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Mechanism-Based Models of Neurons and Synapses for Multi-Level Simulations of Brain Functions

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Abstract– The conductance-based simulation approach is highlighted as a most valuable method for the examination of neuronal functions by means of mathematical models in close relation to the physiological and pathophysiological mechanisms. This approach, mostly used for single neuron simulations, can be extended to consider subcellular mechanisms as well as higher level activities at the level of neuronal networks, interactions between different brain nuclei, and relations to behavioral functions. Strategies of physiologically justified simplifications and adjustments to specific tasks with regard to experimentally and clinically relevant measures are illustrated, and novel technologies to overcome the inherent limitations of time consuming calculations are presented.

1. Introduction: The Multiple Levels of Brain Functions and their Nonlinear Interdependencies

Modeling of brain functions requires considering different functional levels and scales, from subcellular processes of gene expression and second messenger systems to ion channels, neurons, and synapses, further up to neuronal networks and interaction between different brain nuclei, and finally to the behavioral level with cognitive and mental functions [1,2]. For example, cognitive functions of learning and memory are apparently related to cellular and subcellular processes of ion channel modulation with successive alterations of ion channels' density and synaptic efficacy. Likewise, neurological and psychiatric disorders are typically manifested at the behavioral level while drug treatment interferes with synaptic transmission, ion channels, and gene expression.

Bringing together these different levels is a major challenge in neurobiology. The task is further aggravated by the fact that the functional interdependencies at all levels and between them are highly nonlinear. Moreover, there is an enormous meshing of different functions at the same level as well as across the levels, i.e. along a horizontal as well as a vertical scale. Additionally, biological systems are notoriously noisy and the reaction of individual elements exhibits enormous diversity. Conductance-based approaches can deal with such complicated interdependencies by introducing physiologically justified simplifications. This study presents an example of such a modeling approach for neuronal current activation. A second example will show how the problem of time-consuming simulations can further be reduced by the use of a digital FPGA hardware core for the calculations.

2. Model Simplifications and the Relations between Nonlinearities and Randomness

The conductance-based approach, going back to the ingenious work of Hodgkin and Huxley [3], provides the physiologically most realistic simulations of neuronal functions, because each model variable and parameter has a clearly defined physiological correlate. In the original Hodgkin-Huxley (HH)-equations the determinant parameters are the rate constants of the opening and closing of ion channels which are functions of the membrane voltage. Most HH-type models are still designed in this form. We have simplified the original approach arriving at a two- instead of four-dimensional model for spike-generation [2,4]. Among others, we have made the model parameters easier to adjust by replacing the unhandy equations that calculate current activations from the rate constants by sigmoid steady-state activation curves:

$$a = 1/(1 + \exp(-(V - V_h)/s)) \ , \qquad (1)$$

where a is the steady state activation variable and V is the actual voltage with V_h as the half-activation potential and s the slope of the sigmoid curve.

Notably, these simplifications do not weaken the connections to physiological mechanisms, but instead bring the equations closer to experimental reality. In the vast majority of nowadays patch-clamp experiments, whole cell currents are recorded and their activation curves are typically fitted by sigmoid Boltzmann functions. Rate constants can be derived from the activation curves what, by the way, was also done by Hodgkin and Huxley. Their aim, at that time, was to

understand how the shape of an action potential can be explained - with exceptional success. All their major assumptions have fully been confirmed during recent decades. However, actual research is more focused on subthreshold mechanisms to understand how the firing rates and spiking patterns are modulated, generally adjusted by alterations of slope, half-activation, and maximum value of the Boltzmann function.

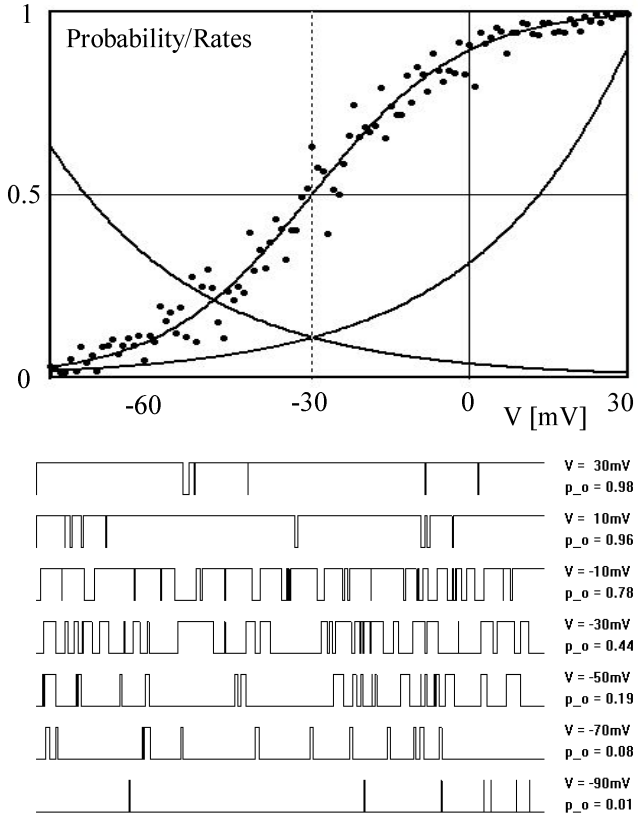

Fig. 1: Upper diagram: Exponential curves of rate constants of ion channel closing and opening probabilities as a function of the membrane voltage V, adjusted to a sigmoid current activation curve. The dots show the values of opening probabilities obtained from 40ms simulation runs as illustrated by examples in the lower diagrams. The numbers indicate the membrane voltage (V) and the relative time of open states (p_o).

The relations between an ion channel dynamics and neuronal current activation are illustrated in Fig. 1 by means of a simple channel type that only switches between two states, open and closed. As an example, we have taken a sigmoid curve with half activation voltage V_h *=-30* mV and slope of *s=0.07*. The exponential curves of opening and closing probabilities p_o and p_c are given by

$$p_o = a \exp(b\,(V - V_h))\,, \qquad (2)$$

$$p_c = a \exp(-b\,(V - V_h)). \qquad (3)$$

For simplicity, the parameter values for opening and closing probabilities are chosen to be the same. With $a = 0.11$ (here per ms) and $b = 0.035$ (mV^{-1}) (Fig. 1top panel) transitions between open and closed states are obtained as shown in Fig. 1 bottom. When the percentage of open states is calculated the points are distributed along the original sigmoid curve (Fig. 1 top).

Although a neuronal model that is composed of such nonlinear functions is considered deterministic, one should bear in mind that Boltzmann curves are probability functions and that the background of the neurons' nonlinearities is the randomness of ion channel opening and closing. This leads to partly significant deviations of the simulated values from the calculated curve (Fig. 1 top), especially when the simulation runs (or experimental recordings) are short. Likewise, with a limited number of ion channels in a real neuron, the percentage of open states will show fluctuations over time. To consider also this aspect of randomness a time-varying stochastic term is needed. Such a term is mostly implemented by a mathematical realization of noise, typically by Gaussian white noise, added to one or more of the model variables. In this way, noisy simulations are obtained. Tese "dynamic" aspects of randomness with a "noise" term can lead to significant changes of the neuronal behavior in cooperation with the "static" randomness, i.e. the system's nonlinearities [5] what can be seen not only in computer simulations but also in experimental recordings [6]. In real neurons, it is an artificial distinction because it is the same source from which (deterministic) nonlinearities and noise originate.

Noteworthy, the functionally essential nonlinearities are often implemented by sigmoid curves also in more simplified higher level models without any action potentials, e.g. in Hopfield nets [7,8] where the neurons' output reflects an integrated firing rate. In this case, sigmoid functions, of course, immediately remind on the output of a noisy neuron in response to an increasing input. At even higher levels when, for example, the interaction between different brain nuclei is simulated by mean field models [9] the output of a complete nucleus is often summarized in a single term of a compound firing rate. In this case, another type of randomness may additionally be comprised, namely the individual neurons diversity, best known to all experimentalists from enormous differences in individual neurons' activity and responsiveness even in exactly identical situations. Similar to the "static" form of noise, the sigmoid curves may reflect a "global" diversity. To consider "individual" diversity, according to "dynamic" noise, requires to additionally consider the diversity of individual elements which, as demonstrated by recent studies [10], can again can have significant effects on the system's dynamics.

3. Multi-Level Simulations and Impulse Patterns

Without neglecting the above mentioned higher level simulations and other modeling approaches, we have made particular attempts to adjust our simplified, conductance-based model neuron for use in multi-level

simulations. The connections to the next lower levels of ion channels, as demonstrated above, can easily be made considering the physiological background of the model's structure. Additionally, similar to the neuron model, we have designed a simplified, but nevertheless physiologically justified, version of a chemical synapse that can account for a manifold of experimentally and clinically relevant changes at the synaptic membranes as well as of subcellular processes [11]. Towards higher levels, e.g. to study the interaction between functionally different brain structures, we have represented them by single, conductance based neurons and synapses which allowed us to relate alterations of brain functions to activity dependent changes of the synaptic efficacy and underlying alterations of subcellular processes [4]. Recently, we have extended these multi level approaches considering a larger number of neurons also to account for the above mentioned "individual" diversity [12].

Conductance-based models of individual neurons have the major advantage compared to models with mean firing rates and compound activity outputs that they also allow considering the functionally important alterations of the spike pattern. We are specifically interested in transitions from single-spike activity (tonic firing) to grouped discharges (bursts) which, for example, can regularly be observed at the transitions from wake to sleep states or during epileptic seizures, which are also, most interestingly, accompanied by neuronal synchronization. To examine these interrelations, we have been running neuronal network simulations with four-dimensional model neurons that, in addition to the spike generating currents, include subthreshold currents for slow membrane potential oscillations. These model neurons, originally developed for the simulation of peripheral cold receptor discharges [13], have proved to be most flexible single neurons pattern generators that are perfectly suited to examine the relations between neuronal impulse pattern and synchronization [14,15].

Admittedly, such a realistic HH-type modeling approach seems to be "computationally prohibitive, since we can simulate only a handful of neurons in real time" [16]. In search for a solution of this problem, a digital FPGA hardware core has been designed on which actually up to 400 conductance-based neurons with four voltage-dependent currents can be implemented for real-time simulations. A PC interface allows free parameter adjustment including data storage and on-line display of conventional synchronization measures [17]. An example of real-time displayed graphics of synchronization studies is given in Fig. 2.

The simulation in Fig. 2 shows the effects of increasing nearest neighbor gap-junction coupling in a network of Hodgkin-Huxley type neurons with subthreshold currents operating in a pacemaker-like tonic firing regime. Interestingly, gap-junction coupling initially lengthens the interspike intervals and introduces irregularities of spike generation (Fig. 2c) before more regular pattern with shorter interspike intervals are generated. This is accompanied by continuously increasing synchronization (e.g. Fig. 2b) although still far away from in-phase spike discharges.

The raster plot (Fig. 2a) indicates the spike timing of a selected number of neurons. Its structure can provide rough information about the type of synchronization. The field potential (Fig. 2b) gives the mean voltage of all neurons showing increasing deflections with increasing in-phase synchronizations. Beyond these standard procedures voltage traces of up to four selected neurons (two in Fig. 2c) can be plotted for more detailed insights. The diagram of interspike intervals (ISI, Fig. 2d) of one of the selected neurons can provide elucidative information about the relations between impulse pattern variations and neuronal synchronization.

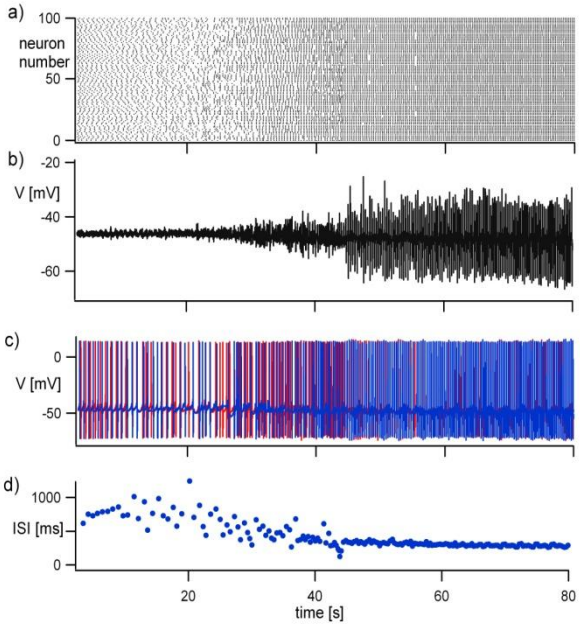

Fig. 2: Real-time graphics of synchronization analysis using a digital FPGA hardware core with a PC interface. Illustrated by an 80s simulation run of 400 nearest neighbor coupled neurons when the coupling strength is linearly increased from 0 to 20nS/cm^2. a) Spike times of 100 neurons indicated by dots. b) Field potential calculated as the mean voltage of all 400 neurons. c) Voltage traces of two neurons. d) Interspike-intervals (ISI) of one of the neurons.

Further attempts will be made to produce the digital hardware as very large scale integrated circuits (VLSI). In parallel, an analogue circuit of, so far, a single neuron, acting as the impulse pattern generator, has been designed [18]. Integrated circuits of a multiple of them would solve any problems related to calculation time. In analogue circuits the reaction time does not depend on the network's size, i.e. the number of implemented neurons. Everything is going in parallel, as in the brain and the speed in electronic circuits is much higher because information is transmitted with light speed. However, any computational or electronic model's structure, also for conductance-based simulations, is still light years away from the brain's complexity.

4. Summary: The Conductance-Based Modeling Approach as a Physiologically Justified Mid-out Strategy for Multi-Level Simulations

In the introduction, we have recapped the particular problems of the modeling of biological functions, specifically in neurophysiology, arising from the multiple levels and the nonlinear interdependencies between different functions at each level as well as across the levels that need to be considered. Indeed, a multitude of computational approaches for studying biological systems already exist and they all may have a specific value for specific problem to be solved. However, a mathematical model towards a better understanding of real brain functions needs to represent the biologically relevant parameters. This is the reason why we have emphasized on the conductance-based approach as a valuable mid-out strategy that allows physiologically justified simplifications as well as model extensions whenever they are required. We have given an example of physiologically justified model simplifications, specifically considering the neurons' nonlinearities. We have been referring to recent successful approaches towards multi-level simulations demonstrating that the applicability of conductance-based simulations beyond the single neuron level can further be enhanced by the use of appropriate computer technologies and the development of new computational strategies.

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