Constructing detailed biophysical models of hippocampal pyramidal cells

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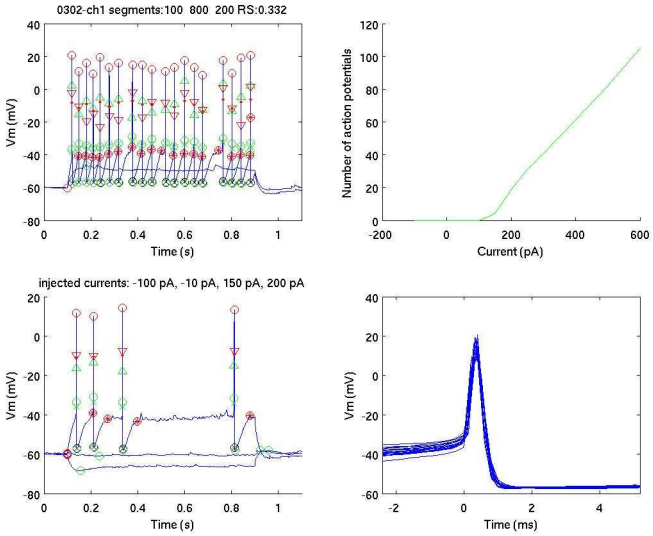
March 31, 2015

Talk outline

- Relevant experimental data sets at IEM HAS
- Hippocampal models in our lab
- Examples of critical data and existing models
- Critical elements in faithful single cell models
- Our current approach to developing models
- Towards a community model of the CA1 pyramidal cell

Cellular and synaptic databases at IEM HAS

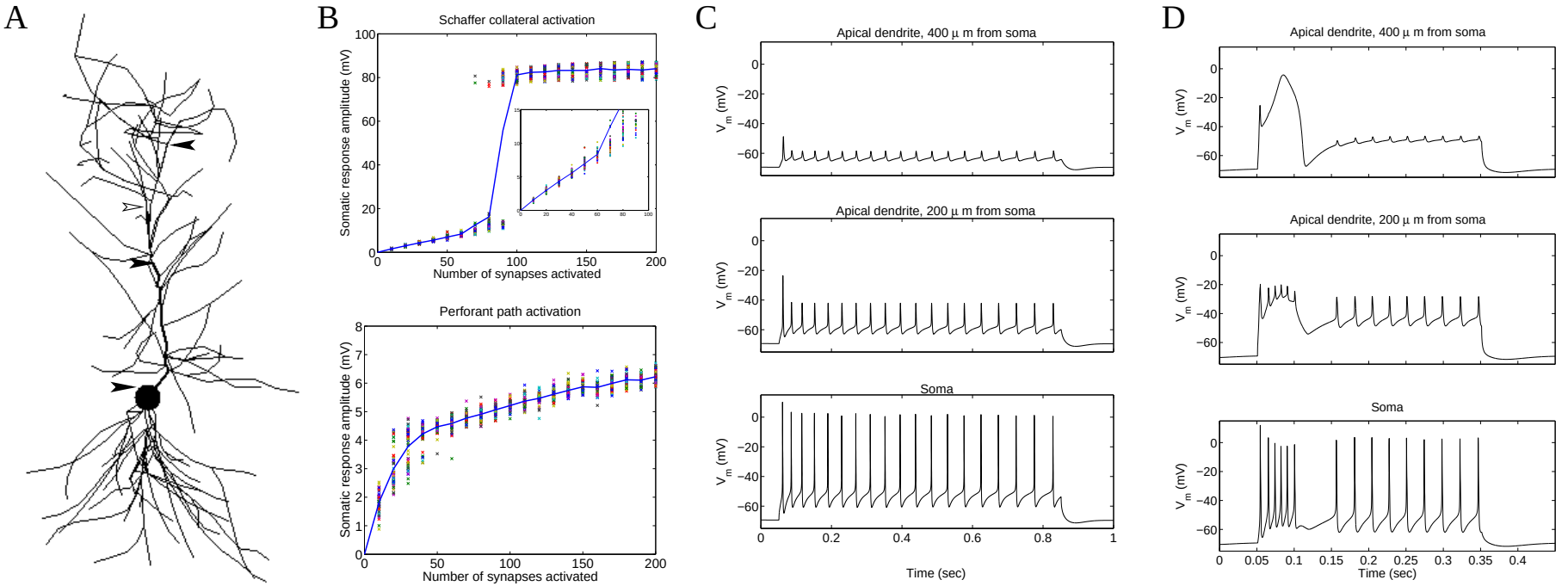
- a large database (> 500 experiments) of somatic whole-cell recordings from a variety of cell types (in CA1 and CA3) in hippocampal slices using a standardized current step protocol



- database of synaptic connections (including short-term plasticity)
- morphological reconstructions of CA1 PCs and several interneuron types (in rat)
- morphological reconstructions of various cell types with associated physiological (step protocol) data (in mouse – HBP)

Our hippocampal models 1: CA1 pyramidal neuron

Reconstructed CA1 pyramidal cell from Megias et al. (2001), with a wide variety of active conductances in all compartments.



Káli and Freund, 2005

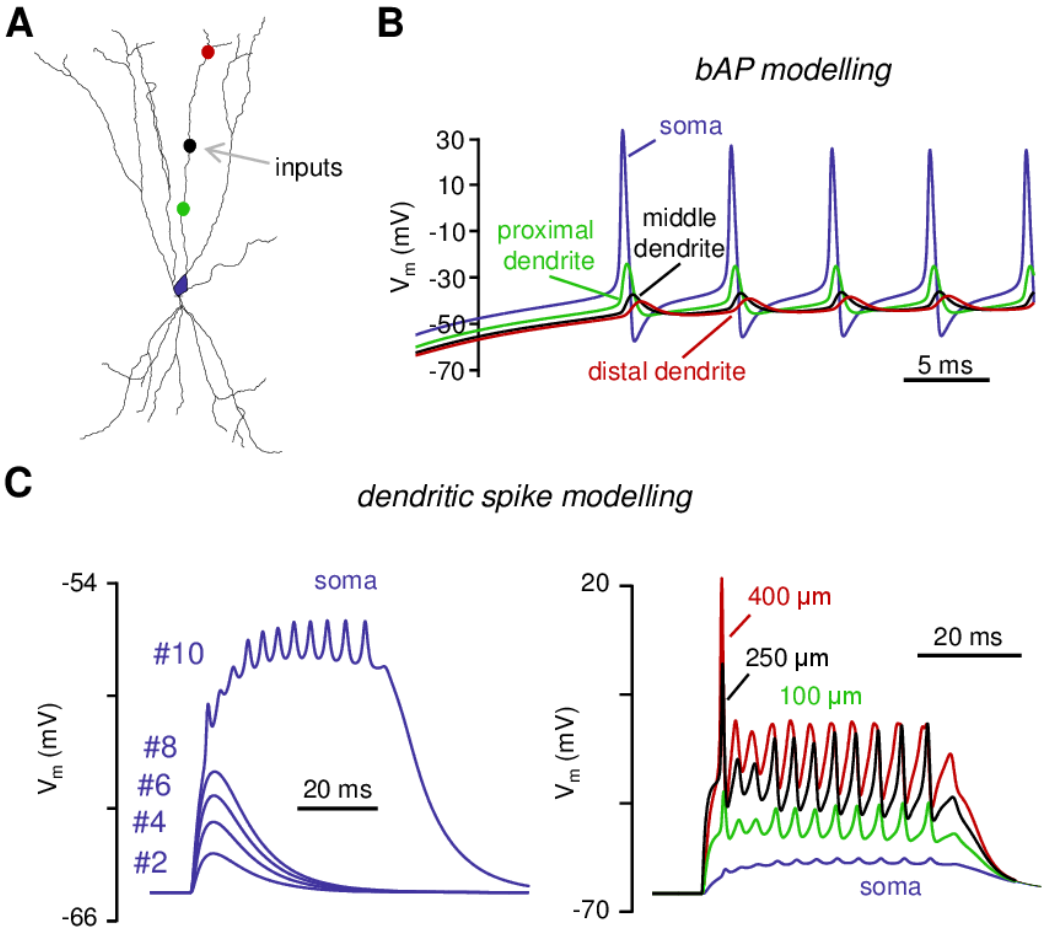
Main features of our original CA1 PC model

- SC and PP inputs are integrated differently due to both electrotonic and active properties
- in the absence of Ca^{2+}spikes, PP inputs are modulatory
- Ca^{2+}spikes can carry an all-or-none message about the result of distal dendritic integration
- the modulation of K(A) can switch dendrites into a different mode of processing, where synaptic input-triggered dendritic APs can propagate in the forward direction (confirmed experimentally by Losonczy et al. (2008))

Our hippocampal models 2: CA1 PV+ basket cell

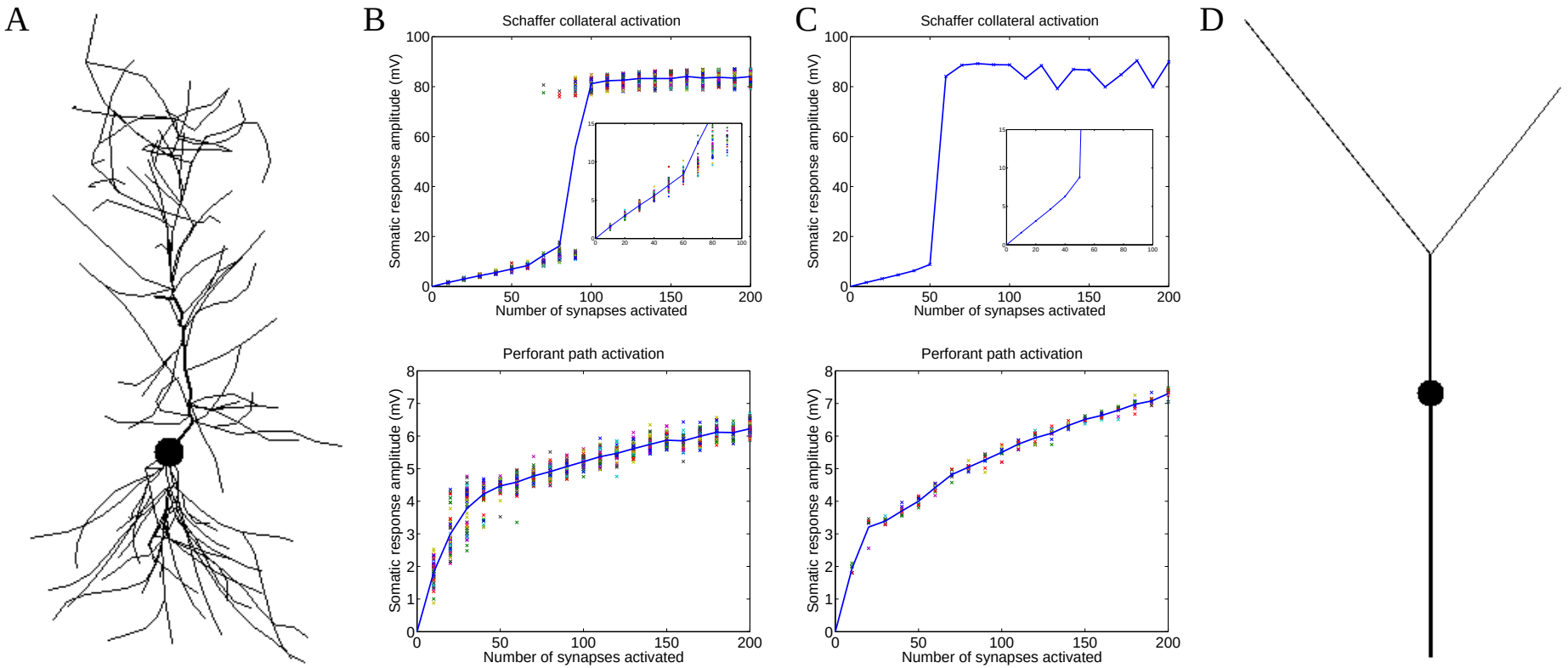
Reconstructed CA1 PV+ basket cell from Gulyás et al. (1999), with Na, K(DR), and HVA Ca conductances in all compartments.

Reproduces experimentally observed fast oscillations in response to strong dendritic input.



Chiovini et al., 2014

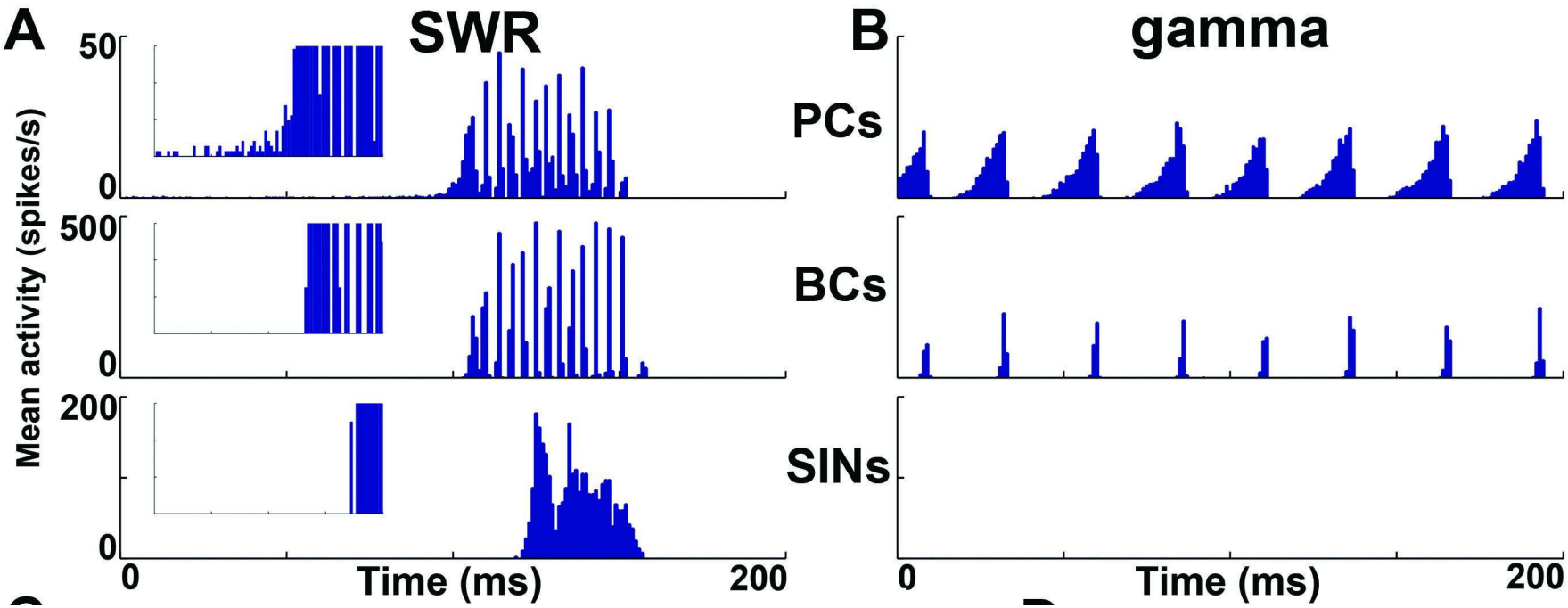
Our hippocampal models 3: systematically simplified CA1 PC (spatial summation in non-bursting models)



Optimized aspects of the behavior of a reduced 5-compartment model were similar to the morphologically detailed model.

Our hippocampal models 4: single-compartment models

- Single-compartment conductance-based (HH) models of CA1 FSBCs and O-LM cells
- Phenomenological (adaptive exponential integrate-and-fire) models of CA3 PCs and FSBCs, used in a network model which captures sharp wave-ripples, gamma oscillations, and epileptic events



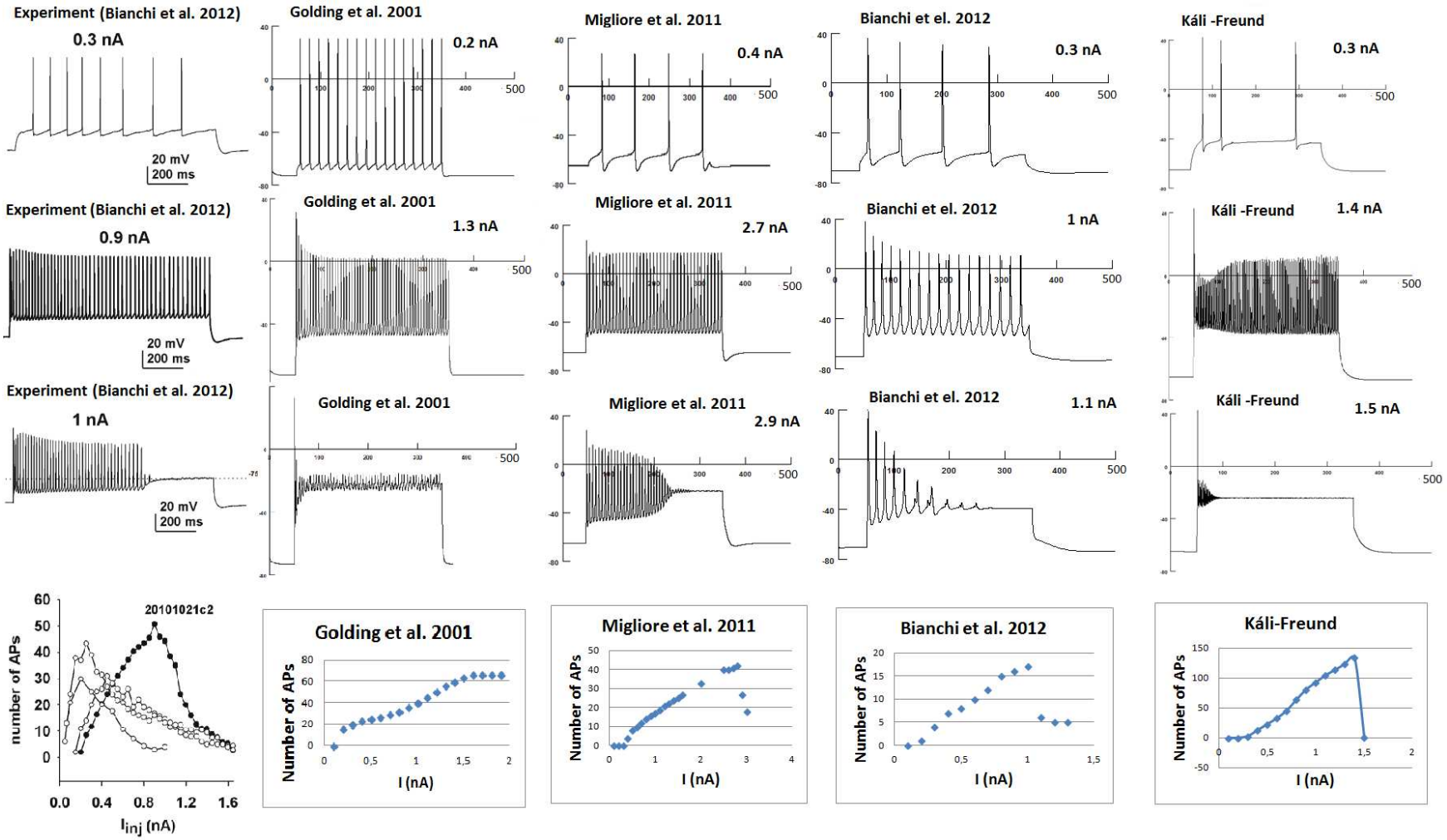
Some examples of other CA1 PC models

- a series of models by Migliore and coworkers (1999 - 2014)
- Poirazi et al. (2003) and derivatives
- Traub et al.
- Kath, Spruston et al. (2001-2009)
- Lyle Graham
- etc.

90 models in ModelDB...

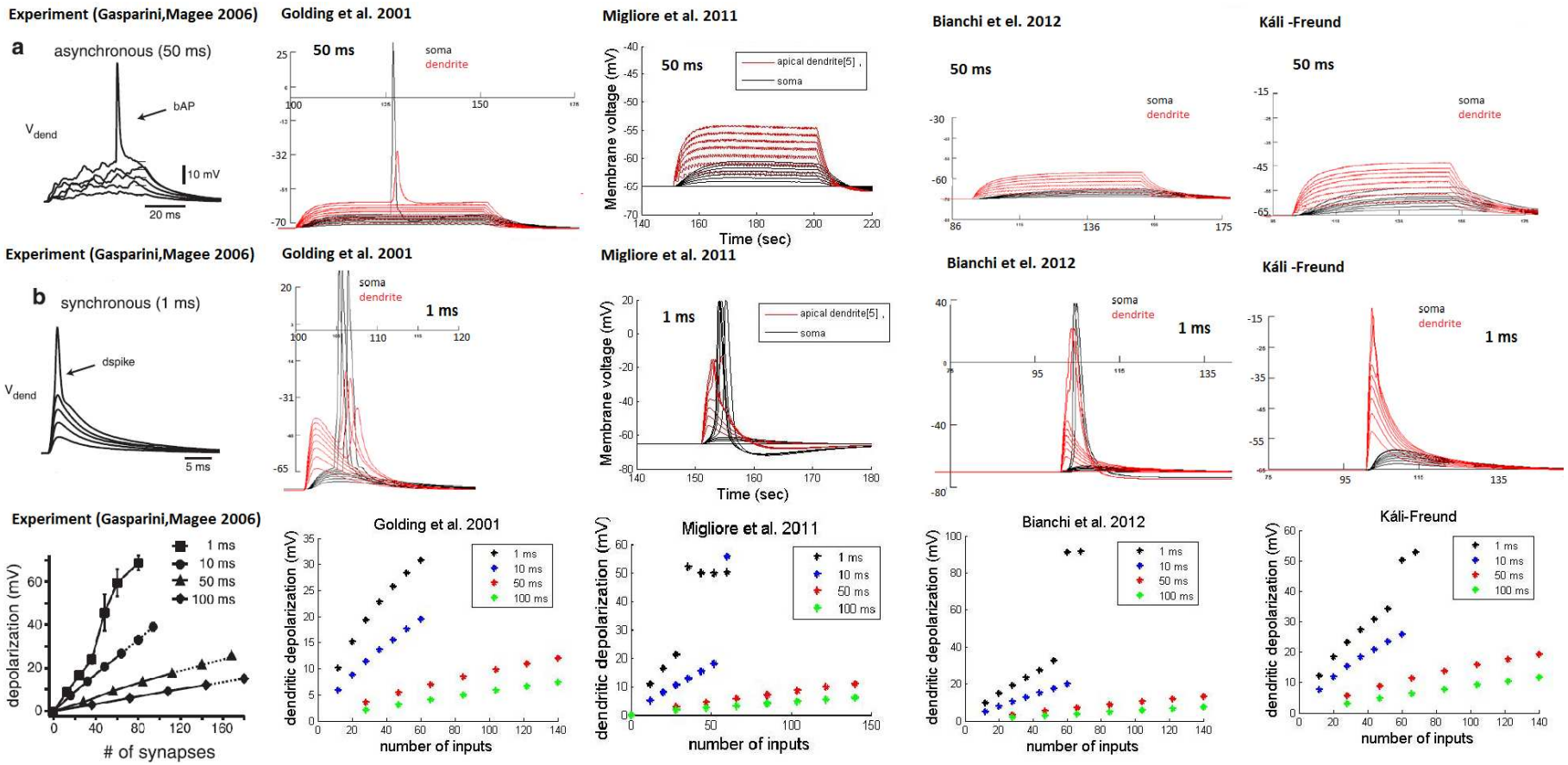
Many of these models nicely capture some aspects of the behavior of CA1 PCs — but how do they generalize to data sets they were not built to reproduce?

Comparison of critical data and existing models (1)



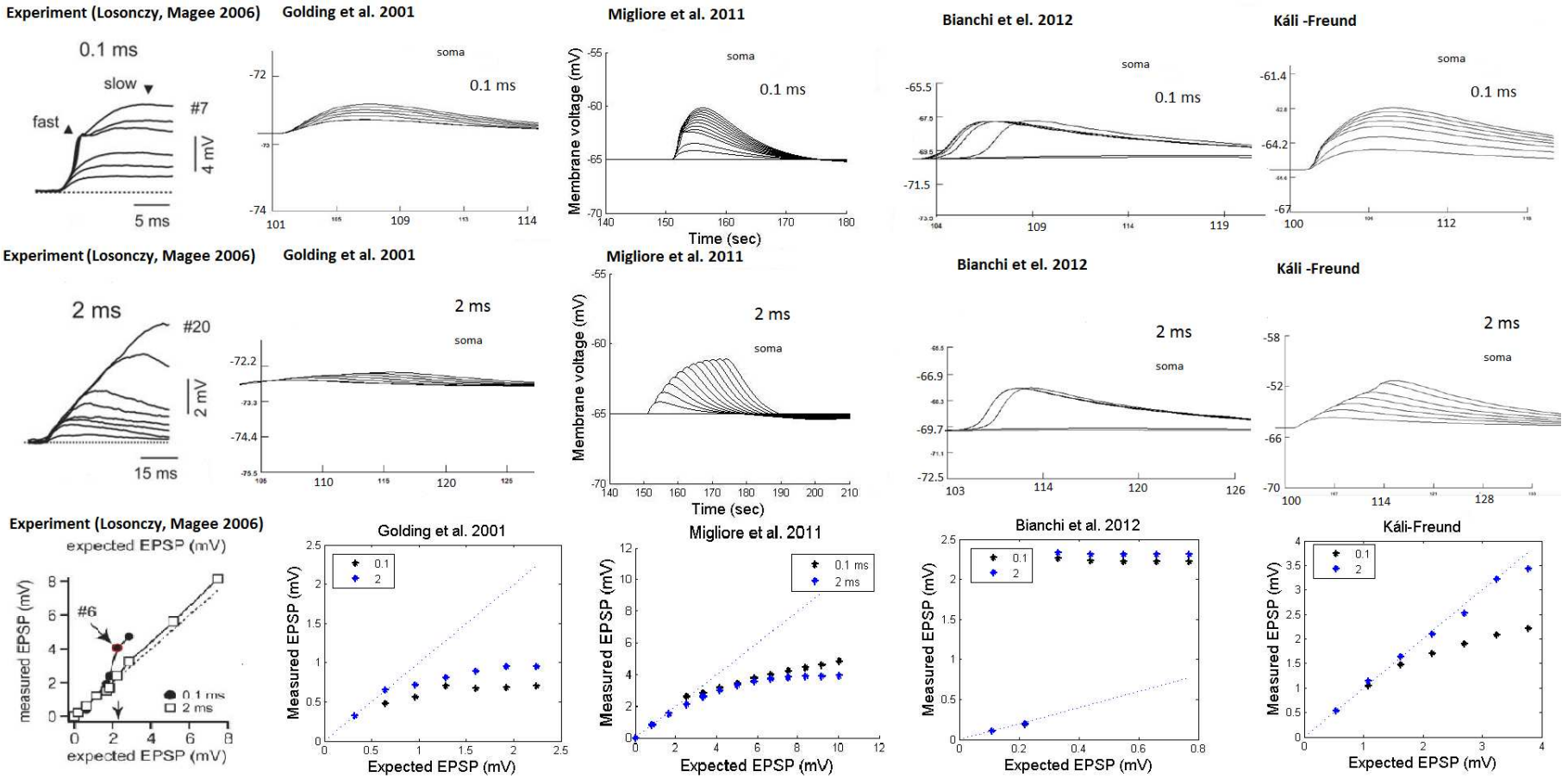
Somatic step current injections: f-I curve and depolarization block

Comparison of critical data and existing models (2)



Synaptic integration in the apical trunk.

Comparison of critical data and existing models (3)



Synaptic integration in apical oblique dendrites.

Qualitative comparison of data and models

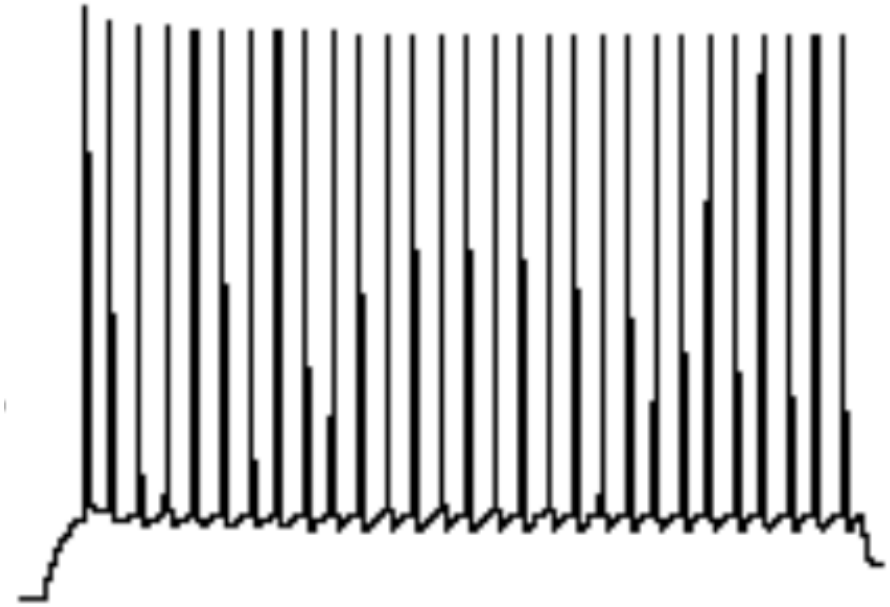
Experimental results	Golding et al. 2001	Migliore et al. 2011	Bianchi et al. 2012	Káli-Freund
Depolarization block (Bianchi et al. 2012)	☒	☑	☑	☑
If an appropriate number of synchronous inputs arrive to the apical **trunk**, dendritic spike is generated. (Gasparini Magee 2006. Fig. 1. b)	☒	☑	☑	☑
If an appropriate number of synchronous inputs arrive to the apical **trunk**, not only dendritic spike is generated, but somatic action potential as well (Gasparini Magee 2006. Fig. 1. D)	☒	☑	☑	☒
In the case of synchronous inputs arriving to the **trunk**, dendritic spike is generated, and their amplitude decreases if the inputs are distributed. (Gasparini Magee 2006. Fig. 2. d,e)	☒	☐	☒	☑
In the case of the most synchronous inputs arriving to the **trunk** the form of signal integration is supralinear. (Gasparini Magee 2006. Fig. 1. e)	☒	☑	☑	☑
If an appropriate number of asynchronous inputs arrive to the apical **trunk**,no dendritic spike is generated, but backpropagating action potential appeares. (Gasparini Magee 2006. Fig. 1. a)	☑	☒	☒	☒
In the case of synchronous inputs arriving to the **radial oblique dendrites** the summation is supralinear. (Losonczy Magee 2006 Fig. 1. J)	☒	☒	☑	☒
In the case of asynchronous inputs arriving to the **radial oblique dendrites** the summation is linear. (Losonczy Magee 2006 Fig. 1. J)	☒	☒	☒	☑
In the case of synchronous, distributed inputs arriving to the **radial oblique dendrites** the summation becomes more supralinear, compared to the clustered inputs. (Losonczy Magee 2006 Fig. 1. J)	☑	☐	☒	☑

Quantitative comparison of data and models

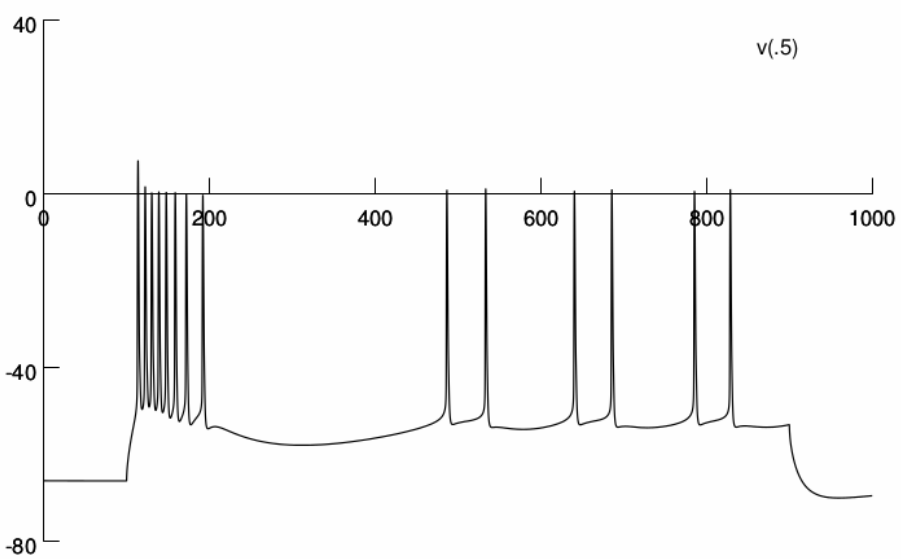
Experimental result	Golding et al. 2001	Migliore et al. 2011	Bianchi et al. 2012	Káli-Freund
Depolarization block occures at an I value between 200pA-0.95nA (Bianchi et al. 2012)	☒	☒ (2.9 nA)	☑	☒ (1.5 nA)
On the apical **trunk** dendritic spike threshold is 52 ± 5 synchronous inputs. (Gasparini, Magee 2006)	☒	☒ (about 36 inputs)	☑	☑
For highly synchronos, clustered inputs arriving to the **trunk** the amplitude of the local spike generated is 64 ± 3 mV. (Gasparini, Magee 2006)	☒ (no spike)	☒ (53 mV)	☒ (90 mV)	☒ (50-53 mV)
The mean voltage threshold for dendritic spike generation on **oblique dendrites** is 3.4 ± 0.2 mV at the soma.	☒	☒	☒	☒ (1.05 mV)

Regressions are common with conventional approaches

Response to 220 pA somatic current injection:



Poirazi et al. (2003)



Gomez Gonzalez et al. (2011)

Elements of a detailed neuronal model

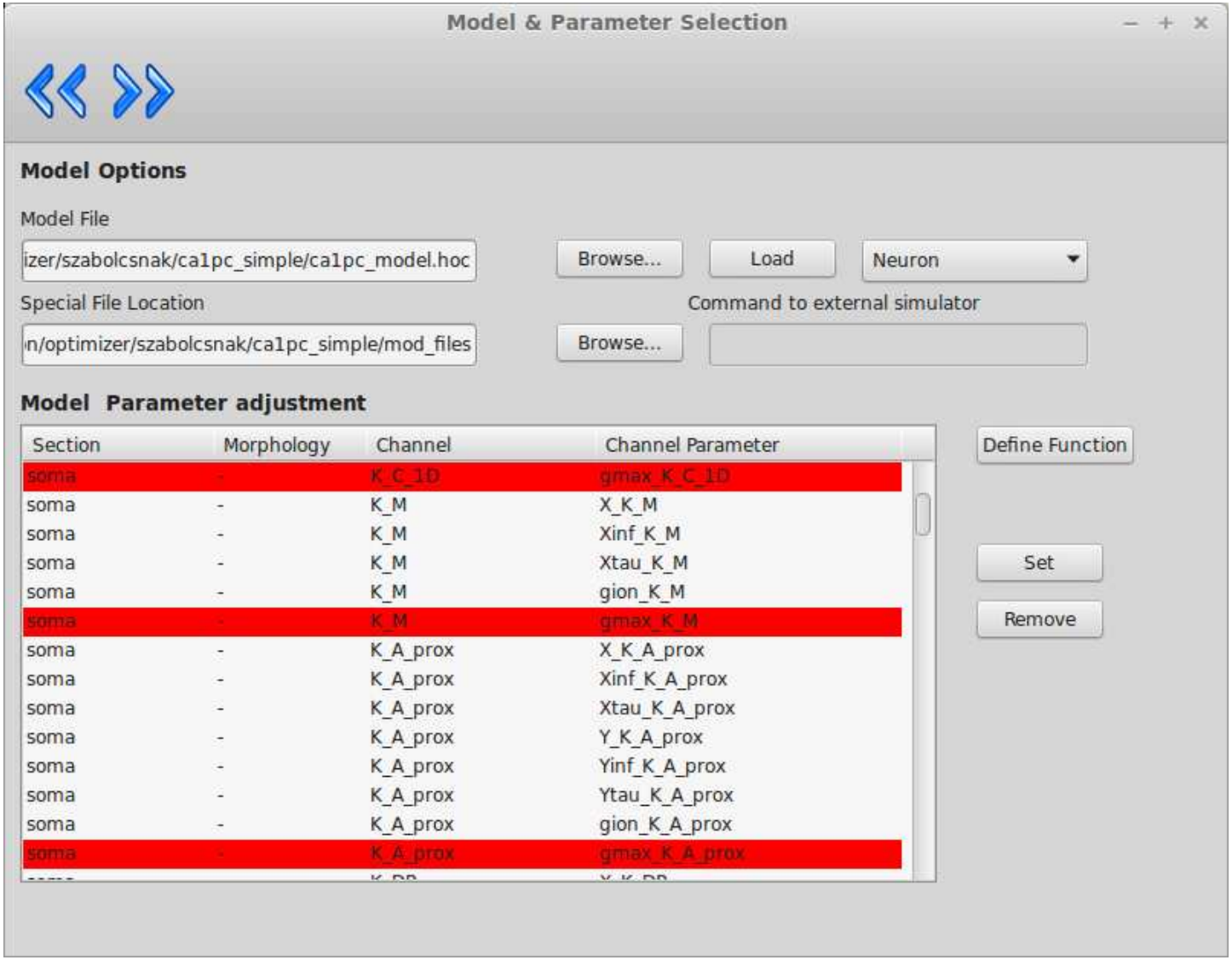
- Morphology – difficult to achieve high quality (ask Attila Gulyás)
- Passive properties (axial resistance is notoriously hard to estimate)
- Voltage-gated channels: types, kinetics (can vary between cell types), modulation, distribution
- We (in collaboration with Zoltán Nusser) are using a combination of morphological reconstructions, patch-clamp physiology, pharmacology, compartmental modeling, optimization, and statistical inference to plan maximally informative experiments, and determine critical parameters (such as the sub-cellular distribution of ion channels) in a step-by-step manner.

Our current approach

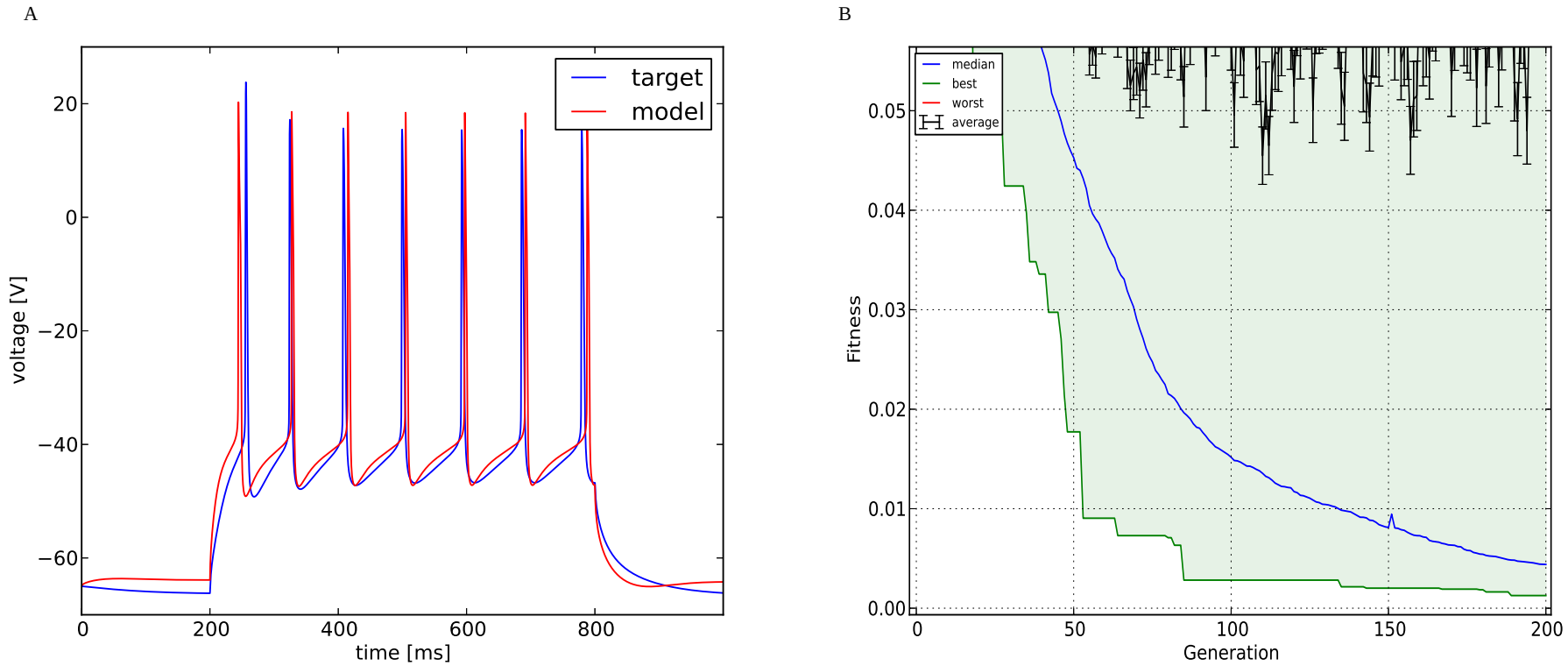
- try to use experimental data directly (rather than from the literature) – ideally, many types of data from the same cell
- use multiple benchmarks concurrently
- use automated optimization

- We have developed a software tool to fit the parameters of neuronal models
  - GUI mode
  - batch mode

The Optimizer GUI



Model simplification results using Optimizer's evolutionary algorithm



A community-based strategy to develop reliable CA1 PC models

- Gather high-quality data from many types of experiments in multiple labs
- Come up with a set of generally accepted defining criteria for CA1 PCs based on discussion of data involving experts
- Evaluate all candidate models automatically, based on the same (quantitative) criteria
- Make models and their results on the benchmarks public
- Discuss results, combine and improve models

Conclusions

- It is extremely difficult to build faithful compartmental models of complex neurons (such as cortical pyramidal cells)
  - no reliable model exists for CA1 PCs despite considerable efforts
  - there are a lot of free parameters, so it is relatively easy to reproduce a few selected results, but it is much more difficult to satisfy all available constraints
  - probably no single lab has all the required resources and expertise

  But: the community as a whole has all the required expertise and resources - so let us try to do it together!

Acknowledgements

- Attila Gulyás
- Norbert Hájos
- Tamás Freund

- Péter Friedrich
- Mátyás Forián Szabó
- Sára Sáray
- Norbert Majubu
- Boglárka Szőke
- Ádám Divák
- András Ecker