A GENERAL SYSTEMS OUTLOOK TO THE PREDICTION-INFERENCE DILEMMA OF NEUROSCIENCE MODELS.

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ABSTRACT

As the predictions made by a mathematical model gets validated, the level of confidence on the model grows with every successful prediction. With this rise in confidence one is tempted to make inferences from the more abstract parts of the model. This may result in perceived notion of contradictions or paradoxes. For an ontologically oriented non-general system theorists the relation between model and real-world such that the model results are applied, is a complex one. Let me illustrate this using one of the most famous models in computational neuroscience, the Hodgkin-Huxley model.

Since its unveiling 67 years ago, the system of the four differential equations have successfully modelled other axons and entire neurons based on the modelling schema. For the typical model the equations are such that one is a derivative of the membrane voltage. This is coupled to the remaining three derivatives of the probability that three different ion gates are open. Consider the case of a single channel with four charged particles. And the probability that each charged particle is in a position to open the channel is 0.5. But a real cell membrane has more than one channel of the same type, say ten. Does that mean there are only four charged particles for all the ten channels combined? How can a single channel have four charged particle and at the same time the number of charged particles in the remaining nine channels is also ten?

This contradiction leads to the prediction-inference dilemma. The dilemma that the model makes successful predictions yet, inferences from the model results in inconsistencies. If we waited until someone produced a type of channel with four charged particles and also four charged particles for an arbitrary number of the channel we would not be using the Hodgkin-Huxley model today. This would be like, not using geometry until someone produces a point with no dimension.

From the perspective of a general system theorists the prediction-inference dilemma is resolved. This is because from a general system view, a mathematical model has two facets; principal quantity/ies and secondary quantity/ies or constructs. The principal quantity agrees with the measurable quantity. For instance, membrane voltage variable in the system of equations. The principal quantity and the measured quantity are two different quantities. The model and real-world relation is provided by the agreement between the quantities. Secondary quantities are the result of mathematical abstractions; concepts, operations and symbols of which there are no counterpart in the real-world. This is the Slepian's two-world view from information theory.

In the interdisciplinary field of neuroscience the role of computational neuroscience (also, theoretical or mathematical neuroscience) is to join the disciplinary rungs of the neuroscience ladder. The computational neuroscientist must therefore be a general system

theorists and also be proficient in the science of modelling. This paper will present the solution to the prediction-inference dilemma as an illustration of the general systems approach to the science of modelling in computational neuroscience.

Keywords: general systems theory, model making, computational neuroscience, neural network, portable concepts.

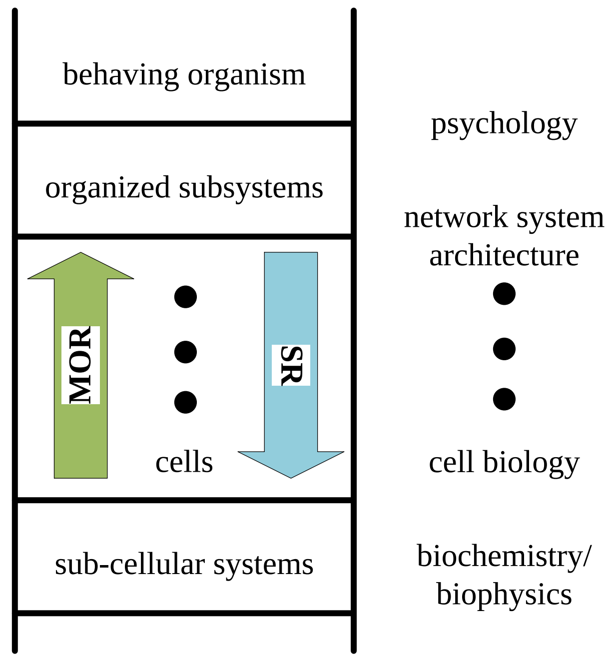

Figure 1. The neuroscience ladder. SR stands for scientific reduction and MOR for model order reduction.

QUANTITATIVE MODELING IN NEUROSCIENCE

Model making in neuroscience involves at least two levels of modelling: component modelling and system modelling. The component modeller is able to dig more deeply into a particular field, like biology. For instance, Hodgkin and Huxley (1952) developed innovative experiments to study the ionic compositions and its dynamics with respect to the electrical potential across the cell membrane. The knowledge led to the derivation of a model of the giant squid axon, popularly known as the Hodgkin and Huxley model (HH). Therefore, physical measurements from the *real-world* is reduced to a mathematical form. This is scientific reduction (Figure 1). It is an approach commonly employed in specialized disciplines, most notably, physics.

A system consists of both the object of study and the model of that object. Therefore, a component model is a system, albeit a smaller scale one. Every system is contained in a larger system. The systems modeller trained in the overall view aims to tie the components of the system together. Fields of applied mathematics greatly help the effort. However, it is a necessary but insufficient requirement. For instance, although a systems modeller can tie together few HH models in a system, adding a few more HH models will eventually lead to the unavoidable barrier in the form of a limit on the power of any computing device. Weinberg calls this the “Square Law of Computation” (Weinberg, 1975, p6-8). The amount of involved computation increased at least as fast as the square of the number of equations (Figure 2). Therefore, with double the number of equations, solving it in the same amount of time will require a new computer that must be four times as powerful.

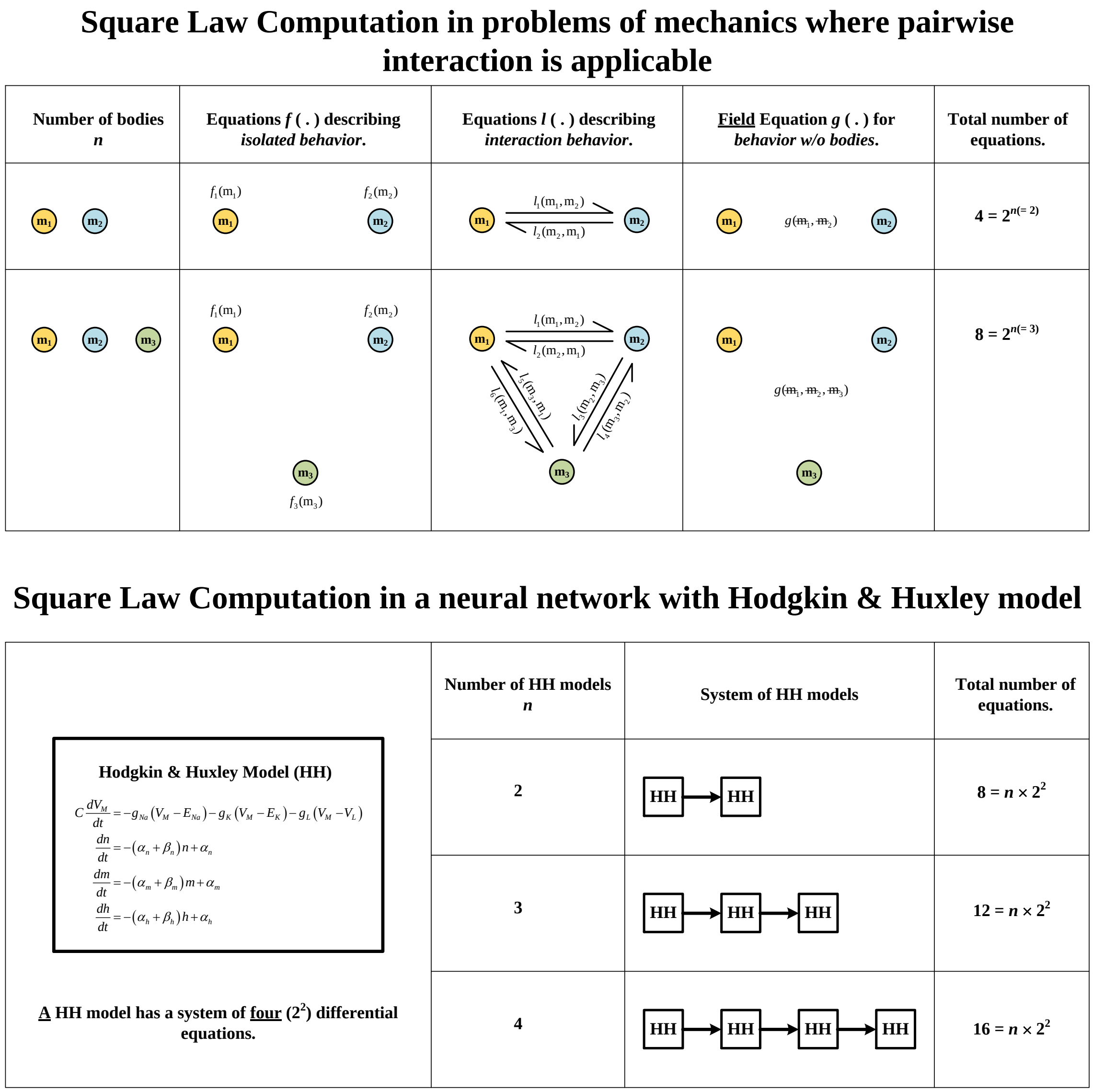

Figure 2. Illustration of the square law of computation. For the first (top) case the law is 2^n and for the other is $n2^2$. The idea is that, as the system grows in size the amount of required computation increases by some multiple of 2.

When confronted with the issue of the square law of computation, wisdom from past experiences show that some simplification must be made. The simplification when done right is not the simplification of science. "Doing it right" is the science of simplification. Weinberg uses Newton's analysis of planetary orbits to illustrate this. Newton successfully reduced the number of equations required solving on the order of $10^{30,000}$ to just about 10 equations, resulting in what some call "the greatest generalization achieved by human mind." Weinberg says that Newton's genius was,

"… his ability to simplify, idealize, and streamline the world so that it became, in some measure, tractable to the brains of perfect ordinary men. By studying the methods of simplification that have succeeded and failed in the past, we hope to make the progress of human knowledge a little less dependent on genius." (Weinberg, 1975, p12)

The simplification of component models to build a larger system is called model order reduction. If we concern ourselves only with the general characteristics, complexity and randomness of any system, most neuroscience models will come under Weinberg's region of organized complexity (Figure 3). The region where systems are too complex for analysis and too organized for statistics (Weinberg, 1975, p17-19). Weinberg calls this the "vast no-man's land of medium numbers." In systems of organized complexity the gross effects of interaction among a huge number of variables tend to produce measurable results or observables that cluster tightly around a very small numerical range of values (Wells, 2010, p173). This is why model order reduction is possible with neuroscience models.

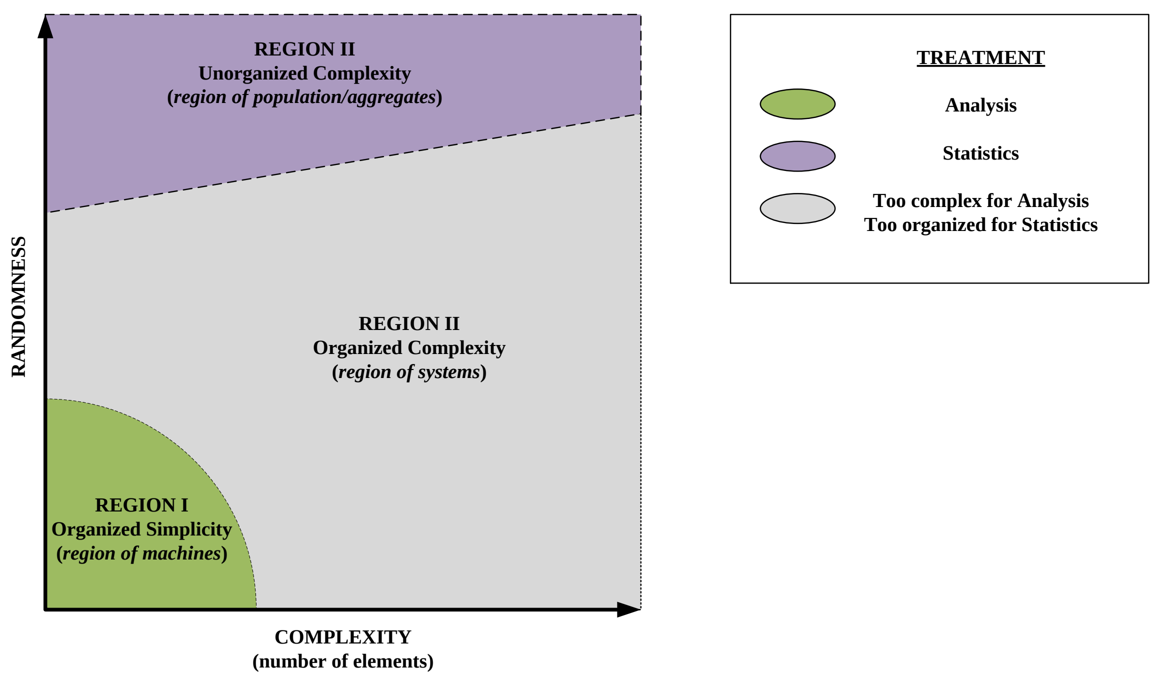

Figure 3. Types of systems based on complexity and randomness.

THE PREDICTION-INFERENCE DILEMMA

Suppose a model has garnered much confidence due to its successes in making predictions. Are some inferences drawn from the model incongruent with physical measurements? The answer seems to be no, and yet they seem so.

Movements of ions through the resistance of the cell membrane results in current flowing through the cell membrane. This resistance is a reflection of “permeability” of the ions. Compared to other ions the concentrations of the sodium ions (Na^+) and the potassium ions (K^+), make the bulk of the ionic concentrations, extracellular and intracellular respectively. Therefore, the collective Na^+ and the collective K^+ flowing through the membrane are considered; I_{Na} and I_K . And the flow of rest of the ions are lumped as I_L .

This simplification makes possible the description of ionic current across the membrane with just three components, $I = I_K + I_{Na} + I_L$. Using K^+ flow I will illustrate the concept of the prediction-inference dilemma. The model is shown in Figure 4.

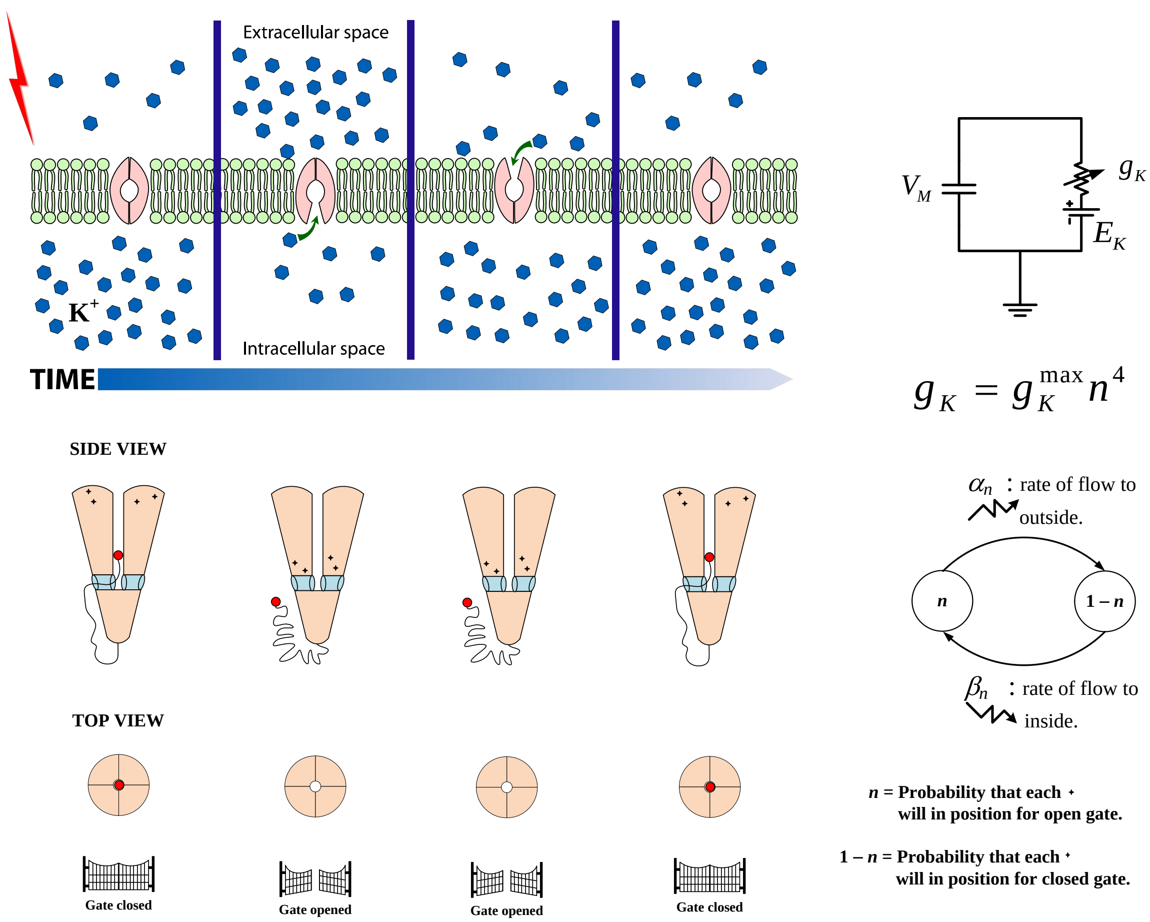

Figure 4. Illustration of K^+ flow through the “resistance” of the membrane. When a disturbance is created such that the membrane voltage (V_M) is changed from rest, K^+ flows out. After sometime it flows in to return to equilibrium.

The Model

Permeability is the freedom with which the membrane allows K^+ to pass. For charged solutes like K^+, their permeability takes into account the electrical forces. The driving force is the resultant of the equilibrium potential (E_K) yielded by the concentration difference (in and out the cell) and the potential difference across the membrane (membrane potential, V_M) due to all the ions. Let us define it as $V_{DF} = V_M - E_K$.

The permeability coefficient has the dimension of a conductance (mho or Siemens). For K^+ ions they are referred to by the conductance g_K.

Whatever the relation of I_K and V_{DF}, the definition $g_K = I_K / V_{DF}$ is valid. However the degree to which g_K measures real properties depends on how they are measured. When the measurements are made fast enough that the membrane has no time to change, then g_K is the constant of proportionality to $I_K \propto V_{DF}$. Thus, V_K is taken constant and the conductance for a range of V_M can be measured.

Although the above definition of conductance helps provide a measurement of the physical property, it is lacking as a source of insight. To study the possible cause of K^+ flowing in and out the cell based on g_K vs. V_M measurements, Hodgkin and Huxley employed kinetic theory with the assumption of a first order reaction. Based on this simplification,

$$g_K = g_K^{\max} n^4 \qquad [1]$$

where, the constant $g_K^{\max}$ is the maximum conductance, the exponent 4 is the number of similarly charged particles and $n \in [0,1]$ is a dimensionless variable representing the proportion of charged particles in a certain position say, position to open for K^+ to flow. Hence, the proportion in a position to close is $1-n$. The variable is given by,

$$\frac{dn}{dt} = \alpha_n (1-n) + \beta_n n \qquad [2]$$

where, α_n and β_n represent the rates; α_n, the rate at which the proportion of charged particles in a position to open transitions to a position to close, and β_n, the rate in the opposite direction. They are given by,

$$\alpha_n = \frac{0.01\left[10 - \left(V_M - V_{rest}\right)\right]}{e^{\left[\frac{10-\left(V_M - V_{rest}\right)}{10}\right]} - 1} \qquad [3]$$

$$\beta_n = 0.125 e^{\left[\frac{-\left(V_M - V_{rest}\right)}{80}\right]}$$

where, the constant V_{rest} is the resting membrane potential. Therefore g_K is the conductance of the voltage-dependent potassium channel.

The Predictability

Experimental observations shows that the model is congruent with conductance from physical measurements. Since the introduction of the model 67 years ago different species of voltage-dependent potassium channel has been discovered. Investigators have found that different values of the exponent of n can represent various species.

The seemingly conjuring term n has proven prescient in describing how the channel functions. When Hodgkin and Huxley first introduced the term not much was known about what we now call as K-channels. The equation [2] is a form of the first-order rate equation

$$\frac{dp_0}{dt} = \alpha(1 - p_0) + \beta p_0 \qquad [4]$$

where, p_0 is the probability that the process is open and $1 - p_0$ is the probability for closed process. The use of n therefore introduces the idea of some gating mechanism in the channel. Biologists have discovered that this process is performed by a gate-like mechanism in the pore of the potassium channel (Figure 4). Thus, n is the probability that the gate is open. It cannot be emphasized enough that the n variable was part of the model years before the discovery of gates. Because n is a function of time and voltage (V_M) these channels come under the family of channels called voltage-gated channels.

With all the success in predictions accrued by the model over the years, it is not a surprise that the HH model garners much confidence with regards to how well it represents or reflects the electric neuron. One researcher after another over the years have successfully modelled other axons and entire neurons based on the HH model schema. A reason why it may not be used to model larger systems is because of the aforementioned square law of computation (Figure 2).

The Dilemma

We have a model that is not only congruent with physical measurements and a model that covers a gamut of varying channel species, but a model that is able to describe deep seated functional mechanisms. Based on the confidence of the model suppose that the probability that the gate is open $n = 0.5$. Also consider just one channel. The term n^4 is the distribution of all the four charged particles, the probability that all four particles are in a position to open the gate assuming that they have equal probabilities. Is it sensible to infer that there would be only four charged particles in a channel? What if there are more than one channel?

Although this might appear to some as an extreme or exaggerated example one such experience regardless of how much confidence one has on a model can lead to the dilemma. That is, either continue to have confidence in the model or discard the model. A reason why one gets into this kind situation is due to Bacon's idols. Bacon says,

"The human understanding, when any proposition has been one laid down, forces everything else to add fresh support and confirmation; and although most cogent and abundant instance may exists to the contrary, yet either does not observe or despises them, or gets rid of and rejects them by some distinction, with violent and injurious prejudice, rather than sacrifice the authority of its first conclusions." (Bacon, 1620, p15)

He continues,

"The human understanding is most excited by that which strikes and enters the mind at one and suddenly, and by which the imagination is immediately filled and inflated. It then begins almost imperceptibly to conceive and suppose that everything is similar to the few objects which have taken possession of the mind, whilst it is very slow and unfit for the transition to the remote and heterogeneous instances …" (Bacon, 1620, p16)

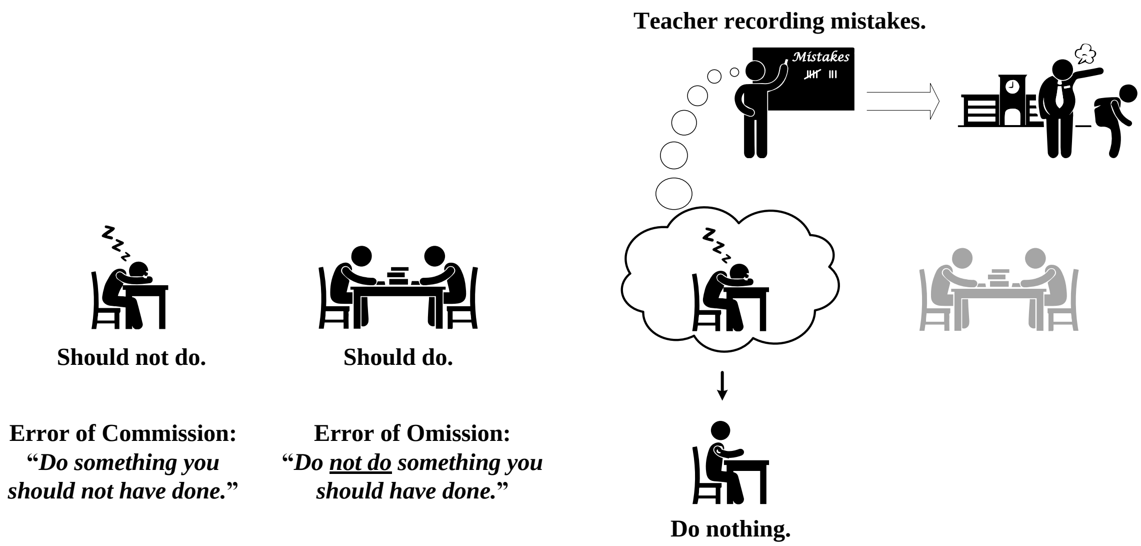

Figure 5. Illustration of Ackoff's errors of commission and errors of omission. Most cost-profit analysis only record the mistakes. Thus, to maintain one's position, say as a student or an employee, the simplest way to maintain stability is to do nothing.

The ontology centred when faced with such a dilemma will consider two choices; accept or reject the cause of the dilemma. However going with either of these choice would be a mistake. Ackoff (2006) calls these respectively as the "error of commission", you do something you should not have done, and the "error of omission", you do not do something you should have done (Figure 5). Since most cost-profit analysis record mistakes, it is very common to zone in on the error of commission. In such situations the easiest way to maintain stability in the sense that you don't get judged (for the mistakes) is to do nothing. Although this treatment of mistake can lead to stability, it prevents change, that is, understanding of the system.

Therefore most neuroscientist when confronted with examples like the one illustrated here, will do nothing. Thus, not committing the error of commission. But, as a result they will be committing the error of omission. The error that they do not resolve the dilemma.

Though our model is mathematical, the contradiction is not in math but how we relate to the real phenomenon. We are not limited like in math where, to avoid mathematical contradiction one must hold yes or no. There is a third alternative, resolve the dilemma.

MATHEMATICAL MODELS APPLIES TO IDEALIZED SYSTEMS

Before discussing how to resolve the prediction-inference dilemma, let me explore why one may invent a mathematical model. At different stages of consideration of a body of real phenomenon one may try to develop, a set of inventions and a resulting body of theory. That is, invent a mathematical model such that it applies to an *idealized* physical system which seem close enough to the *real* physical system. The hope of the inventor is that the idealized system will *explain* the real phenomenon. It is often the case that with the growth and development of the model many modellers tend to forget that the model is a representation of an idealized system, or worst fails to recognize.

Mathematics is a language for saying things precisely. The mathematical relation *indicate* real relation in a condensed way. It is also economical because one can in a relatively cheap manner carry out paper equivalent of real experiments. Calculations that *would* happen under certain assumed conditions.

The relation between the model and the real-world is complex. Ask an engineer building hard disk drives how Galileo's laws of inclined planes hold? The engineer dealing with ball-bearings, one set for the rotating discs and another set for the actuator arm, might respond saying that the law applies to the special and simple case of inclined planes. What he means to say is that it is modelled on the idealized system of inclined planes. In other words, the law holds *precisely* for a mathematical model and *approximately* for actual material. As Weaver puts it,

"… a great many "scientific laws" that we tend to forget that very many of them are really the theorems which hold strictly only for mathematical models, though they are obeyed closely enough by actual phenomena so that they are highly useful." (Weaver, 1963, p58)

Just because a model holds precisely only for the idealized system and approximately for the real phenomenon does not mean we do not use the model or even discard the model. This would be like not using geometry because there are no physical points without dimensions and lines with no thickness. Theoretically one could continue to search for a phenomena that conforms to the assumptions of the theory/model, i.e., search for the ideal physical system. But, if we did so we would not be using geometry and most of the fundamental ideas of human knowledge and discovery.

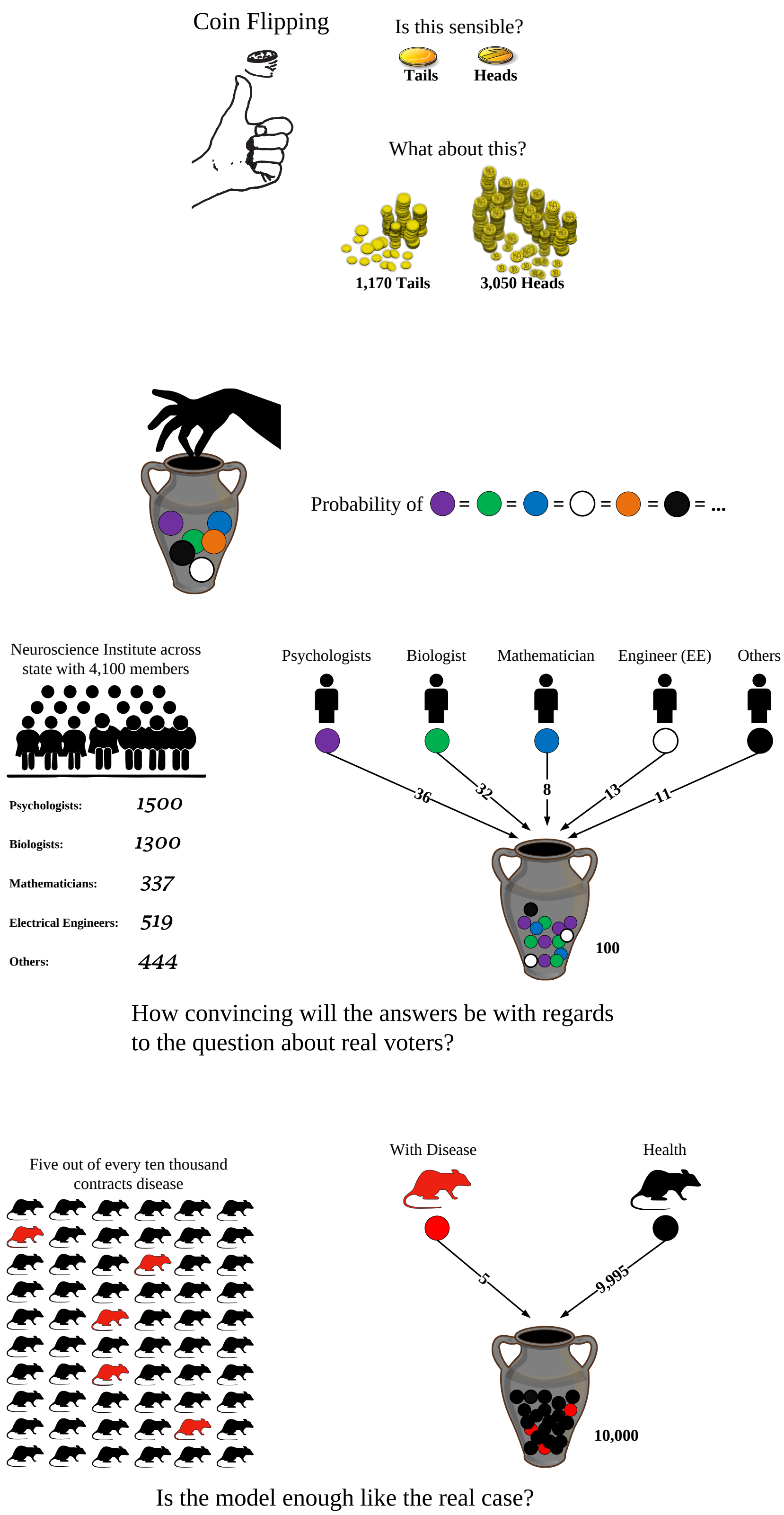

Figure 6. Some models based on probability theory.

However, if one wants to use the model it is important to keep in the vanguard of one's thought the relationship between mathematical model and the events of the real world. If one keeps in mind the model-real world concept, the confusion and difficulties will vanish. Let me illustrate this using probability theory, a branch of mathematics that may appear magical, and that which have led to many debates among mathematicians, philosophers and logicians.

Toss a coin, a large number of times. It seems sensible to believe that half of them will end up as heads and the other half, tails. It may also seem impossible to suppose that the actual number of heads would exceed those of tails by thousands. You would be wrong with the latter supposition. One reason is because the first supposition is based on an idealized system where all the events are *equally* probable. However that does not mean that a model based on an idealized system can't apply usefully to a real situation.

Take the example of the fictitious and idealized urns and balls. The probability of drawing any one ball from the urn is the same as for any other. Consider the scenario where one is interested in the voting for the director of a neuroscience institute composed of psychologists, biologists, mathematicians and electrical engineers. The idea is to select a representative sample. How likely will the chosen sample be a fair representation of the community?

Create a model such that in an urn you put a proper proportion of, purple balls (psychologists), green balls (biologists), blue balls (mathematicians) and white balls (electrical engineers). Based on varying these numbers such that they are proportionate to those in the community, one can produce a model that produces convincing answers with regards to the question about real voters.

Consider a different scenario where it has been known in the past few years that about 5 out of every 10,000 rats in a relevant age range contracts disease across the laboratories. As a person that uses rats in the laboratory you are worried about the possibility that one of your rats will contract the disease within the calendar year.

Suppose you create a model with an urn containing 10,000 balls such that 5 are black (diseased rats) and 9,995 balls are white. Is the model enough like the real case? Would drawing the balls out simulate the real situation of contracting or not contracting the disease? What is the probability of drawing four black balls in succession? Isn't the probability of contracting the disease dependent on number of factors like, lab conditions, veterinarians trained in rat medicine, and so on…? Have these factors been taken into account.

These two scenarios highlights the fact that the probability calculations apply only to fictitious models on which they are based. One must always keep in mind this when inventing models, regardless of whether the theoretical calculations concerning the model mean much and apply usefully to real situations.

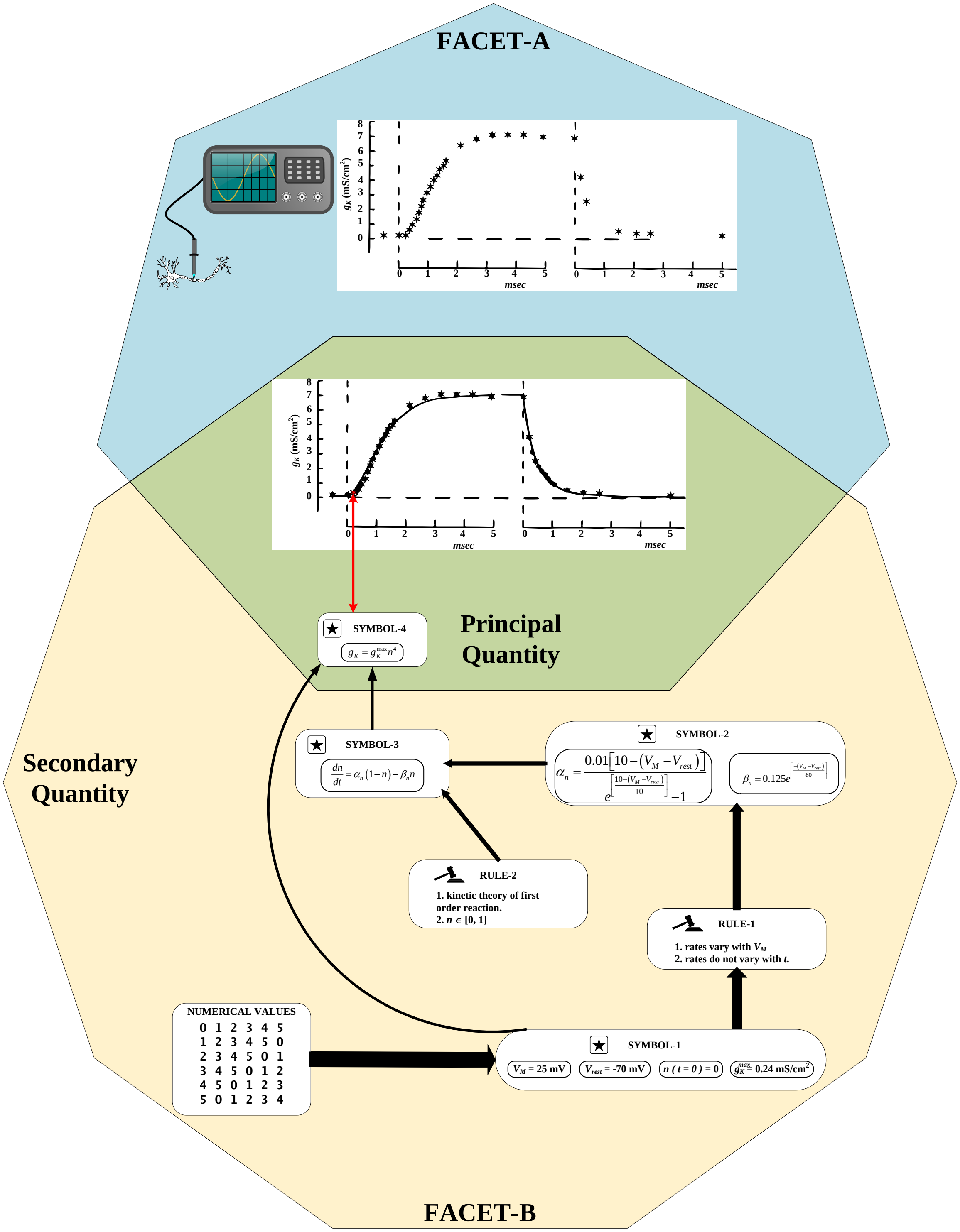

Figure 7. Slepian's two world view on the mathematical world – real world relation. Facet-B is the mathematical world. It comprises of secondary quantities which do not correspond to physical measurement. The principal quantities correspond to physical measurement, but it is still a different quantity from the measured value.

What is this a model of? → n

A

Mathematical Model

$$g_K = g_K^{max} n^4$$

$$\frac{dn}{dt} = \alpha_n (1-n) + \beta_n n$$

$$\alpha_n = \frac{0.01\left[10-\left(V_M - V_{rest}\right)\right]}{e^{\left[\frac{10-\left(V_M-V_{rest}\right)}{10}\right]}-1}$$

$$\beta_n = 0.125 e^{\left[\frac{-\left(V_M-V_{rest}\right)}{80}\right]}$$

What is the behavior and function of the containing whole?

A

Voltage-dependent gated K Channel.
The gate is either open or closed with the rate α_n from open to closed and β_n in the opposite direction.

What role does *n* play in the whole?

A

n is a secondary quantity.
It is the probability (equal) of each of all the four charged particle that they will be in a suitable position for gate to open.

Figure 8. Synthetic thinking to prediction-inference dilemma.

MODEL-REAL WORLD CONCEPT AND RESOLVING THE DILEMMA

David Slepian (1976), one of the early pioneers in information theory at a lecture given at an Information Theory Symposium presented a practical more concrete account to this two world view. The concept is summarized as follows.

There are two *distinctly* different components of a quantitative science. They are called facets-A and B, made of totally different stuffs. Facet-A which encompass the real world, is comprised of observation on the real world and manipulations of the real world. Numbers describing the state of the real world are derived from measuring instruments. They are recorded in notebooks as rational real numbers.

Facet-B encompasses the mathematical model (Figure 7). It is comprised of the mathematical symbols and equations describing the model and also means for operating the model. Therefore when numerical values are given to some symbol, the rules for manipulating them prescribe numerical values for other symbols.

A theoretician or a modeller becoming too comfortable with a model can find quantities within facet-B *very real*. One would like to think that there is an intimate relationship between facet-A and facet-B of a given science. For instance, under test cases the measured K^+ conductance agree with the numerical value of the symbol g_K. The modeller gets so confident that he/she starts saying for both, "the conductance of K^+ across the membrane." Regardless of how confident one may get, the fact is that these are two very *different quantities*. Using same name to describe them confounds this distinction.

Why are these quantities distinct? The correspondence between them are incomplete and imprecise. This mismatch goes both ways; details from facet-A do not appear in facet-B and details of facet-B may not have any counterpart in facet-A. Details from facet-A like laboratory details (table height of the measuring instrument) are usually ignored in the model. This usually cause little problem in terms of the model being convincingly useful.

Mathematical models are full of concepts, symbols and operations. Most of these details of facet-B have no counterpart in facet-A. This can be troublesome. With some training and practice one may perform mental exercises to understand and agree upon. But the difficulty persists and continues to perplex. This is because there is a fundamental lack of correspondence between the two facets.

From a facet-A facet-B perspective the prediction-inference dilemma is resolved. This is because it does not try to force an agreement between the two worlds. Rather, it accepts the fundamental lack of correspondence between the two worlds. However that does not mean that a person with this perspective surrenders the mission to find a relation between the model and the real phenomena.

The details within facet-B that have no counterpart in facet-A are called secondary quantities (Figure 7). The symbol values in facet-B that correspond with measurements in facet-A are called principal quantities. However as noted earlier one should always keep in mind that the principal quantity and the measured quantity are not the same. It is not uncommon for the value of a principal quantity to be an irrational number (as result of mathematical operations). The measurement value is in rational real number. The principal quantity is made to correspond to the measurement value by simple schemes like round-off, k -significant digits etc.

The presence of the secondary constructs or quantities introduces mathematical abstractions which makes the model tractable. For the model to be useful a necessary condition is that the principal quantities are insensitive to small changes in the secondary quantities. One would be suspicious of the model if it made one prediction when the value of the secondary quantity $g_K^{\max} = 0.24$ but made a very different prediction when say $g_K^{\max} = 0.23095$. For the model maker the proper application of the principle of making principal quantities insensitive to secondary quantities is paramount to the robustness of the model.

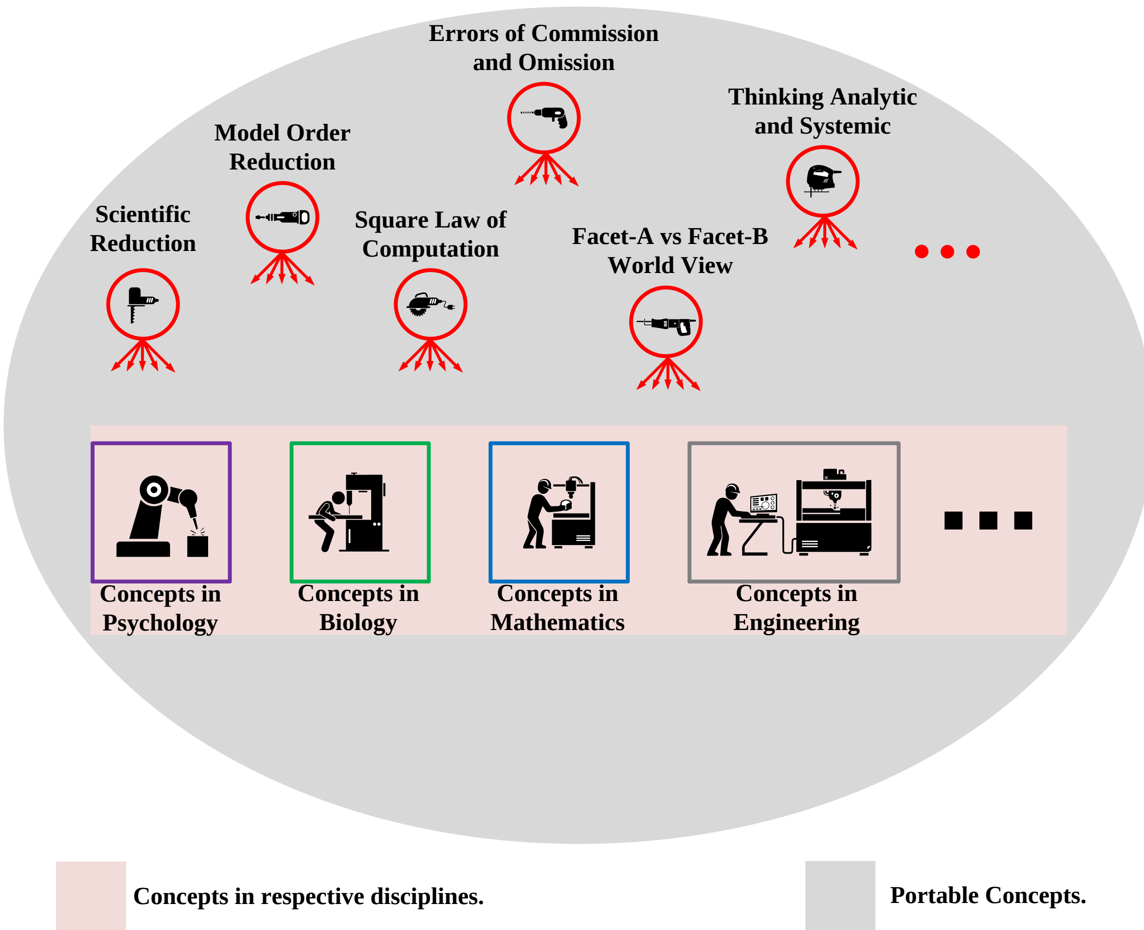

Figure 9. Portable concepts are indispensable to a general systems thinker.

GENERAL SYSTEMS AND THE SCIENCE OF MODELLING

Neuroscience as a product of being an interdisciplinary science has its practitioners with varied background. Specialized technical terms learned from years of training in their respective disciplines creates a major roadblock in communication and hence collaboration among the neuroscientists. I am of the school of thought that the role of computational neuroscience (also known as theoretical or mathematical neuroscience) is to join the disciplinary rungs of the neuroscience ladder. Joining the rungs help explain the behaviour of a system. Explanation of the system generally lies outside the system. Understanding is its product. Ackoff (1994) calls this “synthetic thinking”.

The task of joining the rungs comes in various forms. One of them is to resolve confusions and conflicts like the prediction-inference dilemma. These are a side-effect of analytic thinking. Analysis takes apart the object of interest in the system, identify its behaviour and properties, and then aggregate the knowledge of the parts. Analytic thinking produces the knowledge, how does it work? But, this is not understanding.

Synthetic thinking on the other hand is the opposite of analytic thinking (Figure 8). It identifies the containing whole of the object of interest, explain the behaviour of the whole, and then disaggregate the explanation of the containing whole.

The objectives of a neuroscience system are usually not clear initially in the mind of the model maker. This is mostly due to the fact that in most practical cases the objectives are modified on the basis of better knowledge of what is available. Therefore the model maker requires a broad background of alternatives presented with crude evaluation. That is, the model maker must first put together a simplified rough model with the primary objective to get it "to work". Detailed consideration requires an extensive set of assumptions which is only justified after considerable study of the problem.

Model design and invention or model derivation are integral tasks of a model maker. However they depend more on concept than quantity. A model maker with general system training will therefore be equipped with a set of transferrable concepts (Figure 9). Linvill calls this portable modelling concepts (Linvill, 1962). Portable concepts are necessary because of the wide technical range of system problems. The aforementioned concepts are all portable concepts because they are transferrable to other disciplines or interdisciplinary studies. It is essential for a general system theorist to accumulate portable concepts.

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