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Small is beautiful: models of small neuronal networks

Damon G Lamb and Ronald L Calabrese

Modeling has contributed a great deal to our understanding of how individual neurons and neuronal networks function. In this review, we focus on models of the small neuronal networks of invertebrates, especially rhythmically active CPG networks. Models have elucidated many aspects of these networks, from identifying key interacting membrane properties to pointing out gaps in our understanding, for example missing neurons. Even the complex CPGs of vertebrates, such as those that underlie respiration, have been reduced to small network models to great effect. Modeling of these networks spans from simplified models, which are amenable to mathematical analyses, to very complicated biophysical models. Some researchers have now adopted a population approach, where they generate and analyze many related models that differ in a few to several judiciously chosen free parameters; often these parameters show variability across animals and thus justify the approach. Models of small neuronal networks will continue to expand and refine our understanding of how neuronal networks in all animals program motor output, process sensory information and learn.

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Introduction

Models of the small neuronal networks of invertebrates, especially rhythmically active central pattern generators (CPG), have proven to be fruitful subjects of investigation, revealing general principals of neuronal network function and generating hypotheses later supported by the living systems they represent. Over the past two decades, models of 'simple' networks, powered by efficient desktop computing and a wealth of physiological data, have provided guiding insights into how neuronal networks function. Over the past decade, theoretical studies, but now supported by experimental analysis in several different networks and species, have shown that reliable network output can result from networks in which parameters (e.g. the intrinsic membrane properties (maximal conductances) of the neurons and the strengths of the synaptic connections) show 2–5-fold animal-to-animal variability [1–3]. Consequently, to understand a neuronal network through biophysical modeling, we must construct populations of models with multiple sets of parameter values corresponding to parameters from different individuals [4–6]. A sobering consequence is that the computational effort needed to produce a state of the art biophysical model is vastly increased. The situation is clearly still fluid [4,5], but the reaction in the modeling community has ranged from a continued pursuance 'ideal parameter sets' or sticking to averaged values for parameters to what Prinz [6], calls ensemble modeling, where multiple functional instances are identified and examined. In this review we sample the diversity of small network modeling approaches to highlight how each continues to contribute significant new insights.

A note on models and parameters

Before we continue, we should distinguish between models and parameters. The models discussed in this review consist of differential equations that describe the dynamics of state variables, for example, membrane potential (V_m) and the gating variables of voltage dependent conductances. Embedded in these equations are a number of parameters, including maximal conductances as well as half activation voltages and time constants of channel gates. Some of these parameters are considered free, or variable between instances, while the remaining parameters are fixed. For example, in the pioneering work of Prinz *et al.* [2,3], only maximal conductances were considered free parameters. Even with powerful computing resources, it is not possible or desirable to consider all instances of a model. Making a model then involves deciding on a neuronal structure (single or multiple compartments), network connectivity, descriptive equations (often derivatives of the Hodgkin–Huxley formalism), which parameters are free and the range over which each may vary. These decisions will all be driven by the data available and by the investigators' intuition for which parameters are likely to be significant in controlling neuronal activity. In short, the ability to consider multiple instances of a model does not free one from making a good model, and making a good model requires detailed knowledge of the system and judgment about what details can be ignored and which parameters fixed.

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Swimming in *Tritonia*

The swimming CPG of *Tritonia* has long been the object of experimental analyses and modeling [7,8]. Calin-Jageman *et al*. [9••], updated the Getting model [10] to reflect new data on synaptic connectivity, intrinsic properties and intrinsic neuromodulation with a careful refitting of intrinsic and synaptic parameters, only to find that the network model did not produce the swim motor pattern in either the unmodulated or modulated state. Undeterred, they first compared their model's parameters to those of the original model and adjusted those that significantly differed to the values of the original model. This process restored the ability of the model to produce the swim pattern. They also performed a brute force parameter space investigation of the differing parameters and identified all models that produced the swim pattern (2%). They showed that all parameters sets leading to proper network function were contiguous in parameter space. Then, using discriminant analysis and dimensional stacking, they identified key parameters contributing to proper network function. Somewhat at a loss to explain how their carefully fitted model failed while the Getting model was successful, they suggest that, 'even if it reflects a nonphysiological configuration, it has still been a useful sign-post toward understanding the conditions that could enable the swim-motor program.'

Feeding in *Lymnea*

The feeding CPG of *Lymnea* is well characterized [11] and has been analyzed for mechanisms of associative learning in the form of single-trial, food-reward classical conditioning [12,13]. Vavoulis *et al*. [14], developed a model of the core CPG with fixed parameters selected to match excitability criteria and other physiological data. This model captured feeding activity and predicted physiological phenomena that were later verified experimentally. Corresponding work in the *Aplysia* feeding CPG [15] failed to capture feeding activity without an additional putative neuron which has yet to be identified physiologically. An interesting aspect of the *Aplysia* study is the extensive sensitivity analysis, including perturbations during simulations, which demonstrated the model activity's robustness to parameter variation.

Vavoulis *et al*. [16•], have continued the *Lymnea* work by focusing on the mechanisms of persistent depolarization of the cerebral giant cells (CGCs) that underlies single-trial, food-reward classical conditioning. To construct the model CGC neuron they used a combination of fitting to available voltage-clamp data and parameter optimization techniques for determining maximal conductances and dynamic parameters. Remarkably, optimization led to tight ranges for most parameters, though some time constant parameters were not tightly constrained. A model based on median parameter values captured CGC depolarization without altered excitability, observed in the living system, and identified two critical maximal conductances in this process; simultaneous increases in $max g_{NaP}$, a persistent sodium current, and $max g_{D}$, a delayed rectifier.

Heartbeat in *Hirudo*

The heartbeat CPG of *Hirudo* has been analyzed [17] and modeled, for example [18], extensively. Weaver *et al*. [19], presented a model of the entire core CPG that shows the utility of systematic parameter variation of a small subset of parameters in network analysis. Two bilateral pairs of premotor interneurons, phased differently with respect to the timing kernel of the CPG, show a phase progression on one side and near synchrony on the other. These phase differences are achieved by blending inhibitory synaptic input and electrical coupling. Making simplifying assumptions based on symmetry in the network, these investigators probed a range of maximal conductances for the inhibitory synapse and the electrical coupling to each premotor interneuron. The analysis established parameter values that produced model activity within the range observed in a large number of preparations. The relative parameter values predicted by this model were confirmed physiologically in voltage-clamp experiments [19] (see Figure 1).

The control of motor neurons by this CPG has also been extensively analyzed and modeled [20,21,22•]. Garcia *et al*. [23] used averaged data to define input phasing and synaptic strength profiles and a simplified single compartment model for the motor neurons. That model failed to achieve quantitatively accurate average output phasing [23,24]. An analysis of 12 preparations for the timing of the activity of the four premotor interneurons of the CPG (input phasing) and of their strength of inhibitory output (synaptic strength profiles) onto motor neurons, and the timing (output phasing) of the motor neurons revealed wide animal-to-animal variability in synaptic strengths and input and output phasing [20]. Wright and Calabrese [22•], used input phasing, synaptic strength profiles and phasing targets from individual animals as inputs to the Garcia model [23], but were still not able to achieve greater accuracy. Those results, as well as dynamic clamp experiments also using individualized synaptic input patterns, indicated the involvement of motor neuron intrinsic properties not encompassed by the motor neuron model, thus leading to the conclusion that a multi-compartmental motor neuron model with more sophisticated intrinsic properties was required [21,22•].

Respiration in vertebrates

The respiratory CPG of vertebrates has been studied in detail at many levels. It is a complex system consisting of millions of neurons with a great diversity of intrinsic and synaptic properties [25]. Moreover, the CPG is influenced by myriad extrinsic inputs, primarily related to

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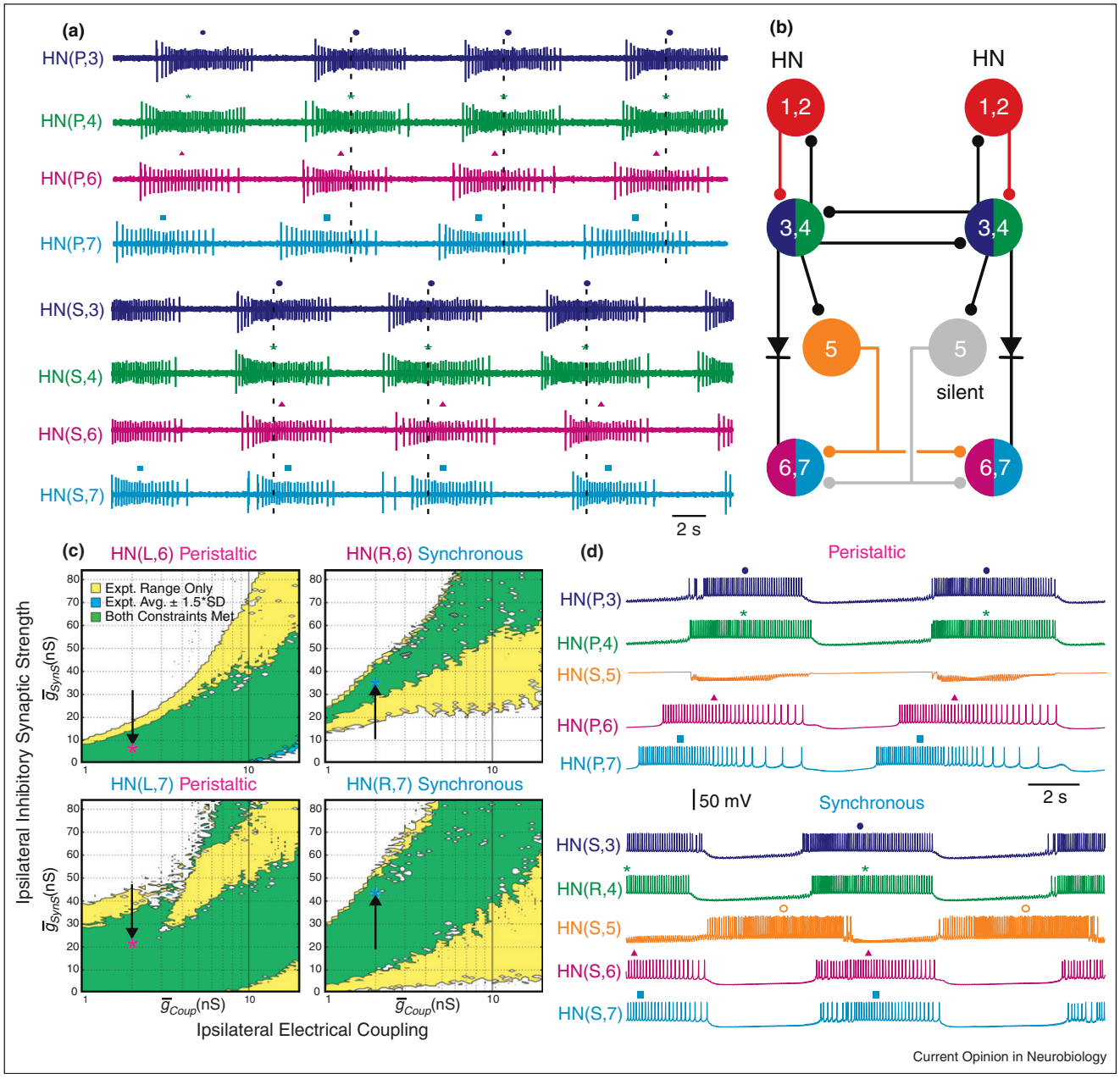
Figure 1



(a) Bilateral activity (recorded extracellularly) in the premotor heart interneurons (HN(3), HN(4), HN(6) and HN(7) interneurons) of the core heartbeat CPG showing these neurons in peristaltic (P) and synchronous (S) coordination modes. The middle spike of the peristaltic HN(4) interneuron is used as a reference to compute phase: vertical dashed lines ease comparison of relative (unilateral) phase in the two coordination modes. The bilateral record is artificially reconstructed from a unilateral recording that switched between coordination modes and aligned so that peristaltic and synchronous HN(4) interneurons fire out of phase (0.5). **(b)** Circuit diagram showing synaptic connections among interneurons of the core heartbeat CPG. Small colored/black circles indicate inhibitory chemical synapses, and diodes indicate rectifying electrical junctions. For simplicity, in the CPG diagram, cells with similar input and output connections and function are combined. Only one HN(5) interneuron is rhythmically active at a time, and it determines synchronous coordination ipsilaterally and peristaltic coordination contralaterally. **(c)** Covarying maximal conductances for the inhibitory synapse and the electrical coupling to identify appropriate values (colored asterisks and arrows). For every combination of maximal conductances, phase and duty cycle for that middle premotor interneuron were calculated and compared with those of individual neuron's experimentally recorded values (see graph legend). **(d)** Core CPG model activity (bilateral) with parameters selected in (c). After Weaver *et al*. [19].

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relevant respiratory signals such as pCO_2. A large-scale computational model of the respiratory CPG [26] successfully reproduced data from arterially perfused brainstem-spinal cord rat preparations in which transections sequentially removed rostral components of the respiratory network. That model was based on populations of Hodgkin–Huxley style neurons in the Bötzinger complex (BötC), pre-Bötzinger complex (pre-BötC), and ventral respiratory group, with excitatory drive from the pons and retrotrapezoid nucleus (RTN).

Building on this work, Rubin *et al.* [27••,28], reduced the complexity and employed the small network approach used for invertebrate models. The authors used activity-based, non-spiking, single neuron models to represent populations of spiking neurons, allowing for the application of bifurcation analysis. The reduced model reproduced the three major dynamic regimes observed in previous experimental studies and large-scale models [26,29], supporting the idea that the proposed architecture and drive structure are reasonable. Similar to experimental studies using brain stem transections, the removal of pontine drive converted the initial three-phase oscillations characteristic of *in vivo* respiration to two-phase oscillations, which lack the post-inspiratory phase, characteristic of *en bloc* preparations that retain rostral nuclei. Subsequent removal of inhibition from BötC expiratory neurons associated with removal of tonic drive from RTN converted the two-phase oscillations to one-phase inspiratory oscillations characteristic of slice preparations of the pre-BötC.

Two oscillatory mechanisms appear to underlie these oscillatory patterns at the cellular level, in particular in the pre-BötC complex: a persistent sodium-driven oscillation and a calcium-driven oscillation. Two recent papers [30,31•] present models which include both Na_p and Ca driven oscillatory behavior, although the specifics of the models presented differ. An important aspect of the Toporikova and Butera model [31•] is that several important responses to neuromodulator, pharmacological, and environmental influences are replicated, despite its relatively simple construction.

Food processing in Crustaceans

The food processing CPGs in the stomatogastric nervous system (STN) of decapod crustaceans continue to be a focus of modeling studies with wide implications for how neuronal networks achieve functional output. Early last decade, researchers began to use the STG system to address questions of model degeneracy, where the same functional output resulted from models with widely differing underlying parameters. This raised the question of how reliable network activity as well as sensitivity to neuromodulation and perturbation could be achieved in these small neural networks.

Recent investigation by Grashow *et al.* [32], used a simplified neuronal model to approach the broad question of how underlying neural parameters contribute to overall network performance. The authors coupled a Morris Lecar model neuron with a pharmacologically isolated living STG neuron via dynamic clamp, and then varied the maximal conductance of the artificial synapses and a model I_h current injected into the STG neuron. Echoing Prinz [3], the results showed that diverse parameter values can lead to similar network output. In other cases, however, the same parameter values can also result in wildly different network output, showing that differences between the intrinsic properties of the biological neurons can drastically alter the resulting pattern in the hybrid network. Thus, network activity is more resilient to variations in some regions of parameter space than others, strongly supporting earlier modeling work [1].

Nadim *et al.* [33•], also used a simplified model to investigate how a specific synapse influences network activity. Their stripped down model of a primary STN pacemaker network, composed of the anterior burster (AB) and pyloric dilator (PD) neurons, allowed them to apply phase plane analysis to investigate the role of the only known chemical synapse onto this network, the lateral pyloric (LP) to PD synapse. In the living system, the removal of this synapse has no effect under control conditions, although it was proposed that the LP-PD synapse would stabilize the AB/PD cycle period [34,35]. Nadim *et al.* [33•], verified this experimentally, and then used their model to help explain how. Essentially, the synapse reinforces the stability of the pacemaker by overriding the influence of perturbations — either slowing down incipient advances or speeding up incipient delays.

Moving from highly reduced to more complicated models, Taylor *et al.* [36••], uses what is variously referred to as ensemble [6], family [4], or population modeling. In this approach, many similar models are considered and each instance, or individual, is a different combination of free parameter values. They constructed a biophysical baseline model, tuned to a subset of experimental data, and then explored the parameter space around this model. By randomly sampling the parameter space and then simulating and perturbing each instance, they could identify models which were acceptable across all of several metrics. Those acceptable models had widely differing parameters, but did not have the strong correlations between these parameters that were expected based on experimental correlations between channel mRNA [37–39].

Conclusions

Each of these models has advantages and limitations, but all contribute to our understanding of neuronal networks — from circuit-specific findings, such as putative new members, to broad conclusions about the likely

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structure and regulation of network topology and cellular properties. We were only able to present a selection of small network models, leaving out many other fascinating systems which are actively modeled, especially neuronal circuits underlying locomotion [40–45,46•,47•]. The ability of small network models to facilitate a mechanistic understanding of such a broad array of complex systems speaks to their heuristic power.

As we move forward, models of small networks will no doubt clarify many interesting issues. For example, although some studies find that variability of intrinsic properties at the cellular level becomes less important at the network level [32], others suggested that network topology and neural dynamics strongly interact and both are of critical importance [48]. Furthermore, we know that neuromodulation plays a key role in pattern generation in many systems, yet much of the research on the small neural networks which underlie behavior appears to touch only superficially on the 2nd messenger systems involved. The levels of regulation available to neurons are myriad: epigenetics, transcription and translation regulatory mechanisms, splice variation, interrupted or delayed translation, and post-translational modification. The next logical step is to extend our investigations into the 2nd messenger pathways which drive observable change in electrophysiological properties. Not only will a more complete understanding of the cellular pathways which influence electrophysiological activity help us understand the unperturbed state of small neural networks, but also the effects of and interactions between neuromodulators and extrinsic perturbations. In addition to expanding the complexity of our models to include more cellular complexity, the ensemble modeling approach is likely to expand as we move forward, especially given the ever-increasing computational capabilities available.

Models of small networks are beautiful windows into how neuronal networks in all animals function, and we look forward to exciting new models that will continue to expand and challenge our understanding of them.

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- • of special interest
- •• of outstanding interest

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