

INCORPORATING ANATOMICALLY REALISTIC CELLULAR-LEVEL CONNECTIVITY IN NEURAL NETWORK MODELS OF THE RAT HIPPOCAMPUS

Giorgio A. Ascoli

Krasnow Institute for Advanced Study and Psychology Department, George Mason University
MS2A1, 4400 University Dr., Fairfax, VA 22039, USA
ascoli@gmu.edu - www.krasnow.gmu.edu/L-Neuron (case sensitive)

John Atkeson

Krasnow Institute for Advanced Study and Psychology Department, George Mason University
MS2A1, 4400 University Dr., Fairfax, VA 22039, USA
jatkeson@gmu.edu

ABSTRACT

Classical neural network models are usually based on extremely simple connectivity patterns (e.g. all-to-all or random sparse; layered or symmetric) and a very small number of cell classes. Yet one of the most striking elements of complexity in the brain is the connectivity among neurons. In the rat hippocampus, for example, each principal cell can establish synapses with over 10,000 other neurons over a dozen of distinct cell classes. While the presence of individual connections between any two neurons is likely to be substantially stochastic, each different (sub)region of the brain is overall characterized by its own peculiar connectivity patterns. What is the role of specific connectivities in subserving network activity, coding, and function? In order to address this question directly, it is necessary to implement (quasi-)real-scale neural network models based on plausible system-level anatomy and cellular-level connectivity. This approach implies the adoption of simple computational implementations of single-cell activity. A variety of efficient dynamical systems are available, including McCulloch-Pitts units augmented with electrotonic properties [2] and/or ionic channel models [13], integrate-and-fire neurons [1], and low-dimension systems of differential equations [9]. Each of these models disregards important elements of single-cell behavior. However, depending on the scientific question pursued, these approximations may be preferred to drastically simplifying connectivity or scaling down the network (in the extreme, to single neurons), as becomes necessary with the more biophysically detailed models typically adopted in computational neuroscience.

Anatomically realistic neural network models of the hippocampal formation have been attempted for the dentate gyrus [11], Ammon's Horn [4], and area CA1 [12]. However, only in one case were simulations of network dynamics actually performed [5]. The major hurdle to these efforts is the lack of complete anatomical data of connectivity among all neuronal classes, and of detailed physiological data of synaptic activity (e.g. potential amplitude, kinetics, and frequency). Nonetheless, a wealth of data have been accumulated in recent years on the hippocampus, including connectivity patterns for numerous classes of interneurons [7] and postsynaptic potential parameters for all principal cells [e.g. 14]. A much simplified summary of the hippocampal formation connectivity is shown in Figure 1 (excitatory and inhibitory connections are represented as full and empty arrows, respectively). The general loop, from the entorhinal cortex (EC) to the dentate gyrus (DG), to CA3, to CA1, to the subicular complex (SC), and back to EC, contains at least three shortcuts (the perforant pathway – PP – from EC to CA3 and CA1, and the CA1-EC connection), and is mostly unidirectional (counterclockwise in Figure 1). Within each subregion of the hippocampus proper (DG, CA3, CA1), only the principal neurons (granule cells – gc – in DG, and pyramidal cells in CA) project to other areas, while interneurons (all inhibitory with the exception of DG mossy cells) establish local connections. EC and SC have not been expanded into complex cellular-level connectivity patterns.

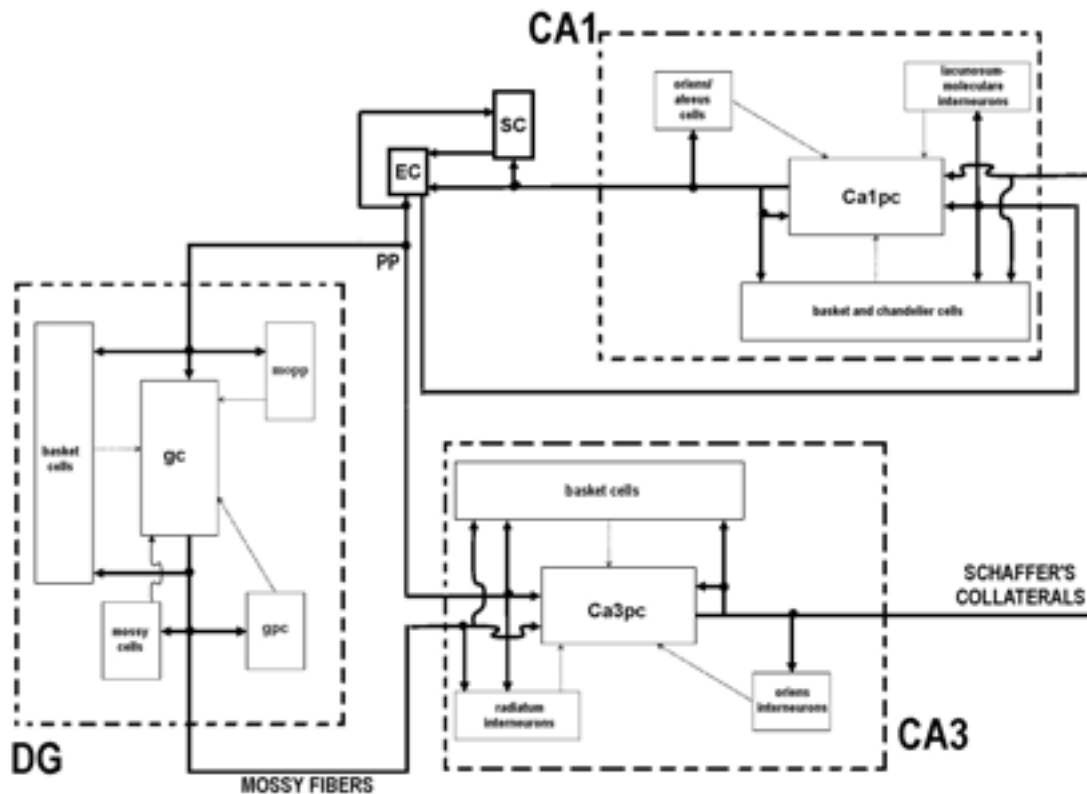


Figure 1

Interestingly, several basic motifs are repeated throughout all subregions. For example, both CA3 and CA1 pyramidal cells establish recurrent connections (and DG granule cells also achieve excitatory feedback via mossy cells). Each region has multiple classes of interneurons providing distinct inhibitory mechanisms. For example, DG mopp (molecular layer perforant pathway associated neurons), CA3 radiatum interneurons, and CA1 lacunosum-moleculare interneurons, provide purely feedforward inhibition to the respective principal cells. The same principal neurons receive instead purely feedback inhibition by gpc (gabaergic polymorphic cells), oriens and oriens/alveus interneurons. Each of the three subregions also include basket cells, which inhibit the principal neurons both with a feedforward and feedback mechanism. The presence of repeated motifs may be indicative of specific functional units [3, 10]. Neural network motif analysis has been carried out at the regional level both in general terms [8], and on the hippocampal formation [6]. However, insofar as we maintain neurons to be the brain computational units, it is essential to study the correlation between structure and function at the level of neuronal connectivity.

We characterize the connectivity from one cellular class to another with seven key parameters:

- 1) Synaptic type. This can simply distinguish between excitatory and inhibitory presynaptic neuron, or include the type of neurotransmitter and of postsynaptic receptor.
- 2) Numbers of neurons (presynaptic and postsynaptic).
- 3) Stoichiometry of the connection, expressed as number of postsynaptic cells contacted by each presynaptic cell, or number of presynaptic cells contacting each postsynaptic cell.
- 4) Electrotonic distance on the postsynaptic neuron. According to cable theory, this parameter affects integration through delay, attenuation, and duration of the signal. A more thorough description would include active channel distributions.
- 5) Axonal distance of the presynaptic neuron (possibly affecting transmission delay and failure probability).
- 6) Location of presynaptic and postsynaptic cells and specificity of the connection. The stoichiometry of connections is partly a result of the layer organization of cells and fibers, but various subtypes of axonal appendices may target specific cell classes.
- 7) Topography of the connection. Given the spatial arrangements of presynaptic and postsynaptic neurons, and a mapping between the two, the topographical relationship can vary from near 1:1 to completely random. This (set of) parameter(s) also characterizes “anti-topographic” connections (e.g. mossy cells to granule cells [11]).

In the general case, most of these parameters will be described by statistical distributions including expected variation across individual cells within a class. We have collected quantitative data from the available literature for parameters 1-3 for each of the cellular classes represented in figure 1 (see <http://www.krasnow.gmu.edu/ascoli/CNG/main.html>). Collection of data for parameters 4-7 is underway. A number of scientific questions can be already asked at this stage, including the following:

- What role do feedback and feedforward inhibitory cells play in shaping network dynamics?
- How does each neuronal class constrain emergent network rhythms?
- What is the effect of passive dendritic integration on network activity [2]?
- How robust are network properties to scaling?
- How does connectivity affect the acquisition and storage of information via simple plasticity mechanisms (e.g. Hebbian rule)?

As an example of this approach, we speculate on a putative role of feedforward inhibition in the dentate gyrus. We propose that the mopp interneurons can “stabilize” the granule cell “output” around the known firing rate over a range of entorhinal “input” firing rates. Specifically, given the known numbers, firing frequencies, and stoichiometries of the entorhinal-to-granule cell excitatory connection, and of the entorhinal-to-mopp-to-granule cell feedforward inhibition, we show with a simple binomial model that, in the presence of mopp activity, the firing rate of granule cells remains nearly constant upon a 10% variations of entorhinal input. In the absence of mopp activity, the same range of entorhinal input results in a several-fold variation of granule cell firing rate (Figure 2).

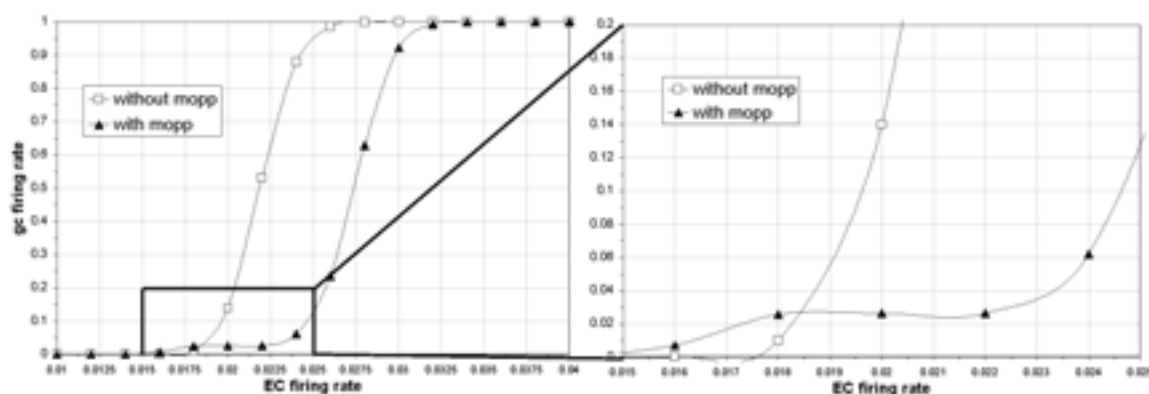


Figure 2

Keywords: Hippocampus, Neural networks, Neuroanatomy.

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