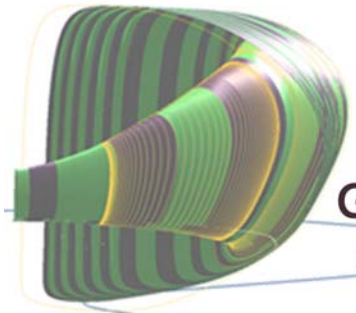
Book of Abstracts



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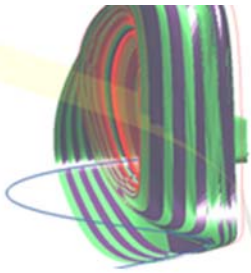

Georgia State University,
Atlanta April 7-8, 2006

Origin and Regulation of Bursting Activity in Neurons

http://www.mathstat.gsu.edu/~meetings

Department of Physics and Astronomy

Georgia State University

Keynote speakers:

Bard Ermentrout	University of Pittsburgh
John Guckenheimer	Cornell University
Eve Marder	Brandeis University
Nino Ramirez	University of Chicago
John Rinzel	New York University
David Terman	Ohio State University

Scientific and Organizing Committee:

Ron Calabrese	Igor Belykh
Gennady Cymbalyuk	Donald Edwards
Andrey Shilnikov	Paul Katz

Student Body of Local Organizing Committee:

James Bates	Easther Meyer
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Rutgers University
Salk Institute for Biological Studies
University of Alberta
University of California, San Diego
University of Chicago
University of Houston-Clear Lake
University of New Orleans
University of Pittsburgh
University of Utah

PROGRAM

Friday, April, 7.

8:00-9:00	Registration and Breakfast.
9:00-9:05	Opening Remarks
9:05-9:10	**Paul Katz** *Center for Neural Communication and Computation at GSU*
9:10-10:00	Morning lecture I: **Eve Marder** *Variability, homeostasis, and compensation in neural oscillators.*
10:00-10:50	Morning lecture II: **David Terman** *Dynamic Clustering in a Model for an Insect's Antennal Lobe*
10:50-11:15	Coffee Break
	Short Talks
11:15-11:40	**Gennady Cymbalyuk** *Bifurcations and regulation of bursting activity*
11:40-12:05	**Astrid Prinz** *Distribution of bursting model neurons in an eight-dimensional conductance space*
12:05-12:25	**Attila Szücs** *Synaptic and cellular properties shaping the intraburst spike dynamics of pyloric neurons.*
12:30-13:50	Lunch
13:50-14:40	Afternoon lecture: **Nino Ramirez** *The differential roles of pacemaker neurons in controlling different parameters of the respiratory rhythm*

	Short Talks
14.40-15:05	**Thomas Nowotny** *Can we build accurate conductance based models to investigate the origin of bursting?*
15:05-15:30	**Jorge Golowasch** *Pacemaker activity recovery after decentralization: role of neuromodulators and calcium pump*
15:40-16:00	Coffee break
16:00-16:25	**Andrey Olypher** *Inactivation rate of the low-threshold Ca^{2+} current controls burst duration in the leech heart interneurons*
16:25-16:50	**Mark Pernarowski** *Map characterizations of a model of bursting exhibiting bistability*
16:50-17:15	**Dieter Jaeger** *Bursting properties of deep cerebellar nucleus neurons: induced, driven, rebound.*
17:15-17:40	**Nikolai Rulkov** *Replicating spiking-bursting behavior with map-based models*
17:40-18:05	**Georgi Medvedev** *Transition to bursting via deterministic chaos*
18:05- 18:30	Evening break, posters
18:30-19:20	Evening lecture: **John Guckenheimer** *A Mathematician Tries to Walk: Modeling Locomotion.*
19:30-22:00	Reception and Dinner. Posters

Saturday, April, 8.

8:00-9:00	Breakfast
9:00-9.50	Morning lecture I: **Bard Ermentrout** *Why a duck: Hopf bifurcations, canards, and elliptic bursters*
9:50-10:40	Morning lecture II: **John Rinzel** *Network bursting without cellular burst mechanisms*
10:40-11:10	Coffee Break
	Short Talks
11:10-11:35	**Igor Belykh** *Synchronized bursting: what matters in the network topology*
11:35-12:00	**Carmen Canavier** *Independent Regulation of Firing Pattern and Rate in a Model of a Midbrain Dopamine Neuron*
12:00-12:25	**Andrey Shilnikov** *Homoclinic chaos on a spike adding route into bursting in a neuronal model*
12:25-13:45	Lunch
13:45-14:35	Afternoon lecture: **Jeffrey C. Smith** *Oscillatory bursting mechanisms in respiratory neurons*
	Short Talks
14:35-15:00	**Robert Butera**, *Significance of pacemaker vs. non-pacemaker neurons in an excitatory rhythmic network*

15:00-15:25	**Ilya Rybak** *Bursting and tonic activity states of the pre-Bötzinger complex and respiratory rhythm generation*
15:25-16:05	Coffee break
16:05-16:30	**Maxim Bazhenov** *Coexistence of tonic firing and bursting in cortical neurons*
16:30-16:55	**Victor Matveev** *Multistability in a two-cell inhibitory network with T-like currents*
16:55-17:20	**Joel Tabak** *Low dose of dopamine may stimulate prolactin secretion by increasing fast potassium currents*
17:20-17:45	**Janet Best** *Bursting versus episodic firing in hypothalamic neurosecretory cells*
17:45-18:15	Evening break, posters
18:15-18:40	**Paul Katz** *A role for intrinsic neuromodulation in the Tritonia swim central pattern generator*
18:40-18:45	**Donald Edwards** *Brain and Behaviors Program at GSU*
18:45-19:10	**Donald Edwards** *ANIMATLAB: a physically accurate 3-D environment for behavioral neurobiology research.*
19:10-21:00	Dinner. Posters

ABSTRACTS

LECTURES

Why a duck: Hopf bifurcations, canards, and elliptic bursters

G. Bard Ermentrout

University of Pittsburgh

Cortical slices produce propagating waves when disinhibited or when treated with medium low in magnesium. The lowered magnesium unblocks the NMDA receptors allowing for long lasting synaptic depolarization. We describe two possible mechanisms for these oscillations: (i) depolarization block leading to an "elliptic burster" and (ii) after-hyperpolarization with persistent sodium leading to a "square-wave" burster. Predictions allowing us to distinguish these two possibilities are made.

A Mathematician Tries to Walk: Modeling Locomotion

John Guckenheimer

Cornell University

Walking is a complex phenomenon that has proved to be difficult to model. This lecture will discuss computational problems that arise in modelling both the biomechanics and neural control of locomotion. It will emphasize the role of multiple time scales and combinations of discrete and continuous phenomena in walking.

Variability, homeostasis, and compensation in neural oscillators

Eve Marder

Brandeis University

I will discuss a combination of computational and experimental studies designed to ask a series of questions about the dependence of oscillatory behavior on the parameters of the processes that give rise to those behaviors. In particular, I will discuss data that indicate that similar behavior, both at the single neuron and network level can arise from different combinations of conductances, and therefore that similar behavior in different animals may be associated with different solutions to the production of a given pattern of activity.

The differential roles of pacemaker neurons in controlling different parameters of the respiratory rhythm

J.M. Ramirez, Andrew Hill, Jean-Charles Viemari

Committee on Neurobiology, Department of Organismal Biology and Anatomy, University of Chicago, Chicago, IL, USA

The respiratory network of mammals isolated in transverse slice preparations is reconfigured during the transition from normoxia into hypoxia. The network generates normal respiratory activity (=fictive eupneic activity) in normoxia, and gasping in hypoxia. The transition from eupneic into gasping activity is associated with a change in the dependence on pacemaker activity. Eupneic activity depends on at least two types of respiratory pacemakers. Bursting by one type is dependent on the persistent sodium current, which can be blocked by riluzole (i.e. riluzole-sensitive, RS), while the other relies on CAN current and can be blocked by flufenamic acid (FFA) (i.e. FFA-sensitive (FFAS)). Blockade of both pacemaker types abolishes eupneic activity. While blockade of either RS or FFAS pacemakers alone is insufficient to block eupneic activity, our data indicate that FFAS pacemakers control burst shape and amplitude, whereas RS pacemakers control frequency and stability of respiratory network activity. During gasping KATP channels inhibit FFAS pacemakers. By contrast, RS pacemakers remain rhythmically active, and some additional RS pacemakers are recruited during hypoxia. Fictive gasping is blocked by riluzole, but not by FFA, suggesting that gasping relies only on RS-pacemakers. These RS pacemakers are dependent on endogenously released serotonin acting on 5-HT2A receptors. In the presence of 5HT2A receptor antagonists RS bursting (Pena and Ramirez 2003), and gasping is abolished (Tryba and Ramirez, 2006). We conclude that the number of active pacemakers in the respiratory network is state-dependent, and that pacemakers play differential roles in controlling different forms of respiration and different parameters of respiratory activity. These differential roles are regulated by endogenously released neuromodulators and the metabolic state of the network.

Network bursting without cellular burst mechanisms

John Rinzel

NYU, Center for Neural Science and Courant Institute

The frameworks that have been developed for understanding and generating bursting dynamics have relied primarily on cellular mechanisms: fast-spiking dynamics and slow negative feedback processes, intrinsic to a cell. Some models have addressed synchronization in networks of such intrinsic bursters. I will describe a network model in which individual cells have no slow processes; they are conditional tonic spikers. Our mean field model describes the spontaneous episodic activity in developing chick spinal cord. Slow negative feedback in this functionally excitatory-coupled network is due to slow synaptic depression. The mathematical structure is that of square-wave bursting; the time scales are minutes, rather than seconds. A cell-based integrate-and-fire network displays some features of the idealized mean field model.

Oscillatory bursting mechanisms in respiratory neurons

Jeffrey C. Smith, H. Koizumi, and S. Smerin

Cellular and Systems Neurobiology Section, NINDS, NIH, Bethesda, MD, USA

A heterogeneous network of excitatory neurons in the brainstem pre-Bötzinger complex contributes to respiratory rhythm generation in the mammalian nervous system. This network exhibits autorhythmic properties arising from dynamic interactions of excitatory synaptic currents and intrinsic cellular currents, which endow intrinsic rhythmic bursting properties to a subset of neurons when isolated from synaptic inputs. Our experimental and modeling analyses of intrinsic cellular current mechanisms indicate that two subthreshold neuronal conductances in particular contribute importantly to cellular and network-level oscillatory bursting: a persistent sodium conductance (NaP) and a potassium-dominated Leak conductance. NaP has voltage-dependent activation/ inactivation properties with very slow inactivation kinetics at subthreshold voltages. This kinetics gives rise to the slow recovery process that underlies regenerative bursting at cellular and network levels. Leak is voltage-independent and due in part to TASK channels– a subclass of two-pore potassium channels that are modulated by a variety of neurotransmitters and physiological regulatory signals including hydrogen ion. NaP is also modulated by physiological signals, particularly low oxygen. Our analyses indicate that rhythm generation and modulation in the pre-Bötzinger complex network can be understood to an important extent by considering the contributions of NaP and Leak.

Supported by the Intramural Research Program of NINDS, NIH.

Dynamic clustering in a model for an insect's antennal lobe

David Terman

Department of Mathematics and Mathematical Biosciences Institute, Ohio State University

Experiments have demonstrated that the projection neurons (PNs) within a mammal's olfactory bulb or insect's antennal lobe (AL) produce complex firing patterns in response to an odor. The firing patterns may consist of epochs in which a subset of PNs fire synchronously. At each subsequent epoch, PNs drop in and drop out of the ensemble, giving rise to "dynamic clustering". I will present a biologically motivated model of the AL that produces dynamic clustering, as well as other complex features of AL activity patterns. For example, the model exhibits of form of spatial decorrelation in which the temporal representations of similar odors evolve to distinct patterns. Using singular perturbation methods, we reduce the analysis of the model to an algorithm based on a directed graph. The algorithm allows us to systematically study how properties of the attractors depend on parameters including network architecture.

SHORT TALKS

Coexistence of Tonic Firing and Bursting in Cortical Neurons

F. Frohlich and **Maxim Bazhenov**

Salk Institute

Sustained neuronal activity can be broadly classified as either tonic firing or bursting. These two major patterns of neuronal oscillations are state dependent and may coexist if the system displays bistability. Dynamics and intracellular mechanisms of transitions between tonic firing and bursting in cortical networks remain poorly understood. Here, we use a computational model of a neocortical circuit with extracellular potassium dynamics to show that activity-dependent modulation of intrinsic excitability can lead to sustained oscillations with slow transitions between two distinct firing modes - fast tonic spiking and slow bursting. Transitions between two stable fixed points mediated by slow changes of the calcium dependent potassium current, IK(Ca), underlie burst generation in an isolated cortical neuron. Existence of the tonic firing mode is determined by stability of a limit cycle within a range of IK(Ca) fluctuations occurred during fast tonic oscillations. The study explains ionic and dynamical mechanisms underlying transition between two different oscillatory modes as a function of neuronal excitability mediated by extracellular potassium concentration.

Supported by: NIDCD

Bursting versus episodic firing in hypothalamic neurosecretory cells

J.A.Best[1] , C.B.Roberts[2], K.J.Suter[2]

1. *Mathematical Biosciences Inst., Ohio State Univ., Columbus, OH, USA*
2. *Biology, Emory Univ., Atlanta, GA,USA*

Intermittent firing in hypothalamic GnRH neurons likely underlies the pulsatile hormone secretion that supports sexual reproduction. The mechanisms that initiate and terminate episodic firing are uncertain. One possibility is that GnRH neurons share the classical bursting mechanisms of other neurosecretory neurons. Alternatively, GnRH neurons may require distinct mechanisms; indeed, emerging evidence suggests that the classical mechanisms that sustain bursting in other neurosecretory neurons are not operant in these. We present recent progress on an alternative model for the GnRH pulse generator and discuss implications for the regulation of hormone release.

Support Contributed By: NSF Agreement No. 00112050 and by HD045436.

Synchronized bursting: what matters in the network topology

Igor Belykh

Department of Mathematics and Statistics, Georgia State University

We study the influence of coupling strength and network topology on synchronization behavior of square-wave bursters coupled via fast excitatory synapses. Surprisingly, we find that the stability of the completely synchronous state in such networks only depends on the number of signals each neuron receives, independent of all other details of the network topology. This is in contrast with electrically coupled bursting neurons where complete synchrony strongly depends on the network structure and number of cells. Through analysis and numerics, we show that the onset of synchrony in a network with *any* coupling topology admitting complete synchronization is ensured by one single condition. We also show that fast inhibition can lead to stable bursting clusters of complete synchrony.

Supported by the GSU internal research grant (RIG).

Significance of pacemaker vs. non-pacemaker neurons in an excitatory rhythmic network

Robert Butera
Georgia Tech

Liston Purvis, *Georgia Tech*; Michael Wright, *Emory University*

The transverse brainstem slice containing the preBotzinger complex is a rhythmically active in vitro system that contains a subcircuit of the respiratory pattern generator circuitry. The slice rhythm is remarkably stable and the neural circuitry within the slice and its mechanism for generating rhythmic bursts has been the subject of much experimental, as well as computational, study. Much of the current controversy is with regard to the significance of the presence of pacemaker (endogenously bursting) neurons to the generation of network-wide bursts of electrical activity. While it is generally agreed that pacemaking neurons exist and that a persistent Na current underlies the bursting process at the single cell level, some experimental studies have suggested that endogenous bursting of single neurons is not necessary for network-wide bursting, and modeling studies have also shown that such an idea is feasible, but has not been robustly explored. In our present study we consider heterogeneous networks with a variable number of pacemaker (PM) and non-pacemaker neurons (NPM); the properties of the model neuron are randomly assigned and biased by the statistics of known conductance differences between PMs and non-PMs. The network simulations show that network bursting can occur even with no pacemakers, however, when the % of PMs is 50% or greater, the bursting is more robust (defined by the size of parameter space where bursting is supported) and can occur at the large range of frequencies exhibited by the slice (which is not the pace for few PMs). The simulations also suggest multiple modes of burst generation, which have been validated qualitatively with simulations of pairs of neurons and are currently being investigated using numerical bifurcation analysis tools.

Independent Regulation of Firing Pattern and Rate in a Model of a Midbrain Dopamine Neuron.

Carmen C. Canavier

Neuroscience Center, LSU Health Sciences Center, New Orleans, LA USA

A stylized, symmetric, compartmental model of a dopamine neuron *in vivo* shows how rate and pattern can be modulated either concurrently or independently. An increase in the AMPA/NMDA ratio produces an example of a concurrent modulation of rate and pattern, whereas blocking the small conductance (SK) channel is an example of a modulation that primarily affects pattern. Doubling AMPA produces a modest increase in both rate and fraction of spikes in bursts, but blocking SK produces a much more dramatic increase in fraction of spikes fired in bursts than in rate. Blocking SK evokes additional bursts by allowing a depolarization that previously produced only a single spike to elicit two or more, and elongates existing bursts by the same principle. Hence the proportion of spikes fired in bursts is more strongly affected than the total number of spikes, or rate. The increase in number of spikes is partially offset by quiescent intervals that often follow bursts due to the lingering effects of the slow hyperpolarizing processes evoked by a burst. On the other hand, the AMPA current is short-lived relative to burst duration, and evokes additional spikes without regard to pattern, producing comparable small increases both in spike frequency and fraction fired in bursts. The effect of the SK current is dependent upon the background level of GABA receptor activation: when GABA activation is high, the SK current represents a smaller fraction of the total current and its effects are much less noticeable. In the model, a strong correlation exists (r=0.99) between pattern and rate when only a single parameter is varied, consistent with experimental observations. However, if two parameters are varied concurrently, rate and pattern become decorrelated, providing an explanation for the lack of a tight correlation *in vivo*. Under these conditions, **changes** in pattern and rate are very weakly correlated (r=0.14), comparable to experimental observations

Supported by NINDS grant NS37963 to CCC.

Bifurcations and regulation of bursting activity

G. Cymbalyuk, J. Bates, T. Malashchenko and A. Shilnikov

Georgia State University

Bursting activity has been reported in many different neurons and associated with a various functions of the nervous system. Our study is focused on determining the generic biophysical and bifurcational mechanisms underlying the onset and evolution of bursting activity from tonic spiking and quiescence regimes.
Bifurcation analysis of the dynamics of neurons under pharmacological reductions allows one to study comprehensively the general mechanisms of metamorphoses of temporal characteristics of the neuronal activity. It provides the qualitative and quantitative description of the evolution of waveforms on a control parameter. Predictions do not count on specifics of a model or a neuron. For example, among a few basic characteristics of bursting activity are the burst duration, the interburst interval and the spike frequency in a burst. We consider a model describing the dynamics of the single leech interneuron under pharmacological conditions, that leave only I_{Na} and I_{K2} currents. In this model, a variation of a single parameter, which is a shift of the activation curve I_{K2} can cause a neuron to vary smoothly the temporal characteristics of its bursting activity. The plasticity ranges from bursting with an arbitrarily large interburst interval and short burst duration to bursting with large burst duration and short interburst interval; i.e. in other words, the duty cycles moves from zero to infinity. Both transitions are featured in accordance with dynamical laws imposed by the saddle-node bifurcation both for equilibria and periodic orbits. The outputs of these transitions are nevertheless radically different: the silent hyperpolarized neuron and the tonic spiking neuron, respectively. Results are compared to the complete 14D model of the heart interneuron and to other models under different pharmacological reductions.

ANIMATLAB: A PHYSICS BASED 3-D GRAPHICS ENVIRONMENT FOR BEHAVIORAL NEUROBIOLOGY RESEARCH

D.W.Cofer[1]; J.Reid[2]; O. Pochapinskyy[1], Y.Zhu[2]; G.Cymbalyuk[3]; W.J.Heitler[4]; D.H. **Edwards**[1]

Departments of Biology[1], Computer Science[2], and Physics and Astronomy[3], Georgia State University, PO Box 4010, Atlanta, GA, USA 30302, and School of Biology[4], Univ. of St. Andrews, Scotland, United Kingdom KY16 9TS

Understanding neural mechanisms of behavior has frequently depended on comparisons between detailed descriptions of freely behaving animals and fictive motor programs displayed by neurons in anesthetized, restrained, and dissected preparations. We have developed a software toolkit, AnimatLab, to help researchers determine whether their descriptions of neural circuit function can account for how specific patterns of behavior are controlled. AnimatLab enables one to build a virtual body from simple LEGO™-like building blocks, situate it in a virtual 3-D world subject to the laws of physics, and control it with a multi-cellular, multi-compartment neural circuit model. A Body Editor enables adjustable blocks, balls, truncated cones, and cylinders to be connected through a variety of joints to form a body. Sensors enable extrinsic and intrinsic signals to be detected, and virtual muscles governed by Hill muscle models span the joints to produce movement. The body and other objects are subject to gravity, buoyancy, drag, friction, contact collision, and muscle tension. A Neural Editor enables a neural network to be constructed from a menu of neurons and synapses, and then linked to sensors and effectors on the body. We are currently using AnimatLab to study the neural control of locomotion and the escape behavior of crayfish. Several simulations have been built that demonstrate how small neural networks can produce complex behaviors like walking over rough terrain, navigation around obstacles, and using olfactory cues to find and consume food in an unpredictable environment.

Pacemaker activity recovery after decentralization: role of neuromodulators and calcium pump

Jorge Golowasch *Dept. Biological Sciences, Rutgers University and Dept. Mathematical Sciences, NJIT*

The rhythmic activity produced by the pyloric network of crustaceans depends on the release of neuromodulatory substances by axon terminals from adjacent ganglia. After action potential transmission along these axons is inhibited (decentralization), rhythmic pyloric activity recovers spontaneously, but this recovery follows a very complex temporal dynamics that involves the alternating turning on and off of the pyloric rhythm (termed "bouting"). This bouting period lasts several hours after which a stable pyloric rhythm reemerges. We want to understand the biophysical mechanism of pacemaker activity recovery after a massive perturbation such as the removal of all central input to the network.

A previous theoretical study used a network model to characterize the process of activity recovery after decentralization. This study showed that long-term activity-dependent regulation of ionic conductances was necessary and sufficient to enable this recovery. However, it did not capture the complex temporal dynamics that follows decentralization and that precedes the final stable recovery. Here we built a model of a single conditional pacemaker neuron whose ionic conductances as well as the activity of Ca^{++} uptake into internal stores are slowly regulated by activity. To this end we modified the previously described model but included a simple yet realistic network of intracellular Ca^{++} sequestration into, and release from, intracellular stores. This occurs via a Ca^{++} pump and IP_3-dependent Ca^{++} channel. Intracellular Ca^{++} sensors, representing enzymatic pathways, regulate the Ca^{++} pump activity and the maximal Ca^{++} and K^{+} conductances. The model reproduces the dynamic process of bouting that leads to the stable rhythmic state observed in the biological system. It also reproduces the effects of long term preincubation with neuromodulators on the recovery process. This model suggests that the role of Ca^{++} sequestration plays an important role in the process of activity recovery, via either intracellular Ca^{++} pump regulation or the regulation of Ca^{++} release from intracellular stores. These are predictions that should now be tested experimentally. *Supported by NIMH 64711 and NSF IBN-0090250.*

Bursting properties of deep cerebellar nucleus neurons: induced, driven, rebound

Dieter Jaeger

Department of Biology, Emory University

Neurons in the DCN are usually in a spontaneous tonic spiking mode when recorded in brain slices. However, a minority of neurons is spontaneously bursting under the same recording conditions. Strong endogenous bursting is induced in all neurons by blocking Sk current with apamin. The propensity of these neurons to continuous bursting may be related to their ability to show strong single rebound bursts after short periods of hyperpolarization. These rebound bursts have both fast T-type calcium current dependent and slow persistent sodium current dependent components. Rebounds have been hypothesized to be important for synaptic responses to strong inhibition in vivo. Thus, an important question may be how strong single rebounds can be elicited, but continuous bursting can be dampened in most circumstances. Nevertheless, even in vivo these neurons can exhibit strong bursting, for example during ketamine-xylazine anesthesia. A phase plane analysis of the different bursting and rebound regimes has not been carried out to date.

A Role for Intrinsic Neuromodulation in the Tritonia Swim Central Pattern Generator

Paul S. Katz, Robert J. Calin-Jageman, Akira Sakurai, Evan S. Hill

Department of Biology, Georgia State University

Neuromodulatory input can alter rhythmic behavior but it remains unclear how intrinsic neuromodulation shapes the dynamics of rhythmic systems. The central pattern generator (CPG) underlying swimming in the mollusc, *Tritonia diomedea*, has been characterized as a network oscillator comprised of three cell types (DSI, VSI, and C2). The serotonergic DSIs modulate the cellular and synaptic properties of other neurons in the circuit; these intrinsic neuromodulatory actions appear to be essential for initiation of the motor pattern and play important roles in the maintenance and termination of rhythmic activity as well. Re-analysis of an earlier integrate-and-fire simulation of the circuit (Getting, J. Neurophysiol. 49:1017-1035, 1983), using a parameter mapping approach, suggests the unmodulated circuit cannot produce the swim motor pattern and that the production of the pattern depends on modulation of multiple circuit elements. Furthermore, the revised model suggests that switching out of the oscillatory state may also involve modulation of cellular or synaptic properties. Physiological and pharmacological experiments further indicate that second messenger signaling plays an integral role in maintaining the motor pattern and determining the periodicity. Thus, intrinsic neuromodulation and second messenger signaling may be directly involved in the initiation, maintenance, and termination of rhythmic activity in this CPG.

Multistability in a Two-Cell Inhibitory Network with T-like Currents

Victor Matveev and Amitabha Bose

Department of Mathematical Sciences, NJIT

Farzan Nadim, NJIT, Newark, NJ and Rutgers University

Networks of neurons coupled through reciprocal inhibition are ubiquitous, and are of crucial importance for maintaining rhythmic activity in such diverse systems as invertebrate central pattern generators, and the mammalian subcortical and cortical circuits. We explore the dynamics of a network of two neurons with type-I excitability, each endowed with a T-like current, and reciprocally coupled by inhibitory synapses. For sufficiently strong synaptic coupling, it is known that the T-currents allow such a circuit to maintain a stable antiphase bursting state, in which a burst in one cell causes a rebound burst in the other cell. In addition, the network we consider can maintain a low-frequency tonic state, whereby a single low-frequency spike is not sufficient to cause a postinhibitory rebound in the partner cell. Finally, this two-cell network can also exhibit an irregular chaotic firing regime, corresponding to certain intermediate, partial level of T-current activation.

In a certain parameter range, the network is bistable, exhibiting two of these three stable activity states. Moreover, distinct bursting states with different number of spikes per burst can be co-stable for the same parameter values. We find that such multistability of bursts can be captured by a one-dimensional Poincaré map relating the lengths of the successive bursts of the two neurons with the level of T-current inactivation at the start of the burst. Further, we show that incorporating short-term synaptic facilitation into the model can significantly enlarge the bistability between bursting and tonic firing, since facilitation would serve to strengthen the synaptic coupling during a burst, increasing the entrainment of the two cells in the burst state, while allowing the synaptic currents to remain below rebound activation threshold during the low-frequency firing. Finally, we find that in the presence of facilitation the irregular chaotic burst state becomes metastable, and can co-exist with the two stable periodic firing states.

Support contributed by: NSF DMS-0417416 (V.M.), NSF DMS-0315862 (A.B.), and NIH MH60605 (F.N.)

Transition to bursting via deterministic chaos

Georgi S. Medvedev

Department of Mathematics, Drexel University

We study statistical properties of the irregular bursting arising in a class of neuronal models close to the transition from spiking to bursting. Prior to the transition to bursting, the systems in this class develop chaotic attractors, which generate irregular spiking. The chaotic spiking gives rise to irregular bursting. The duration of bursts near the transition can be very long. We describe the statistics of the number of spikes and the interspike interval distributions within one burst as functions of the distance from criticality.

This work was partially supported by the National Science Foundation under Grant No. 0417624

Can we build accurate conductance based models to investigate the origin of bursting?

Thomas Nowotny

University of California San Diego

Experience has shown that in many cases the direct assembly of fits to voltage clamp data fails in constructing accurate conductance based neuron models. Typically the resulting models reproduce some aspects of the neuron dynamics but tend to break apart under perturbations, e.g., the blocking of one current. Other approaches, including enumeration of models ("database approach") and automatic fitting procedures, have been suggested. Here, we describe our latest attempt of an automatic fitting procedure and its success in building an accurate conductance based neuron model of the lobster LP neuron. The promising first results emphasize the critical role of sufficiently rich data as well as an adequate fitting procedure and cost function. The resulting model(s) should allow insight into the mechanisms of burst formation in the LP neuron, which is known for its wide chaotic bursting regime.

Inactivation rate of the low-threshold Ca2+ current controls burst duration in the leech heart interneurons

Andrey V. Olypher, Ronald L. Calabrese *Emory University*

Gennady S. Cymbalyuk *Georgia State University*

The aim of our research is to determine biophysical mechanisms that regulate bursting, which is a fundamental mode of neuronal activity. Bursting is integral to central pattern generators; neuronal networks controlling rhythmic behavior. We studied the heartbeat pattern generator of the medicinal leech, and focused on the control of the bursting pattern by the slowly inactivating low-threshold calcium current, I_{CaS}. The heartbeat rhythm is based on alternating bursting in two pairs of reciprocally inhibitory heart interneurons. To explore the I_{CaS} regulation of bursting in such a pair, we assembled a hybrid system consisting of a living heart interneuron and its corresponding mathematical model running in real time. The living interneuron and the model were connected with artificial inhibitory synapses using dynamic clamp, which was also used, in some experiments, to implement artificial I_{CaS} in the living interneuron. The natural inhibitory synapses were blocked pharmacologically. We varied the inactivation time constant of I_{CaS} unilaterally in either the living or in the model heart interneuron and assessed changes in major burst characteristics: burst duration and period, and the final spike frequency in the burst. We found that in oscillator heart interneurons the time constant of I_{CaS} inactivation determined the burst duration in the varied interneuron. The time constant of the I_{CaS} inactivation determined the time constant of spike frequency decline in a burst. Spike frequency in a burst declined until reaching a final spike frequency set by the opposite neuron (Sorensen et al. 2004). Varying I_{CaS} inactivation time constant did not affect the final frequency of either interneuron. When I_{CaS} inactivation time constant was short, spike frequency declined slowly and bursts were long, and when I_{CaS} inactivation time constant was long, spike frequency declined quickly and bursts were short. This mechanism did not depend on synaptic interaction with an opposing interneuron; synaptically isolated living or model interneurons with the varied I_{CaS} inactivation time constant behaved similarly.

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Map characterizations of a model of bursting exhibiting bistability

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Many recent models of bursting require two or more slow variables to explain the biological phenomena they are intended to describe. In this talk we examine a phenomenological model with two slow and two fast variables. We outline the singular perturbation construction of bursting solutions using a one dimensional return map. Fixed points of the map are shown to correspond to bursting solutions. However, for some parameter values, the maps are not defined everywhere. In one instance, this restricted domain is shown to correspond to a bistability between stable equilibria and bursting solutions of the entire system. Some biological implications of this new dynamic will be discussed.

Distribution of bursting model neurons in an eight dimensional conductance space

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Brute force computational exploration of highdimensional neuronal parameter spaces provides a tool that can complement bifurcation analysis in the investigation of the role of different neuronal parameters in shaping neuronal behavior. The neuronal model databases resulting from such parameter explorations are high-dimensional datasets with millions of entries, and can be analyzed with the help of visualization methods to determine where in parameter space models with a given behavior are located, and how characteristics of that behavior depend on the underlying properties. I will use the distribution of 1,120,235 bursting model neurons in the eightdimensional maximal conductance space of a crustacean stomatogastric model neuron to illustrate this approach, to introduce a visualization method for highdimensional data based on dimensional stacking, and to investigate how characteristics of bursting behavior, such as burst period, burst duration, number of spikes per burst, etc., depend on the composition of membrane currents in the neuronal membrane.

Replicating spiking-bursting behavior with map-based models

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A simple two-dimensional map is designed to replicate waveforms of spiking-bursting activity of neurons. The map-based model consists of fast and slow subsystems. The fast subsystem captures spikes generation while the slow one controls transient dynamics and the onset of bursting activity. The paper discusses how form of the map shapes the properties of both autonomous and response behavior of the model.

Bursting and tonic activity states of the pre-Bötzinger complex and respiratory rhythm generation

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A series of *in vitro* studies has demonstrated that pre-Bötzinger complex (pBC) can generate an endogenous bursting activity that is dependent on the expression of the persistent sodium current (INaP) in pBC neurons. At the same time, in the intact system *in vivo*, the pBC is embedded into a wider brainstem respiratory network and its functional state and firing behavior are dependent on the interactions with other neural compartments involved in the respiratory rhythmogenesis and control of respiration. As a result, the brainstem respiratory network can operate in multiple functional states engaging different state-dependent neural mechanisms. A computational model of the brainstem respiratory network has been developed to study state-dependent mechanisms for respiratory rhythm generation and to reproduce and explain our recent experimental data. The model incorporates several interacting neural compartments including the pons, Bötzinger complex (BC), pBC, and rostral VRG. We suggest that the rhythmogenic mechanism (i.e. pacemaker-driven, network, or hybrid), operating within the network in each mode, depends on the functional state of the pBC (expression of INaP-dependent bursting activity), which in turn is defined by the excitatory inputs from other compartments, including the pons, and the activity of post-inspiratory neurons of the BC that provide phasic inhibition of the pBC and other respiratory compartments. The model predicts a continuum of respiratory network states, defining competition and cooperation of different cellular and network mechanisms and their roles in the generation and control of the respiratory rhythm and pattern.

Homoclinic chaos on a spike adding route into bursting in a neuronal model

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Bursting is a manifestation of the complex, multiple time scale dynamics observed in diverse neuronal models. A description list of the nonlocal bifurcations leading to its onset is far from being complete and presents a dare need for interdisciplinary science of neurobiology. There was a recent breakthrough in this direction that explains a few novel mechanisms of transitions between tonic spiking and bursting activity, as well as their co-existence in models of leech interneurons through homoclinic saddle-node bifurcations of periodic orbits including a blue sky catastrophe. Here we report and describe another such mechanism in a model of a leech heart interneuron, the so-called a spike adding route: as a parameter shifting the membrane potential of half-inactivation slow potassium current is monotonically changed, a sequence of bifurcations occurs causing incremental change of the number of spikes in a burst. Of our special interest is the origin of the sequence, where each transition is accompanied by chaos within a narrow parameter window. To figure out the transition dynamics we construct a one-parameter family of the Poincare return mappings on the central manifolds of slow motions. We show that the transitions in question are due to the bifurcations of homoclinics of a repelling point of the map that is a threshold between tonic spiking and hyperpolarized states of the neuron model. A symbolic description applied to the trajectory behavior of the map allows us to systemize the order of interburst spike variations.

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Synaptic and cellular properties shaping the intraburst spike dynamics of pyloric neurons

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The pyloric network of the crustacean stomatogastric nervous system is one of the best known assemblies of neural oscillators producing rhythmic bursts. The temporal patterns of bursts and their modulation by synaptic and chemical factors have been main subjects of investigation in such neural systems. Recent work from our laboratory also showed that the pyloric neurons express characteristic, cell-specific firing patterns within their bursts termed as 'interspike interval signatures'. The characteristic intraburst spike patterns are closely related to the neurons' voltage waveform and they depend both on the intrinsic cellular properties of the neurons and on the synaptic inputs they receive. Manipulations of either the intrinsic properties of the neurons or their synaptic connectivity results in characteristic changes in their spike dynamics. Neuromodulators and blockers of neurotransmission affect the intraburst spike patterns at concentrations far lower than those effectively changing the overall burst pattern of the network. Accordingly, the spike dynamics of the bursting neurons appears as a main target of synaptic and chemical neuromodulation. The observed sensitivity of intraburst spike dynamics to synaptic inputs also suggests a novel way of temporal coding in bursting neurons. In the present talk I will describe the interspike interval signatures of several identified pyloric neurons from the lobster stomatogastric ganglion in normal conditions and under the manipulation of the synaptic connectivity of the system. I will also discuss the cellular and synaptic properties, which play a central role in forming and reshaping the cell-specific spike patterns.

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Low dose of dopamine may stimulate prolactin secretion by increasing fast potassium currents

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Dopamine (DA) is the main inhibitor of prolactin secretion by pituitary lactotrophs. DA hyperpolarizes the lactotroph membrane, preventing action potentials and the associated calcium entry that would cause exocytosis. However, at a lower dose (i.e. ~1000-fold less than the inhibitory dose), DA has been shown to increase intracellular calcium levels ($[Ca^{++}]_i$) and prolactin secretion. This is surprising since DA mostly increases K^+ currents, which generally decrease membrane excitability and therefore decrease $[Ca^{++}]_i$.
To explain this paradoxical effect, we modeled the effect of low DA by adding a fast potassium current to a minimal lactotroph model. This minimal model incorporated a bursting mechanism but operated in a spiking mode. The fast potassium current could be either inactivating (I_A) or non-inactivating (I_{BK}). Addition of either fast K^+ current to the minimal model could transform the spike pattern from spiking to bursting. However, while I_{BK} caused a reliable increase in $[Ca^{++}]_i$, I_A did not. This difference could be explained by analyzing how each fast K^+ current affected the spiking pattern. While I_{BK} allowed the cell to continue spiking at higher Ca^{++} levels (compared to the spiking level), I_A forced the cell to decrease its $[Ca^{++}]_i$ before spiking could start. However, for certain combinations of the model parameters, I_A could induce bursting through a different mechanism than the classical "bistability + slow variable(s)" mechanisms,. In these conditions, increasing I_A could provoke an increase in $[Ca^{++}]_i$.

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POSTERS

The effect of coupling on a one-dimensional bursting map

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Bursting is a complex oscillatory phenomenon in which periods of rapid oscillation (or chaotic behaviour) alternate with periods of relative quiescence. Bursting is observed in nature, for example in the electrical potential across the membrane of some living cells. A desirable feature of models for bursting is that bursting persists when coupling is introduced. Continuous-time bursting models (ODEs) have been well studied. In general, bursting persists when such models are coupled. Discrete-time bursting models (maps) also exist, and can be much less computationally expensive, though they have not been studied in much detail. We investigate the one-dimensional Izhikevich-Hoppensteadt bursting map. Interestingly, we find that bursting disappears when two such maps are coupled. Instead, we find simple oscillations, including in-phase and anti-phase 2-cycles, 3-cycles, etc., depending on initial conditions and coupling strength. This seems to suggest that discrete-time models may not be a suitable alternative to continuous-time models for the purpose of modelling bursting.

ANIMATLAB: a physics based 3-D graphics environment for behavioral neurobiology research

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Understanding neural mechanisms of behavior has frequently depended on comparisons between detailed descriptions of freely behaving animals and fictive motor programs displayed by neurons in anesthetized, restrained, and dissected preparations. We have developed a software toolkit, AnimatLab, to help researchers determine whether their descriptions of neural circuit function can account for how specific patterns of behavior are controlled. AnimatLab enables one to build a virtual body from simple LEGO™-like building blocks, situate it in a virtual 3-D world subject to the laws of physics, and control it with a multi-cellular, multi-compartment neural circuit model. A Body Editor enables adjustable blocks, balls, truncated cones, and cylinders to be connected through a variety of joints to form a body. Sensors enable extrinsic and intrinsic signals to be detected, and virtual muscles governed by Hill muscle models span the joints to produce movement. The body and other objects are subject to gravity, buoyancy, drag, friction, contact collision, and muscle tension. A Neural Editor enables a neural network to be constructed from a menu of neurons and synapses, and then linked to sensors and effectors on the body. We are currently using AnimatLab to study the neural control of locomotion and the escape behavior of crayfish. Several simulations have been built that demonstrate how small neural networks can produce complex behaviors like walking over rough terrain, navigation around obstacles, and using olfactory cues to find and consume food in an unpredictable environment.

A class of neurons in the pre-Bötzinger complex become bursting pacemakers when exposed to severe hypoxia

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In vivo, the respiratory response to acute hypoxia follows a characteristic sequence. An initial increase in frequency and amplitude of inspiration is followed by primary apnea, gasping, and finally terminal apnea. Gasping, which is characterized by large amplitude, short-duration inspiratory breaths that occur at a low frequency, is an important mechanism for survival during hypoxemia and for auto-resuscitation. Here we explore the changes that occur within the pre-Bötzinger complex that are responsible for the change from eupnea to gasping. Previous work has shown that the inspiratory neurons may be divided into two broad classes: follower cells and pacemakers. The initial increase in burst frequency is due to a change in the burst frequency of the pacemakers. Additionally, among the pacemaker neurons there are two classes: those that cease bursting during prolonged hypoxia and those that continue to burst. The neurons that continue to burst in hypoxia are sensitive to riluzole, a persistent Na+ channel blocker, while the others are sensitive to Cd2+ and flufenamic acid, a blocker of the CAN current. We have recently discovered another class of pacemaker neurons that only become pacemakers under severe hypoxia. In hypoxia and when isolated pharmacologically from the network, these neurons show changes in their burst properties that are consistent with gasping: an increase in the instantaneous spike frequency within a burst, a decrease in burst duration, and a decrease in burst frequency. Similar to the pacemaker neurons that were found to continue bursting after prolonged hypoxia, these neurons are insensitive to Cd2+ but sensitive to riluzole. Interestingly, within the intact network these neurons may also contribute to the initial increase in amplitude of fictive eupnea during the hypoxic response. We hypothesize that these neurons may be important for the reconfiguration of the network necessary to produce gasping.

A model of long period bursting activity

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Some neurons exhibit bursting activity with a period of several hours. Frequently, the long-periodic activity is attributed to dynamic transcription of clock genes (Hastings and Herzog, 2004). In this work we explore properties of a model of endogenously bursting neuron with dynamics based on the long-period oscillations of cytosolic Ca^{2+} concentration. First, we analyze Ca^{2+} dynamics described by the Friel model (Friel, 1995). It is a "minimal" model describing dynamics of two variables: cytosolic Ca^{2+} concentration and concentration of Ca^{2+} in internal store. The Friel model accounts the fluxes of Ca^{2+} ions between cytoplasm and extracellular medium and cytoplasm and endoplasmatic reticulum. In our work we perform the bifurcation analysis and determine the parameter regions of three stable states: two distinct stationary and one oscillatory. Of our special interest is the parameter region corresponding to the periodic oscillations. We identify a parameter that can linearly control the period of the oscillations of cytosolic Ca^{2+} concentration. Its increase causes the linear increase of the period from 30 seconds through several hours. Second, we propose a neuron model employing voltage-dependent currents involved in spikes generation and the CAN (Calcium Activated Nonselective cation) current. This current has been detected in various neurons (Cho et al., 2003). Its conductance depends on cytosolic Ca^{2+} concentration, so that the increase of cytosolic Ca^{2+} concentration opens the CAN channels. The CAN current possesses a negative reversal potential E_{CAN} about -20mV. Therefore, in this model the cytosolic Ca^{2+} concentration may drive the bursting activity. Regulations and transformations of the bursting activity are analyzed in the model as well. The Friel model can exhibit long-periodic Ca^{2+} oscillations in the range from 30 seconds through several hours. Dependence of the period of $[Ca^{2+}]$ oscillations on the rate of the SERCA pump is proven to be linear. The biophysical mechanism describing this phenomenon is based on that the increase of the rate of the SERCA pump causes linear increase of amplitude of oscillations of Ca^{2+} concentration in the endoplasmatic reticulum, which in turn leads to the linear increase of the length of the periodic closed orbit. Complete bifurcation analysis of stationary and oscillatory states of the Friel model is carried out. Dependence of the temporal oscillatory properties on some experimentally accessible parameters is described. A model of calcium driven bursting activity of a neuron is proposed and analyzed. The same controlling parameters regulate the period linearly in the range from 30 seconds through several hours while duty cycle remains constant.

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Burst firing in dopamine neurons of the substantia nigra

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The firing pattern of midbrain dopamine (DA) neurons determines basal ganglia output and allows for coordinated motor behavior. In particular, the transition from tonic to burst firing profoundly increases the amount of dopamine and co-peptides released into the striatum. The ionic mechanisms underlying bursting are not entirely clear, and at least two alternate mechanisms have been proposed based on either calcium- or sodium- dependent conductances. Burst firing in dopamine cells was characterized *in vitro* using whole-cell patch-clamp recordings of Substantia Nigra pars compacta (SNC) slices from adult mice. NMDA-induced bursting was found to be cadmium-insensitive, suggesting that voltage-gated calcium channels are not strictly required for the maintenance of burst mode. However, bursting was completely disrupted by flufenamic acid, a specific blocker of the calcium-activated non-specific cation current (I_{CAN}). Therefore, I_{CAN} may be a novel component of *in vitro* bursting in DA neurons. We propose that NMDA-induced calcium-influx activates the CAN current which in turn leads to the non-linear amplification of the NMDA component. For decades, DA neurons of the SNC have been described as a fairly homogenous population with respect to their basic electrical properties and network connectivity. However, both the tonic pacemaker activity and burst firing recorded *in vitro* varies quantitatively among the neurons sampled in this study. Firing patterns differed in several parameters, including: frequency, regularity, inter-spike interval, burst duration, and number of spikes per burst. Moreover, cells within the population exhibited non-uniform pharmacological profiles in response to excitatory transmitters (i.e. glutamatergic, cholinergic) and channel blockers (i.e. Apamin). Therefore, we propose that SNC neurons possess a previously unappreciated heterogeneity in intrinsic membrane properties that may be important for the functioning of the SNC under physiological and pathophysiological conditions, such as Parkinson's disease.

Smooth and Lurching Pulses in Two-Layer Thalamocortical-Reticular Integrate-and-Fire-or-Burst Networks

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Ferret slices of lateral geniculate neucleus (LGN) and its companion reticular structure the perigeniculate nucleus (PGN) are known to generate "spindle" wave oscillations in the 7-10 Hz. range. These oscillations are due to synaptic connections between the glutametergic thalamocortical (TC) neurons in the LGN and GABAergic reticular (RE) neurons in the PGN, and intrinsic transient low-threshold calcium "T"-currents that when activated cause bursts of action potentials in both of these cell types \cite{thalmoAssem}. Lateral connections in these structures serve to propagate this activity [1].

Simulated integrodifferential equation models of propagating "spindle" waves in one-dimensional networks comprised of distinct thalamocortical (TC) and reticular (RE) cell layers have observed both smooth and lurching wave pulses depending on the types of synaptic connectivity used [2,3,4]. In the present study we use a reduced two-layer TC-RE network comprised of integrate-and-fire-or-burst (IFB) neuronal populations to explore the existence of smooth and lurching pulses analytically. First, we show analytically, under generic conditions, that smooth pulses cannot exist with an "on-centered" synaptic connection topology consisting of a wide RE to TC synaptic footprint and narrow TC to RE synaptic footprint. Second, we solve for exact smooth and lurching pulse singular solutions in two-layer TC-RE IFB networks. To this end we use techniques similar to those employed by Coombes (2003) [5] to study wave-pulses in single-layer IFB networks in combination with singular perturbation methods where synaptic variables tend quickly to their asymptotic values. Smooth pulses are solved for in the case of off-center wide TC to RE and narrow on-center RE to TC footprints. We solve for lurching pulses in the case of wide on-center RE to TC and narrow on-center TC to RE synaptic footprints. These solutions corroborate the numerical observations in Terman, Ermentrout, and Yew (2001)

[3] . Furthermore, these exact solutions provide the wave speed of the pulse and how the speed depends on parameters of the synaptic footprint and physiological parameters. The solutions show that the speed of wave propagation in the smooth case depend on parameters in the RE layer whereas the propagation in the case of a lurching pulse depends primarily on parameters in the TC layer. Additionally these analytical results corroborate the findings from simulations of biophysically detailed models studied in Golomb, Wang, and Rinzel (1997) [2], where the speed of the lurching front depends primarily on sum of the width of the synaptic footprints between the TC and RE layers and the T-current decay time constants.

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Periodic Bursting in Two Identical Coupled Cell Systems

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Analysis in terms of fast-slow dynamical systems gives insights into mechanisms for generation of bursting behavior. Bursting behavior in neurons can be generated due to interactions between neurons in a network. For example, brain functions such as motor control, information processing and memory formation frequently involve bursting behavior of neurons. On the other hand, periodic bursting in fast-slow system can be viewed as closed paths through the unfolding parameters of degenerate singularities. Using this approach we show that bursting in coupled systems can have interesting behavior. Here we study and focus on the analysis of two identical cell systems, and use the Z_2 symmetry present in such systems to illustrate surprisingly interesting bursting phenomena. In particular, we show that Hopf bifurcation and Hopf bifurcation mode interactions can lead to bursting between in phase and out of phase periodic solutions, and symmetry-breaking Takens-Bogdanov singularities can lead to bursting that randomly chooses between two symmetrically related limit cycles.

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Analysis of the lobster pyloric pacemaker kernel via computational exploration of the parameter space of its multi-compartment model

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The lobster pyloric network produces rhythmic activity generated by a pacemaker group of electrically coupled neurons AB and PD. The AB neuron is an intrinsic burster and is smaller than the two PD neurons, which spike tonically if isolated from AB. We explored the 23-dimensional parameter space of a 4-compartment model of this pacemaker kernel to examine why the pacemaker includes two types of neurons with different properties, and how its behavior depends on their cellular and synaptic properties. The model consisted of one AB coupled to one PD model neuron, each with a somato-neuritic and an axonal compartment. Our computational exploration started with a hand-tuned pacemaker model (Soto-Treviño et al, J Neurophysiol 94: 590-604, 2005) and systematically varied maximal conductances of membrane currents. In future work, variations of axial conductances as well as the electrical coupling strength will be investigated. To reduce computation time, the parameter space of each individual neuron was first explored separately. Every parameter set for an individual model neuron was simulated and classified as functional if that parameter set produced spiking (for PD) or bursting (for AB) activity and proper responses to the model equivalent of deafferentation (i.e., neuromodulator deprivation) within the range observed in the isolated biological AB and PD neurons. Many different parameter sets performed successfully under all tested conditions, suggesting that the properties of a pacemaker kernel with multiple neurons do not have to be narrowly tuned to achieve functional and robust pacemaker output.
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The role of $5HT_{2\ bPan}$ and $5HT_{1\ aPan}$ receptors in mediating the 5-HT induced change in pyloric cycle frequency in the spiny lobster, Panulirus interruptus.

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Rhythmogenic neurons rely heavily on neuromodulators to initiate, terminate and shape a burst; therefore, a comprehensive understanding of pattern generation requires knowledge of the transduction cascades that underlie modulatory effects. To this end we are examining the roles of the $5\text{-}HT_{2\ Pan}$ and $5\text{-}HT_{1\ Pan}$ receptors in mediating the 5-HT induced changes in the cycle frequency of the pyloric network. Application of 5-HT had variable effects on pyloric cycle frequency and could either significantly increase (class I response, 7/18 preparations) or decrease (class II response, 11/18 preparations) cycle frequency by 29+3% and 59$\pm$12%, respectively. Interestingly, the mean cycle frequency of class I responders was significantly faster than class II responders in the intact preparation (1.25$\pm$0.09 Hz vs. 0.89$\pm$0.08 Hz, $p<0.02$), but was identical when modulatory input was removed (0.77$\pm$0.06Hz.). These data suggest that there is a stable difference in the pyloric circuit between the class I and class II responders, and that this difference is only uncovered when neuromodulators are present, and in particular 5-HT. To determine if and how $5\text{-}HT_{1\ Pan}$ and $5\text{-}HT_{2\ Pan}$ receptors contribute to the differences between the classes, we first sought to obtain pharmacological tools that would allow us to define their roles in mediating the class I and class II response. Using cloned receptors in a heterologous expression system we found that (+)butaclamol, cinanserin and ritanserin were specific antagonists for $5\text{-}HT_{2\ Pan}$. On the other hand, mCPP was a specific agonist for $5\text{-}HT_{1\ Pan}$ receptors. Using these drugs we were able to show that $5\text{-}HT_{2\ Pan}$ receptors mediate the early portion of the 5-HT response in both class I and class II responders. Interestingly, when the $5\text{-}HT_{2\ Pan}$ receptors are pharmacologically blocked there is no longer a significant difference between class I and class II responders in the presence of 5-HT, suggesting that state determination could be associated with the $5\text{-}HT_{2\ Pan}$ transduction cascade. On the other hand, $5\text{-}HT_{1\ Pan}$ receptors may be involved in the later portion of the 5-HT response in all preparations. We are now investigating whether differences in gene expression can account for the variability in the 5-HT response.

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Respective contributions of two negative feedback processes in neuronal rhythms

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Neuronal systems involve a large number of dynamical processes interacting to generate a given activity pattern. To analyze the role of a process, neuroscientists often "remove" it from the system. However, this may change the system's dynamical mode. Instead, we propose to assess the role of a dynamic process by varying the speed of that process. We look at a relaxation oscillator model of neuronal episodic activity, whereby the system with autocatalysis switches between a high and a low activity state due to two slow negative feedback processes. One negative feedback process acts as a divisive factor, i.e. it directly decreases the gain in the autocatalysis loop, while the other process acts as a subtractive factor. To assess the role of each process, we vary the corresponding variable's time constant. If a particular process is responsible for terminating a given phase of the oscillation, then slowing down that process should lengthen this phase of the activity accordingly. This analysis shows that for Hodgkin-Huxley-type models of neuronal oscillations, the subtractive process corresponding to the outward (potassium) current sets the length of the silent phase of the oscillations, while the divisive process corresponding to inward (sodium) current inactivation mainly contributes to the length of the active phase.

Bursting: an intrinsic switching mechanism of synchronous neuronal firing

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The brain signals such as local field potentials often display the gamma-band (30-70 Hz) oscillations in a variety of cognitive tasks. These oscillatory activity possibly reflect synchronization of cell assemblies that are engaged in a specific cognitive function. A type of pyramidal neurons, i.e., chattering neurons, show fast rhythmic bursting (FRB) in the gamma frequency range, and can be the origin of the stimulus-dependent gamma-band oscillations in the cerebral cortex. Several different mechanisms have been proposed for FRB. Some experimental results suggested that calcium-activate nonselective cationic current contributes to the generation of FRB, while other experimental studies suggested that the electric interactions between soma and dendrite play a crucial role in generating FRB. Here, using phase-response analyses of multi-compartment models, we demonstrate synchronization and desynchronization among FRB neurons are governed by the changes in the FRB patterns irrespective of the detailed biological mechanisms of bursting. Generally, synchronization and desynchronization are exchanged rapidly when the bursting mode is changed between singlet, doublet and, so on. These results suggested that the chattering neurons may significantly contribute to the rapid establishment of synchrony at the gamma frequencies. To investigate this possibility in further details, we analysis the phase-response of the simple neuron model proposed by Izhikevich. The model can exhibit a variety of firing patterns including FRB. We found that the synchronization properties of the model in FRB firing patterns are similar to those shown by complex conductance based FRB neuron models. Therefore, we may conclude that the model is suitable for simulating the dynamic behavior of large-scale networks.

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Bursting without a slow variable in a model of the pituitary lactotroph

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Prolactin (PRL) is a hormone secreted by lactotrophs, which are excitable cells located in the anterior lobe of the pituitary gland. Dopamine (DA) is a well known prolactin inhibitor. When DA is added in a high (micromolar) concentration to lactotrophs in cell culture, it inhibits the cells' activity, which results in a decrease of PRL release. But when a low (nanomolar) concentration of DA is used, PRL release is increased. It has been shown that DA increases the activation of A-type K^+ channels. In our model, an increase in the conductance of A-type K^+ channels results in a qualitative change of the lactotroph electrical activity: the cell switches from spiking to bursting. Thus our model provides a possible mechanism for the stimulatory effect of DA: at low concentrations, DA converts spikers to bursters, which may increase the release of PRL. In most models of endocrine cells, activity-dependent changes in a slow process provides the mechanism for switching between a spiking and a silent phase, producing a bursting pattern. In contrast, our three variable model produces bursting with fast variables only.

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