

## **Conductance Imbalances Link Diverse Symptoms of Demyelination Diseases**

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White matter in both the central and peripheral nervous systems is susceptible to damage that results in the disruption of myelin insulation. Demyelination upsets the normal saltatory propagation of action potentials resulting in slowed, blocked, desynchronized or paradoxically excessive spiking that may underlie negative (loss-of-function) and positive (gain-of-function) symptoms observed in demyelination diseases. The diversity and timing of such symptoms are poorly understood, often intermittent, and uncorrelated with disease progress. We have examined the effects of demyelination and related ionic conductance alterations on intrinsic axonal excitability using a Hodgkin-Huxley (HH) based multi-compartment model of a mammalian myelinated axon and a reduced Morris-Lecar (ML) model.

Our modeling reveals a simple explanation for the breadth of symptoms and reveals how the ratio of sodium to leak conductance,  $g_{Na}/g_L$ , acts as a four-way-switch that governs complex excitability patterns in partially demyelinated axons including (from lowest to highest  $g_{Na}/g_L$ ): spike-failure, single spikes, afterdischarge, or spontaneous spiking. Our results demonstrate that afterdischarge requires a slow inward current that renders the system bistable, i.e. with two coexisting attractor states, one corresponding to quiescence and the other to repetitive spiking. The bistability required for afterdischarge can result from smaller departures in the  $g_{Na}/g_L$  ratio from the single spike zone than those required to destabilize the system so that it spikes spontaneously. A neuron prone to afterdischarge may function normally unless a trigger switches the system to its “pathological” attractor state; although the underlying pathology may develop slowly, switching between attractor states happens abruptly and may account for paroxysmal symptoms (e.g. pain, paresthesias, spasms).

Overall, our results demonstrate how continuous changes in membrane conductances can, because of nonlinearities, cause discontinuous changes in axonal excitability. Thus, negative symptoms as well as tonic and paroxysmal positive symptoms may be a consequence of the  $g_{Na}/g_L$  ratio taking different values following demyelination.

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