First passage time problems in stochastic hybrid systems

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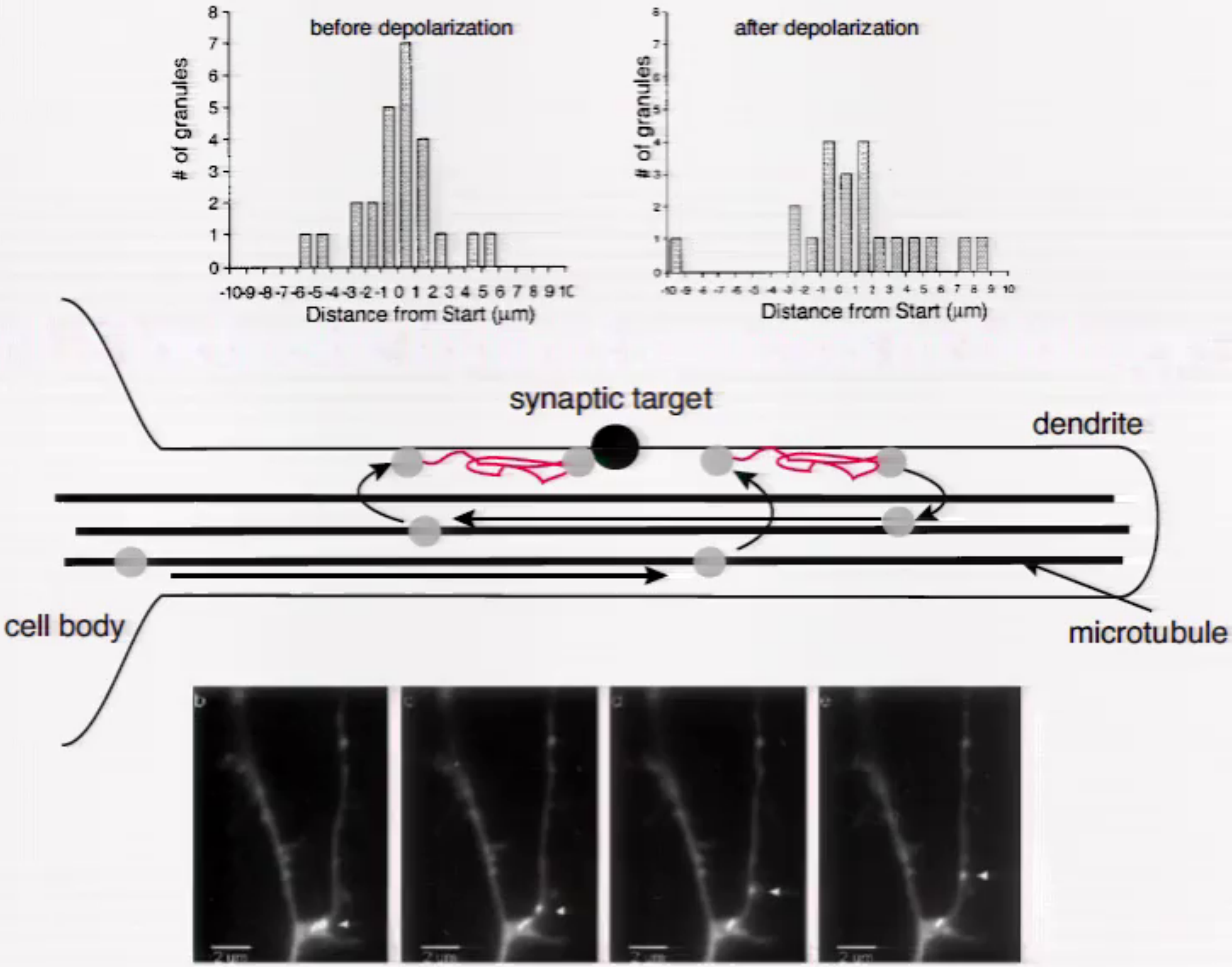
[A] Bidirectional motor-driven intracellular transport



Rook et al J. Neurosci. (2000)

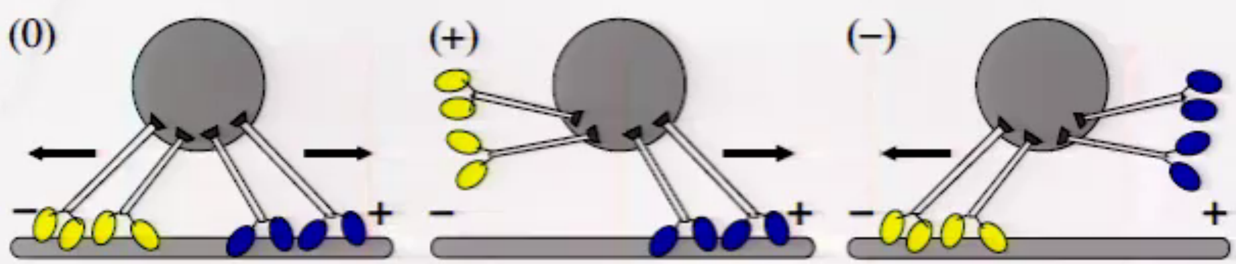
eg. mRNA transport along dendrites

[A] Tug-of-war model

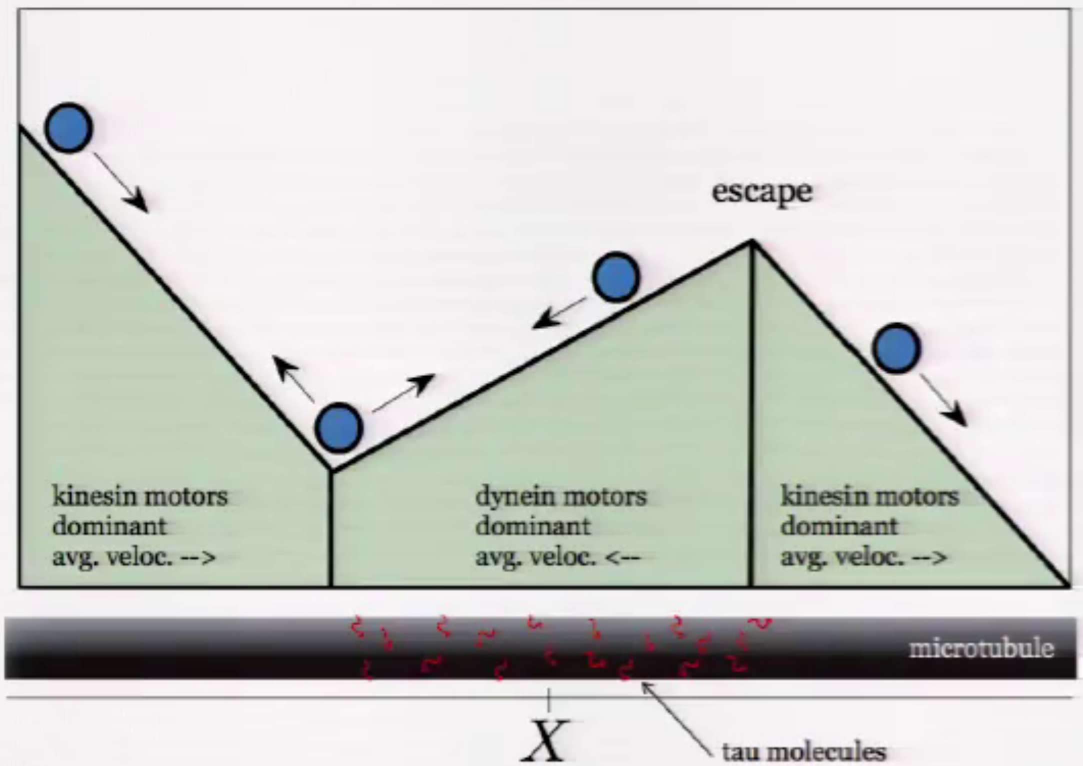
- Let $X(t)$ denote position of motor-cargo complex on MT track.
- Discrete state given by (n_+, n_-) where n_+ (n_-) is number of kinesin (dynein) motors bound to MT
- Let $v(n_+, n_-)$ be velocity of motor complex in state (n_+, n_-)
- Piecewise deterministic dynamics of motor complex is

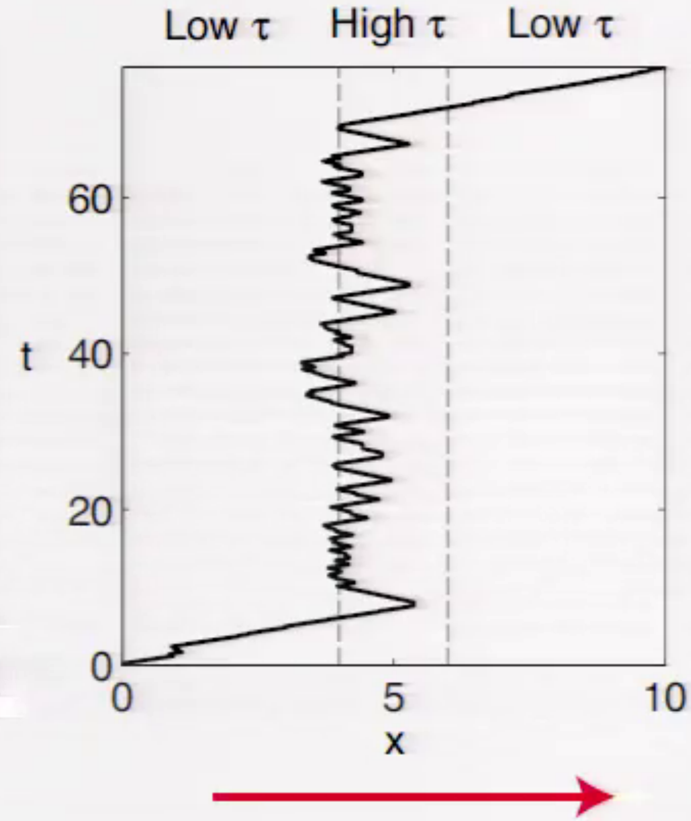
$$\frac{dX}{dt} = v(n_+, n_-)$$

- Transitions between different states described by a jump Markov process (Klumpp et al)



[A] LOCAL SIGNALING AND AN ESCAPE PROBLEM (NEWBY/PCB 2010)

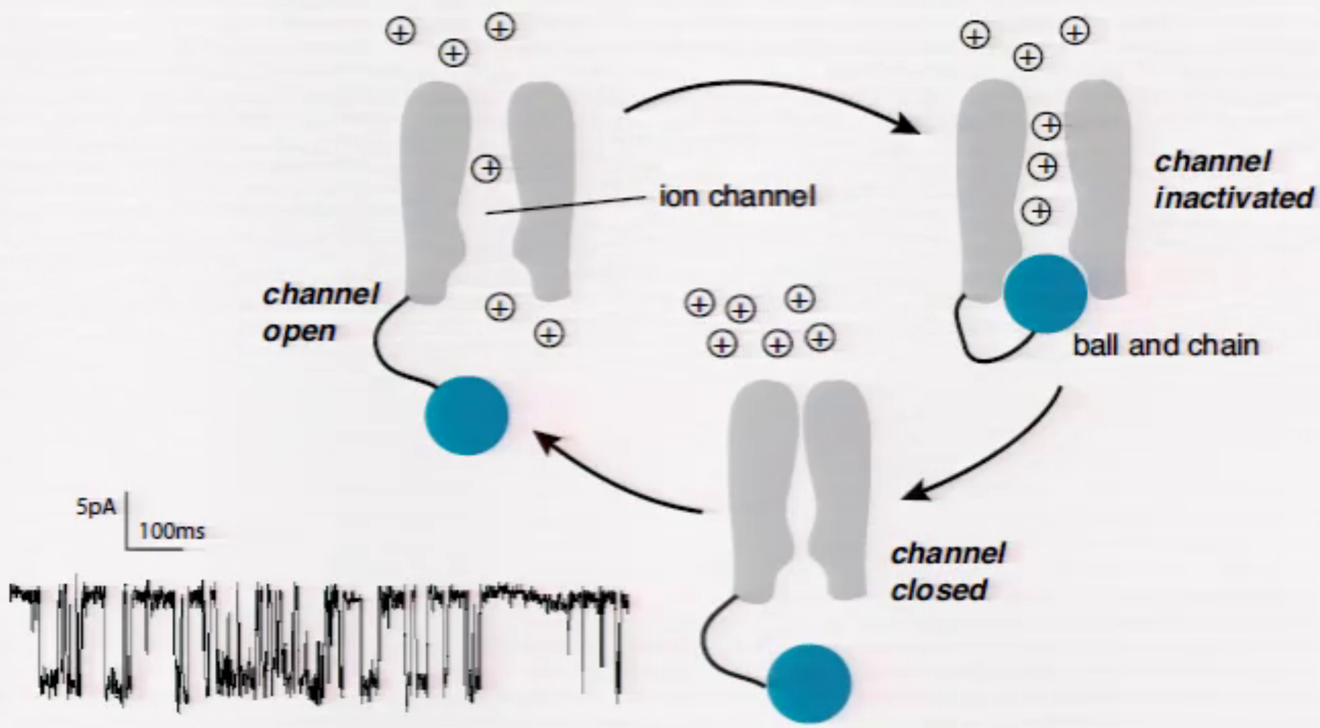




- MAPs (tau, MAP2) can bind to microtubules and reduce the binding rate of kinesin
- Provides a possible explanation for experimentally observed oscillatory motion of motor complexes
- Now have X-dependent velocities $v = v(n_+, n_-, X)$ and transition rates.

[B] Stochastic ion channels and voltage fluctuations

- Single ion channels fluctuate rapidly between open and closed states in a stochastic fashion.



[B] STOCHASTIC CONDUCTANCE-BASED MODEL (PCB/NEWBY/KEENER 2013)

- Suppose a neuron has $n \le N$ open Na^+ channels and $m \le M$ open K^+ channels
- Voltage $V(t)$ evolves according to piecewise deterministic dynamics

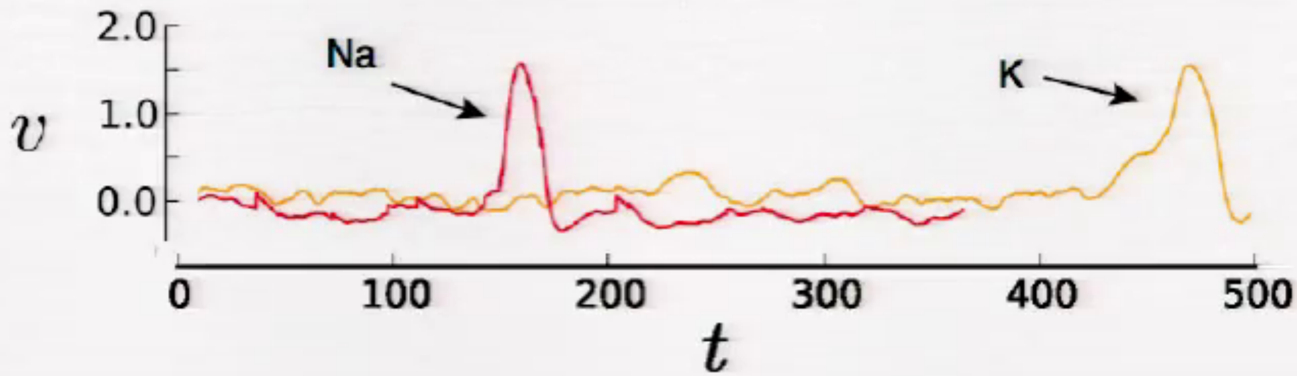
$$\frac{dv}{dt} = F(v, m, n) \equiv \frac{n}{N} f_{Na}(v) + \frac{m}{M} f_K(v) - g(v).$$

with $f_i(v) = \bar{g}_i(v_i - v)$

- Assume each channel satisfies the simple kinetic scheme

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

- Ion channel fluctuations can induce spontaneous action potentials.



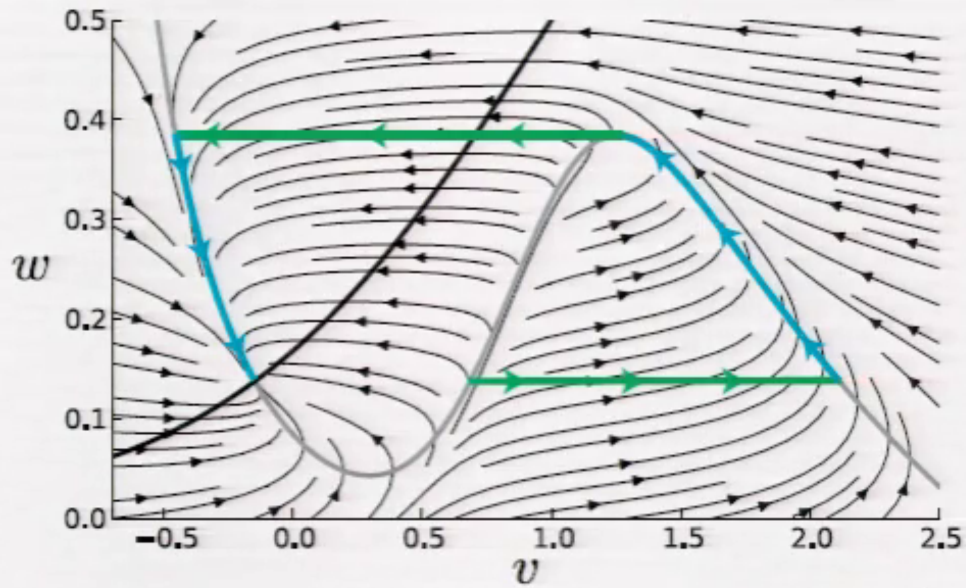
[B] MORRIS-LECAR MODEL OF NEURAL EXCITABILITY

- In the limit of fast Na^+ channels and infinite K^+ channels ($M \to \infty$) we obtain the deterministic Morris-Lecar (ML) model

$$\frac{dv}{dt} = \frac{\alpha_{Na}(v)}{\alpha_{Na}(v) + \beta_{Na}(v)} f_{Na}(v) + w f_K(v) - g(v)$$

$$\frac{dw}{dt} = \alpha_K(v)(1 - w) - \beta_K(v) w,$$

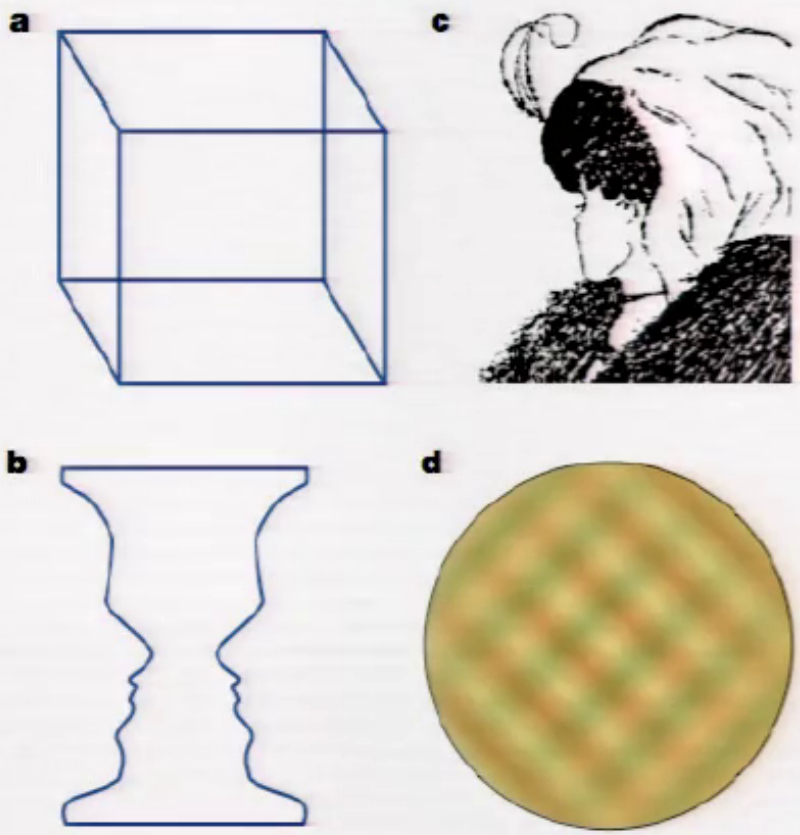
- Examine excitability using slow/fast analysis
- Require large perturbations (rare events) to induce an action potential

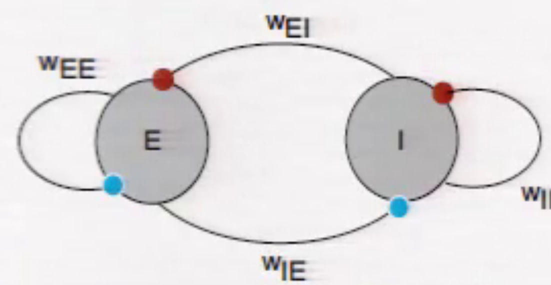


[C] GENETIC SWITCHES/BISTABLE NEURAL NETWORKS

continuous variable
= promoter protein concentration

discrete variable
= state of promoter

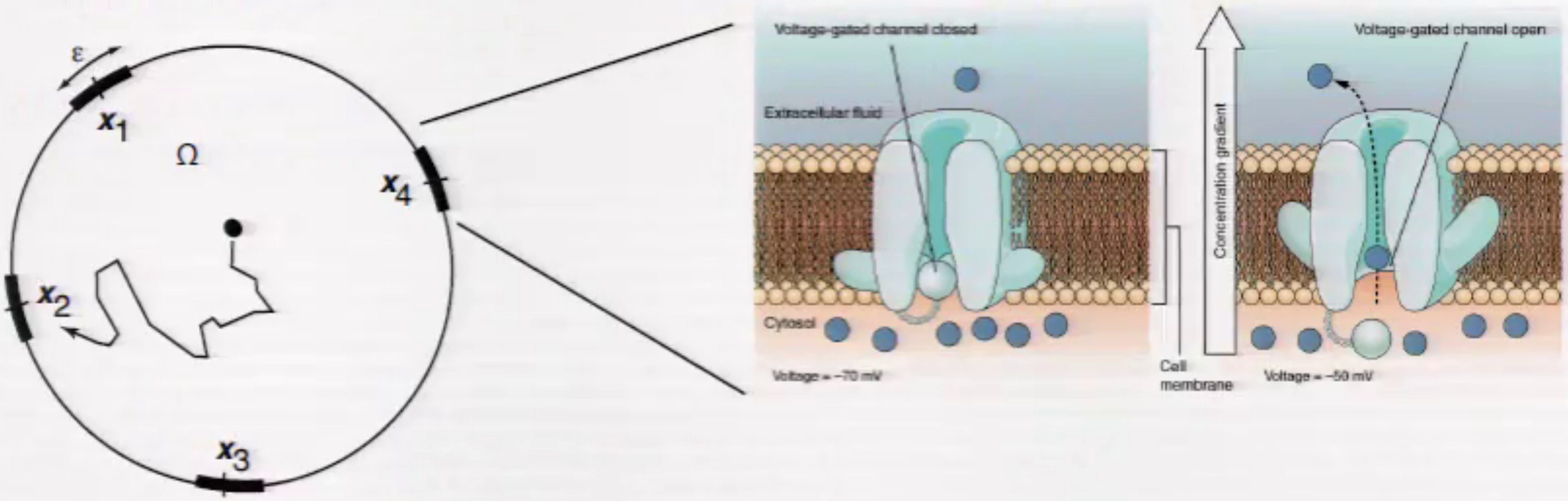




continuous variables
= synaptic currents in
each population

discrete variables
= number of spiking neurons
in each population

[D] ESCAPE FROM SUBCELLULAR DOMAINS WITH SWITCHING BOUNDARIES



- Diffusion of molecules within a subcellular domain Ω with stochastic channels in the membrane $\partial\Omega$
- Consider N narrow gates $\partial\Omega_k^\varepsilon$, $k \in \{1, \ldots, N\}$, with the kth gate given by the $\varepsilon > 0$ neighborhood of $\mathbf{x}_k \in \partial\Omega$ defined according to

$$\partial\Omega_k^\varepsilon := \{\mathbf{x} \in \partial\Omega : |\mathbf{x} - \mathbf{x}_k| < \varepsilon\}.$$

- Let $\mathbf{n}(t) \in \{0, 1\}^N$ be an irreducible Markov process whose k-th component, $n_k(t) \in \{0, 1\}$, controls the state of the k-th gate.

Part II. Analysis of first passage time problems

1D STOCHASTIC HYBRID SYSTEM

- Consider the 1D system

$$\frac{dx}{dt} = \frac{1}{\tau_x}F_n(x), \quad x \in \mathbb{R}, \quad n = 1, \ldots, K$$

- Jump Markov process $m \to n$ with transition rates $W_{nm}(x)/\tau_n$.
- Set $\tau_x = 1$ and introduce the small parameter $\epsilon = \tau_n/\tau_x$
- Chapman-Kolmogorov (CK) equation for $p_n(x,t) = \mathbb{E}[p(x,t)1_{n(t)=n}]$ is

$$\frac{\partial p_n}{\partial t} = -\frac{\partial [F_n(x)p_n(x,t)]}{\partial x} + \frac{1}{\epsilon}\sum_{m=1}^{K} A_{nm}(x)p_m(x,t)$$

where

$$A_{nm}(x) = W_{nm}(x) - \sum_{k=1}^{K} W_{kn}(x)\delta_{m,n}.$$

- Assume that there exists a unique stationary density $\rho_n(x)$ with

$$\sum_m A_{nm}(x)\rho_m(x) = 0$$

QUASI-STEADY-STATE APPROXIMATION (PCB/NEWBY)

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

$$\frac{dx}{dt} = \mathcal{F}(x) \equiv \sum_{n=1}^{K} F_n(x)\rho_n(x),$$

- Decompose the probability density as

$$p(x,n,t) = C(x,t)\rho_n(x) + \epsilon w_n(x,t),$$

where $\sum_n p_n(x,t) = C(x,t)$ and $\sum_n w_n(x,t) = 0$.

- Asymptotic expansion in ϵ yields FP equation

$$\frac{\partial C}{\partial t} = -\frac{\partial}{\partial x}(\mathcal{F}C) + \epsilon \frac{\partial}{\partial x}\left(\mathcal{D}\frac{\partial C}{\partial x}\right),$$

- Drift term given by mean-field equation, and diffusion coefficient

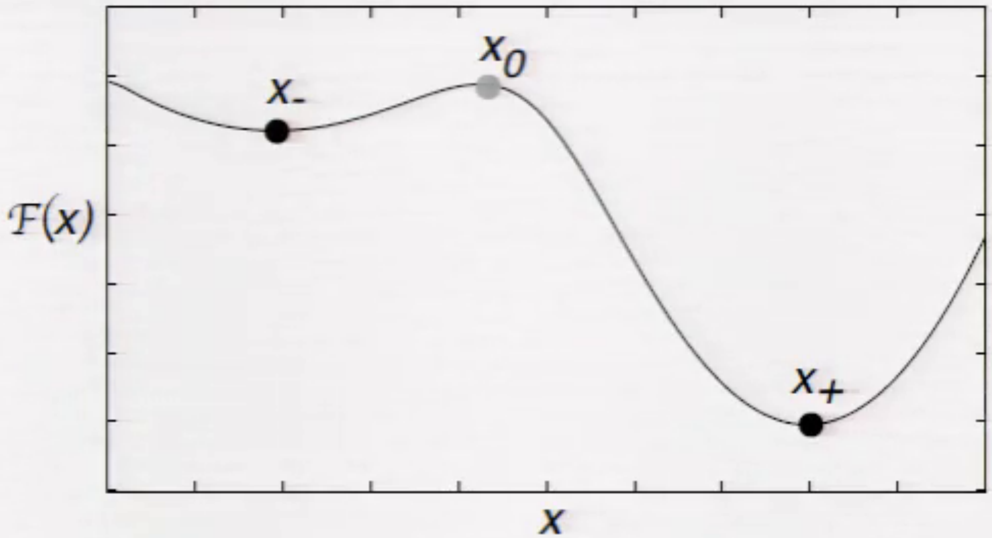
$$\mathcal{D}(x) = \sum_n Z_n(x)F_n(x),$$

where

$$\sum_m A_{nm}(x)Z_m(x) = -[\mathcal{F}(x) - F_n(x)]\rho_n(x)$$

First-passage time (FTP) problem I

- Suppose that mean field equation is bistable



- Let $T(x)$ be the stochastic time for the particle to exit at x_0 starting at x
- Introduce the survival probability $\mathbb{P}(x,t)$ that the particle has not yet exited at time t:

$$\mathbb{P}(x,t) = \int_0^{x_0} \sum_n p_n(x',t|x,0)dx'.$$

and define the first passage time (FPT) density

$$f(x,t) = -\frac{\partial \mathbb{P}(x,t)}{\partial t}.$$

First-passage time (FTP) problem II

- The mean first passage time (MFPT) $\tau(x)$ is

$$\tau(x) = \langle T(x) \rangle \equiv \int_0^\infty f(x,t) t dt = \int_0^\infty \mathbb{P}(x,t) dt,$$

- In limit $\epsilon \to 0$, expect MFPT to have the Arrhenius-like form

$$\tau(x_-) = \frac{2\pi\Gamma(x_0, x_-)}{\sqrt{|\Phi''(x_0)|\Phi''(x_-)}} e^{[\Phi(x_0) - \Phi(x_-)]/\epsilon}.$$

  where $\Phi(x)$ is a **quasipotential** and Γ is a prefactor.
- QSS approximation yields the approximate quasipotential

$$\Phi_{QSS}(x) \equiv -\int^x \frac{\mathcal{F}(x')}{\mathcal{D}(x')} dx'$$

  $\Longrightarrow$ may generate exponentially large errors in MFPT
- FP equation is 2nd-order, whereas CK equation is K-th order $\Longrightarrow$ QSS can breakdown at boundaries

Path-integral representation (PCB/Newby 2014)

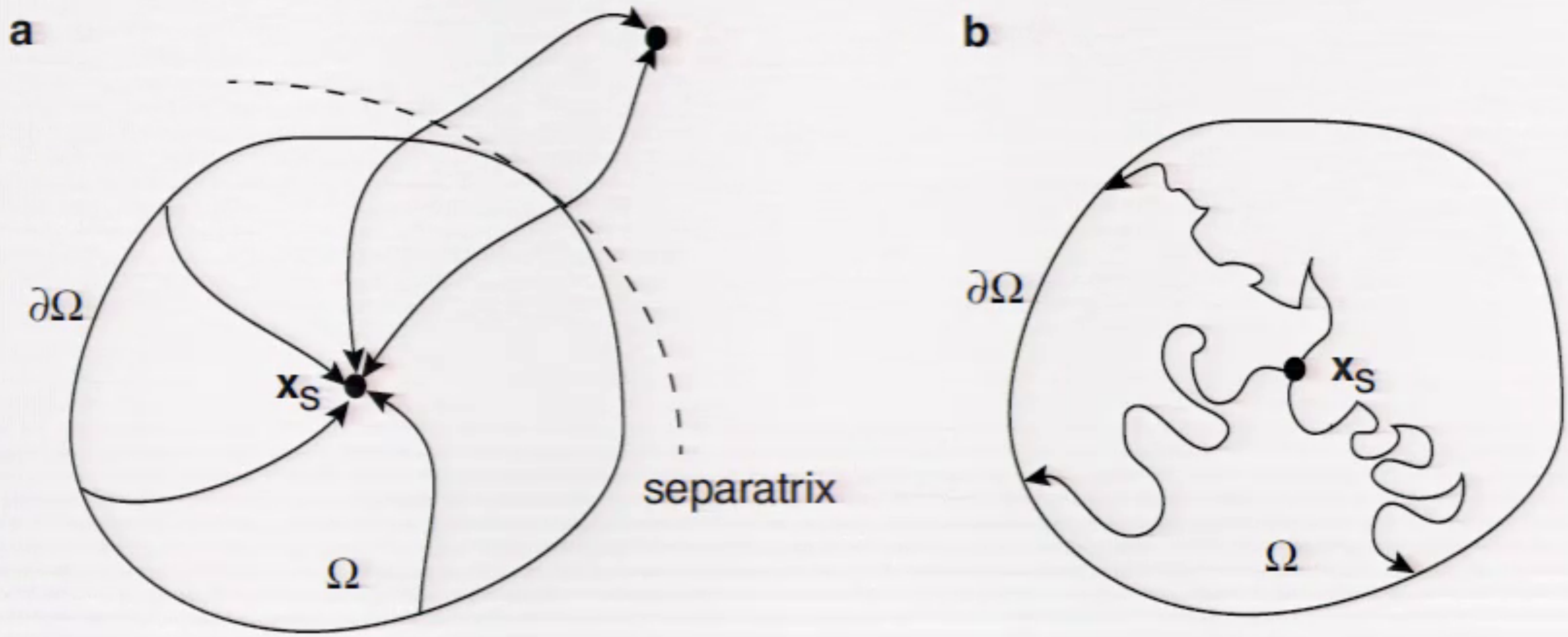
- Determine $\Phi(x)$ using large deviation theory/path integrals/WKB
- Consider the eigenvalue equation

$$\sum_m [A_{nm}(x) + q\delta_{n,m}F_m(x)]\, R_m^{(s)}(x,q) = \lambda_s(x,q) R_n^{(s)}(x,q),$$

  and let $\xi_m^{(s)}$ be the adjoint eigenvector.
- Perron-Frobenius theorem shows that there exists a real, simple Perron eigenvalue labeled by $s=0$, say, such that $\lambda_0 > \mathrm{Re}(\lambda_s)$ for all $s > 0$
- Path-integral representation of PDF

$$P(x,\tau) = \int_{x(0)=x_*}^{x(\tau)=x} \exp\left(-\frac{1}{\epsilon}\int_0^\tau [p\dot{x} - \lambda_0(x,p)]dt\right) \mathcal{D}[p]\mathcal{D}[x]$$

"ZERO ENERGY" 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

MEAN-FIELD EQUATIONS

- We have the trivial solution $p = 0$ and $R_m^{(0)}(x, 0) = \rho_m(x)$ with

$$\sum_m A_{nm}(x)\rho_m(x) = 0$$

- Differentiating the eigenvalue equation with respect to p and then setting $p = 0$, $\lambda_0 = 0$ shows that

$$\left.\frac{\partial \lambda_0(x,p)}{\partial p}\right|_{p=0} \rho_n(x) = F_n(x)\rho_n(x) + \sum_m A_{nm}(x) \left.\frac{\partial R_m^{(0)}(x,p)}{\partial p}\right|_{p=0}$$

- Summing both sides wrt n and using $\sum_n A_{nm} = 0$,

$$\left.\frac{\partial \lambda_0(x)}{\partial p}\right|_{p=0} = \sum_n F_n(x)\rho_n(x)$$

- Hamilton's equation $\dot{x} = \partial \lambda_0(x,p)/\partial p$ recovers mean-field equation

$$\dot{x} = \sum_n F_n(x)\rho_n(x).$$

Maximum-likelihood paths of escape

- Unique non-trivial solution $p = \mu(x)$ with positive eigenvector $R_m^{(0)}(x, \mu(x)) = \psi_m(x)$:

$$\sum_m [A_{nm}(x) + \mu(x)\delta_{n,m}F_m(x)]\, \psi_m(x) = 0$$

- Yields quasipotential $\Phi(x)$ with $\Phi'(x) = \mu(x)$ and

$$S[x,p] \equiv \int_{-\infty}^{\tau} [p\dot{x} - \lambda_0(x,p)]\, dt = \int_{x_s}^{x} \Phi'(x) dx.$$

- Equivalent to WKB quasipotential obtained using ansatz for quasistationary solutions

$$p_n(x) = R_n(x) \exp\left(-\frac{1}{\epsilon}\Phi(x)\right),$$

Part III. Stochastic ion-channels revisited

Reduced Morris-Lecar model

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

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

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

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

$$n \to n \pm 1,$$

with rates

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

- Take

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

for constants β, v_1, v_2.

Chapman-Kolmogorov equation

- CK equation is

$$\frac{\partial p_n}{\partial t} = -\frac{\partial [F_n(v) p_n(v,t)]}{\partial v} + \frac{1}{\epsilon} \sum_{n'} A_{nm}(v) p_m(v,t),$$

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

- There exists a unique steady state density $\rho_n(v)$ for which

$$\sum_m A_{nm}(v) \rho_m(v) = 0$$

where

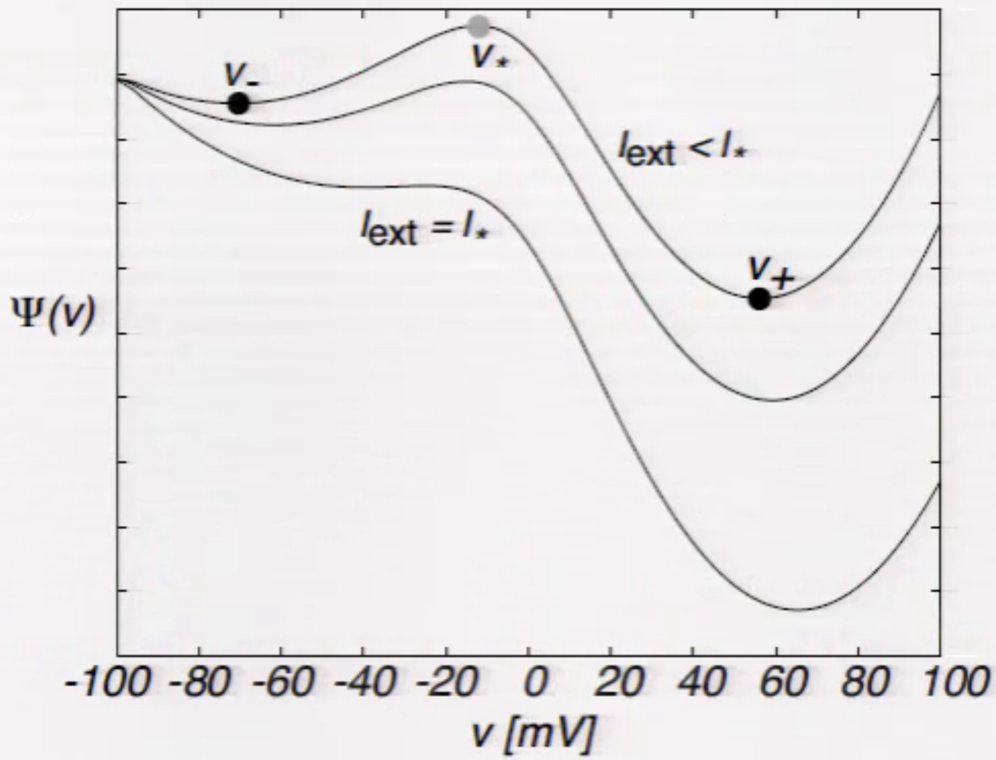
$$\rho_n(v) = \frac{N!}{(N-n)!n!} a(v)^n b(v)^{N-n}, \quad a(v) = \frac{\alpha(v)}{\alpha(v)+\beta},\ b(v) = 1 - a(v).$$

MEAN-FIELD LIMIT

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

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

- Assume deterministic system operates in a bistable regime



Perron eigenvalue I

- Eigenvalue equation for λ_0 and $R^{(0)} = \psi$:

$$(N-n+1)\alpha\psi_{n-1} - [\lambda_0 + n\beta + (N-n)\alpha]\psi_n + (n+1)\beta\psi_{n+1} = -p\left(\frac{n}{N}f - g\right)\psi_n$$

- Consider the trial solution

$$\psi_n(x,p) = \frac{\Lambda(x,p)^n}{(N-n)!n!},$$

- Yields the following equation relating Λ and μ:

$$\frac{n\alpha}{\Lambda} + \Lambda\beta(N-n) - \lambda_0 - n\beta - (N-n)\alpha = -p\left(\frac{n}{N}f - g\right).$$

- Collecting terms independent of n and terms linear in n yields

$$p = -\frac{N}{f(x)}\left(\frac{1}{\Lambda(x,p)} + 1\right)(\alpha(x) - \beta(x)\Lambda(x,p)),$$

and

$$\lambda_0(x,p) = -N(\alpha(x) - \Lambda(x,p)\beta(x)) - pg(x).$$

THE QUASIPOTENTIAL

- Non-trivial solution ryields

$$p = \mu(x) \equiv N \frac{\alpha(x) f(x) - (\alpha(x) + \beta) g(x)}{g(x)(f(x) - g(x))}.$$

- The corresponding quasipotential Φ is given by

$$\Phi(x) = \int^x \mu(y) dy.$$

- Analogous result in full ML model

Stochastic Morris-Lecar model

- Take $n \le N$ open Na^+ channels and $m \le M$ 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

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

- 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 $\mathbb{L}_j$, $j = \text{Na, K}$, are defined according to

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

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

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

WKB APPROXIMATION

- Introduce quasistationary solution of the form

$$\varphi(v,w,n) = R_n(v,w)\exp\left(-\frac{1}{\epsilon}\Phi(v,w)\right),$$

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

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