Unraveling the key ion channels shaping the excitability of projection neurons in pain circuits

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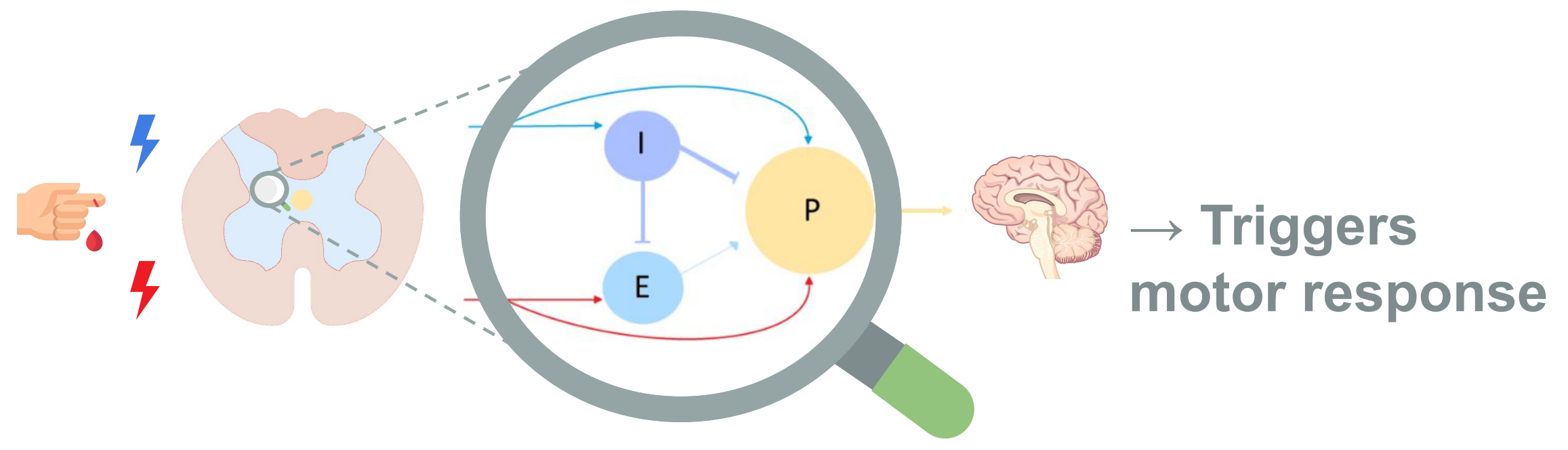
Our work

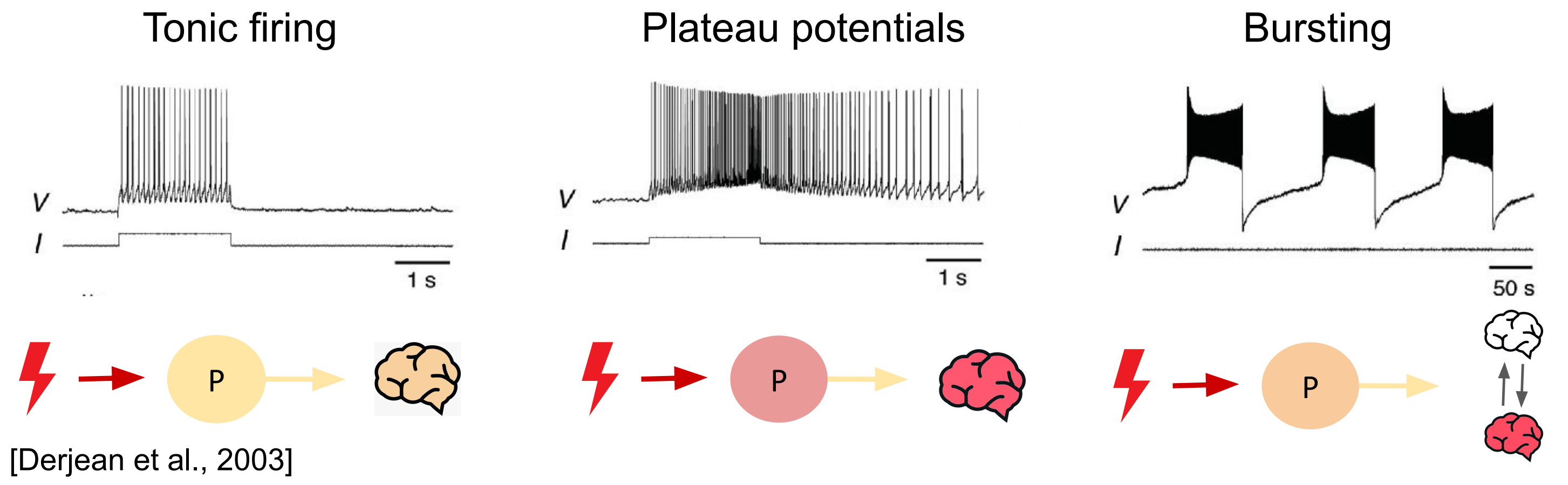
This work aims at understanding the excitability of projection neurons in the dorsal horn. For this purpose, we built a conductance-based model and reduced it to extract the model key dynamics. This allows studying the roles of CaL and Kir channels in shaping excitability.

Background

- During an injury, warning inputs are sent to the spinal cord, the first relay of the pain system.
  These signals are processed by excitatory (**E**) and inhibitory (**I**) interneurons, and sent by projection (**P**) neurons to the brain.

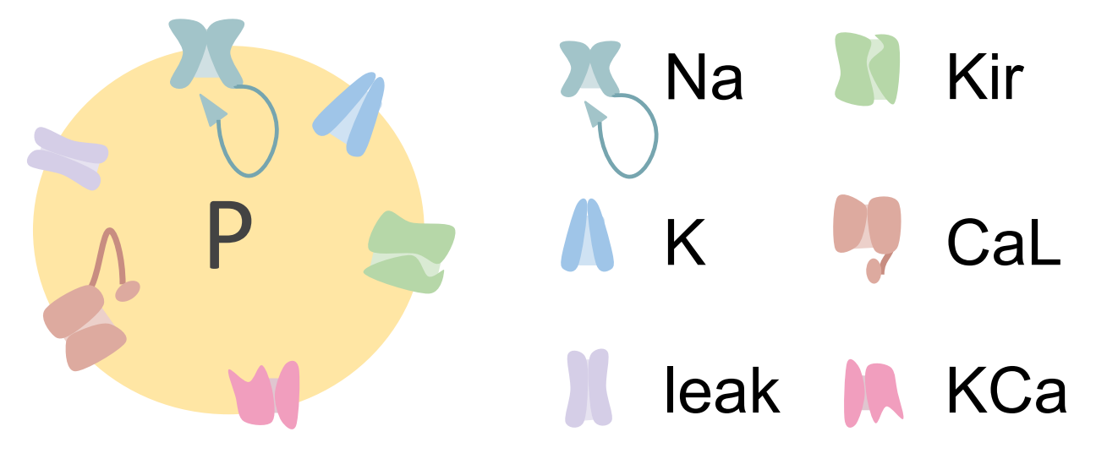


- Projection neurons exhibit 3 types of firing patterns. Each of them has different coding properties. It captures the functional state of the pain system in the spinal cord.



[Derjean et al., 2003]

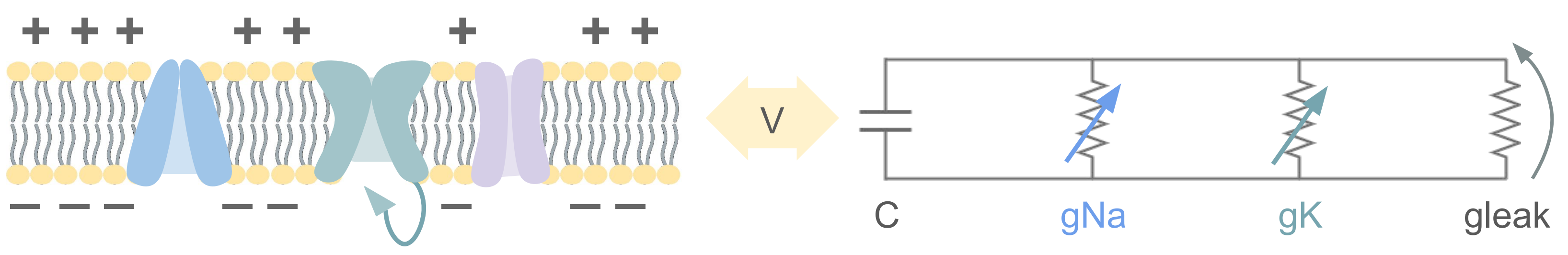
- The **E/I** balance controls projection neurons excitability. This control is achieved through the modulation of key ion channels conductances.



[Le Franc et Le Masson, 2010]

Conductance-based modeling

- Neuronal excitability relies on ions moving in and out the cell thanks to ion channels activation *m* and inactivation *h*.
  In 1952, Hodgkin & Huxley modeled membrane currents flowing in these channels as an electrical circuit.

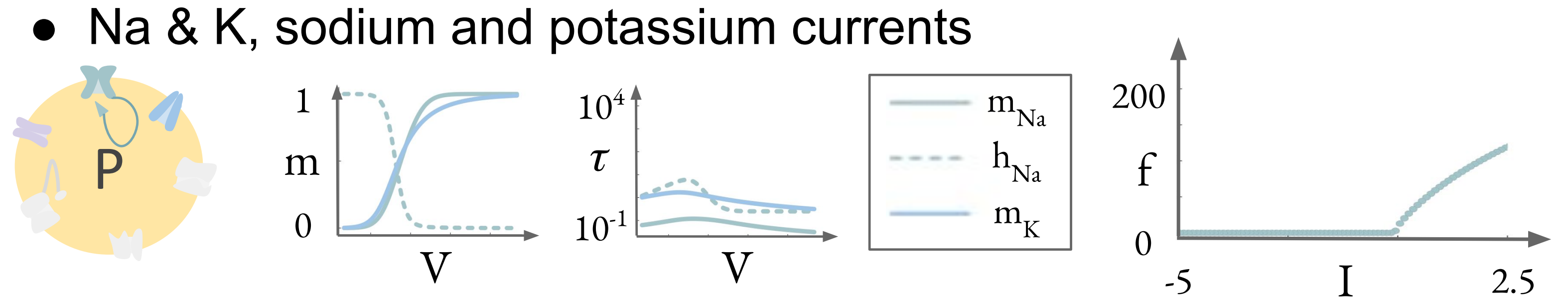


- This approach is the basis of conductance-based modeling, and it is valid for any ion channel.

Excitability

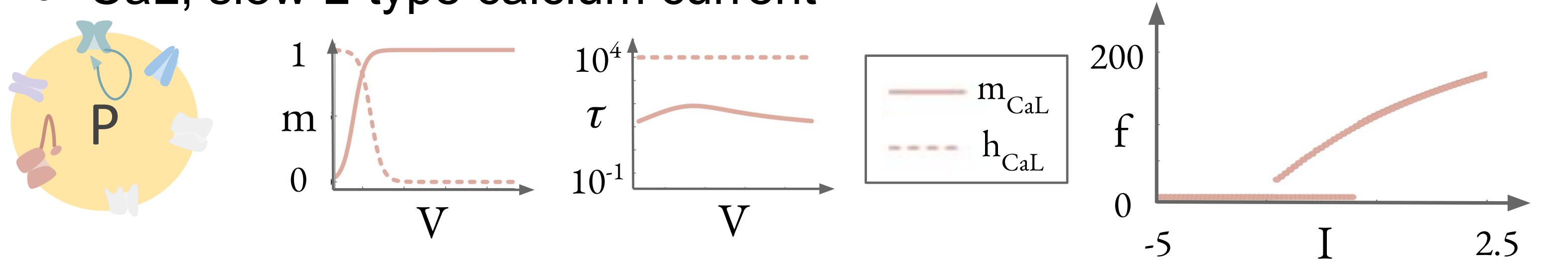
We built a conductance-based model of projection neurons. To reveal its excitability, we show its f-I curve and the gates used at each step.

- Na & K, sodium and potassium currents



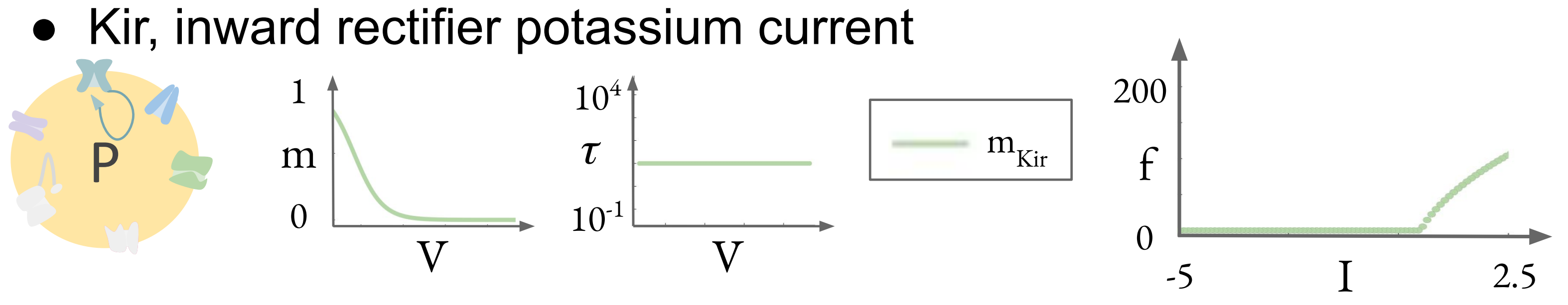
They are the basic building blocks to mode action potentials.

- CaL, slow L-type calcium current



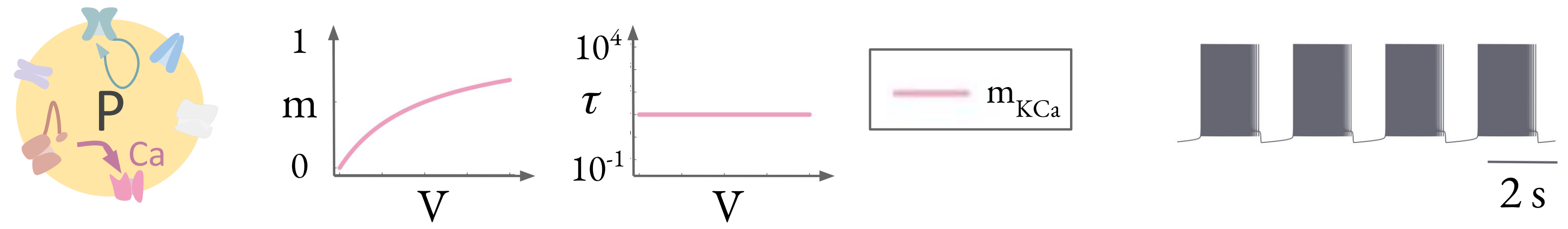
This channel provides strong bistability, and accelerates spiking.

- Kir, inward rectifier potassium current



They slow down spinking and bring little bistability.

- KCa, calcium-activated potassium current

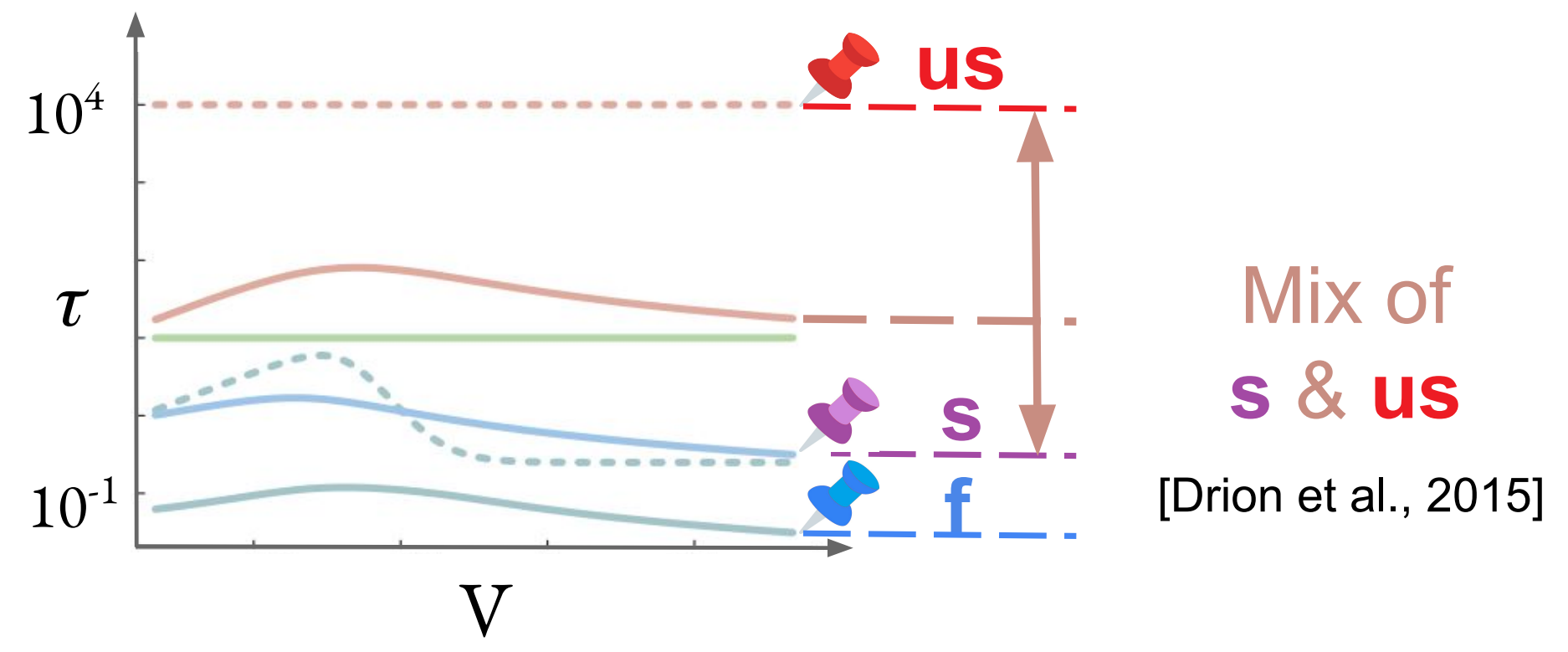


When activated by CaL channels, KCa channels induce bursting.

We want to understand how bistability is created by the CaL and the Kir currents.

Model reduction

The reduction exploits the timescale separation between the gates with a fast potential V, a slow potential V_s, and an ultraslow potential V_{us}.

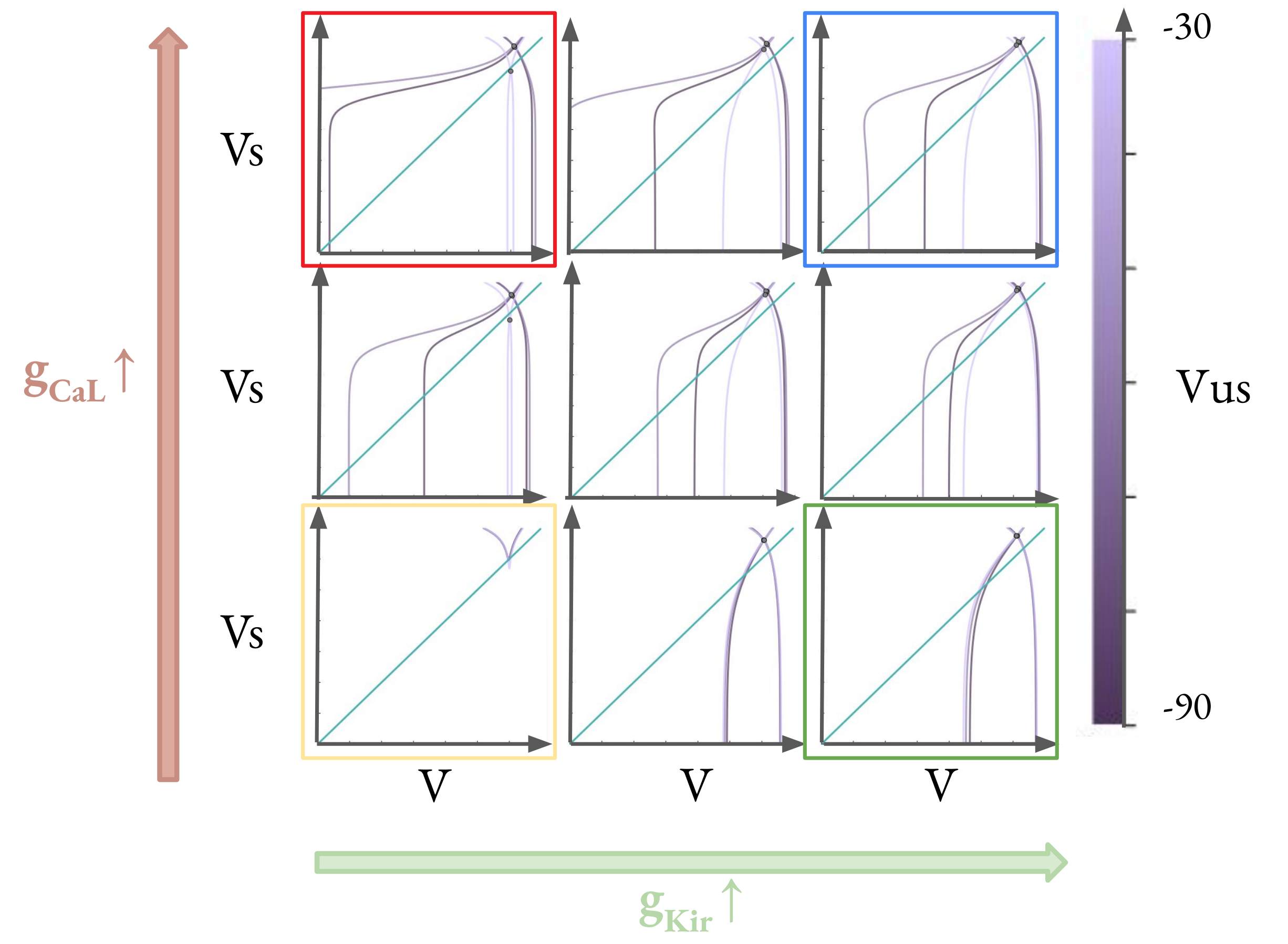


[Drion et al., 2015]

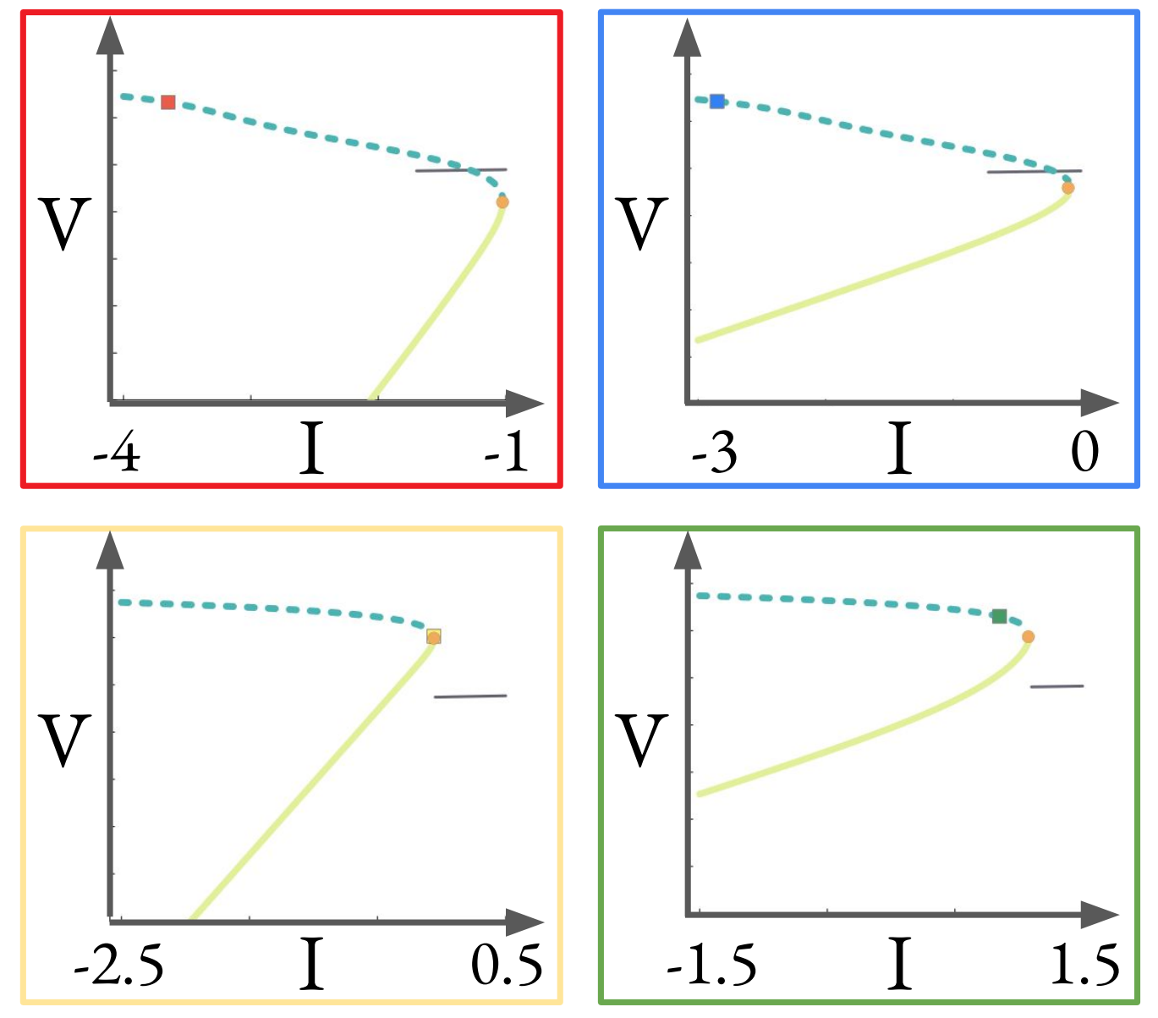
- ☐ <u>Choice of reference:</u> m_{Na}, m_K, and h_{CaL}
- ☐ <u>Weight the other gates:</u> The logarithmic distance between gates and the two closest references is computed.
- ☐ <u>Compute the all gates:</u> Each gate is a weighted sum of the steady-state at each reference potential.

Dynamical study

- To extract the key features of CaL and Kir channels, we will study the stability of the fast-slow (f-s) system for multiple CaL and Kir maximum conductances (gCaL and gKir). The ultra-slow potential V_{us} is considered much slower and fixed to a constant value.
- We can draw the phase plane of the f-s system for several values of (gCaL;gKir). The current is chosen so that the upper and lower branch collide on each other.



- The intersections between the blue and each the purples lines denote a steady-state of the f-s system, for the value of V_{us} chosen.
- To assess its bistability, we can modify the current of the f-s system and observe how it evolves around its phase plane.



- Taking 4 couples (gCaL;gKir) and a mid-range V_{us}, we can spot the steady-states and limit cycle minimum (grey line) for each current.

Conclusions & Perspectives

- CaL and Kir have opposite effects on spiking frequency excitability.
- When Kir channels are alone, they provide barely no bistability.
- When CaL channels are alone, they create strong bistability but the more the bistability needed, the less physiological the steady-states
- Taken together, CaL and Kir channels are complementary to create robust bistability in a physiological range.