Key ion channels complement each other to promote robust bistability in dorsal horn projection neurons

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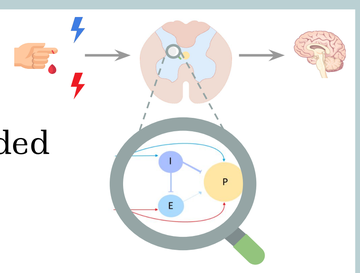
Context

Nociception begins when an event threatens the integrity of the body. The threat is sensed and translated into sensory signals. These inputs are encoded by many interneurons in the spinal cord and sent to the brain by projection (**P**) neurons to trigger pain.

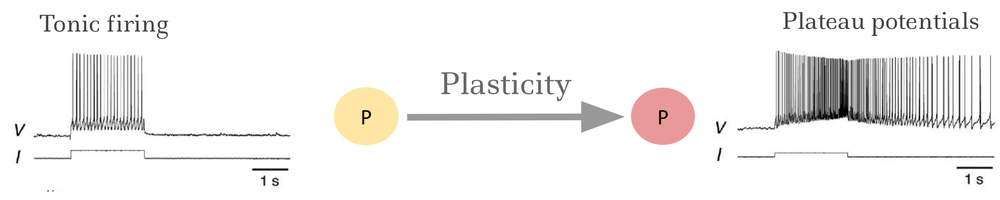


Our work

The present work aims at understanding how projection neurons, a key relay in pain processing, manifest robust bistability in the scope of central sensitization.
In this work, we built a conductance-based model and explored the effect of CaL and Kir channels on the bistability window.

1. Excitability

Through plasticity mechanisms, projection neurons change their excitability and alter signal transmission properties.[1,2] A key feature contributing to this switch is the emergence of robust bistability.



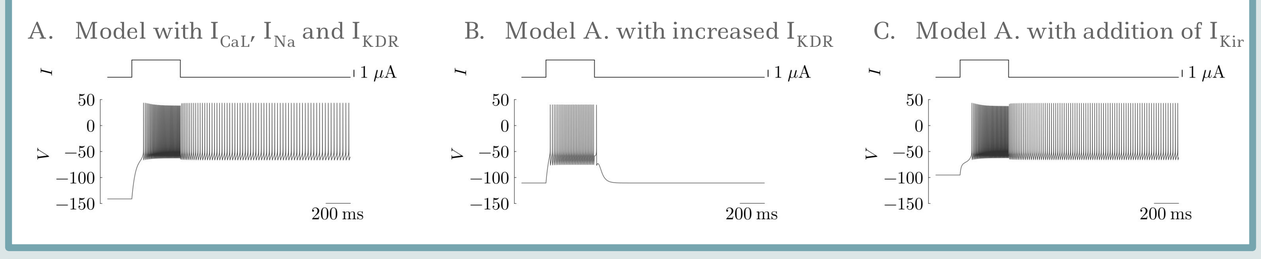
To explain how robust bistability emerge at the single cell level, we built a conductance-based model regrouping the following ion currents :

$$C\dot{V} = -I_{CaL}(V,t) - I_{Na}(V,t) - I_{KDR}(V,t) - I_{Kir}(V,t) - I_{leak}(V) + I$$

where I_{Na} is a sodium current, I_{KDR} a potassium current, I_{CaL} a L-type calcium current, and I_{Kir} an inward rectifier potassium current.

Bistability is observed when the model behavior changes after a pulse of current and depends on the set of conductances chosen.

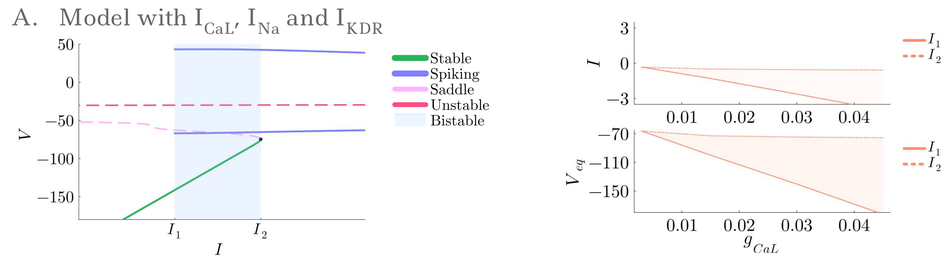
- I_{CaL} creates bistability but with unrealistic equilibrium potentials.
- I_{KDR} seems to improve these equilibriums, but breaks bistability.
- I_{Kir} both preserves bistability and improves the corresponding equilibrium potentials.



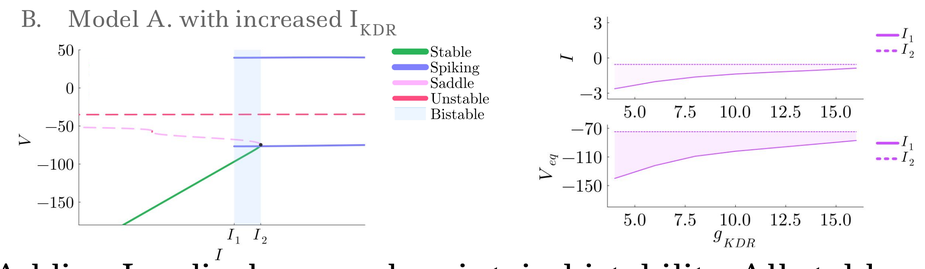
2. Bistability window

In a bifurcation diagram, the bistability window is defined by the range of current where spiking coexists with a stable equilibrium potential.

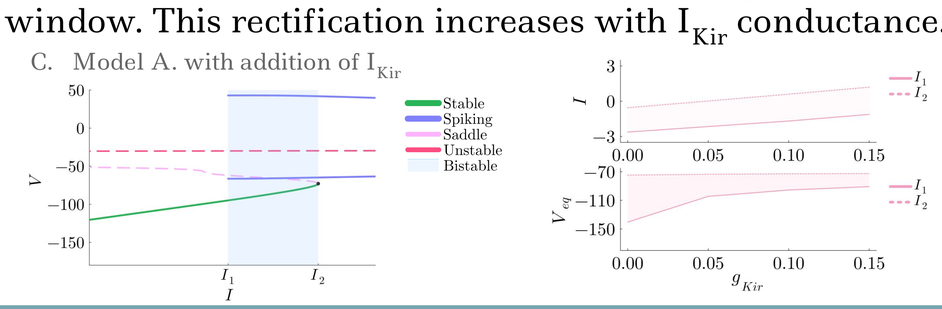
- As I_{CaL} conductance increases, the bistability window gets wider, but at equilibrium potentials that are more and more unrealistic.



- Increasing I_{KDR} conductance improves the equilibrium potentials actually by shrinking the bistability window.



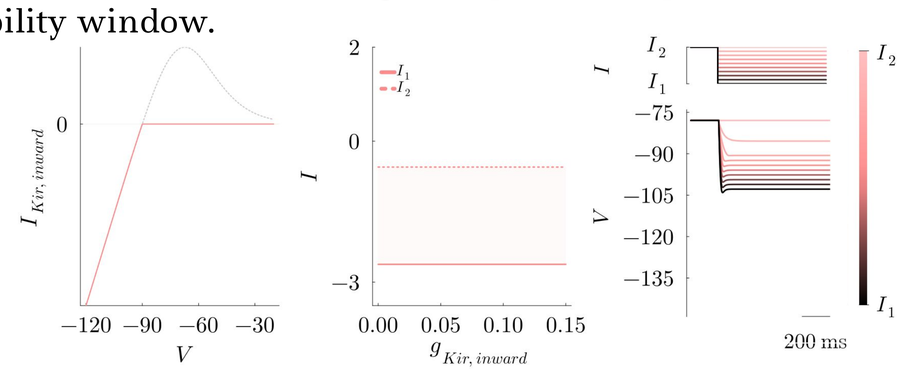
- Adding I_{Kir} displaces and maintain bistability. All stable equilibrium potentials are increased, including in the bistability window. This rectification increases with I_{Kir} conductance.



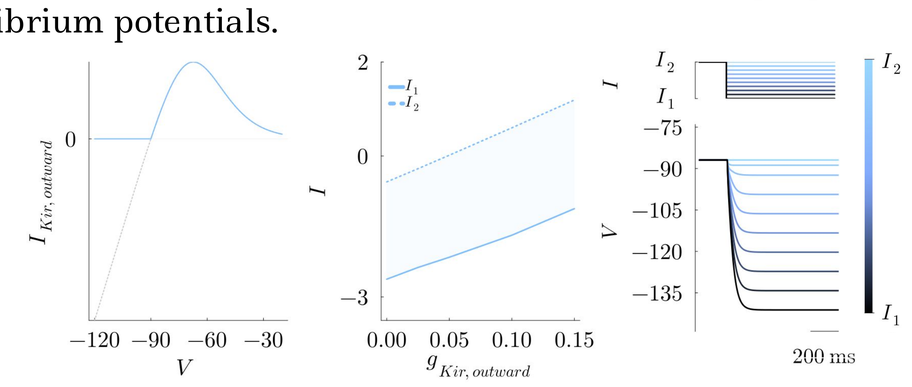
3. Steady-state properties

I_{Kir} differs from other families of potassium currents because it displays a strong inward current and a small outward current. By blocking one of them at the time, we can investigate the role of each contribution.

- The inward current does not contribute to spiking dynamics. Therefore, it leaves the bistability window unchanged. This contribution aims at rectifying the equilibrium potentials in the bistability window.



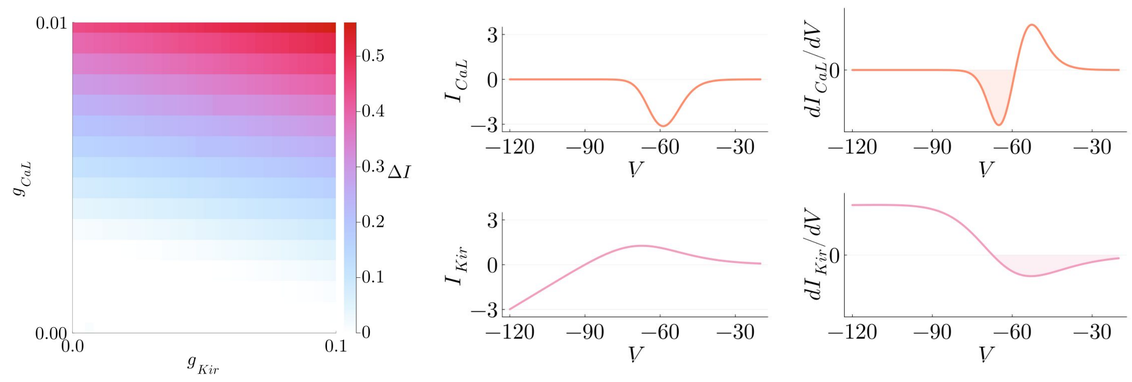
- The outward current contributes to spiking dynamics. This contribution acts both on I_1 and I_2 to maintain the bistability window. Also, the outward current rectifies a small proportion of equilibrium potentials.



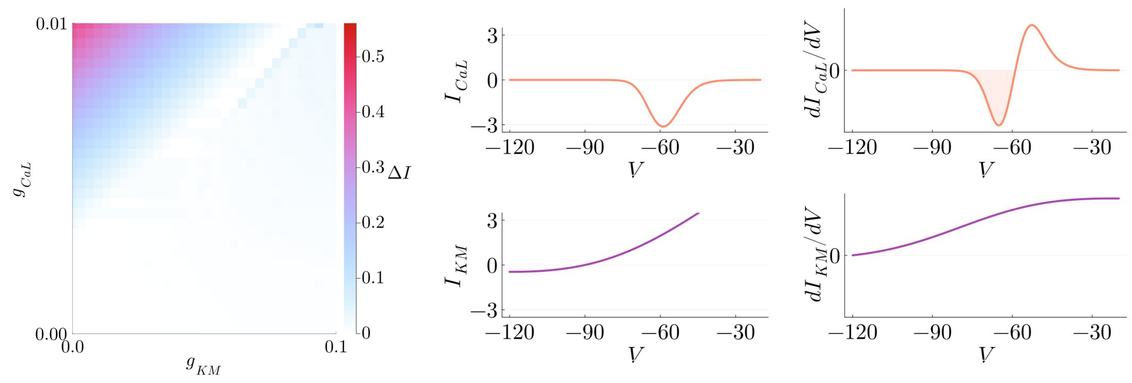
4. Negative conductance

The size of the bistability window computed over a wide range of conductances reveals that the Kir conductance also increases bistability.

In fact, just as I_{CaL}, the outward part of I_{Kir} displays a region of negative conductance around spike threshold, that is key to create bistability.



If I_{Kir} is replaced by another potassium current (I_{KM}) that acts at a similar timescale but does not display a region of negative conductance, I_{CaL}-induced bistability is completely destroyed.



Conclusion

Bistability increases with CaL conductance, but as it increases, the corresponding equilibrium potentials get out of physiological ranges.
Kir channels display a large inward current that rectifies the equilibrium potentials in the bistability window, and a small outward current with a region of negative conductance that promotes bistability.
CaL and Kir channels together creates physiological bistability.

References & Acknowledgments

[1] Derjean D, Bertrand S, Le Masson G, Landry M, Morisset V, Nagy F. Dynamic balance of metabotropic inputs causes dorsal horn neurons to switch functional states. Nat Neurosci. 2003
[2] Latremoliere A, Woolf CJ. Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. The Journal of Pain. 2009

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