How a neuron model can demonstrate co-existence of tonic spiking and bursting?

Andrey Shilnikov,

Department of Mathematics and Statistics
Georgia State University, Atlanta, GA 30303

Ronald L. Calabrese and

Department of Biology, Emory University, Atlanta, GA 30322

Gennady Cymbalyuk

Department of Physics and Astronomy ,
Georgia State University, Atlanta, GA 30303

Abstract

Tonically spiking as well as bursting neurons are frequently observed in electrophysiological experiments. The theory of slow-fast dynamical systems can describe basic scenarios of how these regimes of activity can be generated and transitions between them can be made. Here we demonstrate that a bifurcation of a codimension one can explain a transition between tonic spiking behavior and bursting behavior. The bifurcation of a saddle-node periodic orbit with non-central homoclinics [10] is behind the phenomena of bi-stability observed in a Hodgkin-Huxley type neuron model. This model can exhibit two coexisting types of oscillations: tonic spiking and bursting.

Key words: Bi-stability, bifurcations, medicinal leech, saddle-node, homoclnics

Neurons are observed in one of three fundamental, generally defined modes: silence, tonic spiking and bursting. The functional role of bursting has been actively discussed in recent theoretical and experimental studies. There is agreement that it is an important mode for control of rhythmic movements and is frequently observed in central pattern generators, neuronal networks controlling motor behavior [12]. Also, bursting has been widely observed in sleep and pathological brain states [17]. More recently bursting has begun to be identified with other functions. It has been proposed to improve reliability of memory formation [9]. The co-existence of bursting tonic spiking modes and of different bursting modes with each other has been observed in modeling [2,3,5] and experimental [7,8,19] studies and this complexity adds potential flexibility to the nervous system. Such multistability may be controlled by

neuromodulators and thus reflect the functional state of the nervous system. Multistability has many potential implications for dynamical memory and information processing in a neuron [3,19,11]. A mathematical model of a single neuron may demonstrate similar regimes, and variations of certain biophysical parameters in the model can cause transitions between these regimes. These regimes co-exist in certain parameter ranges depending on initial conditions or perturbation. Bursting behavior is well described and has been classified within a framework of the methods of qualitative theory of slow-fast systems; see comprehensive reviews in [14]. Of special interest here are various mechanisms for chaotic bursting analyzed in detail in [18,20], which occur in transitions from the regime of continuous spikes to bursting. Here we report a distinct case in which the bifurcation behind the transition from tonic spiking into bursting is homoclinic but involves a saddle-node periodic orbit instead of saddle equilibria. We refer to identified oscillator interneurons that are part of the leech heartbeat central pattern generator. When isolated pharmacologically from the rest of the network these neurons show autonomous bursting behavior [5]. In these neurons, eight voltage dependent ionic currents have been identified and characterized, see [13,6] and references therein. Classified by their ionic specificity, these currents are two sodium currents, a fast sodium current (I_{Na}) and a persistent sodium current (I_{NaP}); three potassium currents, a delayed rectifier-like potassium current (I_{K1}), a persistent potassium current (I_{K2}) and a fast transient potassium (I_{KA}); two low-threshold calcium currents, one rapidly (I_{CaF}) and one slowly inactivating (I_{CaS}) and a hyperpolarization-activated current (I_h). A canonical model of a single neuron has been constructed and tuned to reproduce experimentally observed behaviors [5,6]. As alluded to above a comprehensive analysis of this model would be quite difficult. Blockade of groups of currents in living heart interneurons simplifies neuronal dynamics, and elicit characteristic behaviors, like that observed under blockade of Ca^{2+} currents. In leech neurons, application of divalent ions like Co^{2+}, which block Ca^{2+} currents, along with partial block of outward currents, elicit slow plateau-like oscillations with up to $60s$ period and up to 20 second plateau duration [1,13]. This phenomenon persists after a blockade of I_h, [13].

Previously, in our modeling studies [4] we addressed the question of how these slow temporal characteristics are produced by a system with dynamics based on much faster time scales (time constants of the ionic currents involved do not exceed one second). We derived a simplified neuron model taking into account that the experimental conditions eliminated or reduced the contribution of certain currents into the dynamics of the neuron. This simplified model can produce slow plateau-like oscillations with a sufficiently long plateau phase. To bring the canonical model developed in [6] in accordance with the experimental conditions described above we remove from the model the equations and terms describing blocked currents: I_{CaF}, I_{CaS}, and I_h. For simplicity, we assume that the partial block of outward currents completely removes I_{K1} and I_{KA}, whereas it reduces I_{K2}. I_{NaP} is removed for simplicity. Here we employ the model described in [4]. In terms of dynamical systems, co-existence of tonic spiking and bursting corresponds to the co-existence of two distinct attractors in the phase space of the system. Here we describe a codimension-one bifurcation of a saddle-node periodic orbit with noncentral homoclinics, which explains this phenomenon. We present a mechanism for this type of bi-stability in a general slow-fast 3D system, as well as provide a qualitative understanding for how either attractor can be observed by varying initial conditions. Our analysis explains also a smooth transition between the regimes. Furthermore, through the analysis we
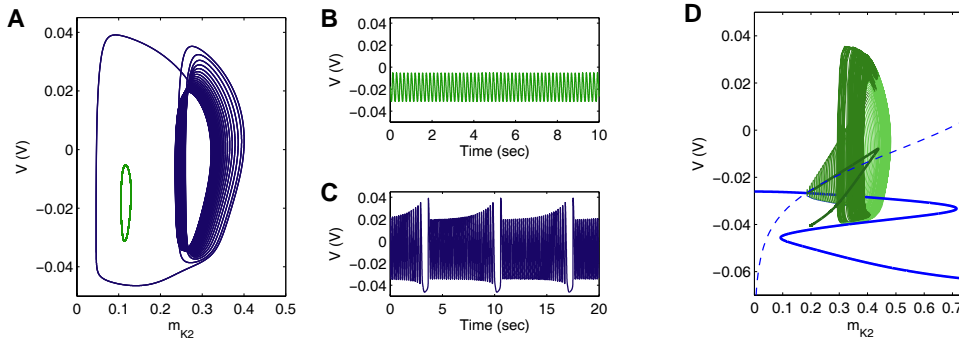
2

Fig. 1. Co-existence of spiking and bursting modes in the model in the (V, m_{K2})-projection at the control parameter $V_{h_{1/2}} = 0.03367$ V. The small round periodic orbit in A corresponds to the tonic-spikes shown in B; the larger complex orbit in A corresponds to the bursting cycle shown in C. The topology of this bursting cycle (B) is illustrated in Figs 2 below. (D) Slow motion surface found through continuation of the periodic orbits translated by the nullcline $\langle \dot{m}_{K2} \rangle = 0$ (shown dashed). The curve that originates at the Andronov-Hopf bifurcation and terminates at the homoclinic one is the averaged coordinate $\langle V \rangle$ on the periodic orbit vs. $\langle m_{K2} \rangle$. To make it visible the part of the surface adjoining the homoclinic point is not graphed.

identify physiologically plausible parameters that can control the duration of the burst phase and the number of spikes in a burst. Our results present feasible predictions for experimental studies. We construct a prototype dynamical system with bifurcation features essential for the phenomenon of bi-stability of tonic spiking and bursting. We show that the bifurcations in our biophysically realistic model are analogous to those in a generic slow-fast $3D$ system of ODEs written in the form:

$$\dot{\mathbf{x}} = F(\mathbf{x}, \alpha) - z, \quad \dot{z} = \mu G(\mathbf{x}, z, \alpha), \tag{1}$$

where $\mathbf{x} = (x, y)$ and z are phase space variables, α is a vector of control parameters, and $0 < \mu << 1$. The function $G(\mathbf{x}, z, \alpha)$ is supposed to be linear in $\mathbf{x}$, and smooth in z. The first restriction is not essential for our analysis and is introduced only for sake of simplicity. At $\mu = 0$, the *fast* subsystem decouples from the second *slow* one. In this case, the slow variable z becomes a parameter in the fast subsystem. As for the function F, we will require some typical assumptions, like enough smoothness; its essential properties are illustrated in Fig. 2. First, it ensures that the fast subsystem has either one or three equilibrium states, depending on z. The branch M_{eq} of the equilibria curve for the fast subsystem has a distinctive Z-shape in its projection onto the (z, x)-phase plane. Its equation is given by $z = F(\mathbf{x}, \alpha)$. The two turning points of M_{eq}, at z_{SN} and z_{SN}^*, correspond to the saddle-node bifurcations in the fast subsystem where two equilibrium states coalesce forming a double one. Thus the fast subsystem has three equilibria within the interval $z_{SN} < z < z_{SN}^*$. The middle branch of M_{eq} is comprised of saddle points. The upper branch of M_{eq}, when stable, corresponds to a depolarized state of the model, whereas the lower one corresponds to a hyperpolarized state. The stable focus on the upper branch M_{eq} is presumed to become unstable through the supercritical Andronov-Hopf bifurcation at $z = z_{AH}$. This means that the stability of the upper branch of M_{eq} will be imparted, as z increases, onto the parabolic-like surface M_{lc} composed of limit cycles of the fast subsystem. As z increases further, the forthcoming evolution of the stable limit cycle can follow either of two potential scenarios. In the first case, the stable limit cycle is terminated at the homoclinic bifurcation at some z_H when the saddle point on the middle

3

branch of M_{eq} has a homoclinic orbit. In addition the saddle value which is the sum of the two characteristic exponents at the saddle point has to be negative. This means that the stable periodic obit may merge into the homoclinic loop. In the second case, which is realized in the considered model, a homoclinic bifurcation also occurs, but the saddle value is *positive*. This means that the unstable limit cycle bifurcates from the homoclinic orbit as z goes through z_H. As z grows further, the stable and the unstable limit cycles get closer, and they merge into a double limit cycle at some z_{SN}^{lc}. This is a saddle-node bifurcation for limit cycles in the fast subsystem. After z_{SN}^{lc} is passed there exists no limit cycle. This scenario makes the surface M_{lc} look like as being turned inside out, compare Figs. 1(b) and 2. After the stable limit cycle disappears for $z > z_{sn}^{lc}$, a nearby phase point moves to another attractor. Such an attractor is a stable equilibrium state on the lower branch of the curve M_{eq}. Now if the parameter z is decreased the phase point will follow the lower branch towards the saddle-node bifurcation at z_{SN}. Then the steady state attractor disappears and the phase point jumps to the stable limit cycle on M_{lc}. Now that we have described the bifurcation structure of the fast subsystem, let us consider the complete 3D system when $\mu \neq 0$. It follows from the work by Fenichel that when $0 < \mu \ll 1$, the manifold M_{eq}, whenever it is hyperbolic (i.g. far from bifurcations), will persist in the form of some μ-close invariant manifold in the singulary perturbed system. Introduce a nullcline $G(\mathbf{x}, z, \alpha) = 0$ on which the z-variable does not change, i.e. $\dot{z} = 0$, see Fig. 2. Below $G(\mathbf{x}, z, \alpha) = 0$ the time derivative $\dot{z}$ is negative, while $\dot{z} > 0$ on upper branch of M_{eq} and the surface M_{lc}. If the above conditions are fulfilled, then the phase point of the 3D system will behave as follows. It drifts slowly along the lower branch of M_{eq} leftward till the fold. Then it makes a rapid jump up onto the perturbed surface M_{lc}. Afterwards, it drifts slowly rightward in circular motion around M_{lc}. After its z-component passes through the critical value z_{sn}^{lc}, the phase point falls down onto the lower branch M_{eq}, and the cycle starts over again. Such behavior of a trajectory is associated with bursting in neuron models. The number of spikes in a burst is a number of complete revolutions around M_{lc}. A point where the null-cline crosses M_{eq} is an equilibrium point in the singularly perturbed system. The coordinates of this point can be found from the system $G(\mathbf{x}, z, \alpha) = 0$ and $F(\mathbf{x}, \alpha) - z = 0$. We presume that null-cline $\dot{z} = 0$ crosses M_{eq} just once where M_{eq} represents unstable equilibria.

Let us first discuss the behavior of the trajectories near the surface M_{lc} in the singularly perturbed system. By construction, the outer surface M_{lc}^s is spanned by the stable limit cycles of the fast system at $\mu = 0$. Define the average value $\langle \mathbf{x} \rangle$ on a such limit cycle $\varphi(t; z, \alpha)$ over its period T for a given value of z as follows: $\langle \mathbf{x} \rangle (z, \alpha) = \frac{1}{T(z,\alpha)} \int\limits_{0}^{T(z,\alpha)} F(\varphi(t; z, \alpha), z) dt$. By the construction, the curve $\langle \mathbf{x} \rangle (z)$ originates from the Andronov-Hopf bifurcation at z_{AH} and terminates at the homoclinic bifurcation at z_{sn}^{lc} as described above. Note that the curve has a distinctive fold where the stable and unstable limit cycles coalesce (Fig. 2). Thus, in terms of the Pontryagin averaged fast subsystem, its equilibrium state corresponds to a limit cycle in the fast subsystem and the fold corresponds to the saddle-node bifurcation of limit cycles. The slow system is defined on the slow manifold, denoted by $\langle \mathbf{x} \rangle$ corresponding to equilibria of the averaged fast subsystem. Note that the upper segment of $\langle \mathbf{x} \rangle$ linking the Andronov-Hopf and fold bifurcation points consists of the stable equilibria of the averaged subsystem. Its lower segment between the fold and homoclinic bifurcation points consists of the repelling equilibria which are the images of the unstable limit cycles. Suppose next that the upper branch of $\langle \mathbf{x} \rangle$ is

crossed transversally by the null-cline $\langle \dot{z} \rangle = 0$. The intersection point is an equilibrium state of the averaged system. The equilibrium state will be stable if the curve crosses $\langle \mathbf{x} \rangle$ from below, and unstable in z otherwise. The stable equilibrium state of the averaged system is the image of the stable periodic orbit in the 3D singularly perturbed system. This stable periodic orbit corresponds to periodic tonic spiking activity of a neuron model. When the surface $\langle \dot{z} \rangle = 0$ is crossed by the curve $\langle \mathbf{x} \rangle$ twice, then the intersection points will correspond to the two periodic orbits, one stable and one of the saddle type, see Fig. 2. Here, of a very special interest is an interplay between the stable manifold of the saddle periodic orbit that is shown as a grey disk in this figure, and the way the phase point jumps up at $\sim z_{sn}$ (the left fold on the Z-shape curve of equilibria of the fast subsystem) onto the surface M_{lc}. Two robust situations are possible here. The first shown in Fig. 2(a) is when the phase point gets, once or after some intermediate phase, into the attraction basin of the stable periodic orbit. The system will generate tonic spikes. In the second case illustrated in Fig. 2(b), the stable manifold of the saddle cycle does separate the attraction basin of the stable periodic orbit. This corresponds to the bi-stability in the system, where the the tonic-spike solution co-exists with the bursting solution, see the numerical results presented in Fig. 1(a). The choice of the regime is determined by the initial condition. The periodic orbits merge when t $\langle \dot{z} \rangle = 0$ becomes tangent to $\langle \mathbf{x} \rangle$. The point of the
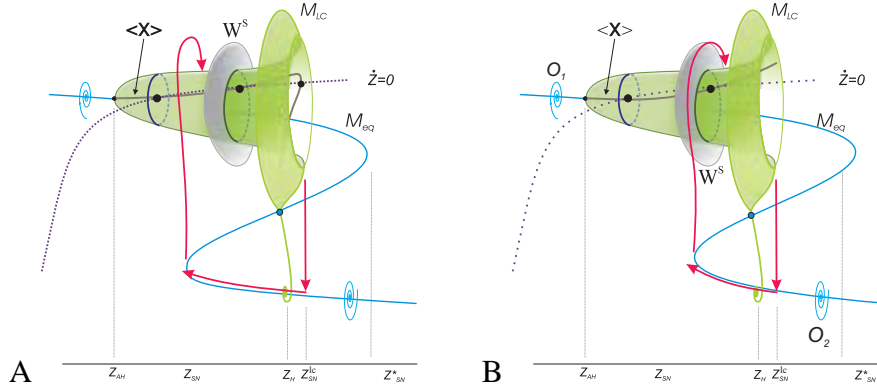

Fig. 2. (A) Points of transverse intersections of $\langle \dot{z} \rangle = 0$ with $\langle \mathbf{x} \rangle$ are the images of the two periodic orbits: one stable and one saddle in the phase space of the 3D singularly perturbed system. (B) Bi-stability starts when the stable manifold of the saddle periodic orbit bounds the attraction basin of the stable orbit.

contact corresponds to the saddle-node periodic orbit in the phase space of the 3D singularly perturbed system [16]. This orbit vanishes as $\langle \dot{z} \rangle = 0$ moves below $\langle \mathbf{x} \rangle$. Therefore, there is no bi-stability after the saddle-node bifurcation in the system which starts firing bursts only. After both periodic orbits disappear through the saddle-node bifurcation only the bursting mode will persist.

Conclusion We have described a mechanism for the transition between tonic spiking and bursting. This mechanism also explains possible bi-stability in the system, where bursting mode co-exists with tonic spiking and a particular mode can be attained by appropriate choice of initial conditions. The core of the mechanism is based on a saddle-node bifurcation of codimension one for periodic orbits. We argue that the scenario and the geometry of the bifurcation are both quite typical for fast-slow systems based on the Hodgkin-Huxley formalism.

5

References

[1] J. Angstadt and W. Friesen, J. Neurophysiol. **66**, 1858 (1991).

[2] R. Bertram, Biol. Cybern. **69** 257 (1993).

[3] C.C. Canavier, D.A. Baxter, L. Clark, J. Byrne. J. Neurophysiol. **69**, 2252 (1993).

[4] G.S. Cymbalyuk and R.L. Calabrese. Neurocomputing, 159 (2001).

[5] G.S. Cymbalyuk, Q. Gaudry, M.A. Masino, R.L. Calabrese J. Neuroscience **22**, 10580, 2002.

[6] A. Hill, J. Lu, M. Masino, O. Olsen, R.L. Calabrese, J. Comput. Neuroscience **10**, 281 (2001).

[7] J. Hounsgaard, O. Kiehn, J. Physiol. **414**, 265 (1989)

[8] H. Lechner, D. Baxter, C. Clark, J. Byrne, J. Neurophysiol. **75** 957 (1996).

[9] J. Lisman (1997) Trends Neurosci. **20**, 38 (1997).

[10] V. Lukaynov and L. Shilnikov, Soviet Math. Dokl. **19**(6), 1314 (1978)

[11] E. Marder, L. Abbott, G. Turrigiano, Z. Liu, J. Golowasch, Proc. Natl. Acad. Sci. USA **26-93**(24), 13481 (1996).

[12] E. Marder , R.L. Calabrese, Physiol. Rev. **76**, 687 (1996).

[13] C.A. Opdyke and R.L. Calabrese, J. Comp. Physiol. *175*, 781 (1994).

[14] J. Rinzel, Lecture Notes in Mathematics **1151**, 304 (1985)

[15] A. Shilnikiov, L. Shilnikov and D. Turaev, Moscow Math. Journal (2004) to appear.

[16] L. Shilnikov, A. Shilnikiov, D. Turaev and L. Chua Methods qualitative theory in nonlinear dynamics, Volumes I and II. World Scientific, (1998 and 2001)

[17] M. Steriade, D.A. McCormick, T.J. Sejnowski, Science **262**, 679, 1993.

[18] D. Terman, J. Nonlinear science **2**, 135 (1992).

[19] G. Turrigiano, E. Marder, L. Abbott, J. Neurophysiol. **75** 963 (1996).

[20] X.J. Wang, Physica D **62**, 263 (1993).