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What Can a Mathematician do in Neuroscience?

Abstract Mammalian brain is one of the most complex objects in the known universe, as it governs every aspect of animal's and human behavior. It is fair to say that we have a very limited knowledge of how the brain operates and functions. Computational Neuroscience is a scientific discipline that attempts to understand and describe the brain in terms of mathematical modeling. This user-friendly review tries to introduce this relatively new field to mathematicians and physicists by showing examples of recent trends. It also discusses briefly future prospects for constructing an integrated theory of brain function.

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1. Introduction. The purpose of this review article is to present a relatively new field of Computational Neuroscience (or Theoretical Neurobiology) to mathematicians or physicists, who would like to do a non-traditional research in theoretical biology but do not know how and where to start. The primary audience for this review are graduate students who have their MSc in mathematics, theoretical physics, or computer science, and are ambitious enough to think about their PhD (doctorate) in Computational Neuroscience.

I still remember myself in the mid 1990s when I was finishing my PhD in theoretical physics (condensed matter) and thinking that I would not spend the rest of my life doing this type of research. At that time it became clear to me that physics was an "old science" and all exciting theoretical problems that could be solved and later verified experimentally had been already solved. (Of course there was string theory but that appeared to me as an extremely abstract fantasy with its 11 or so dimensions and with no chance for any sort of verification in my lifetime). In my search, I turned to biology, which at about that time was depicted in a popular press as the science that would dominate the 21 century. Judging by the percent of biological papers published in every issue of highly prestigious Nature and Science magazines, this prediction has turned out to be correct. In particular, neurobiology seemed very interesting to me, because it dealt with the brain, which is the organ

generating all of our behavior, as well as higher cognitive states (e.g. the ability to solve math equations). I made my transition from theoretical physics to theoretical neurobiology when I was a postdoc at Boston University. That transition was relatively quick and painless, and I have never regretted my decision. My example shows that it is possible to switch successfully scientific fields, if somebody is highly motivated and hard working. Thus, if a young reader of this article possesses these two traits, such a transition can be possible as well.

2. General overview of Computational Neuroscience.

2.1. Grand challenges of Computational Neuroscience. One of the major goals of contemporary Neuroscience is to understand human behavior and action through understanding certain physical processes in the brain [4]. The challenge here is to provide quantitative description or "theory" that would make far-reaching testable predictions, much the same way as it has happened in physical sciences with the understanding of non-living matter. There is no need to elaborate that such putative understanding would be beneficial for society at large, and might have technological implications (e.g. for constructing "intelligent" computational devices). However, because of the brain structural complexity (about 10^{10} neurons and 10^{15} synapses in the human brain), this task is extremely difficult. One might note that this fact in itself should not be a big obstacle because even 1 mole of non-living matter contains about 10^{23} atoms, and somehow statistical physics deals efficiently with that. However, there are several fundamental differences between non-living and living matter, in particular the brain.

First, the brain, which can be viewed as an electro-chemical system of ionic mixture, is far from thermodynamic equilibrium with the environment and also within different brain components. This inequilibrium is maintained by the brain itself through various self-regulatory biochemical and sensory feedback loops, which use energy from the environment (animals have to eat). Nothing like that appears in non-living matter composed of a huge number of atoms, and mostly successfully described by equilibrium statistical physics (there are also exceptions, e.g. weather phenomena that are often described by non-equilibrium thermodynamics).

Second, neurons interact in a non-linear manner and the degree of this interaction changes over time (neuromodulation). Moreover, neurons and synapses undergo structural changes over vastly different time scales (from minutes to years). This process is known as brain plasticity and it is to a large extent environmentally (externally) driven, and therefore it has a strong non-deterministic component. This environmental stochasticity introduces non-stationarity into brain dynamics, which is difficult to capture theoretically. In contrast, non-living physical systems described by equilibrium statistical physics are composed of elements that interact in a predictable and on average static ways, which are relatively easy to formulate mathematically.

Third, neurons process information, i.e. they store information and recall it when necessary. A similar function can be also performed by some non-living man-made devices, e.g. computers, but only rather passively. The point is that brains do it naturally and adaptively, with a high degree of effectiveness, which is a result of a long process of evolution and self-organization (see e.g. [25] for the latter topics). A related issue is that brains (at least human brain) use information in a specific way to create abstract representations of the outside world. This is implemented by the so-called "higher cognitive states" or consciousness, which form the basis of

our daily existence and experience. Unfortunately, these cognitive states are rather elusive and therefore they have been much more investigated using the methods of psychology rather than those of exact sciences.

Given all that, one could speculate that the future integrated "grand theory" of brain function (provided such a theory is possible at all) should contain elements of stochastic dynamical systems [14, 34] combined in some innovative way with non-equilibrium statistical physics [32], and information theory [17] possibly with some elements of game theory (psychologically motivated). All these three or four disciplines already exist and have solid theoretical foundations. Nevertheless, they are still actively developed and have many open questions, especially in the context of neuroscience. Thus, I believe that we have enough theoretical tools at hand for describing brain functional mysteries, and there is no need to invent "new kinds" of mathematics or physics for that particular goal (see however [11] and [37] for the opposite points of view on the brain and general complex biological systems, respectively). It seems that the main challenge in constructing the grand theory of the brain is in appropriately adopting and integrating already existing separate concepts from these disciplines into a coherent theoretical picture that would be useful for brain description, rather than to invent completely new and unchecked concepts.

2.2. Historical remarks. Up to recent years Neuroscience has been predominantly an experimental science, in which scientists have been accumulating painstakingly, mostly separate, experimental facts. In this field there was no room for any sort of theory or mathematical model, partly because of incomplete or evolving knowledge and partly because of neuroscientists' reluctance to mathematics. Consequently, the majority of neurobiological models had qualitative, verbal character. The first example that theory can be useful in neuroscience came with the formulation of the so-called Hodgkin-Huxley model [16], which "mechanistically", i.e. physically, explains the generation and propagation of action potential in squid axon in terms of Na^+ and K^+ ions flow through neuron's membrane. That mathematical model agreed perfectly with the data and subsequently has become a classic. Hodgkin and Huxley were later awarded the Nobel Prize in Medicine or Physiology (1963) for their combined experimental, computational and explanatory efforts of neural spiking biophysics. However, despite this early success, the mathematical modeling in general and the Hodgkin-Huxley model in particular, were for a long time an exception rather than a rule in the neuroscience research. The exceptions in the 1960s and 1970s were in part due to people like Stephen Grossberg, Walter Freeman, and slightly later Terry Sejnowski (to name just a few), who made some lasting contributions to computational neuroscience, but nevertheless, did not inspire big crowds of computational scientists. Such an inspiration wave among physicists came later with the so-called Hopfield models in the early 1980s [18]. That huge initial wave subsided significantly later because the Hopfield's models and their extensions were not too realistic. It seems that the main value of these simple models is in the fact that they helped to realize that mathematics, physics, and computer science with their quantitative and rigorous methodologies, can offer a lot in understanding the brain. As a result of this thinking a new field called Computational Neuroscience has emerged, which is still in progress and which provides a link between theoretical and experimental work in neuroscience from a physical perspective [10, 26]. It seems that at present Neuroscience has matured enough so that it is possible, and even necessary, to try to find mechanistic explanation of brain dynamics and function.

The current models used in Computational Neuroscience are far more complex and realistic than they were in the 1980s and 1990s. It should be also mentioned that this new interdisciplinary field is practiced only to a limited extent in Poland by a handful of people. Nevertheless, I do hope that a popularity of this exciting field will grow over time in Poland as well.

3. Examples of research topics in Computational Neuroscience. In this section I present a short description of selected topics in Computational Neuroscience that might be of a particular interest to the mathematical and physical communities. The choice of these topics reflects author's interest, and for that reason it should not be viewed as the whole field of Computational Neuroscience.

3.1. Dynamics of a single neuron and networks of neurons. The most popular area of research in Computational Neuroscience is neural dynamics. Neurophysiological studies show that the brain exhibits different activity patterns, from regular oscillations, often with synchronous activities across different brain regions, to highly irregular or chaotic behavior. In this area the typical questions of interest are: (i) What are the mechanisms of oscillations in neural systems? (ii) What conditions must be satisfied to obtain synchronization in neural activities? (iii) Is chaotic neural activity relevant functionally? (iv) What is the mechanism of generating the so-called bursts of action potentials? These and similar questions are investigated both on a single neuron level and on a network level. In general, the single neuron study involves modeling realistic neurons with complicated voltage dynamics due to primarily sodium and potassium channels located on neuron's membrane. The basic equations of this approach, called Hodgkin-Huxley (HH) equations are of the form:

$$C\frac{dV}{dt} = -g_L(V - V_L) - g_{Na}(V - V_{Na}) - g_K(V - V_K) + I_{syn} \tag{1}$$

where C is the membrane electric capacity, V is the membrane voltage, I_{syn} is the synaptic input current, g_{Na}, g_K, and g_L are sodium, potassium and the so-called leak conductances through the membrane. These ions have their specific equilibrium voltages (Nerst potentials) for balance of their concentration gradients with electrostatic forces. These voltages are denoted as V_{Na}, V_K, and V_L, respectively. The Na and K conductances are dynamical parameters in this model, and are given by $g_{Na} = \bar{g}_{Na}m^3h$, and $g_K = \bar{g}_K n^4$, where $\bar{g}_{Na}$ and $\bar{g}_K$ are maximal conductances (all positive). The variables m, h, and n are the so-called gating variables, and each of them is described by a similar differential equation of the type:

$$\frac{dm}{dt} = ff_m(1 - m) - fi_m m \tag{2}$$

where ff_m and fi_m depend on voltage V in a non-linear manner. The gating variables describe complicated ion channels kinetics such as channel opening, closing, and inactivation through voltage dependence of the parameters ff and fi (for details see [10, 26]).

Let us try to provide some physical picture behind Eqs. (1) and (2). When neuron does not get a synaptic input ($I_{syn} = 0$), its voltage V is at a resting potential, which is close to V_L (about -65 mV). This is a consequence of the fact that for very negative voltages, Na^+ and K^+ channels are practically closed and do not conduct

ions. Mathematically this means that the gating variables m and n, characterizing channels openings, are approximately to zero (hence g_{Na} and $g_K \to 0$). However, when synaptic input I_{syn} 0, then voltage V increases due to sodium channels opening and Na^+ influx to neuron's interior. Mathematically speaking, V grows because g_{Na} increases and $V - {}_{Na}$ 0 ($V_{Na} \approx 50$ mV). If I_{syn} is sufficiently strong, then V can reach a threshold ($V_{th} \approx -44$ mV) for generation of an action potential (action potentials are abrupt changes "spikes" in V, and are the means to communicate signals between neurons). After crossing the threshold, the voltage increases further sharply, and this is because a positive feedback loop between g_{Na} and V (both drive each other through the gating variable m). With some delay the potassium channels start to open, i.e. the gating variable n starts to grow. However, since $V - {}_K$ 0 ($V_K \approx -90$ mV), the potassium current is negative (K^+ ions escape from the neuron's interior) and counteracts the positive Na^+ current. Therefore, the activation of potassium channels results in slowing down the rise of V, and ultimately its decay after reaching $\sim 20 - 30$ mV to negative values below V_L. From there the voltage slowly relaxes to its resting value V_L. The whole process of the action potential lasts about $2 - 3$ msec.

Note that the Hodgkin-Huxley HH model involves four differential equations (one for V, and 3 equations for the gating variables). The modern single neuron research takes this model as a base and extends it by including a whole range of new (recently discovered) channels, such as different types of calcium channels, calcium activated potassium channel, etc, to study neural dynamics. Such models are more realistic but at the same time more complex (and require more computing time in simulations). The interesting thing is that sometimes the presence of one channel type can have a dramatic impact on single neuron dynamics [1, 27]. That is, this dynamics can vary from highly ordered to extremely irregular.

On the other hand, studies on a network level involve simplified models of neurons. The most popular of these is the so-called integrate-and-fire (IF) model, of the form

$$\frac{dV}{dt} = f(V) + I_{syn} \qquad (3)$$

where   is the membrane time constant, and the function $f(V) = -(V - {}_r)$, with V_r denoting the resting membrane potential (i.e. when there is no synaptic input). In this model an action potential is generated when voltage V reaches a certain threshold, after which V is immediately reset by hand to a value below V_r. Then V starts to relax back to value V_r. This resetting procedure introduces a discontinuous jump in V, which is to mimic the decay phase of V during an action potential observed in real neurons. Additionally, the resetting jump in V leads to a non-linearity in the model, which otherwise would be perfectly linear. The advantage in using this simple model over the HH type model (Eqs. 1 and 2) is that a simulation time on a computer is much shorter because less equations have to be solved. This allows simulation of a huge number of connected IF neurons. Another benefit of using IF model is that, unlike HH model, it can be solved analytically, which provides in some cases a huge intuitive advantage. On the other hand, the drawback of this model is that "an interesting" neural dynamics is generated only by an interesting synaptic input, unlike in HH base models (which could be highly nonlinear even with constant I_{syn}).

Extensions of IF model have been proposed that involve different forms of the function f (V). For example, the so-called quadratic integrate-and-fire or its modification known as an Izhikevich model has $f(V) = aV^2 + bV + c$, where a b, and c are some numerical coefficients [7, 19]. Another example was proposed by the author [20] that can be called an absolute integrate-and-fire, which is piece-wise linear with $f(V) = | \quad - _r|$. These extended models have features that make them slightly more realistic than the traditional IF model, and hence should describe the dynamics of real neural networks a little more faithfully.

3.2. Models of learning and memory in the brain. One of the most important aspects of the brain is that it can learn and remember different events in the real world. These dynamic processes take place in the synapses, i.e. in the tiny volumes connecting two neurons (the term I_{syn} in Eqs. 1 and 3). Despite a huge experimental progress in the last 30 years, the detailed mechanisms of learning and memory are still poorly known. What we do know, however, is that synaptic structure and conductance are not static but change over time with different time constants ranging from 0.1 sec to $\sim 50 - 70$ years (human lifetime). That process is known as synaptic plasticity, and it can be activated when two neurons connected by a given synapse are simultaneously (or almost simultaneously) active. It is suspected that memories are encoded in these structural synaptic changes.

There exist a traditional model of memory based on the Hopfield model [18]. In this model the network learns different patterns by a training, and there is a close correspondence of memory states to the basins of attractors known from the dynamical systems. The problem with this and similar models is that they are quite abstract, i.e. memories can last forever, and moreover they have rather low capacity for the number of memory patterns they can store. In recent years, there have appeared other models of learning and memory [3,13,30] that are based on an experimental finding that synapses can exist in many discrete states, not in a continuum of states [31]. In these models [3,13,30], which usually have large memory capacities, plasticity is associated with transitions between these discrete states, and memories can naturally fade away, as it happens in the real world. As was stated above, there is a stochastic component to these transitions, which involves considering probabilities of synaptic states. The dynamics of synaptic probabilities are described by differential equations of the Master equation type known from non-equilibrium statistical physics [14]. Anther formulation of synaptic plasticity through the Fokker-Planck equation is also possible. This example shows that stochastic effects are present in the brain and can have some functional role (in this case in learning and memory).

3.3. Models of brain metabolism and visualization of brain function.
Brain is an expensive organ in terms of metabolic energy it uses [2, 5]. Moreover, as brain increases in size on an evolutionary scale its metabolic consumption grows slightly faster than metabolic needs of the whole body [22, 24]. This suggests that metabolism is an important part of brain function. The majority of energy used by neurons goes to maintaining concentration gradients of Na^+ and K^+ ions across neural membranes. These gradients are necessary for keeping the brain in the out of equilibrium state, which is the pre-condition for the ability to generate action potentials, which are necessary for efficient neural communication. One can relate the amount of metabolic energy used to the underlying neurophysiological processes such as the firing frequency of action potentials and activities of synapses. This involves solution of a system of differential equations for a balance in ionic flow of Na^+

and K$^+$ [23]. This relationship can have a practical aspect, because by measuring metabolic activity of certain brain regions one could say something more definitive about physiological state of neurons there. This is important, since the only way to visualize regional brain function in humans is through techniques such as PET (positron emission tomography) and fMRI (functional magnetic resonance imaging). Both of them are based primarily on brain metabolic activity, and therefore it is good to have a model that maps brain metabolism into an underlying electrical (neural) and chemical (synaptic) signaling. In my opinion, this branch of neuroscience will develop fast in the coming years, as is it visible in recent conferences and workshops agendas (e.g. Computational Neuroscience Meeting in Stockholm CNS 2011, or INCF Congress in Munich 2012).

3.4. Models of brain connectivity patterns. The mammalian brain is organized hierarchically. On the most basic level, there are neurons that are connected by synapses. Typically, there are two major classes of neurons, excitatory and inhibitory, determined by the type of synapses (neurotransmitters) they make with other neurons. It is commonly believed that neurons are organized into the so-called columns (about $10^3 - 10^4$ neurons). Neurons belonging to a single column behave dynamically similar in response to a specific stimulation, and different columns are activated differentially by the same stimulus. Columns are organized into macrocolumns and these, in turn, form functional "areas". Human brain contains about hundred areas, each one is thought to process a different type of information. For example, visual areas process visual input coming to the brain through the eyes. Motor areas guide movement of hands and legs, whereas frontal areas (located in front of the brain) are associated with higher cognitive functions.

If the brain is to perform its functions coherently, different areas have to communicate efficiently, i.e. on time, so that information is globally integrated [21,29]. This means that a certain level of connectivity between neurons and areas should be maintained. Too low connectivity would imply too large separation between areas, which is not good for integration of information. On the other hand, too high connectivity would unnecessarily merge distinct areas causing their functional disintegration. Studies in recent years have shown that brain has a "small world" architecture [6], which is a name given to organization in which there are many local connections and only few long-range connections [36].

A common theoretical tool for investigating these topics is graph theory, which provides quantitative means for characterizing anatomical and functional separation and integration in a network [8]. Research in this field is centered around questions of how to relate brain functioning to parameters characterizing brain connectivity. For example, there are studies claiming that certain brain abnormalities and disorders, like schizophrenia and autism, may be a result of an altered connectivity between brain regions [9].

4. Concluding remarks. It is important to stress a difference between understanding the main ideas of the field of Computational Neuroscience and doing an ambitious research on theories of brain function. For the former, one does not need overly complicated or sophisticated mathematics. In fact, it seems that the most common theoretical tool across the whole theoretical neuroscience is the ability to solve and analyze systems of non-linear differential equations on a computer (simulations). By mastering this relatively simple technique (there are even open source free softwares that do it for you), one acquires in principle a sufficient technical back-

ground to comprehend the basics of theoretical neuroscience. For a general overview of mathematics used in neuroscience see the book by Ermentrout and Terman [12].

On the other hand, constructing influential theories of brain functioning requires in my opinion a mixture of different skills (as it was signalled in Section 2). It is not enough to just know how to solve differential equations on a computer, one has also to know how to analyze such equations analytically, at least approximately and qualitatively, to gain an intuition about what they really describe. The more analytical techniques one knows the better. However, even this can be insufficient without a solid knowledge of physics and traditional neurobiology. Physics teaches how to describe in mathematical terms the non-living matter, and borrowing certain concepts from this discipline may be highly beneficial. In particular, the ideas of non-equilibrium thermodynamics and electromagnetism applied in a new context to the brain may yield new insights of how the brain works. Knowledge of neurobiology on some decent level should also help. Neurobiology (or biology in general) teaches researchers from the so-called "exact sciences" which processes are possible and which are not, and additionally that biological phenomena are generally governed by many factors (or parameters), often conflicting in outcome.

The current Computational Neuroscience is very fragmented. Virtually almost all theoretical papers in this field focus on a specific neurobiological phenomenon or on a narrow class of phenomena (no exception are the examples presented in Sec. 3). This narrowness of the scope probably reflects the degree of difficulty in constructing theories that would have a broader unifying impact. This difficulty is a consequence of the fact, already mentioned in Sec. 2, that "grand theories" require a comprehensive approach that would have a chance to integrate concepts from different disciplines into a coherent framework with testable (quantitative) predictions. That is probably too much for the present-day Computational Neuroscience. For example, it is currently not clear at all how to pass from molecular (neurotransmitters, channels) and cellular (neuron) levels of description to the description of macroscopic cognitive states. I do not think we can even properly address this question at present. The point is that we are unsure about which microscopic details to include and which to abandon in the theoretical description. Similarly, on the macroscopic level, it is often unclear how to precisely define distinct cognitive states, and which parameters should characterize them.

The research topics discussed in Sec. 3 and almost all other (see [4]) are satisfactory described in terms of classical physics. However, since neurons and synapses are so small (micrometers), one can wonder if quantum mechanics (describing the world of atoms and molecules) is relevant for the brain description (I mean here functional or dynamical description not just a mere structural description of various microscopic parts of channels and synapses). About two decades ago a prominent mathematician Roger Penrose published a book [33] in which he claimed that quantum effects might underlie neural activities that lead to consciousness. The book was totally criticized by almost every neuroscientist for the author's lack of basic neurobiological knowledge, but nevertheless caused the people to ask questions about the relationship between quantum theory and brain function [15, 28, 35]. At present, it is rather commonly believed that quantum coherence effects are too short ($10^{-10} - 10^{-15}$ sec) to be important for brain dynamics (10^{-3} sec), and thus they cannot control brain function. The very short quantum coherence times are caused by frequent ionic (Na^+, K^+, Cl^-, Ca^{++}) collisions with each other and water molecules, which

is additionally amplified by a relatively high brain temperature of 300 K [28, 35].

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Jak matematyk może pomóc w badaniach nad systemem nerwowym?

Streszczenie. Mózg ssaków jest jednym z najbardziej złożonych obiektów we wszechświecie. Jest odpowiedzialny za sterowanie wszystkimi aspektami zachowań zwierzęcia i człowieka. Obecnie usprawiedliwione wydaje się stwierdzenie, że nasza wiedza na temat pracy mózgu i jego funkcjach jest dość ograniczona. Neurobiologia obliczeniowa jest dyscypliną naukową, która próbuje zrozumieć i opisać mózg w kategoriach modelowania matematycznego. W tej pracy zawarto przyjazny dla czytelnika przegląd zagadnień, który ma na celu wprowadzenie w ten stosunkowo nowy dla matematyków i fizyków obszar badawczy, pokazując przykłady najnowszych trendów w tej dziedzinie. Artykuł omawia także krótko przyszłe perspektywy dla budowy zintegrowanej teorii funkcji mózgu.

Neurobiologia Obliczeniowa ma wiele osiągnięć w modelowaniu procesów neurofizjologicznych. W szczególności, realistyczne modelowanie dynamiki pojedynczych neuronów osiągnęło wysoki poziom wierności z danymi eksperymentalnymi. Wielkim wyzwaniem pozostaje natomiast kluczowe zagadnienie, jak przejść od opisu dynamiki pojedynczych neuronów do realistycznego opisu dynamiki całej sieci neuronów. Generalnie, poznanie i zrozumienie funkcjonowania mózgu w oparciu o modele matematyczne może mieć kolosalne znaczenie praktyczne dla społeczeństwa. Po pierwsze, w medycynie w radzeniu sobie z neurologicznymi schorzeniami takimi jak autyzm, schizofrenia, czy Alzheimer, które są coraz powszechniejsze. Mechanizmy biofizyczne tych chorób nie są znane, i być może dobra teoria funkcjonalna mogłaby w tym pomóc. Po drugie, w technologii tzw. inteligentnych urządzeń. Obecnie nawet najszybsze superkomputery nie są w stanie poradzić sobie z wydawało by się prostym zadaniem takim jak efektywne rozpoznawanie twarzy czy obiektów, z czym dość wolny ludzki mózg nie ma żadnych problemów. Bez wątpienia, inteligentne urządzenia skonstruowane na bazie mózgu miałyby bardzo wiele zastosowań, w różnych sferach działalności człowieka. Wydaje się, że zintegrowana teoria pracy mózgu mogłaby wiele wnieść w tym kierunku[1].

Słowa kluczowe: mózg, modelowanie systemu nerwowego, neurobiologia obliczeniowa, neurony, procesy mózgowe

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[1]Literatura uzupełniająca:

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