Bridging single cell and network dynamics

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Abstract:

The dynamics of networks can be predicted from the dynamics of the neurons and their connections. To better understand the dynamics of small networks of neurons, we measure the dynamics of stellate cells in the entorhinal cortex, estimated with a spike time response curve (STRC), and then couple them thorough a dynamic clamp. Using our dynamical description of the neurons, we can simulate the network and compare it to the network of real neurons. We find that the STRC can capture the essential dynamics of the neurons and can successfully simulate the network behaviors.

Summary:

The dynamics of neural networks depends on the dynamics of both the neurons and their synapses. The effects of both of these properties can be measured using spike time response curves (STRCs). STRCs are estimated by making the neuron fire periodically and measuring how a "synaptic-like" stimulus advances or delays the neuron from its periodic behavior. An example of STRCs measured with excitatory and inhibitory synaptic currents are displayed in figure 1. The amount the next spike advances depends on the timing of the synaptic input with respect to the last firing time of the neuron. We have measured STRCs from pairs of stellate cells in the entorhinal cortex and then coupled the cells through a dynamic clamp to make two-cell networks. Predicted phase relationships from STRCs match observed behavior in two-cell networks very well.

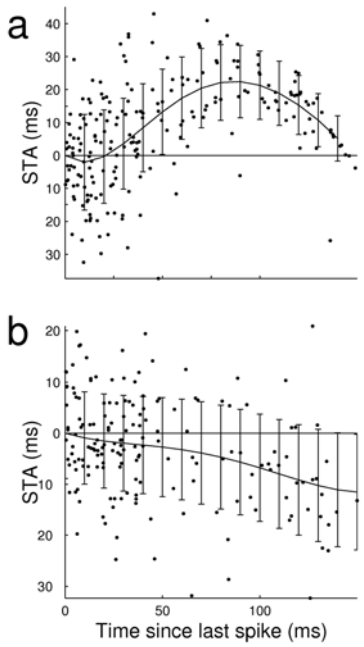

Figure 2. (Netoff)

Figure 1. Spike time response curve (STRC) measured from a layer 2 stellate cell in entorhinal cortex. Periodically firing neurons (firing at theta frequency with 150 msec interspike intervals) are stimulated with synaptic like conductances at different phases (measured as time since last spike). Response to synaptic input is measured as the spike time advance (STA) from its normal period. Excitatory synaptic conductances (panel **a**) advance the next spike time while inhibitory synaptic conductances (panel **b**) delay the next spike time, both in a phase dependent manor.

In initial studies, STRCs were measured with artificial synaptic inputs of constant size and kinetics, delivered only once per firing period. These constraints simplify the analysis, but constrain predictions to relatively simple cases. To develop the STRC method further, we measure how STRCs change with varying synaptic amplitude and kinetics, shown in figure 2. STRCs scale fairly linearly to synaptic conductances that vary in amplitude over a large range spanning the full range of natural spontaneous synaptic inputs. The effects of synaptic kinetics are minimal, as long as the synapse decays within one firing period.

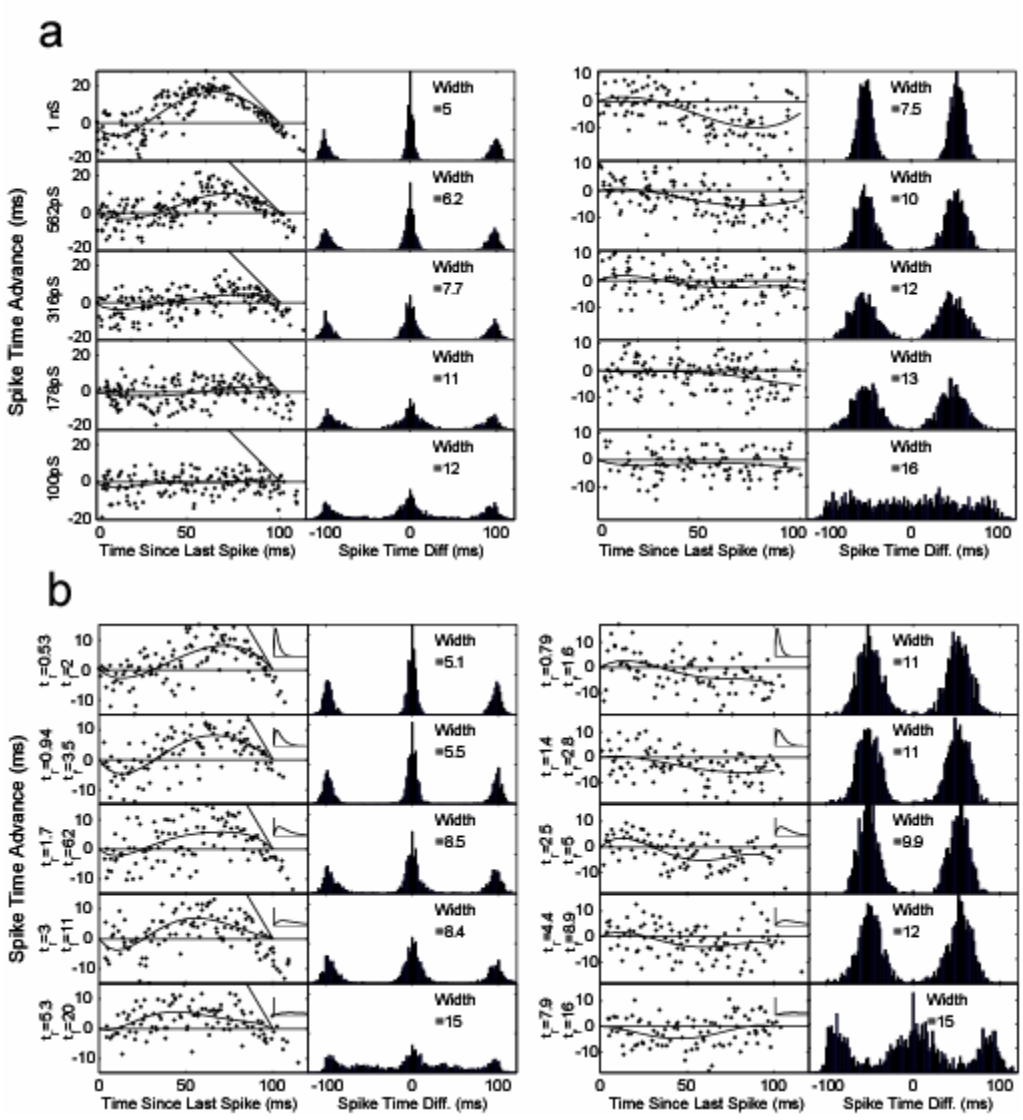

Figure 2. STRCs measured using synaptic conductances with varying kinetics. Panel **a** shows STRCs measured with varying amplitude synaptic conductancs, starting with amplitudes comparable to the size of a mini, roughly the size of the current caused by a single synaptic vesicle release (bottom), to a maximum size of approximately 10 vesicular releases (top). Left panels are from excitatory synaptic inputs while right panels are inhibitory synaptic inputs. Histograms are of spike time differences from itereative simulations of the network, time 0 is the time the reference cell fired with previous firing at approximately -100 and next firing time at 100 ms, the bars indicate the density of firing of the other neuron with respect to the reference cell. Panel **b** shows STRCs measured using varying synaptic time constants but preserving the total conductance, starting with very short and fast at top, to very long and slow at bottom, the middle panel is approximately the size and shape of spontaneous synaptic events measured in slice. Insets show the synaptic conductances to scale. For all synaptic strengths and shapes, we find that excitatory synapses synchronize in phase while inhibitory synchronize out of phase except for the very weakest and longest synaptic currents.

Next, we measured how neurons respond to multiple synaptic inputs by stimulating them with a Poisson train of synaptic inputs. To predict the next spike time with multiple synaptic inputs, we rescaled the STRC after each synaptic input to the new ISI to make more accurate predictions of the advance caused by the next synaptic input. Actual advances vs. predicted advances are shown in figure 3. This stretched STRC is as successful at predicting the advance to multiple synaptic inputs as the STRC is at predicting the advance of a single synaptic input. We conclude that the STRC method, developed under strict assumptions, can be used to predict network behaviors in more realistic conditions.

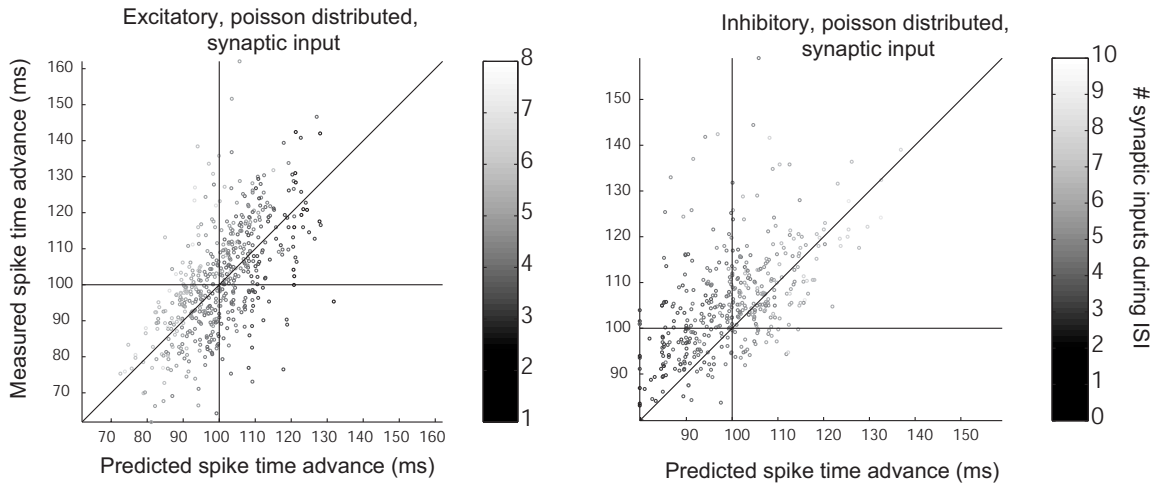

Figure 3. Response of neuron to multiple synaptic inputs. Response of neuron to multiple synaptic inputs is predicted by stretching or shrinking STRC after each synaptic input occurs. To test this hypothesis, we stimulated the neuron with Poisson train at 5 times the rate of the neuron's firing. We then predicted the spike time advance using the stimulus train and plotted it against the actual interspike interval. Colors indicate the number of synaptic inputs per interspike interval. Predictions did much better than assuming an average advance per synaptic input (data not shown).

In conclusion, we demonstrate that the activity of small networks of two cells can be accurately predicted using spike time response curves measured from the neurons. The behaviors of the neurons are generally stereotypical with excitatory networks synchronizing in phase, inhibitory networks synchronizing out of phase and heterogeneous networks being unstable. These network behaviors appear to hold true for a wide range of synaptic kinetics. To lay the groundwork for predicting larger networks,

we have measured how neurons respond to multiple synaptic inputs and find that we can predict the response of a neuron to multiple synaptic inputs as accurately as we can predict its response to a single synaptic input.

Acknowledgements: Grants: NIH: F32 MH066555-01A2, R01-NS34425, R01-MH47150