Cellular mechanisms of dorsal horn neurons shape the functional states of nociceptive circuits

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Our interest

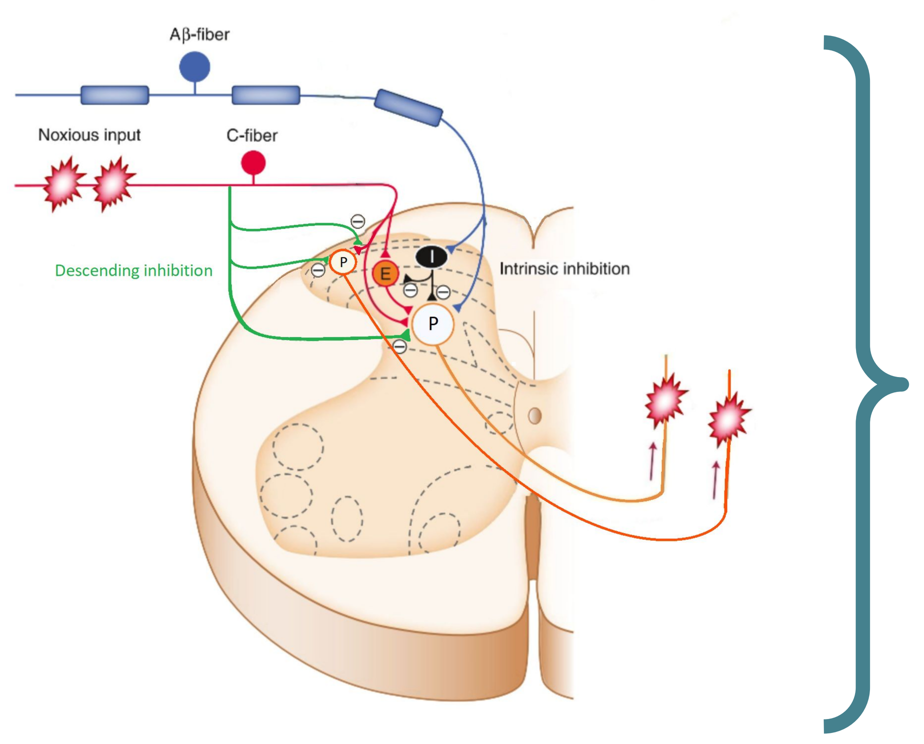
- Nociceptive circuits in the dorsal horn are a **key relay** for pain processing, that are able to trigger and maintain **central sensitization** - a state of hyperexcitability and a major contributor to clinical pain states.

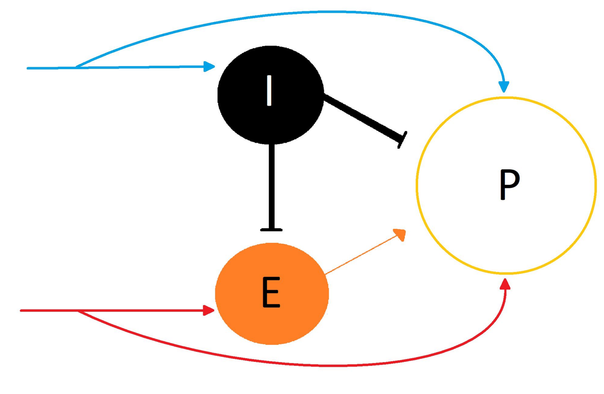
Our work

- Our goal is to build a **low-dimensional model** of the projection neurons of nociceptive circuits to capture the rich dynamics of their functional states.

I. Nociceptive circuits in the dorsal horn process pain signals

- Nociceptors and mechanoreceptors inputs are processed by a network of inhibitory (**I**) and excitatory (**E**) interneurons.
- The **E/I balance** sets the functional state of the pain system by modulating key cellular mechanisms of **projection** (**P**) neurons, which changes their firing patterns.



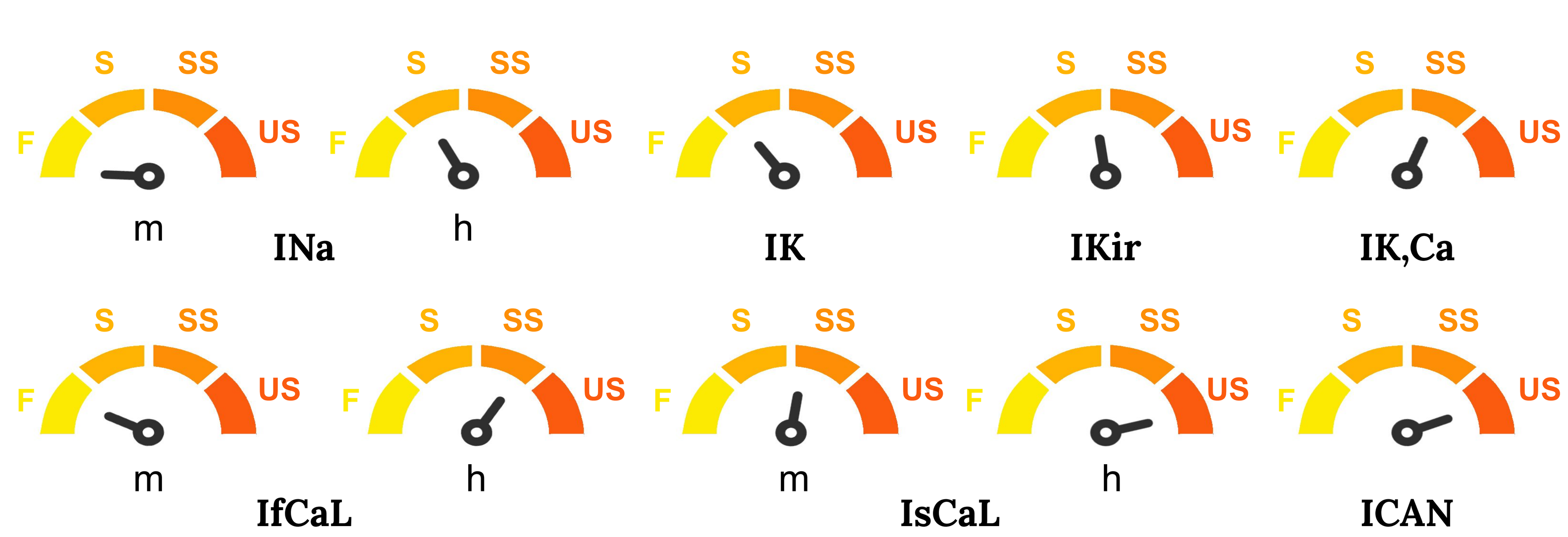


Simplified circuit

- Projection neurons exhibit three types of firing patterns: **tonic firing**, **burst** and **plateau potentials**.

II. Functional states rely on cellular mechanisms over 4 timescales

- The ion channels found at the projection neurons membrane can be listed and split into **4 groups**:
  - Fast channels (**F**),
  - Slow channels (**S**),
  - Super-slow channels (**SS**),
  - Ultra-slow channels (**US**).
- The **timescale separation** between these cellular mechanisms is the basis to build our low-dimensional model.

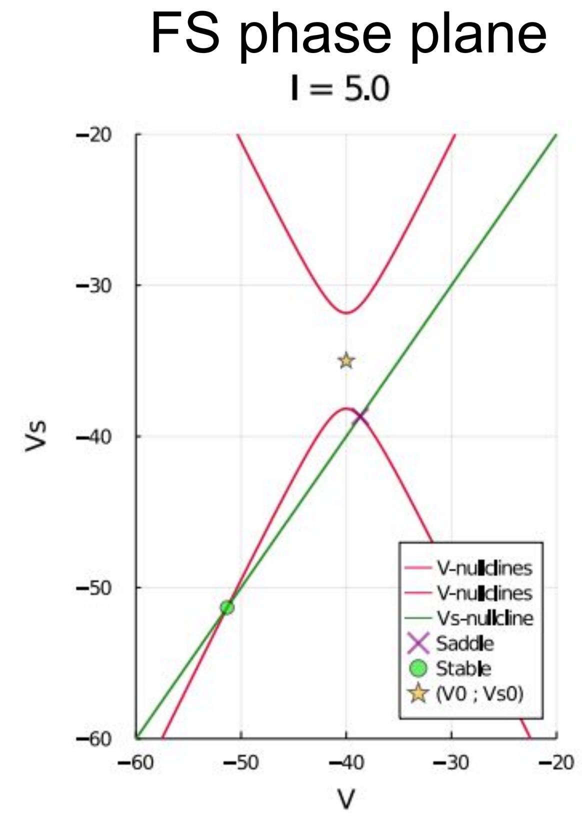


III. MQIF model with 2 timescales sets the fast-slow dynamics

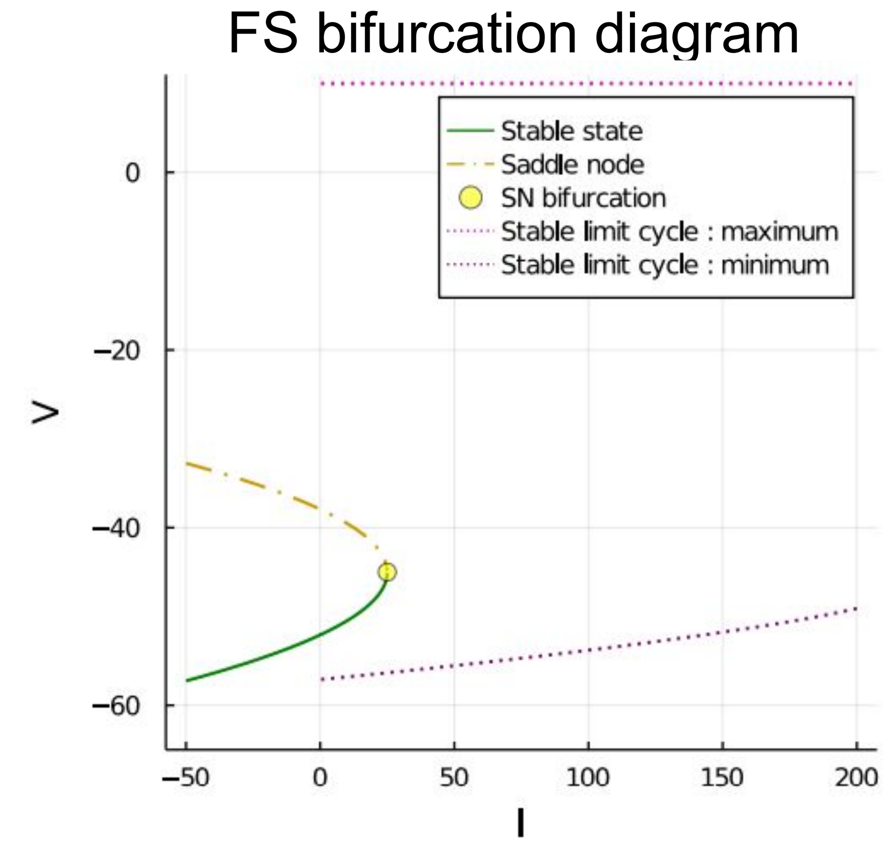
- The low-dimensional model we chose is a Multiple Quadratic Integrate and Fire (**MQIF**) model. [Van Pottelbergh et al., 2018]
- We started by implementing the **fast-slow** dynamics of the model to induce the **bistability** needed.

$$C\dot{V} = \underbrace{\bar{g}_f(V-V^0)^2 - \bar{g}_s(V_s-V_s^0)^2}_{FS(V,V_s)} + I_{\text{app}}$$
$$\tau_s\dot{V}_s = V - V_s$$
$$\text{if } V \geq V_{\max}, \text{ then } V \leftarrow V_r, V_s \leftarrow V_{s,r}$$

FS phase plane



FS bifurcation diagram



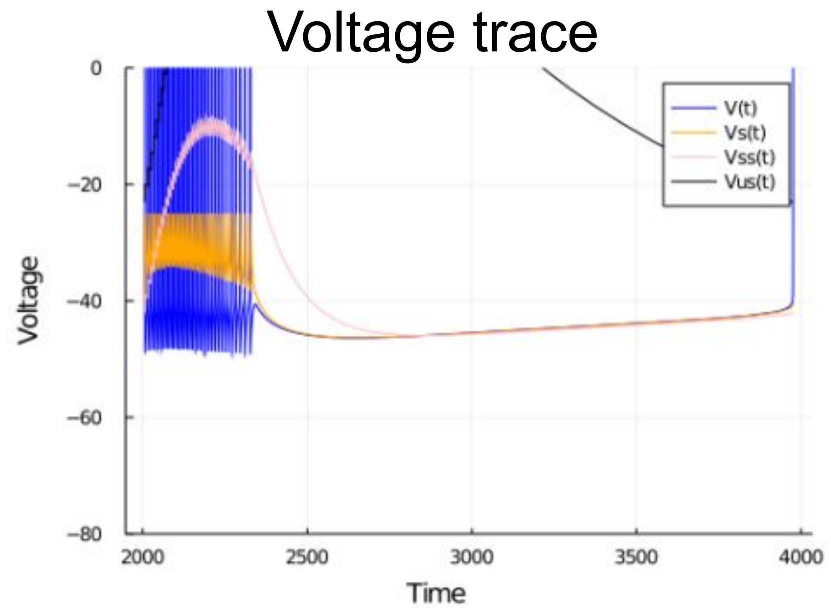
IV. MQIF model with 4 timescales captures all three functional states

- The super-slow and ultra-slow timescales are added to build the **final MQIF** model of the projection neurons.This model is seen as the fast-slow model with a **varying Iapp**.

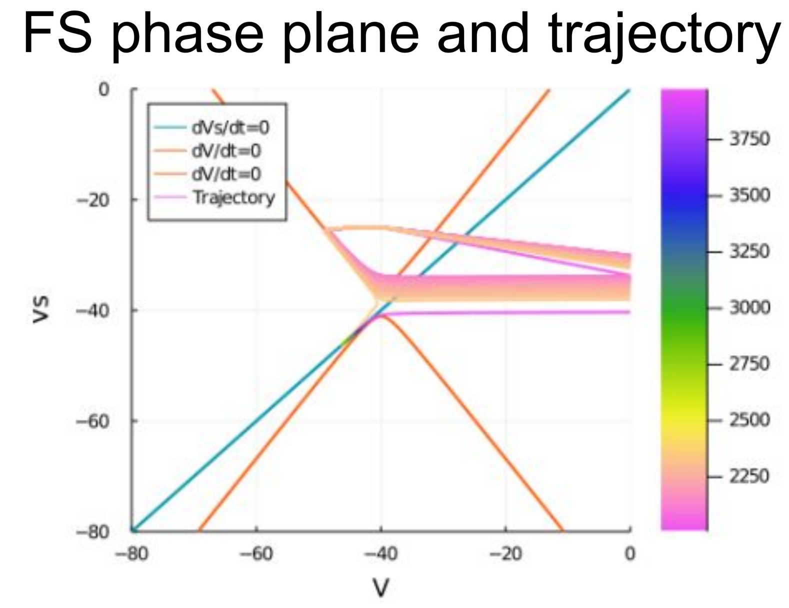
$$C\dot{V} = FS(V,V_s) - \bar{g}_{ss}(V_{ss}-V_{ss}^0)^2 - \bar{g}_{us}(V_{us}-V_{us}^0)^2 + I_{\text{app}}$$
$$\tau_s\dot{V}_s = V - V_s$$
$$\tau_{ss}\dot{V}_{ss} = V - V_{ss}$$
$$\tau_{us}\dot{V}_{us} = V - V_{us}$$
$$\text{if } V \geq V_{\max}, \text{ then } V \leftarrow V_r, V_s \leftarrow V_{s,r}, V_{ss} \leftarrow V_{ss} + \Delta V_{ss} \text{ and } V_{us} \leftarrow V_{us} + \Delta V_{us}$$

- The model response is characterized by a **movement on the bifurcation diagram** of the fast-slow model.

Voltage trace



FS phase plane and trajectory



Conclusion

- Our model captures the dynamics of the three firing patterns shown by the projection neurons of dorsal horns.
- The E/I balance plays on the strength of the super-slow and ultra-slow feedbacks to change the functional state of nociceptive circuits.
- A possible mechanism for central sensitization in nociceptive circuits is the modulation of super-slow and ultra-slow ion channels at the projection neurons membrane.