Simulating cortical network activity states constrained by intracellular recordings

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Abstract

We present a method for studying states of network activity while incorporating constraints provided by intracellular measurements. Taking into account measurements of the average membrane potential, input resistance changes and membrane potential fluctuations, narrows down the possible region of parameter space (connectivity, quantal conductances) where this activity can appear in networks. Searching in those specific regions greatly enhances the efficiency of the network level modeling because irrelevant parameter combinations are automatically eliminated. We illustrate this approach by modeling self-sustained stochastic states in networks of excitatory and inhibitory neurons, based on intracellular recordings *in vivo*.

Our goal is to identify network mechanisms implicated in the genesis of self-sustained states of activity in the cerebral cortex. The common approach is to simulate networks and perform unconstrained variations of their connectivity and connection strength in order to map the genesis of states by such networks, and finally identify the regions of parameter space which are consistent with experimental measurements. We propose here a different approach, consisting in the use of intracellular measurements in order to obtain constraints on possible architectures in which these states are possible. This procedure allows us to considerably reduce the parameter space in network simulations and ultimately obtain states of activity consistent with intracellular measurements.

We illustrate this approach for the case of the genesis of self-sustained stochastic states of activity, as found in neocortex *in vivo* during activated states [5], or during persistent activity [8]. The high degree of connectivity in neocortex, with thousands of synaptic connections for each pyramidal neuron, together with the spontaneous (irregular) firing of a small fraction of cortical neurons, are probably responsible for generating these states through recurrent interactions, as indicated by the observation of similar states of spontaneous activity in cortical slices [7]. Indeed, a number of computational models have reported states of self-sustained stochastic activity resulting from recurrent interactions between excitatory and inhibitory neurons [1, 2, 3, 6].

To constrain the network simulations, we use a number of measurements of this network activity which were obtained from intracellular recordings *in vivo* [5]. *(i)* The resting value of the neurons after suppression of network activity was about -80 mV. *(ii)* The average V_m during network activity was about -65 mV. *(iii)* The average V_m during network activity using chloride-filled pipettes was about -51 mV; in this case, the inhibitory reversal potential was moved from -75 mV (control) to -55 mV. *(iv)* The input resistance was

reduced by about 5-fold by network activity. *(v)* The standard deviation of the V_m was about 4 mV on average. *(vi)* The average firing rate during these states is between 1 and 20 Hz.

From *(i)* to *(iv)*, and assuming a reversal potential of 0 mV for excitation, we can deduce the relative amount of excitatory (g_e) and inhibitory (g_i) conductances, namely:

$$g_i \;=\; 3.27\; g_L \qquad g_e \;=\; 0.73\; g_L \;, \tag{1}$$

where g_L is the resting conductance without network activity. In other words, these *in vivo* measurements directly show a dominance of inhibition, which is in this case about 4.5 times larger than excitatory conductances.

The total conductance resulting from network activity is given by: $g_e = n_{ee} f_e Q_e$, where n_{ee} is the number of excitatory synapses per neuron, f_e is their average release rate, and Q_e is the total conductance (integral) of a single synaptic event. Similarly, for inhibition we have $g_i = n_{ie} f_i Q_i$. Assuming that all synapses have the same quantum (q_e for excitation and q_i for inhibition), that inputs are uncorrelated, and taking into account that the integral of an exponential synapse is $Q_e = q_e \tau_e$, $Q_i = q_i \tau_i$, we obtain the set of constraints:

$$\left\{ \begin{array}{rcl} g_e &=& n_{ee}\, f_e\, q_e\, \tau_e \\ g_i &=& n_{ie}\, f_i\, q_i\, \tau_i \end{array} \right. \tag{2}$$

Next, we used the conditions (1) and (2) in order to constrain the combinations of parameters consistent with *in vivo* measurements. To this end, we also used the measurement *(v)*: $\sigma_{V_m} = 4$ mV [5]. We ran simulations of single excitatory neurons described by Hodgkin-Huxley type models, with synapses simulated by kinetic models [4], taking into account AMPA, NMDA and $GABA_A$ receptor types. The neurons were subject to random synaptic activity of parameters $\{n_{ee}, f_e, n_{ie}, f_i\}$ and we identifed the regions producing membrane potential activity consistent with intracellular measurements (correct value of g_e and g_i, correct σ_V, firing rate consistent with f_e). These parameters of "synaptic bombardment" were then tested in inhibitory neurons in order to verify that the obtained firing rate is consistent with f_i. This procedure was repeated for a large range of possible values for the number of synapses $\{n_{ee}, n_{ie}\}$ and for the connection strength $\{q_e, q_i\}$, until we identified the region of parameter space where these states are possible (all parameters must be consistent).

Finally, the possible regions that remain were tested using numerical simulations. In the case of self-sustained stochastic states, we obtained a continuum of possible network configurations, which range from small networks with few strong connections, up to large networks with many synapses of small quantal size. These various network architectures were then simulated numerically using the same single-neuron models as above.

Our simulations for networks showed that predictions for connectivity based on single neuron dynamics may work for some values of $\{n_e, n_i\}$, when n_e is weak compared to n_i. If the excitation is strong enough to synchronize the network, the method can not be applied because uncorrelated input was assumed in order to get the quantal values. Simulations for networks of increasing sizes up to 4000 neurons showed the augmentation of the recurrent firing as a fonction of size. This suggests the attainability of self-sustained active states for larger networks, even in the presence of dominant inhibition.

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