

# NNET: Linking small and large-scale network models<sup>1</sup>

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## Abstract

To examine how mechanistic principles derived in small networks are manifest in larger networks, we developed a versatile neuronal network simulator, NNET, in portable C++ code. NNET allows easy, fast and accurate characterization of any neuronal population and coupling pattern of electrical and chemical synapses. Using NNET, we simulated 30-cell networks of interneurons coupled with both gap junctions and GABAergic synapses, based on a mechanism derived in two-cell networks.

*Keywords:* neuronal network simulator, gap junction, interneuron, synchrony, hippocampus.

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# 1 Introduction

The complexity of brain networks and the many details inherent at the many levels make it a monumental challenge to understand the many interacting dynamics that give rise to the different patterns that have been recorded in the brain. One major aspect of computational neuroscience is the use of well-constructed computer simulations as a mode of mathematical expression to understand the operation of the brain [15]. Although it is not clear how much model detail (and subsequent simulations) is appropriate and required to determine underlying principles in neuronal network operation, it is clear that small networks with some biophysical detail can provide insight and understanding in larger networks. For example, the mechanistic understanding of synchrony in inhibitory networks determined by [20] has been invoked in large thalamic and hippocampal networks [6, 19].

Networks of inhibitory interneurons or GABAergic cells are recognized as being essential units in cortical functioning, likely responsible for controlling the various EEG rhythmic frequencies [2, 13]. However, it is also abundantly clear that interneurons form a diverse population of neurons in terms of morphology, biochemical characteristics, channel types and distribution and connectivity profiles [16]. In particular, it is known that interneurons form networks via both GABAergic synapses and gap junctions (g.j.) (e.g., [7, 8, 9, 10]) and that g.j.s are critical for synchronous activity [4, 11].

Experimental work indicates the involvement of bursting oscillations in interneuronal networks with both gap junctional and inhibitory coupling in setting a slow population rhythm [22]. This motivated us to develop a mechanism by which this could occur. We found that synchronized bursting could be produced robustly in two-cell networks connected by both GABAergic and g.j. synapses in which persistent sodium and slowly inactivating potassium currents ( $I_{K_{s-i}}$ ) were present in the individual neurons [17]. With such intrinsic properties, synchronized bursting occurs when inhibition sufficiently removes the potassium inactivation. The g.j. coupling acts to stabilize the synchronous, intraburst spiking, so that synchronized bursting occurs. However, with only a two-cell network we could not examine how the connectivity architecture contributes to possible population bursting.

In this paper we describe a newly developed neuronal simulator software, NNET, which can be used to build networks of arbitrary size and connectivity, and in which the

individual neurons have a conductance-based formalism. We use NNET to simulate large networks of interneurons connected with g.j.s and GABAergic synapses based on the mechanism derived in [17].

## 2 NNET Software

**Design Goal and “intermediate level of detail” model networks.** Most neuronal network simulation packages place emphasis either the connective configuration of networks of simple nodes (i.e, artificial neural networks) or the elaborate physiological and molecular details of the membrane current dynamics of a single neuron (e.g., NEURON or GENESIS). Neither genre suits our purpose of examining an intermediate level (of detail) neuronal network with sufficient details to achieve the phenomenological characterization of each individual neuron but rid of the staggering details which hinder the study of a network of meaningful size and architecture. We designed and implemented a software package, NNET, to bridge this gap [14]. Furthermore, within this realm of models, we were not aware of any network simulators that included g.j.s as a feature.

**Outline of Design and Implementation.** NNET (N-cell NETwork) is portable, scalable, and re-usable. It solves a prototyped system of stiff ordinary differential equations (ODEs) (which must be a subset of the equations in [17]) using CVODE [3]. The network can have both synaptic and g.j. couplings of arbitrary architectures. The default output is a binary file readable by MATLAB. Output includes dynamic variables, coupling currents and field potentials. As in [5], the extracellular field potential,  $V_{ext}$ , is calculated as  $V_{ext} = \frac{R_e}{4\pi} \sum \frac{I_k}{r_k}$  where  $R_e$  is the extracellular resistivity,  $I_k$  is the total postsynaptic current on the  $k$ th cell and  $r_k$  is the distance between the location of the probe and the  $k$ th cell.

Fig. 1 illustrates NNET’s design. The C++ NNET program provides a scripting environment (neuBASIC) in which the values for the coefficients of the equations and various parameters for the manipulation of CVODE are set for later retrieval. Essentially, NNET provides a versatile programming environment for constructing and numerically solving a prototyped system of stiff initial value set of ODEs. Given a set of equations that describes the neuron and one connection between any two neurons, called an Equation Prototype, NNET parses a script (neuBASIC) that is similar to the BASIC procedural programming

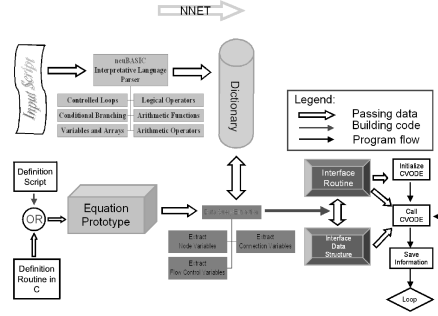


Figure 1: *Schematic of NNET design.*

language, in which the coefficients of the equation system are specified and then extracted to construct an abstract data structure and associated routines that are subsequently supplied to the CVODE numerical solver to generate the results. The support for loops, conditional branching and common arithmetic functions eases the effort and shortens the time in specifying a system. NNET is freely available (send email to FKS).

### 3 Application to Inhibitory Network Simulations

The effect of gap-junctional coupling in the generation and maintenance of slow field potentials in inhibitory networks was examined. Using model cell and couplings as described in [17], we built networks of up to 30 cells using our NNET software.

**Scalability, Multistability and Bursting.** As noted in our earlier work, our two-cell model network can exhibit other stable solutions besides the synchronized bursting solution (for which  $I_{K_{s-i}}$  must actively participate, i.e., be sufficiently deinactivated). Other solutions of antiphase spiking and unsynchronized firing can be uncovered via perturbations of the g.j.-coupling (not shown). Since we wanted to examine the synchronized bursting mechanism, we started with the same parameters as in the two-cell network of [17]. We then performed a scalability study of 3 to 10 all-to-all coupled networks (in total, 46 networks were examined). We found that population bursting was maintained only if the maximal g.j. conductance,  $g_{gap}$ , was increased as the network size was increased (possibly due to accumulation of numerical errors), approaching an asymptotic factor of 3 (see Fig.2). (Note that a normalization of synapses is done such that the total synaptic drive per cell on average

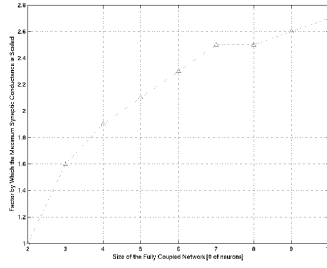


Figure 2: *Scaling factor necessary to maintain population bursts in a network of  $N$  fully coupled cells.*

remains the same as network size is changed, i.e.,  $g_{gap}$  (or  $g_{syn}$ ) is divided by the number of synapses ( $M$ ) in the network. Thus  $M_{syn} = N$  for all-to-all coupling and  $p = M_{syn}/N$  is the coupling probability (similarly for  $M_{gap}$ .) Thus, in subsequent network simulations, we increased  $g_{gap}$  by a factor of 3 so that we know that our networks can exhibit synchronized bursting with all-to-all inhibitory and g.j.-coupling via the mechanism described in [17].

**Large network bursting possible with minimal g.j. connectivity.** Fig.3 shows plots of field potentials in 30-cell networks for various g.j. coupling architectures ( $M_{syn}$  the same). Population bursts (P.B.s) occur with similar frequencies and durations as in the two-cell case. Bursting cells are perfectly synchronized, but the number of cells that are bursting during the P.B. changes (not shown). One can get at least one P.B. with as little as 10% g.j. connectivity (Fig.3,  $M_{gap} = 3$ ). We know from the two-cell work that the g.j.s are playing a stabilizing role, i.e., with a large enough  $g_{gap}$ , synchronized bursts can occur and be stably maintained in the face of perturbations (see Fig.8 in [17] and Fig.2 in [18]). In the 30-cell network simulations, we see that the amount of g.j. connectivity plays a similar (stabilizing) role. Note that in Fig.3,  $g_{gap}$  per se is not being changed, just the degree of g.j. connectivity, or the number of cells connected by g.j.s. In the two-cell case, the presence of stable bursts relies on a large enough  $g_{gap}$ . In the large 30-cell networks, the presence of P.B.s also requires g.j.s, but the degree of g.j. connectivity dictates the length of time for which P.B.s occur (as shown in Fig.3).

**Mechanism of P.B.** In the two-cell situation, the bursting behaviour terminates because of the removal of the inactivation leading to an increase in the potassium current

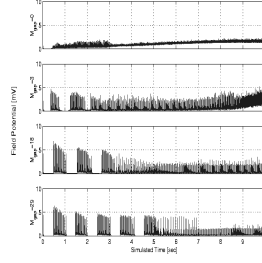


Figure 3: *P.B.s occur in larger networks and require g.j. connectivity. Field potentials of four 30-cell networks with (top to bottom)  $M_{gap}=0$ , no g.j.s;  $M_{gap}=3$ ;  $M_{gap}=18$ ; and  $M_{gap}=29$ , all-to-all coupling ( $M_{syn} = 18$  in all cases).*

which eventually prevents the individual cell from spiking. This is also true in the large network, but because of the particular (not all-to-all) connectivity, all cells do not have g.j.s and so some are tonically firing and others are suppressed (as would be the case without g.j.s and other possible stable solutions). Unlike the two-cell network, the P.B.s decline in amplitude since less cells are participating as the burst progresses. In summary, the field potential decreases during a burst due to the gradual loss of network synchrony, which leads to a suppression of a subpopulation of neurons and ultimately the loss of P.B.s.

**Heterogeneity.** In the above simulations, all cells in the network are identical. However, theoretical work indicates that heterogeneity makes synchrony fragile [21]. Therefore, we might expect that for the same g.j. coupling, but with heterogeneous cells, P.B.s would not last as long. In 30-cell network simulations, we found that this was not necessarily the case. Indeed, it was possible for P.B.s to last longer with less g.j. connectivity. To understand this, we performed a preliminary study with smaller (6 and 12 cell) networks in which we examined exactly which cells were interconnected. We found that this phenomenon occurred when g.j. connections were present between cells that had more diverse firing patterns, presumably because then an appropriate balance between high and low firing cells could be achieved to extend the length of time for which P.B.s could occur.

## 4 Discussion and Conclusion

In summary, a versatile network simulator, NNET, has been developed. There is no limit on network size except for memory and computing power, which is not a formidable issue nowadays. Besides the simulations described here, NNET has been modified for other specific uses [1, 12]. Future plans include the incorporation of synaptic plasticity and parallel versions of CVODE. Since NNET includes g.j.s, networks of simple multi-compartment cells can also be simulated.

Although 30 cells is still a relatively small network, it is large enough to allow us to make some assessment of connectivity issues. It is intriguing to think about g.j.s as “switches” for controlling the frequency of network output, i.e., output can switch from slow rhythms (synchronized bursts) to faster rhythms (no bursts) by manipulating the g.j. connectivity. Given that gap junctions are not static pores, this suggests an interesting mode of control of network frequency (over orders of magnitude).

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### ***Biosketches***

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