Training deep neural density estimators to identify mechanistic models in science

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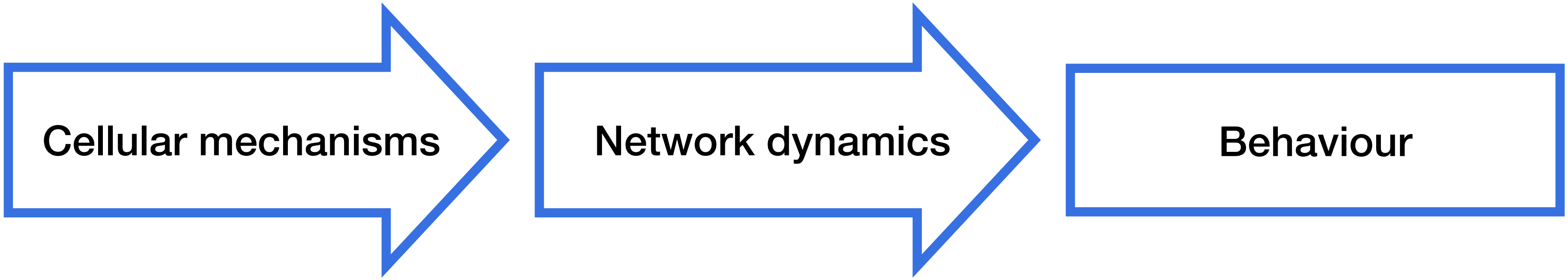
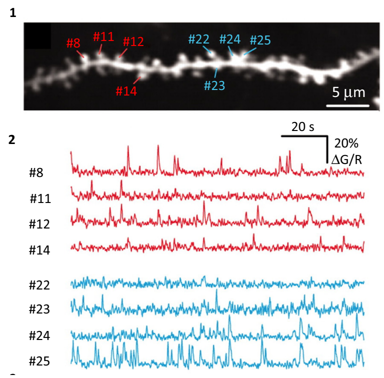
Joint work with Jan-Matthis Lueckmann, Michael Deistler, Marcel Nonnenmacher, Giacomo Bassetto, Kaan Öcal, David Greenberg, Jakob H. Macke

caesar
center of advanced european studies and research

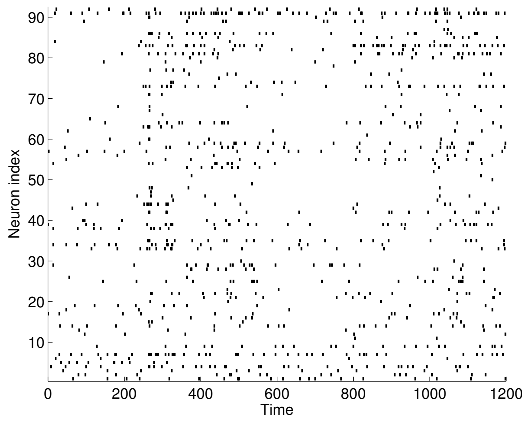
EBERHARD KARLS UNIVERSITÄT TÜBINGEN

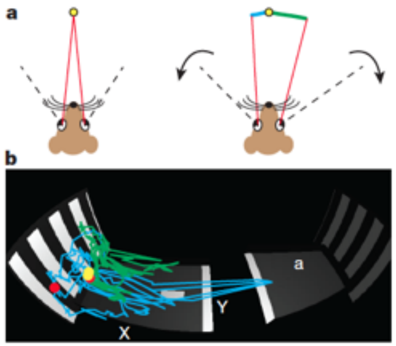
SFB 1089


Cellular mechanisms
Network dynamics
Behaviour



Takahashi et al 2012



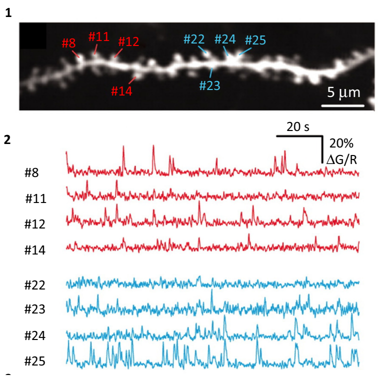


Wallace, Greenberg, Sawinsinki et al 2013

Cellular mechanisms

Network dynamics

Behaviour



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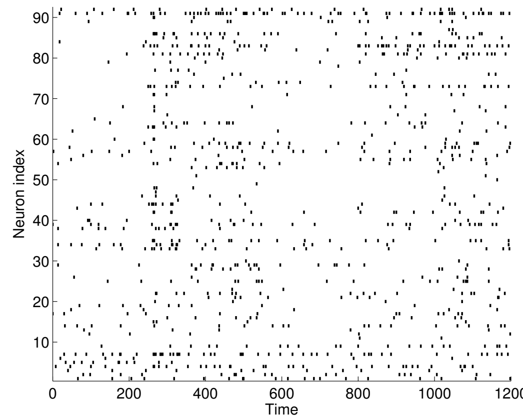
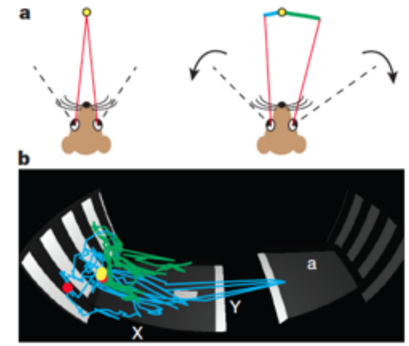
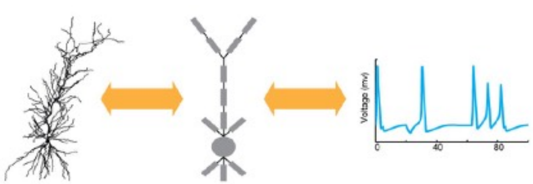




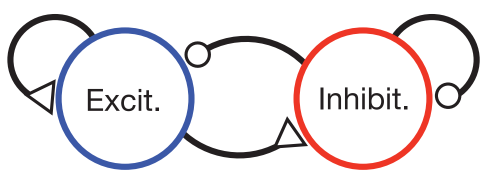
Wallace, Greenberg, Sawinsinki et al 2013

Cellular mechanisms → **Network dynamics** → **Behaviour**

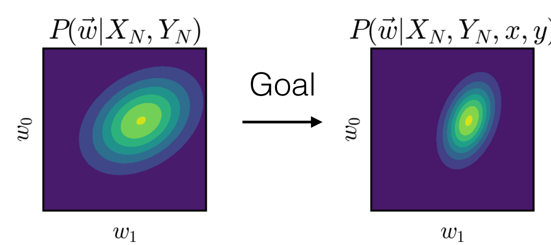
$$C\frac{\dot{V}(t)}{dt} = \sum_c \bar{g}_c g_c(t)[E_c - V(t)] + I(t)$$



$$\tau_m \frac{dV_i}{dt} = V_{rest} - V_i + RI_i(t)$$



$$\arg\max_{\boldsymbol{x}} \mathrm{H}[\boldsymbol{\theta}|\mathcal{D}] - \mathbb{E}_{y\sim p(y|\boldsymbol{x}\mathcal{D})}\left[\mathrm{H}[\boldsymbol{\theta}|y, \boldsymbol{x}, \mathcal{D}]\right]$$



Mechanistic models vs. Statistical/ML models

Hodgkin-Huxley model

Multi-compartment model

Conductance-based LIF

Balanced networks

Biophysical network simulations

Mechanistic models vs. Statistical/ML models

Mechanistic models

- Hodgkin-Huxley model
- Multi-compartment model
- Conductance-based LIF
- Balanced networks
- Biophysical network simulations

Statistical/ML models

- Generalized linear models
- RNNs
- Maximum Entropy models
- Gaussian Process Factor Analysis
- Deep Nets

Mechanistic models vs. Statistical/ML models

Hodgkin-Huxley model

Multi-compartment

- designed using mechanistic principles

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- built with statistical convenience in mind

Analysis

Deep Nets

Mechanistic models vs. Statistical/ML models

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Generalized linear models

RNNs

- built with statistical convenience in mind
- can be directly fit to data

Analysis

Deep Nets

How can we make statistical inference tractable for mechanistic models of neural dynamics?

How can we make statistical inference tractable for mechanistic models of neural dynamics?

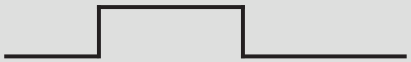
1) An algorithm
2) A couple of applications

Bayesian inference: finding parameters of a model which are consistent with data and prior knowledge

model

$$C_m \frac{dV}{dt} = \sum_c \bar{g}_c g_c [E_c - V] + I$$

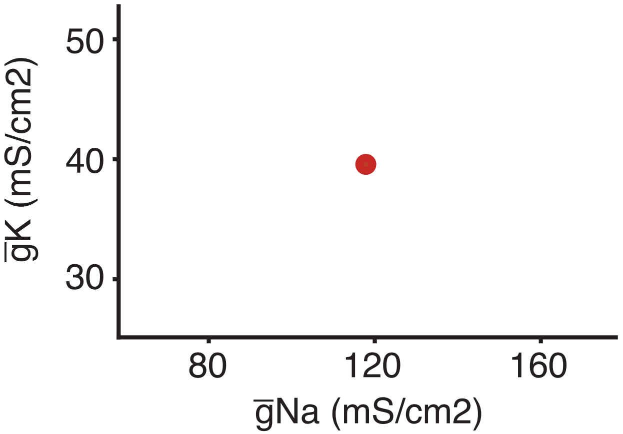
input (e.g. step current)



Bayesian inference: finding parameters of a model which are consistent with data and prior knowledge

parameters

$$\theta = [\bar{g}_{Na}, \bar{g}_K, ...]$$



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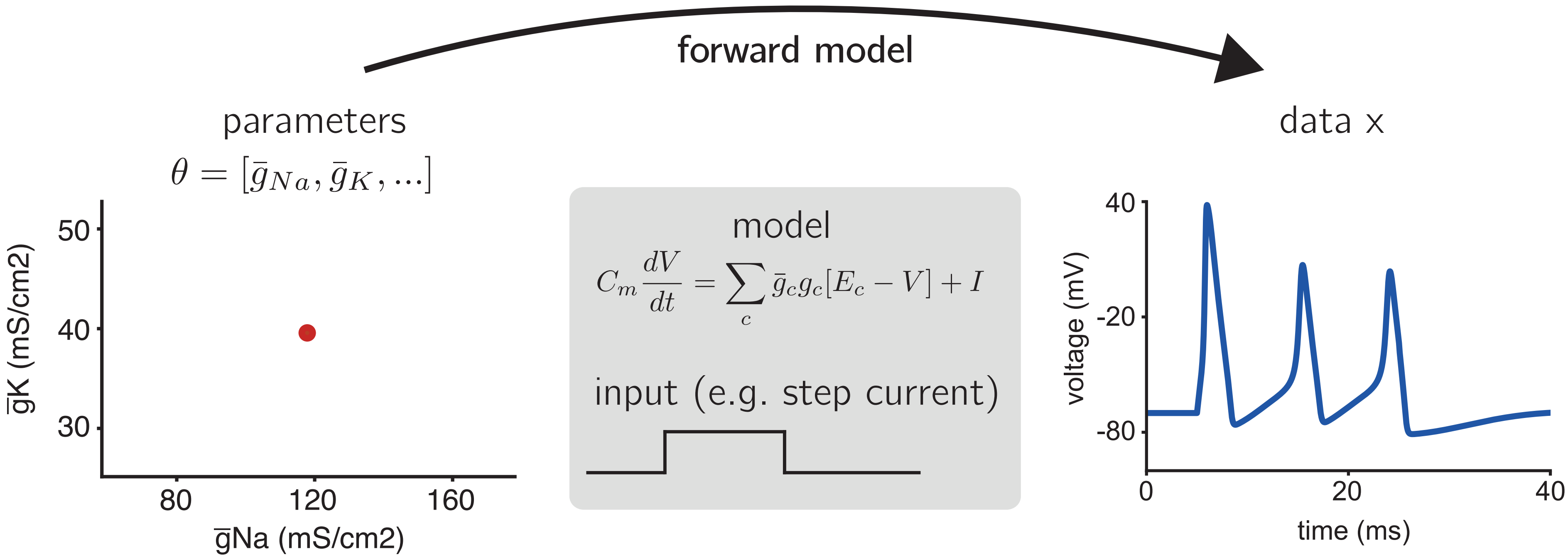
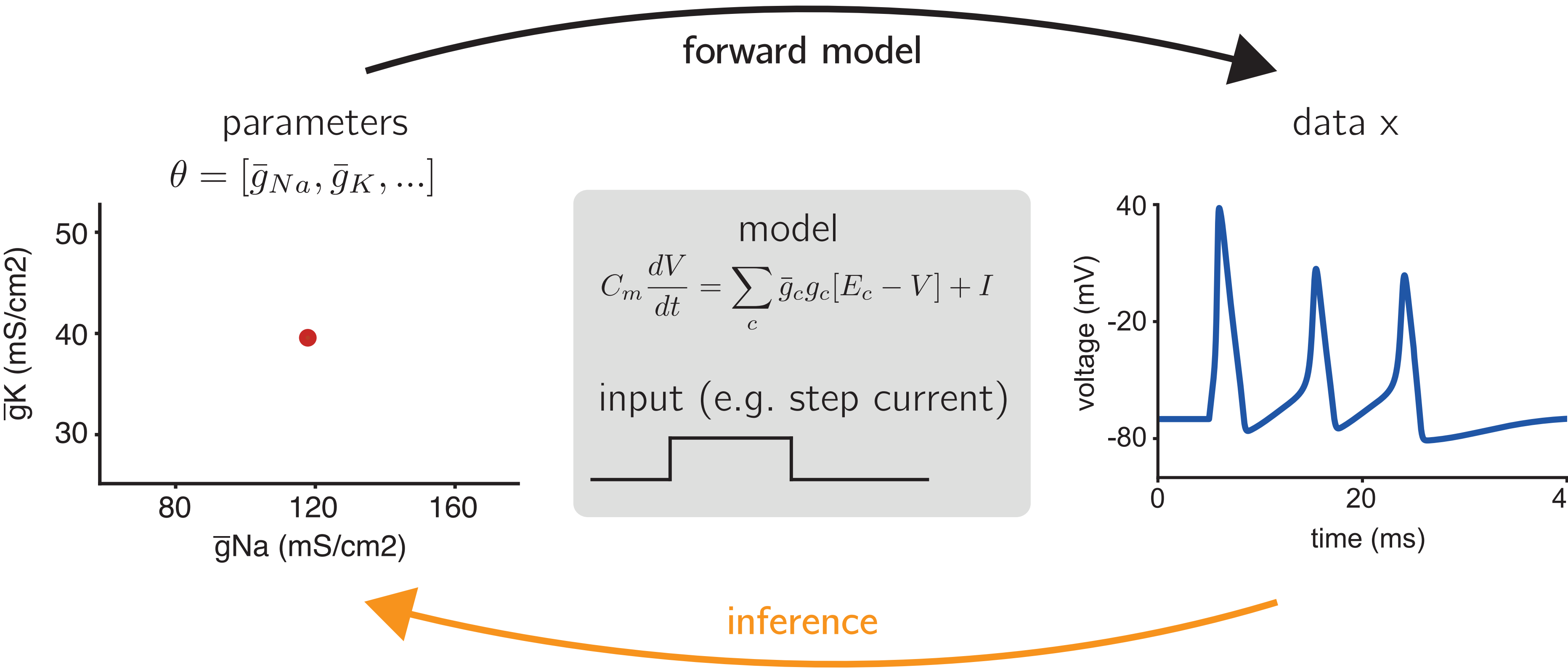


Bayesian inference: finding parameters of a model which are consistent with data and prior knowledge



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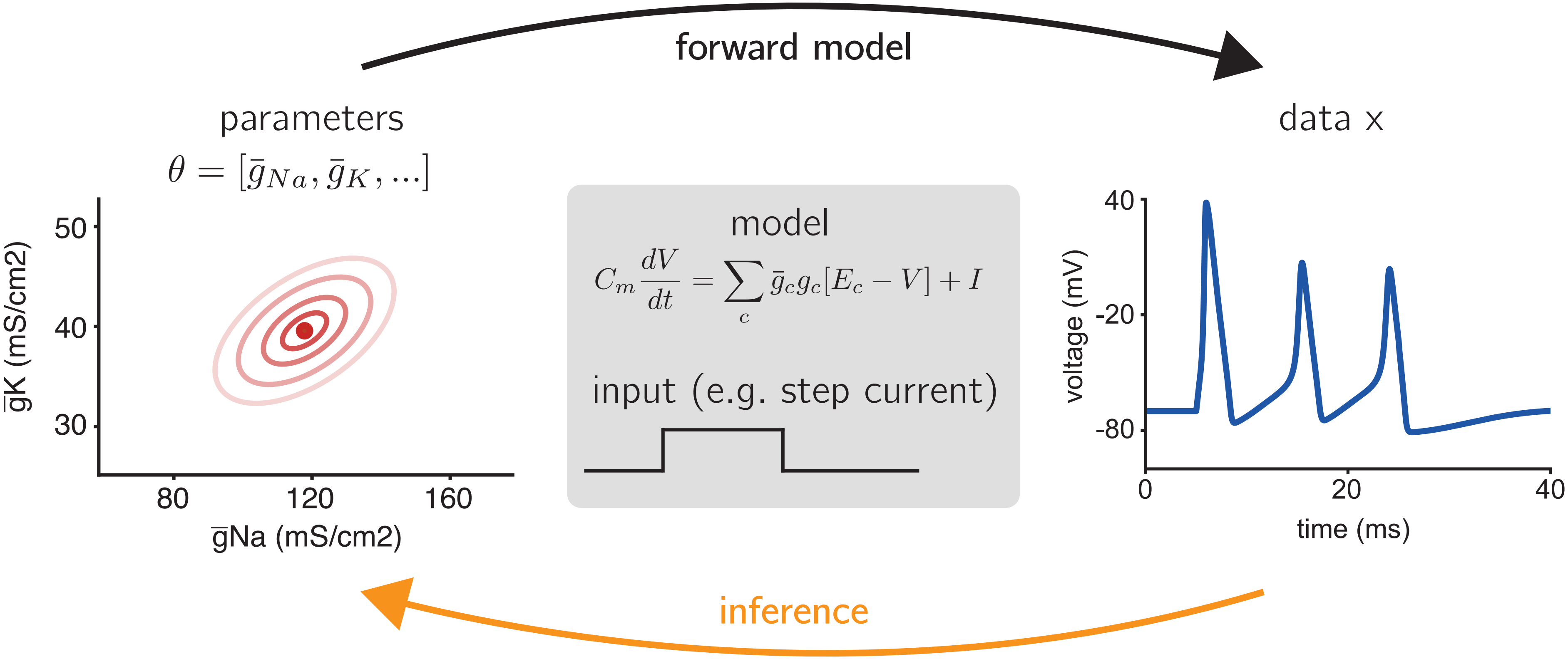

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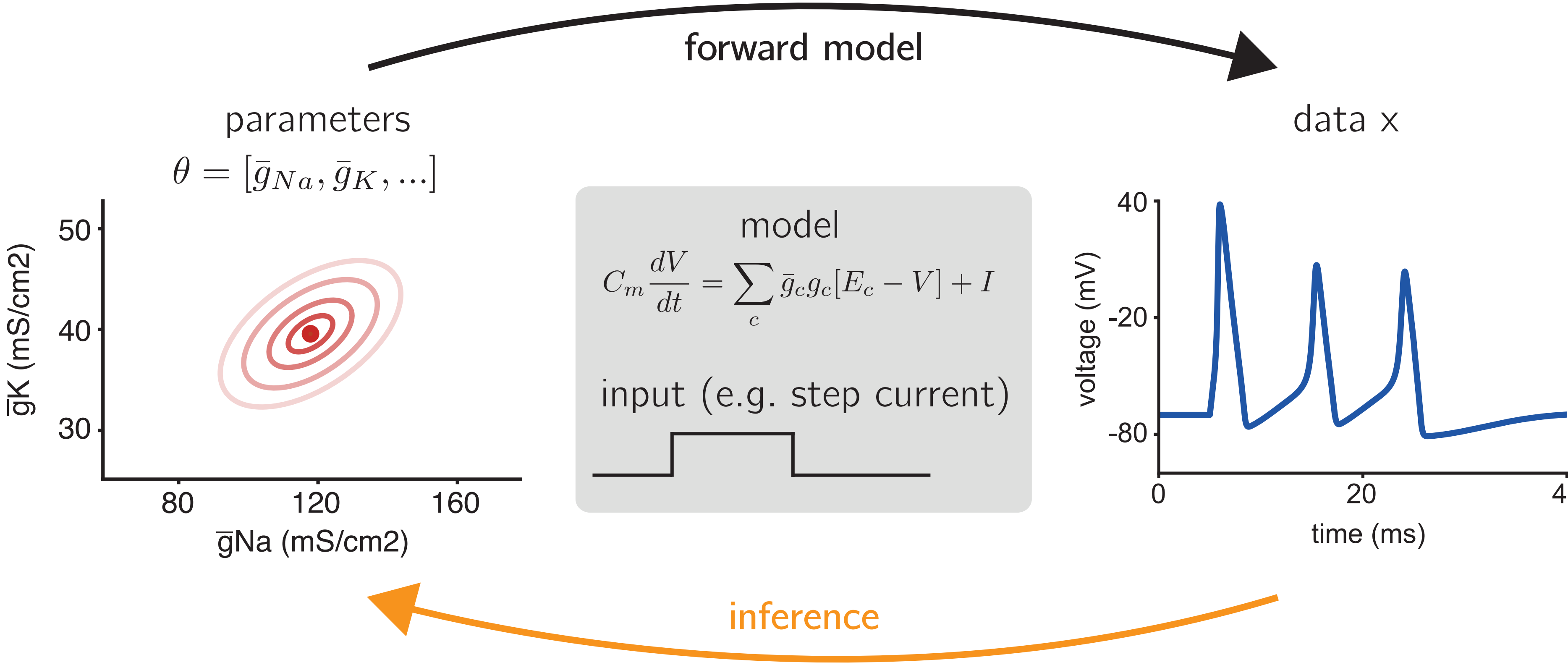
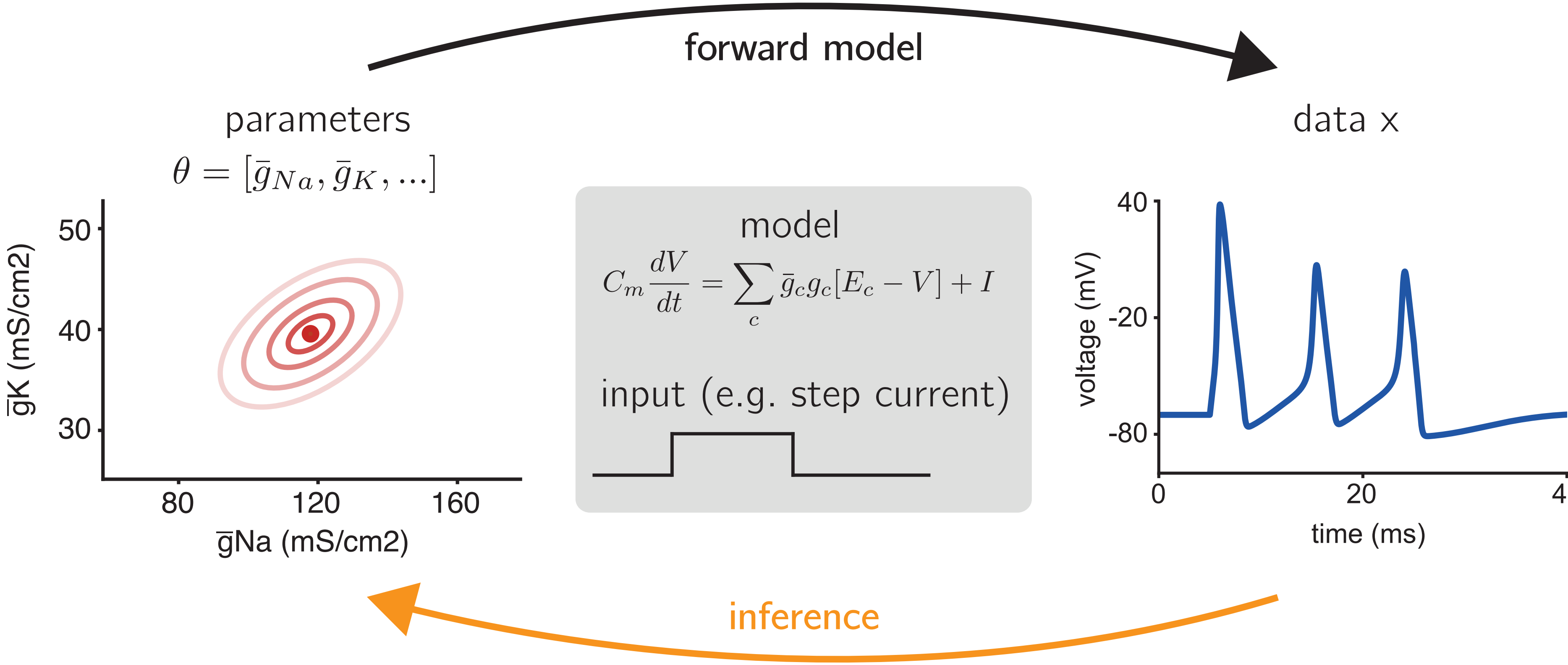


posterior distribution: $p(\theta|x) \propto p(x|\theta)p(\theta)$

Bayesian inference: finding parameters of a model which are consistent with data and prior knowledge



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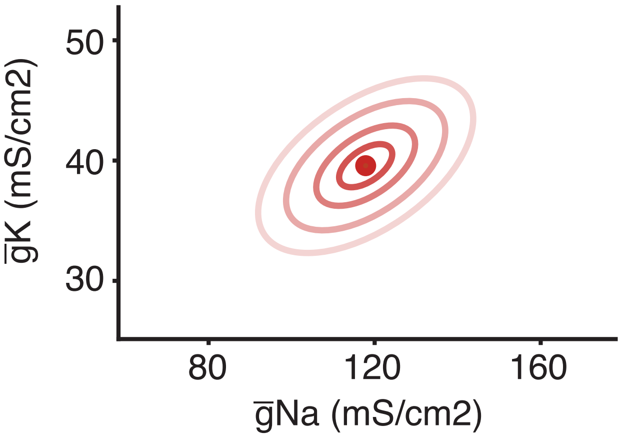
Challenging! Simulation-based inference comes to the rescue

Bayesian inference in simulation based models



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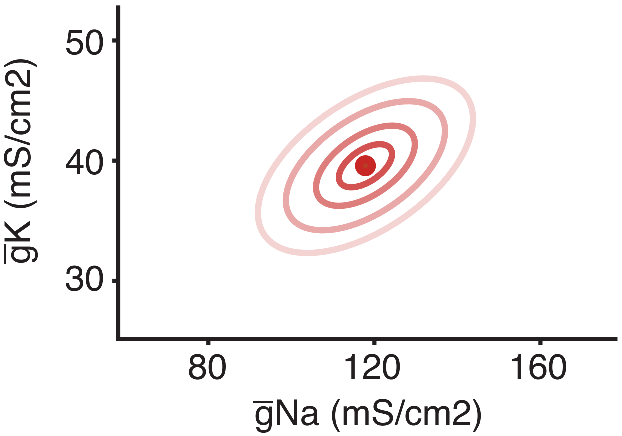
Bayesian inference in simulation based models



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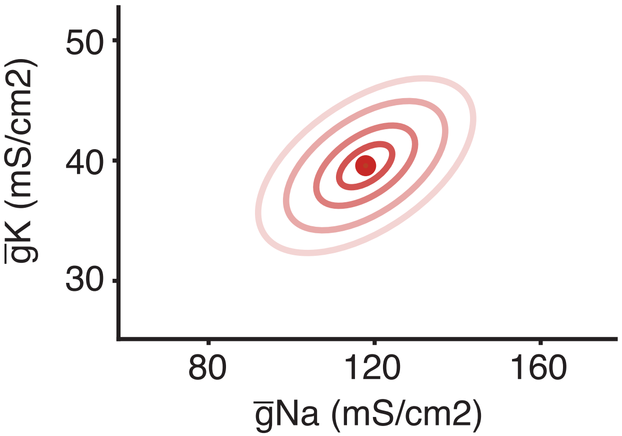
Bayesian inference in simulation based models



$$p(\theta|x) \propto p(x|\theta)p(\theta)$$

likelihood: often not tractable

posterior: hard to compute

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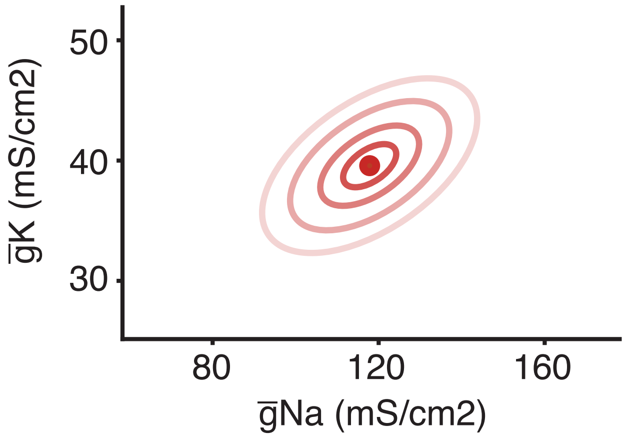

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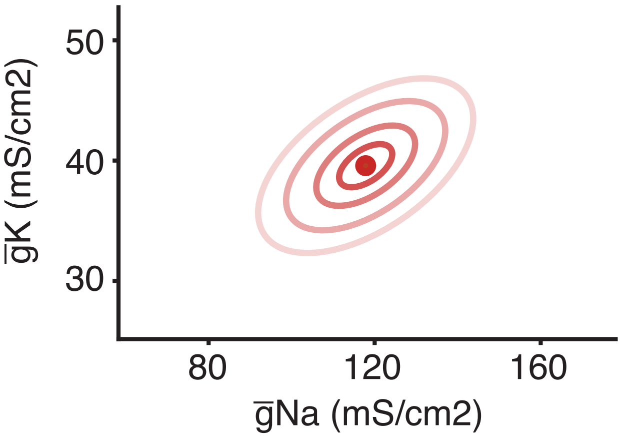
For ‘simulation based’ models (and neuroscience models in particular), we can simulate x, but we cannot evaluate the likelihood **p(x|θ)**.

Bayesian inference in simulation based models



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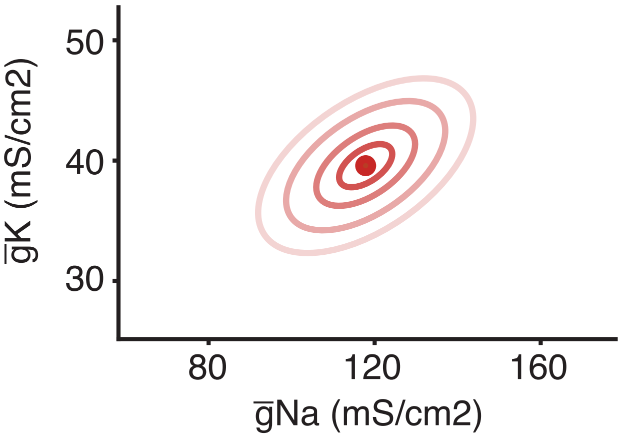
How can we do **Bayesian inference**, if all we have is a **simulator**, but **no explicit likelihoods**?

Bayesian inference in simulation based models



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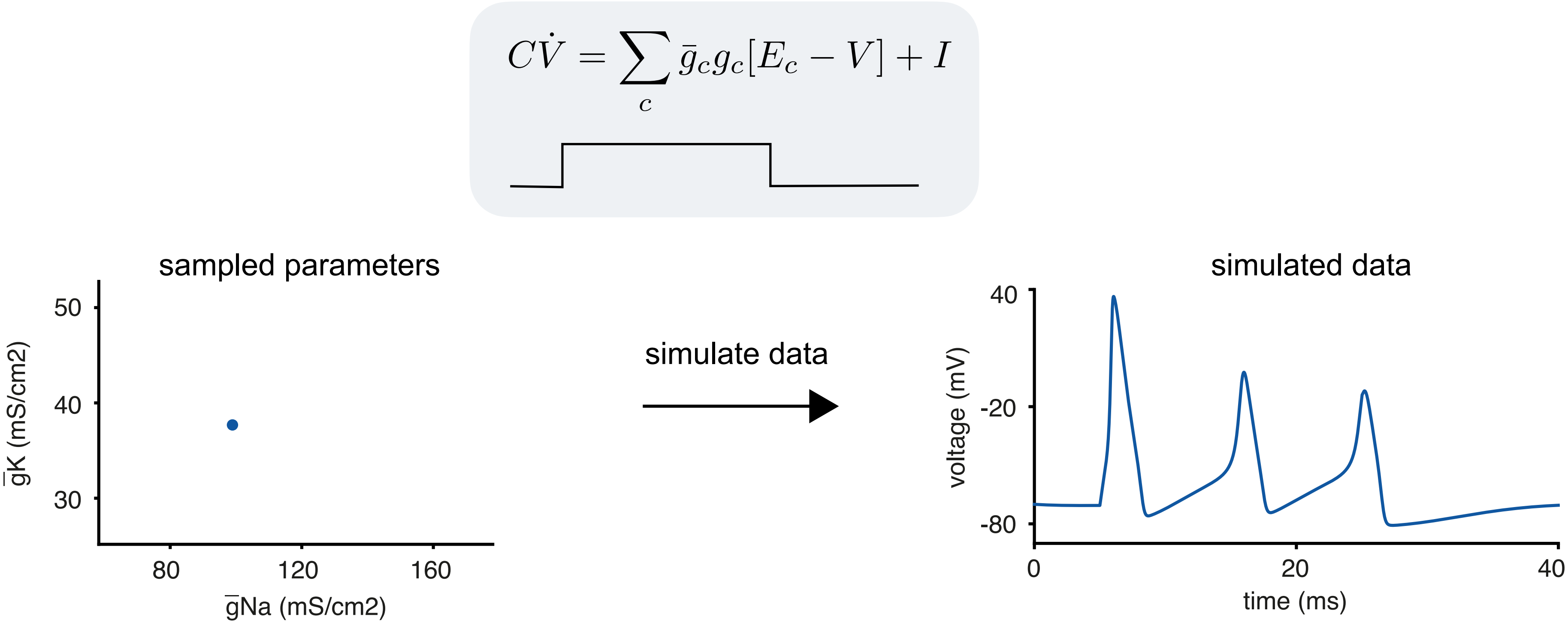
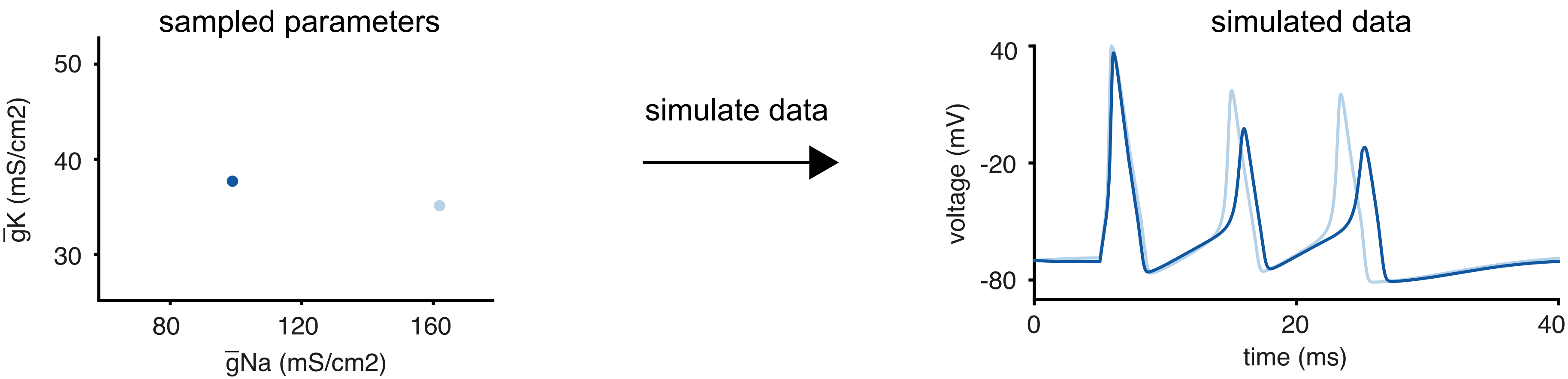
Likelihood-free Bayesian Inference or Approximate Bayesian Computation (ABC)
Blum & Francois 2010, Papamakarios & Murray 2016

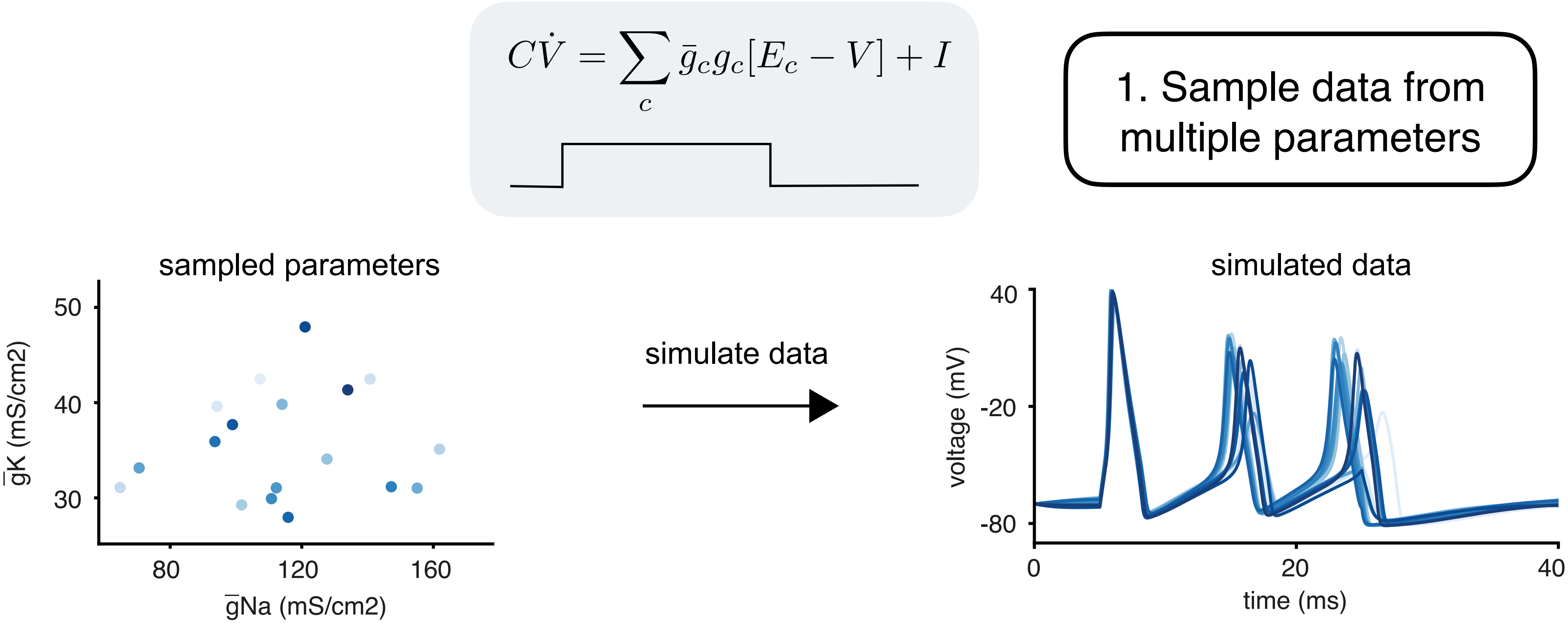
$$C\dot{V} = \sum_c \bar{g}_c g_c [E_c - V] + I$$


$C\dot{V} = \sum_c \bar{g}_c g_c [E_c - V] + I$
sampled parameters
50
40
30
80
120
160
$\bar{g}$K (mS/cm2)
$\bar{g}$Na (mS/cm2)
simulate data
simulated data
40
-20
-80
voltage (mV)
0
20
40
time (ms)

$$C\dot{V} = \sum_c \bar{g}_c g_c [E_c - V] + I$$

1. Sample data from multiple parameters





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sampled parameters
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50
40
30
80
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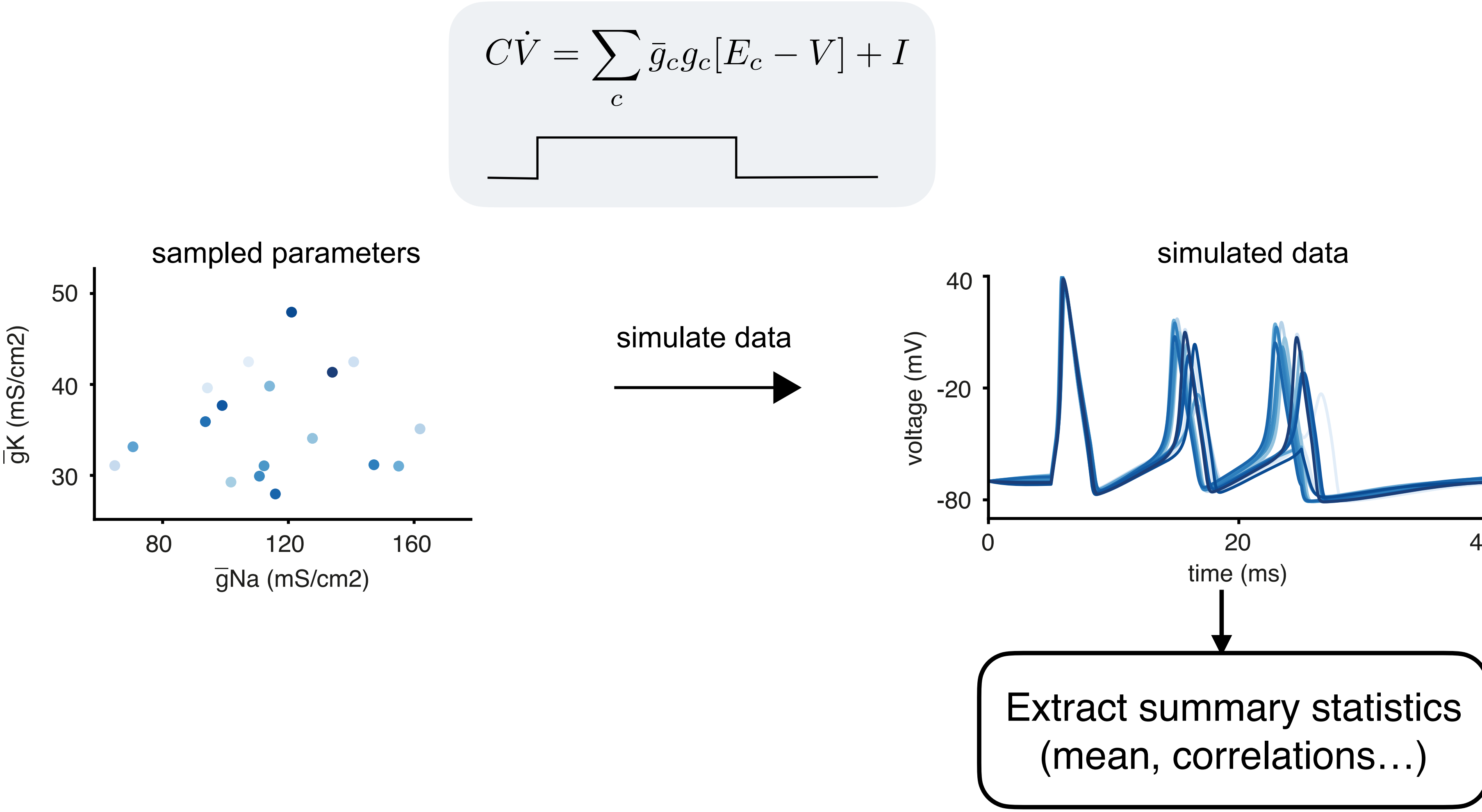
160
$\bar{g}$Na (mS/cm2)
simulate data
simulated data
voltage (mV)
40
-20
-80
0
20
40
time (ms)


$C\dot{V} = \sum_c \bar{g}_c g_c [E_c - V] + I$
sampled parameters
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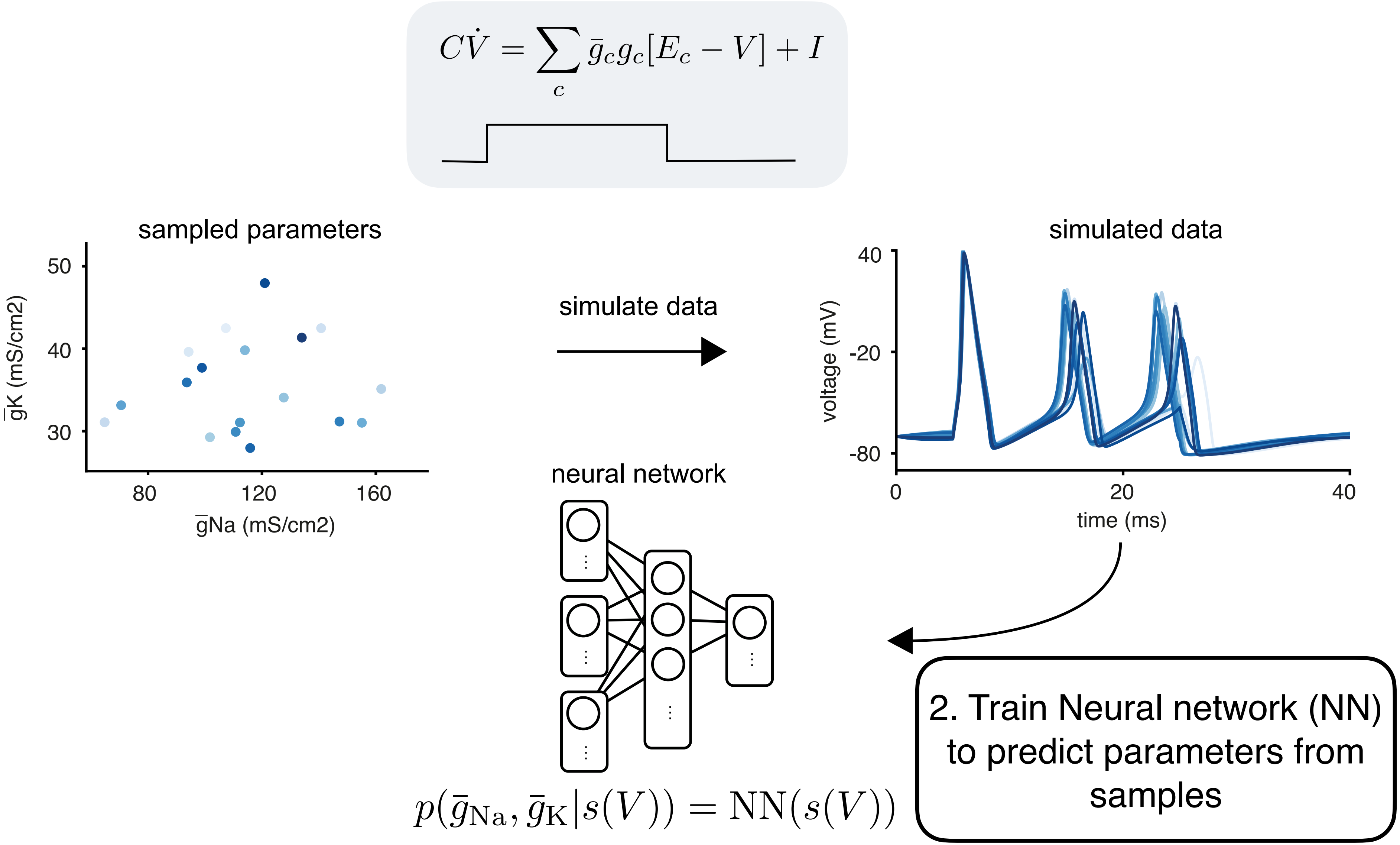
$\bar{g}$Na (mS/cm2)
simulate data
simulated data
40
-20
-80
voltage (mV)
0
20
40
time (ms)
Extract summary statistics
(mean, correlations…)



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simulated data
40
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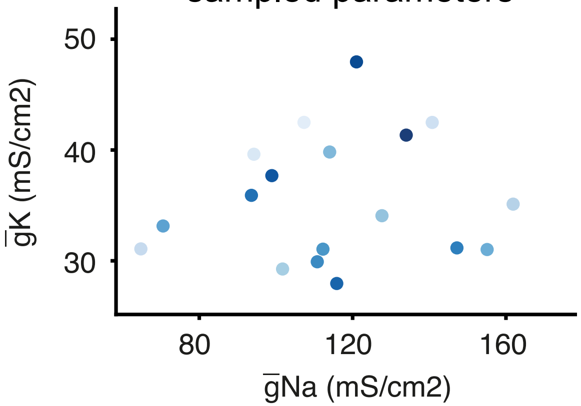
-80
voltage (mV)
0
20
40
time (ms)
neural network
$p(\bar{g}_{\mathrm{Na}}, \bar{g}_{\mathrm{K}} | s(V)) = \mathrm{NN}(s(V))$
2. Train Neural network (NN) to predict parameters from samples

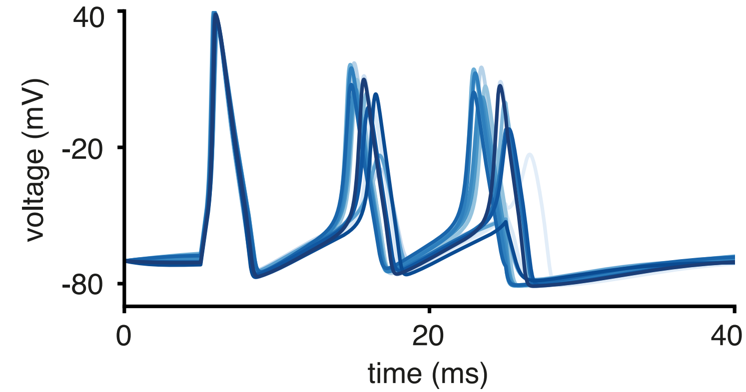
$$C\dot{V} = \sum_c \bar{g}_c g_c [E_c - V] + I$$

sampled parameters

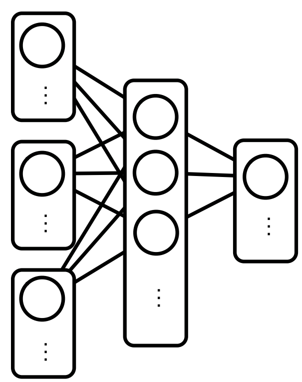


simulate data

simulated data



neural network

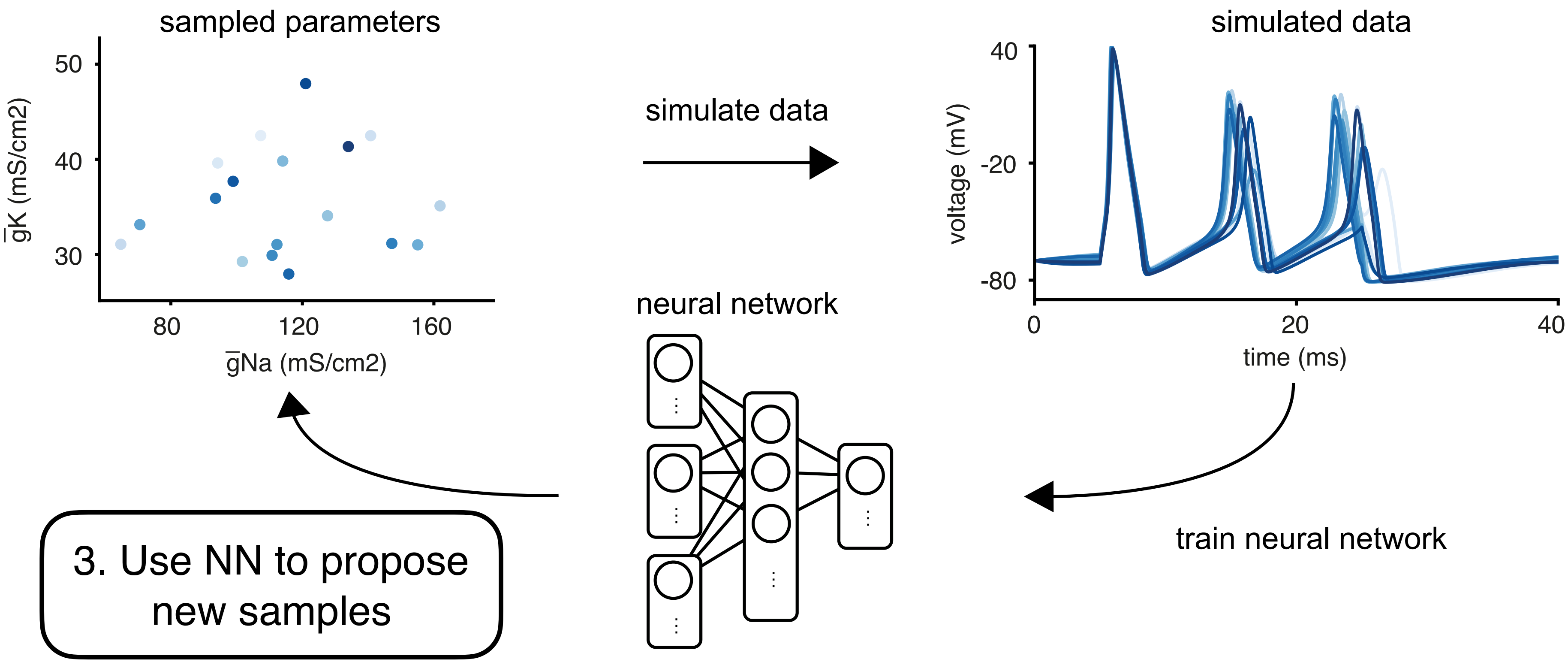


$$p(\bar{g}_{\mathrm{Na}}, \bar{g}_{\mathrm{K}} | s(V)) = \mathrm{NN}(s(V))$$

2. Train Neural network (NN) to predict parameters from samples

$$\boxed{p(\bar{g}_{\mathrm{Na}}, \bar{g}_{\mathrm{K}} | s(V_o)) = \mathrm{NN}(s(V_o))}$$

$$C\dot{V} = \sum_c \bar{g}_c g_c [E_c - V] + I$$



$$p(\bar{g}_{\mathrm{Na}}, \bar{g}_{\mathrm{K}} | s(V)) = \mathrm{NN}(s(V))$$

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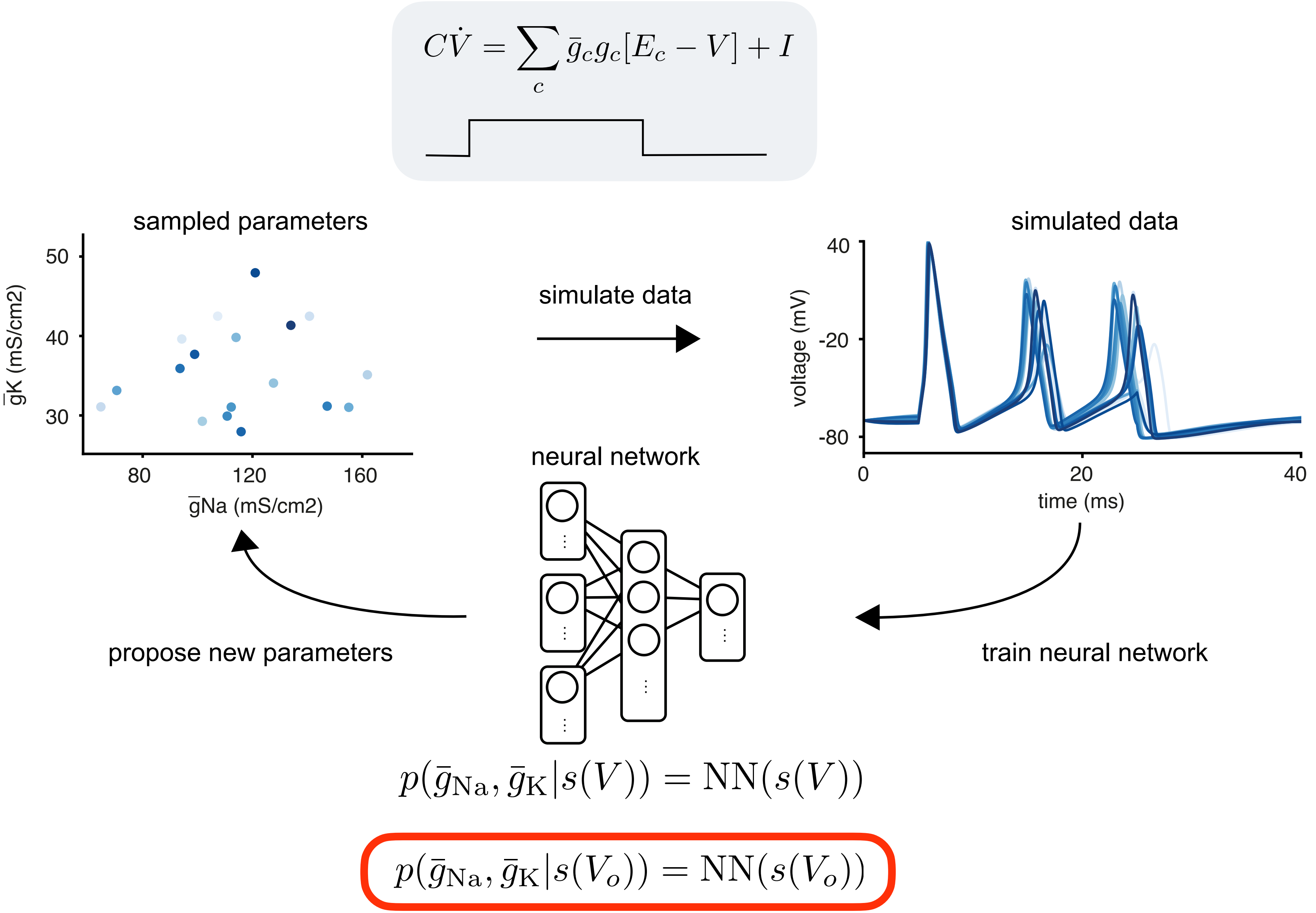
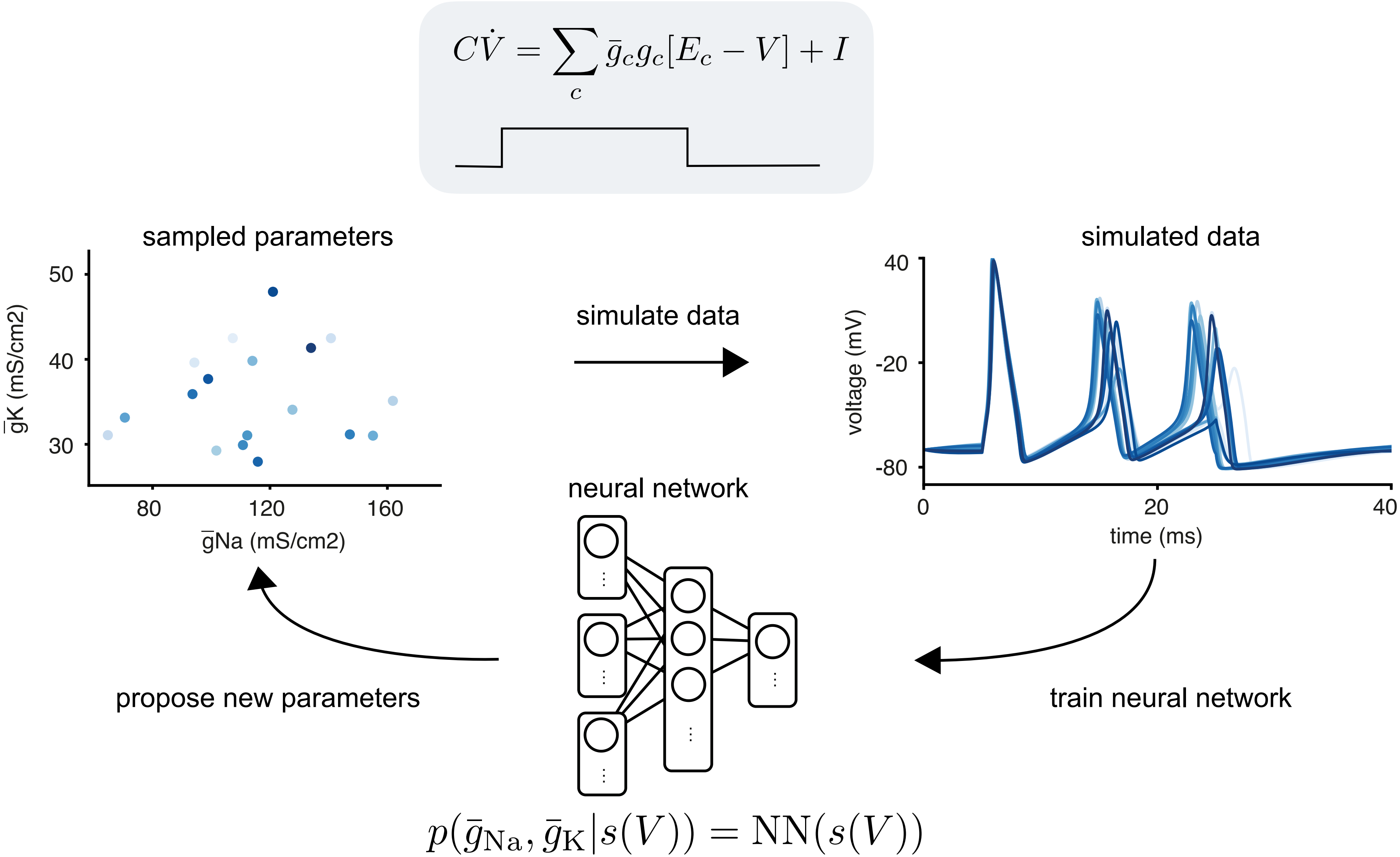


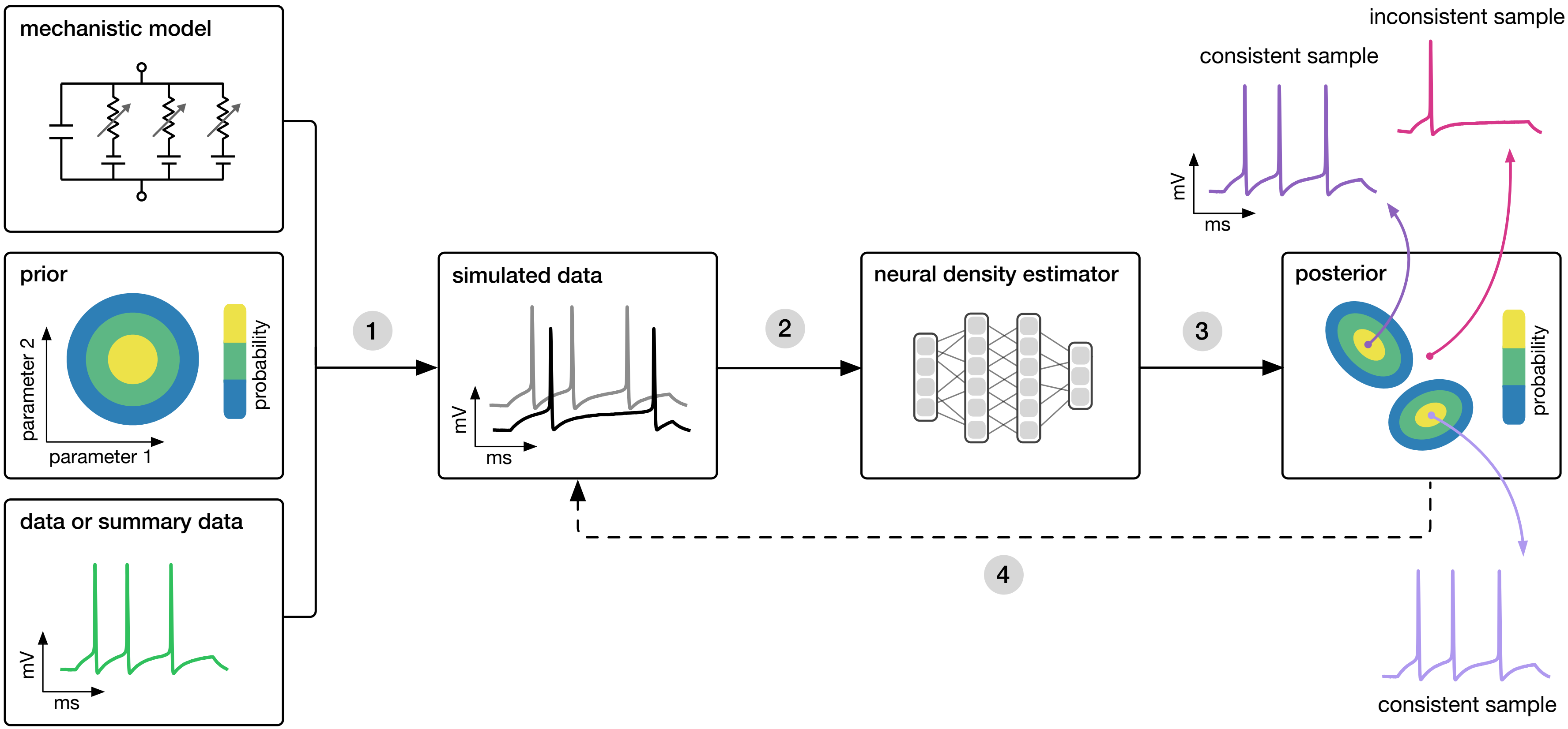
Sequential Neural Posterior Estimation, SNPE



JM Lückmann*, PJ Goncalves* et al, NeurIPS 2017

PJ Goncalves*, JM Lückmann*, M. Deistler* et al (2020) eLife

github.com/mackelab/delfi; https://www.mackelab.org/sbi/



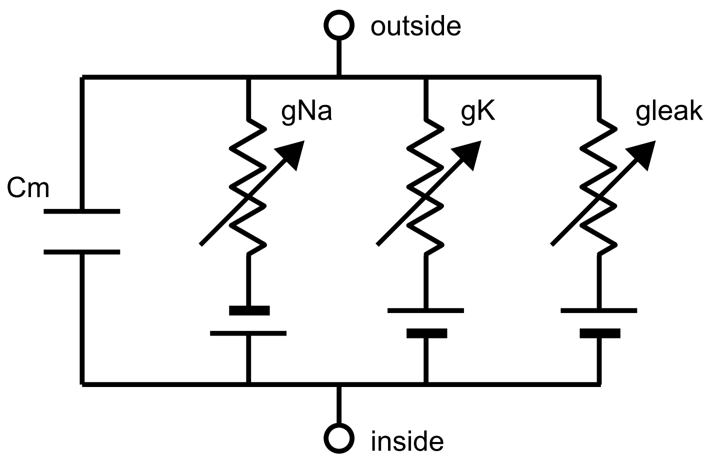
mechanistic model
prior
parameter 2
parameter 1
probability
data or summary data
mV
ms
1
simulated data
mV
ms
2
neural density estimator
3
posterior
probability
4
inconsistent sample
consistent sample
mV
ms
consistent sample

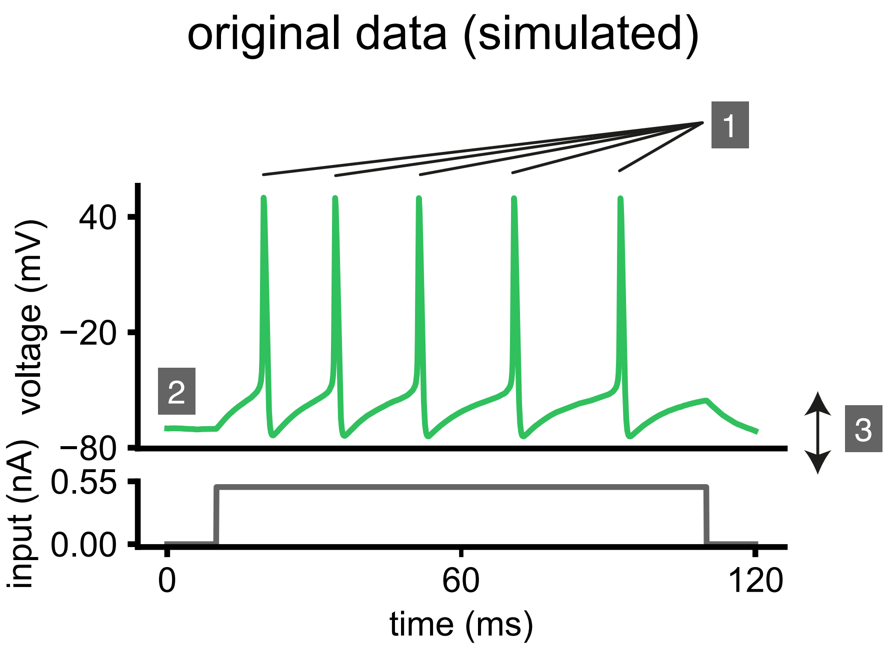
A couple of applications

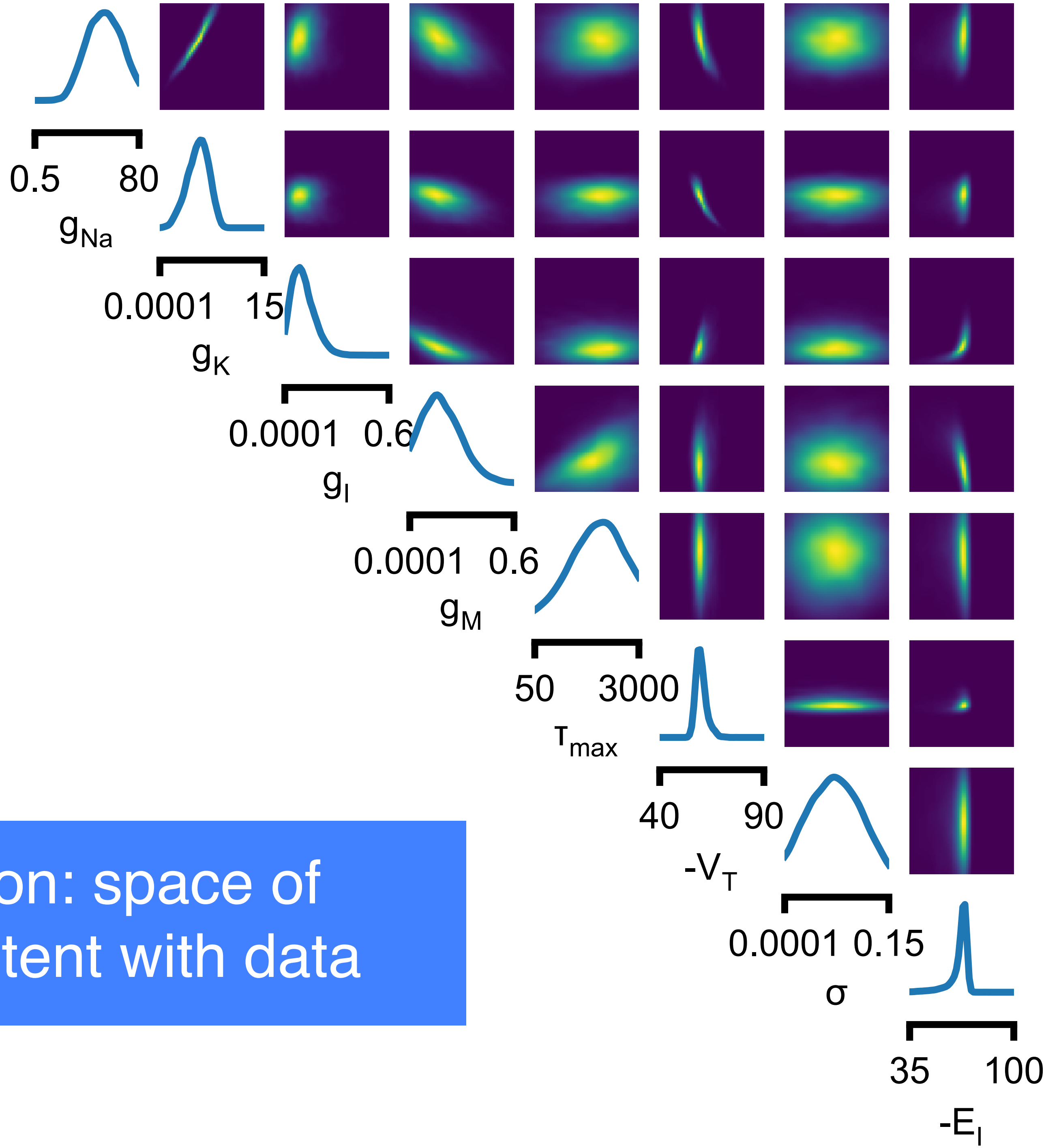
→ Identification of parameters in canonical neural model

→ Sensitivity to perturbations in a neural network model

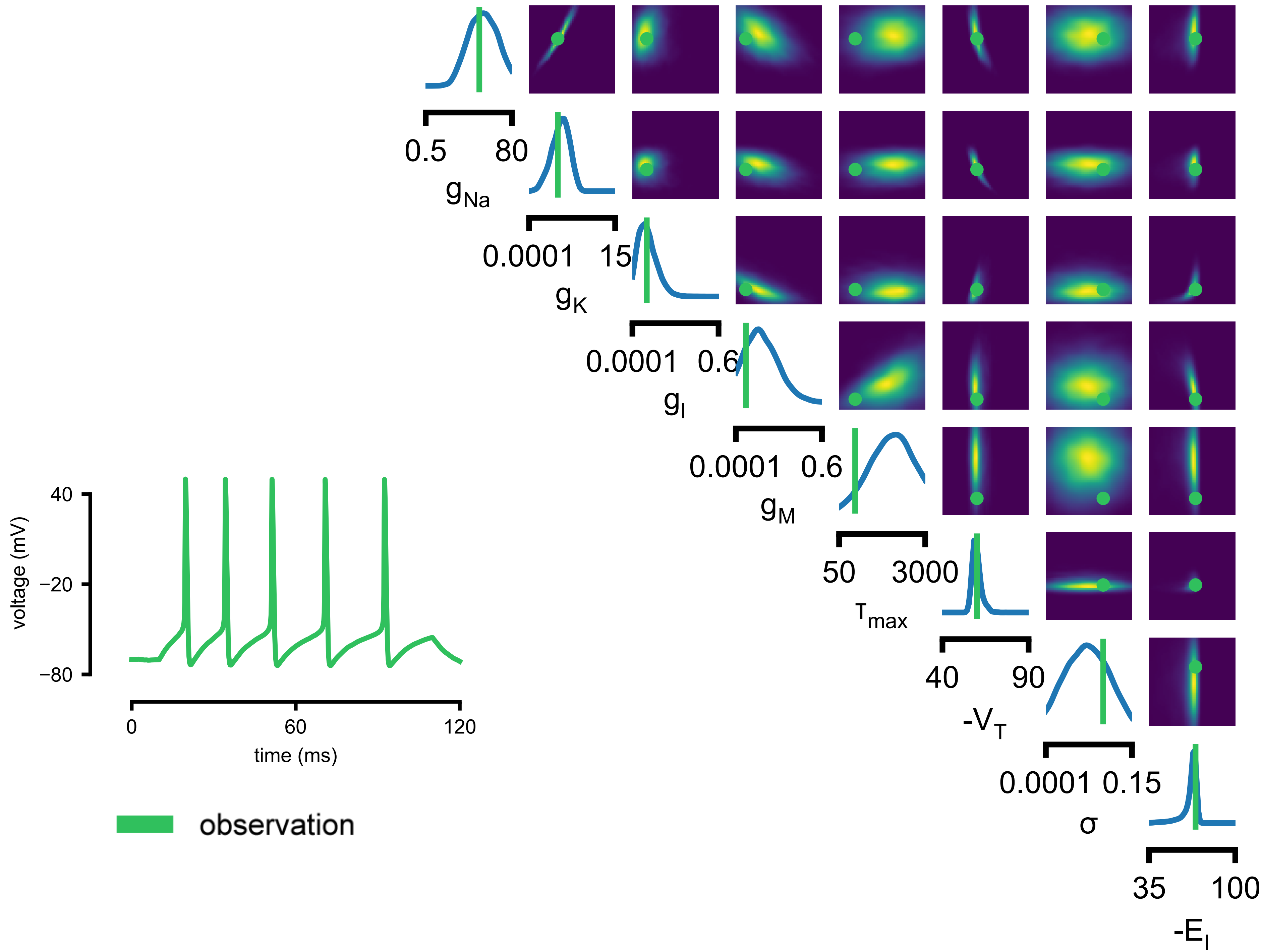
Inference of 8 biophysical parameters in Hodgkin-Huxley models



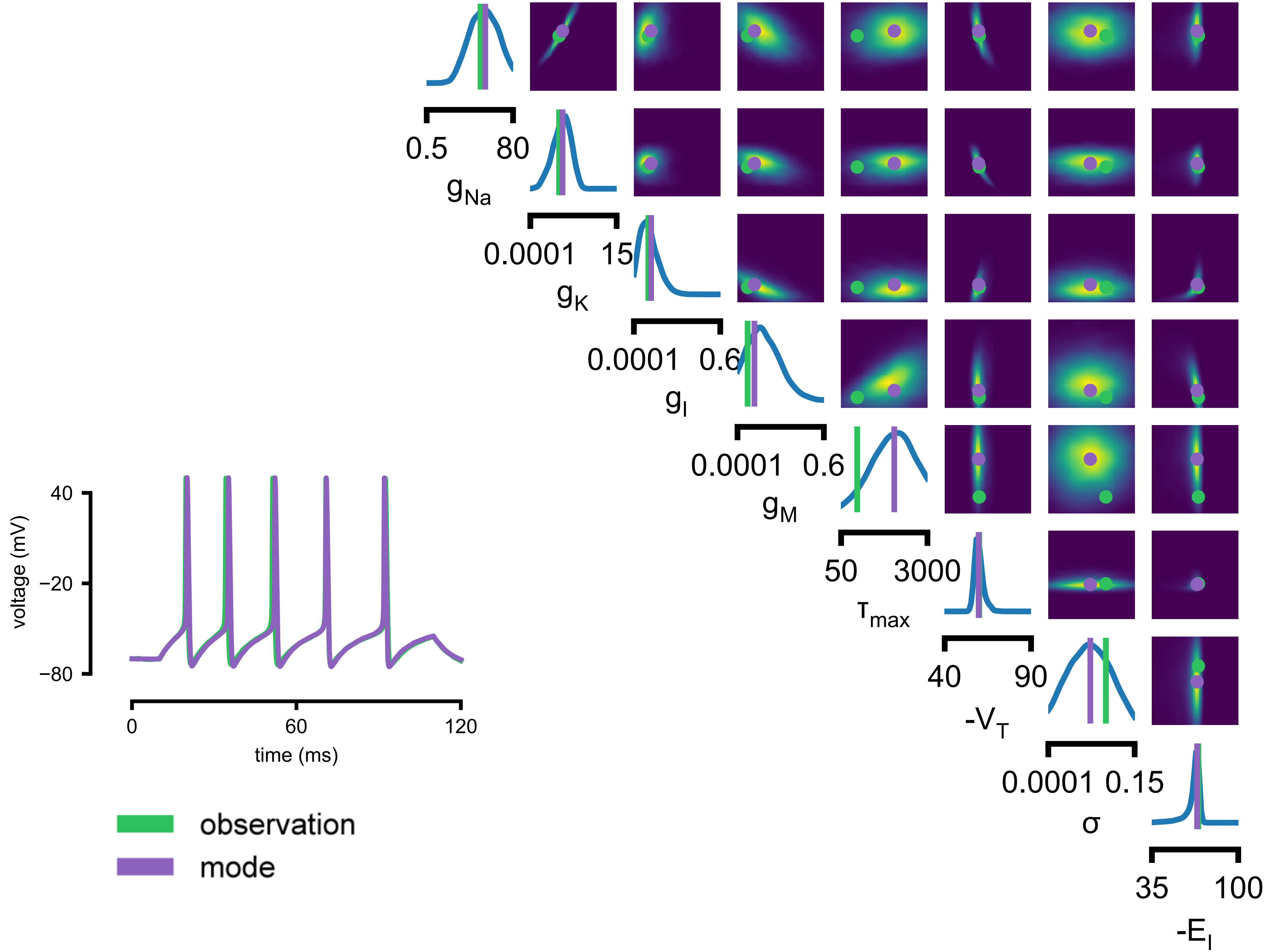




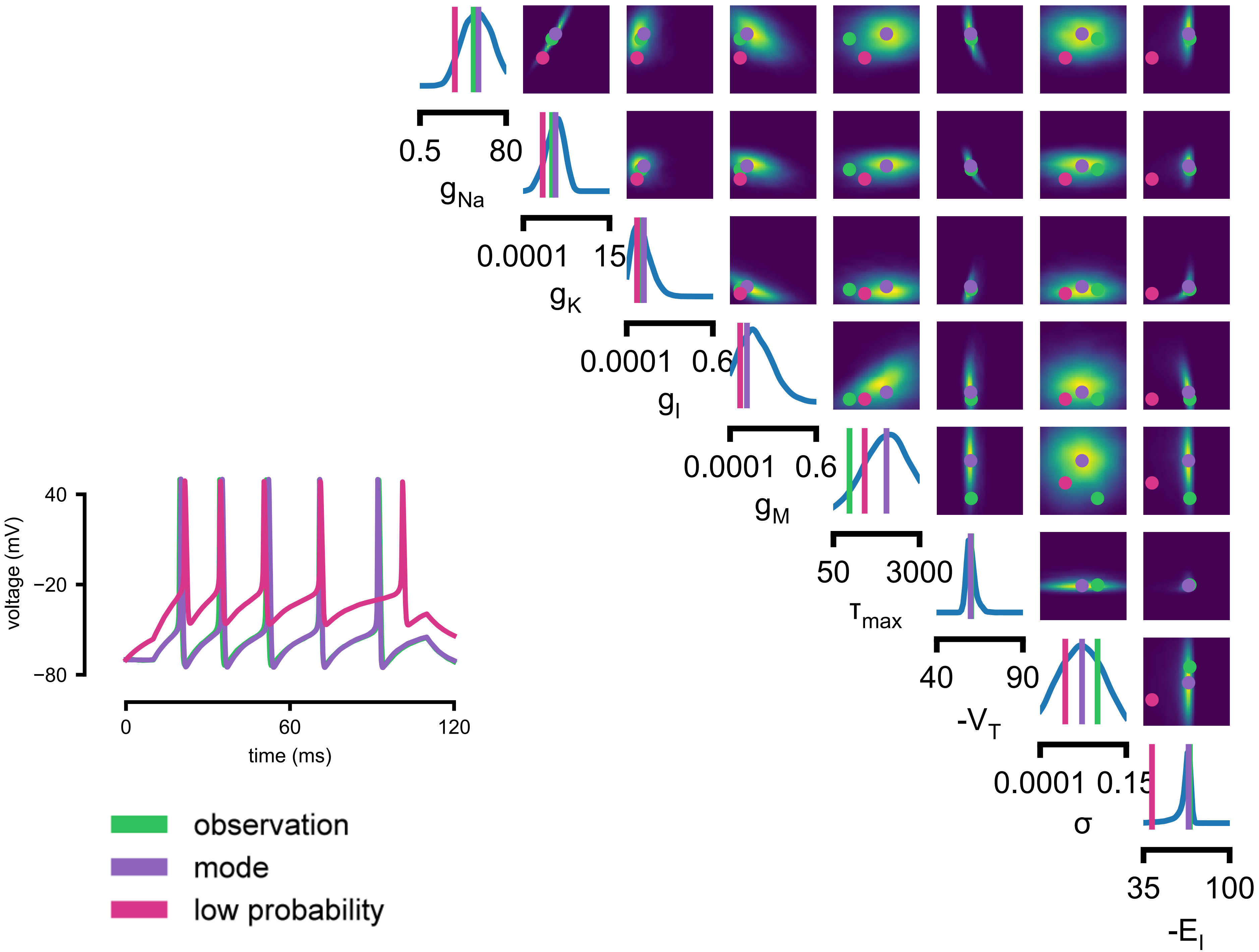
Posterior distribution: space of parameters consistent with data



0.5
80
g_{Na}
0.0001
15
g_K
0.0001
0.6
g_l
0.0001
0.6
g_M
50
3000
τ_{max}
40
90
$-V_T$
0.0001
0.15
σ
35
100
$-E_l$
40
−20
−80
voltage (mV)
0
60
120
time (ms)
observation



0.5
80
g_{Na}
0.0001
15
g_K
0.0001
0.6
g_l
0.0001
0.6
g_M
50
3000
τ_{max}
40
90
$-V_T$
0.0001
0.15
σ
35
100
$-E_l$
40
−20
−80
voltage (mV)
0
60
120
time (ms)
observation
mode


0.5
80
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35
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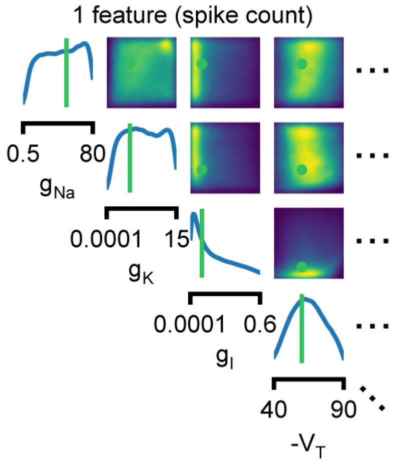
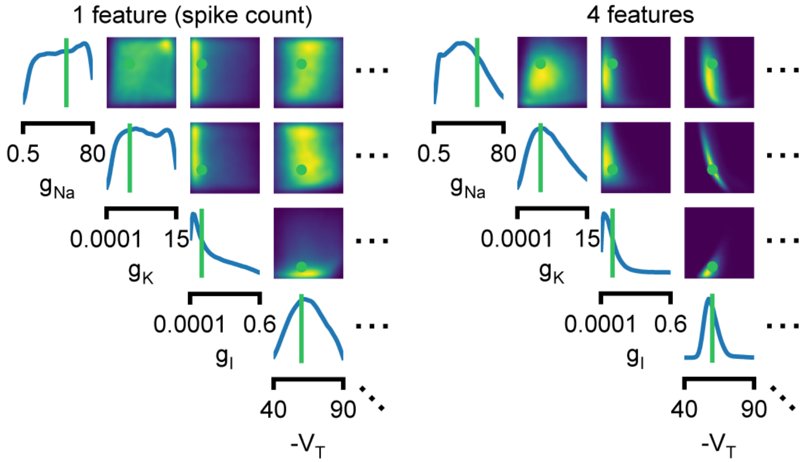
voltage (mV)
40
−20
−80
0
60
120
time (ms)
observation
mode
low probability

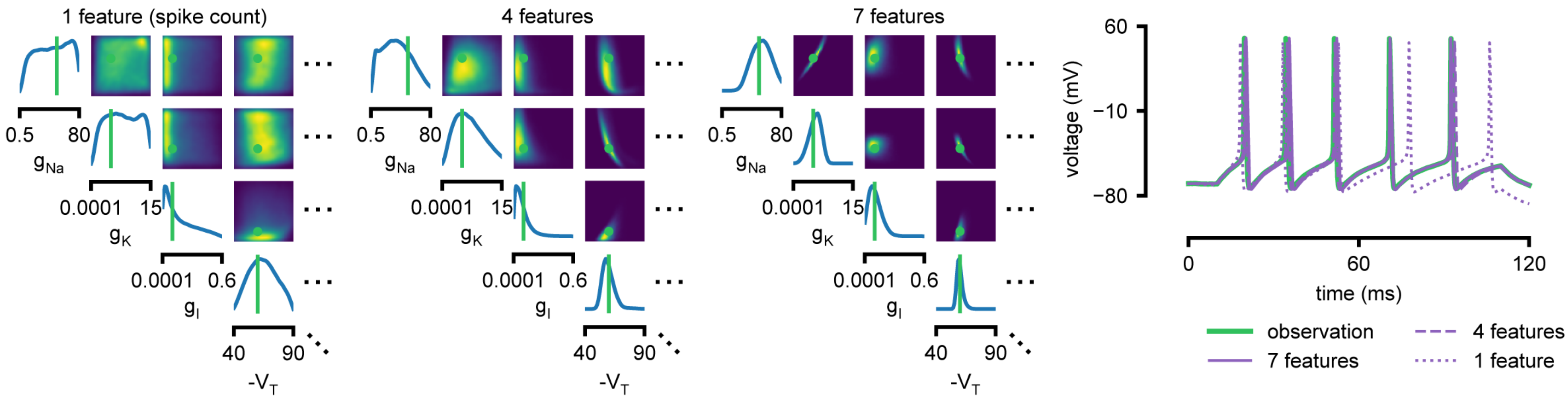
Stronger constraints from additional data features



Stronger constraints from additional data features



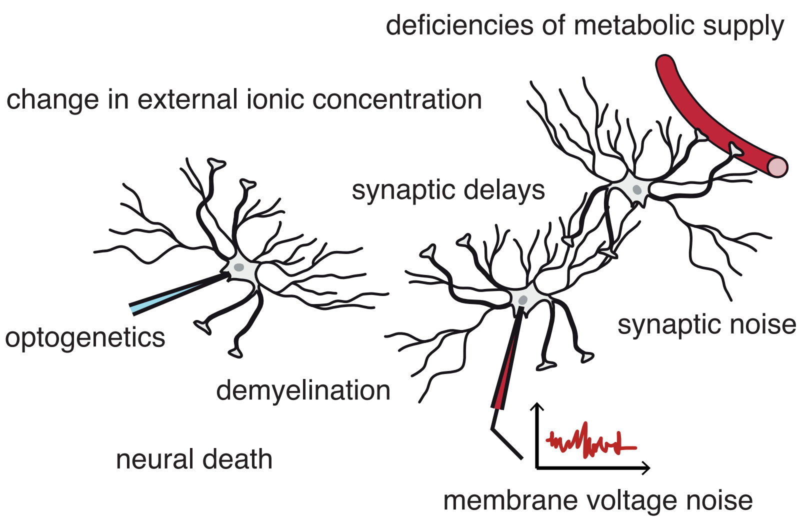
Stronger constraints from additional data features



Sensitivity to perturbations in a neural network model

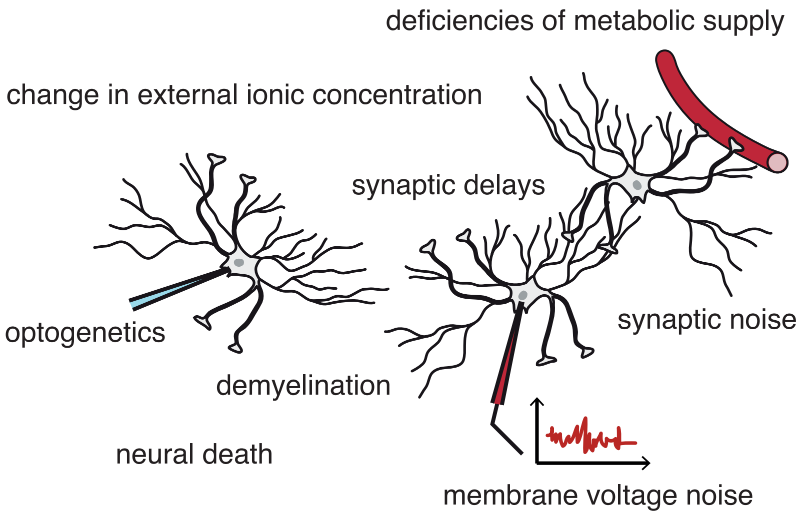
Michael Deistler

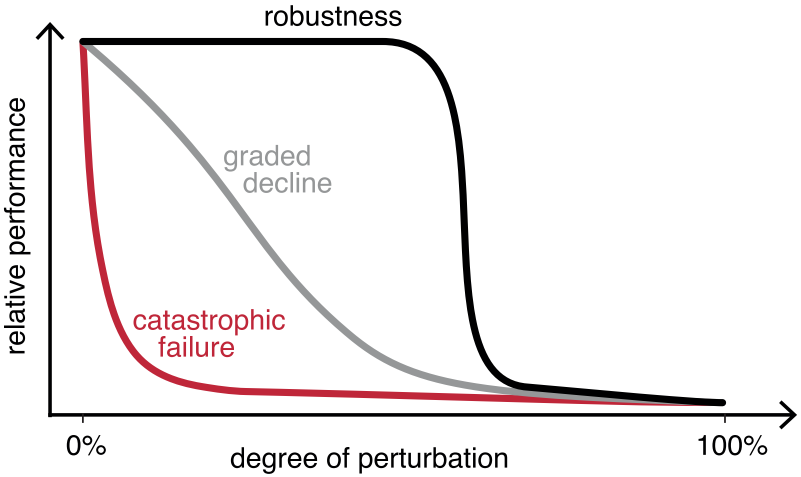
Neural systems operate under multiple perturbations



N Calaim*, FA Dehmelt*, PJ Goncalves*, CK Machens (2021) bioRxiv

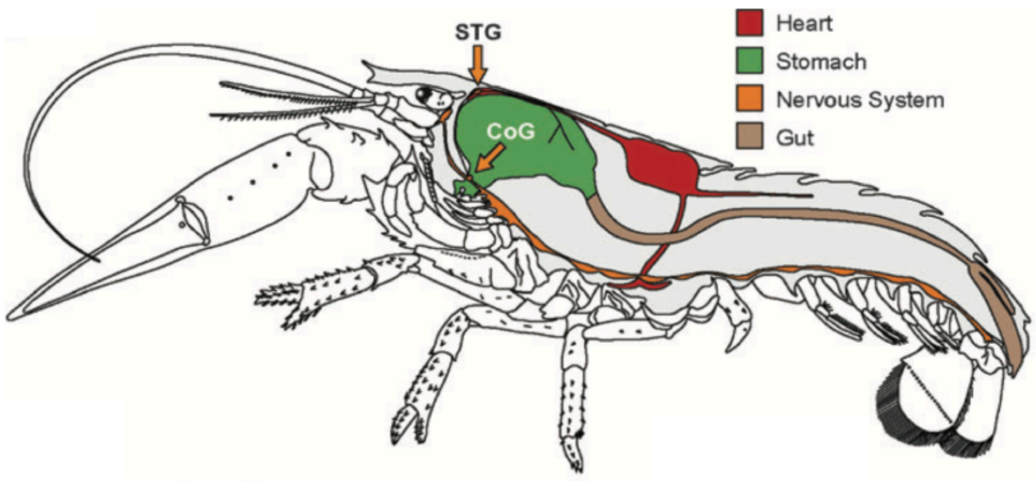
Neural systems operate under multiple perturbations

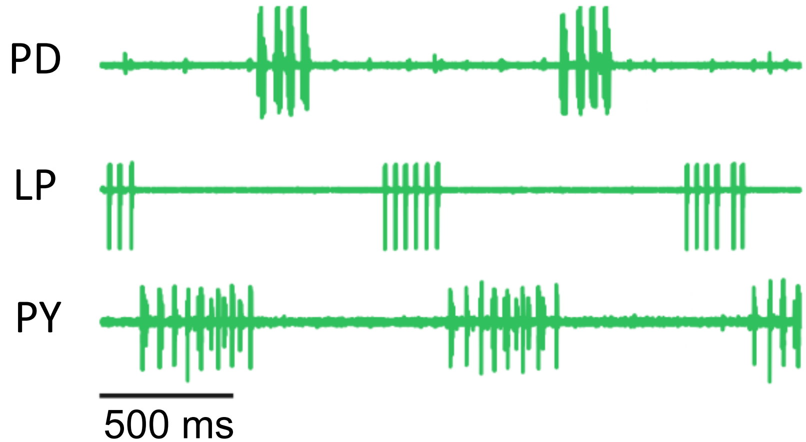




N Calaim*, FA Dehmelt*, PJ Goncalves*, CK Machens (2021) bioRxiv

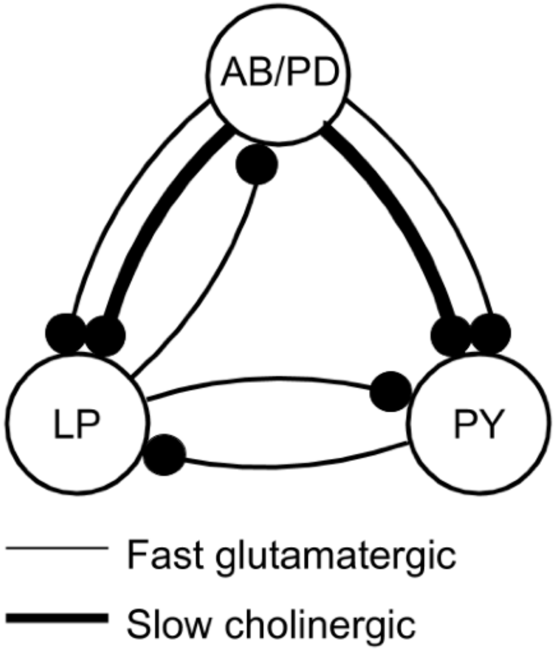
Pyloric network





Marder and Bucher 2007; Haddad and Marder 2018

Model of the pyloric network

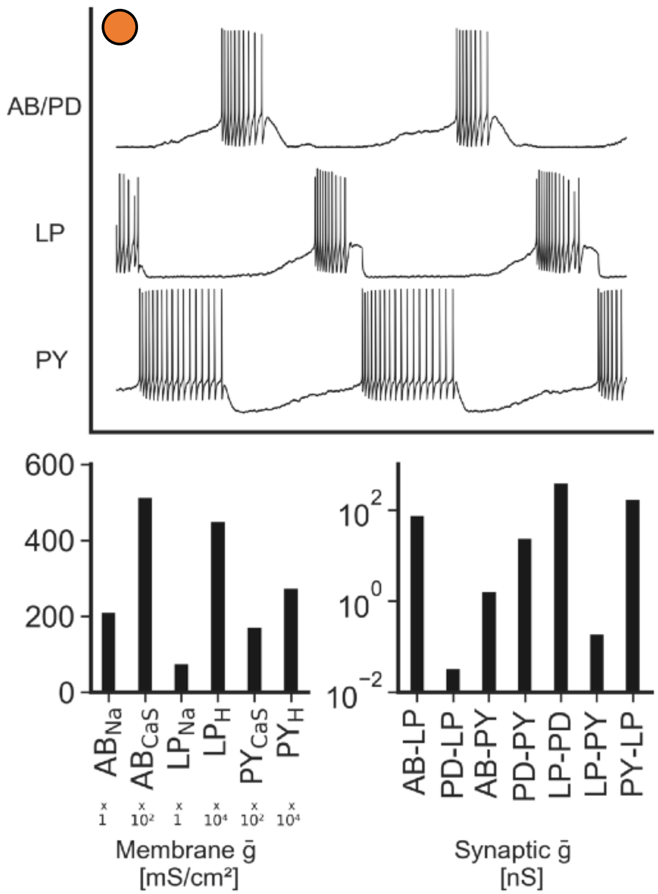


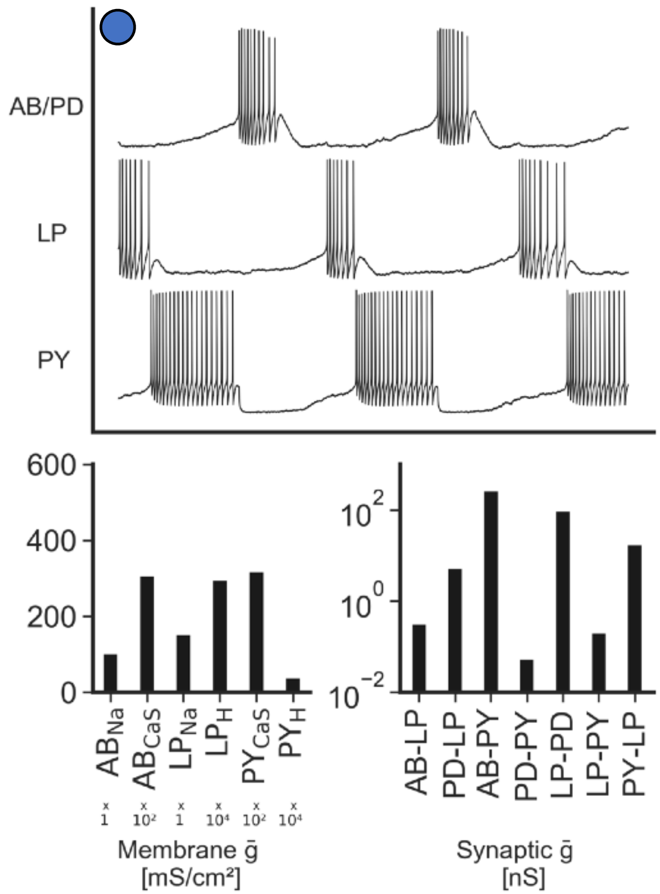
31 parameters:

- 8 maximal membrane conductances per neuron
- 7 synaptic strengths

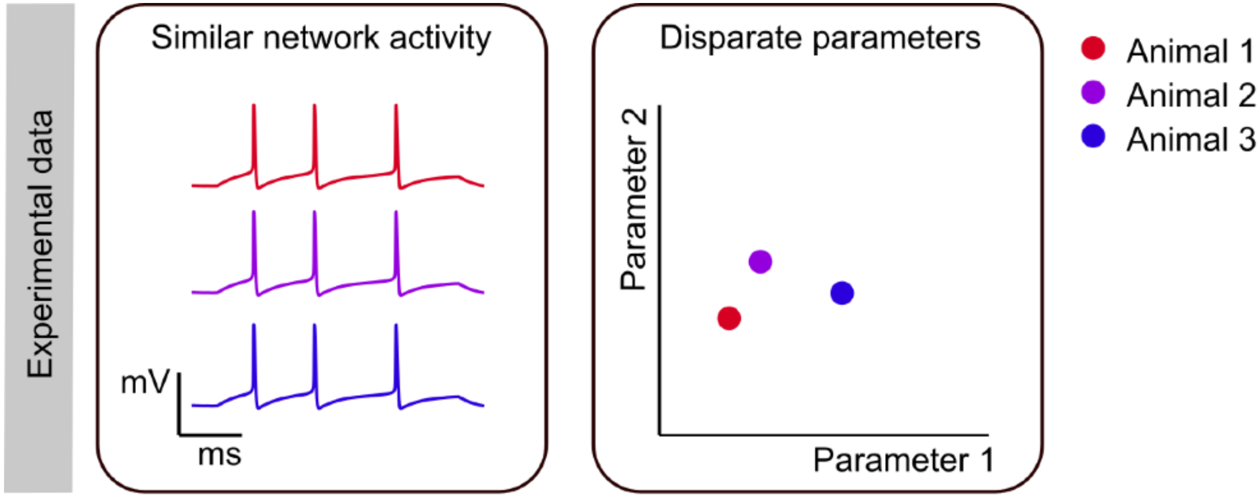
Prinz, Bucher, Marder 2004

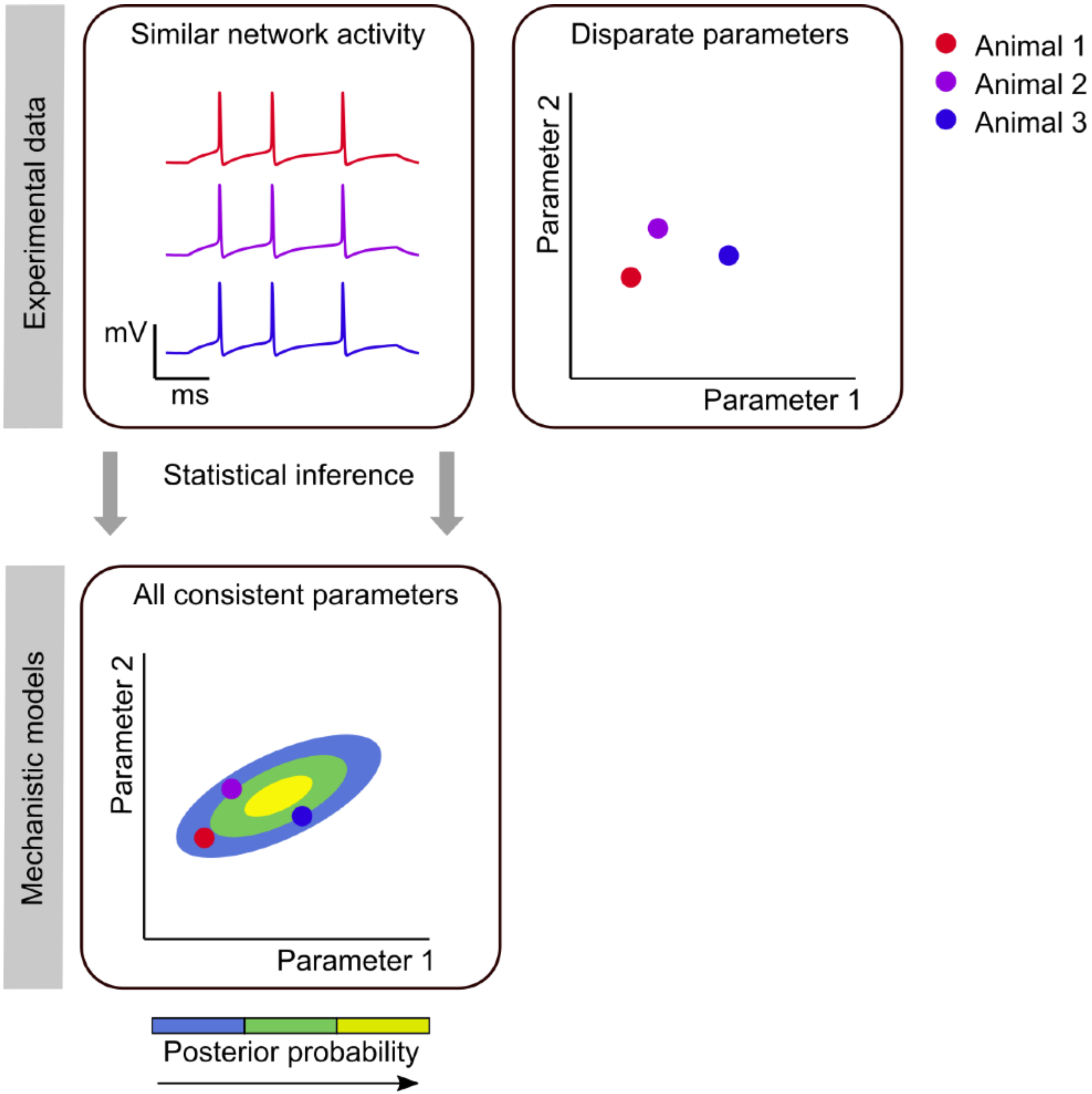
Model of the pyloric network



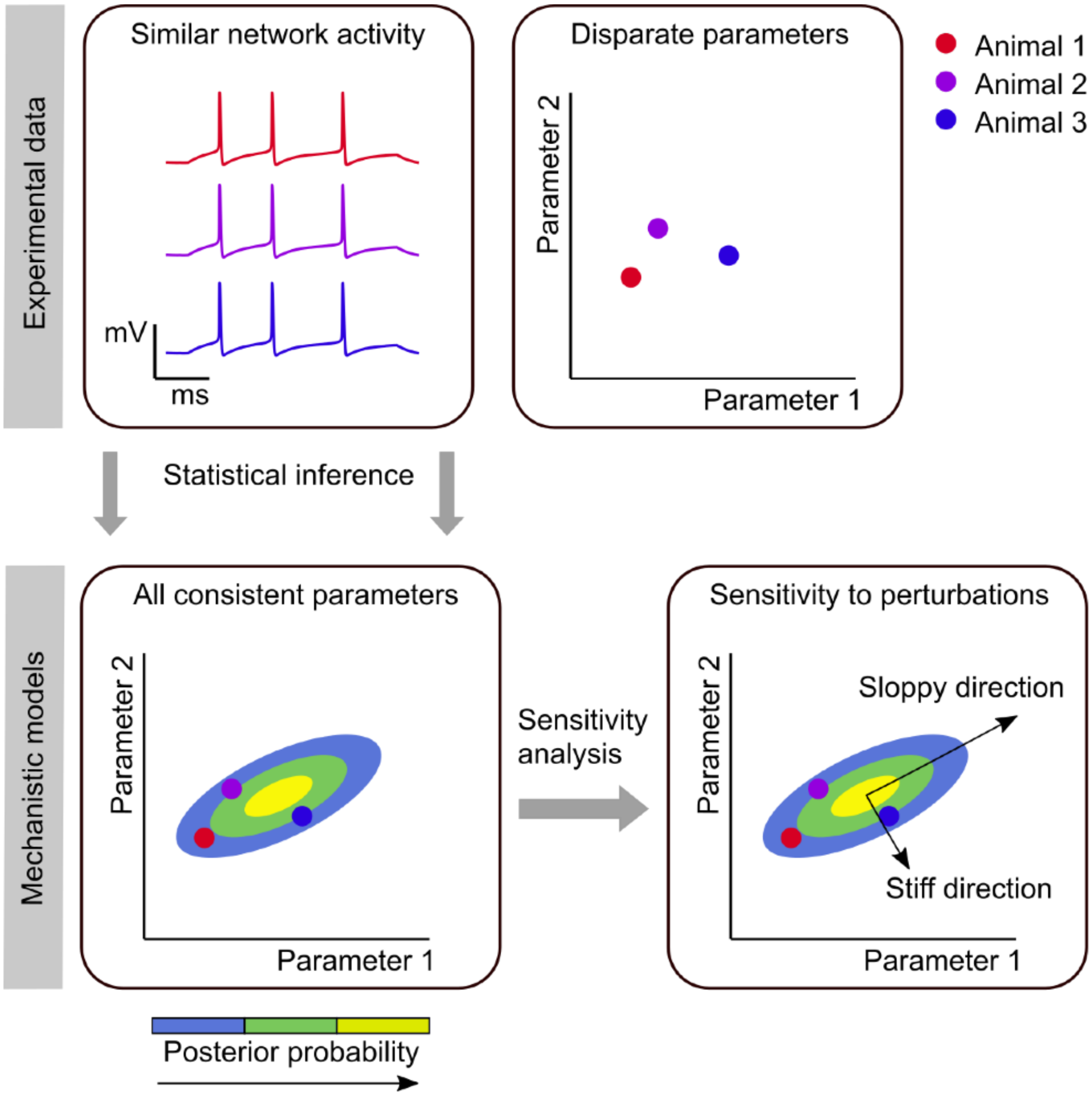


Prinz, Bucher, Marder 2004

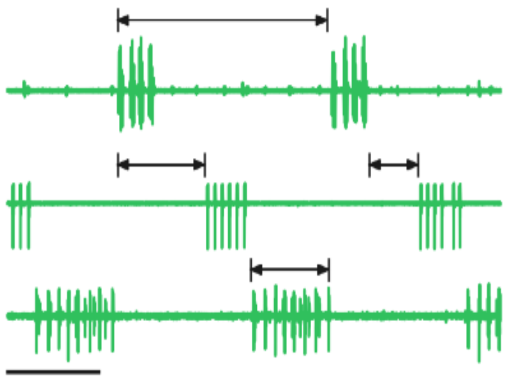

Experimental data
Similar network activity
mV
ms
Disparate parameters
Parameter 2
Parameter 1
Animal 1
Animal 2
Animal 3

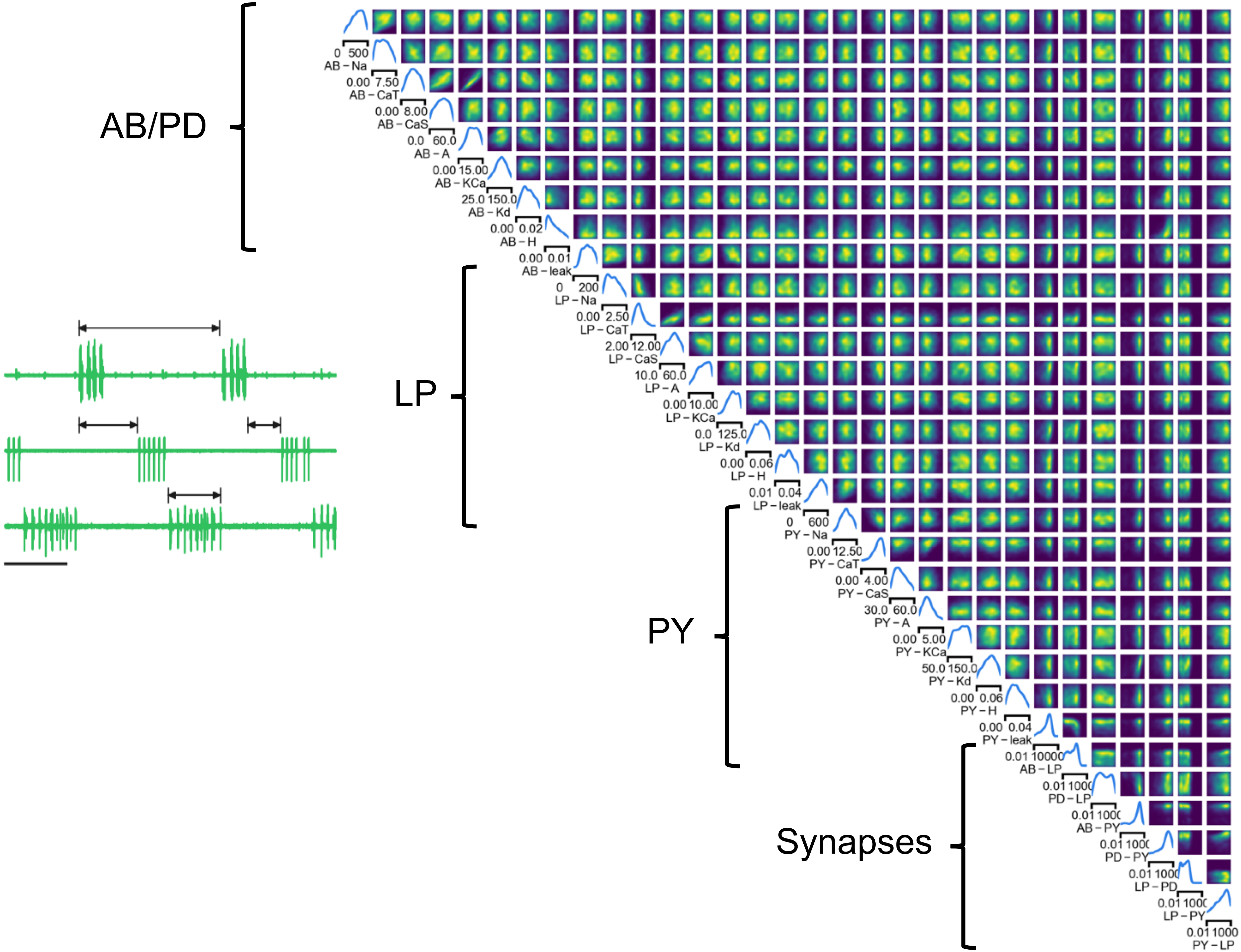


Experimental data
Similar network activity
mV
ms
Disparate parameters
Parameter 2
Parameter 1
Animal 1
Animal 2
Animal 3
Statistical inference
Mechanistic models
All consistent parameters
Parameter 2
Parameter 1
Posterior probability

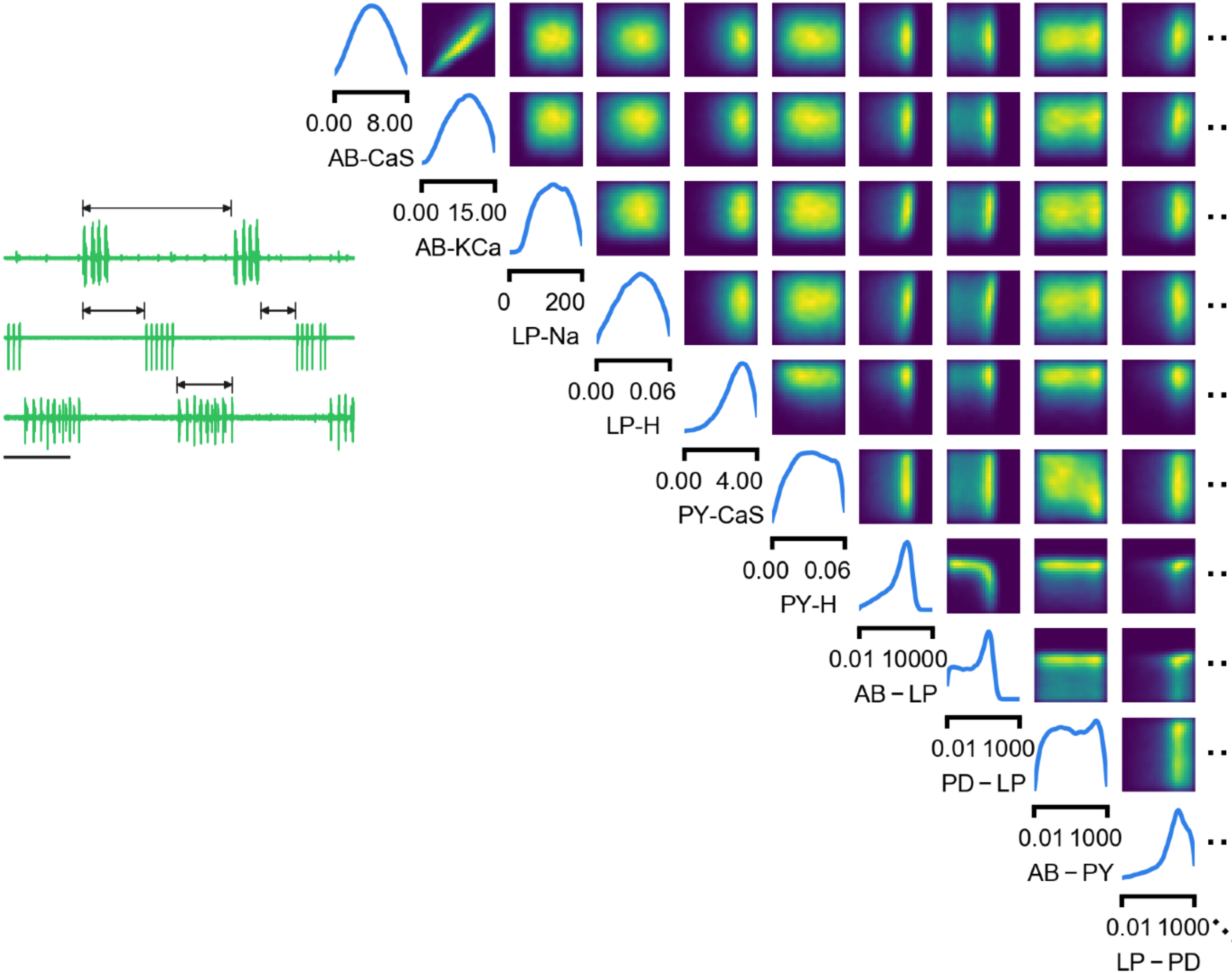


Experimental data
Similar network activity
mV
ms
Disparate parameters
Parameter 2
Parameter 1
Animal 1
Animal 2
Animal 3
Statistical inference
Mechanistic models
All consistent parameters
Parameter 2
Parameter 1
Posterior probability
Sensitivity analysis
Sensitivity to perturbations
Parameter 2
Sloppy direction
Stiff direction
Parameter 1

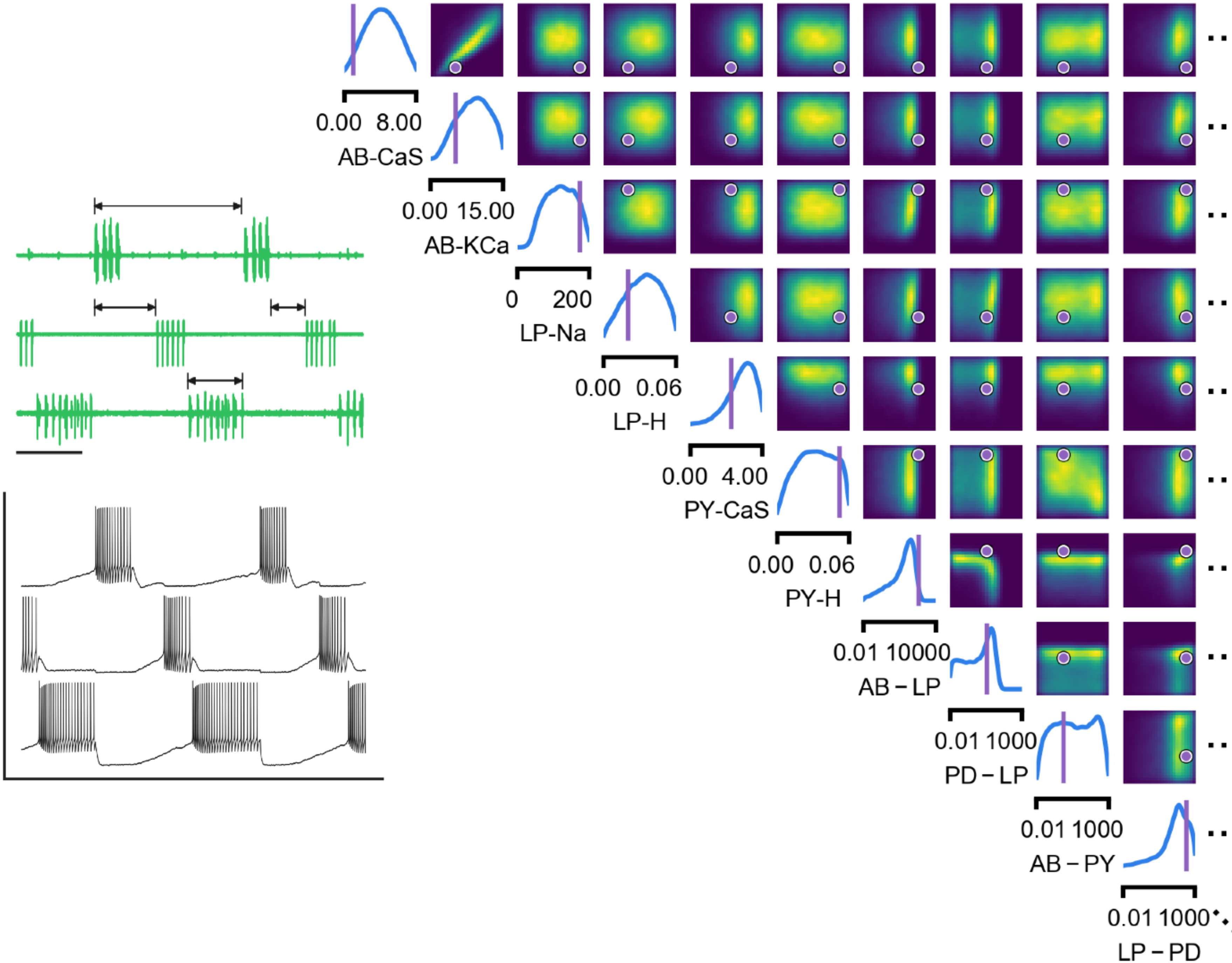




AB/PD
LP
PY
Synapses
0 500
AB – Na
0.00 7.50
AB – CaT
0.00 8.00
AB – CaS
0.0 60.0
AB – A
0.00 15.00
AB – KCa
25.0 150.0
AB – Kd
0.00 0.02
AB – H
0.00 0.01
AB – leak
0 200
LP – Na
0.00 2.50
LP – CaT
2.00 12.00
LP – CaS
10.0 60.0
LP – A
0.00 10.00
LP – KCa
0.0 125.0
LP – Kd
0.00 0.06
LP – H
0.01 0.04
LP – leak
0 600
PY – Na
0.00 12.50
PY – CaT
0.00 4.00
PY – CaS
30.0 60.0
PY – A
0.00 5.00
PY – KCa
50.0 150.0
PY – Kd
0.00 0.06
PY – H
0.00 0.04
PY – leak
AB – LP
PD – LP
AB – PY
PD – PY
LP – PD
LP – PY
0.01 1000
PY – LP



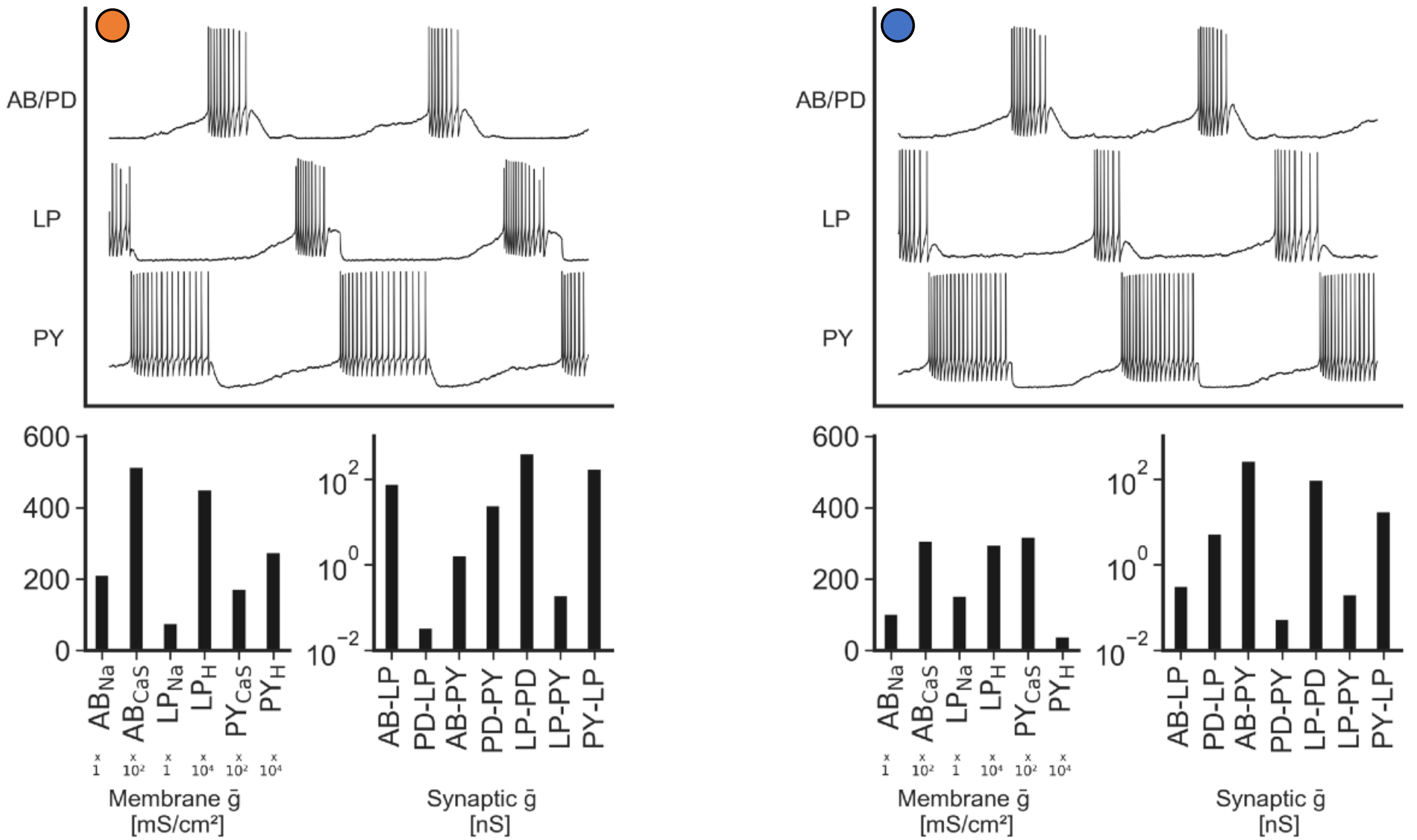
0.00 8.00
AB-CaS
0.00 15.00
AB-KCa
0 200
LP-Na
0.00 0.06
LP-H
0.00 4.00
PY-CaS
0.00 0.06
PY-H
0.01 10000
AB – LP
0.01 1000
PD – LP
0.01 1000
AB – PY
0.01 1000
LP – PD



0.00 8.00
AB-CaS
0.00 15.00
AB-KCa
0 200
LP-Na
0.00 0.06
LP-H
0.00 4.00
PY-CaS
0.00 0.06
PY-H
0.01 10000
AB – LP
0.01 1000
PD – LP
0.01 1000
AB – PY
0.01 1000
LP – PD

Analysing the posterior

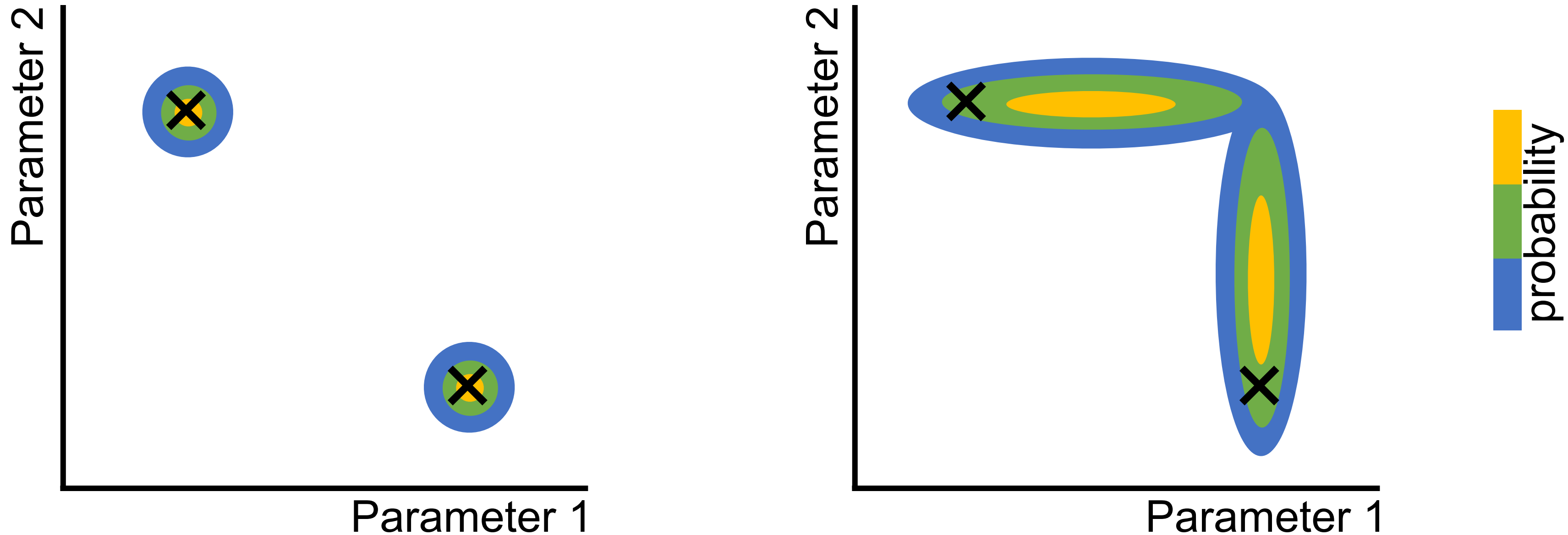
Robustness to perturbations



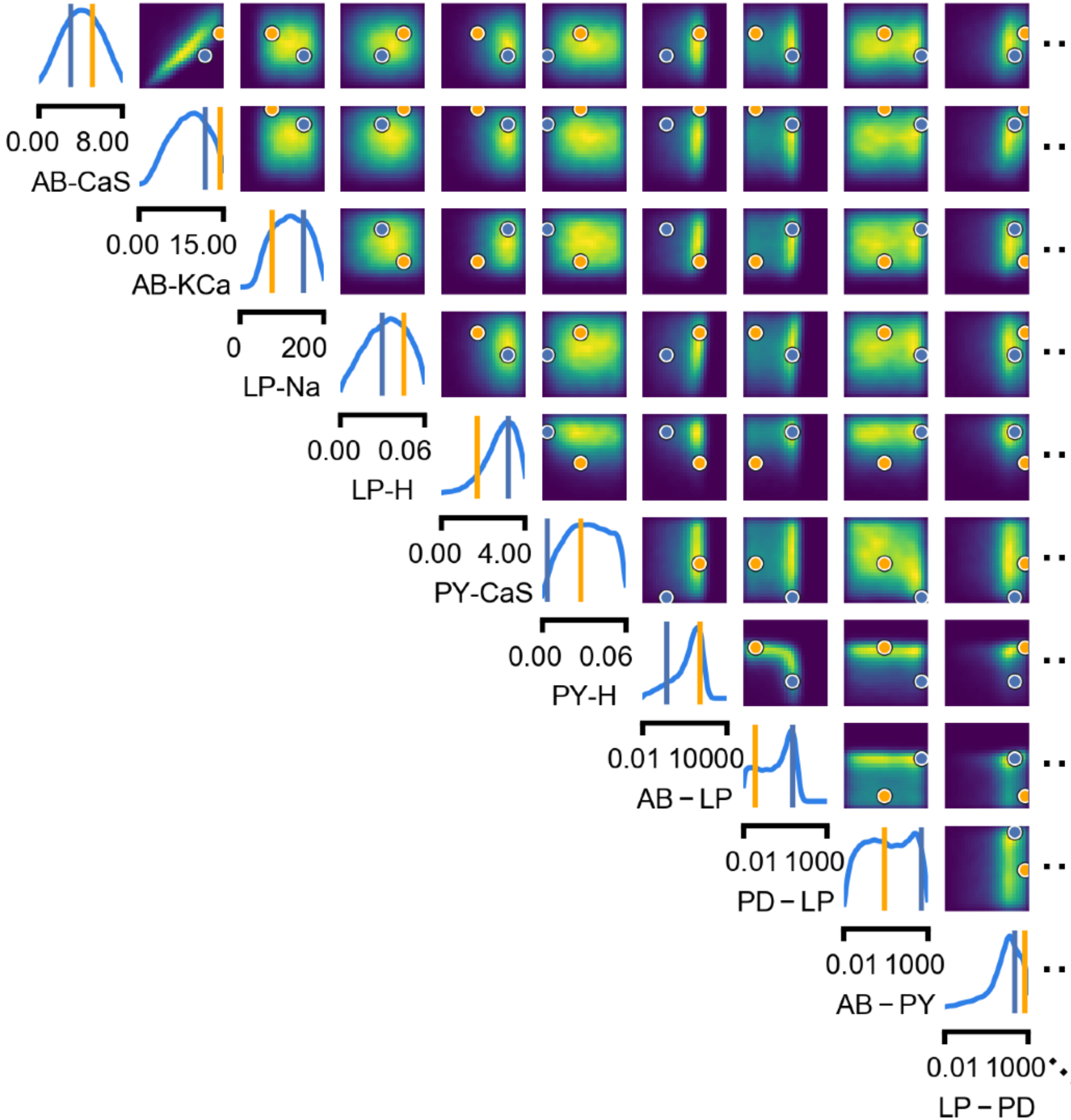
Taylor et al. 2006

Scenario 1: parameter sets lie on separate islands

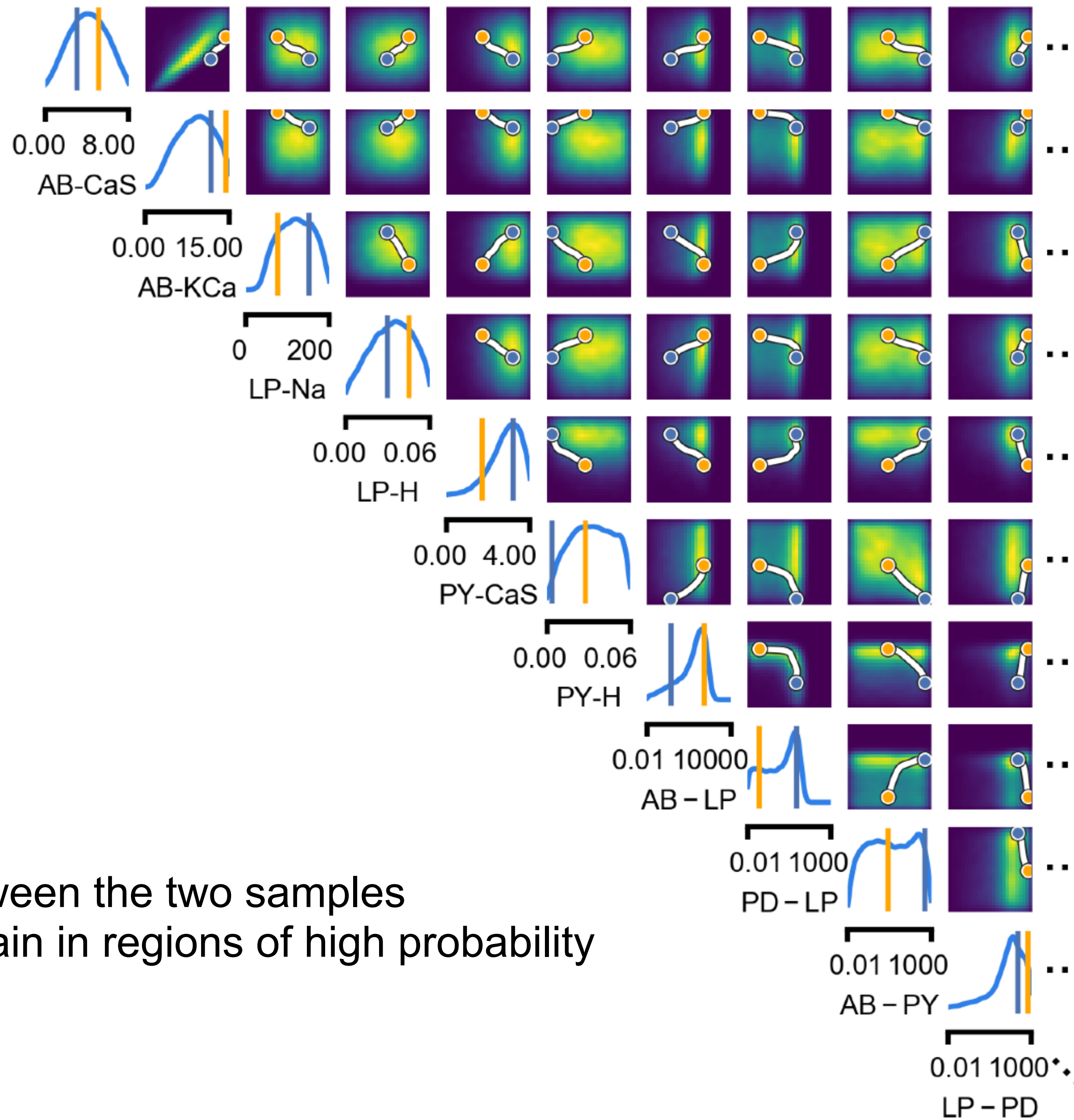
Scenario 2: parameter sets are connected



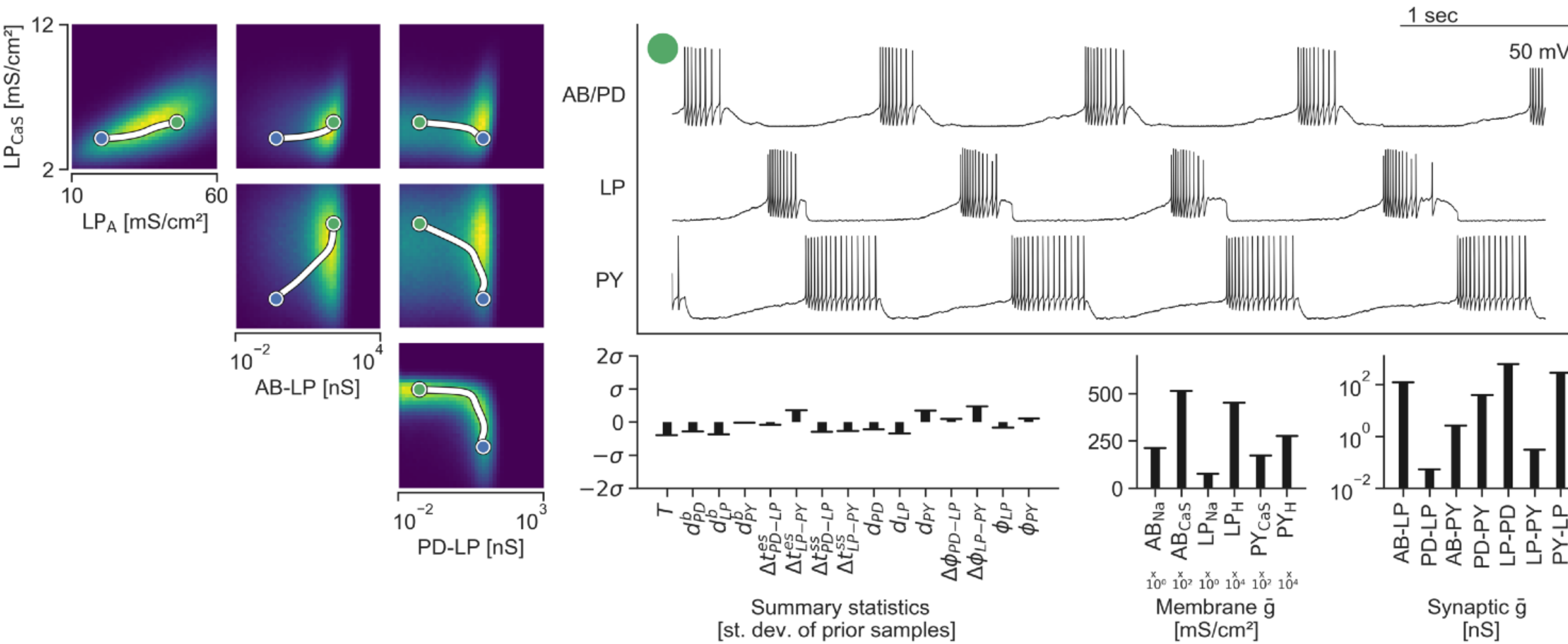
✕ Consistent parameter sets



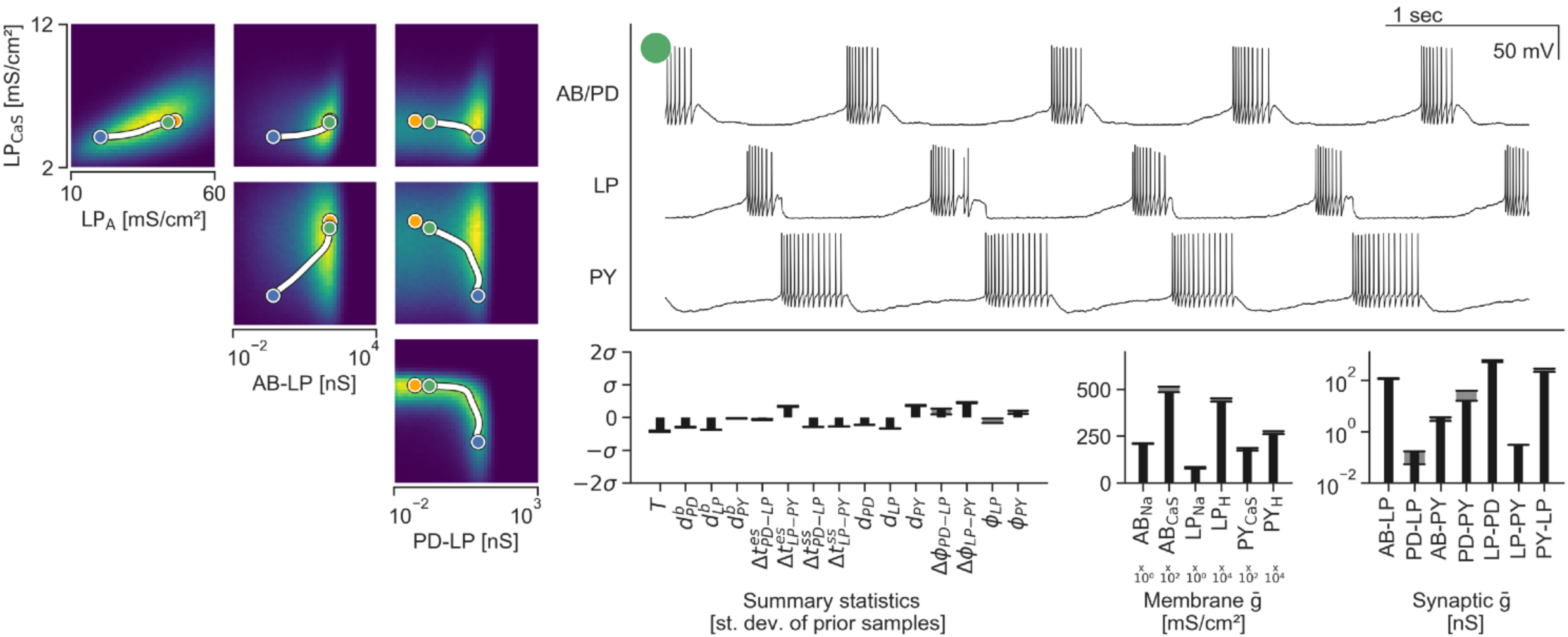
0.00 8.00
AB-CaS
0.00 15.00
AB-KCa
0 200
LP-Na
0.00 0.06
LP-H
0.00 4.00
PY-CaS
0.00 0.06
PY-H
0.01 10000
AB − LP
0.01 1000
PD − LP
0.01 1000
AB − PY
0.01 1000
LP − PD



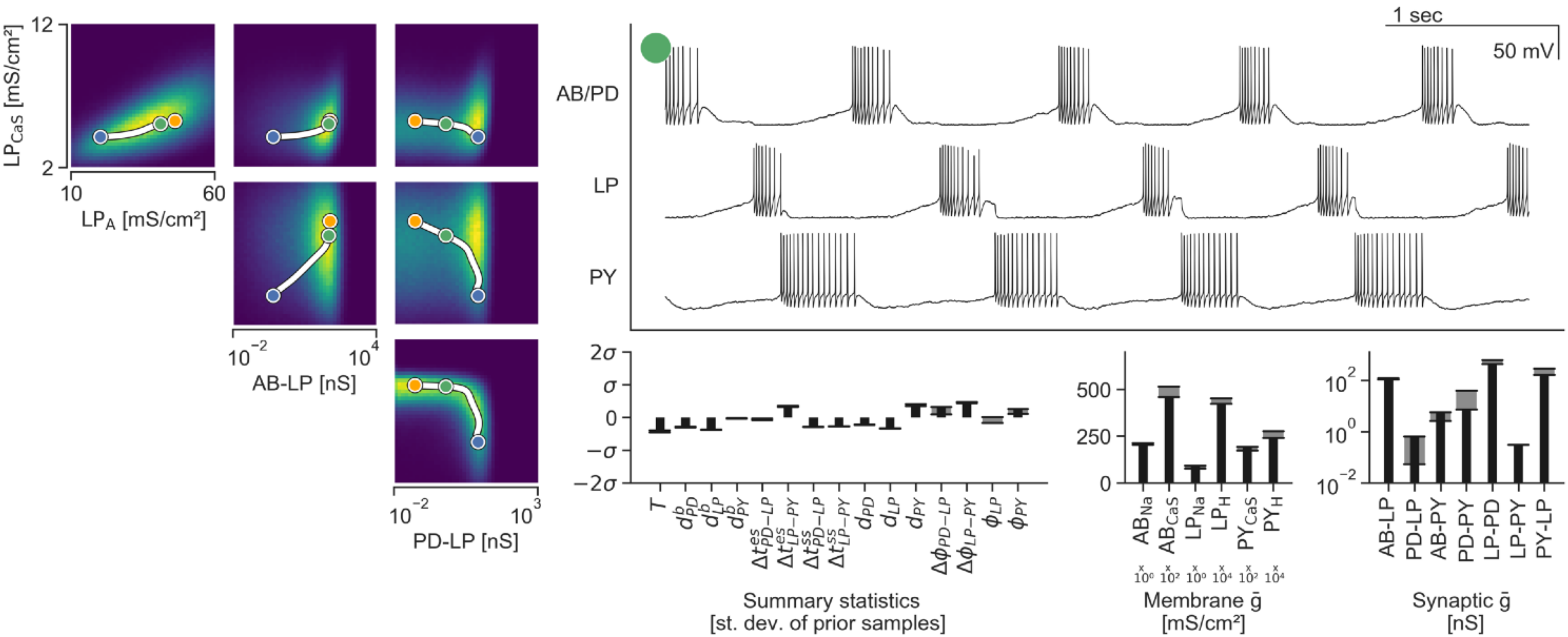
- Find a ‘path’ between the two samples
- Path should remain in regions of high probability



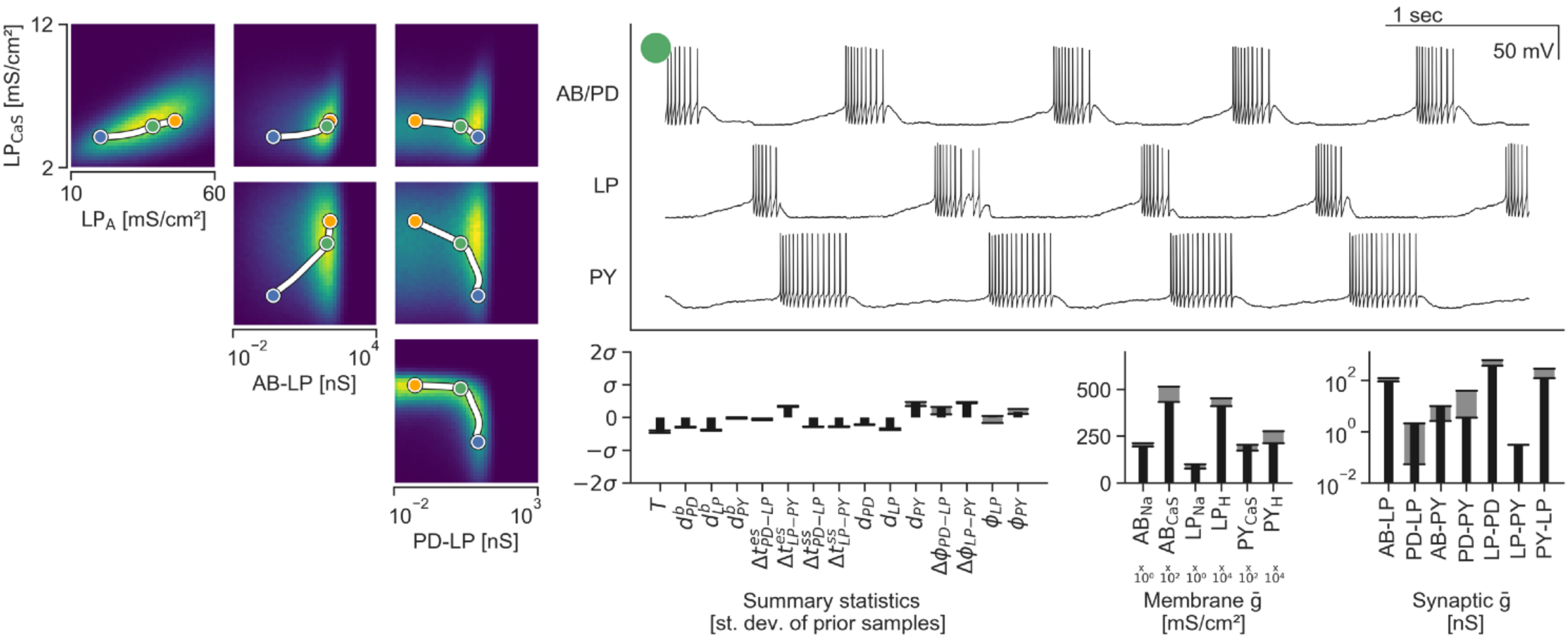
LP_{CaS} [mS/cm²]
12
2
10
60
LP_A [mS/cm²]
10^{-2}
10^{4}
AB-LP [nS]
10^{-2}
10^{3}
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
2σ
σ
0
$-\sigma$
-2σ
T
d^b_{PD}
d^b_{LP}
d^b_{PY}
Δt^{es}_{PD-LP}
Δt^{es}_{LP-PY}
Δt^{ss}_{PD-LP}
Δt^{ss}_{LP-PY}
d_{PD}
d_{LP}
d_{PY}
$\Delta\phi_{PD-LP}$
$\Delta\phi_{LP-PY}$
ϕ_{LP}
ϕ_{PY}
Summary statistics
[st. dev. of prior samples]
500
250
0
AB_{Na}
AB_{CaS}
LP_{Na}
LP_H
PY_{CaS}
PY_H
x 10^0
x 10^2
x 10^0
x 10^4
x 10^2
x 10^4
Membrane $\bar{g}$
[mS/cm²]
10^{2}
10^{0}
10^{-2}
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP
Synaptic $\bar{g}$
[nS]



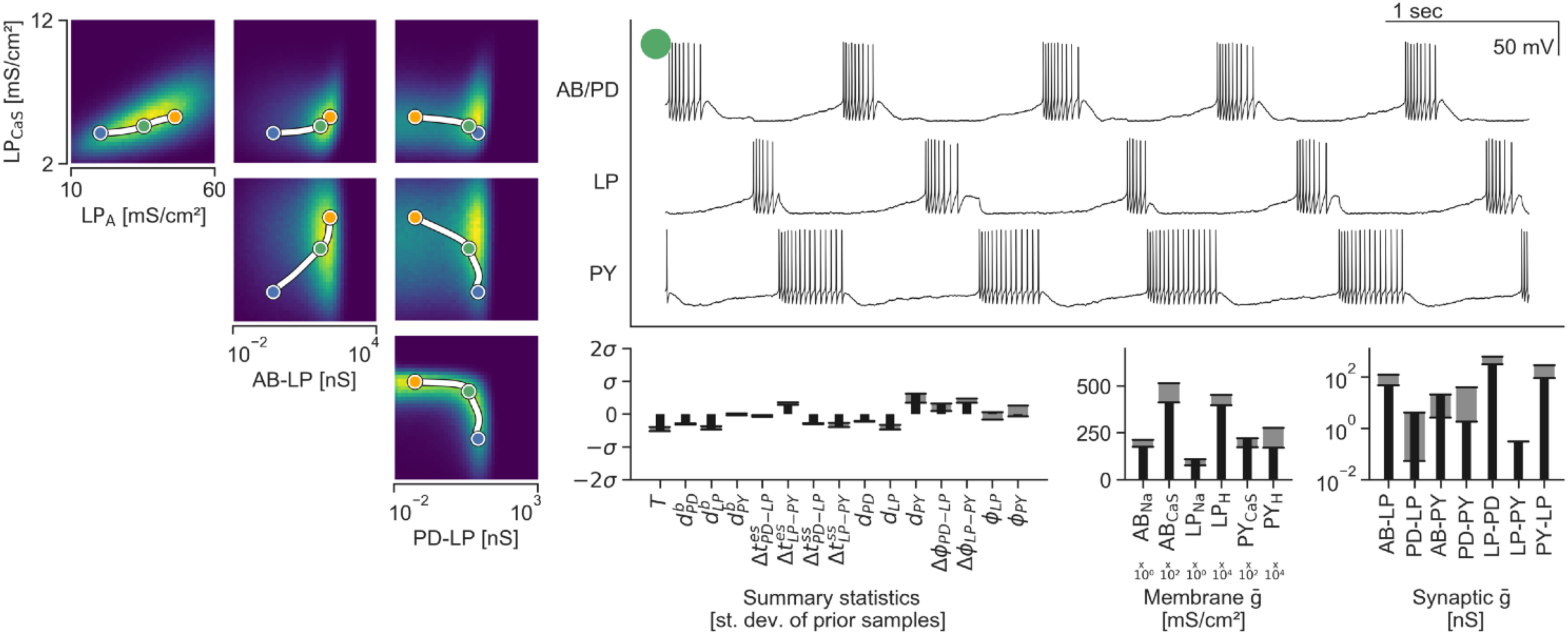
LPCaS [mS/cm²]
12
2
10
60
LPA [mS/cm²]
AB-LP [nS]
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
Summary statistics
[st. dev. of prior samples]
Membrane ḡ
[mS/cm²]
Synaptic ḡ
[nS]
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP



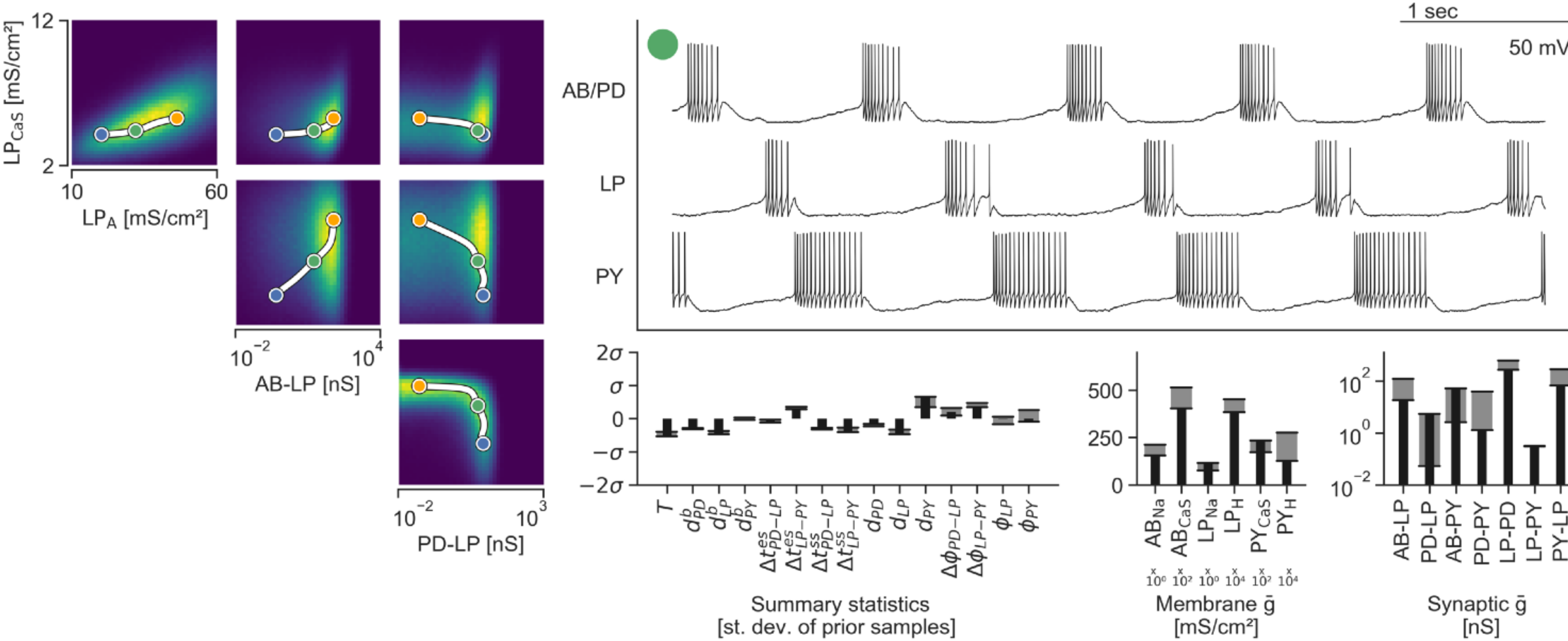
LP$_{CaS}$ [mS/cm²]
12
2
10
60
LP$_A$ [mS/cm²]
10^{-2}
10^4
AB-LP [nS]
10^{-2}
10^3
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
2σ
σ
0
$-\sigma$
-2σ
T d^b_{PD} d^b_{LP} d^b_{PY} Δt^{es}_{PD-LP} Δt^{es}_{LP-PY} Δt^{ss}_{PD-LP} Δt^{ss}_{LP-PY} d_{PD} d_{LP} d_{PY} $\Delta\phi_{PD-LP}$ $\Delta\phi_{LP-PY}$ ϕ_{LP} ϕ_{PY}
Summary statistics
[st. dev. of prior samples]
500
250
0
AB$_{Na}$ AB$_{CaS}$ LP$_{Na}$ LP$_H$ PY$_{CaS}$ PY$_H$
x 10^0 x 10^2 x 10^0 x 10^4 x 10^2 x 10^4
Membrane $\bar{g}$
[mS/cm²]
10^2
10^0
10^{-2}
AB-LP PD-LP AB-PY PD-PY LP-PD LP-PY PY-LP
Synaptic $\bar{g}$
[nS]



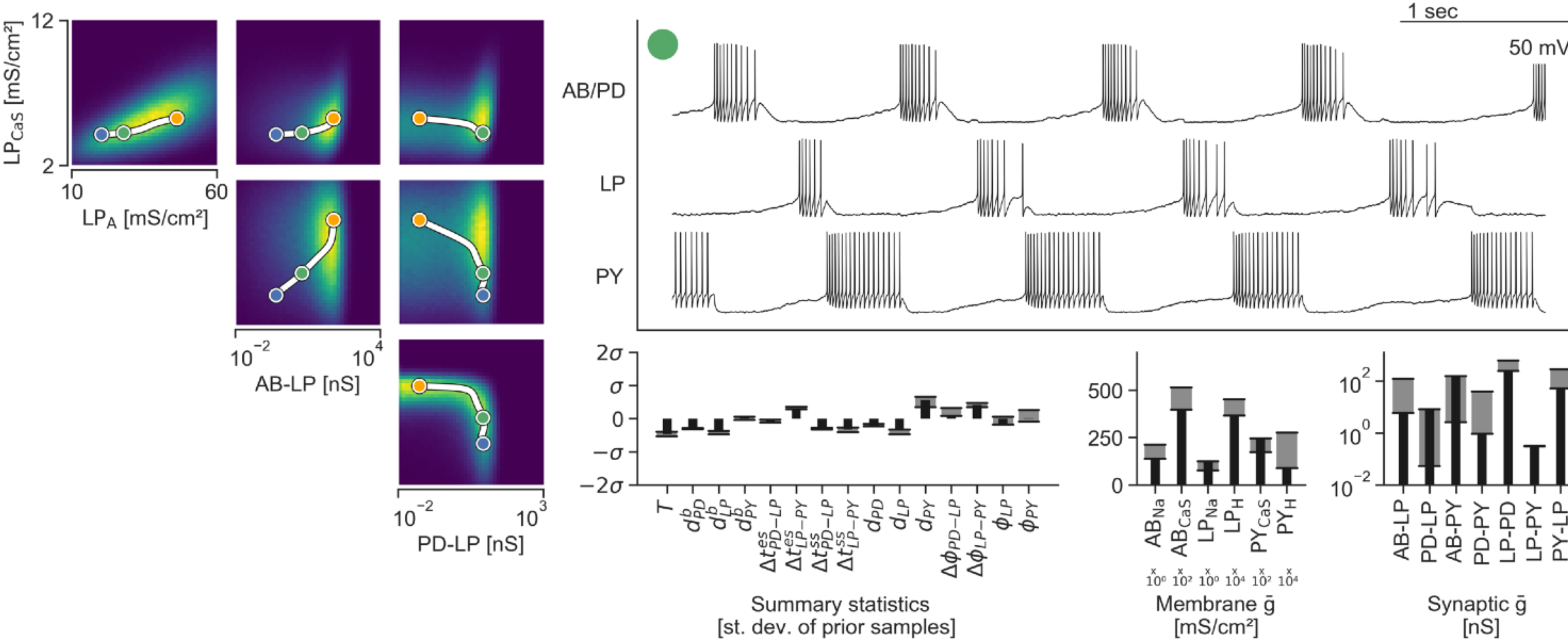
LPCaS [mS/cm²]
12
2
10
60
LPA [mS/cm²]
AB-LP [nS]
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
2σ
σ
0
−σ
−2σ
Summary statistics
[st. dev. of prior samples]
500
250
0
ABNa
ABCaS
LPNa
LPH
PYCaS
PYH
Membrane ḡ
[mS/cm²]
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP
Synaptic ḡ
[nS]



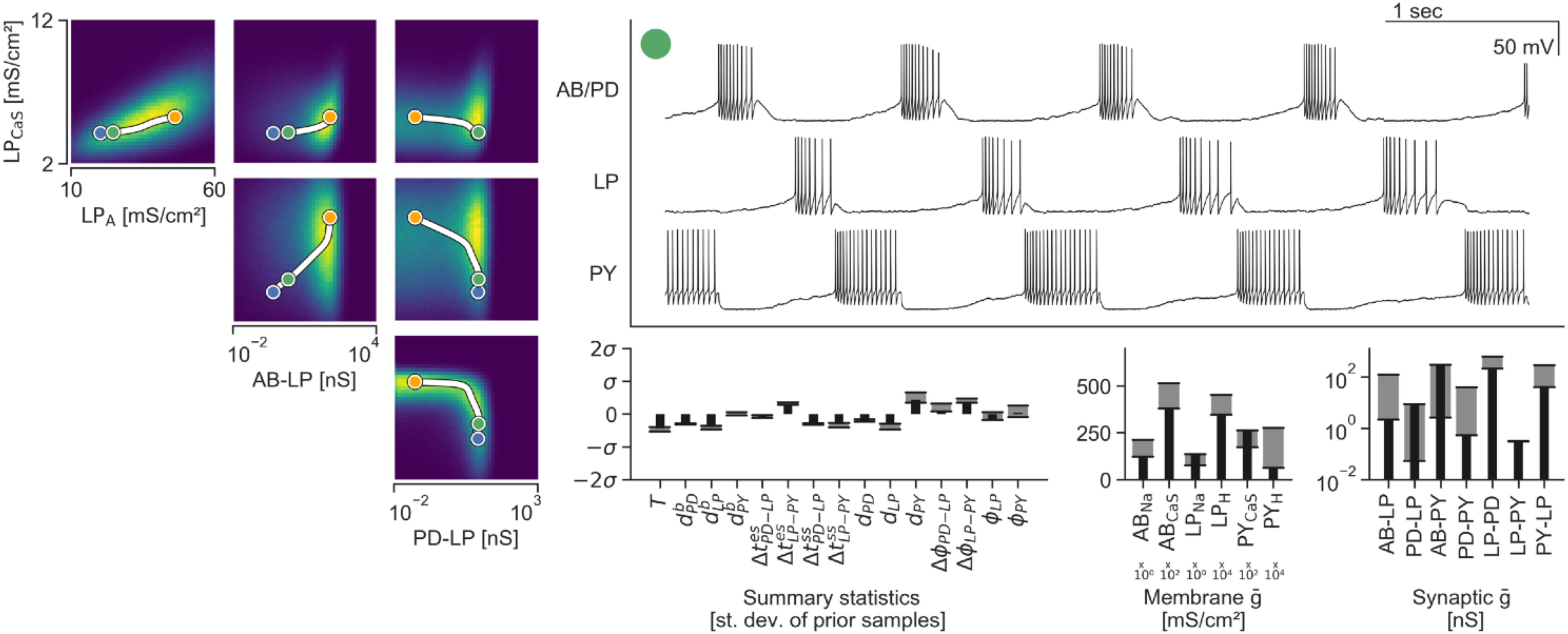
12
2
LPCaS [mS/cm²]
10
60
LPA [mS/cm²]
AB-LP [nS]
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
Summary statistics
[st. dev. of prior samples]
Membrane ḡ
[mS/cm²]
Synaptic ḡ
[nS]



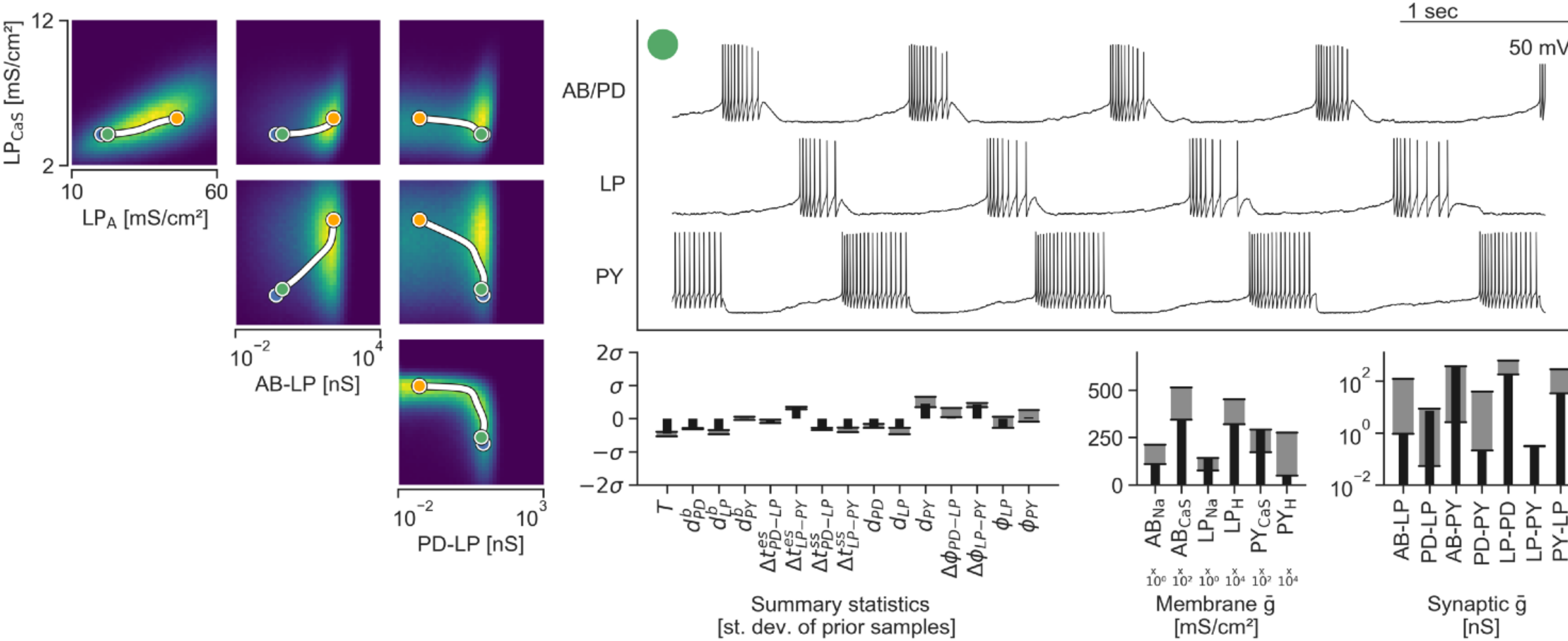
LP_{CaS} [mS/cm²]
12
2
10
60
LP_A [mS/cm²]
10^{-2}
10^4
AB-LP [nS]
10^{-2}
10^3
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
Summary statistics
[st. dev. of prior samples]
Membrane $\bar{g}$
[mS/cm²]
Synaptic $\bar{g}$
[nS]



LPCaS [mS/cm²]
12
2
10
60
LPA [mS/cm²]
AB-LP [nS]
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
2σ
σ
0
−σ
−2σ
Summary statistics
[st. dev. of prior samples]
500
250
0
Membrane ḡ
[mS/cm²]
Synaptic ḡ
[nS]
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP

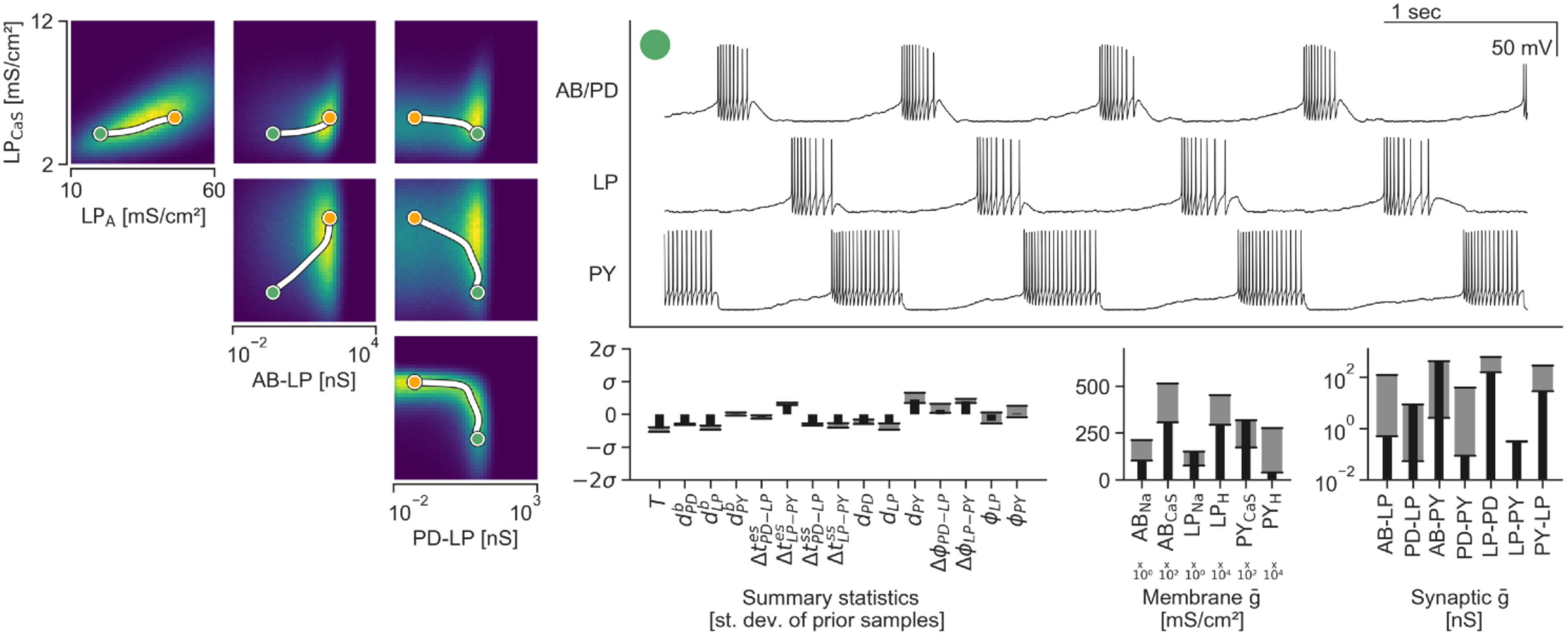


LPCaS [mS/cm²]
12
2
10
60
LPA [mS/cm²]
AB-LP [nS]
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
Summary statistics
[st. dev. of prior samples]
Membrane ḡ
[mS/cm²]
Synaptic ḡ
[nS]
ABNa
ABCaS
LPNa
LPH
PYCaS
PYH
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP

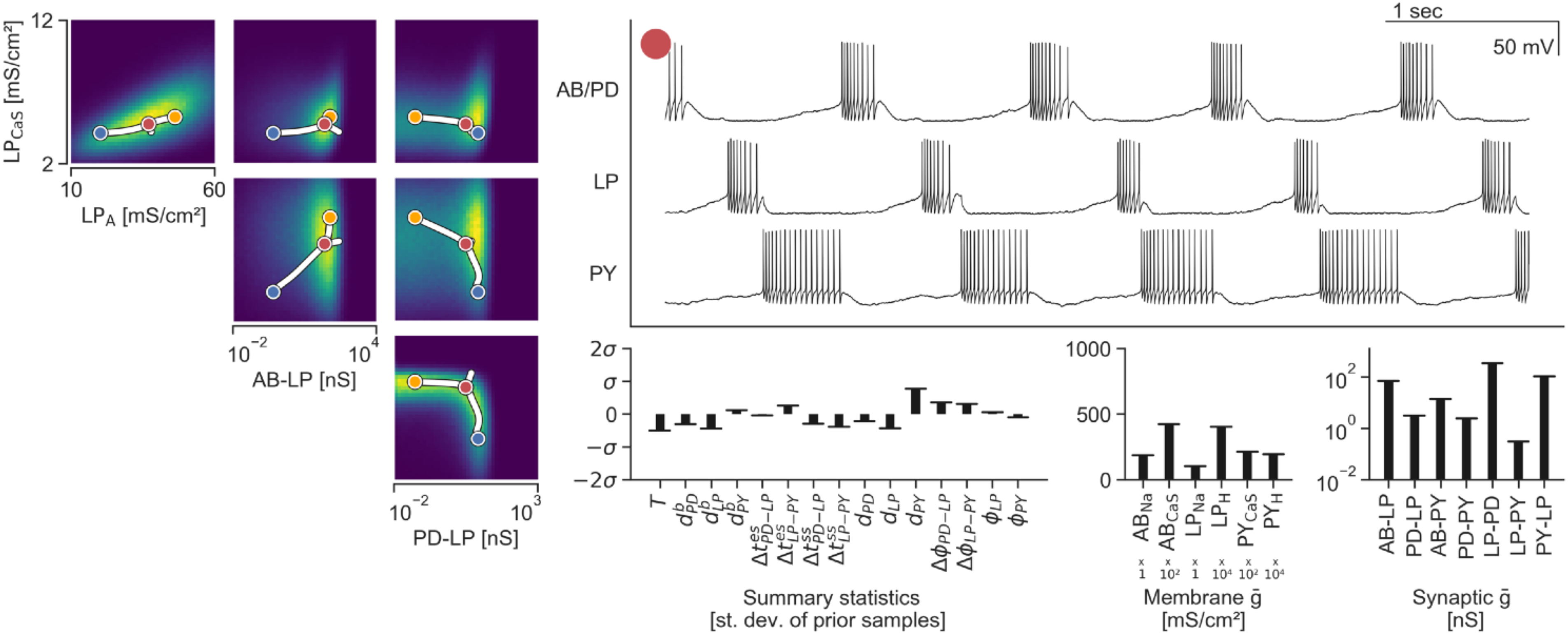


LPCaS [mS/cm²]
12
2
10
60
LPA [mS/cm²]
AB-LP [nS]
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
Summary statistics
[st. dev. of prior samples]
Membrane ḡ
[mS/cm²]
Synaptic ḡ
[nS]
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP

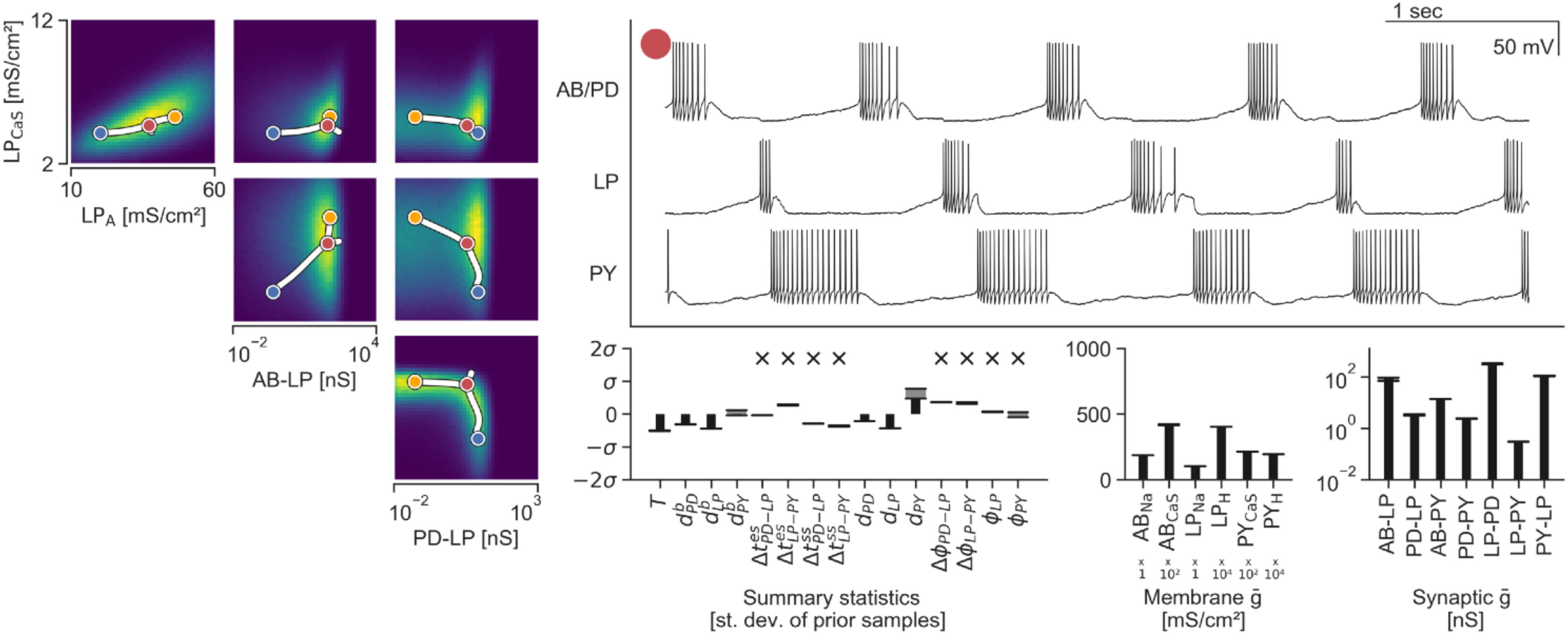
Parameter sets producing similar outputs are connected in parameter space: no 'islands'



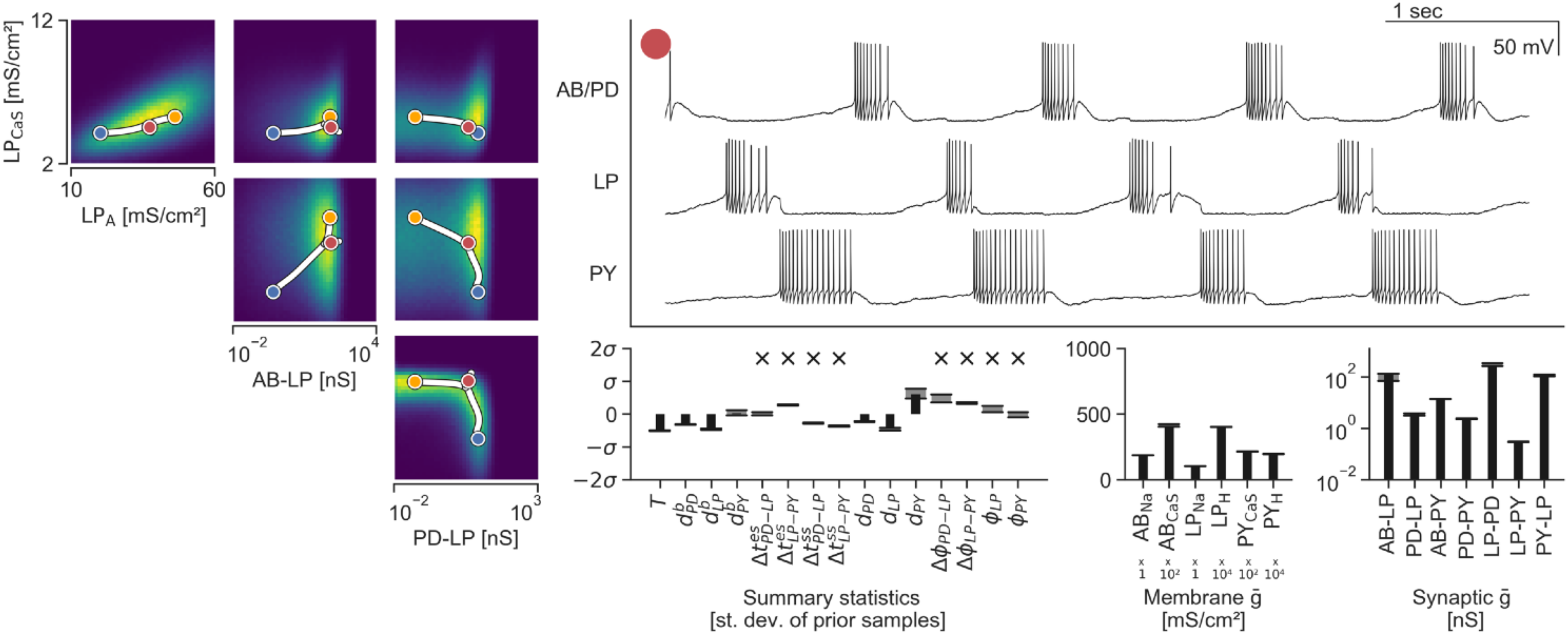
Can small perturbations lead the circuit to break down?



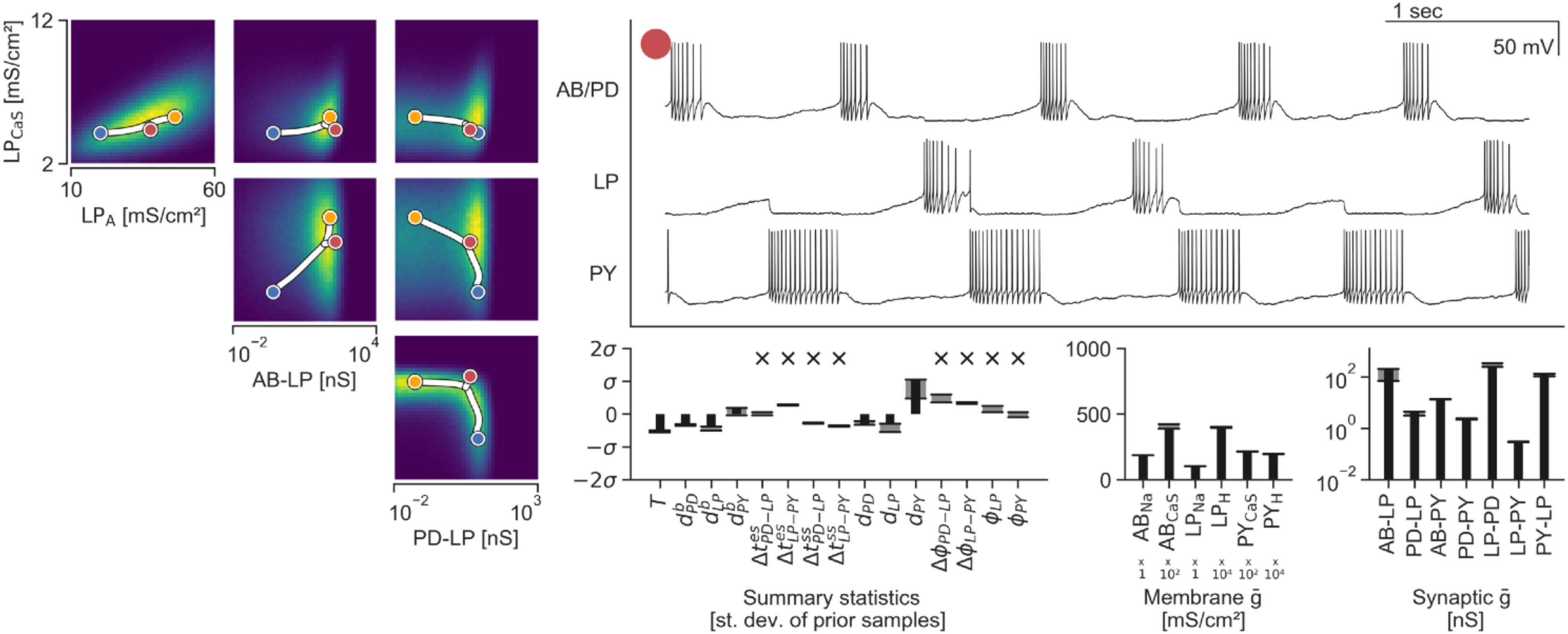
LP_CaS [mS/cm²]
LP_A [mS/cm²]
AB-LP [nS]
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
Summary statistics
[st. dev. of prior samples]
Membrane ḡ
[mS/cm²]
Synaptic ḡ
[nS]



LP$_{CaS}$ [mS/cm²]
12
2
10
60
LP$_A$ [mS/cm²]
10^{-2}
10^4
AB-LP [nS]
10^{-2}
10^3
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
2σ
σ
0
−σ
−2σ
Summary statistics
[st. dev. of prior samples]
1000
500
0
AB$_{Na}$
AB$_{CaS}$
LP$_{Na}$
LP$_H$
PY$_{CaS}$
PY$_H$
Membrane ḡ
[mS/cm²]
10^2
10^0
10^{-2}
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP
Synaptic ḡ
[nS]

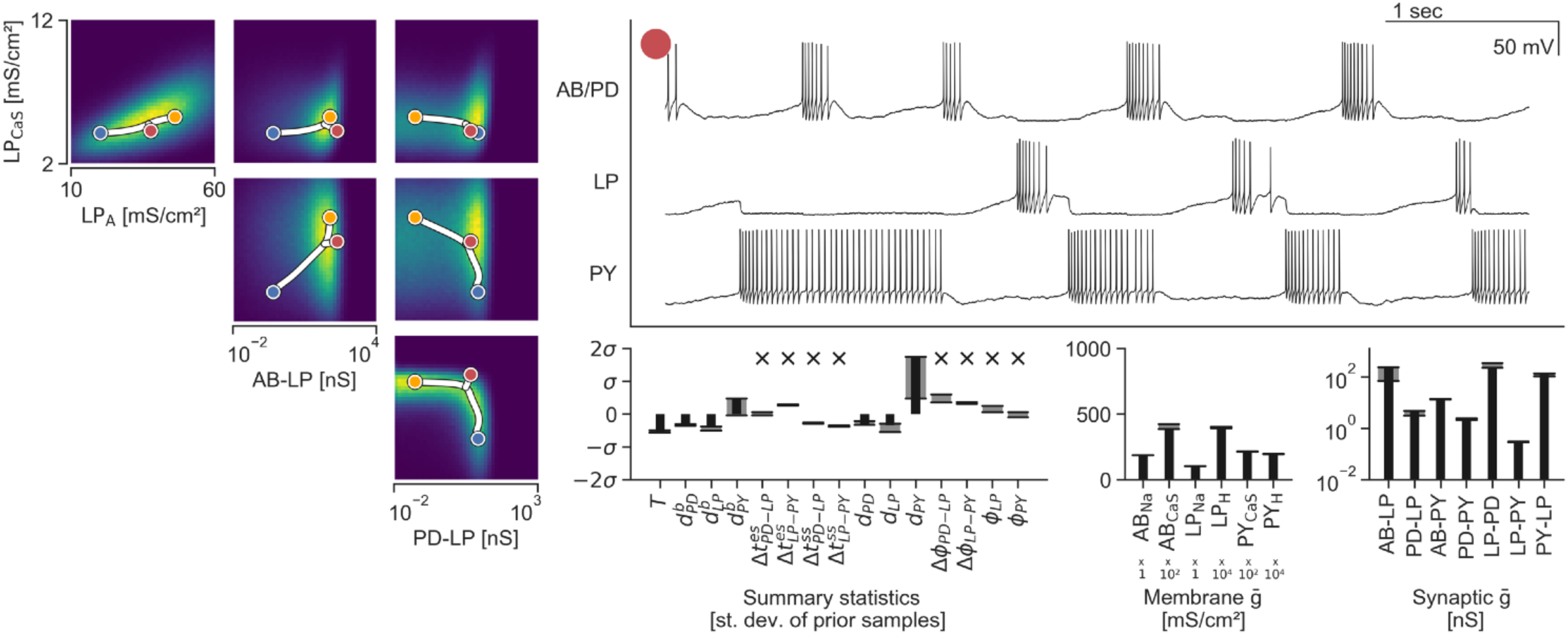


LP$_{CaS}$ [mS/cm²]
12
2
10
60
LP$_A$ [mS/cm²]
10^{-2}
10^{4}
AB-LP [nS]
10^{-2}
10^{3}
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
2σ
σ
0
$-\sigma$
-2σ
T d^b_{PD} d^b_{LP} d^b_{PY} Δt^{es}_{PD-LP} Δt^{es}_{LP-PY} Δt^{ss}_{PD-LP} Δt^{ss}_{LP-PY} d_{PD} d_{LP} d_{PY} $\Delta\phi_{PD-LP}$ $\Delta\phi_{LP-PY}$ ϕ_{LP} ϕ_{PY}
Summary statistics
[st. dev. of prior samples]
1000
500
0
AB$_{Na}$ AB$_{CaS}$ LP$_{Na}$ LP$_H$ PY$_{CaS}$ PY$_H$
x 1 x 10^2 x 1 x 10^4 x 10^2 x 10^4
Membrane $\bar{g}$
[mS/cm²]
10^{2}
10^{0}
10^{-2}
AB-LP PD-LP AB-PY PD-PY LP-PD LP-PY PY-LP
Synaptic $\bar{g}$
[nS]



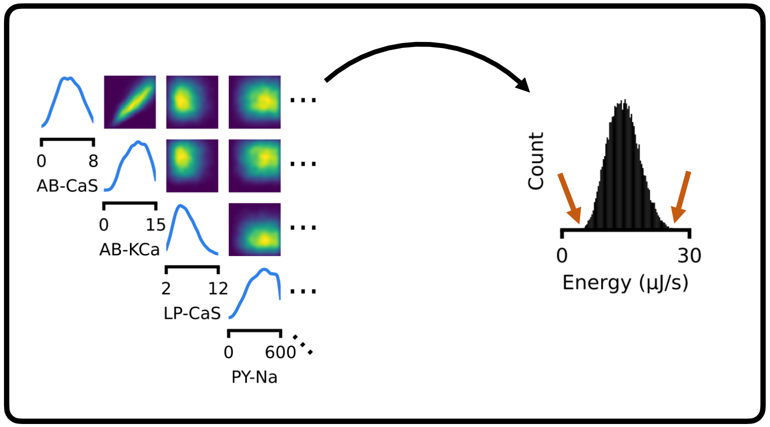
LP$_{CaS}$ [mS/cm²]
12
2
10
60
LP$_A$ [mS/cm²]
10^{-2}
10^4
AB-LP [nS]
10^{-2}
10^3
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
2σ
σ
0
$-\sigma$
-2σ
T d^b_{PD} d^b_{LP} d^b_{PY} Δt^{es}_{PD-LP} Δt^{es}_{LP-PY} Δt^{ss}_{PD-LP} Δt^{ss}_{LP-PY} d_{PD} d_{LP} d_{PY} $\Delta\phi_{PD-LP}$ $\Delta\phi_{LP-PY}$ ϕ_{LP} ϕ_{PY}
Summary statistics
[st. dev. of prior samples]
1000
500
0
AB$_{Na}$ AB$_{CaS}$ LP$_{Na}$ LP$_H$ PY$_{CaS}$ PY$_H$
x 1 x 10^2 x 1 x 10^4 x 10^2 x 10^4
Membrane $\bar{g}$
[mS/cm²]
10^2
10^0
10^{-2}
AB-LP PD-LP AB-PY PD-PY LP-PD LP-PY PY-LP
Synaptic $\bar{g}$
[nS]

Small perturbations can lead the circuit to break down



Flexibility of simulation-based inference

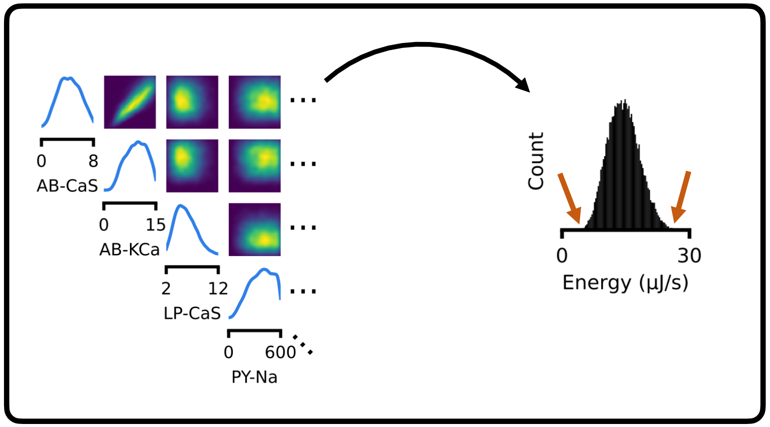
Energy efficiency and robustness



M Deistler, JH Macke*, PJ Goncalves* (2021) biorXiv

Flexibility of simulation-based inference

Energy efficiency and robustness

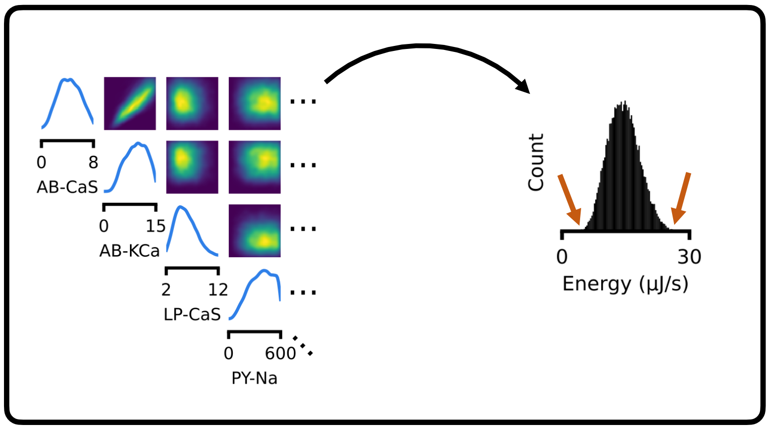


M Deistler, JH Macke*, PJ Goncalves* (2021) biorXiv

But other projects ongoing at different scales in the brain. Also, cosmology and climate sciences.

Flexibility of simulation-based inference

Energy efficiency and robustness



M Deistler, JH Macke*, PJ Goncalves* (2021) biorXiv

But other projects ongoing at different scales in the brain. Also, cosmology and climate sciences.

Workshop on simulation-based inference for scientific discovery, 09/2021, Tübingen.

Discussion

- **Flexibility:** inference approach does not depend on specifics of mechanistic model, works with simulation-based models

PJ Goncalves*, JM Lückmann*, M. Deistler* et al (2020) eLife
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github.com/mackelab/delfi; https://www.mackelab.org/sbi/

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- Sensitivity analysis
- Lots of challenges: scaling number of parameters, model misspecification…

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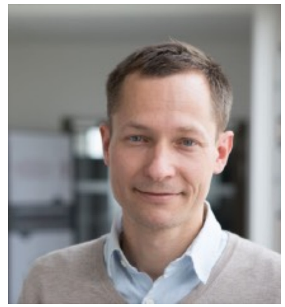
Acknowledgments

Jakob Macke's group

Giacomo Bassetto
Sebastian Bischoff
Jan Boelts
Álvaro Tejero Cantero (former)
Michael Deistler
Richard Gao
Jaivardhan Kapoor
Janne Lappalainen
Jan-Matthis Lueckmann
Kaan Oecal (former)
Poornima Ramesh
Cornelius Schröder
Auguste Schulz
Artur Speiser
Julius Vetter



Jakob Macke

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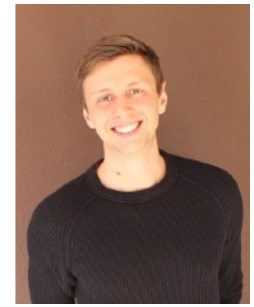

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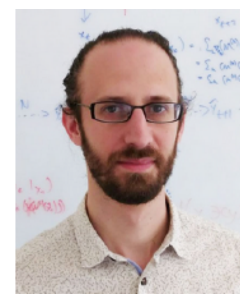

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