Training deep neural networks to identify mechanistic models of neural dynamics

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

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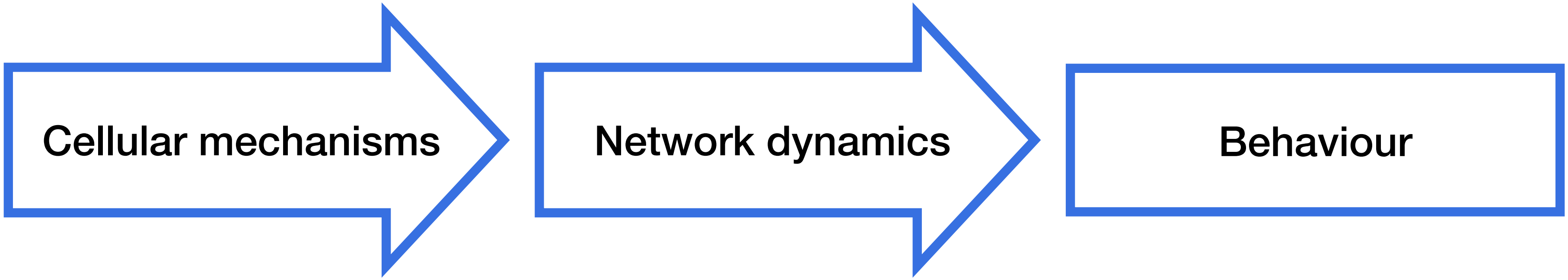
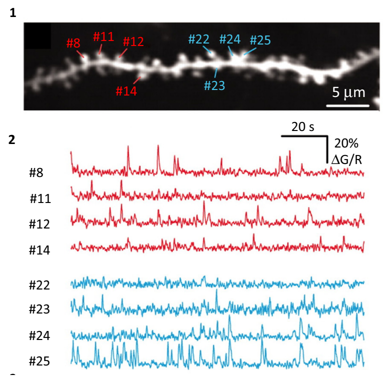
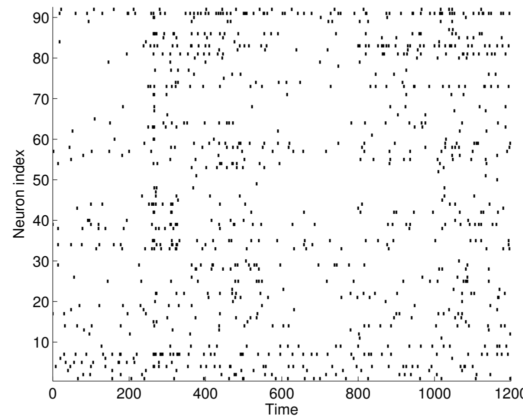
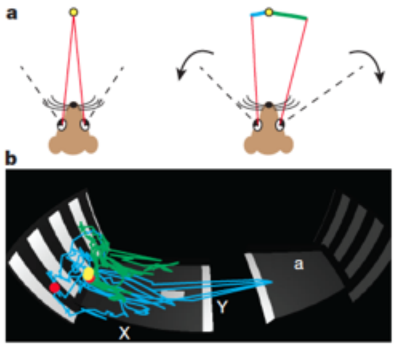
SFB 1089


Cellular mechanisms
Network dynamics
Behaviour



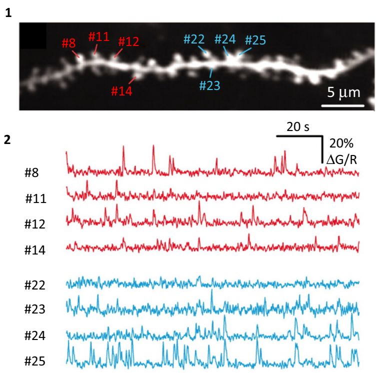
Takahashi et al 2012





Wallace, Greenberg, Sawinsinki et al 2013

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



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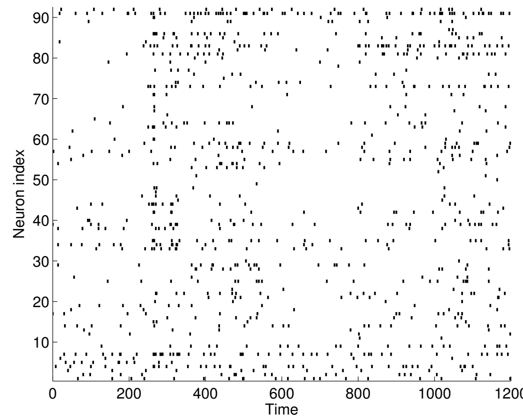
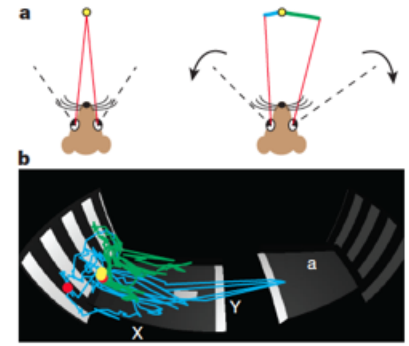
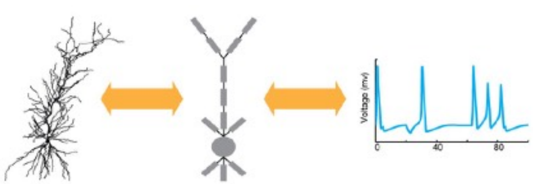




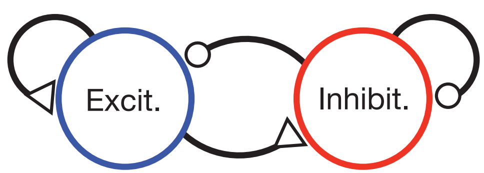
Wallace, Greenberg, Sawinsinki et al 2013

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

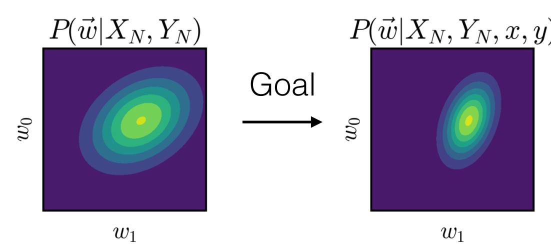
$$C\frac{\dot{V}(t)}{dt} = \sum_c \bar{g}_c g_c(t)[E_c - V(t)] + I(t)$$



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



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



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

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Multi-compartment

- designed using mechanistic principles

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- hard to fit to data

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Generalized linear models

RNNs

- built with statistical convenience in mind

Analysis

Deep Nets

Mechanistic models vs. Statistical/ML models

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- hard to fit to data

Biophysical network simulations

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?

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→ Simulation-based inference comes to the rescue!

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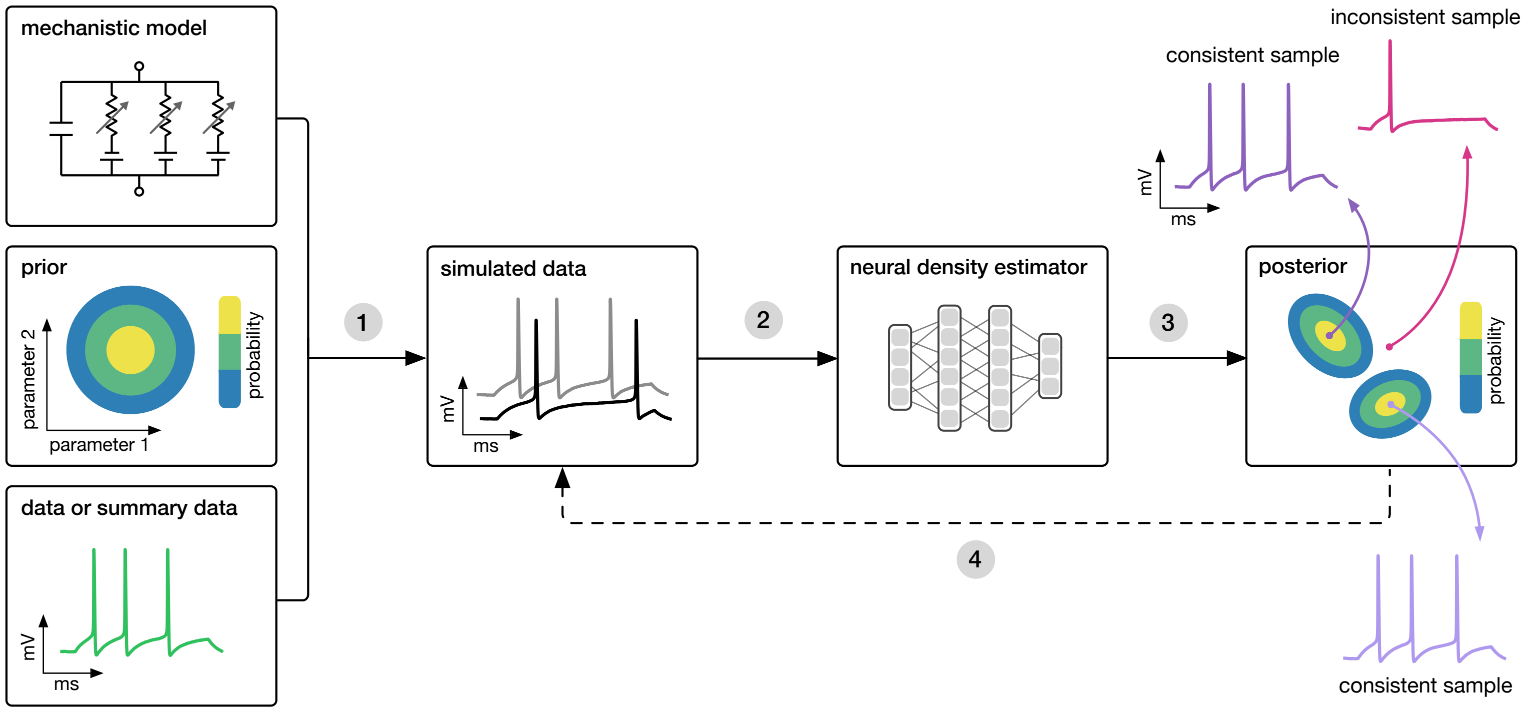
→ Simulation-based inference comes to the rescue!

→ A couple of applications

Train neural networks to identify mechanistic models which are consistent with data and prior knowledge

Sequential Neural Posterior Estimation, SNPE (details later in the workshop)



Lueckmann*, Goncalves* et al, NeurIPS 2017
Greenberg et al, ICML 2019
Goncalves*, Lueckmann*, Deistler* et al, eLife 2020

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

Hodgkin-Huxley type voltage dynamics:

$$C_m \frac{dV}{dt} = g_{\mathrm{leak}}(E_{\mathrm{leak}} - V) + \bar{g}_{\mathrm{Na}} m^3 h (E_{\mathrm{Na}} - V) + \bar{g}_{\mathrm{K}} n^4 (E_{\mathrm{K}} - V) + \bar{g}_M p (E_{\mathrm{K}} - V) + I_{\mathrm{inj}} + \sigma(t)$$

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Channel kinetics (Pospischil et al. 2008):

Activation **m** and inactivation **h** of sodium

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(V)\,(1-m) \;-\; \beta_m(V)\,m$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(V)\,(1-h) \;-\; \beta_h(V)\,h$$

$$\alpha_m = \frac{-0.32\,(V - V_T - 13)}{\exp[-(V - V_T - 13)/4] - 1}$$

$$\beta_m = \frac{0.28\,(V - V_T - 40)}{\exp[(V - V_T - 40)/5] - 1}$$

$$\alpha_h = 0.128\,\exp[-(V - V_T - 17)/18]$$

$$\beta_h = \frac{4}{1 + \exp[-(V - V_T - 40)/5]}.$$

Activation **n** of potassium

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(V)\,(1-n) \;-\; \beta_n(V)\,n$$

$$\alpha_n = \frac{-0.032\,(V - V_T - 15)}{\exp[-(V - V_T - 15)/5] - 1}$$

$$\beta_n = 0.5\,\exp[-(V - V_T - 10)/40]$$

Slow activation **p** of potassium

$$\frac{\mathrm{d}p}{\mathrm{d}t} = (p_\infty(V) - p)/\tau_p(V)$$

$$p_\infty(V) = \frac{1}{1 + \exp[-(V + 35)/10]}$$

$$\tau_p(V) = \frac{\tau_{\max}}{3.3\,\exp[(V + 35)/20] + \exp[-(V + 35)/20]}$$

Inference of 8 biophysical parameters in Hodgkin-Huxley models

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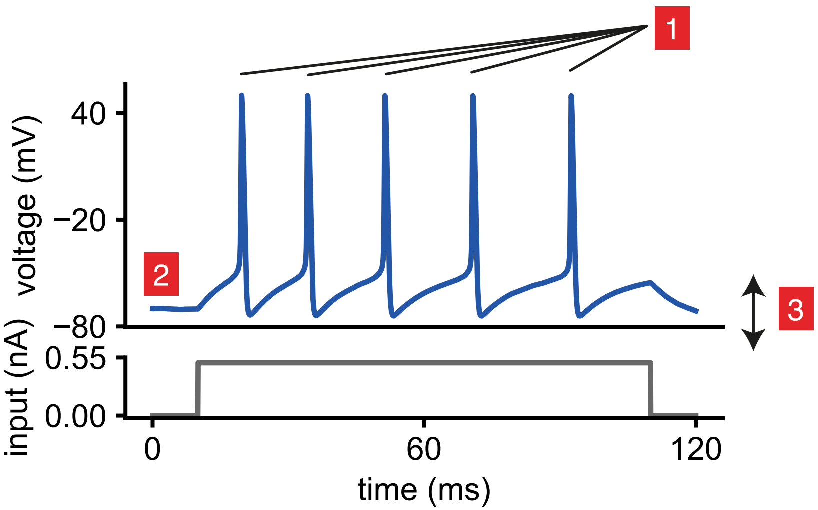
Summary statistics of interest

original data (simulated)



(1) number of spikes
(2) mean resting potential
(3) STD of resting potential
(4-7) the first four voltage moments

Summary statistics of interest

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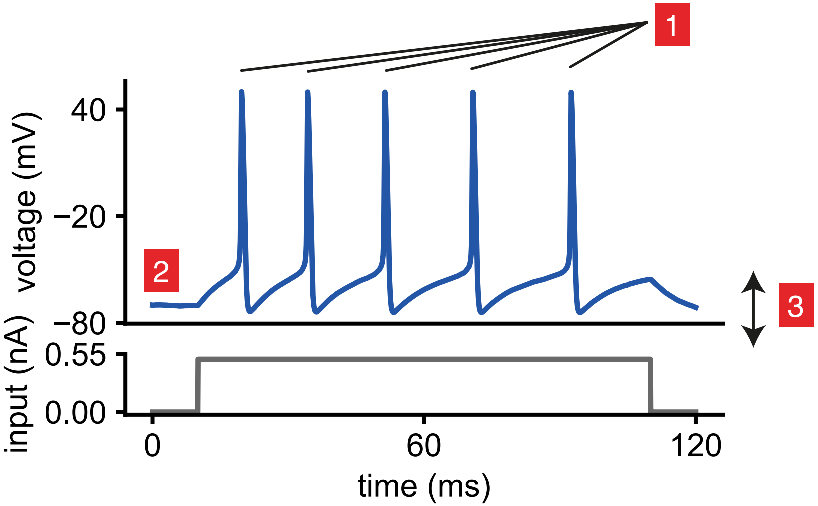

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Why **these** summary statistics?

Summary statistics of interest

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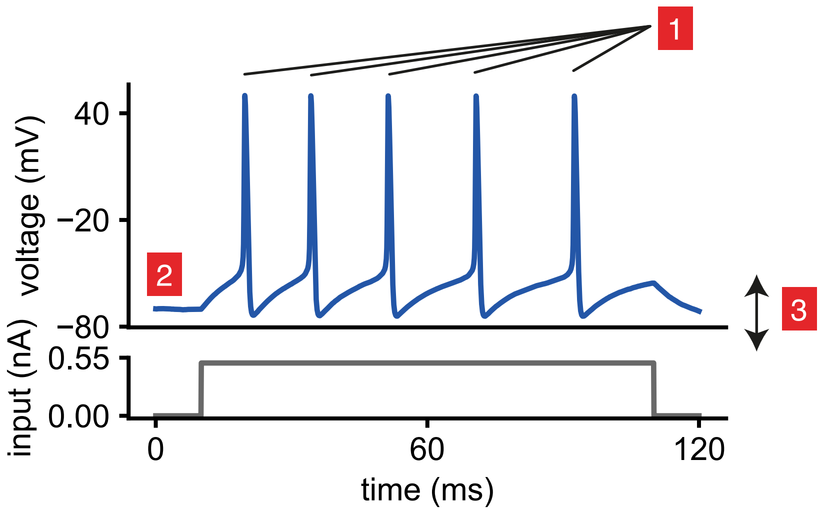


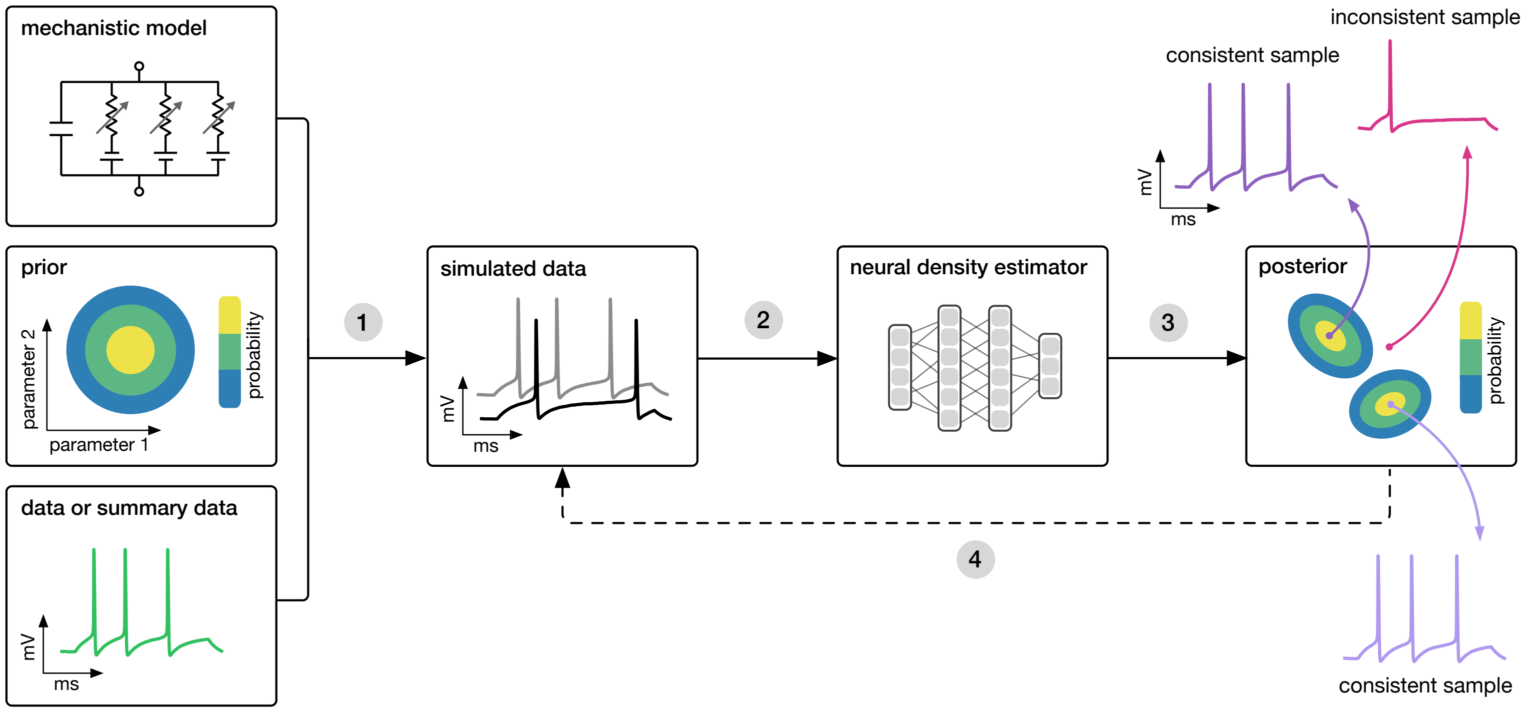
(1) number of spikes
(2) mean resting potential
(3) STD of resting potential
(4-7) the first four voltage moments

Why **these** summary statistics?

- prior modelling work suggests that some are related to the parameters of interest
- exploration of new summary statistics

Train neural networks to identify mechanistic models which are consistent with data and prior knowledge

Sequential Neural Posterior Estimation, SNPE



Lueckmann*, Goncalves* et al, NeurIPS 2017
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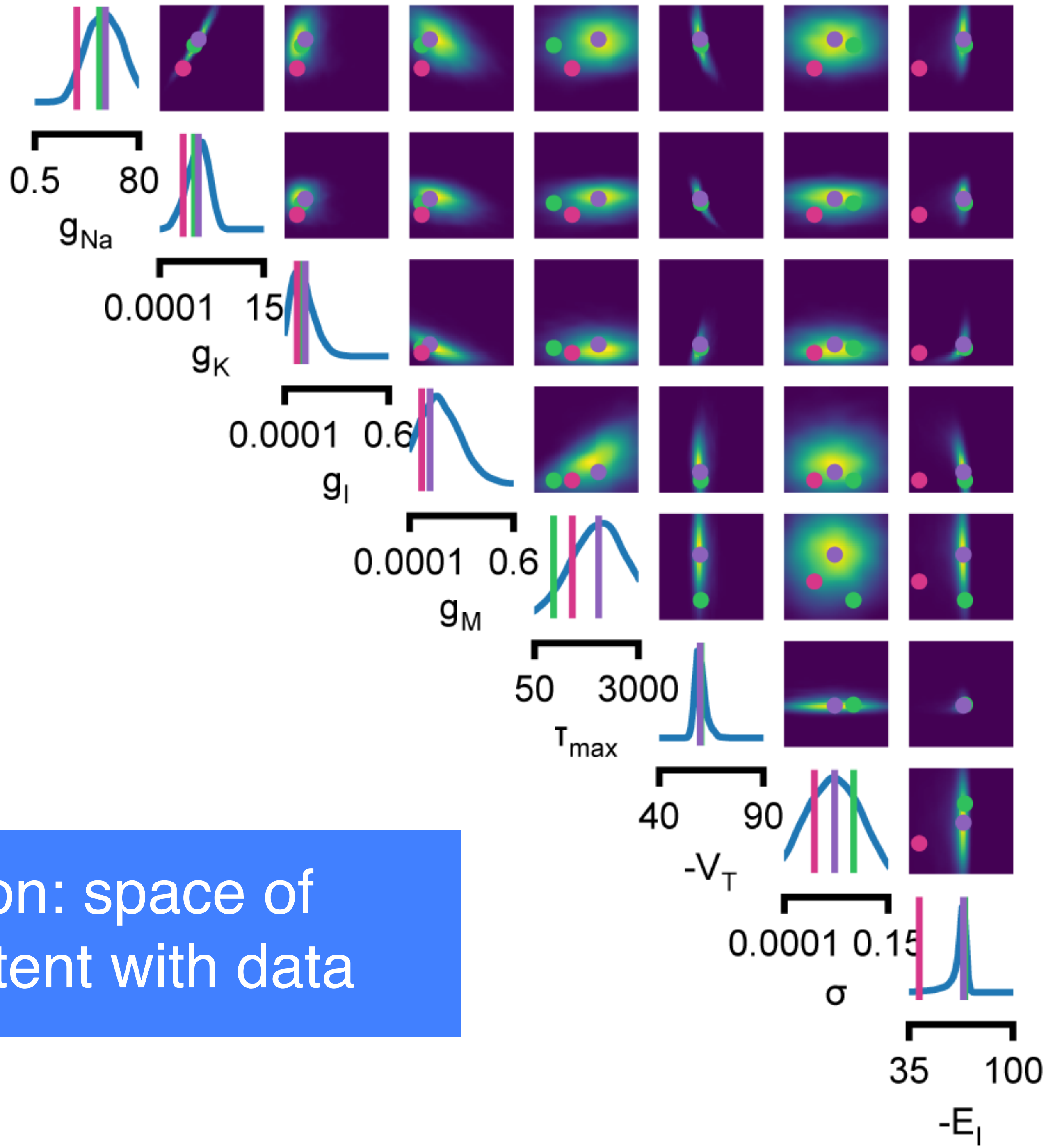
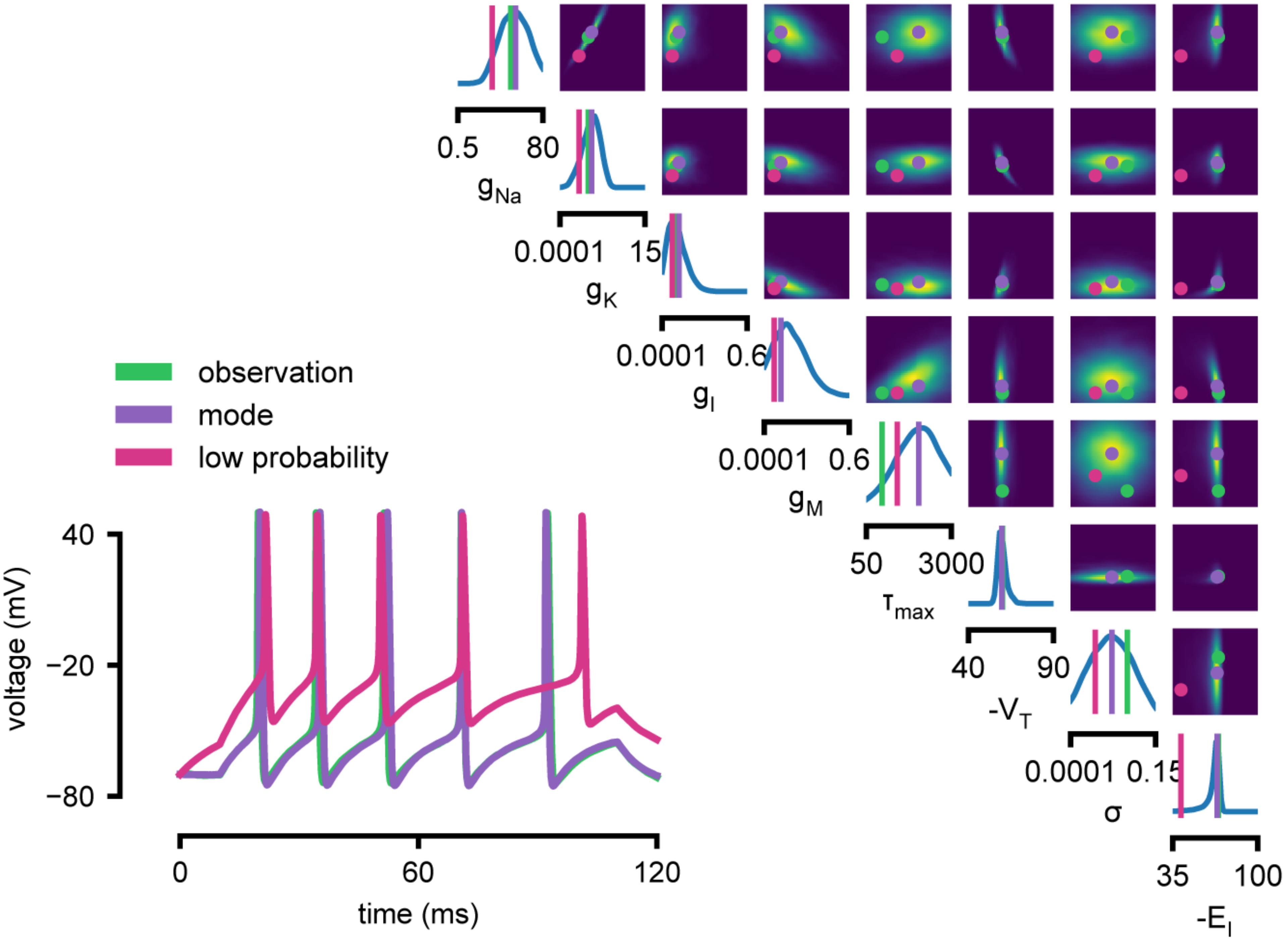
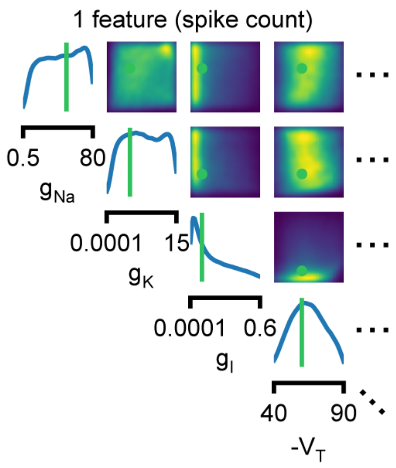


Posterior distribution: space of parameters consistent with data



observation
mode
low probability
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)

Stronger constraints from additional data features



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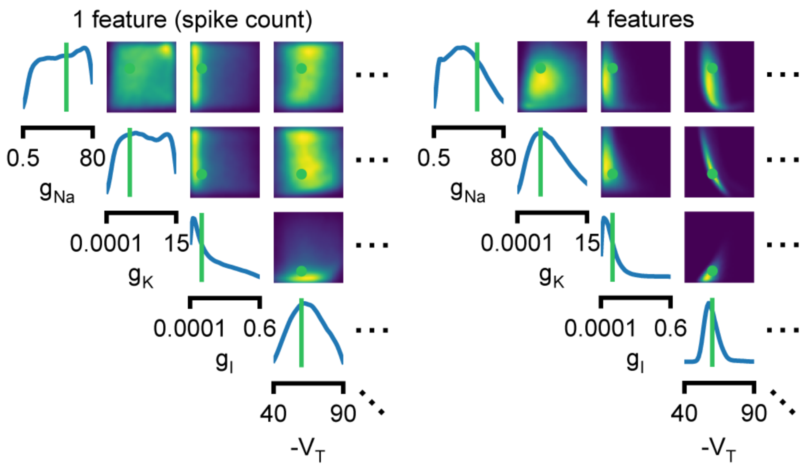
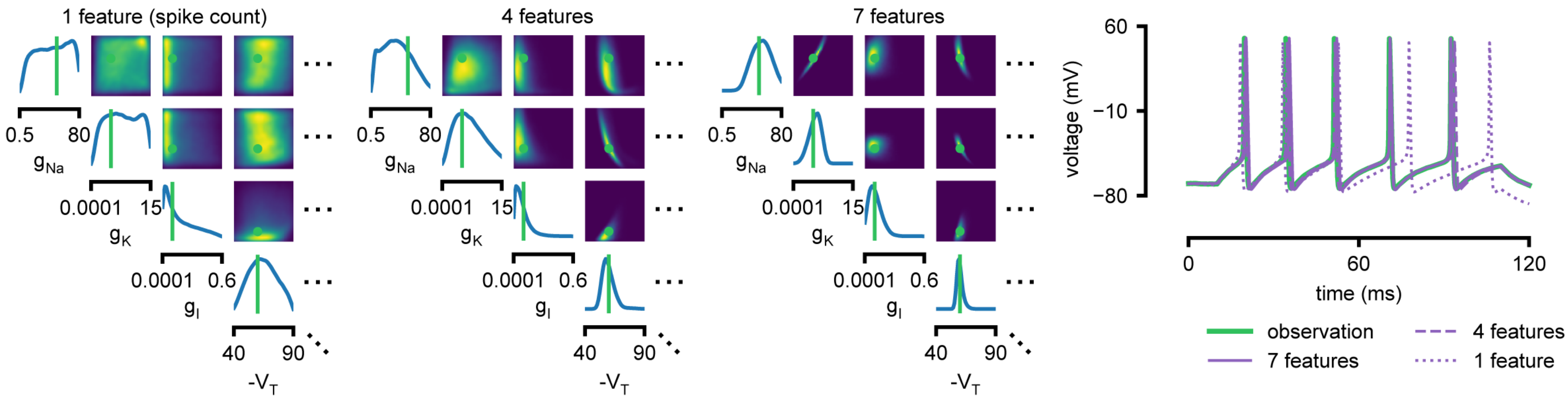


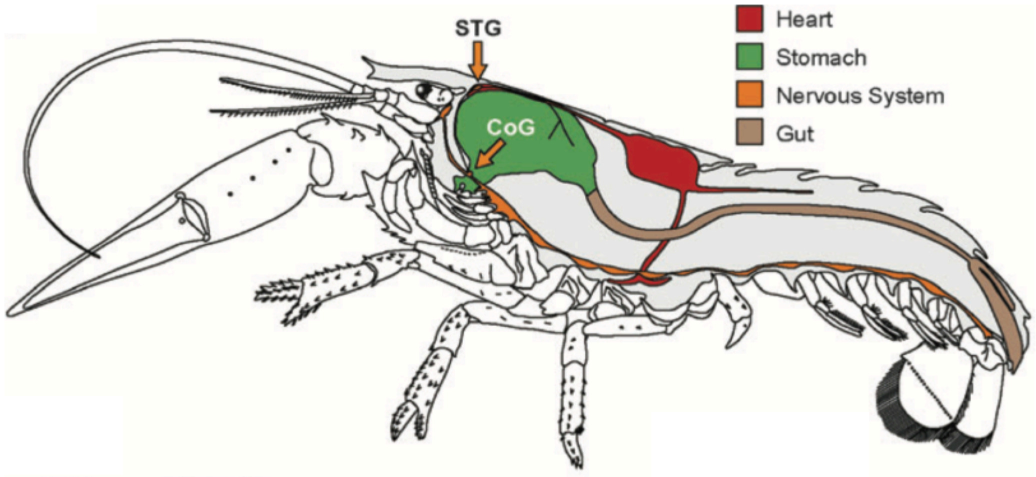
Stronger constraints from additional data features

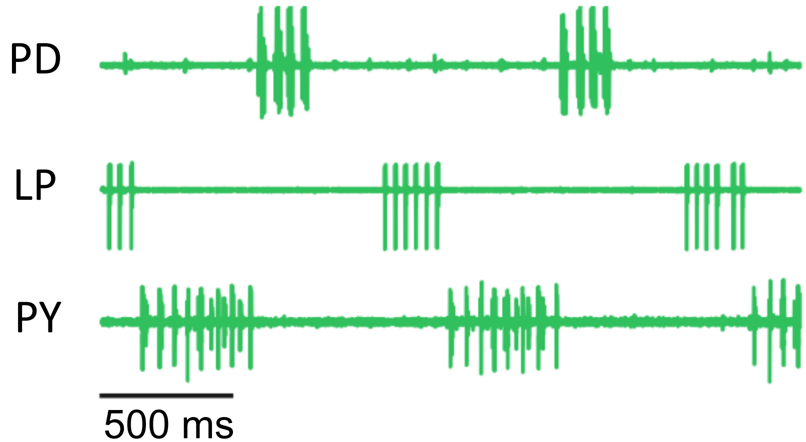


Sensitivity to perturbations in a neural network model

Michael Deistler (work and slides), Kaan Oecal

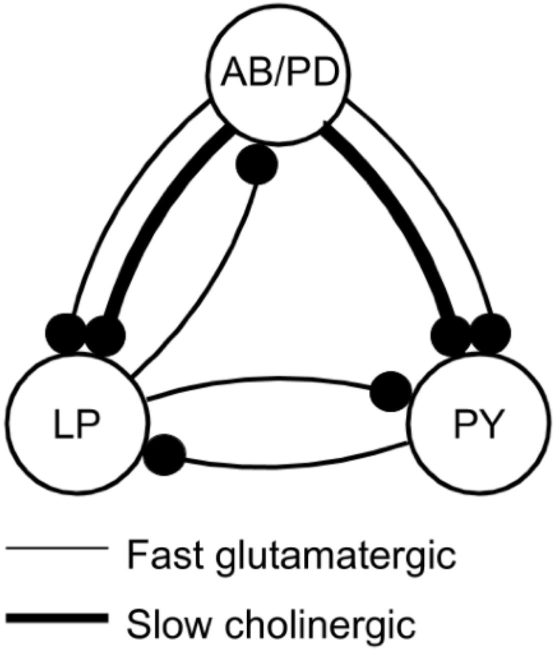
Pyloric network





Marder and Bucher 2007; Haddad and Marder 2018

Model of the pyloric network

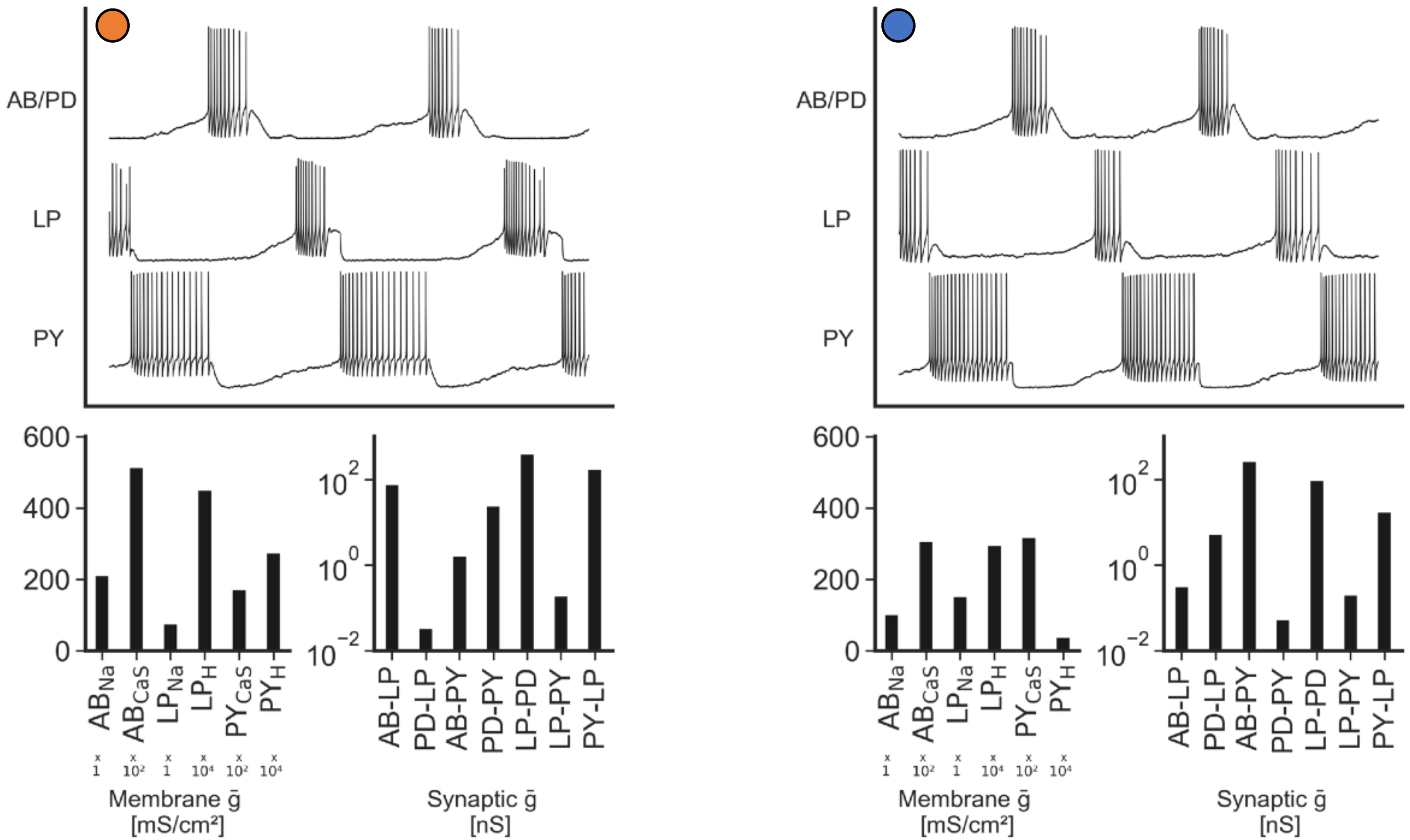


31 parameters:

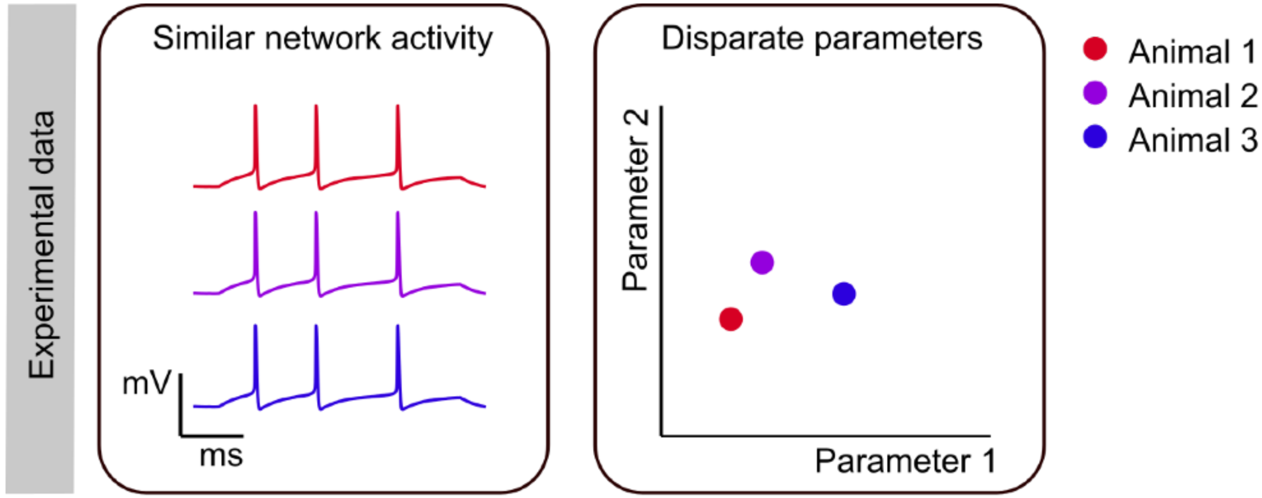
- 8 maximal membrane conductances per neuron
- 7 synaptic strengths

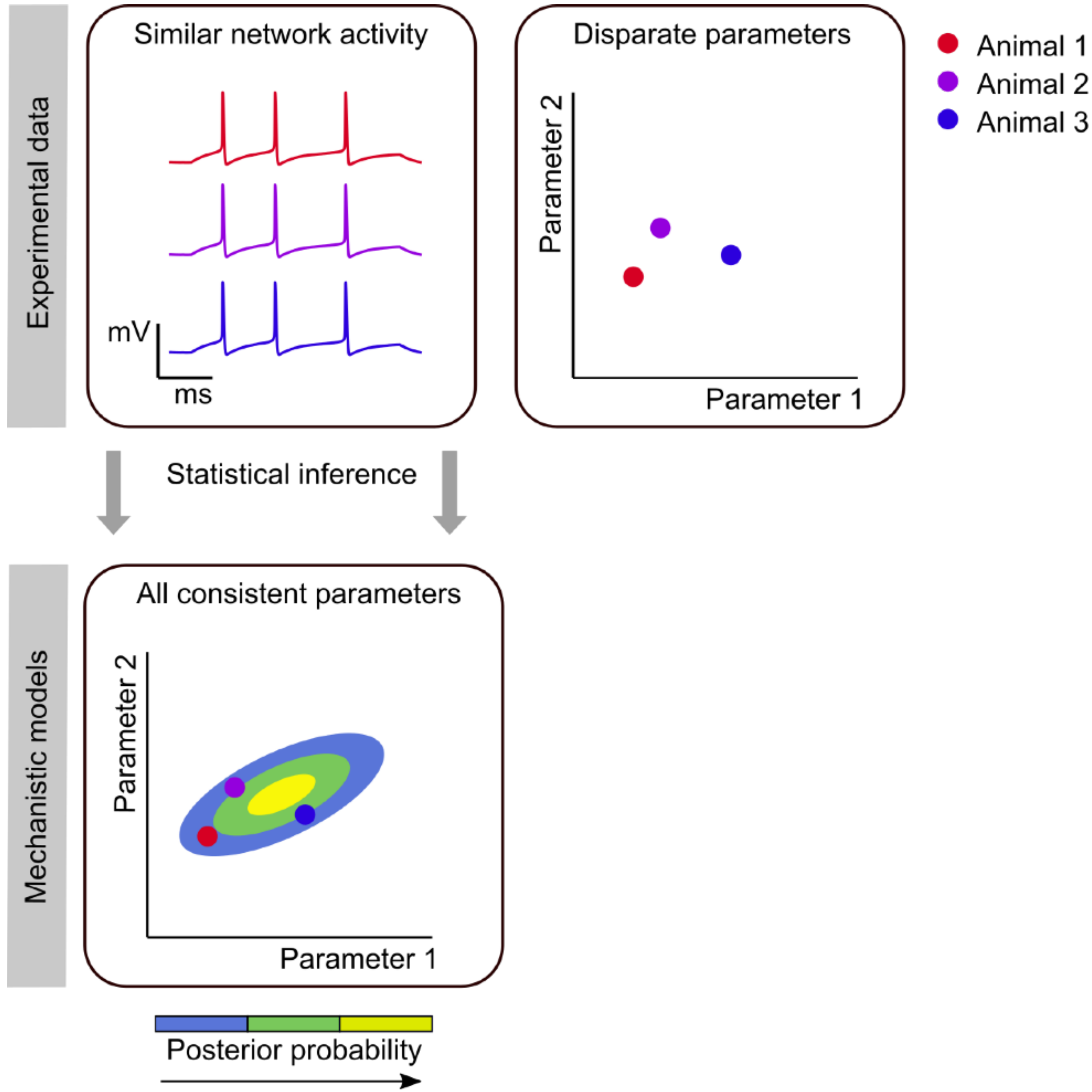
Prinz, Bucher, Marder 2004

Model of the pyloric network

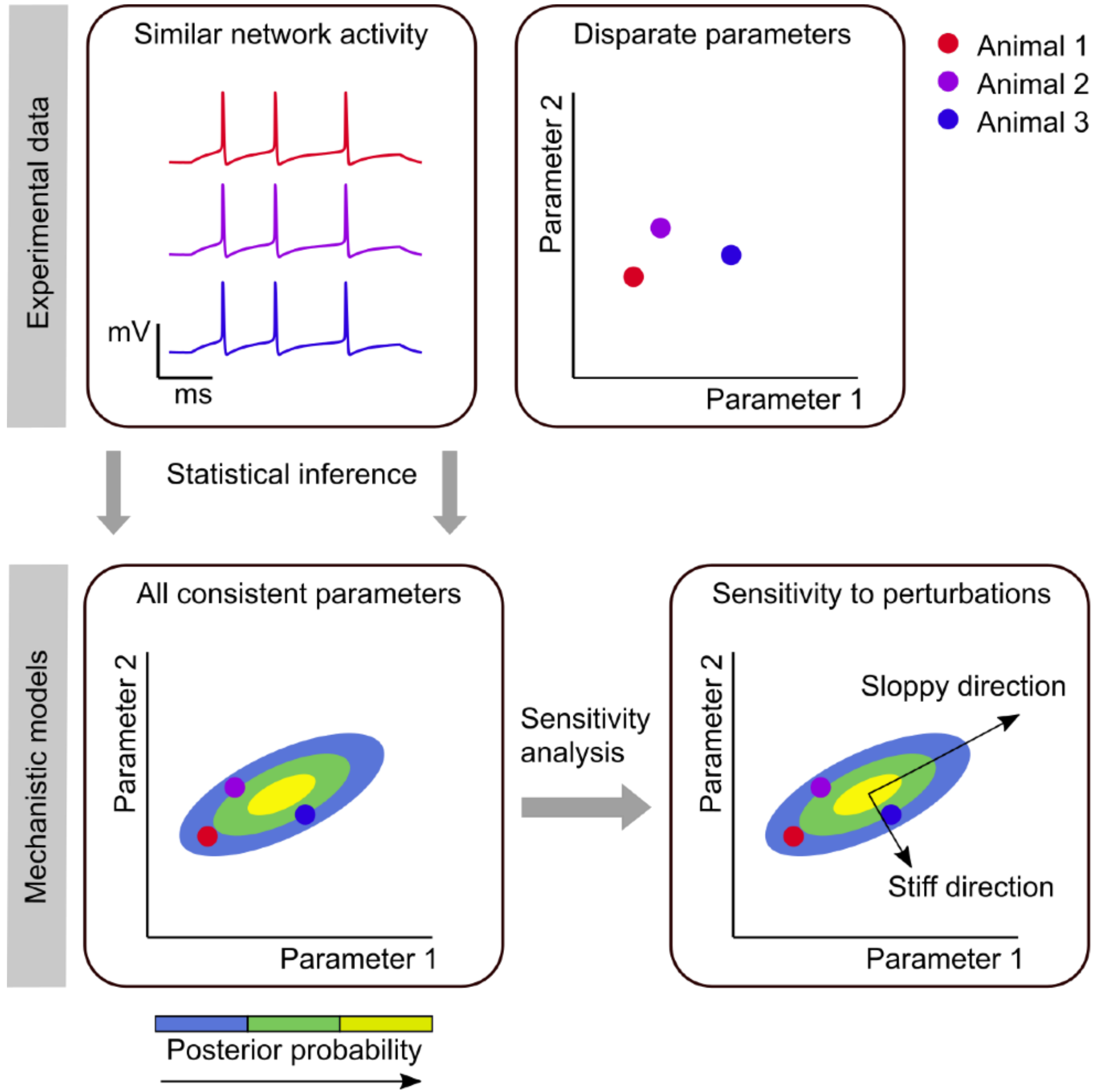


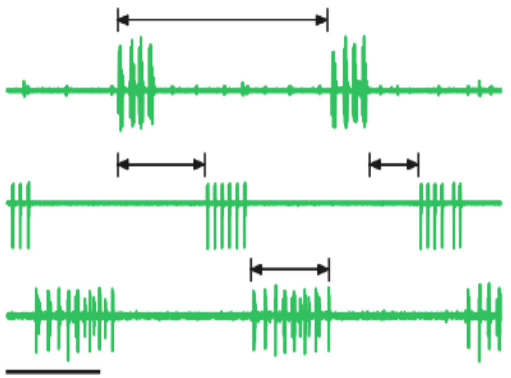
Prinz, Bucher, Marder 2004

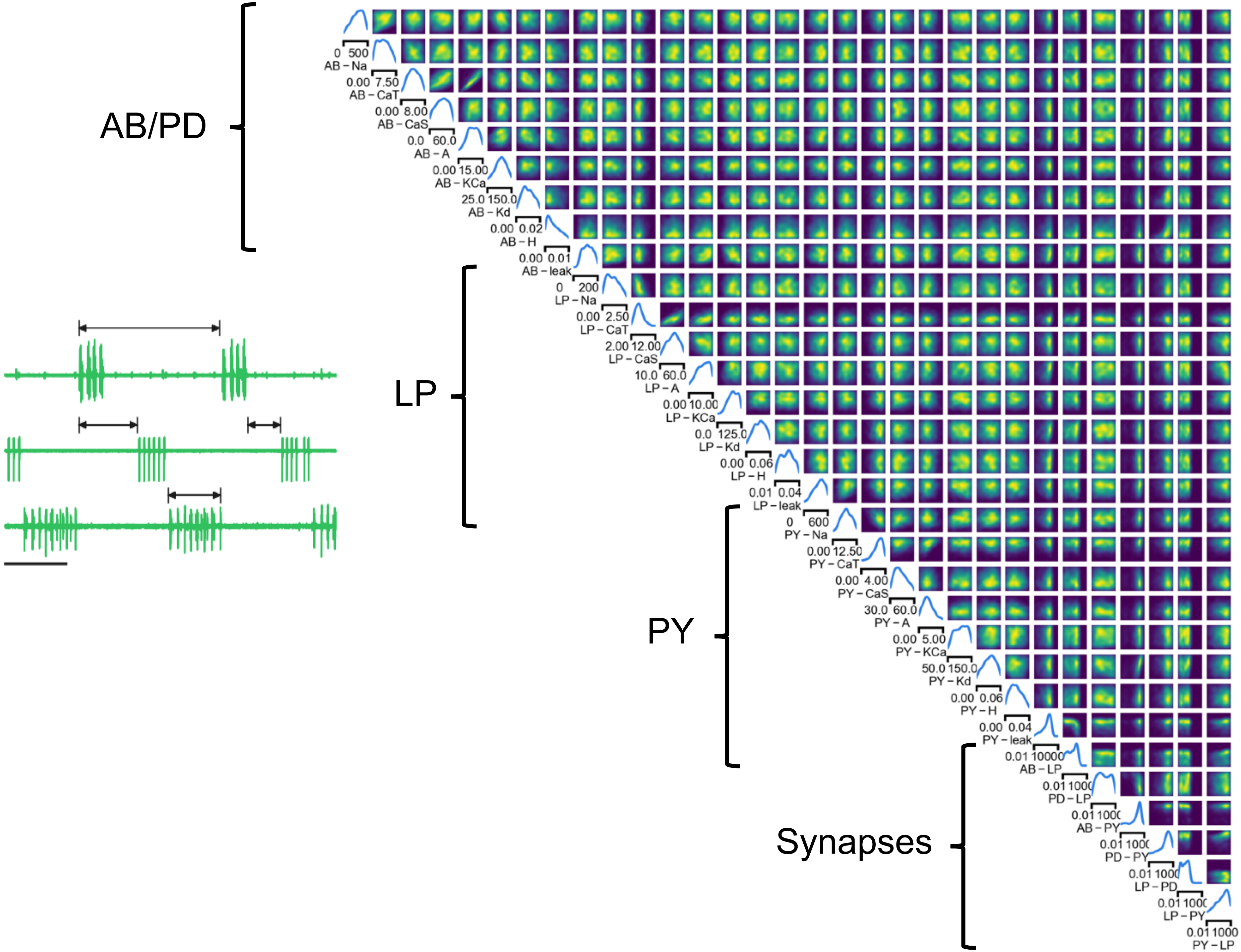

Experimental data
Similar network activity
mV
ms
Disparate parameters
Parameter 2
Parameter 1
Animal 1
Animal 2
Animal 3



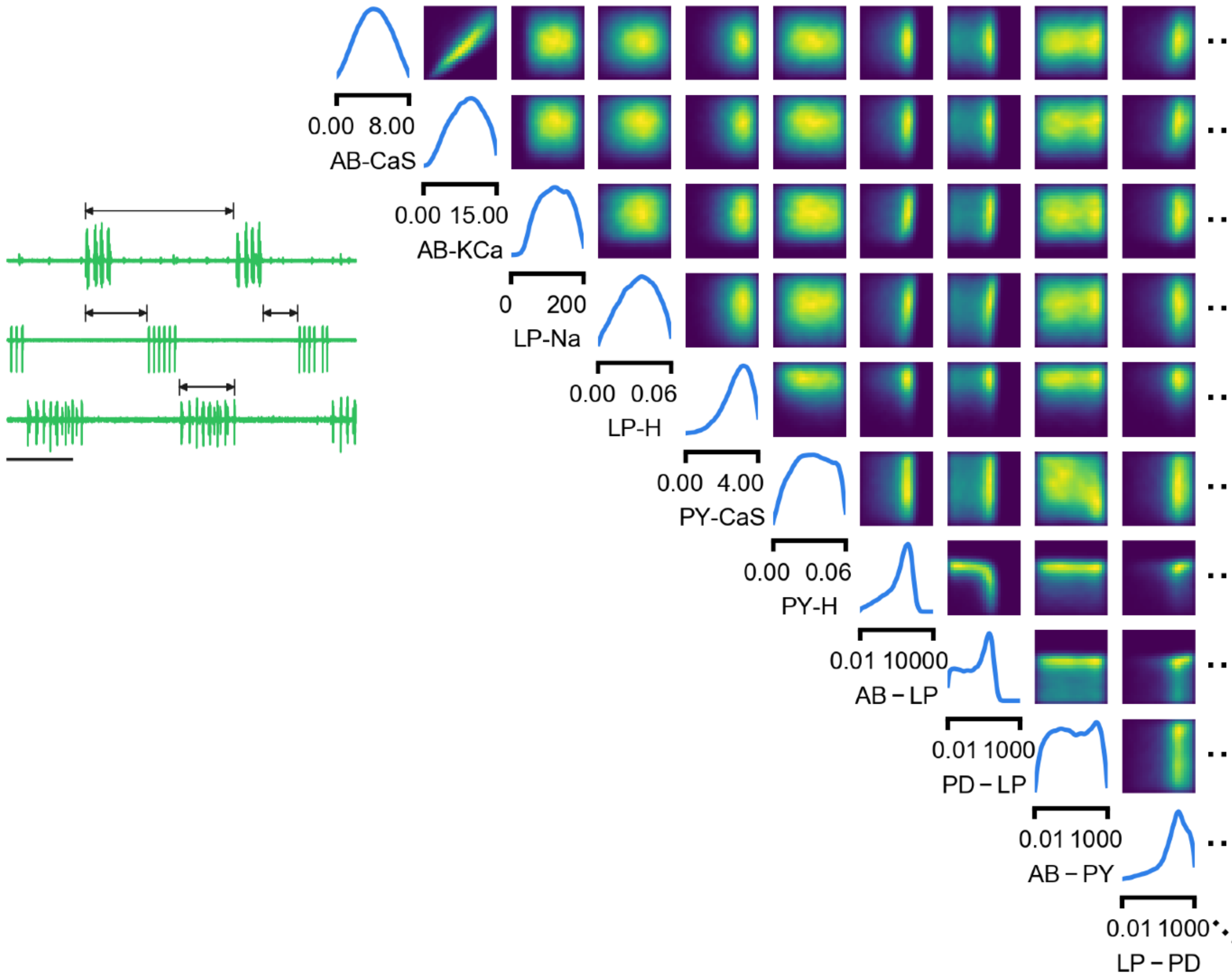
Experimental data
Similar network activity
mV
ms
Disparate parameters
Parameter 2
Parameter 1
Animal 1
Animal 2
Animal 3
Statistical inference
Mechanistic models
All consistent parameters
Parameter 2
Parameter 1
Posterior probability


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
Sensitivity analysis
Sensitivity to perturbations
Parameter 2
Sloppy direction
Stiff direction
Parameter 1
Posterior probability

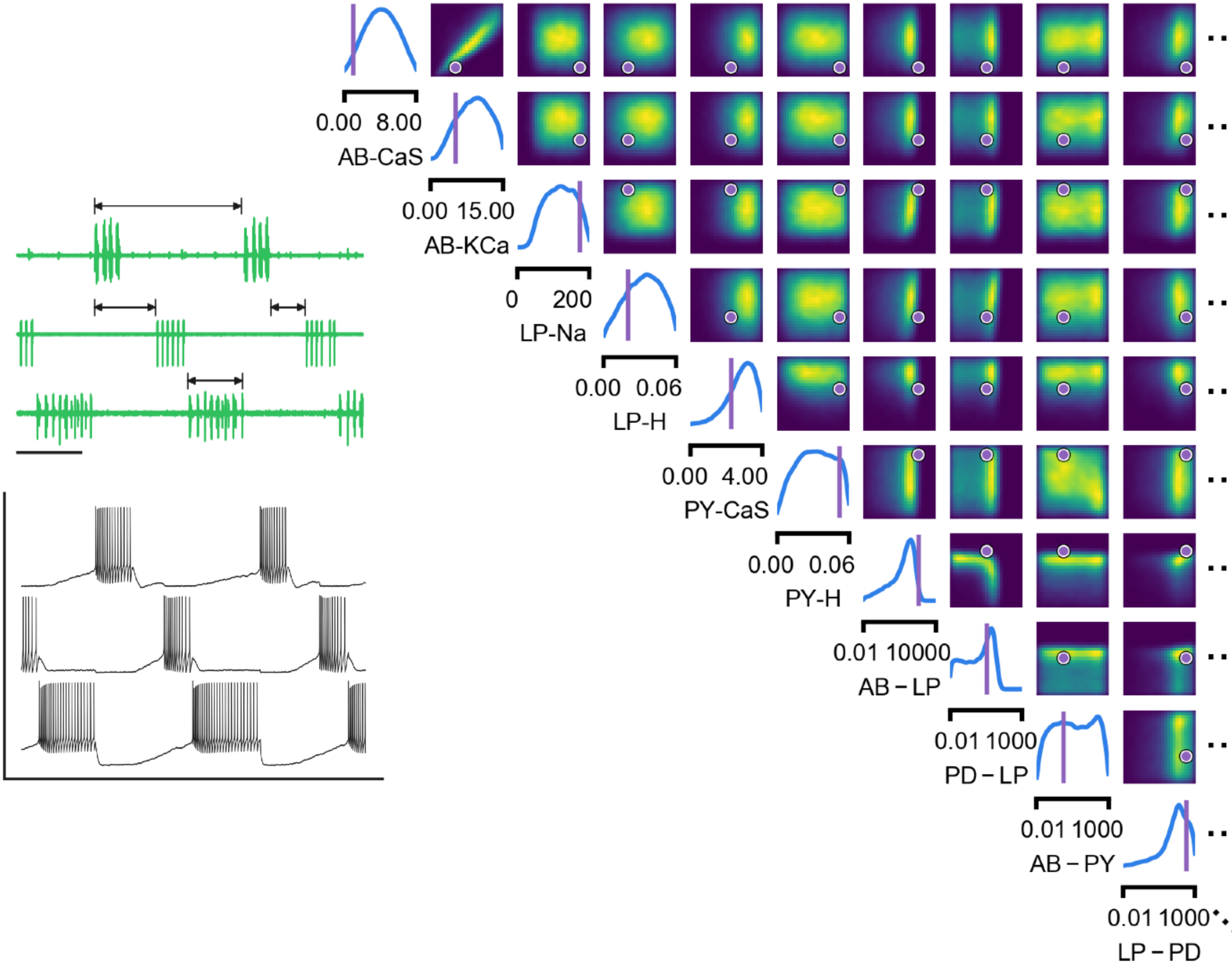




AB/PD
LP
PY
Synapses
0 500
AB – Na
0.00 7.50
AB – CaT
0.00 8.00
AB – CaS
0.0 60.0
AB – A
0.00 15.00
AB – KCa
25.0 150.0
AB – Kd
0.00 0.02
AB – H
0.00 0.01
AB – leak
0 200
LP – Na
0.00 2.50
LP – CaT
2.00 12.00
LP – CaS
10.0 60.0
LP – A
0.00 10.00
LP – KCa
0.0 125.0
LP – Kd
0.00 0.06
LP – H
0.01 0.04
LP – 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
0.01 10000
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

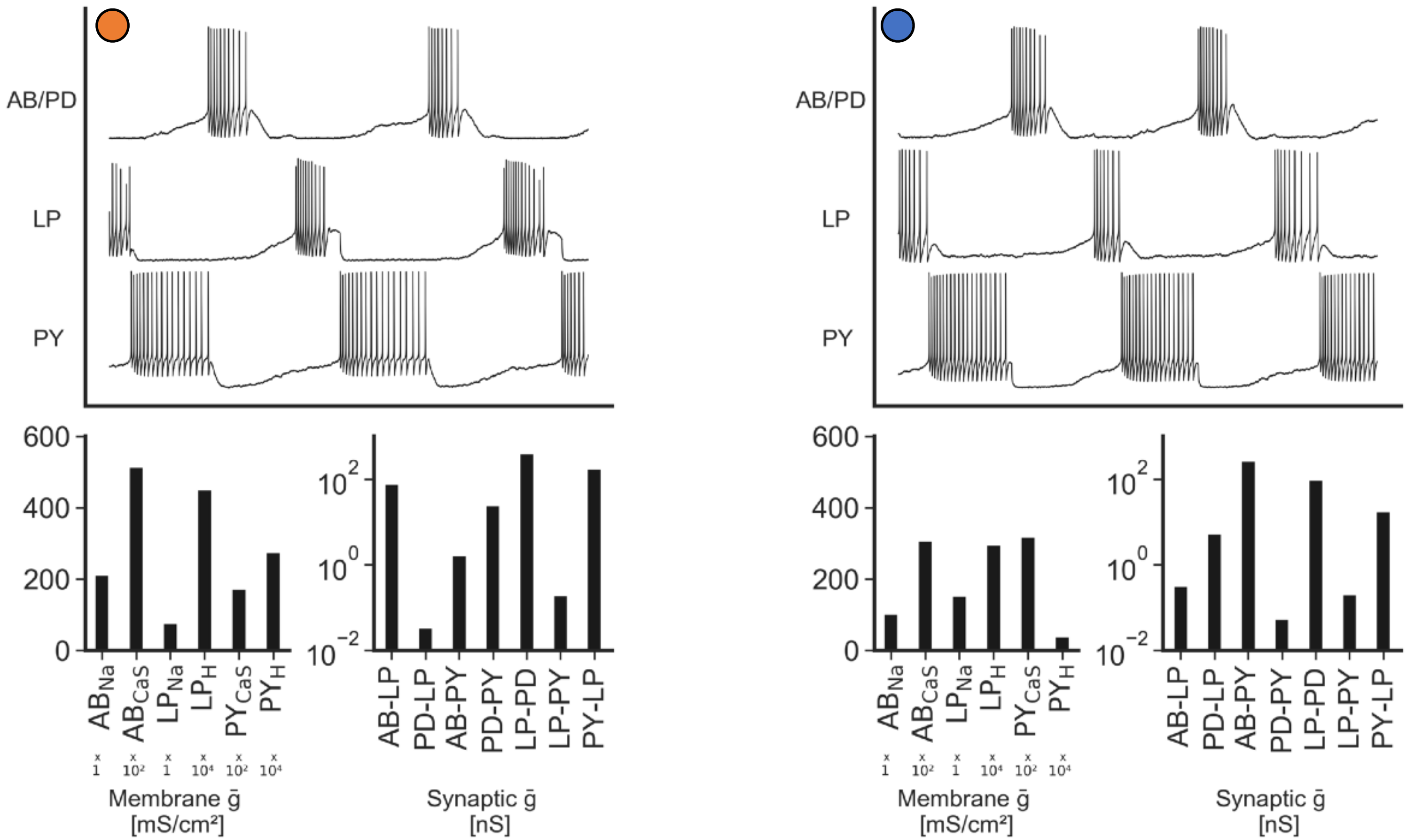


0.00 8.00
AB-CaS
0.00 15.00
AB-KCa
0 200
LP-Na
0.00 0.06
LP-H
0.00 4.00
PY-CaS
0.00 0.06
PY-H
0.01 10000
AB − LP
0.01 1000
PD − LP
0.01 1000
AB − PY
0.01 1000
LP − PD

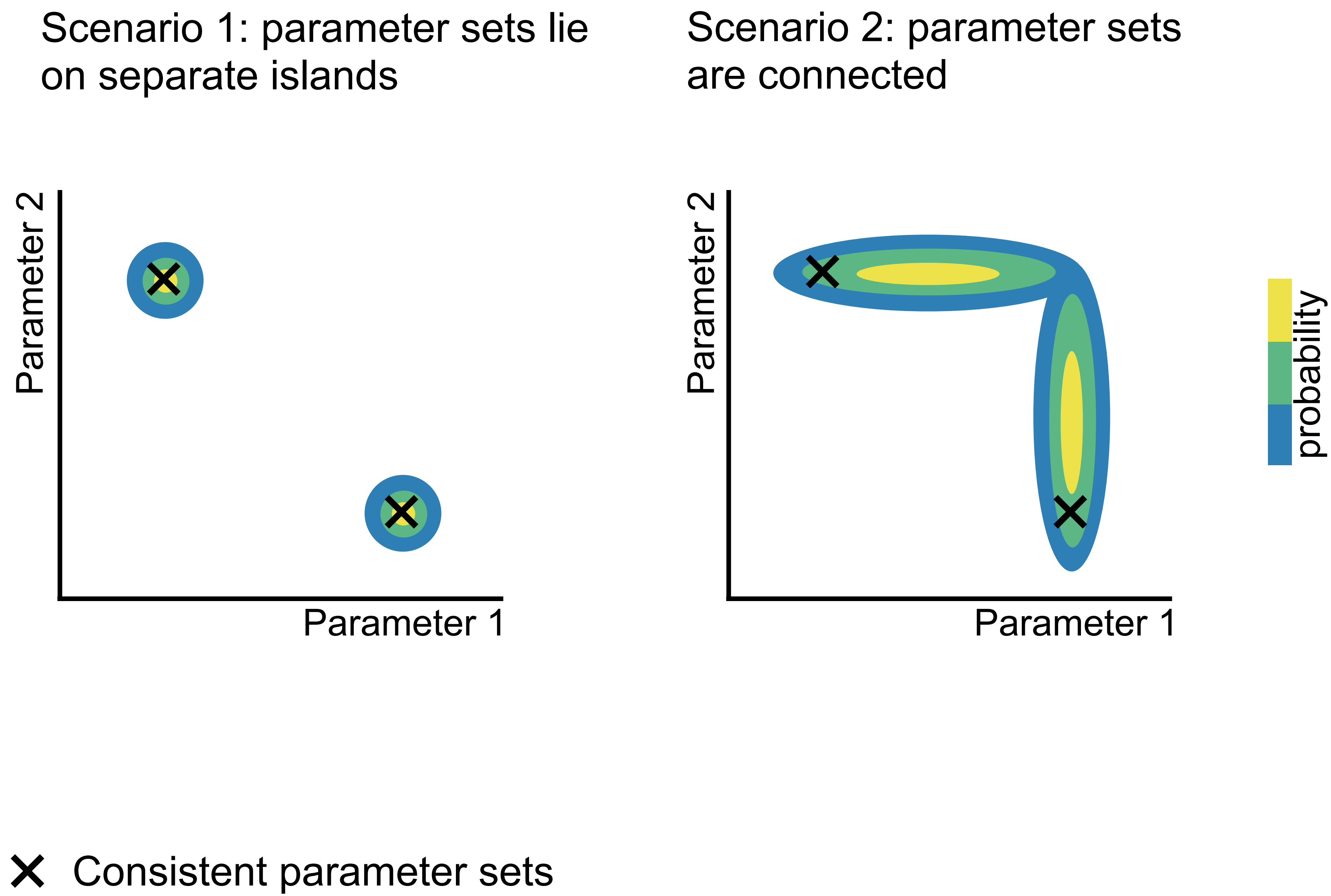
Analysing the posterior

Michael Deistler (work and slides), Kaan Oecal

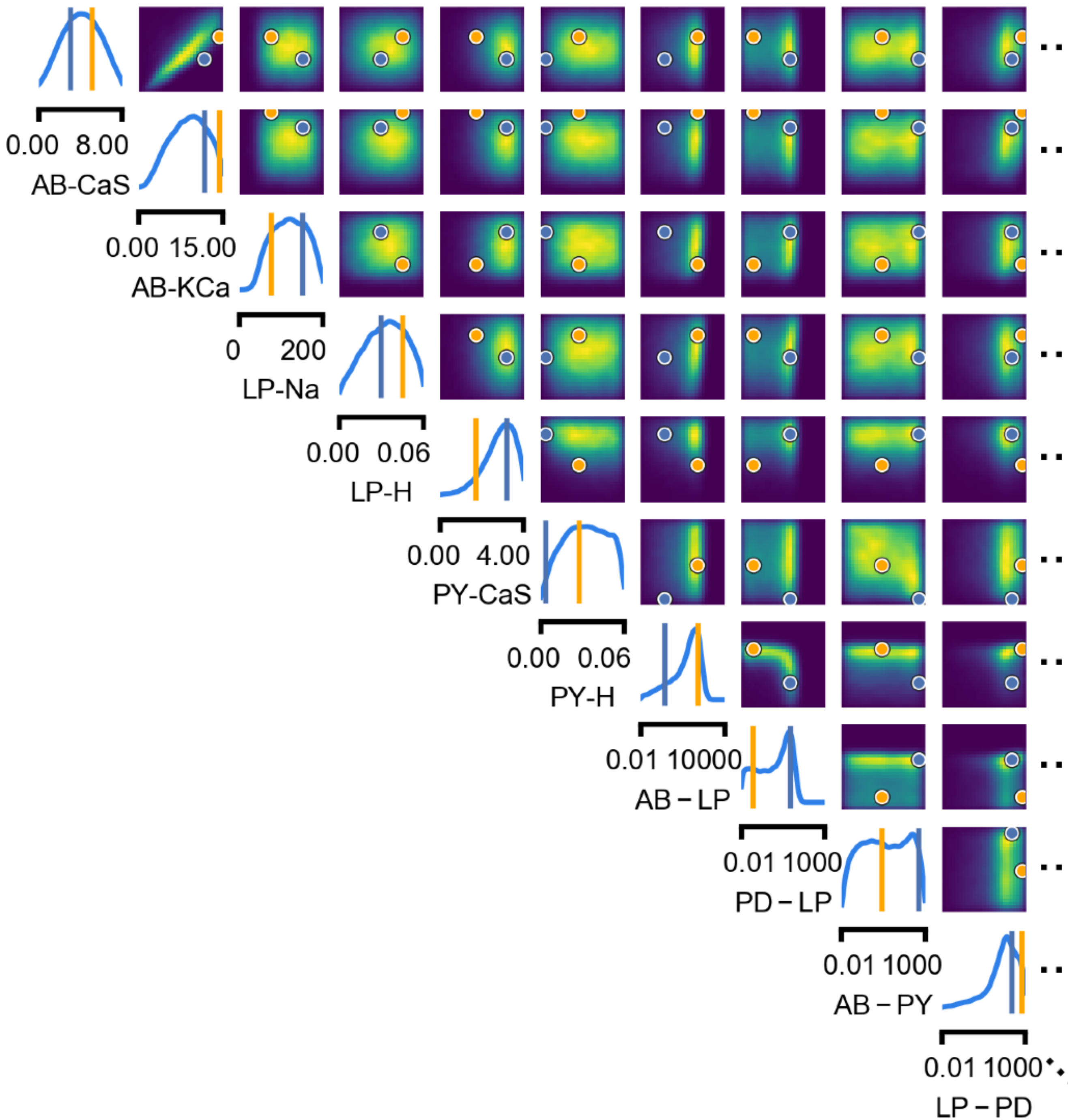
Robustness to perturbations



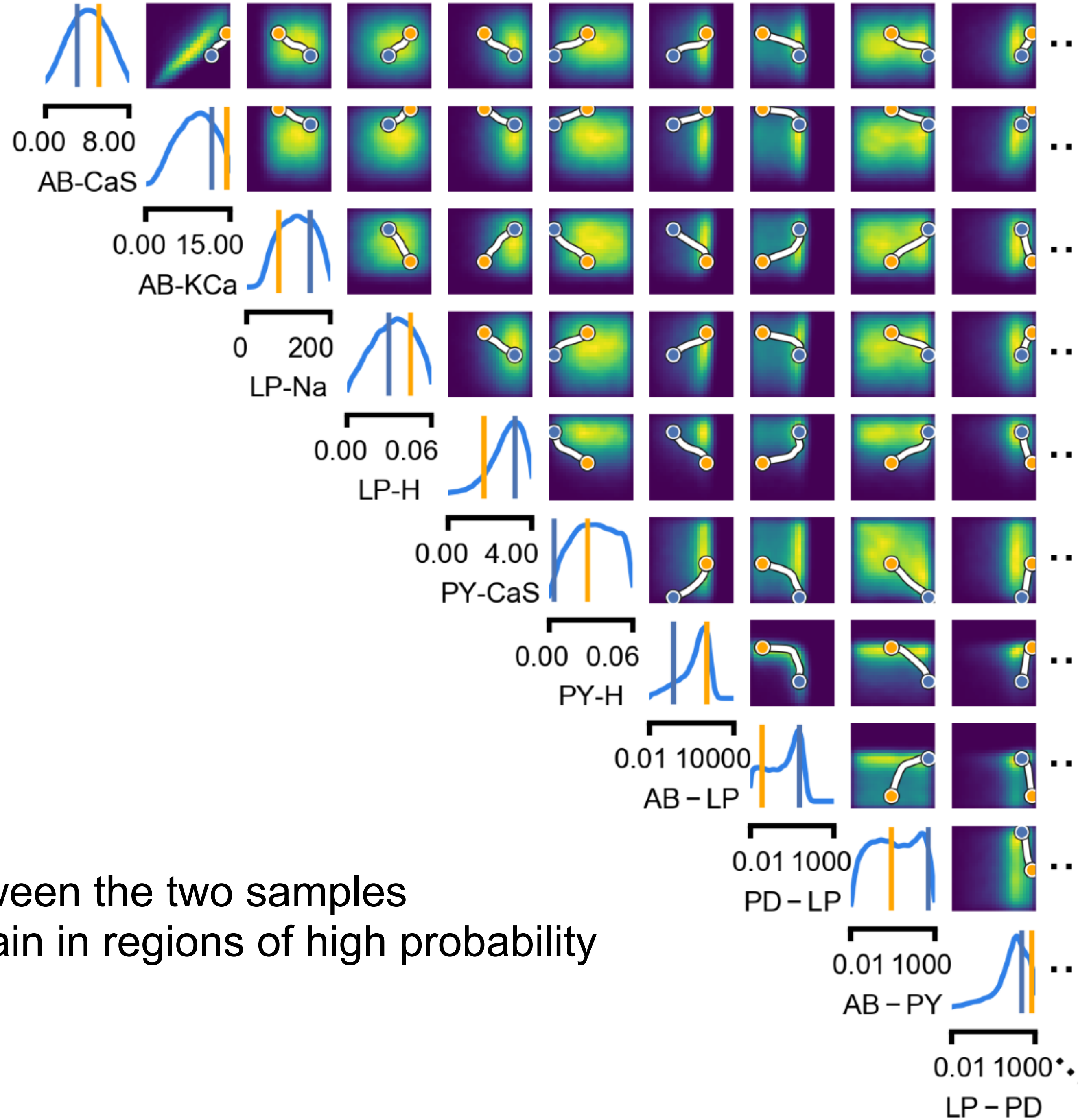
Taylor et al. 2006



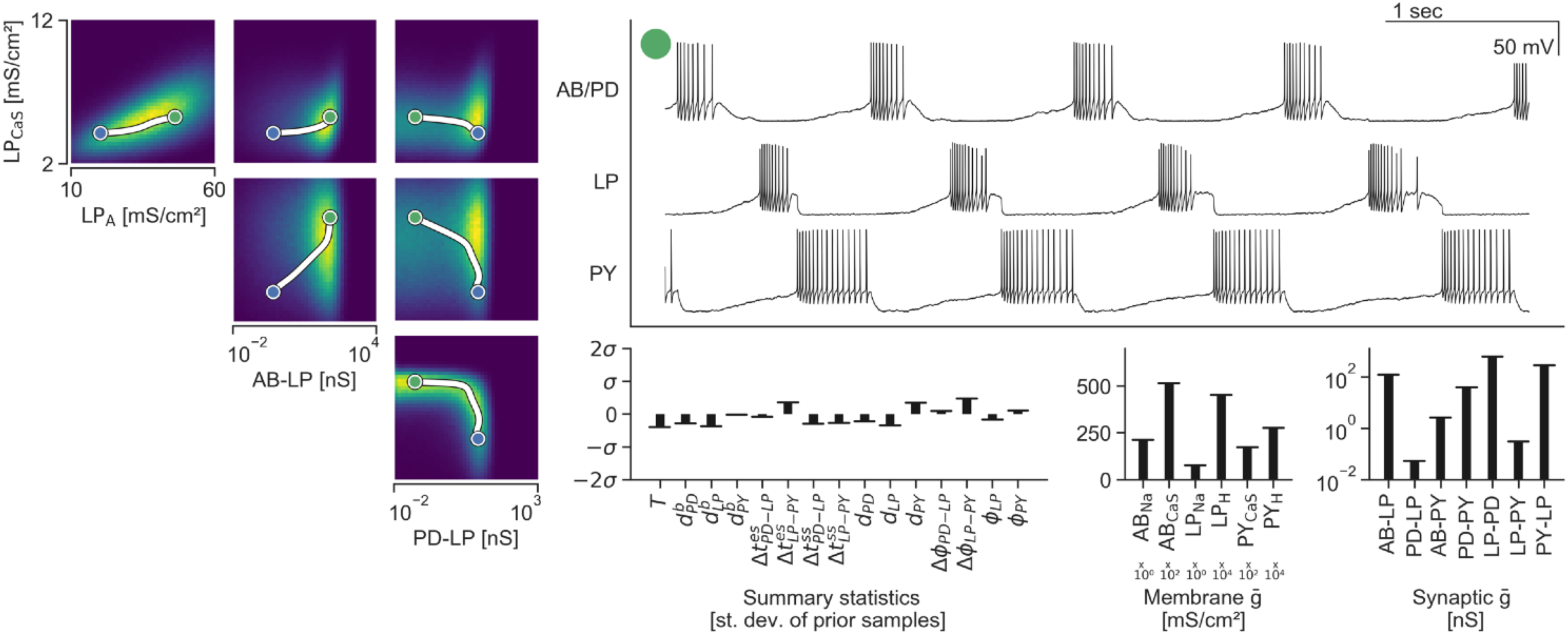
Scenario 1: parameter sets lie on separate islands
Scenario 2: parameter sets are connected
Parameter 2
Parameter 1
Parameter 2
Parameter 1
probability
Consistent parameter sets



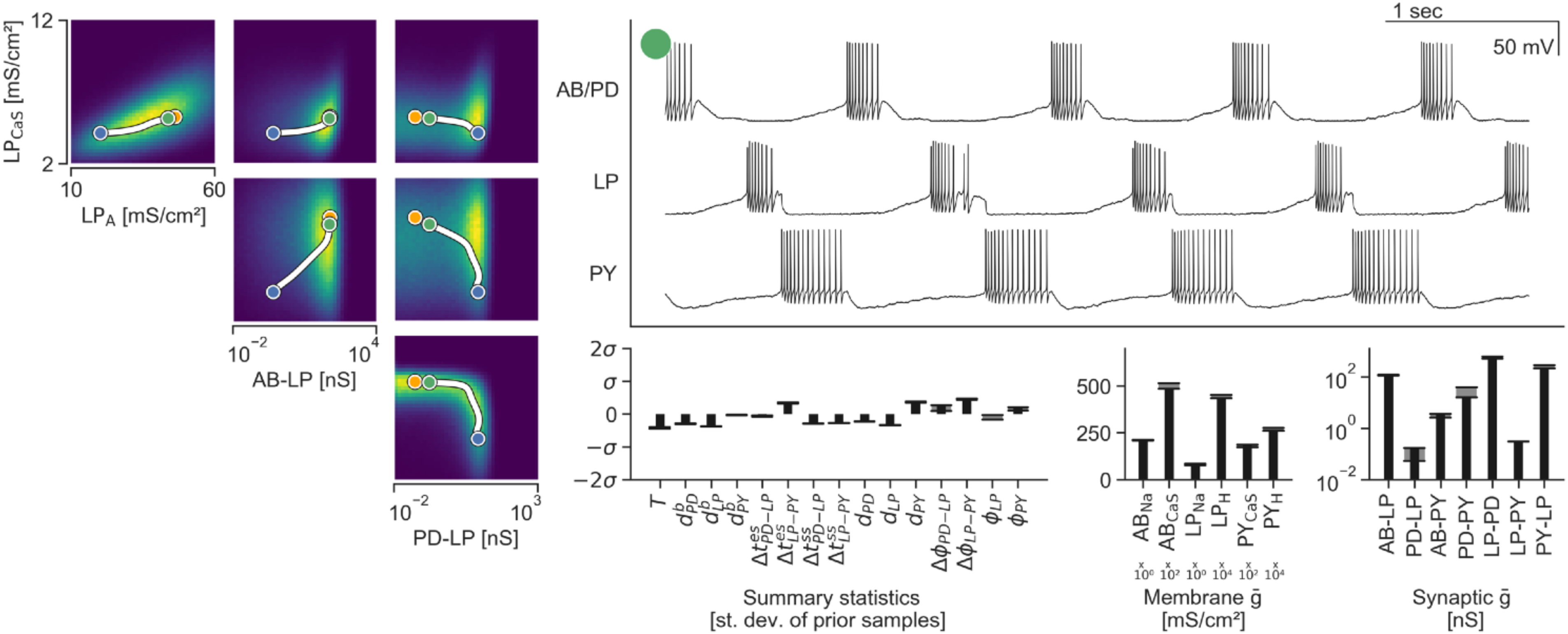
0.00 8.00
AB-CaS
0.00 15.00
AB-KCa
0 200
LP-Na
0.00 0.06
LP-H
0.00 4.00
PY-CaS
0.00 0.06
PY-H
0.01 10000
AB – LP
0.01 1000
PD – LP
0.01 1000
AB – PY
0.01 1000
LP – PD



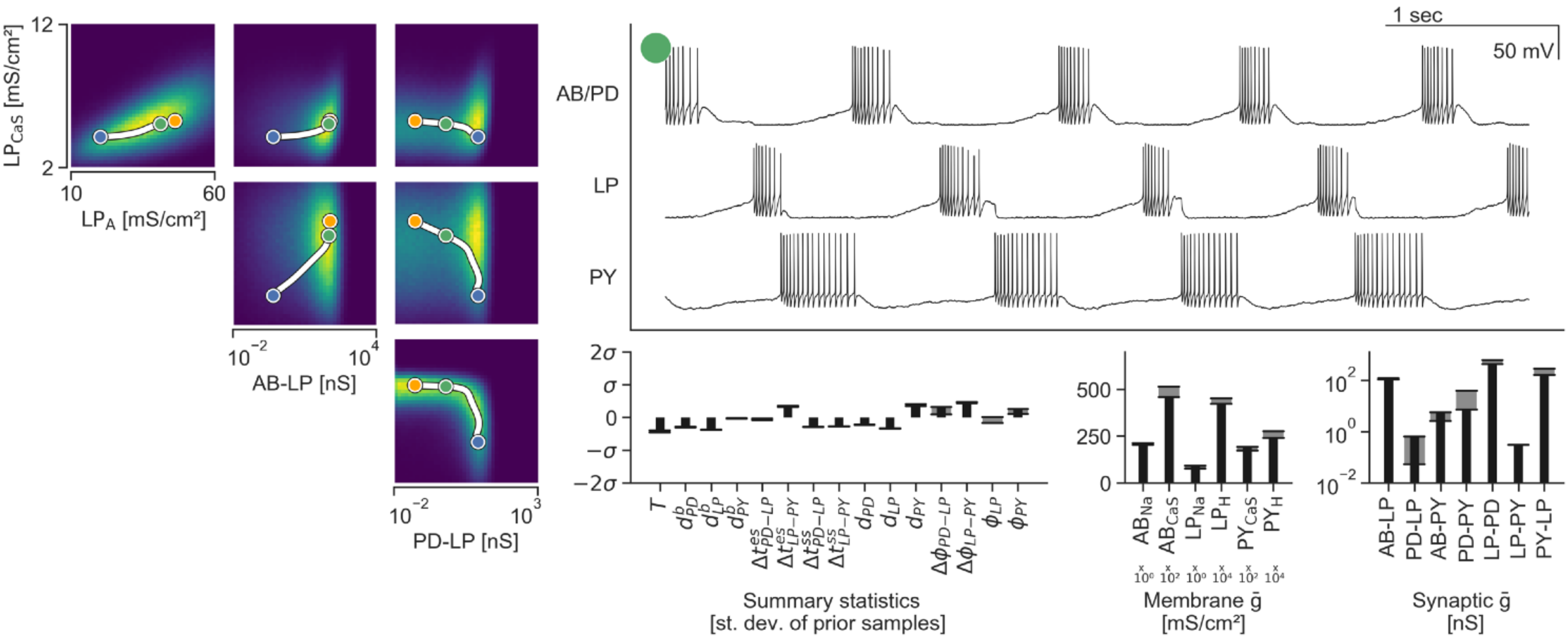
- Find a ‘path’ between the two samples
- Path should remain in regions of high probability



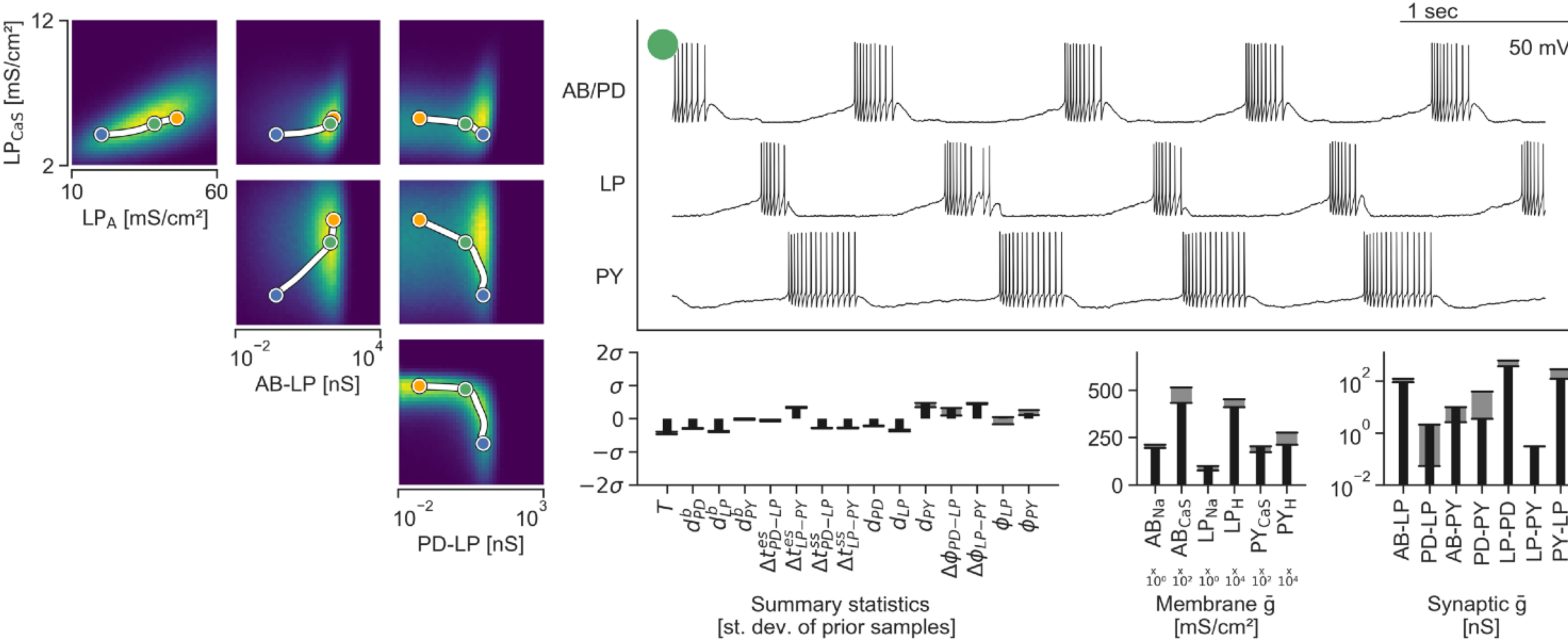
LP$_{CaS}$ [mS/cm²]
12
2
10
60
LP$_A$ [mS/cm²]
AB-LP [nS]
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
Summary statistics
[st. dev. of prior samples]
Membrane ḡ
[mS/cm²]
Synaptic ḡ
[nS]
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP



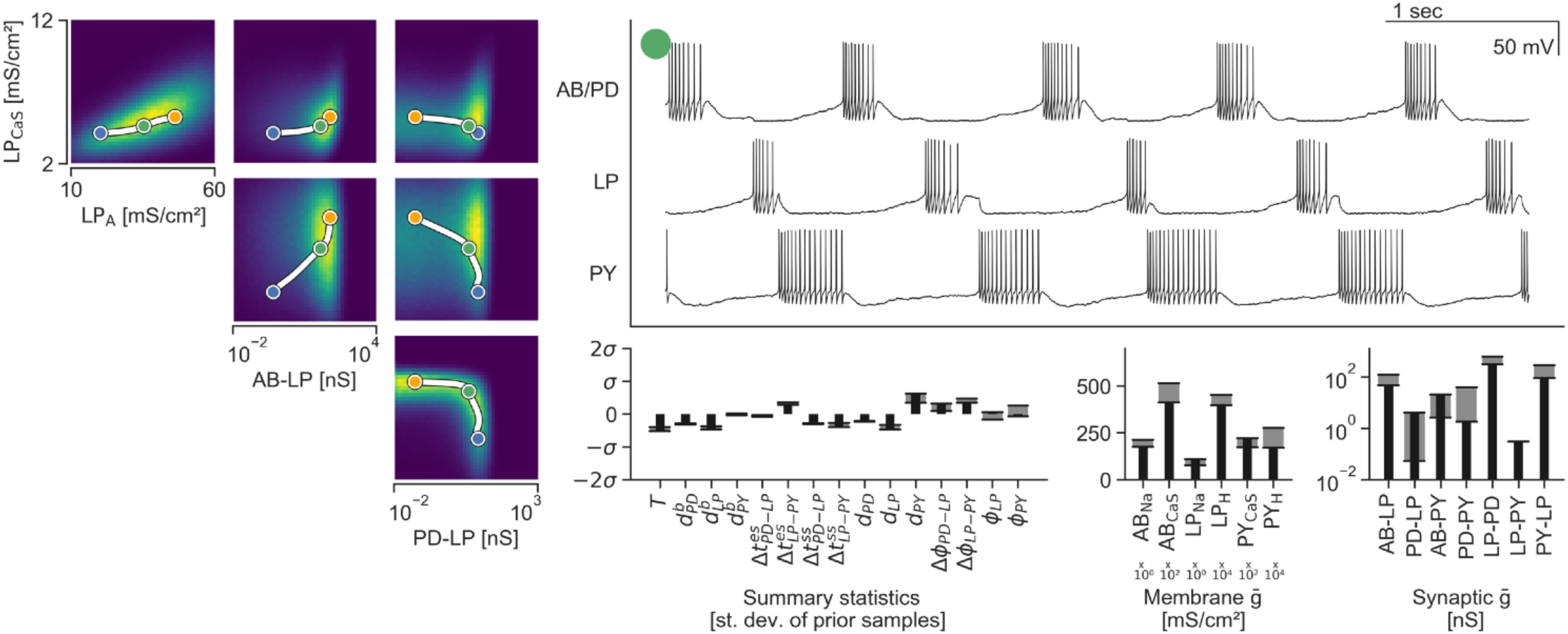
12
2
LPCaS [mS/cm²]
10
60
LPA [mS/cm²]
AB-LP [nS]
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
2σ
σ
0
−σ
−2σ
Summary statistics
[st. dev. of prior samples]
500
250
0
Membrane ḡ
[mS/cm²]
Synaptic ḡ
[nS]
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP

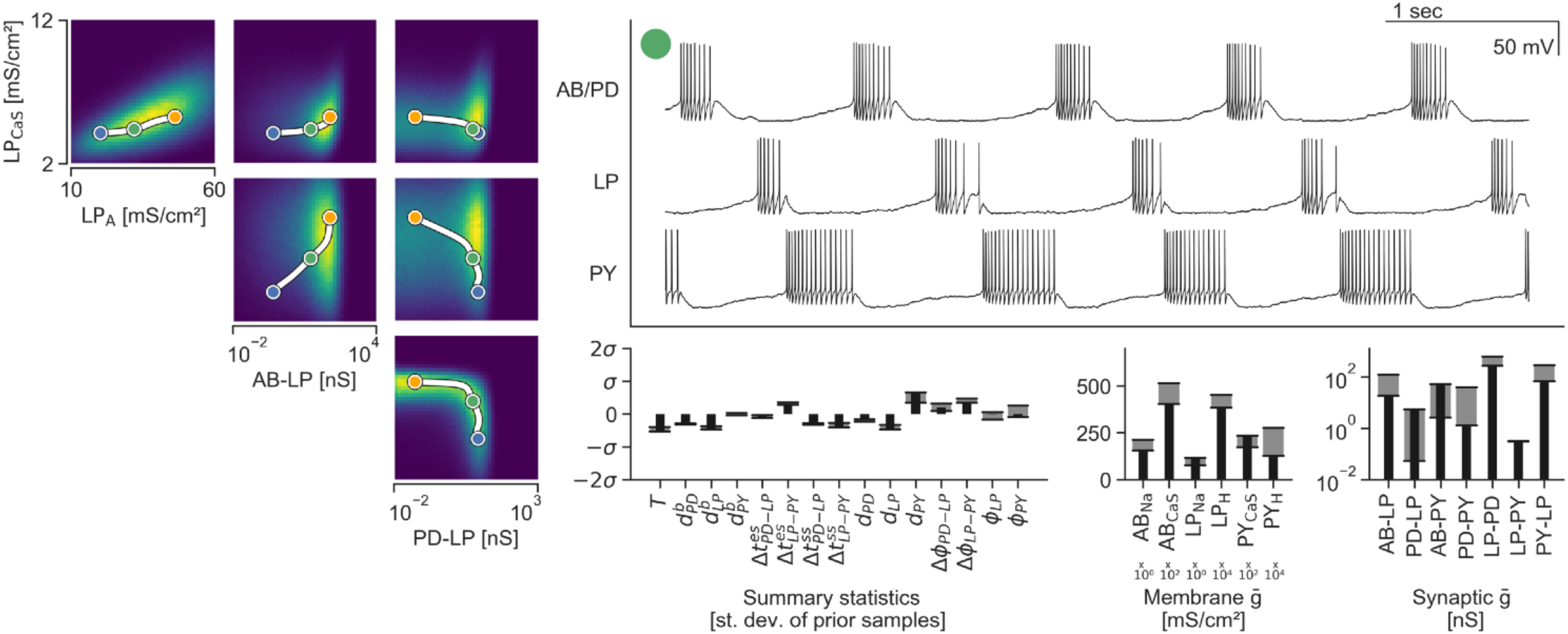


LPCaS [mS/cm²]
12
2
10
60
LPA [mS/cm²]
AB-LP [nS]
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
Summary statistics
[st. dev. of prior samples]
Membrane ḡ
[mS/cm²]
Synaptic ḡ
[nS]
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP

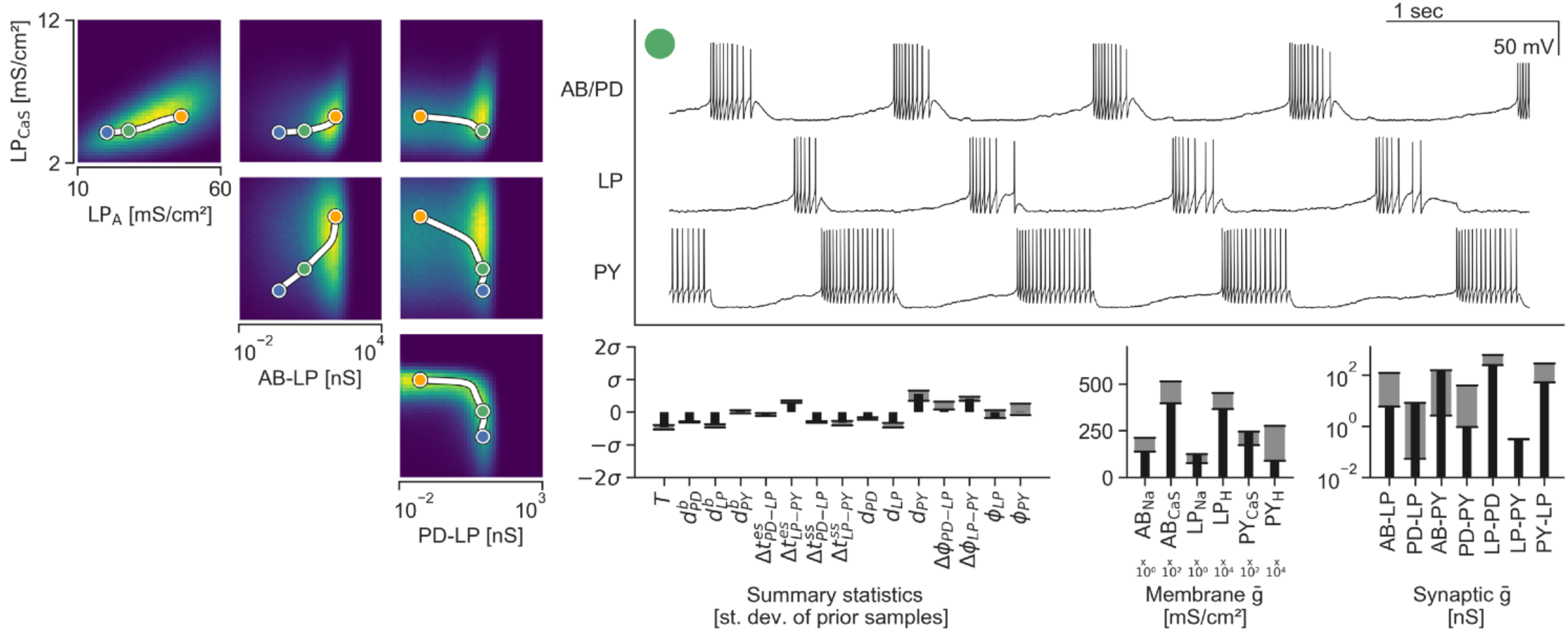


LP_CaS [mS/cm²]
12
2
10
60
LP_A [mS/cm²]
AB-LP [nS]
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
Summary statistics
[st. dev. of prior samples]
Membrane ḡ
[mS/cm²]
Synaptic ḡ
[nS]
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP

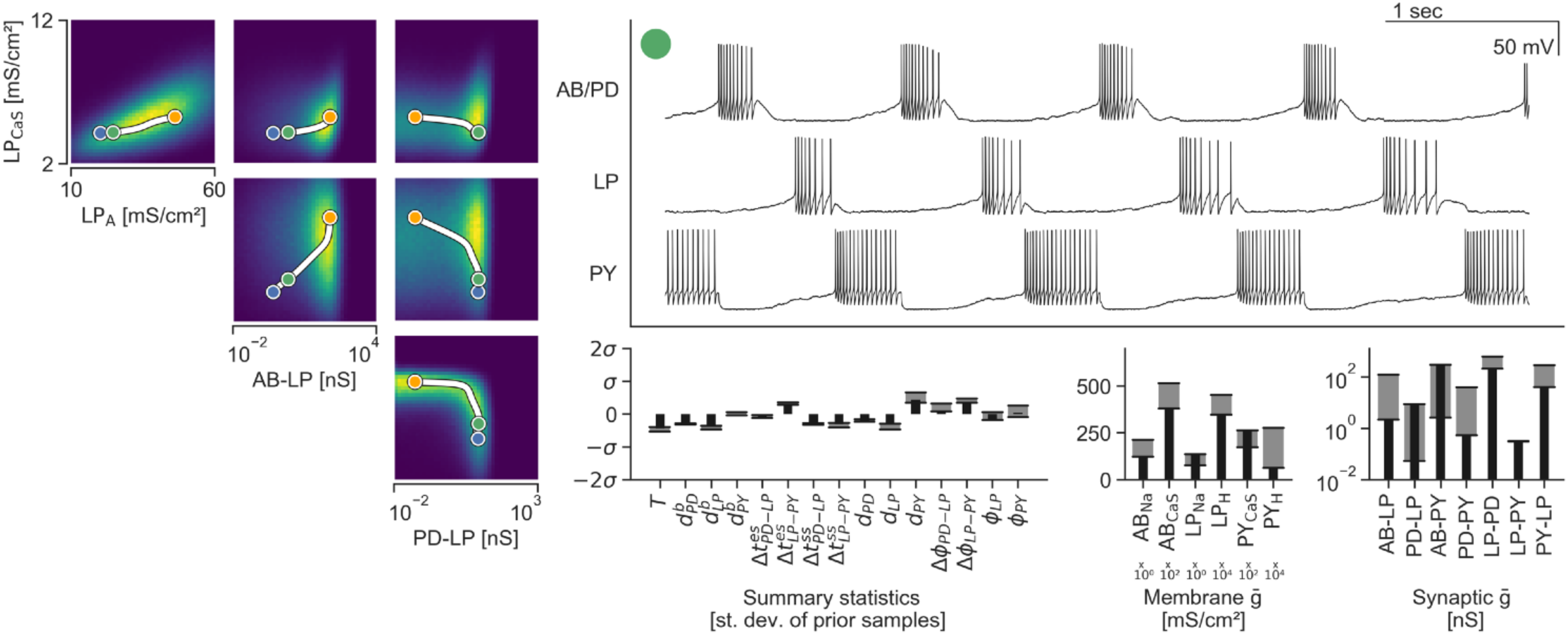

LPCaS [mS/cm²]
12
2
10
60
LPA [mS/cm²]
10−2
104
AB-LP [nS]
10−2
103
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
2σ
σ
0
−σ
−2σ
500
250
0
102
100
10−2
Summary statistics
[st. dev. of prior samples]
ABNa
ABCaS
LPNa
LPH
PYCaS
PYH
x 100
x 102
x 100
x 104
x 102
x 104
Membrane ḡ
[mS/cm²]
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP
Synaptic ḡ
[nS]



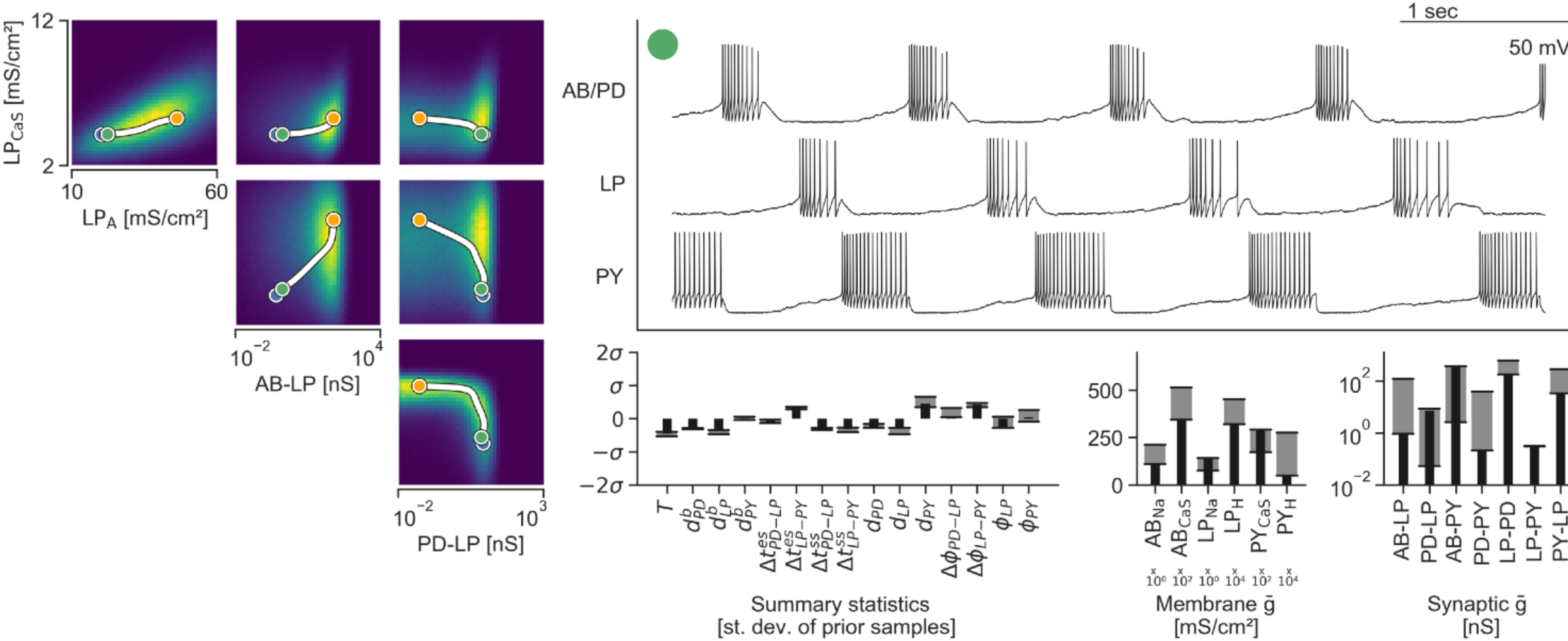
LP_CaS [mS/cm²]
12
2
10
60
LP_A [mS/cm²]
AB-LP [nS]
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
Summary statistics
[st. dev. of prior samples]
Membrane ḡ
[mS/cm²]
Synaptic ḡ
[nS]
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP



LPCaS [mS/cm²]
12
2
10
60
LPA [mS/cm²]
AB-LP [nS]
10^-2
10^4
PD-LP [nS]
10^-2
10^3
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]
10^2
10^0
10^-2
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP
Synaptic ḡ
[nS]

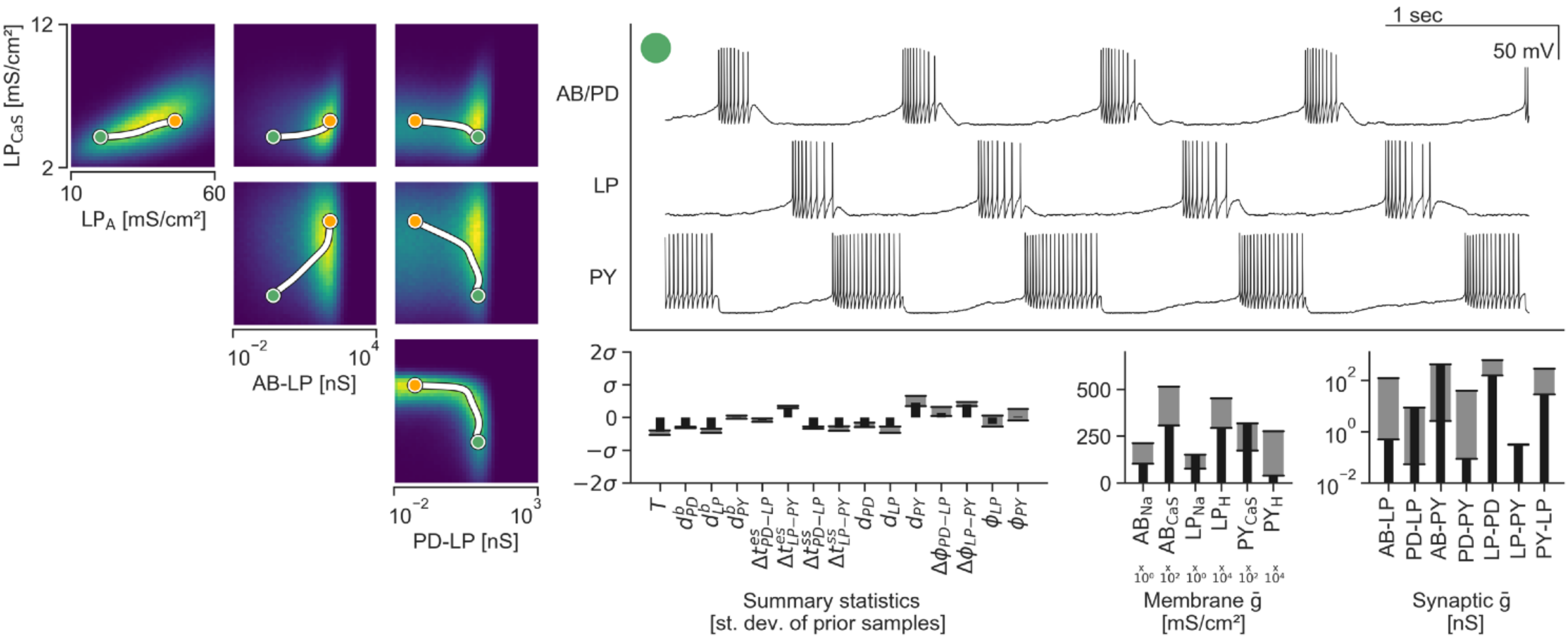


LPCaS [mS/cm²]
12
2
10
60
LPA [mS/cm²]
10^-2
10^4
AB-LP [nS]
10^-2
10^3
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
2σ
σ
0
−σ
−2σ
Summary statistics
[st. dev. of prior samples]
500
250
0
AB_Na
AB_CaS
LP_Na
LP_H
PY_CaS
PY_H
Membrane ḡ
[mS/cm²]
10^2
10^0
10^-2
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP
Synaptic ḡ
[nS]



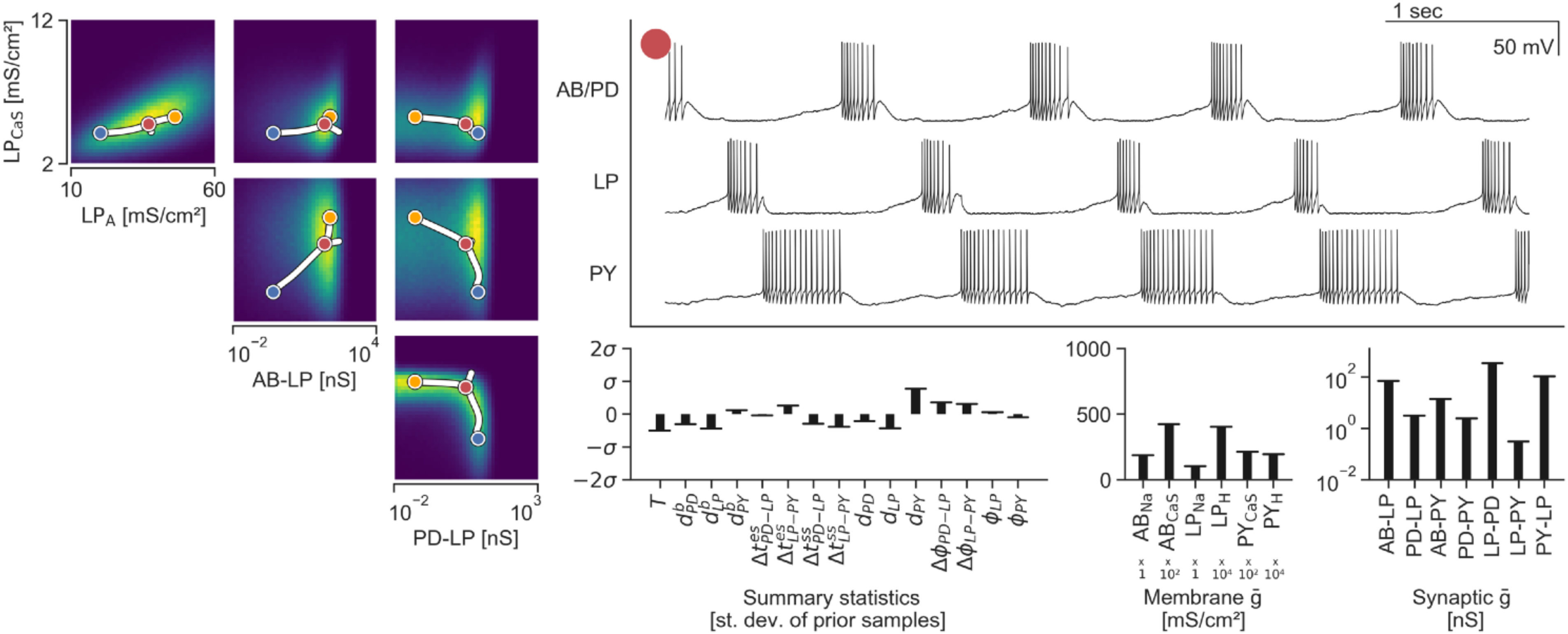
LPCaS [mS/cm²]
12
2
10
60
LPA [mS/cm²]
10⁻²
10⁴
AB-LP [nS]
10⁻²
10³
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
2σ
σ
0
−σ
−2σ
Summary statistics
[st. dev. of prior samples]
500
250
0
ABNa
ABCaS
LPNa
LPH
PYCaS
PYH
Membrane ḡ
[mS/cm²]
10²
10⁰
10⁻²
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP
Synaptic ḡ
[nS]

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

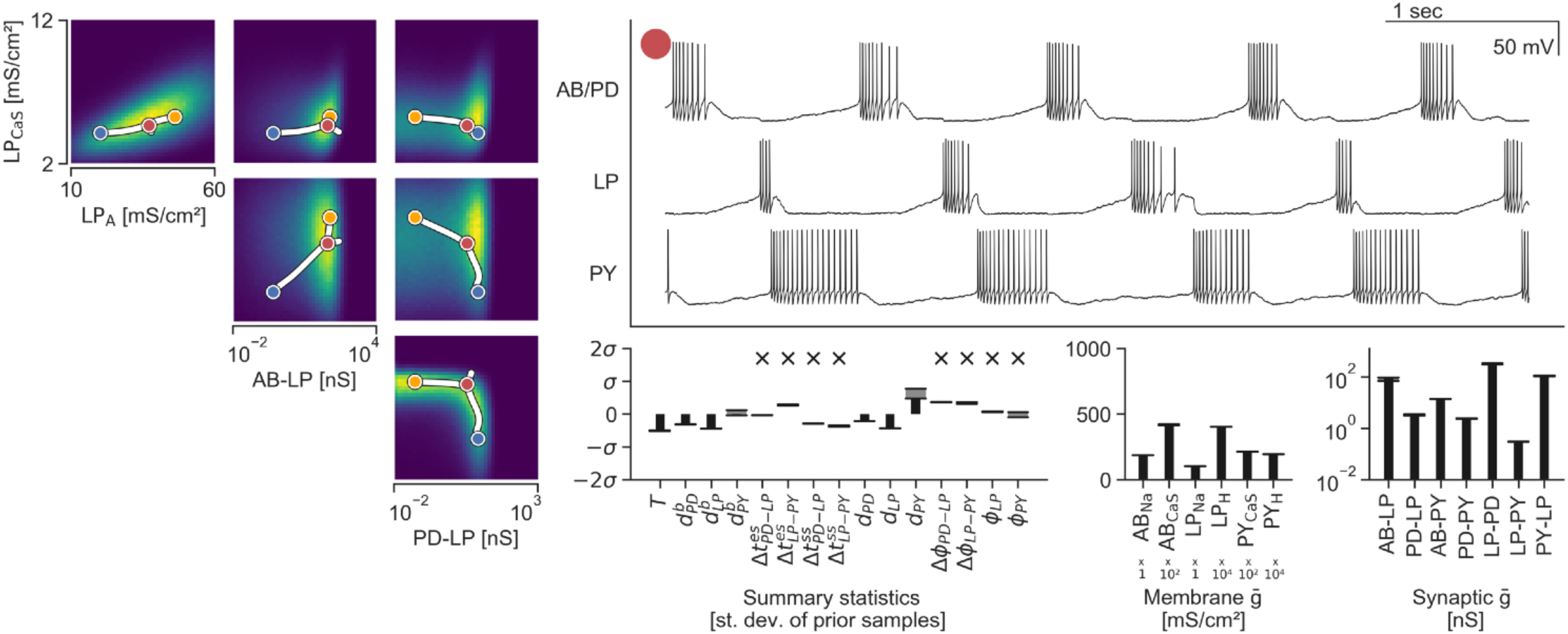


Can small perturbations lead the circuit to break down?

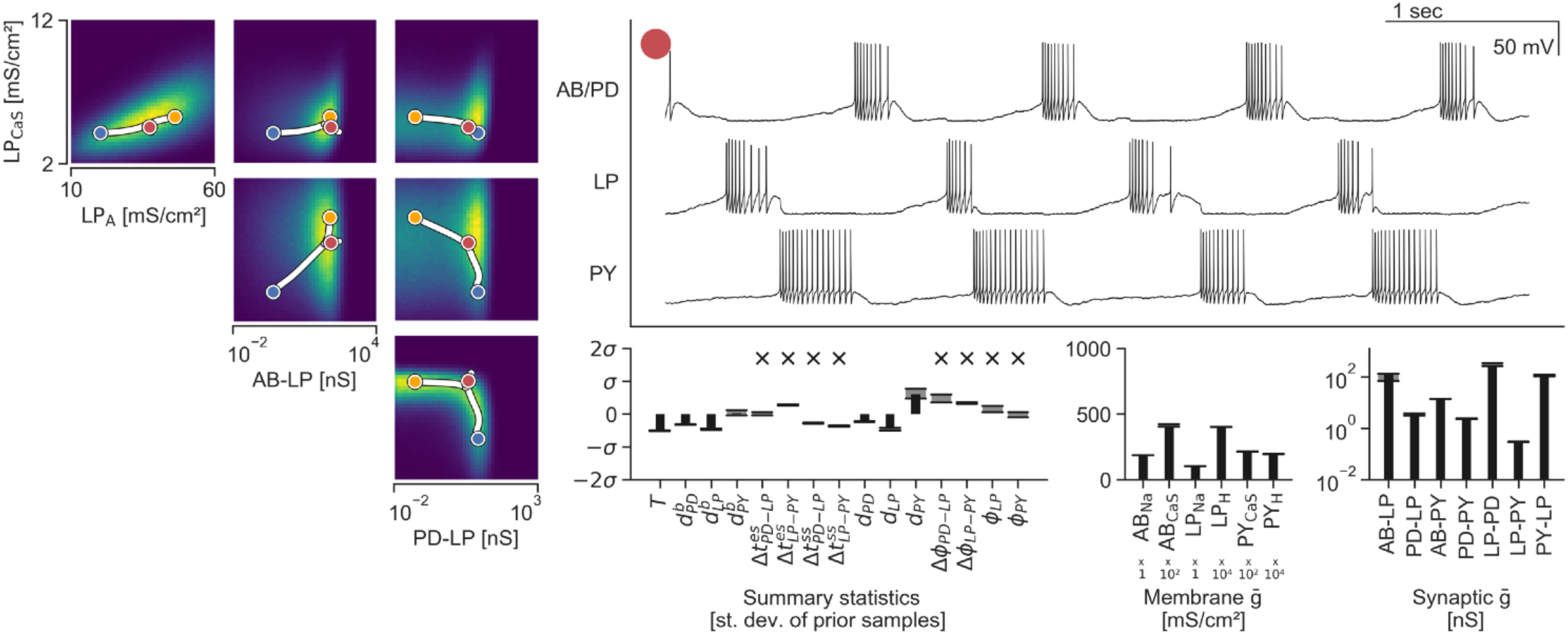
Michael Deistler (work and slides), Kaan Oecal



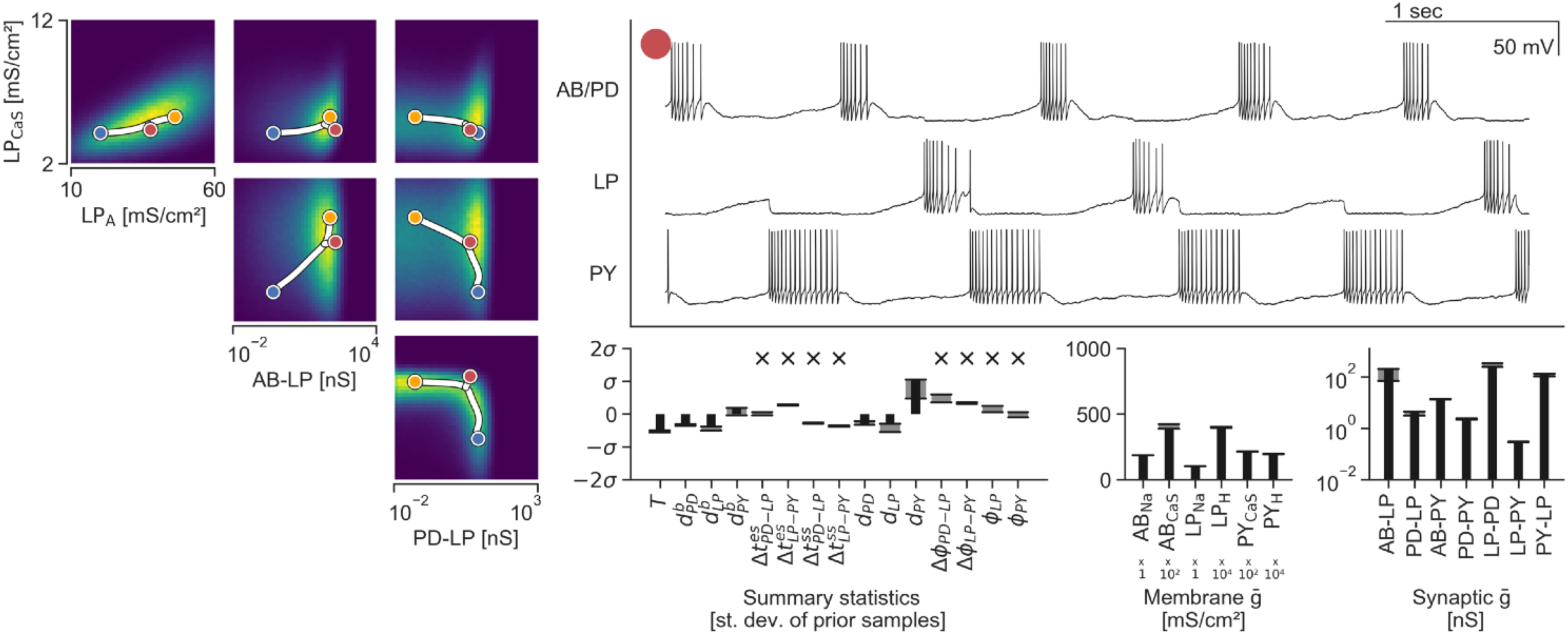
12
2
10
60
LP_{CaS} [mS/cm²]
LP_A [mS/cm²]
10^{-2}
10^4
AB-LP [nS]
10^{-2}
10^3
PD-LP [nS]
AB/PD
LP
PY
1 sec
50 mV
2σ
σ
0
$-\sigma$
-2σ
Summary statistics
[st. dev. of prior samples]
1000
500
0
AB_{Na}
AB_{CaS}
LP_{Na}
LP_H
PY_{CaS}
PY_H
x 1
x 10^2
x 1
x 10^4
x 10^2
x 10^4
Membrane $\bar{g}$
[mS/cm²]
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]
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]
1000
500
0
AB_Na
AB_CaS
LP_Na
LP_H
PY_CaS
PY_H
Membrane ḡ
[mS/cm²]
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP
Synaptic ḡ
[nS]

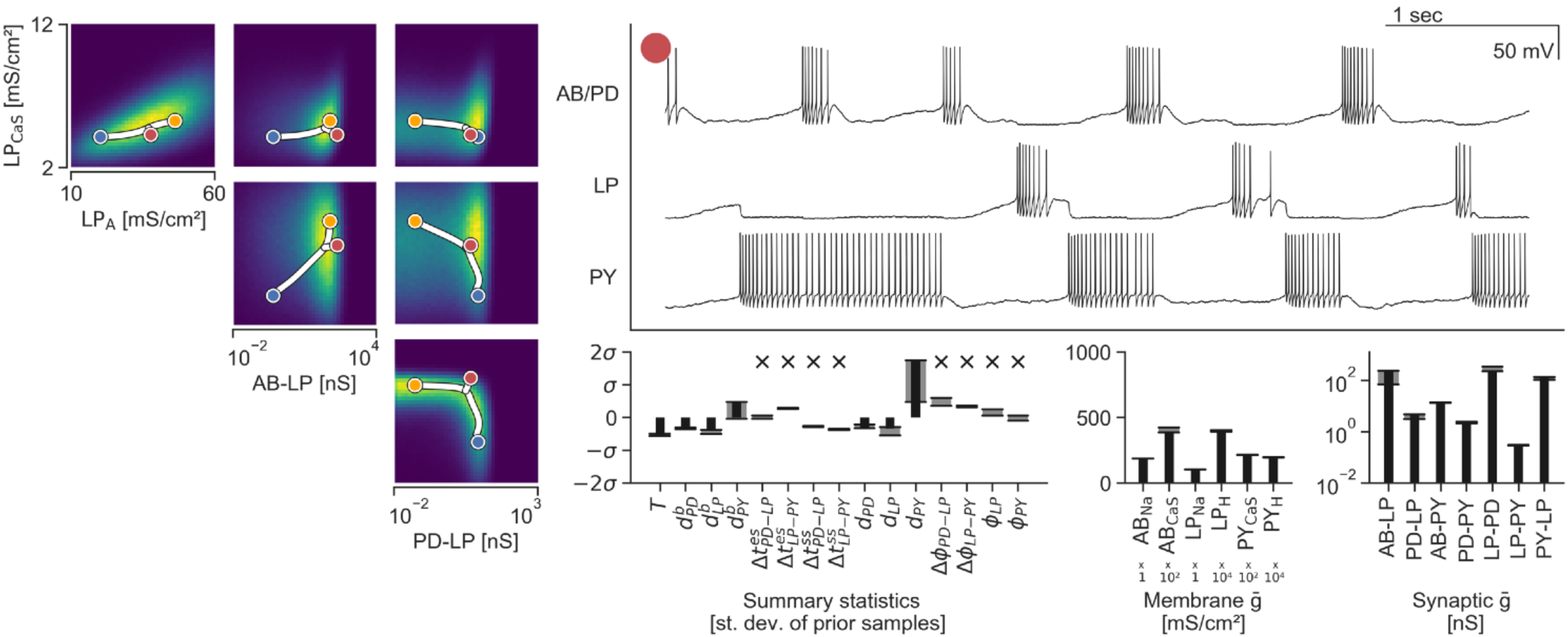


LPCaS [mS/cm²]
12
2
10
60
LPA [mS/cm²]
AB-LP [nS]
PD-LP [nS]
1 sec
50 mV
AB/PD
LP
PY
2σ
σ
0
−σ
−2σ
Summary statistics
[st. dev. of prior samples]
1000
500
0
Membrane ḡ
[mS/cm²]
Synaptic ḡ
[nS]
AB-LP
PD-LP
AB-PY
PD-PY
LP-PD
LP-PY
PY-LP



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]
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



Discussion

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

Goncalves*, Lückmann*, Deistler* et al, eLife 2020

Discussion

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- Simulation-based inference allowed us to fit non-linear neural models, with lots of parameters and complex relationships between parameters and outputs

Goncalves*, Lückmann*, Deistler* et al, eLife 2020

Discussion

- **Flexibility:** inference approach does not depend on specifics of mechanistic model, works with simulation-based models
- Simulation-based inference allowed us to fit non-linear neural models, with lots of parameters and complex relationships between parameters and outputs
- Sensitivity analysis

Goncalves*, Lückmann*, Deistler* et al, eLife 2020

Discussion

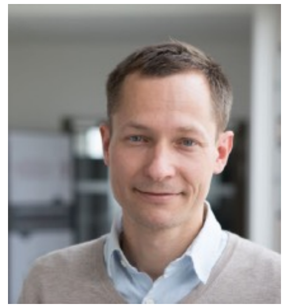
- **Flexibility:** inference approach does not depend on specifics of mechanistic model, works with simulation-based models
- Simulation-based inference allowed us to fit non-linear neural models, with lots of parameters and complex relationships between parameters and outputs
- Sensitivity analysis
- Lots of challenges: scaling number of parameters, model misspecification…

Goncalves*, Lückmann*, Deistler* et al, eLife 2020

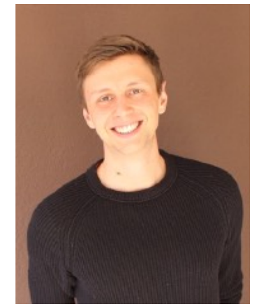
Acknowledgments

Jakob Macke's group

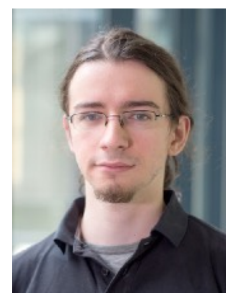
Giacomo Bassetto
Sebastian Bischoff
Jan Boelts
Álvaro Tejero Cantero (former)
Michael Deistler
Richard Gao
Jaivardhan Kapoor
Janne Lappalainen
Jan-Matthis Lueckmann
Kaan Oecal (former)
Poornima Ramesh
Cornelius Schröder
Auguste Schulz
Artur Speiser
Julius Vetter

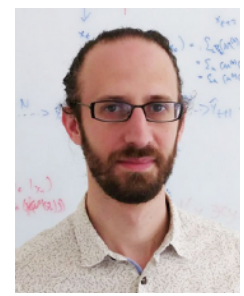

Jakob Macke


Jan-Matthis Lueckmann


Michael Deistler


Giacomo Bassetto


Marcel Nonnenmacher


David Greenberg

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center of advanced european studies and research

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