

Looking for Newton: Realistic Modeling in Modern Biology

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Introduction

This article introduces a series of tutorials originally presented at the first annual World Association of Modeling - Biologically Accurate Modeling Meeting (WAM-BAMM*05) held in the spring of 2005 in San Antonio, Texas (<http://www.wam-bamm.org>). This meeting was specifically designed to support and promote “realistic” biological modeling. This form of modeling, which is core to the GENESIS simulation project (<http://www.genesis-sim.org/GENESIS/>), is premised on the assumption that models should FIRST incorporate known anatomical and physiological features of biological systems, and THEN be used as tools to generate NEW ideas and experimental directions in exploring structure / function relationships. The meeting was attended by close to 100 participants. We were particularly pleased to have both the GENESIS and NEURON (Hines and Carnevale, 1997) modeling environments represented.

Because there seems to be continuing confusion regarding the definition, application, and appropriateness of realistic modeling, I have decided in this introductory article to provide some of the historical and philosophical underpinnings for this effort as I see them. The views expressed are certainly not shared by all participants of the WAM-BAMM meeting, or all contributors to the tutorials that follow. This is the perceived view, however, of the World Association of Modeling, of which I as High Po-Bah, and David Beeman, as Chief Minister of Propaganda, are currently the only members.

Very broadly speaking, I think that modeling efforts in biology can be categorized into those that are intended to demonstrate a preconceived concept or idea, and those that are intended as tools to discover new structure / function relationships. By definition, the later variety are realistic models, in that the biological structure must first be placed in the model, in order for novel functional relationships to emerge. In contrast, the demonstration type models are typically more abstract, explicitly include

numerous biological simplifications, and typically carefully select which features of the known biology should be included in the model. They also remain the majority modeling effort within computational biology. The primary purpose of these types of models is to convince others that the modeler understands something important about the system under study. As a result, the modeler often doesn't know how to respond to the question: "what do you know about the system post-model, that you didn't know pre-model?". When asked: "how would you test this model experimentally?" the answer is usually either that an experimentalist should figure this out (which of course they almost always can't or don't bother to do), or a suggestion is made that is experimentally implausible ("if you record from 10% of the neurons in cerebral cortex, you should see the effect"). When asked: "you have indicated all the data your model does explain, what data doesn't it explain?" the answer is usually "the model accurately replicates all the known data". When questioned about the level of realism of the model (for example, "why are you using integrate and fire neurons when there is little experimental evidence that they exist in nature?") the abstract / demonstration type theorist usually says that these assumptions make the model computationally or analytically tractable.

Back in Time

After many years of debating what type of biological modeling is most likely to advance the field (c.f. [Bower, 1990](#)), and in particular arguing for the importance of *a priori* (not *post facto*) biological realism, several years ago I decided to look back into the history of science to see whether this debate had occurred or been resolved in other sciences. In particular, I decided to focus on physics, a field generally considered to support a fairly close working relationship between experimental and theoretical studies, and also generally accepted as the first science to have attained "modern" (i.e. paradigmatic: [Kuhn, 1962](#)) status. Specifically, I was looking for a circumstance where a computationally challenging "physically realistic" model had been in competition with a more computationally tractable and therefore inherently more abstract model. Better yet if the abstract model was (1) built on deeply held assumptions for which there was, in fact, little experimental evidence, (2) was therefore primarily constructed as an existence proof for a preexisting idea, and (3) nevertheless, was highly successful in replicating and predicting experimental data. It did not take long to find such a case – and, more than that, a case it could be argued actually provided the very foundation for the evolution of physics as a paradigmatic science.

The case in point is, of course, the competition in the 16th and 17th centuries between earth-centered Ptolemaic epicycle models of planetary motion, and heliocentric models of the sort proposed by Copernicus in the mid 16th century. For more than 1,000 years previous, the dominant model for planetary motion had been based on Ptolemaic epicycles. Similar, I would claim, to more abstract models in biology today, the Ptolemaic model relied on existing well understood mathematics (the mathematics of circular motion), its structure could be relatively easily extended to account for new experimental data (as Arabic and European scholars did by adding additional epicycles or other features); and the model was completely consistent and in fact directly reflected preexisting fundamental (although experimentally unverified) assumptions about the underlying physical reality (the earth does not move and is at the center of a mathematically perfect universe). It is important to especially emphasize that the Ptolemaic models were quite adept at predicting the experimental data, i.e. the changing positions of the planets, especially over the short term. In fact, Ptolemaic models provided the most accurate predictions for the position of the planets in the night sky for hundreds of years after heliocentric Copernican models were introduced ([Kuhn, 1957](#)). They thus excelled at what

many of today's biological modelers, journal editors, and grant review panels hold as the highest measure of a model's value: its ability to replicate experimental data. Accordingly, it seems highly unlikely that SCIENCE, NATURE, or any other "leading" journals of the day, had they existed, would have published a paper titled, "The Earth Moves: An alternative model of the solar system." submitted by Nicholas Copernicus. In fact, the majority of the manuscript Copernicus did publish was, in effect, an apology to the dominant expert scholarly review organization of his day, the Roman Catholic Church.

Of course, to be fair, Copernicus had scant experimental evidence that his model was more physically realistic than that of Ptolemy. Instead, his motivation for proposing that the earth moved around the sun was that Ptolemaic models had become too Baroque in their efforts to account forever better experimental data. In a letter to the Pope (i.e. Chief Editor), which became the forward to his book, he wrote: "... it is as though an artist were to gather the hands, feet, head and other members for his images from diverse (human) models, and since they in no way match each other, the result would be a monster rather than a man". Thus, Copernicus' stated motivation was to generate a simpler, less complex, model which only required a violation of the underlying assumption that the earth didn't move (an assumption of considerable interest to the church, thus his long winded apology). In this sense, the abstract biological model makers of today might very well see their efforts as consistent with those of Nicholas's. They too argue that their models avoid the Baroque, aiming to provide (or reveal) a more fundamental underlying simplicity of structure. Of course, in the case of Biology, it is natural selection that makes structures Baroque – whereas biological-style natural selection does not operate on planetary systems. In any event, the simplicity (and associated inaccuracy) of Copernican models was short lived as Kepler (despite his own natural inclinations towards harmony and simplicity) soon realized that he would have to invent and apply the much messier mathematics of ellipses to account for the extraordinarily good planetary data provided him by Tycho Brae. For this Kepler is firmly in the ranks of those very rare scientists who are willing to let data push them into violating their own intuitive sense about how things work. To wit, quoting verbatim from an anonymous review of one of our own recent cerebellar papers: "*The data concerning the vertical organization of the cerebellar cortex have been around for over 20 years, and the arguments have been laid down elsewhere (e.g. Bower 2002) and should be well-known by all investigators in the field. The present data and discussion will probably do little to change the minds of those investigators still set on the predominance of the PF beam*". (Paper eventually published as: [Lu et al., 2005](#)).

Anyway, returning to models of planetary motion, one can argue that the seminal scientific event for the history of physics was not the original proposal for a helio-centered solar system, or even the extraordinary mathematical contribution of Kepler to the model (and mathematical methods): but instead, the subsequent contribution of a natural experimentalist, who was fortunately advised early in his career to learn mathematics. Of direct relevance to this discussion, I contend that the seminal scientific accomplishment of this experimentalist (first) mathematician/theorist (second), explicitly involved the construction of a physically realistic model capturing what was known at the time about planetary relationships. That scientist was, of course, Isaac Newton (at the time 19) and the model was what is generally referred to in the writings of historians as a mathematical "graph" (c.f. [White, 1997](#)). This graph is actually a mathematical representation of what was then known about the actual movement of the moon around the earth. This graph fits well within the standard I propose for realistic models for several reasons: First, it was *de novo* constructed from what Newton knew about the physical relationship between the movement of the moon and the earth; Second and perhaps most importantly, Newton built the model to try to understand the relationship buried within this structure without knowing in advance what he would find. That relationship was, of course, the inverse square relationship between the force of the earth on the moon and the distance between them. While there are various aspects of the historical timing of this understanding which remain subject to debate– it is

absolutely clear that Newton didn't know about the inverse square relationship before he built the model: instead it fell out of the model because Newton had faithfully reproduced the physical relationship between the position of the earth with respect to the movement of the moon. To Quote from Michael White, one of Newton's more recent biographers (White, 1997): *"together (the available) documents show a step by step development of the idea of the inverse square law "*. That step-by-step process was fundamentally dependent on his realistic model.

The inverse square relationship he discovered, iteratively, became the basis for Newton's Universal Theory of Gravitation whose success lead directly to his work on mechanics resulting in publication of the *Principia*, the work largely regarded today as the foundation of modern physics. While these events took place 350 years ago, I believe they represent an important lesson for biological science, which I believe to be in a very similar state to Physics prior to Newton. First, Newton and colleagues, in effect, replaced an abstract computationally tractable model that quite accurately predicted experimental data with a much messier realistic model that didn't replicate the experimental data nearly as well but from which Newton extracted an important principle for the organization of the physical world; Second, the messiness of the model required the development of new analysis tools whose structure and features were driven by the modeling effort itself as well as the physical nature of the system under study (thus, the importance of the area under the curve in calculated centripetal and centrifugal forces). Perhaps most importantly, it must be emphasized once again that Newton did not understand the functional relationships in the system prior to constructing the model – but instead discovered those relationships by capturing what was known about the physical relationship between the models components.

It is my claim that the initial physical insights that drive the conversion of a field to a paradigmatic science can only be discovered by constructing models that first and foremost capture the physical structure of the system. For this reason, the most important evaluation for a model is not primarily its ability to replicate or predict experimental data (although replication of data is important) and it is certainly not its ability to be easily understandable or mathematically tractable: instead, the measure of a model should be in what you learn through its construction that you did not understand previously. I assert that THE ONLY WAY a model can accomplish this feat is if it includes, from the outset, the known physical properties of the system unadulterated to the extent possible by preconceived functional ideas. Certainly, a model constructed only to demonstrate a pre-existing idea about how something works, falls very far from this mark. Such models, I would claim are fundamentally Ptolemaic and subject to the same intellectual limitations.

Moving Foreword

The WAM-BAMM meeting, whose tutorial presentations follow this article, like the GENESIS project itself, are specifically designed to foster and promote the kind of modeling that I think was key to the transformation of physics in the 16th and 17th centuries. Like that earlier time, I believe this transition will depend on the construction and analysis of models imbued FIRST with physical (biological) realism and THEN analyzed and explored with an open mind for the emergent functional relationships found in the embedded structure. As in earlier times, the construction and analysis of these models will require the invention of new technologies, methods of mathematical and general quantitative analysis, as well as new mechanisms for describing, reporting and sharing results. Further, these

technologies and tools must emerge from an analysis of biological systems themselves as captured in realistic models. They cannot simply be imported from other fields (like physics).

The explicit objective of this effort, therefore, is to start constructing a theoretical framework for biological science of the sort the *Principia* provided for physics, but which, like that earlier effort, is fundamentally derived from the physical structure of the systems we study. Without such a framework, there is no real basis for communication and collaboration and forward progress. In fact, without such a common quantitative infrastructure, there doesn't even exist in biology today a common set of definitions for terms many currently believe to be central to our effort to figure out how biology works. A few such terms include: "spike synchrony", "dendritic integration", "cortical columns", "cognition", and even "gene". How can we be expected to make theoretical or experimental progress without clear and common definitions? Once again, I assert that it is only through the construction of models that terms can be quantitatively defined – and it is only through the construction of realistic models that it will become clear what terms and relationships are most likely to be most relevant and appropriate for biology.

As was the case for physics in the 16th and 17th centuries, biology also needs to develop new, discipline-appropriate forms of communication, collaboration, and education. Newton and his colleagues invented the scientific journal. While this type of communication device is appropriate for descriptions of simple things (like models of planetary motion) it is entirely inappropriate for describing either biological data, or biological models. It is in fact ironic, as well as a symptom of the current confusing state of biology, that in recent years the gold standard for biological experimental and theoretical publications has become articles in short publication journals such as NATURE and SCIENCE. I have previously suggested that this is a symptom of a much larger problem, as it is difficult, perhaps even impossible to say anything valuable about biology in 1½ published pages (Bower, 1996). In fact, text-based publication is sadly lacking altogether as a means for real communication and collaboration in biology. Again, just as in Newton's times, we need to invent new forms of communication and collaboration appropriate to our own new science.

Critically, we also need to invent new ways to educate our experimentalists, computationally, because, as in the case of Newton, I am convinced that the transformation of biology into a paradigmatic science will require the expanded education of scientists who are experimentalists first, and computational / theoretical second. It is only after a computational / theoretical structure begins to emerge from our realistic models, that we can begin to think about separate career tracks in experiment and theory as now exists in physics. Further, this new form of education must itself be built on the use of biologically realistic models (i.e. the essential tool for moving us forward). There is no longer any reason for neuroscientists to learn about biology by reading books and attending lectures. Both forms are as outmoded and inappropriate as are journal articles. In addition, tutorials built on realistic models provide not only a more dynamic and appropriate substrate for understanding what is currently known (and not known) about biology, but simultaneously exposes students to the modeling technology necessary to make biology a true science (cf the structure of *The Book of GENESIS: Bower and Beeman, 1994, 1998*, now available to all online: <http://www.genesis-sim.org/GENESIS/bog/bog.html>). Accordingly, it is my hope this journal, and the tutorial articles that follow represent first steps in a new form of communication appropriate for learning about and studying biological systems: a process in turn critical to biology finally becoming a quantitative science.

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