Path-integrals and large deviations in stochastic hybrid systems

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Part I. Path-integral representation of an SDE

Langevin equation with weak noise

- Consider the scalar SDE

$$dX(t) = A(X)dt + \sqrt{\epsilon}dW(t),$$

for $0 \leq t \leq T$ and initial condition $X(0) = x_0$. Here $W(t)$ is a Wiener process and the noise is taken to be weak ($\epsilon \ll 1$).

- Discretizing time by dividing the interval $[0, T]$ into N equal subintervals of size Δt such that $T = N\Delta t$ and setting $X_n = X(n\Delta t)$, we have

$$X_{n+1} - X_n = A(X_n)\Delta t + \sqrt{\epsilon}\Delta W_n,$$

with $n = 0, 1, \ldots, N-1$, $\Delta W_n = W((n+1)\Delta t) - W(n\Delta t)$

$$\langle \Delta W_n \rangle = 0, \quad \langle \Delta W_m \Delta W_n \rangle = \Delta t \delta_{m,n}.$$

- Let **X** and **W** denote the vectors with components X_n and W_n respectively.

Conditional probability density

- Conditional probability density function for $\mathbf{X} = \mathbf{x}$ given a particular realization $\mathbf{w}$ of the stochastic process $\mathbf{W}$ (and initial condition x_0) is

$$P(\mathbf{x}|\mathbf{w}) \quad = \prod_{n=0}^{N-1} \delta\left(x_{n+1} - x_n - A(x_n)\Delta t - \sqrt{\epsilon}\Delta w_n\right).$$

- Inserting the Fourier representation of the Dirac delta function,

$$\delta(x_{m+1} - z_m) = \frac{1}{2\pi}\int_{-\infty}^{\infty} \mathrm{e}^{-i\tilde{x}_m(x_{m+1}-z_m)}\, d\tilde{x}_m,$$

gives

$$P(\mathbf{x}|\mathbf{w}) = \prod_{m=0}^{N-1}\left[\int_{-\infty}^{\infty} \mathrm{e}^{-ip_m\left(x_{m+1} - x_m - A(x_m)\Delta t - \sqrt{\epsilon}\Delta w_m\right)} \frac{dp_m}{2\pi}\right].$$

- The Gaussian random variable ΔW_n has the probability density function

$$P(\Delta w_n) = \frac{1}{\sqrt{2\pi\Delta t}}\mathrm{e}^{-\Delta w_n^2/2\Delta t}.$$

JOINT PROBABILITY DENSITY

- Setting

$$P(\mathbf{x}) = \int P[\mathbf{x}|\mathbf{w}] \prod_{n=0}^{N-1} P(\Delta w_n) d\Delta w_n$$

and performing the integration with respect to Δw_n by completing the square, we obtain the result

$$P(\mathbf{x}) = \prod_{m=0}^{N-1} \left[\int_{-\infty}^{\infty} \mathrm{e}^{-ip_m\left(x_{m+1}-x_m-A(x_m)\Delta t\right)} \mathrm{e}^{-\epsilon p_m^2 \Delta t/2} \frac{dp_m}{2\pi} \right].$$

- Performing the Gaussian integration with respect to p_m, we have

$$\begin{aligned} P(\mathbf{x}) &= \prod_{m=0}^{N-1} \frac{1}{\sqrt{2\pi\epsilon\Delta t}} \mathrm{e}^{-\left(x_{m+1}-x_m-A(x_m)\Delta t\right)^2/(2\epsilon\Delta t)} \\ &= \mathcal{N} \exp\left[-\frac{1}{2\epsilon} \sum_{m=0}^{N-1} \left(\frac{x_{m+1}-x_m}{\Delta t} - A(x_m) \right)^2 \Delta t \right], \end{aligned}$$

with $\mathcal{N} = \frac{1}{(2\pi\epsilon\Delta t)^{N/2}}$.

ONSAGER-MACHLUP PATH INTEGRAL

- Define expectations according to

$$\mathbb{E}[F(\mathbf{X})] = \int F(\mathbf{x})P(\mathbf{x})dx_1 \dots x_N$$

  for any integrable function F.

- Take the continuum limit $\Delta t \to 0, N \to \infty$ with $N\Delta t = T$ fixed. Now $P[x]$ is a probability density *functional* over the different paths $\{x(t)\}_0^T$ realized by the original SDE with $X(0) = x_0$:

$$\boxed{P[x] \sim \exp\left[-\frac{1}{2\epsilon}\int_0^T (\dot{x} - A(x))^2 dt\right],}$$

- The expectation of a functional $F[x]$ is given by the Onsager-Machlup path integral

$$\mathbb{E}[F[x]] = \int F[x]P[x]\mathcal{D}(x),$$

  where $\mathcal{D}[x]$ is an appropriate measure.

VARIATIONAL PRINCIPLE

- The conditional probability density that the stochastic process $X(t)$ reaches a point x at time $t = \tau$ given that it started at x_0 at time $t = 0$ is

$$P(x, \tau | x_0) = \int_{x(0)=x_0}^{x(\tau)=x} \exp\left[-\frac{1}{2\epsilon}\int_0^\tau (\dot{x} - A(x))^2 dt\right] \mathcal{D}[x].$$

- In the limit $\epsilon \to 0$, we can use the method of steepest descents to obtain the approximation

$$P(x, \tau | x_0) \sim \exp\left[-\frac{\Phi(x, \tau | x_0)}{\epsilon}\right],$$

where Φ is the quasipotential

$$\Phi(x, \tau | x_0) = \inf_{x(0)=x_0, x(\tau)=x} S[x],$$

with

$$S[x] = \int_0^\tau L(x, \dot{x}) dt, \quad L(x, \dot{x}) = \frac{1}{2}(\dot{x} - A(x))^2$$

VARIATIONAL PRINCIPLE II

- Variational problem that minimizes the functional $S[x]$ over trajectories from $\{x(t)\}_0^\tau$ with $x(0) = x_0$ and $x(\tau) = x$ (most probable path)
- We can identify $S[x]$ as a "classical action" with corresponding Lagrangian $L(x, \dot{x})$
- Most probable path is given by the solution to the Euler-Lagrange equation

$$\frac{d}{dt}\frac{\partial L}{\partial \dot{x}} = \frac{\partial L}{\partial x}.$$

- Substituting for L yields

$$\ddot{x} = A(x)A'(x)$$

that is,

$$\dot{x}(t)^2 = A(x(t))^2 + \text{constant}$$

Steady-state density

- Suppose that in the zero noise limit there is a globally attracting fixed point x_s such that $A(x_s) = 0$.
- Approximation of steady-state density can be obtained by solving the Euler-Lagrange equation with $x(-\infty) = x_s$ and $x(\tau) = x$. This yields $\dot{x} = -A(x)$.
- The quasipotential is

$$\Phi(x, \tau) = -2 \int_{-\infty}^{\tau} A(x)\dot{x}dt = 2 \int_{-\infty}^{\tau} U'(x)\dot{x}dt = 2 \int_{x_s}^{x} U'(x)dx = 2U(x).$$

- Hence, we obtain the expected result that the stationary density is

$$P(x) \sim \mathrm{e}^{-2U(x)/\epsilon}.$$

MULTI-VARIATE PATH-INTEGRAL

- Consider the multivariate SDE

$$dX_i(t) = A_i(\mathbf{X})dt + \sqrt{\epsilon}\sum_j b_{ij}(\mathbf{X})dW_i(t),$$

for $i = 1, \ldots, d$ with $W_i(t)$ a set of independent Wiener processes.

- Generalizing the path integral method to higher dimensions, one obtains the action functional

$$\boxed{S[\mathbf{x}] = \frac{1}{2}\int_0^T \sum_{i,j=1}^{d} (\dot{x}_i(t) - A_i(\mathbf{x}(t)))D_{ij}^{-1}(\dot{x}_j(t) - A_j(\mathbf{x}(t)))dt,}$$

where $\mathbf{D} = \mathbf{b}\mathbf{b}^{\text{tr}}$ is the diffusion matrix.

Fokker-Planck equation

- Consider the FP equation corresponding to the scalar SDE:

$$\boxed{\frac{\partial p}{\partial t} = -\frac{\partial[A(x)p(x,t)]}{\partial x} + \frac{\epsilon}{2}\frac{\partial^2 p(x,t)}{\partial x^2} \equiv -\frac{\partial J(x,t)}{\partial x},}$$

where

$$J(x,t) = -\frac{\epsilon}{2}\frac{\partial p(x,t)}{\partial x} + A(x)p(x,t).$$

- Suppose that the deterministic equation $\dot{x} = A(x)$ has a stable fixed point at x_-, $A(x_-) = 0$, with $0 < x_- < x_0$.
- Impose an absorbing boundary condition at x_0 and a reflecting boundary condition at $x = 0$:

$$p(x_0, t) = 0, \quad J(0, t) = 0$$

WKB approximation

- We seek a quasistationary solution of the WKB form

$$\phi^{\epsilon}(x) \sim K(x;\epsilon)\mathrm{e}^{-\Phi(x)/\epsilon},$$

with $K(x;\epsilon) \sim \sum_{m=0}^{\infty} \epsilon^m K_m(x)$.
- Substitute into the stationary FP equation and Taylor expand with respect to ϵ.
- Lowest order equation is

$$\boxed{\frac{1}{2}\left(\frac{\partial\Phi(x)}{\partial x}\right)^2 + A(x)\frac{\partial\Phi(x)}{\partial x} = 0.}$$

- Similarly, collecting $O(\epsilon)$ terms yields the following equation for the leading contribution K_0 to the pre factor:

$$\left[\frac{\partial\Phi}{\partial x} + A(x)\right]\frac{\partial K_0}{\partial x} = -\left[A'(x) + \frac{1}{2}\frac{\partial^2\Phi(x)}{\partial x^2}\right]K_0(x).$$

Hamilton-Jacobi equation

- Introducing the time-independent "Hamiltonian"

$$H(x,p) = \frac{p^2}{2} + A(x)p,$$

  we can rewrite lowest order equation as

$$H(x, \Phi'(x)) = 0.$$

- Hamiltonian H describes a "particle" with position x and conjugate momentum p evolving according to Hamilton's equations

$$\dot{x} = \frac{\partial H}{\partial p} = p + A(x), \quad \dot{p} = -\frac{\partial H}{\partial x} = -pA'(x).$$

- Performing the Legendre transformation

$$H(x,p) = p\dot{x} - L(x,\dot{x}), \quad p = \frac{\partial L}{\partial \dot{x}}$$

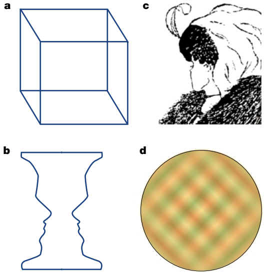
  we recover Lagrangian of Onsager-Machlup path integral:

$$L(x,\dot{x}) = \frac{1}{2}(\dot{x} - A(x))^2$$

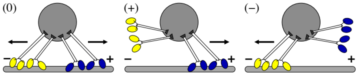
Part II. Path-integral representation of a stochastic hybrid system

Examples of stochastic hybrid systems

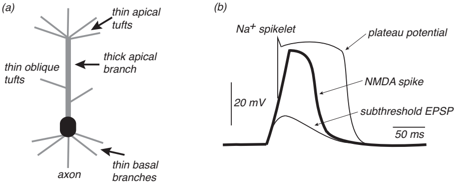
Stochastic neural populations (PCB/Newby 2013)



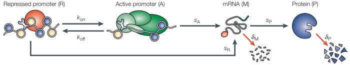
Motor-driven intracellular transport (PCB/Newby 2011),



Dendritic NMDA spikes (PCB/Newby 2014)



gene networks (Newby 2012)



1D STOCHASTIC HYBRID SYSTEM

- Consider the 1D system

$$\frac{dx}{dt} = \frac{1}{\tau_x} F_n(x), \quad x \in \mathbb{R}, \quad n = 0, \ldots, K-1$$

- Jump Markov process $n' \to n$ with transition rates $W_{nn'}(x)/\tau_n$.
- Set $\tau_x = 1$ and introduce the small parameter $\epsilon = \tau_n/\tau_x$
- CK equation is

$$\boxed{\frac{\partial p}{\partial t} = -\frac{\partial [F_n(x) p_n(x,t)]}{\partial x} + \frac{1}{\epsilon} \sum_{n'=0}^{K-1} A_{nn'}(x) p_{n'}(x,t)}$$

where

$$A_{nn'}(x) = W_{nn'}(x) - \sum_{m=0}^{K-1} W_{mn}(x) \delta_{n',n}.$$

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

$$\frac{dx}{dt} = \mathcal{F}(x) \equiv \sum_{n=0}^{K-1} F_n(x) \rho_n(x),$$

PATH-INTEGRAL I

- Discretize time by dividing a given interval $[0, T]$ into N equal subintervals of size Δt such that $T = N\Delta t$ and set

$$x_j = x(j\Delta t), n_j = n(j\Delta t)$$

- The conditional probability density for $x_1, \ldots, x_N$ given x_0 and a particular realization of the stochastic discrete variables $n_j, j = 0, \ldots, N-1$, is

$$P(x_1, \ldots, x_N | x_0, n_0, \ldots, n_{N-1}) = \prod_{j=0}^{N-1} \delta\left(x_{j+1} - x_j - F_{n_j}(x_j)\Delta t\right)$$

- Using the Fourier representation of the Dirac delta function,

$$\begin{aligned} P(x_1, \ldots, x_N | x_0, n_0, \mathbf{n}) &= \prod_{j=0}^{N-1} \left[\int_{-\infty}^{\infty} \mathrm{e}^{-ip_j\left(x_{j+1} - x_j - F_{n_j}(x_j)\Delta t\right)} \frac{dp_j}{2\pi}\right] \\ &\equiv \prod_{j=0}^{N-1} \left[\int_{-\infty}^{\infty} H_{n_j}(x_{j+1}, x_j, p_j) \frac{dp_j}{2\pi}\right] \end{aligned}$$

Path-integral II

- On averaging with respect to the intermediate states $\mathbf{n} = (n_q, \ldots, n_{K-1})$, we have

$$P(x_1, \ldots, x_N | x_0, n_0) = \left[\prod_{j=0}^{N-1} \int_{-\infty}^{\infty} \frac{dp_j}{2\pi} \right] \sum_{n_1, \ldots, n_{N-1}} \prod_{j=0}^{N-1} T_{n_{j+1}, n_j}(x_j) H_{n_j}(x_{j+1}, x_j, p_j)$$

where

$$\begin{aligned} T_{n_{j+1}, n_j}(x_j) &\sim A_{n_{j+1}, n_j}(x_j) \frac{\Delta t}{\epsilon} + \delta_{n_{j+1}, n_j} \left(1 - \sum_m A_{m, n_j}(x_j) \frac{\Delta t}{\epsilon} \right) + o(\Delta t) \\ &= \left(\delta_{n_{j+1}, n_j} + A_{n_{j+1}, n_j}(x_j) \frac{\Delta t}{\epsilon} \right). \end{aligned}$$

Path-integral III

- Consider the eigenvalue equation

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

and let $\xi_m^{(s)}$ be the adjoint eigenvector.

- Insert multiple copies of the identity

$$\sum_s \xi_m^{(s)}(x,q)R_n^{(s)}(x,q) = \delta_{m,n}$$

into the discrtetized path-integral with $(x,q) = (x_j,q_j)$ at the jth time-step

Path-integral IV

- Find that

$$P(x_N, n_N|x_0, n_0) \equiv \prod_{j=1}^{N-1} \int_{-\infty}^{\infty} dx_j P(x_1, \ldots, x_N, n_N|x_0, n_0)$$

$$= \left[\prod_{j=1}^{N-1} \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} dx_j \frac{dp_j}{2\pi} \right] \sum_{n_1, \ldots, n_{N-1}} \sum_{s_0, \ldots, s_{N-1}} \left[\prod_{j=0}^{N-1} R_{n_{j+1}}^{(s_j)}(x_j, q_j) \xi_{n_j}^{(s_j)}(x_j, q_j) \right]$$

$$\exp\left(\sum_j \left[\lambda_{s_j}(x_j, q_j) - i\epsilon p_j \frac{x_{j+1} - x_j}{\Delta t} \right] \frac{\Delta t}{\epsilon} \right) \exp\left([i\epsilon p_j F_{n_j}(x_j) - q_j F_{n_j}(x_j)] \frac{\Delta t}{\epsilon} \right).$$

- Discretized path integral is independent of the q_j. Set $q_j = i\epsilon p_j$ for all j and eliminate the final exponential factor.
- Sum over the intermediate discrete states n_j using the orthogonality relation

$$\sum_n R_n^{(s)}(x, q) \xi_n^{(s')}(x, q) = \delta_{s,s'}.$$

Path-integral V (PCB and Newby 2014)

- 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 $s > 0$

- Hence, set $s_j = 0$ and take the continuum limit to obtain the following path-integral from $x(0) = x_0$ to $x(\tau) = x$ (after performing the change of variables $i\epsilon p_j \to p_j$ (complex contour deformation):

$$\boxed{P(x, n, \tau | x_0, n_0, 0) = \int_{x(0)=x_0}^{x(\tau)=x} \exp\left(-\frac{1}{\epsilon}\int_0^\tau [p\dot{x} - \lambda_0(x, p)]dt\right) \mathcal{D}[p]\mathcal{D}[x]}$$

- Dropped factor $R_0^{(s)}(x, p(\tau))\xi_{n_0}^{(0)}(x_0, p(0))$

Variational principle

- Applying steepest descents to path integral yields a variational principle in which optimal paths minimize the action

$$S[x,p] = \int_0^\tau [p\dot{x} - \lambda_0(x,p)]\,dt.$$

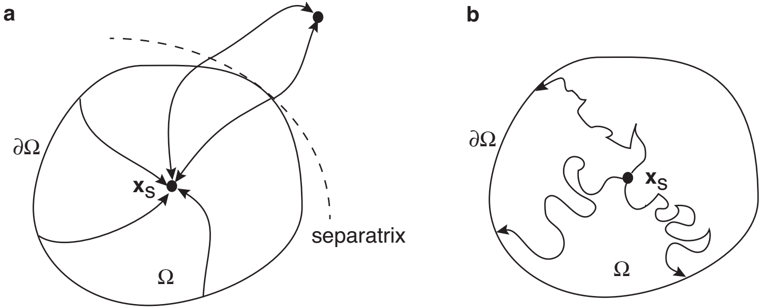
- Hence, we can identify the Perron eigenvalue $\lambda_0(x,p)$ as a Hamiltonian and the optimal paths are solutions to Hamilton's equations

$$\dot{x} = \frac{\partial \mathcal{H}}{\partial p}, \quad \dot{p} = -\frac{\partial \mathcal{H}}{\partial x}, \quad \mathcal{H}(x,p) = \lambda_0(x,p)$$

- Deterministic mean field equations and optimal paths of escape from a metastable state both correspond to zero energy solutions.
- Setting $\lambda_0 = 0$ in eigenvalue equation gives

$$\boxed{\sum_m [A_{nm}(x) + p\delta_{n,m}F_m(x)]\, R_m^{(0)}(x,p) = 0}$$

"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 $R_m^{(0)}(x, \mu(x)) = \psi_m(x)$:

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

- Recovers leading order equation for WKB quasipotential $\Phi(x)$ with $\Phi'(x) = \mu(x)$ and

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

Part III. Stochastic ion-channels revisited

Stochastic 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 $f(v) = g_{\mathrm{Na}}(V_{\mathrm{Na}} - v)$ 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

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

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 I

- Introduce the joint probability density

$$\mathrm{Prob}\{v(t) \in (v, v + dv), n(t) = n\} = p_n(v, t)dv,$$

for given initial data

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

$$\frac{\partial p_n}{\partial t} = -\frac{\partial [F_n(v)p_n(v,t)]}{\partial v}$$
$$+\frac{1}{\epsilon}[\omega_+(n-1)p_{n-1}(v,t) + \omega_-(n+1)p_{n+1}(v,t) - (\omega_+(n) + \omega_-(n))p_n(v,t)]$$

- 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

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

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

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

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

where

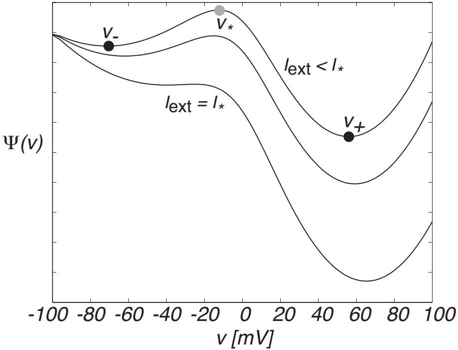
$$\rho_n(v) = \frac{N!}{(N-n)!n!} a(v)^n b(v)^{N-n}, \quad a(v) = \frac{\alpha(v)}{\alpha(v)+\beta},\ b(v) = 1 - a(v).$$

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

- 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

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

Perron eigenvalue II

- Eliminating Λ from these equation gives

$$p = \frac{1}{f(x)}\left(\frac{N\beta(x)}{\lambda_0(x,p)+N\alpha(x)+pg(x)}+1\right)(\lambda_0(x,p)+pg(x))$$

- Obtain a quadratic equation for λ_0:

$$\lambda_0^2+\sigma(x)\lambda_0-h(x,p)=0.$$

with

$$\sigma(x)=(2g(x)-f(x))+N(\alpha(x)+\beta(x)),$$

$$h(x,p)=p[-N\beta(x)g(x)+(N\alpha(x)+pg(x))(f(x)-g(x))].$$

- The "zero energy" solutions imply that $h(x,p)=0$

RECOVERS WKB QUASIPOTENTIAL

- Non-trivial solution recovers result of WKB analysis

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

- The corresponding quasipotential Φ is given by

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

- Analogous result in full ML model

Part IV. Higher-dimensional systems

D-DIMENSIONAL STOCHASTIC HYBRID SYSTEM

- Consider the system

$$\frac{dx_i}{dt} = \frac{1}{\tau_x} F_n^{(i)}(\mathbf{x}), \quad \mathbf{x} \in \mathbb{R}^D, \quad i = 1, \ldots, D$$

- Jump Markov process $n' \to n$ with transition rates $W_{nn'}(\mathbf{x})/\tau_n$.
- Set $\tau_x = 1$ and introduce the small parameter $\epsilon = \tau_n/\tau_x$
- CK equation is

$$\boxed{\frac{\partial p_n}{\partial t} = -\sum_i \frac{\partial [F_n^{(i)}(\mathbf{x}) p_n(\mathbf{x}, t)]}{\partial x_i} + \frac{1}{\epsilon} \sum_{n'} A_{nn'}(\mathbf{x}) p_{n'}(\mathbf{x}, t)}$$

$$A_{nn'}(\mathbf{x}) = W_{nn'}(\mathbf{x}) - \sum_m W_{mn}(\mathbf{x}) \delta_{n',n}.$$

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

$$\frac{dx_i}{dt} = \mathcal{F}_i(x) \equiv \sum_n F_n^{(i)}(\mathbf{x}) \rho_n(\mathbf{x}),$$

where $\sum_{m \in I} A_{nm}(\mathbf{x}) \rho_m(\mathbf{x}) = 0$.

PATH-INTEGRAL

- Proceeding as in the 1D case find that

$$p_n(\mathbf{x}, \tau|\mathbf{x}_0, \mathbf{n}_0, 0) = \int_{\mathbf{x}(0)=\mathbf{x}_0}^{\mathbf{x}(\tau)=\mathbf{x}} \mathcal{D}[\mathbf{p}]\mathcal{D}[\mathbf{x}] \exp\left(-\frac{1}{\epsilon}S[\mathbf{x}, \mathbf{p}]\right)$$

$$\times R_n^{(0)}(\mathbf{x}, \mathbf{p}(\tau))\xi_{n_0}^{(0)}(\mathbf{x}_0, \mathbf{p}(0))$$

  with action

$$S[\mathbf{x}, \mathbf{p}] = \int_0^\tau \left[\sum_{i=1}^D p_i\dot{x}_i - \lambda_0(\mathbf{x}, \mathbf{p})\right] dt.$$

- Here λ_0 is the Perron eigenvalue of the following linear operator equation

$$\sum_m \left[A_{nm}(\mathbf{x})R_m{}^{(0)}(\mathbf{x}, \mathbf{p}) + \delta_{n,m}\sum_{i=1}^D p_i F_m^{(i)}(\mathbf{x})\right] R_m^{(0)}(\mathbf{x}, \mathbf{p}) = \lambda_0(\mathbf{x}, \mathbf{p})R_n^{(0)}(\mathbf{x}, \mathbf{p}),$$

  and $\xi^{(0)}$ is the corresponding adjoint eigenvector.

Stochastic Morris-Lecar model revisited

- 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

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

- 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

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

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

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**

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

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

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:

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

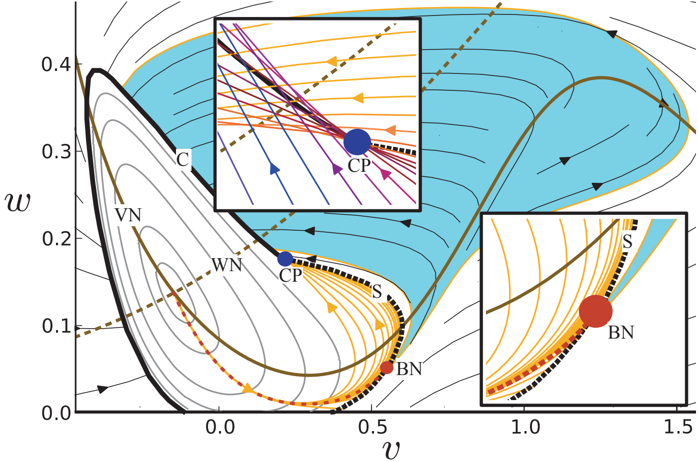
- Solve for Φ using **method of characteristics**. Satisfy Hamilton's equations

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

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 $(v,w) = \mathbf{x}(t)$.

SOLUTIONS OF HJ EQUATION (NEWBY,PCB,KEENER 2013)



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

PATH-INTEGRAL FOR STOCHASTIC ML

- Path-integral action is

$$S[x, w, p_x, p_w] = \int_0^\tau [p_x \dot{x} + p_w \dot{w} - \lambda_0(x, w, p_x, p_w)]dt$$

  where λ_0 is the Perron eigenvalue of the following linear operator equation

$$\lambda_0 R_n = \left[\mathbb{L}_{Na} + F_n(x, w)p_x + h(x, w, p_w)\right] R_n^{(0)}.$$

  with $F_n(x, w) = F(x, Mw, n)$
- The path-integral representation of the stationary density is then

$$p_n(x, w, \tau | x_0, w_0, 0) = \iint_{\mathbf{x}(0)=\mathbf{x}_0}^{\mathbf{x}(\tau)=\mathbf{x}} \exp\left(-\frac{1}{\epsilon} S[x, w, p_x, p_w]\right)$$

$$R_n^{(0)}(\mathbf{x}, \mathbf{p}(\tau))\xi_{n_0}^{(s)}(\mathbf{x}_0, \mathbf{p}(0))\, \mathcal{D}[\mathbf{p}]\mathcal{D}[\mathbf{x}]$$

PERRON EIGENVALUE DIFFERS FROM WKB HAMILTONIAN

- Introduce the ansatz

$$R_n^{(0)}(v,w) = \frac{\Lambda(v,w)^n}{(N-n)!n!}$$

  into eigenvalue equation.
- Collecting terms linear in n gives

$$\begin{aligned} A(x,w) &= \alpha_{Na}(x) \\ &\quad - \frac{1}{N}(p_x g(x,w) + h(x,w,p_w) - \lambda_0(x,w,p_x,p_w)), \end{aligned}$$

- Collecting terms independent of n
  and substituting for $A(x,w)$ gives the following quadratic equation for λ_0:

$$\lambda_0^2 - (2h(x,w,p_w) + \sigma(x,w,p_x))\lambda_0 + \mathcal{H}(x,w,p_x,p_w) = 0,$$

  with

$$\sigma(x,w,p_x) = (2g(x) + f(x))p_x - N/(1 - w_\infty(x))$$

  and $\mathcal{H}$ the WKB Hamiltonian.

References

1. PCB. Mean field theory and effects of fluctuations in stochastic hybrid neural networks. (2014)
2. PCB and J. M. Newby. Path-integrals and large deviations in stochastic hybrid systems. Phys. Rev. E (2014)
3. PCB and J. M. Newby. Stochastic hybrid model of spontaneous dendritic NMDA spikes. Phys. Biol. **11** 016006 (2014).
4. J. M. Newby, PCB and J. P. Keeener. The effect of Potassium channels on spontaneous action potential initiation by stochastic ion channels. Phys. Rev. Lett. **111** 128101 (2013).
5. PCB and J. M. Newby. Metastability in a stochastic neural network modeled as a jump velocity Markov process SIAM J. Appl. Dyn. Syst. **12** 1394-1435 (2013).