Transistor Analogs of Emergent Iono-Neuronal Dynamics

Supplementary Material

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Parameter tunability: digital vs. analog simulations

Traditional software-based computer models are powerful because of the ease with which one can adjust simulation parameters. This advantage pales as model complexity or the required simulation time increases. When using software-based simulations, practical considerations place constraints on: 1) the order and type of the differential equations used to describe dynamic biological processes; 2) the number of such equations to be included in the model; 3) the stiffness and robustness of the model equations; and 4) the precision, stability and speed of the simulation software and numerical routines. These issues must be judiciously optimized even when using state-of-the-art computers. The present iono-neuronal models are highly demanding in that they require both high sampling rates to capture physiological behaviors of ion-channel dynamics and long run times to capture the development of chaotic dynamics. Each 40 second run (in biological time) required >10 min in real time for a NEURON simulation and >30 minute on the MATLAB simulation package (The Mathworks, Natick, MA).

Moreover, software simulations must allow the system to relax to "dynamical steady state" before getting useful data for each run, rendering the initial simulation time unusable. This cost is paid each time a parameter is changed. This run-stop-restart methodology consumes valuable computational time, causing vast regions of the parameter space to remain unexplored, and important behaviors to be overlooked.

Hardware-based models, on the other hand, compute in real time at high speed independent of model complexity. This is a tremendous advantage that allows rapid parameter space exploration of even highly complex models. Importantly, the tuning of parameters on-chip does not require the simulation to be aborted and restarted. Instead, the effects of tuning are revealed instantaneously such that a large parameter space may be explored in an interactive fashion. By contrast, the high-precision, low-noise advantages of digital computation are less important insofar as iono-neuronal dynamics are intrinsically analog and noisy. The use of hardware-based analog models with limited precision but real-time computation is therefore prudent for large-scale iono-neuronal simulations.

Pacemaker bursting mechanisms explored by parameter tuning

The on-chip pacemaker model allowed us to generate a variety of bursting behaviors by systematically tuning all model parameters in real time. Each portion of the burst generation mechanism was modified independently, and the effects on burst duration, frequency, interburst intervals (IBI) and interspike intervals (ISI) were readily quantified.

Table S1 lists the tunable parameters of the bursting model. The $Ix\text{-}_{\mathrm{REST}}$ parameters are DC bias current required for proper operation of the log-domain filter (tunable picoampere-nanoampere levels). An important use of the bias current is to provide the persistent depolarizing current of the persistent Na (NaP) channel. In other channels, they act as leak current paths that can be nulled by tuning the AP circuit's I_{LEAK} node as desired. The τ_{x} node represents the activation and inactivation dynamics of ionic channels. Thus, tuning the I_{τ} node of a log-domain filter can be thought of as affecting the channel's opening and closing kinetics. Finally, we can modify each channel's reversal potential and investigate the effects of changing neuronal excitability.

Figure S1 shows the effects of modifying I_{NaP} at rest, $\tau_{\mathrm{NaP},}$ and E_{Na} on burst duration and burst frequency. Importantly, we found that slower activation dynamics results in longer bursts that exhibit higher irregularity, along with longer interburst intervals. This parameter space was analyzed by tuning the excitability for each ion channel and changing the activation/inactivation kinetics for each portion of burst mechanism. Here are some qualitative observations:

1. For a given set of NaP parameters, tuning $\underline{\tau}_{\mathrm{KCa}}$ dynamics allowed the neuron to transition from silence through bursting (with 2-200 spikes/burst) to tonic firing.
2. For a given set of calcium-activated K channels (KCa) parameters, tuning $I_{\mathrm{NaP\text{-}rest}}$ allows modification of IBI (from 300 ms to >10 seconds). Tuning $\underline{\tau}_{\mathrm{NaP}}$ allows us to increase burst length independent of bursting frequency. Moreover, tonic firing frequency was

dependent on both parameters, allowing us to generate firing rates from 1 – 80 Hz, as desired.

3. Modification of calcium dynamics by tuning τ_{Ca} allowed bursts length from 2-20 spikes/burst. Very slow calcium channel kinetics produced slow calcium summation that together with slow KCa dynamics produced regular bursts and long IBI (>3 sec).
4. We were able to recreate a variety of bursting behaviors. By modifying the slow kinetics of calcium channels, we were able to see an incrementing ISI pattern, and an incrementing-decrementing ISI pattern (Fig S2).

Table S1: Tunable Bursting Parameters			
AP Mechanism	**Excitatory connections**	**Slow mediator**	**Inhibitory connections**
I_{LEAK}	$I_{\mathrm{NaP\text{-}REST}}$	$I_{\mathrm{Ca\text{-}REST}}$	$I_{\mathrm{KCa\text{-}REST}}$
	τ_{NaP}	τ_{Ca}	τ_{KCa}
	E_{Na}	E_{Ca}	E_K

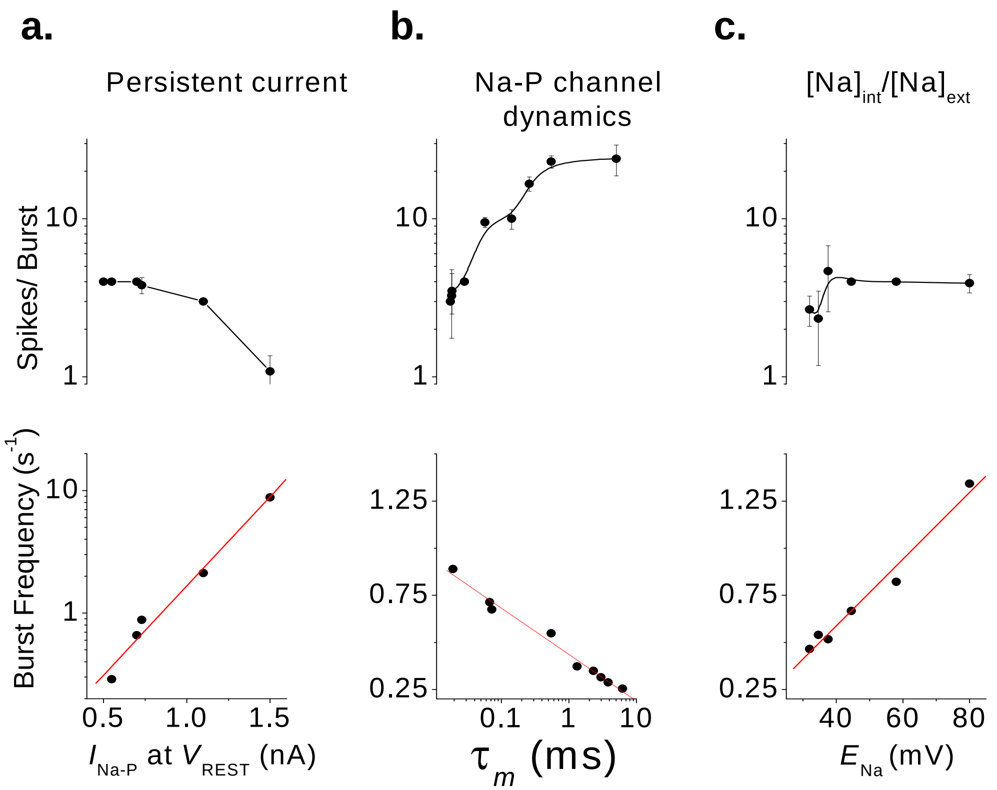

Fig S1.. Modification of burst length and burst frequency as a function of various Na-P parameters. **a.** Response to changes in the resting $I_{\mathrm{Na\text{-}P}}$ levels. Top: spike per burst stayed relatively constant with increasing depolarization current; bottom: bursting frequency increases exponentially with increased depolarization current.. **b** . Response to changing the persistent Na channel.activation dynamics. Top: slower dynamics produced exponentially more spikes per burst. Bottom: faster dynamics linearly increased burst frequency. Blue circle indicates parameter space that showed chaotic dynamics. **c.** Response to changes in excitability (by modification of the Na-P channel reversal potential E_{REV}). Top: spikes per burst increased in response to larger electrochemical gradient. Bottom: spiking frequency linearly increased with changes in reversal potential.

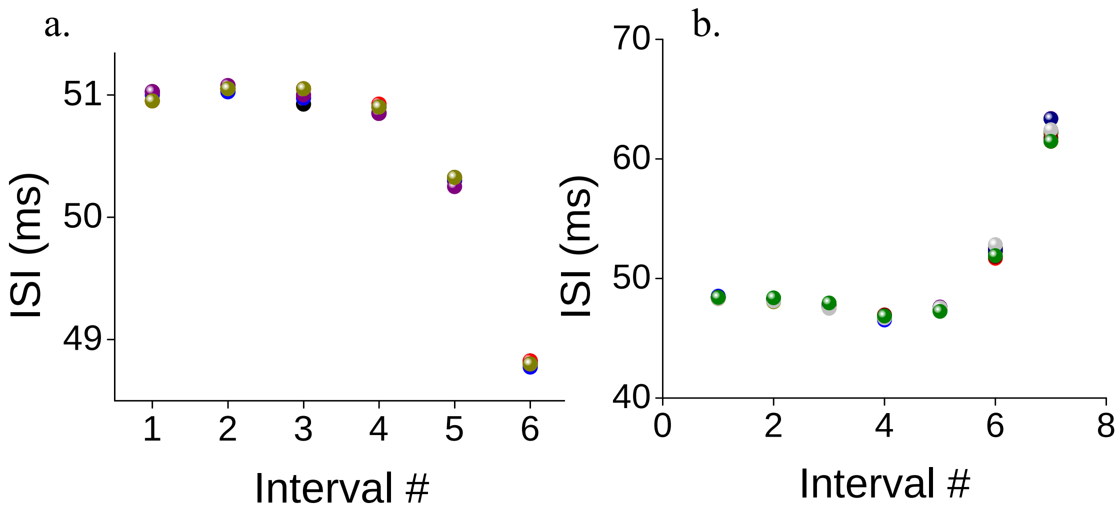

Fig S2. Modeling a variety of bursting patterns. Each burst in one run was overlaid on top of each other (each burst is color-code). **a**) Incrementing ISI pattern. **b**) Incrementing - decrementing ISI pattern.