Principles of Motor Pattern Generation:
Experiments and Modeling

Organizers: Carmen Canavier (LSUHSC) and Andrey Shilnikov (GSU)

July 26, 2012

Tentative schedule

9:00 - 9:40 Allen Selverston (UCSD) "New ways for experimentalists and modelers to look at CPGs"

9:40: - 10:20 Akira Sokurai (GSU) "A natural example of different circuit architectures for analogous behaviors in different species"

Coffee break - 15min

10:30 - 11:10 Andrey Shilnikov (GSU) "Bifurcation of polyrhythmic patterns in 3-cell bursting motifs"

11:10 - 11:50 Thomas Nowotny (Sussex, UK) "Central patterns generation with heteroclinic orbits"

Lunch break

13:00 - 13:40 Brian Mulloney (UC Davis) "Experimental and computational analysis of an intersegmental coordination circuit"

13:40 - 14:20 Carmen Canavier (LSU) "Functional phase resetting and the pyloric circuit"

Coffee break – 20 min

14:40 - 15:20 Maxim Bazhenov (UCR) "Ionic dynamics mediate tonic-clonic pattern generation in epilepsy"

15:30 - 17:30 Panel discussion – "CPG modeling and verification feedback"

18:30 Dinner at "The Iberian Pig"
121 Sycamore Street
Decatur, GA 30030 (404) 371-8800
http://www.iberianpigatl.com/index.php
http://www.theiberianpigatl.com/pdf/Menu.pdf

New ways for experimentalists and modelers to look at CPGs

Allen Selverston (UCSF)

Abstract: The central pattern generators (CPGs) of invertebrates have features that make them uniquely profitable for examining the cellular mechanisms underlying rhythm generation and pattern formation. Early ideas about hard wired circuits have been replaced by circuits that demonstrate a high degree of flexibility in response to neuromodulators and sensory feedback. Identified neurons and synapses, a hallmark of invertebrate CPGs, are now thought to have a range of conductances and strengths permiting degenerate solutions to neuronal computations. These advances will have significant impact on modeling studies, a necessary component of CPG research. To illustrate this, I will demonstrate how standard modeling techniques were used to examine the dynamics of a three neuron network in the lobster stomatogastric ganglion. Neurons were connected with asymmetrical synapses similar to the LP-PD-PY network. Considerable insight was gained regarding the relative roles of intrinsic bursters, networks and hybrid circuits as the basis for rhythmogenesis and pattern formation. The results also provided some insight into the robustness-flexibility dilemma. Other models have started to examine networks with variable parameters and suggest how clusters of different conductance parameters can lead to similar patterns of activity. Finally I will suggest future research trends for the analysis of invertebrate CPGs that incorporate new molecular techniques.

A natural example of different circuit architectures for analogous behaviors in different species

Akira Sakurai and Paul S. Katz
Neuroscience Institute, Georgia State University

Recent modeling studies have shown that neuronal circuits with considerably different membrane and synaptic parameters might produce relatively similar network outputs. However, there is still a general assumption that similar behaviors in related animal species originate from a common neural architecture. In this study, we show that two species produce similar behaviors using homologous neurons connected in circuits having distinct architectures and dynamics.

The nudibranch molluscs *Melibe leonina* and *Dendronotus iris* exhibit swimming behaviors consisting of rhythmic left-right body flexions. It was previously shown in *Melibe* that the central pattern generator (CPG) for swimming consists of two bilaterally symmetric neurons, Swim Interneuron 1 ($Si1_{Mel}$) and Swim Interneuron 2 ($Si2_{Mel}$). $Si1_{Mel}$ and $Si2_{Mel}$ are electrically coupled ipsilaterally and mutually inhibitory with both contralateral counterparts. Their homologues ($Si1_{Den}$ and $Si2_{Den}$) have been identified in *Dendronotus* but their synaptic connections are fundamentally different. The $Si1_{Den}$ neurons do not form mutual inhibitory synapses but are electrically coupled to all other swim interneurons. $Si1_{Den}$ does not function as the member of the swim CPG; rather its tonic firing initiates and accelerates the swim motor program.

In addition to Si1 and Si2, we recently found an additional bilateral pair of neurons, Si3, in both species. The Si3 pair forms another half-center oscillator element that is interconnected with the Si1/2 complex. In *Melibe*, $Si3_{Mel}$ receives excitatory input from the ipsilateral $Si1_{Mel}$, and makes inhibitory synapses onto the contralateral $Si1_{Mel}$. This causes $Si3_{Mel}$ bursts to be approximately 25% phase delayed from the contralateral Si1/2 bursts. Injecting hyperpolarization current into $Si3_{Mel}$ slowed down but did not stop the rhythm, suggesting that $Si3_{Mel}$ plays an important role in pattern generation, but is not critically necessary for rhythm generation. In contrast, in *Dendronotus*, each $Si3_{Den}$ drives the contralateral $Si2_{Den}$ via strong electrical and chemical excitatory synapses, making the $Si3_{Den}$ burst slightly phase-advanced to the contralateral $Si2_{Den}$ burst. A hyperpolarizing current injection into $Si3_{Den}$ suppressed the rhythm, suggesting their critical role in the rhythm generation. Thus, despite having homologous neurons producing similar two-phase motor outputs, there are substantial differences in network architecture, phase relationships, and internal dynamics between these two CPGs.

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Bifurcation of polyrhythmic patterns in 3-cell bursting motifs

Jeremy Wojcik, Robert Clewley and Andrey Shilnikov
Neuroscience Institute and Department of Mathematics
Georgia State University, Atlanta, GA, 30303

We examine multistability of several coexisting bursting patterns in a central pattern generator network composed of three Hodgkin-Huxley type cells coupled reciprocally by inhibitory synapses.
It is established that the control of switching between bursting polyrhythms and their bifurcations are determined by the temporal characteristics, such as the duty cycle, of networked interneurons and the coupling strength asymmetry.
A computationally effective approach to the reduction of dynamics of the nine-dimensional network to two-dimensional Poincare return mappings for phase lags between the interneurons is presented. We describe the effective way educe detailed models of central pattern generators to equation-less return mappings for the phase lags between the constituting bursting interneurons. Such mappings are studied geometrically as the model parameters, including coupling properties of inhibitory and excitatory synapses, or external inputs are varied. Bifurcations of the fixed points and invariant curves of the mappings corresponding to various types of rhythmic activity are examined. These changes uncover possible biophysical mechanisms for control and modulation of motor-pattern generation. Our analysis does not require explicit phase equations that model the system, and so provides a powerful new approach to studying detailed models, applicable to a variety of biological phenomena beyond motor control.
We demonstrate our technique on a motif of three reciprocally coupled, inhibitory and excitatory, cells that is able to produce multiple patterns of bursting rhythms. Motifs of three coupled cells are a common network configuration including models of biological central pattern generators.
The family of 2D mappings reveals the organizing centers of emergent polyrhythmic patterns and their bifurcations, as the asymmetry of the synaptic coupling is varied.

[1] Shilnikov A.L., Gordon R. and Belykh I.V., Polyrhythmic synchronization in bursting network motifs, J. Chaos, 18, 037120, 2008, DOI: 10.1063/1.2959850. Virtual Journal of Biological Physics Research: biological networks. 16(7), 2008.

[2] Wojcik J., Clewley R, and Shilnikov A., Order parameter for bursting polyrhythms in multifunctional central pattern generators. Physics Review E 83, 056209-6, 2011

[3] Belykh I.V. and Shilnikov, A.L., When weak inhibition synchronizes strongly desynchronizing networks of bursting neurons, Phys. Rev. Letters 101, 078102, 2008. Virtual Journal of Biological Physics Research: biological networks, 16(4), 2008.

[4] Wojcik J., Clewley R, and Shilnikov A., Principle bifurcation of polyrhythmic patterns in 3-cell bursting motifs, submitted to J. Neuroscience, 2012.

Title: Central patterns generation with heteroclinic orbits

Abstract:
Heteroclinic orbits have been suggested [1] as a dynamical systems construct underlying the generation of stable yet flexible motor patterns by central pattern generators (CPGs) in the nervous system. In this talk I will review the original models underlying these ideas, the mathematical formulation in the form of modified Lotka-Volterra models and how heteroclinic dynamics relates to the trade-off between stability to perturbations against sensitivity to meaningful inputs.
In the second part of the talk I will present results on extensions of the heteroclinic ideas to Hodgkin-Huxley type conductance based models [2] and discuss our recent paper [3] on the structural stability of heteroclinic orbits in this model class.

[1] Valentin S. Afraimovich, Mikhail I. Rabinovich, P. Varona. Heteroclinic Contours in Neural Ensembles and the Winnerless Competition Principle. Intern. J. Bifurcat. Chaos 14(4): 1195-1208 (2004).

[2] Thomas Nowotny, Mikhail I. Rabinovich. Dynamical origin of independent spiking and bursting activity in neural microcircuits, Phys Rev Lett 98: 128106 (2007).
[3] Peter Ashwin, Ozkan Karabacak, Thomas Nowotny. Criteria for robustness of heteroclinic cycles in neural microcircuits, J. Math. Neurosci. 1: 13 (2011).

“Experimental and computational analysis of an intersegmental coordination circuit”

B. Mulloney[1], Jiawei Zhang[2], T.M. Wright, Jr.[1], C Smarandache-Wellmann[3], and T.J. Lewis[2]
[1] Dept. Neurobiology, Physiology, and Behavior, and [2] Dept. Mathmatics, Univ. California, Davis. [3] Zoological Institute, Biocenter, University of Cologne, Germany

Many behavioral tasks require synchronization of distributed neural circuits, but details of the neural mechanisms that synchronize them are largely unknown. In the crayfish CNS, the modular local circuits that control swimmerets are distributed in four segments, but when the swimmeret system is active, the motor output from these modules are synchronized with a stable intersegmental phase-difference of 0.25, an example of metachronal synchronization. This phase difference is unaffected by changes in the system's period, an example of phase-constancy.

In each module, coordinating neurons encode detailed information about each cycle of the module's motor output as bursts of spikes, and export this information to modules in other segments. In a comprehensive set of recordings, we mapped the synaptic connections of two types of coordinating neurons onto their common target neurons in other segments – the intersegmental coordinating circuit. Each axon made its strongest synapse onto the target neuron in the nearest neighboring segment. Its synapses onto homologous targets in more remote segments were progressively weaker, a segmental gradient of synaptic strength. The shape-indices of these synaptic potentials (EPSPs) are tuned to transmit the coordinating information from each axon precisely. In each target neuron's own module, these bursts of EPSPs modified the phase of the module's motor output. Each target neuron decodes information from several coordinating axons, and the strengths of their synapses differ systematically. These differences in synaptic strength weight information from each segment differently, which we postulate can account for features of the system's characteristic metachronal synchronization.

The pattern-generating kernel of each swimmeret module has properties of a “half-center oscillator” in that it contains two sets of reciprocally-inhibitory local neurons that establish the key features of the module’s output. In one approach to understanding the system's phase-constant properties, we modeled it as a chain of local circuits constructed with conductance-based neuron models. First, we examined the phase-response properties of these circuits for two fundamentally different mechanisms that produce anti-phase activity in individual circuits: the "escape" and "release" mechanisms. We demonstrated that these different mechanisms give rise to very different phase-response properties, and we used phase-plane arguments to explain the different shapes of the phase-response curves. We then compare properties of these models to properties of the swimmeret system’s coordinating circuit, and consider the system’s synchrony and phase constancy.

Functional phase resetting and the pyloric circuit

Carmen Canavier (Louisiana State, HSC)

Phase resetting theory was developed for oscillators. Within the context of a central pattern generator (CPG), the oscillatory elements, or pacemakers, are often bursting neurons. Burst phase resetting curves, or the resetting of burst timing in response to a burst in another neuron, have been used to characterize pacemakers such as the AB/PD kernel in the pyloric circuit of the stomatogastric ganglion of the crab and lobster. However, not all components of CPGs are endogenous bursters. Other elements, such as post-inhibitory rebound (PIR) neurons or other types of follower neurons can be analyzed using the phase resetting formalism is the phase response is measured in response to a contingent pulse repeatedly applied at a fixed delay after burst initiation. We call this type of phase resetting curve a functional phase resetting curve. The contribution of the nonpacemakers, LP and PY, to the pyloric triphasic rhythm can be better understood using this protocol.

Ionic dynamics mediate tonic-clonic pattern generation in epilepsy

Many types of epileptic seizures involve repetitive periods of tonic (fast spiking) and clonic (bursting) activity. We found that the coexistence of tonic spiking and bursting states for a range of extracellular K+ concentrations is critical for the maintenance of seizure-like activity. Increase of intracellular sodium concentration causing the disappearance of bistability between tonic spiking and bursting leads to a quick termination of seizures. We further report that reducing sodium spiking currents in pyramidal cell dendrites rids of bistability as well. In terms of dynamics of the model, the mechanism underlying the smooth transition is due to a safe bifurcation of a homoclinic orbit of a saddle-node equilibrium state terminating the quiescence period of bursting. We hypothesize that a similar topology of quiescence and tonic spiking manifold in a phase space of other high-order models guarantees an absence of sustainable seizure-like activity. Our results will likely have implications onto drug development and deepen our understanding of the origin of seizure.