A Mathematical Investigation of Chemotherapy-Induced Peripheral Neuropathy

Parul Verma1, Achim Kienle2, Dietrich Flockerzi2, Doraïswami Ramkrishna1

1Davidson School of Chemical Engineering, Purdue University, USA
2Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany

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: Na1,7 and Na1.8, delayed rectifier KDR, A-type transient KA and a leak channel

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

\[ \frac{dV}{dt} = I_{\text{ext}} - (g_{\text{Na1.7}}m_{\text{Na1.7}}h_{\text{Na1.7}}(V - V_{Na}) + g_{\text{Na1.8}}m_{\text{Na1.8}}h_{\text{Na1.8}}(V - V_{Na}) + g_{\text{K}}(V - V_{K}) + g_{\text{Leak}}(V - V_{Leak})) \]

Some dynamic simulations for different values of \( g_{\text{Na1.8}} \). For specific values of \( g_{\text{Na1.8}} \), mixed-mode oscillations (MMO) are observed.

Bifurcation Diagrams for Spontaneous Firing

- Dynamical systems analysis with \( \theta \) as primary bifurcation parameters
- Steady state till Hopf bifurcation point
- Full-blown oscillations beyond cyclic limit point

Continuation of Bifurcation Points

- Two parameter continuation for Hopf bifurcation and limit points
- Na1.8 blocker and KDR enhancer may reduce spontaneous firing

Mixed-Mode Oscillations

- MMO for region between HB and CLP of A: \( g_{\text{Na1.8}} \), B and C: \( K_A \)
- Voltage dynamics and corresponding phase portraits

Paclitaxel-Induced Excitability

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

  \[ G_{\text{Na}} = g_{\text{Na}} \frac{2}{1 + e^{-P}}, \ G_{\text{K}} = g_{\text{K}} \frac{2}{1 + e^{-P}} \]

  \( P \): dimensionless Paclitaxel amount,
  \( G_{\text{Na}}, G_{\text{K}} \): 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

