



Model- and scale-independent performance of a hippocampal CA3 network architecture

Elliot D. Menschik^{a,*} Shih-Cheng Yen^b, Leif H. Finkel^{a,b}

^a*Institute of Neurological Sciences, 301 Hayden Hall, 3320 Smith Walk, University of Pennsylvania, Philadelphia, PA 19104, USA*

^b*Department of Bioengineering, 301 Hayden Hall, 3320 Smith Walk, University of Pennsylvania, Philadelphia, PA 19104, USA*

Received 15 October 1998

Abstract

The hippocampus is known to be a critical structure for memory function, but how its anatomical, physiological, and cellular elements endow it with this function remains a mystery. As such, even less is known about how neuropathological changes associated with Alzheimer's disease, epilepsy or traumatic brain injury lead to the clinical manifestations of disease. To begin to address these issues, we have constructed a biophysically-detailed model of the CA3 region of the hippocampus that incorporates many of the well-characterized but, from a functional standpoint, poorly understood properties and phenomena into a functioning network. These include cholinergic neuromodulatory regulation, theta (4-6 Hz) oscillations, gamma (20-80 Hz) oscillations, diversity of interneuron classes, regular spiking vs. bursting pyramidal cells, and lamina-specific inputs and characteristic anatomy. We have found that the integration of these hippocampal elements results in a biological analog to the "connectionist" autoassociative attractor network where memories are represented as spatial patterns of temporally-precise spikes across CA3. In addition, simulating the cholinergic modulation of this network model and its constituent cellular components suggests novel mechanisms for memory dysfunction in Alzheimer's disease [8, 9]. Here we demonstrate such networks to be robust and accurate in memory function, insensitive to the choice of neuronal model from a 64-compartment cell with numerous ionic conductances [11] to a reduced dual-compartment model [10], and scalable from small to large networks.

Keywords: hippocampus; CA3; acetylcholine; interneurons; oscillations; Alzheimer's disease

1. Introduction

The characteristic anatomy of the CA3 region of the hippocampus, in particular the dense recurrent collaterals between pyramidal cells [7], has long prompted investigators to suggest that this area could be a neural substrate for an autoassociative memory [15]. Much of this thinking has stemmed from artificial neural network research, especially those results related to autoassociative attractor networks [1, 6]. While there are many variations on the original theme proposed by Hopfield, this general class of networks remains our best conception of how neurons might interact to store and recall memories in a robust fashion. The mathematics provide us with powerful analytical tools for such networks, however the applicability of the theory to biological neurons, with all of their biophysical complexity, has remained in question. We have attempted to see if some regulatory elements of CA3, in particular interneurons, oscillations, and cholinergic neuromodulation, are sufficient to control detailed biophysical cellular models such that they can operate in an analogous fashion to their artificial counterparts. In addition to learning how detailed cellular-level models can be harnessed to function in networks by an appropriate control structure, we have also been able to examine the effects of cholinergic deprivation, a major early component of

* Corresponding author. Tel.: +1 215 8980822; fax: +1 215 5732071; e-mail: menschik@neuroengineering.upenn.edu

Alzheimer's disease [8, 9]. Our results not only demonstrate that detailed biophysical networks can function as attractor networks, but also suggest ways in which cholinergic denervation may contribute to the decline of memory function.

2. Methods

Compartmental simulations were constructed using the GENESIS development package and PGENESIS, its recent implementation for parallel platforms [4]. Simulations were performed on a four-processor Silicon Graphics Origin 2000. Two sets of biophysical neuronal models were chosen for the network simulations: 1) The 66-compartment hippocampal CA3 pyramidal cell and the 51-compartment hippocampal interneuron developed by Traub and colleagues [11, 12] and 2) the 2-compartment reduced "Traub" pyramidal cell of Pinsky and Rinzel [10] and a single compartment interneuron described by Wang and Buzsáki [16]. For the most part, synapses were implemented as described by Traub and colleagues [13]. Excitatory synapses were implemented to simulate both AMPA and NMDA receptors which always colocalized at a given excitatory synapse. Inhibitory synapses were implemented to simulate the GABA_A receptor. Cholinergic neuromodulation was introduced at the cellular level by inhibiting intrinsic membrane currents (I_{AHP} , I_C , and I_{Ca}), suppressing excitatory synaptic transmission [5], and depolarizing cells (for details see [8]).

In constructing the model network we have attempted to be as faithful as practically possible to known hippocampal anatomy, and the resulting design is sketched in Fig. 1A. Networks of varying sizes were investigated from as large as 1,032 cells to as small as 24. In all simulations there were N pyramidal cells, N stratum radiatum interneurons and 8 basket cells. Neither entorhinal nor septal cells were explicitly modeled; perforant input was generated as a spatial pattern of spikes at the presynaptic terminals, and oscillatory theta-band inhibition was modeled by somatic current injection to basket cells.

We begin with a pre-wired network storing arbitrarily chosen memories. This is intended to be an approximation of a more biologically-faithful network that would have already undergone Hebbian associative learning, presumably via LTP and LTD. For a network of N pyramidal cells, we choose unbiased, random N -bit binary strings ξ to store as memories. These patterns are then used to determine the fixed connectivity of the recurrent synapses using Hopfield's original algorithm for storing binary patterns [6] in a network of N neurons where the $N \times N$ elements of the synaptic matrix T are a function of the p different patterns ξ .

$$T_{ij} = \begin{cases} \sum_p (2\xi_i^p - 1)(2\xi_j^p - 1), & i \neq j \\ 0, & i = j \end{cases} \quad (1)$$

This synaptic matrix is implemented using AMPA- and NMDA-mediated synapses of the recurrent collaterals in the stratum radiatum for positive T_{ij} values and GABA_A-mediated synapses (via stratum radiatum interneurons) for negative ones. The T_{ij} value is used to scale the maximal conductances of the receptors.

Note that by the term "memory" we refer to the spatially-distributed pattern of spiking activity in pyramidal cells of CA3 for a very small window of time. That is, we are concerned with temporally-precise representations of information as opposed to "rate coded" information. In our model (which in its present state omits input from the dentate gyrus which we believe is part of a long-term learning stage), this pattern of activity is a function of the transient inputs arriving from entorhinal cortex, the recurrent connections between pyramidal cells, and the regulation by two classes of inhibitory interneurons as well as cholinergic neuromodulation from the medial septal nuclei.

3. Results

3.1 Network function

The network elements outlined in Fig. 1A interact as follows: As has been observed in a variety of single pyramidal cell models [8, 9] and *in vitro* [2], cholinergic input is capable of switching cells from a bursting to a regular spiking mode. It also provides a general depolarizing drive to pyramidal and basket cells alike. In the network of mutually connected GABA_Aergic basket cells, spiking leads to intrinsic synchronization of firing in the gamma-band range as has been previously reported [3, 14, 16]. Pyramidal cells also spike at the gamma frequency due to the coordination of cholinergic drive and basket cell inhibition. These oscillations are further modulated however by slower, theta-band rhythmic inhibition from septal GABA_Aergic neurons. The effect of this externally-

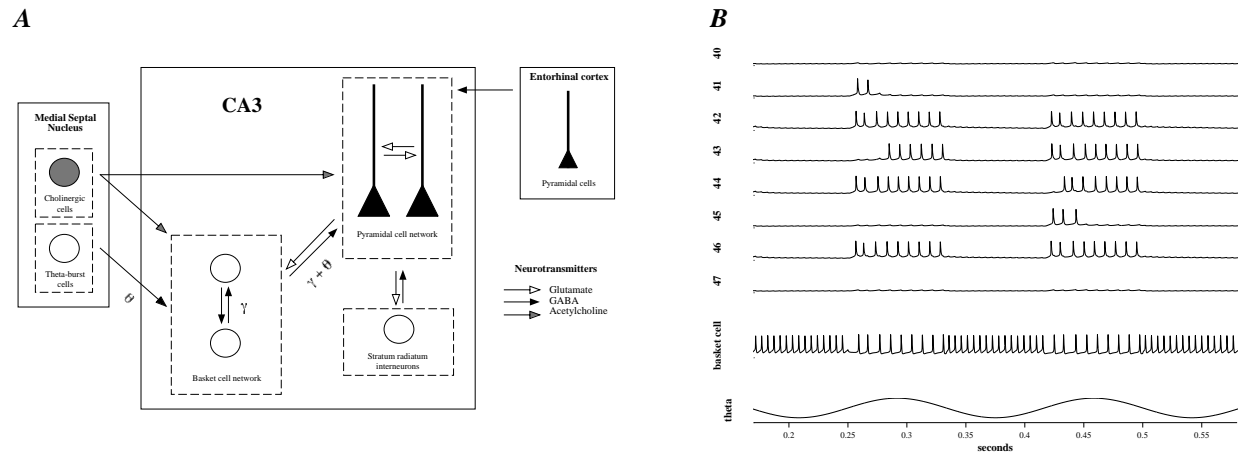


Fig. 1. Architecture and function of the CA3 network model. (A) The model captures several major components of hippocampal anatomy. Memories, represented by the spatial pattern of activity of the CA3 pyramidal cell network, are encoded in the recurrent synapses between pyramidal cells. Recall is elicited by perforant path activation from superficial entorhinal pyramidal cells, and the CA3 pyramidal cell activity is regulated by interneurons, theta- and gamma-band oscillations, and cholinergic neuromodulation. Theta oscillations are generated extrinsically in the medial septum, while gamma-band oscillations are generated intrinsically by mutually-inhibitory basket cells. See the text for a detailed explanation of the interactions between network components. (B) Network function in a 136-cell model of CA3 using Traub and colleagues' pyramidal cell and interneuron models. Shown are somatic voltage traces from 8 of a total of 64 pyramidal cells (labeled 40 to 47) along with a single trace from a basket cell and an idealized theta rhythm of two complete cycles. At the start of each theta cycle, a new transient input arrives over the perforant pathway in the form of a spatial pattern of single spikes impinging on the distal dendrites of the pyramidal cells. This input causes some subset of pyramidal cells to spike, and, over each subsequent gamma-cycle (here approximately 10 ms) the pattern of spikes is determined by the recurrent connectivity of the network. In some cases a firing cell becomes quiescent, while in other cases a silent pyramidal cell begins to spike. Well before the theta rhythm declines, the pattern of activity across the network reaches a stable pattern (i.e. the fixed-point attractor state or "memory") that repeats with each gamma-cycle until theta inhibition of the basket cells declines, basket cells fire more vigorously, and the pyramidal cell network is shut down and reset before the next entorhinal input arrives.

derived theta-band inhibition is to modulate the firing rate of the basket cell network. When theta inhibition is low, basket cells fire at high frequency having been strongly depolarized by the diffuse spread of ACh in the *stratum oriens*. This activity prevents pyramidal cells from spiking and thereby "resets" the network before each new perforant path input arrives. When theta inhibition rises, basket cell spiking is slowed (even in the presence of the cholinergic depolarization) and the mutual interactions between basket cells dominate. In this phase the emergent gamma-band synchrony of the interneurons regulates the pyramidal cell firing as input arrives to the network from entorhinal cortex (EC). These transient inputs are presented to CA3 pyramidal cells in synchrony with theta along the perforant path by AMPA- and NMDA- mediated synapses in the most distal dendrites. The final component of the model network, the recurrent connections between pyramidal cells, is mediated by monosynaptic excitatory contacts between pyramidal cells and disynaptic inhibition mediated by stratum radiatum interneurons. As in attractor neural networks, the pattern of these recurrent excitatory and inhibitory synapses defines the attractor states (i.e. memories).

An example of the attractor-type behavior in a sub-network of 64 Traub pyramidal cells is shown in Fig. 1B where somatic membrane voltage traces from eight of the cells are shown with a single basket cell somatic recording and an idealized theta rhythm drawn for reference. At the start of the theta rhythm, synaptic input from the perforant path causes a particular set of pyramidal cells to spike. The recurrent excitation and inhibition then directs which pyramidal cells will spike on subsequent "gamma cycles" within the single theta cycle until the closest memory is reached. Memories are fixed-point attractors in that partially correct patterns of spikes will progress to one of the stored patterns with each successive gamma cycle. Once the correct pattern of spikes is obtained, that pattern recurs on each gamma cycle until the theta input declines, basket cell inhibition rises, and the pyramidal cell network is hyperpolarized and reset.

3.2 Stability of the stored memories

Our first step in the evaluation of the network model, regardless of the size or the cellular models used, was to ascertain the stability of the stored memories; that is, if the pattern of spikes induced by transient entorhinal input is

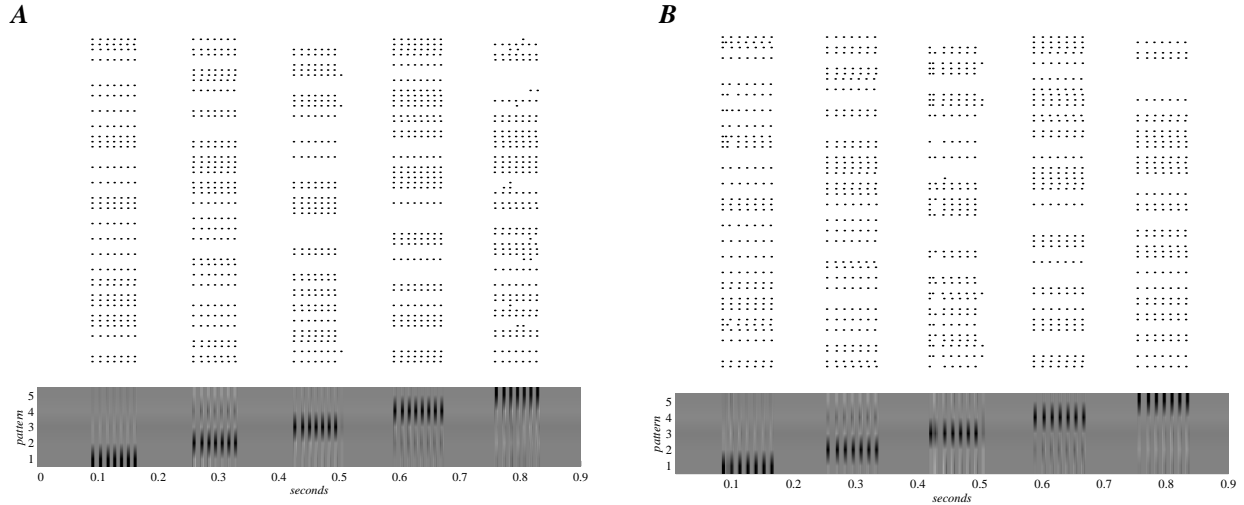


Fig. 2. Stability of stored memories in a 136-cell CA3 network comprised of either Traub pyramidal cells and interneurons (A) or Pinsky-Rinzel pyramidal cell and Wang-Buzsáki interneurons (B). *Top*. Shown is a raster plot of the spikes of each of the 64 pyramidal cells as a function of time. *Bottom*. Shown is a density plot of the overlap m_p of the network with the 5 stored memories as a function of time. Black denotes a perfect correlation between network state and the particular memory, while white denotes perfect anticorrelation. At the beginning of each theta cycle, one of the stored memories is presented to the network over the perforant pathway. On each subsequent gamma cycle, the induced pattern of pyramidal cell activity persists and shows perfect overlap with the input.

identical to one of the stored memories, this same pattern should repeat with each gamma oscillation. For arbitrarily large networks, examining spike traces as shown in Fig. 1B becomes too burdensome for comparison with the stored N -bit memories, so a convenient metric for determining the state of the network relative to the stored memories is the "overlap" or "magnetization" function commonly applied to artificial attractor networks. The overlap m with a given pattern p is defined by

$$m_p = \frac{1}{N} \sum_{i=1}^N (2\xi_i^p - 1)(2S_i - 1) \quad (2)$$

where S_i is the binary state (1 or 0, spike or no spike) of the i -th neuron.

Shown in Fig. 2A is a raster plot of the spike history of the 64 pyramidal cells in a network of Traub cells (*top*) and the overlap with each of 5 stored memories as a function of time (*bottom*) as a different memory is presented over the perforant path on each new theta cycle. Here the overlaps are shown in a density plot where black represents 1.0 (perfect correlation), white -1.0 (perfect anti-correlation), and shades of gray for intermediate values. Each of the stored memories is indeed a fixed point attractor as can be seen either by the repetition of the same pattern in the raster plot with each new gamma cycle or, directly, in the overlap plot. This stability occurs in spite of the fact that there is considerable overlap between different stored memories. In this particular example, there are 9 gamma cycles available for computation each theta cycle. Similar results are shown in Fig. 2B for the same size network using Pinsky-Rinzel pyramidal cells but the same recurrent connectivity. In addition, we have observed the same degree of fidelity in a much larger 1,032-cell network using Pinsky-Rinzel pyramidal cells and the Wang-Buzsáki interneurons where 40 randomly chosen 512-bit patterns were stored (*data not shown*).

3.3 Autoassociative recall of memories

One method of probing the autoassociative capability of our network is to provide corrupted versions of the stored memories as input and then observe the ability of the network to recall the correct memory (i.e. error-correction). "Noisy" memories were created by randomly flipping some percentage of the bits of the original pattern. The degree of corruption is reflected in the initial overlap between the network state on the first gamma cycle and the stored memory. Fig. 3A shows the result for the network of Traub pyramidal cells where progressively more corrupted versions of a single memory are presented on each successive theta cycle. Even when the initial overlap is approximately 50%, the network still reaches the appropriate attractor. The network utilizing the Pinsky-Rinzel pyramidal cells can be seen to demonstrate similar error-correcting capabilities for the same inputs as shown in Fig. 3B.

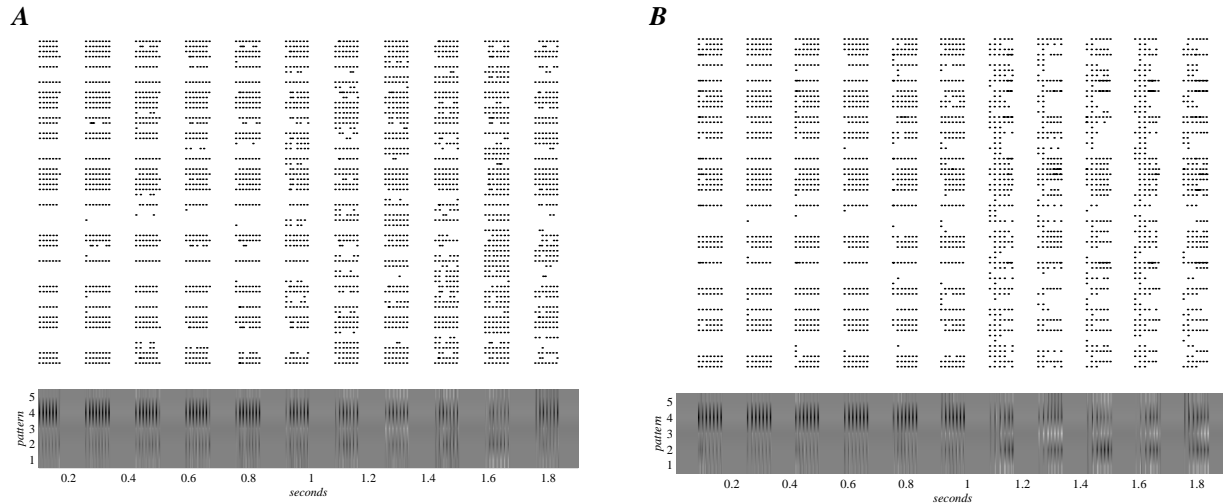


Fig. 3 Autoassociative behavior of the Traub-based 136-cell CA3 network (A) and its correlate using Pinsky-Rinzel pyramidal cells (B). With each theta cycle a progressively more corrupted version of the 4th memory is presented to the network. Even with heavily (approximately 50%) corrupted inputs, over several gamma cycles nested in the theta rhythm the network is able to reconstruct the correct memory. As inputs are corrupted even further, however, the network can no longer recall the correct, or any, memory before the theta rhythm declines and the network is reset.

We should note that, in these preliminary simulations, we have always stored fewer than Hopfield's maximal capacity of $0.15N$ memories. We have yet to chart the memory capacity of these networks as a function of the number of neurons. An additional shortcoming of this preliminary network is our mimicry of the original Hopfield model with its deterministic dynamics, a reliance on all-to-all, symmetric connections, and non-sparsely coded representations of information. All of these issues have been addressed by the generations of attractor models that followed Hopfield's seminal paper [6] resulting in models with sparse information representations, much larger memory capacities, stochastic dynamics, and more biologically-plausible synaptic interactions. At this early stage of our investigation, we have yet to try using any of these modifications for a biophysical network simulation, but given our success with the original Hopfield model, we expect these other architectures to be amenable to similar biophysical implementations.

4. Conclusions

Our results demonstrate that large networks of biophysically-based neurons, under an appropriate control structure, can demonstrate memory function and perform the same computations as their artificial "connectionist" counterparts. A sufficient control structure, and one that is consistent with the biology of the hippocampus, consists of locally-generated synchronous oscillations (e.g. gamma-band oscillations via mutual inhibition), neuromodulatory substances of subcortical and local origin (e.g. acetylcholine from the medial septum/diagonal band of Broca complex) and external pacemaking (i.e. theta-band inhibition from the medial septal nuclei). We have found that this architecture scales well from 24 to 1,032 cells and can be applied to different neuronal models with essentially no modification. Finally, at least in the context of this network, the Pinsky-Rinzel pyramidal cell is just as useful as the Traub pyramidal cell for biophysical simulations in its response to EPSPs, IPSPs, and cholinergic neuromodulation and allows for the investigation of much larger networks with the same computational resources.

References

- [1] D.J. Amit, *Modeling Brain Function: The world of attractor neural networks* (Cambridge University Press, New York, 1989).
- [2] R. Azouz, M.S. Jensen, and Y. Yaari, Muscarinic modulation of intrinsic burst firing in rat hippocampal neurons, *Eur J Neurosci* 6 (1994) 961-6.
- [3] P. Bush and T.J. Sejnowski, Inhibition synchronizes sparsely connected cortical neurons within and between columns in realistic network models, *Journal of Computational Neuroscience* 3 (1996) 91-110.
- [4] N.H. Goddard and G. Hood, Large Scale Simulation Using Parallel GENESIS, in: J.M. Bower and D. Beeman, eds., *The Book of GENESIS: Exploring Realistic Neural Models with the General NEural Simulation System*, (TELOS, Santa Clara, 1998) 349-379.

- [5] M.E. Hasselmo and E. Schnell, Laminar selectivity of the cholinergic suppression of synaptic transmission in rat hippocampal region CA1: computational modeling and brain slice physiology, *Journal of Neuroscience* 14 (1994) 3898-914.
- [6] J.J. Hopfield, Neural networks and physical systems with emergent collective computational abilities, *Proceedings of the National Academy of Sciences of the United States of America* 79 (1982) 2554-8.
- [7] X.G. Li, P. Somogyi, A. Ylinen, and G. Buzsáki, The hippocampal CA3 network: an in vivo intracellular labeling study, *Journal of Comparative Neurology* 339 (1994) 181-208.
- [8] E.D. Menschik and L.H. Finkel, Neuromodulatory control of hippocampal function: Towards a model of Alzheimer's disease, *Artificial Intelligence in Medicine* 13 (1998) 99-121.
- [9] E.D. Menschik and L.H. Finkel, Cholinergic neuromodulation and Alzheimer's disease: from single cells to network simulations, in: J. Reggia, E. Ruppin, and D. Glanzman, eds., *Progress in Brain Research* (Elsevier, New York, in press) .
- [10] P.F. Pinsky and J. Rinzel, Intrinsic and network rhythmogenesis in a reduced Traub model for CA3 neurons, *Journal of Computational Neuroscience* 1 (1994) 39-60.
- [11] R.D. Traub, J.G.R. Jefferys, R. Miles, M.A. Whittington, and K. Tóth, A branching dendritic model of a rodent CA3 pyramidal neurone, *Journal of Physiology* 481 (1994) 79-95.
- [12] R.D. Traub and R. Miles, Pyramidal cell-to-inhibitory cell spike transduction explicable by active dendritic conductances in inhibitory cell, *Journal of Computational Neuroscience* 2 (1995) 291-8.
- [13] R.D. Traub, M.A. Whittington, S.B. Colling, G. Buzsáki, and J.G.R. Jefferys, Analysis of gamma rhythms in the rat hippocampus in vitro and in vivo, *Journal of Physiology* 493 (1996) 471-484.
- [14] R.D. Traub, M.A. Whittington, I.M. Stanford, and J.G.R. Jefferys, A mechanism for generation of long-range synchronous fast oscillations in the cortex, *Nature* 383 (1996) 621-4.
- [15] A. Treves and E.T. Rolls, Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network, *Hippocampus* 2 (1992) 189-99.
- [16] X.J. Wang and G. Buzsáki, Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model, *Journal of Neuroscience* 16 (1996) 6402-13.



Elliot Menschik received his B.S.E. and M.S.E. degrees in Electrical and Computer Engineering from the Johns Hopkins University in 1993 where his research involved the construction of analog VLSI models of active biological cells. He is currently in the Medical Scientist Training Program at the University of Pennsylvania, School of Medicine as an M.D./Ph.D. candidate in Neuroscience. His doctoral research uses biophysical-level models of single cells and networks to examine the role of neuromodulation in the function and dysfunction of the hippocampus.



Shih-Cheng Yen received his B.S.E. and M.S.E. in Bioengineering from the University of Pennsylvania in 1993 and his Ph.D. in Bioengineering from the University of Pennsylvania in 1998. He studied the role of visual cortical circuits in the perception of salient contours for his doctoral thesis. He is currently a postdoctoral fellow at University of California, Davis, where he is conducting physiological experiments in primates to test the predictions of his model.



Leif Finkel received his B.S. in Physics from the University of Maryland in 1976 and his M.D. and Ph.D. in Biophysics from the University of Pennsylvania in 1985. He has worked in a number of areas in computational neuroscience, most recently in cortical mechanisms of visual perception and the development of models of clinical disease. Additional information is available from our web site at www.neuroengineering.upenn.edu.