Construction of Predictive Neuron Models using Large Scale Data Assimilation

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Overview

Building neuron models with data assimilation:

- Multichannel conductance model
- Assimilation of electrophysiological data
- Model validation through prediction
- Bayesian inference boost – single valued model

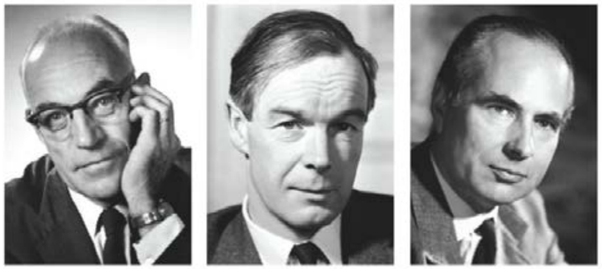
DA for conditioning neural networks:

- Adaptive Bioelectronics
  $\Rightarrow$ *New therapies for cardiorespiratory disease*
- Control of switching between chaotic attractors to produce specific motor patterns e.g. gaits
  $\Rightarrow$ *Validation of the command neuron hypothesis*

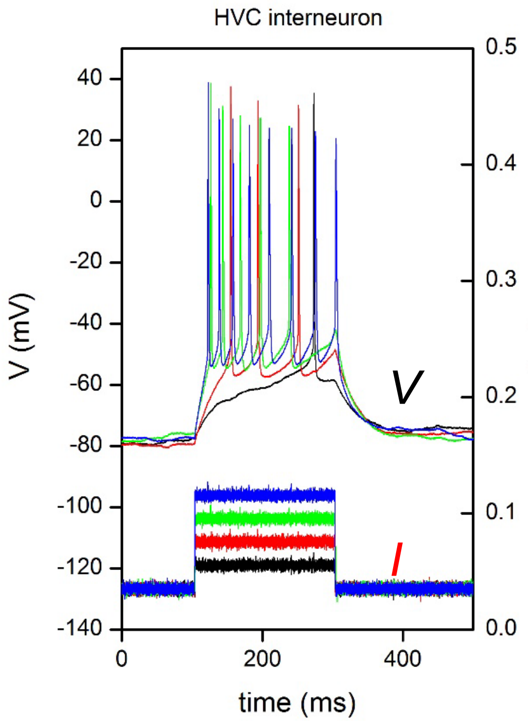
Neuron: a current driven non-linear oscillator

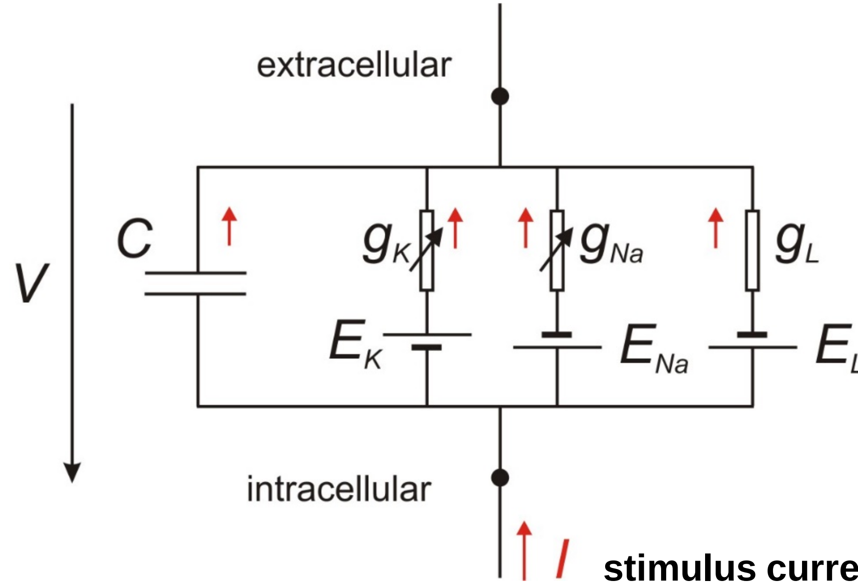
The Nobel Prize in Physiology or Medicine 1963

"for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"



Sir John Carew Eccles | Alan Lloyd Hodgkin | Andrew Fielding Huxley



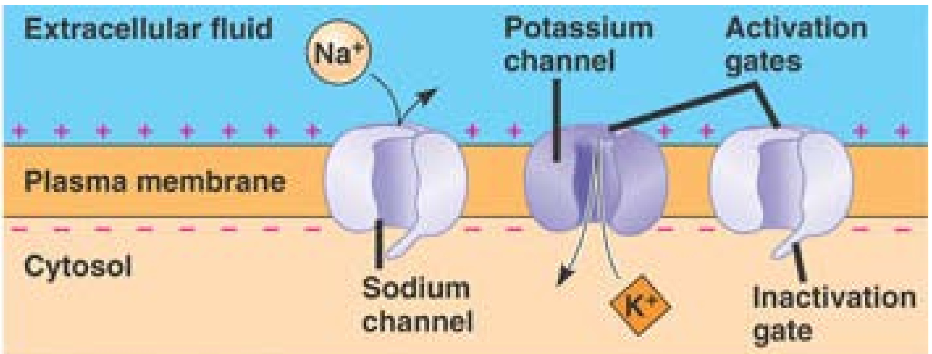


stimulus current or **synaptic current** injected through the membrane.

Hodgkin-Huxley model:

$$C\dot{V} = \bar{g}_{Na} m^3 h (E_K - V) + \bar{g}_K n^4 (E_{Na} - V) + g_L (E_L - V) + I$$
$$\tau_m \dot{m} = m_\infty - m(t)$$
$$\tau_h \dot{h} = h_\infty - h(t)$$
$$\tau_n \dot{n} = n_\infty - n(t)$$

Kinetics of ionic gates



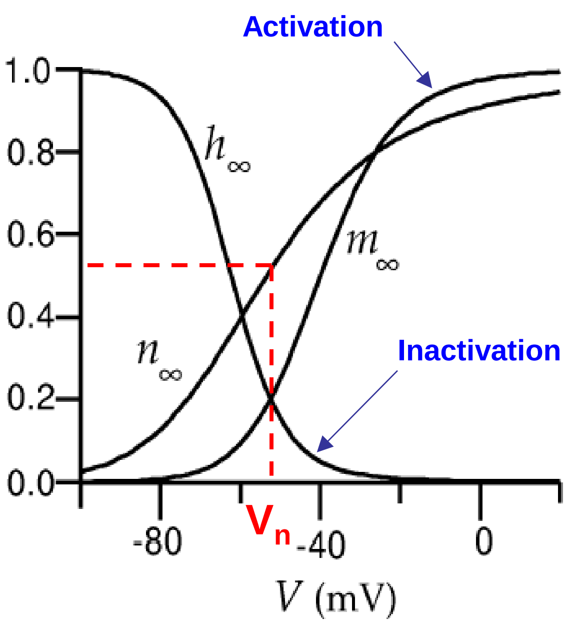
Dynamics of the Potassium-activation gate:

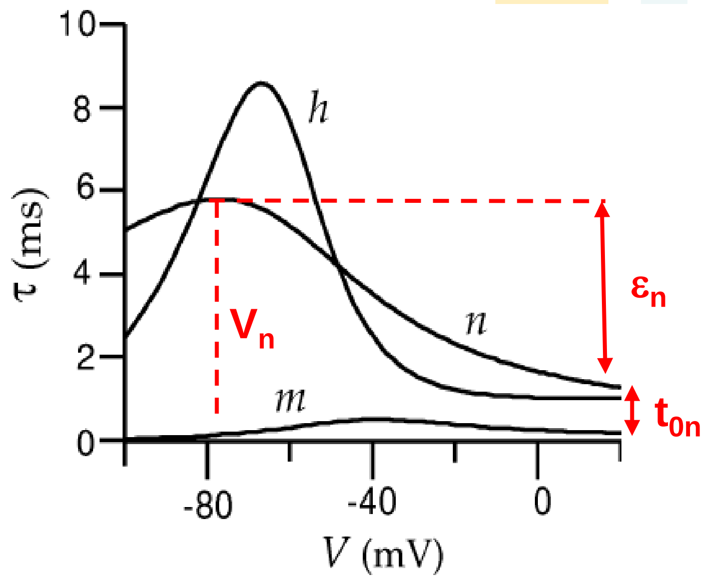
$$\frac{dn(t)}{dt} = \frac{n_\infty(V) - n(t)}{\tau_n(V)}$$

$$n_\infty(V) = \frac{1}{2}\left[1 + \tanh\left(\frac{V - V_n}{dV_n}\right)\right]$$

$$\tau_n(V) = t_{0n} + \varepsilon_n\left[1 - \tanh^2\left(\frac{V - V_n}{dV_{nt}}\right)\right]$$

5 model parameters



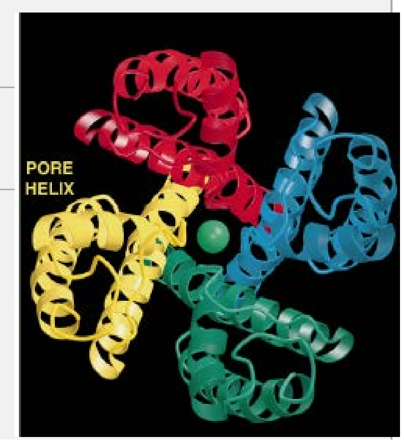


Sodium activation and inactivation gates:

10 model parameters

Ion channels are highly specialized proteins

Function	Protein name (associated gene)
Delayed rectifier Slowly activating or non-inactivating	$K_v\alpha1.x$ - Shaker-related: $K_v1.1$ (KCNA1), $K_v1.2$ (KCNA2), $K_v1.3$ (KCNA3), $K_v1.5$ (KCNA5), $K_v1.6$ (KCNA6), $K_v1.7$ (KCNA7), $K_v1.8$ (KCNA10) $K_v\alpha2.x$ - Shab-related: $K_v2.1$ (KCNB1), $K_v2.2$ (KCNB2) $K_v\alpha3.x$ - Shaw-related: $K_v3.1$ (KCNC1), $K_v3.2$ (KCNC2) $K_v\alpha7.x$: $K_v7.1$ (KCNQ1) - KvLQT1, $K_v7.2$ (KCNQ2), $K_v7.3$ (KCNQ3), $K_v7.4$ (KCNQ4), $K_v7.5$ (KCNQ5) $K_v\alpha10.x$: $K_v10.1$ (KCNH1)
A-type potassium channel rapidly inactivating	$K_v\alpha1.x$ - Shaker-related: $K_v1.4$ (KCNA4) $K_v\alpha3.x$ - Shaw-related: $K_v3.3$ (KCNC3), $K_v3.4$ (KCNC4) $K_v\alpha4.x$ - Shal-related: $K_v4.1$ (KCND1), $K_v4.2$ (KCND2), $K_v4.3$ (KCND3)
Outward rectifying passes current more easily outwards	K,α10.x: $K_v10.2$ (KCNH5)
Inward rectifying passes current more easily inwards	$K_v\alpha11.x$: $K_v11.1$ (KCNH2), $K_v11.2$ (KCNH6), $K_v12.3$ (KCNH7)
Slowly activating	$K_v\alpha12.x$: $K_v12.1$ (KCNH8), $K_v12.2$ (KCNH3), $K_v12.3$ (KCNH4)
Modifier / silencer heterotetramerize with $K_v\alpha2$ family members to form conductive channels	$K_v\alpha5.x$: $K_v5.1$ (KCNF1) $K_v\alpha6.x$: $K_v6.1$ (KCNG1), $K_v6.2$ (KCNG2), $K_v6.3$ (KCNG3) $K_v6.4$ (KCNG4) $K_v\alpha8.x$: $K_v8.1$ (KCNV1), $K_v8.2$ (KCNV2) $K_v\alpha9.x$: $K_v9.1$ (KCNS1), $K_v9.2$ (KCNS2), $K_v9.3$ (KCNS3)



Individual ion channels have specific threshold voltages and kinetics.

The 9 ion channel conductance model

$$C_m \frac{dV}{dt} = -J_{ion} + \frac{I_{app} + V / R_s}{area}$$

where: $$-J_{ion} = J_{NaT} + J_{NaP} + J_{K1} + J_{K2} + J_{K3} + J_{CaL} + J_{CaT} + J_{HCN} + J_L$$

and $C_m = C / area$ membrane capacitance per unit area.

$J_{ion} = I_{ion} / area$ ion current density

ID	Channel	Current density	Nominal conductance
NaT	Fast and transient Na^+ current	$J_{NaT} = g_{NaT} m^3 h (E_{Na} - V)$	g_{NaT}=110mS.cm^{-2}
NaP	Persistent Na^+ current	$J_{NaP} = g_{NaP} m (E_{Na} - V)$	g_{NaP}=0.064mS.cm^{-2}
K1	Transient depolarization activated K^+ current	$J_{K1} = g_{K1} m^4 (E_K - V)$	g_{K1}=5mS.cm^{-2}
K2	Rapidly inactivating K^+ current (A current)	$J_{K2} = g_{K2} m^4 h (E_K - V)$	g_{K2}=12mS.cm^{-2}
K3	Ca^{2+} activated K^+ current	$J_{K3} = g_{K3} m (E_K - V)$	g_{K3}=9.1mS.cm^{-2}
CaL	High threshold Ca^{2+} current	$J_{CaL} = \rho m^2 J_{Ca}$	-
CaT	Low threshold Ca^{2+} current	$J_{CaT} = m^2 h J_{Ca}$	-
HCN	Hyperpolarization-activated cation current	$J_{HCN} = g_{HCN} h (E_{HCN} - V)$	g_{HCN}=0.092mS.cm^{-2}
Leak	Leakage channels (K & Na)	$J_L = g_L (E_L - V)$	g_L=0.066mS.cm^{-2}

Calcium current prefactor: $J_{Ca} = \left(\frac{g_{out} - g_{in} \exp(V / V_T)}{\exp(V / V_T) - 1} \right) \times V$ Goldman-Hodgkin-Katz equation

12 state variables, 71 parameters
12 coupled non linear differential equations

Model equations

$$\textbf{Voltage}: dy_1/dt = ((p_2 y_2^3 y_3 + p_3 y_4)(p_4 - y_1) + (p_5 y_5^4 + p_6 y_6^4 y_7 + p_7 y_8)(p_8 - y_1)$$

$$+ (p_{71} y_9^2 + p_{72} y_{10}^2 y_{11}) 19.2970673 (p_{11} - 0.0001 \exp(y_1/13))/\mathrm{GHK}(y_1)$$

$$+ p_9 (p_{10} - y_1) + p_{12} y_{12} (-43 - y_1) + I_{inj}/p_{13})/p_1 + u(t)(V_{data}(t) - y_1)$$

$$\textbf{NaT}, m: \; dy_2/dt = 0.5(1 + \tanh((y_1 - p_{14})/p_{15}) - 2y_2)/(p_{17} + p_{18}(1 - \tanh^2((y_1 - p_{14})/p_{16})))$$

$$\textbf{NaT}, h: \; dy_3/dt = 0.5(1 + \tanh((y_1 - p_{19})/p_{20}) - 2y_3)/(p_{22} + p_{23}(1 - \tanh^2((y_1 - p_{19})/p_{21})))$$

$$\textbf{NaP}, m: \; dy_4/dt = 0.5(1 + \tanh((y_1 - p_{24})/p_{25}) - 2y_4)/(p_{27} + p_{28}(1 - \tanh^2((y_1 - p_{24})/p_{26})))$$

$$\textbf{K1}, m: \; dy_5/dt = 0.5(1 + \tanh((y_1 - p_{29})/p_{30}) - 2y_5)/(p_{32} + p_{33}(1 - \tanh^2((y_1 - p_{29})/p_{31})))$$

$$\textbf{K2}, m: \; dy_6/dt = 0.5(1 + \tanh((y_1 - p_{34})/p_{35}) - 2y_6)/(p_{37} + p_{38}(1 - \tanh^2((y_1 - p_{34})/p_{36})))$$

$$\textbf{K2}, h: \; dy_7/dt = 0.5(1 + \tanh((y_1 - p_{39})/p_{40}) - 2y_7)/(p_{42} + p_{44} + 0.5(1 - \tanh(y_1 - p_{39}))$$

$$\cdot (p_{43}(1 - \tanh^2((y_1 - p_{39})/p_{41})) - p_{44}))$$

$$\textbf{K3}, m: \; dy_8/dt = 0.5(1 + \tanh((y_1 - p_{45})/p_{46}) - 2y_8)/(p_{48} + p_{49}(1 - \tanh^2((y_1 - p_{45})/p_{47})))$$

$$\textbf{CaT}, m: \; dy_9/dt = 0.5(1 + \tanh((y_1 - p_{50})/p_{51}) - 2y_9)/(p_{53} + p_{54}(1 - \tanh^2((y_1 - p_{50})/p_{52})))$$

$$\textbf{CaL}, m: \; dy_{10}/dt = 0.5(1 + \tanh((y_1 - p_{55})/p_{56}) - 2y_{10})/(p_{58} + p_{59}(1 - \tanh^2((y_1 - p_{55})/p_{57})))$$

$$\textbf{CaL}, h: \; dy_{11}/dt = 0.5(1 + \tanh((y_1 - p_{60})/p_{61}) - 2y_{11})/(p_{64} + p_{65}(1 + \tanh((y_1 - p_{60})/p_{62}))$$

$$\cdot (1 - \tanh((y_1 - p_{60})/p_{63}))(1 - \tanh(y_1 - p_{60}) \tanh((1/p_{62} + 1/p_{63})(y_1 - p_{60})))$$

$$/(1 + \tanh((y_1 - p_{60})/p_{62}) \tanh((y_1 - p_{60})/p_{63})))$$

$$\textbf{HCN}, h: \; dy_{12}/dt = 0.5(1 + \tanh((y_1 - p_{66})/p_{67}) - 2y_{12})/(p_{69} + p_{70}(1 - \tanh^2((y_1 - p_{66})/p_{68})))$$

Constrained nonlinear optimization

Takens embedding theorem: all information required to constrain the model is contained in the observation of one state variable – the membrane voltage $V(t)$ – over a finite time window of duration T.

Record time series data to be fitted: $V(t_1)$, $V(t_2)$, $V(t_3)$, … $V(t_N)$ induced by the current protocol injected in the neuron $I(t_1)$, $I(t_2)$, $I(t_3)$, … $I(t_N)$.

Define a cost function to minimize:

$$C(y_1(0), \vec{p}) = \frac{1}{2}\sum_{i=0}^{N}\left\{\left(V(t_i) - y_1(t_i, \vec{p})\right)^2 + u(t_i)^2\right\}$$

Observed voltage — Model variable — Convergence acceleration function

Creveling et al, Phys. Lett. A, **372**, 2640 (2008)

under:

- **Equality constraints:** the 12 differential equations linearized at each point of the discretized time window $t_i=iT/N$. Typically N=100,000 mesh points ⇒ 1.2 million constraints
- **Inequality constraints:** the search intervals of the 72 parameters

Build the Lagrangian by replacing the inequality constraints with logarithmic barriers
⇒ Karush-Kuhn-Tucker system: sparse systems of linear equations

Interior point optimization: iteratively seek the extremum of the KKT Lagrangian using Newton's method.
At each iteration reduce the height of the logarithmic barrier until convergence is achieved.

When data assimilation has converged ~ 2 days of run time on a workstation:

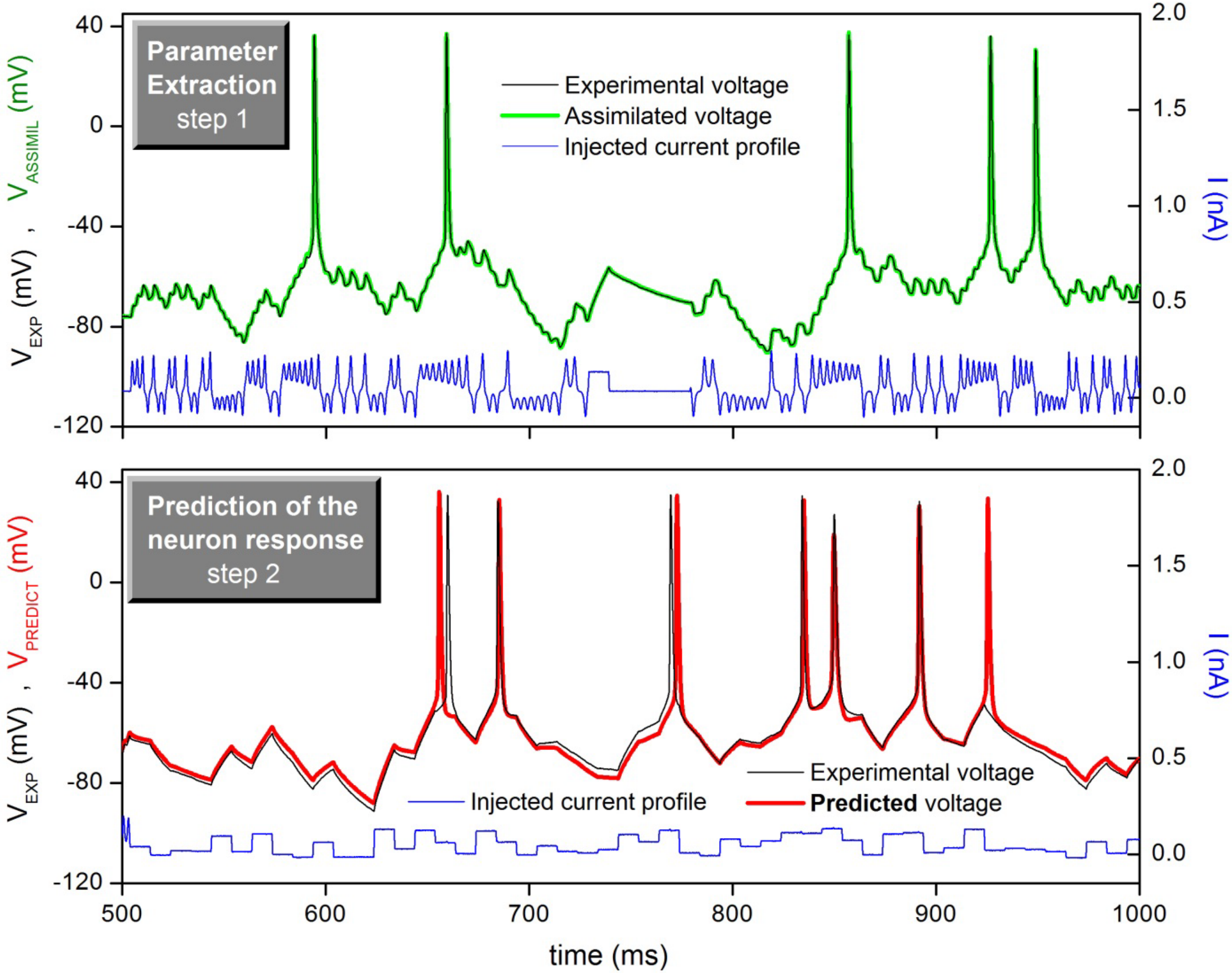
- The $\boldsymbol{p}$={C_m, g_{Na}, E_{Na}, g_K, E_K …} vector solution of the problem is obtained – 71 parameters.
- $u(t)$=0

Example of extracted parameter sets

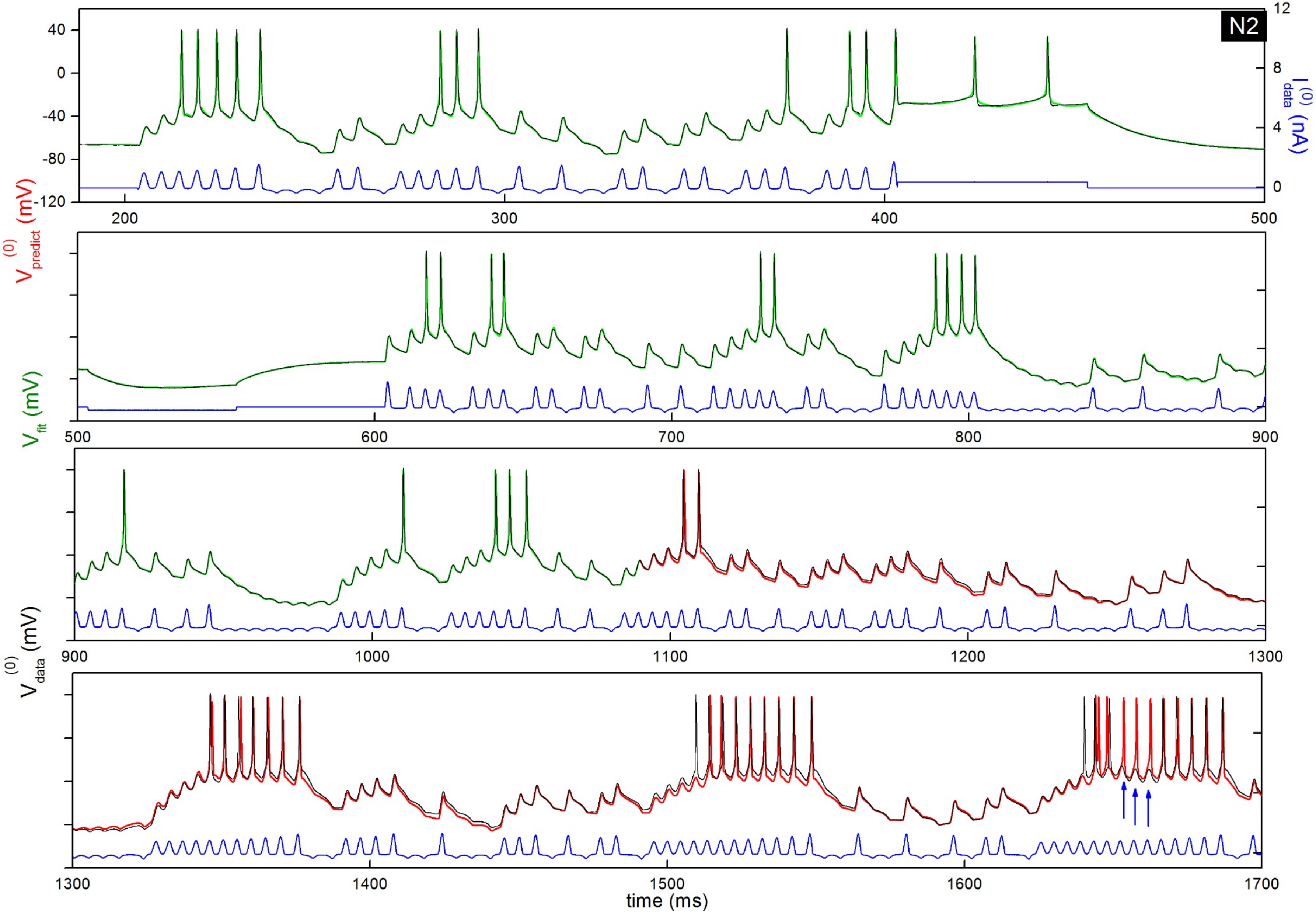
param. number	param. 'name'	units	lower bound	upper bound	neuron N1	neuron N2	neuron N3
p_1	Cm[1]	μF/cm^2	0.900	1.100	1.100	1.032	1.035
p_2	NaT:g[2]	nS/cm^2	5.000	170.000	7.545	85.364	9.736
p_3	NaP:g	nS/cm^2	0.000	20.000	0.008	0.086	0.075
p_4	E_{Na}	mV	45.000	55.000	55.000	55.000	55.000
p_5	K1:g	nS/cm^2	0.000	80.000	0.096	0.216	0.000
p_6	K2:g	nS/cm^2	0.000	80.000	5.687	14.708	1.074
p_7	K3:g	nS/cm^2	0.000	12.000	0.438	0.191	6.482
p_8	E_K	mV	-85.000	-70.000	-75.001	-85.000	-85.000
p_9	Leak:g	nS/cm^2	0.010	0.600	0.010	0.036	0.047
p_{10}	E_{Leak}	mV	-65.000	-48.000	-65.000	-65.000	-65.000
p_{11}	$[\mathrm{Ca}]_{\mathrm{ext}}$	mM	0.010	9.000	0.020	9.000	8.996
p_{12}	HCN:g	nS/cm^2	0.000	10.000	0.017	0.011	0.000
p_{13}	I_{SA}[3]	cm^2	15.00	250.0	38.0	81.0	78.0
p_{14}	NaT,m[4]:$V_{1/2}$	mV	-45.000	-15.000	-34.738	-18.495	-38.400
p_{15}	NaT,m:κ	mV	0.500	25.000	21.682	22.457	17.327
p_{16}	NaT,m:σ	mV	0.500	25.000	0.500	0.500	0.500
p_{17}	NaT,m:τ_0	ms	0.010	0.700	0.010	0.194	0.010
p_{18}	NaT,m:τ_{max}	ms	0.012	7.000	0.012	0.158	0.012
p_{19}	NaT,h:$V_{1/2}$	mV	-75.000	-35.000	-43.132	-38.452	-57.314
p_{20}	NaT,h:κ	mV	-25.000	-0.500	-9.400	-4.487	-25.000
p_{21}	NaT,h:σ	mV	5.000	25.000	6.401	22.344	5.000
p_{22}	NaT,h:τ_0	ms	0.020	2.000	0.554	0.207	0.841
p_{23}	NaT,h:τ_{max}	ms	1.000	30.000	30.000	4.427	21.173
p_{24}	NaP,m:$V_{1/2}$	mV	-69.000	-29.000	-64.537	-37.719	-57.822
p_{25}	NaP,m:κ	mV	5.000	25.000	5.000	5.349	11.042
p_{26}	NaP,m:σ	mV	5.000	25.000	25.000	5.194	25.000
p_{27}	NaP,m:τ_0	ms	0.020	2.000	2.000	0.020	1.088
p_{28}	NaP,m:τ_{max}	ms	0.012	7.000	7.000	7.000	0.012
p_{29}	K1,m:$V_{1/2}$	mV	-69.000	-21.000	-67.970	-54.343	-67.597
p_{30}	K1,m:κ	mV	5.000	25.000	6.734	15.528	24.998
p_{31}	K1,m:σ	mV	5.000	25.000	7.908	5.000	24.992
p_{32}	K1,m:τ_0	ms	0.020	2.000	2.000	0.052	1.998
p_{33}	K1,m:τ_{max}	ms	1.000	30.000	30.000	1.000	29.979
p_{34}	K2,m:$V_{1/2}$	mV	-90.000	-21.000	-52.893	-41.932	-66.958
p_{35}	K2,m:κ	mV	5.000	48.000	13.597	10.972	19.837
p_{36}	K2,m:σ	mV	5.000	48.000	11.528	48.000	45.659
p_{37}	K2,m:τ_0	ms	0.020	2.000	0.020	0.020	2.000
p_{38}	K2,m:τ_{max}	ms	1.000	30.000	1.838	1.000	30.000

param. number	param. 'name'	units	lower bound	upper bound	neuron N1	neuron N2	neuron N3
p_{39}	K2,h[5]:$V_{1/2}$	mV	-90.000	-35.000	-66.425	-52.586	-73.699
p_{40}	K2,h:κ	mV	-39.000	-5.000	-30.417	-11.517	-24.863
p_{41}	K2,h:σ	mV	-39.000	-5.000	-39.000	-20.389	-5.000
p_{42}	K2,h:τ_0	ms	0.020	2.000	2.000	1.989	0.020
p_{43}	K2,h:τ_{max}	ms	0.500	100.000	68.490	100.000	0.663
p_{44}	K2,h:δ^2	ms	0.000	30.000	2.113	0.000	22.460
p_{45}	K3,m:$V_{1/2}$	mV	-15.000	40.000	-15.000	-15.000	5.976
p_{46}	K3,m:κ	mV	5.000	65.000	65.000	65.000	37.251
p_{47}	K3,m:σ	mV	5.000	70.000	70.000	20.202	6.190
p_{48}	K3,m:τ_0	ms	0.020	55.000	55.000	0.020	1.106
p_{49}	K3,m:τ_{max}	ms	1.000	150.000	150.000	128.333	2.561
p_{50}	CaT,m:$V_{1/2}$	mV	-56.000	-8.000	-55.999	-49.049	-55.998
p_{51}	CaT,m:κ	mV	5.000	49.000	48.995	29.827	48.991
p_{52}	CaT,m:σ	mV	5.000	55.000	54.990	54.855	54.909
p_{53}	CaT,m:τ_0	ms	0.020	2.000	1.966	0.020	1.863
p_{54}	CaT,m:τ_{max}	ms	1.000	295.000	294.917	6.273	294.835
p_{55}	CaL,m:$V_{1/2}$	mV	-80.000	-35.000	-71.954	-44.457	-71.213
p_{56}	CaL,m:κ	mV	5.000	39.000	38.987	30.094	20.336
p_{57}	CaL,m:σ	mV	5.000	57.000	56.983	22.726	57.000
p_{58}	CaL,m:τ_0	ms	0.020	2.000	1.975	0.020	2.000
p_{59}	CaL,m:τ_{max}	ms	1.000	150.000	149.945	110.617	19.396
p_{60}	CaL,h:$V_{1/2}$	mV	-90.000	-55.000	-72.996	-56.002	-55.000
p_{61}	CaL,h:κ	mV	-34.000	-5.000	-33.759	-7.789	-34.000
p_{62}	CaL,h:σ_+	mV	3.000	55.000	54.853	55.000	55.000
p_{63}	CaL,h:σ_-	ms	3.000	55.000	54.824	4.362	55.000
p_{64}	CaL,h:τ_0	ms	5.000	190.000	189.147	59.808	190.000
p_{65}	CaL,h,τ_{max}	ms	0.500	7000.000	6959.019	7000.000	7000.000
p_{66}	HCN,h:$V_{1/2}$	mV	-90.000	-40.000	-89.061	-63.231	-67.150
p_{67}	HCN,h:κ	mV	-40.000	-5.000	-6.416	-5.000	-38.150
p_{68}	HCN,h:σ	mV	5.000	40.000	13.075	40.000	38.297
p_{69}	HCN,h:τ_0	ms	0.020	2.000	2.000	2.000	1.029
p_{70}	HCN,h:τ_{max}	ms	100.000	2000.000	2000.000	2000.000	1925.350
p_{71}	CaL:p	μm/s	0.000	10.000	0.000	0.010	0.000
p_{72}	CaT:p	μm/s	0.000	10.000	0.000	0.003	0.004

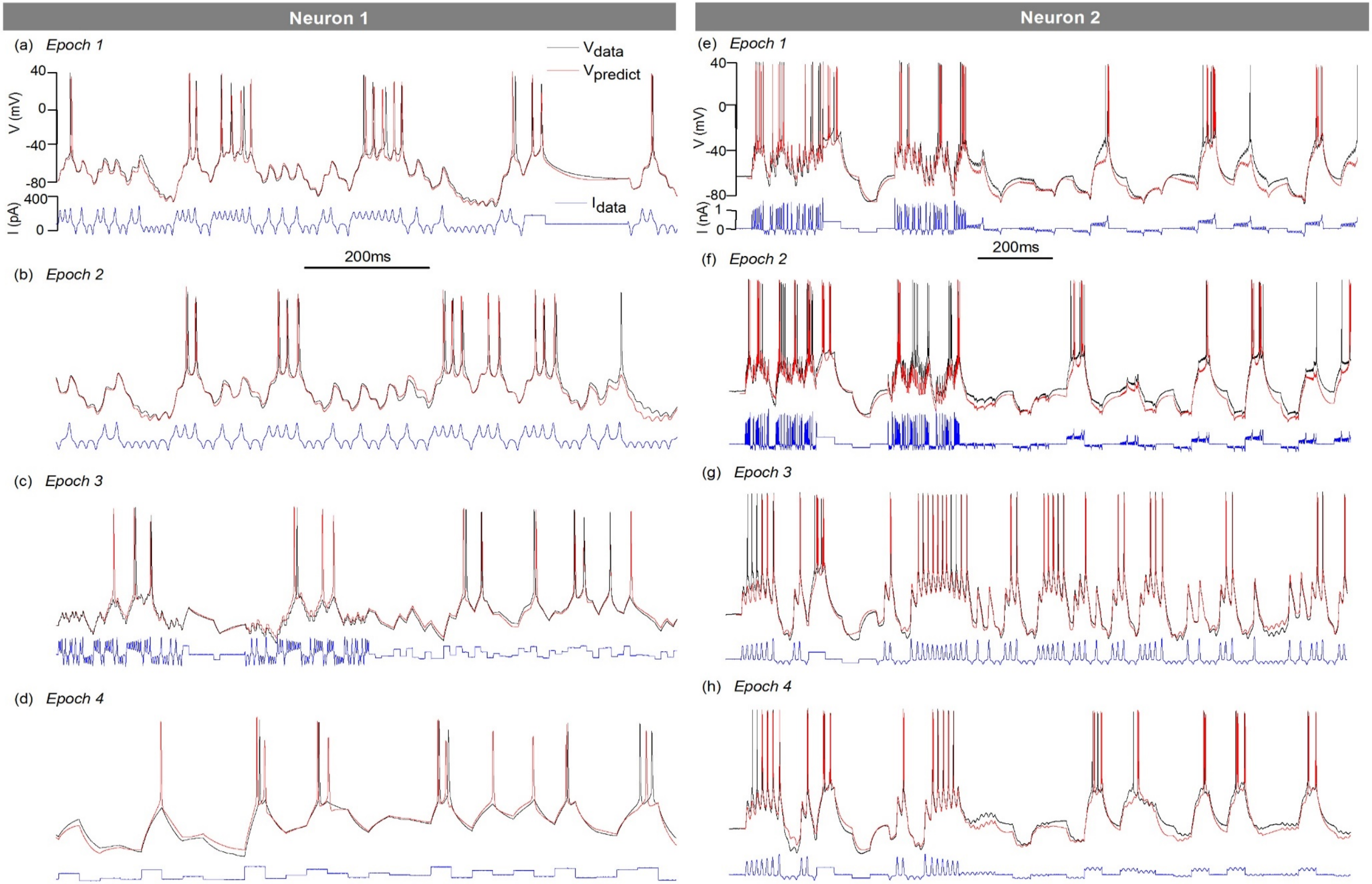
Assimilation and prediction of neuron output – N1



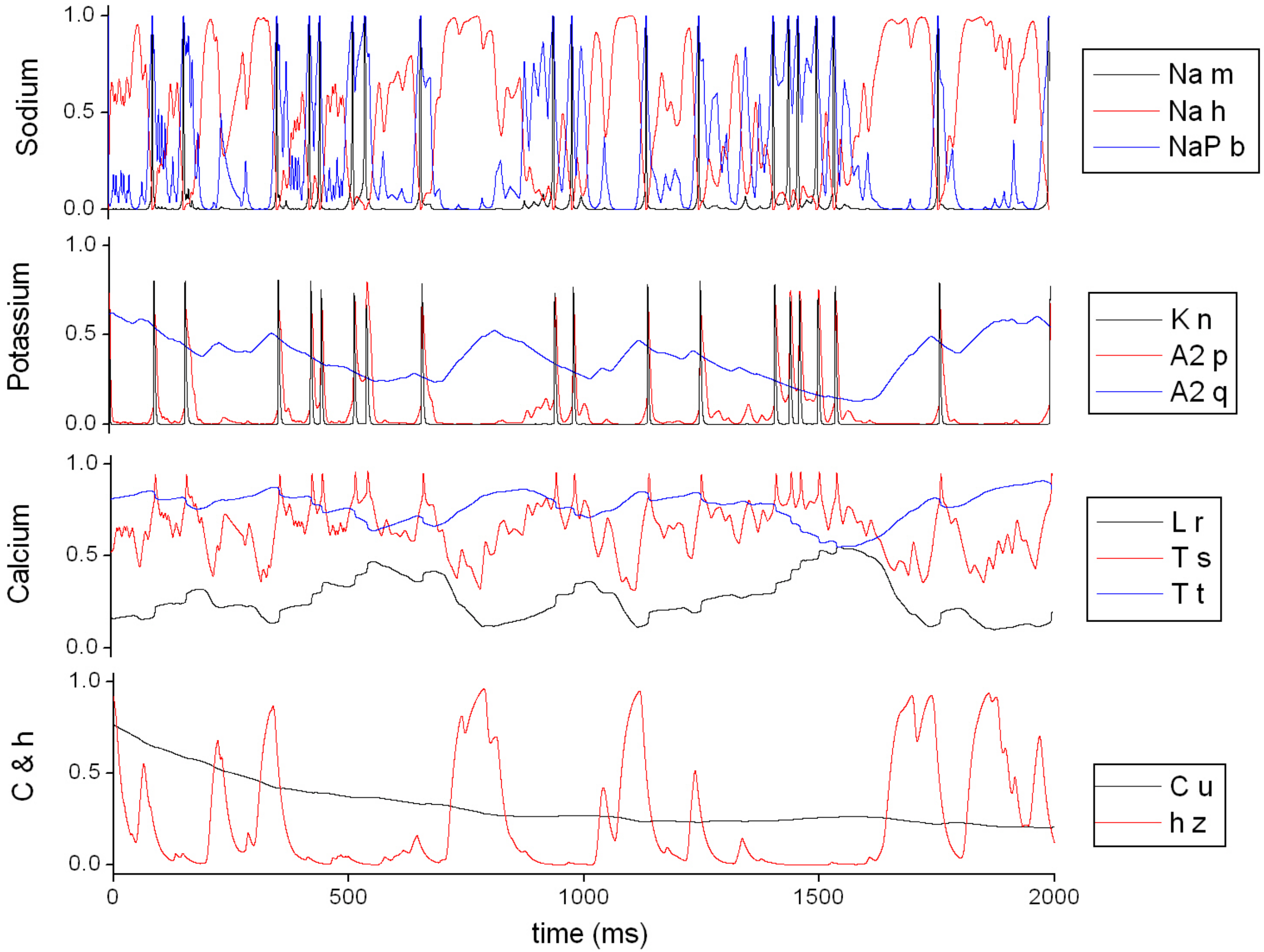
Assimilation and prediction of neuron output – N2



Prediction neuron response to arbitrary current stimulation



Prediction of the state of ionic gates



Predicting the state of the gate variables of the 9 ion channels – **not accessible to the experiment!**

Uncertainty on parameter field

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Separate the experimental signal $V_{data}(t)$ into the useful signal $V_{use}(t)$ and the noise component $v_n(t)$.

Insert in the cost function:

$$
\begin{aligned}
c(\vec{x}(0),\vec{p}) &= \frac{1}{2}\sum_{i=0}^{i=N}\left(V_{data}(t_i) - V(t_i,\vec{x}(0),\vec{p})\right)^2 \\
&= \frac{1}{2}\sum_{i=0}^{i=N}\left(V_{use}(t_i) + v_n(t_i) - V(t_i,\vec{x}(0),\vec{p})\right)^2 \\
&= \frac{1}{2}\sum_{i=0}^{i=N}\left(V_{use}(t_i) - V(t_i,\vec{x}(0),\vec{p})\right)^2 + \frac{1}{2}\sum_{i=0}^{i=N}\left(v_n(t_i)\right)^2
\end{aligned}
$$

The cross term cancels as it is proportional to the noise average which is zero. The second term on the RHS gives th variance of the membrane voltage which when driven by thermal fluctuations is given by Nyquist theorem:

$$
\langle v_n^2 \rangle = \frac{1}{N+1}\sum_{i=0}^{i=N}\left(v_n(t_i)\right)^2 = 4R\,k_B T\,\Delta f
$$

Entropy

$$
c(\vec{x}(0),\vec{p}) = \frac{1}{2}\sum_{i=0}^{i=N}\left(V_{use}(t_i) - V(t_i,\vec{x}(0),\vec{p})\right)^2 + 2(N+1)R\,k_B\,\Delta f\;\; T
$$

Total energy: U

Free energy: F

Random energy: TS

F=0 achieved by direct parameter search

T=0 achieved by statistical inference

Hence:

$$
\delta c = ST
$$

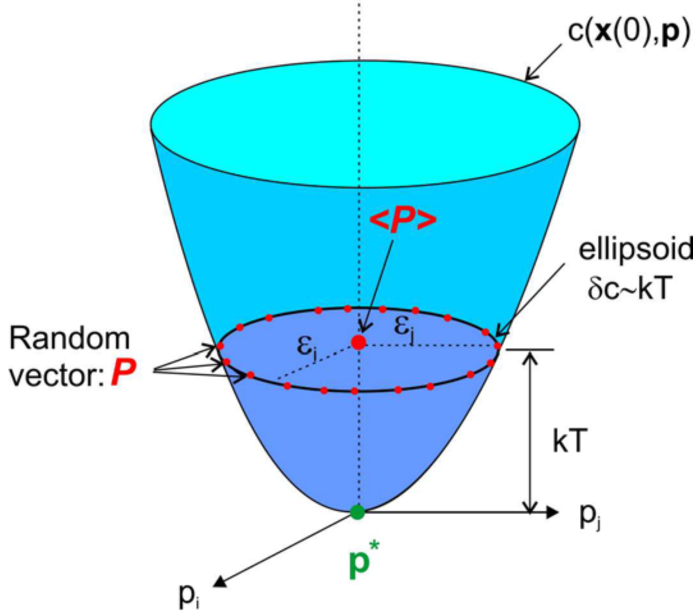
Noise behaves as a residual temperature that prevents reaching the global minimum through direct parameter search

Statistical inference of the "global" minimum

Provided the noise temperature T is not too large that the second order Taylor expansion is accurate:

$$\delta c = \frac{1}{2}(\boldsymbol{p} - \boldsymbol{p}^*)^T \hat{\boldsymbol{H}} (\boldsymbol{p} - \boldsymbol{p}^*)$$

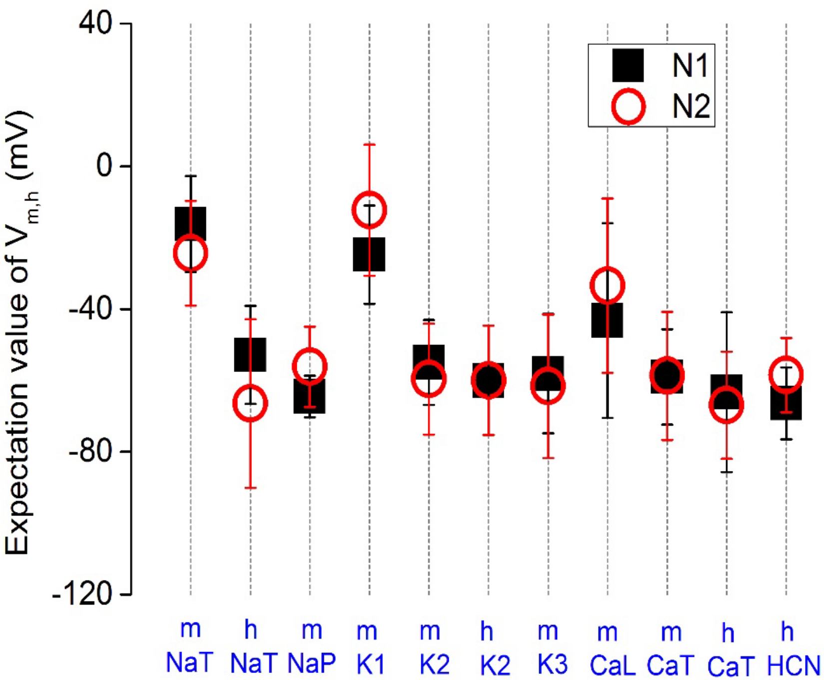
the true global minimum $\boldsymbol{p}^*$ may be estimated taking a statistical average <***P***> of the multivalued solutions of the data assimilation



$\boldsymbol{p}^* = <\boldsymbol{P}>$

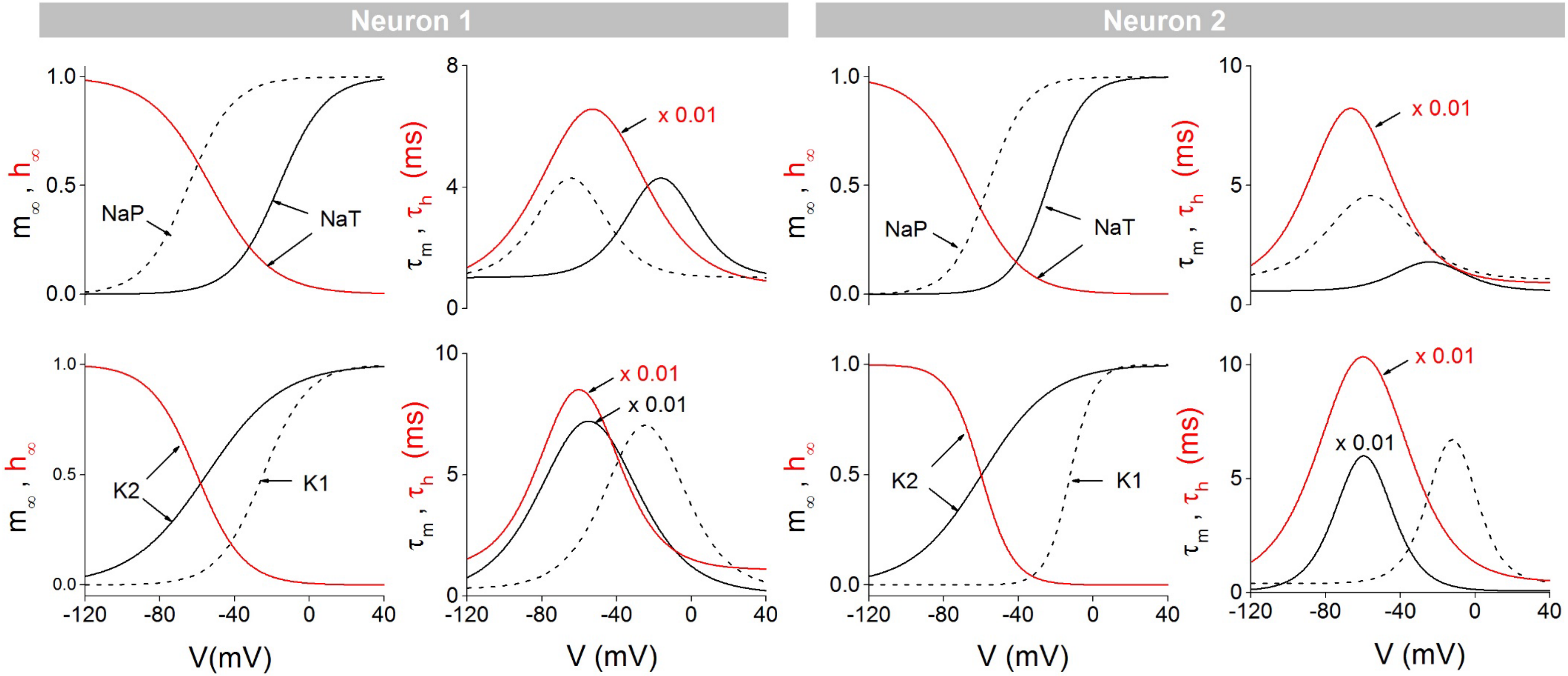
Global minimum

Nogaret et al, *Sci.Rep*. **6**,32749 (2016)



Excellent agreement between the threshold voltages extracted from 2 HVC neurons!
Physiologically meaningful parameter solutions

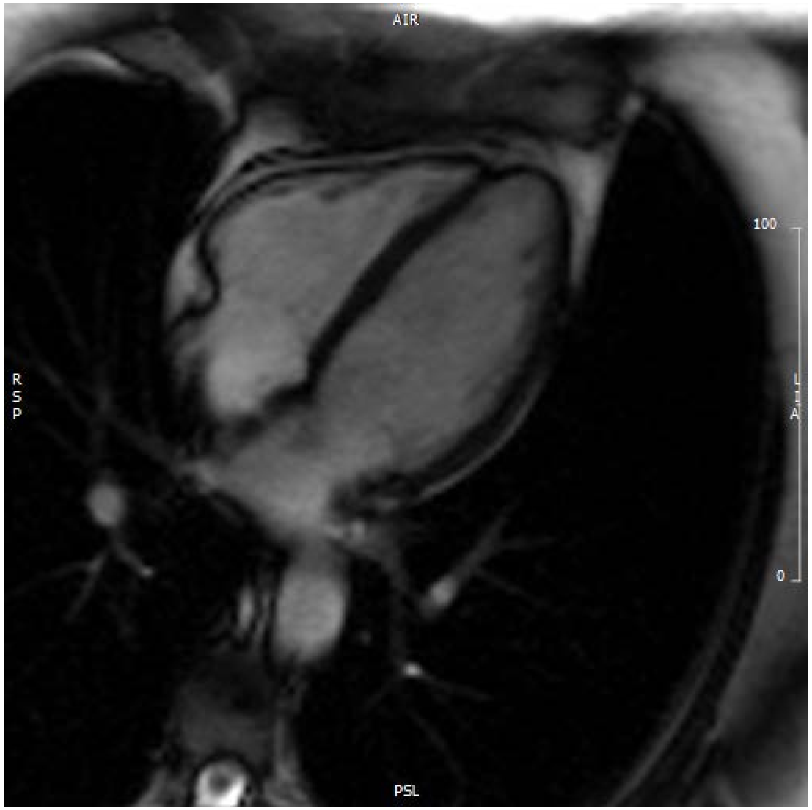
Uncertainty on parameters



Similarity of the activation curves of 2 HVC neurons reconstructed from the inferred global minimum.

DA + Bayesian inference consistently achieves single valued, biologically plausible models.
The method is fully automatic, requiring minimal biological intuition.
It absorbs intrinsic fluctuations of biological neurons to make predictions with sufficient accuracy to evidence trial-to-trial fluctuations in neuron behaviour.

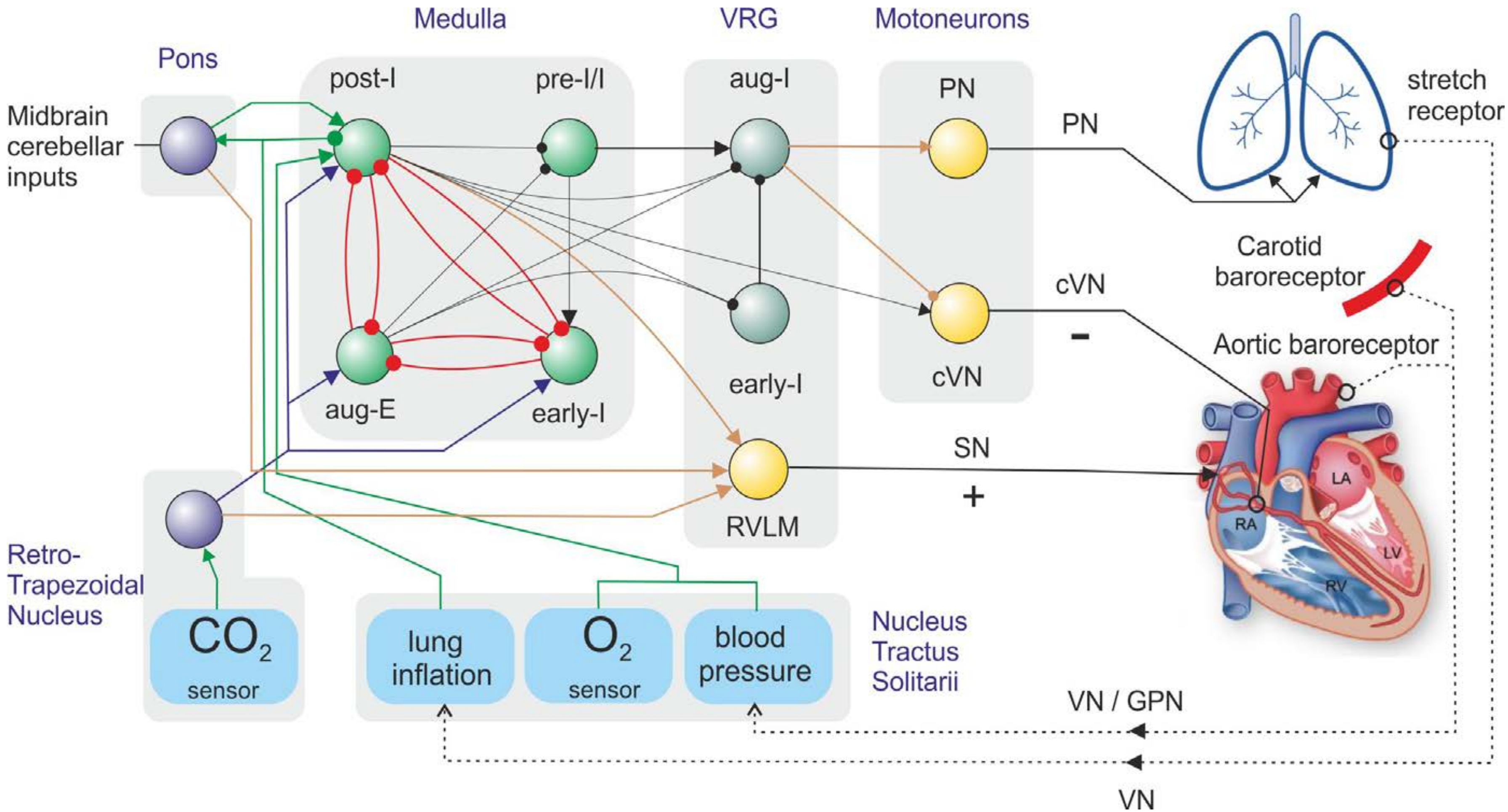
Healthy Heart



Heart Failure

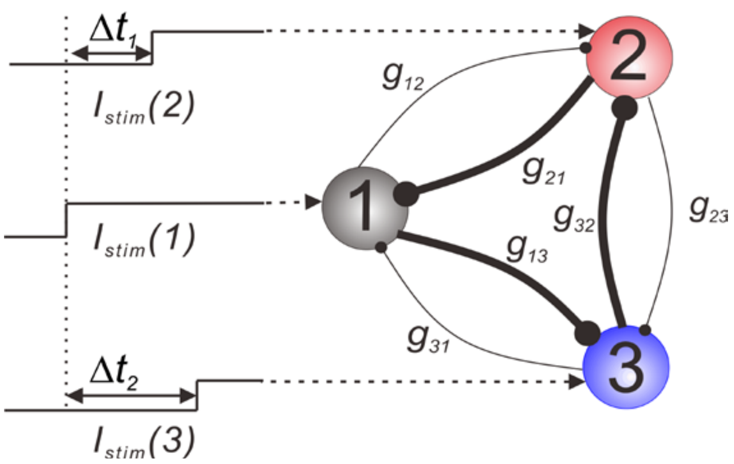
Loss of Heart rate variability is a prognosis of heart-failure

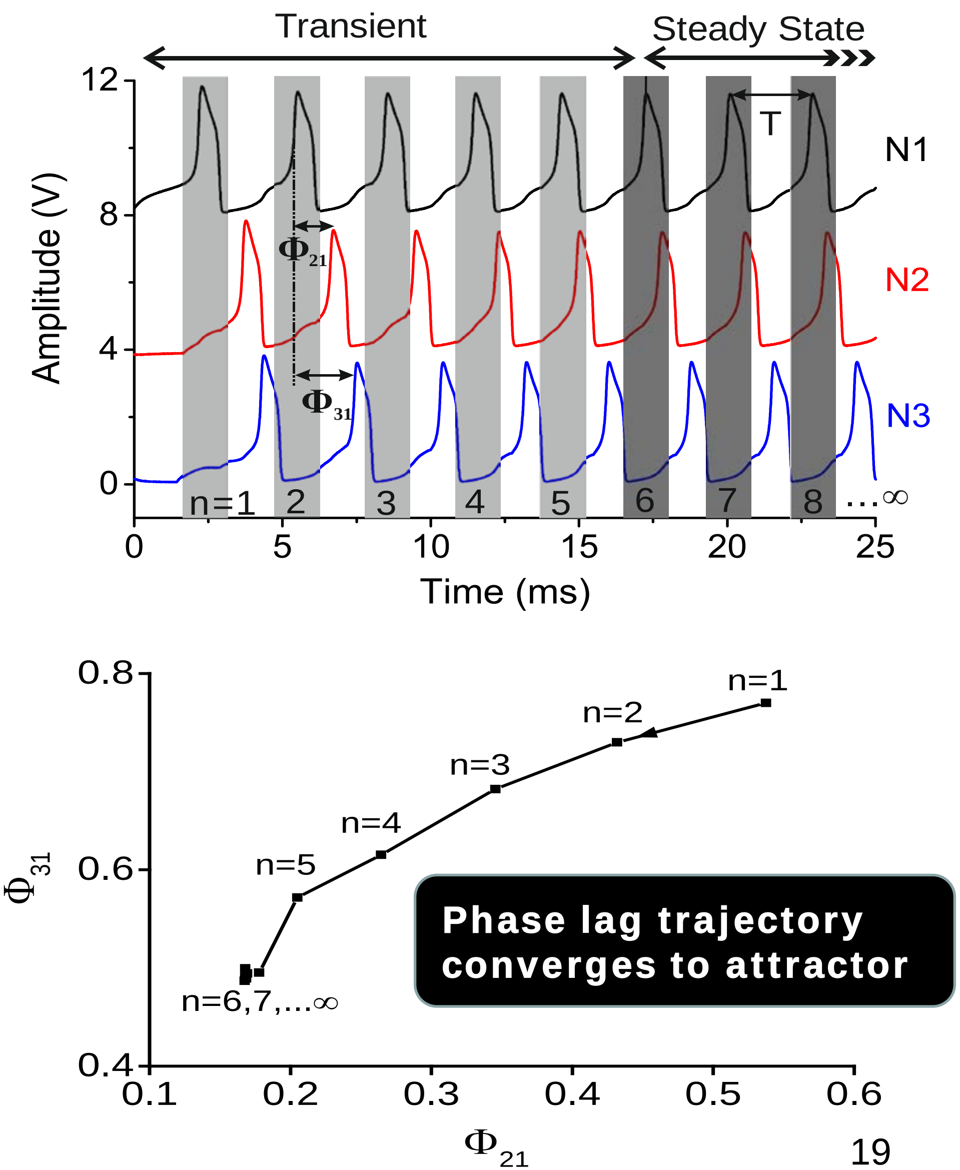
Medullary Central Pattern Generators control Heart Pacing

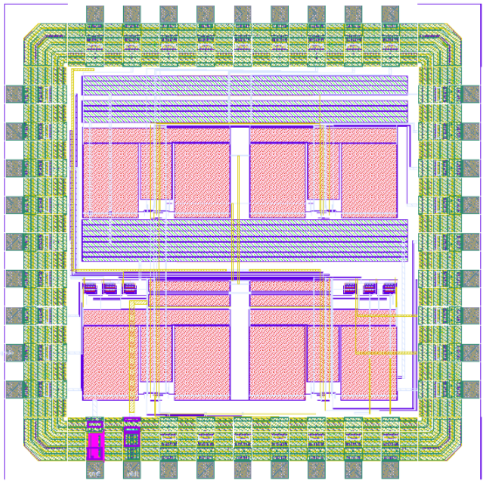


DA can infer the network connectivity that restores accurate adaptation to physiological feedback

Application of DA: machine learning





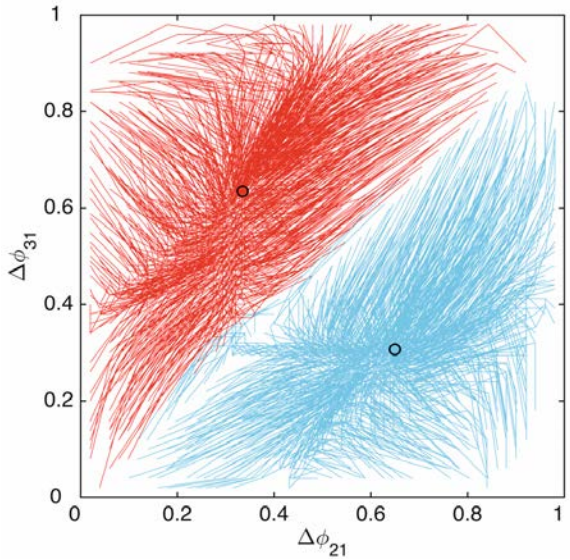


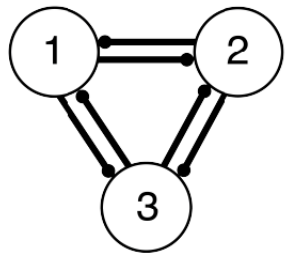
4 HH neuron VLSI platform

3N Central Pattern Generator

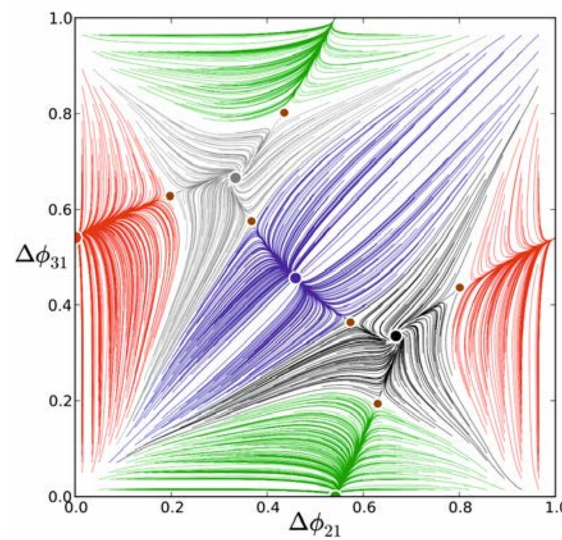
Experiment

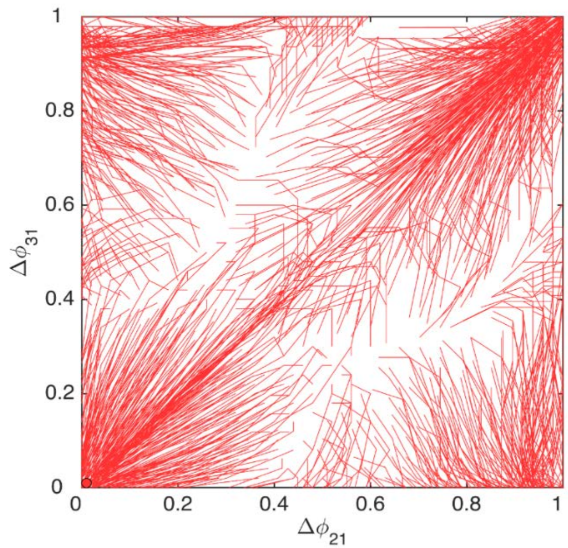
Theory

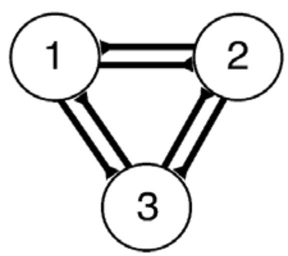




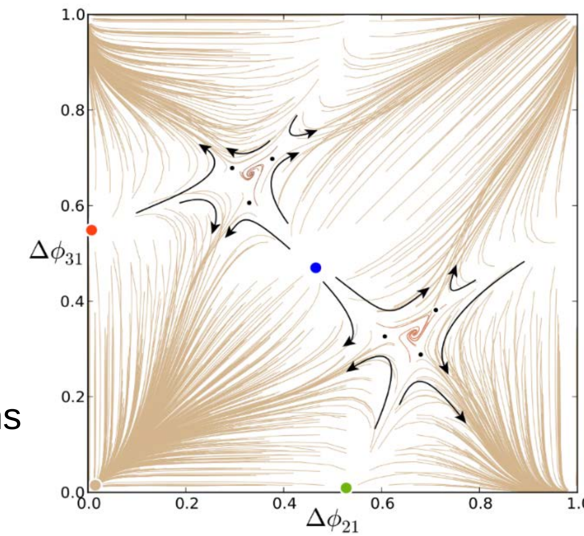
Competing neurons
(inhibition)







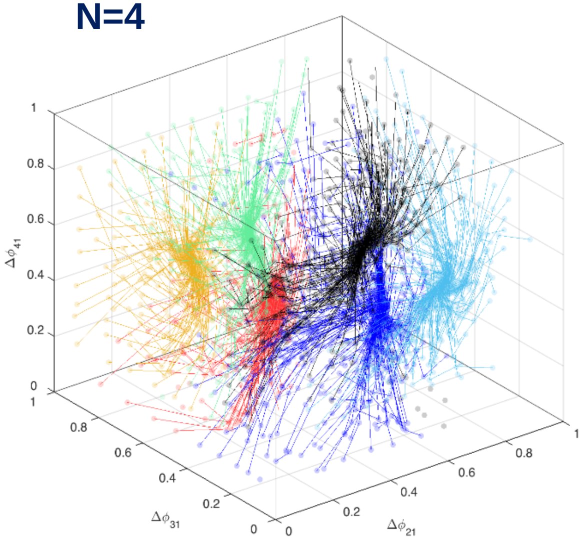
Cooperative neurons
(excitation)

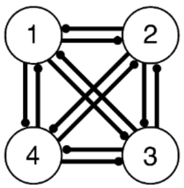


Wojcik et al., Phys. Rev. E **83**, 056209 (2011)

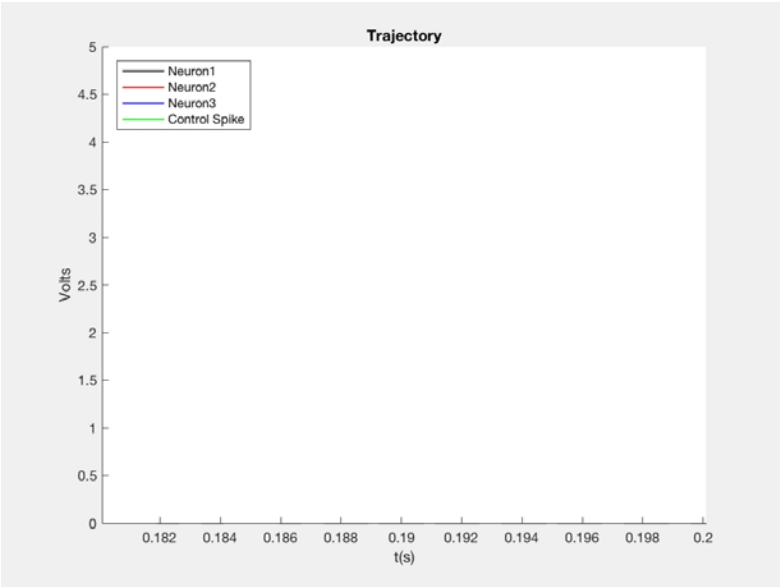
4-6 neuron CPGs – electrical switching of motor patterns

N=4

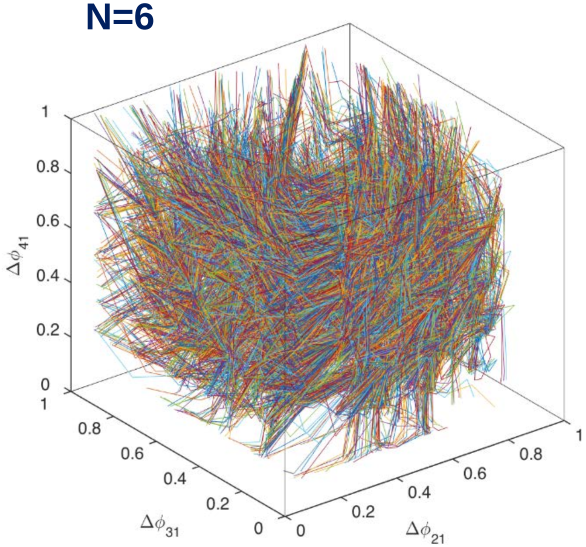




(N-1)! = 6 Attractors



N=6



(N-1)! = 120 Attractors

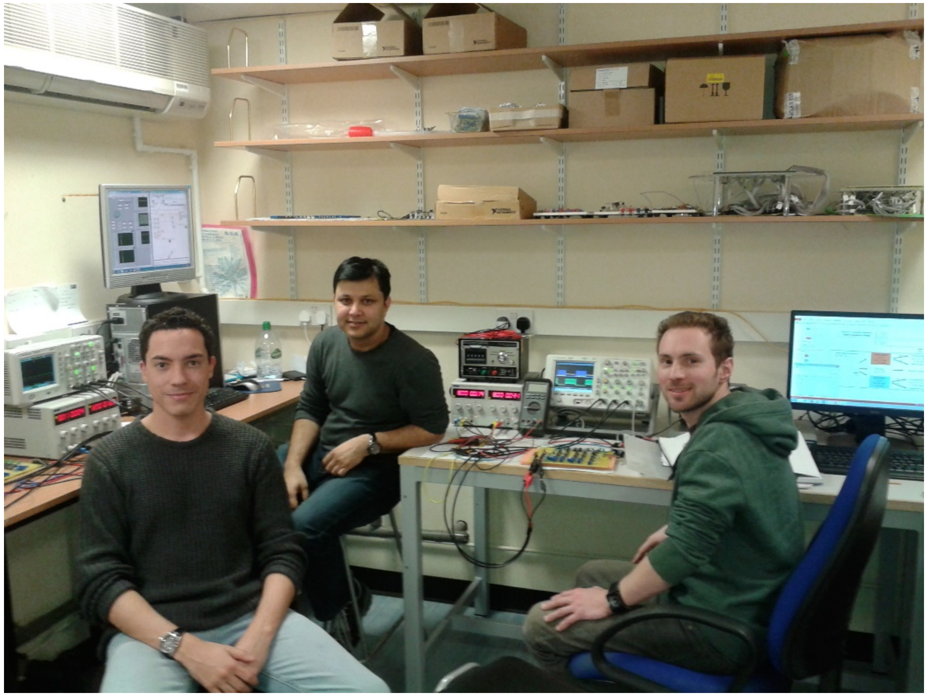
Stimulus induced switching between attractors
Demonstration of *command neuron action* to switch motor patterns e.g. gaits

- **Scaling of attractors ~(N-1)!**
- **Switching between attractors is induced by command pulses**
- **Analog CPGs integrate instantly**

DA may “engineer” basins of attraction to produce specific gaits.

Acknowledgements

UNIVERSITY OF BATH



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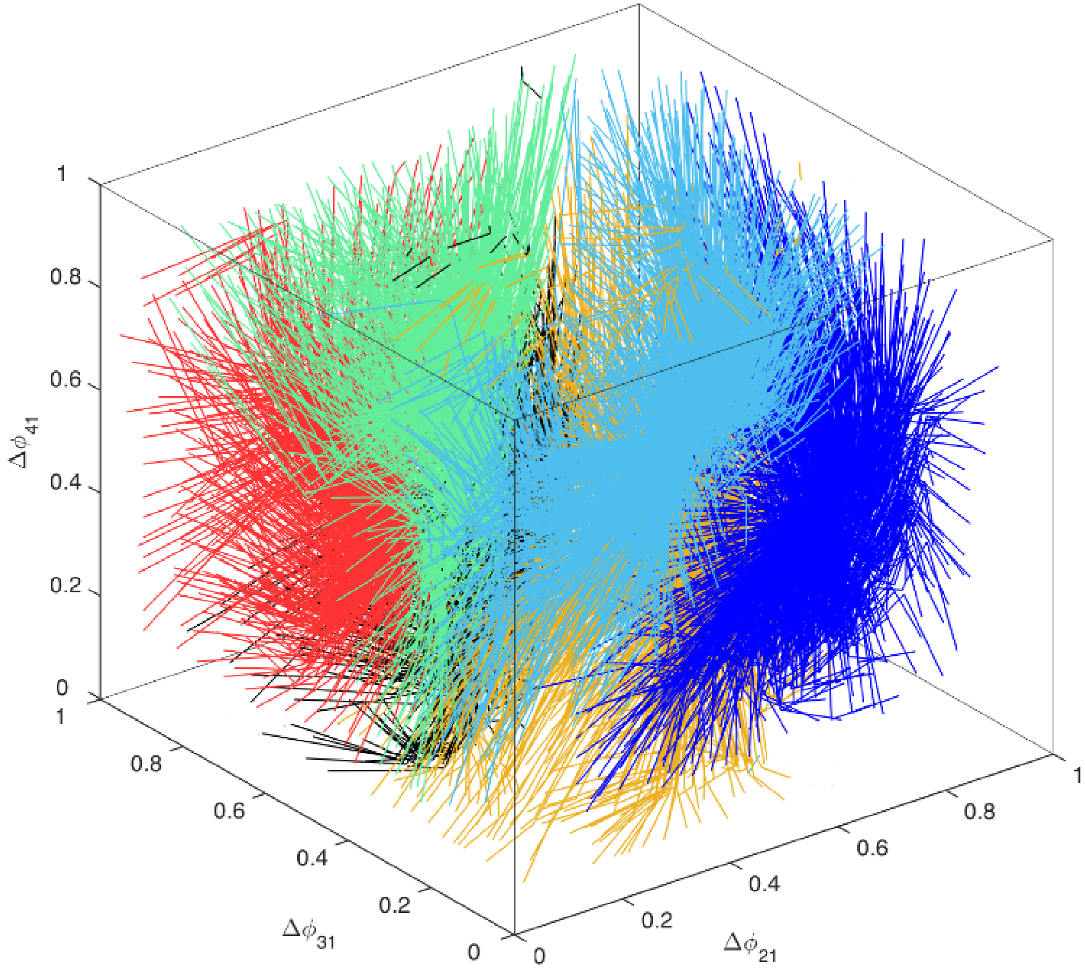
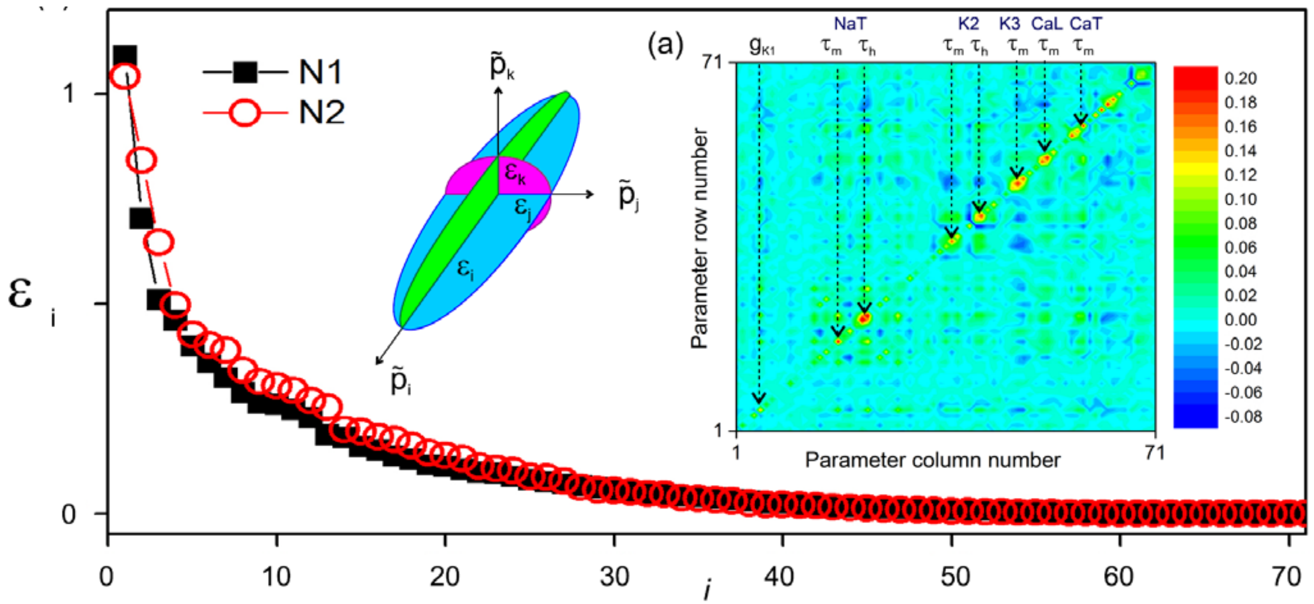
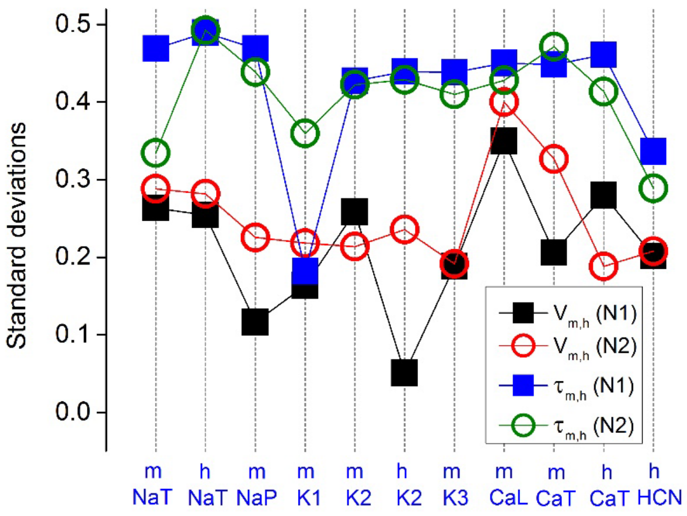
H2020 FET

Phase map of 3N winnerless network



Covariance matrix of the data misfit Hessian





The eigenvalues of the Hessian matrix **H** are the half-axes of the 71D-ellipsoid:

The spectrum of eigenvalue decays exponentially.

The "sloppiest" – most loosely constrained – are the time constants of the model, the most tightly constrained are the gate voltage thresholds.