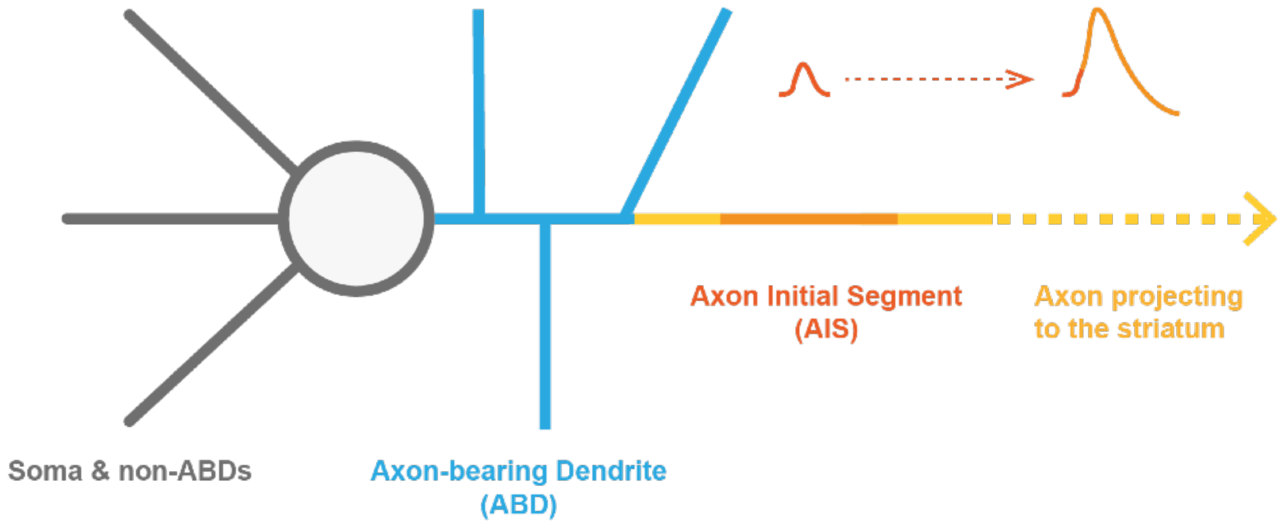
Contribution of morphological and biophysical parameters to activity modification in dopaminergic neurons

Jean-Marc Goaillard & Cyprien Dautrevaux

CONTEXT

Electrophysiological and morphological properties of SNc DA neurons



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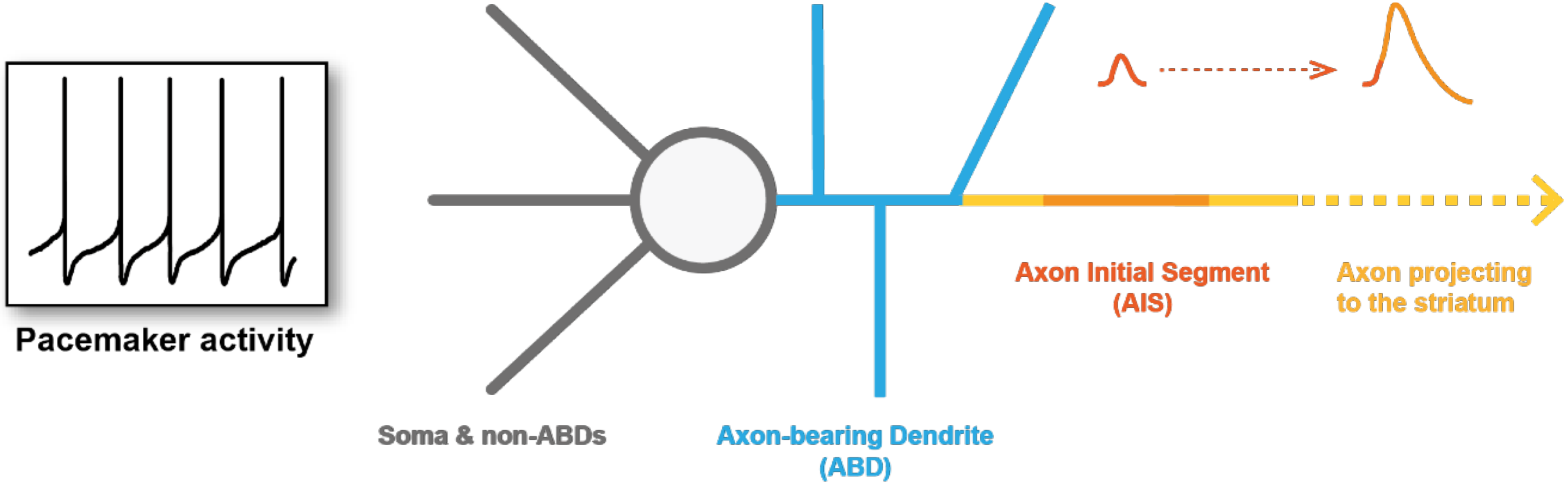
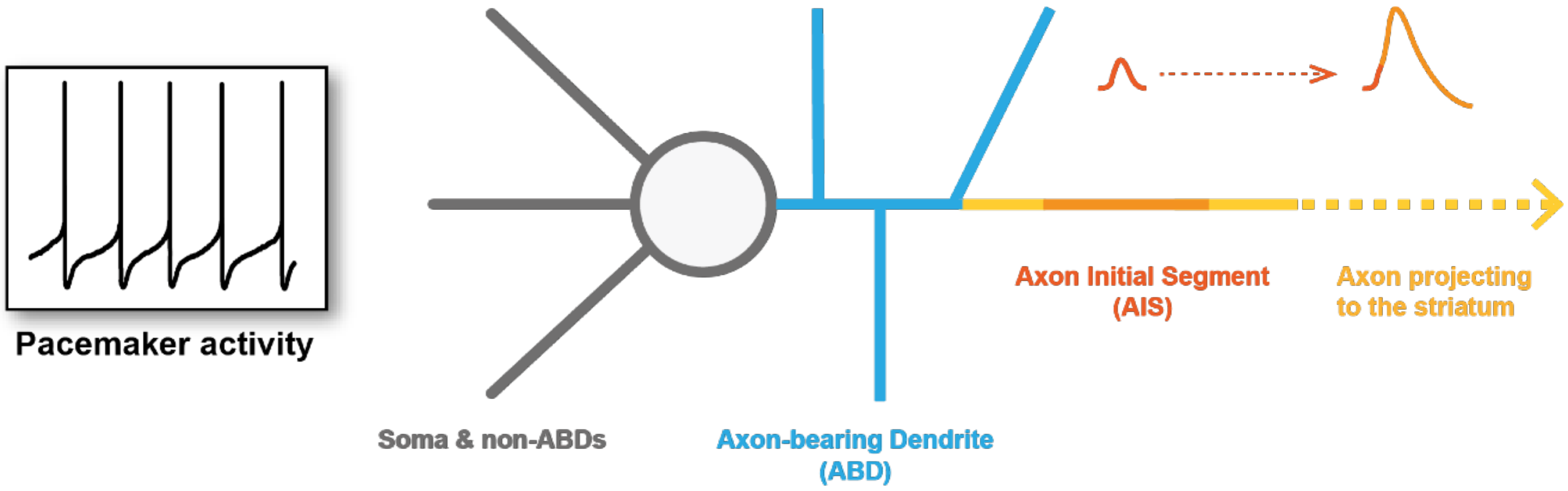


1) Pacemaker activity

Hausser et al. (1995), Gentet & Williams (2007), Jang et al. (2014), Moubarak et al. (2019, 2022)

Electrophysiological and morphological properties of SNc DA neurons



1) Pacemaker activity

2) Axon bearing dendrite (ABD)

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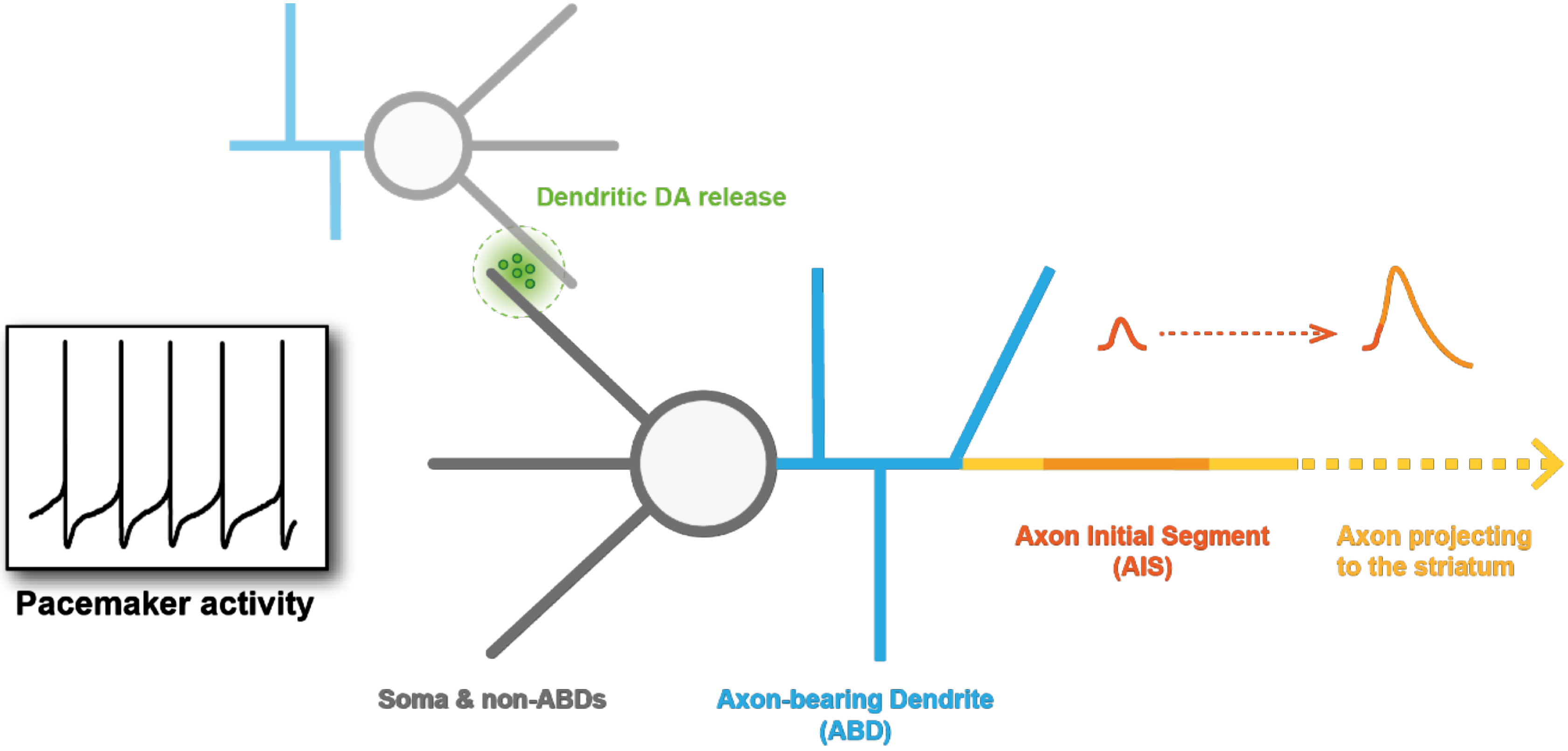

1) Pacemaker activity

2) Axon bearing dendrite (ABD)

3) Dendritic release of dopamine

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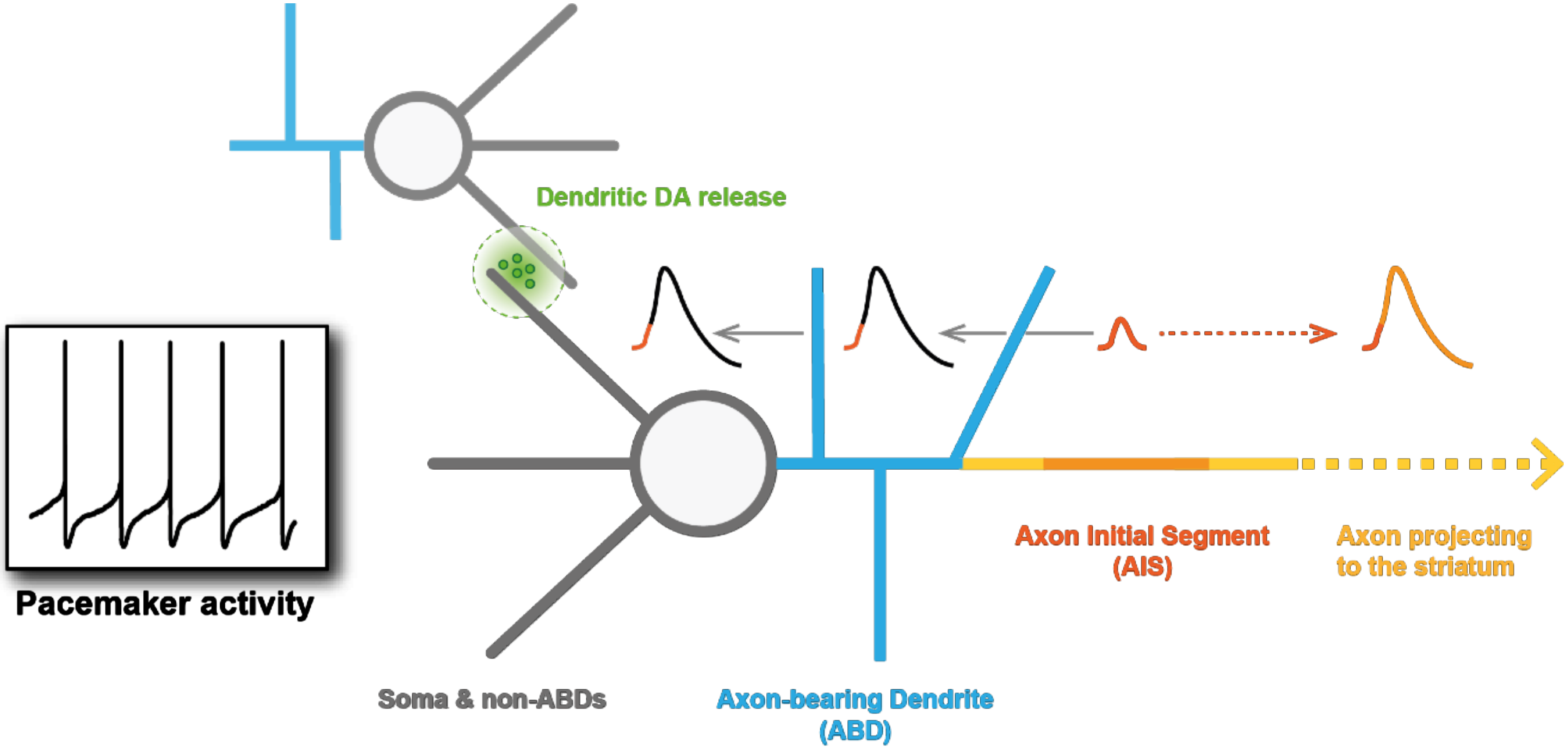

1) Pacemaker activity

2) Axon bearing dendrite (ABD)

3) Dendritic release of dopamine

4) Faithful back-propagation of action potential

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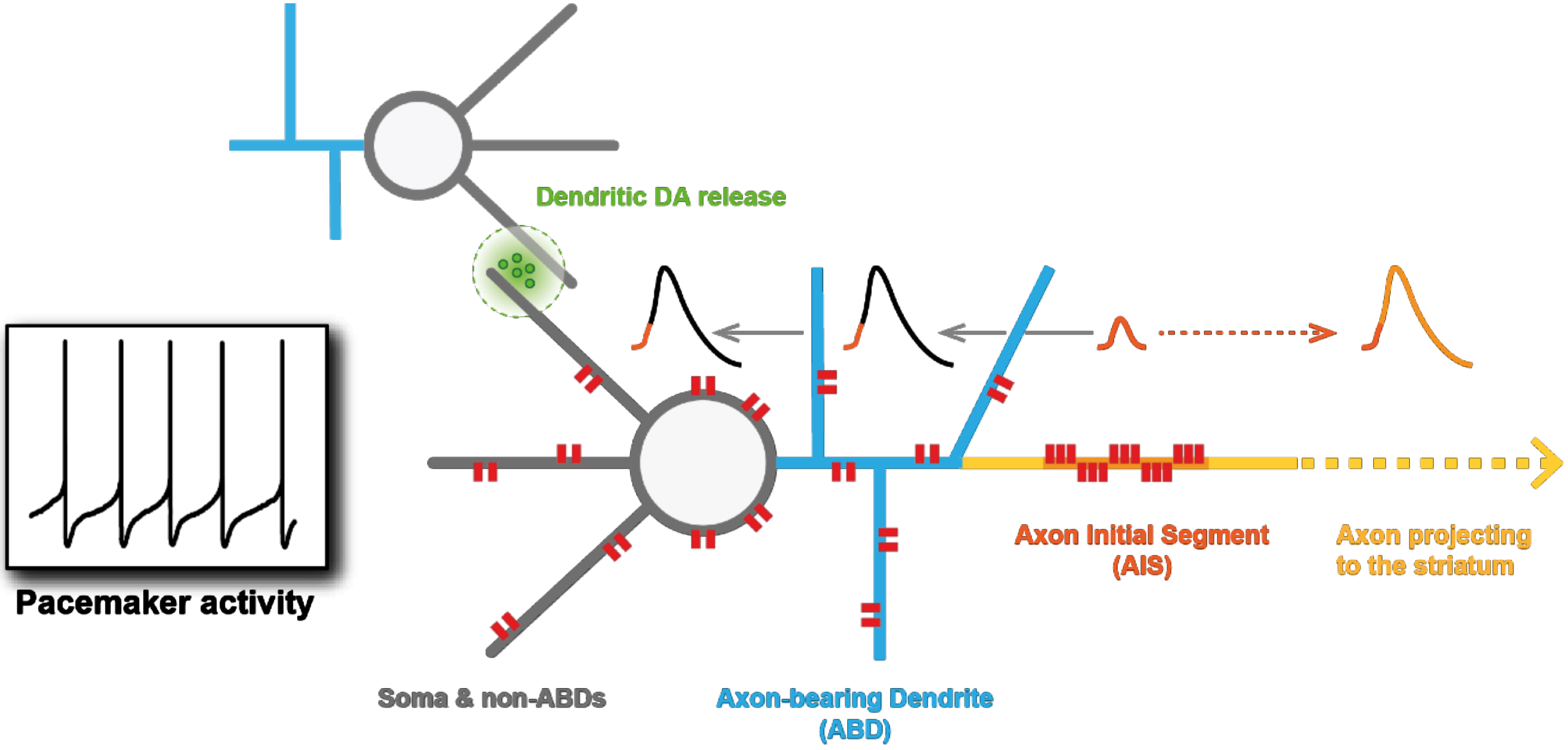


1) Pacemaker activity

2) Axon bearing dendrite (ABD)

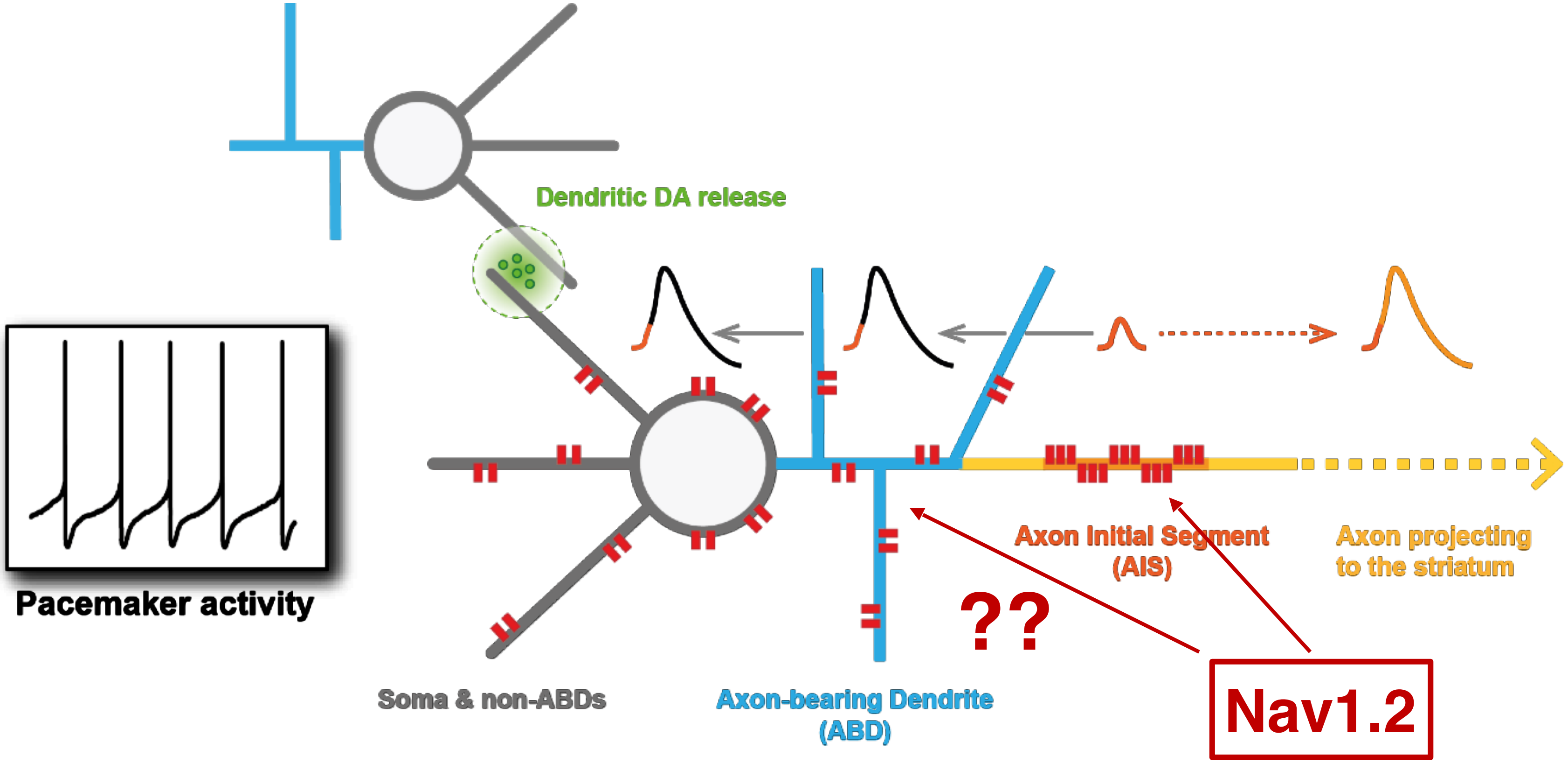
3) Dendritic release of dopamine

4) Faithful back-propagation of action potential

5) High density of sodium channels in the soma and dendrites

Hausser et al. (1995), Gentet & Williams (2007), Jang et al. (2014), Moubarak et al. (2019, 2022)

Electrophysiological and morphological properties of SNc DA neurons



1) Pacemaker activity
2) Axon bearing dendrite (ABD)
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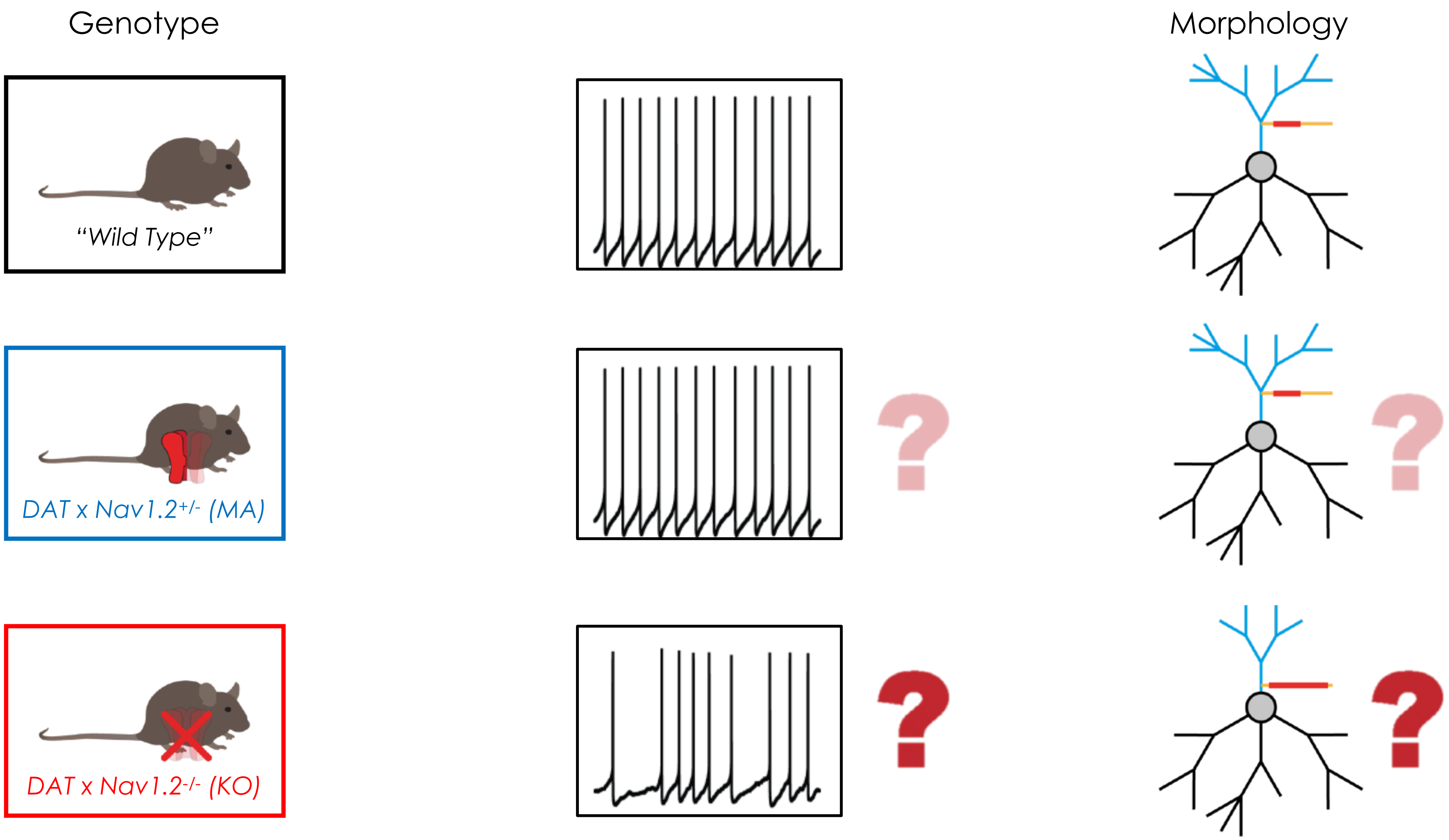
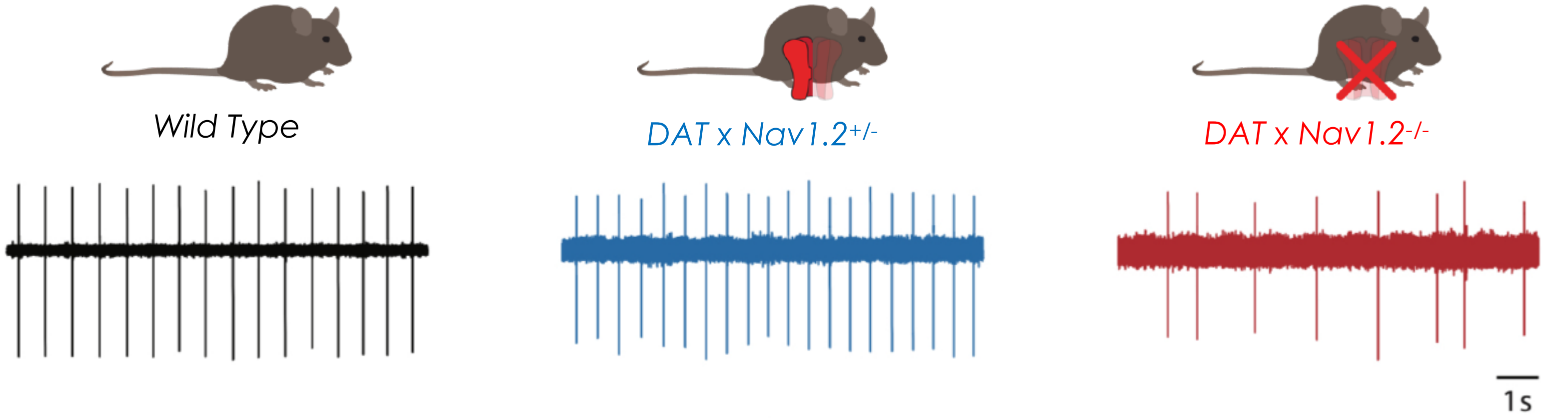
CONTEXT

Using Nav1.2 transgenic mice to investigate the function of Nav1.2 in dendrites



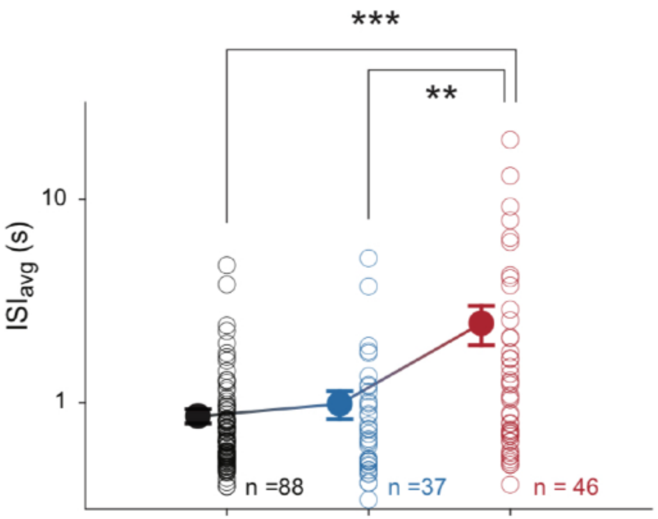
CONTEXT

Pacemaking is altered in Nav1.2 KO neurons



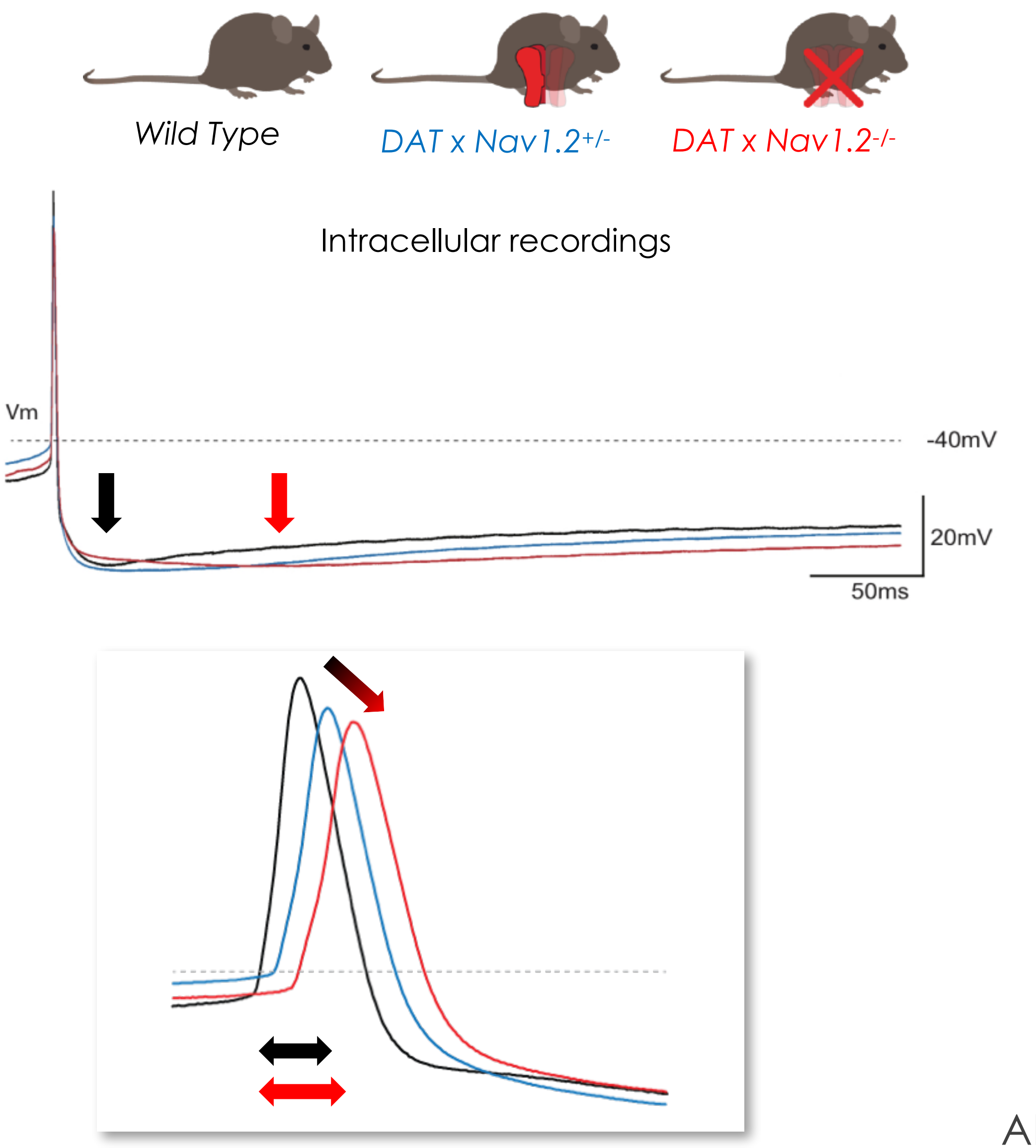
-65% in frequency

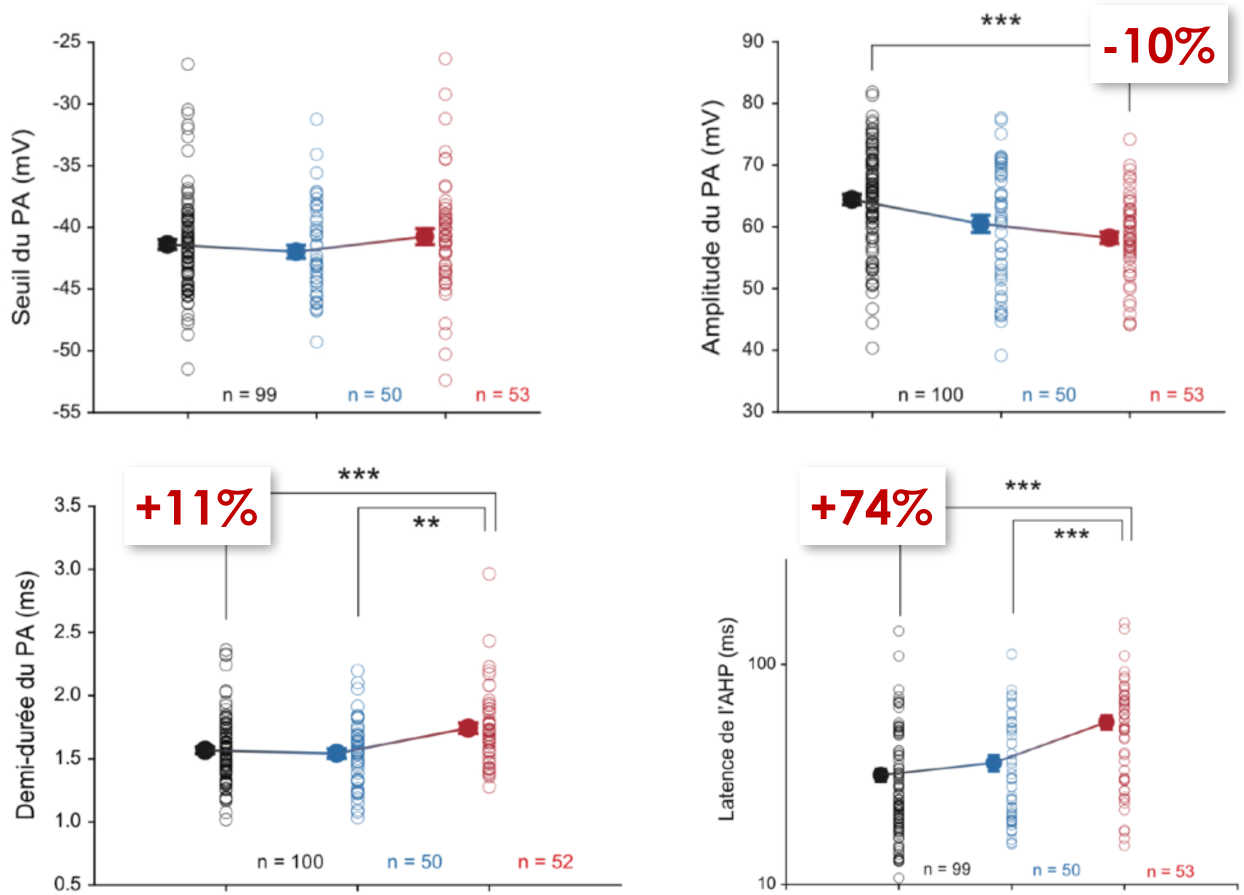
+172%



Nav1.2 total deletion induces a decrease in spontaneous firing rate and an increase in irregularity

Action potential shape is altered in Nav1.2 KO neurons



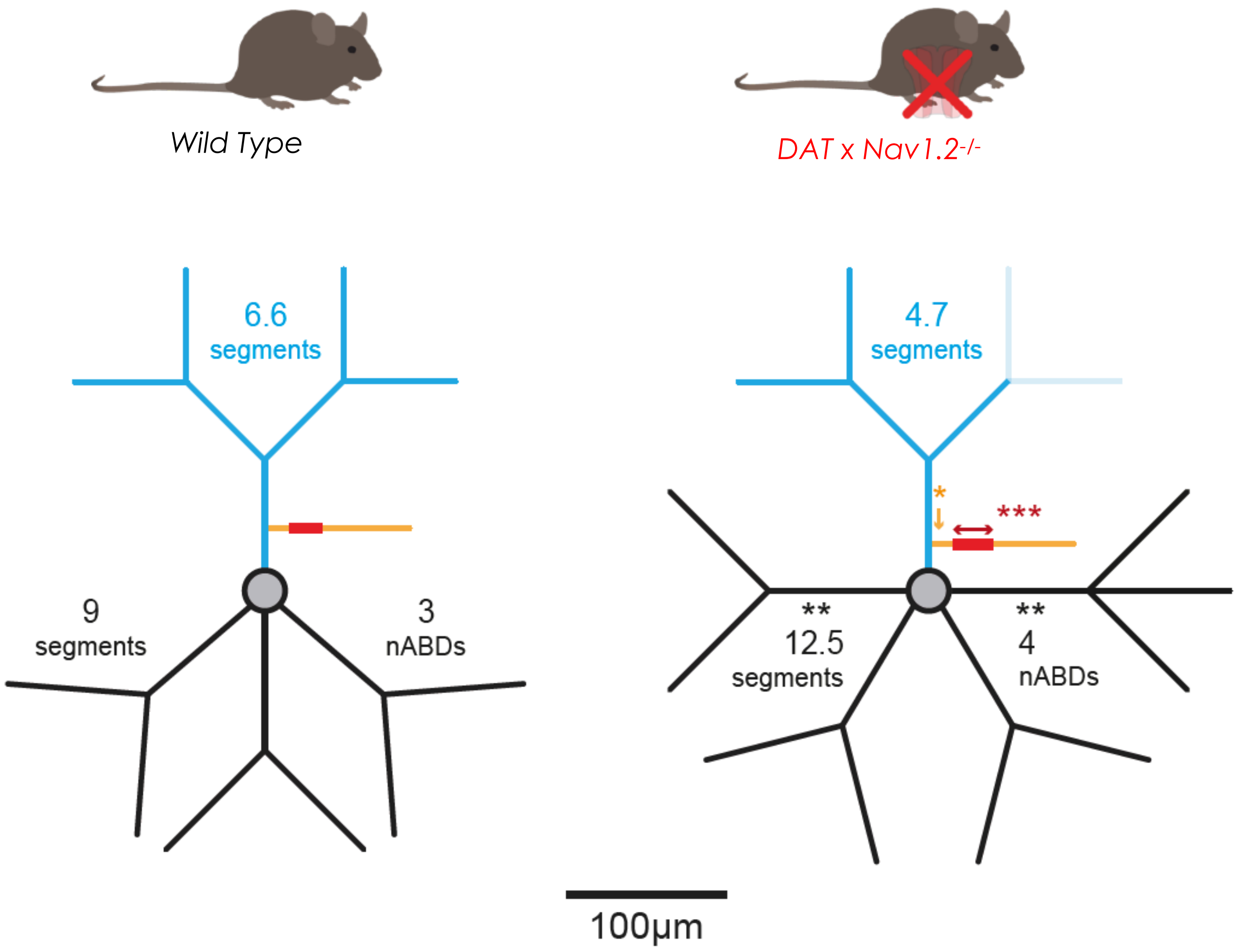


Nav1.2 total deletion alters AP properties :

AP amplitude decreases, AP half-width & AHP latency increase

CONTEXT

Morphology is altered in Nav1.2 KO neurons



ABD complexity

Axon-soma distance

AIS length

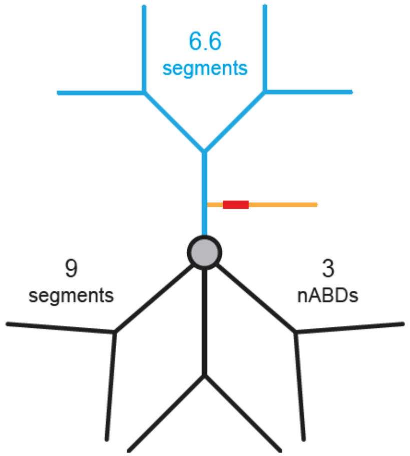
nABD complexity

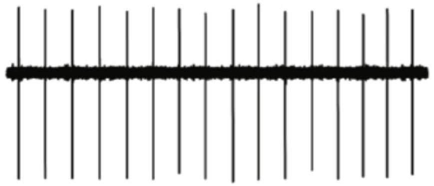
Can we decipher the complex interplay between morphology and biophysical parameters to explain electrophysiological results?

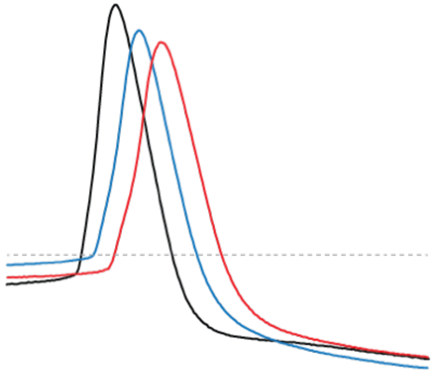
Altered morphology

Altered neuronal output

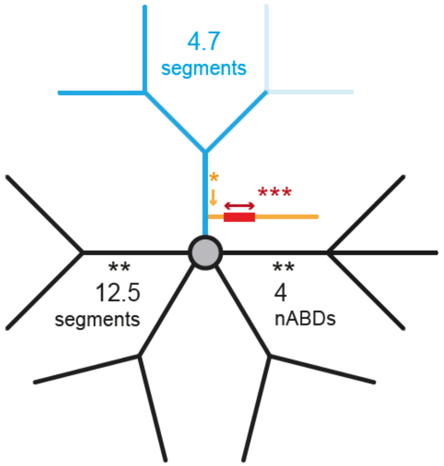
Wild Type





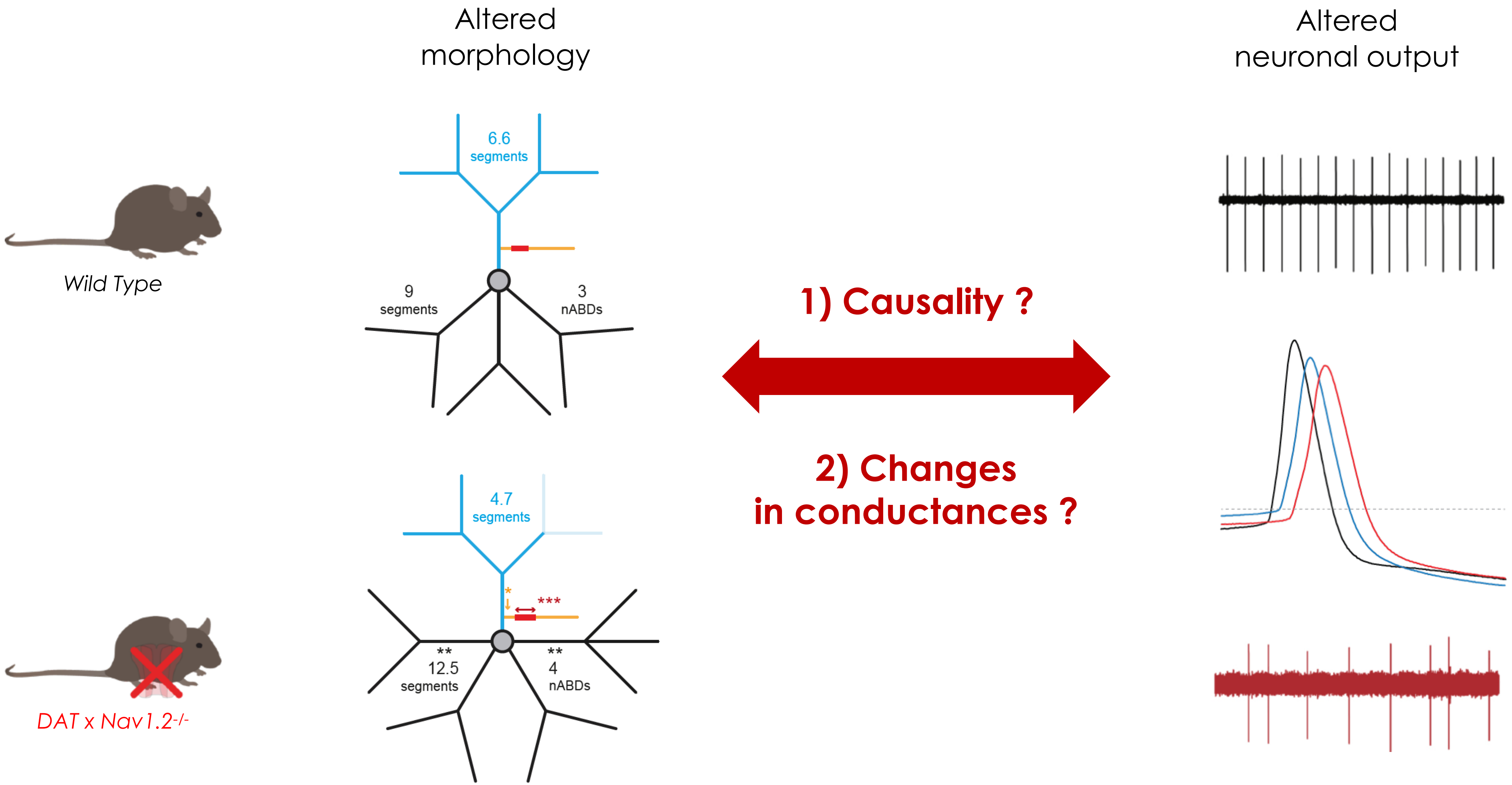


DAT x Nav1.2$^{-/-}$



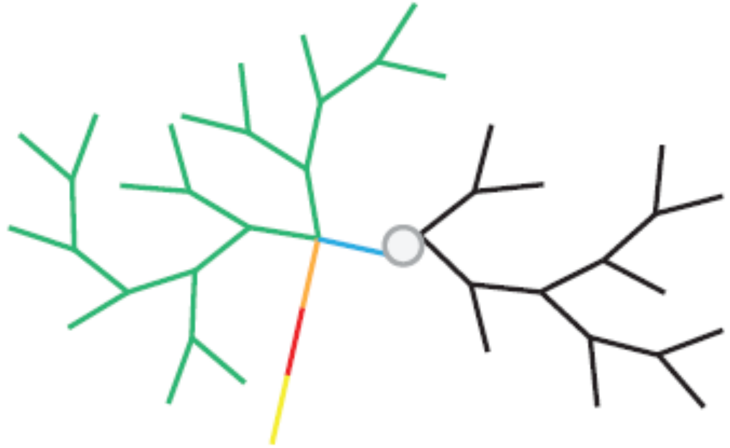
PROJECT

Can we decipher the complex interplay between morphology and biophysical parameters to explain electrophysiological results?

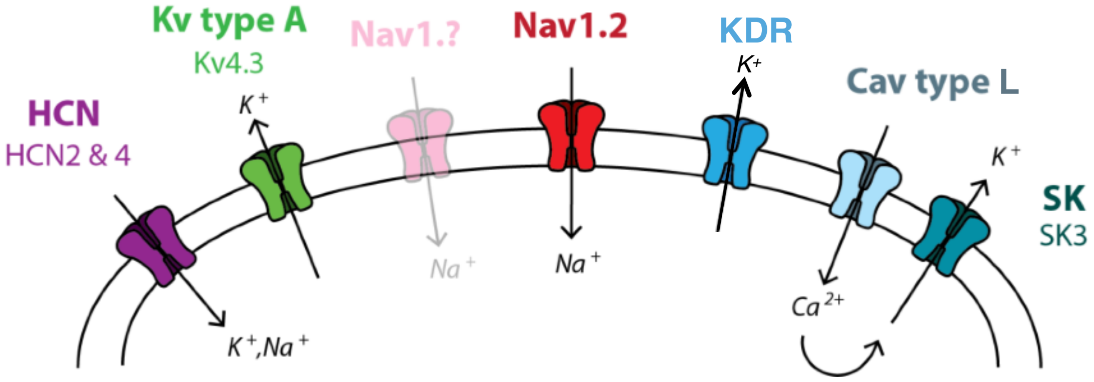


General approach: multicompartment HH model

Neuron multicompartment morphological model



Extended Hodgkin Huxley model



Current general equations (except for I_{SK}): $I(V,t) = g_{max} \times m^a(V,t) \times h^b(V,t) \times (V - E_{rev})$

$$m_\infty(V) = \frac{1}{\left(1 + exp\left[\left(\frac{-(V - V_m)}{k_m}\right)\right]\right)} \qquad h_\infty(V) = \frac{1}{\left(1 + exp\left[\left(\frac{-(V - V_h)}{k_h}\right)\right]\right)}$$

$$dm(V,t)/dt = \frac{[m_\infty(V) - m(V,t)]}{\tau_m} \qquad dh(V,t)/dt = \frac{[h_\infty(V) - h(V,t)]}{\tau_h} \qquad dt = 10\ \mu s$$

Current	V_m (mV)	k_m (mV)	a	V_h (mV)	k_h (mV)	b	E_{rev} (mV)	Specific equations (τ_m and τ_h are expressed in ms)	g_{max} (pS/μm^2) Soma	ABD	nABD	aD	Ax-st	AIS	Axon
I_{Na}	−28	8	3	−50	−10	1	60	$\tau_m = 0.01 + (0.33/(1 + ((V + 20)/30)^2))$ $\tau_h = 0.7 + (16/(1 + ((V + 50)/8)^2))$	25–200	25–200	25–200	25–200	25–200	1000–8000	400
I_{KDR}	−30	9	4	—	—	0	−90	$\tau_m = (4 \times exp(-(0.000729) \times ((V + 32)^2))) + 4$	50–400	50–400	50–400	50–400	50–400	1000–8000	400
I_A (soma)	−30	7	1	−75	−7	1	−90	$\tau_m = 1.029 + (4.83/(1 + exp((V + 57)/6.22)))$	150	0	0	0	0	0	0
I_A (dendrite)	−30	7	1	−85	−7	1	−90	$\tau_h = 25 + (120 + (78.4/(1 + exp(V + 68.5)/$ $5.95)) - 25)/(1 + exp((-V + 90) \times 5))$	0	100	100	100	100	0	0
I_H	−92	−7,25	1	—	—	0	−40	$\tau_m = 556 + 1100 \times exp(-0.5 \times ((V)/11.06)^2)$	3	3	3	3	3	0	0
I_{CaL}	−31	7	1	—	—	0	120	$\tau_m = 1/((-0.209 \times (V + 39.26)/(exp(-(V + 39.26)/4.111)$ $- 1) + (0.944 \times exp(-(V + 15.38)/224.1))))$	1	1	1	1	1	0	0
I_{SK}	—	—	—	—	—	—	−90	$I(V,Ca_i) = g_{max} \times O_\infty(Ca_i) \times (V - E_{rev})$ $O_\infty(V) = (Ca_i)^4/((Ca_i)^4 + (0.00019)^4)$	0.1	0.1	0.1	0.1	0.1	0	0
Calcium buffering and pump (Desthexe et al., 1993)															

NEURON

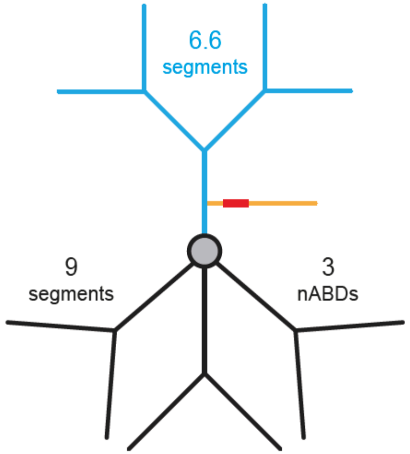
Yale NEURON simulator

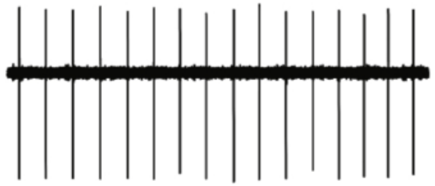
General approach: Model inversion framework

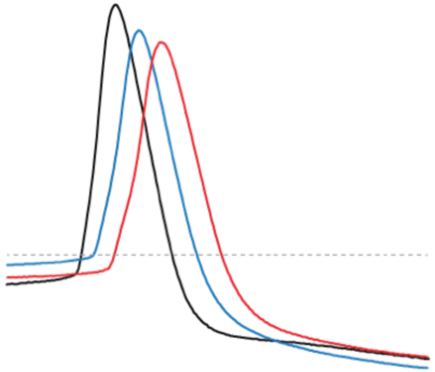
Altered average morphology

Altered neuronal output

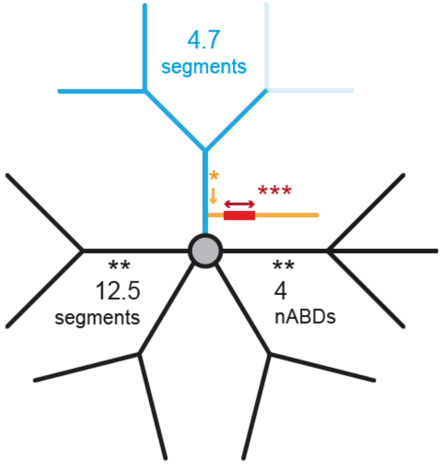
Wild Type







DAT x Nav1.2-/-



Mitra ED, Hlavacek WS. (2019), Moubarak et al. (2019, 2022)

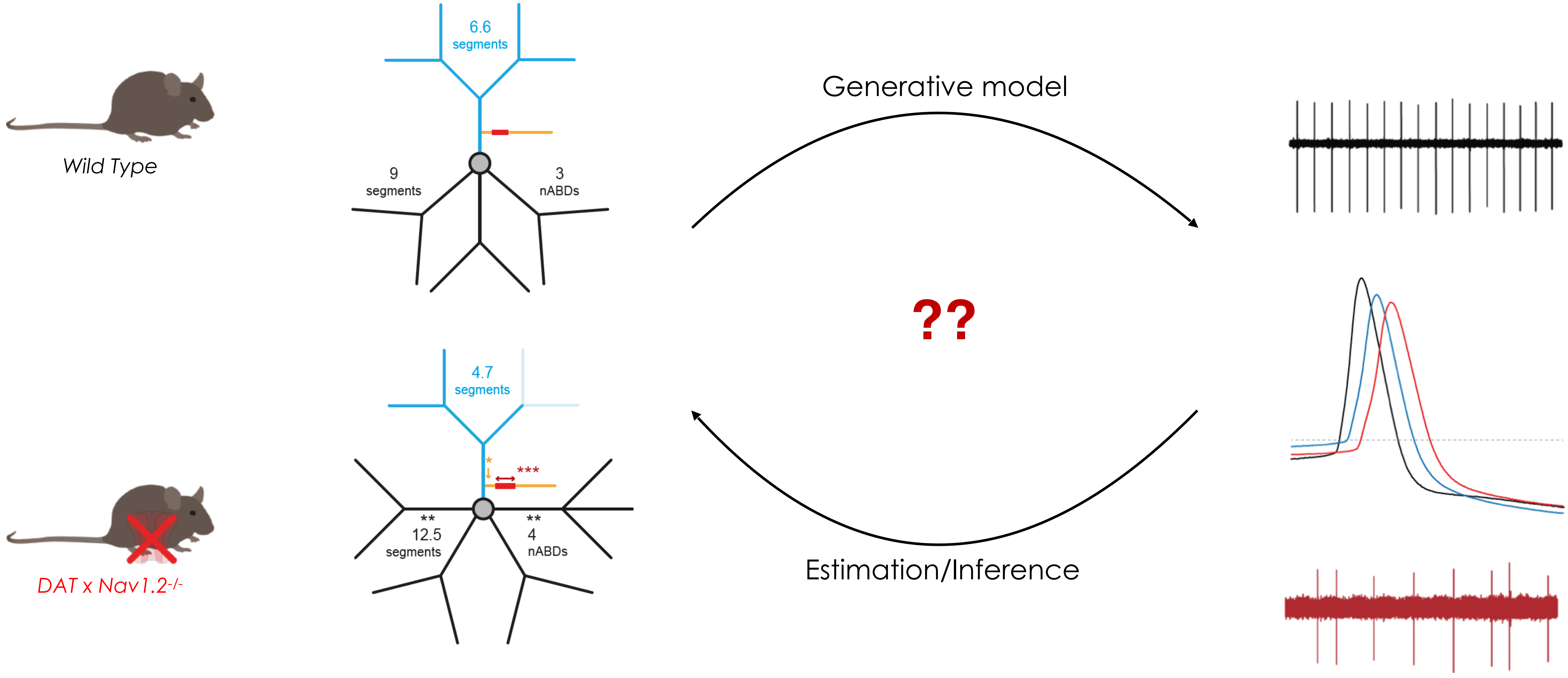
METHODS

General approach: Model inversion framework

Altered average morphology

Model inversion method

Altered neuronal output



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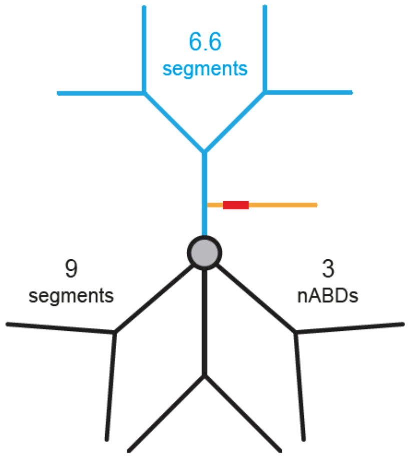

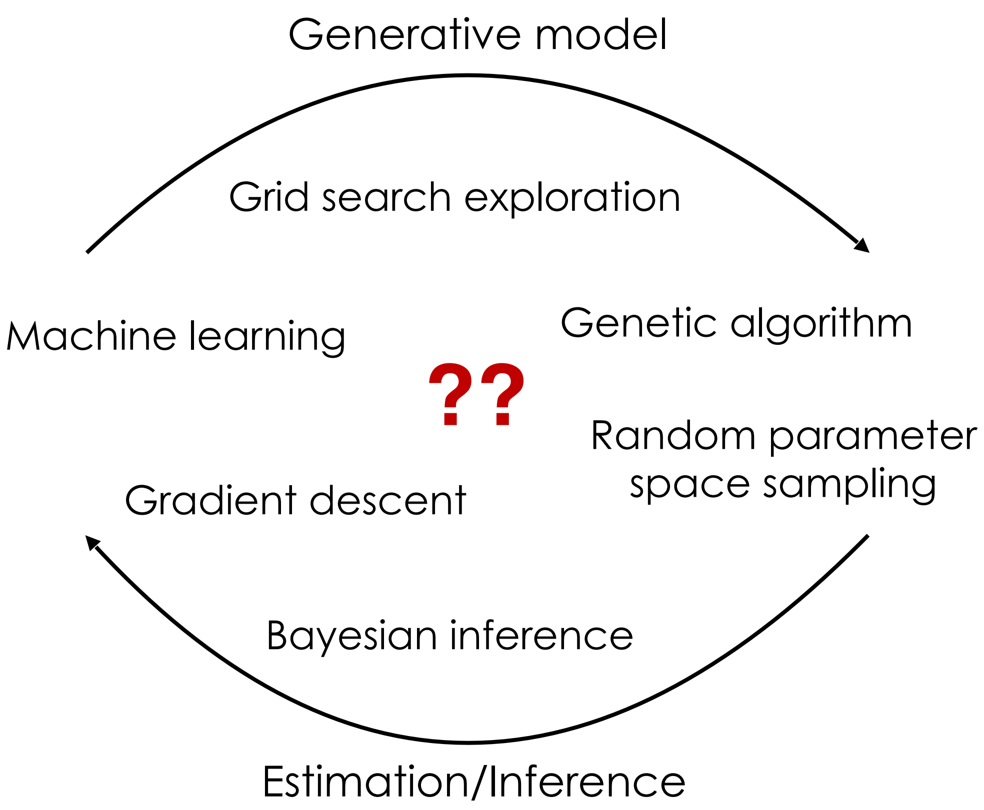

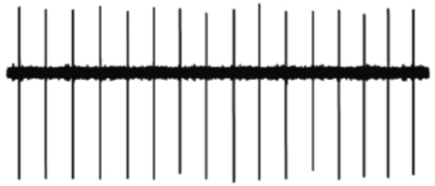

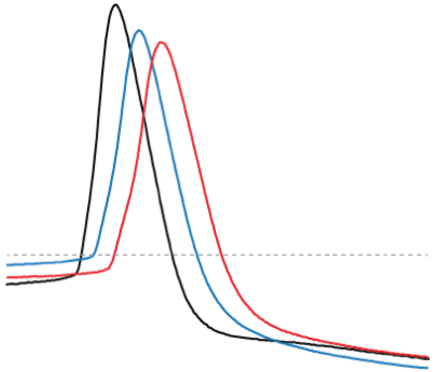

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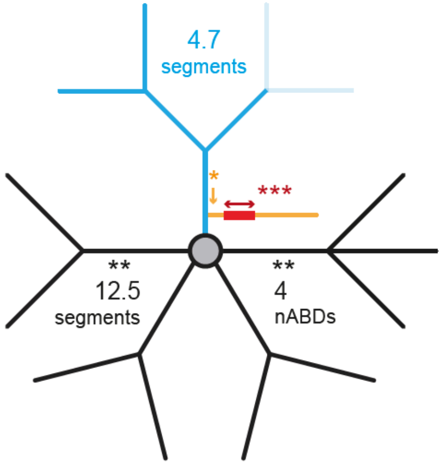

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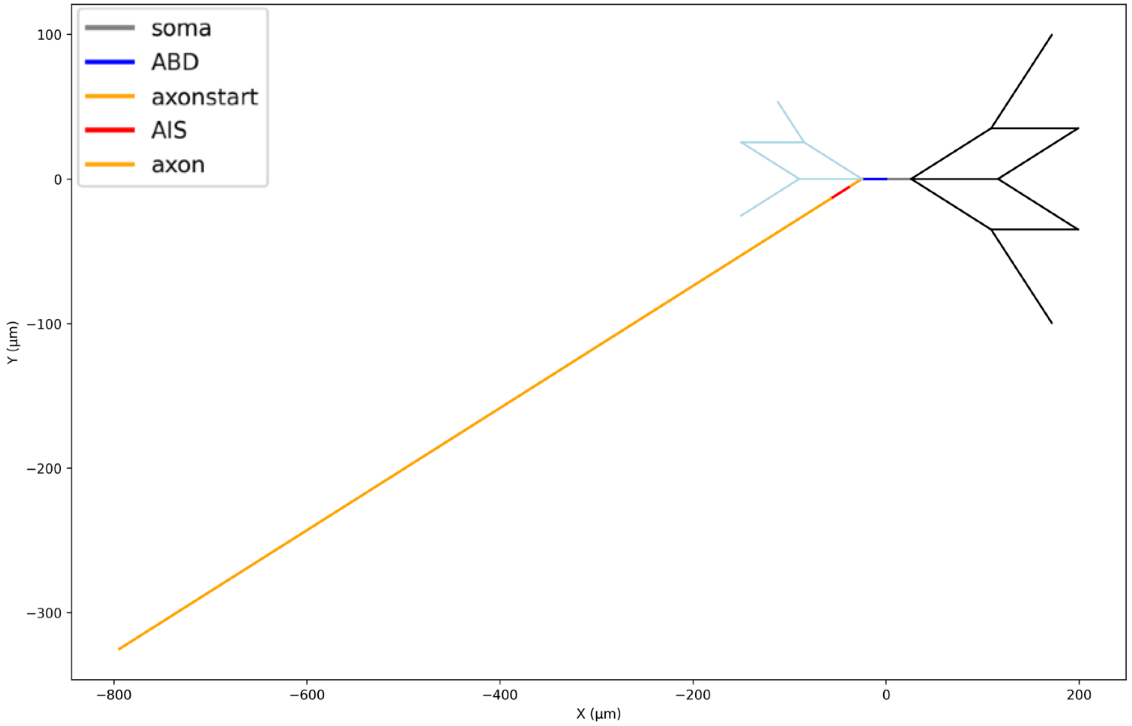
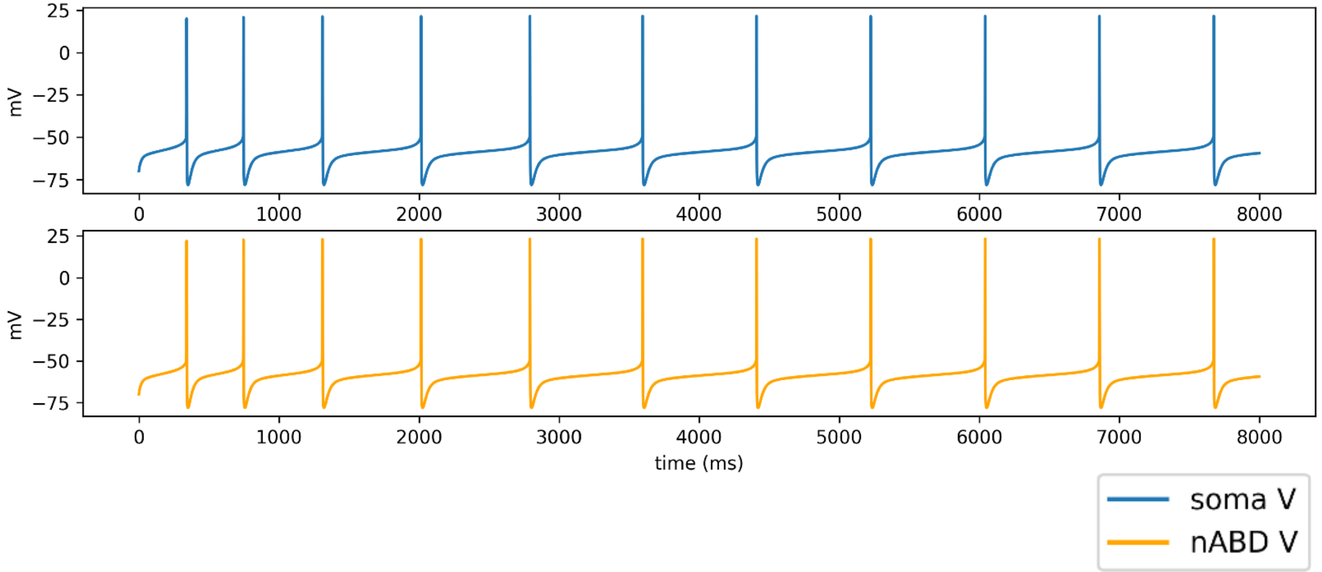
General approach: Project feasibility

Average Wild type
Neuron morphology

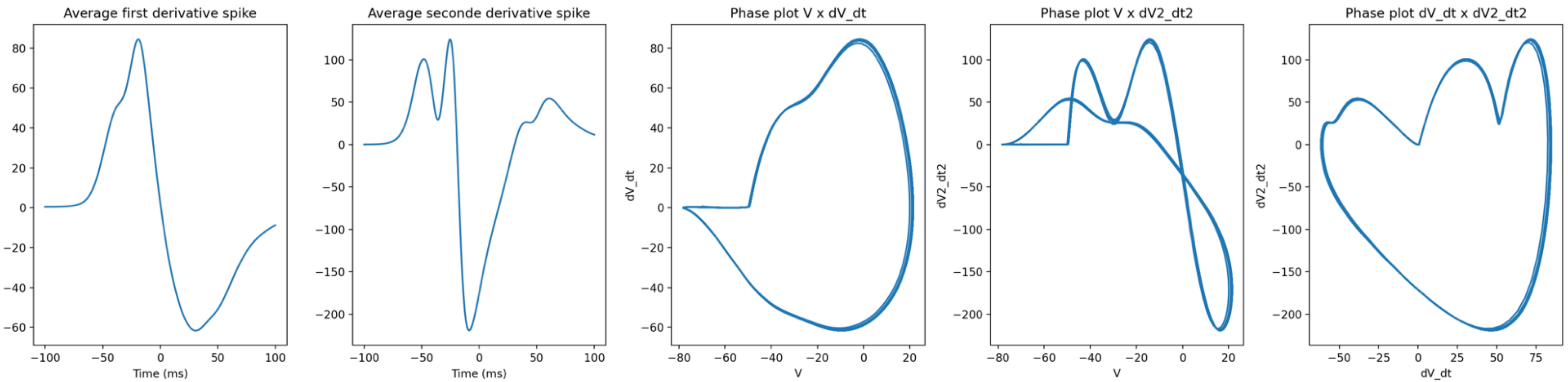


Pacemaker simulated activity



General approach: Project feasibility

Average Wild type Neuron



Extracted features from simulated recordings:

- Spike_frequency
- Average_ISI
- CV_ISI
- Spike_onset
- Spike_max_potential
- Spike_amplitude
- Half_width

- Max_rise
- max_decay
- AHP_trough
- AHP_latency
- IS_peak
- SD_peak
- IS_SD_latency

- Onset_slope_potential
- Offset_slope_potential
- Onset_slope_duration
- Offset_slope_duration

Bibliography

Biology

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Computational

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