Breakdown of fast-slow analysis in an excitable system with channel noise[1]

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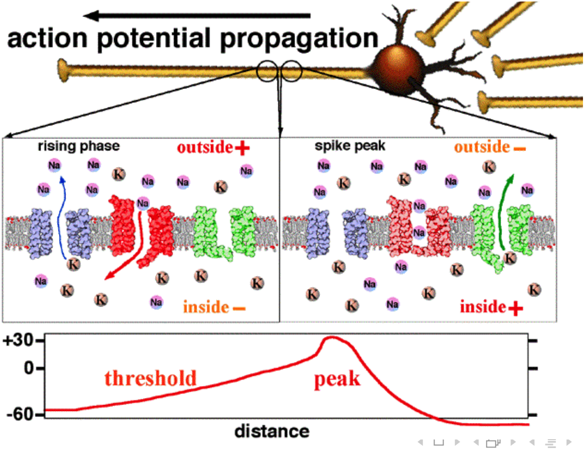
Part I. Neural excitability

THE ACTION POTENTIAL

- Generation and propagation of an action potential based on nonlinearities associated with active membrane conductances.
- Recordings of the current flowing through single ion channels indicate that channels fluctuate rapidly between open and closed states in a stochastic fashion.

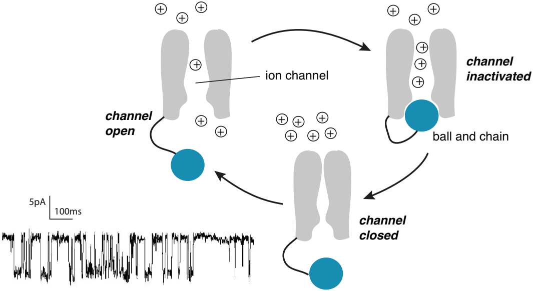


Ion channels I

- Usually assume that there are a large number of approximately independent channels of each type - law of large numbers
- The conductance for an ion channel of type i

$$g_i = \bar{g}_i X_i$$

where $\bar{g}_i$ is the density of channels in the membrane multiplied by the conductance of a single channel and X_i is the fraction of open channels.



ION CHANNELS II

- Model kinetics of X in terms of voltage-dependent transitions between an open and closed state:

$$\frac{dX}{dt} = \alpha_X(v)(1 - X) - \beta_X(v)X,$$

where

$$C(\text{closed}) \underset{\beta_X(v)}{\overset{\alpha_X(v)}{\rightleftharpoons}} O(\text{open}).$$

- From basic thermodynamics, the opening and closing rates are expected to be exponential functions of the voltage.
- Kinetics can be rewritten in the alternative form

$$\tau_X(v)\frac{\mathrm{d}X}{\mathrm{d}t} = a_X(v) - X,$$

where

$$\tau_X(v) = \frac{1}{\alpha_X(v) + \beta_X(v)}, \qquad a_X(v) = \alpha_X(v)\tau_X(v).$$

It follows that X approach the asymptotic value $a_X(v)$ exponentially with time constant $\tau_X(v)$,

MORRIS-LECAR MODEL OF NEURAL EXCITABILITY

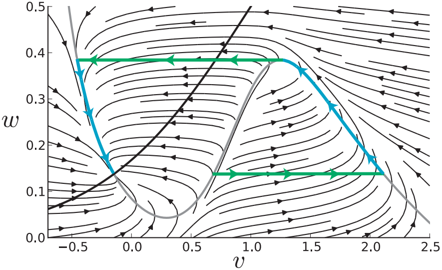
- Morris-Lecar (ML) model describes voltage dynamics driven by fast sodium (Na) (or Ca) and slow potassium (K) channels

$$\begin{aligned}\frac{dv}{dt} &= a(v)f_{\mathrm{Na}}(v) + wf_{\mathrm{K}}(v) - g(v)\\ \frac{dw}{dt} &= \frac{w_{\infty}(v) - w}{\tau_w(v)},\end{aligned}$$

- Here $f_i(v) = \bar{g}_i(v_i - v)$ and w represents the fraction of open K^+ channels.
- The fraction of Na^+ channels is assumed to be in quasi steady-state.
- Analyze the generation of action potentials using a fast/slow analysis

Fast/slow analysis of excitability

- Fast variable v has a cubic-like nullcline and slow variable w has a monotonically increasing nullcline
- Assume nullclines have a unique intersection point - stable resting state
- Excitable system: sufficiently large perturbations of the resting state result in a time-dependent trajectory taking a prolonged excursion through state space before returning to the resting state - the action potential (AP)
- Rapid transition ($w \approx$ constant) during initiation of AP



Fundamental issues

- For fixed w, 1D system is bistable with a well-defined threshold for initiation of an AP
- How does one analyze the effects of sodium ion channel fluctuations on spontaneous action potential (SAP) generation? - first passage time problem
- Is the fast/slow decomposition still valid when potassium ion channel fluctuations are taken into account?
- How does one formulate spontaneous action potential generation for an excitable system in terms of a first passage time problem - there is no well-defined separatrix for escape from the resting state?

Part II. First passage time problem for SAP formation

STOCHASTIC ION CHANNEL MODEL

- Let n, $n = 0, \ldots, N$ be the number of open sodium channels:

$$\frac{dv}{dt} = F(v, n) \equiv \frac{1}{N} f(v) n - g(v),$$

with $f(v) = g_{\mathrm{Na}}(V_{\mathrm{Na}} - v)$ and $g(v) = -g_{\mathrm{eff}}[V_{\mathrm{eff}} - v] + I_{\mathrm{ext}}$.

- The opening and closing of the ion channels is described by a birth-death process according to

$$n \to n + 1, \quad n \to n - 1$$

at rates

$$\omega_+(v, n) = \alpha(v)(N - n), \quad \omega_-(n) = \beta n$$

- Take

$$\alpha(v) = \beta \exp\left(\frac{2(v - v_1)}{v_2}\right)$$

for constants β, v_1, v_2.

Chapman-Kolmogorov equation I

- Introduce the joint probability density

$$\mathrm{Prob}\{v(t) \in (v, v + dv), n(t) = n\} = p(v, n, t | v_0, n_0, 0) dv,$$

- **Differential Chapman-Kolmogorov** (CK) equation (dropping the explicit dependence on initial conditions)

$$\begin{aligned}\frac{\partial p}{\partial t} = -&\frac{\partial [F(v, n) p(v, n, t)]}{\partial v} \\ &+ \frac{1}{\epsilon}[\omega_+(v, n-1) p(v, n-1, t) + \omega_-(n+1) p(v, n+1, t) \\ &- (\omega_+(v, n) + \omega_-(n)) p(v, n, t)],\end{aligned}$$

- Introduced small parameter ϵ - opening and closing of sodium channels much faster than relaxation dynamics of voltage

Chapman-Kolmogorov equation II

- Rewrite CK equation in the more compact form

$$\frac{\partial p}{\partial t} = -\frac{\partial [F(v,n)p(v,n,t)]}{\partial v} + \frac{1}{\epsilon}\sum_{n'} A(n,n';v)p(v,n',t),$$

$$A_{n,n-1;v} = \omega_+(v,n-1),\ A_{n,n;v} = -\omega_+(v,n) - \omega_-(n),\ A_{n,n+1;v} = \omega_-(n+1).$$

- There exists a unique steady state density $\rho(v,n)$ for which

$$\sum_m A(n,m;v)\rho(v,m) = 0$$

where

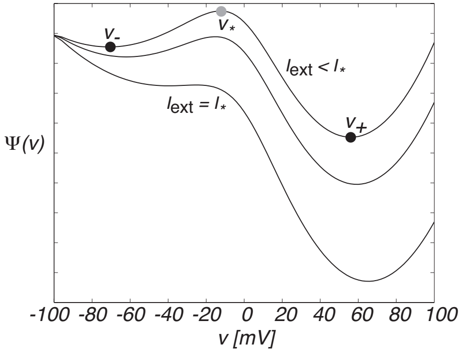
$$\rho(v,n) = \frac{N!}{(N-n)!n!}a(v)^n b(v)^{N-n}, \quad a(v) = \frac{\alpha(v)}{\alpha(v)+\beta},\ b(v) = 1-a(v).$$

Mean-field limit

- In the limit $\epsilon \to 0$, we obtain the mean-field equation

$$\frac{dv}{dt} = \sum_n F(v,n)\rho(v,n) = a(v)f(v) - g(v) \equiv -\frac{d\Psi}{dv},$$

- Assume deterministic system operates in a bistable regime



First-passage time (FTP) problem

- Assume particle starts at stable fixed point v_-
- Absorbing boundary conditions at v_*:

$$p(v_*, n, t) = 0 \quad \text{for all } n \leq k$$

such that $F(v_*, n) < 0$.

- Let T be FPT with density $f(t)$
- Introduce survival probability

$$S(t) = \int_0^{v_*} \sum_n p(v, n, t) dv \equiv \text{Prob}\{t < T\}.$$

- It follows that

$$f(t) = -\frac{dS}{dt} = -\int_0^{v_*} \sum_n \frac{\partial p}{\partial t}(v, n, t) dv = \sum_n F(v_*, n) p(v_*, n, t),$$

SPECTRAL PROJECTION METHOD I (WARD 1998,NEWBY/KEENER 2011,PCB/NEWBY 2013/2014)

- Introduce the inner product

$$\langle f, g\rangle = \sum_{n=0}^{\infty} \int_0^{v_*} f(v,n) g(v,n) dv$$

- Consider eigenfunctions of CK linear opertor $\widehat{L}$

$$\begin{aligned} \widehat{L}\phi_r(v,n) &\equiv \frac{d}{dv}(F(v,n)\phi_r(v,n)) - \frac{1}{\epsilon}\sum_m A(n,m;v)\phi_r(v,n) \\ &= \lambda_r \phi_r(v,n), \end{aligned}$$

together with the boundary conditions

$$\phi_r(v_*, n) = 0, \text{ for } n \leq k$$

Spectral projection method II

- Assume the spectrum of $\widehat{L}$ satisfies the following:

  (i) $\widehat{L}$ has a complete orthonormal set of eigenfunctions ϕ_r

  (ii) The eigenvalues λ_r all have positive real part and the smallest eigenvalue λ_0 is simple. Thus we can introduce the ordering $0 < \lambda_0 < \mathrm{Re}[\lambda_1] \leq \mathrm{Re}[\lambda_2] \leq \ldots$.

  (iii) λ_0 is exponentially small, $\lambda_0 \sim \mathrm{e}^{-C/\epsilon}$, whereas $\mathrm{Re}[\lambda_r] = \mathcal{O}(1)$ for $r \geq 1$. In particular, $\lim_{\epsilon\to 0} \lambda_0 = 0$ and $\lim_{\epsilon\to 0} \phi_0(v,n) = \rho(v,n)$.

- Introduce the eigenfunction expansion

$$p(v,n,t) = \sum_{r=1}^{N} C_r \mathrm{e}^{-\lambda_r t} \phi_r(v,n),$$

Spectral projection method III

- At large times we have the **quasistationary approximation**

$$p(v,n,t) \sim C_0 \mathrm{e}^{-\lambda_0 t} \phi_0(v,n).$$

- Hence

$$f(t) \sim \mathrm{e}^{-\lambda_0 t} \sum_n \phi_0(v_*,n) v(v_*,n), \quad \lambda_1 t \gg 1.$$

- It can be shown that

$$\lambda_0 = \frac{\sum_{n=0}^{\infty} F(v_*,n)\phi_0(v_*,n)}{\langle 1,\phi_0\rangle}.$$

- Hence, (normalized) first passage time density reduces to

$$f(t) \sim \lambda_0 \mathrm{e}^{-\lambda_0 t}$$

and $\langle T\rangle = \int_0^\infty t f(t) dt \sim 1/\lambda_0$.

QUASISTATIONARY DENSITY I

- **Quasistationary density** ϕ_ϵ approximates ϕ_0 up to exponentially small terms at the boundary

$$\widehat{L}\phi_\epsilon = 0, \quad \phi_\epsilon(v_*, n) = \mathcal{O}(\mathrm{e}^{-C/\epsilon}).$$

- Express λ_0 in terms of the quasistationary density ϕ_ϵ by considering the eigenfunctions of the adjoint operator

$$\widehat{L}^\dagger \xi_r(v,n) \quad \equiv \quad -F(v,n)\frac{d\xi_r(v,n)}{dv} - \frac{1}{\epsilon}\sum_m A(m,n;v)\xi_r(v,m) = \lambda_r \xi_r(v,n)$$

and the boundary conditions

$$\xi_r(v_*, n) = 0, \quad n > k.$$

- The eigenfunctions $\{\phi_r\}$ and $\{\xi_r\}$ form a biorthogonal set:

$$\langle \phi_r, \xi_s \rangle \equiv \int_{-\infty}^{v_*} \sum_n \phi_r(v,n)\xi_s(v,n)dv = \delta_{r,s}$$

Quasistationary density II

- Consider the identity

$$\langle \boldsymbol{\phi}_\epsilon, \widehat{L}^\dagger \boldsymbol{\xi}_0 \rangle = \lambda_0 \langle \boldsymbol{\phi}_\epsilon, \boldsymbol{\xi}_0 \rangle.$$

- Integration by parts then gives

$$\boxed{\lambda_0 = -\frac{\sum_n \phi_\epsilon(v_*, n)\xi_0(v_*, n)F(v_*, n)}{\langle \boldsymbol{\phi}_\epsilon, \xi_0 \rangle}.}$$

- Determine ϕ_ϵ using the WKB method and ξ_0 using matched asymptotics (Keener and Newby 2011, Newby and Chapman 2013).

WKB Method I

- Seek a solution of the form

$$\phi_\epsilon(v,n) \sim R(v,n)\exp\left(-\frac{\Phi(v)}{\epsilon}\right)$$

- Substitution yields

$$\sum_m \left(A(n,m;v) + \Phi'(v)\delta_{n,m}F(v,m)\right) R(v,m) = \epsilon \frac{dF(v,n)R(v,n)}{dv}$$

- Asymptotic expansions $R \sim R^{(0)} + \epsilon R^{(1)}$ and $\Phi \sim \Phi_0 + \epsilon\Phi_1$
- The leading order equation is

$$\boxed{\sum_m A(n,m;v)R^{(0)}(v,m) = -\Phi_0'(v)F(v,n)R^{(0)}(v,n).}$$

WKB METHOD II

- One positive solution is $R^{(0)} = \rho$, for which $\Phi_0' = 0$.
- There exists one other positive solution, for which $\Phi_0' = 0$ at the deterministic fixed points (Newby and Keener 2011)
- Next order in the asymptotic expansion:

$$\sum_m \bar{A}(n,m;v)R^{(1)}(v,m) = \frac{dF(v,n)R^{(0)}(v,n)}{dv} - \Phi_1'(v)F(v,n)R^{(0)}(v,n)$$

with

$$\bar{A}(n,m;v) = \left(A(n,m;v) + \Phi_0'(v)\delta_{n,m}F(v,m)\right)$$

- Matrix operator $\bar{A}(n,m;v)$ has a 1D null space spanned by the positive WKB solution $R^{(0)}$

WKB Method III

- Fredholm Alternative Theorem yields solvability condition

$$\sum_n S(v,n)\left[\frac{dF(v,n)R^{(0)}(v,n)}{dv} - \Phi_1'(v)F(v,n)R^{(0)}(v,n)\right] = 0,$$

$$\boxed{\sum_n S(v,n)\left(A(n,m;v) + \Phi_0'(v)\delta_{n,m}F(v,m)\right) = 0.}$$

- Given $R^{(0)}$, S and Φ_0, the solvability condition yields the following equation for Φ_1:

$$\Phi_1'(v) = \frac{\sum_n S(v,n)[F(v,n)R^{(0)}(v,n)]'}{\sum_n S(v,n)F(v,n)R^{(0)}(v,n)}.$$

WKB METHOD IV

- Define

$$k(v) = \exp\left(-\int_{v_-}^{v} \Phi_1'(y)dy\right),$$

- To leading order in ϵ,

$$\boxed{\phi_\epsilon(v,n) \sim \mathcal{N} k(v) \exp\left(-\frac{\Phi_0(v)}{\epsilon}\right) R^{(0)}(v,n),}$$

- Normalization

$$\mathcal{N} = \left[\int_0^{v_*} k(v) \exp\left(-\frac{\Phi_0(v)}{\epsilon}\right) dv\right]^{-1}.$$

- Laplace's method gives

$$\mathcal{N} \sim \frac{1}{k(v_-)} \sqrt{\frac{|\Phi_0''(v_-)|}{2\pi\epsilon}} \exp\left(\frac{\Phi_0(v_-)}{\epsilon}\right).$$

ADJOINT EIGENFUNCTION I

- Leading order adjoint equation

$$\epsilon F(v,n)\frac{d\xi_0(v,n)}{dv} + \sum_m A(m,n;v)\xi_0(v,m) = 0,$$

  with boundary conditions

$$\xi_0(v_*,n) = 0, \quad n > k.$$

- Boundary layer: set $v = v_* - \epsilon z$ and $Q(z,n) = \xi_0(u_* - \epsilon z)$:

$$F(v_*,n)\frac{dQ(z,n)}{dz} + \sum_m A(m,n;v_*)Q(z,m) = 0$$

- Inner solution has to be matched with the outer solution $\xi_0 = 1$

$$\lim_{z\to\infty} Q(z,n) = 1$$

Adjoint eigenfunction II

- Consider the eigenvalue equation

$$\sum_n \left(A(n,m;v) - \mu_r(v)\delta_{n,m}v(u,m)\right) S_r(v,n) = 0,$$

$$S_0(v,n) = 1,\ \mu_0 = 0, \quad S_1(v,n) = S(v,n),\ \mu_1(v) = -\Phi_0'(v)$$

- Zero eigenvalue is degenerate at $v = v_*$, since $\Phi_0'(v_*) = 0$.
- Introduce the generalized eigenfunction expansion

$$Q(z,n) = c_0 + c_1(\widehat{S}(v_*,n) - z) + \sum_{r\geq 2} c_r S_r(v_*,n)\mathrm{e}^{-\mu_r(v_*)z}$$

$$\boxed{\sum_n A(n,m;v_*)\widehat{S}(v_*,n) = -F(v_*,m).}$$

ADJOINT EIGENFUNCTION III

- Eliminate secular term $-c_1 z$ using an alternative scaling in the boundary layer of the form (Newby and Chapman 2013)

$$x = x_* + \epsilon^{1/2} z$$

- Find that

$$c_1 \sim \sqrt{\frac{2|\Phi_0''(v_*)|}{\pi}} + \mathcal{O}(\epsilon^{1/2}), \quad c_r = \mathcal{O}(\epsilon^{1/2}) \text{ for } r \geq 2$$

- Only need c_1, since the quasistationary approximation ϕ_ϵ is proportional to $R^{(0)}$, which is orthogonal to all eigenvectors S_r, $r \neq 1$.

PRINCIPLE EIGENVALUE

- Principal eigenvalue is

$$\lambda_0 \sim \frac{1}{\pi}\frac{k(v_*)B(v_*)}{k(v_-)}\sqrt{\Phi_0''(v_-)|\Phi_0''(v_*)|}\exp\left(-\frac{\Phi_0(v_*)-\Phi_0(v_-)}{\epsilon}\right).$$

$$B(v_*) = -\sum_n \widehat{S}(v_*,n)v(u_*,n)\rho(v_*,n)$$

$$\sum_m A(n,m;v)R^{(0)}(v,m) = -\Phi_0'(v)F(v,n)R^{(0)}(v,n).$$

$$\sum_n S(v,n)\left(A(n,m;v)+\Phi_0'(v)\delta_{n,m}F(v,m)\right) = 0.$$

$$\sum_n A(n,m;v_*)\widehat{S}(v_*,n) = -F(v_*,m).$$

CALCULATION OF PRINCIPAL EIGENALUE

1. Find eigenfunction $R^{(0)}(v,n)$ and eigenvalue $\mu(v) = -\Phi_0'(v)$.

$$R^{(0)}(v,n) = \frac{N!}{(N-n)!n!}\frac{(f(v)-g(v))^{N-n}g(v)^n}{f(v)^N}.$$

and

$$\mu(v) = N\frac{\alpha(v)f(v)-(\alpha(v)+\beta)g(v)}{g(v)(f(v)-g(v))},$$

2. Calculate the prefactor $k(v)$ from the null eigenfunction

$$S(v,n) = \left(\frac{b(v)g(v)}{a(v)(f(v)-g(v))}\right)^n$$

3. Calculate the generalized eigenfunction $\widehat{S}(v^*,n)$:

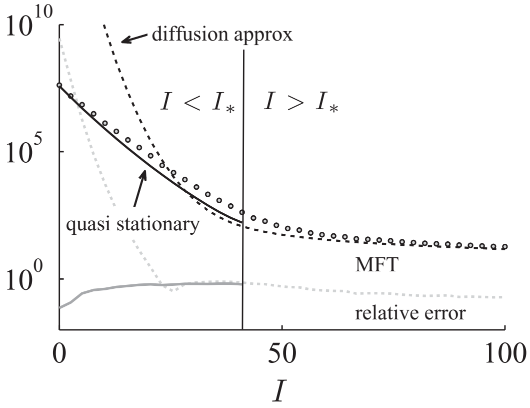
$$\widehat{S}(v^*,n) = \frac{f(v_*)}{N(\alpha(v_*)+\beta)}n.$$

4. Calculate the factor $B(v*)$:

$$B(v_*) = \frac{f(v_*)^2\alpha(v_*)\beta}{N(\alpha(v_*)+\beta)^3}$$

Comparison with numerics (Keener and Newby 2011)

- Compare analytical results with Monte Carlo simulations
- Good agreement in super threshold and sub threshold regimes
- A corresponding diffusion approximation breaks down in the sub threshold regime



Part III. Breakdown of fast/slow analysis

Stochastic Morris-Lecar model

- Take $n \leq N$ open Na^+ channels and $m \leq M$ open K^+ channels:

$$\frac{dv}{dt} = F(v,m,n) \equiv \frac{n}{N} f_{Na}(v) + \frac{m}{M} f_K(v) - g(v).$$

- Each channel satisfies the kinetic scheme

$$C \underset{\beta_i(v)}{\overset{\alpha_i(v)}{\rightleftarrows}} O, \quad i = \mathrm{Na},\ \mathrm{K},$$

- The Na^+ channels fast relative to voltage and K^+ dynamics.
- Chapman–Kolmogorov (CK) equation,

$$\frac{\partial p}{\partial t} = -\frac{\partial (Fp)}{\partial v} + \mathbb{L}_K p + \mathbb{L}_{Na} p.$$

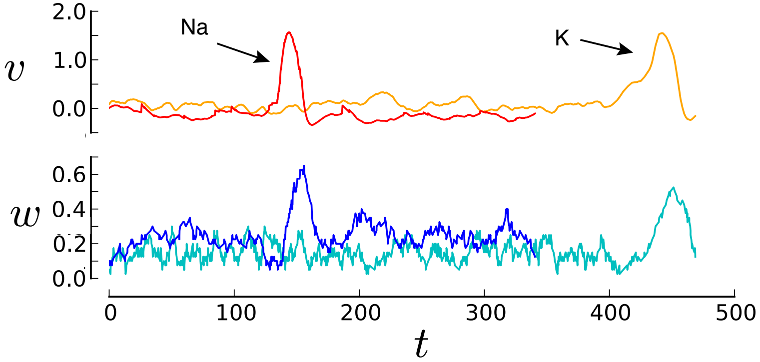
- The jump operators $\mathbb{L}_j$, $j = \mathrm{Na}, \mathrm{K}$, are defined according to

$$\mathbb{L}_j = (\mathbb{E}_n^+ - 1)\omega_j^+(n,v) + (\mathbb{E}_n^- - 1)\omega_j^-(n,v),$$

with $\mathbb{E}_n^{\pm} f(n) = f(n \pm 1)$, $\omega_j^-(n,v) = n\beta_j$ and $\omega_j^+(n,v) = (N-n)\alpha_j(v)$.

K^+ channel fluctuations can induce SAPs

- The deterministic ML model is recovered in the limit $\beta_{Na} \to \infty$, $M \to \infty$ with $\lambda_M = \beta_{Na}/M$ fixed.
- Find spontaneous SAPs can be generated for finite M and/or finite β_{Na}



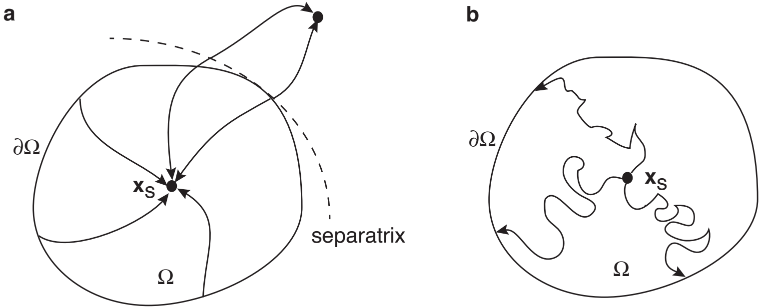
Small noise limit

- Introduce a small parameter $\epsilon \ll 1$ such that (in dimensionless units)

$$\beta_{Na}^{-1} = \epsilon, \quad M^{-1} = \lambda_M \epsilon,$$

- Set $w = m/M$ and write $(m \pm 1)/M = w \pm M^{-1}$
- Perturbation expansion in ϵ combines a **system size expansion** with a **slow/fast analysis**
- We would like to determine the most probable or **optimal paths** of escape from the resting state in the (v, w)-plane for small ϵ
- For chemical master equations, the **quasipotential** of the WKB approximation satisfies a **Hamilton-Jacobi equation** - the optimal paths given by solutions to an effective **Hamiltonian dynamical system**
- There is an underlying **variational principle** derived using **large deviation theory** or **path-integrals**

OPTIMAL PATHS



- (a) Deterministic trajectories converging to a stable fixed point $\mathbf{x}_S$. Boundary of basin of attraction formed by a union of separatrices
- (b) Noise-induced paths of escape

WKB APPROXIMATION

- Introduce quasistationary solution of the form

$$\phi_\epsilon(v,w,n) = R(n|v,w)\exp\left(-\frac{1}{\epsilon}\Phi(v,w)\right),$$

where $\Phi(v,w)$ is the **quasipotential**

- To leading order,

$$\left[\mathbb{L}_{Na} + p_v + h(v,w,p_w)\right]R(n|v,w) = 0,$$

where

$$p_v = \frac{\partial \Phi}{\partial v}, \quad p_w = \frac{\partial \Phi}{\partial w}$$

and

$$h(v,w,p_w) = \frac{\beta_K}{M\lambda_M}\left[(e^{-\lambda_M p_w} - 1)\omega_K^+(Mw,v) + (e^{\lambda_M p_w} - 1)\omega_K^-(Mw,v)\right]$$

Hamilton-Jacobi equation

- Introducing the ansatz

$$R_n(v,w) = \frac{\Lambda(v,w)^n}{(N-n)!n!},$$

yields a **Hamilton-Jacobi** equation for Φ:

$$0 = \mathcal{H}(v,w,p_w,p_v) \equiv (a(v)f_{Na}(v)+g(v))p_v + h(v,w,p_w)$$
$$-\frac{b(v)}{N}\left[((2g(v)+f_{Na}(v))p_v h(v,w,p_w) + (f_{Na}(v)+g(v))g(v)p_v^2 + h(v,w,p_w)^2\right)$$

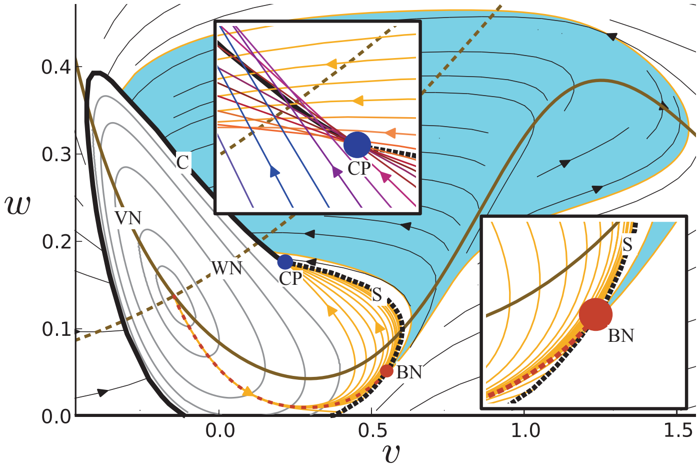
- Solve for Φ using **method of characteristics**. Satisfy Hamilton's equations

$$\dot{\mathbf{x}} = \nabla_{\mathbf{p}}\mathcal{H}(\mathbf{x},\mathbf{p}), \quad \dot{\mathbf{p}} = -\nabla_{\mathbf{x}}\mathcal{H}(\mathbf{x},\mathbf{p}).$$

for $\mathbf{x} = (v,w)$ and $\mathbf{p} = (p_v,p_w)$

- Interpret $\Phi(t)$ as the **action** with $\dot{\Phi}(t) = \mathbf{p}(t)\cdot\dot{\mathbf{x}}(t)$, is a strictly increasing function of t, and the **quasipotential** is given by $\Phi(v,w) = \Phi(t)$ at the point $(v,w) = \mathbf{x}(t)$.

RESULTS I: SOLUTIONS OF HJ EQUATION



- Caustic (C), v nullcline (VN), and w nullcline (WN), metastable separatrix (S), bottleneck (BN), caustic formation point (CP)

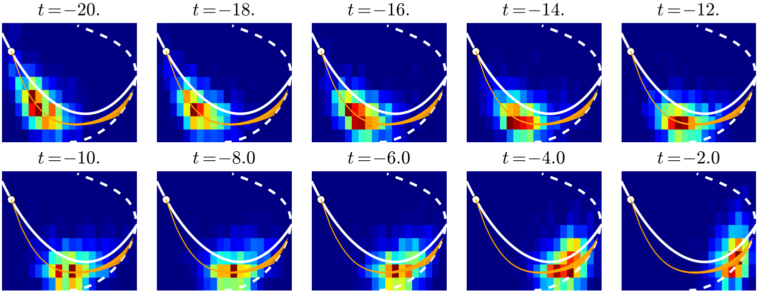
RESULTS II

- Φ takes the shape of a potential well in a neighborhood of resting state with convex level curves.
- Once Φ reaches a threshold, a **caustic** is formed along which every point is connected to two equally likely metastable trajectories
- Most probable paths of escape dip significantly below the resting value for w, indicating a **breakdown** of the deterministic slow/fast decomposition.
- Escape trajectories pass through a narrow region of state space that acts like a **bottleneck or stochastic saddle node**
- Hence, although there is no well-defined **separatrix** for an excitable system, one can formulate an escape problem by determining the MFPT to reach the bottleneck from the resting state.
- Curves that don't pass through SN are bounded by a curve (S) that acts like a **stochastic separatrix**.

RESULTS III

- Identify SAP trajectories as those metastable trajectories that cross the separatrix.

- SAP trajectories begin at the fixed point as a single trajectory and then fan out just before reaching the metastable separatrix.
- Result confirmed by Monte-Carlo simulations



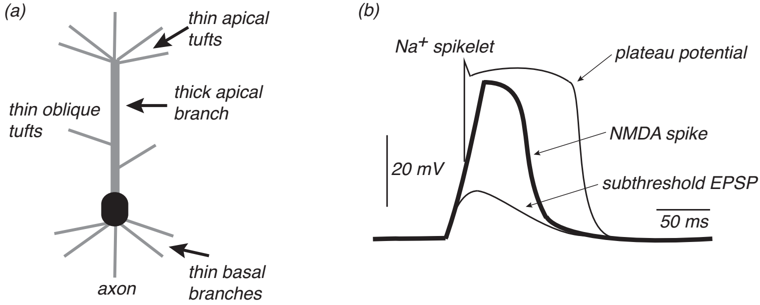
SUMMARY OF RESULTS

- Fluctuations in the slow recovery dynamics of K^+ channels significantly affect spontaneous activity in the ML model.
- The maximum likelihood trajectory during initiation of a SAP drops below the voltage nullcline so that w is not constant - breakdown of fast/slow analysis
- SAP initiation mechanisms is a burst of simultaneously-closing K^+ channels that causes v to increase.
- Constraining the paths by fixing w alters the effective energy barrier for SAP initiation, which significantly affects determination of the spontaneous firing rate.
- There is an effective metastable separatrix that can be used to formulate an FPT problem for an excitable system

Part IV. Dendritic NMDA spikes

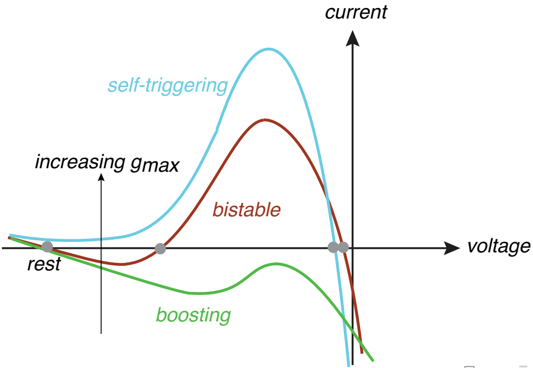
NMDA spikes in thin dendrites

- A pyramidal neuron has a thick apical dendrite and various thin dendrites. The latter support the initiation of dendritic NMDA spikes
- A strong glutamatergic input can trigger a dendritic plateau potential of duration 100 msec.
- The plateau potential consists of several dendritic conductances, the most predominant being due to NDMAR channels. Pharmacologically blocking *Na* and *Ca* channels reveals the pure dendritic NMDA spike



VOLTAGE CHARACTERISTICS OF DENDRITIC MEMBRANE

- Following strong stimulation and removal of the Mg^+ block, the maximum conductance $g_{\max}$ of the NMDARs is high so that the N-shaped I-V curve has only a stable depolarized fixed point.
- As $g_{\max}$ decreases due to glutamate unbinding, two additional fixed points arise via an SN bifurcation – bistability
- As $g_{\max}$ is further reduced, a second SN bifurcation results in a rapid return to the resting state.



DETERMINISTIC CONDUCTANCE-BASED MODEL

- The dendritic voltage v evolves as

$$C\frac{dv}{dt} = g_x(t)a_x(v)(V_x - v) + \bar{g}_y a_y(v)(V_y - v) + \bar{g}_L(V_L - v),$$

  where x, y label NMDA and Na channels, respectively, and C is the membrane capacitance.

- The glutamate-bound NMDA receptors act like sodium channels,with non-ohmic voltage-dependent conductances

$$a_r(v) = \frac{1}{1 + e^{-\gamma_r(v-\kappa_r)}}, \quad r = x, y.$$

  Here $a_r(v)$ represents the fraction of open ion channels of type r in the limit of fast channel kinetic

- The time-dependent deactivation of the NMDA channels following the binding of glutamate is incorporated by taking the maximal conductance of the NMDA receptors to be a slowly decaying function of time t:

$$g_x(t) = \bar{g}_x e^{-t/\tau},$$

STOCHASTIC MODEL

- Fix g_x and set $C = 1$. Have a stochastic hybrid system

$$\frac{dV}{dt} = I(V, n_x, n_Y) \equiv \bar{g}_x \frac{n_x(t)}{N}(V_x - V) + \bar{g}_y \frac{n_y(t)}{N}(V_y - V) + \bar{g}_L(V_L - V),$$

- Only holds between jumps in the discrete random variables n_x, n_y: birth-death processes

$$n_r \underset{\omega_+^r(n_r,V)/\epsilon}{\rightarrow} n_r + 1, \quad n_r \underset{\omega_-^r(n_r)/\epsilon}{\rightarrow} n_r - 1.$$

- The transition rates are

$$\omega_+^r(n_r, V) = \alpha_r(V)(N - n_r), \quad \omega_-^r(n_r) = \beta_r n_r,$$

  after rescaling α_j, β_j by a factor $1/\epsilon$.
- Introduce the associated probability density

$$p(v, n_x, n_y, t)dv = \mathbb{P}[v \le V(t) \le v + dv, n_x(t) = n_x, n_y(t) = n_y],$$

Stochastic model II

- The differential Chapman-Kolmogorov (CK) equation is

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial v}\left[I(v,n_x,n_y)p(v,n_x,n_y,t)\right] + \frac{1}{\epsilon}\mathbb{L}p(v,n_x,n_y,t),$$

where $\mathbb{L} = \mathbb{L}_x + \mathbb{L}_y$,

$$\mathbb{L}_r = (\mathbb{E}_r^{+} - 1)\omega_{-}^{r}(n_r) + (\mathbb{E}_r^{-} - 1)\omega_{+}^{r}(n_r, V).$$

and $\mathbb{E}_r^{\pm}$ are ladder operators defined according to

$$\mathbb{E}_r^{\pm}F(n_r) = F(n_r \pm 1)$$

STOCHASTIC MODEL III

- Can rewrite CK equation as

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial v}\left[I(v,\mathbf{n})p(v,\mathbf{n},t)\right] + \frac{1}{\epsilon}\sum_{\mathbf{m}} A(\mathbf{n},\mathbf{m};v)p(v,\mathbf{m}),$$

where $\mathbf{n} = (n_x, n_y)$ and the matrix A has the non–zero entries

$$\begin{aligned}
A(n_x,n_y,n_x-1,n_y;v) &= \omega_+^x(n_x-1,v),\\
A(n_x,n_y,n_x,n_y-1;v) &= \omega_+^y(n_y-1,v),\\
A(n_x,n_y,n_x+1,n_y;v) &= \omega_-^x(n_x+1),\\
A(n_x,n_y,n_x,n_y+1;v) &= \omega_-^y(n_y+1),\\
A(n_x,n_y,n_x,n_y;v) &= -\left[\omega_-^x(n_x)+\omega_-^y(n_y)+\omega_+^x(n_x,v)+\omega_+^y(n_y,v)\right].
\end{aligned}$$

- Note that $\sum_{\mathbf{m}} \equiv \sum_{m_x=0}^{N}\sum_{m_y=0}^{N}$.

STOCHASTIC MODEL IV

- The transition matrix satisfies

$$\sum_{\mathbf{n}} A(\mathbf{n},\mathbf{m};v) = 0, \quad \sum_{\mathbf{m}} A(\mathbf{n},\mathbf{m};v)\rho(v,\mathbf{m}) = 0.$$

- The steady-state density ρ is

$$\rho(v,n_x,n_y) = \prod_{r=x,y} \frac{N!}{(N-n_r)!n_r!} a_r(v)^{n_r} b_r(v)^{N-n_r}$$

$$a_r(v) = \frac{\alpha_r(v)}{\alpha_r(v)+\beta_r}, \; b_r(v) = \frac{\beta_r}{\alpha_r(v)+\beta_r}.$$

- In the deterministic limit $\epsilon \to 0$

$$\frac{dv}{dt} = F(v) = \frac{\bar{n}_x}{N} f_x(v) + \frac{\bar{n}_y}{N} f_y(v) - g(v) \equiv -\frac{d\Psi}{dv}.$$

  where $\bar{n}_r$ is the mean number of open channels,

$$\bar{n}_r = \sum_{n_x=1}^{N} \sum_{n_y=1}^{N} n_r \rho(v,n_x,n_y) = N a_r(v).$$

WKB APPROXIMATION

- Seek a WKB solution of the form

$$\varphi_\epsilon(v, \mathbf{n}) = R(v, \mathbf{n}) \exp\left(-\frac{\Phi(v)}{\epsilon}\right),$$

  where $\Phi(v)$ is the quasipotential.

- Substituting into the equation $\widehat{L}\phi_\epsilon = 0$, we have

$$\sum_{\mathbf{m}} \left(A(\mathbf{n}\, m; v) + \Phi'(v)\delta_{\mathbf{n},\mathbf{m}} I(v, \mathbf{m})\right) R(v, \mathbf{m}) = \epsilon \frac{dI(v, \mathbf{n})R(v, \mathbf{n})}{dv},$$

  where $\Phi' = d\Phi/dv$.

- Introducing the asymptotic expansions $R \sim R^{(0)} + \epsilon R^{(1)}$ and $\Phi \sim \Phi_0 + \epsilon\Phi_1$, the leading order equation is

$$\sum_{\mathbf{m}} A(\mathbf{n}, \mathbf{m}; v) R^{(0)}(v, \mathbf{m}) = -\Phi_0'(v) I(v, \mathbf{n}) R^{(0)}(v, \mathbf{n}).$$

Calculation of the quasipotential

- Try a normalized positive solution of the form

$$R^{(0)}(v,\mathbf{n}) = \frac{1}{[1+\Lambda_x(v)]^N}\frac{1}{[1+\Lambda_y(v)]^N}\frac{N![\Lambda_x(v)]^{n_x}}{(N-n_x)!n_x!}\cdot\frac{N![\Lambda_y(v)]^{n_y}}{(N-n_y)!n_y!},$$

  with $\sum_{n_x,n_y} R^{(0)}(v,\mathbf{n}) = 1$ for all v
- Substitute into zeroth order equation and collect terms independent of $\mathbf{n}$ and terms linear in n_x, n_y
- Three equations in three unknowns $\Lambda_x, \Lambda_y, \Phi_0$.
- Find that Λ_x satisfies a quadratic with

$$\Lambda_x^{\pm} = -\frac{b}{2a} \pm \frac{\sqrt{b^2-4ac}}{2a}, \quad \Lambda_y = \frac{\alpha_x+\alpha_y-\beta_x\Lambda_x}{\beta_y}$$

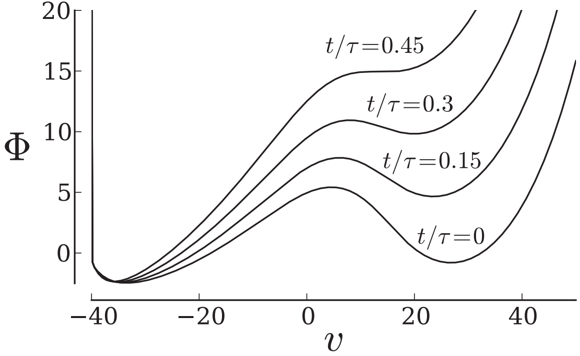
  with

$$\begin{aligned} a &= \beta_x(f_x+f_y), \quad c = -(\alpha_x+\alpha_y)f_y \\ b &= -(\alpha_x+\alpha_y)(f_x+f_y)+\beta_x f_y - f_x\beta_y \end{aligned}$$

- Only one root yields positive solution

Effect of glutamate unbinding on quasipotential

- MFPT for spike initiation calculated using similar methods to ML model
- Need to account for glutamate unbinding to determine mean duration of a spike
- Quasipotential is a function of slowly varying maximum NMDA conductance $g_x(t) = \bar{g}_x e^{-t/\tau}$
- Using an adiabatic approximation, we can take Φ to vary slowly with time t

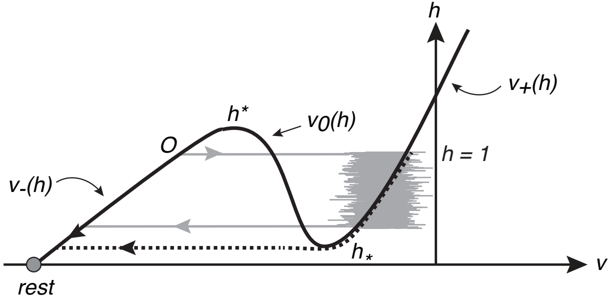


Stochastic phase-plane analysis

- With glutamate unbinding have a planar system

$$\frac{dv}{dt} = ha_x(v)(V_x - v)/\tau_x + a_y(v)(V_y - v)/\tau_y + (V_L - v)/\tau_L \equiv J(v,h),$$
$$\frac{dh}{dt} = -\frac{h}{\tau}, \quad h(0) = 1.$$

- Assume a separation of time-scales $\tau_j \ll \tau$ and use an adiabatic approximation.
- Let $\lambda_0(t)$ be the MFPT to jump from RH to LH branch given $h(t) = e^{-t/\tau}$.



Phase-plane analysis

- Let $P(s) = \mathbb{P}(T > s)$ where T is the random spike duration.
- The probability that a spike terminates in an infinitesimal time interval δs is $\lambda_0(s)\delta s$, so that

$$P(s + \delta s) = P(s)(1 - \lambda_0(s)\delta s).$$

- Taking $\delta s \to 0$ and integrating gives $P(s) = \exp\left(-\int_0^s \lambda_0(t)dt\right)$, and

$$p(s) = -\frac{dP}{ds} = \lambda_0(s)\exp\left(-\int_0^s \lambda_0(t)dt\right).$$