Ensembles of membrane proteins as statistical mixed-signal computers

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***Abstract*— The paper presents a formalism that connects functional properties of neurons with the properties of membrane proteins treated as abstract probabilistic machines. The machines are referred to as Probabilistic Molecular Machines (PMM). It is shown that ensembles of PMMs (EPMM) provide robust statistical implementation of mixed-signal computers combining the dynamical capabilities of analog computers with the sequencing capabilities of state machines. The classical Hodgkin and Huxley model is reformulated in terms of two EPMMs and is used as a detailed example illustrating the structure and the representational possibilities of the PMM/EPMM formalism.**

I. Introduction

Computational theory of neural networks studies dynamical systems described by large sets of nonlinear differential equations. *Where do these "neural" differential equations come from?* Some differential equations describe the accumulation of charges on the surfaces of cell membranes or the accumulation of atoms and molecules in cellular compartments. Others deal with kinetics of chemical reactions. The majority of the differential equations employed in today's neural network models come from these sources.

A less utilized source of neural differential equations is associated with the kinetics of conformations of membrane proteins (especially ion channels). The three differential equations describing the behavior of the n-, m-, and h-gates in the classical Hodgkin and Huxley (HH) model [1] give an example of the differential equations of this type.

What is the information processing significance of such differential equations? This paper develops the *known* general idea – the idea is implicitly present in the HH model and has been discussed elsewhere – that, at the information processing level, some membrane proteins can be treated as abstract probabilistic machines (the first-order Markov systems). Such machines are referred to in this paper as Probabilistic Molecular Machines (PMM). It is shown that ensembles of PMMs (EPMM) provide a robust statistical implementation of a class of mixed-signal computers combining the dynamical capabilities of analog computers with the sequencing capabilities of state machines.

The paper is organized as follows. Section II gives a formal definition of the concept of a PMM. Section III defines the concept of an ensemble of PMMs (EPMM). Section IV describes a model of a cell with several ensembles of ion channels represented as EPMMs interacting via common membrane potential. The model is implemented as an interactive C++ program that allows the user to simulate a cell with up to 10 ion channels represented as PMMs with up to 18 states each. The program has two simulation modes: the continuous mode for the infinite number of PMMs, and the Monte-Carlo mode for the number of PMMs from 1 to 10000 for each channel. Unlike the previously developed programs employing the notion of a membrane protein as a first-order Markov system – see, for example, [2], [3] – the above program allows one to simulate patch-clamp experiments and study effects of fluctuations.

Section V reformulates the HH model in terms of two EPMMs corresponding to the ensembles of potassium and sodium channels. The potassium channel is represented as a 16-state PMM corresponding to 4 independent n-gates, and the sodium channel is represented as a 16-state PMM corresponding to 3 independent m-gates and one independent h-gate. These 16-state PMMs are reduced, respectively, to the equivalent 5-state and 8-state PMMs – this leads to $5+8-2=11$ kinetic equations vs. the 3 kinetic equations used in the HH model (see [4], p. 585). Quite remarkably, both models produce close (but not identical) simulation results. (Note that the HH mathematical model doesn't follow rigorously from the HH gate model.)

Section VI discusses some implications of the PMM/EPMM formalism for the theory of information processing in the brain.

II. Concept of a Probabilistic Molecular Machine

DEFINITION. A *Probabilistic Molecular Machine* (PMM) is a system $(\mathbf{X}, \mathbf{Y}, \mathbf{S}, \alpha, \omega)$, where

- $\mathbf{X}$ and $\mathbf{Y}$ are the sets of real input and output vectors, respectively
- $\mathbf{S}$= $\{s_0, ..s_{n-1}\}$ is a finite set of states
- $\alpha : \mathbf{X} \times \mathbf{S} \times \mathbf{S} \rightarrow \mathbf{R}'$ is a function describing the input-dependent conditional probability densities of state transitions, where
  $\alpha(x, s_i, s_j)dt$ is the conditional probability of transfer from state s_j to state s_i during time interval dt,
  $x \in \mathbf{X}$ is the value of input, and $\mathbf{R}'$ is the set of non-negative real numbers. The components of x are called *generalized potentials*. They can be interpreted as membrane potential and/or concentrations of different neurotransmitters.
- $\omega : \mathbf{X} \times \mathbf{S} \rightarrow \mathbf{Y}$ is a function describing output. The components of y are called *generalized currents*. They

can be interpreted as ion currents and/or the flows of second messengers.

Let $x \in \mathbf{X}$, $y \in \mathbf{Y}$, $s \in \mathbf{S}$ be, respectively, the values of input, output, and state at time t, and let P_i be the probability that $s = s_i$. The work of a PMM is described as follows:

$$\frac{dP_i}{dt} = \sum_{j \neq i} \alpha(x, s_i, s_j) P_j - P_i \sum_{j \neq i} \alpha(x, s_j, s_i) \quad (1)$$

$$at\ t = 0 \qquad \sum_{i=0}^{n-1} P_i = 1 \quad (2)$$

$$y = \omega(x, s) \quad (3)$$

Summing the left an the right parts of equations 1 for $i = 0, ..n-1$, it is easy to verify that condition 2 holds for any t.

III. Concept of an Ensemble of PMMs (EPMM)

DEFINITION. An *Ensemble of Probabilistic Molecular Machines* (EPMM) is a set of identical independent PMMs with the same input vector, and the output vector equal to the sum of output vectors of individual PMMs.

Let N be the total number of PMMs, N_i be the number of PMMs in state s_i (the occupation number of state s_i), and let $e_i = N_i/N$ be the relative occupation number of state s_i. We have

$$y = N \sum_{i=0}^{n-1} e_i \omega(x, s_i) \quad (4)$$

The behavior of the average $\overline{e}_i$ is described by the equations similar to (1) and (2).

$$\frac{d\overline{e}_i}{dt} = \sum_{j \neq i} a_{ij}(x) \overline{e}_j - \overline{e}_i \sum_{j \neq i} a_{ji}(x) \quad (5)$$

$$at\ t = 0 \qquad \sum_{i=0}^{n-1} \overline{e}_i = 1 \quad (6)$$

where $a_{ij}(x) = \alpha(x, s_i, s_j)$ describes the rate constant of transfer between states s_j and s_i.

The structure of equations 5 is illustrated in Figure 1. The diagram suggests that an EPMM provides a statistical implementation of a mixed-signal computer with the rate constants serving as input-controlled coefficients (that can serve as switches). This implementation is extremely robust because the properties of the whole computer are determined by the properties of a single PMM. No interaction among PMMs is needed. Variable external connections are replaced by variable internal probabilities, and statistics does the trick. It is tempting to say that, in the same way as statistical mechanics of simple molecules leads to thermodynamics, the statistical mechanics of very complex molecule-machines leads to neural computations.

IV. Cell model with several ion channels

The block diagram of a one-compartment cell model with several ion channels is shown in Figure 2. The cell membrane is represented by a single integrator with the coefficient $1/C$, where C is the capacitance of the cell membrane ($C \approx 1\mu F/cm^2$). The black boxes CH^0,..CH^{m-1} represent ensembles of ion channels described as EPMMs. (The "Leak" is treated as a 1-state channel.) All boxes have the same input, u (membrane potential), and different outputs, I^0,..I^{m-1} representing ion currents. Let N^k be the number of molecules (PMMs) in CH^k, and let n^k be the number of states in the PMM representing the $k-th$ channel. Let N_i^k and e_i^k=N_i^k/N^k be, respectively, the occupation number and the relative occupation number of the $i-th$ state of the $k-th$ channel. Let us assume, for the sake of simplicity, that $N^k \to \infty$, so we don't need to distinguish between e_i^k and its average $\overline{e}_i^k$ in equation 5 from section III. The dynamics of the cell model of Figure 2 is described by the following equations, where $k = 0, ..m-1$ and $i, j = 0, ..n^k - 1$.

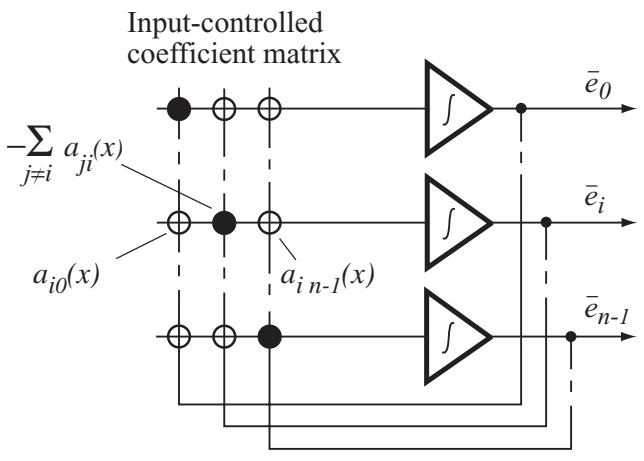

Fig. 1. EPMM as a mixed-signal computer

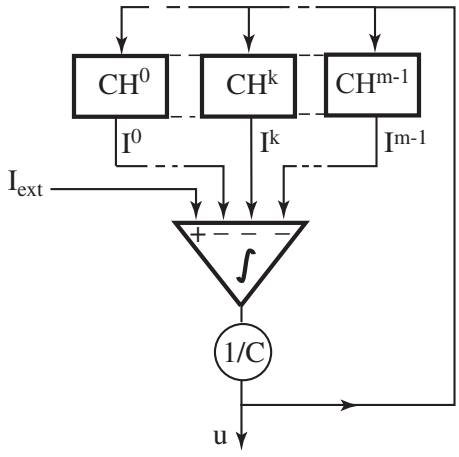

Fig. 2. Dynamical model of a cell with several ion channels

$$C\frac{du}{dt} = I_{ext} - \sum_{k=0}^{m-1} I^k \tag{7}$$

$$\frac{de_i^k}{dt} = \sum_{j\neq i} a_{ij}^k(u)e_j^k - e_i^k \sum_{j\neq i} a_{ji}^k(u) \tag{8}$$

$$\sum_{i=0}^{n^k-1} e_i^k = 1 \tag{9}$$

$$I^k = \sum_{i=0}^{n^k-1} e_i^k \gamma_i^k (u - E^k) \tag{10}$$

where

- $a_{ij}^k(u)$ is the rate constant of transfer between state j and state i of the $k-th$ channel. This rate constant is a function of membrane potential u.
- γ_i^k is the conductance of the $k-th$ channel in the $i-th$ state.
- E^k is the reversal potential for the $k-th$ ion.

V. Reformulating the HH model in terms of two EPMMs

To illustrate some representational possibilities of the PMM formalism we will reformulate the HH model in terms of two EPMMs interacting via common membrane potential.

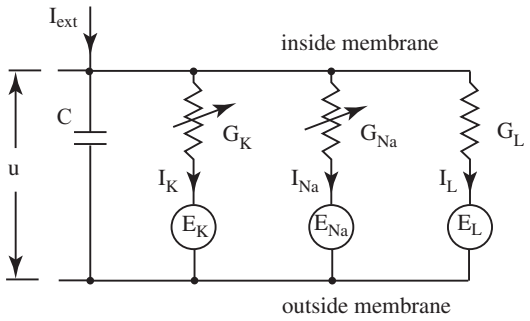

Fig. 3. Relationship between membrane current and membrane potential

A formal description of the HH model is presented below. This description is equivalent to that in [5] if one shifts u by $-65mV$. Equations 11-14 describe the relationship between membrane currents and membrane potential. This relationship can be understood with the help of the circuit shown in Figure 3. The potassium and sodium conductances (G_K and G_{Na}) depend on membrane potential via the "gate variables" n, m, h (the factors n^4 and m^3h in equations 12 and 13). The "Leak" conductance, G_L, is treated as a constant, g_L. (This conductance is determined mainly by the Cl^- ions.) Equations 15, 16, and 17 describe the dynamics of n, m, and h variables, respectively.

$$C\frac{du}{dt} = I_{ext} - I_K - I_{Na} - I_L \tag{11}$$

$$I_K = G_K(u - E_K) = g_K n^4(u - E_K) \tag{12}$$

$$I_{Na} = G_{Na}(u - E_{Na}) = g_{Na}m^3h(u - E_{Na}) \tag{13}$$

$$I_L = G_L(u - E_L) = g_L(u - E_L) \tag{14}$$

$$\frac{dn}{dt} = \alpha_n(u)(1 - n) - \beta_n(u)n \tag{15}$$

$$\frac{dm}{dt} = \alpha_m(u)(1 - m) - \beta_m(u)m \tag{16}$$

$$\frac{dh}{dt} = \alpha_h(u)(1 - h) - \beta_h(u)h \tag{17}$$

The parameters in equations 11-14 have the following values. The membrane capacitance $C = 1\mu F/cm^2$. The reversal potentials $E_K = -77mV$, $E_{Na} = 50mV$, $E_L = -54.4mV$. The conductances $g_K = 36mS/cm^2$, $g_{Na} = 120mS/cm^2$ and $g_L = 0.3mS/cm^2$.

The rate constants $\alpha_x(u)$ and $\beta_x(u)$, where $x \in \{n, m, h\}$, are functions of membrane potential, u. These functions are described by the following equations. The numbers in these equations were found by Hodgkin and Huxley to fit the data obtained in the experiments with the giant axon of the squid.

$$\alpha_n(u) = 0.01(u + 55)/(1 - exp(-(u + 55)/10)) \tag{18}$$

$$\beta_n(u) = 0.125exp(-(u + 65)/80) \tag{19}$$

$$\alpha_m(u) = 0.1(u + 40)/(1 - exp(-(u + 40)/10)) \tag{20}$$

$$\beta_m(u) = 4.0exp(-(u + 65)/80) \tag{21}$$

$$\alpha_h(u) = 0.07exp(-(u + 60)/20) \tag{22}$$

$$\beta_h(u) = 1.0/(1 + exp(-(u + 35)/10)) \tag{23}$$

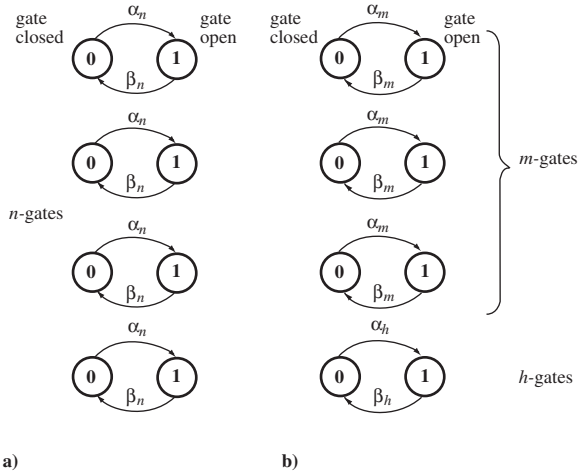

Fig. 4. The Hodgkin and Huxley gate model
a) Potassium channel with four n-gates.
b) Sodium channel with three m-gates and one h-gate.

A model of a potassium channel with four statistically independent n-gates is shown schematically in Figure 4a. The structure of the corresponding 16-state PMM is shown in Figure 5a. The states of the PMM are represented as 4-digit

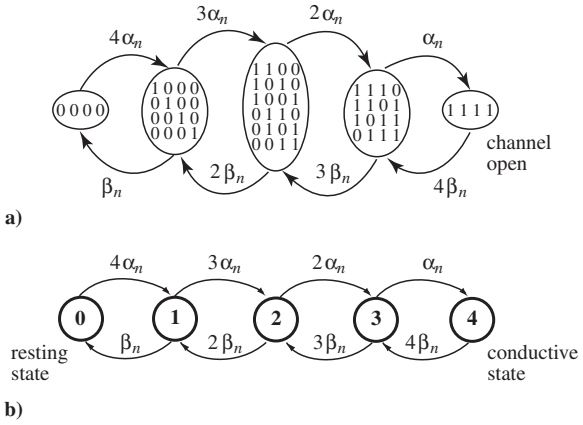

Fig. 5. PMMs corresponding to potassium channel in the HH gate model
a) 16-state PMM with equivalent states grouped
b) Equivalent 5-state PMM

binary numbers, each binary digit describing the state of one of four n-gates: 0 means that the gate is closed and 1 means that the gate is open.

Let $a_{10}dt$ be the probability that an n-gate in state 0 jumps into state 1 (opens) and $a_{01}dt$ be the probability that an n-gate in state 1 jumps into state 0 (closes) during the time interval dt. The probabilities of transitions between two states with the Humming distance $k > 1$ have factor dt^k, so these transitions can be ignored. This explains the structure of the state diagram shown in Figure 5a. The coefficients 4, 3, 2, and 1 describe the number of transfers between the subsets of equivalent states

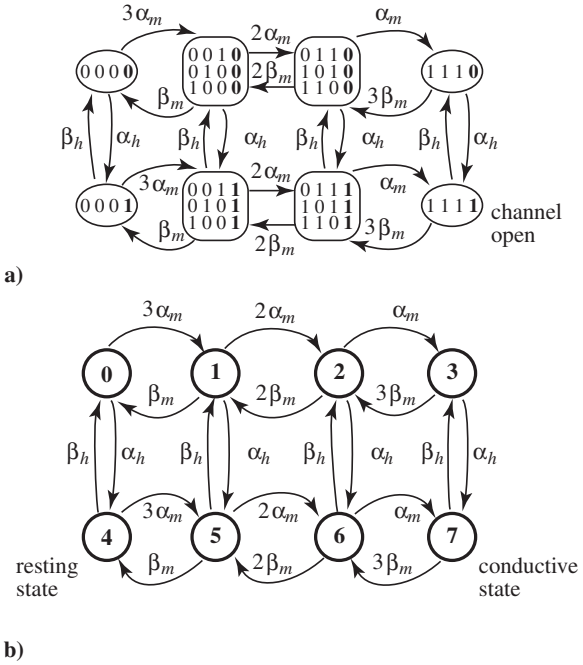

Fig. 6. PMMs corresponding to sodium channel in the HH gate model
a) 16-state PMM with equivalent states grouped (bold binary digit represents h-gate)
b) Equivalent 8-state PMM

(the states with the same number of open gates). For example, each molecule with one open gate (e.g., state 0001) can jump into three possible states with 2 open gates (states 0011, 0101, and 1001), etc. Replacing the subsets of equivalent states with single states we get the 5-state PMM shown in Figure 5b. Using a similar reasoning, one can go from the 4-gate model of the sodium channel shown in Figure 4b, to the 16-state PMM shown in Figure 6a, to the 8-state PMM shown in Figure 6b. The state diagram is more complex than that for potassium channel because the h-gates are different from the m-gates.

The dynamical model of a cell corresponding to the above 5-state potassium and 8-state sodium PMMs is described by equations 7-10 from section IV and equations 18-23 from this section. The model has 11 independent first-order differential equations describing kinetics of channels (8 equations (8) for Na^+ channel (k=0) plus 5 equations (8) for K^+ channel (k=1) minus 2 equations (9) for k=0,1), vs. the 3 first-order differential equations 15-17 describing the kinetics of gates in the HH model. The conductances γ_i^k have the following values: $\gamma_i^0 = 0$ for $i = \{0, ..6\}$; $\gamma_7^0 = g_{Na} = 120mS/cm^2$; $\gamma_i^1 = 0$ for $i = \{0, ..3\}$; $\gamma_4^1 = g_K = 36mS/cm^2$, and $\gamma_0^2 = g_L = 0.3mS/cm^2$. (The "Leak" is represented as an ion channel, k=2, with a single state, $i = 0$.) The relative occupation numbers e_i^k play the same role as the variables n, m, and h in the HH model. The important difference is that the ion currents depend linearly on e_i^k, whereas in the HH model there are nonlinear factors n^4 and m^3h. The linear relationship expresses the fact that the conductance of N channels is N times greater than the conductance of a single channel. There is no such simple interpretation of the above nonlinear factors, though they work quite well.

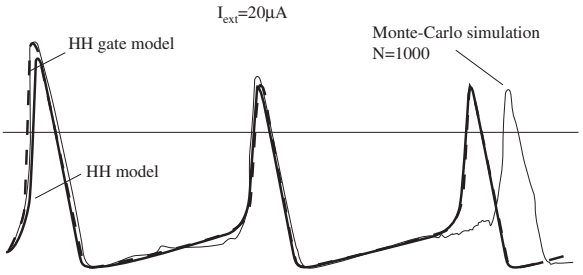

Fig. 7. Comparison of the HH gate model expressed in terms of two EPMMs with the HH model

I studied the behavior of the HH gate model with the above PMMs using the cell simulation program mentioned in section I. Just to make sure that there were no bugs, I simulated the EPMMs with both the (16,16)-state PMMs and the (5,8)-state PMMs – there was no difference between these two theoretically equivalent cases. Then I compared the EPMM model with the HH model. The results of this comparison are illustrated in Figure 7. As the plots show, the behavior of the HH-gate model represented in terms of EPMMs is remarkably similar to the behavior of the HH mathematical model – this is in spite of the fact that these behaviors are produced by quite different sets of equations (11 kinetic equations vs. 3 kinetic

equations). A discussion of the relationship between the HH gate model and the HH mathematical model can be found in [4], p. 585.

The generation of spikes is a very robust phenomenon that can be produced with many different PMM models for the K^+ and Na^+ channels. Figure 8 shows 5-state PMMs that produced simulation results shown in Figure 9. In this figure, a^k_{ji} are constants, $\theta(u - u^k_{up})$ and $\theta(u^k_{dn} - u)$ are step-up and step-down functions, where $\theta(x)$ is the Heaviside step function: $\theta(x) = 0$ for $x \leq 0$ and $\theta(x) = 1$ for $x > 0$. Parameters have the following values:

- Sodium channel (superscript $k = 0$): $a^0_{10} = a^0_{21} = a^0_{32} = 8.0msec^{-1}$, $u^0_{up} = u^0_{dn} = -52mV$, $a^0_{43} = 2.5msec^{-1}$, $a^0_{04} = 1.3msec^{-1}$, $\gamma^0_0 = \gamma^0_1 = \gamma^0_2 = \gamma^0_4 = 0$, $\gamma^0_3 = 120mS$, $E^0 = 50mV$.
- Potassium channel (superscript $k = 1$): $a^1_{10} = a^1_{21} = a^1_{32} = a^1_{43} = 5.0msec^{-1}$, $u^1_{up} = -52mV$, $a^1_{04} = .25msec^{-1}$, $\gamma^1_0 = \gamma^1_1 = \gamma^1_2 = \gamma^1_3 = 0$, $\gamma^1_4 = 36mS$, $E^1 = -77mV$.
- Leak channel ($k = 2$): $\gamma^2_0 = .3mS$, $E^2 = -54.4mV$.

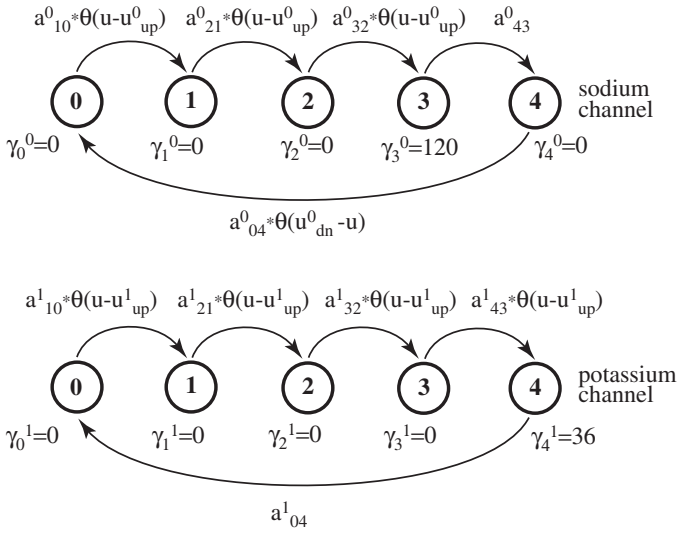

Fig. 8. The 5-state PMMs with the ring structure used in the simulation shown in Figure 9

VI. Discussion

To simulate the work of a computing system similar to the human brain in real time one needs to implement a very large set of differential equations. These differential equations must have time constants ranging from a split millisecond to years. *How can such broad range of time constants be implemented in neural networks?* The formalism discussed in this paper suggests that many of these time constants can be naturally associated with conformational kinetics of membrane proteins.

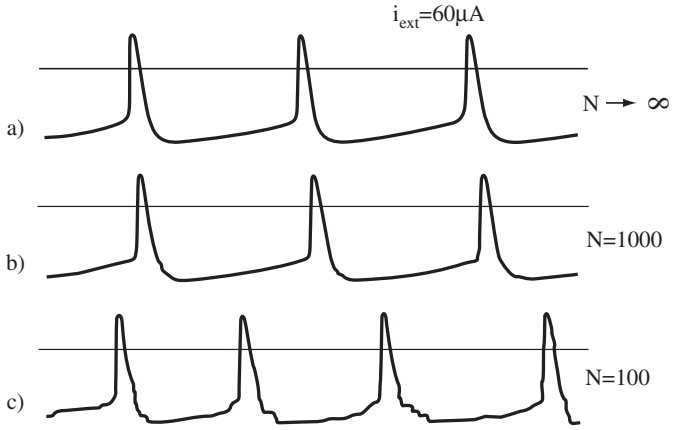

Fig. 9. Spikes produced by the model with the 5-state sodium and potassium PMMs shown in Figure 8

The big picture appears as follows:

1) A single membrane protein molecule implements a probabilistic molecular machine (PMM) defined in section II. There can be many different types of PMMs corresponding to different proteins. Note that a specific "physical" implementation of a PMM is not essential!
2) Due to the laws of statistics, an ensemble of PMMs (EPMM) embedded in a cell membrane implements a mixed-signal computer described in section III. The properties of this computer are determined by the properties of a single PMM. No interaction among PMMs is needed, so this statistical implementation is extremely robust. As mixed-signal systems, EPMMs combine the dynamical capabilities of analog computers with the sequencing capabilities of state machines.
3) A cell with several embedded EPMMs interacting via electrical and/or chemical messages implements a complex mixed-signal dynamical system. The HH model gives a simple example of such system. Note that a single nerve cell have several (many) embedded EPMMs, so such cell should be viewed as a complex integrated block rather than a simple atomic unit.
4) Neurons with different functional properties can be implemented in a uniform way by simply changing the properties of embedded EPMMs. Such neurons can be easily tailored to match different computational needs. This helps to understand why the brain needs many different membrane proteins and many different neurotransmitters.
5) Complex nerve cells are organized in neural networks that interact with sensory and motor devices to produce complex behavior. There are many interesting ideas as to how the networks built from complex mixed-signal neurons can account for various phenomena of context-sensitive associative memory, learning, and thinking [6], [7], [8]. These important topics are beyond the scope of this paper.

Modern neuroscience provides ample evidence in favor of the notion of a single neuron as a complex computing element the properties of which have direct behavioral (psychological) implications. See, for example, [9], [10], [11], [12], [4], [13].

Why does the brain need complex neurons? The simplest general answer to this question is that there is not enough neurons in the whole brain to implement the required amount of brain hardware computation in the networks built from simple neurons (although anything can be computed by such networks, in principle). An obvious problem arises, for example, when one tries to explain the complex dynamical properties of the brain's very large context-sensitive associative memory [7], [2].

How can the differential equations describing the dynamics of such memory be implemented in the brain? The EPMM formalism suggests that the states of short-term memory (STM), and intermediate-term memory (ITM) are represented by the relative occupation numbers, e_i, in equations 5. In the case of long-term memory (LTM), the absolute numbers of PMMs are also involved (growth), so equation 6 should be replaced by equations describing the dynamics of N. This general approach allows for very complex dynamical models of memory – each memory cell can afford several embedded EPMMs. The title of this paper emphasizes the *mixed-signal* character of the statistical computer implemented as an EPMM. *What is the advantage of a mixed-signal EPMM as compared with a purely analog dynamical system?* The main advantage is that an EPMM can work as a sequencer. Consider, for example, the 5-state PMM shown in Figure 10. The rate constants of transfers $0 \rightarrow 1$ and $3 \rightarrow 4$ depend on input u, say, the membrane potential. The rate constants of transfers $0 \rightarrow 3$ and $1 \rightarrow 2$ depend on input s, say, the concentration of a second messenger. For the sake of simplicity, let us assume that $a_{10}(u) = a_{43}(u) = const_1\theta(u - u_0)$ and $a_{30}(s) = a_{21}(s) = const_2\theta(s - s_0)$, where $\theta(x)$ is the Heaviside step function. Let the PMM be in state 0. If event $u > u_0$ precedes event $s > s_0$, the PMM goes to state 2. If event $s > s_0$ precedes event $u > u_0$, the PMM goes to state 4. Using this idea, it is easy to represent quite complex temporal phenomena the outcome of which depends on the order of input events. Such temporal phenomena present a difficult problem for the computational models that don't have discrete states and cannot switch these states depending on inputs.

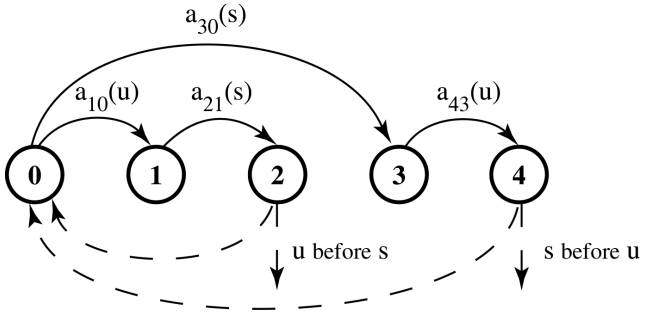

Fig. 10. Representing effects that depend on the order of input events

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