

# Theories, Models, and Equations in Systems Biology

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*Abstract:* This paper begins with a review of some claims made by biologists such as Waddington and von Bertalanffy, and others, that biology should seek general theories similar to those found in physics, for example in Newton's theory of gravitation and its elaboration in the *Principia*, some treatments of Maxwell's electromagnetic theory, or thermodynamics, quantum mechanics, and relativity theories. In these domains, broadly applicable differential equations system states and potential trajectories are found. I disagree with that view, and describe an alternative framework for biological theories as collections of prototypical interlevel largely qualitative causal models that can be extrapolated by analogy to different organisms. However, in the rare area of intersection between prototypical models which are largely qualitative and the equation-based models of physics, there are some significant accomplishments that may point the way toward important systems approaches in biology.

I look at two cases in particular in this intersection area: the development of the Hodgkin-Huxley giant squid model for action potentials, and at a more recent model of Ferré and Lockery for worm (*C. elegans*) chemotaxis. The Hodgkin-Huxley strategy uses equations, but in specialized ways involving empirical curve-fitting and heuristic approximations, to build their model. In the worm example, model building proceeds from the organismal level down. It starts from a model of the nematode body which captures the head and neck turning movements (head-sweep), then seeks a neural implementation of the head-sweep mechanism using tools from compartment theory. The proponents of this model argue that their neural model is well-based on the worm's neurophysiology but only weakly, at this point, on the organism's neuroanatomy. Though both approaches use some of the tools of biophysics and other mathematically sophisticated theories of physics, the manner of their implementation is quite different from physics, but may be generalizable as an approach for systems biology.

**1. Introduction: The Structure of Biological Theories.** Until quite recently, much of the analysis of theories in the biological and biomedical sciences had subscribed to what I term the "Euclidean Ideal." This notion assumes that the ideal structure of a scientific theory resembles Euclid's approach to geometry: a small number of fundamental definitions and axioms constitute the essence of a theory. The axioms are mathematically precise, and are then elaborated deductively in the form of theorems and applications that cover a broad (scientific) domain. This view of theory structure obtains fairly strong support in the physical sciences, and is exemplified by Newton's theory of gravitation and its elaboration in the *Principia*, (1942 [1726]), by some treatments of Maxwell's electromagnetic theory

(see Stratton, 1941), thermodynamics, and by quantum mechanics (see von Neumann, 1955). A similar orientation toward general theory in biology also can be found in the work of von Bertalanffy on "general systems theory" and his sets of multiple partial differential equations.

Biologists -- especially those biologists seeking a methodological unity with the physical sciences such as Waddington in his (1968) -- and philosophers of biology, such as the *early* Michael Ruse (1973), have maintained that the laws and theories of biology have the exact same logical structure as do those of the physical sciences (though recently there have been some changes -- see Kitcher (1984), Rosenberg (1985), Culp and Kitcher (1989), and van der Steen and Kamminga (1990)). This simple *unity* view is only supportable if one restricts one's attention to those few -- but very important -- theories in biology which in point of fact have a very broad scope and are characterizable in their more simplified forms as a set of "laws" which admit of mathematically precise axiomatization and deductive elaboration. Examples are certain formulations of Mendelian genetics and of population genetics. I maintain that a deeper analysis of even these theories, however, will disclose difficulties with a strong methodological parallelism with the physical sciences (see Schaffner, 1980 and 1986, and Kitcher, 1984). I believe that a close examination of a wide variety of other biological theories in immunology, physiology, embryology, and the neurosciences will suggest that the typical theory in the biomedical sciences is a structure of overlapping interlevel causal temporal prototypical models.

The models of such a structure usually constitute a series of idealized *prototypical* mechanisms and variations (some of which may be mutants) that bear family or *similarity resemblances* to each other, and characteristically each has a (relatively) narrow scope of straightforward application to (few) pure types. The models are typically *interlevel* in the sense of levels of aggregation, containing component parts which are often specified in intermingled body part (e.g., head or tail), cellular (e.g., neuron or axon), and biochemical (e.g., receptor or ions) terms. Stages of temporal development in the models may represent either deterministic, causally probabilistic, random (Markovian), or even mixed connections. This probabilistic character of some causal connections (*a failure of strict determinism*) should be distinguished from the *conceptually distinct failure* of the exact *match* of a model to a non-pure type to which, nonetheless, it is closest given available knowledge. Such a match can be close, however, exhibiting a *strong analogy* between a model and an organism (or population of organisms). I argued at length (in my 1980) that this new type of theory, which I termed a "theory of the middle range" (with apologies to R.K. Merton (1968) who first used that term in a somewhat different context), both is found and should be expected to be found in the biomedical sciences. The term "middle range" seemed appropriate for two reasons: first the theories were not broad sweeping general theories but they were not summaries of data either; they were mid-way between these extremes. Second, in terms of levels of aggregation of the entities in such theories, the theories were not about high level populations evolving in evolutionary time and not about specific DNA sequences or specific enzymes functioning in well defined biochemical pathways, but were at the level of the organelle, the gene as characterized by functional products, the cell, and the organ. Thus though *interlevel*, their levels of aggregation tended to concentrate in the "middle range."

Though the Waddington and von Bertalanffy programs have not been confirmed in

the typical accomplishments and representations in molecular biology in general, and molecular genetics in particular, there are interesting advances that fall between those searches for broad theories couched in mathematically precise differential equation form, and the narrow classes of mechanisms, usually described in qualitative multilevel causal language, that constitute the vast majority of current biomedical explainers. In traditional population genetics, one important exception is the ability to develop a powerful axiomatization of the subject that does bear strong analogies to equation based theories of physics. (For a detailed example see the Jacquard axiomatization of population genetics summarized in my (Schaffner 1993a), chapter 8.)

There are several other theories that are equation-based which can be identified in contemporary biomedicine, and in the remainder of this paper I discuss two of these in detail. My view is that these can disclose some important ways that very general and quantitative principles can be applied fruitfully in biology and medicine. They also disclose the limitations of this kind of physics-oriented approach to biology, and a comparison of those areas where mathematical modeling works and at what points it begins to fail may indicate ways that systems biology can approach the issues of theories, models, and equations in this nascent area.

I will begin my discussion with a brief account of the development of the Hodgkin-Huxley Giant Squid Model for Action Potentials, a stunning accomplishment for which Hodgkin and Huxley shared the Nobel Prize in physiology or medicine in 1963. One of the current standard textbooks of neuroscience, (Kandel et al. 2000) states that fifty years after it's publication, "the Hodgkin-Huxley model stands as the most successful quantitative computational model in neural sciences if not all of biology"<sup>1</sup> (p. 156).

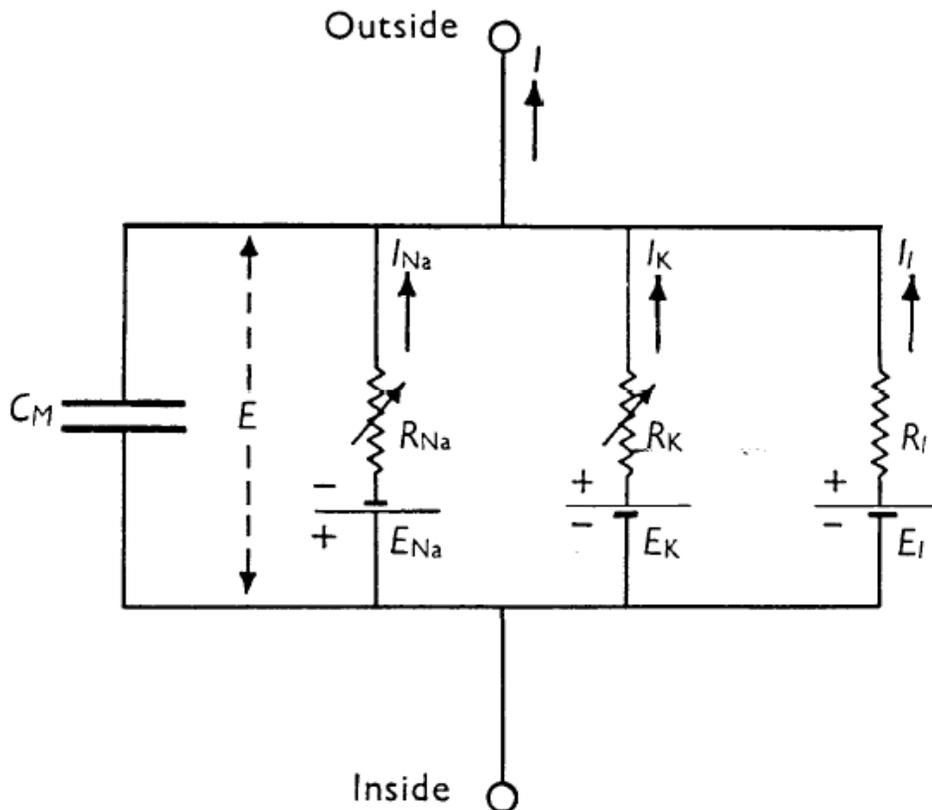
## **2. The Development of the Hodgkin-Huxley Giant Squid Model for Action Potentials as a Classical Example of Systems Biology.**

Action potentials (APs) are waves of potential difference (or voltage) that move down nerve axons, communicating the effect of a stimulus from the receptors located near the beginning of the neuron to the termination of the nerve cell. To a first approximation, APs are the result of a rapid (millisecond) changes in the membrane's permeabilities to sodium and potassium ions, changes which underlie the wave of potential difference. Hodgkin and Huxley's work on the action potential in nerve cells began from Hodgkin's earlier work on electric currents on the shore crab in the late 1930s (Hodgkin 1964). He teamed up with Huxley, who was his student at Cambridge University, and they jointly turned their attention to the giant squid axon, which was a much more tractable experimental system in which to investigate the movement of specific ions, including sodium and potassium. Though their work was interrupted by World War II, they resumed their project in 1946, and in the late 1940s through to the early 1950s they conducted their classical experimental and theoretical investigations (Huxley 1964). A series of papers culminated in their extraordinary 1952 article in the *Journal of Physiology* in which they systematically lay out the steps and their reasoning that culminates in the classical action potential model of nerve transmission (Hodgkin 1952).

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<sup>1</sup> The philosophy of science literature has just recently begun to address the Hodgkin-Huxley action potential model as an important exemplar. Weber in his 2004/5 book discusses it at some length in chapter 2 of his book, and Bogen (2005) and Craver (2006) analyze it as well.

The 1952 paper closely parallels their more historical account of their steps toward their quantitative model that appears in the two Nobel Prize lectures (Hodgkin 1964) (Huxley 1964). They begin by first discussing their careful experimental results which had employed the voltage clamp apparatus, developed in 1949 by Kenneth Cole. This experimental device permits the establishment of a set of different potential differences across the squid nerve cell membrane, and recording of the effects that the different membrane potential have on the state of the cell. (A detailed description of the apparatus and technique can be found in the textbox on page 152 of (Kandel et al. 2000).) Their earlier papers had indicated that the movement of currents based on ions across nerve cell membrane could be well represented by an “equivalent circuit” involving a capacitor and three resistors, all in parallel, and with each resistor in series with a source of an electrical potential difference. This circuit captures the sodium (Na) and potassium (K) currents, as well as a small leakage current ( $I$ ). This equivalent circuit from their 1952 paper is shown in the figure below, though this particular representation is from (Huxley 1964).



Equivalent circuit of a small area of membrane of the giant axon.  $R_K$  and  $R_{Na}$  obey Ohm's law for rapid changes in the potential difference across the membrane, but change their values in times of the order of a millisecond if the membrane potential is held at a new value.  $R_l$  is constant.

The “laws of working” ( a term originally used by John Mackie, but see my discussion of the phrase in my 1993, pp. 287, 306-307) that govern this circuit are the standard physical laws including Ohm's law as noted in the legend to the figure above. Additionally the

potential difference across the membrane established by differences in the Na and K ions is as required by the Nernst equation:

$$V_{\text{ion}} = RT/zF \ln (X_o/X_i),$$

where V is the potential difference (voltage), R and F are the universal Boltzmann and Faraday constants, T is the temperature, z is the valence of the ion, and X<sub>o</sub> and X<sub>i</sub> are the concentrations of the ion outside and inside the cell. (Such laws are constraints and foundations, but are not the complete derivational source, for the later H and H equations I introduce further below (also see Bogen (2005) and Craver (2005) on this point.)

Part II of the Hodgkin-Huxley paper is a “mathematical description of membrane current during a voltage clamp.” Equations for the sodium and potassium currents, as conductances are developed. The equations do *not* come from “first principles” but rather are *empirical equations fitted from the voltage clamp data*. They are typically chosen based on simplicity, with a first order equation being preferred over a second order, etc.. A first order equation is satisfactory to represent a portion of the time course of nerve depolarization (a rapid change of voltage across the membrane), but a fourth order equation is needed to represent the beginning of the potassium depolarization process. The equation for potassium conductance, in the form that it could be compared with the empirical results, was chosen as:

$$g_K = (g_{K\infty})^4 - [(g_{K\infty})^4 - (g_{K0})^4] \exp(-t/\tau_n)^4,$$

It is a *theoretical* equation, to use H and H’s language, based on the equivalent circuit and the general empirically found form of the rise and fall of ion conduction during depolarization and repolarization. H and H doubt it gives a “correct picture” of the membrane, though they do provide a possible physical basis for the equation (see pp. 506-507 of the 1952 article). The equation contains a constant  $\tau_n$  that can then be specified to be the best fit to *experimentally determined* depolarizations of different potential membrane differences. Hodgkin and Huxley found that there was reasonable agreement between theoretical and experimental curves. H and H then go on to develop the somewhat more complex reasoning leading to the equation for sodium conductance, which I shall not discuss, but which can be found on pp. 512-515 of their 1952 paper. They also develop equations for rate constants  $\alpha$  and  $\beta$ , and the dimensionless proportions n, m, and h, of ions inside and outside the membrane, in part II as well.

At the beginning of Part III of their (1952) paper, titled “Reconstruction of Nerve Behavior,” H and H summarize the equations they have developed in Part II of that paper. The summary is from from the H and H (1952) article) and the numbering of the equations in parentheses comes from their original equation numbers. The summary looks like this:

$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l), \quad (26)$$

where

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n, \quad (7)$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m, \quad (15)$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h, \quad (16)$$

and

$$\alpha_n = 0.01 (V + 10) \left/ \left( \exp \frac{V + 10}{10} - 1 \right) \right., \quad (12)$$

$$\beta_n = 0.125 \exp (V/80), \quad (13)$$

$$\alpha_m = 0.1 (V + 25) \left/ \left( \exp \frac{V + 25}{10} - 1 \right) \right., \quad (20)$$

$$\beta_m = 4 \exp (V/18), \quad (21)$$

$$\alpha_h = 0.07 \exp (V/20), \quad (23)$$

$$\beta_h = 1 \left/ \left( \exp \frac{V + 30}{10} + 1 \right) \right.. \quad (24)$$

The first four of these equations are the differential equations which govern the system's behavior. The many computer simulations of the H and H model involve programs that repeatedly step through those first four equations (see Fodor, 2005, for one example).

Equation (26) is then applied to the action potential. We are most interested in the "propagated action potential," as distinguished from a uniform membrane action potential. In the propagated action potential, the local circuit currents have to be provided by the net membrane current. At this point in their (1952) paper, H and H appeal to a well known partial differential equation from cable theory (which is a variant of Laplace's well known heat diffusion partial differential equation) relating the current to the second partial derivative of the potential difference (V) with respect to distance (x). This equation is given by the expression:

$$i = [ 1/(r_1 + r_2) ] \partial^2 V / \partial x^2 \quad (27)$$

There are some simplifications then invoked, e.g., since  $r_1 \ll r_2$ ,  $r_1$  can be dropped. The expression for the current density for the fiber with a radius of  $a$  then allows the equation to be rewritten as:

$$I = [ a/2r_2 ] \partial^2 V / \partial x^2$$

This relation is then substituted into equation (26), which yields a partial differential equation that is "not practical to solve as it stands" (p. 522). But a similarity is noted for the condition of steady propagation, one which permits the equation to be converted into an ordinary differential equation that can be solved numerically, if laboriously given the computational tools available in 1952. This *is the propagated action potential equation* and was written as:

$$(30) \quad \underline{a} \quad \underline{d^2V} = C_M \underline{dV} + g_K n^4 (V - V_K) + g_{Na} m^3 h (V - V_{Na}) + g_l (V - V_l)$$

$$2R\theta^2 \frac{d^2}{dt^2}$$

Where  $\theta$  is a parameter that has to be estimated numerically, based on the behavior of the equation at extreme boundary conditions (see p. 522 of H and H for details). A section on numerical methods of solution of such equations is interpolated in the 1952 article, and after a minor (abbreviational) substitution, equation (30) is rewritten as equation (31) (not shown here, but see p. 524 of the original article). This equation (either 30, or the equivalent 31, is solved numerically, and graphs of the membrane conductances during a propagated action potential are depicted. H and H's graphical results are shown in their figure 17, inserted just below:

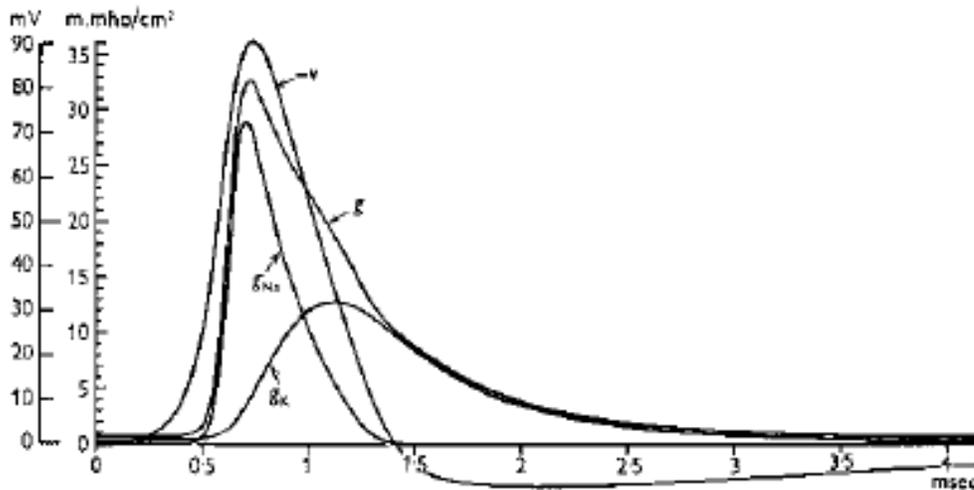


Fig. 17. Numerical solution of eqn. (31) showing components of membrane conductance ( $g$ ) during propagated action potential ( $-V$ ). Details of the analysis are as in Fig. 15.

Readers will recognize these graphs of the conductances as THE classical action potential result, which is re-presented, based on largely qualitative considerations, in typical neuroscience textbooks.

### 3. Implications of the Hodgkin-Huxley Model and their Methodology.

#### 3.1 One basic mechanism with many types of molecular realizations?

An examination of the *form* of the key equations, especially the batch summarized beginning with (26) on page 8 above and then numbers (30-31) might suggest that H and H's accomplishment is not that different than, say, James Clerk Maxwell's articulation of the electromagnetic theory of light and Maxwell's derivation of the wave equation for an electromagnetic disturbance. (That disturbance importantly had the transverse wave features and the same velocity as light, which led Maxwell to postulate that light was an electromagnetic wave.) But the H and H equations are not universal equations as were Maxwell's – the H and H equations were empirically generated from curve fittings to the squid action potential changes read using the voltage clamp technique. Hodgkin and

Huxley remarked on the limitations of their model a number of times during the course of their (1952) article, limitations that are well summarized by Bogen (2005) and Craver (2005).

Toward the very end of the 1952 paper, H and H wrote:

*Applicability to other tissues.* The similarity of the effects of changing the concentrations of sodium and potassium on the resting and action potentials of many excitable tissues (Hodgkin, 1951) suggest that the *basic mechanism* of conduction may be the *same* as implied by our equations, but the *great differences* in the shape of action potentials show that even if equations of the same form as ours are applicable in other cases, some at least of the parameters must have *very different* values (p.xxx) (my emphases).

In addition, toward the end of his Nobel lecture, Hodgkin returned to this issue and the related theme of a specific or “definite” model of the membrane when he wrote:

To begin with we hoped that the analysis might lead to a definite molecular model of the membrane. However, it gradually became clear that different mechanisms could lead to similar equations and that no real progress at the molecular level could be made until much more was known about the chemistry and fine structure of the membrane. On the other hand, the equations that we developed proved surprisingly powerful and it was possible to predict much of the electrical behaviour of the giant axon with fair accuracy. Examples of some of the properties of the axon which are fitted by the equations are: the form, duration and amplitude of the action potential; the conduction velocity; impedance changes; ionic movements; and subthreshold phenomena including oscillatory behaviour. (1962, p. 42)

A review of contemporary molecular models of various ion channels capable of supporting action potentials suggests that H and H happened on a most remarkable level of abstraction/aggregation that would support very broad generalization in terms of the specificity of membrane currents, though not any specific molecular mechanisms. For example, the chapter by Koester and Siegelbaum on “Propagated Signaling: The Action Potential” in Kandel et al 2000 states somewhat “teleologically” that:

The squid axon can generate an action potential with just two types of voltage-gated channels. Why then are there so many *different types* of voltage-gated channels found in the nervous system? The answer is that neurons with the expanded set of voltage-gated channels have much more complex information-processing abilities than those with only two types of channels. (p. 159). (my emphasis)

The number and types of ion channels are explained, and to an extent unified, by the underlying genetics (and epigenetics) of ion channel diversity, a topic to which I turn next.

## 2. Genetic and epigenetic diversity accounts for ion channel diversity.

Hille recounts the history of ion channel research over the course of the last half-century following H and H's classic paper. The progress he writes has been "phenomenal," and "the field has become highly interdisciplinary, combining approaches of biophysics, pharmacology, protein chemistry, molecular and medical genetics, and cell biology" (Hille 2001) p. 61. Several recent Nobel prizes have, in point of fact, been awarded for ion channel research, including to Neher and Sakmann in 1991, who developed the "patch clamp method" that provided direct evidence of ion channels, and to MacKinnon in 2003, for structural and mechanistic studies of ion channels, including his pore model.

Genetic studies that began in the 1980s have indicated that there are three general genetic "superfamilies" of ion channels, comprising ligand-gated, gap-junction, and the H and H type of action-potential generating voltage gated channels. This last class, which are activated by depolarization, also contains three subclasses of channels selective for  $\text{Na}^+$  and  $\text{K}^+$  and  $\text{Ca}^{++}$  (Siegelbaum 2000). (Siegelbaum 2000) describe the similar architecture of this class of channels writing:

They contain four repeats of a basic motif composed of six transmembrane segments [known as] (S1-S6). The S5 and S6 segments are connected by a loop, through the extracellular face of the membrane, the P-region, that forms the selectivity filter of the channel. A single subunit of voltage gated  $\text{Na}^+$  and  $\text{Ca}^{++}$  channels contains four of these repeats. Potassium channels are composed of four subunits, each containing one repeat. ( p. 119).

Additional ion family channels are in the process of being discovered and characterized, including a class of  $\text{Cl}^-$  channels. But already the number of different channel types is according to (Siegelbaum 2000) "enormous." The diversity is accounted for in part because "most channels are made up of multiple subunits that can be combined in different permutations to produce channels with different functional properties" (p. 119). Additionally, the variability is "produced by differential expression of two or more closely related genes, by alternative splicing of mRNA transcribed from the same gene, or by editing of mRNA" (p. 120).

Some simplification of this extensive diversity occurs in the axonal region of the neuron where just the two major channel types,  $\text{Na}^+$  and  $\text{K}^+$  are involved. However, even here, Hille also describes an extensive "diversity of K channels" in different tissues and even within single-cells. He sums up this "microheterogeneity of K channels," noting that "such results are typical of experimental discoveries today. The finer the method of analysis, the more apparent subtypes of channels are discovered" ((Hille 2001) p. 74). In spite of this extensive diversity and variation, genetics can provide a rationale for generalization, at least involving similarity modeling. On this point Hille writes: "The NA, Ca, and K families of voltage gated channels form a homologous gene superfamily, as may be expected from their broad apparent functional similarity. This means that many findings for one type of channel can be generalized to the others" (Hille 2001), p. 85.

### *3. The H and H "basic mechanism" as an emergent simplification.*

The account of the extensive diversity of specific mechanisms of ion channel types just summarized raises the question of how unity can be effectively achieved amid such natural

variation. In a significant sense, H and H achieved that unification and simplification in advance of the more recent molecular knowledge by working at a *higher* level of abstraction. Their accomplishment suggests that in certain areas of biology, investigators can capture what might be termed “emergent simplifications” that transcend the specific workings of the molecular details. In a way, a more abstract mechanism can be a “basic mechanism,” even if it is clearly realized that there are as yet unknown molecular details of the mechanism. Possibly such a basic mechanism is more like a “prototypical” mechanism, which identifies and characterizes salient core features of a biological entity and its actions.

In some circumstances, the core features of those simplifications can be generated by quantitative investigations and represented by mathematical equations that are formally analogous to what we find in the Euclidean types of theories discussed in section 1. But they lack that very broad universality, and instead serve their functions by being prototypes for analogical modeling to similar prototypes, albeit in this case, analogical modeling to other quantitative prototypes. In addition, they are not usually uni-level, but instead mix levels of aggregation. In the H and H work, the discussion is focused on current flows and potential difference changes due to ions and inferred ion channels, but as situated in an axon of a particular species. Further reflection of the H and H systems-level methodology may provide important generalizable heuristics that can inform biology pursued at the level of general systems.

#### **4. A Neuroscientific Account of Behavior in *C. elegans*.**

An interesting comparison with the above H and H account can be found in a recent essay by Ferrée and Lockery. Whereas the typical study of the behavior of the model organism, *C. elegans*, tries to identify genes, and molecular sequences that are characterized as “causes” of behaviors, the example to be discussed in this section is more akin to the H and H inquiry and their mode of modeling. For an example of the more typical approach to worm behavior modeling, see Mario de Bono and Cori Bargmann’s (1998) *Cell* paper with their focus on a DNA nucleotide change as the “cause” of a behavioral phenotype involving social versus solitary feeding.) Ferrée and Lockery, in contrast, provide an analysis that attempts to model the factors and interactions that govern the neurons not the genes. Ferrée and Lockery’s general task was to determine “the behavioral strategy for chemotaxis in *C. elegans*,” and their specific approach was to “derive a linear neural network model of the chemotaxis control circuit” in *C. elegans*, and then to “demonstrate that this model is capable of producing nematode-like chemotaxis” (Ferrée and Lockery, 1999, 2). This then is a simulation study, but one based on a considerable amount of empirical work.

Ferrée and Lockery utilized a “candidate neural network” based on Bargmann’s earlier work on the worm (see figure 1). Lockery’s own investigations (Goodman et al, 1998) have shown that the neural signals in *C. elegans* are encoded by graded electrical potentials (not by classic sodium action potentials). The individual neurons display nonlinear transfer functions, but Ferrée and Lockery propose that one can look at a simplified linearization of the chemotaxis system that can give some insights about this behavior, albeit as a first approximation.

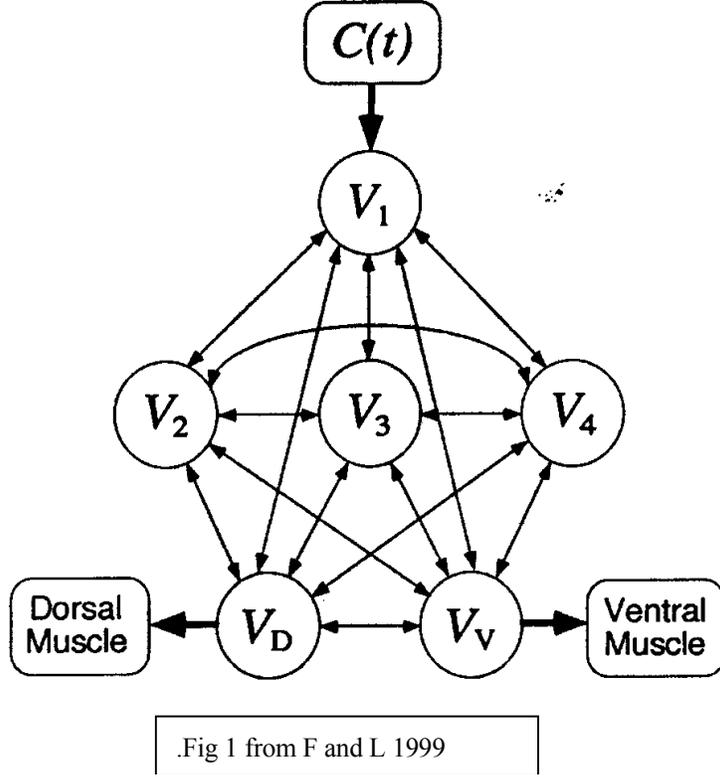


Figure 1: Neural network model for the chemotaxis control circuit of *C. elegans*. The state variable of each neuron (circle) is voltage ( $V_i$ ). The model contains one chemosensory neuron ( $V_1$ ), three interneurons ( $V_2$  to  $V_4$ ), and two motor neurons ( $V_D, V_V$ ). The chemosensory neuron receives input equal to the chemical concentration  $C(t)$  at the tip of the nose, and the motor neurons innervate dorsal (D) and ventral (V) neck muscles. (From Ferré and Lockery, 1999, 267, with permission.)

The model building proceeds from the organismal level down. It starts from a model of the nematode body which captures the head and neck turning movements (head-sweep), then seeks a neural implementation of the head-sweep mechanism. Ferré and Lockery argue that their neural model is based on the worm's neurophysiology, but only – at this point -- weakly on the neuroanatomy. Citing Goodman et al., 1998, they suggest the neurons can be represented as single electrical compartments. (Compartment models, like the simpler cable theory models that backgrounded some of H and H's investigation, are one of the traditional strategies used in neuroscience; see Bower and Beeman, 1995.) An equation for the voltage  $V_i$  of the  $i^{\text{th}}$  neuron can be written using standard compartment modeling as:

$$C_i^{cell} dV_i/dt = -G_i^{cell} \cdot (V_i - E_i^{cell}) - I_i^{elec}(V) - I_i^{chem}(V) - I_i^{sens}(t) \quad (1)$$

where  $C_i^{cell}$  is the whole-cell capacitance,  $G_i^{cell}$  is the effective ohmic conductance associated with the linear region of the I-V curve, and  $E_i^{cell}$  is the resting potential of an isolated neuron. Here  $I_i^{elec}(V)$  and  $I_i^{chem}$  represent electrical and chemical synaptic currents,  $V = (V_1, \dots, V_N)$  is an N-dimensional vector comprised of the voltages of all  $N$

neurons in the network, and  $I_i^{sens}(t)$  represents chemosensory input (from Ferrée and Lockery, 14).

They then borrow from data on *Ascaris*, since as frequently noted in the worm literature, synaptic neurophysiological data are not yet available for *C. elegans*, so a closely related worm, *Ascaris*, is used). This data allows them to assert that the chemical synapses between cells  $i$  and  $j$  can be modeled by the a sigmoidal functional equation:

$$I_i^{chem}(V) = \sum_{j=1}^N G_{ij}^{chem} \cdot \sigma(\beta_{ij}(V_j - \bar{V}_j)) \cdot (V_i - E_{ij}) \quad (2)$$

where  $G_{ij}^{chem}$  is the maximum conductance in the cell  $i$  due to synaptic connections from cell  $j$  and  $E_{ij}$  is the reversal potential for the corresponding postsynaptic current.

Electrical synapses are similarly modeled by another slightly simpler third equation.

Further, chemical inputs to the system are captured by:

$$I_i^{sens}(t) = -\delta_{i1} \kappa_{sens} C(t) \quad (3)$$

where  $C(t)$  is the chemical concentration at the tip of the worm's nose,  $\delta_{i1}$  is the standard Kronecker delta and  $\kappa_{sens}$  is a constant parameter.

The total synaptic model can be further simplified by representing only the chemical synapses. Equation (2), which is then governing, is nonlinear, but it can be linearized by using a Taylor series expansion (familiar to elementary calculus students) and retaining only the linear terms. This process yields the following set of equations:

$$dV_i/dt = \sum_{j=1}^N A_{ij} V_j + b_i + c_i(t) \quad (4)$$

( The matrix  $A_{ij}$  and  $b_j$  are complicated functions of the  $G$ 's,  $V$ 's, and  $E$ 's introduced in equations (1)-(2) and are not reproduced here; see Ferrée and Lockery, 1999, pp. 16-17.) This linearized equation and two quite simple body model equations are then combined with an equation representing the chemical environment,  $C$ , and the equations solved to yield a state trajectory  $S(t)$  that begins from some specified initial state  $S_0$ . The simulation solutions were obtained by numerical integration, akin to h and H's work, though now using powerful computer tools, and some other tricks employed to eliminate transients. Figures 2a and 2b, below, show a comparison between real and simulated worms.

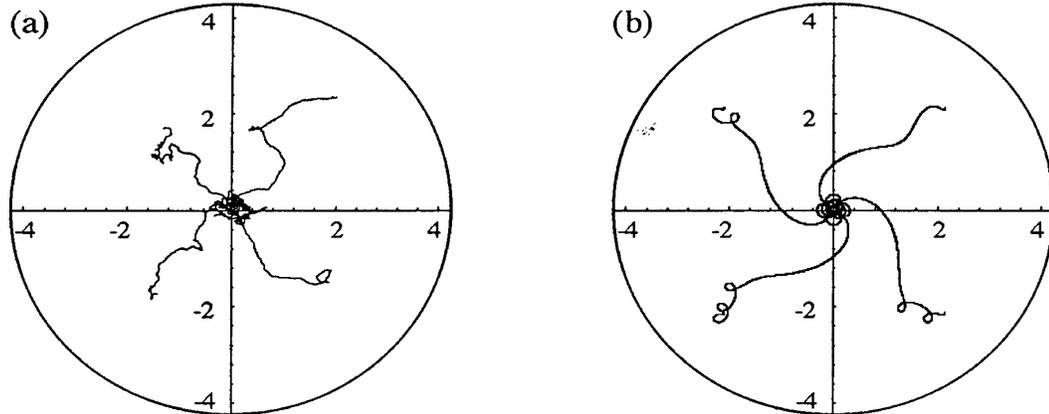


Figure 2.: Chemotaxis control by neural networks: (a) biological nematodes, (b) model nematodes controlled by network  $\Gamma_1$ . In both cases, simulation time  $T = 5$  min. Axes labels are in cm. (From Ferrée and Lockery, 1999, 270, with permission.)

Next, Ferrée and Lockery explored the linearized equation solution to develop a more intuitive result, since they note that “distributed representations” often lack this property of intuitability. This part of their paper provides a “simple rule for chemotaxis control which relates the body rate of turning ... to time derivatives of the chemosensory input....” (p. 23). Based on the analysis, Ferrée and Lockery argue that their network uses strategies both of klinotaxis (alignment with a vector component of the stimulus field) and klinokinesis (change in turning rate in response to the scalar value of a stimulus field) to produce the behavior represented in figure 2b. (Here the definitions of klinotaxis and klinokinesis follow Dunn, 1990. These strategies also suggest seeking additional experimental worm stimulus and movement data to confirm or disprove the models.

Ferrée and Lockery’s approach does not use genes, and it does not employ structural data from molecular biology. It does utilize physiology and neuroscientific compartment analysis to formulate a mathematical model of a neural network that qualitatively agrees with the worm’s observed behavior. It is perhaps more similar to a biophysics approach such as H and H’s action potential model than a biomolecular approach.

## 5. Implications of the Ferrée and Lockery Model for *C. elegans* Chemotaxis.

The F and L model is a mathematical simulation, of *C. elegans* chemotaxis relying on a simplified neural circuit, and on generally accepted model-building strategies found in the neurosciences. Like H and H, it seeks to identify an appropriate level of abstraction from the much more complicated details that might constitute the specific mechanisms of neural interplay. But thus far it has not enjoyed the broad acceptance and heuristic

fertility of the H and H model. Why that is the case, needs further thought, since the general strategies appear to be similar. Possibly what seems to be the idiosyncratic aspects of the model arises because F and L are not dealing with a constituent low-level mechanism that could be found in multiple instances and more easily generalized to similar ion channel activities in related type of cells. Rather F and L deal with an intentionally *particular* wiring diagram that may restrict the generalizability of the results of their model. However, the more methodological modeling and equation building and solving strategies may have broader applicability, such as the reliance on an empirically confirmed circuit, and the application of compartment modeling to such interactive networks.

## **6. Eight Implications of the Two Exemplars for Systems Biology.**

I can think of eight implications of the above discussion for philosophical issues in systems biology; other may see additional implications.

1. In biology, the roles that general theories have in physics (as explainers, organizers of domains of inquiry, and experimental fertility) is carried out by a series of prototypes (think of these as models or as mechanisms) which are causal-temporal multilevel systems and are analogically related to other prototypes.
2. Those prototypes *may* be formulated in quantitative terms, though typically they are not, and in their quantitative variants these may even appear in a mathematical form that is very much like that found in general physical theories, such as in Maxwell's equations or the axioms of quantum mechanics. But the equations describing the prototypes are not universal ones, rather they are tied closely to the specific organisms on which they are based, though they can be extended. Such equations are also typically approximations rather than exact equations.
3. Biological prototypes are applied, in the sense of being used as explainers or as extending the application to another biological organism, more by *analogical reasoning* than by determining the mathematically expressed initial conditions (or boundary conditions) and proceeding deductively, by inserting those conditions into equations to particularize and thus apply the general system.
4. Biological prototypes need not be only gene-based. The H and H and the F and L exemplars are not gene-based, but do their work well, though the H and H model is much more generalizable, for reasons speculated on in the text above. Genetic information may assist in specifying highly particular variants of mechanisms, such as receptors, and even in identifying classes of control mechanisms, but a genetic dimension is not always needed.
5. Biological prototypes incorporate critical *structural information*. This structural information is "biological" in nature, as opposed to simple physical and chemical structural information. In an important sense, the explanation for biological structure requires an implicit appeal to billions of years of evolution, but working biologists need to assume that

structure as an “emergent” given in investigating any biological system, and need to characterize the prototype being studied at the appropriate levels with such structure assumed. We saw this in the H and H example in terms of accepting a cable model for the giant squid axon, constructed in part out of a structured membrane permitting sodium and potassium ion passage. In the F and L *C. elegans* example, we encountered a pre-existing wiring diagram of connected neurons, in addition to pre-existing compartments characterizing the neurons. See Kitano (2001) for the importance of taking structural information into account in systems biology.

6. Biological prototypes may be most useful when they display dynamical or behavioral features, in addition to structural organization, whether these dynamical/behavioral aspects are presented as temporal-causal sequences or as a dynamics that can be captured mathematically and in simulations, as in the H and H and F and L exemplars discussed in this paper. The importance behavior and dynamics for systems biology is also stressed by Kitano (2001).

7. In the case where the systems are characterized quantitatively, as in the H and H and F and L exemplars, simulations can be constructed fairly easily, and these can be valuable both in testing a prototype and in possibly extending it, by allowing for variation of parameters in a precise manner and their application to experimental systems. These simulations, however, need to be controlled both by specific data and by general biological principles, and not be purely speculative exercises in mathematical model building, as in much of von Bertalanffy’s (1968) writings.

8. The two exemplars discussed above go some way toward identifying some potentially useful philosophical issues in systems biology, but they need to be supplemented with *other exemplars*, in order to provide a more comprehensive picture. One such additional area might involve gene-based systems together with high-throughput data. A valuable proof of principal paper along these lines is the Ideker et al.’s (2001) galactose metabolism model for yeast, -- one that points toward additional features, such as gene-protein and protein-protein interactions, that are likely to be important in a philosophy of systems biology.

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