of a subacute myelo-neuropathy (SMON), primarily in Japan (Tabira, 2001; Tateishi, 2000). CQ iron chelates were initially implicated because they were found in urine of SMON patients and shown to increase lipid peroxidation. Further, SMON symptoms and distal axonopathy could be reproduced with high-dose CQ administration to dogs and cats with marked variation in the response due to dose and species (Matsuki et al., 1997). More recent findings have led to the hypothesis that CQ zinc chelates were the neurotoxin involved in SMON (Arbiser et al., 1998). As with most drugs, toxicity may occur at very high doses, but for useful agents, not within their effective therapeutic window. Because of the potential oxidative damage from metal chelates, their use may require appropriate dietary or supplementary antioxidants that were inadequate in postwar Japan. For example, for deferrioxamine to control oxidative damage in diabetic rats, an ascorbic acid supplement was required (Young et al., 1995). An alternative theory discussed by Kaur et al. is that indiscriminate high-dose CQ use aggravated B_{12} deficiency in postwar Japan and led to SMON in a subset of vulnerable patients. They have found no evidence for CQ toxicity with effective dosing in mice. More significantly, in a phase II clinical trial, therapeutic CQ has been coadministered with B_{12} to Alzheimer patients with no evidence of drug-dependent adverse events. Whether or not the toxicity issues with CQ can be ironed out, Andersen and colleagues' work with the ferritin transgenics provides strong evidence that control of oxidative damage by nontoxic iron chelation may be a viable approach for PD and perhaps other neurodegenerative diseases. Based on its success in animal models for both AD and PD and its apparent safety and possible efficacy in the clinic with AD patients, there is growing reason for the ironic hope that the drug CQ, once withdrawn from the market for causing neurodegeneration, may be used to prevent it.

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Interpolating between Cellular Biophysics and Computation in Single Neurons

What types of computations are performed on synaptic inputs within the dendritic trees of single neurons? In this issue of *Neuron*, Poirazi et al. (2003a, 2003b) present a systematic method to reduce complex, biophysically realistic neuron models to more tractable, simplified two-layered neural networks that could shed some light on this issue.

The complexity of synaptic integration mechanisms within single neurons has become mind-boggling following the explosive increase in databases on dendritic recordings in slice preparations during the past decade (Stuart et al., 1999; Reyes, 2001). Yet, to understand how ionic channels and their distribution are utilized by single cells to process information will require some abstraction from biophysical detail toward simpler models and a shift in focus from a faithful description to a more abstract representation of the relation between synaptic inputs and neuronal firing rate (Segev and London, 2000). Two papers in this issue of *Neuron* (Poirazi et al., 2003a, 2003b) address this question using the example of CA1 pyramidal cells. The results provide a general and explicit method to reduce biophysical complexity without losing the input/output relation of single neurons that could potentially lead to a better understanding of how neurons process synaptic inputs.

The authors start by constructing a detailed biophysical model of a CA1 hippocampal pyramidal cell based on anatomical and electrophysiological data from various laboratories. The model includes many of the conductances thought to play a role in synaptic integration, including I_h and I_A, as well as sodium conductances responsible for backpropagating action potentials, and several types of Ca^{2+} conductances. To calibrate the model, Poirazi et al. simulated current injection protocols from both somatic and dendritic locations and compared the results with experimental data under various conditions, including the use of pharmacological blockers (see the Supplemental Data for Poirazi et al., 2003a, available online at http://www.neuron.org/cgi/content/full/37/6/977/DC1).

The next step, described in Poirazi et al. (2003a), consisted in reproducing synaptic stimulation experiments in which pairs of inputs were activated simultaneously

at various positions in the apical dendritic tree of CA1 pyramids (Cash and Yuste, 1999). In addition to such pairs of inputs, high-frequency synaptic stimulation trains were also investigated. The results suggest that linear summation of excitatory postsynaptic potentials at the soma—as reported by Cash and Yuste—could be compatible with strong nonlinear summation when several inputs are activated simultaneously in a single dendritic branch in the presence of active membrane conductances. In the authors' simulations and data analysis, nonlinear summation was most evident in the dendritic membrane potential recorded at the site of stimulation but could also be detected in the somatic membrane potential. An experimental verification of these predictions using similar methods as in Cash and Yuste (1999) should therefore be possible. An alternative but technically more difficult approach would be to directly stimulate two distinct presynaptic inputs and record from the postsynaptic target neuron as in Tamas et al. (2002). Poirazi et al. go on to show that summation of inputs distributed across more distant branches in their model follows a much more linear characteristic.

These results set the stage for the reductionist approach exposed in the second article (Poirazi et al., 2003b). The authors postulate that individual inputs sum linearly within a dendritic branch before being transformed by a sigmoidal transfer function $s(\bullet)$ similar in shape to nonlinear branch summation described above. The outputs of each branch are then combined to determine the firing rate according to

$$f = g\left(\sum_{i=1}^{m} \alpha_i s(n_i)\right).$$

In this equation, the index i runs over each dendritic branch, n_i is the total input to the branch, and α_i measures its coupling to the somatic membrane potential. Finally, the output nonlinearity g converts the intermediate sum, a measure of somatic depolarization, into firing rate. This description is formally identical to a two-layered neural network. The fact that two-layered neural networks can fit the input/output relation of a pyramidal cell would not in itself constitute a surprise: although simple in appearance, they are powerful objects known to approximate arbitrary functions with high accuracy (Bishop, 1995). The interesting observation made by Poirazi et al. is rather that the coefficients of such a model can be constrained by and mapped onto biophysically measurable quantities, such as the number of branches in the dendritic tree and their somatic coupling. This suggests a systematic procedure to reduce multicompartmental models to more tractable ones for analyzing the computations performed by neurons. The authors proceed to establish the superiority of this model against several challengers by using an elegant and efficient method. To test the various models under consideration, they select synaptic input patterns designed to optimally challenge their predictive power. A similar strategy is often used in more conventional statistical tests.

The work of Poirazi et al. suggests that the dendritic branches of neurons could act as localized nonlinear summing subunits and brings us closer to understanding how single neurons—the fundamental building blocks of the nervous system—could process information. It also leaves open several questions. As noted by the authors themselves, it will be interesting to know if their results generalize beyond mean firing rate averaged over 250 ms, the neuronal output variable predicted in their simulations. It is likely that in many cases processing of sensory information occurs on a faster timescale. An extension of their results would allow us to address such situations as well. Another challenge is to investigate whether such reductions can be obtained directly from experimental data. Pyramidal cells might not be the neuron type most easily amenable to testing, since it is currently difficult to selectively stimulate single synaptic inputs at different positions in their dendritic tree and to simultaneously monitor dendritic integration. The method should however be applicable to other neurons where computational dendritic subunits are thought to exist and where integration of synaptic inputs across the cell could be nonlinear (Egelhaaf et al., 2002). In this context, the authors' method should provide a useful complement to traditional compartmental modeling methods in understanding dendritic integration and the relative role played by various dendritic branches and conductances in this process. Finally, one would like to relate the properties of the synaptic weights, α_i, to aspects of computing performed by single neurons and, ideally, compare their values among neurons performing different computations on identical inputs.

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Sequence Learning: What's the Hippocampus to Do?

The medial temporal lobe is crucial for some forms of memory, but its role in implicit learning has remained