A Mathematical Investigation of Chemotherapy-Induced Peripheral Neuropathy

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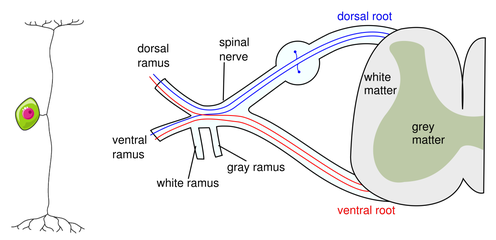
Chemotherapy-Induced Peripheral Neuropathy

- Chemotherapy-induced peripheral neuropathy: a numbing and tingling sensation in palm and feet, arising as a side-effect due to specific chemotherapy drugs (vincristine, paclitaxel, oxaliplatin, etc.)
- Indicated by an increase in excitability of sensory neurons, due to alteration in various areas such as voltage-gated ion channels [1]
- **Aim:** Use dynamical systems theory to investigate role of voltage-gated ion channels and chemotherapy drug Paclitaxel in controlling small dorsal root ganglia (DRG) neuron excitability

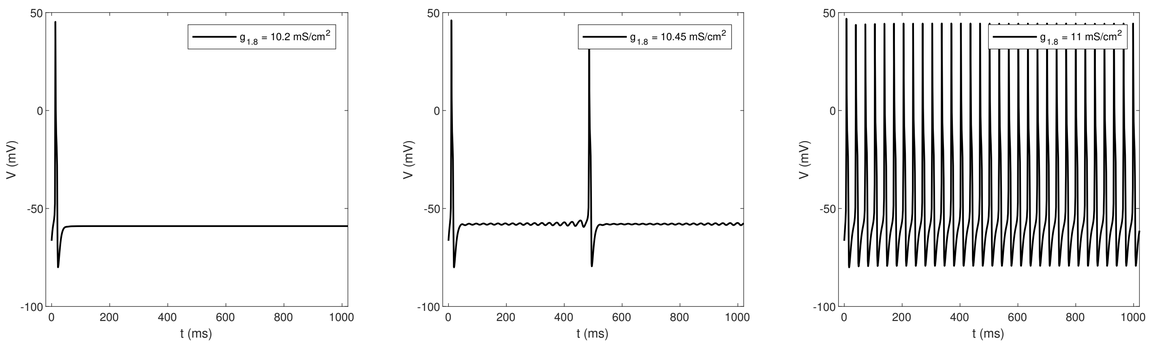


Mathematical Model of Small DRG Neuron

A model of small DRG neuron, consisting of voltage-gated ion channels: $Na_{1.7}$ and $Na_{1.8}$, delayed rectifier K_{DR}, A-type transient K_A and a leak channel

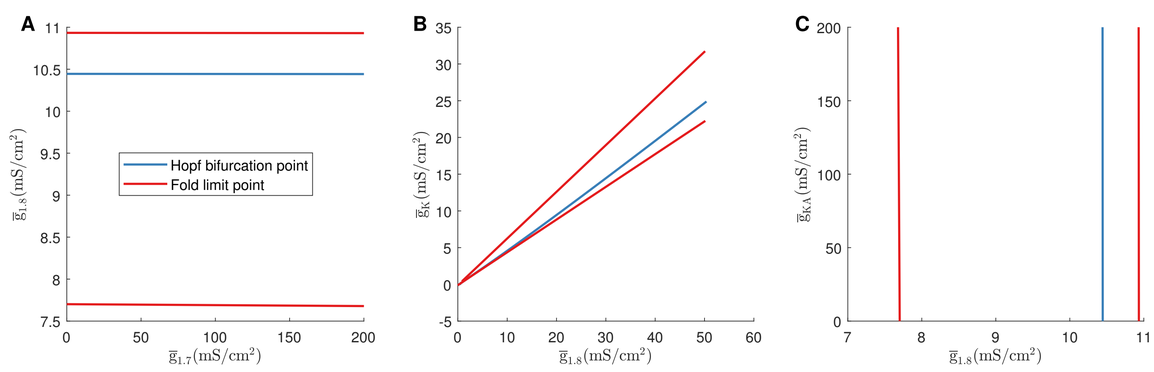
Model is of Hodgkin-Huxley formalism [2,3] with the main equation as the following, where $I_{ext} = 0$ for spontaneous firing:

$$C\frac{\mathrm{d}V}{\mathrm{d}t} = I_{ext} - (\overline{g}_{1.7}m_{1.7}^3 h_{1.7}s_{1.7}(V - V_{\mathrm{Na}}) + \overline{g}_{1.8}m_{1.8}h_{1.8}(V - V_{\mathrm{Na}}) + \overline{g}_{\mathrm{K}}n_{\mathrm{K}}(V - V_{\mathrm{K}}) + \overline{g}_{\mathrm{KA}}n_{\mathrm{KA}}h_{\mathrm{KA}}(V - V_{\mathrm{K}}) + g_{\mathrm{Leak}}(V - V_{\mathrm{Leak}}))$$



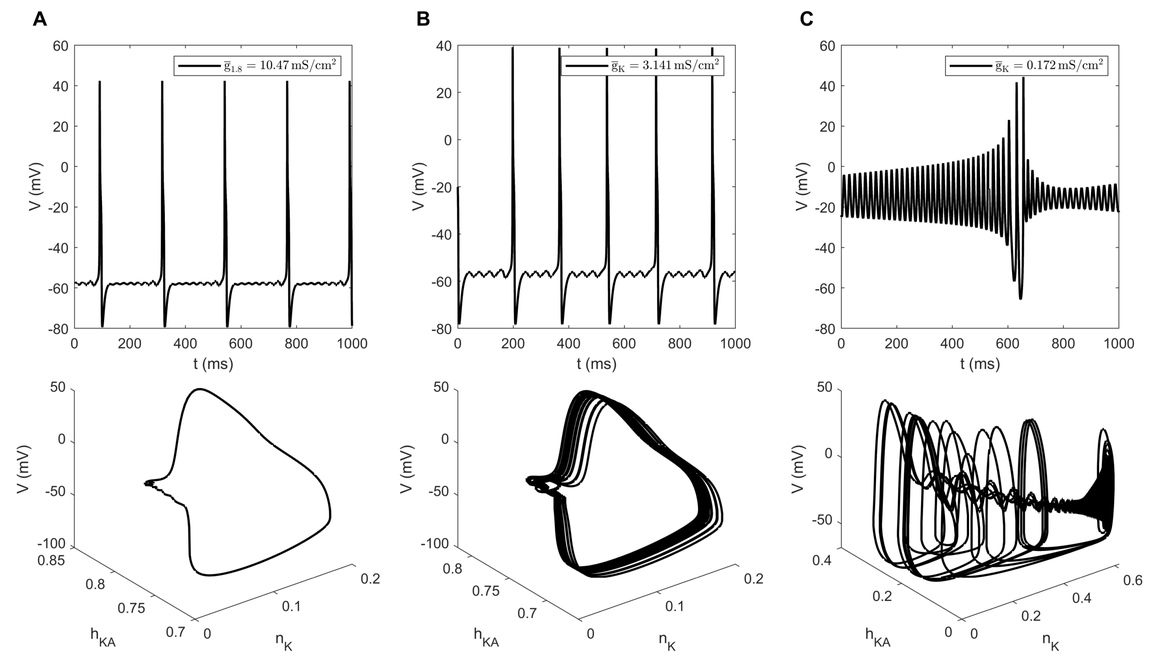
Some dynamic simulations for different values of $\overline{g}_{1.8}$. For specific values of $\overline{g}_{1.8}$, mixed-mode oscillations (MMO) are observed.

Continuation of Bifurcation Points



- Two parameter continuation for Hopf bifurcation and limit points
- $Na_{1.8}$ blocker and K_{DR} enhancer may reduce spontaneous firing

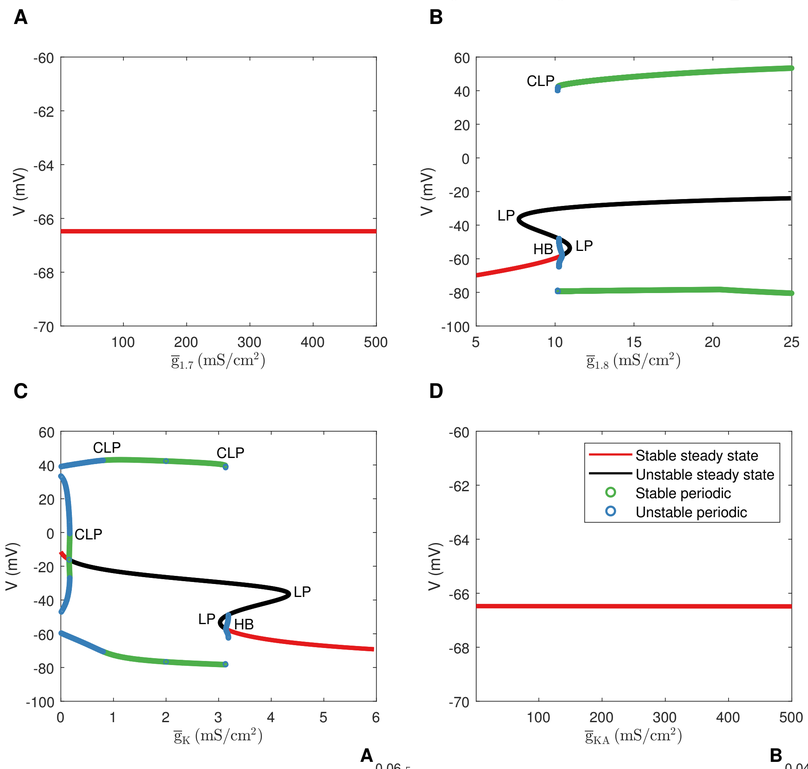
Mixed-Mode Oscillations



- MMO for region between HB and CLP of A: $\overline{g}_{1.8}$, B and C: $\overline{g}_{\mathrm{K}}$
- Voltage dynamics and corresponding phase portraits

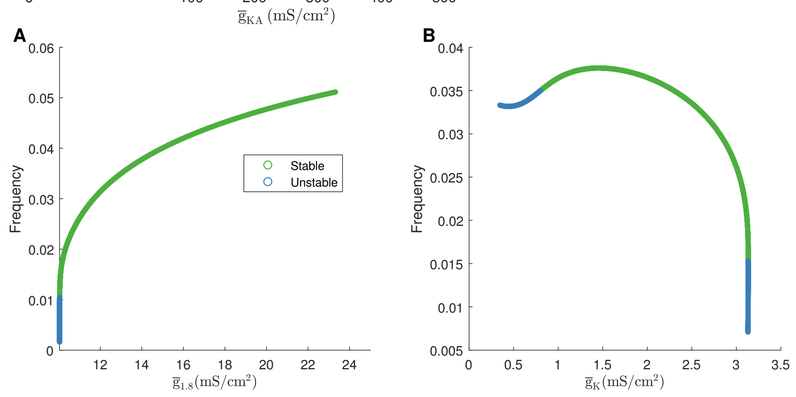
Bifurcation Diagrams for Spontaneous Firing

- Dynamical systems analysis with $\overline{g}$ as primary bifurcation parameters
- Steady state till Hopf bifurcation point
- Full-blown oscillations beyond cyclic limit point



Bifurcation diagrams keeping
A: $\overline{g}_{1.7}$
B: $\overline{g}_{1.8}$
C: $\overline{g}_{\mathrm{K}}$
D: $\overline{g}_{\mathrm{KA}}$
as bifurcation parameters.
HB: Hopf bifurcation point,
LP: limit point,
CLP: cyclic limit point

Frequency plots for A: $\overline{g}_{\mathrm{Na}}$ and B: $\overline{g}_{\mathrm{K}}$. Frequency tending to 0 may imply period infinity solution, explaining the break in continuation plot above.

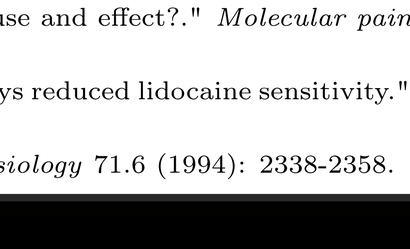


Paclitaxel-Induced Excitability

- Paclitaxel introduced into the model
- Assume all Na, K channels' maximal conductance updated as:

$$G_{\mathrm{Na}} = \overline{g}_{\mathrm{Na}}\frac{2}{1 + e^{-kP}},\ G_{\mathrm{K}} = \overline{g}_{\mathrm{K}}\frac{2}{1 + e^{kP}}$$

P: dimensionless Paclitaxel amount,
G_{Na}, G_{K}: updated conductance



Conclusions

- Dynamical systems theory can potentially unravel role of ion channels and chemotherapy drug in controlling neuron excitability, and provide strategies to reverse peripheral neuropathy
- This is a preliminary study which needs experimental validation. Moreover, other events such as calcium oscillations need to be included for a thorough investigation of the mechanism

References

[1] Aromolaran, Kelly A., and Peter A. Goldstein. "Ion channels and neuronal hyperexcitability in chemotherapy-induced peripheral neuropathy: Cause and effect?." *Molecular pain* 13 (2017): 1744806917714693.

[2] Sheets, Patrick L., et al. "A Nav1. 7 channel mutation associated with hereditary erythromelalgia contributes to neuronal hyperexcitability and displays reduced lidocaine sensitivity." *The Journal of physiology* 581.3 (2007): 1019-1031.

[3] Schild, J. H., et al. "A-and C-type rat nodose sensory neurons: model interpretations of dynamic discharge characteristics." *Journal of Neurophysiology* 71.6 (1994): 2338-2358.