Reciprocal role of network connectivity and cellular excitability in excitatory networks

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Abstract: How do cellular and synaptic properties contribute to network activity? We study two models of burst generation based on a purely excitatory network and a slow negative feedback due to either 1) synaptic depression or 2) cellular adaptation. Specifically, how do two parameters -- mean cellular excitability and network connectivity -- affect burst duration and interburst interval? We show that varying each parameter has reciprocal effects on models 1) and 2). These dual effects of cellular excitability and connectivity allows experimental distinction of the two bursting mechanisms in excitatory networks.

Spontaneous, episodic activity is a general feature of developing and disinhibited networks. This activity is patterned as bursts during which the whole network is recruited, separated by intervals during which cells are silent. It is generated by a purely excitatory network (a fast positive feedback loop), which is bistable, ie it can be either in a high activity state or a low activity state (interval). A slow network depression acts as a negative feedback and allows the network to switch between high and low states, ie between bursts (active phase) and interburst intervals (silent phase). During the active phase, the network slowly depress until the level of depression is such that activity cannot be maintained. The network then falls to the silent phase, during which it recovers from depression, until network excitability is so high that a new episode starts. This mechanism is general, ie it does not depend on whether the slow network depression is synaptic or represents adaptation of cellular excitability. Indeed we have developed two classes of model utilizing either synaptic depression or cellular adaptation as the slow negative feedback and each class is capable of generating episodic activity similar to the observed activity. So how can we distinguish experimentally whether the slow negative feedback is operating at the cellular or synaptic level? In this study, we show that two parameters, network connectivity and bias current have different effects on each model. In addition we note that the effect of a parameter (ie connectivity) on a given model mechanism (ie cellular adaptation) is analoguous to the effect of the other parameter (ie bias current) on the other model (ie synaptic depression).

We start with a mean field representation of the network activity, ie we use an average (over time and population) of the synaptic drive received by individual cells. The input-output relationship of the network has a sigmoidal shape which depends on both the effective connectivity in the network and the average cellular firing threshold. Making either 1) synaptic efficacy (s) or 2) cellular threshold (tha) a slow variable depending on activity will slowly modify the input-output function of the network such that episodic activity is generated. For each of these two model, we study how the two following parameters: network connectivity (n) and bias current (i) affect the activity pattern. [Note: these models do not include a fast synaptic depression that is responsible for oscillatory behavior during the episodes, as previously published. This simplification allows us to concentrate on the slow episodic behavior and permits an analytical study.]

We show analytically that connectivity strongly affects when episodes of the cellular adaptation model terminate (ie the value that tha has to reach to terminate episodes), but not when they start.

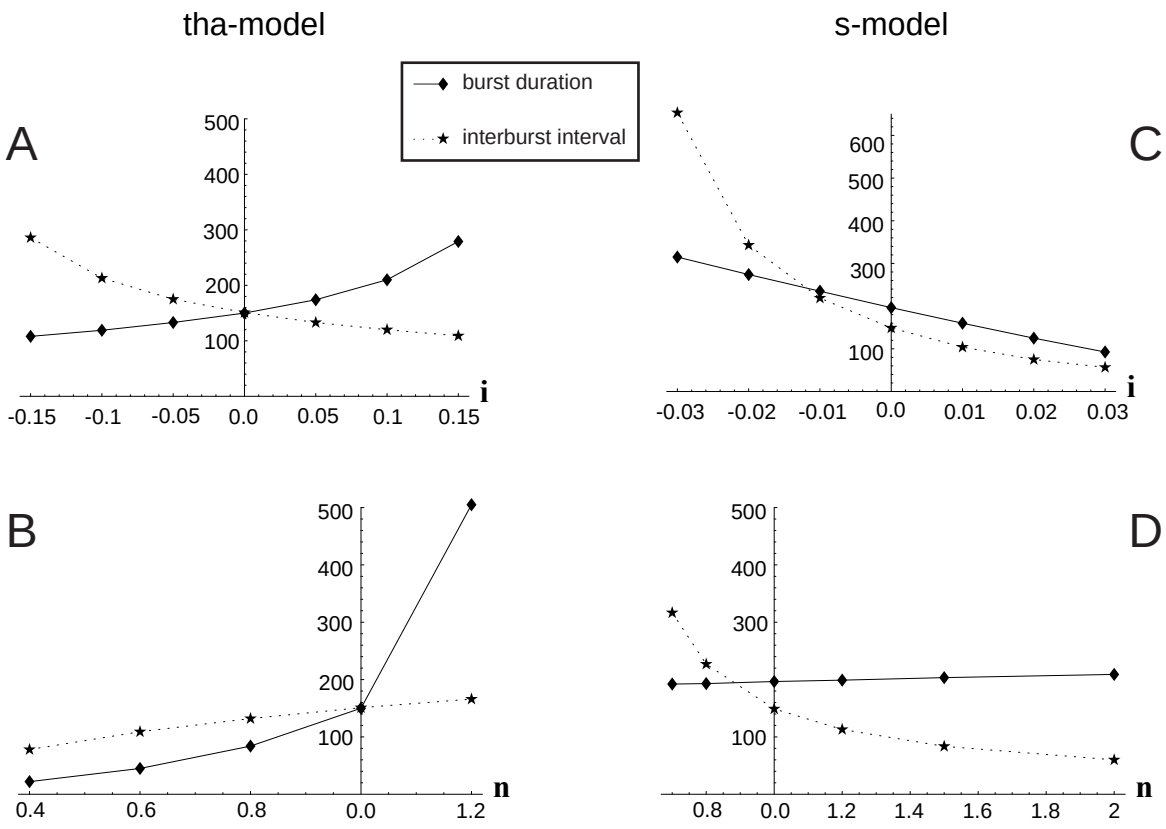
It is intuitively understood as greater connectivity implies greater synaptic inputs during the active phase and therefore the cellular threshold has to reach a higher value before episodes are terminated. On the other hand, during the silent phase cells do not receive much synaptic input and connectivity is less relevant, an episode will only start when cellular threshold is so low that a few cells start firing. The consequence is that the range of tha values covered during both active and silent phases is increased, so both active and silent phase increase when connectivity is increased (Figure B).

Bias current has a similar effect on the synaptic depression model. During the active phase, neurons receive large synaptic currents, so bias current does not have a strong influence and therefore does not affect much episode termination (episodes terminate when the synaptic efficacy, s, becomes too low). However, during the interburst interval, when most neurons are silent, a strong positive bias current will help start a new episode (that is, the higher parameter i is, the smaller the value of slow variable s needed to start an episode). As above, this affect the range of values covered by the slow variable, and therefore active and silent phase duration will be affected in the same way by a change in bias current. For instance, they both decrease when i is increased (Figure C).

We now look at the effect of bias current on the cellular adaptation model. This current shifts the input-output relationship of the network in the same way that cellular threshold does. Therefore, varying i will simply shift the range covered by tha. Even though the length of the range does not change, the lengths of the active and silent phases will vary, because the speed at which this range is covered will vary. If bias current is increased, tha will move more slowly during an episode (because it is closer to its asymptotic value) and faster during the interepisode interval. Therefore, the durations of active and silent phase will vary in an OPPOSITE way: the increased bias current leads to longer active phases and shorter silent phases (Figure A). Connectivity has a similar effect on the synaptic depression model, an increase in n increases episode duration, but decreases interepisode interval (Figure D).

To summarize, the effect of one of these parameters on a model is similar to the effect of the other parameter on the other model (cf Fig A vs D, or B vs C). However, each parameter has different effects on the two models (cf Fig A vs C, or B vs D), which allows to distinguish experimentally between them. For example, we can decrease connectivity with a low dose of a pharmacological agent that will block a fraction of the excitatory synaptic receptors. If the physiological mechanism of the depression is synaptic, this will induce LONGER interepisode intervals (and shorter episode duration). But if the slow negative feedback is due to cellular adaptation, the same pharmacological manipulation will lead to SHORTER intervals (and episode durations).

Finally, we present similar results obtained with networks of Integrate & Fire neurons and will perform the suggested experiments on disinhibited mice spinal cord in vitro at different stages of development (pre- and post-natal).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