Breakdown of fast-slow analysis in an excitable system with channel noise\textsuperscript{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

- 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

$$C(\text{closed}) \xrightarrow{\alpha_X(v)} O(\text{open}).$$

- 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

$$\tau_X(v) \frac{dX}{dt} = a_X(v) - X,$$

where

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

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

\[
\frac{dv}{dt} = a(v)f_{Na}(v) + wf_K(v) - g(v)
\]

\[
\frac{dw}{dt} = \frac{w_\infty(v) - w}{\tau_w(v)}
\]

- Here \(f_i(v) = \tilde{g}_i(v_i - v)\) 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 $f(v) = g_{Na}(V_{Na} - v)$ and $g(v) = -g_{eff}[V_{eff} - v] + I_{ext}$.

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

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

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 $\beta, v_1, v_2$. 
Chapman-Kolmogorov Equation I

- Introduce the joint probability density

\[
\text{Prob}\{v(t) \in (v, v + dv), n(t) = n\} = p(v, n, t|v_0, n_0, 0)dv,
\]

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

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

- Introduced small parameter $\epsilon$ - 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

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

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

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

\[
\sum_{m} A(n, m; v)\rho(v, m) = 0
\]

where

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

![Graph showing bistable regime](image-url)
**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 operator \( \hat{L} \)

  \[
  \hat{L}\phi_r(v, n) \equiv \frac{d}{dv} (F(v, n)\phi_r(v, n)) - \frac{1}{\epsilon} \sum_{m} A(n, m; v) \phi_r(v, n)
  \]

  \[ = \lambda_r \phi_r(v, n), \]

  together with the boundary conditions

  \[ \phi_r(v_*, n) = 0, \text{ for } n \leq k \]
Spectral projection method II

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

  (i) $\hat{L}$ has a complete orthonormal set of eigenfunctions $\phi_r$

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

  (iii) $\lambda_0$ is exponentially small, $\lambda_0 \sim e^{-C/\epsilon}$, whereas $\text{Re}[\lambda_r] = \mathcal{O}(1)$ 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

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

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

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

- Hence

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

- 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

  \[ f(t) \sim \lambda_0 e^{-\lambda_0 t} \]

  and \( \langle T \rangle = \int_0^{\infty} tf(t) dt \sim 1/\lambda_0. \)
**Quasistationary density I**

- **Quasistationary density** $\phi_\epsilon$ approximates $\phi_0$ up to exponentially small terms at the boundary

  \[ \hat{L}\phi_\epsilon = 0, \quad \phi_\epsilon(v_*, n) = \mathcal{O}(e^{-C/\epsilon}). \]

- Express $\lambda_0$ in terms of the quasistationary density $\phi_\epsilon$ by considering the eigenfunctions of the adjoint operator

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

  and the boundary conditions

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

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

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

$$\langle \phi_\epsilon, \hat{L}^\dagger \xi_0 \rangle = \lambda_0 \langle \phi_\epsilon, \xi_0 \rangle.$$ 

Integration by parts then gives

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

Determine $\phi_\epsilon$ using the WKB method and $\xi_0$ 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
  \[ \sum_m (A(n, m; v) + \Phi'(v)\delta_{n,m}F(v, m)) R(v, m) = \epsilon \frac{dF(v, n)R(v, n)}{dv} \]

- Asymptotic expansions \( R \sim R^{(0)} + \epsilon R^{(1)} \) and \( \Phi \sim \Phi_0 + \epsilon \Phi_1 \)

- The leading order equation is
  \[ \sum_m A(n, m; v)R^{(0)}(v, m) = -\Phi'_0(v)F(v, n)R^{(0)}(v, n). \]
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:

$$
\sum_m \bar{A}(n, m; \nu) R^{(1)}(\nu, m) = \frac{dF(\nu, n)R^{(0)}(\nu, n)}{d\nu} - \Phi'_1(\nu)F(\nu, n)R^{(0)}(\nu, n)
$$

with

$$
\bar{A}(n, m; \nu) = (A(n, m; \nu) + \Phi'_0(\nu)\delta_{n,m}F(\nu, m))
$$

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

Fredholm Alternative Theorem yields solvability condition

\[ \sum_{n} S(v, n) \left[ \frac{dF(v, n) R^{(0)}(v, n)}{dv} - \Phi'_1(v) F(v, n) R^{(0)}(v, n) \right] = 0, \]

\[ \sum_{n} S(v, n) (A(n, m; v) + \Phi'_0(v) \delta_{n,m} F(v, m)) = 0. \]

Given \(R^{(0)}, S\) and \(\Phi_0\), the solvability condition yields the following equation for \(\Phi_1\):

\[ \Phi'_1(v) = \frac{\sum_{n} S(v, n) [F(v, n) R^{(0)}(v, n)]'}{\sum_{n} S(v, n) F(v, n) R^{(0)}(v, n)}. \]
WKB Method IV

- Define

\[ k(v) = \exp \left( - \int_{v_-}^{v} \Phi'_1(y) dy \right), \]

- To leading order in \( \epsilon \),

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

- Normalization

\[ \mathcal{N} = \left[ \int_{0}^{v^*} k(v) \exp \left( - \frac{\Phi_0(v)}{\epsilon} \right) dv \right]^{-1}. \]

- Laplace’s method gives

\[ \mathcal{N} \sim \frac{1}{k(v_-)} \sqrt{\frac{\left| \Phi''_0(v_-) \right|}{2\pi \epsilon}} \exp \left( \frac{\Phi_0(v_-)}{\epsilon} \right). \]
ADJOINT EIGENFUNCTION I

- Leading order adjoint equation

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

with boundary conditions

\[ \xi_0(\nu_*, n) = 0, \quad n > k. \]

- Boundary layer: set \( \nu = \nu_* - \epsilon z \) and \( Q(z, n) = \xi_0(u_* - \epsilon z) \):

\[ F(\nu_*, n) \frac{dQ(z, n)}{d \nu} + \sum_m A(m, n; \nu_*) Q(z, m) = 0 \]

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

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

\[ Q(z, n) = c_0 + c_1 \left( \hat{S}(v_*, n) - z \right) + \sum_{r \geq 2} c_r S_r(v_*, n) e^{-\mu_r(v_*)z} \]

\[ \sum_n A(n, m; v_*) \hat{S}(v_*, n) = -F(v_*, m). \]
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

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

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

\[ \lambda_0 \sim \frac{1}{\pi} \frac{k(v_*) B(v_*)}{k(v_-)} \sqrt{\Phi'_0(v_-) |\Phi''_0(v_*)|} \exp \left( -\frac{\Phi_0(v_*) - \Phi_0(v_-)}{\epsilon} \right). \]

\[ B(v_*) = -\sum_n \hat{S}(v_*, n) v(u_*, n) \rho(v_*, n) \]

\[ \sum_m A(n, m; v) R^{(0)}(v, m) = -\Phi'_0(v) F(v, n) R^{(0)}(v, n). \]

\[ \sum_n S(v, n) (A(n, m; v) + \Phi'_0(v) \delta_{n,m} F(v, m)) = 0. \]

\[ \sum_n A(n, m; v_*) \hat{S}(v_*, n) = -F(v_*, m). \]
CALCULATION OF PRINCIPAL EIGENVALUE

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 \( \hat{S}(v^*, n) \):

\[
\hat{S}(v^*, n) = \frac{f(v^*)}{N(\alpha(v^*) + \beta)} n.
\]

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 $\text{Na}^+$ channels and $m \leq M$ open $\text{K}^+$ channels:
  \[
  \frac{dv}{dt} = F(v, m, n) \equiv \frac{n}{N} f_{\text{Na}}(v) + \frac{m}{M} f_{\text{K}}(v) - g(v).
  \]
  - Each channel satisfies the kinetic scheme
    \[
    C \xleftarrow{\alpha_i(v)} \xrightarrow{\beta_i(v)} O, \quad i = \text{Na}, \text{K},
    \]
  - The $\text{Na}^+$ channels fast relative to voltage and $\text{K}^+$ dynamics.
  - Chapman–Kolmogorov (CK) equation,
    \[
    \frac{\partial p}{\partial t} = -\frac{\partial (Fp)}{\partial v} + \mathbb{L}_{\text{K}} p + \mathbb{L}_{\text{Na}} p.
    \]
  - The jump operators $\mathbb{L}_j$, $j = \text{Na}, \text{K}$, 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 $\beta_{Na}$
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 $\epsilon$ 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 $\epsilon$

- 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 $x_s$. 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,

\[ [\mathbb{L}_Na + p_v + h(v, w, p_w)] R(n|v, w) = 0, \]

where

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

and

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

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

yields a Hamilton-Jacobi equation for \( \Phi \):

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

- Solve for \( \Phi \) using method of characteristics. Satisfy Hamilton’s equations

\[ \dot{x} = \nabla_p \mathcal{H}(x, p), \quad \dot{p} = -\nabla_x \mathcal{H}(x, p). \]

for \( x = (v, w) \) and \( p = (p_v, p_w) \)

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

- $\Phi$ takes the shape of a potential well in a neighborhood of resting state with convex level curves.

- Once $\Phi$ 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 \(g_{\text{max}}\) of the NMDARs is high so that the N-shaped I-V curve has only a stable depolarized fixed point.

- As \(g_{\text{max}}\) decreases due to glutamate unbinding, two additional fixed points arise via an SN bifurcation – bistability.

- As \(g_{\text{max}}\) 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

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

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 $t$:

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

\[
\begin{align*}
    n_r &\xrightarrow{\omega^+_{r}(n_r,V)/\epsilon} n_r + 1, \quad n_r &\xrightarrow{\omega^-_{r}(n_r)/\epsilon} n_r - 1.
\end{align*}
\]

- The transition rates are

\[
\begin{align*}
    \omega^+_{r}(n_r, V) = \alpha_r(V)(N - n_r), \quad \omega^-_{r}(n_r) = \beta_r n_r,
\end{align*}
\]

after rescaling $\alpha_j, \beta_j$ by a factor $1/\epsilon$.

- Introduce the associated probability density

\[
p(v, n_x, n_y, t)dv = \mathbb{P}[v \leq V(t) \leq v + dv, n_x(t) = n_x, n_y(t) = n_y],
\]
**Stochastic model II**

- The differential Chapman-Kolmogorov (CK) equation is

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

where \( \mathbb{L} = \mathbb{L}_x + \mathbb{L}_y \),

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

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

\[
\frac{\partial p}{\partial t} = - \frac{\partial}{\partial v} [I(v, n)p(v, n, t)] + \frac{1}{\epsilon} \sum_m A(n, m; v)p(v, m),
\]

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

\[
A(n_x, n_y, n_x - 1, n_y; v) = \omega^x(n_x - 1, v),
\]

\[
A(n_x, n_y, n_x, n_y - 1; v) = \omega^y(n_y - 1, v),
\]

\[
A(n_x, n_y, n_x + 1, n_y; v) = \omega^x(n_x + 1),
\]

\[
A(n_x, n_y, n_x, n_y + 1; v) = \omega^y(n_y + 1),
\]

\[
A(n_x, n_y, n_x, n_y; v) = - [\omega^x(n_x) + \omega^y(n_y) + \omega^x(n_x, v) + \omega^y(n_y, v)].
\]

- Note that \( \sum_m \equiv \sum_{m_x=0}^N \sum_{m_y=0}^N \).
**STOCHASTIC MODEL IV**

- The transition matrix satisfies
  \[ \sum_n A(n, m; v) = 0, \quad \sum_m A(n, m; v) \rho(v, m) = 0. \]

- The steady-state density \( \rho \) is
  \[ \rho(v, n_x, n_y) = \prod_{r=x,y} \frac{N!}{(N - n_r)! n_r!} a_r(v)^{n_r} b_r(v)^{N-n_r} \]
  \[ a_r(v) = \frac{\alpha_r(v)}{\alpha_r(v) + \beta_r}, \quad b_r(v) = \frac{\beta_r}{\alpha_r(v) + \beta_r}. \]

- 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

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

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

Substituting into the equation $\hat{L}\varphi_\epsilon = 0$, we have

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

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

$$\sum_m A(n, m; v)R^{(0)}(v, m) = -\Phi_0'(v)I(v, n)R^{(0)}(v, n).$$
Calculation of the Quasipotential

- Try a normalized positive solution of the form

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

with \( \sum_{n_x, n_y} R^{(0)}(v, n) = 1 \) for all \( v \)

- Substitute into zeroth order equation and collect terms independent of \( n \) and terms linear in \( n_x, n_y \)

- Three equations in three unknowns \( \Lambda_x, \Lambda_y, \Phi_0 \).

- Find that \( \Lambda_x \) 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

\[ a = \beta_x (f_x + f_y), \quad c = -(\alpha_x + \alpha_y)f_y \]
\[ b = -(\alpha_x + \alpha_y)(f_x + f_y) + \beta_x f_y - f_x \beta_y \]

- 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 $\Phi$ to vary slowly with time $t$
STOCHASTIC PHASE-PLANE ANALYSIS

- With glutamate unbinding have a planar system

\[
\frac{dv}{dt} = hax(v)(Vx - v)/\tau_x + ay(v)(Vy - v)/\tau_y + (VL - v)/\tau_L \equiv J(v, h),
\]

\[
\frac{dh}{dt} = -\frac{h}{\tau}, \quad h(0) = 1.
\]

- 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 \( h(t) = e^{-t/\tau} \).

\[ v_{-}(h) \quad v_{0}(h) \quad v_{+}(h) \]

\[ h = 1 \quad h^* \quad v_0(h) \quad v_+(h) \]

\[ h_{*} \quad O \quad rest \]
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 \( \delta s \) 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

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