Update on Figures

Firing Characterization:

Question figure addresses:

Firing is a complicated phenomenon. How can it be simply characterized to compare the effects of changes in current properties?

Method by which data is generated:

Schematic diagram that does not contain underlying data - contains different square root functions.

Conclusion from Figure:

Firing can be characterized by the rheobase and the AUC (proprotional to the increase in firing after the rheobase). The rheobase and firing in a small range above it (AUC) are likely important for determining network excitability (I think this makes sense, would need references to support this).

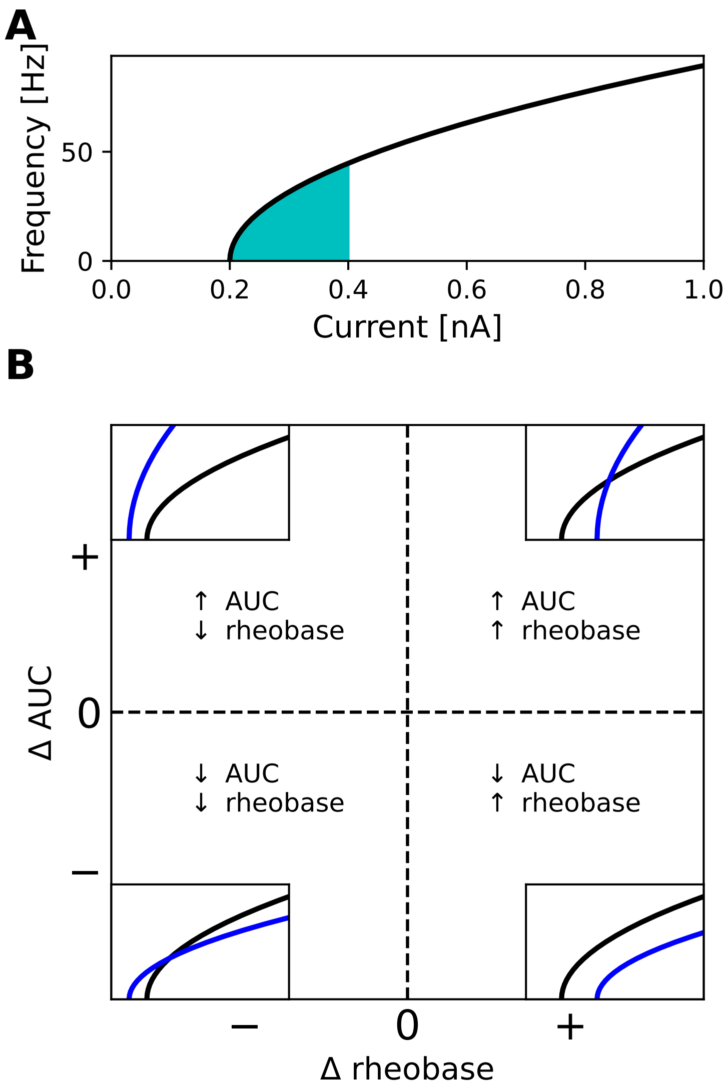

Figure 1: A. Demonstrates AUC in cyan. B. Demonstrates what combinations of increased and decreased rheobase and AUC look like in terms of fI curves.

Diversity in Model Firing:

We have used a number of neuronal models that do not burst to look at the effects of changes in current properties in firing given different cell types/current environments

Question figure addresses:

Which model is used?

Rationale:

The effect of a change in a current property cannot be assessed in only one cell type to understand the general effects of this change and to assess whether differences occur across cell types.

Method by which data is generated:

Models from different sources are used and an example spike train is shown for each model along with a fI curve. The black dot on the fI curve indicates where the spike train is taken from and the green and red dots indicate the current at which the first and last spike occurs from an increasing and decreasing current ramp respectively. (These ramps can be seen in the ramp figure at the end).

Conclusion from Figure:

The models use are diverse and display a variety of spike shapes, firing behaviours, and fI curve shapes.

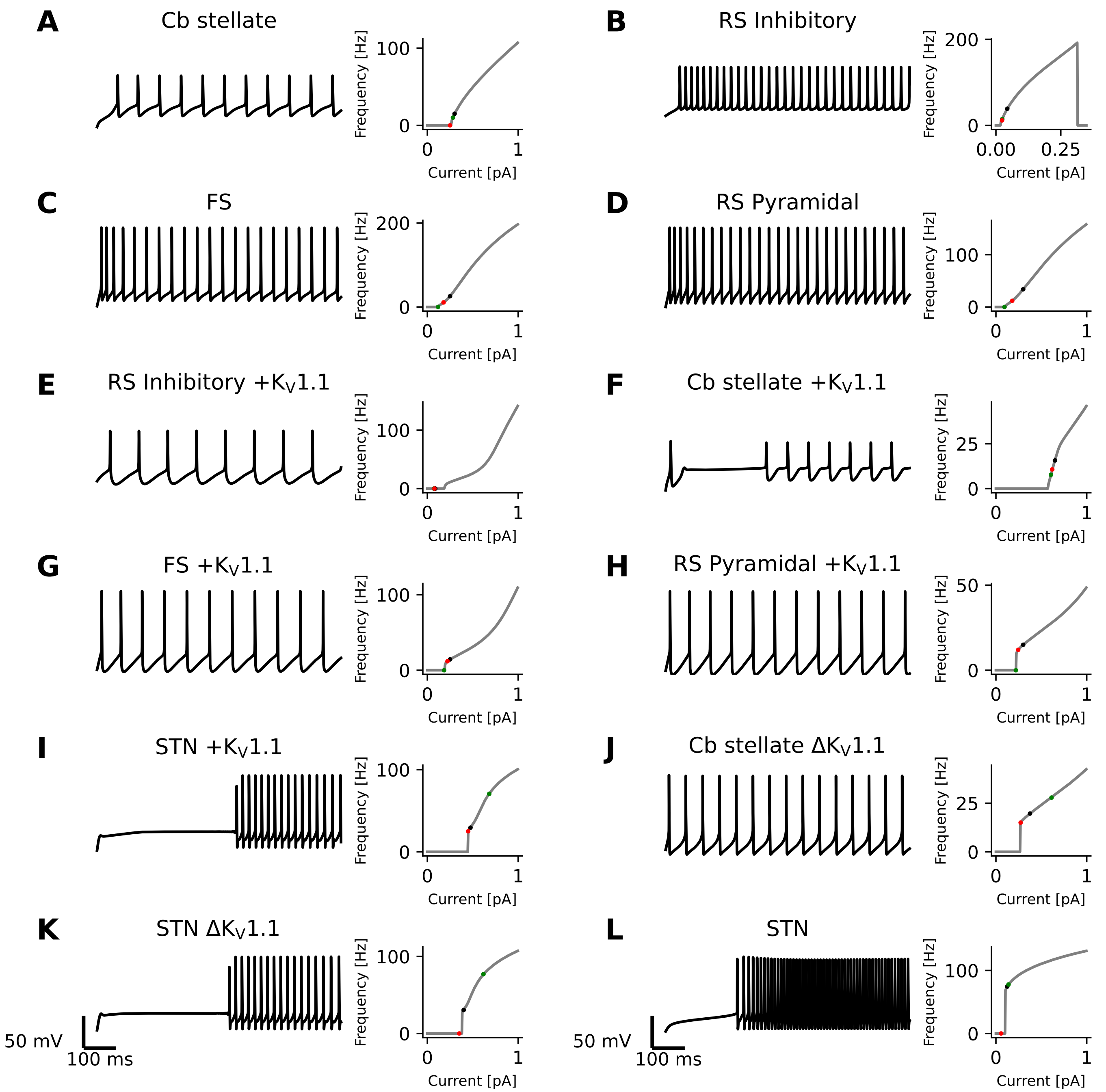

Figure 2: Spike trains and corresponding fI curves from: A. Cb stellate, B. RS Inhibitory, C. FS, D. RS Pyramidal, E. RS Inhibitory $+\mathrm{K_V1.1}$, F. Cb stellate $+\mathrm{K_V1.1}$, G. FS $+\mathrm{K_V1.1}$, H. RS Pyramidal $+\mathrm{K_V1.1}$, I. STN $+\mathrm{K_V1.1}$, J.Cb stellate $\Delta\mathrm{K_V1.1}$, K. STN $\Delta\mathrm{K_V1.1}$, L. STN, where $+\mathrm{K_V1.1}$ indicates the addition of Kv1.1 to the model and $\Delta\mathrm{K_V1.1}$ indicates the exchange of the A type K+ current for Kv1.1. The black dot on the fI curve indicates where the spike train is taken from and the green and red dots indicate the current at which the first and last spike occurs from an increasing and decreasing current ramp respectively.

Rheobase Sensitivity Analysis:

I am not yet happy with this figure's layout

Question figure addresses:

How is rheobase affected by changes in current properties across models? Is the change in rheobase always in the same direction across models?

Method by which data is generated:

A one factor at a time (OFAT) sensitivity analysis was performed on the currents common to all or most models, where one current property was changed systematically at a time, the firing responses simulated and the fI curves computed. From this fI curve the largest injected current at which no firing occurs and the smallest injected current at which firing occurs were obtained. This current interval was then simulated to obtain the rheobase at greater resolution.

Conclusion from Figure:

Generally the effect on rheobase is similar across all models/current environments

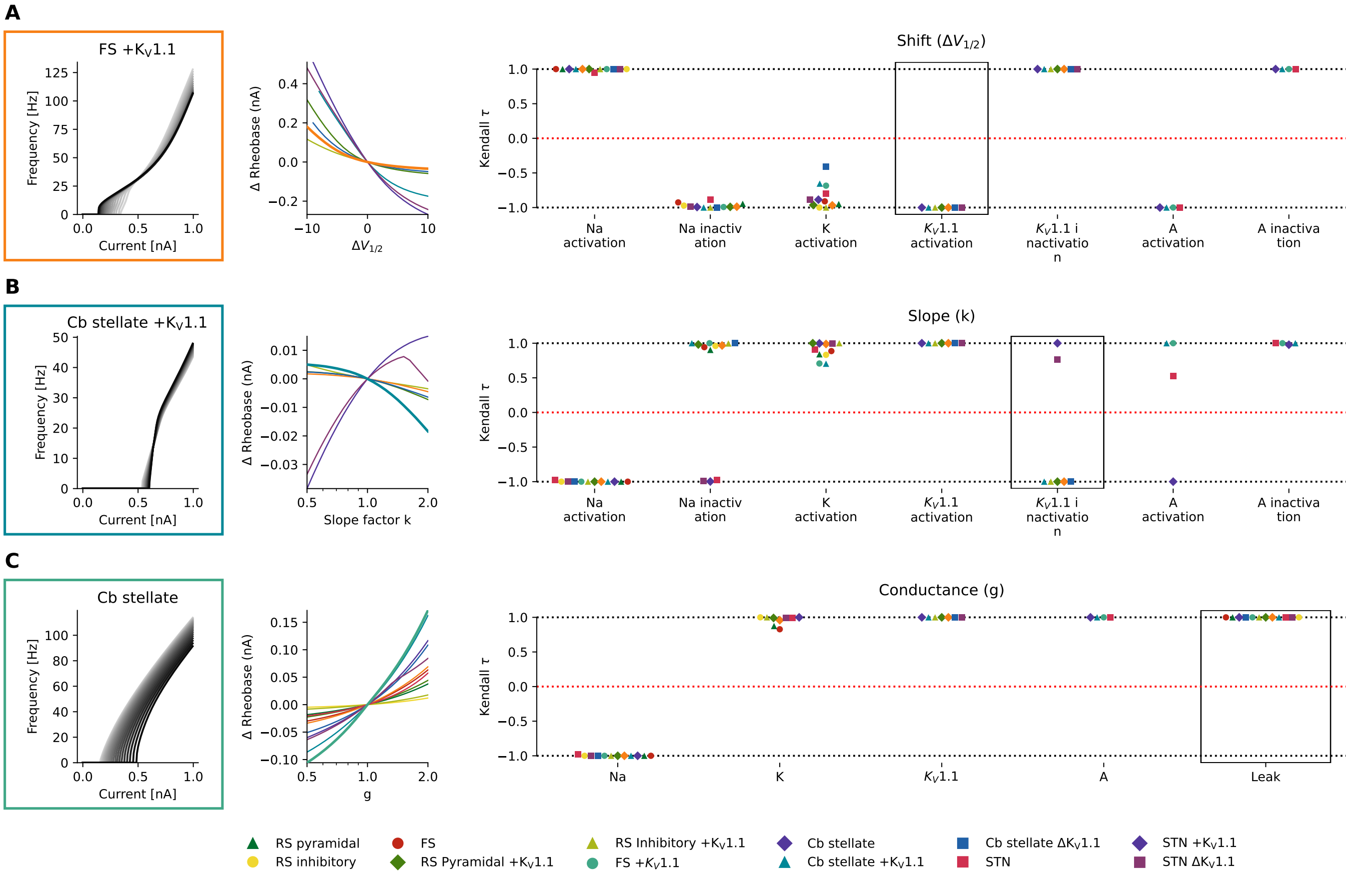

Figure 3:

AUC Sensitivity Analysis:

I prefer the first layout

Question figure addresses:

How is AUC affected by changes in current properties across models? Is the change in AUC rheobase always in the same direction across models?

Method by which data is generated:

A one factor at a time (OFAT) sensitivity analysis was performed on the currents common to all or most models, where one current property was changed systematically at a time, the firing responses simulated and the steady-state fI curves computed. From this fI curve the largest injected current at which no firing occurs was obtained and the integral from this current using the composite trapezoidal rule for 1/5 of the current range.

Conclusion from Figure:

A given current property change does not necessarily cause the same change in rheobase and as such the outcome of a given change is dependent on the current environment or cell type.

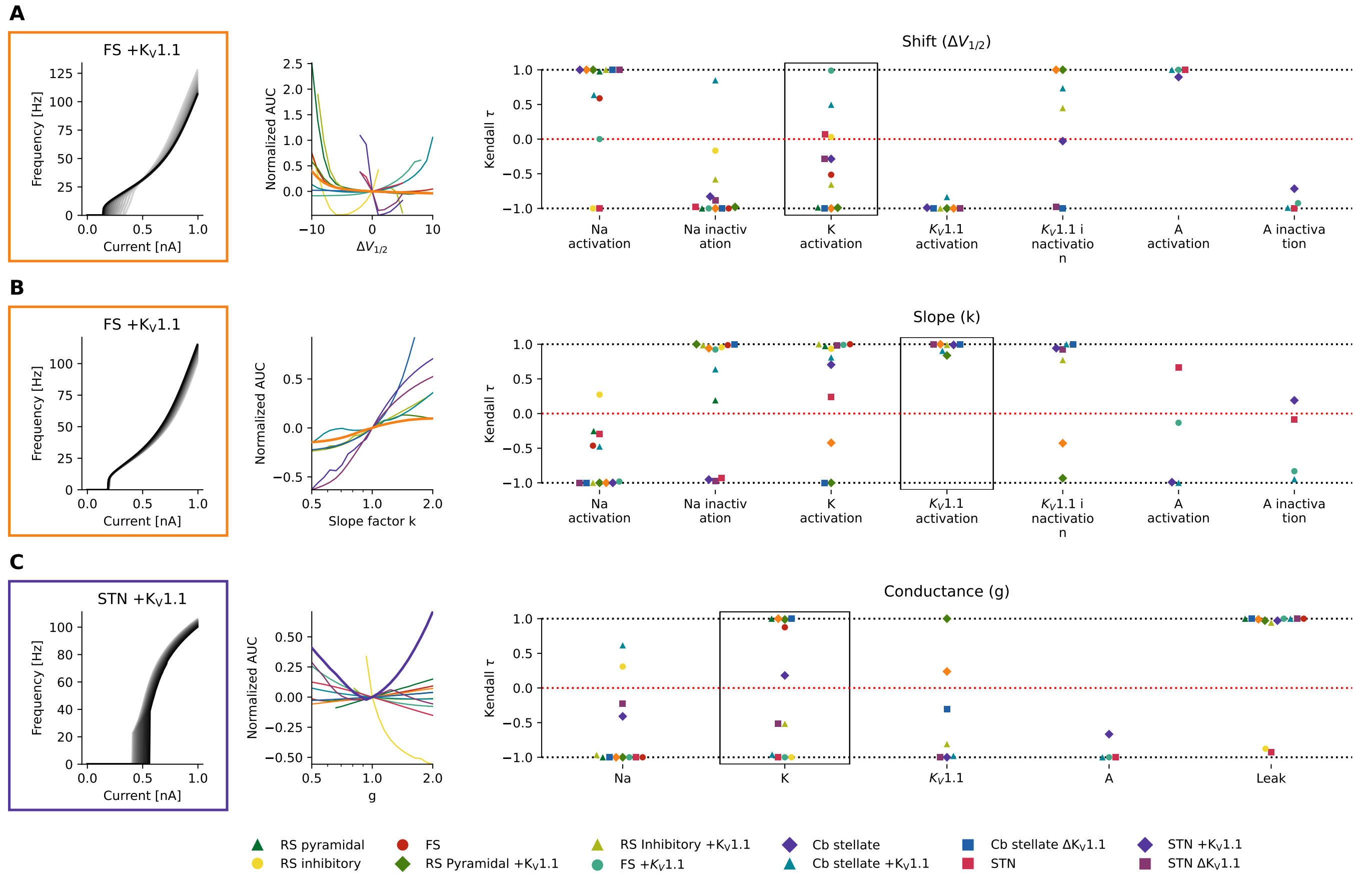

Figure 4:

Kv1.1 mutation simulation:

Question figure addresses:

Do mutations of Kv1.1 cause similar effects on firing across cell types or is the effect cell type (and thus neuronal network) dependent?

Method by which data is generated:

Published Kv1.1 mutations (Lauxmann et al 2021) are simulated in all models containing Kv1.1 or an inactivating Kˆ+ current by altering the current properties according to those experimentally measured for each mutation. The firing of each model for each mutation are then simulated and the rheobase and AUC are computed.

Conclusion from Figure:

The effects of Kv1.1 mutations on rheobase are highly correlated across models indicating that these mutations affect the rheobase in a similar fashion. However, the effect of Kv1.1 mutations vary across models as seen by the different correlation magnitudes between models. Thus although these mutations affect rheobase in a similar manner, the effect on AUC cannot easily be generalized and depends on cell type.

Furthermore, this Figure demonstrates why characterization of mutations in terms of LOF or GOF in relation to firing overlooks potentially important characteristics of the changes in firing seen in different cell types. Thus, the characterization LOF and GOF is useful at a channel level to characterize the effects of a mutation on the current, but cannot and should not be blindly extended to characterize the effects of the mutation on firing as LOF and GOF, not only because the current environment in which this mutation occurs is a key determinant of the firing outcome, but also that firing is complex and not easily characterized as LOF or GOF.

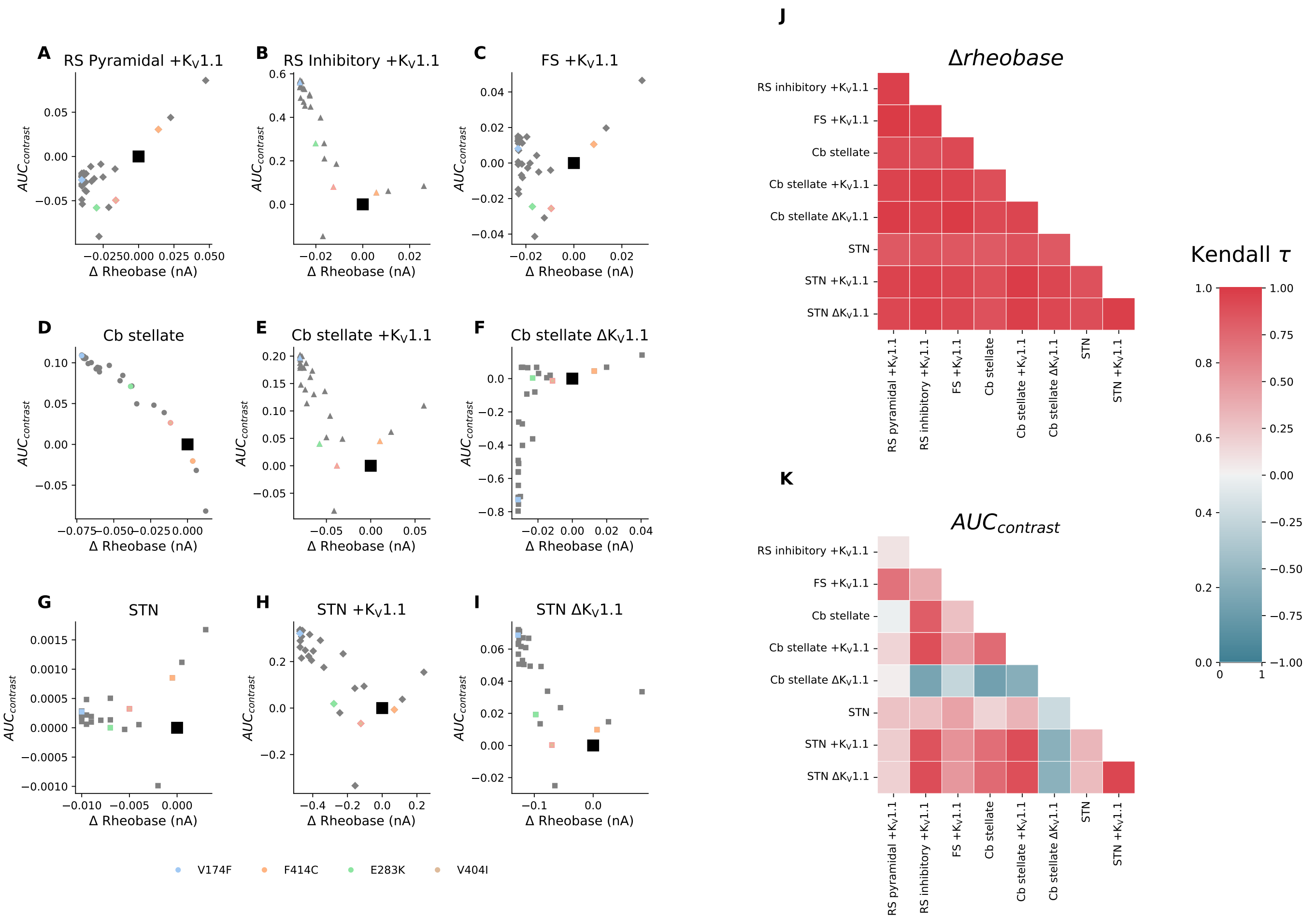

Figure 5:

Ramp Firing - For Supplements?:

Question figure addresses:

How does the firing of the models look like with a ramp protocol?

Method by which data is generated:

A 4 second ramp with the same current range as the step currents used to obtain fI plots is used and the firing of all models is simulated. The resulting spike trains are plotted.

Conclusion from Figure:

The diversity of firing seen with step currents is also seen with current ramps. The ramps highlight the hysteresis in models.

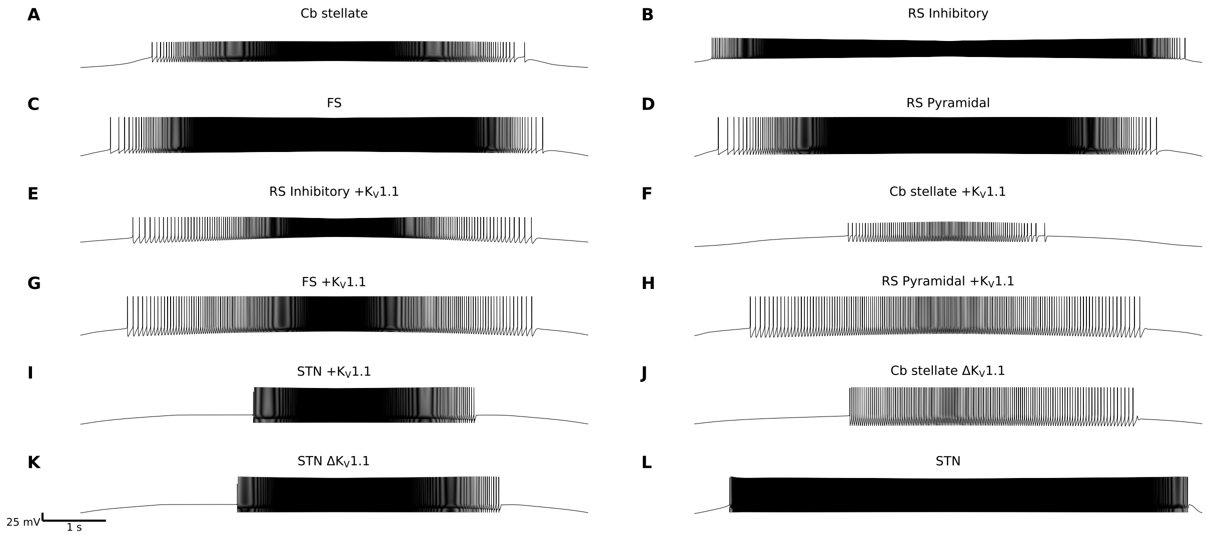

Figure 6: A. Cb stellate, B. RS Inhibitory, C. FS, D. RS Pyramidal, E. RS Inhibitory $+\mathrm{K_V}1.1$, F. Cb stellate $+\mathrm{K_V}1.1$, G. FS $+\mathrm{K_V}1.1$, H. RS Pyramidal $+\mathrm{K_V}1.1$, I. STN $+\mathrm{K_V}1.1$, J.Cb stellate $\Delta\mathrm{K_V}1.1$, K. STN $\Delta\mathrm{K_V}1.1$, L. STN, where $+\mathrm{K_V}1.1$ indicates the addition of Kv1.1 to the model and $\Delta\mathrm{K_V}1.1$ indicates the exchange of the A type K+ current for Kv1.1.