

PHASE AND EXACT MODELS FOR MULTIFUNCTIONAL CENTRAL PATTERN GENERATORS

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ABSTRACT

We compare multistability in central pattern generator (CPG) motifs comprised either of biologically plausible Hodgkin-Huxley models of bursting leech heart interneurons or of phenomenologically reduced phase models. We propose a novel computational tool for detailed examination of polyrhythmic bursting in biophysical CPG models with coupling asymmetries and arbitrary coupling strength. We carry out the comparison of the 3-cell motifs with reciprocally inhibitory asymmetric connections by reducing the consideration to the examination of the qualitative geometric structure of two-dimensional maps for phase lag between the bursting cells.

3-CELL MOTIFS

The ability of distinct neural anatomical circuits, such as central pattern generators (CPG), to generate multiple bursting patterns determining motor behaviors such as heartbeat, respiration, and locomotion is widespread in animals and humans [1, 2]. While a dedicated CPG generates a single pattern robustly, a multifunctional CPG can flexibly produce distinct rhythms, such as temporarily distinct swimming versus crawling, and alternation of blood circulation patterns in leeches, for example [3]. Multistability enhances the flexibility of nervous systems and has far reaching implications for motor control, dynamic memory, information processing, and decision making in humans and animals. Switching between locomotive behaviors can be attributed to switching between various attractors of a CPG network [4]. Each attractor is associated with a definite rhythm on a specific time scale. The emergence of synchronous rhythms in neural networks is closely related to temporal characteristics of the coupled

neurons due to both their intrinsic properties and types of synaptic coupling (inhibitory and excitatory) [5]. When the individual neuron is close to the transition from bursting into tonic spiking, the dynamics of the network become sensitive to small changes in synaptic coupling strengths.

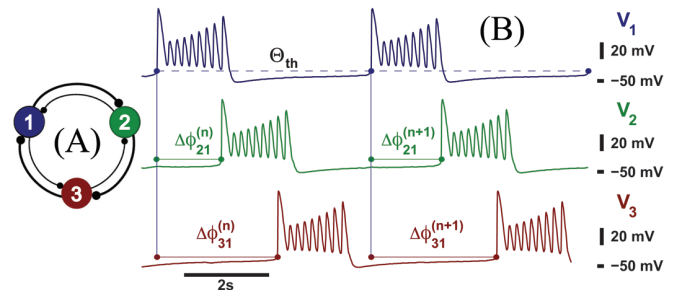


Figure 1. (A) 3-cell bursting motif with unbalanced clockwise and counter-clockwise connection strengths. (B) Voltage clockwisely rhythm generated by the motif of the leech heart interneurons: the phase of reference cell 1 (blue) is reset when V_1 reaches threshold Θ_{th} . The time delays between the burst onset in the reference cell 1 and the burst onset in cells 2 (green) and 3 (red), normalized over the recurrent time of cell 1, define a sequence of phase lags $\{\Delta\phi_{21}^{(n)}, \Delta\phi_{31}^{(n)}\}$ (defined on mod 1).

Elemental circuit configurations for CPG models are often reduced to 3-cell motifs comprised of anatomically and physiologically diverse neurons. Many CPG circuits involve a 3-cell motif, including the spiny lobster pyloric network, the *Tritonia* swim circuit, and the *Lymnaea* respiratory CPGs [2]. The 3-cell motif can be treated as a universal building block for larger, re-

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alistic multifunctional CPGs. We propose a novel computational tool for detailed examination of polyrhythmic bursting in biophysical CPG models with coupling asymmetries and arbitrary coupling strength. The tool reduces the problem of stability and existence of bursting rhythms in large networks to the bifurcation analysis of fixed points (FP) of Poincaré return mappings for phase lags. We demonstrate that a 3-cell motif made of bursting interneuron models and phenomenological phase models can robustly generate similar multistable rhythmic patterns. We show how rhythms of the multistable motif are selected by changing the relative timing of bursts by physiologically plausible perturbations and that the set of possible rhythmic outcomes can be controlled by varying the coupling around the motif.

PHASE-LAG MAPPING FOR BURSTING INTERNEURONS

First we consider a CPG motif comprised of endogenously bursting neurons from the leech heart [6] that are coupled in a reciprocally inhibitory ring using fast synapses described by the fast threshold modulation (FTM) [4]. FTM implies that the post-synaptic current is zero (resp., maximized) when the voltage of a driving cell is below (resp., above) a synaptic threshold. The duty cycle (DC) of bursting oscillations, which is the fraction of the burst period in which the cell is spiking, is known to affect the synchronization properties of coupled bursters [5, 7]. Many physiological parameters, including intrinsic and external currents, can continuously affect the DC of a cell, especially when the latter is close to a transition to tonic spiking (DC=1) or hyperpolarized quiescence (DC=0).

In this study we consider a weakly coupled motif by using an adequately chosen value of maximal conductance for the synapses coupling the cells [4]. Such weak coupling guarantees relatively slow convergence of transients to phase-locked states of the motif, and permits us to visualize “smooth” trajectories that expose in detail the structure of phase-lag return maps, qualitatively resembling time-continuous planar vector fields in this case. The findings obtained for the weak coupling case prepare the basis for understanding more complex patterns in strongly coupled, non-homogeneous motifs with the same technique. Asymmetry in the motif is controlled by another bifurcation parameter, which proportionally enforces (weakens) counter-clockwise (resp., clockwise) coupling strengths.

As the period of oscillations generated by the coupled cell can fluctuate in time, we define delays between the onset of bursting in cell 2 (green) and cell 3 (red) relative to that in the reference cell 1 (blue) at the instances the voltages V_i increase through a threshold (Fig. 1). The subsequent delays normalized over the period of the cell 1 define a forward trajectory $\{\Delta\phi_{21}^{(n)}, \Delta\phi_{31}^{(n)}\}$ of phase-lag return maps on a torus $[0, 1) \times [0, 1)$ with $\Delta\phi_{i1} \bmod 1$. The maps are tabulated on a 40×40 (or more) grid of initial points [8]. We can then study the dynamical properties of the maps, locate fixed points and evaluate their stability, detect periodic and heteroclinic orbits, and identify the underlying bi-

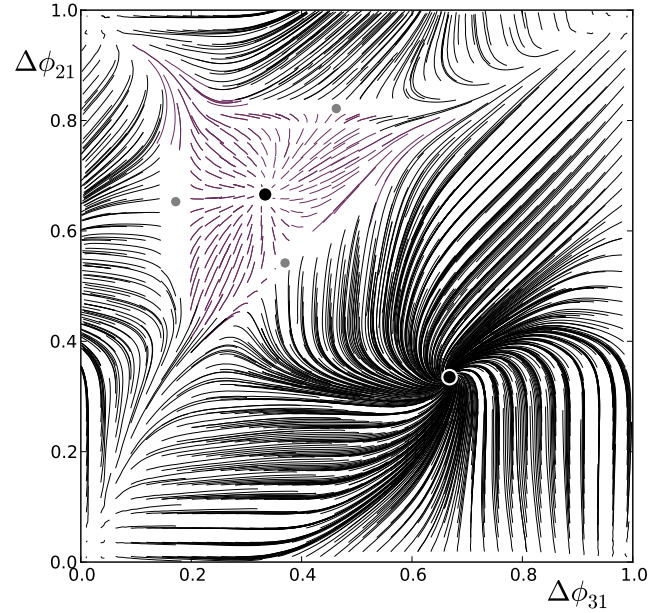


Figure 2. $(\Delta\phi_{31}, \Delta\phi_{21})$ phase lag map for the highly asymmetric ($g_{\ominus} = 0.8$) medium bursting motif depicting two attractors: the one for the clockwise ($1 \prec 2 \prec 3$) rhythms prevails over the attractor for the counter-clockwise ($1 \prec 3 \prec 2$) rhythm.

furcations as the control parameters of the network are varied. Figure 2 shows the $(\Delta\phi_{31}, \Delta\phi_{21})$ phase-lag map for the asymmetric long bursting motif with an 80% duty cycle. The map possesses two stable fixed points corresponding to the coexisting phase-locked bursting patterns: black ($\Delta\phi_{31} \approx \frac{2}{3}, \Delta\phi_{21} \approx \frac{1}{3}$) and purple ($\frac{1}{3}, \frac{2}{3}$). The attraction basins of these points are divided by separatrices (incoming and outgoing sets) of three saddle points (grey dots). While the existence of the $(1 \prec 2 \prec 3)$ and $(1 \prec 3 \prec 2)$ rhythms in a 3-cell motif can hypothetically be deduced using symmetry arguments, the robustness and observability of the rhythms must be justified by accurate computation.

2 Θ PHASE MODEL

The knowledge of the existence, stability and bifurcations of the polyrhythms in the motif of the interneuron is vital for accurate derivations of reduced phenomenological phase models for CPGs. Below, we propose a “2 Θ ”-model for repetitive bursting with two slow-pace states: “on” and “off” corresponding to tonic spiking, at $\Theta = \pi$, and hyperpolarized quiescence, at $\Theta = 0$, on a unit circle. The 2 Θ -model of the 3-cell motif ($i = \{1, 2, 3\}$) is given by

$$\theta_i' = \omega - \cos 2\theta_i - H(\cos \theta_i)(1 + 2 \sin \theta_i) \left[\frac{g_i(i, i-1)}{1 + e^{\cos \theta_{i-1}}} + \frac{g_i(i, i+1)}{1 + e^{\cos \theta_{i+1}}} \right],$$

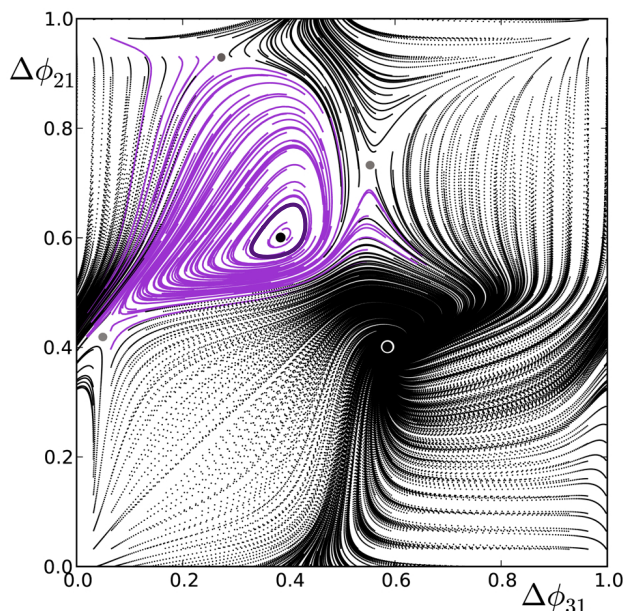


Figure 3. (top) 2D mapping for the angle differences between phase bursters at $\omega = 1.5$ showing two fixed points corresponding to unstable ($1 \prec 2 \prec 3$) and stable ($1 \prec 3 \prec 2$) rhythms due to asymmetry in the motif: $g_{ij} = 0.02$ and $g_{ji} = 0.0088$. The attraction basins, black (of the stable fixed point) and purple (of the stable invariant curve) in the mapping are divided by stable sets of three saddles (gray dots).

where H is the Heaviside function, $g_{(i,i+1)}$ and $g_{(i,i-1)}$ are maximal conductances of the FTM-based clockwise and counter-clockwise oriented synapses across the motif; another control parameter ω determines the frequency of the 2Θ motif.

Figure 3 represents the 2D mapping for the angle differences between phase bursters in the counter-clockwise, asymmetrically biased 3-cell motif. By comparing it with Fig. 2 one can observe that the 2Θ motif qualitatively mimics the bistability properties of the realistic motif comprised of the Hodgkin-Huxley interneuron models. A feature of the mapping for the asymmetric 2Θ motif is the occurrence of a stable invariant curve which is associated with the appearance of slow phase jitters within the ($1 \prec 2 \prec 3$) rhythm in voltage traces. The closed curve emerges from the fixed point through a secondary supercritical Andronov-Hopf (torus) bifurcation as the motif becomes less symmetric.

CONCLUSIONS

We presented a comparison of two 3-cell motifs: one is biophysically plausible and the other is phenomenologically reduced. Both motifs are multistable, i.e. is able to generate polyrhythms that are selected by initial conditions of the individual cells. We characterized the essential properties of each motif by measuring two phase lags between the three oscillators. By

systematic variation of the initial conditions, the computational exploration of the possible rhythmic outcomes led to a reduction of the original systems to a graphical and equationless representation of the 2D mapping for the phase lags. The geometric properties of the mappings, and how they change as control parameters of the network are varied, can be understood through standard qualitative techniques of dynamical systems theory. Thus, the phase locked rhythmic patterns of the motif correspond to stable fixed points of the maps; the basins of attraction for the rhythms are separated by phase thresholds known as saddles. As parameters are varied, bifurcations of the fixed point attractors determine changes in the rhythmic pattern outcomes.

Future investigations will explore asymmetric motifs and stronger coupling regimes, and will consider the addition of simple contextual circuits to the CPG such as proprioceptive feedback from motor control systems. Our approach also naturally generalizes to other regulatory networks involving reciprocal inhibition, which is a form of feedback found in a diversity of biological networks. We believe our approach is applicable to improved understanding of various phenomena featuring multistability such as memory formation, decision making, and enhancing synthetic approaches for generating motor behavior from artificial circuits.

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