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A note on bistability in a simple synapseless 'point neuron' model

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Abstract. Neural network models include at least one synaptic interaction between a pair of neurons so that plasticity can be conferred on the system. The single neuron is usually treated unrealistically in these models, functioning as a simple machine that transforms weighted synaptic input to firing frequency in a sigmoidal fashion. Knowledge gained in the past 15 years about the ways voltage-gated ion channels (the molecules of excitability) work, calls for re-evaluation of the role played by intrinsic neural excitability properties in learning and memory. Here I show that complex memory processes, ranging from seconds to 'lifetime', can be induced in a point neuron by including a realistic gating machinery of a potassium selective voltage-gated ion channel that is known to express in hippocampal cells.

Theories of memory implicate some form of change in excitability. Voltage-gated ion channels, being the functional units of excitability, are obvious candidates to serve also as basic memory units. There is, however, a fundamental obstacle in attributing such a role to voltage-gated ion channels: the time scale of voltage changes during an action potential is in the order of few milliseconds, therefore classical channel gating machinery that is purely voltage dependent and state ('history') independent [1] cannot account for memory processes that last from seconds to lifetime. Consequently, point-neuron models lack memory capacity beyond the millisecond time scale (refractory period). A Hodgkin–Huxley point-neuron fires at a rate that reflects the stimulus amplitude in a certain dynamic range; the stimulus history is of no relevance for this neuronal computation, and there is only one stable state of excitability to which the neuron returns soon after the stimulus is removed.

In recent years the database of voltage-gated ion channel properties has increased remarkably, and it is now clear that channels function in a state-dependent manner [2]. Particularly relevant is the finding of state-dependent and voltage-independent inactivation (a decrease in channel availability) of potassium channels [3–6]. Since potassium channels are the fine-tuners of action potential waveform and stabilizers of membrane potential, any long lasting change in their availability that can be induced by activity is of prime importance. The time course of inactivation in these channels ranges from few milliseconds to seconds, and recovery time can last tens of seconds, depending on the specific channel type [7,8]. These time scales, taken together with state ('history')-dependent gating machinery, suggest that it is possible to bridge a gap of more than three orders of magnitude, between millisecond events (action potential) and events at the seconds time range, at the elementary level of a single synapseless neuronal model. To demonstrate this point, measured gating parameters of a cloned mammalian potassium channel that is known

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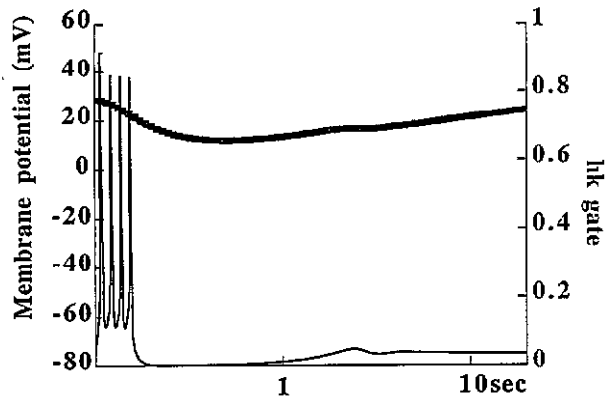

Figure 1. A model of a silent neuron, which includes state-dependent potassium conductance, is given a 50 ms depolarizing current injection from an 'external' source. The cell fires in response and relaxes to its stable silent state soon after the stimulus is removed. The heavy line (denoted hk gate) represents depletion and then recovery of the pool of state-dependent potassium channels.

Computational methods: The simulated cell is assumed to be isopotential and behaves according to the equations developed by Hodgkin and Huxley [1] modified as in Marom and Abbott [10]: $I = m^3 h G_{Na}(V - V_{Na}) + (1 - f)n^4 G_K(V - V_K) + f n_3^4 h_{K_3} G_K(V - V_K) + G_{leak}(V - V_{leak})$; $dV/dt = -I/C_m$, where I is the total ionic current, G_X is the maximum conductance, V is membrane potential and V_X is the calculated Nernst potential for the specific ion. C_m stands for membrane capacitance. f stands for the fraction of potassium channels that behave in a state-dependent manner. The gating variables were calculated as follows: $C = 1\ \mu F\,cm^{-2}$; $V_K = -80$ mV, $V_{Na} = +50$ mV, $V_{leak} = -49$ mV, $G_{Na} = 40\,mS\,cm^{-2}$, $G_K = 3$–$6\,mS\,cm^{-2}$, $dt = 0.02$–0.1 ms.

Sodium activation: $\alpha = 0.1(V + 40)/(1 - \exp(-0.1(V + 40)))$, $\beta = 4\exp(-0.0556(V + 65))$, $dm/dt = \alpha(1 - m) - \beta m$;

Sodium inactivation: $\alpha = 0.07\exp(-(V + 65)/20)$, $\beta = 1/(\exp(-(V + 35)/10) + 1)$, $dh/dt = \alpha(1 - h) - \beta h$.

Potassium activation (Hodgkin–Huxley like): $\alpha = 0.01(V + 55)/(1 - \exp(-0.1(V + 55)))$, $\beta = 0.25\exp(-0.0125(V + 65))$, $dn/dt = \alpha(1 - n) - \beta n$.

Potassium activation (state-dependent): $\alpha = -0.021(V + 8.3)/(\exp(-(V + 8.3)/9.8) - 1)$, $\beta = 0.0002\exp(-(V + 23.6)/20.7)$, $dn_3/dt = a(1 - n_3) - \beta n_3$.

Potassium inactivation (state-dependent): $dh_{K_3}/dt = 0.0001(1 - hK3) - 0.0014h_{K_3}n_3^4$.

The simulations were performed using a 'Think C' (Symantec, CA) compiler on a Macintosh (Apple Computers) Quadra 950.

to be expressed in the hippocampus were included in a neuronal model. The model is composed of two major conductances—fast sodium and delayed-rectifier potassium (10:1 ratio). Potassium conductance is subdivided to Hodgkin–Huxley-like conductance [1] (non-inactivating, voltage-dependent state-independent channels) (90%–96%) and state-dependent potassium channels (4%–10%). The parameters for state-dependent conductance are those of Kv3 (RCK3, Kv1.3) channel [7,8]. Kv3 is a particularly interesting channel: it is a voltage-activated potassium selective ion channel, found in the dentate gyrus subfield of the hippocampus, and also transiently expressed in the CA1 and CA3 subfields during development [9]. The inactivation gating machinery of this channel is state-dependent [6] and can be modelled by coupling the entry into the inactivated state to the open probability [10] so that $dh(n)/dt = k_{i0}(1 - h) - k_{0i}n(\upsilon)^4 h$ where k_{0i} and k_{i0} are voltage-independent transition rates into and out from the inactivated state, 1/0.7 s and 1/10 s, respectively, h denotes the probability to be in the inactivated state, and $n(\upsilon)^4$ denotes the probability

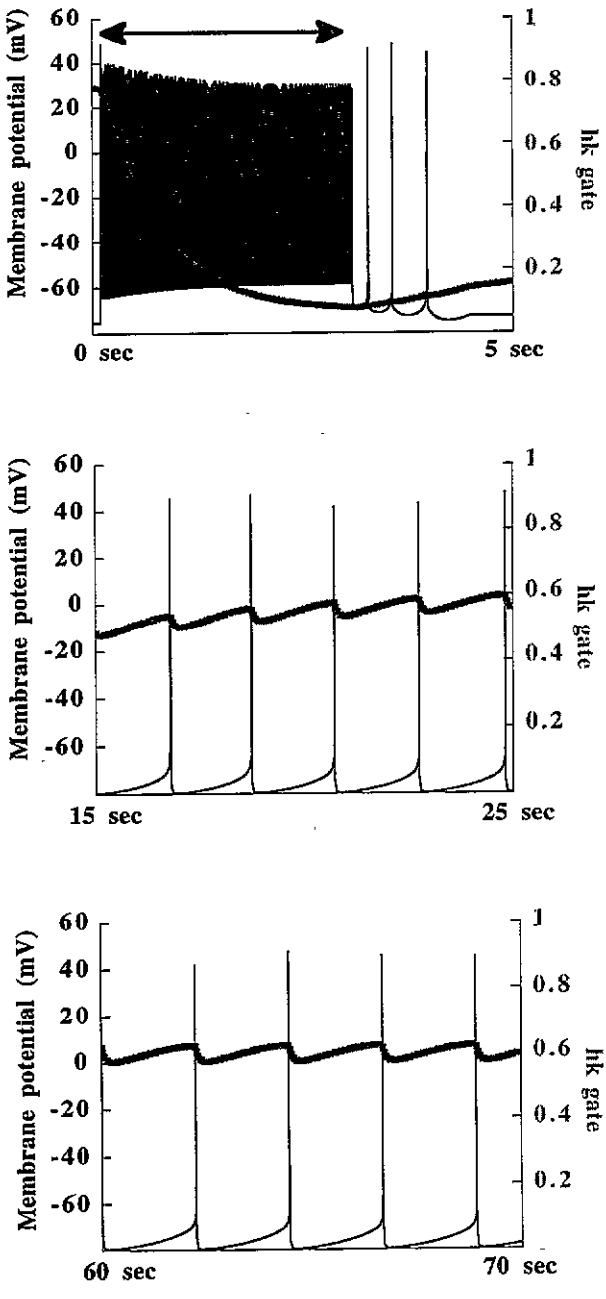

Figure 2. A 3 s depolarizing stimulus (*a*) causes an increase in firing rate during the stimulus as described elsewhere [10], accompanied by a high frequency spike attenuation and after-discharge at the end of the stimulus. Note the massive depletion of state-dependent potassium channels (10% left over). The model does not return to its initial silent mode but rather stabilizes in a constant-frequency firing mode, as shown in (*b*) and (c), where the pool of state-dependent potassium channels is equilibrated around 60% availability (compare to figure 1).

to be in the open state (a complete description of the model is given in the caption for figure 1). Four non-conducting states along a voltage-controlled pathway are used. Under these conditions, the model presents a highly sophisticated input–output function and duration of stimulation becomes a significant factor determining the neuronal response. In figure 1 a silent model neuron is perturbed by a brief (50 ms) depolarizing external current injection. The model neuron responds by firing (note logarithmic time scale) and relaxes to its stable silent state soon after the stimulus is removed because the availability

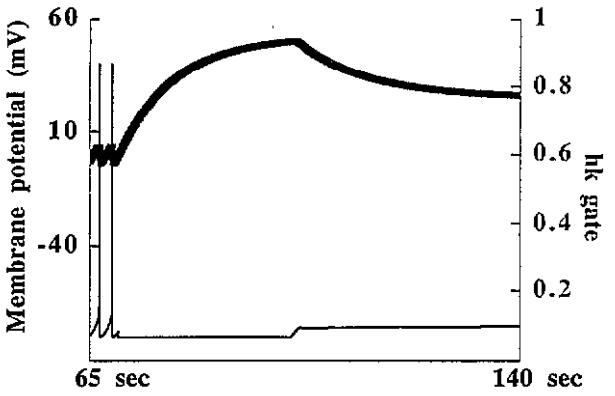

Figure 3. Release of the cell that is shown in figure 2 from the firing mode into the silent mode is achieved by clamping the model for 30 s in −80 mV, allowing the pool of potassium channels (heavy line) to recover.

of state-dependent potassium conductance (heavy line in figure 1) is still high enough so that membrane potential can be pulled down to its initial silent mode. However, most interestingly, if the stimulus lasts long enough (figure 2) the neuron is locked into a new mode of activity—the initially silent cell is transformed to be a pacemaker. This new mode remains stable ('mode lock') after the stimulus is removed (figure 2(*c*)) as if a memory of the massive activity is imprinted on the excitability status of the neuron. The reason for the appearance of a new stable mode of activity is the following: the membrane potential to which a neuron goes to is determined by a fine dynamic balance between available sodium and potassium conductances. In the Hodgkin–Huxley model, the pool of available potassium channels is not affected by firing rate. However, in the present model, massive firing during the stimulus period provides a route for draining state-dependent potassium channels away from the available pool, in an activity-dependent manner, thus creating a new balance between potassium and sodium conductances and a new stable state appears. A prediction of this mechanism is that the lock can be recovered from by a long contradicting (inhibitory) stimulus. As shown in figure 3, clamping the active cell in −80 mV for 30 s allows the pool of state-dependent potassium channels to recover (heavy line) and the model neuron relaxes back to its initial silent mode.

The implications of having a sophisticated input–output function and multiple stable states between which the point neuron is moving according to its stimulation history are most relevant for models of memory and learning in neural network. Yet, are there experimental correlates that suggest existence of such mechanisms in real brain cells? Temporal integration and gradual increase in firing rate were in fact described for hippocampal cells by Storm [11] and are very similar to the model prediction. Gradual decline in action potential amplitude (figure 2(*a*)) is the result of sodium channel inactivation, sometimes termed high-frequency spike attenuation. Mode lock is reminiscent of an observation made by Bliss and Lømo [12] in the hippocampus. In their classic description of long-term potentiation (LTP), these authors suggest that two independent mechanisms are responsible for LTP: (a) an increase in synaptic efficiency, and (b) a long-lasting activity-dependent increase in the excitability of the granule cells. It is very tempting to suggest that the latter results from an activity-dependent decrease in availability of state-dependent potassium conductance, equivalent to the mechanism of mode lock.

Neural models are far from being exact mathematical representations of the brain;

however, they provide a valuable tool for exploring ways which the human brain could have used in order to learn and memorize. In this respect the model described here is educating because it suggests that focusing on realistic properties is productive in terms of understanding the system behaviour: traces of what is usually ascribed to more complex systems (temporal integration and bistability) can be explored in a single point neuron, the most elementary functional unit of the brain.

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