The need for the emergence of mathematical neuroscience: beyond computation and s...

Health & Medicine

Computational neuroscience, broadly defined, is the mathematical and physical modeling of neural processes at a specific chosen scale, from molecular and cellular to systems, for the purpose of understanding how the brain and related structures represent and process information. The ultimate objective is to provide an understanding of how the organism takes in sensory information, how such information is integrated and used in the brain, and how the output of such processing results in meaningful decisions and behaviors by the organism to allow it to function and thrive in its environment. This endeavor involves the building of computational models that aim to replicate and explain observed or measured data in order to arrive at a deeper understanding of the dynamics of brain function.

Beginning with a set of experimental observations or measurements, a model is postulated that aims to provide a set of rules or relationships that if given the initial experimental observations (or at least part of such a set) would be able to describe and explain some desired aspects or properties of the experimental measurements, such as casual, correlative, or mechanistic relationships between the data and underlying molecular, cellular, and systems mechanisms that produced it. In general, this process almost always begins with a qualitative " guess" about how the data fit together and what are the likely rules that govern the relationships between it. This is subject to a number of uncontrollable variables, including the amount and quality (e. g., accuracy and precision) of the data, how general or narrow the acquisition conditions were under which it was collected, which may constrain the generality and applicability of the model, and the degree of understanding and expertise on the part of the investigator constructing the model about the neurobiology which the data describe. This qualitative picture of the model is then “ translated” into a quantitative mathematical framework which almost always involves expressing the hypothesized relationships as ordinary or partial differential equations or related objects, such as difference equations, as state variables that evolve in space and/or time. The model, once constructed, is still nothing more than a guess, and so testing it with the goal of building circumstantial support for it (or against it) is then carried out by numerical simulations of the processes being modeled, often where the answers or outputs are known from experiment and can be compared with the outputs computed by the model. At this point several outcomes are possible, assuming the model is at least partially correct. One possibility is that the model is able to describe the data set used to constructed it but cannot make any novel non-trivial predictions or new hypotheses about the system under study. This outcome often provides a modest contribution to the literature that may give some insights into the mechanisms involved if the model or at least parts of it can be experimentally tested and validated. A less desirable outcome is where a model contains terms or is constructed in a way where further experimental testing of the model cannot occur, for example due to limitations in experimental technologies or terms in the mathematics that have no known real world counterparts. A more productive outcome is when the model results in a novel non-trivial or unexpected experimental hypothesis that can be tested and verified. This may lead to the design and carrying out of new experiments and may lead to potentially significant novel experimental findings. In turn, new data sets allow the fine tuning or modification of the model in an iterative way. But in all cases though, the core of the process is the same: one guesses at a model and uses mathematics to justify the guess. The actual validation of the guess is based on numerical simulations, and in an often iterative approach improves the model. Note however, that in the typical way in which computational neuroscience is practiced, the mathematics involved, while in an applied sense is central to the process, is purely *descriptive* and does not participate in the process of discovery. Given this discussion, we can define computational neuroscience somewhat more provocatively as numerical simulations of postulated models constructed from qualitative hypotheses. In the most limited case this definition extends itself to numerical simulations of postulated models constructed from unverifiable hypotheses. The computational neuroscience literature is full of beautifully mathematically constructed models that have had minimal impact on main stream neuroscience or our understanding of brain function because of this.

Here, we propose to define mathematical neuroscience not as the generation of hypotheses based on numerical simulations of postulated models, but as the systematic analytical investigation of data driven theorems, a term we progressively explain in the rest of this commentary. The principle idea being put forward is that mathematical conjectures can be written down and logically proven who's axioms, i. e., the starting point ground truths, are not unknown or postulated hypotheses about how the system under consideration *might* work, but, within the limits of experimental verification, are the simplest possible set of experimentally verified knowns which allow the construction of the statement of truth being made by the conjecture. (We apologize outright to mathematicians for the considerable abuse of the term “ axiom” here). The initial goal is to set up a conjecture that is mathematically sound and is based on an agreed upon experimentally known set of axioms, and then use any mathematics possible to formally prove it or at least provide a reasonable starting point, such as a sketch of a possible proof. These axioms are the same types of experimental observations and measurements that form the starting point in computational neuroscience, but instead of qualitatively guessing a possible relationship that explain the set of observables, the objective is to translate the set of experimental observations into a corresponding complimentary set of simple mathematical statements. No assumptions or guesses whatsoever regarding the relationship between either the set of experimental observables or their corresponding mathematical representations need be made at this point. Only, as simply as possible, straight forward statements of fact that everyone would agree upon.

For example, consider on-going efforts to decipher the connectome of the mammalian brain; that is, identifying and mapping the structural connectivity of the networks in the brain at various scales. At the cellular scale, no one would disagree that the connections between cells represented by the vast spaghetti of processes that make up the neuropil are a complex intermingling of curves. This represents a universally accepted qualitative anatomical statement of fact about the structural connectivity of cellular networks in the brain that few would argue with. We can translate this agreed upon statement into a mathematical statement. For example, we can say that the set of edges that connects the vertices that make up the network of interest are not represented by Euclidean geodesics but by curves that can be described geometrically as Jordan arcs or some other appropriate mathematical object. We may decide to characterize the turning numbers (from topology) of similar curves in a set or use some other math to describe a different property. The point is that we have taken a simple agreed upon experimental neurobiological statement of fact and have " translated" it into a mathematical statement. We have captured some desirable aspect or property about this " experimental axiom" within the language of mathematics.

The next step is to set up a conjecture that says something about the set of axioms. While this is itself a guess, often the product of much trial and error and finding patterns between the objects under study, it is a mathematical guess. This means that once a plausible conjecture is written down, it can be attempted to be proven. And here is the most significant conceptual deviation from computational neuroscience. In computational neuroscience a model is written down which is a guess about the relationship between a set of data, but there is no formal logical way to " prove" the model correct or incorrect. So numerical simulations are done. But this is never proof of anything. In fact, this exercise often results in an expansion of the model to fit the data. Writing down a valid conjecture on the other hand is a very narrow statement about a very specific set of facts. And it has the potential to be proven; meaning that it can be established as true or false analytically. And once proven it is true forever. One has established a truth about the relationship between the starting point axioms from a logical set of arguments. No simulations or other guesses are required. There is another important consequence of this mathematical neuroscience approach. As mentioned above, much of computational neuroscience is based on time varying differential equations that describe state variables. But this completely misses the fact that other properties or aspects of the neurobiological system under study may be more appropriately and more naturally described by other mathematical objects. Mathematical neuroscience by its very formulation breaks free of differential equations and rewards creativity and imagination. There is no template or rule book to this process, one is free to write down a set of axioms and to construct and prove a conjecture from those axioms using whatever mathematics is deemed appropriate. Of course, this makes it an inherently difficult process, since it is not clear *a priori* what experimental observations can be translated into such mathematical statements let alone what conjectures might arise from such statements. There in lies the challenge but also the reward. There is a large intellectual void in our theoretical understanding of many aspects about how the brain works and how it processes information despite ever accumulating volumes of experimental data. A new approach for dealing with such data is needed.

Then the game becomes how far can the math take you. Starting from the initial theorem, what new theorems can be logically derived given an agreed upon set of experimentally verified axioms without making any new or unknown experimental assumptions. The statements of truth expressed by such theorems then must apply to the neural systems described by the starting axioms and any other proven theorems used to construct the current theorem. The point is that if one is careful in stating the initial axioms and in how those axioms are used to prove conjectures, then the proven statement in the form of a theorem also applies to or says something about the neurobiology the axioms describe. In other words, one can “ work back” to the mechanisms of the neurobiology for which the starting axioms apply. A notable and important difference between mathematical axioms and our use of the term here applied to neurobiological experimental measurements is that mathematical axioms are irreducible and permanent, while such experimental neurobiological axioms may change as new experiments are done and new information accumulates. In this regard, “ proven” theorems that relate to the neurobiology would then have to be revisited to ensure that they still apply in practice if their starting points change. Again, to achieve this, new math not necessarily typical in neuroscience may need to be used or even discovered. This last point is potentially intriguing and there are several examples from theoretical physics where the physics has contributed to the development of new mathematics, even entire new branches of mathematics, out of the necessity of describing the physical system. In this context it is not what can math do for physics but what can physics do for math. We propose that a similar argument can be applied to the relationship between mathematics and neuroscience where it is clear that we either are not using the right mathematical tools to understand the brain or such tools have not yet been discovered. The resultant mathematical descriptions should make non-trivial predictions about the system that can then be verified experimentally. This approach takes advantage and has the potential to use the vast amounts of *qualitative* data in neuroscience and to put it in a quantitative context.

Again, consider the example from above regarding the significant resources and time being put into deciphering the structural connectome of the brain. This massive amount of accumulating data is qualitative, and although everyone agrees it is important and necessary to have it in order to ultimately understand the dynamics of the brain that emerges from the structural substrate represented by the connectome, it is not at all clear at present how to achieve this. Although there have been some initial attempts at using this data in quantitative analyses they are essentially mostly descriptive and offer little insights into how the brain actually works. A reductionist's approach to studying the brain, no matter how much we learn and how much we know about the parts that make it up at any scale, will by itself never provide an understanding of the *dynamics* of brain function, which necessarily requires a quantitative, i. e., mathematical and physical, context. The famous theoretical physicist Richard Feynman once wrote that " people who wish to analyze nature without using mathematics must settle for a reduced understanding." No where is this more true than in attempting to understand the brain given its amazing complexity.