Robust bistability in spinal pain processing neurons

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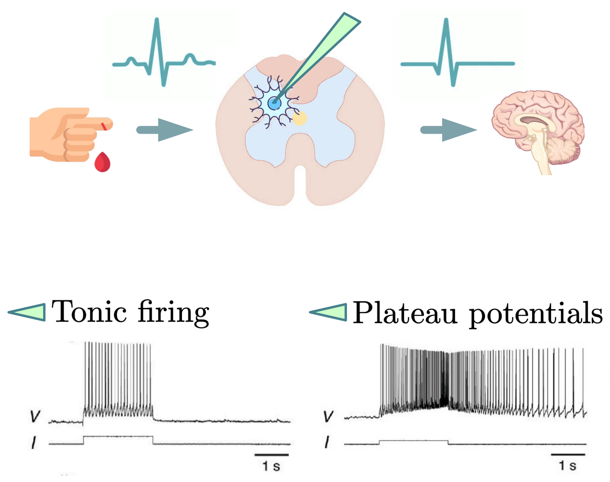
Spinal pain processing

Nociception begins when an event threatens the integrity of the body. As a result, sensory inputs are encoded by many interneurons in the spinal cord and sent to the brain by projection neurons to initiate pain.

Through plasticity mechanisms, projection neurons undergo a change in their excitability. A key feature that emerges during this switch is robust bistability.



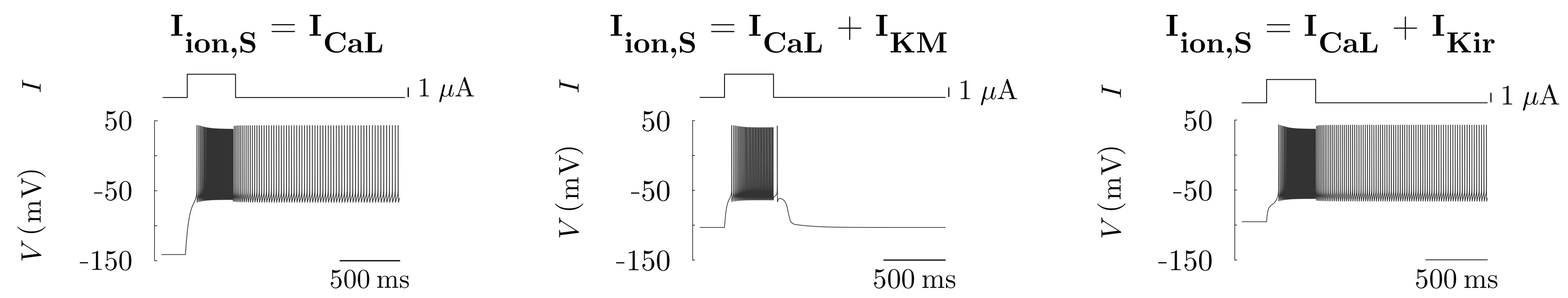
Conductance-based model

We used a conductance-based model to explore the effect of L-type calcium (CaL) channels, M-type potassium (KM) channels, inward rectifier potassium (Kir) channels on the emergence of robust bistability.

$$C\dot{V} = \underbrace{-I_{\mathrm{Na}} - I_{\mathrm{KDR}} - I_{\mathrm{leak}}}_{-\mathbf{I}_{\mathbf{ion,F}}} \underbrace{- I_{\mathrm{CaL}} - I_{\mathrm{Kir}} - I_{\mathrm{KM}}}_{-\mathbf{I}_{\mathbf{ion,S}}} + I$$

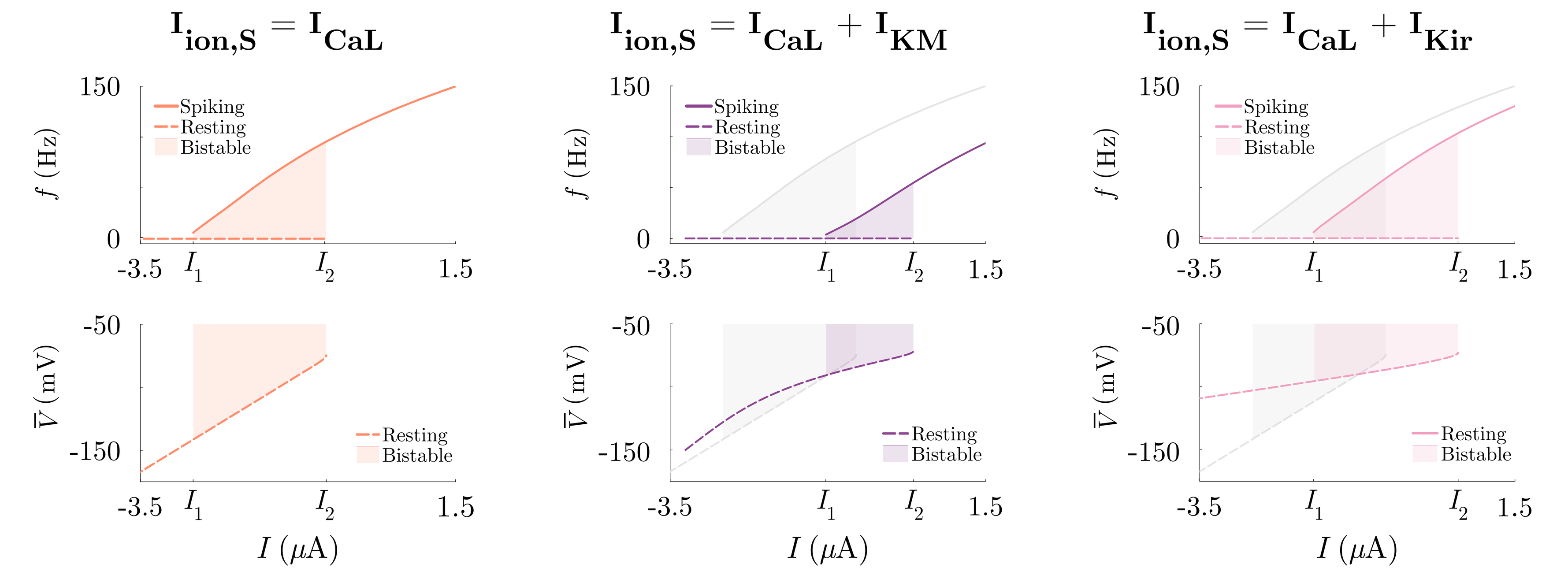
1. Does the excitability shows bistability?

A bistable neuron displays either resting or spiking at the same applied current value depending on the initial conditions. Thus, a pulse of current might trigger the switch from one resting to spiking if the for a range of baseline currents.



The range of currents at which spiking and resting coexist (i.e. the *bistability window*) can be observed on the fI curve. Its size and position depends on the ion channels used.

To capture it, we computed the fI curve and the corresponding range of resting potentials using three sets of ion channels.

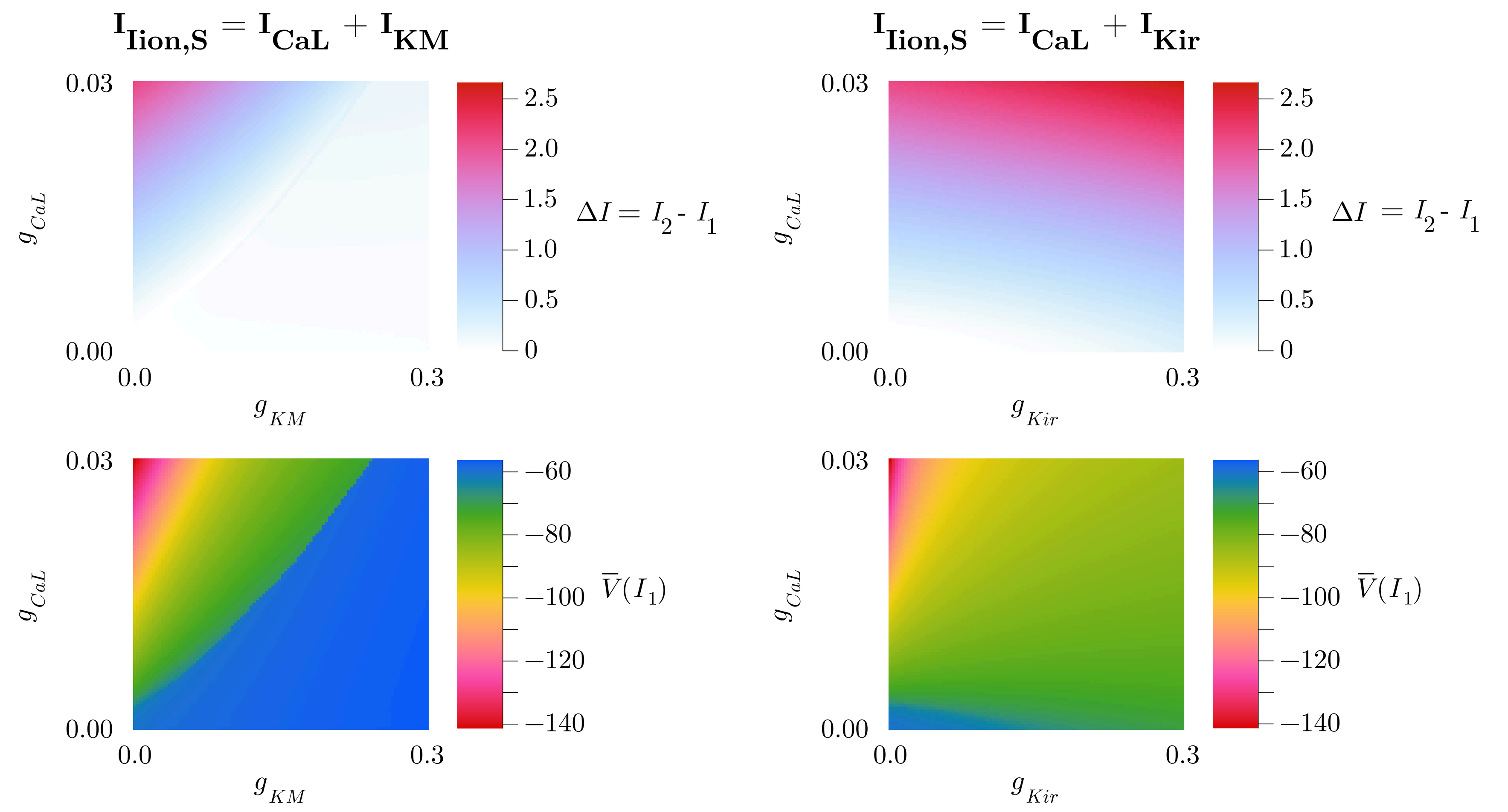


2. How do these channels affect bistability?

CaL channels create a large bistablity window, but at unphysiological resting potentials.

One mechanism through which physiological bistability may arise is the coupling of CaL channels with KM or Kir channels. However, they act differentlty on bistability.

Their effect is well captured as each conductance (g_{CaL} and g_{KM} or g_{Kir}) increases.



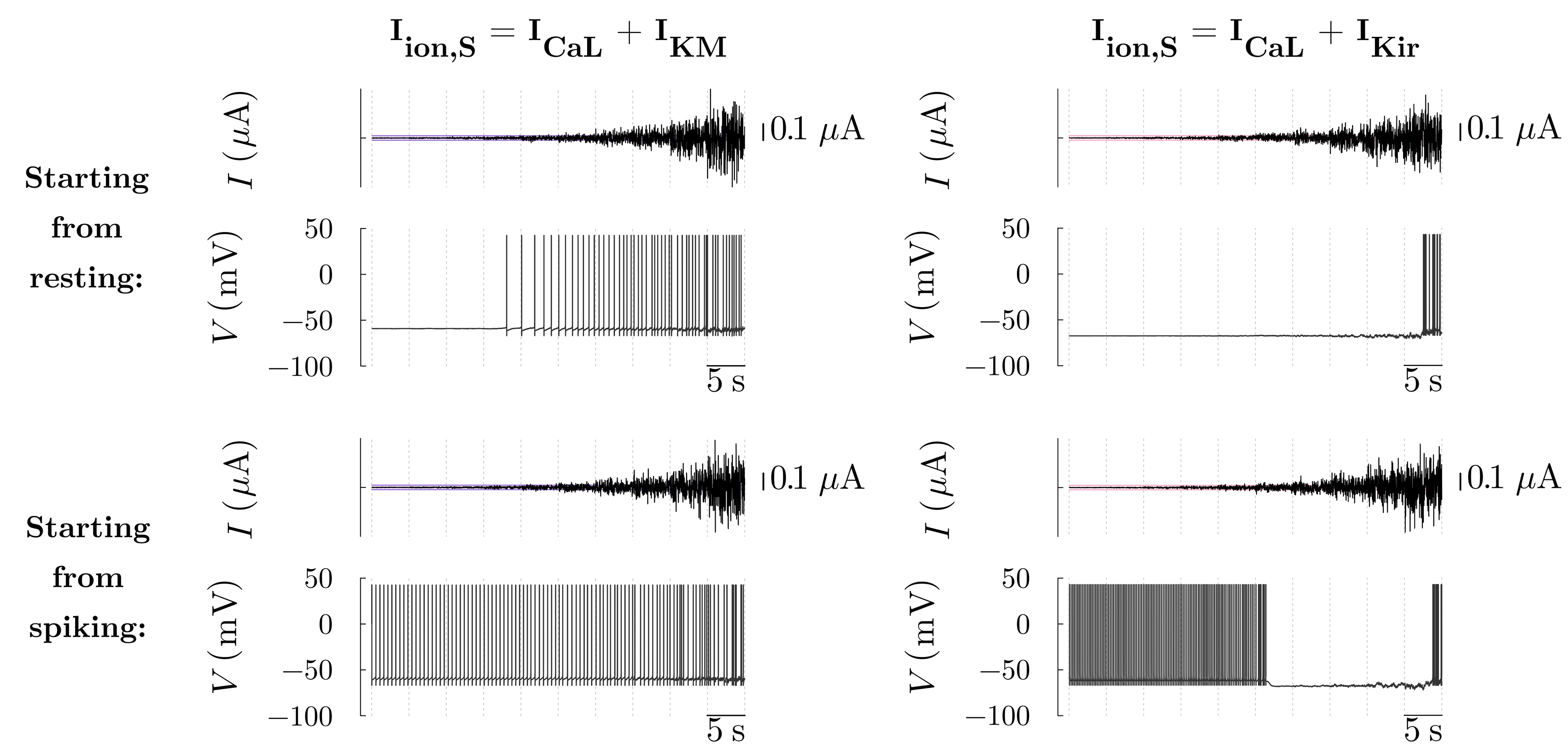
KM channels rectify the resting potentials $\bar{V}$ within the bistability window. However, they narrow this window ($\Delta I \searrow$).

By contrast, Kir channels rectify the equilibriums and expand the bistability window.

3. How robust are the two types of bistability?

Similar levels of bistability are achieved by coupling two values of g_{CaL} with $g_{\mathrm{Kir}} = g_{\mathrm{KM}}$. However, KM and Kir channels create two different types of bistability.

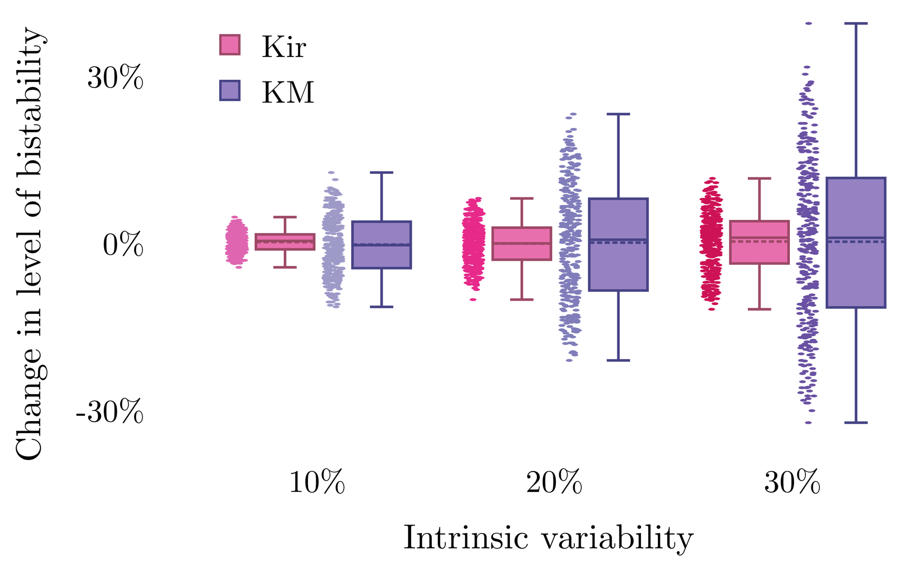
To quantify their robustness, we applied the bistability window center current with superimposed Gaussian noise of increasing amplitude.



KM-bistablity displays a weak resting state, and a robust spiking state. Conversely, Kir-bistability displays a resting state that is more robust than spiking, which withstands perturbations more or less as large as its bistability window.

Identical sets of conductances (g_{CaL};g_{Kir}) or (g_{CaL};g_{KM}) create two types of bistability of *different levels*.

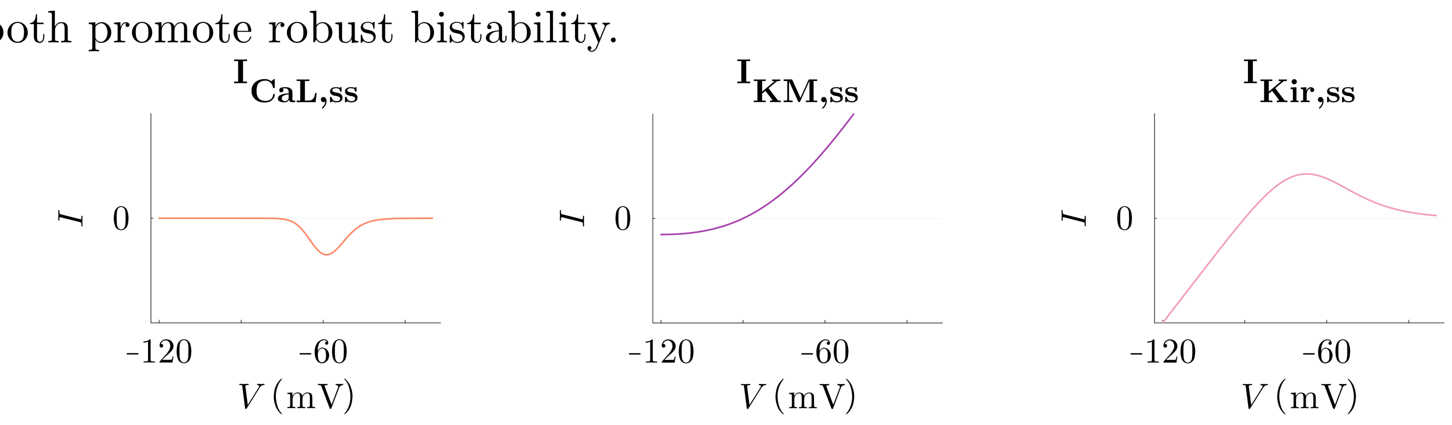
Their robustness can also be assessed by introducing intrinsic variability into the neuron, and computing the relative change in bistability window size.



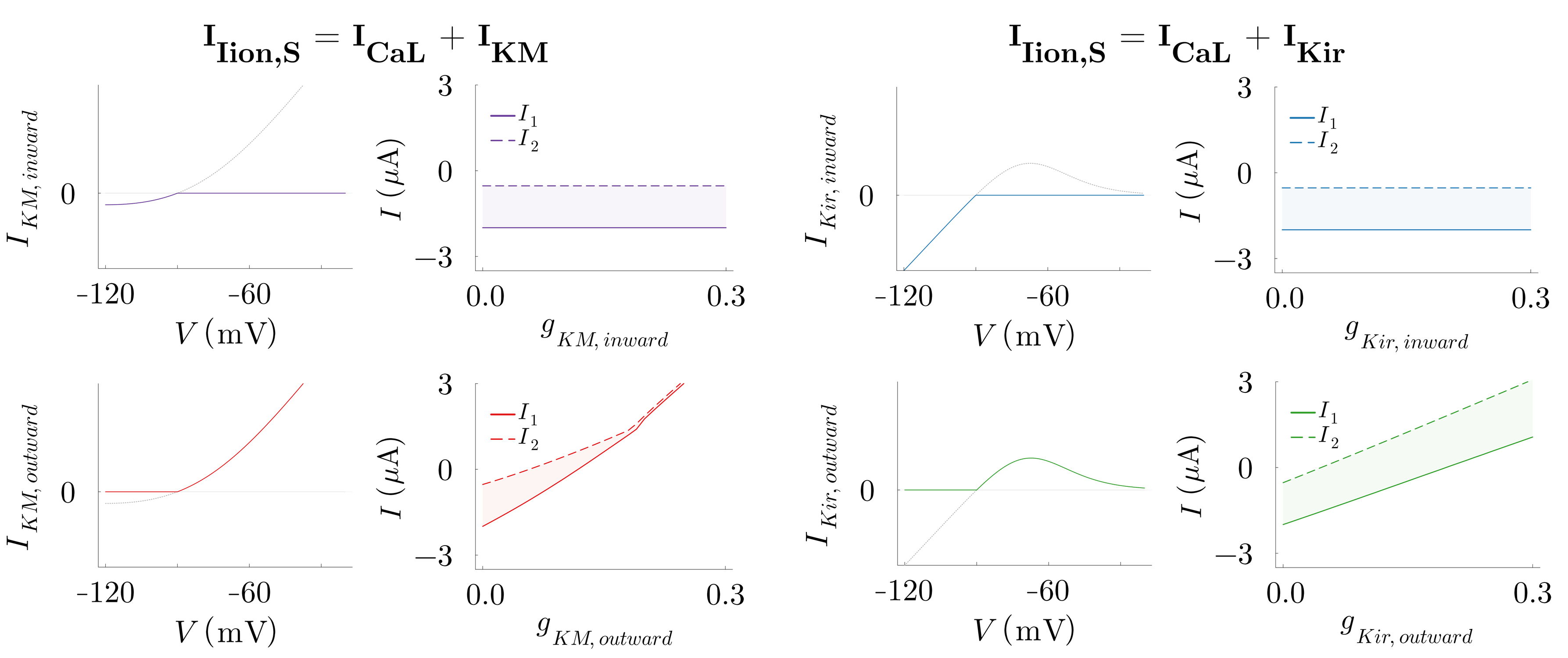
4. Why do the two potassium channels act differently?

To provide for the disparate effects of KM and Kir channels, we analyzed their steady-state current. The KM current impairs robust bistability and diplays a positive slope.

In contrast, Kir and CaL currents show a colocalized region of negative slope, and both promote robust bistability.



To investigate their role, we blocked separately the outward or inward current flowing in KM or Kir channels, and computed the resulting bistability window.



Both the inward KM and Kir currents did not modify the size of the bistability window. However, the outward KM and Kir current acted on it in opposite directions.

Conclusion

When CaL and Kir channels are combined, bistability is observed over a wide range of conductances. However, this does not hold when combining CaL and KM channels.

The resulting type of bistability is robust to intrinsic variability and noise amplitudes as large as the bistability window itself.

Kir channels promote robust bistability through a region of negative slope.