The processing and integration of excitatory and inhibitory signals in models of hippocampal neurons and networks

Szabolcs Káli (with Tamás F. Freund)

Institute of Experimental Medicine
Hungarian Academy of Sciences

kali@koki.hu

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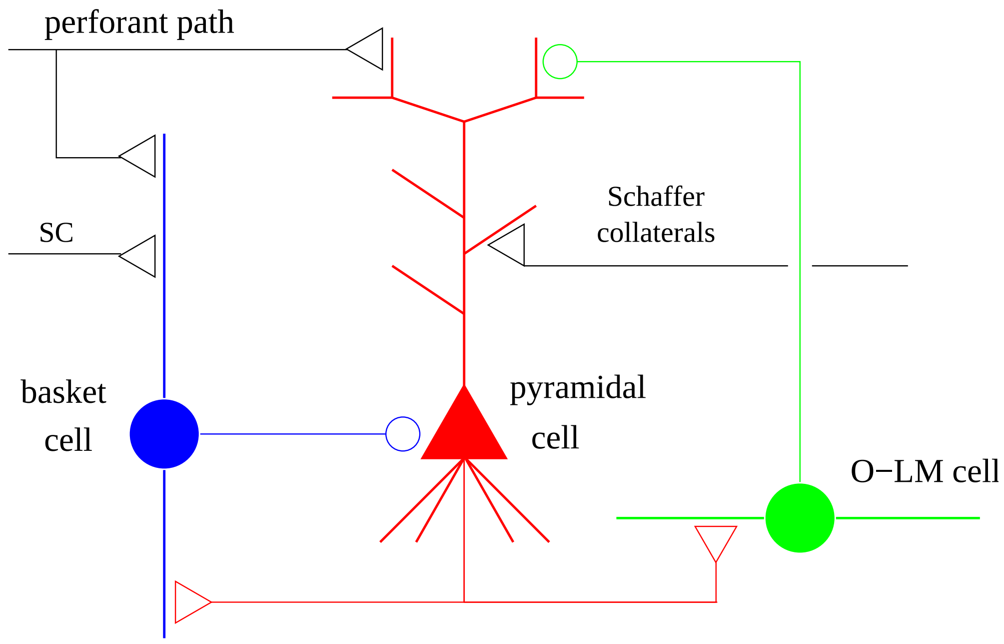
Introduction

Question: How do various types of inhibitory interneuron influence information processing in cortical pyramidal neurons?

Example:
CA1 region
in hippocampus



Focus: dendritic inhibitory neurons (e.g., O-LM cells) — comparison with basket cells

Models at two different levels:

- interactions between various kinds of unitary events (postsynaptic potentials, action potentials) in a single (pyramidal) cell
  - intrinsic properties (e.g., signal propagation)
  - integration of (excitatory and inhibitory) synaptic events

- interactions between populations of pyramidal cells and interneurons (+ intrinsic properties of interneurons)

- a necessary technical step: the systematic reduction of compartmental neuronal models

Dendritic processing in CA1 pyramidal cells

What happens in pyramidal cell dendrites?

- generation, spread and integration of EPSPs — passive and active processes
- backpropagation of somatic action potentials
- interactions of the above $\longrightarrow$ plasticity

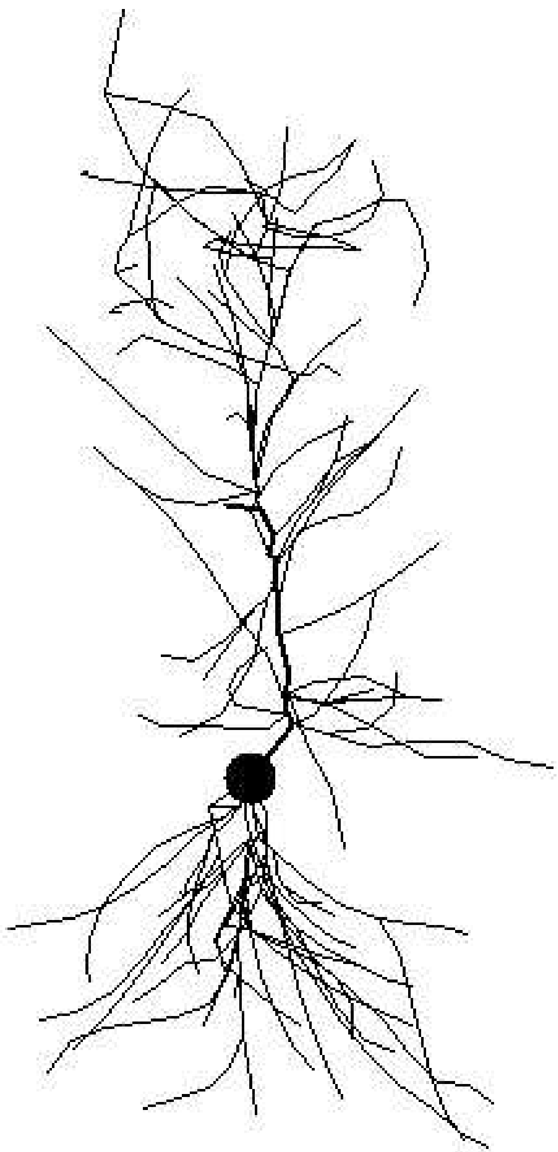
Effects of inhibition may depend on:

- relative position of sites of initiation, inhibition, and measurement; spread of inhibition
- relative timing (and temporal extent)
- strength of excitatory and inhibitory inputs

in the context of

- the morphology of the neuron and the spatial distribution of ionic conductances
- the kinetic properties of the membrane and ionic conductances

CA1 pyramidal cell model

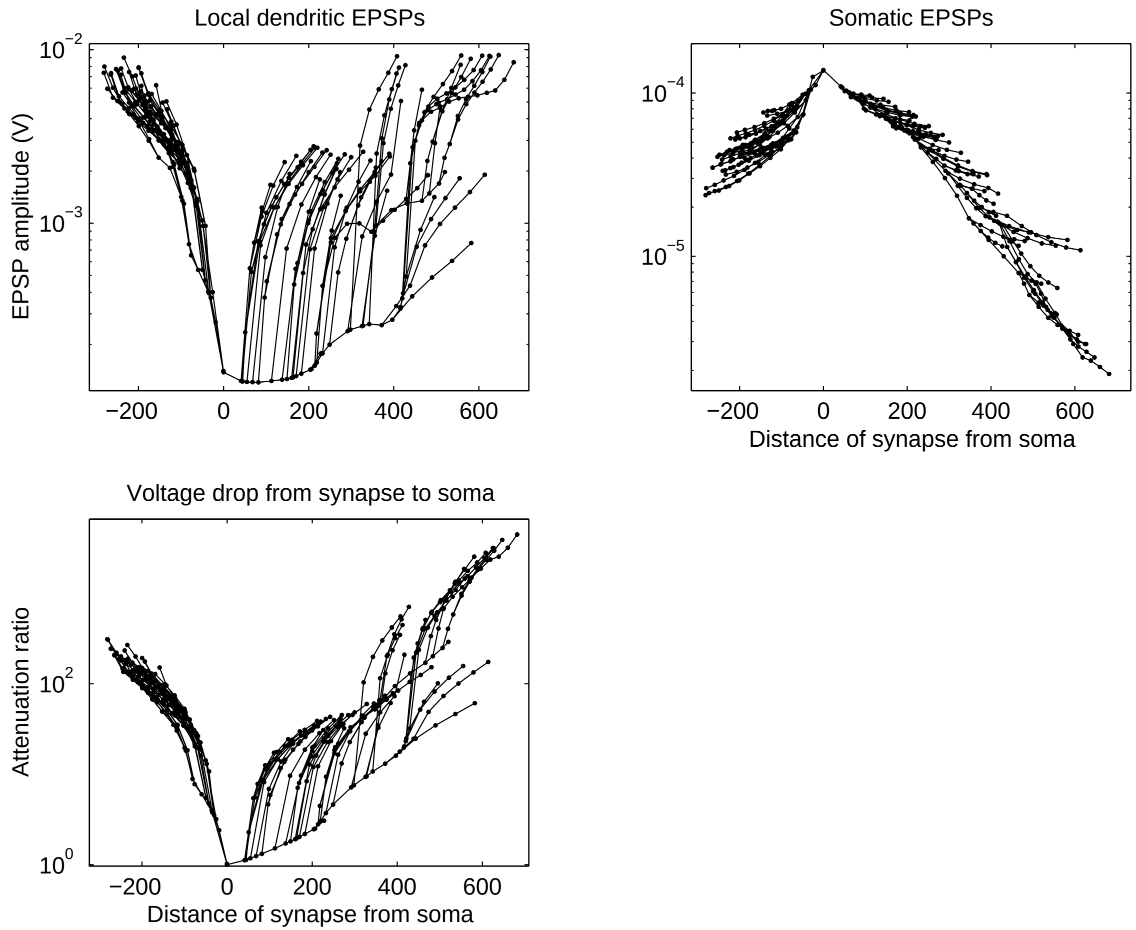


Reconstructed CA1 pyramidal cell from Megias et al. (2001), re-compartmentalized more coarsely (into 455 segments) for computational efficiency, with a wide variety of active conductances in all compartments.

Voltage- and calcium-dependent conductances:

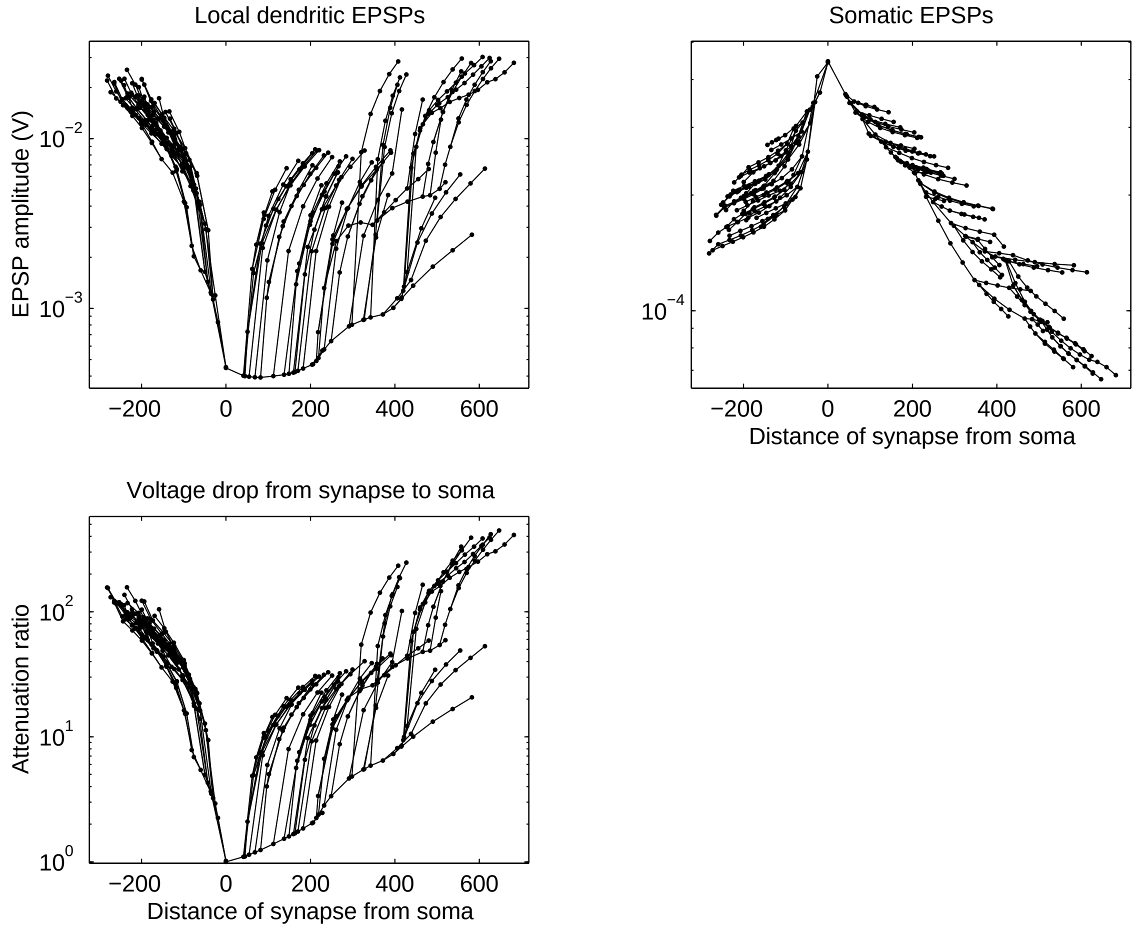
- Na^+
  - fast, transient (also includes persistent)
- Ca^{2+}
  - high-threshold (L, N, R subtypes)
  - low-threshold (T-type)
- K^+
  - delayed rectifier
  - transient A-type (proximal and distal variants)
  - persistent M-type
  - voltage- and Ca^{2+}-gated C-type
  - Ca^{2+}-dependent slow afterhyperpolarization current
- mixed cation
  - h-current (proximal and distal variants)

Forward propagation of EPSPs



Distal dendritic EPSPs are severely attenuated in the baseline model. The results are in agreement with data on Schaffer collateral input, but would render the perforant path input to CA1 essentially ineffective.

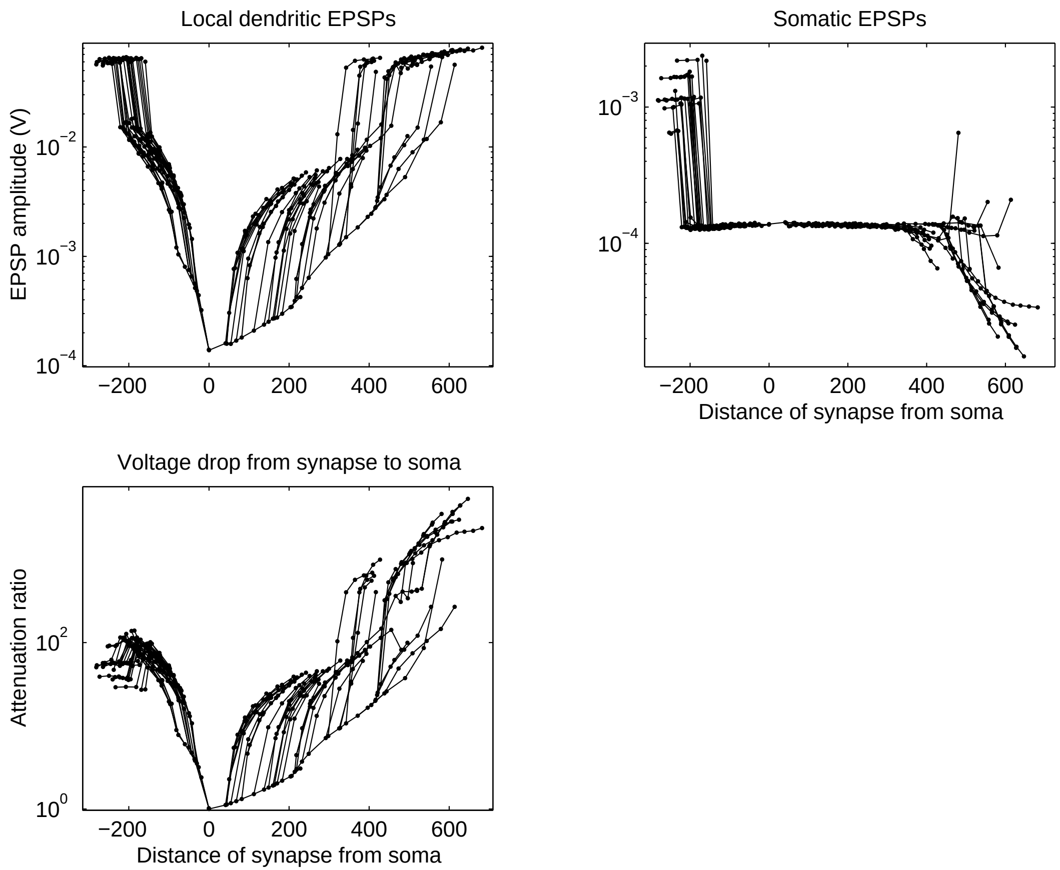
Passive model



Main reason for large attenuation: increased density in the distal dendrites of channels active in the subthreshold range (e.g., K_A, I_h). These reduce baseline membrane resistance and decrease the membrane space constant.

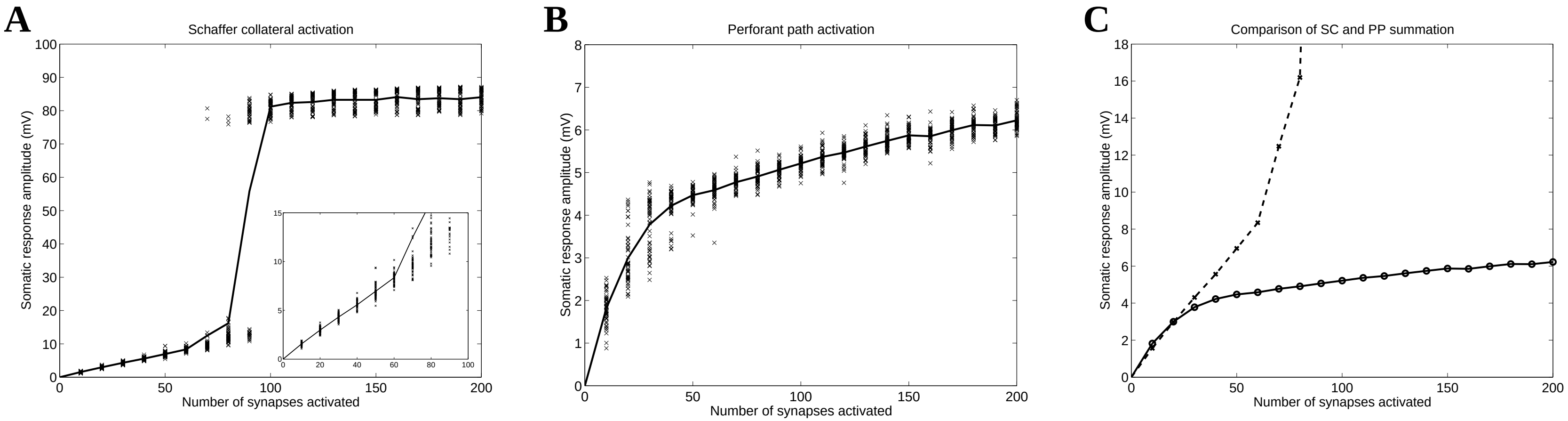
Is it just a matter of synaptic efficacy?

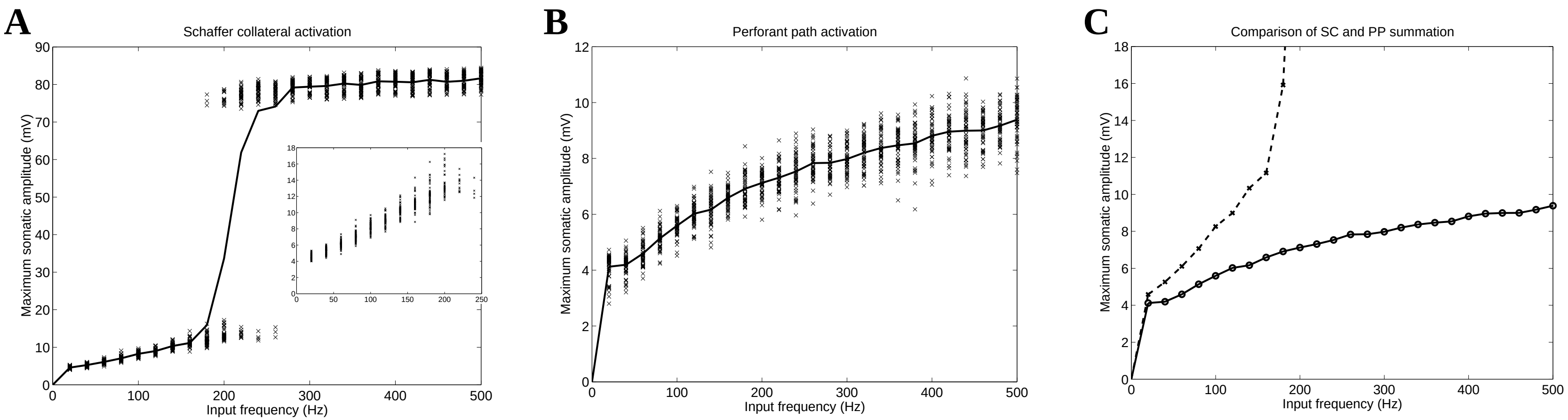
Can we solve the problem by evoking synaptic scaling?



Well, single synaptic responses saturate, and...

The spatial and temporal summation of inputs

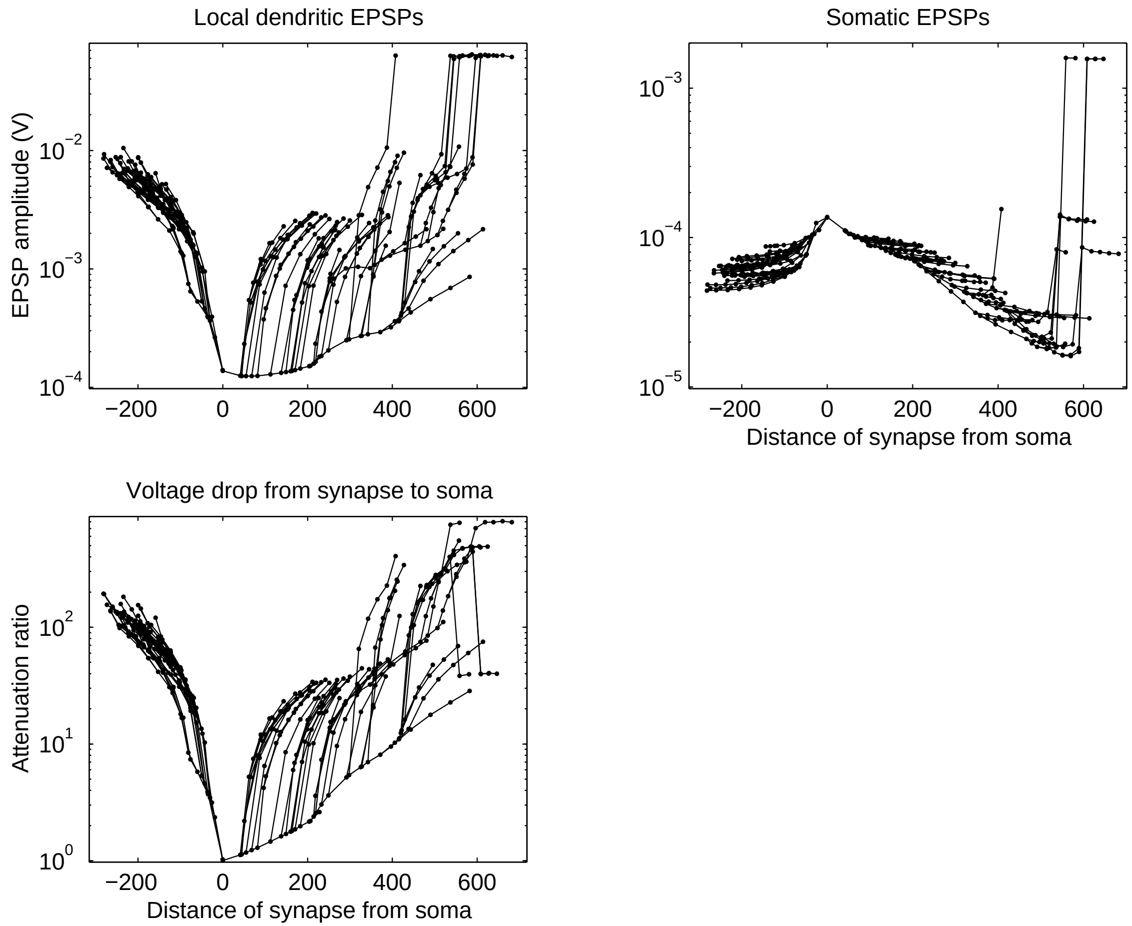




Summation of large distal dendritic signals is highly sublinear!

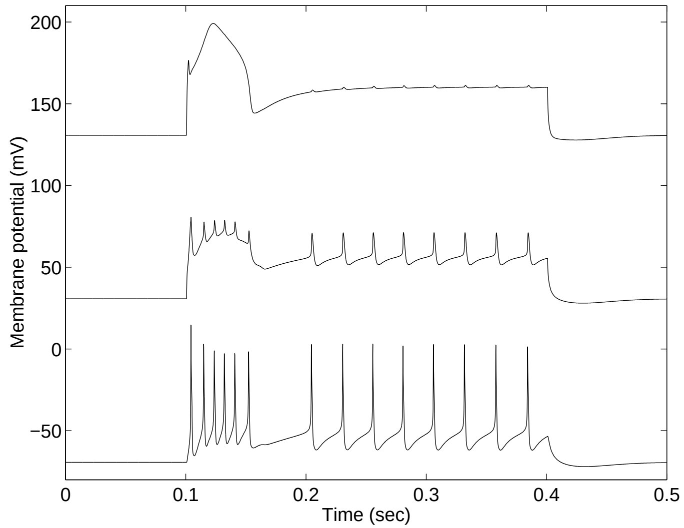
The modulation of K(A)

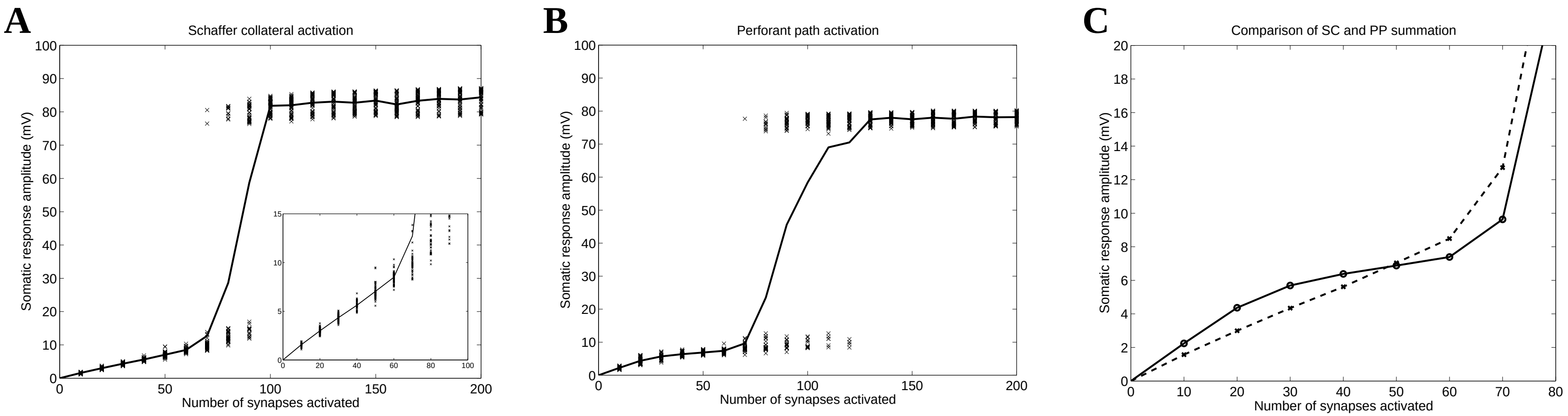
K(A) can be modulated by several metabotropic neurotransmitter receptors, which shifts the voltage dependence of its activation. This greatly enhances the efficacy of distal inputs in the model.



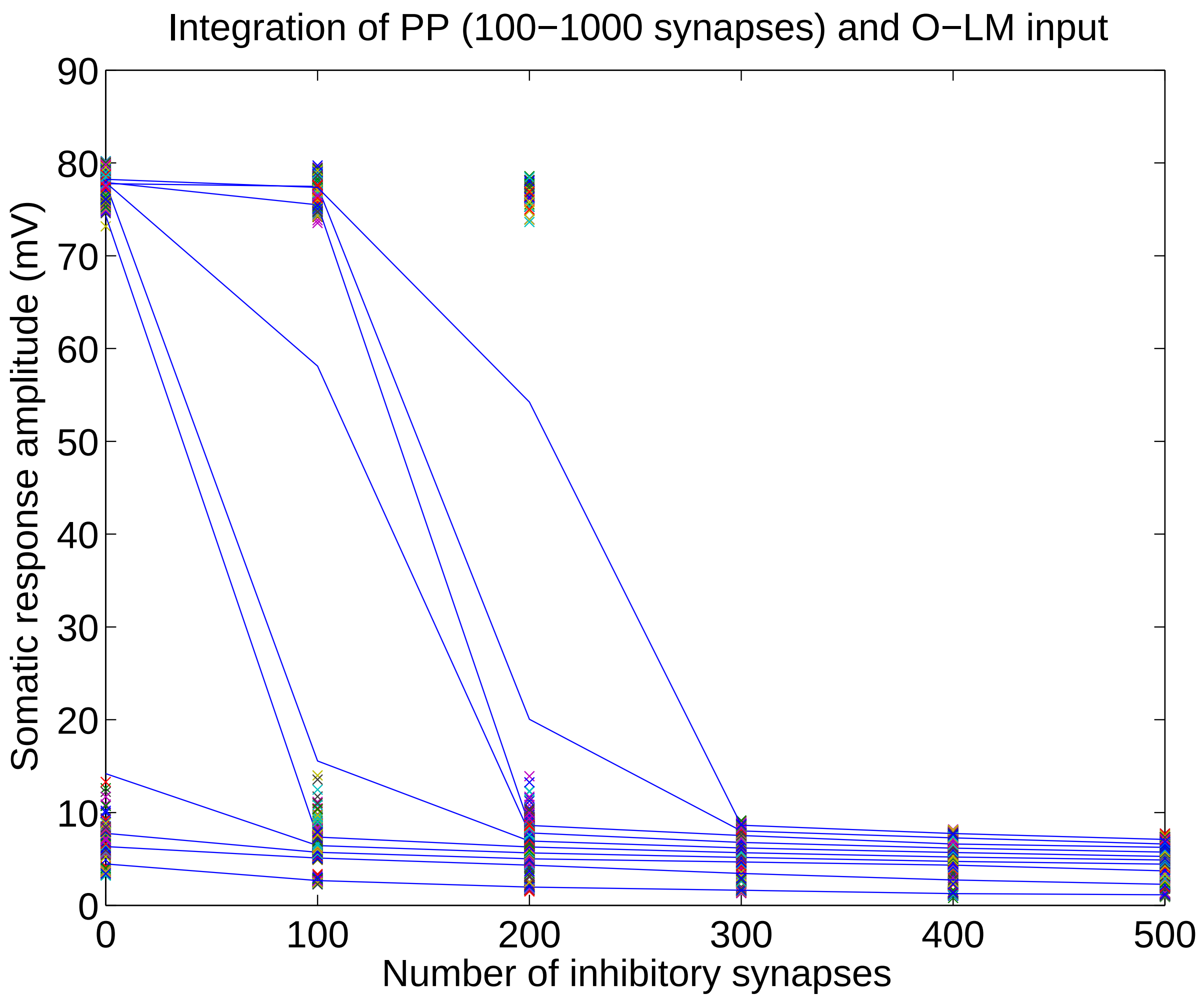
The effect of dendritic Ca^{2+}spikes

By increasing the density of dendritic Ca(R) channels, dendritic Ca^{2+}spikes and somatic bursts become possible. This also enhances the potential impact of the perforant path input.





Integration of excitatory and inhibitory inputs (full bursting model)



Systematic reduction of compartmental models

Detailed multicompartmental model neurons

+ provide an accurate description of single cell behavior
− are too complex to be used in network simulations

Abstract model neurons used in network models

− either lack the distinctive features of individual cell types, or
− are developed using *ad hoc* procedures

Goal: to develop a systematic procedure for finding simplified models which provide an optimal approximation of the behavior of complex compartmental model neurons.

(What aspects of behavior? Optimal in what sense?)

Methods

Two-step procedure:

1. Assign the compartments of the full model to clusters which then define the compartmental structure of the reduced model. This assignment also determines the appropriate placement of synapses. The clusters may also be used in defining the target for the second phase.

2. Optimize the parameters of the reduced model so that some given aspects of its behavior are as close as possible to those of the full model.

Step I: Clustering

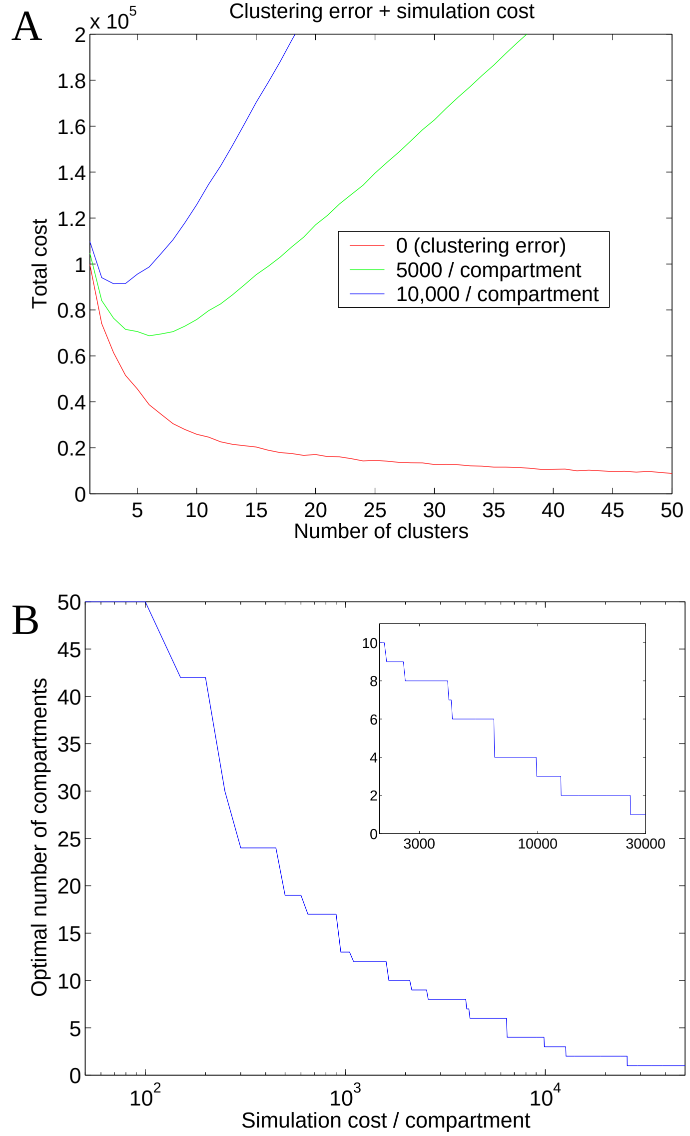
- compartments were characterized by their voltage response to the activation of synapses at various locations — other characterizations (e.g., by the pattern of voltage response in the cell to synaptic activation in the compartment, or by the response to other types of input) are also possible
- the logarithm of the response was used in most cases to enable the algorithms to focus on global patterns
- algorithms used:
  - K-means clustering (iterative algorithm, maximizes the similarity within clusters and the differences between clusters) with various distance measures (Eucledian, i.e., norm l_2, city block, i.e., norm l_1, etc.)
  - Gaussian mixture model, fit using the expectation-maximization (EM) algorithm
  - hierarchical clustering (arranges compartments as the leaves of a binary tree according to pairwise similarity) — results in a series of possible clusterings
- if clustering works right, the geometry of the reduced model also becomes evident

Step II: Parameter Optimization

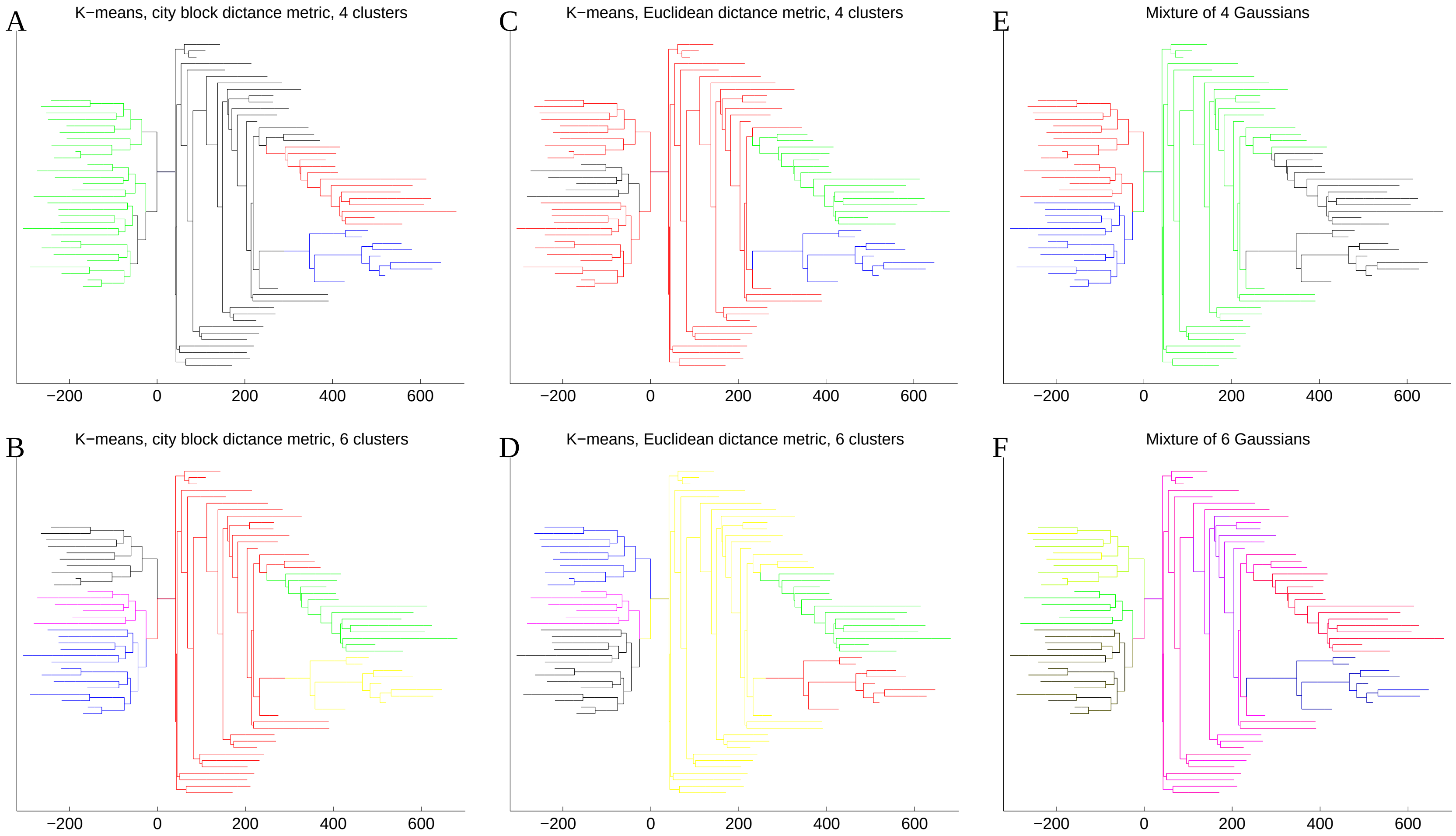
- either current injections or synaptic inputs were used for stimulation
- the (arithmetic or geometric) mean responses of compartments of the full model in each cluster were calculated and used as a target for the internal dynamics of the simplified model
- a set of parameters (up to 20) in the reduced model was varied using a parameter search algorithm so that the responses of the reduced model match this average as closely as possible (amplitude, temporal features, or entire waveforms may be matched)
- algorithms used:
  - simulated annealing (with a simplex method implementation) over the "energy landscape" — noisy gradient descent with decreasing "temperature"
  - genetic algorithm — "evolution" of a population of models

Results I: Clustering

- clustering revealed a meaningful compartmentalization within the dendritic tree, partly corresponding to functional subregions
- different methods and distance measures gave somewhat different results with some conserved features
- K-means and Gaussian mixture models worked best with logarithmic data
- the optimal number of clusters can be determined if the simulation cost per compartment is known

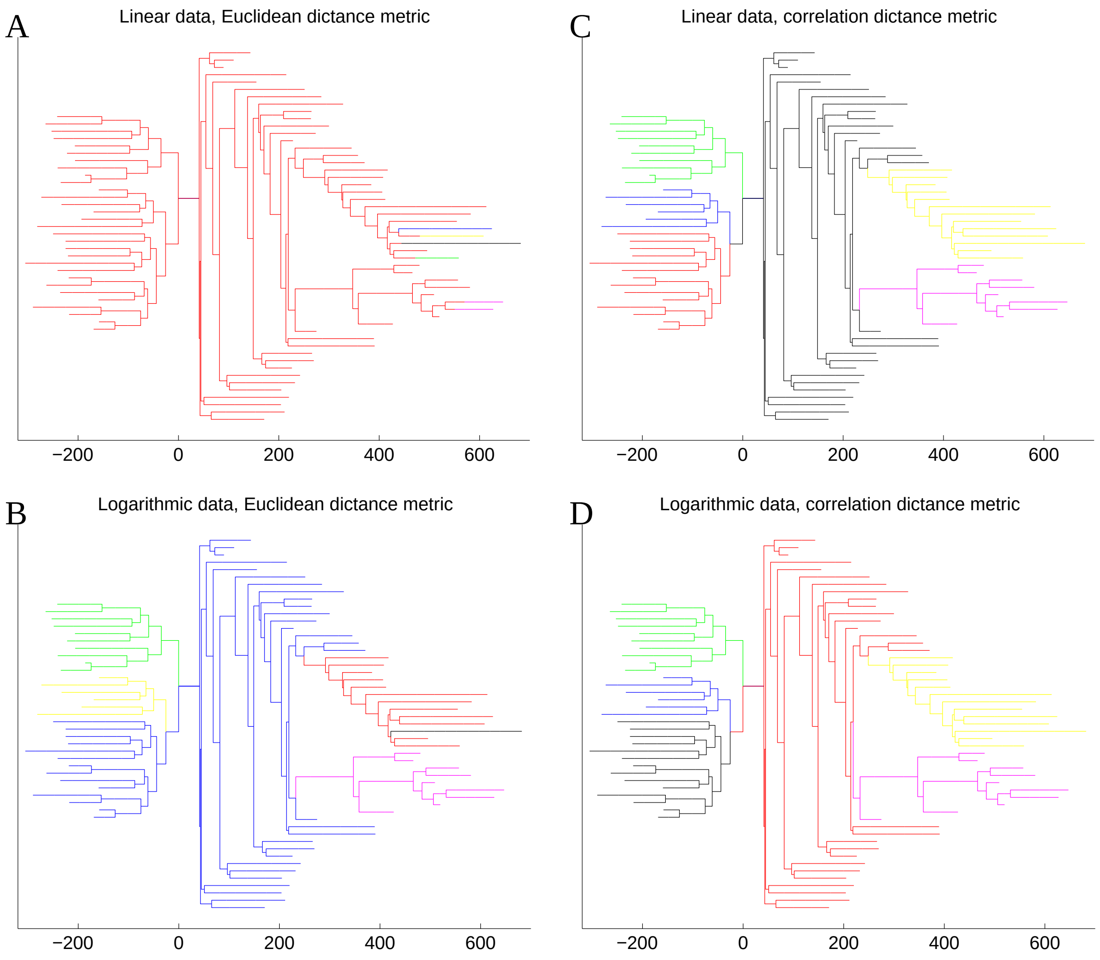


K-means and Gaussian mixture clustering results



Hierarchical clustering results

- some versions of hierarchical clustering also gave satisfactory results, but there were substantial differences between different variants (distance measures, linkage methods, linear vs. log data)

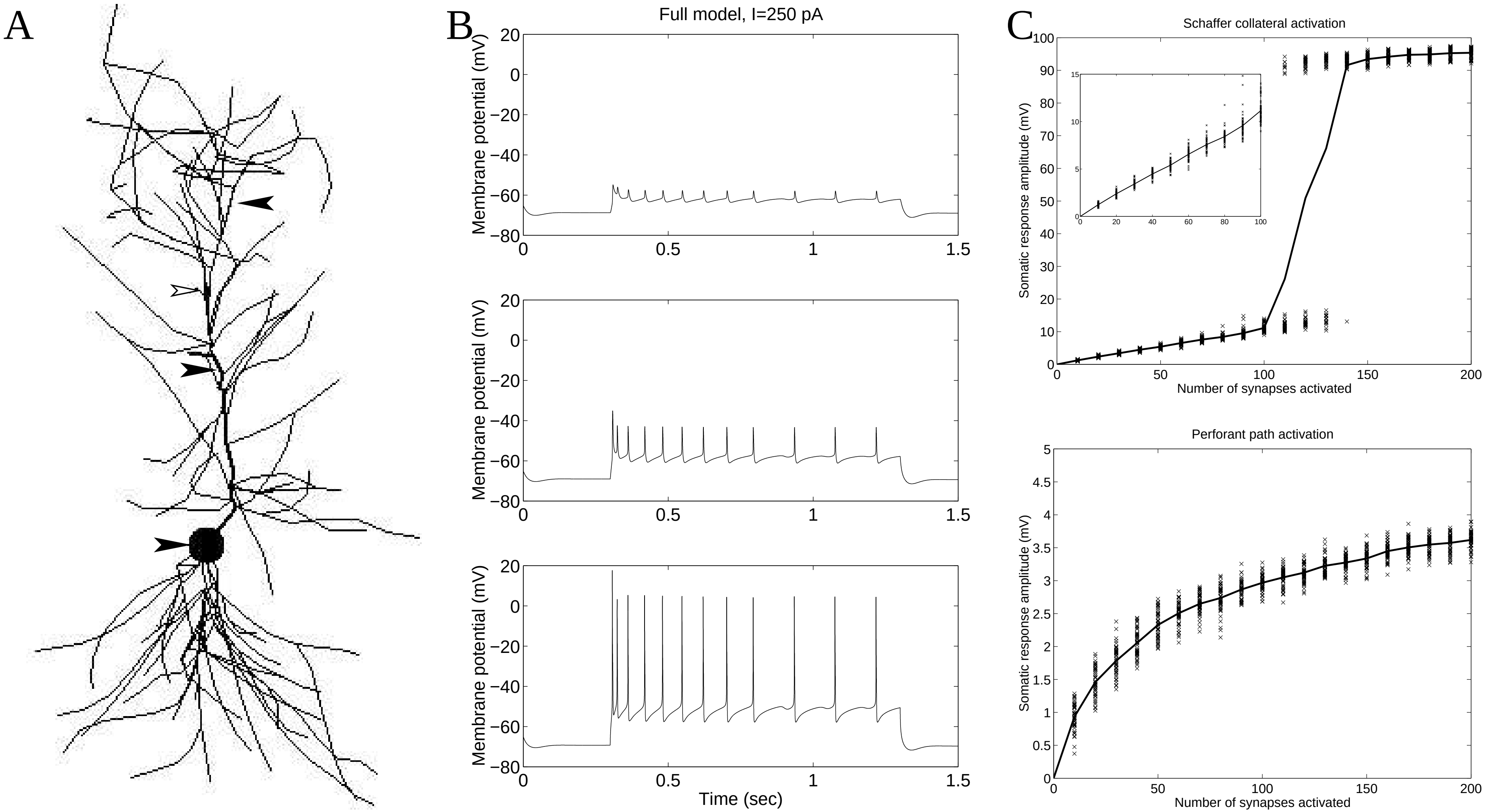


Results II: Parameter Optimization

- passive characteristics of the reduced cell (dendritic dimensions, R_M, C_M) and the densities of active conductances (Na, K(A), I(h)) were optimized
- non-optimized parameters were set to their average values within the cluster
- we first fit a passive version of the model to the passive version of the full model to provide initial guesses for passive parameters
- the target was either
  - (the geometric average of) the amplitude of the voltage response in the corresponding compartments to synaptic stimulation in various compartments
  - or the voltage trace in all compartments in response to somatic and dendritic current injections

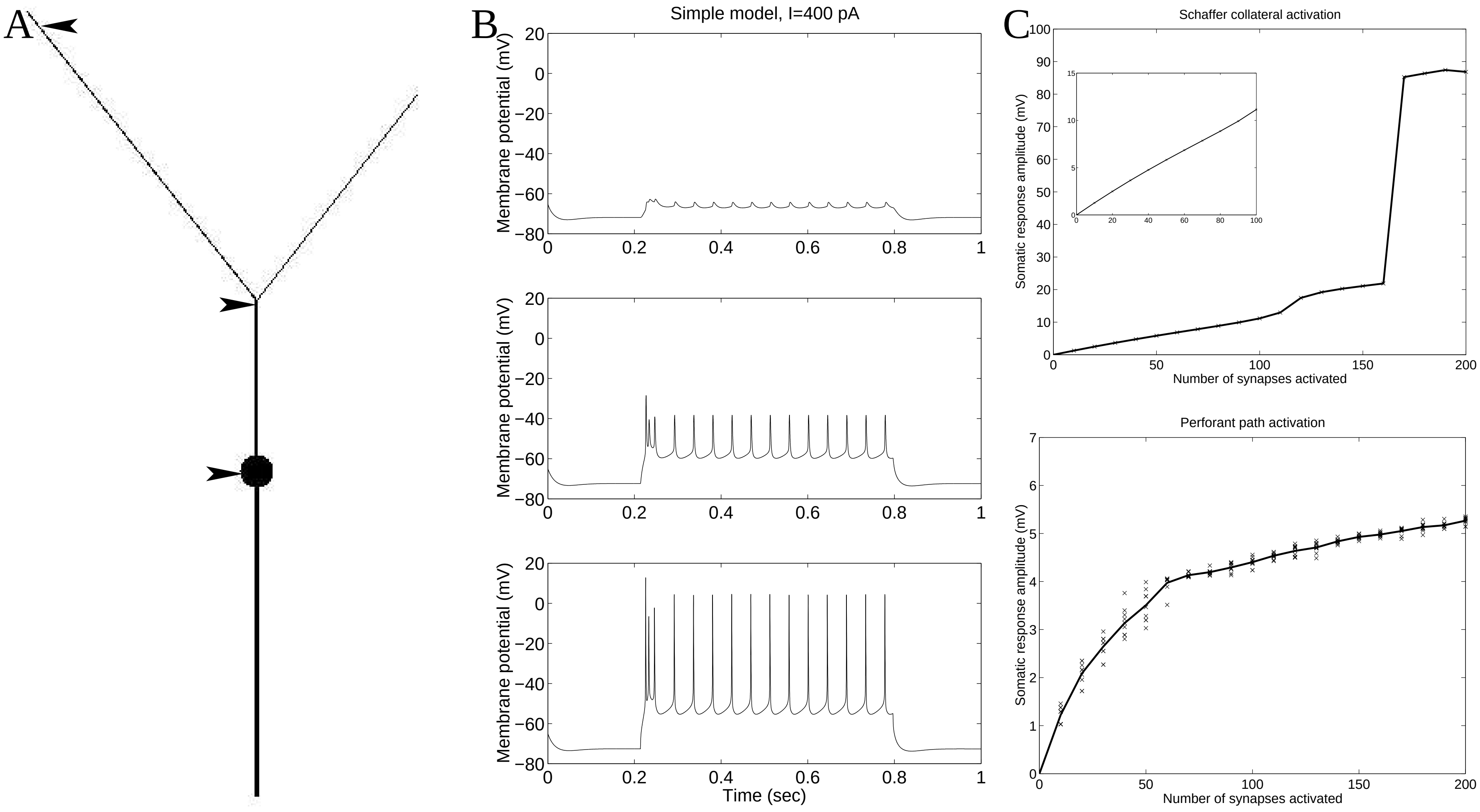
- both simulated annealing and the genetic algorithm often found good solutions
- however, in repeated runs, solutions were rather variable, and both algorithms occasionally failed to find a good solution
- simulated annealing appeared to be the most reliable
- when signal attenuation between different parts of the cell was optimized, the behavior of the resulting model was quite similar to that of the original model in several other respects:
  - response to step current injection to the soma
  - summation of proximal (Schaffer collateral) and distal (perforant path) synaptic inputs
- but failed to reproduce other phenomena such as bursting

Full model

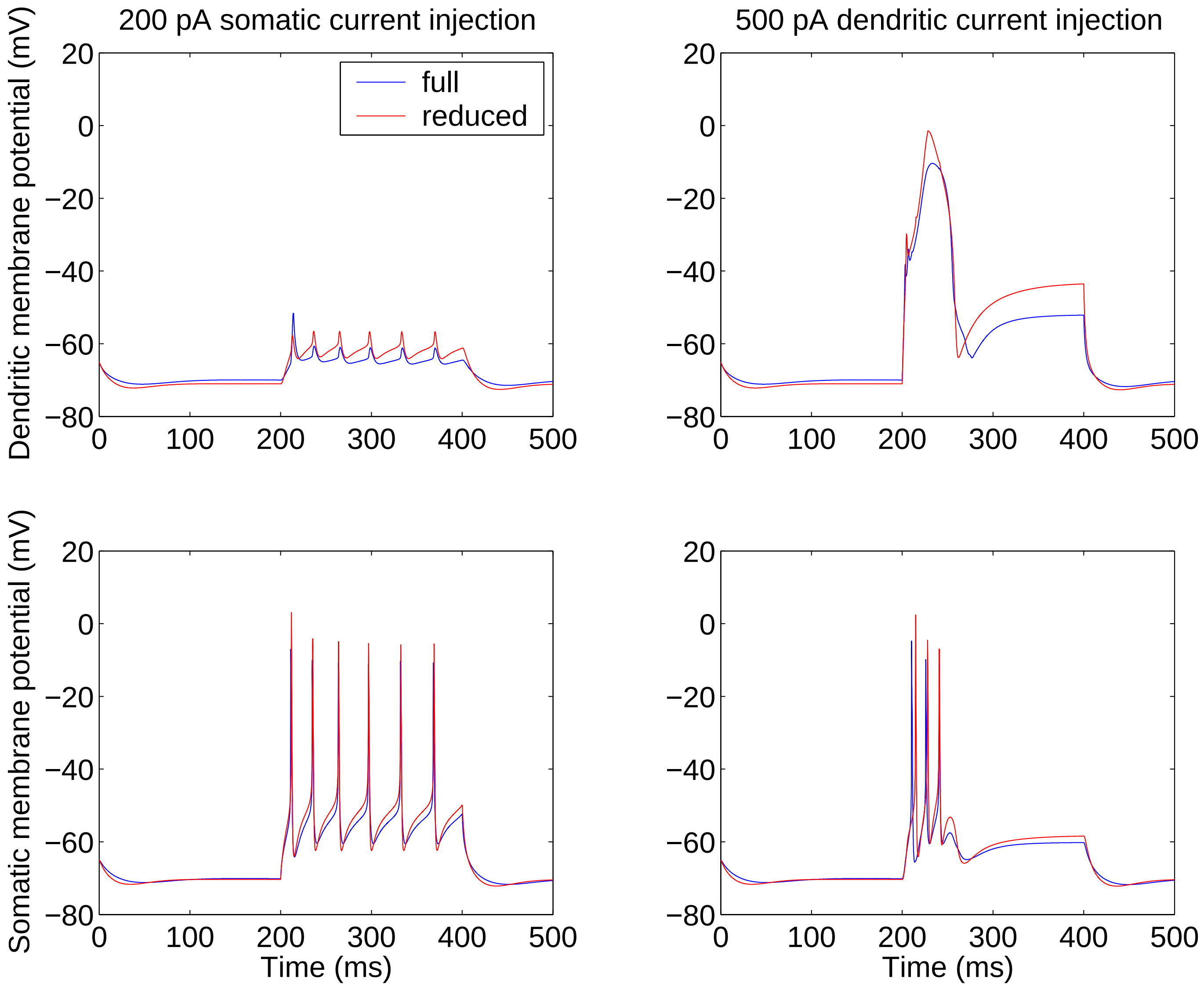


A
B
Full model, I=250 pA
Membrane potential (mV)
Time (sec)
C
Schaffer collateral activation
Somatic response amplitude (mV)
Number of synapses activated
Perforant path activation
Somatic response amplitude (mV)
Number of synapses activated

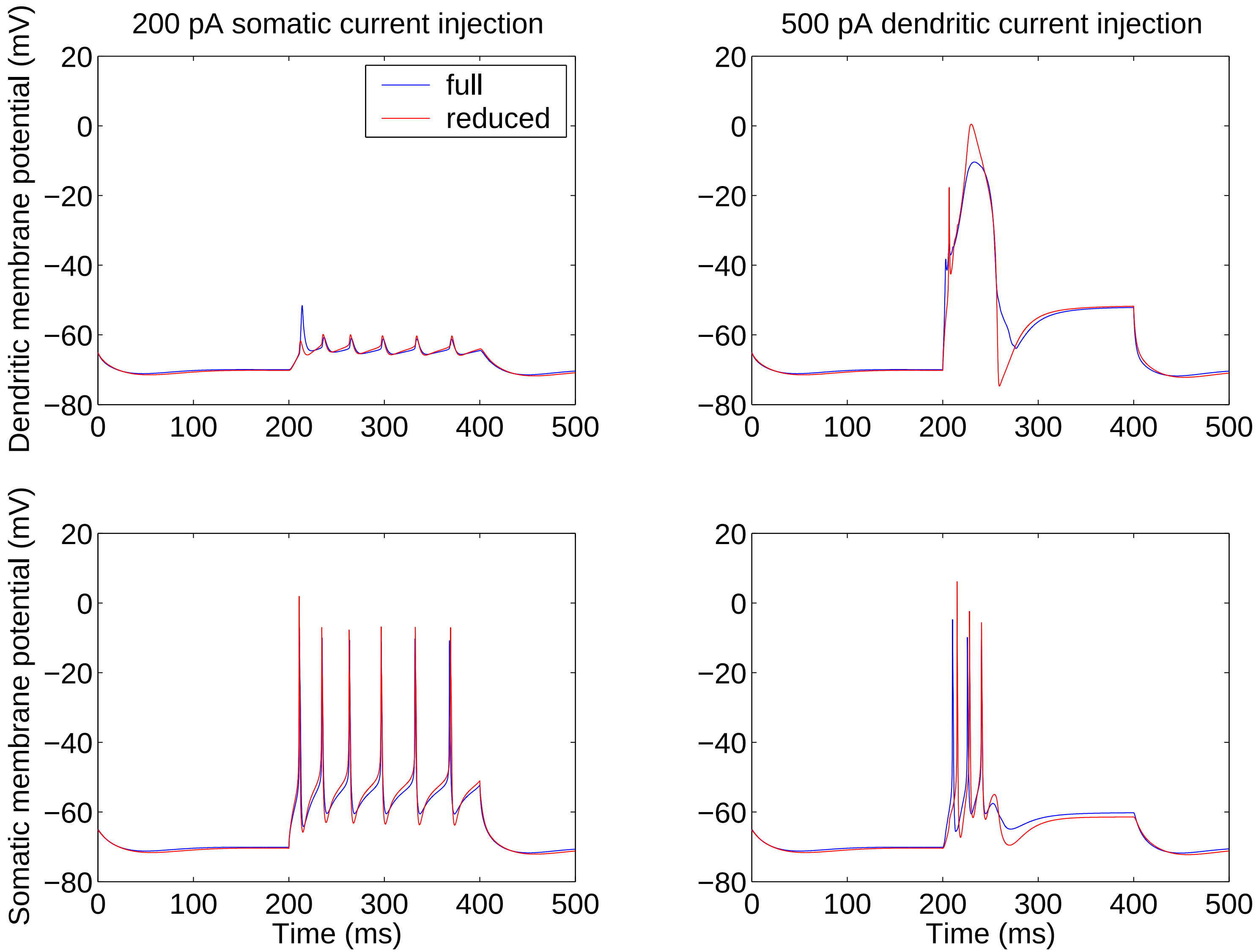
Reduced model, optimal small-amplitude transfer



Reduced model, optimal spiking response (simulated annealing)

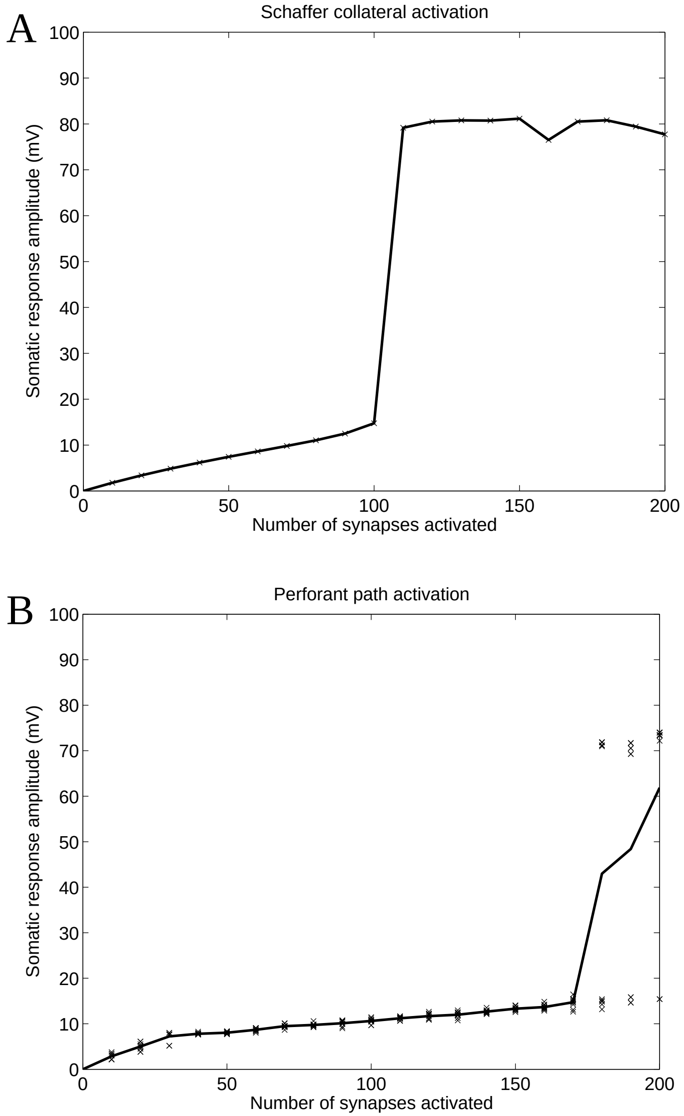


Reduced model, optimal spiking response (genetic algorithm)



- when the response to suprathreshold (somatic and dendritic) current injections was optimized, target voltage traces were fairly precisely fit

- however, other aspects of behavior, such as the response to synaptic activation, were not reproduced correctly



Discussion and conclusions (model reduction)

- the outlined procedure is a viable way of automatically creating arbitrarily simplified versions of complex compartmental models
- no single variant of the procedure is clearly superior to the others
- local minima can cause serious problems at both stages

- no single reduced model can reproduce all aspects of the real cell's behavior, so the exact method of reduction should be tailored to the intended use of the simplified model neuron
- the case of localized active events appears to be especially problematic

Conclusions

- inputs impinging on different parts of the dendritic tree may be processed in very different ways
- dendritic inhibition can selectively modulate the efficacy of different input pathways

- active conductances in pyramidal cell dendrites play a major role in these processes;
- in particular, they enable relatively independent local dendritic computations, only the end result of which is communicated to the soma
- active dendritic processing may play a role in the generation of network oscillations
- modulation of voltage-gated conductances may switch CA1 pyramidal neurons between different information processing modes