal. Negroes and women, as well as fossil apes, were seen to connect white men to the apes (Stepan 1982; Haller 1995). The Great Chain could be a very dangerous concept.

The Great Chain of Being still frames our world; but rather than extending across the universe, it extends mainly across the university. If I were to ask you what is the lowest natural science, you'd probably say biology. It deals with dirty matter. The next highest—chemistry. It deals with purified matter. The next highest—physics. It deals with idealized matter. And the next highest would be mathematics, which celebrates its separation from matter and material analogy. And there are bridge disciplines. The lowest biology: ecology, which is dependent upon contingent matter. The highest biology, molecular biology, connects to the lowest chemistry, biochemistry. The highest chemistry, physical chemistry, is still dirty physics. The highest, theoretical, physics joins math (see Anderson 1972; Gilbert et al 2000)**.** From dirty matter to pure logic—that is the Great Chain.

This notion of impurity and purity, of material vs ideal, lay behind the reductionist programs of scientific unity that saw mathematics as the goal of all sciences (Cat 2017). Physics came closest to math, and biology was lagging far behind. Galileo wrote that the Book of Nature was written in the language of mathematics and geometrical proofs. Biology was only a science in so far as it could be reduced to physics and mathematics. Besides physics, every other science, in the words of physicists Kelvin and/or Rutherford and/or Feynman (O'Toole 2015) was merely "stamp collecting."

Indeed, the Great Chain of Being is the model that emphasizes the importance of mathematical models. It is the meta-model that causes biology to be seen as an inferior science. It is so engrained in our culture that it often goes unquestioned, and is therefore dangerous. One of the best depictions of this was Randall Munroe’s (2008) XKCD cartoon “Fields Arranged by Purity,” showing the representatives of the sciences on a line. At the far left end of the line, the psychologist looks at the forlorn sociologist, saying, “sociology is just applied psychology,” while the biologist tells him that “psychology is just applied biology.” The chemist tells the biologist next to him says that “biology is just applied chemistry,” only to be told by the physicist that chemistry “is just applied physics.” The physicist says, “It’s nice to be on top.” However, far to the right of this linear group, a mathematician yells to them, “Hey I didn’t see you guys all the way down there.”

3.2. Putting biology on a mathematical foundation: The Geometry of *On Growth and Form*

So “Is biology a science?” was a question in the early 1900s. And for the most part, it wasn’t. It was “natural history” or agriculture. Physics was a science. (One of the differences between the Science and Technology Studies (STS) and History of Science was that STS took biology seriously as a science.) To be a real science, biology needed an overarching theory—which it received with evolution; and evolutionary theory needed to be placed on a mathematical basis. There were two main ways of doing this. One was D’Arcy Thompson’s geometric and physical analysis of organisms. The other was the Modern Synthesis, based on the algebra of population genetics done by Fisher, Haldane, Wright, and Chetverikov.

D’Arcy Thompson was one of the great explicators of the Great Chain in science. His first sentence of *On Growth and Form* (1917) reiterates Kant’s view that a discipline is a science in proportion to the role played by mathematics. The next thousand pages are ways of bringing mathematics and physics into biology, and the last chapter brings us back to this goal, where the dominion of mathematics said to be the proper study of the physical world, “within this range, her dominion is supreme…” (p. 1097).

Indeed, in science, mathematics will replace the language of description: “We begin by defining the shape of an object in the simple words of common speech: we end by defining it in the precise language of mathematics... we are brought by means of it in touch with Galileo’s aphorism (as old as Plato, as old as Pythagoras, as old perhaps as the wisdom of the Egyptians), that the Book of Nature is written in Geometry.” (p. 1026). Moreover, once the geometry is known, “we rise from the conception of form to an understanding of the forces that gave rise to it…and the direction of the forces which have sufficed to convert the one form into the other.”

These forces are those of physics, and these physical laws are mathematical. Citing Poincare, Thompson writes (P. 1028) that only mathematics can account for the approximation of perfect geometry and the deviations from them that one sees in nature. Biologists, he writes, claim separation from mathematics by invoking the departure from mathematical regularity in nature. “This seems to me to involve a misapprehension. There is no essential difference between the phenomena of organic form and those which are manifest in portions of inanimate nature…”

And here, on p. 1032, is an important point: Mathematics may be able to tell us the shape of a snail shell and the twist of a horn, but we should not get lost in the details of individuals. “Even to do this, we must learn from the mathematician to eliminate and to discard: to keep the type in mind and leave the single case, with all its accidents, alone; and to find in this sacrifice of what matters little and conservation of what matters much one of the peculiar excellences of the method of mathematics.”

This is a mathematical biology that finds the ideal, that abstracts away the contingent and the individual. It is a biology that seeks similarities, and sees the actual biological entities as accidents, secondary deviations. This was a difficult chore, and the biologists were not interested in it. I would argue that Thompson’s work doesn’t enter developmental biology until Alan Turing (1952) references it (without citation) in his *Chemical Morphogenesis* paper. As we will see, population genetics provided an alternative mathematical method. Indeed, the notion that physical changes can cause changes in development and provide the variation needed for natural selection didn’t become part of the modern developmental biology until the beginning of the 21st century. At that time, the reaction-diffusion models of morphogenesis (Meinhardt 1982), the physical models of Gurwisch and Beloussov from the Soviet Union (Beloussov 1997), and the generic and physical models of Ray Keller (2012) and Stuart Newman (2012; Newman et al 2006) began to be integrated into the genetic models that had characterized the science.

3.3. The Algebra of the Modern Synthesis

Rather, the mathematicization of biology that succeeded was that of genetics. Genetics dealt specifically with what Thompson told us to avoid: Deviations from the norm. Genetics was the mathematical science of biological differences, and its unit was the *allele*, which means “that which differs.”

Recall that Mendel’s work on peas was experimentation that enabled him to make a quantitative model of inheritance and to make quantitative predictions based on his model. Morgan then formulated gene mapping through crossovers; again, a quantitative method that predicted the distance of genes from each other on a chromosome. Morgan (1932a) linked the propagation of allelic differences directly to evolution, reinforcing the ideas of population geneticists with substantial data. Embryology would be excluded from evolution because it was neither mathematical or lawful in the sense of genetics (Morgan 1932b). Morgan is particularly nasty about this: Biology finally had laws, starting with Mendel’s, and he claimed that the biologist’s genes were like the chemist’s atoms. The phenotype was the readout of these genes, and that evolution was genetics writ large over huge swaths of time. Embryology, which had been seen as the motor of evolution, was to be thrown out and its place taken over by genetics (see Gilbert 1998).

Dobzhansky (1973) famously said. “Nothing in biology makes sense except in the light of evolution.” He also said (Dobzhansky 1951), “The study of the mechanisms of evolution falls within the province of population genetics.” Thus, nothing in biology appears to make sense except as seen in the light of population genetics. Equations and laws were fundamental. Biology was to imitate physics. Indeed, in other places, Dobzhansky (1962, p. 500-501) was explicit about this:

> Genetics is the first biological science which got in the position in which physics has been in for years. One can justifiably speak about such a thing as a theoretical mathematical genetics, and experimental genetics, just as in physics…. Since the times of Wright, Haldane, and Fisher, evolutionary genetics has been in a similar position.

Fisher's original fundamental theorem alluded to genes as atomized entities whose frequencies were dependent on the antagonistic principles of natural selection and mutation. He felt that the achievements of statistical mechanics were the ideals to which the statistical treatment of gene frequencies might someday reach. The goal was nothing less than the reformulation of biology along mathematical principles (and not the application of mathematical techniques to biology). However, Fisher realized the limits of his theories. The Preface to *The Genetic Theory of Natural Selection* (Fisher 1930) begins, "Natural Selection is not evolution."

Morgan and his laboratory, however, were to claim that development and evolution were the epiphenomenon of the laws of genetics, and I think it is fair to say that the genetic approach to the mathematicization of biology won over all others. It won by the reductionist strategy of reducing phenotype to genotype. Discussing the work of Fisher, Haldane, and Wright, Harvard systems theorist Jeremy Gunawardena (2014b) writes:

> The key step in setting up their formal model of population genetics was figuring out how to deal with selection, which in contrast to recombination and mutation, acted on the phenotype. Phenotypes are extraordinarily complicated, arising as they do from an intricate dialogue between genotypes, development, and the environment. …The solution they found was simplicity, itself. The phenotype—the organism, in other words—was omitted from the formal model, and selection was assumed to work on the genotype. Mathematically speaking, it was a stroke of genius, which set up a rigorously formulated problem of allele frequency dynamics while avoiding the morass of organismal biology. Biologically speaking, well, that was another matter…The stroke of genius in leaving the organism out now comes back to haunt a later generation of biologists.

There's a wonderful little story (Squier 2017) told by Lynn Margulis about a lecture Richard Lewontin gave on evolutionary theory to an economics class at the University of Massachusetts. When she asked him why he presented to the students a mathematical model of evolution that was "devoid of chemistry and biology," Lewontin answered—"physics envy…a syndrome in which scientists in other disciplines yearn for the mathematically explicit models of physics."

4. Non-Mathematical Models of Development and Evolution.

In addition to the formal, mathematical models, evolutionary developmental biology has inherited some “informal”, intellectual models and metaphors. Two of them are “landscapes.” The other involves musical performance, a type of mathematics far distant and more physical than the geometry of Thompson or the algebra of the Modern Synthesis.

4.1. The Epigenetic Landscape

Evolutionary developmental biology has no model, and D’Arcy Thompson’s transformations did not help. Although the evolutionary aspect of D’Arcy Thompson’s transformations can be traced to Thomas Huxley’s view of evolution, Thompson had no formulae for his shape changes; nor did it even try to relate these changes to development—he has no intermediate stages. Ontogeny does not recapitulate phylogeny, and the morphospace of Thompson’s crabs and fish are related to nothing genetic or developmental. So Evo-devo has had to contend with the two competing visual models that it inherited from its two major parents, evolutionary biology and developmental biology. These visual models are both landscapes—the fitness landscape and the epigenetic landscape. Donna Haraway (2105) calls this type of model a “figure.”

> Figuring is a way of thinking or cogitating or meditating or hanging out with ideas. I’m interested in how figures help us avoid the deadly fantasy of the literal...Figures help us to avoid the fantasy of “the one true meaning.” They are simultaneously visual and narrative as well as mathematical. They are very sensual.

The two landscapes are opposites in many ways, and they are similar in many ways. As Silvia Caianiello (2008) has adroitly shown, both these models aim at visualizing the behaviors of complex dynamic systems in terms of spatial relationships; and thus, both models are convolutions mapping migrating equilibria. Moreover, their strategy is to collapse multidimensional phase-spaces into a three-dimensional diagrammatic representation.

However, there are profound differences. The fitness landscape originated as a model for the shifting balance theory of evolution, and it served as a tool for biomathematical modeling. The fitness landscape is a visualization of population genetics, where a contour map is created to portray the relative fitness of individuals within a population. Sewall Wright helped construct these. However, according to Will Provine (1986)—no one really knows what the fitness landscape is, and it is "meaningless in any precise sense." If each dot on the landscape represents a particular combination of genes, the landscape cannot be continuous. There is a problem with the fitness landscape resembling anything, and Sewall Wright (1988, p. 118), in his last publication, notes that while his representations were "useless for mathematical purposes," "an intellectual representation depends on some enormous simplification" (McCandish 2011).

The epigenetic landscape is almost the negative space of the adaptive landscape. Indeed, if the fitness landscape is coded masculine—rugged peaks needed to be scaled by progressively fitter genotypes—the epigenetic landscape is coded feminine-- clefts into which phenotypes settle[5]. In the epigenetic landscape, the dynamic equilibrium is not in the landscape itself, but in the ball or river rolling down a hill (Waddington 1940, 1957). The ball represents—what?-we don't really know . It represents the possibilities of cell types—an early embryo—and the cells within that embryo (Gilbert 1991; Noble 2015; Borish and Gilbert 2016). But then, again, in 1957, Waddington added the guy ropes of genes, making the landscape into a competent cell type.

> The pegs represent the genes, and the tensions on the guy ropes the chemical forces which the genes exert…The course and slope of any particular valley is affected by many genes; and if any gene mutates, altering tension in a certain set of guy ropes, the result will not depend on that gene alone, but on its interaction with all the other guys.

Here, Waddington is using a geometric representation to frame a notion of a developmental landscape dependent on the coordinated interaction of genes.

Interestingly, the epigenetic landscape also originates, in part, from the mathematical modeling of development. Specifically, it comes from the discussions of the Theoretical Biology Group about Lotka (Caianiello 2008). These discussions appear in Joseph Needham's book *Order and Life* (1936), where he relates Lotka's equations to "Waddington's cones," something Waddington never published. But Needham's discussions about them indicate that these cones

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[5] The coding of genetics as masculine and embryology as feminine has a long history (see Gilbert 1988.)

are epigenetic landscapes wherein a ball rolling down them flows into more channeled states. In Lotka's 1925 diagrams—re-presented in Needham's book--equilibrium is depicted as the bottom of a valley, and the language is remarkably similar to that which Waddington would print. Needham also took the liberty of representing Lotka's and Waddington's ideas graphically as a volcano and as a train switching yard.

The epigenetic landscape has been used—as Waddington proposed—to look at cell type differentiation; but Waddington also used them to model evolution; for evolution, he thought, was brought about by changes in development. These changes in development could arise through genetic mutations or through environmental perturbations. Waddington used the epigenetic landscape to model the canalization and developmental assimilation of phenotypes, and the evolution of one type of animal into another.

The epigenetic landscape is an active model that is still being modified for use. Mathematical modeling has re-entered epigenetic landscape models through the extension of the clefts into "attractor basins" (Thom 1969, 1976; Huang et al 2009; Verd et al 2014). Denis Noble (2015) has recently added an ecological dimension to Waddington's model by having guy ropes extending not only downward to the genes, but upward from the environment. The epigenetic landscape has become a frequently used representation of stem cells, showing the progressive restriction of their potency, and the generation of pluripotent stem cells from adult differentiated cells (Fagan 2012). It was used explicitly by Nobel Prize winner S. Yamanaka (2009) and his colleague K. Takahashi (2012) to explain the generation and properties of induced pluripotent stem cells. At least two representations (Goldberg 2007; Sareen and Svendsen 2010) have converted the epigenetic landscape into the epigenetic pinball games, where the Takahashi-Yamanaka transcription factors act as levers to propel the differentiated cell type back up to the pluripotent state.

One of the most interesting interpretations of the epigenetic landscape has recently been proposed by Susan Squier (2017), who returns to the original Waddingtonian idea of the river carving the channels (Waddington 1940). Here, the epigenetic landscape is interpreted as showing the relationality between the hills and the river, between context and content. The rivers (and balls) create the landscape as much as the landscape creates the rivers and the channels in which the balls flow. This co-creative interplay between agents is characteristic of Waddington, who used the epigenetic landscape to model developmental-environmental interactions, such as genetic assimilation.

4.2. Induced Fitness

This brings us to the principle of dependent co-origination. Basically, it is a principle enunciated by the Indian philosopher Nagarjuna that all things emerge by mutual dependence and are nothing in themselves. In Western thought, this is a principle of dialectics, and it extends from the molecular to the social levels (Levins and Lewontin 1985; Gilbert and Tauber 2016). Here, nothing originates or exist independently of its context, and there are always interactions and often interpenetrations between environmental and internal agents.

In biochemistry, this dialectic is called the “induced fit” model (Koshland 1958; 1995), wherein the substrate helps make the enzyme fit it. In embryology, this dialectic is called “reciprocal embryonic induction” (Dye 2017). In physiology, it becomes manifest in the principle of “biological relativity” (Noble 2011), and in immunology, it is seen as “ecological immunity” (Tauber 2016, 2017). In evolutionary biology, this notion finds itself at the heart of niche construction, where

> Parts and wholes evolve in consequence of their relationship, and the relationship, itself, evolves…that one thing cannot exist without the other and that one acquires its properties from its relation to the other, that the properties of both evolve as a consequence of their interpenetration. (Levins and Lewontin, 1985, p. 3)

This passage could have been taken directly from Nagarjuna’s texts, where identity arises through interactions. This principle of mutual dependence has also been used as a way of organizing closure in biological systems (Montevil and Mossio 2015).

5. Speculations: Mathematics made physical

These dialectical interactions have often been compared to a musical composition (often, a symphony) or a dance (since the entities are physical beings that interact through their shapes). Hence, Stuart Kauffman (1995) writes, "Molecules of all varieties join in a metabolic dance to make cells. Cells interact with cells to form organisms; organisms interact with organisms to form ecosystems, economies, societies." The dance metaphor has also been recently used by Denis Noble (2017) as the title of his book, *Dance to the Tune of Life*. In developmental biology, such metaphors are common (Gilbert and Bard 2014), and at the beginnings of modern embryology, Karl Ernst von Baer (1864) used music as his metaphor for development.

> For that reason, I believe I can compare the various life-processes to musical thoughts or themes and call them creative ideas, which construct their own bodies themselves. What we call in music harmony and melody is here type (the combination of parts) and rhythm (the sequence of forms).

The idea of music constructing bodies takes us back to D'Arcy Thompson's hero, Pythagoras. Pythagoras was fascinated by the correspondence of mathematics and music. He is credited with discovering that the intervals between harmonious musical notes always have whole number ratios. (The oldest way of tuning the 12-note chromatic scale is known as Pythagorean tuning.) Pythagorean ideas, refracted through Plato's *Republic*, became the foundation for the Quadrivium that included astronomy, arithmetic, geometry, and music. If Thompson's mathematics was geometry, the modern synthesis' mathematics was algebra, and Turing's morphogenesis was the Calculus, then the next mathematical model might be music.

Here, each organism is thought of as a performance (Gilbert and Bard 2014). The genome is the score, not a text; and it is not decoded. Rather, it is interpreted. Identical twins are, thus, different interpretations of the same score. We inherit a score, a means of interpreting the score, and a means of improvising when the score is deficient (about 50% of mouse gene knockouts are phenotypically normal) or when it is played in a different environment (developmental plasticity). Chord progressions can be seen as the underlying unities pervading the apparent diversity, i.e., the homologies of music. This is how Thomas Huxley (1882) thought of them:

> I remember perfectly well...the intense satisfaction and delight which I had in listening, by the hour together, to Bach's fugues. It is a pleasure which remains with me, I am glad to think; but, of late years, I have tried to find out the why and wherefore, and it has often occurred to me that the pleasure derived from musical compositions of this kind is essentially of the same nature as that which is derived from pursuits which are commonly regarded as purely

> intellectual. I mean, that the source of pleasure is exactly the same as in most of my problems in morphology—that you have the theme in one of the old master's works followed out in all its endless variations, always appearing and always reminding you of unity in variety.

And, as each organism is a developmental performance of billions of interacting parts, we are left with Yeat's (1929) conundrum, "How can we know the dancer from the dance?"

So, must biologists learn code? Maybe as part of a lab course. Math is a tool, not a telos. Perhaps biologists had best be taught to compose music and dance. Let the programmers learn code, like the electron microscopists learn their skills and X-ray crystallographers learn theirs. To learn code means the continual learning of code. My wizardry of Fortran IV (taken as a language requirement for grad school!) does not provide me much help with the C++ programs. One must continuously unlearn and re-learn. Moreover, biology is a physical, even carnal, science, involving shapes fitting other shapes. Abstractions can obliterate the specifics that make the evolving biological processes possible. As R. A. Fisher noted on the first page of his 1932 paper, "…the first duty of a mathematician, like that of a lion tamer, is to keep his mathematics in their place." Similarly, models are not reconstructions or depictions of reality. They are like rafts. They are to get you from one point to another, but they must be jettisoned once they have served their purpose. Unfortunately, as the epicycles of the Ptolomeic system demonstrate, a well-crafted model is difficult to jettison. Indeed, at a recent conference, philosopher Rasmus Winter concluded: Scientists are like artists. They tend to fall in love with their models.

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