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Significance of Pacemaker vs. Non-Pacemaker Neurons in an Excitatory Rhythmic Network

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Abstract— **This modeling study investigates the functional role of pacemaker neurons in generating stable rhythms in the pre-Botzinger complex, a subcircuit of the respiratory pattern-generating circuitry in mammals. While the presence of pacemakers within the network is without doubt, the percentage and significance of such pacemakers is still unresolved. Here we revisited earlier network simulations by varying the fraction of pacemaker and non-pacemaker neurons within the network, and quantifying the robustness of the input parameter space and range of frequencies output by the network. Stable network rhythms were possible even with no pacemakers. However, we found that a network of at least 50% pacemakers produced the greatest range of output frequencies and had the more robust input space.**

I. Introduction

THE transverse brainstem slice containing the pre-Botzinger complex is a rhythmically active in vitro system that contains a subcircuit of the respiratory pattern generator circuitry [1]. The slice rhythm is remarkably stable and the neural circuitry within the slice and its mechanism for generating rhythmic bursts has been the subject of much experimental, as well as computational, study. Much of the current controversy is with regard to the significance of the presence of pacemaker (endogenously bursting) neurons to the generation of network-wide bursts of electrical activity [2-4]. While it is generally agreed that pacemaking neurons exist and that a persistent Na^+ current underlies the bursting process at the single cell level, some experimental studies have suggested that endogenous bursting of single neurons is not necessary for network-wide bursting, and modeling studies have also shown that such an idea is feasible, but has not been robustly explored. This study investigates the functional significance of the contribution of pacemaker neurons to the rhythm.

II. Methods

Our lab previously developed models of bursting pBC neurons [5,6]. In our present study we use these model neurons to explore heterogeneous networks with a variable number of pacemaker (PM) and non-pacemaker (NPM) neurons. The properties of the model neurons are randomly assigned and biased by the statistics of known conductance differences between PMs and NPMs. While keeping the total number of neurons in the network constant, the fraction of the population made up of PMs is varied from 0 to 100%. The amount of respiratory drive to the network and the level of synaptic conductance in this all-to-all connected excitatory network are also varied. The robustness of the network is measured in terms of the input range and output range. The input range is the size of parameter space where network-wide synchronous bursting occurs, and the output range is the range of bursting frequencies that the network produces across this input range.

III. Results

Fig. 1 illustrates the existence and frequency of network-wide bursting as the number of PMs and respiratory drive (g-tonic) are varied for five values of excitatory synaptic coupling. Each point is the result of a single simulation with a new randomly generated set of parameters. The color indicates the frequency of regular, network-wide bursting. A frequency of zero (black portions of Fig. 1) is given to any simulation that does not produce regular network-wide bursting. Fig. 1 reveals that the likelihood of producing network-wide bursting is increased as the number of PMs in the network is increased.

At lower levels of synaptic conductance (top panels of Fig. 1), more PMs are required to generate network-wide bursting. At higher levels of synaptic conductance (bottom panels of Fig. 1), network-wide bursting is seen with fewer PMs, but the range of frequencies produced by the network is reduced. Therefore, increasing synaptic conductance increases the input range of the network but at the cost of the output range. Alternatively, increasing the number of PMs in the network, in general, increases both the input and the output range.

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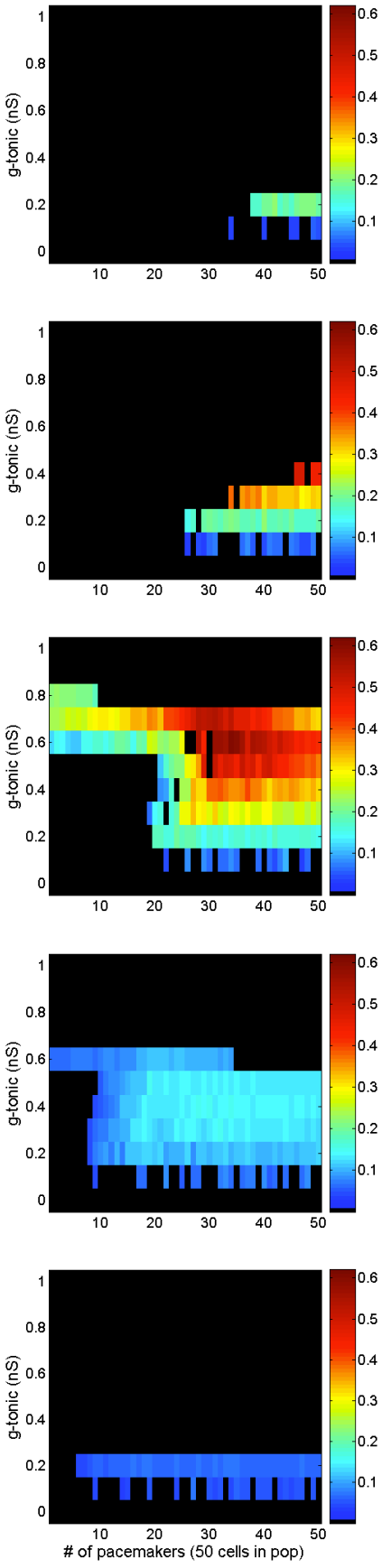

Fig. 1. Frequency of network-wide bursting at various levels of excitatory synaptic coupling (top to bottom: 0.05 nS, 0.075 nS, 0.1 nS, 0.2 nS, and 0.3 nS), various levels of respiratory drive or g-tonic (y-axis), and various numbers of pacemakers (x-axis). Frequency is displayed on the colorbar in Hz.

IV. Conclusions

The network simulations show that network bursting can occur even with no pacemakers, however, when the % of PMs is 50% or greater, the bursting is more robust (defined by the size of parameter space where bursting is supported) and can occur at the large range of frequencies exhibited by the slice (which is not the case for few PMs). The simulations also suggest multiple modes of burst generation, which have been validated qualitatively with simulations of pairs of neurons and are currently being investigated using numerical bifurcation analysis tools.

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