Robust and tunable bursting requires slow positive feedback

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Abstract

We highlight a critical regulatory loop of neuronal bursting, controlling among other things a sweeping modulation between tonic firing and bursting. This regulatory loop is simple to assess experimentally or in a computational model but it is also subtle and sometimes overlooked because of its dynamical nature: it relies on a distinction between ionic currents that provide slow positive feedback and those that provide fast positive feedback. Our results suggest that currents that provide slow positive feedback are essential to the robustness and modulation of intrinsic modes of neuronal activity. Because of its cellular nature, this regulatory loop has implications on neuromodulation of rhythmic circuits at any broader scale.

Significance statement. Nervous systems functions rely on the modulation of neuronal activity between different rhythmic patterns. The mechanisms of this modulation are still poorly understood. Using single cell computational modeling, we show the critical role of a regulatory loop that provides slow positive feedback, distinct from the fast positive feedback necessary for spike generation. The distinction between slow and fast is basic and has a clear physiological signature. Yet its significance for regulation is often overlooked, leading to computational models that are rigid, i.e. lack modulation capabilities, and fragile, i.e. sensitive to small perturbations. These results are particularly relevant for neuromodulation studies that simulate large neural circuits with simplified cellular models.

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Introduction

While the function of neuronal bursting is still debated and probably diverse, the continuous modulation between distinct firing patterns is an important signaling component of many nervous functions. Those include muscle contraction orchestrated by central pattern generators [1], control of sleep, wakefulness and attention in thalamocortical circuits [2, 3], and electrosensing of the electric fish [4]. Voltage recordings in those references suggest that the bursting type varies a lot from one system to another but that the transition from spiking to bursting is robustly regulated in all of them. All transitions share a sharp separation between the low frequency of spikes in tonic firing and the high frequency of spikes during bursts.

The mechanisms of this regulation are still poorly understood. At the physiological level, they seem to involve a variety of ionic currents and neuromodulators, see e.g. the review [5]. At the modeling level, most textbooks on computational and mathematical neuroscience include a chapter on bursting, but mathematical models focus on a particular bursting mode rather than on modulating between distinct firing patterns. How to generate a particular bursting trace is a question that has received far more attention than how to robustly regulate the physiological transition between tonic firing and bursting, or between different bursting types.

We propose that the regulation of bursting critically relies on a distinction between intrinsic currents that provide slow positive feedback and currents that provide fast positive feedback. This distinction is basic but also subtle because of its dynamical nature. In an experimental study, it cannot be assessed from a static information such as the I-V curve. Instead, it requires dynamic information, such as the transient current response of a step voltage-clamp experiment. In a computational study, a model can accurately capture the balance of different ionic currents at steady-state and yet completely miss the dynamical distinction between slow and fast positive feedback by disregarding the difference in activation time constants. This frequently happens due to the lack of dynamic data or in a effort to simplify cellular models for network simulations.

Our results show that the slow positive feedback loop is central to the regulation of bursting and therefore a primary target for neuromodulators. In particular, it is the primary regulatory loop that is modulated in a sweeping transition between spiking and bursting. Furthermore, the balance of the slow positive feedback loop with respect to the other regulatory loops of a bursting neuron is what determines modulatory paths between different types of bursting as well as degeneracy paths along...
which large variations of conductance parameters can be tolerated without affecting the firing pattern. Bursting models that lack a slow positive feedback loop are rigid and fragile. They require different mathematical models for different types of neuronal activity and lead to aberrant firing patterns in the presence of small parameter variations or external noise.

While the analysis in this paper is performed at the single cell level, the discussion provides evidence that slow positive feedback at the cellular level critically impacts the robustness and tunability of circuit and network rhythms as well. This suggests that accounting for the dynamical difference highlighted in this paper is strongly relevant for neuromodulation studies at every scale and therefore a feature that merits attention both from experimentalists and modelers.

Results

The dynamical signature of robust and tunable bursting

Figure 1.A uses a computational model to illustrate a physiological transition from tonic firing to bursting and the corresponding change in a voltage clamp experiment around threshold potential: the current response carries a distinctive transient marker of the neuronal rhythm. We call this transient signature slow in that it separates the early or fast response present in every excitable cell from the late or ultraslow convergence to steady-state. We propose that the control of this slow transient is a critical ingredient of bursting regulation. In bursting mode, the slow transient is inverse i.e. opposite to the voltage perturbation: it mimicks in a slower time scale the early response. In tonic firing mode, the slow transient is in the same direction as the voltage perturbation: it mimicks the monotone behavior of the late response.

The figure was generated using a computational model from the literature [6] with seven voltage-and time-dependent conductances as well as a leak conductance (see Methods). The modulation from tonic firing to bursting is obtained by varying the relative strength of the calcium conductances (gCa) and A-type potassium conductance (gA). This modulation defines a modulatory path in the parameter space of the two maximal conductances (Path a-b in Figure 1.A ). Other paths in that same plane result in almost no change in the neuronal activity (Path c-d in Figure 1.A ). Both the firing pattern and the slow voltage clamp signature are conserved along such degeneracy paths. The coexistence of degeneracy and modulatory paths has been shown to be critical for robust neuromodulation [7]. We propose that
Figure 1: A. The slow transient in a voltage clamp experiment near threshold is a reliable signature to distinguish bursting from tonic firing: the slow transient is increasing in spiking mode (a signature of slow positive conductance) and decreasing in bursting mode (a signature of slow negative conductance). The signature is modulated along a modulation path (a-b) and conserved along a degeneracy path (c-d, not shown) in the parameter space of maximal conductances. B. The modulation of the slow transient vanishes as calcium activation kinetics, the only source of slow negative conductance in the model, varies from slow to fast. In the limit of instantaneous activation, the model has lost its modulation properties and in particular the transition from tonic firing to bursting.
the slow transient of the voltage clamp is a unambiguous signature for such studies. Experimental evidence of this signature has been reported in the literature. For instance, the modulatory effects of the peptide CabPK in regulating a cellular and circuit bursting rhythm in current clamp were assessed through a slow transient signature in voltage clamp [8]. The same signature was used in [9] to assess the cooperativity of persistent sodium and calcium currents in burst excitability of Purkinje cells.

In the computational model used in Figure 1, the early inverse response of the voltage clamp results from the activation of a sodium current whereas the slow inverse response results from the activation of calcium currents. This means that, in this particular model, the control of the slow transient is through the activation of calcium currents. The two inverse responses are distinct in the voltage clamp experiment because the time scales of the calcium current activations are significantly slower than the time scale of the sodium current activation. Figure 1.B shows the result of merging the two time scales by decreasing the time constants of the calcium activations in the computational model: the distinct inverse responses progressively merge. As a result, both the modulatory and degeneracy paths are lost in the parameter space of maximal conductances. This is because the neuronal model has lost its only control of the slow transient in the voltage clamp current response.

We stress that the modeling difference between Figure 1.A and Figure 1.B is purely dynamical in nature: the three models only differ by a change in two activation time constants. This implies that the static properties of the model are unchanged, meaning for instance an identical balance of ionic currents at steady-state, or an identical I-V curve. The change from Figure 1.A to Figure 1.B thus highlights that the tunability of the firing activity can be lost without affecting the static properties of the model. And it also suggests that it might be difficult to extract the dynamical signature in Fig 1.A from other signatures frequently used in experimental studies of bursting, such as the monotonicity of the I-V curve or the existence of slow oscillatory potentials in the absence of sodium.

Fig 2.A contrasts the dynamical voltage clamp signature with the monotonicity properties of the static I-V curve. A negative static conductance around a given voltage is synonym of an inverse static response in the voltage clamp experiment around the same voltage. It is sometimes used as a reliable signature of bursting. But a static inverse response is neither necessary nor sufficient for bursting. Fig 2.A illustrates four model conditions for which the distinction between tonic firing and bursting is unambiguously predicted by the transient voltage clamp signature but not by the static signature. The slow transient of the voltage clamp is a dynamic feature that cannot be inferred from the asymptotic response of the voltage clamp, with is a static feature.
Bursting and its modulation are also often studied experimentally through slow oscillatory potentials (SOPs) observed in the absence of spikes (by blocking sodium channels). But a slow oscillation is not a reliable signature of bursting per se. Fig 2.B illustrates that a slow oscillation does not necessarily discriminate between tonic firing and bursting because it does not discriminate between fast and slow positive feedback. Fast or instantaneous activation of a calcium channel as in Figure 1.B will generate neither the slow transient voltage clamp signature nor bursting. But it provides a steady-state inward current that can be sufficient to destabilise the resting potential and generate a slow oscillatory potential. Once again, the dynamic role of a given current cannot be inferred from its static properties.

The feedback motif of robust and tunable bursting

Conductance-based modeling provides a direct bridge from a voltage-clamp signature to its mathematical modeling counterpart. In their seminal work, Hodgkin and Huxley modeled the action potential...
voltage-clamp signature as the sum of an early and a late currents: the fast activation of an inward current (sodium) accounts for the early inverse response whereas its slow inactivation combined with the slow activation of an outward current (potassium) accounts for the late monotone response. In the language of circuit theory, the former provides a fast negative conductance whereas the latter provides a slow positive conductance. In a more general modeling framework, the early current provides fast positive feedback (or fast regenerativity) whereas the late current provides slow negative feedback (or slow restorativity).

Following the same approach to describe the voltage-clamp signature of bursting, we see that the distinctive ingredient of a burster is an additional current that provides slow positive feedback (or slow regenerativity). Physiological contributors of such currents include any inward current that activates slowly relative to sodium (for instance the whole family of calcium currents with slow activation or resurgent sodium channels [10]) and any outward current that inactivates slowly (for instance fast potassium channels [11]). In the presence of a slow positive feedback current, the late monotone response of the voltage-clamp requires a current that provides ultraslow negative feedback, such as calcium-activated potassium currents.

When translated into a feedback motif, the voltage clamp signature highlighted in Figure 1 requires four distinct feedbacks: two positive feedbacks, one fast and one slow, and two negative feedbacks, one slow and one ultraslow. In Figure 1, the presence or absence of slow positive feedback is what distinguishes bursting from spiking.

The four feedback loops are essential for robustness and modulation of the firing pattern. The two positive feedback loops are essential for robustness because they ensure that the firing patterns are a mixture of four discrete states: rest, spikes, SOPs, and bursts. Each of the four discrete states corresponds to the positive feedbacks being turned on or off. Figure 3.A illustrates the four discrete states. The property that a continuous behavior has the discrete reading of a finite automaton is a typical feature of the positive feedback motif. The positive feedback of any autocatalytic process is essential to switch-like behaviors. The distinct fast and slow positive feedback loops endow the firing pattern with an endogenous source of fast switch (necessary for robust spiking) and a distinct endogenous source of slow switch (necessary for robust bursting). Physiologically, those observations correlate with the necessity of fast regenerative channels for spiking (typically sodium) and the necessity of slow regenerative channels for bursting (typically calcium).

The two negative feedback loops are essential for modulation because they allow to modulate
Figure 3: The four feedbacks motif (fast +, slow +, slow -, ultraslow -) is necessary and sufficient for mathematical modeling of tunable bursting. A. The two positive feedbacks provide an automaton with two binary states: 1 stands for 'on' whereas '0' stands for 'off'. The first digit refers to the fast positive feedback, the second digit refers to the slow positive feedback.

B: Modulating the four feedback loops provides continuous modulation paths in the parameter space of conductances. Left: Increasing both slow positive and ultraslow negative feedback increases burstiness. Right: Varying the time scale of the slow positive feedback between the two time scales of the negative feedbacks modulates the intraburst frequency pattern from monotonically decreasing (squarewave) to biphasic (parabolic) to monotonically increasing (triangular). See Methods for details about the simulations.
the relative strength of the two positive feedback loops both in time and in amplitude. Figure 3.B illustrates the modulation capabilities of the four feedback motif. All traces shown in Figure 3 are generated from the same model, by continuous paths in the parameter space of maximal conductances. Conductance parameters are not tuned by a random exploration of the parameter space. Instead, they are tuned to modulate the relative strength of the four distinct feedbacks. The negative feedbacks provide a continuous modulation of the firing activity between the four discrete states ensured by the positive feedbacks. The reader will notice that Figure 3.B-right reproduces three different types of bursting that have traditionally be associated to different mathematical models of bursting.

The modeling distinction between the four feedback loops of the motif do not necessarily match the physiological distinction between distinct ion channel types. For instance, sodium channels usually provide a source of fast positive feedback through their activation and a source of slow negative feedback through their inactivation. More generally, a same current can contribute to several of the four feedback loops. But a particular modulation scenario will usually have a clear interpretation in terms of the four feedback loops. Central to this paper, the modulation from spiking to bursting will inevitably involve a balance between the slow positive feedback provided by slow regenerative channels and the slow negative feedback provided by slow restorative channels. The paper [12] computed this balance in six published models of the literature and the conclusion related in all six models to experimental evidence of a transition from spiking to bursting. The paper [13] provides a mathematical analysis of the four feedback motif grounded in singularity theory [14]. The paper [15] introduces the concept of dynamic input conductances to map the modulation of feedback loops to the modulation of conductance parameters in an arbitrary conductance-based model. What is central to the message of the present paper is that the slow positive feedback is key to a feedback motif that robustly accounts for modulation from spiking to bursting.

In the four feedback motif, the slow positive feedback is of particular interest: it plays a prominent role in robustness and modulation and yet it is not necessary to bursting. In fact, most textbook mathematical models of bursting as well as many computational models of bursting lack the slow positive feedback and only rely on a three feedback motif. The rationale is simple: a spiking model only requires two feedback loops (fast positive and slow negative), and an additional ultraslow negative feedback is sufficient to create an oscillation between the two discrete states of a spiking neuron. In this approach, bursting is seen as the result of a slow adaptation between resting and spiking. This minimal three feedback motif is at the core of textbook expositions of bursting such as Chapter 9 in
Chapter 9 in [17], and Chapter 5 in [18]. It was originally proposed in the work of Chay and Keyser [19] on secretory (pancreatic) cells.

The three feedback loop motif is sufficient to reproduce bursting traces but the absence of the slow positive feedback loop makes those models rigid and fragile in the space of parameters: they lack modulation capabilities and small parameter variations strongly affect the bursting pattern. Figure 4 illustrates the striking contrast between the fragility of models of the literature that lack slow positive feedback and the robustness of models that include slow positive feedback. The absence of modulation is a consequence of the fragility of parameters. Rigid models lack modulation or degeneracy paths such as those illustrated in Figure 1. Fragile models easily introduce artefacts in network computational studies. For instance, a main discussion in the recent study [20] is about a modulation of spike height in bursting both in experiment and in computation but all computations rest on the fragile CA1 model at the cellular level (see the large variability of spike height in Figure 4.C).

The modified CA1+ model (see Methods for details) also illustrates that robustness and modulation can be recovered in a three feedback bursting model by adding one distinct source of slow positive feedback. The same is true for many computational models of the literature, that do model sodium and calcium as distinct physiological currents but do not model the distinction between fast and slow regenerative channels by setting both activation variables at steady-state. This practice is common because it reduces the dimension of the conductance-based model. The resulting reduced models lack robustness and modulation but those properties can be recovered by simply restoring the physiological time scale separation between fast and slow regenerative channels.

Discussion

A dynamical signature characterizes the transition from spiking to bursting

The classical voltage clamp experiment of electrophysiology near threshold provides the fundamental signature of a continuous modulation from spiking to bursting. This signature is however subtle because it is dynamic or transient rather than static: while the initial (fast) and final (ultraslow) phases of the voltage clamp might not differ, it is the intermediate transient (slow) phase that distinctly differentiates the two firing patterns. This signature reveals the essential role in neuromodulation of
Figure 4: Bursting models that lack slow positive feedback are fragile. Green models (STG and R15) do include slow positive feedback. Their bursting trace is robust to a small uniform variation of all maximal conductance parameters. Red models (pβC, TC, and CA1) lack slow positive feedback. The same parameter variation of parameters causes large variations in their bursting trace. Robustness of CA1 is recovered by making the calcium activation slow (CA1+). See Methods for details.

Currents that provide a slow negative conductance, or equivalently a slow positive feedback. This role can only be captured in models that respect the time scale separation between ion channels that provide fast positive feedback and those that provide slow positive feedback.

This time scale separation is well acknowledged in the ion channel literature. For instance, activation and inactivation of calcium channels is often described as similar to activation and inactivation of sodium channels, but up to fifty times slower for some of them [21], [22, p.127]. But it is often neglected in mathematical and computational modeling. For instance, Figure 5.6 in the textbook [17] refers to both sodium and calcium activation as fast. The section on calcium channels in the recent textbook [18] also suggests that calcium and sodium channels have similar dynamics. In computational modeling, it is widespread practice to set both the calcium and sodium activation to steady-state when reducing the complexity of a model (See supplementary material for a list of important papers that make that assumption). In fact, the lack of distinction between slow and fast positive feedback is more the rule than the exception in neuronal modeling, suggesting that the role of slow negative conductances in neuromodulation is underappreciated.
Slow positive feedback is necessary and sufficient to make a burster robust and tunable

Slow positive feedback is not necessary to bursting but it endows a burster with robustness and modulation properties. In the absence of a regulatory loop that provides slow positive feedback, a bursting model is necessarily rigid and fragile. It lacks modulatory paths in the space of maximal conductance parameters and tiny perturbations of the model parameters cause large variations in the bursting trace. Adding slow positive feedback in such models is sufficient to make the burster robust and tunable.

This observation points to an important feature that should be retained in computational models aiming at neuromodulation studies. For many of them, the slow positive feedback regulatory loop is recovered by simply restoring the physiological time scale of slow regenerative channels.

This observation is also of significance for the mathematical theory of bursting. Starting with the seminal work of Rinzel [23, 24], the mathematical theory of bursting has relied on a classification based on the possible bifurcations that can govern the transition between rest and spike. The recent work of Izhikevich [17] provides up to 16 different such mechanisms. Most mathematical bursters are however minimal in the sense that they rely on a three rather than four feedback motif and lack the slow positive feedback. Those models lack modulation capabilities and different models are required to model different bursting types. In contrast, the four feedback motif provides a sweeping modulation between the four discrete states that govern any bursting trace. This suggests that regulatory mechanisms might be a valuable complement to bifurcation mechanisms in a mathematical theory of bursting.

Slow positive feedback at the cellular level impacts robustness and tunability at other scales

Studying neuromodulation in a cellular model grounded on the four feedback motif provides novel insight about how different neuromodulators can regulate different firing patterns by targeting different ionic conductances or receptors [15]. But the role of the cellular slow positive feedback has also been demonstrated at broader scales. The recent study [25] illustrates its importance in the classical half-center oscillator, one of the most extensively studied rhythmic circuits. The circuit is shown to be robust and tunable only in the presence of slow positive feedback at the cellular level. This analysis is pursued in [26]. T-type calcium channels are shown to play a critical role in enabling fast transitions...
between brain states over a broad range of temporal and spatial scales. The whole range of network rhythms collapses as soon as the activation of those channels is not slow, illustrating the key role of a cellular slow positive feedback at the network level. All those results suggest that the property studied at the cellular level in the present paper is relevant at other scales as well and an important ingredient of neuromodulation.

### Supporting Information (SI)

**Table 1.** List of papers in which a physiologically slow regenerative variable is set to steady state.

| Reference | Slow regenerative gating variable set to steady state |
|-----------|-----------------------------------------------------|
| [27]      | Activation of T-type and high-threshold $Ca^{2+}$ channels |
| [28]      | Activation of T-type $Ca^{2+}$ channels |
| [29]      | Activation of persistent $Na^+$ channels |
| [30]      | Activation of persistent $Na^+$ channels |
| [31]      | Activation of T-type $Ca^{2+}$ channels |
| [32]      | Activation of T-type $Ca^{2+}$ channels |
| [33]      | Activation of T-type $Ca^{2+}$ channels |
| [34]      | Activation of T-type and high-threshold $Ca^{2+}$ channels |
| [35]      | Activation of persistent $Na^+$ channels |
| [36]      | Activation of T-type $Ca^{2+}$ channels |
| [37]      | Activation of persistent $Na^+$ channels |

### Methods

All simulations and analyses were performed using the Julia programming language. The Julia code is freely available upon request.

Figure 1A is generated using the STG model described in [6]. Briefly, the model is composed of a leak current $I_{\text{leak}}$, a transient sodium current $I_{Na}$, a T-type calcium current $I_{Ca,T}$, a S-type calcium current $I_{Ca,S}$, a delayed rectifier potassium current $I_{K,DR}$, a transient potassium current $I_{A}$, a calcium activated potassium current $I_{K,CA}$. Parameters used in the simulations are as follows.

(a): $C = 1 \mu F/cm^2$, $V_{Na} = 50 \text{ mV}$, $V_{K} = -80 \text{ mV}$, $V_{Ca} = 80 \text{ mV}$, $V_{leak} = -50 \text{ mV}$, $g_{leak} =$
0.1 mS cm$^{-2}$, $\bar{g}_{Na} = 700$ mS cm$^{-2}$, $\bar{g}_{Ca,T} = 6$ mS cm$^{-2}$, $\bar{g}_{Ca,S} = 9$ mS cm$^{-2}$, $\bar{g}_A = 30$ mS cm$^{-2}$, $\bar{g}_{K,DR} = 80$ mS cm$^{-2}$, $\bar{g}_{K,Ca} = 25$ mS cm$^{-2}$. (b): same parameters as (a) except $\bar{g}_{Ca,T} = 1$ mS cm$^{-2}$, $\bar{g}_{Ca,S} = 1.5$ mS cm$^{-2}$, $\bar{g}_A = 240$ mS cm$^{-2}$. (c): same parameters as (a) except $\bar{g}_{Ca,T} = 3$ mS cm$^{-2}$, $\bar{g}_{Ca,S} = 4.5$ mS cm$^{-2}$, $\bar{g}_A = 26$ mS cm$^{-2}$. (d): same parameters as (a) except $\bar{g}_{Ca,T} = 7$ mS cm$^{-2}$, $\bar{g}_{Ca,S} = 10.5$ mS cm$^{-2}$, $\bar{g}_A = 225$ mS cm$^{-2}$. Burstiness is defined as spikes per bursting period. Voltage steps in the voltage clamp experiments are from $-39$ mV to $-40$ mV.

Figure 1B is generated with the same model and parameters as Figure 1A except that $\tau_{m_{Ca,T}}$ and $\tau_{m_{Ca,S}}$ are scaled by 0.5 in the center parameter chart and $m_{Ca,T} = m_{Ca,T,\infty}(V)$, $m_{Ca,T} = m_{Ca,T,\infty}(V)$ (instantaneous calcium activation) in the right parameter chart. Voltage clamp traces are from $-39$ mV to $-40$ mV.

Figure 2A top is generated using the STG model described in [38]. Briefly, the model is composed of a leak current $I_{leak}$, a transient sodium current $I_{Na}$, a T-type calcium current $I_{Ca,T}$, a S-type calcium current $I_{Ca,S}$, a delayed rectifier potassium current $I_{K,DR}$, a transient potassium current $I_A$, a calcium activated potassium current $I_{K,Ca}$, and hyperpolarization-activated cyclic nucleotide-activated $I_H$ current. Parameters used in the simulations are as follow. Tonic firing: $C = 1 \mu F, cm^{-2}$, $V_{Na} = 50$ mV, $V_K = -80$ mV, $V_{Ca} = 80$ mV, $V_{leak} = -50$ mV, $\bar{g}_{leak} = 0.01$ mS cm$^{-2}$, $\bar{g}_{Na} = 800$ mS cm$^{-2}$, $\bar{g}_{Ca,T} = 1$ mS cm$^{-2}$, $\bar{g}_{Ca,S} = 1$ mS cm$^{-2}$, $\bar{g}_A = 50$ mS cm$^{-2}$, $\bar{g}_{K,DR} = 90$ mS cm$^{-2}$, $\bar{g}_{K,Ca} = 60$ mS cm$^{-2}$, $\bar{g}_H = 0.1$ mS cm$^{-2}$. Bursting: same parameters as tonic except $\bar{g}_{Ca,T} = 4$ mS cm$^{-2}$, $\bar{g}_{Ca,S} = 8$ mS cm$^{-2}$. Voltage steps in the voltage clamp experiments are from $-44$ mV to $-42$ mV.

Figure 2A bottom is generated using the same STG model as Figure 1A. Parameters used in the simulations are as in 1A except $\bar{g}_{Na} = 800$ mS cm$^{-2}$, $\bar{g}_{Ca,T} = 10$ mS cm$^{-2}$, $\bar{g}_{Ca,S} = 8$ mS cm$^{-2}$, $\bar{g}_A = 10$ mS cm$^{-2}$, $\bar{g}_{K,DR} = 120$ mS cm$^{-2}$, $\bar{g}_{K,Ca} = 50$ mS cm$^{-2}$ (tonic mode) or $\bar{g}_{Na} = 800$ mS cm$^{-2}$, $\bar{g}_{Ca,T} = 1$ mS cm$^{-2}$, $\bar{g}_{Ca,S} = 1$ mS cm$^{-2}$, $\bar{g}_A = 10$ mS cm$^{-2}$, $\bar{g}_{K,DR} = 120$ mS cm$^{-2}$, $\bar{g}_{K,Ca} = 50$ mS cm$^{-2}$ (bursting mode). Voltage steps in the voltage clamp experiments are from $-44$ mV to $-42$ mV.

Figure 2B bottom is generated using the Plant R15 aplysia model as described in [39]. Briefly, the model is composed of a leak current $I_{leak}$, a transient sodium current $I_{Na}$, a persistent calcium current $I_{Ca}$, a delayed rectifier potassium current $I_{K,DR}$, a calcium activated potassium current $I_{K,Ca}$. Parameters used in the simulation are as follows. $C = 0.8 \mu F, cm^{-2}$, $V_{Na} = 30$ mV, $V_K = -75$ mV, $V_{Ca} = 140$ mV, $V_{leak} = -40$ mV, $\bar{g}_{leak} = 0.003$ mS cm$^{-2}$, $\bar{g}_{Na} = 4$ mS cm$^{-2}$, $\bar{g}_{K,DR} = 4$ mS cm$^{-2}$, $\bar{g}_{Ca} = 0.006$ mS cm$^{-2}$, $\bar{g}_{K,Ca} = 0.04$ mS cm$^{-2}$. Voltage steps in the voltage clamp experiments are
from $-80mV$ to $-40mV$. Figure 2B top is generated using the same model and parameters as Figure 2B bottom, except that the calcium current activation is 100 times faster.

Figure 3 bottom left is generated using the same STG model as Figure 1A. Parameters used in the simulations are as in Figure 1A except the following. Case Weakly Bursting: $\bar{g}_{Na} = 1200 \, mS \, cm^{-2}$, $\bar{g}_{Ca,T} = 1 \, mS \, cm^{-2}$, $\bar{g}_{Ca,S} = 4 \, mS \, cm^{-2}$, $\bar{g}_{A} = 10 \, mS \, cm^{-2}$, $\bar{g}_{K,DR} = 40 \, mS \, cm^{-2}$, $\bar{g}_{K,Ca} = 8 \, mS \, cm^{-2}$. Case Bursting: $\bar{g}_{Na} = 1200 \, mS \, cm^{-2}$, $\bar{g}_{Ca,T} = 1 \, mS \, cm^{-2}$, $\bar{g}_{Ca,S} = 7 \, mS \, cm^{-2}$, $\bar{g}_{A} = 8 \, mS \, cm^{-2}$, $\bar{g}_{K,DR} = 40 \, mS \, cm^{-2}$, $\bar{g}_{K,Ca} = 13 \, mS \, cm^{-2}$. Case Strongly Bursting: $\bar{g}_{Na} = 1200 \, mS \, cm^{-2}$, $\bar{g}_{Ca,T} = 10 \, mS \, cm^{-2}$, $\bar{g}_{Ca,S} = 8 \, mS \, cm^{-2}$, $\bar{g}_{A} = 10 \, mS \, cm^{-2}$, $\bar{g}_{K,DR} = 120 \, mS \, cm^{-2}$, $\bar{g}_{K,Ca} = 40 \, mS \, cm^{-2}$.

Figure 3 bottom right is generated using the same STG model as Figure 1A. Parameters used in the simulations are as in Figure 1A except the following. Case Parabolic: $\bar{g}_{Na} = 1200 \, mS \, cm^{-2}$, $\bar{g}_{Ca,T} = 1 \, mS \, cm^{-2}$, $\bar{g}_{Ca,S} = 32 \, mS \, cm^{-2}$, $\bar{g}_{A} = 40 \, mS \, cm^{-2}$, $\bar{g}_{K,DR} = 150 \, mS \, cm^{-2}$, $\bar{g}_{K,Ca} = 200 \, mS \, cm^{-2}$. Case Square-wave: $\bar{g}_{Na} = 1200 \, mS \, cm^{-2}$, $\bar{g}_{Ca,T} = 10 \, mS \, cm^{-2}$, $\bar{g}_{Ca,S} = 8 \, mS \, cm^{-2}$, $\bar{g}_{A} = 10 \, mS \, cm^{-2}$, $\bar{g}_{K,DR} = 120 \, mS \, cm^{-2}$, $\bar{g}_{K,Ca} = 50 \, mS \, cm^{-2}$. Case Triangular: $\bar{g}_{Na} = 1200 \, mS \, cm^{-2}$, $\bar{g}_{Ca,T} = 1 \, mS \, cm^{-2}$, $\bar{g}_{Ca,S} = 40 \, mS \, cm^{-2}$, $\bar{g}_{A} = 40 \, mS \, cm^{-2}$, $\bar{g}_{K,DR} = 200 \, mS \, cm^{-2}$, $\bar{g}_{K,Ca} = 200 \, mS \, cm^{-2}$.

Nominal models in Figure 4 are given as follows. The STG model is the same as Figure 1A with maximal conductance parameters: $\bar{g}_{leak} = 0.1 \, mS \, cm^{-2}$, $\bar{g}_{Na} = 1200 \, mS \, cm^{-2}$, $\bar{g}_{Ca,T} = 6.5 \, mS \, cm^{-2}$, $\bar{g}_{Ca,S} = 9.75 \, mS \, cm^{-2}$, $\bar{g}_{A} = 100 \, mS \, cm^{-2}$, $\bar{g}_{K,DR} = 80 \, mS \, cm^{-2}$, $\bar{g}_{K,Ca} = 40 \, mS \, cm^{-2}$. The Plant R15 model and parameters are the same as given in [39]. The pancreatic beta cells model and parameters are the same as described in [19]. The thalamocortical (TC) model and parameters are the same as given in [36]. The CA1 model and parameters are the same as given in [37]. The modified CA1+ model is obtained from the nominal model by: the persistent sodium current activation is made dynamic with time constant equal to 6 times the original delayed rectifier activation time constant; the original delayed rectifier activation time constant is scaled by 4; the cell capacitance is scaled by 0.4. Scatter plots in Figure 4 bottom are obtained by scaling the maximal condutance vector $\mathbf{g}$ by a uniformly distributed random number in the range $[0.8, 1.2]$.

References

[1] E. Marder. Neuromodulation of neuronal circuits: back to the future. Neuron, 76(1):1–11, 2012.
[2] S Murray Sherman. Tonic and burst firing: dual modes of thalamocortical relay. *Trends in neuroscience*, 24(2):122–126, 2001.

[3] Tatiana Bezdudnaya, Monica Cano, Yulia Bereshpolova, Carl R Stoelzel, Jose-Manuel Alonso, and Harvey A Swadlow. Thalamic burst mode and inattention in the awake lgn. *Neuron*, 49(3):421–432, 2006.

[4] R. Krahe and F. Gabbiani. Burst firing in sensory systems. *Nature Reviews Neuroscience*, 5(1):13–23, 2004.

[5] E. Marder and D. Bucher. Understanding circuit dynamics using the stomatogastric nervous system of lobsters and crabs. *Annu. Rev. Physiol.*, 69:291–316, 2007.

[6] M. S. Goldman, J. Golowasch, E. Marder, and L. F. Abbott. Global structure, robustness, and modulation of neuronal models. *The Journal of Neuroscience*, 21(14):5229–5238, 2001.

[7] Eve Marder, Timothy O’Leary, and Sonal Shruti. Neuromodulation of circuits with variable parameters: Single neurons and small circuits reveal principles of state-dependent and robust neuromodulation. *Annual Review of Neuroscience*, 37:329–347, 2014.

[8] J.C. Rodriguez, D.M. Blitz, and M.P. Nusbaum. Convergent rhythm generation from divergent cellular mechanisms. *Journal of Neuroscience*, 33(46):18047–18064, 2013.

[9] A. M. Swensen and B. P. Bean. Robustness of burst firing in dissociated purkinje neurons with acute or long-term reductions in sodium conductance. *The Journal of Neuroscience*, 25(14):3509–3520, 2005.

[10] A.M. Swensen and B.P. Bean. Ionic mechanisms of burst firing in dissociated purkinje neurons. *Journal of Neuroscience*, 23(29):9650–9663, 2003.

[11] J. Röper and J.R. Schwarz. Heterogeneous distribution of fast and slow potassium channels in myelinated rat nerve fibres. *The Journal of Physiology*, 416:93, 1989.

[12] A. Franci, G. Drion, V. Seutin, and R. Sepulchre. A balance equation determines a switch in neuronal excitability. *PLoS Comput Biol*, 9(5):e1003040, 2013.

[13] A. Franci, G. Drion, and R. Sepulchre. Modeling the modulation of neuronal bursting: a singularity theory approach. *SIAM Journal on Applied Dynamical Systems*, 13(2):798–829, 2014.

[14] M. Golubitsky and D. G. Schaeffer. Singularities and groups in bifurcation theory. *Appl. Math. Sci*, 51, 1985.
[15] G. Drion, A. Franci, J. Dethier, and R. Sepulchre. Dynamic input conductances shape neuronal spiking. *eneuro*, 2(1), 2015.

[16] J. Keener and J. Sneyd. *Mathematical Physiology*. Springer Verlag, 2009.

[17] E. M. Izhikevich. *Dynamical systems in neuroscience*. MIT press, 2007.

[18] G. B Ermentrout and D. H. Terman. *Mathematical foundations of neuroscience*, volume 35. Springer Science & Business Media, 2010.

[19] T. R. Chay and J. Keizer. Minimal model for membrane oscillations in the pancreatic beta-cell. *Biophysical journal*, 42(2):181, 1983.

[20] Emily B Anderson, Jude F Mitchell, and John H Reynolds. Attention-dependent reductions in burstiness and action-potential height in macaque area v4. *Nature neuroscience*, 16(8):1125–1131, 2013.

[21] P.G. Kostyuk, O.A. Krishtal, and Y.A. Shakhovalov. Separation of sodium and calcium currents in the somatic membrane of mollusc neurones. with an appendix by yu a. shakhovalov. *The Journal of physiology*, 270(3):545, 1977.

[22] B. Hille. *Ion Channels of Excitable Membranes*. Sinauer Associates Inc.,U.S., 2001.

[23] J. Rinzel. Bursting oscillations in an excitable membrane model. In *Ordinary and partial differential equations*, pages 304–316. Springer, 1985.

[24] J. Rinzel. A formal classification of bursting mechanisms in excitable systems. *Mathematical topics in population biology, morphogenesis and neurosciences*, 71:267–281, 1987.

[25] J. Dethier, G. Drion, A. Franci, and R. Sepulchre. A positive feedback at the cellular level promotes robustness and modulation at the circuit level. *J Neurophysiology*, 114:2472–2484, 2015.

[26] G. Drion, J. Dethier, A. Franci, and R. Sepulchre. Cellular control of localized brain states. *Submitted*, 2017.

[27] D. Terman, J. E. Rubin, A. C. Yew, and C. J. Wilson. Activity patterns in a model for the subthalamopallidal network of the basal ganglia. *Journal of Neuroscience*, 22(7):2963–76, January 2002.
[28] Jonathan E. Rubin and David Terman. High frequency stimulation of the subthalamic nucleus eliminates pathological thalamic rhythmicity in a computational model. *Journal of Computational Neuroscience*, 16(3):211–35, January 2004.

[29] Robert J Butera, John Rinzel, and Jeffrey C Smith. Models of respiratory rhythm generation in the pre-bötzinger complex. i. bursting pacemaker neurons. *Journal of neurophysiology*, 82(1):382–397, 1999.

[30] Robert J Butera, John Rinzel, and Jeffrey C Smith. Models of respiratory rhythm generation in the pre-bötzinger complex. ii. populations of coupled pacemaker neurons. *Journal of Neurophysiology*, 82(1):398–415, 1999.

[31] Martin Pospischil, Maria Toledo-Rodriguez, Cyril Monier, Zuzanna Piwkowska, Thierry Bal, Yves Frégnac, Henry Markram, and Alain Destexhe. Minimal hodgkin–huxley type models for different classes of cortical and thalamic neurons. *Biological cybernetics*, 99(4):427–441, 2008.

[32] Maureen E Rush and John Rinzel. Analysis of bursting in a thalamic neuron model. *Biological cybernetics*, 71(4):281–291, 1994.

[33] Gregory D Smith, Charles L Cox, S Murray Sherman, and John Rinzel. Fourier analysis of sinusoidally driven thalamocortical relay neurons and a minimal integrate-and-fire-or-burst model. *Journal of Neurophysiology*, 83(1):588–610, 2000.

[34] Shigeru Kubota and Jonathan E Rubin. Nmda-induced burst firing in a model subthalamic nucleus neuron. *Journal of neurophysiology*, 106(2):527–537, 2011.

[35] D. Golomb and Y. Amitai. Propagating neuronal discharges in neocortical slices: computational and experimental study. *Journal of neurophysiology*, 78(3):1199–1211, 1997.

[36] X-J. Wang. Multiple dynamical modes of thalamic relay neurons: rhythmic bursting and intermittent phase-locking. *Neuroscience*, 59(1):21–31, 1994.

[37] D. Golomb, C. Yue, and Y. Yaari. Contribution of persistent na+ current and m-type k+ current to somatic bursting in ca1 pyramidal cells: combined experimental and modeling study. *Journal of neurophysiology*, 96(4):1912–1926, 2006.

[38] Z. Liu, J. Golowasch, E. Marder, and L.F. Abbott. A model neuron with activity-dependent conductances regulated by multiple calcium sensors. *Journal of Neuroscience*, 18(7):2309–2320, 1998.
[39] John Rinzel and Young Seek Lee. Dissection of a model for neuronal parabolic bursting. *Journal of mathematical biology*, 25(6):653–675, 1987.