Large deviations in stochastic hybrid systems

Paul C Bressloff[1]

Institute for data-free modeling

[1]Department of Mathematics, University of Utah

May 22, 2017

Large deviations in stochastic hybrid systems

Paul C Bressloff[1]

Institute for data-free modeling

[1]Department of Mathematics, University of Utah

May 22, 2017

Outline of talk

Part I. Stochastic hybrid systems in biology

Part II. Analysis of first passage time problems

Part III. Stochastic ion channels

Collaborators: Jay Newby, Sean Lawley

Part I. Stochastic hybrid systems in biology

1D STOCHASTIC HYBRID SYSTEM

- Consider the piecewise deterministic system

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

- $n(t)$ is a discrete Markov process 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

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

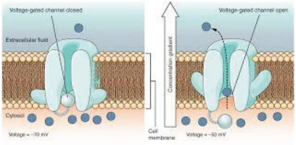
where

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

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

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

[A] STOCHASTIC CONDUCTANCE-BASED MODEL



- Suppose a neuron has $n \leq N$ open Na^+ channels and $m \leq M$ 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

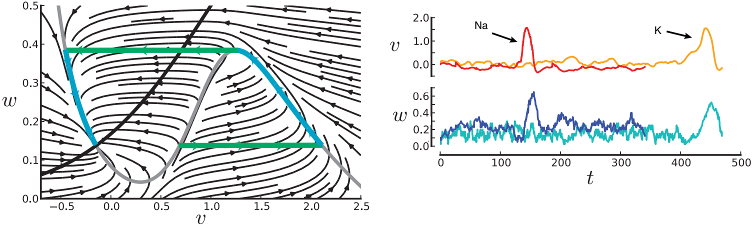
$$C(closed) \underset{\beta_i(v)}{\overset{\alpha_i(v)}{\rightleftharpoons}} O(open), \quad i = \mathrm{Na},\ \mathrm{K},$$

[A] 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

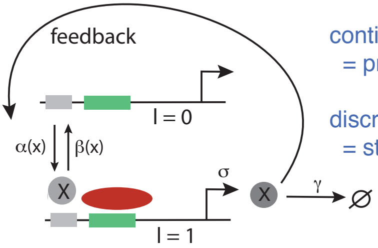
$$\frac{dv}{dt} = \frac{\alpha_{Na}(v)}{\alpha_{Na}(v) + \beta_{Na}(v)} f_{\mathrm{Na}}(v) + w f_{\mathrm{K}}(v) - g(v)$$
$$\frac{dw}{dt} = \alpha_K(v)(1-w) - \beta_K(v) w,$$

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



- Ion channel fluctuations can induce spontaneous action potentials.

[B] Autoregulatory gene network



continuous variable
= promoter protein concentration

discrete variable
= state of promoter

- Protein concentration x and promoter state $n \in \{0, 1\}$:

$$\frac{dx}{dt} = F_n(x) = n\sigma + \sigma_0 - x$$

- Promoter transition rates

$$(\text{off}) \underset{\beta(x)}{\overset{\alpha(x)}{\rightleftharpoons}} (\text{on}) \quad \alpha(x) = \alpha_0 x^2, \quad \beta(x) = \beta_0,$$

[B] AUTOREGULATORY GENE NETWORK

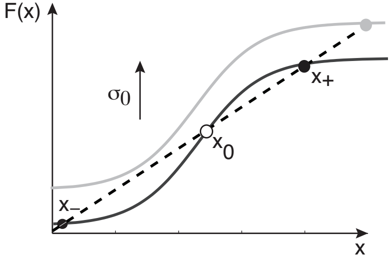
- In the fast switching limit $\varepsilon \to 0$, we obtain the deterministic equation

$$\dot{x} = \sum_{l=0,1} \rho_l(x) F_l(x) \equiv -x + F(x).$$

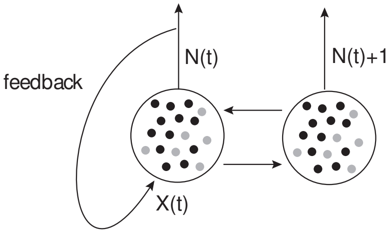
where

$$\rho_0(x) = \frac{\beta(x)}{\alpha(x) + \beta(x)} = 1 - \rho_1(x), \quad F(x) = \sigma_0 + \frac{\sigma \alpha_0 x^2}{\alpha_0 x^2 + \beta_0}.$$

- Hill function $F(x)$ supports bistability



[C] Recurrent excitatory neural network



continuous variable = synaptic current

discrete variable = number of spikes

- Consider a large population of excitatory neurons
- $N(t)$ is number of spiking neurons, and $X(t)$ is synaptic current

$$\tau \frac{dx}{dt} = F_n(x) = -x(t) + wn$$

- Birth-death process $N(t) \to N(t) \pm 1$ with transition rates

$$\Omega_+ = \frac{F(X)}{\tau_a}, \quad \Omega_- = \frac{N(t)}{\tau_a}.$$

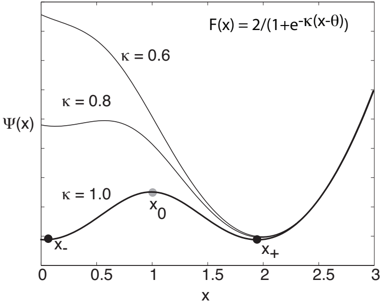
[C] Recurrent excitatory neural network

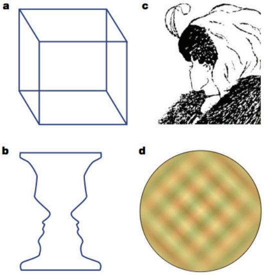
- Stationary density is a Poisson distribution,

$$\rho_n(x) = \frac{[F(x)]^n e^{-F(x)}}{n!},$$

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

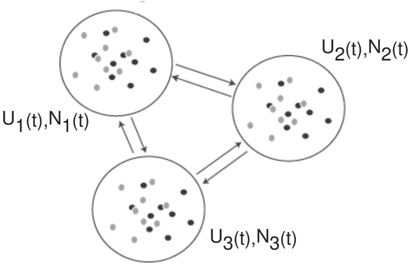
$$\frac{dx}{dt} = \sum_{n=0}^{\infty} F_n(x)\rho_n(x) = -x + wF(x) \equiv V(x) = -\frac{d\Psi}{dx}$$

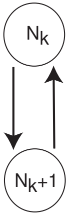




Ambiguous perception and bistability

[C] Extend to multiple populations





- Consider M homogeneous networks labelled $k = 1, \ldots M$, each containing N identical neurons
- $N_k(t)$ is number of spiking neurons, and $U_k(t)$ is synaptic current

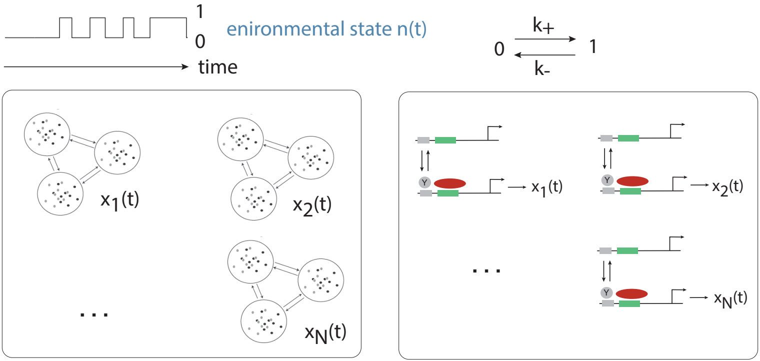
$$\tau \frac{dU_k(t)}{dt} = -U_k(t) + \sum_{k=1}^{M} w_{kl} N_l(t), \quad N_k(t) \to N_k(t) \pm 1.$$

with transition rates

$$\Omega_+ = \frac{F(U_k)}{\tau_a}, \quad \Omega_- = \frac{n_k}{\tau_a}.$$

[D] Metapopulations in randomly switching environments

- Consider a metapopulation of uncoupled neural or gene networks labeled $\ell = 1, \ldots, N$ with state variables $x_\ell(t)$, all being driven by the same external or environmental dichotomous noise $n(t)$



[D] Metapopulations in randomly switching environments

- The state $x_\ell(t)$ could be multi-dimensional, deterministic or stochastic. For concreteness we take $x_\ell \in \mathbb{R}$ and

$$\frac{dx_\ell}{dt} = F_{n(t)}(x_\ell)$$

  for $\ell = 1, \ldots, \mathcal{M}$, with the stochastic variable $n(t)$ independent of ℓ and evolving according to a continuous Markov chain with generator $\mathbf{A}$.

- Take the thermodynamic limit $N \to \infty$, and let $P(x,t)$ denote the density of networks in state x at time t given a particular realization $\sigma(t) = \{n(\tau), 0 \le \tau \le t\}$ of the Markov chain.

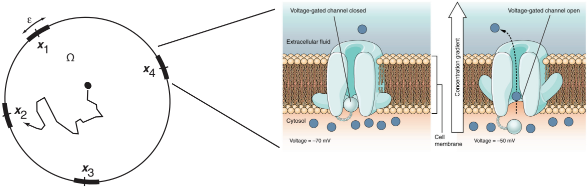
- The population density evolves according to the stochastic Liouville equation

$$\frac{\partial}{\partial t} P(x,t) = \left[-\frac{\partial}{\partial x} F_{n(t)}(x) \right] P(x,t),$$

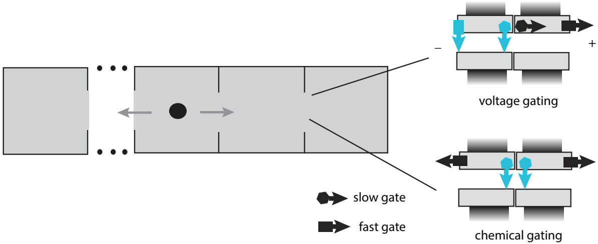
  with $P(x,0) = p_0(x)$.

[D] Many other examples of switching environments

[A] Diffusion in domains with stochastically gated boundaries



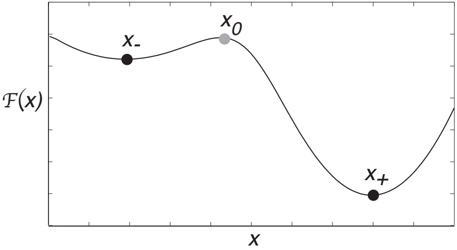
[B] Diffusively coupled cells with stochastically gated gap junctions



Part II. Analysis of first passage time problems

First-passage time (FTP) problem I

- Suppose that mean field equation is bistable



- Let $T(x)$ be the stochastic time for system 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.

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

Path-integral representation (PCB/Newby)

- Consider the eigenvalue equation

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

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

- 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

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

Variational principle

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

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

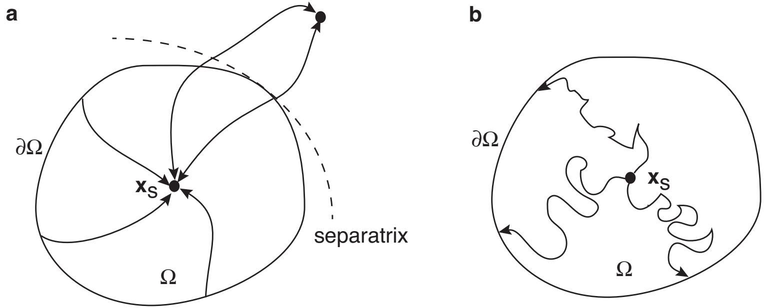
- Hence, we can identify the Perron eigenvalue $\lambda_0(x,p)$ as a Hamiltonian and the optimal paths are solutions to Hamilton's equations

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

- 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

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

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

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

- 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

Reduced Morris-Lecar model

- Adiabatic approximation: freeze K dynamics and absorb into leak current.
- 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

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

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

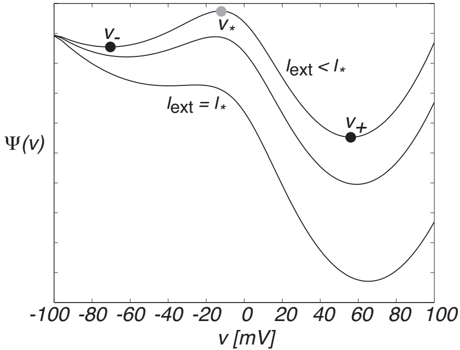
$$\rho_n(v) = \frac{N!}{(N-n)!n!}a(v)^n b(v)^{N-n}, \quad a(v) = \frac{\alpha(v)}{\alpha(v)+\beta},\ b(v) = 1 - a(v).$$

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

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

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:

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

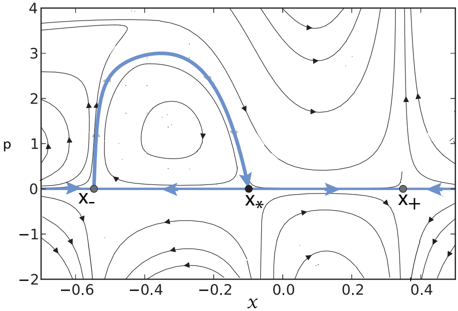
with

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

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

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

THE QUASIPOTENTIAL



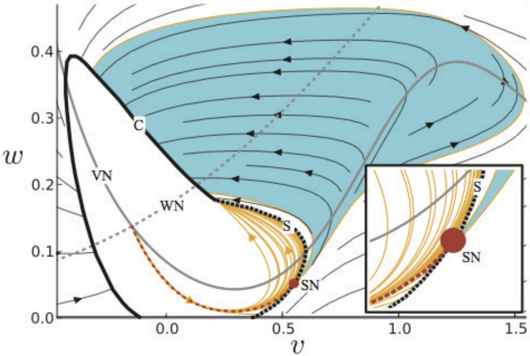
- Non-trivial solution yields

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

- The corresponding quasipotential Φ is given by

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

Stochastic ML (Newby,PCB,Keener)



Caustic (C),

v nullcline (VN),

w nullcline (WN),

metastable separatrix (S),

bottleneck (BN),

caustic formation point (CP)

- Most probable paths of escape dip significantly below the resting value for w, indicating a breakdown of slow/fast decomposition.
- Escape trajectories all pass through a narrow region of state space (bottleneck or stochastic saddle node)
- Inspite of no well-defined separatrix for an excitable system, one can formulate an escape problem by determining the mean first passage time to reach the bottleneck from the resting state.

REFERENCES

1. P. C. Bressloff. Stochastic switching in biology: from genotype to phenotype (Topical Review) J. Phys. A **50** 133001 (2017)
2. PCB and O. Faugeras. On the Hamiltonian structure of large deviations in stochastic hybrid systems. J. Stat. Mech. (2017)
3. PCB. Diffusion in cells with stochastically-gated gap junctions. SIAM J. Appl. Math. **76** 1658-1682 (2016).
4. PCB and S. D. Lawley. Escape from subcellular domains with randomly switching boundaries. Multiscale Model. Simul. **13** 1420-1445 (2015).
5. PCB and S. D. Lawley. Moment equations for a piecewise deterministic PDE. J. Phys. A **48** 105001 (2015).
6. PCB. Path-integral methods for analyzing the effects of fluctuations in stochastic hybrid neural networks. J. Math. Neurosci. **5** (4) 33 pp. (2015)
7. PCB and J. M. Newby. Path-integrals and large deviations in stochastic hybrid systems. Phys. Rev. E **89** 042701 (2014)
8. 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).
9. 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).