Identification of Molecular Pathologies Sufficient to Cause Neuropathic Excitability In Primary Somatosensory Afferents Using Dynamical Systems

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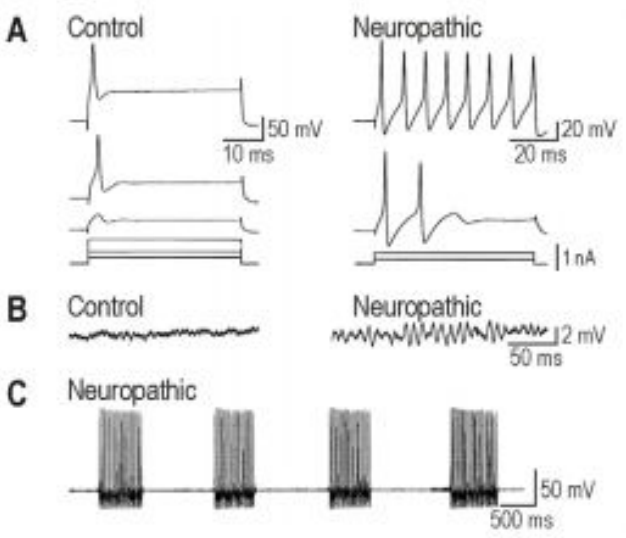
Introduction

- Pain caused by nerve injury associated with neuronal hyperexcitability
- Within primary afferents, injury induced changes identified, but necessary and sufficient molecules for hyperexcitability not yet found
- Three qualitative changes in excitability stand out:
  - a change in spiking pattern
  - membrane potential oscillations
  - bursting
- These changes co-occur and have been documented in dorsal root ganglion (DRG)



Through computational modeling and nonlinear dynamical analysis, we show all 3 arises from a single switch in the nonlinear mechanism responsible for spike initiation.
Also, many distinct molecular changes are sufficient to produce that switch but that no single molecular change is necessary since more than one sufficient change co-occurs after nerve injury

2D Model Used

$$C\,dV/dt = -g_{fast}\,m_\infty(V)(V-E_{Na}) - g_{slow}\,w(V-E_K) - g_{leak}(V-E_{leak}) + I_{stim} + n(t)$$

$$dw/dt = \varphi_w[w_\infty(V) - w]/\tau_w(V)$$

$$m_\infty(V) = 0.5\{1 + \tanh[(V-\beta_m)/\gamma_m]\}$$

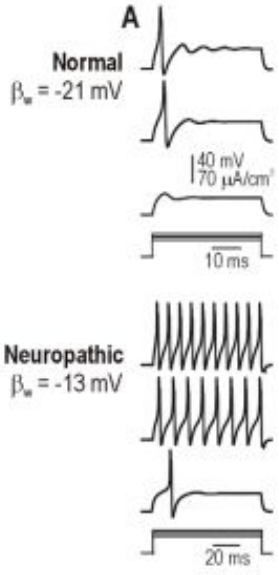
$$w_\infty(V) = 0.5\{1 + \tanh[(V-\beta_w)/\gamma_w]\}$$

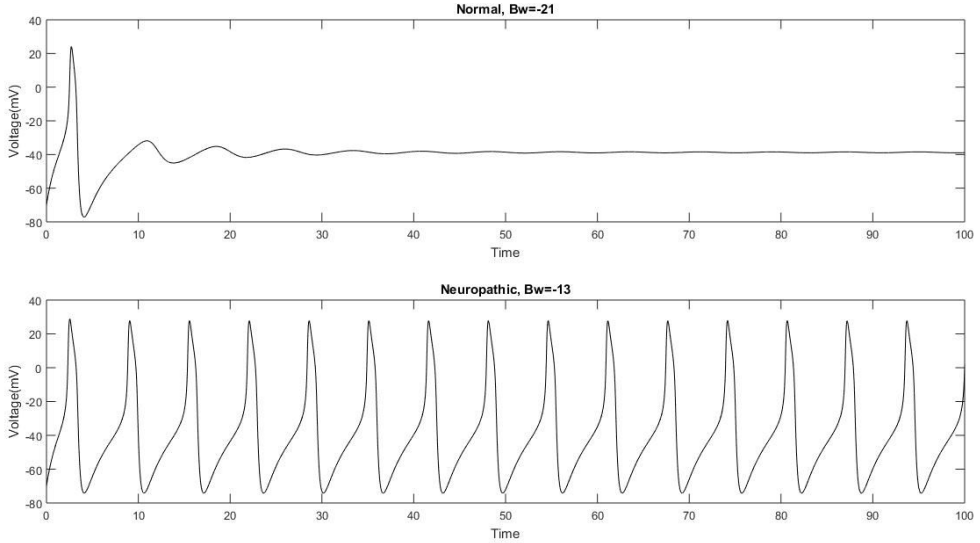
$$\tau_w(V) = 1/[\cosh(V-\beta_w)/2\gamma_w]$$

- The basic model consists of a fast activation variable V and a slower recovery variable w.
- V :membrane potential & m and w: gating variables
- m changes instantaneously with V whereas w changes with a time constant tw.
- Default values for parameters:
  - C = 2 mF/cm2
  - ENa= 50 mV, EK = -100 mV, Eleak= -70 mV,
  - phi_w = 0.15
  - gfast= 20 mS/cm2 , gslow = 20 mS/cm2 , gleak= 2 mS/cm2 ,
  - beta_m = 21.2 mV, gamma_m = 18 mV, gamma_w = 10 mV, and beta_w was varied.
- Istim: injected current.
- n(t): Gaussian white noise with 0 mean and 20 mV2 variance

1. Change in Spiking Pattern

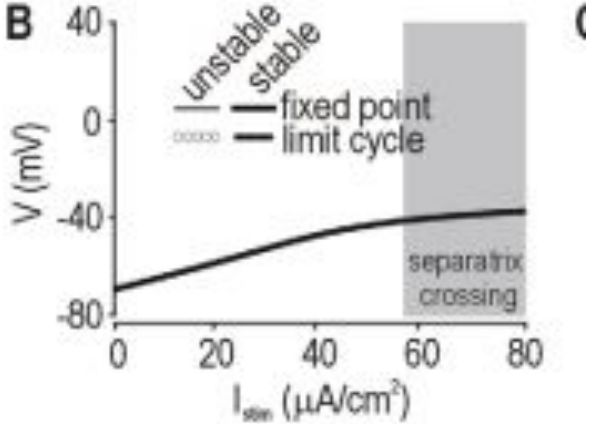
- Spiking pattern during sustained depolarization was converted from onset-only (normal, β_w = -21 mV) to repetitive (neuropathic, β_w = -13 mV) by varying a single parameter.
- Onset-only spiking was observed in the neuropathic model but for only a narrow stimulus range

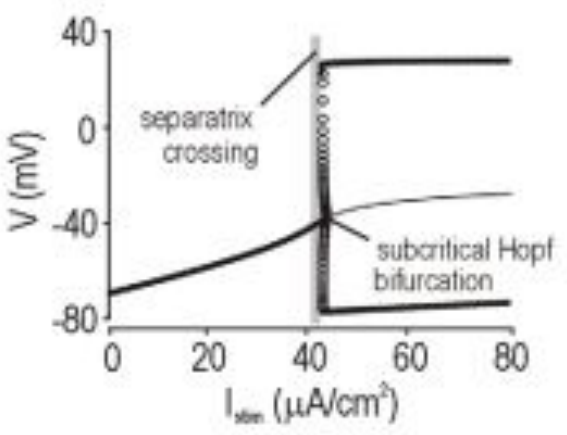




1. Change in Spiking Pattern: Bifurcation Analysis

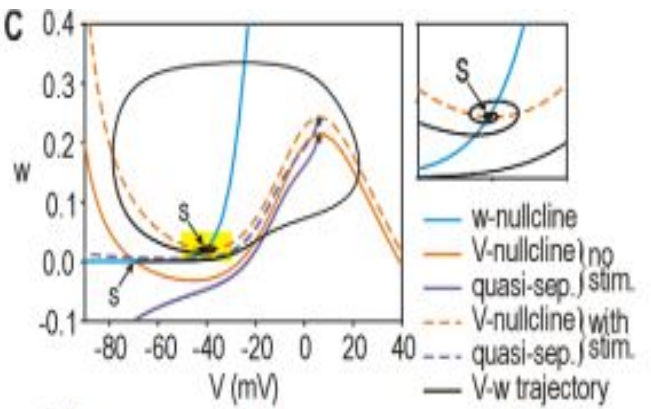
- Stimulation (Istim) was systematically varied, repetitive spiking was produced by the neuropathic model when Istim exceeded a critical value required for a subcritical Hopf bifurcation.
- In contrast, the normal model did not undergo a bifurcation, which means spiking was limited to single spikes generated through a QS crossing

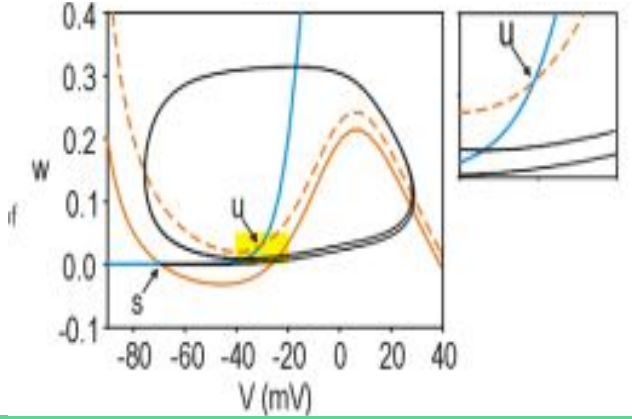


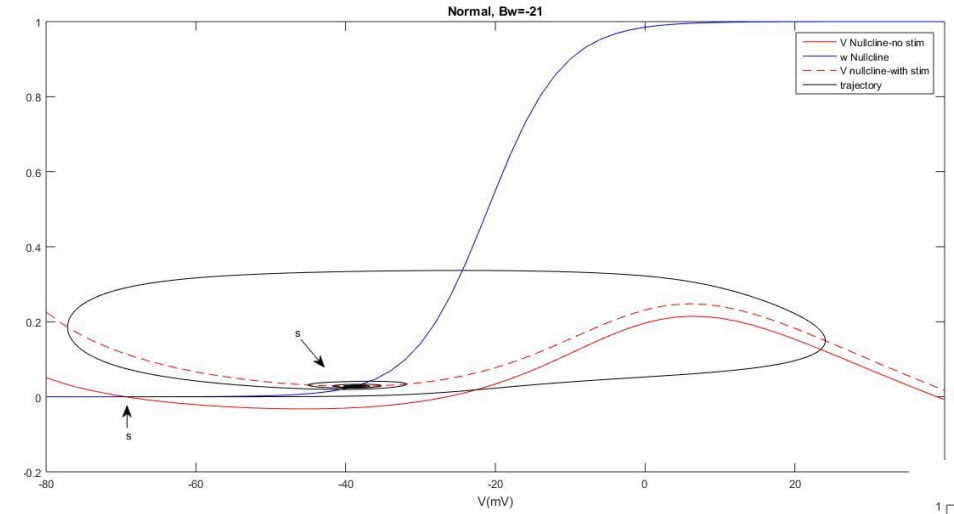


1. Change in Spiking Pattern: Phase-Plane Analysis

- Fast activation variable V plotted against the slower recovery variable w.
- Excitatory stimulation shifts the V-nullcline upward without affecting the w-nullcline.
- In the neuropathic model, stable (s) becomes unstable (u) during stimulation – Hopf bifurcation and is responsible for repetitive spiking.
- In the normal model, the fixed point remains stable despite the V-nullcline shifting, but a single spike can nonetheless be generated depending on how the system moves to the newly positioned fixed point.

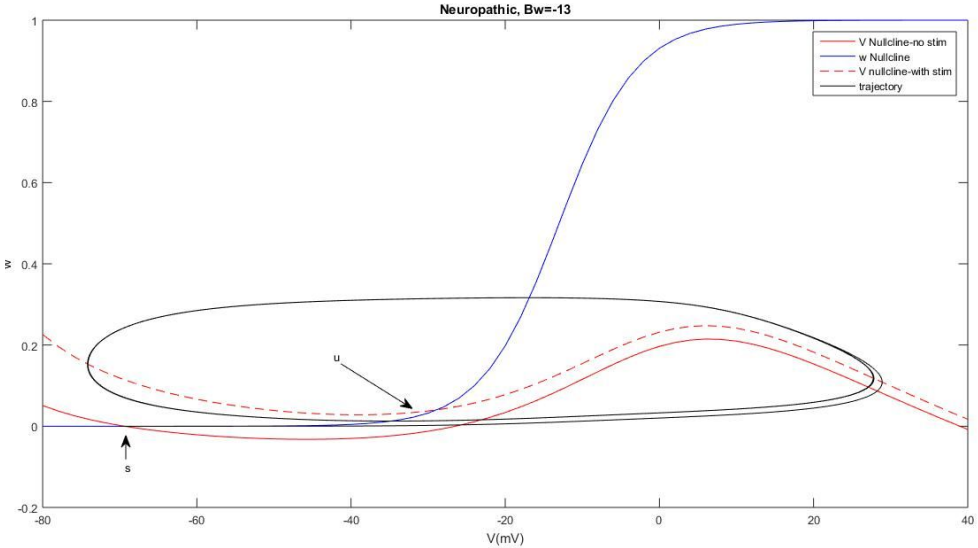






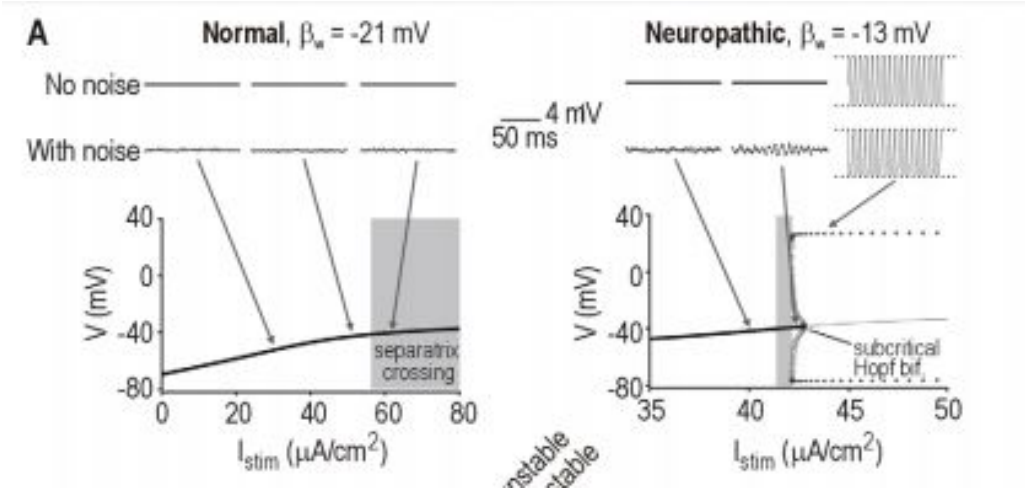
← Normal

Neuropathic →



2. MPO

- Fixed point is a focus - trajectories spiral into or away from that point depending on whether the point is stable or unstable, respectively
- Noise within the system continuously perturbs the system away from its stable fixed point; as the system relaxes, it returns to the fixed point via a spiral trajectory producing oscillations
- A Hopf bifurcation represents destabilization of the fixed point (see above), noise-dependent MPOs prominent near the bifurcation.

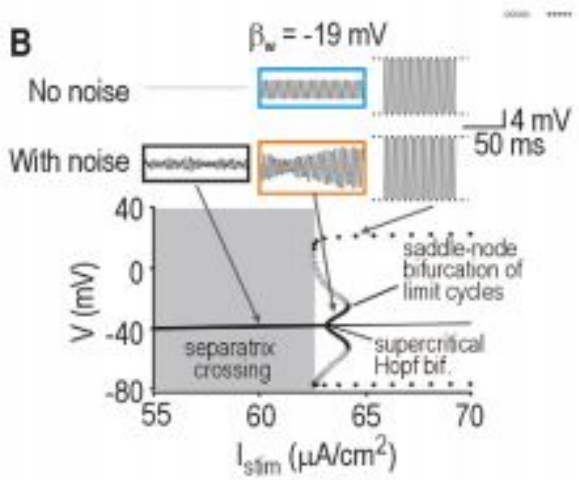


2. MPO

Based on these, 3 predictions made:

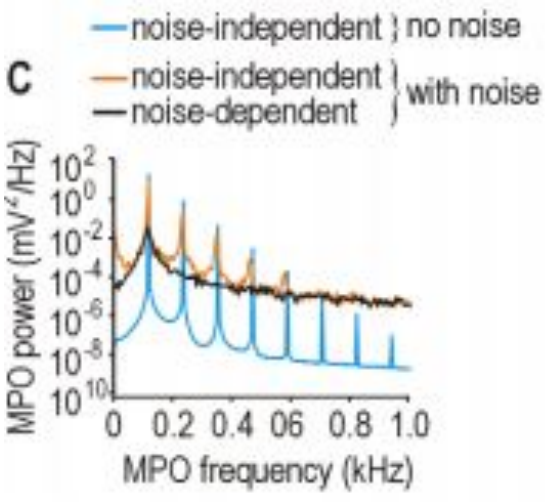
1. noise-dependent MPOs should occur in the neuropathic model when it operates near a subcritical Hopf bifurcation
2. noise dependent MPOs should not occur in the normal model because there is no Hopf bifurcation,
3. noise-independent MPOs should not occur in either model because there is no stable, subthreshold limit cycle on the bifurcation diagrams

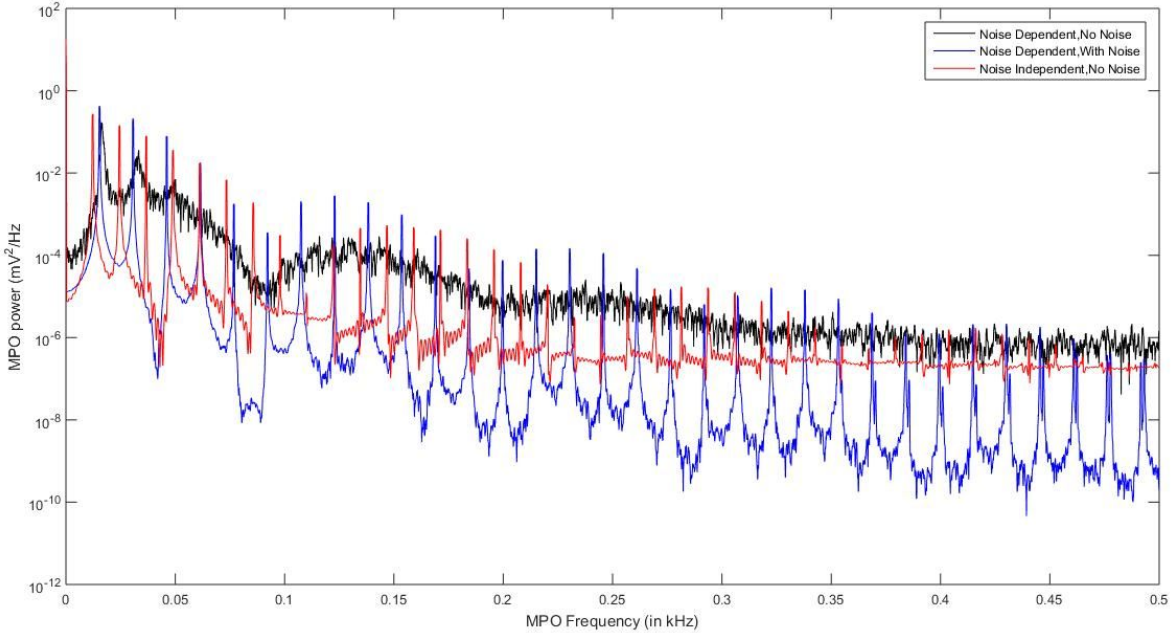
2D model adjusted to produce MPOs in the absence of any noise. In this model, MPOs arose from a stable limit cycle produced through a supercritical Hopf bifurcation



2. MPO

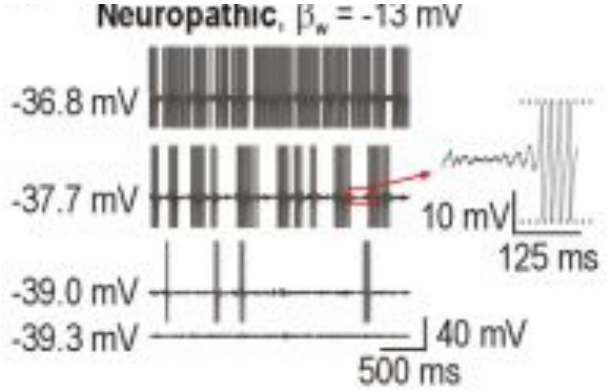
Published power spectra of experimental MPOs are broad like the black power spectrum consistent with noise-dependent MPOs.

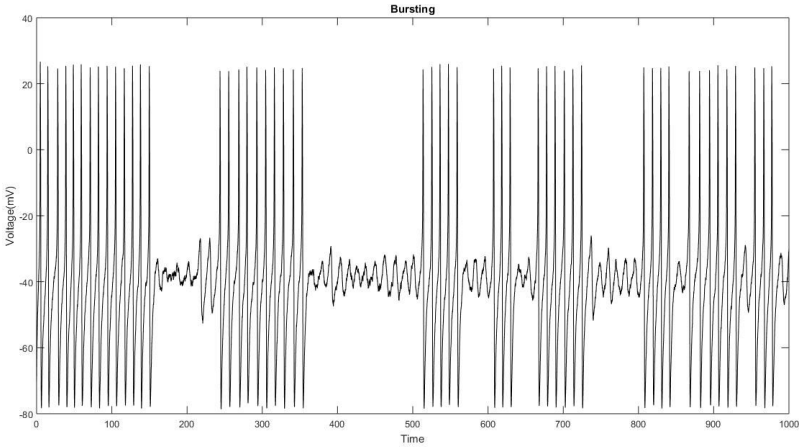




3. Bursting

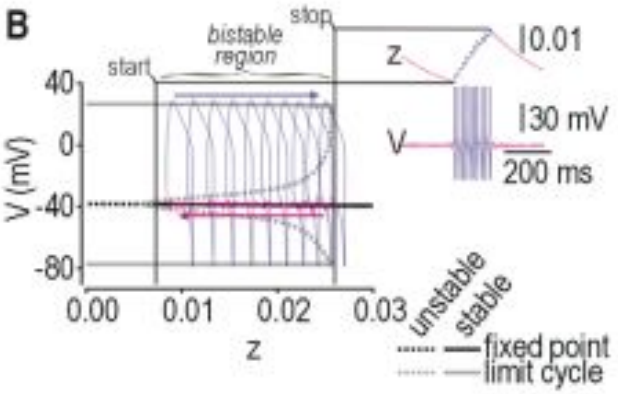
- Bursting is a slow process relative to the timescale of individual spikes - no bursting in 2D because there is no variable with a sufficiently slow time constant
- Subcritical Hopf bifurcation known to allow elliptic bursting when a slow process, like spike frequency adaptation, causes the system to drift back and forth across the bifurcation
- Sample responses at different average membrane potentials in the neuropathic model (bw = -13 mV) with slow adaptation mediated by IAHP.

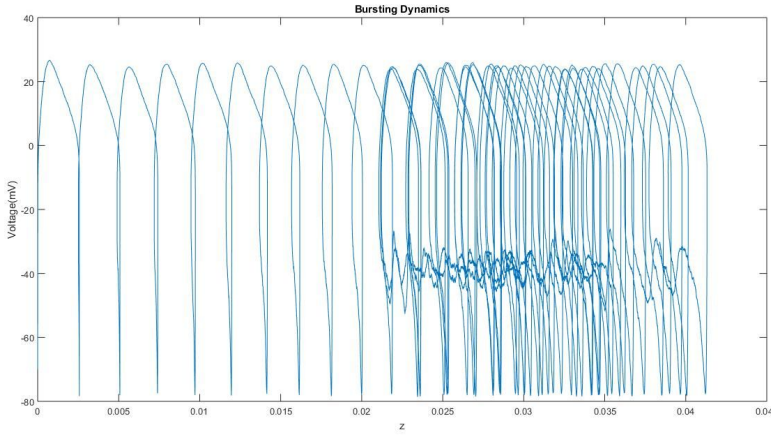




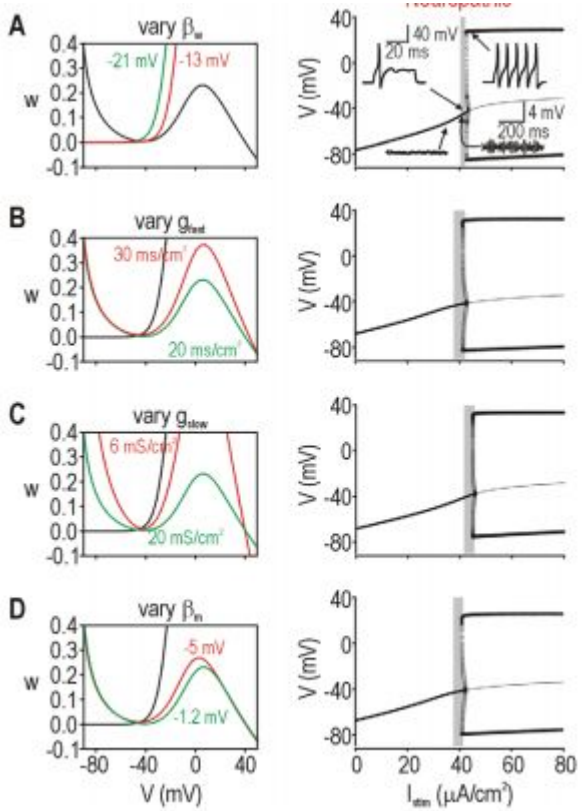
3. Bursting

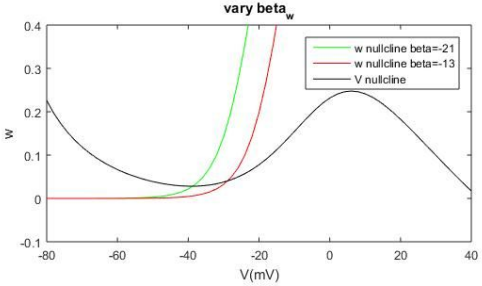
- Hysteresis is evident from the bursts starting and stopping at different values of z.
- The model tracks the stable limit cycle branch, spiking repetitively as z increases until the end of the branch is reached, at which point the burst stops.
- The model then tracks the stable fixed point as z decreases (during which noise-dependent MPOs wax and wane) until the fixed point becomes unstable, at which point another burst starts.

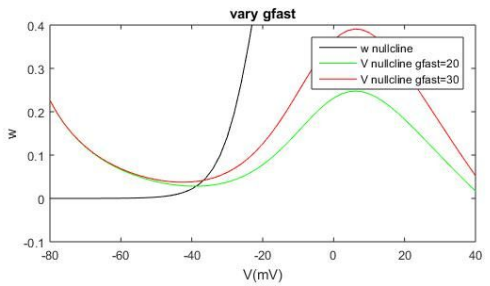


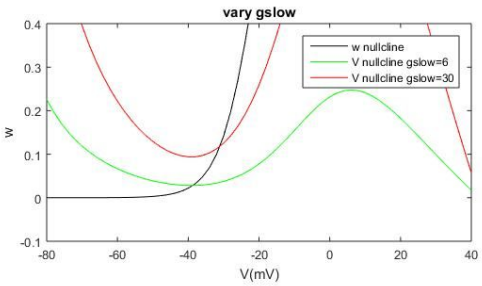


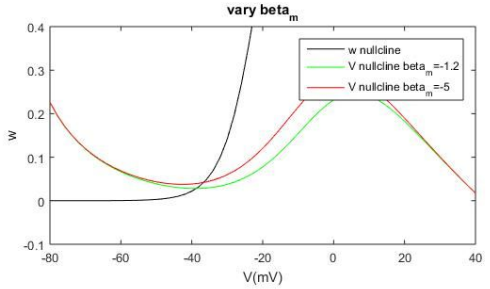
Degeneracy











Distinct molecular pathologies can yield the same pattern of cellular hyperexcitability

Conclusions

- Spiking pattern, MPOs and bursting are mechanistically linked through their mutual dependence on the spike initiation mechanism
- A single parameter change in our minimal 2-D model can represent more than one biological change
- If a conductance that does not influence spike initiation (e.g. one that activates only at suprathreshold potentials) is added to the 2-D model altering that conductance will not affect excitability
- A change in a functionally important parameter might also fail to produce cellular hyperexcitability if that change is offset by a simultaneous change in a second parameter

Conclusions

- A switch in spike initiation mechanism is sufficient and most likely necessary to explain a constellation of neuropathic changes in primary afferent excitability.
- Pathological alteration of the dynamical mechanism responsible for spike initiation, rather than pathological alteration of any one ion channel, is key for explaining cellular hyperexcitability.
- Molecular basis for a change in spike initiation dynamics is highly degenerate insofar as a multitude of different molecular changes, either alone or in combination, can manifest the same change in cellular excitability.
- Strategically intervening to reduce neuropathic pain requires that we thoroughly understand and capitalize on rather than be thwarted by the complexity and degeneracy of the underlying mechanisms.

Thank You

Additional slide: 3D Model with Adaptation

The model with adaptation mediated by an AHP current IAHP [56] was modeled according to

$$C\,dV/dt = -g_{fast}\,m_{\infty}(V)(V-E_{Na}) - g_{slow}\,w(V-E_K)$$
$$-g_{leak}(V-E_{leak}) - g_{adapt}\,z(V-E_K) + I_{stim} + n(t)$$

$$dz/dt = \{1/[1+\exp((\beta_z\text{-}V)/\gamma_z)] - z\}/\tau_z$$

where z controls activation of IAHP current with parameters gadapt= 0.5 mS/cm2 , bz= 0 mV, cz= 4 mV, tz= 300 ms. All other parameters were unchanged from our standard 2-D models.