The Purkinje neuron model parameter landscape: implications for homeostasis and synaptic plasticity

Pablo Achard

Werner Van Geit

Volker Steuber

Erik De Schutter

CNS Unit, Okinawa Institute of Science and Technology, Japan

Theoretical Neurobiology, University of Antwerp, Belgium

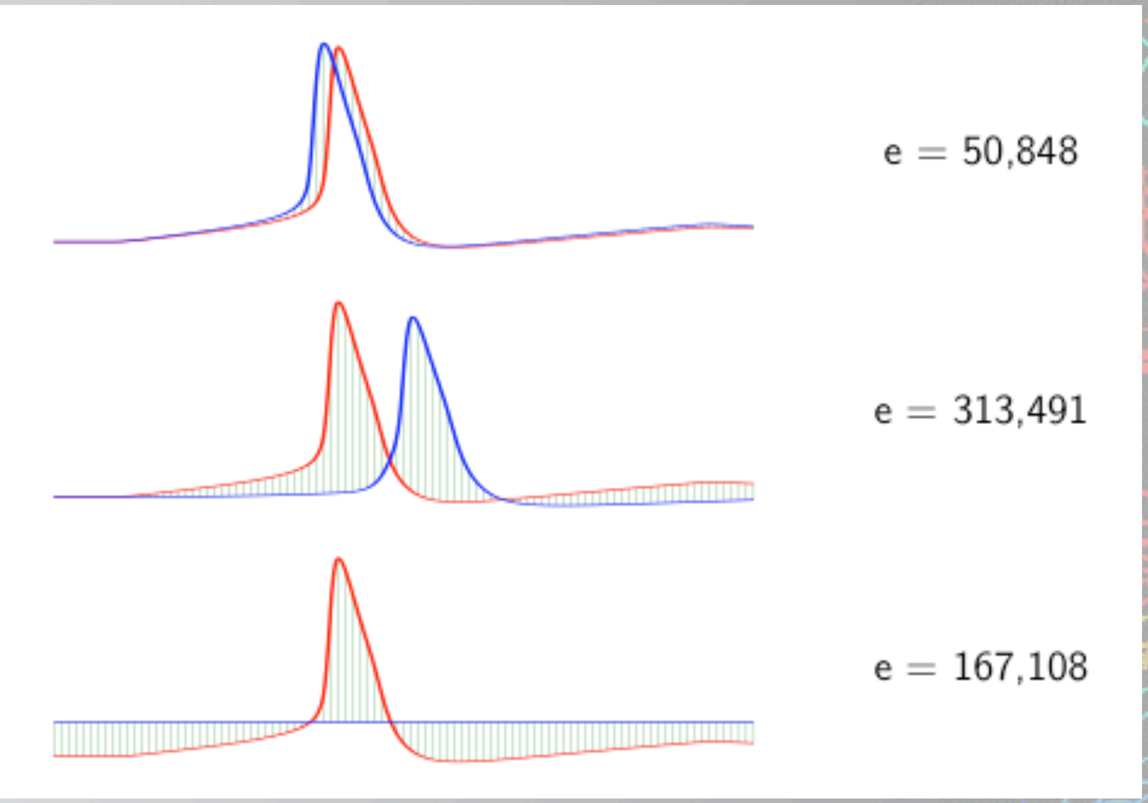
http://www.irp.oist.jp/cns/

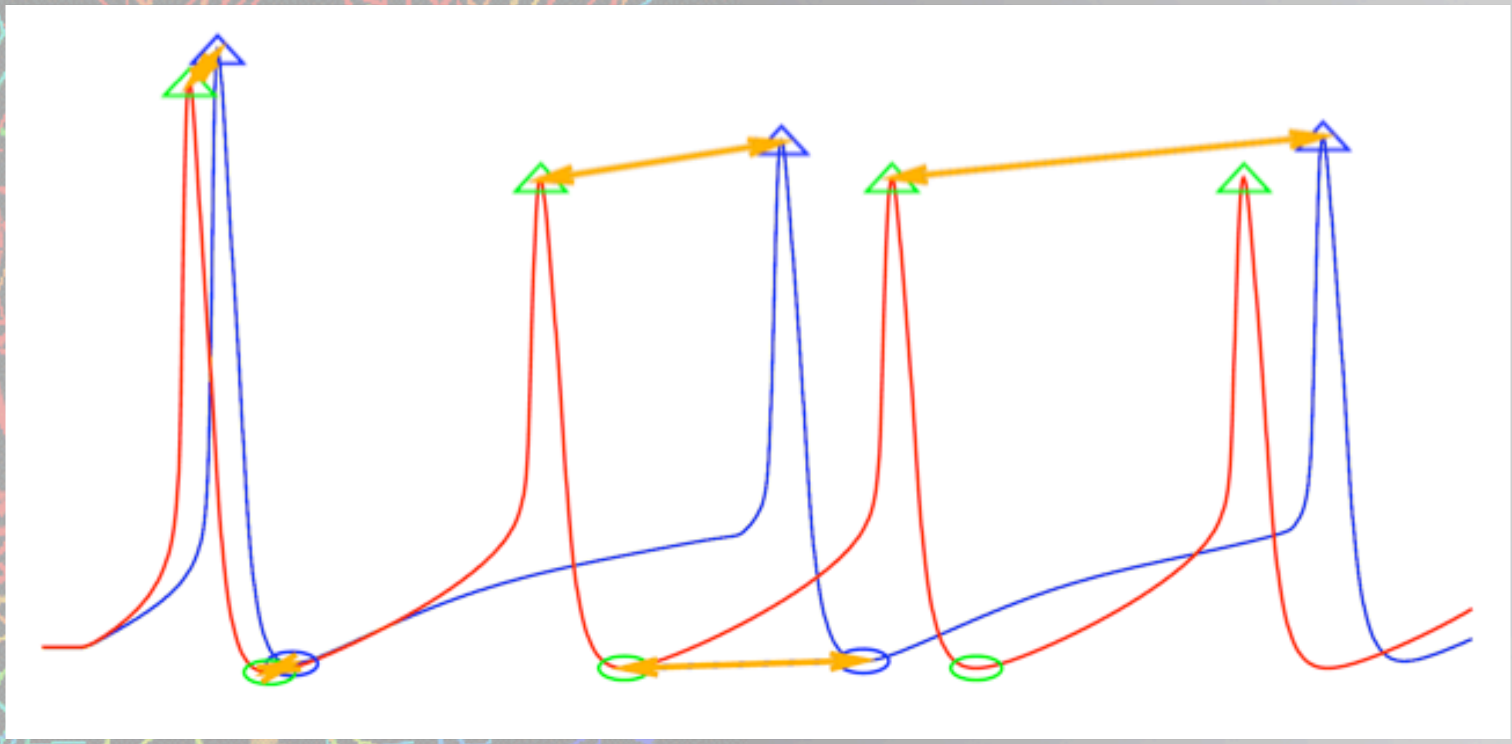
The Purkinje neuron model parameter landscape: implications for homeostasis and synaptic plasticity

- Automated parameter methods (Neurofitter)
- Automated parameter search for new Purkinje model
- Properties of a complex parameter space
- Cerebellar learning: LTD of parallel fiber synapse
- Study I: pattern recognition by Purkinje cells
- Study II: intrinsic excitability, calcium and plasticity

Parameter search: fitness measure

How to compare data and model traces ?





Andrew Davison

Phase shifts in spike trains cause a problem

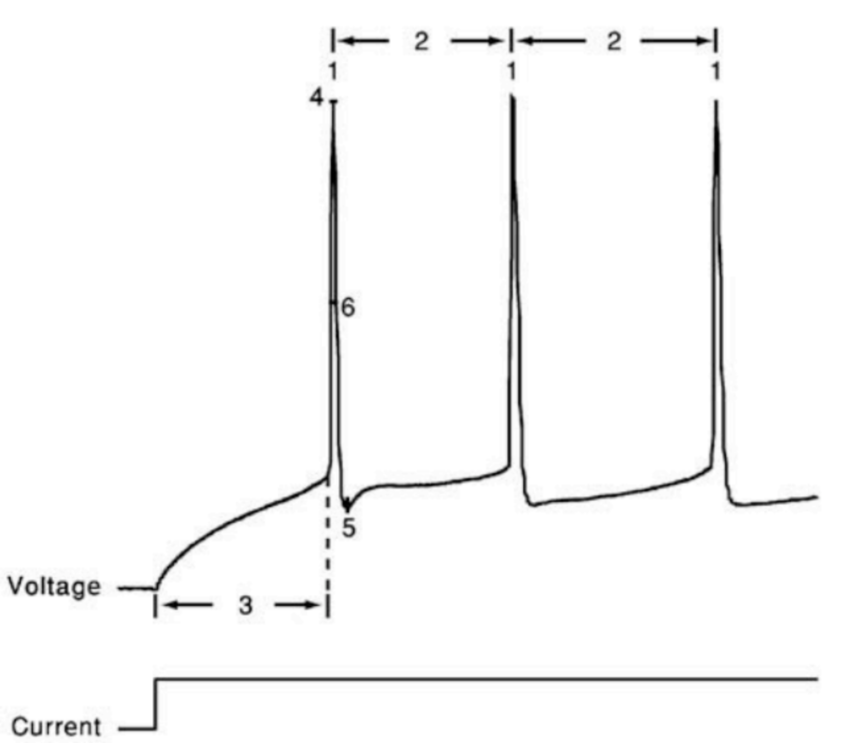
Solution 1: feature based (statistical average)

Solution 2: phase-plane trajectory density

Parameter search: fitness measure

Solution 1: feature based

1. spike rate
2. accommodation index
3. latency to 1st spike
4. action potential overshoot
5. afterhyperpolarization depth
6. action potential width



Druckmann et al. *Frontiers Neuroscience* (2007)

Advantages:

- fitness measure relative to standard deviation
- relative tolerant to poor channel kinetics

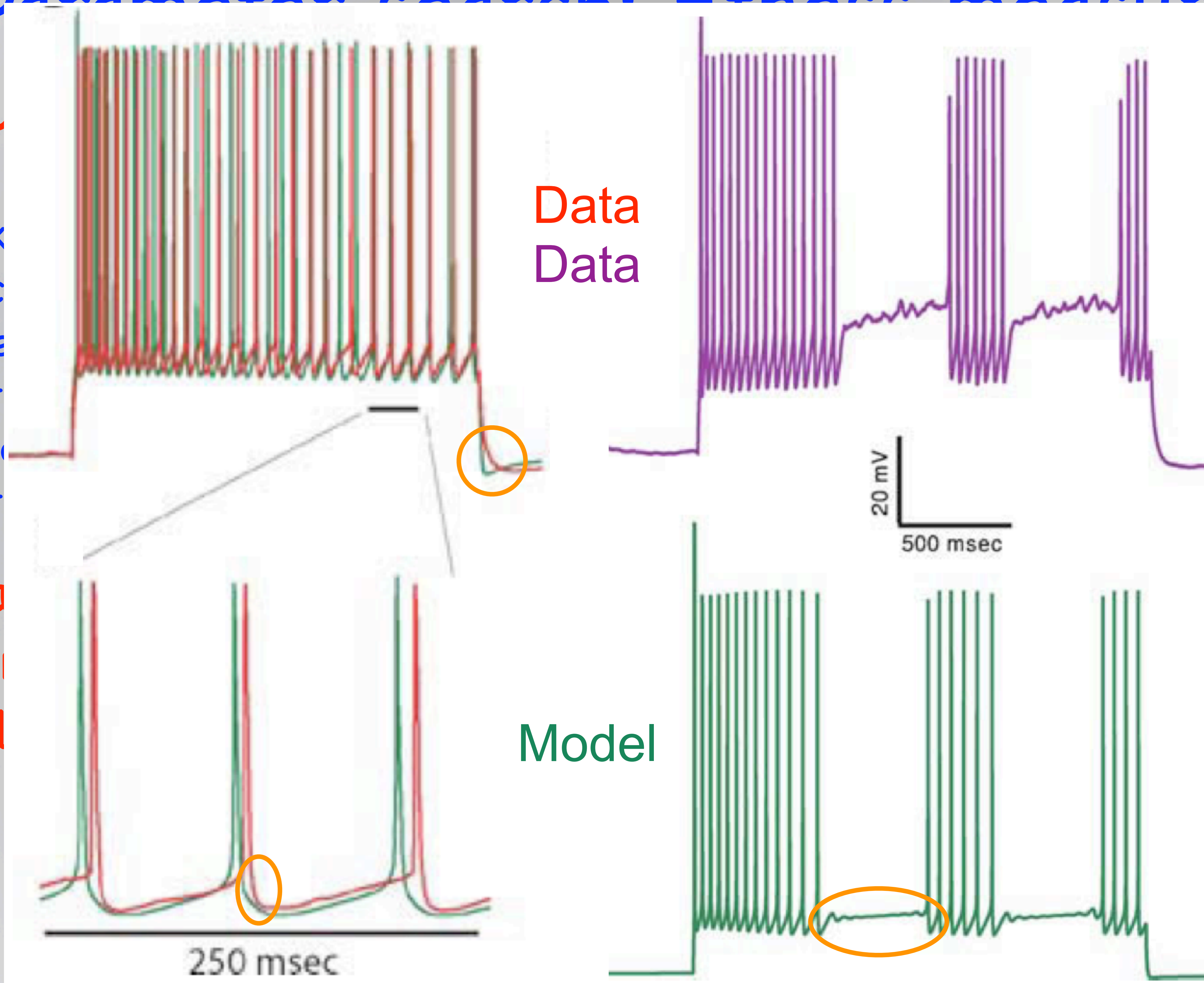
Parameter search: fitness measure

Solu

1. spik
2. acc
3. late
4. act
5. aft
6. act

Adva

- fit
- rel

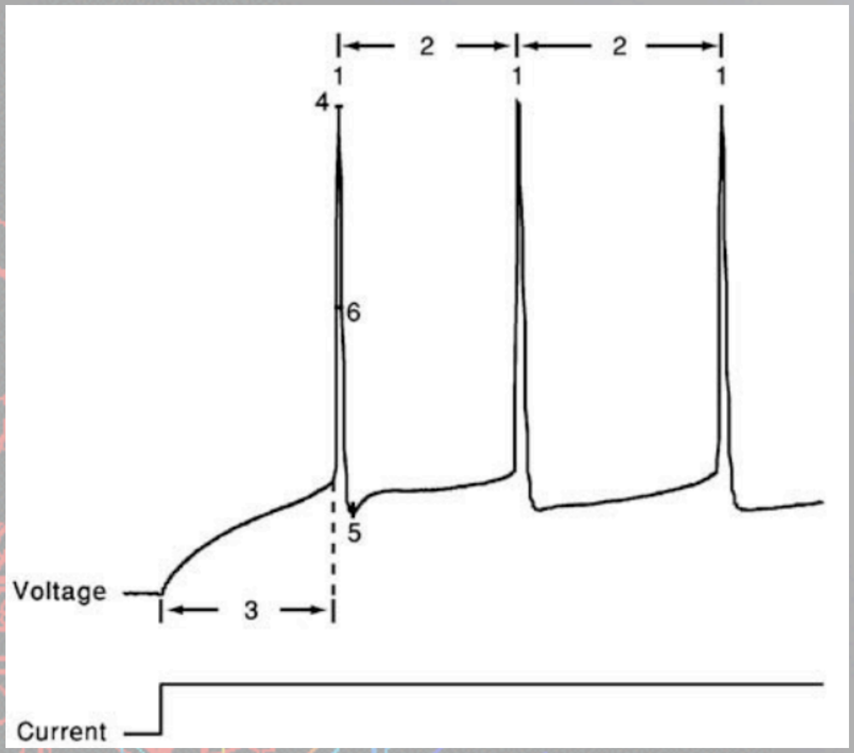


Druckmann et al. *Frontiers Neuroscience* (2007)

Parameter search: fitness measure

Solution 1: feature based

1. spike rate
2. accommodation index
3. latency to 1st spike
4. action potential overshoot
5. afterhyperpolarization depth
6. action potential width



Druckmann et al. *Frontiers Neuroscience* (2007)

Advantages:

- fitness measure relative to standard deviation
- relative tolerant to poor channel kinetics

Disadvantages:

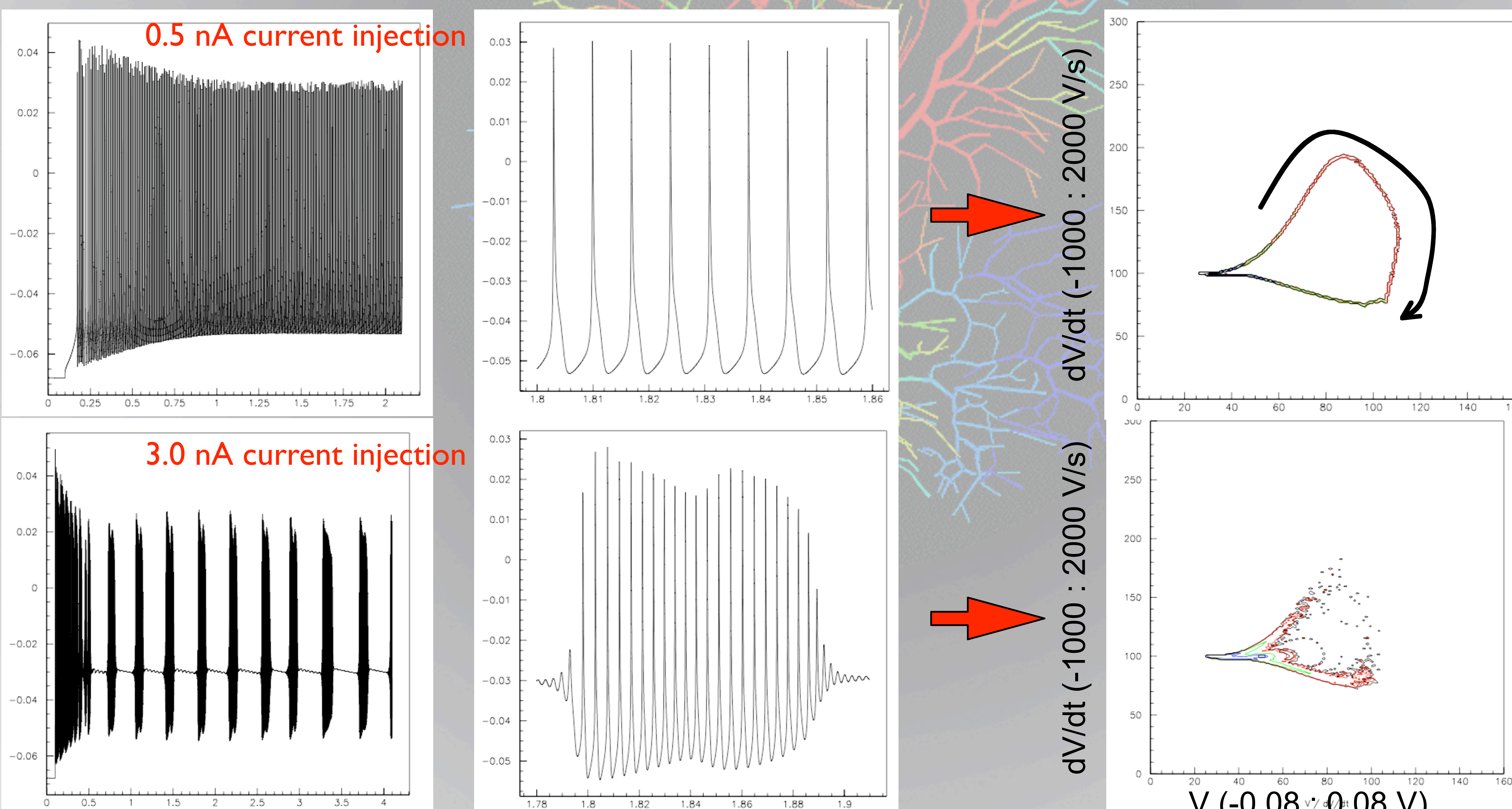
- doesn't fit unmeasured: subthreshold voltage, bursting...
- lot's of data needed to get good statistics
- canonical model: does not capture population variability

Parameter search: fitness measure

Solution 2: phase-plane trajectory density method

Was originally proposed by G. LeMasson in the book "Computational Neuroscience - Realistic modeling for Experimentalists" (EDS ed., 2001).

It allows to compare two electrophysiological traces independently of their relative phase: compared in ${}^{dV}/_{dt}$/V space, relative to number of data points.

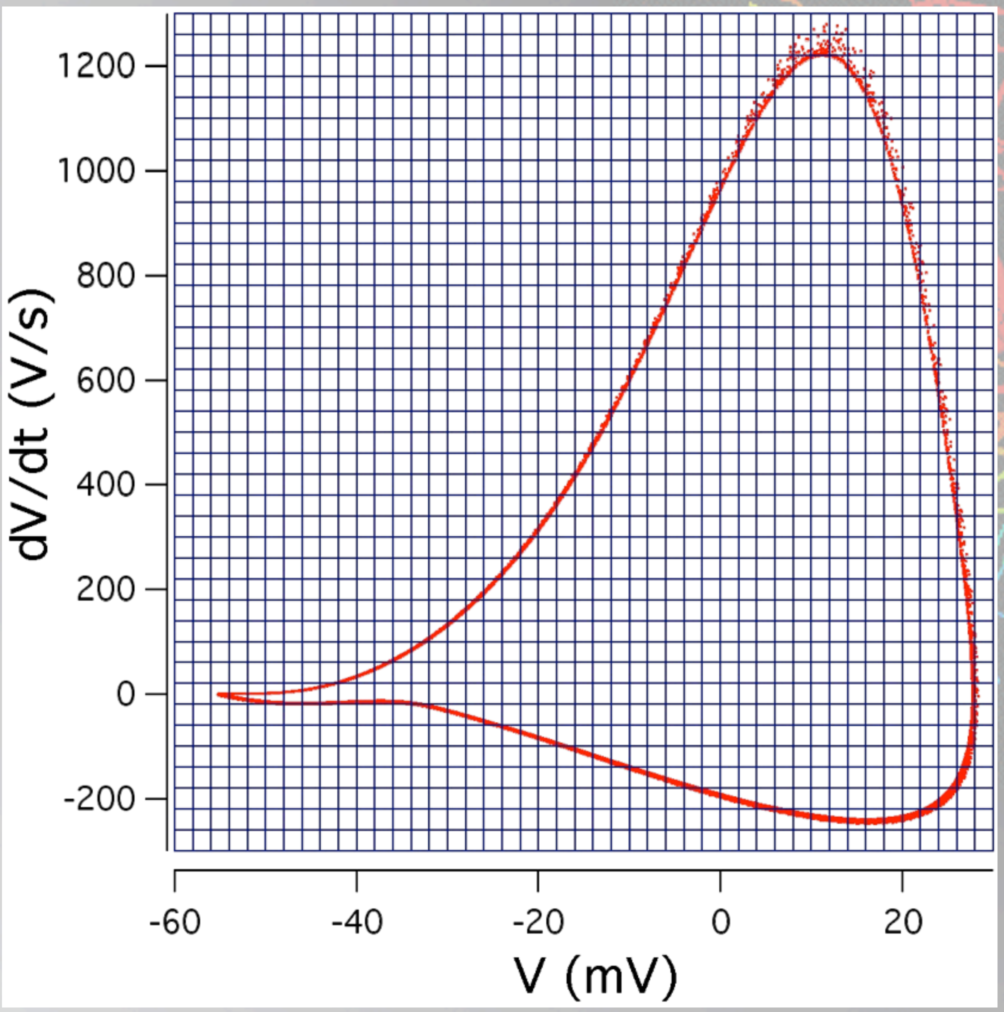


Parameter search: fitness measure

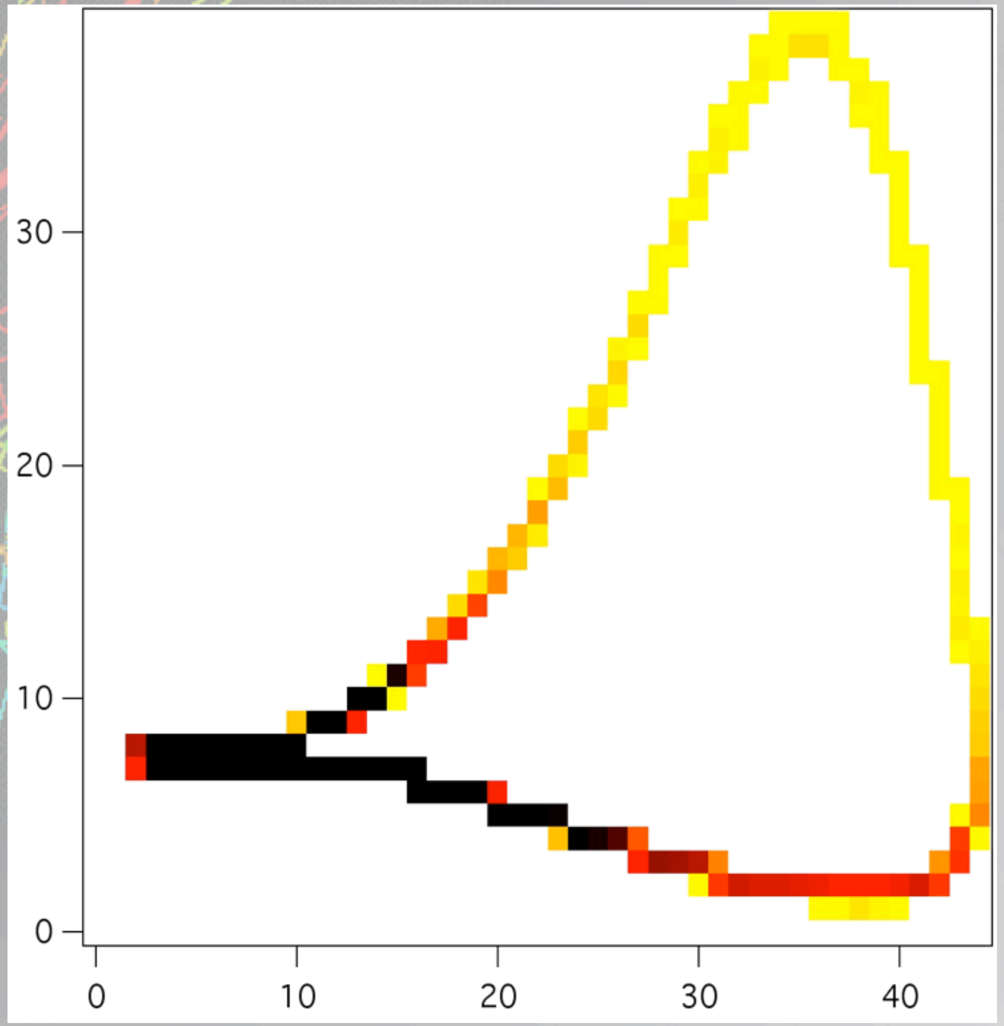
Solution 2: phase-plane trajectory density method

Was originally proposed by G. LeMasson in the book "Computational Neuroscience - Realistic modeling for Experimentalists" (EDS ed., 2001).

It allows to compare two electrophysiological traces independently of their relative phase: compared in ${}^{dV}/_{dt}/V$ space, relative to number of data points.



Binned phase plot



Phase density plot

Parameter search: fitness measure

Solution 2: phase-plane trajectory density method

Was originally proposed by G. LeMasson in the book "Computational Neuroscience - Realistic modeling for Experimentalists" (EDS ed., 2001).

It allows to compare two electrophysiological traces independently of their relative phase: compared in ${}^{dV}/_{dt}/V$ space, relative to number of data points.

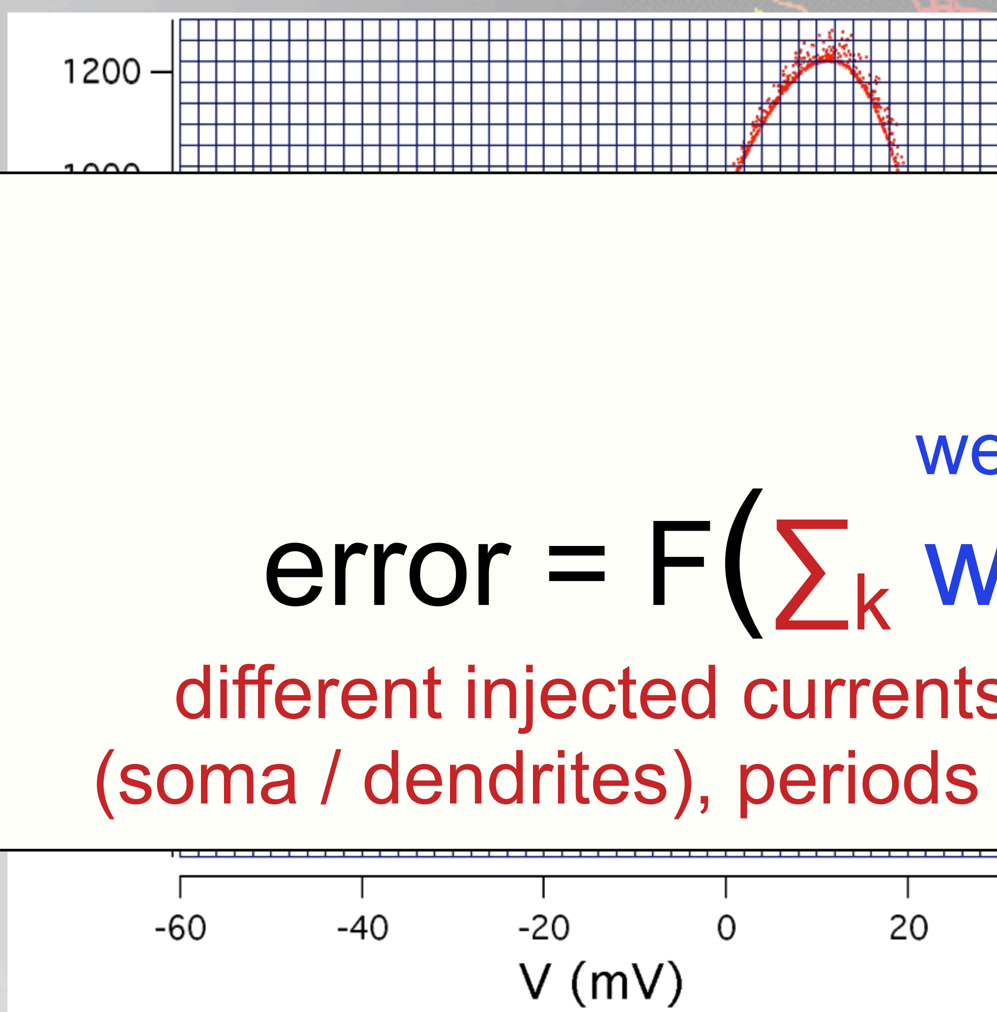
number of points in this bin

(V, dV/dt) matrix

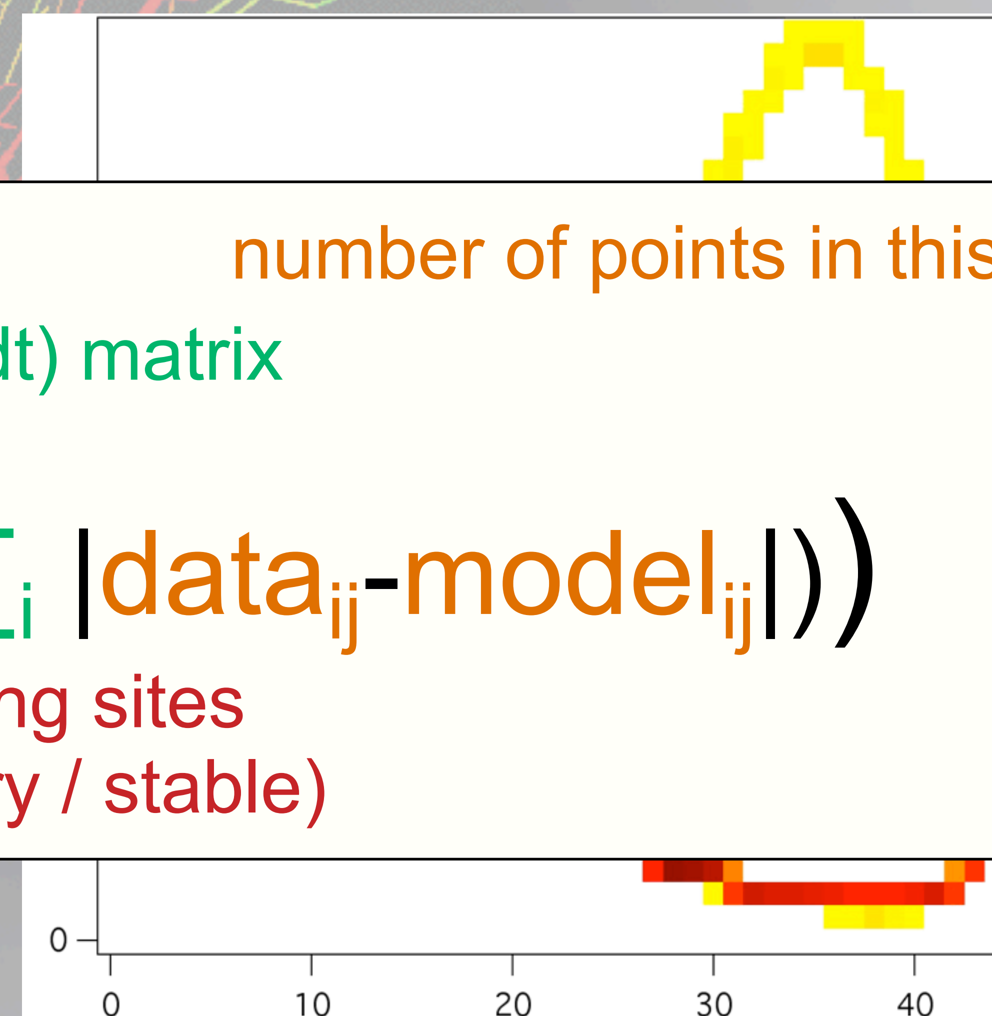
weights

$$\text{error} = F\Big(\sum_k w_k \cdot \big(\sum_j \sum_i |\text{data}_{ij} - \text{model}_{ij}|\big)\Big)$$

different injected currents, recording sites (soma / dendrites), periods (transitory / stable)



Binned phase plot



Phase density plot

Parameter search: Neurofitter

Fitness: phase-plane trajectory density method

Global optimization method:

Grid (or brute-force) method

Random search

Evolution strategy

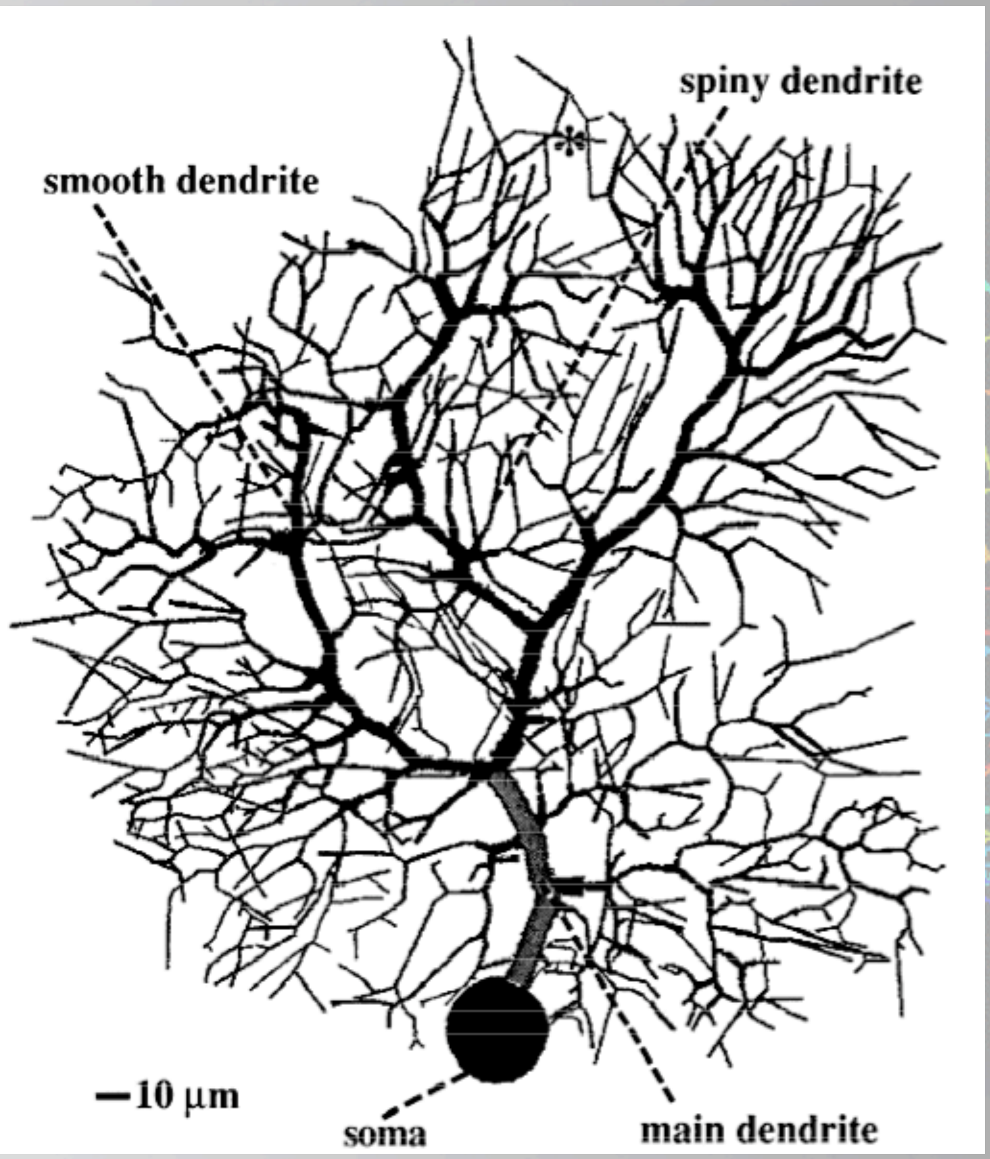
Particle Swarm Optimization

NOMAD (Mesh Adaptive Search)

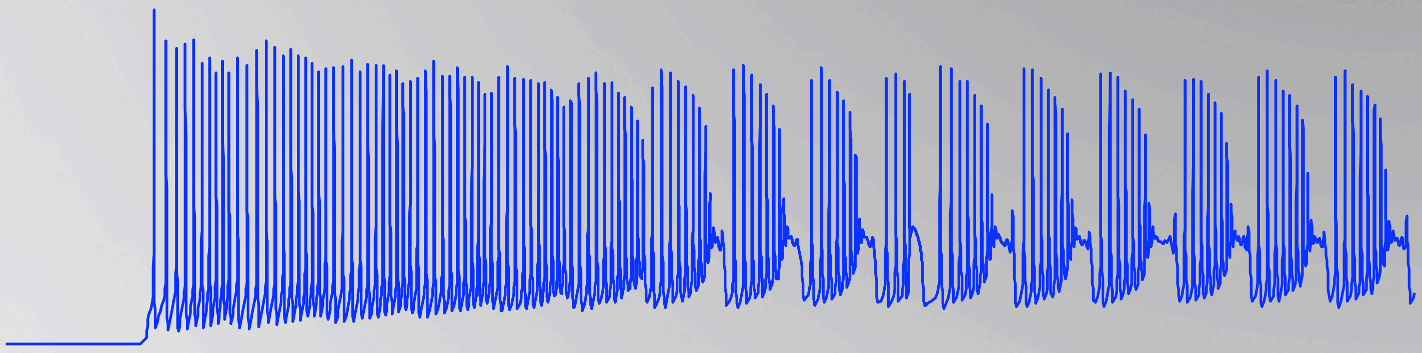
Hybrid (any mixture of the above)

http://neurofitter.sourceforge.net

Surrogate data: the 94 PC model



currents	soma	main	thick	spiny
Fast Na (NaF)	x			
Persistent Na (NaP)	x			
P-type Ca (CaP)		x	x	x
T-type Ca (CaT)	x	x	x	x
Delayed rectifier K (Kdr)	x	x		
Persistent K (KM)	x	x	x	x
A-type K (KA)	x	x		
BK Ca-activated K (KC)		x	x	x
K2 Ca-activated K (K2)		x	x	x
Anomalous rectifier (Kh)	x			



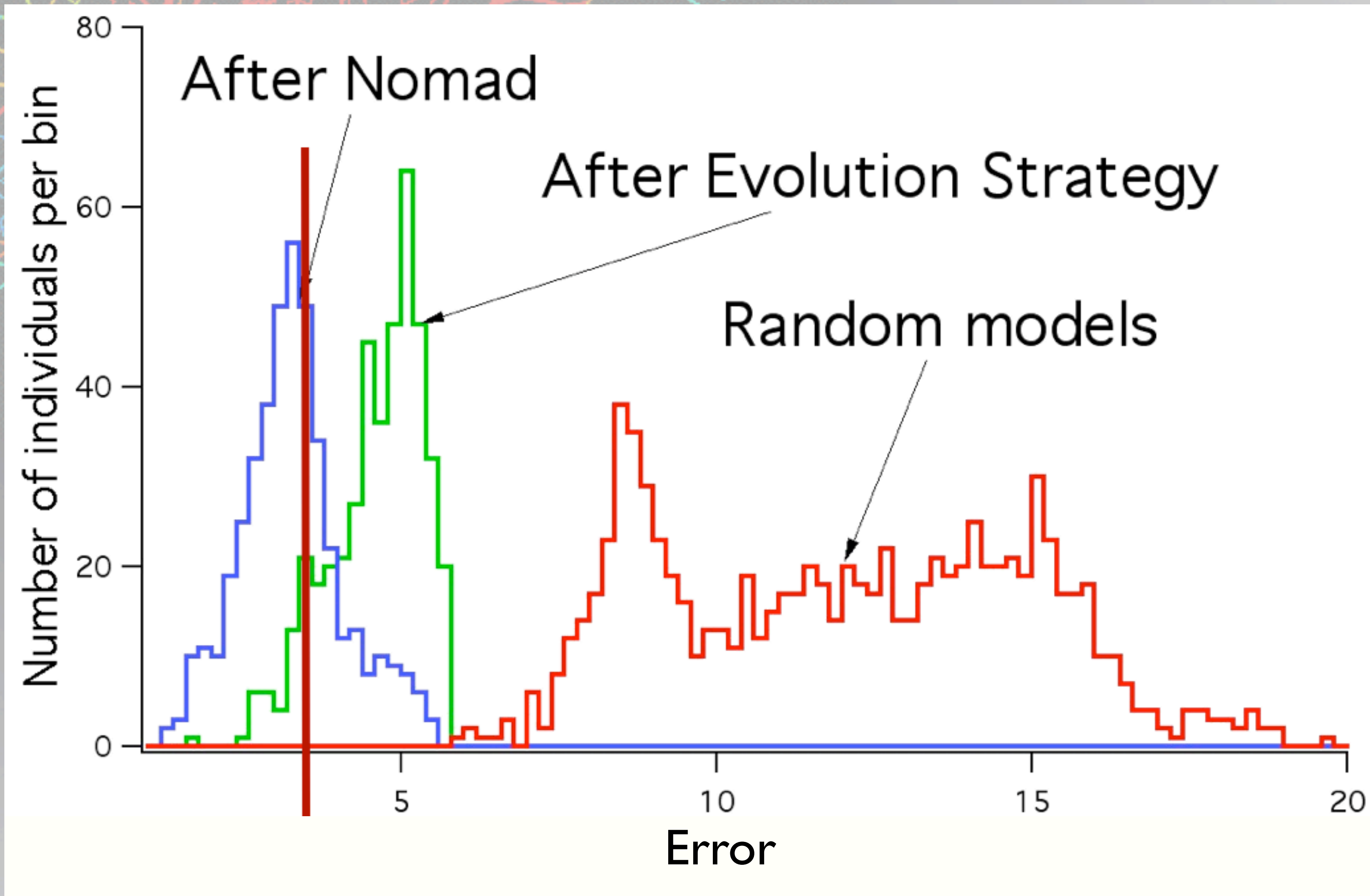
24 conductance densities to adjust

Parameter search: 2007

17 runs of Evolutionary Strategy with 57 or 60 individuals each
~8000 fitness evaluations / run

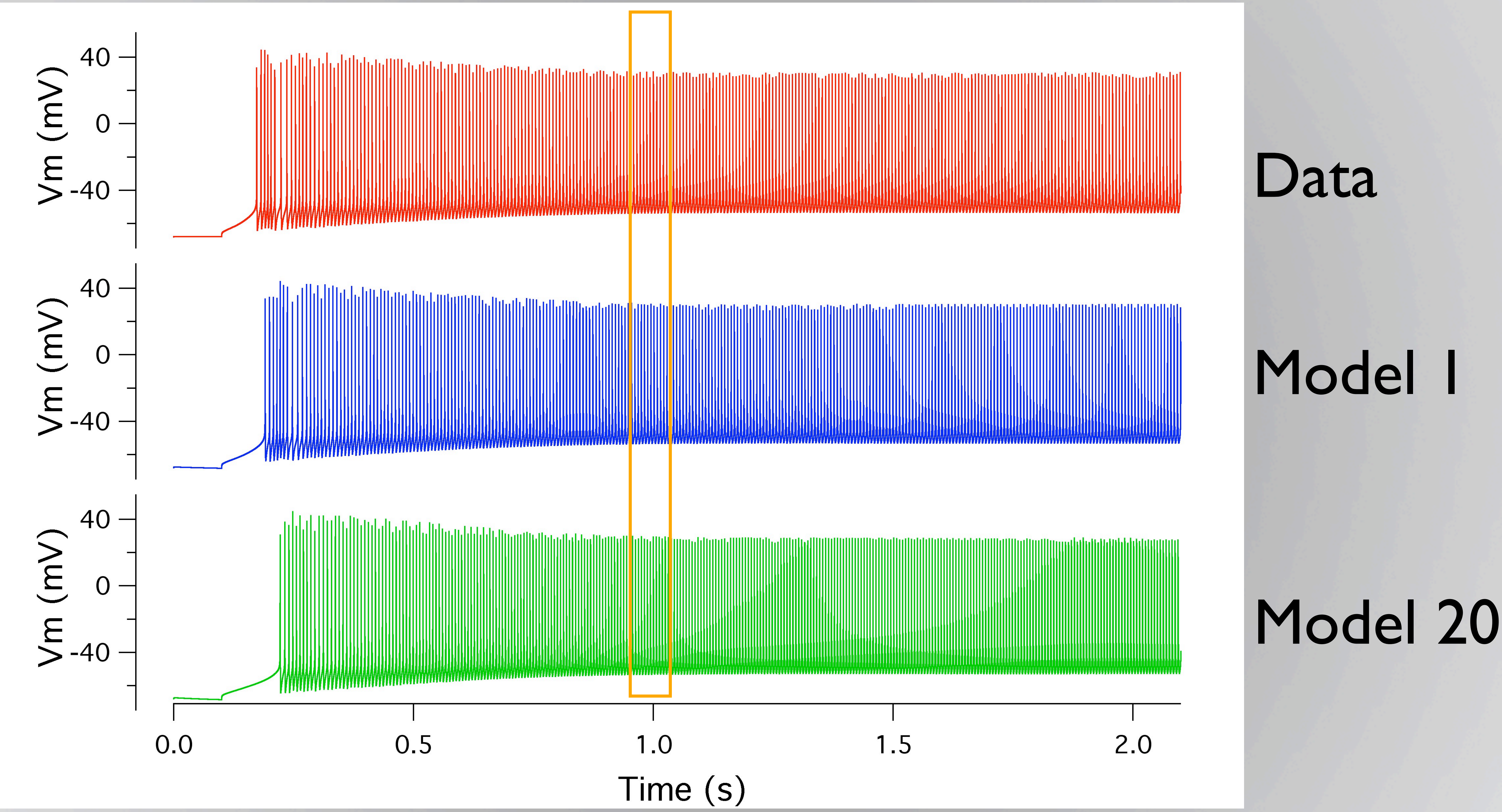
From the pool of 993 individuals, 429 are passed through NOMAD
100 fitness evaluations / individual

The fitness decreases
from 12.1±2.9
to 4.6±0.7
to 3.3±0.8



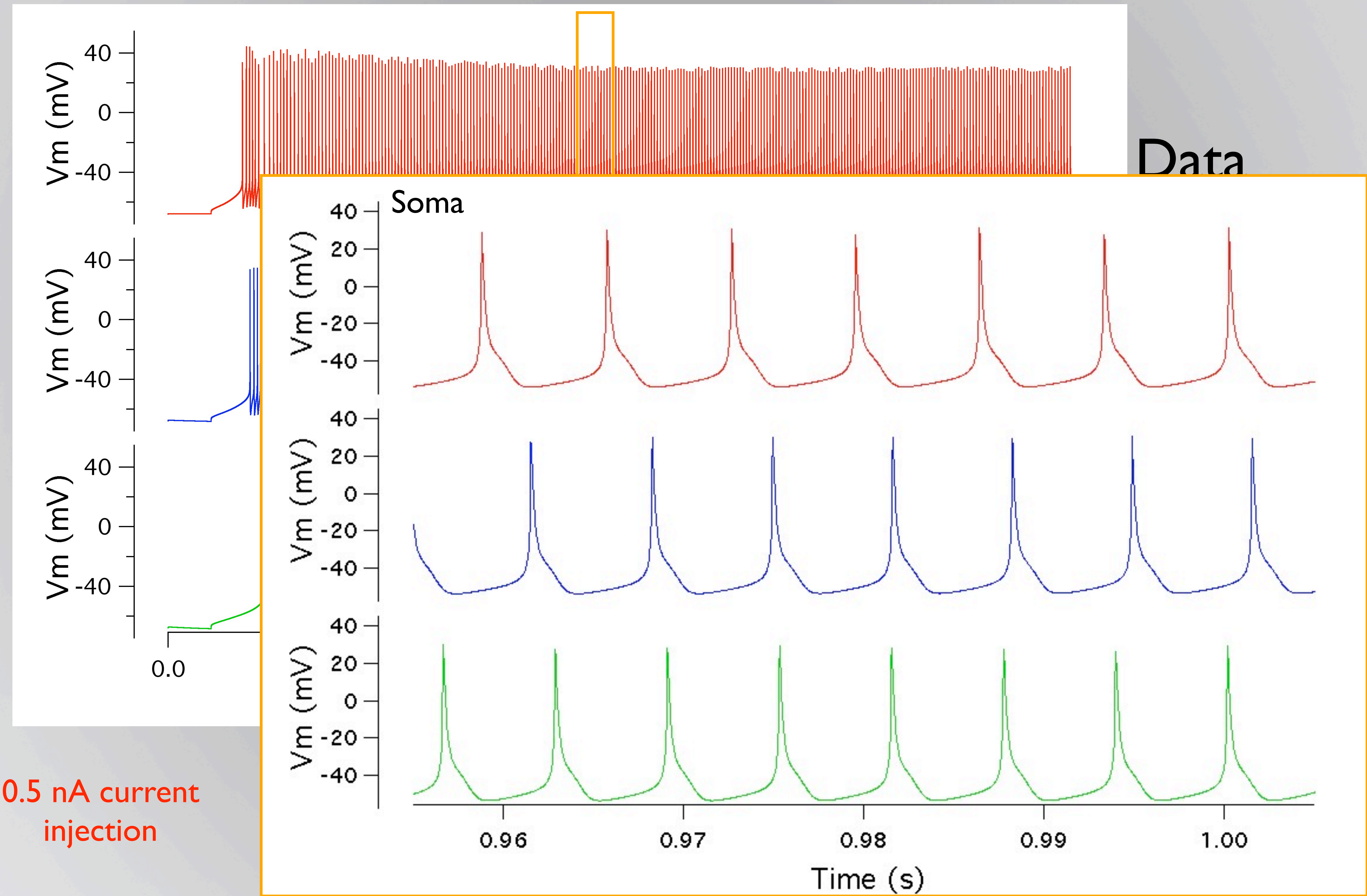
Final selection :
148 individuals
cut-off at 3.0

Properties of good individuals



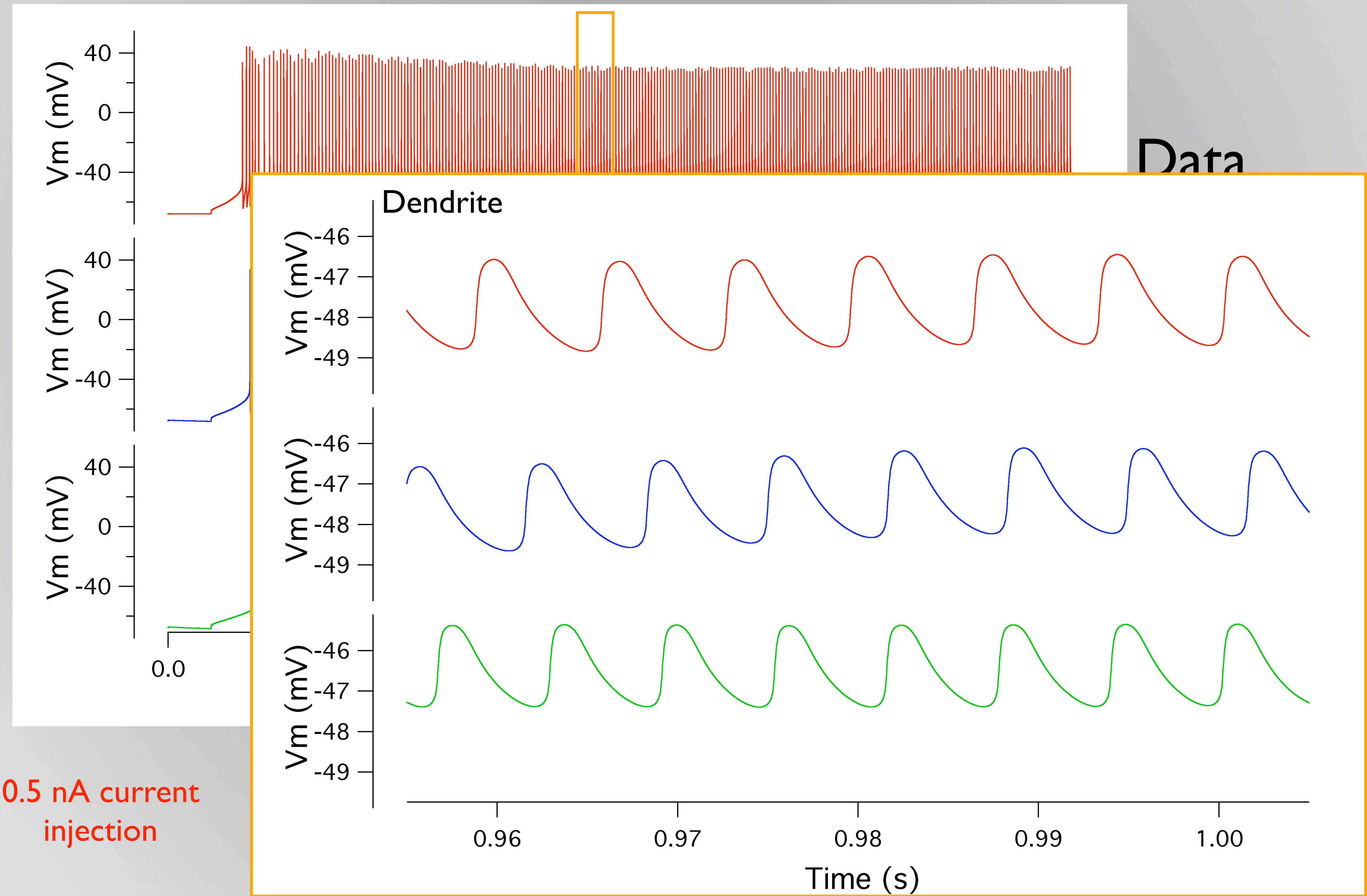
0.5 nA current injection

Properties of good individuals



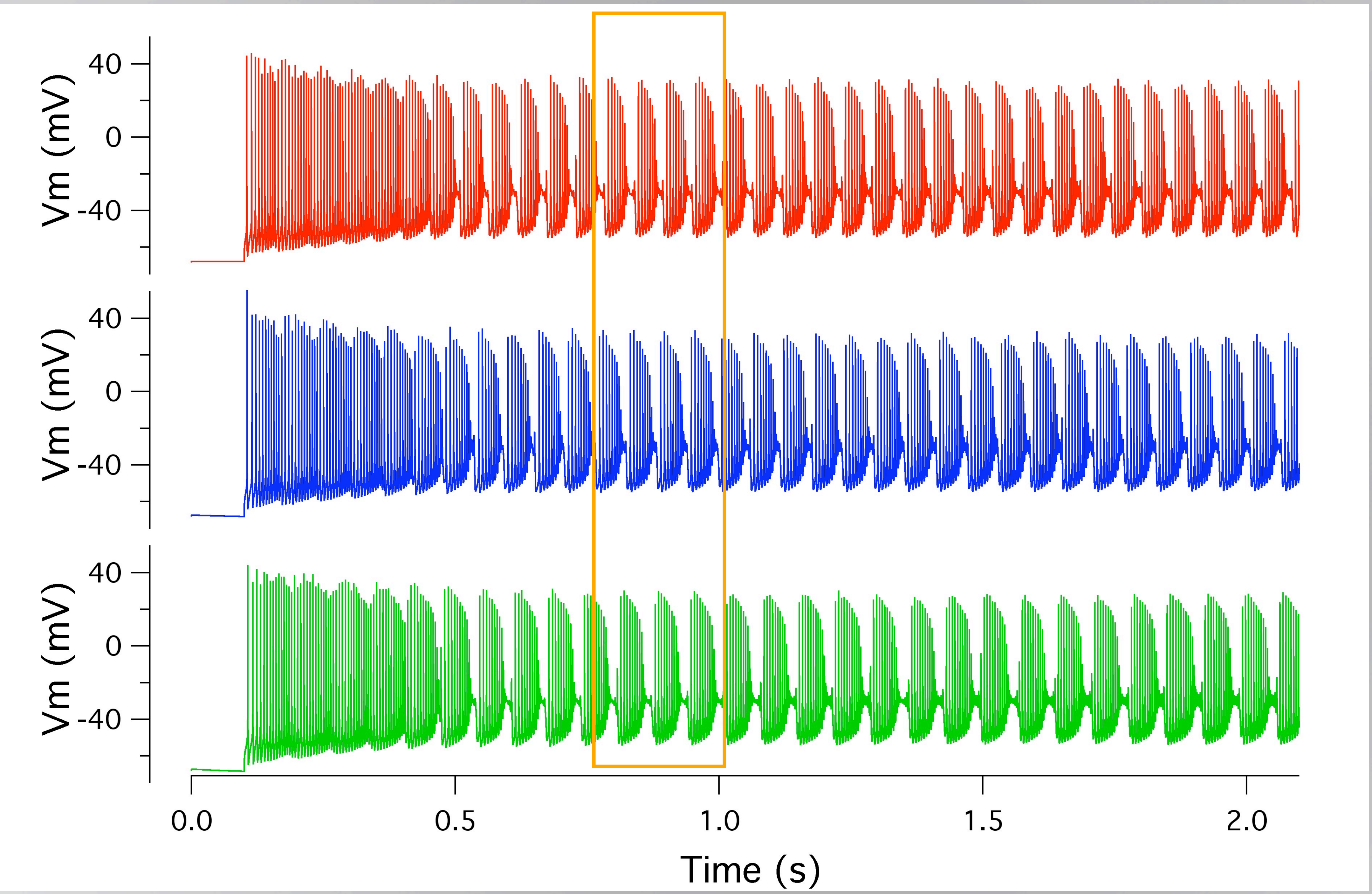
0.5 nA current injection

Properties of good individuals



0.5 nA current injection

Properties of good individuals



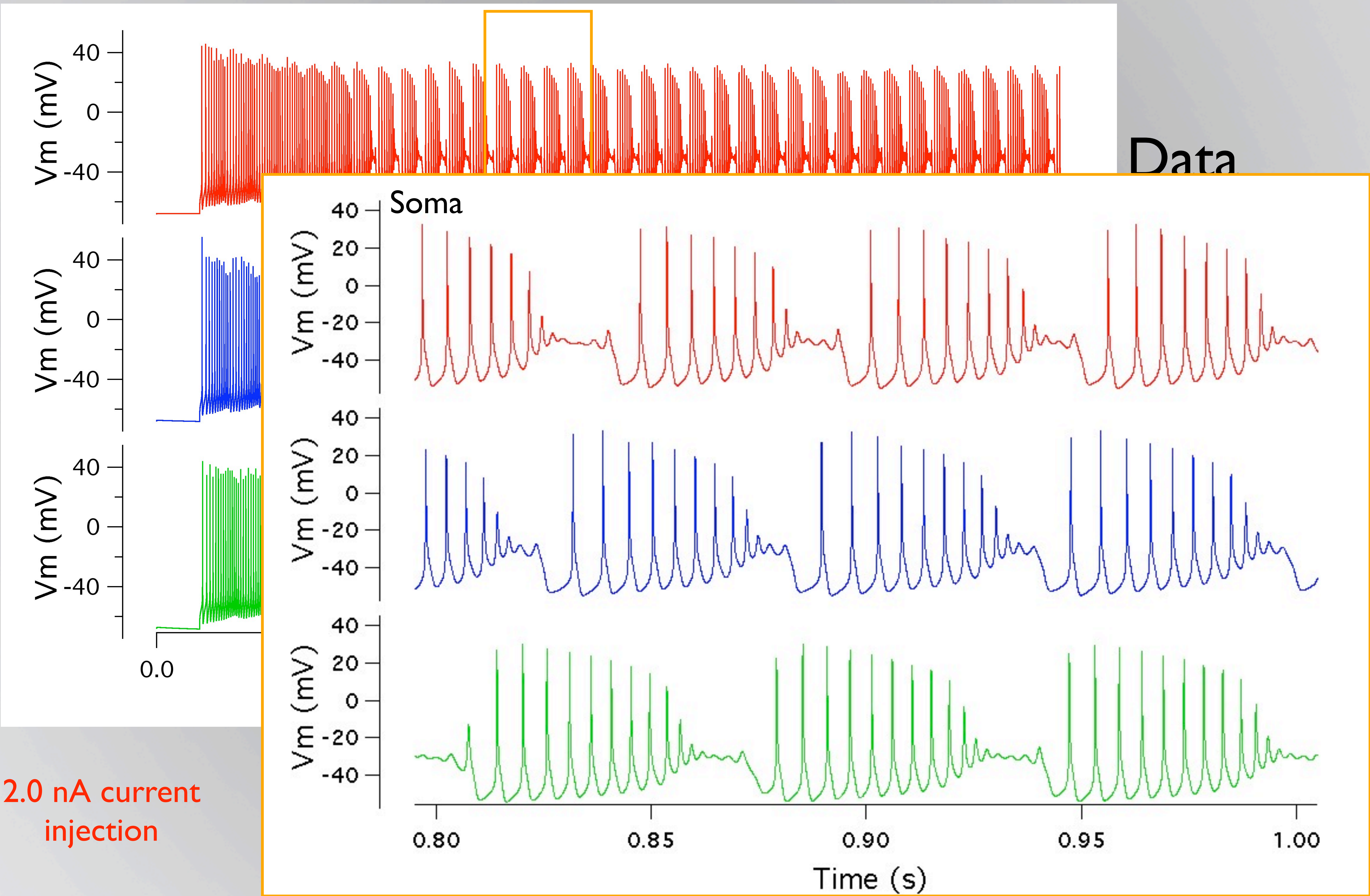
Data

Model 1

Model 20

2.0 nA current injection

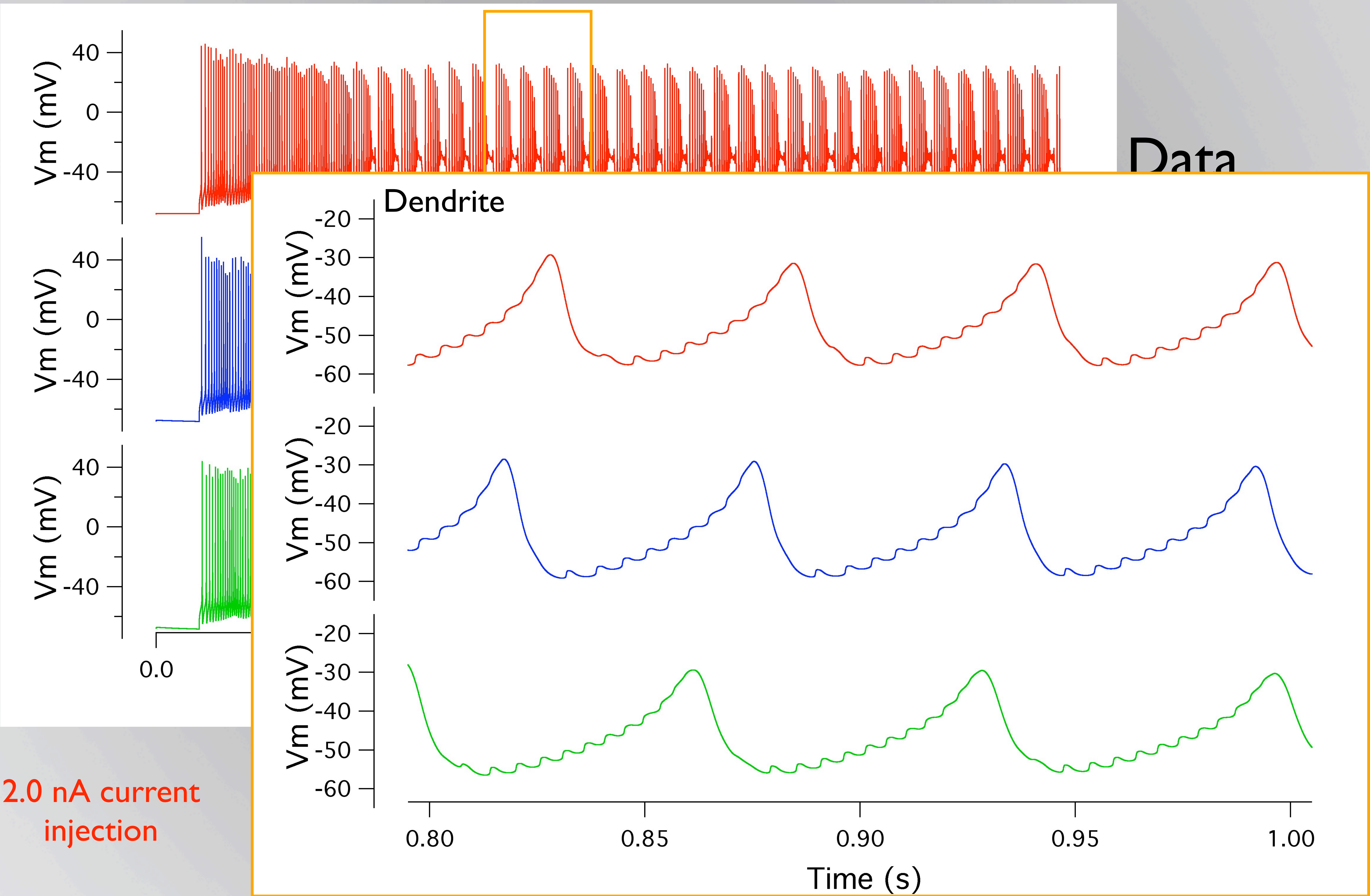
Properties of good individuals



2.0 nA current injection

2006

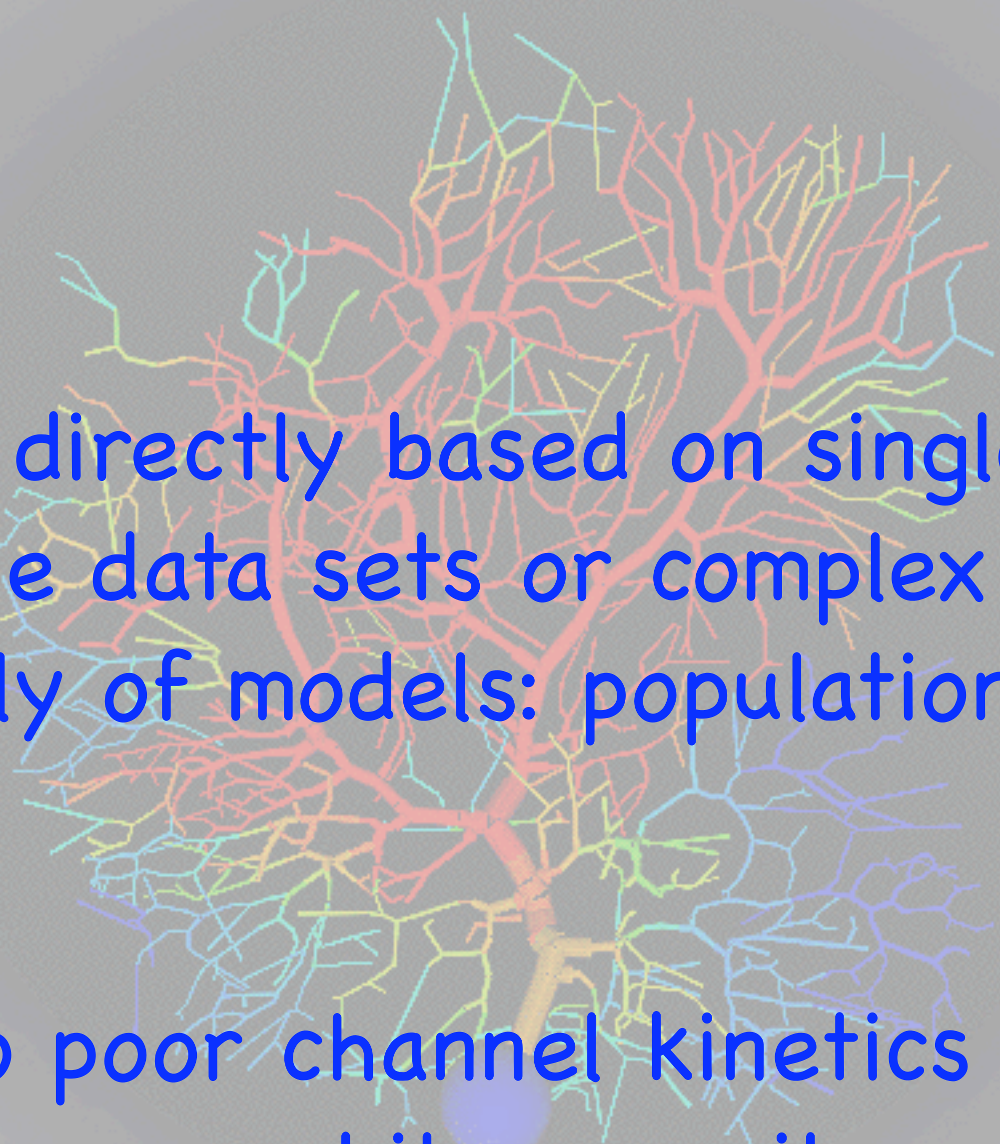
Properties of good individuals



2.0 nA current injection

Parameter search: Neurofitter

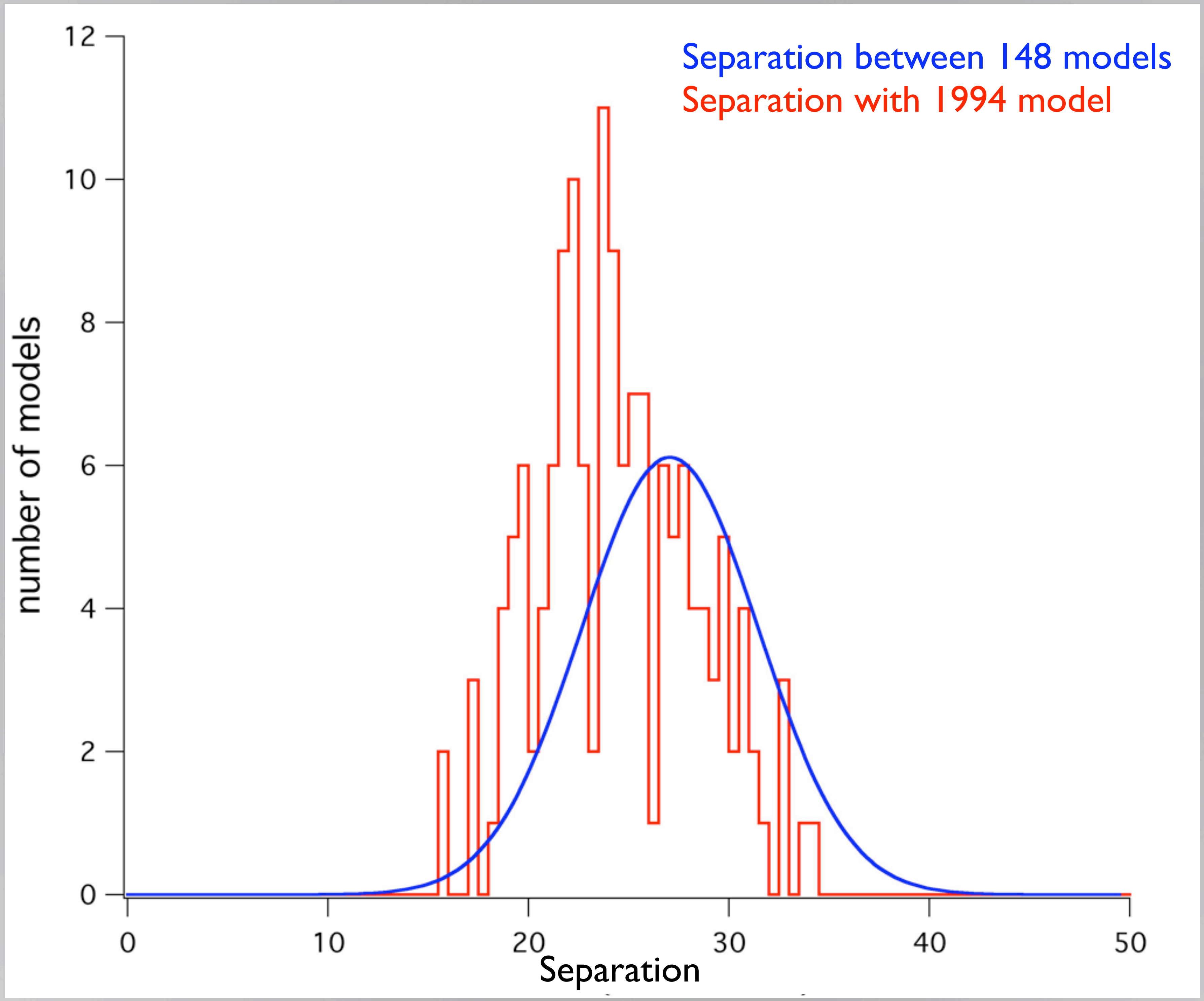
Fitness: phase-plane trajectory density method



Advantages:
- fitness measure directly based on single trace data
- no need for large data sets or complex measurements
- produces a family of models: population variability

Disadvantages:
- very sensitive to poor channel kinetics
- fitness measure uses arbitrary units
- danger of overfitting?

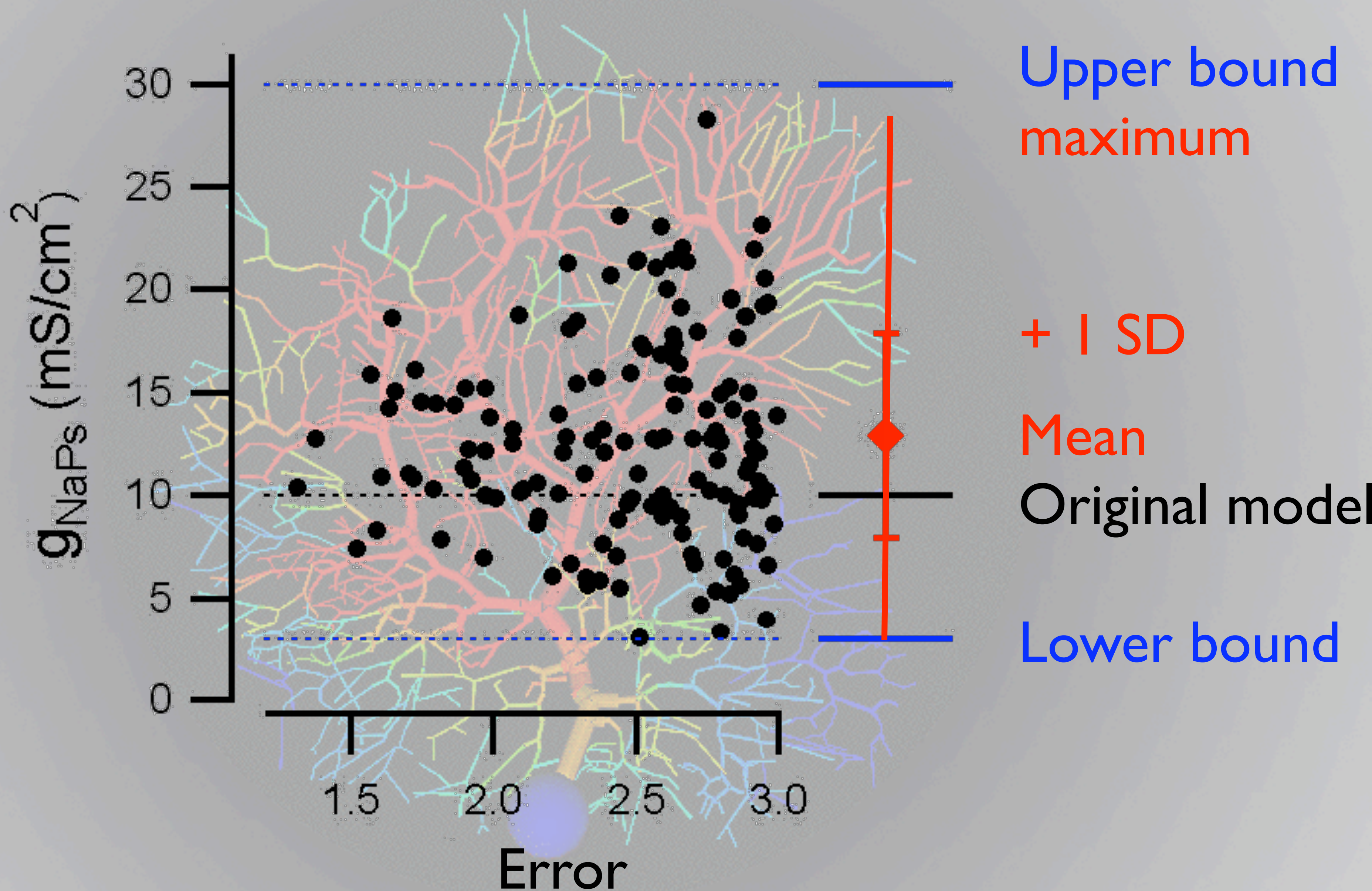
Models are separated



We did not recover the original 1994 model!

➙ our collection is not complete

Large parameter variability

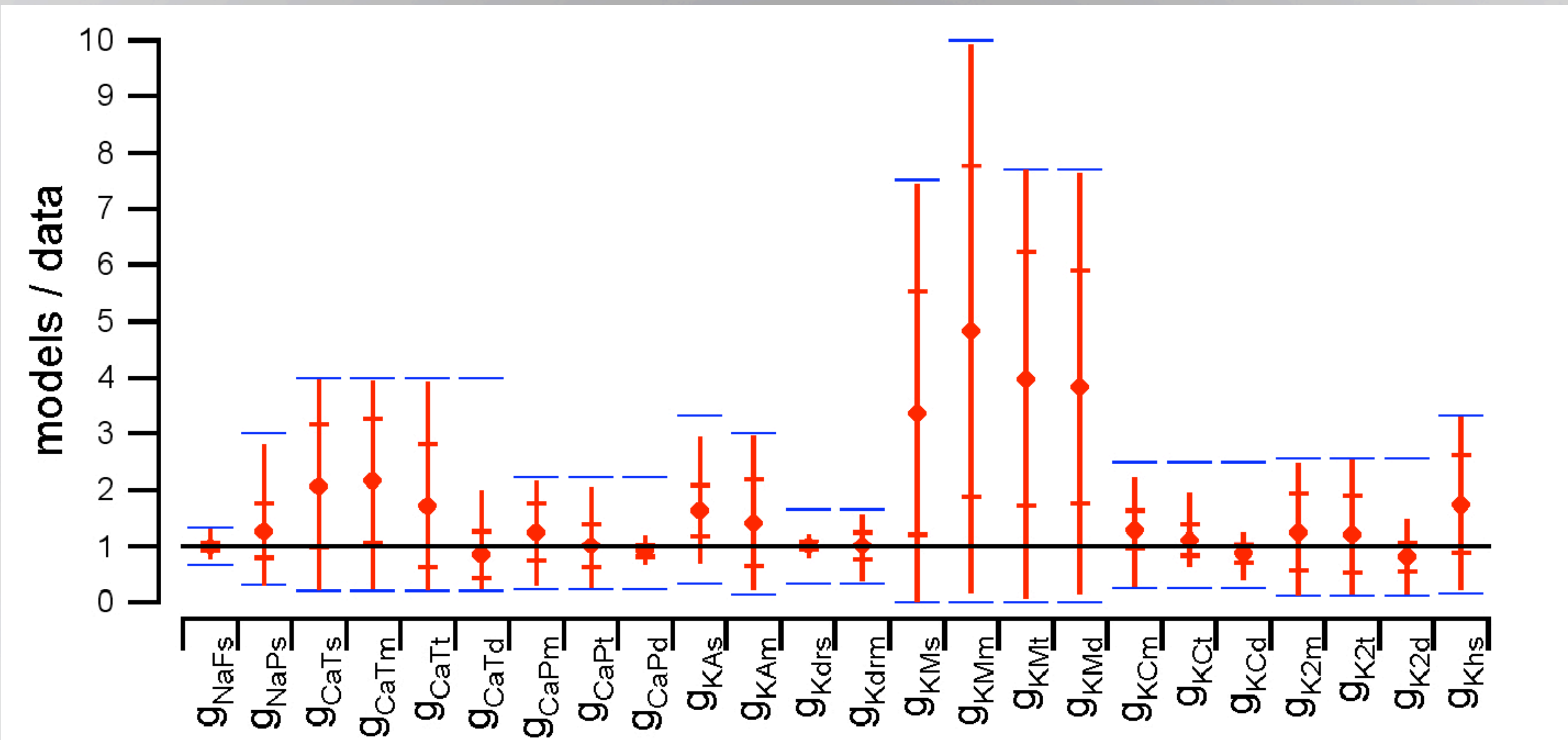


Wide range of values

No correlation between fitness and the value of a single parameter

2007

Large parameter variability



Wide range of values

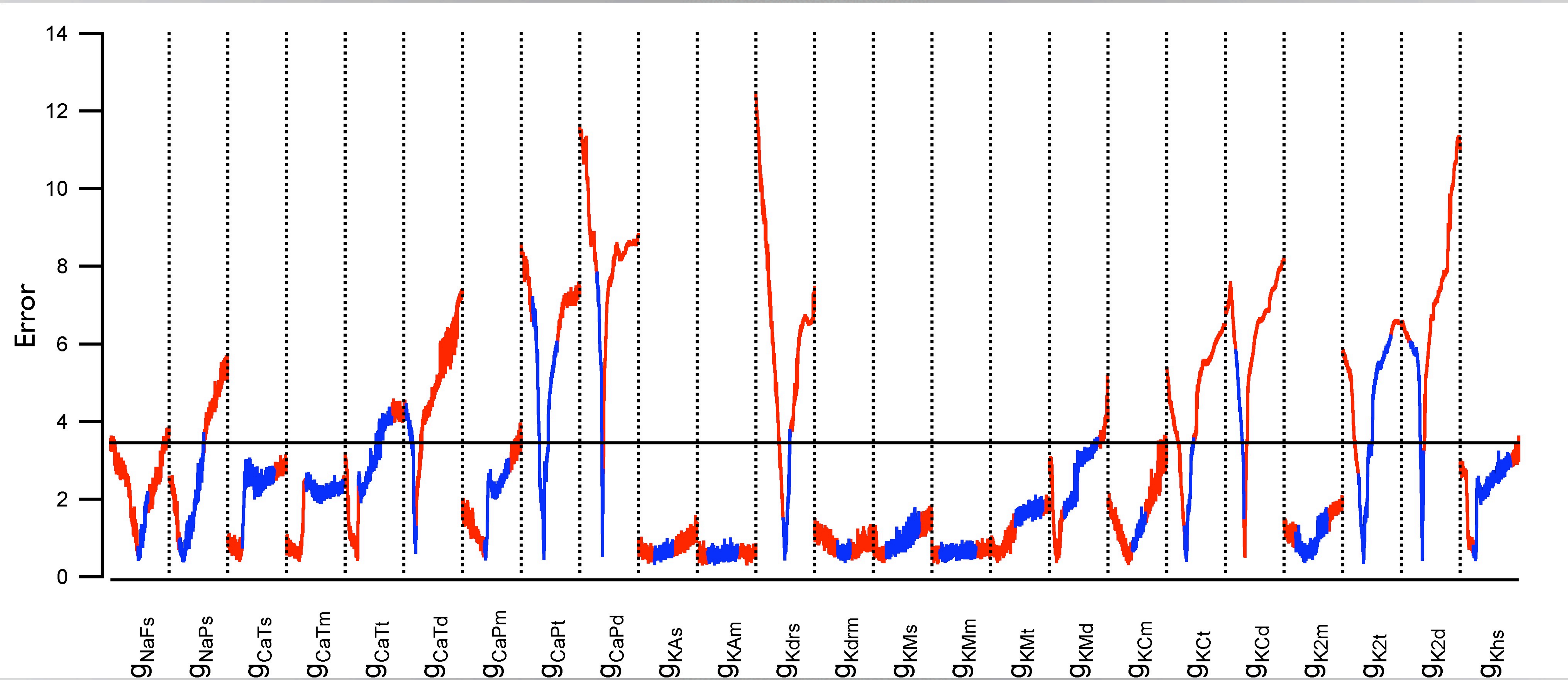
No correlation between fitness and the value of a single parameter

Hypotheses for non-uniqueness

- Too many dimensions: some parameters have very low influence on the neuron electrical behavior.
- All solutions belong to a continuous region of the phase space where models reproduce the data well.
- Strong compensatory mechanisms between some ionic currents: hyperspaces of good solutions exist in the parameter space.
- Oppositely, the solutions belong to small regions which are isolated from each other: discontinuities in the parameter space (due for example to threshold mechanisms).

Effect of varying 1 parameter

All other parameters being equal to the data values: blue ± 1 SD of parameter variability



Most of the parameters have a strong influence on the fitness

Good models do not belong to a continuum around the data

Hypotheses for non-uniqueness

- ~~Too many dimensions: some parameters have very low influence on the neuron electrical behavior.~~
- ~~All solutions belong to a continuous region of the phase space where models reproduce the data well.~~
- Strong compensatory mechanisms between some ionic currents: hyperspaces of good solutions exist in the parameter space.
- Oppositely, the solutions belong to small regions which are isolated from each other: discontinuities in the parameter space (due for example to threshold mechanisms).

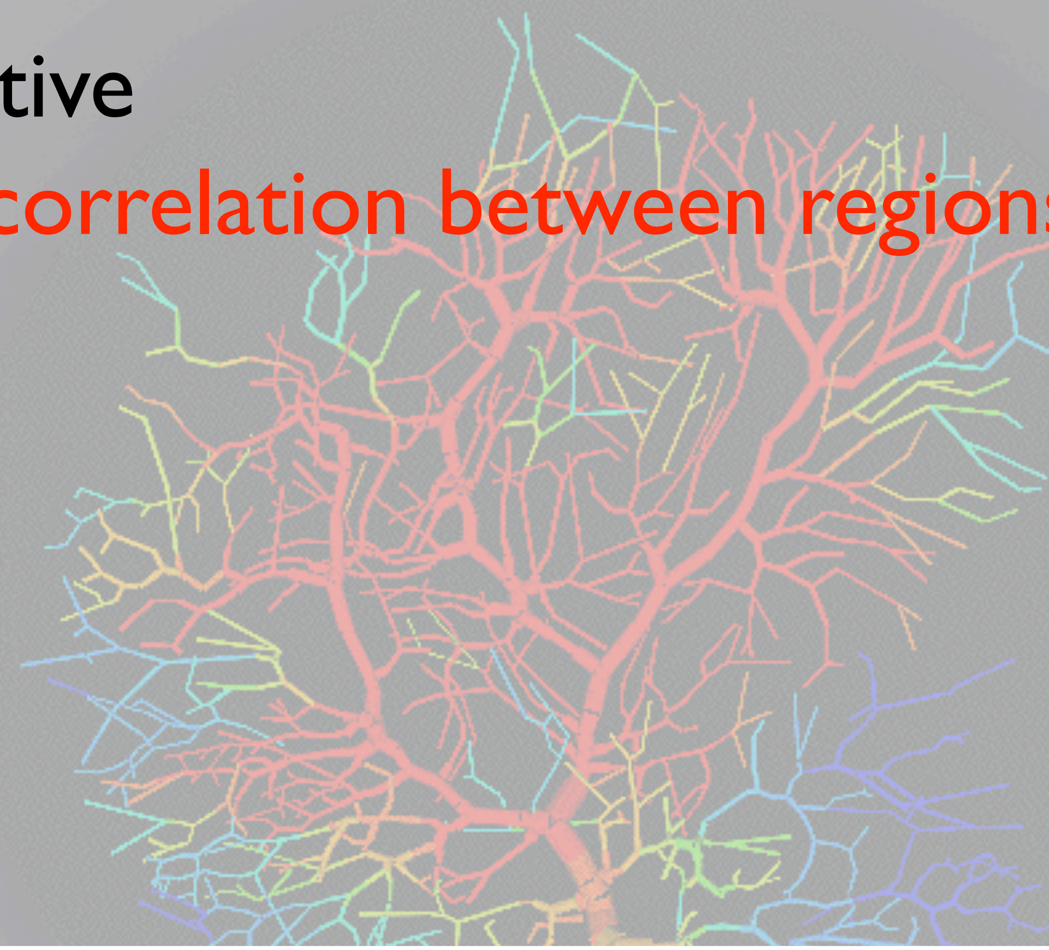
2006

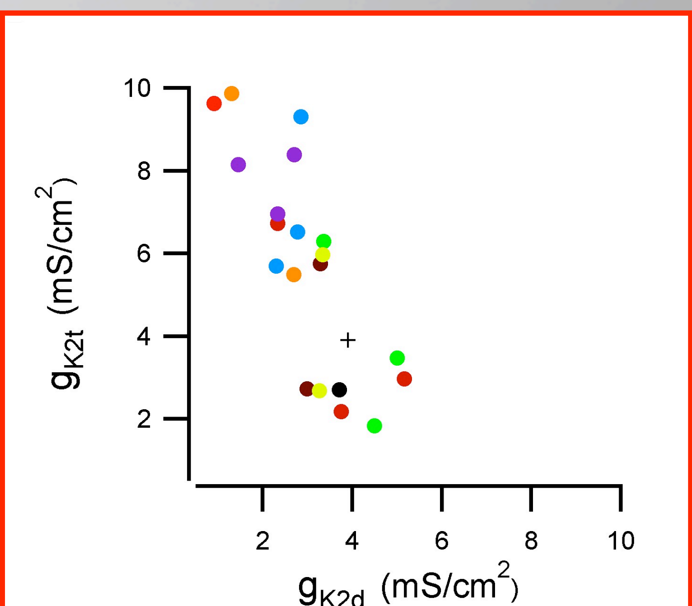
Correlations between parameters

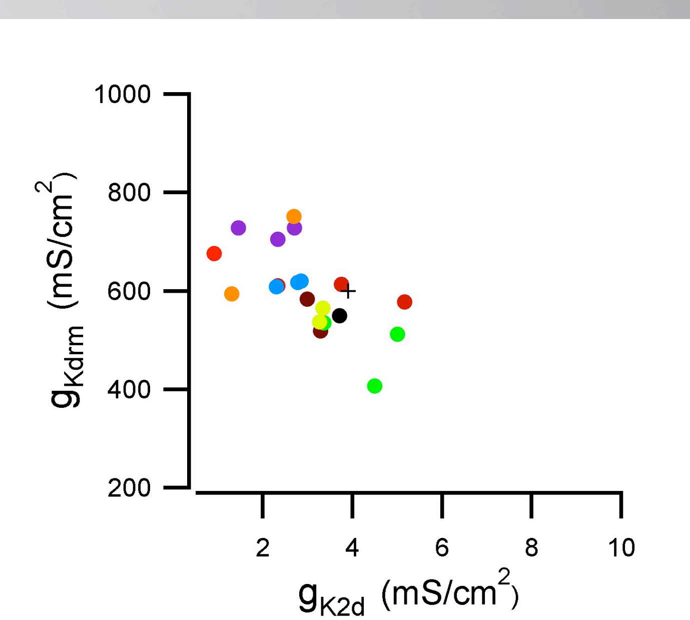
→ only 5 pairs of 276 are correlated

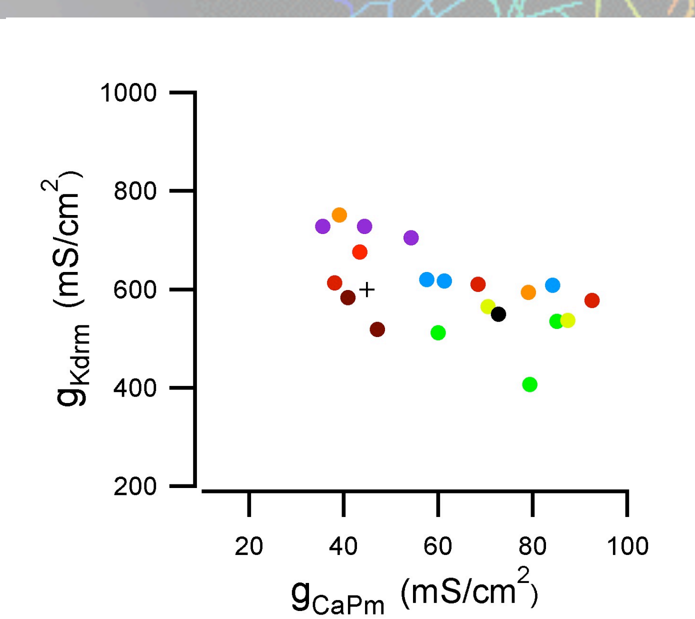
→ not fully transitive

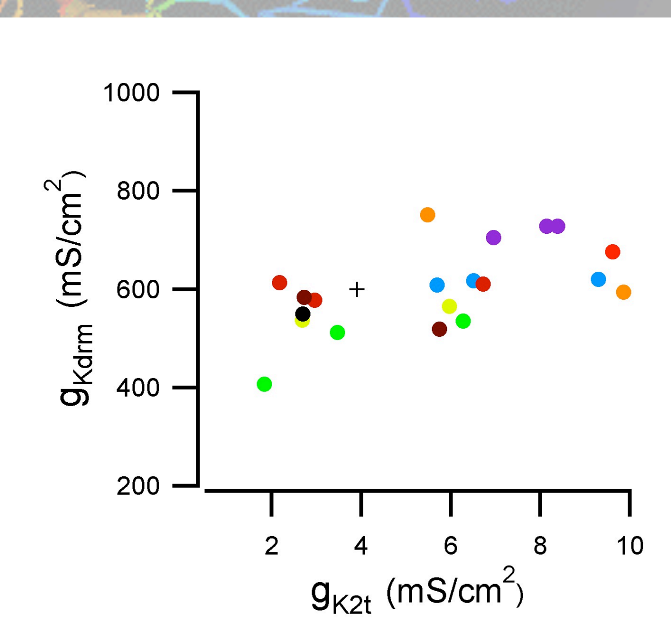
→ 2 pairs = anti-correlation between regions of dendrite

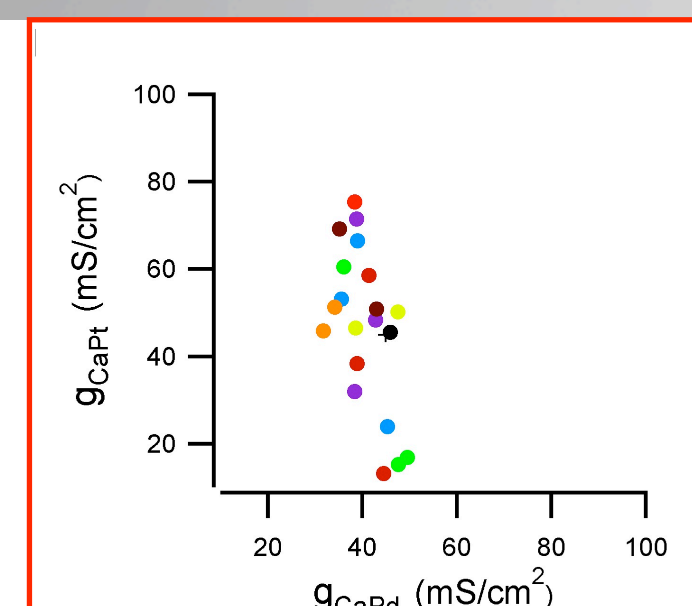






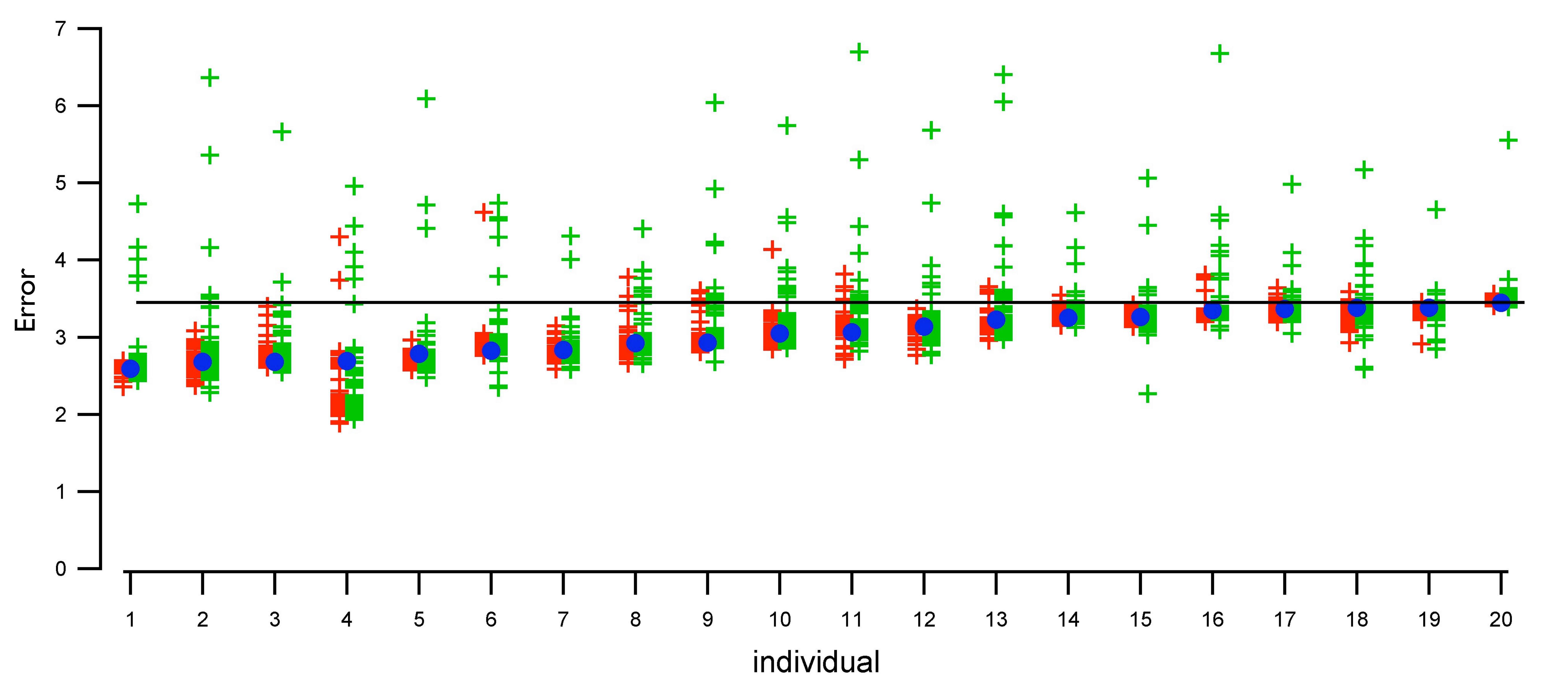






Small regions of good parameters

1%-5% variation of one parameter at a time around our best individuals



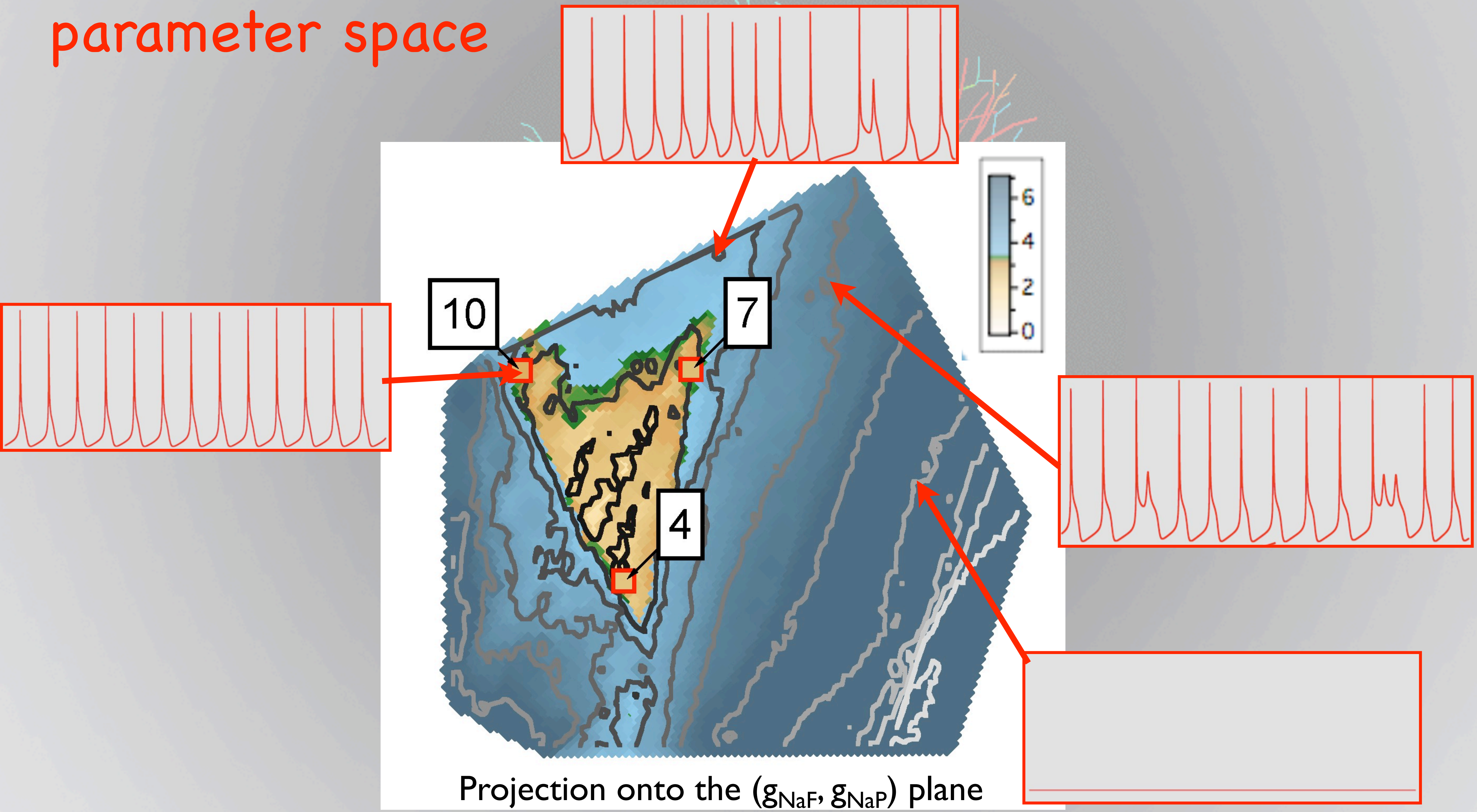
Very sensitive (bad models are very close)

Room for improvement (better models are also close)

2006

Small regions of good parameters

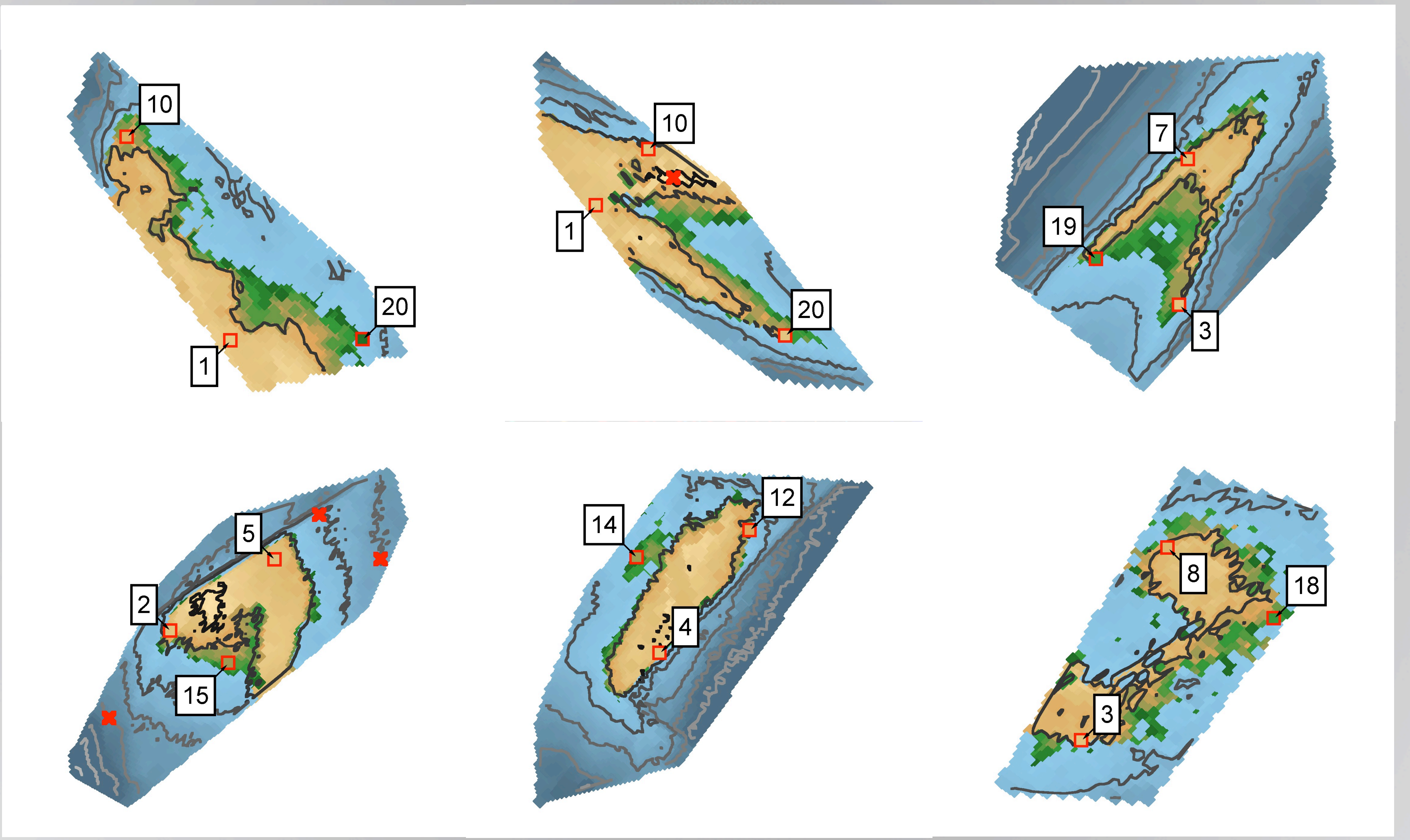
Each triplet of solutions defines a hyperplane in the parameter space



Projection onto the (g_{NaF}, g_{NaP}) plane

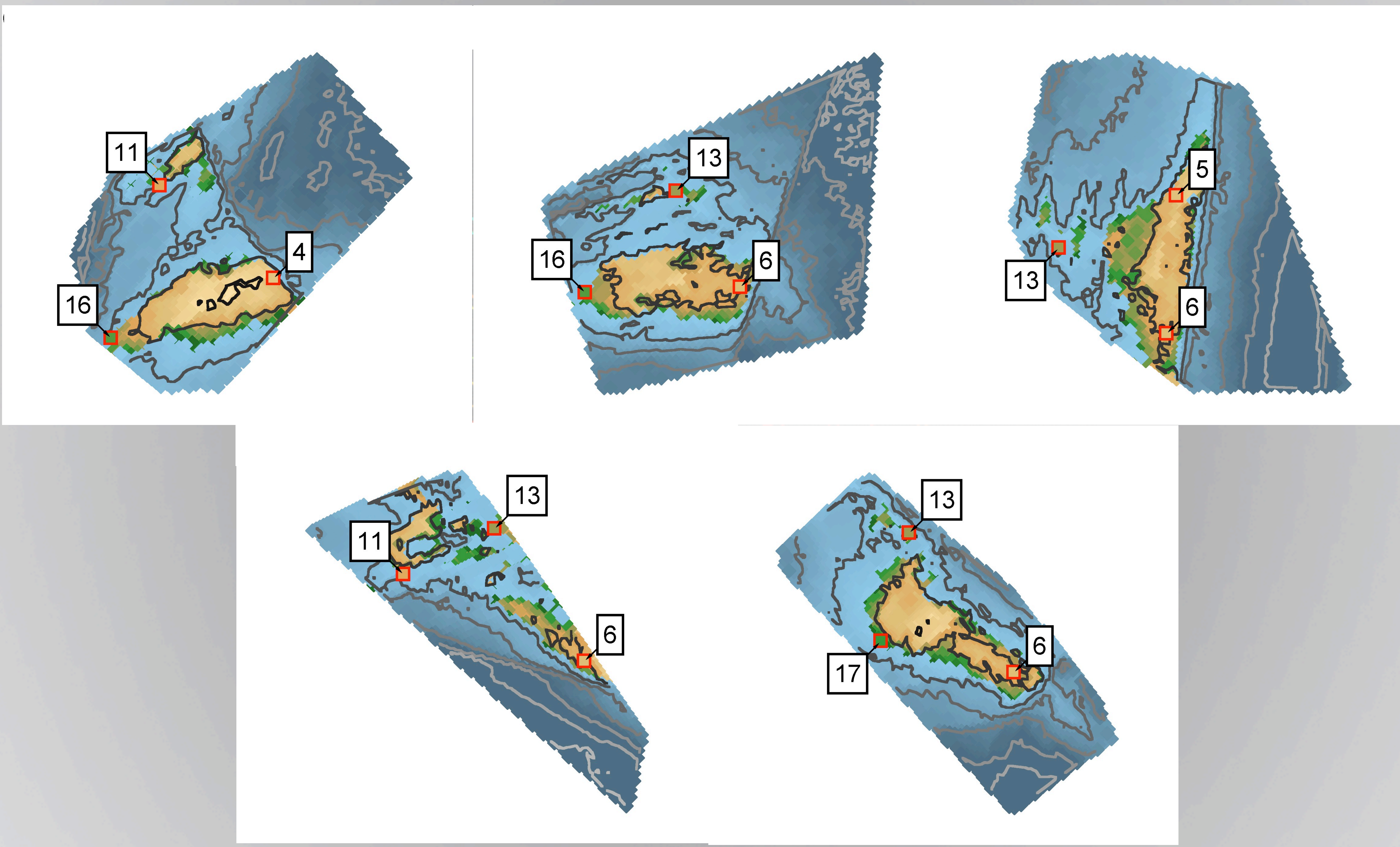
Achard and De Schutter *PLOS Comput. Biol.* 2: e94 (2006)

Small regions of good parameters



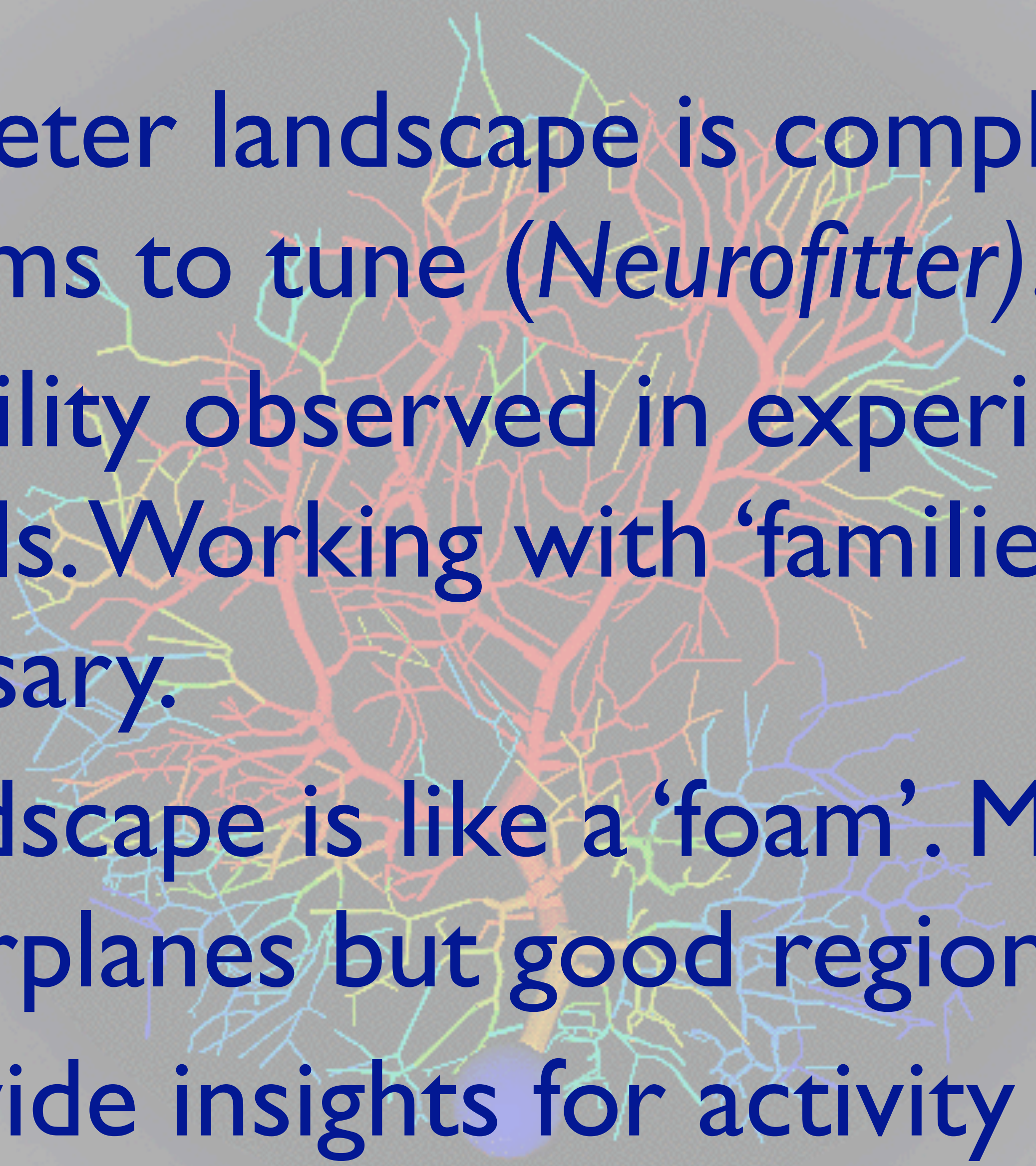
Continuous islands

Small regions of good parameters



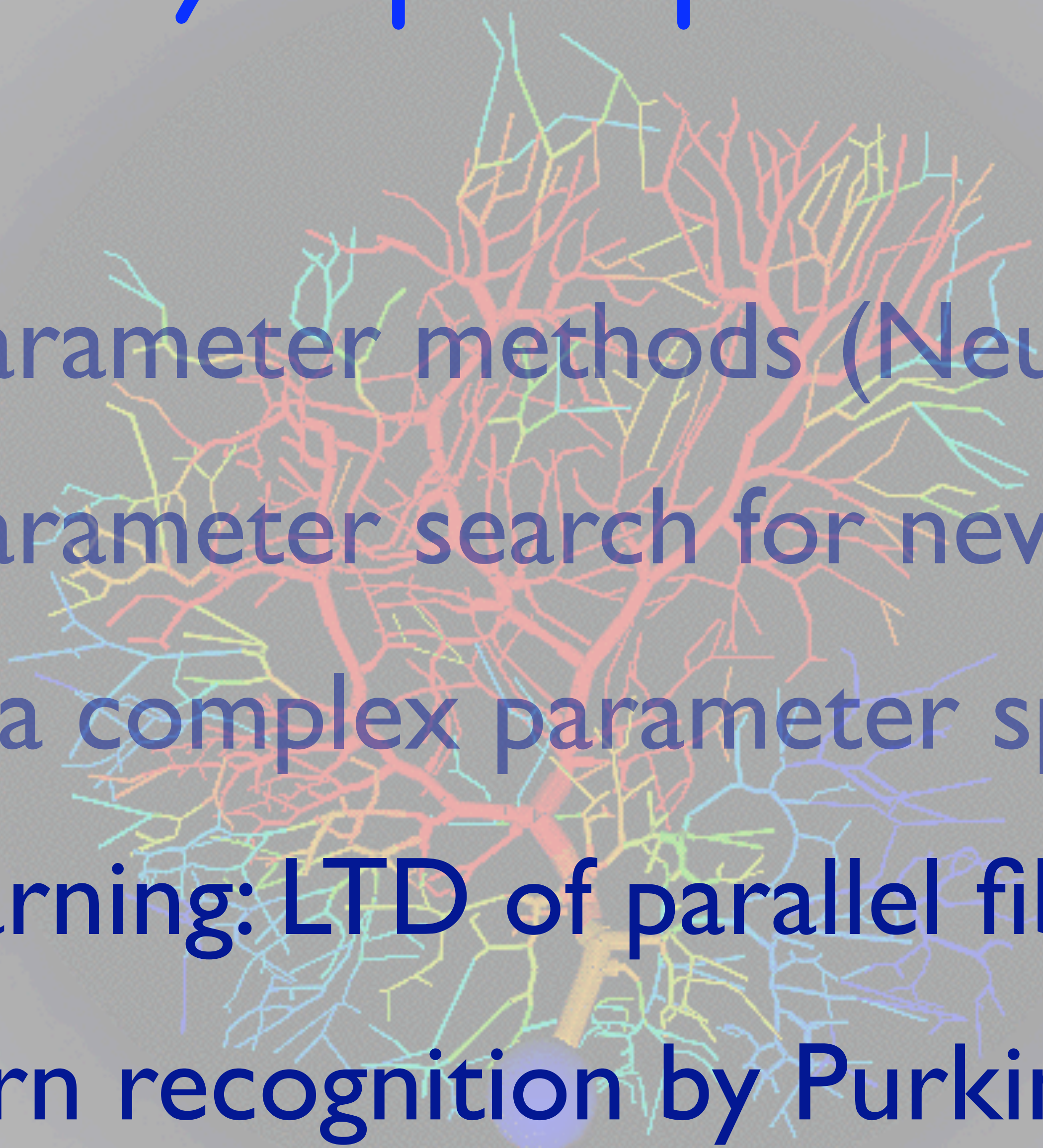
Disconnected islands

A complex parameter space



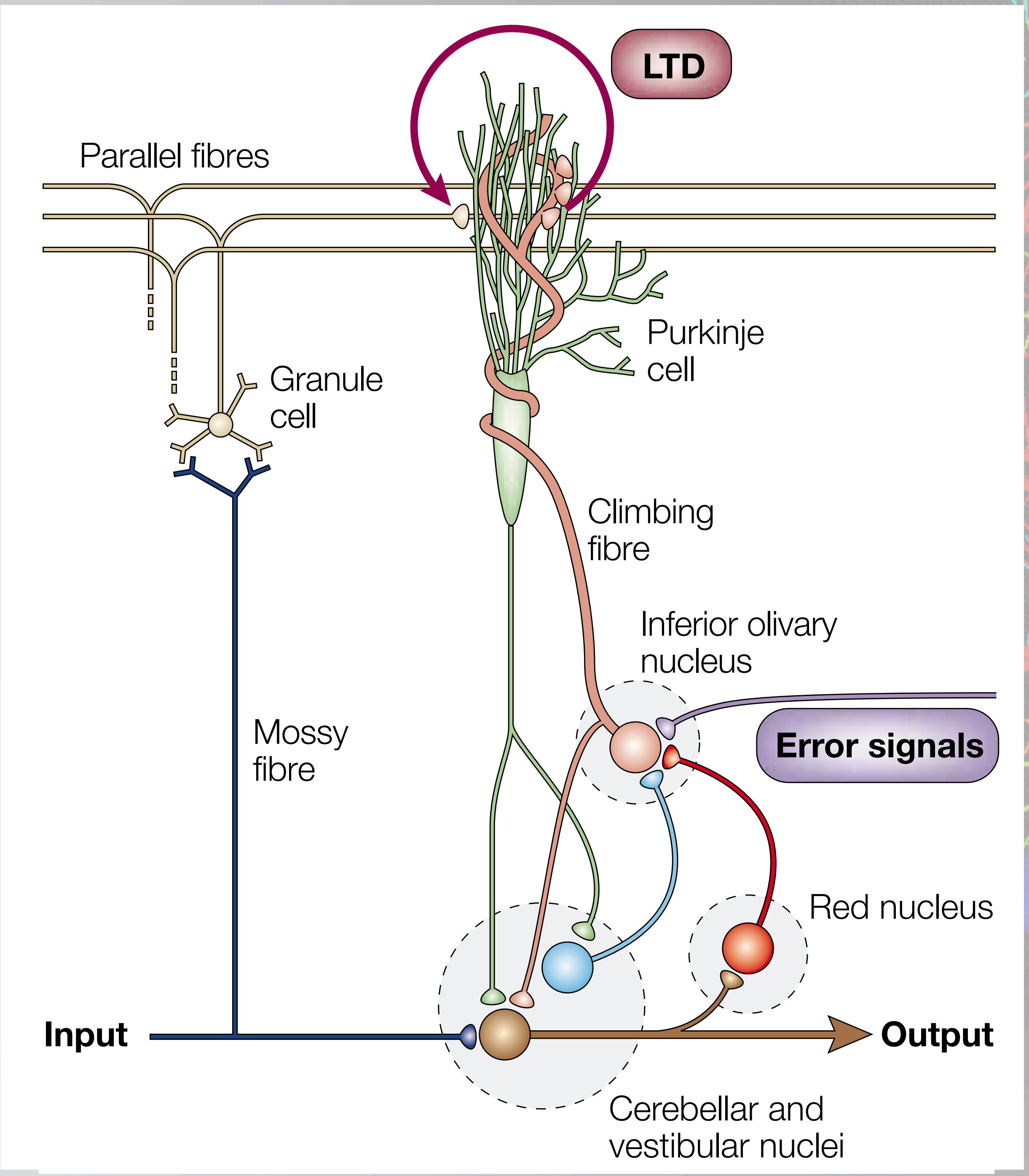
- The PC parameter landscape is complex: it requires clever algorithms to tune (*Neurofitter*).
- The cell variability observed in experiments is also found in models. Working with 'families' of models will become necessary.
- Parameter landscape is like a 'foam'. Many solutions are linked by hyperplanes but good regions are small.
- Does this provide insights for activity homeostasis of voltage-gated channels? How does the neuron navigate through this complex parameter space?

The Purkinje neuron model parameter landscape: implications for homeostasis and synaptic plasticity



- Automated parameter methods (Neurofitter)
- Automated parameter search for new Purkinje model
- Properties of a complex parameter space
- Cerebellar learning: LTD of parallel fiber synapse
- Study I: pattern recognition by Purkinje cells
- Study II: intrinsic excitability, calcium and plasticity

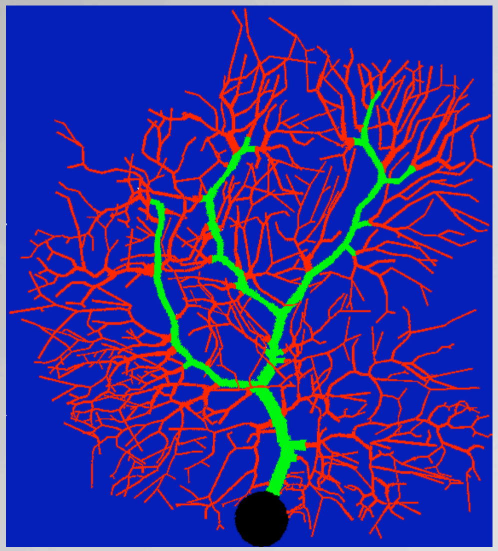
Cerebellar learning: LTD



Ito *Nat. Neurosci. Rev.* 2002

Long-term depression of the parallel fiber synapses on the spiny dendrite is important in cerebellar learning of motor control.

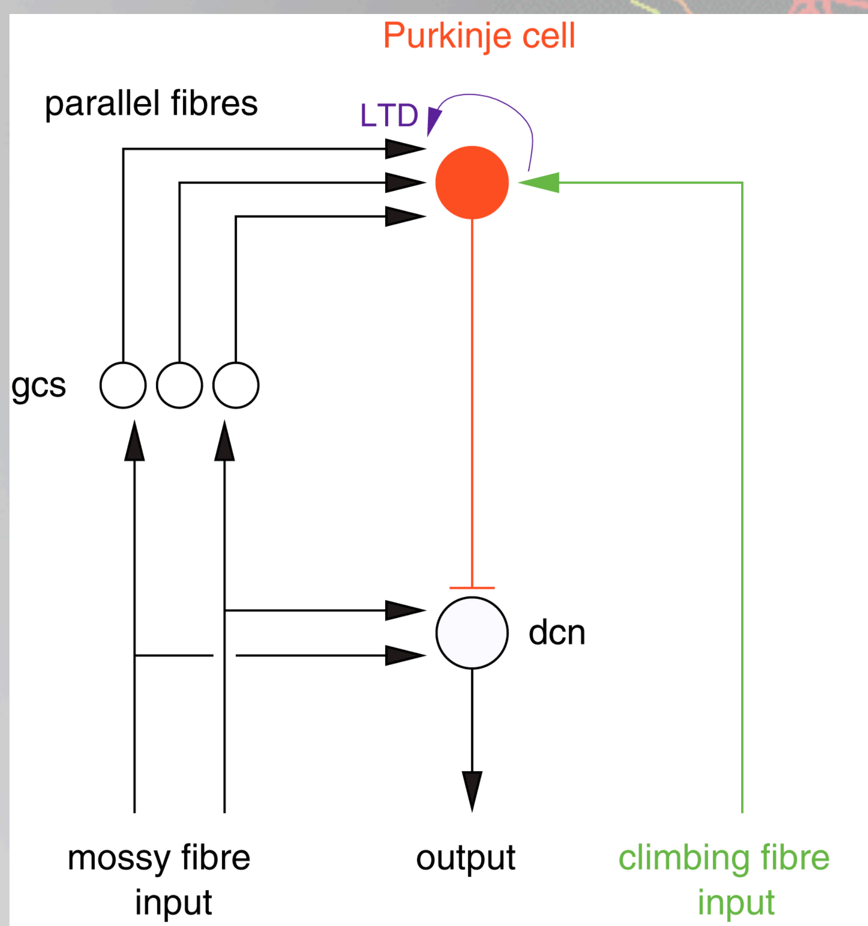
The error signal is carried by the climbing fiber which contacts the smooth dendrite and evokes a complex spike in the Purkinje cell.

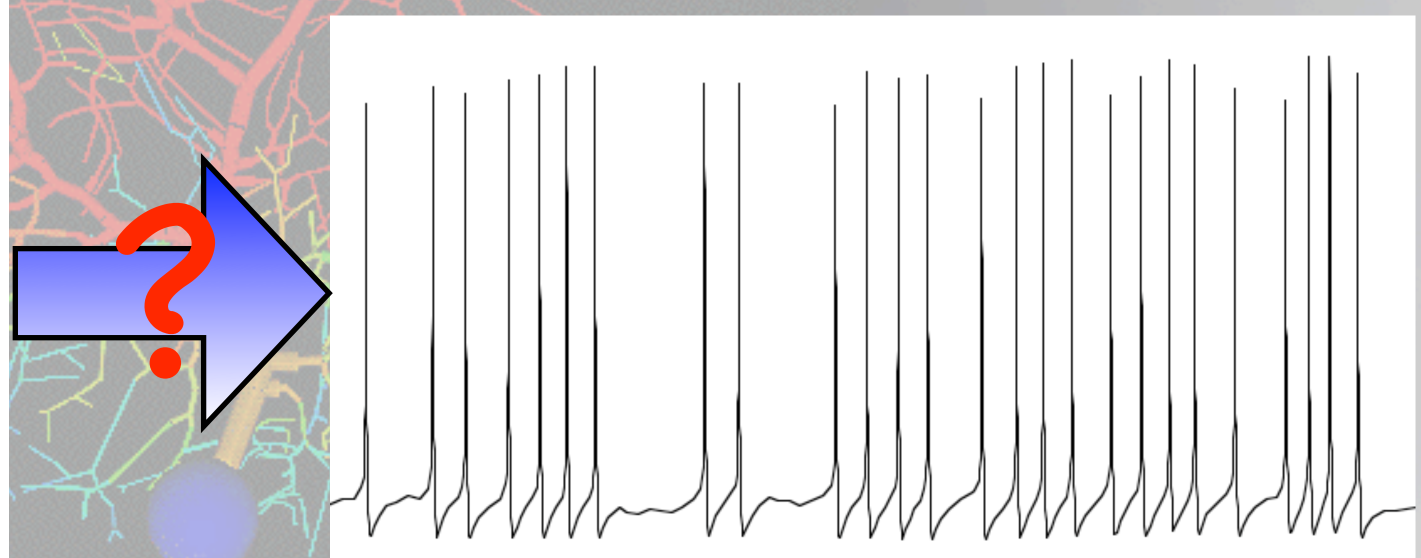


Pattern recognition by LTD

Cerebellar learning by long-term depression PF synapse

- Marr (1969): plasticity at the parallel synapse implements motor learning.
- Ito (1982): Long-Term Depression induced by coincident PF and CF input.
- Simple models: LTD leads to increased output from cerebellum.



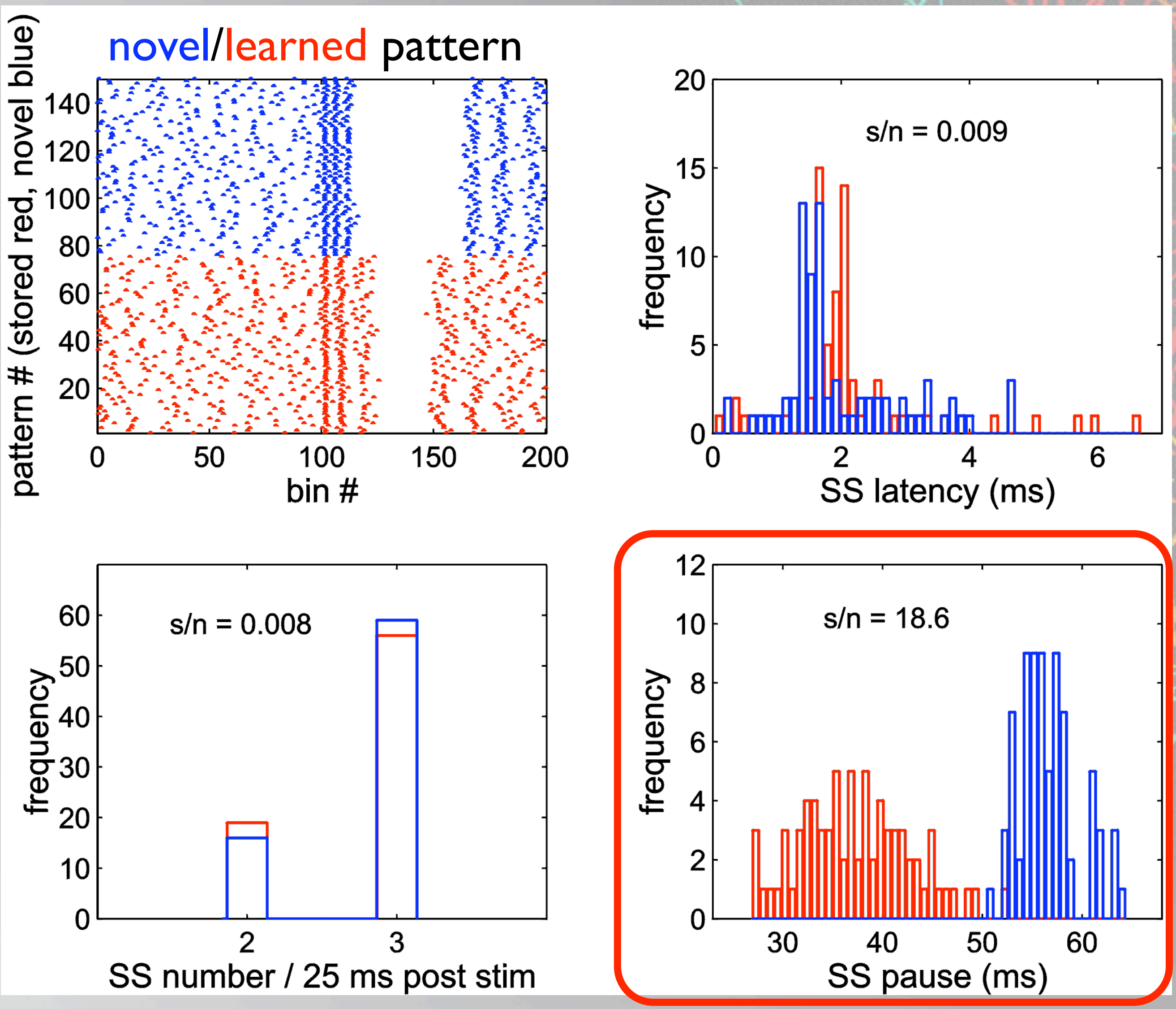


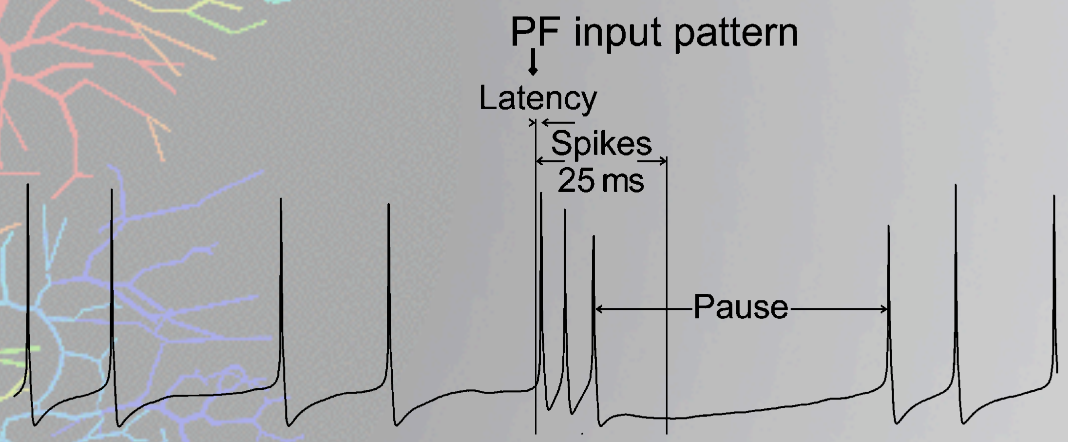
What is the effect of LTD on a spontaneously firing neuron?

Steuber et al. *Neuron* 54: 121–136 (2007)

Pattern recognition by LTD
modeling

- Only reliable recognition measure: simple spike pause following the response.



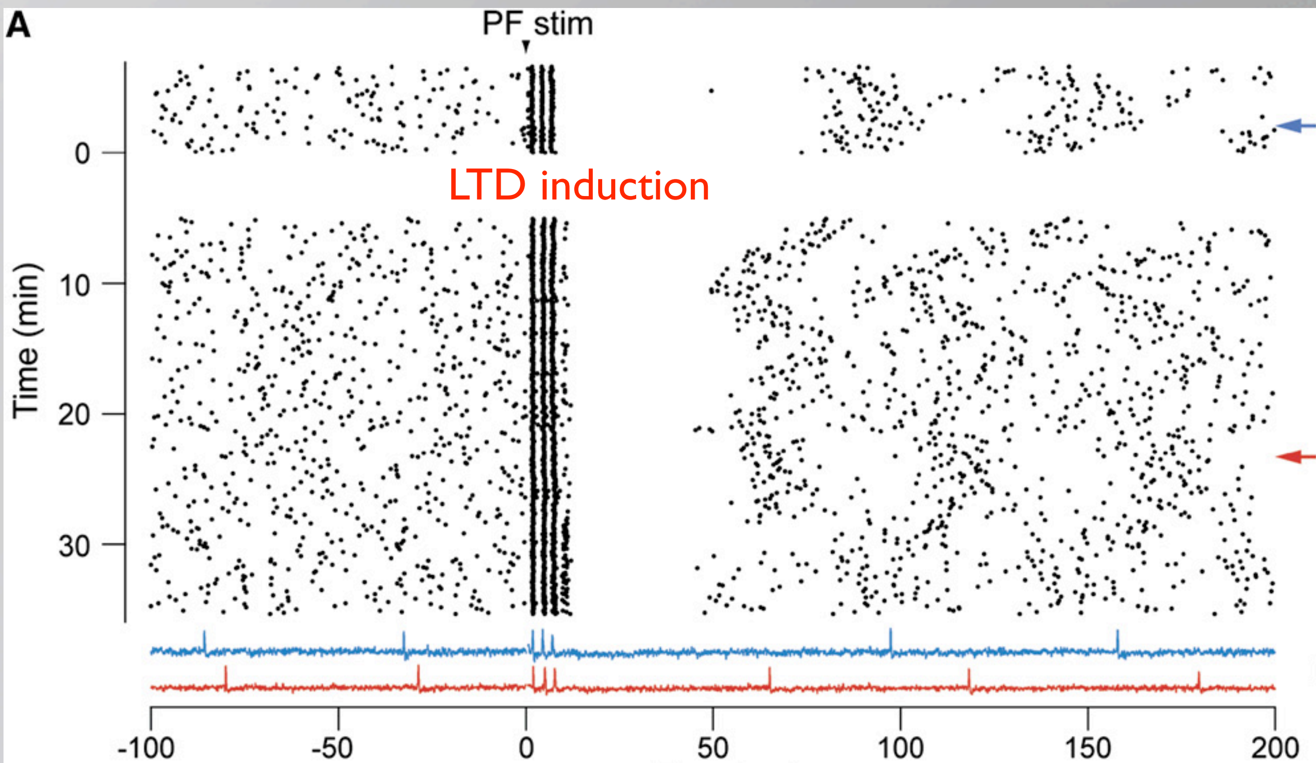


without strong AHP

Reduced pause following induction of LTD → increased output

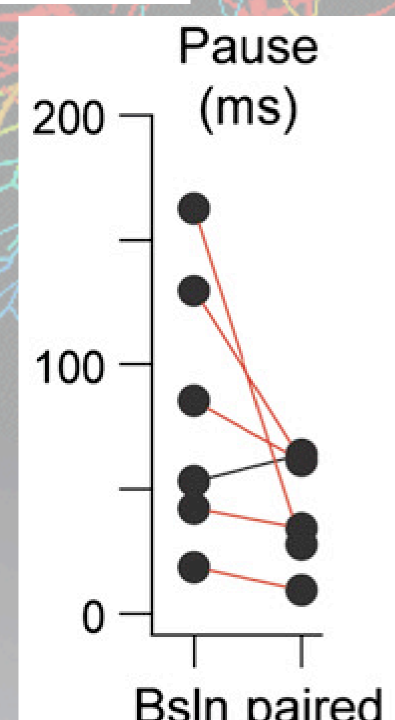
Steuber et al. *Neuron* 54: 121–136 (2007)

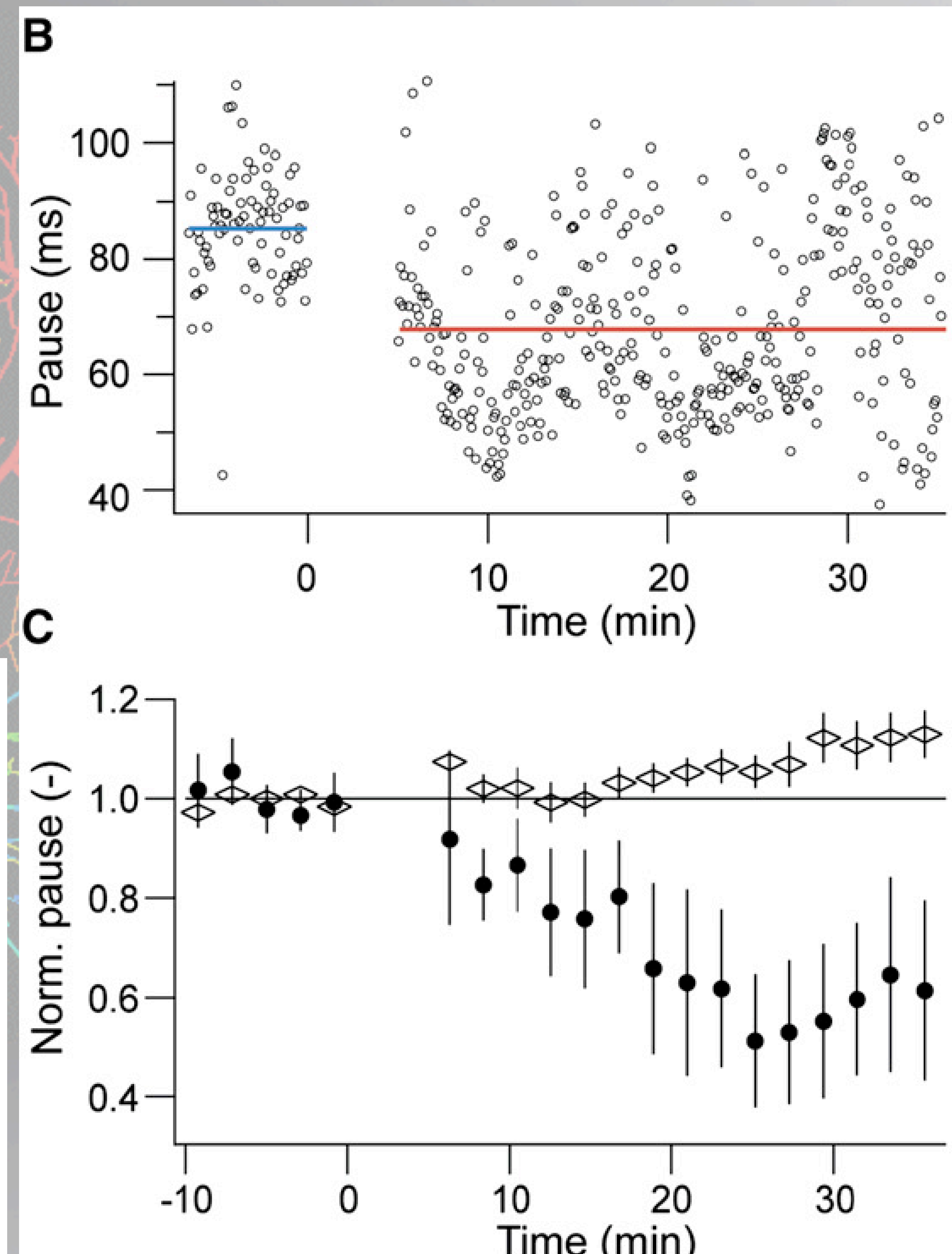
Long-Term Depression changes SS pause
Experimental verification in vitro: LTD



LTD induction:

300 x PF-CF (1 ms interval) at 1 Hz

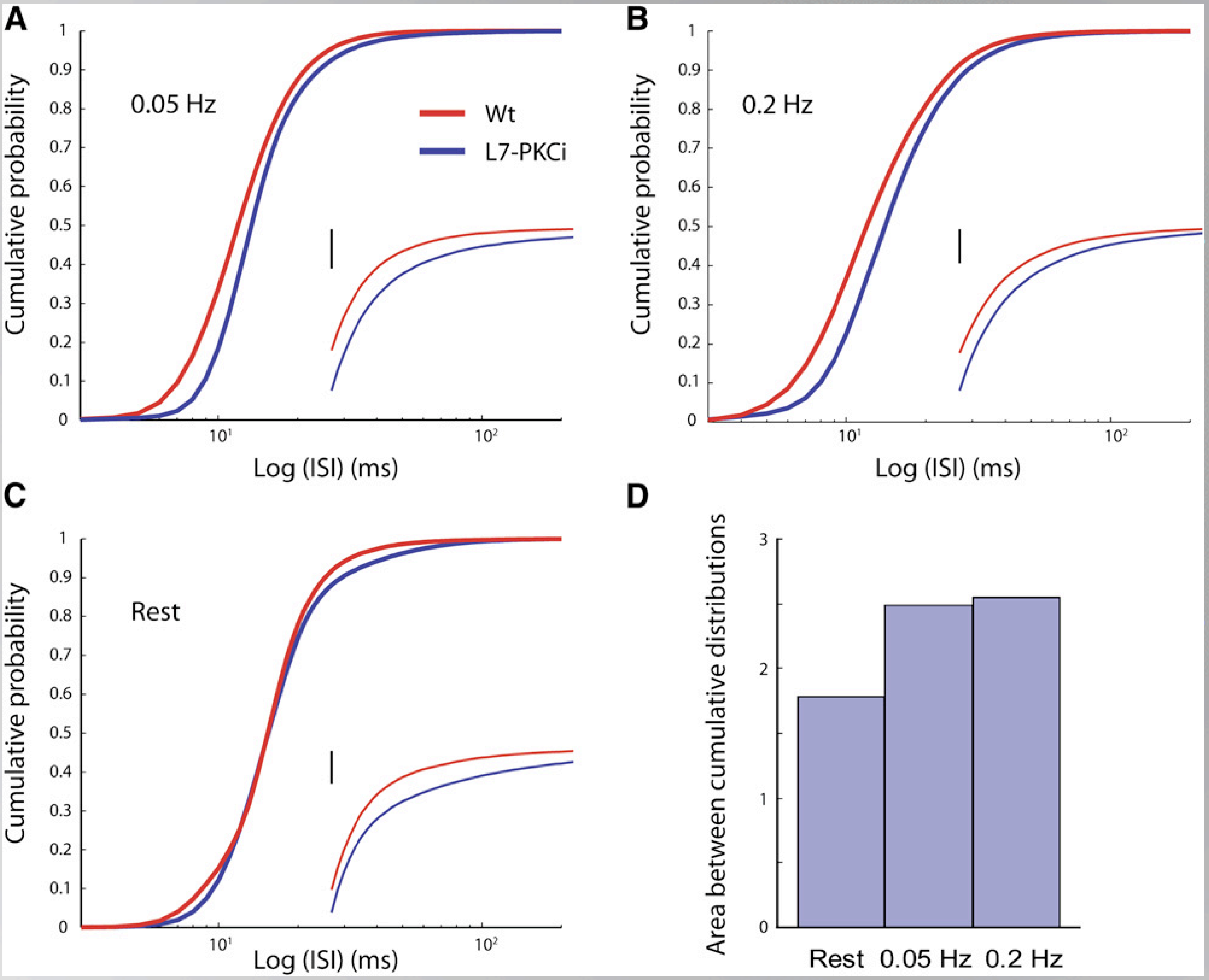




An LTD induction protocol causes shortening of the pause

Steuber et al. *Neuron* 54: 121–136 (2007)

Long-Term Depression changes SS pause Experimental verification in vivo: ISIs



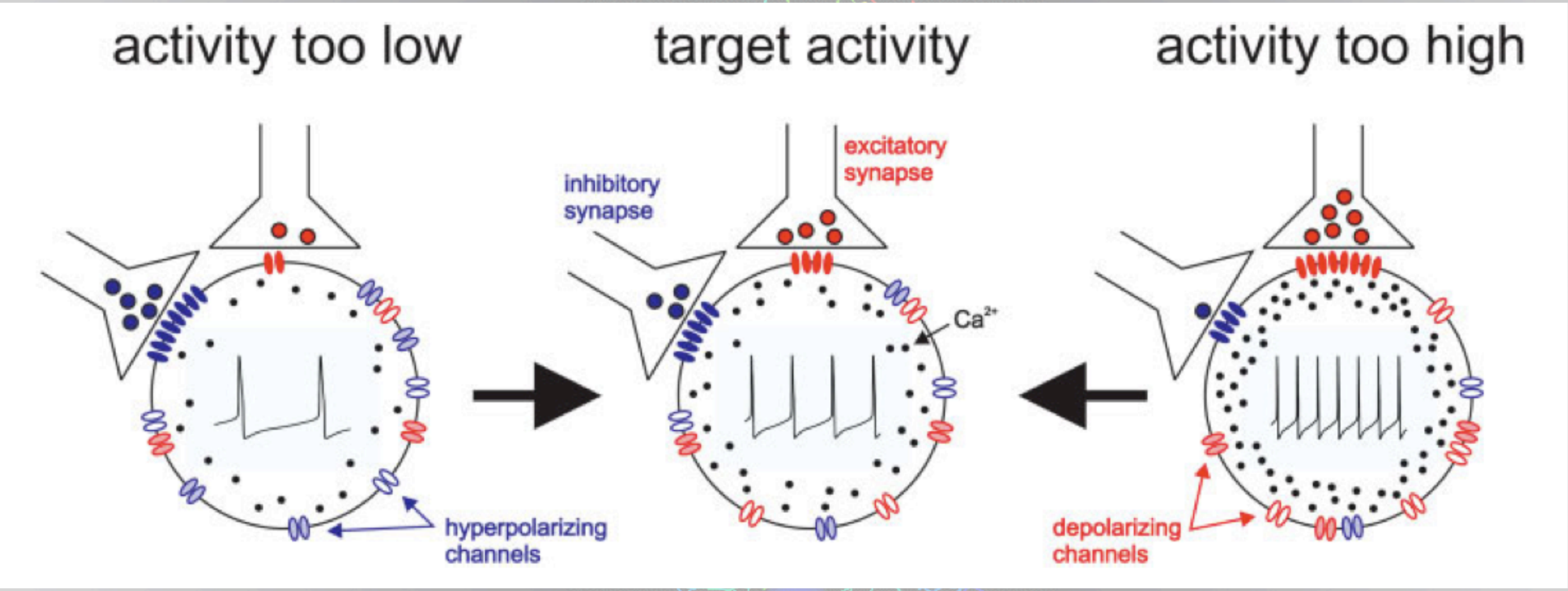
Floccular PCs of transgenic mice lacking LTD have longer pauses in the ISI distribution, more pronounced by oculomotor activity (optokinetic resp.)

Steuber et al. *Neuron* 54: 121–136 (2007)

Pattern recognition by LTD

- Only criterion to distinguish learned and novel patterns after LTD induction is length of simple spike pause.
- Shorter pauses for learned patterns: LTD <u>increases</u> Purkinje cell output → cerebellar output decreases.
- Confirmation in in vitro and in vivo experiments.
- Learning can change duration of pauses.

Calcium as a homeostatic sensor

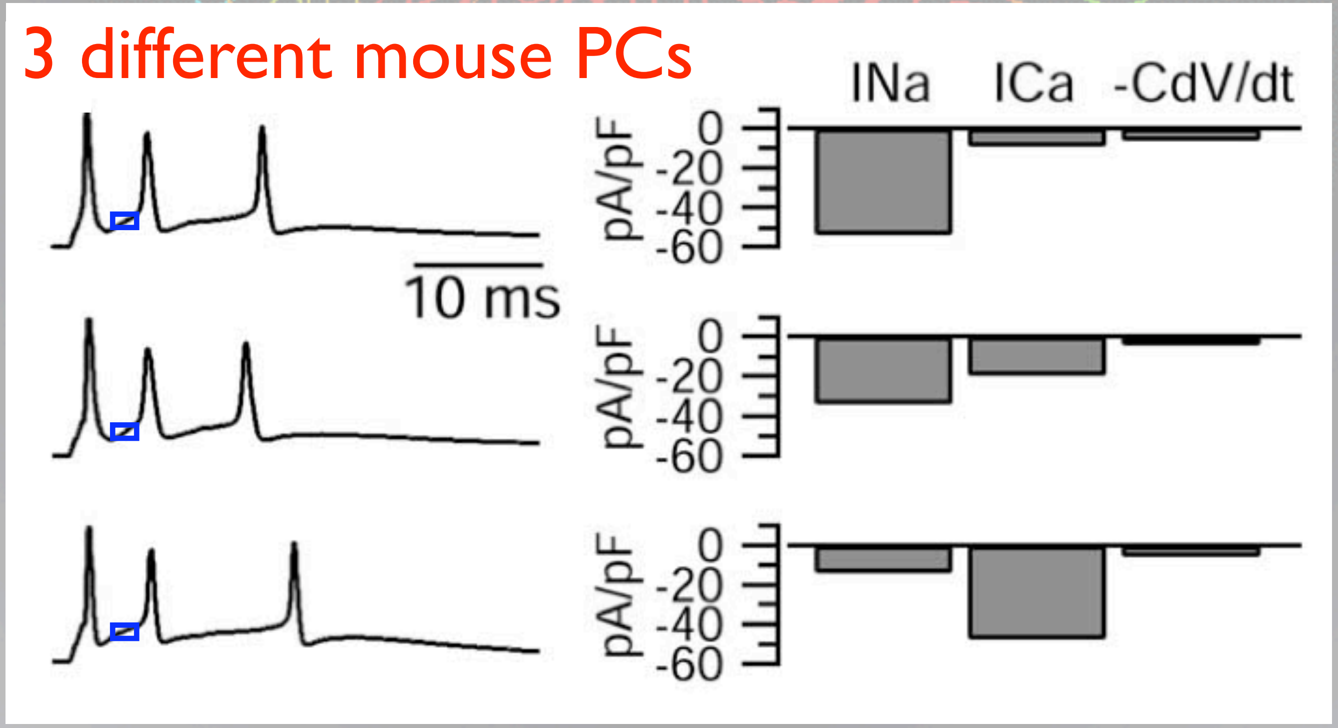


Calcium as a homeostatic sensor

Robustness of Burst Firing in Dissociated Purkinje Neurons with Acute or Long-Term Reductions in Sodium Conductance

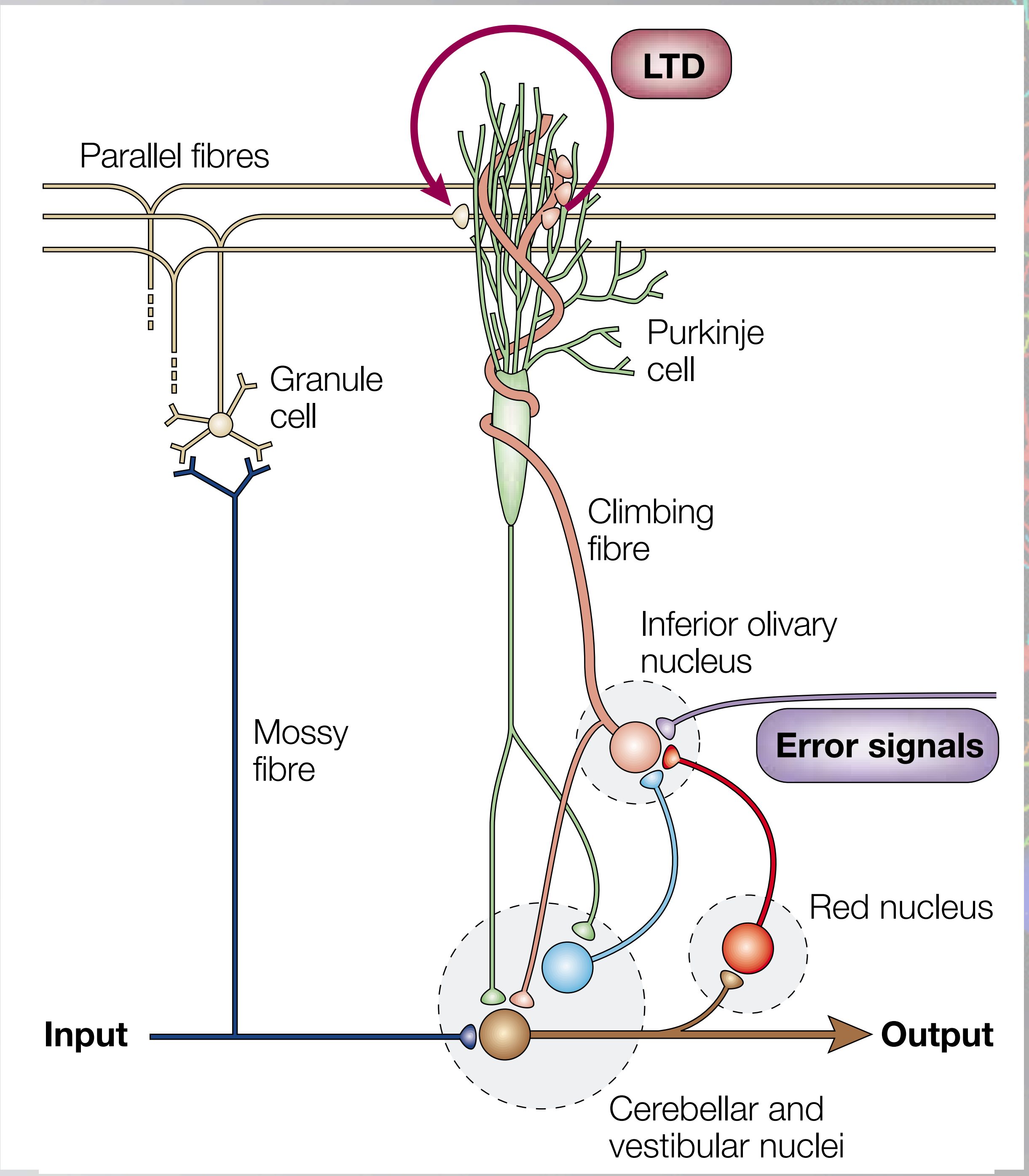
The Journal of Neuroscience, April 6, 2005 • 25(14):3509 –3520

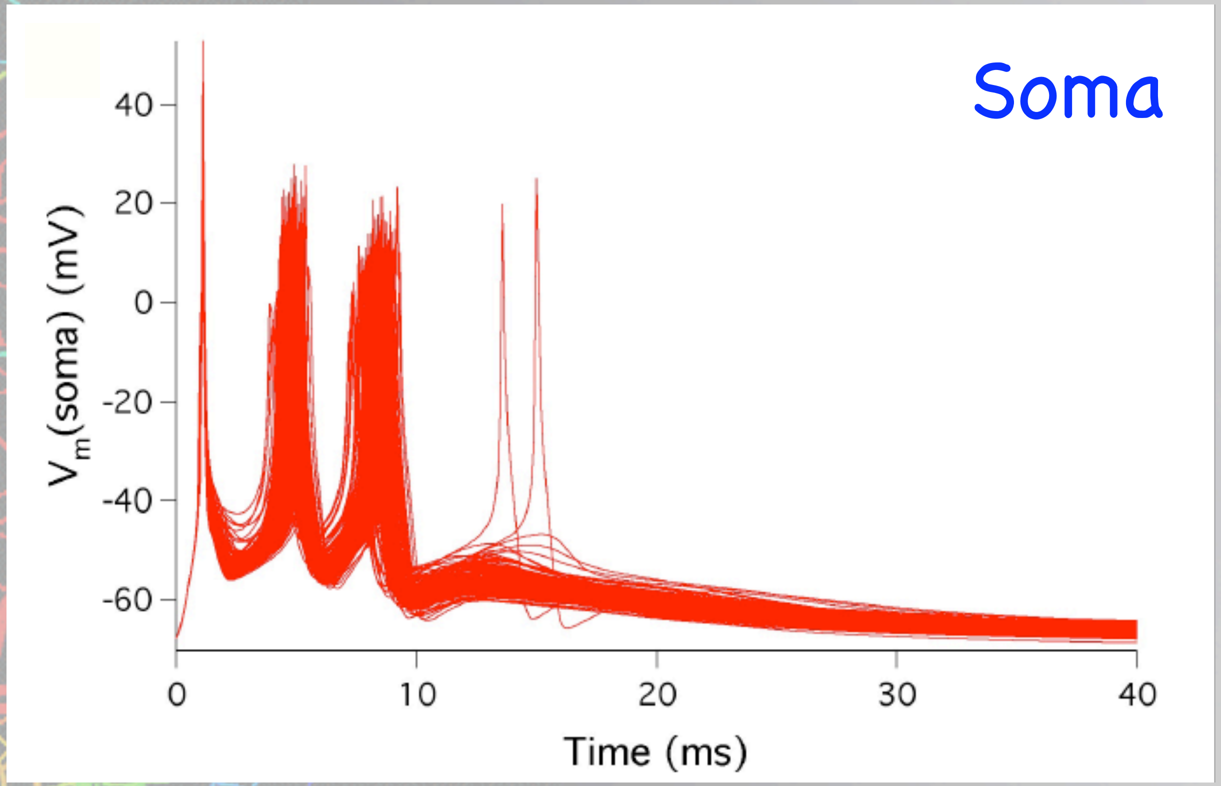
Andrew M. Swensen and Bruce P. Bean

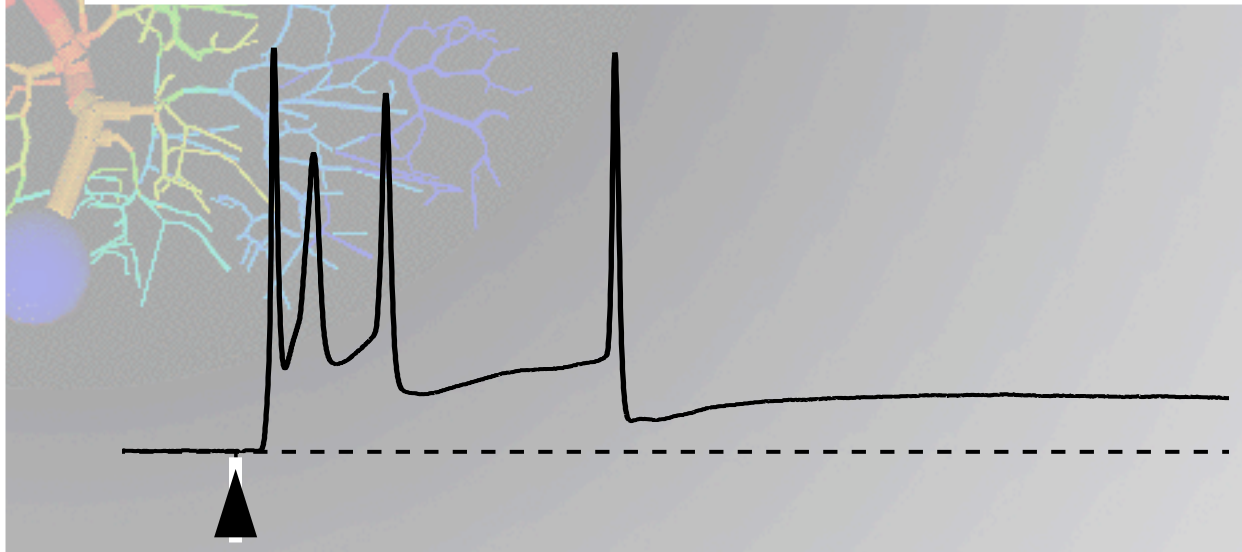


Widely different calcium currents for similar spiking patterns

Calcium and synaptic plasticity





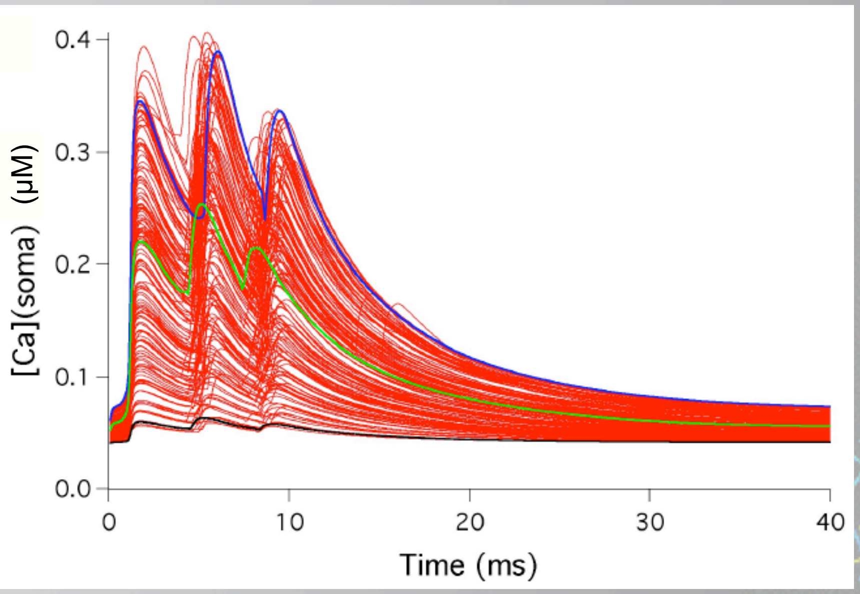


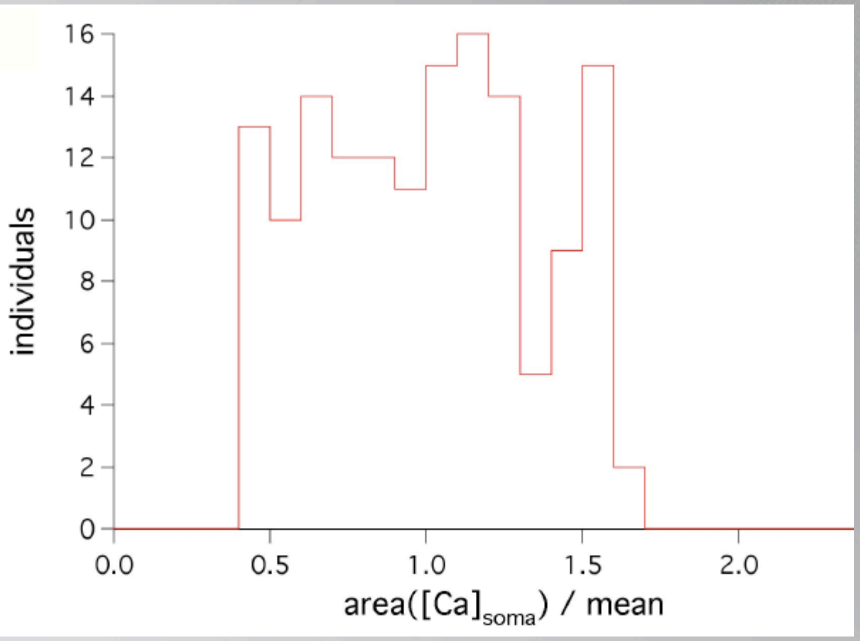
The complex spike voltage transient is fairly constant

Calcium and synaptic plasticity

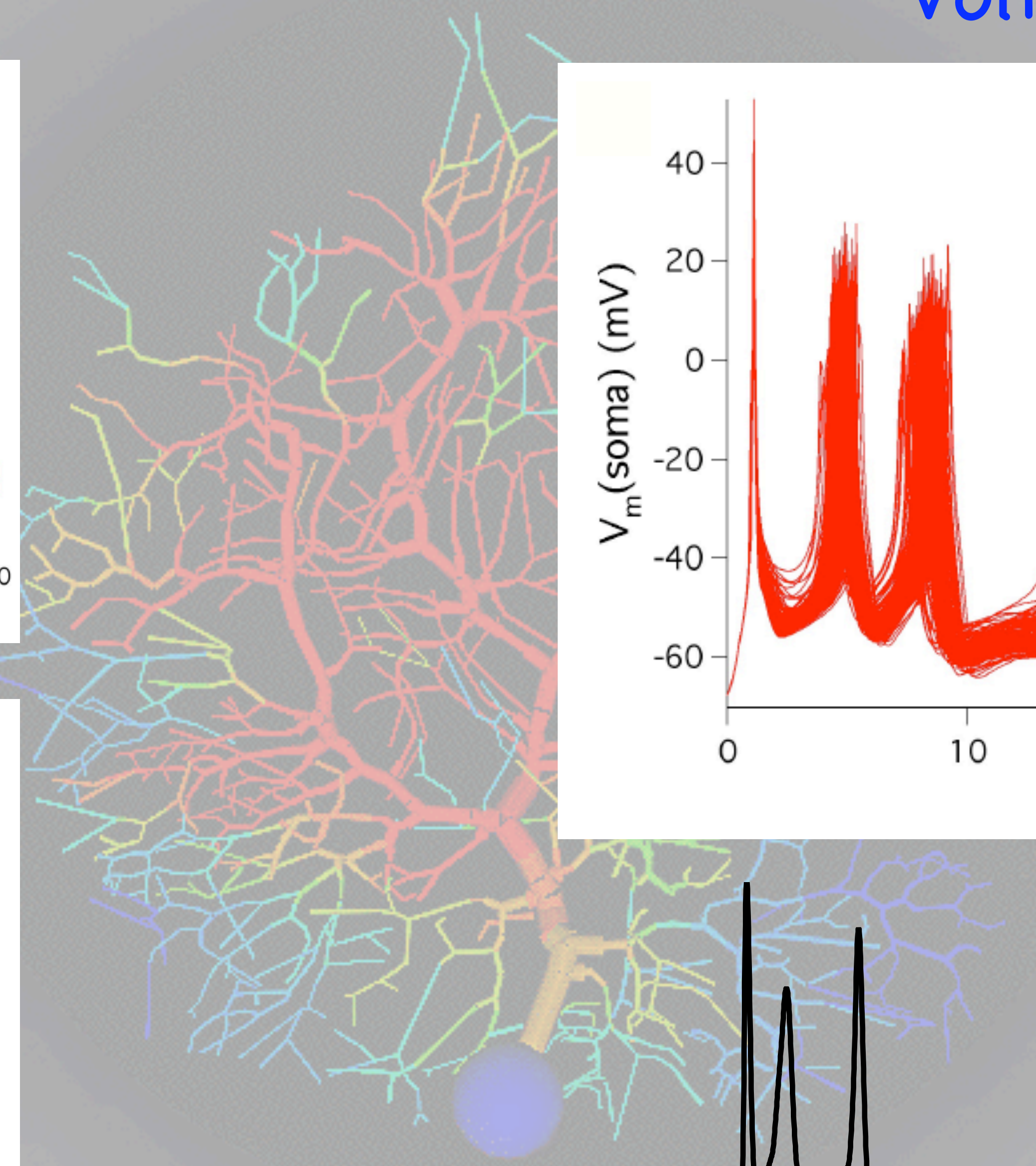
What is the calcium influx caused by the complex spike?

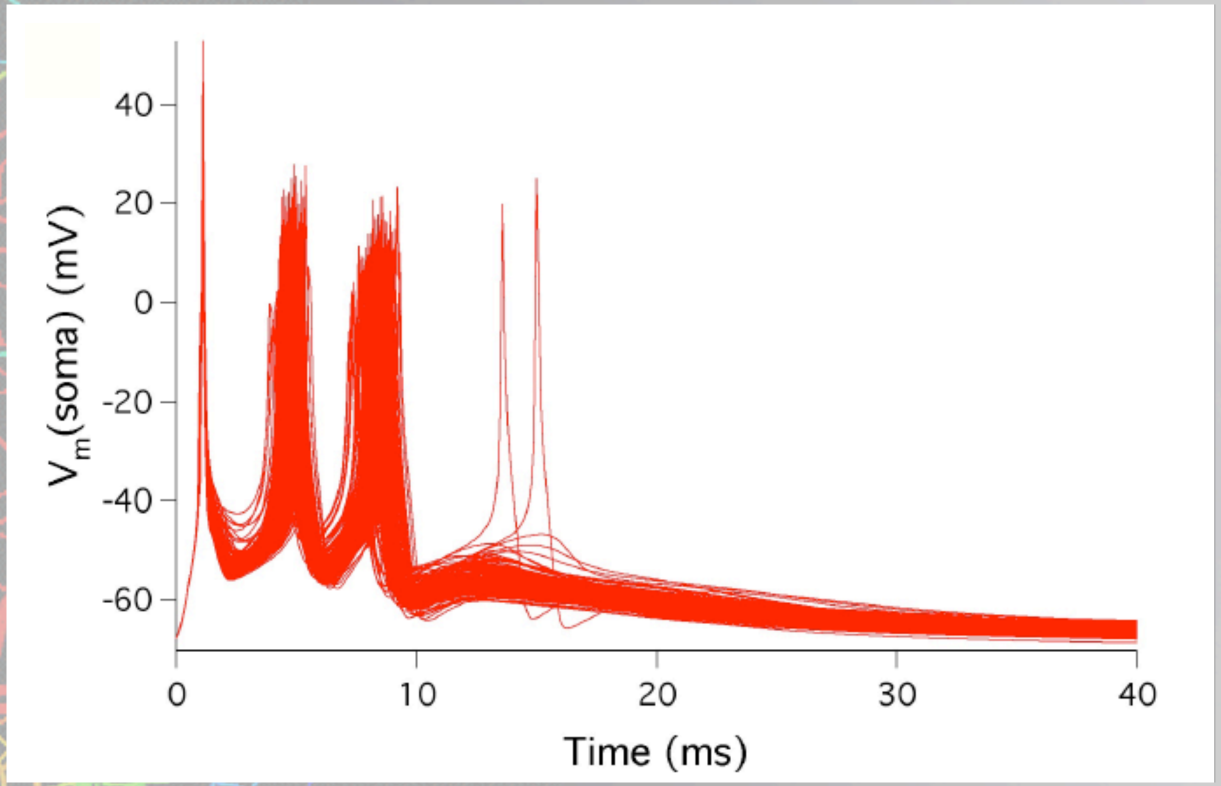
[Ca] soma

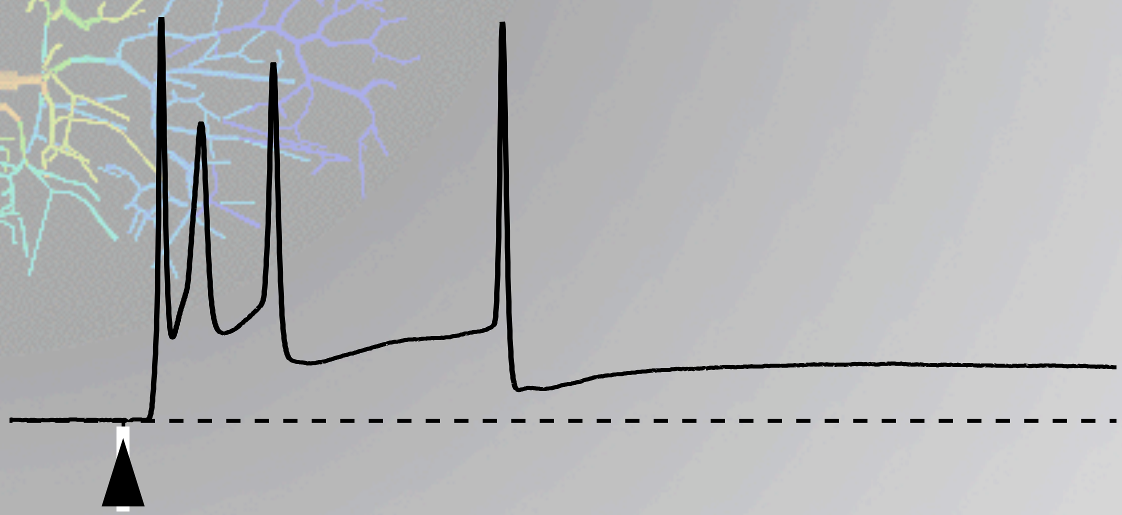




Voltage soma





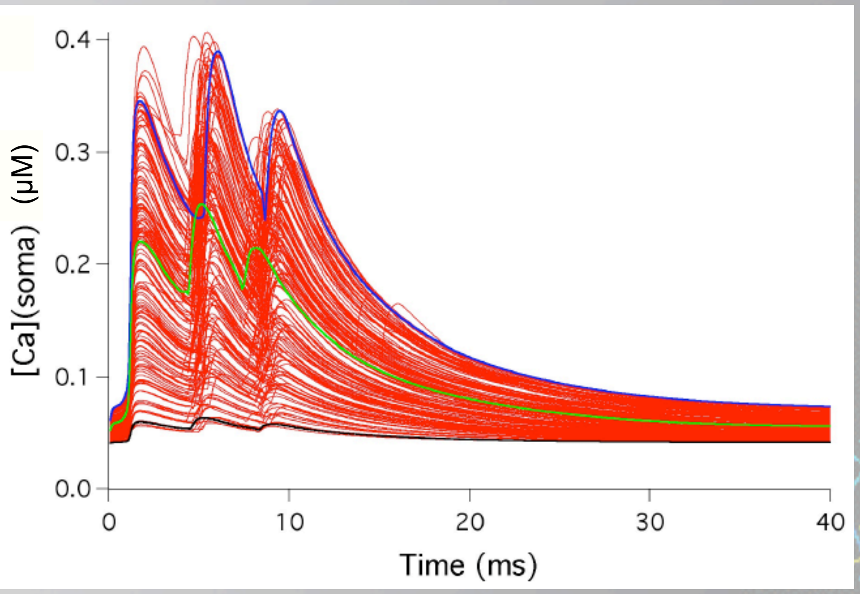


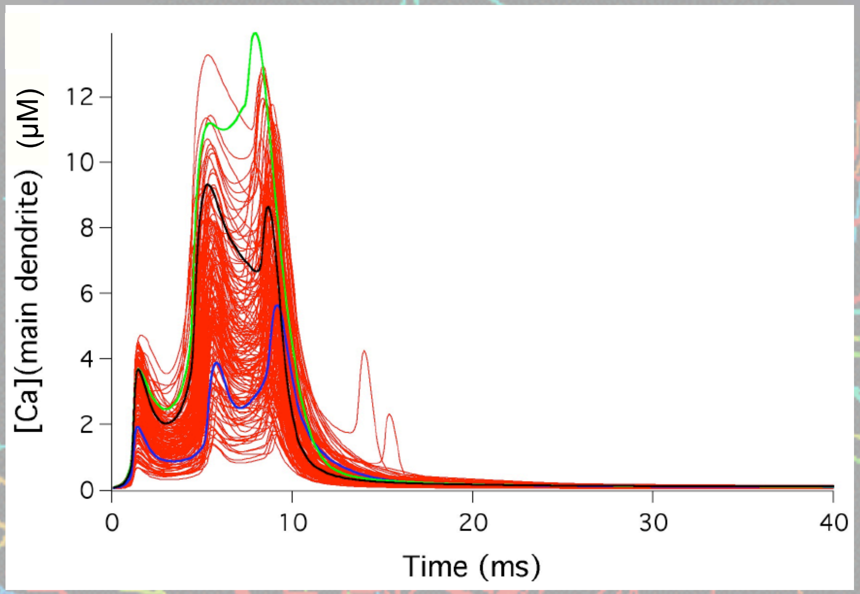
Voltage is constant, but the calcium influx is very variable

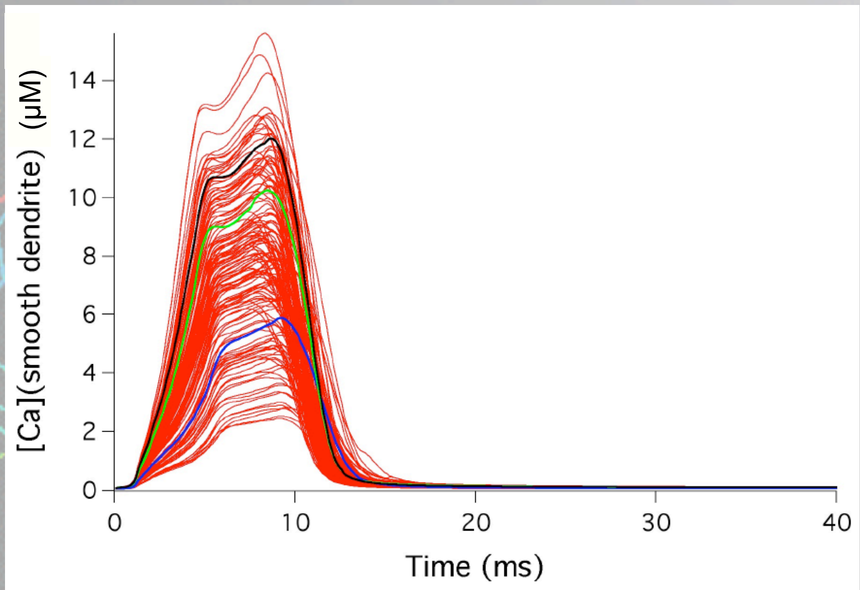
Calcium and synaptic plasticity

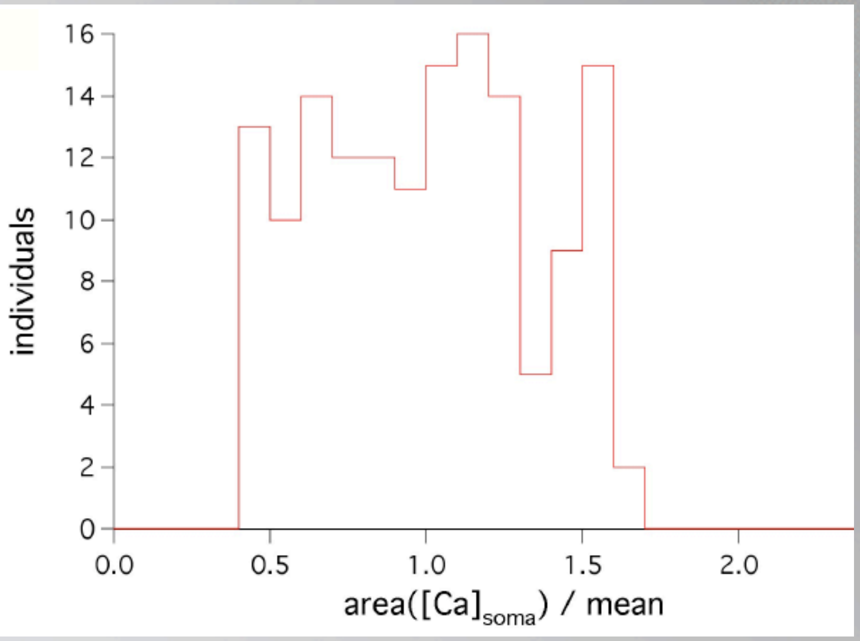
What is the calcium influx caused by the complex spike?

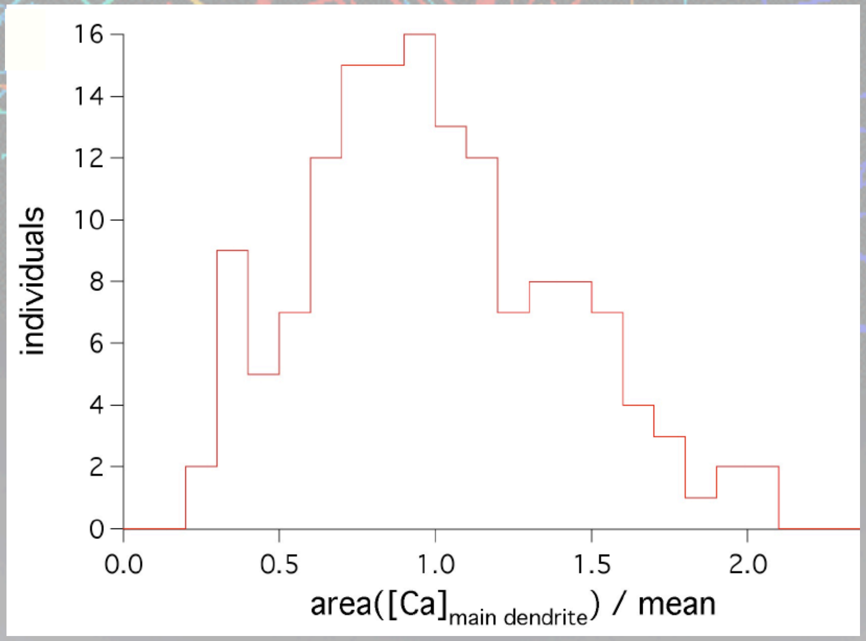
[Ca] soma | [Ca] proximal dendrite | [Ca] smooth dendrite

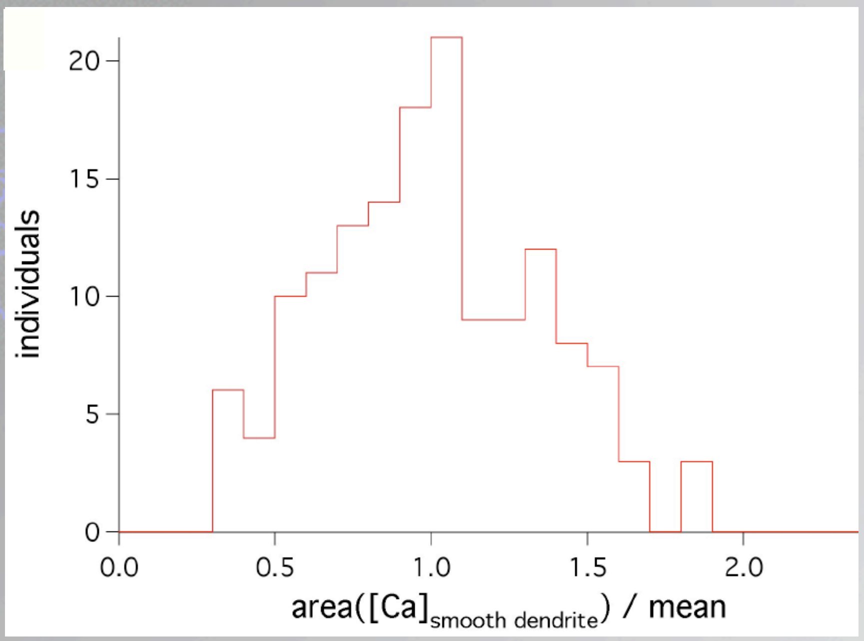








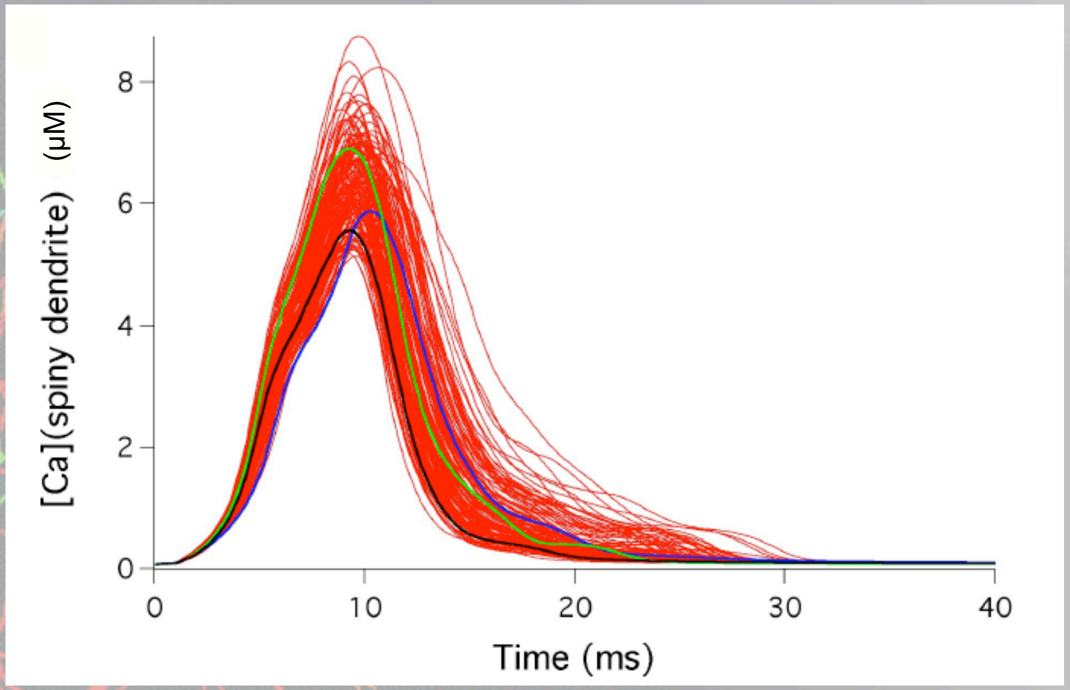




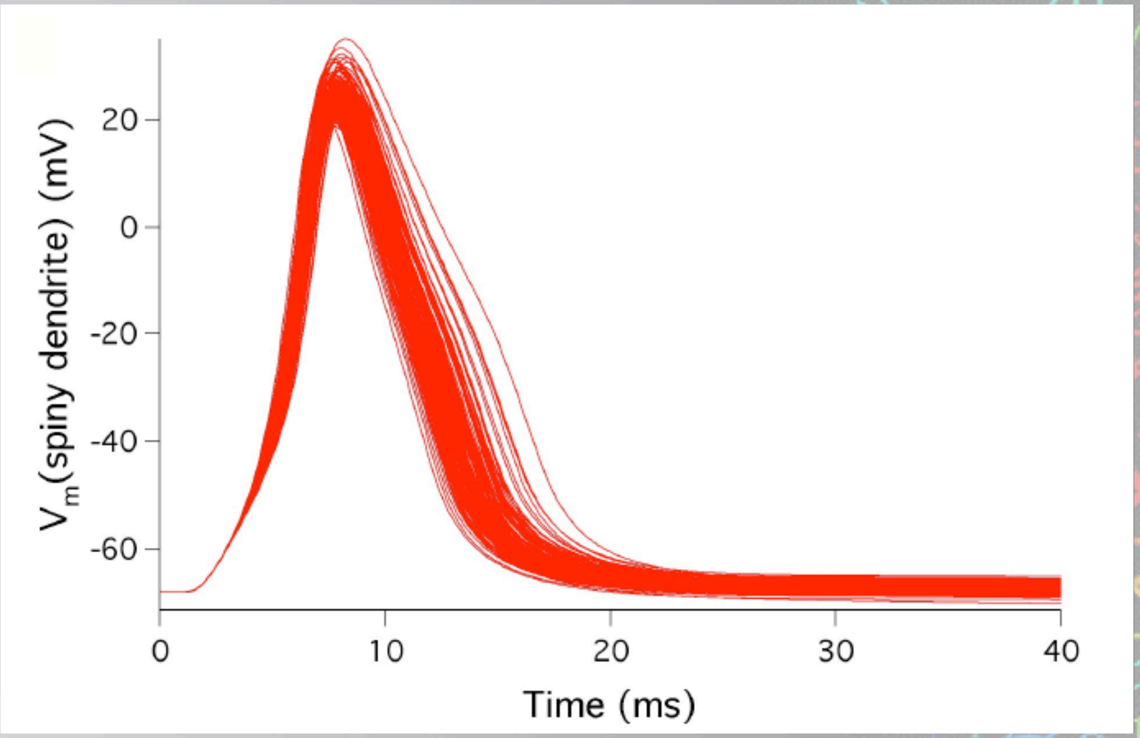
In soma and smooth dendrite calcium influx is very variable

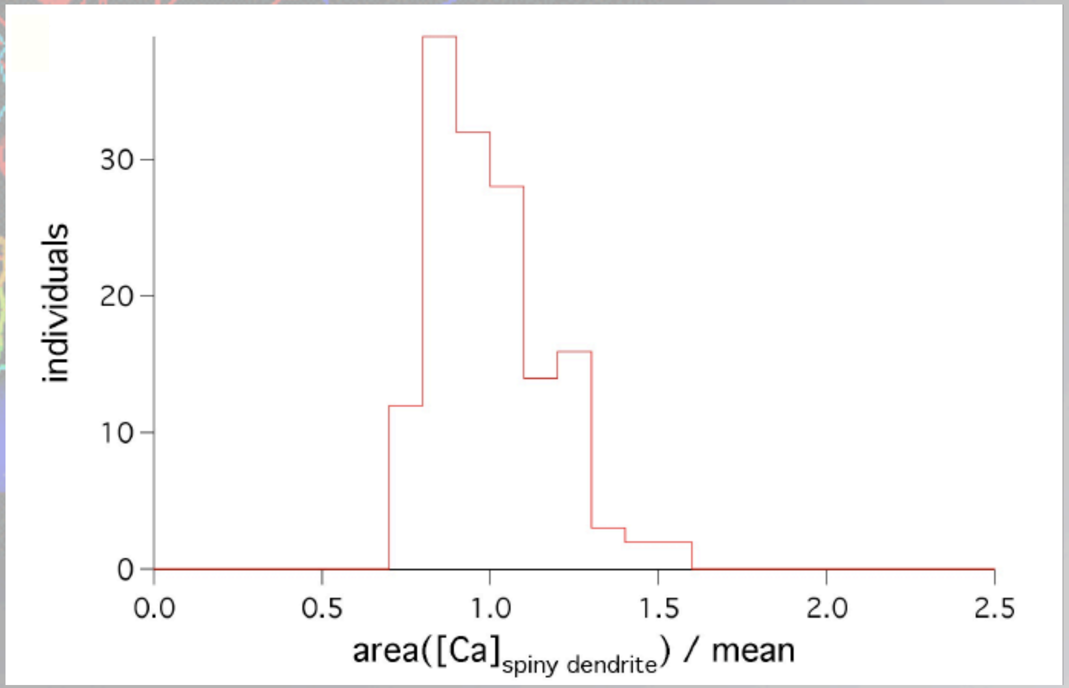
Calcium and synaptic plasticity

[Ca] spiny dendrite



Voltage spiny dendrite



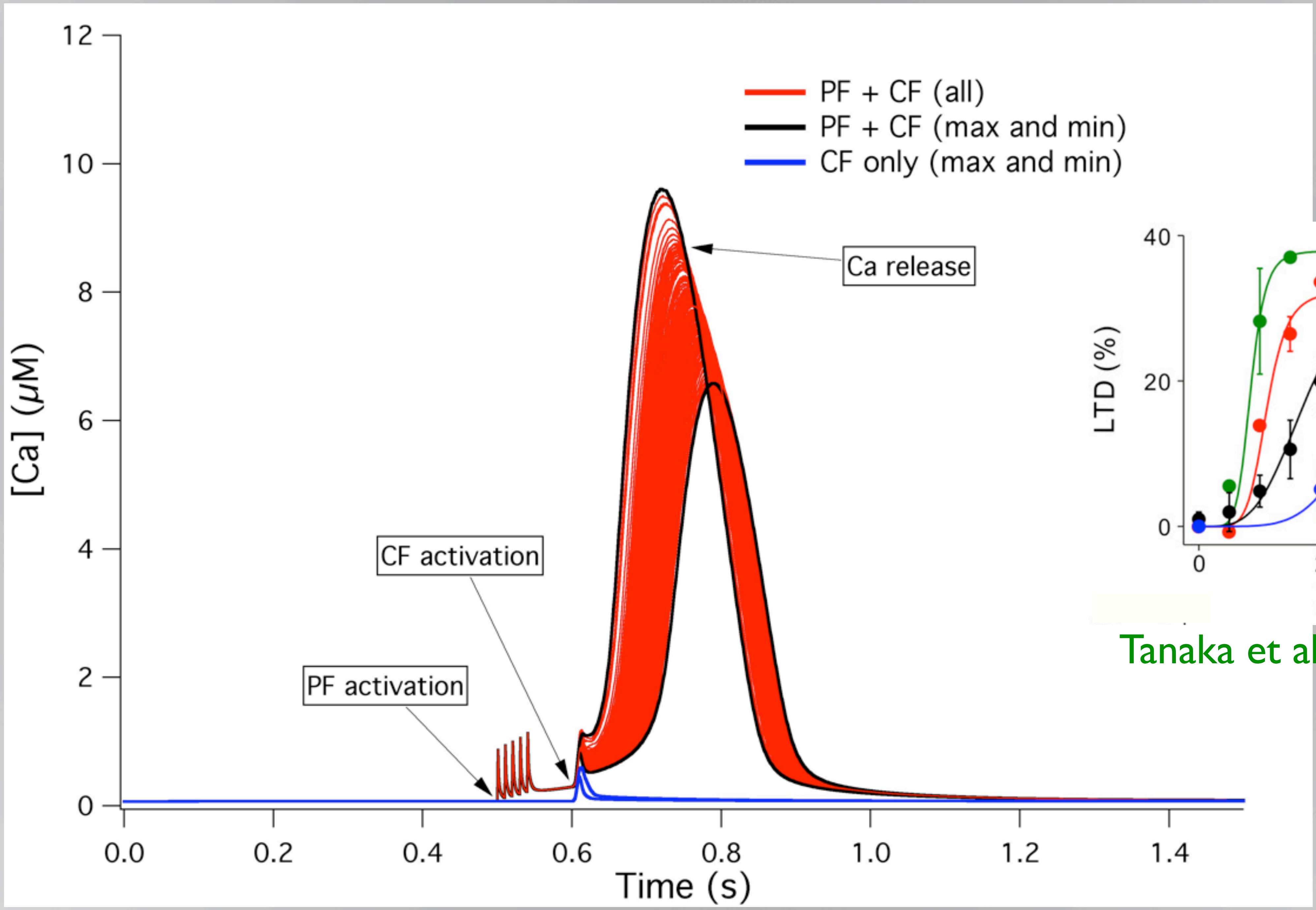


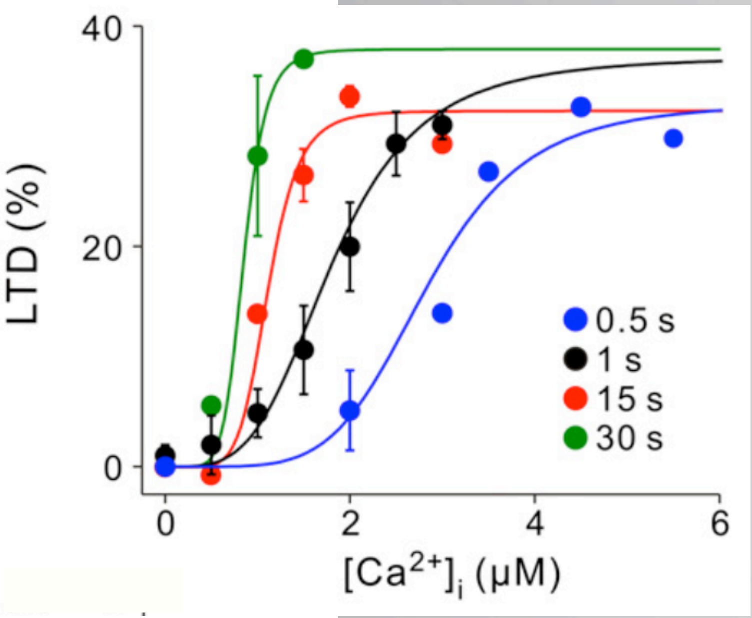
Conversely, in spiny dendrite calcium influx is very robust!

Does this preserve the learning mechanism?

Calcium and synaptic plasticity

Calcium transients evoked by PF + CF for 148 PC models





Tanaka et al. *Neuron* 2007

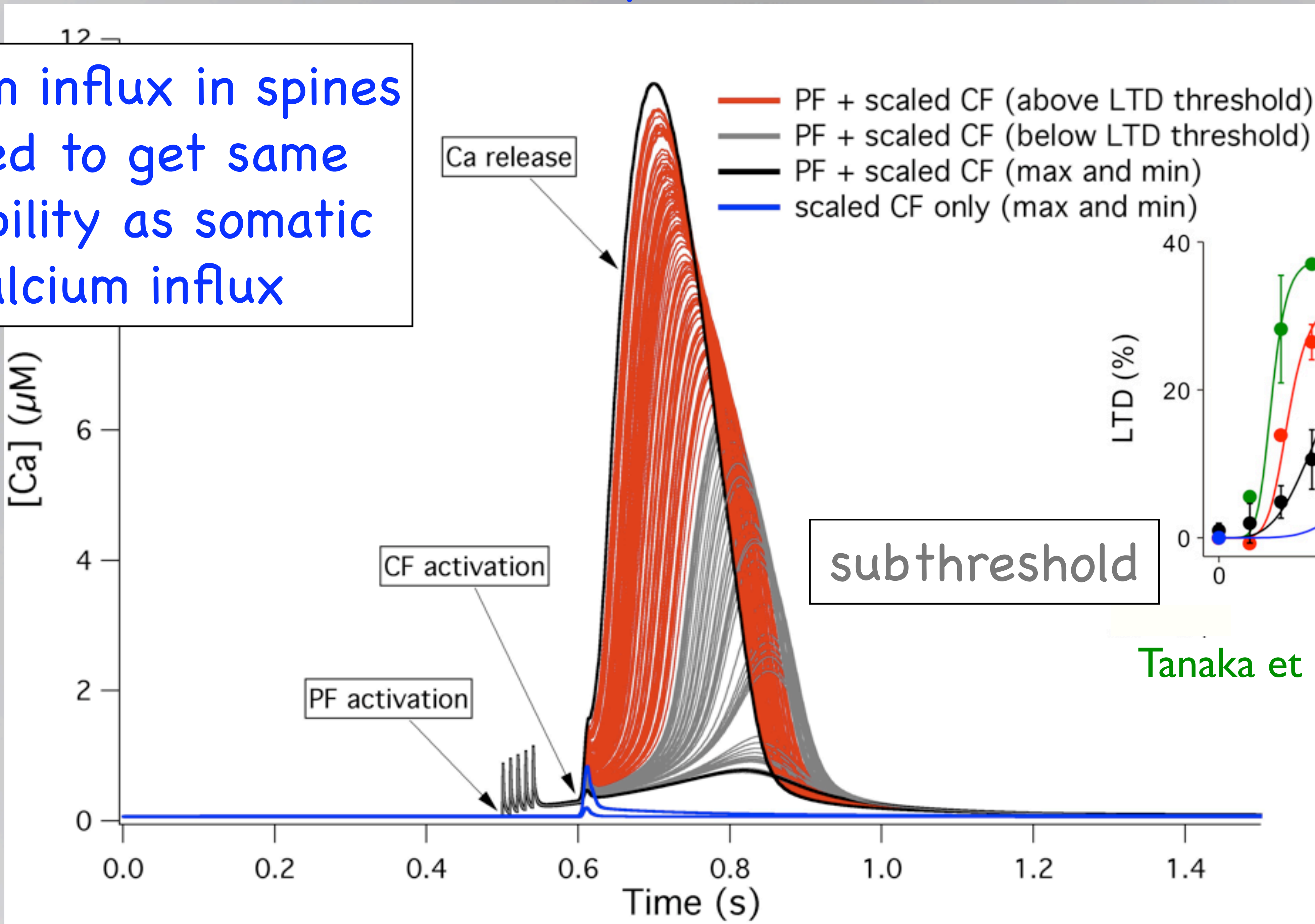
Calcium release model by Doi et al. *J. Neurosci.* 2005

Induction of LTD is preserved in all 148 PC models

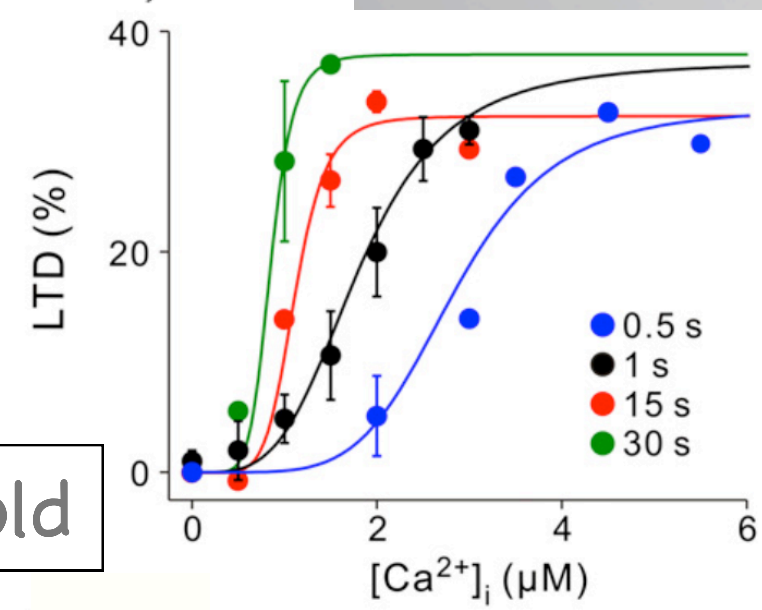
Calcium and synaptic plasticity

Calcium transients evoked by PF + scaled CF for 148 PC models

Calcium influx in spines scaled to get same variability as somatic calcium influx



subthreshold

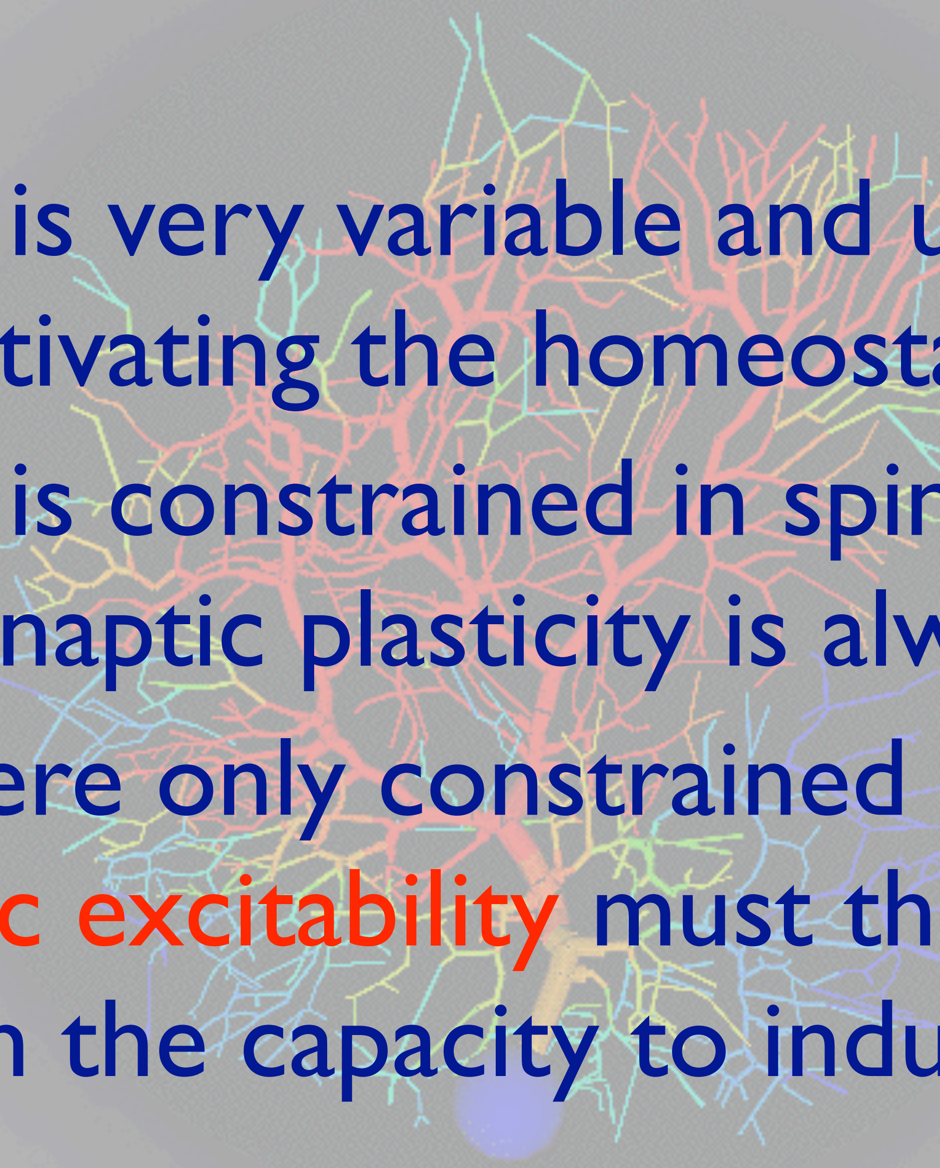


Tanaka et al. *Neuron* 2007

Calcium release model by Doi et al. *J. Neurosci.* 2005

Induction of LTD fails for 37% of the models!

Calcium and synaptic plasticity



- Calcium influx is very variable and unlikely to be the global signal activating the homeostatic sensor.
- Calcium influx is constrained in spiny dendrites so that induction of synaptic plasticity is always possible.
- The models were only constrained by their electrical activity, intrinsic excitability must therefore be strongly correlated with the capacity to induce synaptic plasticity.


Computational Neuroscience Unit
Okinawa Institute of Science and Technology, Japan