Contents

From a dynamical systems perspective, bursting can arise through a variety of mechanisms, including stable limit cycles, chaotic attractors, canard-induced mixed-mode oscillations, and other complex nonlinear dynamics.

1 Conductance Based Models For Bursting Neurons

1.1 Preface

Generally, any model neuron that can spike can also burst under modeulation of time-dependent external input $I(t)$ [4] (***forced burster***, Fig. 2a). However, a neuron can also burst intrinsically under constant input due to the interplay between ionic currents mediated by ion channels present in the membrane of the neuron (***intrinsic burster***, Fig. 2b). Although it is known whether R5 neurons are intrinsic bursters or not [7], as Slow-Wave Activity (SWA) is thought to be generated at the level of R5 [7], in the current work it will be assumed, that R5 neurons exhibit bursting behavior due to intrinsic properties, rather than via time-varied external input.

Resting and spiking states, as well as transition between them can exhibit different features for different models. The examples of bursting neurons in Figures **??** and 2 illustrates the case when the resting state is a stable equilibrium and spiking state is limit cycle attractor. However, generally, the resting state can also be a limit cycle attractor (not shown here). As the eleqtro-physiological recordings of R5 neurons do not show subthreshold oscillations at resting state, this case will be omitted in this chapter. The case when the resting state is a stable equilibrium is referred to as ***'point-cycle burster'*** [3], and will be the main focus in the following. For simplicity, unless stated otherwise, this type of bursting will be referred to as 'bursting'.

1.2 Ohmic vs GHK Current

The current through an ion channel can be modelled useing either Ohm's law, or GHK current equation. Ohmic current assumes linear relationship between voltage and conductance Citation:

$$I_c(V,t) = g_c(V,t)(V - V_c) \tag{1}$$

where V is membrane potential, $g_c(V,t) = \bar{g}_c m^p(V,t)h^q(V,t)$ is conductance calculated as a product of maximal conductance and probabilities of activation (m) and inactivation (h) gates being open, V_c is reversal potential. Here, the concentration between the extracellular and intracellular ion concentrations is hidden inside V_c (see Equation **??** in Section **??** for the case when an ion channel is permeable to one ion). GHK equation on the other hand models nonlinear relationship between the variables in explicit way Citation:

$$I_c(V,t) = g_c(V,t)Pz^2\frac{VF^2}{RT}\frac{[\text{ion}]_{\text{inside}} - [\text{ion}]_{\text{outside}}\exp\left[-zFV/(RT)\right]}{1-\exp\left[-zFV/(RT)\right]} \tag{2}$$

where, P is permeability, R is the universal gas constant (8315 mJ/(K°·Mol)), T is temperature measured in Kelvin, F is Faraday's constant (96480 coulombs/Mol), z is the valence of the ion, whereas $[\text{Ion}]_{\text{in}}$ and $[\text{Ion}]_{\text{out}}$ are ion concentrations inside and outside membrane.

Equation **??** can be obtained from 2 if one considers equilibrium condition, whre the ionic current $I_c = 0$. Nernst equation assumes that ion concentrations are fixed. However, Equation 1 can be still used when ion concentration dynamics are incorporated in the model by recalculating reversal potential at each stimulation step.

For some ion channels Equation 1 is sufficient to reproduce experimentally obtained voltage-current relationships. However, for other channels Ohmic current does not provide good estimates and GHK current equation should be used to obtain better fit between experimental data and simulations Citation (see also Section ??? for *Drosophila* T-type Ca^{2+} ion channels).

1.3 Bifurcations in fast-slow subsystems

Bifurcation analysis is a powerfull tool to investigate the behavior of a dynamical system. Specifically, how given system switches between different states when one or multiple parameters (referred to as **bifurcation parameters**) are varied. As it will be evident throughout this section, the choice of the bifurcation parameter is crucial and depends on what aspects of the system one aims to investigate.

Within the framework of the fast-slow subsystems with single slow variable one can consider the slow variable as a bifurcation parameter and investigate how changing the value of that variable affects the state of the fast subsystem: for what values is the fast subsystem at rest or

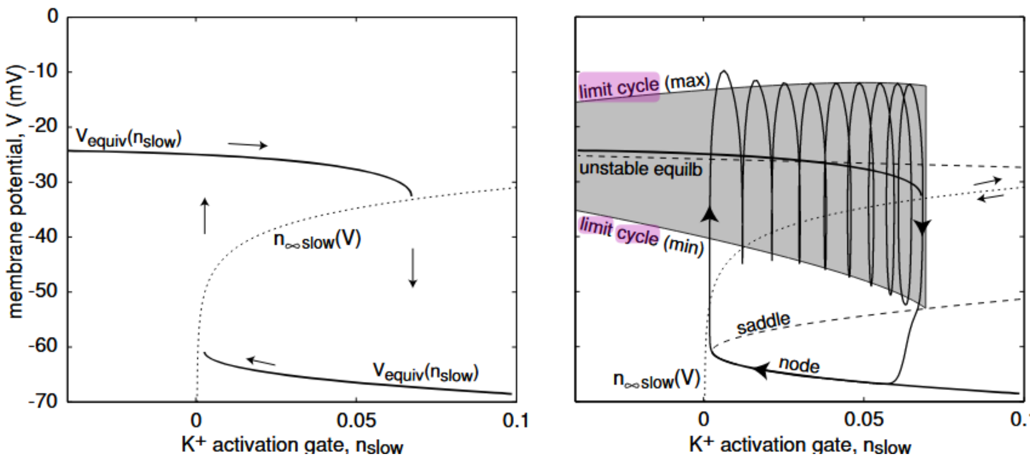


Figure 1: Exampl of fast-slow decomposition. Adapted from [4]. Text

spiking state and how does transition between these states occur. Thus, when the mechanism of bursting is investigated, one can divide the question into two parts: 1) What initiates a burst? 2) What terminates a burst? Before getting deeper into possible mechanisms and suggesting what dynamical properties R5 neurons may have, let us consider one example.

1.3.1 Equivalent voltage and example of fast-slow decomposition

1.3.2 Bifurcations of equilibria and cycles

Burst initiation is transition from resting (when the neuron does not fire action potentials) to spiking state, referred to as **bifurcation of equilibria**.

Transition between spiking to resting state is referred to as **bifurcation of cycles** [3, 4].

Bifurcation of Equilibria	Behavior	Frequency	Amplitude	Operation
Fold	bi-stable	nonzero	fixed	integrator
Saddle-node on Invariant Circle (SNIC)	excitable	zero ($\sqrt{\lambda}$)	fixed	integrator
Supercritical Hopf	excitable	nonzero	zero ($\sqrt{\lambda}$)	resonator
Subcritical Hopf	bi-stable	nonzero	arbitrary	resonator

Table 1: Bifurcations of Equilibria (adapted from [3] with modifications)

1.4 Preliminary Remarks

[2] - Example of bifurcation analysis 4+1 system

Bifurcation of Cycles	Behavior	Frequency	Amplitude
SNIC	excitable	zero ($\sqrt{\lambda}$)	fixed
Supercritical Hopf	excitable	nonzero	zero ($\sqrt{\lambda}$)
Fold Limit Cycle*	bi-stable	nonzero	arbitrary
Saddle Homoclinic Orbit	bi-stable	zero ($1/\|\ln\lambda\|$)	fixed
Saddle-Focus Homoclinic Orbit	bi-stable	zero ($1/\|\ln\lambda\|$)	fixed
Focus-Focus Homoclinic Orbit	bi-stable	zero ($1/\|\ln\lambda\|$)	fixed
Subcritical Flip**	bi-stable	nonzero	arbitrary
Subcritical Neimark-Sacker	bi-stable	nonzero	arbitrary
Blue-sky	excitable	zero ($\sqrt{\lambda}$)	fixed

Table 2: Bifurcations of Cycles (Adapted from [3] with modifications). *Also called Saddle Node of Limit Cycles; **Also called period-doubling bifurcation;

Gating mechanism - probability of ion channel to be in the open state

Bifurcation analysis helpful for: explaining why neuron stays for short period in bursting? Why it is robust to perturbations or noise?

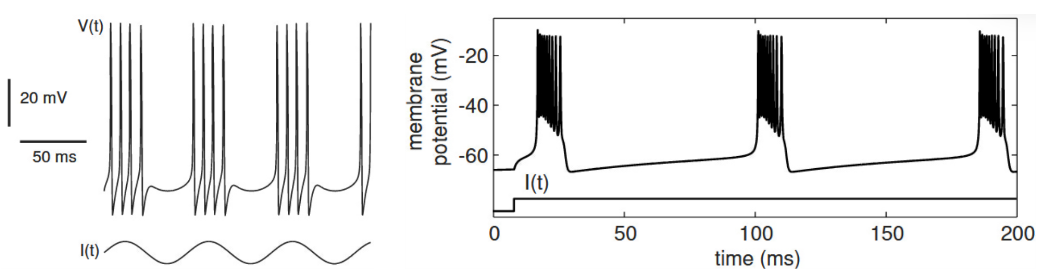
Example of transition from steady state to subthreshold oscillations with increasing currents via Hopf bifurcation [9]

Example of hopf [2]

(Okay, so, if Ca concentration affects the bursting, maybe one should model Ca dependent channels with Goldman-Hodgkin-Katz flux equation ??? It is even second argument for this equation, the first one being that the fit is better!!!) (Liu et al 2016)

Izhikevich - classification based on codimention 1 bifurcation

Write a few workds about the model in Lara's thesis -¿ it is not biologically plausible model -¿ How can it be done with more biologically plausible model? -¿ Generally, the distribuion



(b) Forced Burster (a) Intrinsic Burster

Figure 2: Forced vs intrinsically bursting neurons. Examples of model neurons bursting due to time-varied external input (a) and intrinsic properties (b). Adapted from [4], with modifications.

of ion channels is different along neuron + as it was stated in previos chapter, the soma thing. Here, for simplicity we start from the single compartment neuonal model assuming uniform distribution of the ion channels and ignoring the different compartments of the model. Maybe in the discussion write that the morphology enhances robustness (there is a paper) and maybe find some other pros for multicompartment models. Citations: Laura [5] Richards manuscript [8]

The aim of the current work is to prupose a biologically pausible model for R5 neurons to explain what is written in the previous paragraph.

Different models and approaches have been proposed to study bursting neurons.

One way to study the bursting neurons is to decompose the system into fast and slow subsystems. Here, the fast subsystem corresponds to the spiking state, whereas the slow subsystem acts as the mechanism for the transition between spiking and resting states. Furthermore, based on slow-fast system, neurons can be classified according to corresponding bifurcations of the resting/spiking states [3, 4].

Besides bursting behavior, as it was shown in section **??**, blocking sodium channels with Tetrodotoxin (TTX) resulted in oscillations with an undershoot of the membrane potential before returning to the resting state. Furthermore, the period of the oscillation was approximately three times larger than bursting frequency in the control condition.

Finally, during daytime the R5 neuron exhibited spiking behavior with a peak at 1 Hz in the power spectrum.

However, not every bursting system can be decomposed into fast and slow subsystems (see section xxx).

This chapter contains overview of the literature

Generally, transition between the states can occur in different ways. Early works of Rinzel

When one is talking about conductance based models, one shoud think of two important aspects of bursting: what are the ion channel

1. What is biological basis of the transitions?

Transition between the two states can be characterized by bifurcation and/or phase space analysis of the dynamcial system.

Class 1 for the fast subsystem [6].

Rized restimg membrane potential with T-Type knockdown: impossible unless some other mechanism is involved, or it blocks some other channels - window current of T type channel [1]. Another possibility - how resting membrane potential is defined??

- [3]
- Frequency of emerging/terminating spiking
  - Small initial frequency: circle/*
  - Small terminating frequency */circle or */Homoclinic
  - No significant change fold or andronov-hopf
  - Guckenheimer et al 1997: distinction between */circle and */homoclinic
- Amplitude of emerging/terminating spiking (?)
- Dampted oscillations at rest (?)
- Spike undershoot: not possible
- Spiking and resting:
  - Repetitive spiking in */homoclinic and */fold cycle bursting can be shut down with appropriately timed weak stimulus, however in */circle and */hopf - cannot
  - Weak stimulus can evoke repetitive spiking in fold/* and subHopf/* bursters, but not in circle/* and Hopf/*

1.5 Oscillations after TTX block

ToDo

1.6 Slow-fast decomposition

1.6.1 Ionic Basis

Somewhere should go the inssights about h-current, t-type current, etc. Maybe the last chapter, before summary??

The general idea behind the slow-fast subsystems is coexistance of spiking (fast) state modulated by the

Hysteresis loop: two states - up and down

Phantom bursting ???

1.6.2 Dynamical properties of interest

Forced burster/intrinsic burster - in any case we need similar properties

Bursting can be classified by:

- Modulation of external current
- External input
  - Tonic bursting
  - Phasic bursting
  - Rebound bursting
  - Inhibition-induced bursting

Activation of dSFB Neurons -¿ increased SWA in R5. dSFB are inhibitory...

Electrophysiological orecordings of R5 neurons in *Drsophila melanogaster* revealed

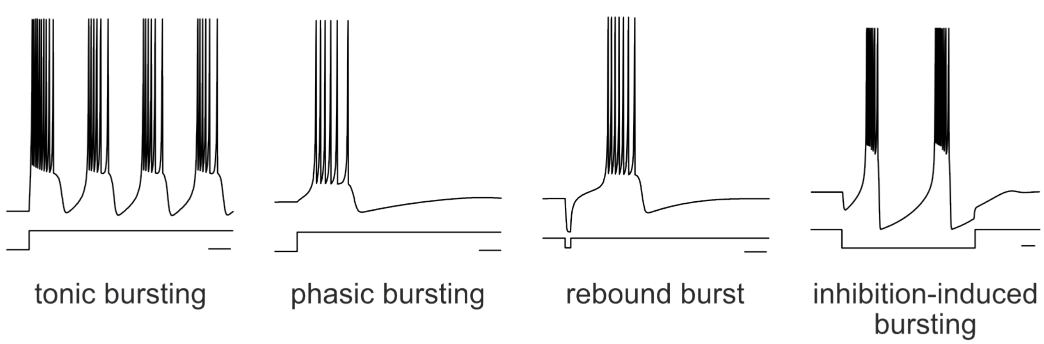


Figure 3: Classification of intrinsically bursting neurons by neuro-computational features. Adapted from [4], with modifications. Electronic version of the figure and reproduction permissions are freely available at `www.izhikevich.com`.

1.7 Phantom Bursting

The ideas behind previous sections were based on decomposition of the dynamical system into slow and fast subsystems. However, firstly, existance of such subsystemts is not a necessary condition to achieve bursting and not all bursting systems can be decomposed into slow and fast subsystems.

- Can be more than one slow variable
- More complex dynamics in the phase space
- Hedgehog limit cycles (Hedgehog limit cycle attractor)
-

1.8 Other Types of Bursting

1.9 Summary