Bursting in Neurons and Small Networks

Definition

Bursting refers to patterns of neural activity consisting of episodes of relatively fast spiking separated by intervals of quiescence. Bursting neurons are ubiquitous in the nervous system and play important roles in the production of motor, sensory, and cognitive behaviors. Because bursting is the predominant mode of activity in central pattern generator (CPG) networks that underlie rhythmic motor activity, bursting neurons have been best characterized in invertebrate CPG networks. Bursting neurons fall into two classes, based on whether bursting is an intrinsic neuronal property, resulting solely from the interaction among ionic currents, or whether it is a network property, emerging from the interaction among ionic and synaptic currents.

Detailed Description

Introduction and Background

Bursting patterns consist of episodes of relatively fast spiking (bursts) separated by intervals of either quiescence or subthreshold activity such as subthreshold oscillations (Kispersky et al. 2010; Malashchenko et al. 2011; Desroches et al. 2013). Bursting is ubiquitous in the nervous system and has been shown to play an important role in the generation of network rhythmic patterns (Nusbaum and Beenhakker 2002). Bursting neurons are of particular importance in rhythmically active CPG networks, which control the ongoing motor behaviors that underlie coordinated activity such as swimming, invertebrate heartbeat, feeding, and limbed locomotion (Friesen and Pearce 1993; Calabrese 1995; Calabrese et al. 1995; Marder and Calabrese 1996; Smarandache et al. 2009).

Extensive research into the mechanisms that generate network bursting activity and its role in motor behavior has been done in invertebrates (Calabrese 1995; Nusbaum and Beenhakker 2002; Selverston 2005). Invertebrate CPG networks are comprised of a relatively small number of neurons and, in many systems, the intrinsic properties of the participating neurons, and the network connectivity is well known. These networks produce multiple complex outputs that control similar behaviors as the much larger CPG networks of vertebrate animals (Marder and Calabrese 1996).

Bursting activity can be generated by individual neurons or through synaptic interactions within networks. Endogenous bursting in individual neurons emerges as the result of the interaction among participating ionic currents, often in the presence of tonic excitatory drive (Harris-Warrick and Flamm 1987; Guckenheimer et al. 1993). Endogenous bursting neurons are often pacemakers of the networks in which they are embedded, which rhythmically drive follower neurons (Selverston 2005). Bursting may also emerge as a network phenomenon through synaptic interactions of individual neurons that are not necessarily endogenous bursters (Selverston et al. 2009). In such networks, the rhythmic properties cannot be ascribed to any individual neuron but emerge as a result of synaptic organization. However, as described below, network bursting can also involve endogenous bursters.

While bursting is a stereotypical mode of neuronal activity, there are qualitatively different types of bursting patterns that differ not only in the bursting attributes (e.g., burst frequency, number of spikes per burst, inter-burst interval, duty cycle) but also in the mechanisms that govern their generation. These mechanisms can be investigated from two different, but complementary, perspectives: membrane biophysics and dynamics. The biophysical mechanisms involve the participating ionic and synaptic currents and neuromodulators that interact to generate bursting activity. The dynamical mechanisms involve nonlinearities, time scales, and bifurcations that govern the initiation and termination of the bursts, the duration of the inter-burst intervals, and additional properties of the bursting patterns. There is no one-to-one correspondence between these two mechanisms. In fact, different sets of ionic currents can give rise to qualitatively similar bursting patterns by the same dynamical mechanism, and, similarly, the same sets of ionic currents can give rise to different bursting patterns. This article focuses on the dynamical mechanisms of bursting and some of the biophysical mechanisms underlying the dynamical behavior.

Endogenous Bursting in Individual Neurons

Bursting patterns can be considered as bursts of spiking activity in otherwise quiescent neurons or, alternatively, as

persistent spiking which is periodically suppressed. These contrasting descriptions can be used to describe the main mechanistic features of bursting: the burst initiation and termination. Additionally, a complete description of bursting activity must include an analysis of spiking properties within a burst, in particular, what determines the intra-burst spike frequency, as well as the dynamical properties of the inter-burst intervals (IBIs).

Classification of Bursting Neurons Using Bifurcation Theory

A classification of mechanisms of spike initiation and termination has been described in terms of bifurcations of dynamical systems (Izhikevich 2000b, 2007). Bifurcations describe the qualitative structural changes in the dynamics of the system. The dynamical systems analysis of neuron and network dynamics is based on the assumption that the output of the system is the solution of a set of differential equations, based on the biophysical properties of the neurons and their synaptic connections. The number of variables in the differential equation is often referred to as the dimension of the system. From a mathematical viewpoint, these equations result in a stable solution trajectory (not necessarily solvable explicitly) that describe the time-dependent changes in the dynamical properties of the neurons, including the voltage trajectories. Using dynamical systems methods, these equations can be analyzed, often in a reduced form, by exploring the transitions between fast and slow kinetics. The resting state of a neuron, for example, may correspond to a stable equilibrium point of the dynamical systems equations. Repetitive spiking, in contrast, corresponds to a stable periodic orbit (limit cycle).

Dynamical systems often evolve in multiple time scales. For instance, the rest state of a neuron can, in a slow time scale, gradually drift to a more depolarized voltage and then suddenly transition to a spiking state. In the fast time scale, these transitions appear as sudden changes in the geometric properties of the system: a stable fixed point (rest state) suddenly changes into an unstable one, and a stable periodic orbit (spiking) appears. These transitions reflect the bifurcations of the underlying dynamical system. A thorough study of the bifurcations underlying the generation and termination of bursting activity can be found in Izhikevich (2000b).

In the classification of bursting dynamics, the underlying bifurcations of the fast dynamics can be used to describe the overall burst structure. For instance, a saddle-node (SN) bifurcation and a homoclinic (HOM) bifurcation govern burst initiation and termination, respectively, in square-wave bursters (Fig. 1). In contrast, both burst initiation and termination in parabolic bursters (Fig. 2) are governed by saddle-node on an invariant circle (SNIC) bifurcation (Rinzel and Lee 1987; Butera et al. 1996; Rinzel and Ermentrout 1998). Elliptic bursters involve a subcritical Andronov-Hopf bifurcation (sub-AH) and an SN bifurcation for burst initiation and termination, respectively (Izhikevich 2000a) (Fig. 4). To a large extent, these bifurcations also govern the dynamics of both the intra-burst spike frequency and the IBIs, for example, the shape and amplitude of spikes, spike-frequency adaptation, and bistability (Cymbalyuk et al. 2002).

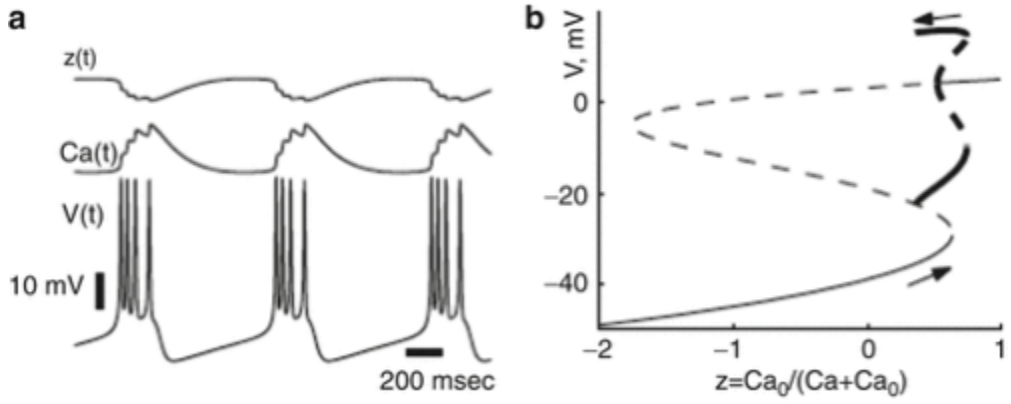

Fig. 1 Square-wave bursting in the modified Morris-Lecar model

. (a) Slow negative feedback via calcium accumulates during the burst and slowly decays during the silent phase. The slow accumulation of calcium activates $I_{K(Ca)}$, which subsequently terminates the burst. Calcium concentration is governed by $Ca' = \varepsilon(-\mu\, g_{Ca}\, m_{\infty}(V)(V - E_{Ca}))$, $Ca_0 = 10$, $\varepsilon = 0{:}005$, $\mu = 0{:}2$. (b) Bifurcation diagram showing the region of bistability and bursting. The bifurcation parameter z is a function of calcium. Arrows indicate the direction of the change in z during silent and active phases of bursting

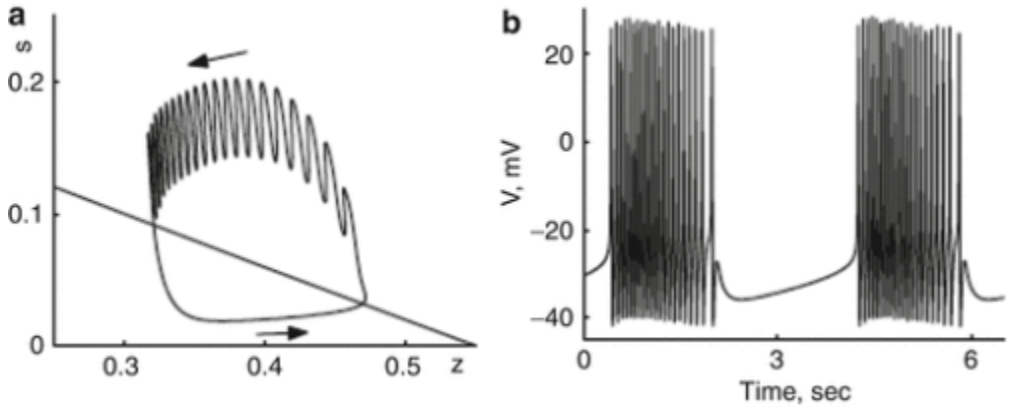

Fig. 2 Parabolic bursting in the modified Morris-Lecar model

. Model is the same as in Fig. 1 with an additional slow variable s to generate the underlying slow oscillation: $I_{Ca,s} = g_{Ca,s}(V - E_{Ca})$.

(a) Projection of the bursting trajectory onto the slow-variable plane. Direction of movement is indicated with arrows. The straight line represents the boundary between equilibria and oscillation for the fast subsystem when the slow variables are fixed; it is where the SNIC bifurcation occurs. Below the low-voltage steady state is the only fast subsystem attractor (silent phase), whereas above this curve there is an oscillation of the fast subsystem (spiking). (b) Time course of parabolic bursting

From a dynamical systems viewpoint, a simple model that is able to generate oscillatory behavior is two-dimensional and involves the interaction of voltage and a recovery variable. Voltage increases due to a positive feedback effect on a relatively fast time scale, typically generated by calcium or sodium. The recovery variable opposes the changes in voltage on a slower time scale and, in biophysical models, corresponds to a state variable of a voltage-gated ionic current such as a potassium current. Although the classical Hodgkin-Huxley model is four-dimensional (Hodgkin and Huxley 1952), the spiking behavior in this model can be reduced to a two-dimensional model (Kepler et al. 1992) without losing significant information.

A simple way to produce bursting activity in a model is to use a two-dimensional system that produces spiking and add one or two slow variables that modulate the spiking activity. The dynamical variables that make up a bursting neuron can then be separated into two subgroups: fast (if they evolve on the time scale of a spike) and slow (if they evolve on the time scale of a burst, roughly determined by the IBI), thus giving these models their name, fast-slow bursters. The bursting model can then be written in the following form:

$$X' = F(X, Y)$$

$$Y' = \mu G(X, Y),$$

where X is a vector of at least 2 fast variables for repetitive spiking. Y is a vector of slow variables that modulates fast spiking. The small parameter $\mu \ll 1$ is a ratio of fast-slow time scales. To determine the type of bursting activity that the dynamical system will exhibit, the slow variable Y is treated as a constant parameter in the fast subsystem equation $X' = F(X, Y)$. The parameter Y is used to determine the bifurcations in the geometric properties of the fast subsystem which correspond to the transitions at the burst onset and termination.

The number of slow variables necessary to produce bursting in a model neuron depends on the underlying generic burst mechanisms that involve additional specific mechanisms of burst initiation and termination. A bursting neuron can be driven by one of the two generic mechanisms: a hysteresis loop such as in the square-wave burster (Fig. 1), or a slow wave, such as in the parabolic burster (Fig. 2). Hysteresis loop refers to the existence of bistable dynamics in the fast subsystem: if the slow variables are kept fixed at a constant value (within some range), the fast subsystem will exhibit two attractors (a stable equilibrium point and a periodic orbit) simultaneously. Hysteresis-loop bursting requires only one slow variable, resulting in three total variables as a minimal model for bursting. The slow variable allows the bistable fast subsystem to transition between its two stable states in either of two ways (Rinzel and Ermentrout 1998). For example, when the trajectory is near the stable fixed point of the fast subsystem, the slow variable grows until this fixed point

becomes unstable (through a fast subsystem bifurcation) and the trajectory transitions to the stable periodic orbit. The slow variable then decays until the stable periodic orbit vanishes or becomes unstable (again through a fast subsystem bifurcation) and the trajectory transitions back to the stable fixed point and the cycle repeats.

In contrast, if the fast subsystem is monostable such as in the parabolic burster (Fig. 2), two slow variables will be necessary to generate bursting activity, resulting in a total of four variables for a minimal model of bursting. In this case, the slow subsystem requires two variables and exhibits an autonomous limit cycle attractor without feedback from voltage changes in the fast subsystem. The neuron bursts because the fast subsystem is driven periodically through SNIC bifurcations.

In what follows, we will think of a fast-slow burster as a slow system driving the fast system through various bifurcations that govern the initiation and termination of bursting activity. There are 16 possible pairs of bifurcations in hysteresis-loop bursters and 8 possible pairs of bifurcations in slow-wave bursters (Izhikevich 2000b). Each one of these bifurcations corresponds to a different topological bursting mode. Although not all these bifurcations have been found in biological neurons, this description has proved to be insightful. We discuss some of them in detail below (for additional information, see Izhikevich (2000b)).

One of the 8 slow-wave bursters can arise from a pair of SNIC bifurcations (both burst onset and termination) and is also known as the circle-circle or parabolic bursting (Fig. 2). The topological type of the hysteresis-loop burster depends on whether the fast system is close to either an SN-homoclinic orbit or a Bautin bifurcation (Figs. 3 and 4). For instance, one of the 16 possible hysteresis-loop bursters involves sub-AH/fold combination of bifurcations to obtain an elliptic burster (Figs. 4 and 5).

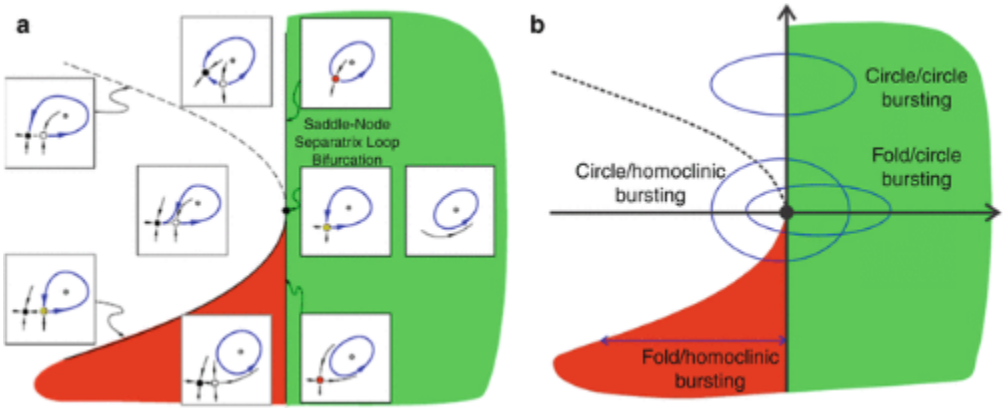

Fig. 3 Pairs of bifurcations in fast-slow hysteresis bursters with the fast subsystem near a saddle-node homoclinic orbit (SN-HOM) bifurcation

. (a) Bifurcation diagram showing changes in the geometry of the fast subsystem as parameters are varied. (b) A system near such an SN-HOM bifurcation may exhibit four different types of fast-slow bursting. Traversing from the red region to the green region leads to square-wave bursting in which burst initiation is through the fold (or SN) bifurcation and the burst termination is through a homoclinic orbit bifurcation

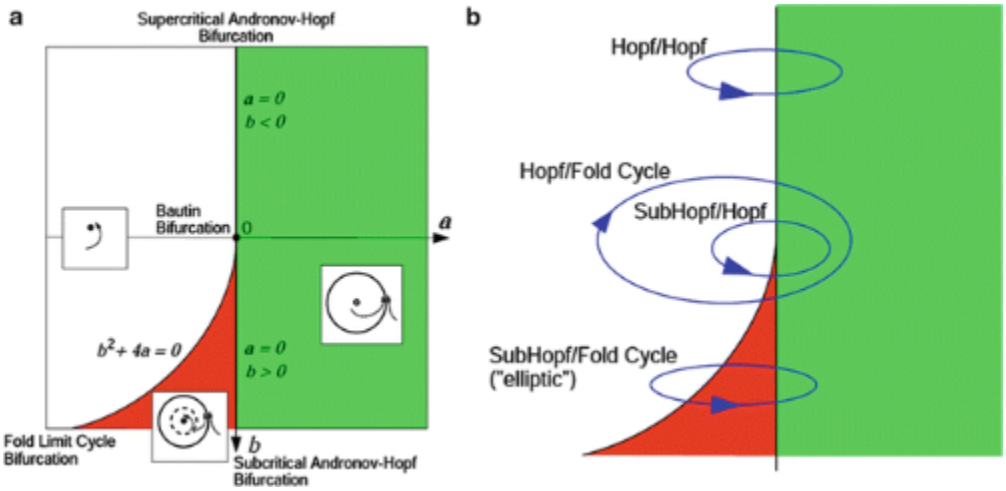

Fig. 4 Pairs of bifurcations in fast-slow hysteresis bursters with the fast subsystem near a Bautin bifurcation . (a) Bifurcation diagram showing changes in the geometry of the fast subsystem as parameters a and b in the topological normal form $z' = (a + i\omega) + bz|z|^2 - z|z|^4$ are varied. When the system is near a Bautin (or Andronov-Hopf) bifurcation it may exhibit four types of bursting when the bifurcation parameters a and b change. In the upper two quadrants, the bifurcation of the rest state takes place via the super-AH and in the lower two quadrants via the sub-AH bifurcation. (b) Four possible topological types of bursting with different bifurcations of the rest and spiking states. Traversing from the red region to the green region leads to elliptic bursting in which the burst initiation is through the sub-AH bifurcation and the burst termination is through the fold bifurcation

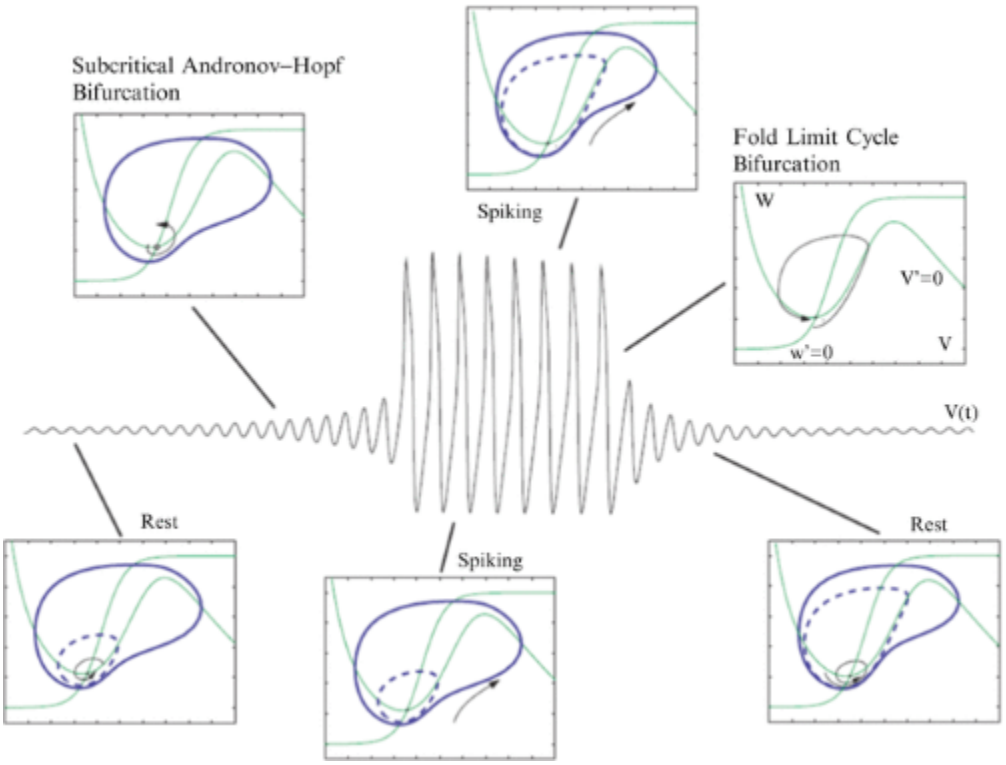

Fig. 5 Elliptic bursting in the Morris-Lecar model (variables V and w) with an additional $I_{K(Ca)}$. Green curves are nullclines $V' = 0$ and $w' = 0$ of the fast subsystem. As the neuron transitions from silence to bursting and back again, there is a clear sequence of changes in the geometry of the phase plane of the fast subsystem. These changes correspond to bifurcations. In the elliptic burster, burst initiation is through the sub-AH bifurcation, and burst termination is through the fold (or SN) bifurcation

The pairs of bifurcations that determine the initiation and termination of a burst can also be used to classify bursting neurons based on their intra-burst spike-frequency content. If the burst onset is through a SNIC bifurcation, the burst shows a progressive increase in spike frequency. If the burst termination is through a homoclinic orbit bifurcation, there is

spike-frequency adaptation (a progressive lengthening of inter-spike intervals (ISIs)) near the end of the burst. This is a prevalent feature in invertebrate bursting neurons. Guckenheimer et al. (1997) studied the scaling properties of ISIs at transitions associated with a homoclinic bifurcation corresponding to the transition from spiking to quiescence. The homoclinic orbit bifurcation results in a spike frequency that decreases as a function of the distance to the saddle. The proximity of homoclinic and a sub-AH bifurcation was used to explain the phenomenon of spike-frequency adaptation. The slow adaptation variable will cause the trajectories of the fast system to track a family of stable periodic orbits until the homoclinic bifurcation is reached, after which they become quiescent (Guckenheimer et al. 1997).

Models of Bursting Neurons

Bursting in neurons is a dynamical mechanism generated by the interplay of different types of ionic currents. There is not a one-to-one mapping between the sets of ionic currents and the stereotypical type of bursting patterns. Bursting mechanisms have been studied using biophysical (conductance-based) models, which include a detailed description of the participating currents, or reduced models, capturing stereotypical bursting patterns in a relatively simple way, but lacking any correspondence to the underlying biophysics. Below, we briefly describe these two approaches with a special emphasis on biophysical models related to invertebrate systems.

Reduced Models

The simplest mechanism to generate bursting activity consists of a sinusoidally forced integrate-and-fire (IF) model (Lapicque 1907) where the subthreshold dynamics are linear. The sinusoidal input brings voltage above threshold for a portion of its period, thus causing persistent firing during an interval within this period and silence outside it. This mechanism can be extended to include models with two- and three-dimensional linear subthreshold dynamics (with or without intrinsic subthreshold oscillations) and the quadratic integrate-and-fire models (Feng 2001). While the subthreshold dynamics in these models can be in principle connected to the biophysical properties of neurons, the spike initiation and termination mechanisms are ad hoc.

The integrate-and-fire-or-burst (IFB) (Smith et al. 2000) model is a generalization of the IF model to include an additional slow variable representing the de-inactivation of a simplified T-type calcium current (I_T) with instantaneous activation. The subthreshold dynamics are, therefore, two-dimensional. This additional current endows the model with the ability to exhibit post-inhibitory rebound (PIR). This model is able to generate bursts of activity when voltage is hyperpolarized enough to de-inactivate I_T. Since the threshold for de-inactivation is more depolarized than the resting voltage, the neuron can respond to a brief input with a burst of spikes. However, the intrinsic dynamics of the model does not produce enough hyperpolarization, and so periodic bursting requires an additional sinusoidal input current.

The FitzHugh-Rinzel (FHR) model (Rinzel 1986) is a three-dimensional generalization of the (two-dimensional) FitzHugh-Nagumo (FHN) model (Fitzhugh 1961; Nagumo et al. 1962; Fitzhugh 1969). The classical FHN forms the fast subsystem, which, to first approximation, produces oscillations when the (unstable) fixed point is located in the middle branch of the cubic V-nullcline. The transition from a stable fixed point to a stable limit cycle occurs through an Andronov-Hopf bifurcation as the tonic (DC) current is increased. In the FHR model, this control parameter is substituted by a slow variable, which governs the generation of elliptic bursting. Modifications to this model could, in principle, generate bursting activity by other mechanisms.

The Hindmarsh-Rose (HR) model (Hindmarsh and Rose 1984; Hindmarsh and Cornelius 2005) is also three-dimensional and slightly more complex than the FHR model. In contrast to the FHN model, the fast subsystem of the HR model has a quadratic recovery-like nullcline that creates extra equilibrium points. This produces bistability through proximity to a saddle-node homoclinic orbit bifurcation. A slow adaptation variable provides the necessary negative feedback to generate square-wave bursting.

Minimal (Phenomenological) Biophysical Models

The two-dimensional version of the Morris-Lecar (ML) model (Rinzel and Ermentrout 1998) describes the generation of oscillatory activity as the result of the interaction of a non-inactivating calcium current with instantaneous activation and a delayed-rectifier potassium current. The mechanisms responsible for the generation of oscillations include the Andronov-Hopf and SNIC bifurcations and depend on the parameters describing the activation/inactivation curves and voltage-dependent time scales. The parameters of the basic ML model can be adjusted to simulate the envelope of

bursting waveforms, which has been carried out in modeling the AB-PD neurons of the pyloric pacemaker in the crustacean stomatogastric ganglion (STG) (Skinner et al. 1994; Kopell et al. 1998). The substitution of a biophysical parameter (I_{app}) by a slow variable endows the ML model with the ability to generate bursting activity. One example is the bursting patterns generated by adding a calcium-activated K^+ current, $I_{K(Ca)}$:

$$I_{K(Ca)} = \overline{g}_{K(Ca)}\left(\frac{Ca^p}{Ca^p+1}\right)(V-E_K)$$

The modified ML model for bursting becomes

$$\frac{dV}{dt} = -\frac{\left(I_{Ca}+I_K+I_L+I_{K(Ca)}\right)}{C}$$

$$\frac{dw}{dt} = \frac{\lambda[w_\infty - w]}{\tau(V)}$$

$$\frac{dCa}{dt} = \varepsilon(-\mu I_{Ca} - Ca)$$

As the calcium concentration varies, the system may become bistable so that the fast subsystem can periodically switch back and forth between repetitive spiking and resting, thus producing bursting. The modified ML model is able to produce either square-wave or elliptic bursting patterns by changing parameter values that alters the type of bistability in the fast subsystem. Burst initiation by a sub-AH bifurcation produces an elliptic burster, whereas burst initiation by a saddle-node bifurcation produces a square-wave burster. To obtain the slow-wave oscillation underlying parabolic bursting in the ML model, the addition of one more variable is required to provide a slow positive feedback that counteracts the slow negative feedback of $I_{K(Ca)}$.

Biophysical Properties of Bursting Neurons

Bursting in neurons arises from a complex interaction between many ionic currents, where the actual ionic mechanisms may vary between different bursting neuron types. In most cases, bursting oscillations involve the presence of a slow inward ionic current. The current-voltage (IV) relationship of this inward current includes a negative slope region and results in an inverted bell-shaped structure which allows the inward current to become active regeneratively. Such currents include the persistent Na^+ current (I Nap) and low-threshold inactivating calcium currents (I_{Ca}). Such currents can work together with other currents such as the slow calcium-activated nonselective cation current (I CAN) and the hyperpolarization-activated inward current (I_h) to depolarize the membrane potential and produce a burst of action potentials. The activation of these inward currents, which leads to a burst of spikes, is counteracted by the slow activation of voltage- and calcium-dependent outward currents which terminate the burst. Moreover, some inward currents, such as the T-type calcium current, inactivate upon depolarization of the membrane potential, and this inactivation may also contribute to the termination of the burst.

Often neurons that do not burst in isolation can produce bursting activity in a network (as described in the next section). The pyloric network LP neuron does not burst endogenously but, in response to inhibitory input, can produce post-inhibitory rebound and plateau potentials that support a burst of action potentials. These properties were described in detailed biophysical models of this neuron, first in a single-compartment model (Buchholtz et al. 1992; Golowasch et al. 1992) and, more recently, in a multi-compartment model that was used to explore how different ionic conductance levels can produce similar bursting output in this neuron (Taylor et al. 2009). In the biological network, the LP neuron receives periodic inhibition from the pacemaker neurons AB and PD which result in the production of bursting activity out of phase with the pacemaker bursts. Plateau potential generation is supported by a similar set of ionic currents as those that

underlie bursting activity. For example, the low-threshold slowly inactivating I_{Ca} is substantially inactive at rest, but inactivation can be removed upon inhibitory input, thus promoting the plateau potential, often together with a burst of spikes. Zhang et al. (1995) showed that, in the dorsal gastric (DG) motor neuron of the STG, I_{CAN}, which is activated by calcium but is carried by Na^+ and K^+, can underlie the plateau potential that results in a long after-depolarization and contributes to burst firing. The current usually acts alongside a low-threshold I_{Ca}, and the dynamical interaction can cause a strong regenerative current that supports plateau potentials.

The pacemaker AB neuron of the crustacean pyloric network is an endogenous burster whose bursting activity depends on the presence of extrinsic neuromodulatory inputs (Hooper and Marder 1987). Early attempts to dissect the ionic mechanism underlying endogenous bursting involved a plateau potential which is initiated and maintained by I_{Nap} and I_{Ca} and terminated by $I_{K(Ca)}$ (Gola and Selverston 1981). Burst frequency in AB is strongly dependent on calcium entry because burst frequency decreases with calcium entry and higher calcium entry results in a larger potassium-mediated post-burst hyperpolarization. The AB neuron employs different mechanisms for bursting under a variety of modulatory conditions (Harris-Warrick and Flamm 1987). A modeling analysis of the AB neuron bursting activity examined the mechanisms that generate and control bursting in this neuron and its electrically coupled partner, the PD neuron (Soto-Trevino et al. 2005). This model demonstrated that the bursting in the AB neuron was crucially dependent on the modulator-activated inward current I_{MI}, and, as discussed in the next section, the PD neuron greatly influences the duty cycle and dynamical range of bursting frequency in the pacemaker group.

Bursting can also occur solely due to the slow inactivation of I_{Ca} without the need for bistability. Two examples of ionic mechanisms underlying burst firing are the R15 neuron, located in the abdominal ganglion of the mollusk Aplysia californica, and the lobster cardiac ganglion interneurons. The essential ingredients for bursting in the R15 neuron are the negative slope region of I_{Ca} that determines the burst onset, together with the calcium-dependent inactivation of this current, which terminates the burst (Adams and Levitan 1985; Kramer and Zucker 1985). A biophysical model of the R15 neuron showed that $I_{K(Ca)}$ and I CAN are not necessary for producing the parabolic-like bursting in this neuron (Canavier et al. 1991). This modeling study also demonstrated the presence of slow oscillations in the absence of action potentials, supporting the parabolic structure (Fig. 2) of the bursting. The parabolic nature of the R15 bursting was further supported by the nonuniform intra-burst spike frequency, even in the absence of $I_{K(Ca)}$. Similar to the R15 neuron, the lobster cardiac ganglion interneurons respond to a steady depolarizing input with slow-wave oscillations called driver potentials. These driver potentials are mediated by slow activation and calcium-dependent inactivation of an I_{Ca} (Tazaki and Cooke 1990).

Bursting in Networks of Neurons

Principles Underlying Rhythmic Bursting in Networks

CPG oscillations can arise either from pacemaker neuron activity or as a network property. In pacemaker-driven networks, one or more neurons can be identified that produce bursting oscillations even when synaptically isolated from the network. The rhythm generated by these pacemaker neurons is then propagated to the network through synaptic interactions. In pacemaker-driven networks, the properties of the pacemaker neurons are the primary determinant of the rhythm frequency. In contrast to pacemaker-driven CPG networks, in other CPG networks, the rhythmic pattern generation is controlled by subnetworks of neurons and thus emerges as a network property. Although network-driven CPGs may also include endogenously bursting neurons, the network frequency in these CPGs is primarily determined by parameters that control the activity of the rhythm-generating subnetwork.

Half-Center Oscillators

Early studies of locomotion in cats by Graham Brown led him to suggest that the alternating activity of flexor and extensor muscles is controlled by a network of two neuron populations in the spinal cord, each of which inhibits the other to produce antiphase alternating activity. He termed these putative central networks that produce antiphase motor activity half-center oscillators (HCOs) (Graham Brown 1911). Later studies have found reciprocal inhibition to be a prevalent feature of CPG networks in both vertebrates and invertebrates (Marder and Calabrese 1996). In invertebrate CPGs,

HCOs are often comprised of two neurons coupled through reciprocal inhibition. The two-cell HCOs provide the simplest network mechanism that is capable of generating stable bursts of alternating activity. Alternating bursting oscillations can arise in HCOs as an emergent network property even when the individual component neurons are not oscillatory (Wang and Rinzel 1992). When the HCO is composed of endogenous bursting neurons, mutual inhibition acts to stabilize the burst period, and bursting occurs over a much wider range of biophysical parameters (Cymbalyuk et al. 2002). Examples of CPG networks whose rhythm-generating mechanism involves HCOs include the CPGs that control leech swimming and heartbeat (segmental oscillators), the crustacean gastric mill network, and the swim networks in lamprey and the gastropod mollusk Tritonia.

Antiphase patterns in HCOs can be generated by various mechanisms that have been classified according to whether intrinsic or synaptic properties are involved and whether the inhibited cell transitions to the bursting regime before or after the termination of inhibition by the other cell. The terms intrinsic release/escape and synaptic release/escape (Wang and Rinzel 1992; Skinner et al. 1994) have been used to describe these mechanisms. Intrinsic release refers to the inhibited cell initiating a burst only when the free cell reaches the end of its burst and turns off inhibition. Intrinsic escape refers to the inhibited neuron generating a burst while it is still inhibited and subsequently shutting off the free neuron. Post-inhibitory rebound (PIR) has been shown to initiate the inhibited cell burst when the neuron is non-oscillatory (Wang and Rinzel 1992), although it has also been shown that a PIR-like current is not required to generate oscillations in HCOs composed of non-oscillatory neurons (Skinner et al. 1994). Synaptic release refers to the free neuron membrane potential falling below the synaptic threshold, thereby allowing the inhibited neuron to transition to a burst. In contrast, synaptic escape refers to the inhibited cell membrane potential depolarizing and crossing a (low) synaptic threshold, thereby inhibiting the free cell. The description of these mechanisms assumes rather restrictive conditions: (i) synapses with well-defined synaptic thresholds and no dynamics and (ii) HCOs that are active in the relaxation regime (very fast transitions for burst onset and termination). When these conditions are relaxed, antiphase patterns may emerge as a result of combinations of escape and release such as in the HCO of the leech heartbeat timing network (Nadim et al. 1995a).

The Role of Electrical Coupling

Computational studies of electrical coupling have provided much insight into the role of gap junctions in networks especially because an inability to cleanly block gap junctions has led to a paucity of experimental data. Electrical coupling is known to promote synchrony in a network. However, more complex and nonintuitive behaviors can arise from electrically coupled networks (Sherman and Rinzel 1992; Chow and Kopell 2000). Electrical coupling between an oscillatory and a bistable neuron can result in a wide variety of behaviors that depend on both the intrinsic biophysical properties and the coupling strengths (Sherman and Rinzel 1992; Kopell et al. 1998). Weak coupling between two identical neurons can induce antiphase oscillation, which extends far beyond the parameter range for oscillation in single neurons, thus making for a more robust oscillator (Sherman and Rinzel 1992). Electrical coupling can also produce oscillatory activity when neurons that are silent in isolation are coupled through gap junctions (Sherman and Rinzel 1992; Manor et al. 1997).

The properties of a non-oscillatory neuron can regulate features such as frequency and amplitude of a bursting neuron to which it is electrically coupled. However, the influence of a non-oscillatory through gap junctions on oscillations of a bursting neuron can be nonintuitive (Kepler et al. 1990). Kepler et al examined the effect of the PD neuron on the bursting activity of the AB neuron and showed that the electrical coupling between these neurons can serve to either increase or decrease the oscillation frequency depending on the voltage waveform of the bursting AB neuron. This effect was further explored through a mathematical analysis of the effect of a bistable neuron coupled to an oscillatory neuron which showed how the network frequency is influenced by the relative voltages of the bistable neuron compared to the voltage range of oscillations in the oscillatory neuron. This influence is dependent on the strength of coupling in a nonlinear manner (Kopell et al. 1998). Using ML neurons in the relaxation-oscillation regime, the authors showed how the electrical coupling can "pin" the voltage trajectory to the low or high branches of the voltage nullcline than compared to the uncoupled oscillator, thus changing the frequency and shape of the oscillations. Unexpectedly, a coupling with higher strength may not necessarily be more effective at influencing the frequency.

The effect of electrical coupling has also been investigated in biophysically realistic model neurons. In the STG pyloric network, for example, electrical coupling between the AB and PD pacemaker neurons causes these neurons to fire in synchrony. Of the two, AB is the only neuron that is capable of endogenous bursting. These two neurons, by virtue of their electrical coupling, fire burst in phase over a wide range of frequencies (Soto-Trevino et al. 2005). The frequency of

the isolated AB neuron can be greater than 2 Hz but limited to 1 Hz in the intact network, i.e., when coupled to the PD neuron (Hooper and Marder 1987). Previous modeling work using reduced models had suggested that the role of the PD neuron in this coupled pair is to regulate the network frequency (Hooper and Marder 1987; Kepler et al. 1990; Abbott et al. 1991). The Soto-Trevino et al. multi-compartment model of the AB-PD pacemaker ensemble demonstrated that increasing the coupling strength caused the slow-wave oscillation and spikes to become near synchronized (Soto-Trevino et al. 2005). For large coupling strengths, the non-oscillatory PD neuron transitioned from tonic spiking to large-amplitude bursting. Coupling of the PD to the AB neuron also increased the frequency of AB oscillation compared to the isolated AB frequency. Thus, the network possesses a way to regulate bursting oscillations that is anatomically separate from the mechanism of the generation of the bursting.

Segmented Networks of Bursting Neurons

In segmented animals, locomotion and other motor functions often require that the movement of different body parts maintain a constant phase relative to adjacent parts, despite changes in frequency. In crayfish and leech, swimming is controlled by the coordinated bursting activity of distributed CPGs in which the undulatory movements appear as a traveling wave. This traveling wave is generated by segmental oscillators with intersegmental phase lags. The neural basis that accounts for the stable intersegmental phase differences has been modeled as linear chains of weakly coupled oscillators (Friesen and Pearce 1993; Skinner et al. 1997; Jones et al. 2003).

The crayfish swimmeret system is a good example of intersegmental coordination. The bursting activity that drives the alternating power and return strokes of individual swimmerets on each segment is driven by a local CPG module. Bursts of impulses in coordinating interneurons control the relative timings of intersegmental bursts and result in a very stable anterior-to-posterior phase progression of bursts that differ in phase by about 90° between adjacent segments (Smarandache et al. 2009; Mulloney and Smarandache 2010).

Swimming in the leech is also involves intersegmental coordination and is characterized by a wave that travels rostro-caudally along the animal. The crests and troughs are produced by antiphase contractions in dorsal and ventral longitudinal muscles in body wall segments. Intersegmental phase lag in body movement is stable at ~20° (Friesen and Pearce 1993). Phase differences are also observed between segmental oscillators in the timing network of the leech heartbeat CPG.

The leech heartbeat pattern is bilaterally asymmetric: on one side, a rostro-caudal wave of muscle contractions causes the peristaltic flow of blood through the heart tube, whereas, on the contralateral side, all segments contract in synchrony. This asymmetric activity switches after 20-50 cycles. Rhythmic activity of the leech heartbeat CPG arises independently in pairs of HCOs located in the third and fourth ganglia (Nadim et al. 1995b; Hill et al. 2002). Rhythmic bursting arises from mutual inhibitory connections between two such neurons. These rhythm-generating subnetworks are coupled via coordinating interneurons from other segmental ganglia to produce a stable phase difference in the range 15-20 % (Hill et al. 2002).

The theory of weakly coupled oscillators (Schwemmer and Lewis 2012) has been used to understand intersegmental coordination. This theory is used to predict phase differences between segmental oscillators under a mathematically described assumption of weak coupling. A chain of such oscillators with nearest-neighbor coupling can support a constant-speed traveling wave. The weak coupling implies that the intrinsic dynamics are dominant, so that the perturbed system remains close to the limit cycle and the coupling only affects the speed with which the neuron moves around its limit cycle. This limit cycle represents the oscillatory spiking activity in the case of a tonic spiking neuron or the slow-wave oscillations in the case of a bursting neuron (as in Jones et al. 2003). The dynamics of each neuron can be reduced to a single-phase equation that describes the phase of the neuron in the limit cycle. This allows for the construction of phase models to investigate the pattern of timings of individual elements in a network and the collective properties of the system.

The key to reducing a high-dimensional model and exploiting the form of the phase equations is the computation of the phase interaction function H (Ermentrout and Kopell 1991; Schwemmer and Lewis 2012), which reduces the interaction between the oscillators to a function of their phase difference $\Delta\varphi$. Methods of singular perturbation theory can often be used as an approach for deriving the interaction function H (Hoppensteadt and Izhikevich 1997). The essential step in deriving H is the infinitesimal phase response curve (iPRC) and its relation to the solution to the adjoint equation. The iPRC quantifies the normalized shift due to an infinitesimally small perturbation delivered at any given phase on the limit cycle so that the oscillator responds in a linear fashion.

In the crayfish swimmeret system, the coupling functions H have been approximated experimentally to understand how multiple oscillator elements coordinate their activity to produce wavelike activity representative of swimmeret locomotion

(Skinner et al. 1997; Jones et al. 2003). In this case, the iPRC was used to approximate the H function and the zeroes of the G function coupling two modules for a model containing two ascending and one descending connection predicted a stable phase difference of 90°. A good agreement with the experimental data showed that the effects of both excitatory and inhibitory ascending connections combine to promote a Stable 90° phase lag between power stroke neuron bursts in neighboring ganglia.

Different strategies are used to achieve the appropriate phase differences between neighboring segments. Phase differences generated by asymmetries in the coupling between segmental oscillators, where ascending and descending interneurons vary in strength and sign (Skinner and Mulloney 1998; Smarandache et al. 2009). On the other hand, the excitability gradient hypothesis states that phase differences arise from the intrinsic frequency or excitability differences between segmental oscillators (Grillner et al. 1993). In the crayfish swimmeret CPG, stable phase differences arise due to the combined effect of excitation and inhibition from ascending and descending coordinating neurons (Jones et al. 2003). In contrast, in the leech heartbeat timing network, a stable phase difference seems to arise from coupling between segmental oscillators of different inherent frequencies. When two segmental oscillators with different intrinsic frequencies were coupled in a model network, the faster one dominated the network frequency and led in phase. The phase difference was directly correlated with the difference in periods (Hill et al. 2002). This phase difference arises because the faster segmental oscillator bursts before the slower one and thereby terminates the activity of the shared coordinating interneuron. There is a brief time in each cycle when the slower segmental oscillator is relieved of inhibition from coordinating interneurons before the faster segmental oscillator ends its burst. Thus, the slow segmental oscillator can be entrained by the fast segmental oscillator through the indirect action of the coordinating interneuron.

Summary

Bursting is a ubiquitous property of neurons in many systems. Bursting in single neurons often results from the interaction of voltage-gated ion channels at various time scales. Bursting can be modeled at different levels of complexity, from abstract reduced models to minimal two- and three-dimensional models and biophysical realistic conductance-based models, often with good agreement with the experimental activity. A bursting neuron is often described by a system of ordinary differential equations operating at two different time scales, also called fast-slow bursters. The different types of bursting in such systems have been classified according to dynamical systems theory in terms of the transitions between the silent and spiking states. The hysteresis-loop bursting is the simplest form of bursting that requires only one slow variable in addition to the fast subsystem that can operate in two stable states: quiescent or tonic spiking. On the other hand, without such fast bistable dynamics, the slow-wave oscillation must be generated independent of the fast spiking and requires at least two slow variables. The classification of different bursting mechanisms is usually done by describing the transitions between the silent and active phases of bursting using bifurcation theory analysis of dynamical systems.

Many oscillatory networks include bursting neurons that are not endogenous bursters. These neurons respond to synaptic input with bursts of spikes that are generated by the activation of regenerative or hyperpolarization-activated inward currents. Even in a two-cell network, the coupling of a bursting neuron to a non-oscillatory neuron can result in phase-locked bursting. In this case, the properties of the non-oscillatory neuron can influence the network frequency and the oscillation amplitude, often in unexpected ways. Electrical coupling of a non-oscillatory neuron to a bursting neuron, for example, can lead to faster or slower bursting oscillations. On the other hand, reciprocally inhibitory coupling can lead to either alternating or synchronized oscillations. In larger networks of bursting neurons, such as those involved in the control of locomotion, the oscillatory activity can be analyzed as a chain of coupled oscillators. These oscillators often represent the bursting activity of the locomotor networks as recorded from the segments of the spinal cord. The theory of weakly coupled oscillators provides a powerful tool for the understanding of how phase-locked oscillations arise in chains of segmental oscillators and can be used to predict which cellular or synaptic parameters control the frequency of the network and the relative phase of the segmental oscillators.

Cross-References

Bifurcations Dynamics of Single Neurons and Small Networks

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Bursting in Neurons and Small Networks

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