Quantifying neuronal spiking patterns using continuous-space Markov chains

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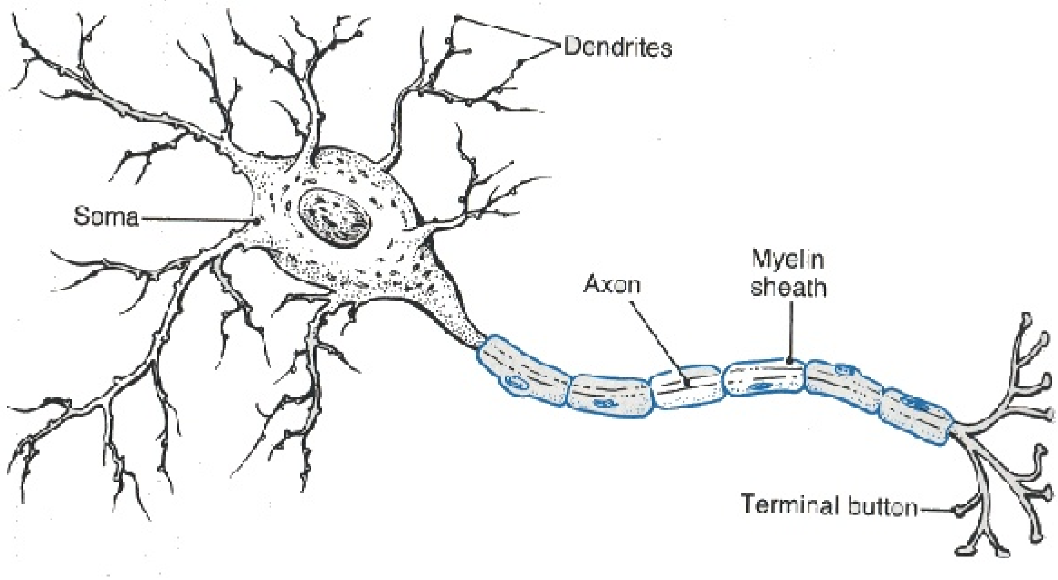
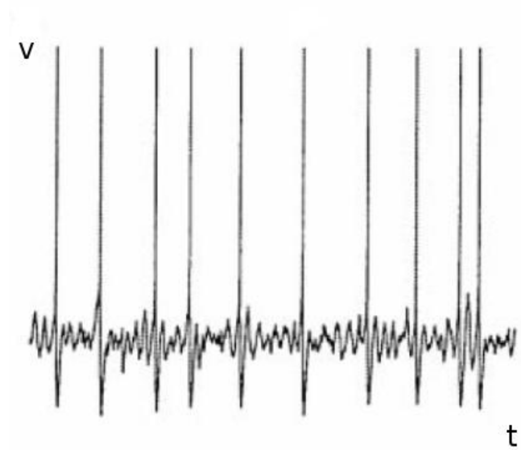
Neurons and action potentials





Action potential [Dickson 00]

- ▷ Neurons communicate via patterns of spikes in action potentials

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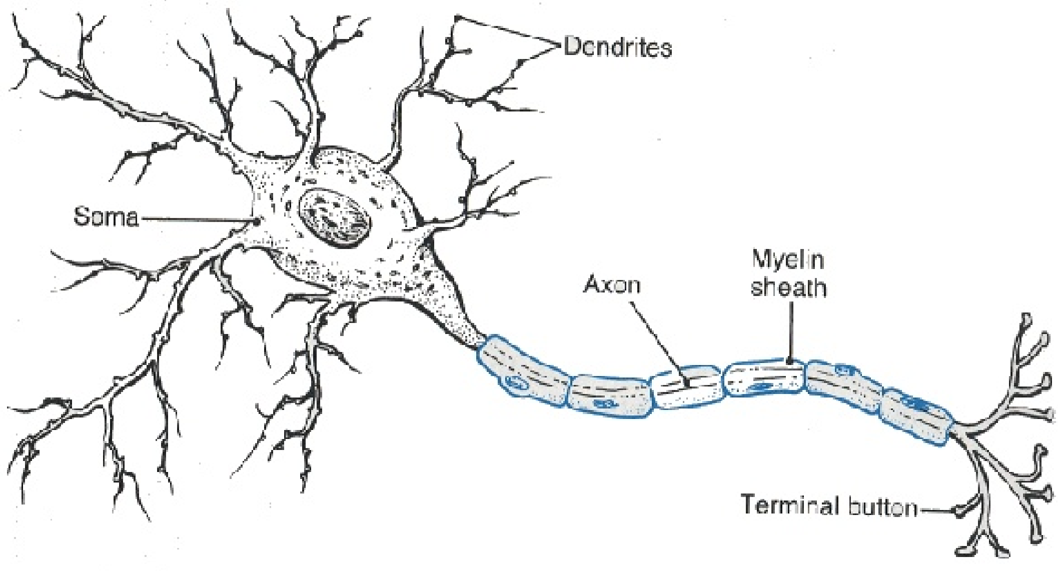

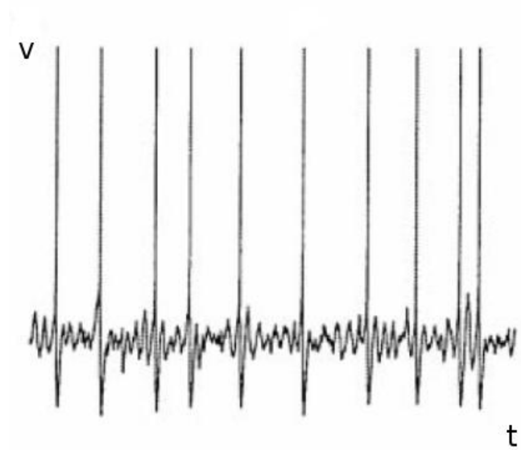

Action potential [Dickson 00]

- ▷ Neurons communicate via patterns of spikes in action potentials
- ▷ Question: effect of noise on interspike interval statistics?
- ▷ Poisson hypothesis: Exponential distribution
  $\Rightarrow$ Markov property

ODE models for evolution of membrane potential

▷ Integrate-and-fire models

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- ▷ Conduction-based models
  - ⋈ Hodgkin–Huxley model (1952)

$$C\dot{v} = \sum_{\text{ion channels } i} I_i(v) \qquad I_i(v) = g_i \varphi_i^{\alpha_i} \psi_i^{\beta_i} (v - E_i)$$

φ_i, ψ_i: Gating variables, satisfy linear ODEs

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$$C\dot{v} = -g_{\text{Ca}} m^*(v)(v - v_{\text{Ca}}) - g_{\text{K}} w(v - v_{\text{K}}) - g_{\text{L}}(v - v_{\text{L}})$$

$$\tau_w(v)\dot{w} = -(w - w^*(v))$$

$$m^*(v) = \frac{1+\tanh((v-v_1)/v_2)}{2}, \quad \tau_w(v) = \frac{\tau}{\cosh((v-v_3)/v_4)},$$

$$w^*(v) = \frac{1+\tanh((v-v_3)/v_4)}{2}$$

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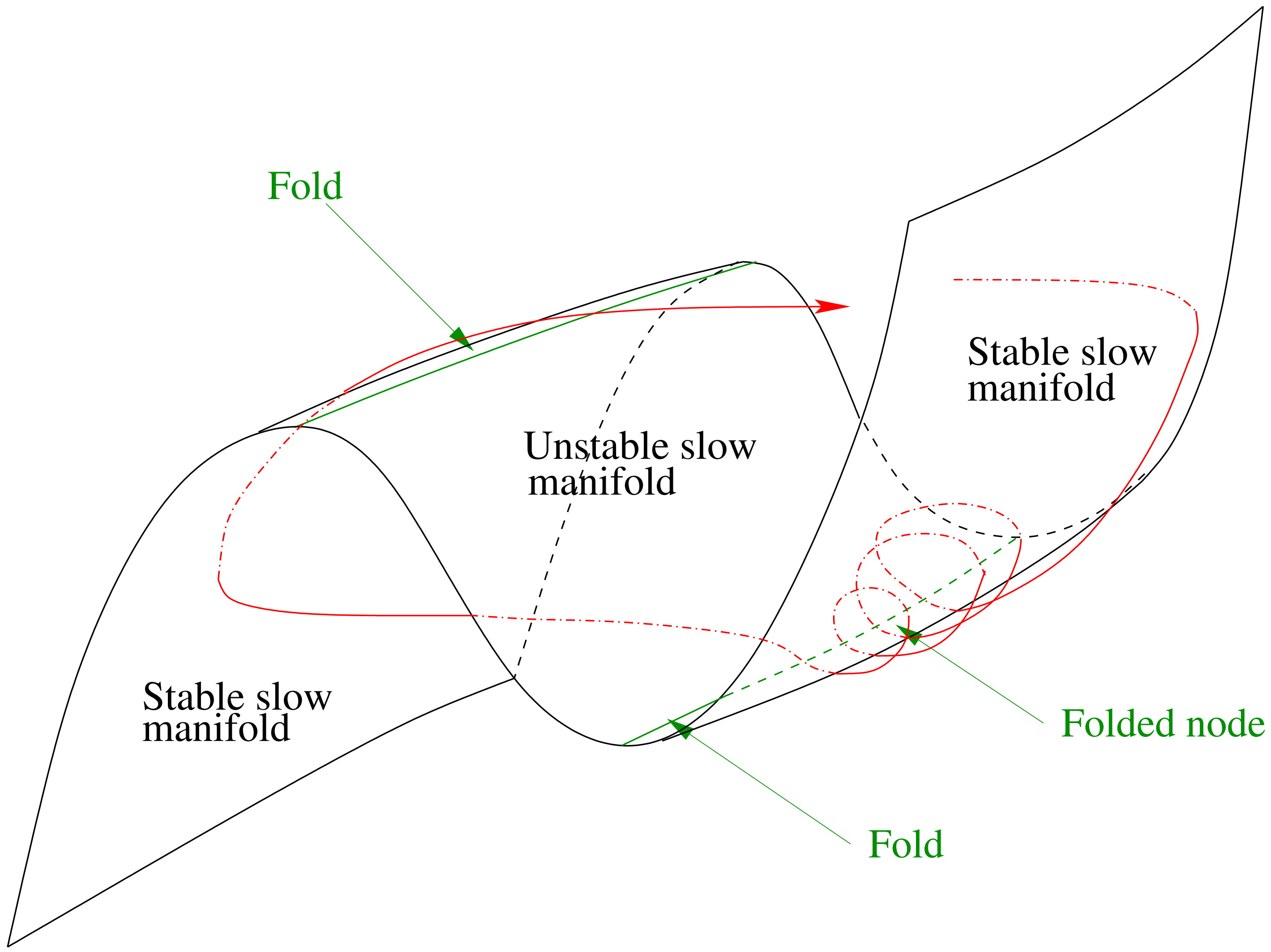
  - ⋈ Fitzhugh–Nagumo model (1962)

$$\frac{C}{g}\dot{v} = v - v^3 + w$$
$$\tau \dot{w} = \alpha - \beta v - \gamma w$$

Random Poincaré map



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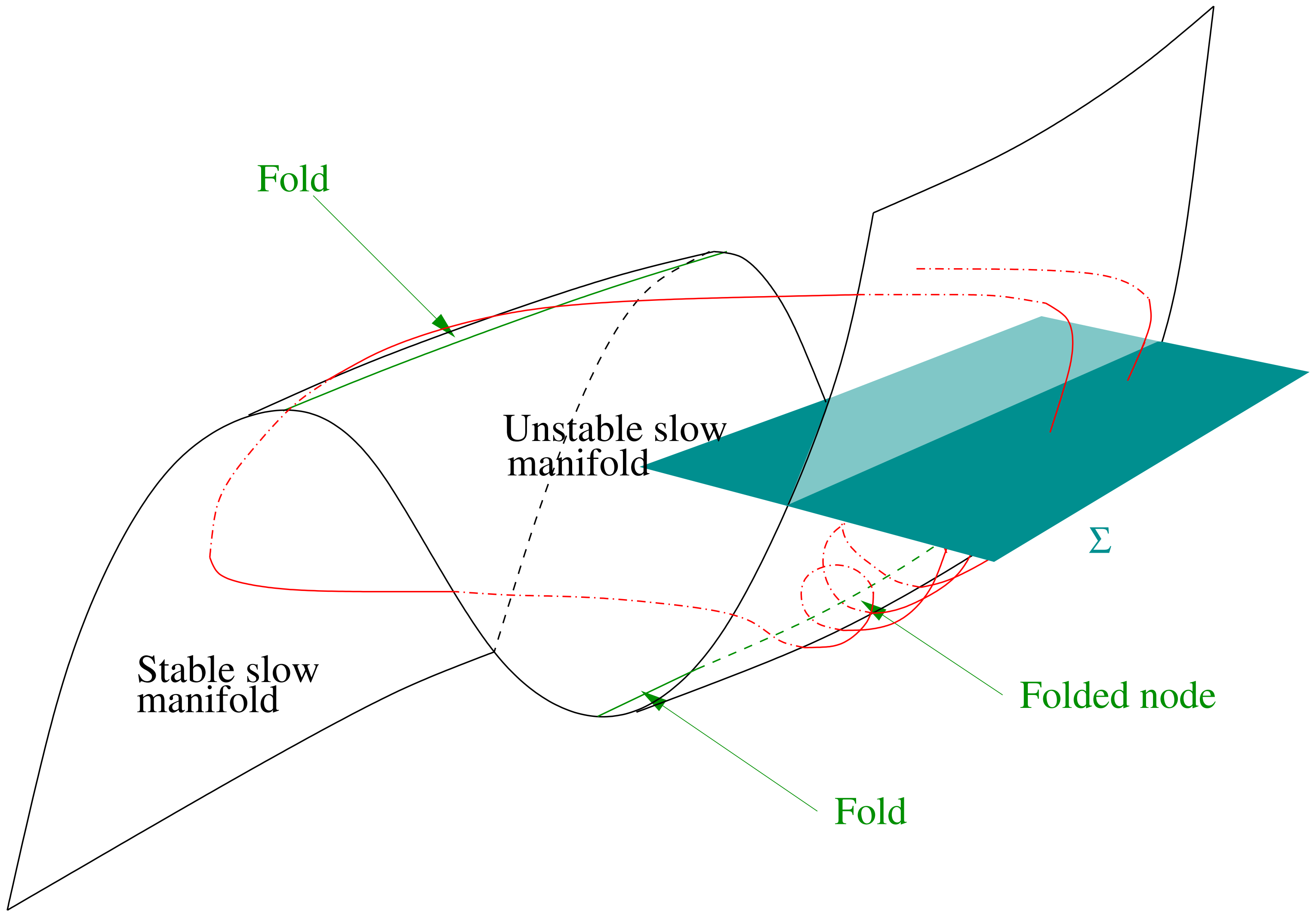

Successive intersections with Σ define Markov chain.

Random Poincaré map

In appropriate coordinates

$$
\begin{aligned}
\mathrm{d}\varphi_t &= f(\varphi_t, x_t)\,\mathrm{d}t + \sigma F(\varphi_t, x_t)\,\mathrm{d}W_t \qquad && \varphi \in \mathbb{R} \\
\mathrm{d}x_t &= g(\varphi_t, x_t)\,\mathrm{d}t + \sigma G(\varphi_t, x_t)\,\mathrm{d}W_t \qquad && x \in E \subset \Sigma
\end{aligned}
$$

▷ all functions periodic in φ (say period 1)
▷ $f \geqslant c > 0$ and σ small $\Rightarrow$ φ_t likely to increase
▷ process may be killed when x leaves E

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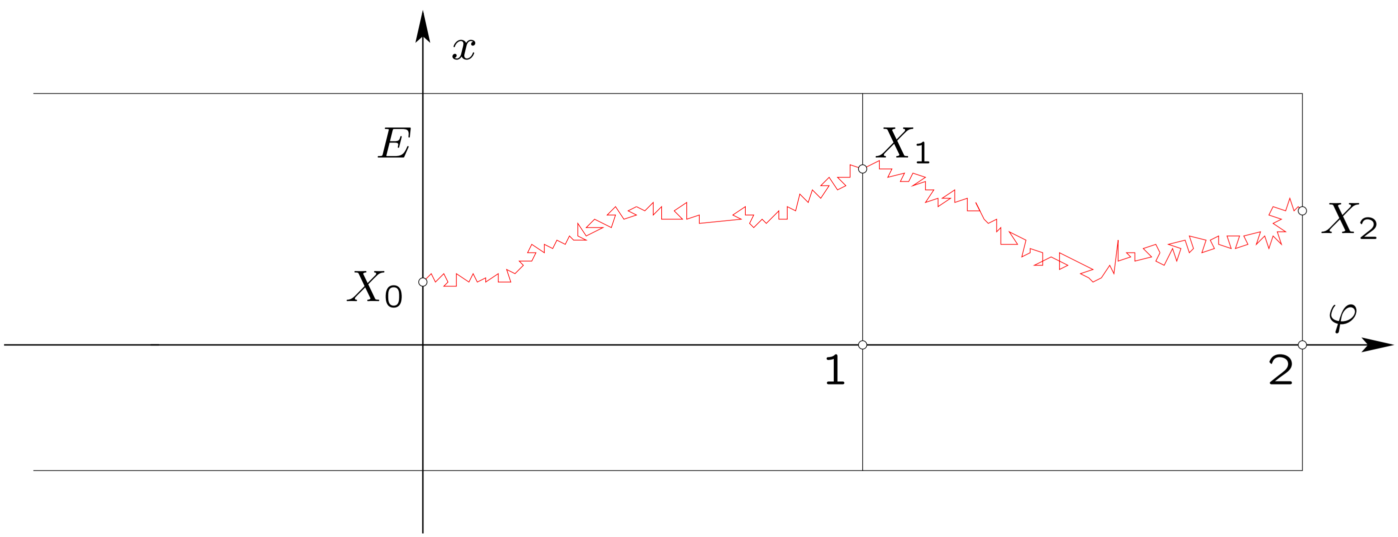
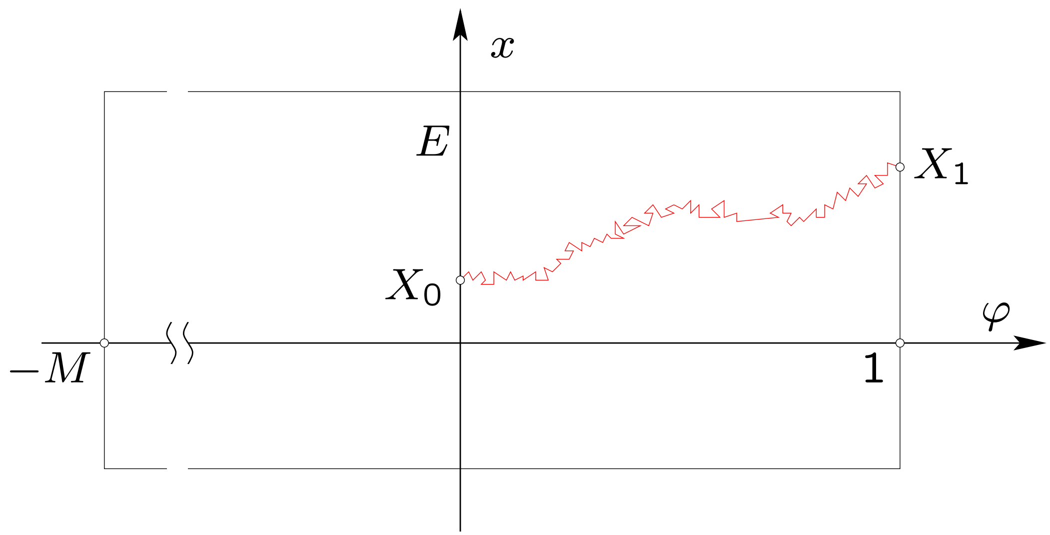


$X_0, X_1, \dots$ form (substochastic) Markov chain

Random Poincaré map and harmonic measure



- ▷ τ: first-exit time of $z_t = (\varphi_t, x_t)$ from $\mathcal{D} = (-M, 1) \times E$
- ▷ $\mu_z(A) = \mathbb{P}^z\{z_\tau \in A\}$: harmonic measure (wrt generator $\mathcal{L}$)
- ▷ [Ben Arous, Kusuoka, Stroock '84]: under hypoellipticity cond, μ_z admits (smooth) density $h(z, y)$ wrt arclength on $\partial\mathcal{D}$

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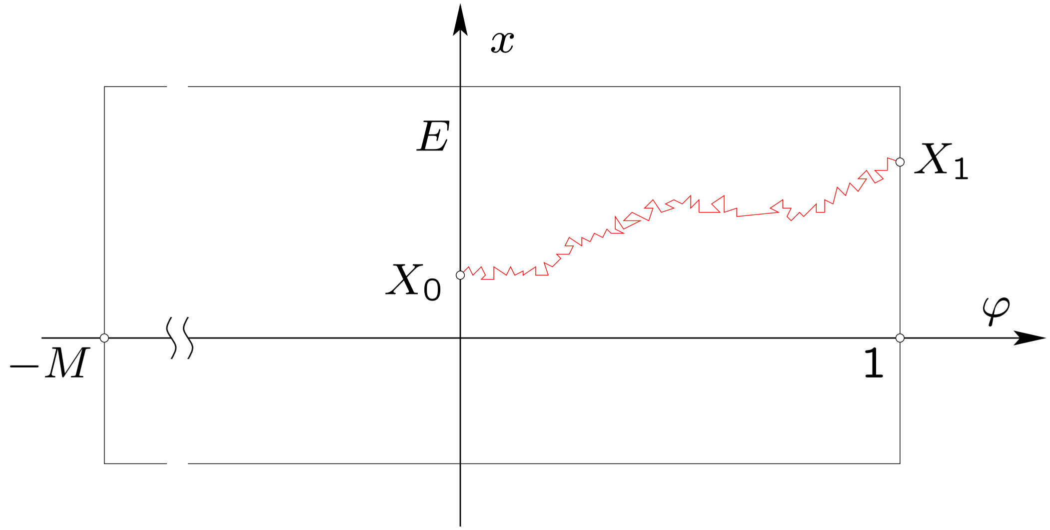

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- [Ben Arous, Kusuoka, Stroock '84]: under hypoellipticity cond, μ_z admits (smooth) density $h(z, y)$ wrt arclength on $\partial\mathcal{D}$
- Remark: $\mathcal{L}_z h(z, y) = 0$ (kernel is harmonic)
- For $B \subset E$ Borel set

$$\mathbb{P}^{X_0}\{X_1 \in B\} = K(X_0, B) := \int_B K(X_0, \mathrm{d}y)$$

where $K(x, \mathrm{d}y) = h((0, x), y)\, \mathrm{d}y =: k(x, y)\, \mathrm{d}y$

Fredholm theory

Consider integral operator K acting

▷ on L^∞ via $f \mapsto (Kf)(x) = \int_E k(x,y) f(y)\,\mathrm{d}y = \mathbb{E}^x[f(X_1)]$

▷ on L^1 via $m \mapsto (mK)(A) = \int_E m(x) k(x,y)\,\mathrm{d}x = \mathbb{P}^\mu\{X_1 \in A\}$

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[Fredholm 1903]:

- ▷ If $k \in L^2$, then K has eigenvalues λ_n of finite multiplicity
- ▷ Eigenfcts $Kh_n = \lambda_n h_n$, $h_n^* K = \lambda_n h_n^*$ form complete ON basis

[Perron, Frobenius, Jentzsch 1912, Krein–Rutman '50, Birkhoff '57]:

- ▷ Principal eigenvalue λ_0 is real, simple, $|\lambda_n| < \lambda_0 \; \forall n \geqslant 1$, $h_0 > 0$

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Spectral decomp: $k(x,y) = \lambda_0 h_0(x) h_0^*(y) + \lambda_1 h_1(x) h_1^*(y) + \dots$

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$$\Rightarrow \mathbb{P}^x\{X_n \in \mathrm{d}y | X_n \in E\} = \pi_0(\mathrm{d}x) + \mathcal{O}((|\lambda_1|/\lambda_0)^n)$$

where $\pi_0 = h_0^* / \int_E h_0^*$ is quasistationary distribution (QSD)
[Yaglom '47, Bartlett '57, Vere-Jones '62, . . .]

How to estimate the principal eigenvalue

▷ "Trivial" bounds: $\forall A \subset E$ with $\mathrm{Lebesgue}(A) > 0$,

$$\inf_{x \in A} K(x, A) \leqslant \lambda_0 \leqslant \sup_{x \in E} K(x, E)$$

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$\lambda_0 \leqslant 1 - \dfrac{1}{\sup_{x \in E} \mathbb{E}^x[\tau_\Delta]}$ where $\tau_\Delta = \inf\{n > 0 \colon X_n \notin E\}$

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▷ Bounds using Laplace transforms (see below)

Application: Stochastic FitzHugh–Nagumo equations

$$\mathrm{d}x_t = \frac{1}{\varepsilon}[x_t - x_t^3 + y_t]\,\mathrm{d}t + \frac{\sigma_1}{\sqrt{\varepsilon}}\,\mathrm{d}W_t^{(1)}$$
$$\mathrm{d}y_t = [a - x_t]\,\mathrm{d}t + \sigma_2\,\mathrm{d}W_t^{(2)}$$

▷ $x \propto$ membrane potential of neuron

▷ $y \propto$ proportion of open ion channels (recovery variable)

▷ $W_t^{(1)}, W_t^{(2)}$: independent Wiener processes

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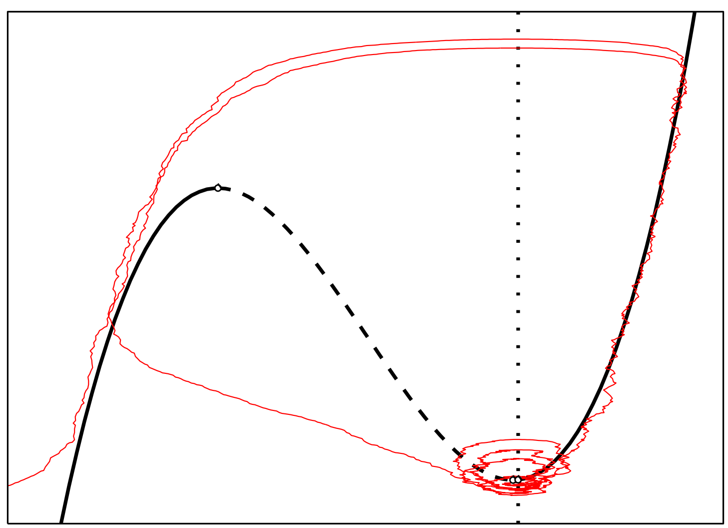
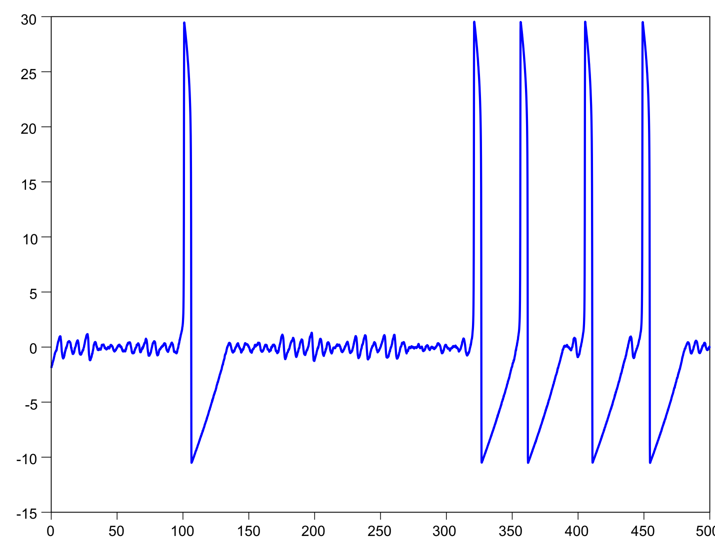
$\varepsilon = 0.1$
$\delta = \frac{3a^2-1}{2} = 0.02$
$\sigma_1 = \sigma_2 = 0.03$





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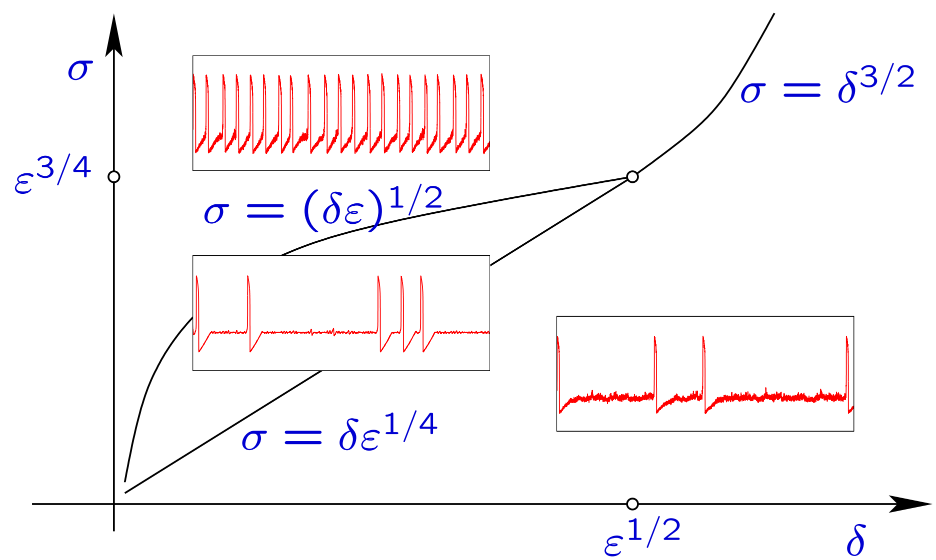
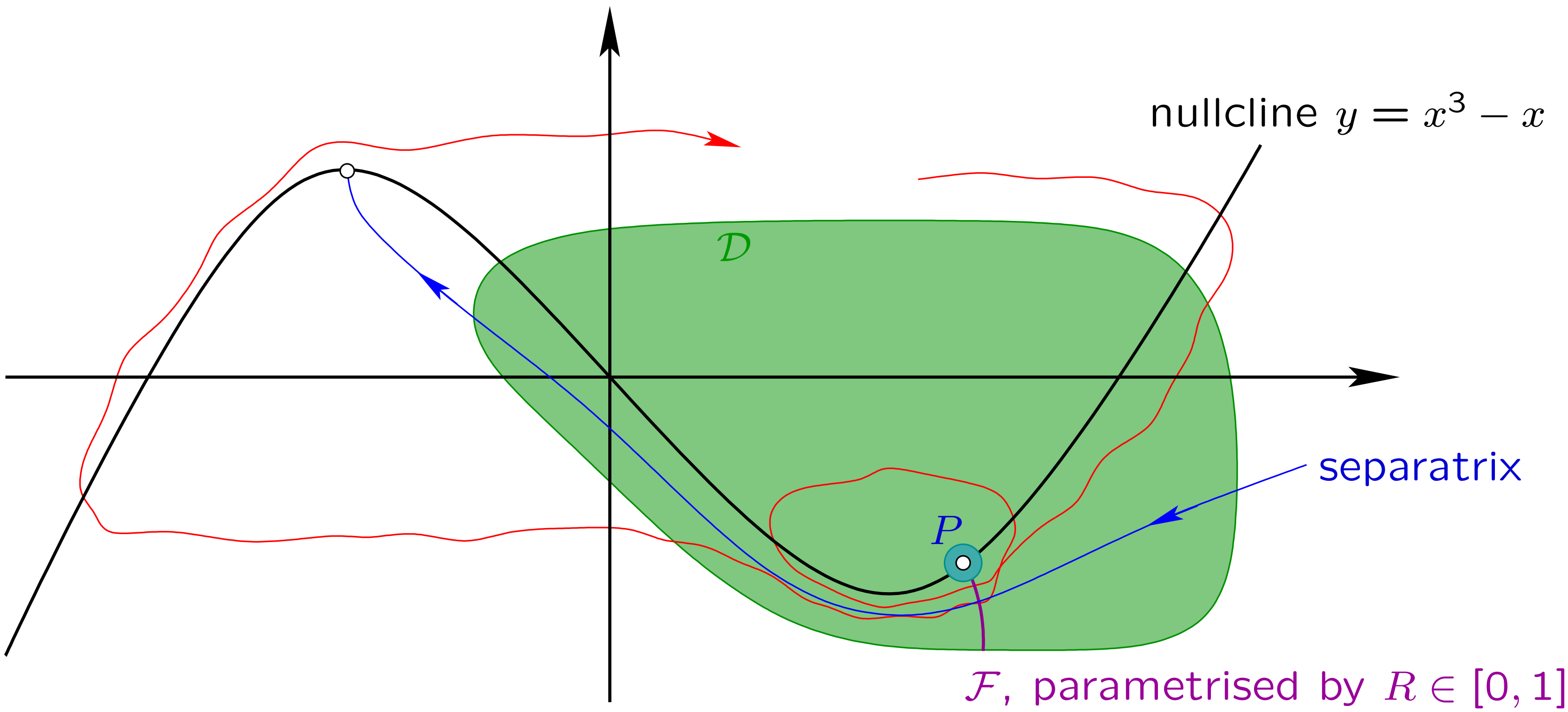
Different regimes

[Muratov & Vanden Eijnden '08]



Small-amplitude oscillations (SAOs)

Definition of random number of SAOs N:



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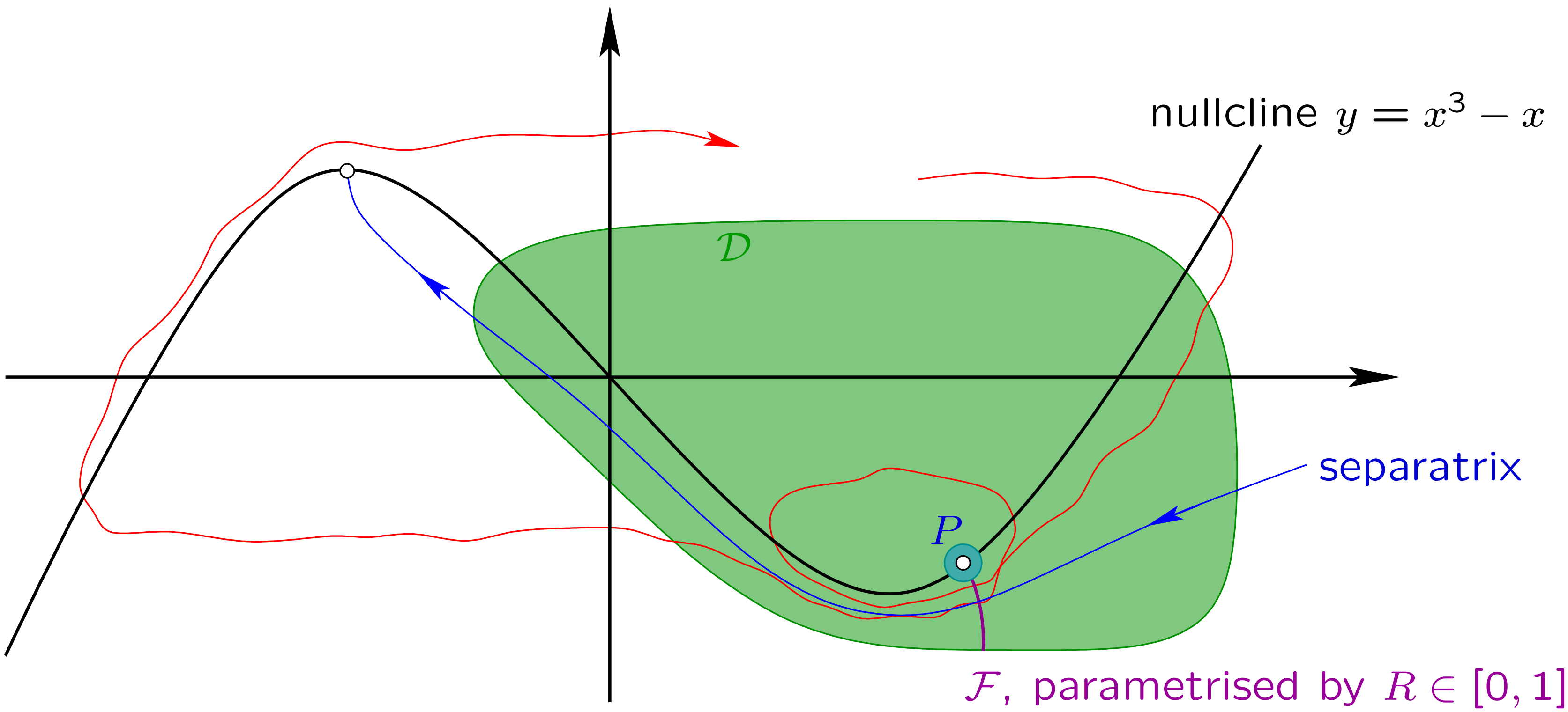

$(R_0, R_1, \dots, R_{N-1})$ substochastic Markov chain with kernel

$$K(R_0, A) = \mathbb{P}^{R_0}\{R_\tau \in A\}$$

$R \in \mathcal{F}$, $A \subset \mathcal{F}$, τ = first-hitting time of $\mathcal{F}$ (after turning around P)

N = number of turns around P until leaving $\mathcal{D}$

Main result 1

Theorem 1: [B & Landon, 2012]

If $\sigma_1, \sigma_2 > 0$, then $\lambda_0 < 1$ and N is asymptotically geometric:

$$\lim_{n\to\infty} \mathbb{P}^{\mu_0}\{N = n+1 | N > n\} = 1 - \lambda_0$$

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Proof:

▷ $\lambda_0 \leqslant K(x^*, E) < 1$ by ellipticity (k bounded below)

▷ $$\begin{aligned}\mathbb{P}^{\mu_0}\{N > n\} = \mathbb{P}^{\mu_0}\{X_n \in E\} &= \int_E \mu_0(\mathrm{d}x) K^n(x,E) \\ &= \int_E \mu_0(\mathrm{d}x) \lambda_0^n [1 + \mathcal{O}((|\lambda_1|/\lambda_0)^n)] \\ &= \lambda_0^n [1 + \mathcal{O}((|\lambda_1|/\lambda_0)^n)]\end{aligned}$$

▷ $$\begin{aligned}\mathbb{P}^{\mu_0}\{N = n+1\} &= \int_E \int_E \mu_0(\mathrm{d}x) K^n(x, \mathrm{d}y)[1 - K(y,E)] \\ &= \lambda_0^n (1-\lambda_0)[1 + \mathcal{O}((|\lambda_1|/\lambda_0)^n)]\end{aligned}$$

▷ Existence of spectral gap follows from positivity condition

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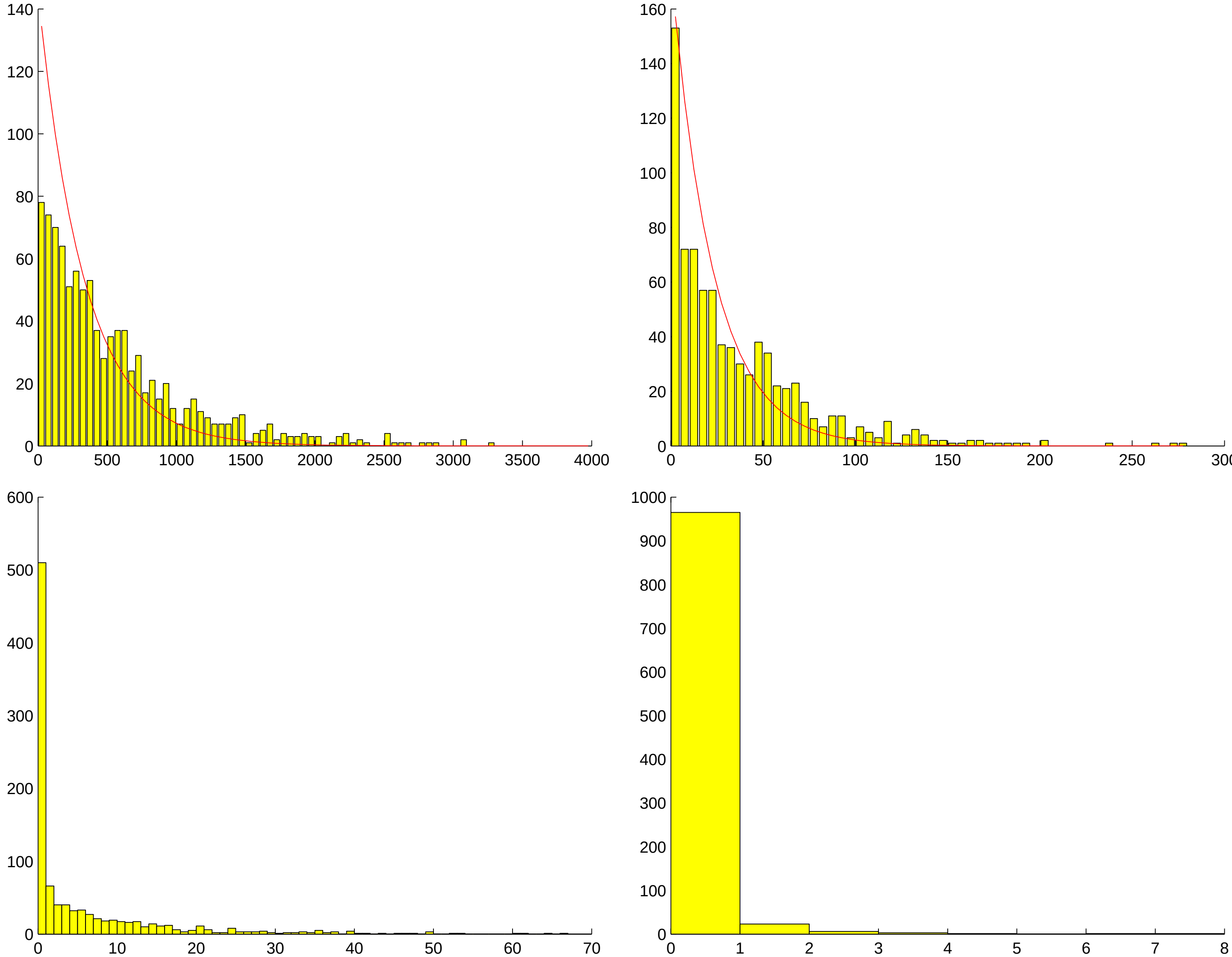
Remark: If $\mu_0 = \pi_0$ then N has geometric distribution and

$$\mathbb{P}^{\pi_0}\{N = 1\} = 1 - \lambda_0 = \frac{1}{\mathbb{E}^{\pi_0}[N]}$$

Histograms of distribution of SAO number N (1000 spikes)

$\sigma = \varepsilon = 10^{-4}, \delta = 1.2 \cdot 10^{-3}, \ldots, 10^{-4}$



Main result 2

Theorem 2: [B & Landon 2012]
Assume ε and $\delta/\sqrt{\varepsilon}$ sufficiently small
There exists $\kappa > 0$ s.t. for $\sigma^2 \leqslant (\varepsilon^{1/4}\delta)^2/\log(\sqrt{\varepsilon}/\delta)$

▷ Principal eigenvalue:

$$1 - \lambda_0 \leqslant \exp\biggl\{-\kappa \frac{(\varepsilon^{1/4}\delta)^2}{\sigma^2}\biggr\}$$

▷ Expected number of SAOs:

$$\mathbb{E}^{\mu_0}[N] \geqslant C(\mu_0) \exp\biggl\{\kappa \frac{(\varepsilon^{1/4}\delta)^2}{\sigma^2}\biggr\}$$

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Proof:

▷ Construct a set $A \subset E$ that the process is unlikely to leave
▷ Use the fact that for $\delta = 0$, the deterministic system admits a first integral
▷ Apply the trivial bound

Transition from weak to strong noise

Linear approximation near separatrix:

$$\mathrm{d}z_t^0 = \left(\frac{\delta - \sigma_1^2/\varepsilon}{\varepsilon^{1/2}} + t z_t^0\right)\mathrm{d}t - \frac{\sigma_1}{\varepsilon^{3/4}} t\,\mathrm{d}W_t^{(1)} + \frac{\sigma_2}{\varepsilon^{3/4}}\,\mathrm{d}W_t^{(2)}$$

$$\Rightarrow \quad \mathbb{P}\{N = 1\} \simeq \Phi\left(-\pi^{1/4}\frac{\varepsilon^{1/4}(\delta - \sigma_1^2/\varepsilon)}{\sqrt{\sigma_1^2 + \sigma_2^2}}\right) \qquad \Phi(x) = \int_{-\infty}^{x} \frac{\mathrm{e}^{-y^2/2}}{\sqrt{2\pi}}\,\mathrm{d}y$$

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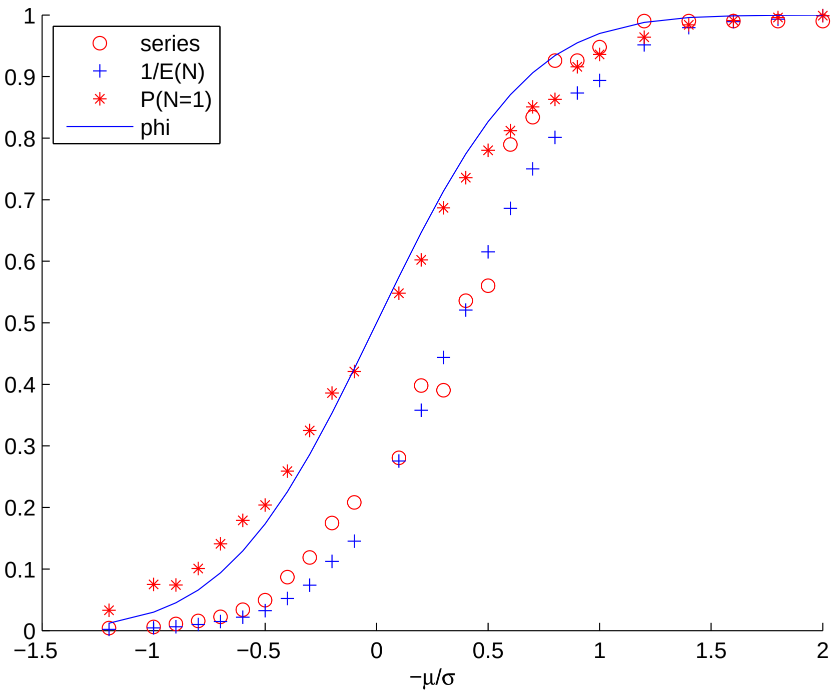

$*$: $\mathbb{P}\{\text{no SAO}\}$

$+$: $1/\mathbb{E}[N]$

$\circ$: $1-\lambda_0$

curve: $x \mapsto \Phi(\pi^{1/4}x)$

Back to the general case

[Joint work with Barbara Gentz, Christian Kuehn, in progress]

▷ Consider system of dim$\geqslant 3$ with several stable periodic orbits

▷ Noise can cause transitions between these orbits

▷ E.g. [Höpfner, Löcherbach & Thieullen '12] show that a HH system with noise will track any det solution with positive probability for some time

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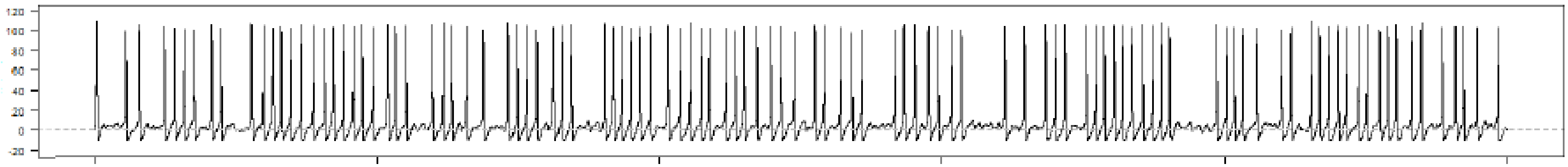

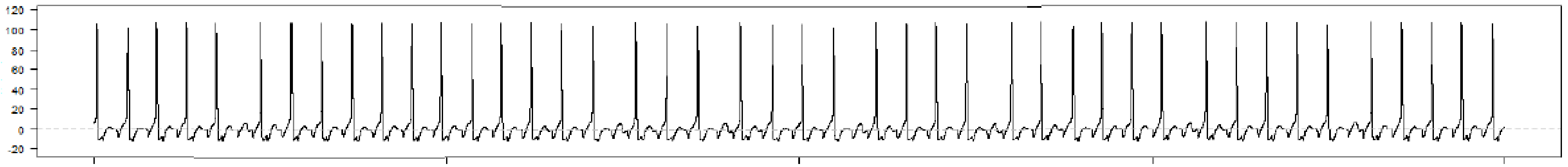

Pictures courtesy of K. Endler, master thesis, directed by R. Höpfner & M. Birkner

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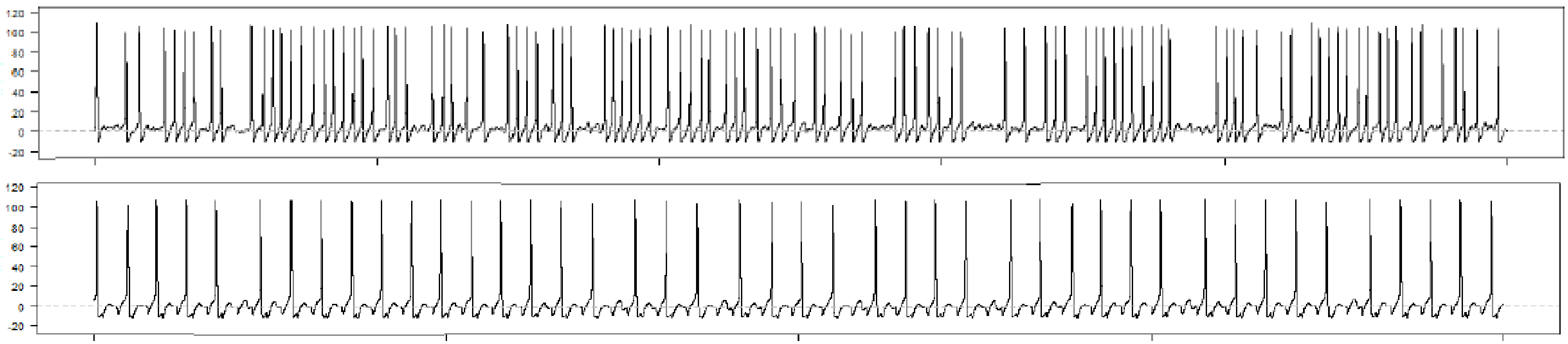

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▷ Can we quantify transitions between deterministic patterns?

▷ Does the dynamics resemble some kind of Markov process jumping between patterns?

▷ Spectral-theoretic approach inspired from reversible case

Laplace transforms

Given $A \subset E$, $B \subset E \cup \{\Delta\}$, $A \cap B = \emptyset$, $x \in E$ and $u \in \mathbb{C}$, define

$$\tau_A = \inf\{n \geqslant 1 \colon X_n \in A\} \qquad G^u_{A,B}(x) = \mathbb{E}^x[\mathrm{e}^{u\tau_A} 1_{\{\tau_A < \tau_B\}}]$$
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▷ $G^u_{A,B}(x)$ is analytic for $|\mathrm{e}^u| < \Big[\sup_{x\in(A\cup B)^c} K(x,(A\cup B)^c)\Big]^{-1}$

▷ $G^u_{A,B} = H^u_{A,B}$ in $(A \cup B)^c$, $H^u_{A,B} = 1$ in A and $H^u_{A,B} = 0$ in B

▷ Feynman–Kac-type relation

$$K H^u_{A,B} = \mathrm{e}^{-u} G^u_{A,B}$$

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$$KH^u_{A,B} = \mathrm{e}^{-u} G^u_{A,B}$$

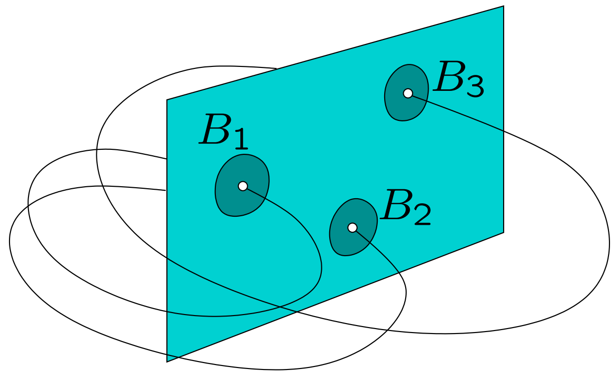
Proof:

$$\begin{aligned}
(KH^u_{A,B})(x) &= \mathbb{E}^x\Bigl[\mathbb{E}^{X_1}\bigl[\mathrm{e}^{u\sigma_A} 1_{\{\sigma_A < \sigma_B\}}\bigr]\Bigr] \\
&= \mathbb{E}^x\Bigl[1_{\{X_1 \in A\}}\mathbb{E}^{X_1}\bigl[\mathrm{e}^{u\sigma_A} 1_{\{\sigma_A < \sigma_B\}}\bigr]\Bigr] + \mathbb{E}^x\Bigl[1_{\{X_1 \in A^c\}}\mathbb{E}^{X_1}\bigl[\mathrm{e}^{u\sigma_A} 1_{\{\sigma_A < \sigma_B\}}\bigr]\Bigr] \\
&= \mathbb{E}^x\bigl[1_{\{1 = \tau_A < \tau_B\}}\bigr] + \mathbb{E}^x\bigl[\mathrm{e}^{u(\tau_A - 1)} 1_{\{1 < \tau_A < \tau_B\}}\bigr] \\
&= \mathbb{E}^x\bigl[\mathrm{e}^{u(\tau_A - 1)} 1_{\{\tau_A < \tau_B\}}\bigr] = \mathrm{e}^{-u} G^u_{A,B}(x)
\end{aligned}$$

$\Rightarrow$ if $G^u_{A,B}$ varies little in $A \cup B$, it is close to an eigenfunction

Heuristics (inspired by [Bovier, Eckhoff, Gayrard, Klein '04])

- Stable periodic orbits in $x_1, \dots, x_N$
- B_i small ball around x_i, $B = \bigcup_{i=1}^N B_i$
- Eigenvalue equation
  $(Kh)(x) = \mathrm{e}^{-u} h(x)$
- Assume $h(x) \simeq h_i$ in B_i



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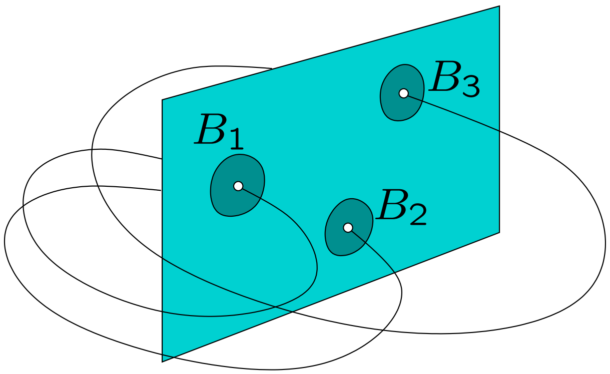

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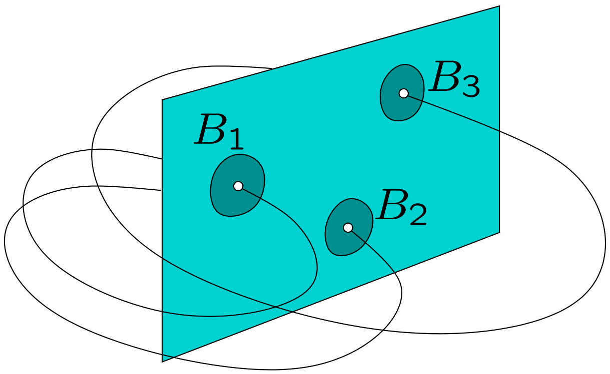

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- ▷ $x \in B_i$: $h(x) = h_i + r(x)$
- ▷ $x \in B^c$: eigenvalue equation is satisfied (by Feynman–Kac)
- ▷ $x = x_i$: eigenvalue equation yields by Feynman–Kac

$$h_i = \sum_{j=1}^{N} h_j M_{ij}(u) \qquad M_{ij}(u) = G^u_{B_j, B\setminus B_j}(x_i) = \mathbb{E}^{x_i}[\mathrm{e}^{u\tau_B} 1_{\{\tau_B = \tau_{B_j}\}}]$$

$\Rightarrow$ condition $\det(M - 1\!\!1) = 0 \Rightarrow N$ eigenvalues exp close to 1

If $\mathbb{P}\{\tau_B > 1\} \ll 1$ then $M_{ij}(u) \simeq \mathrm{e}^u \, \mathbb{P}^{x_i}\{\tau_B = \tau_{B_j}\} =: \mathrm{e}^u P_{ij}$ and $Ph \simeq \mathrm{e}^{-u} h$

Control of the error term

The error term satisfies the boundary value problem

$$(Kr)(x) = \mathsf{e}^{-u}\, r(x) \qquad\qquad x \in B^c$$
$$r(x) = h(x) - h_i \qquad\qquad x \in B_i$$

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Proof:

- ▷ Show that $\mathcal{T} f(x) = \mathbb{E}^x[\mathrm{e}^u\, \theta(X_1) 1_{\{X_1 \in B\}}] + \mathbb{E}^x[\mathrm{e}^u\, f(X_1) 1_{\{X_1 \in B^c\}}]$ is a contraction on $L^\infty(B^c)$
- ▷ Set $\psi_0(x) = 0$, $\psi_{n+1}(x) = \mathcal{T}\psi_n(x) \quad \forall n \geqslant 0$
- ▷ Show by induction that $\psi_n(x) = \mathbb{E}^x[\mathrm{e}^{u\tau_B}\, \theta(X_{\tau_B}) 1_{\{\tau_B \leqslant n\}}]$
- ▷ $\psi(x) = \lim_{n\to\infty} \psi_n(x)$ is fixed point of $\mathcal{T}$ $\Rightarrow$ satisfies the bndry value problem

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$\Rightarrow$ $r(x) = \mathbb{E}^x[\mathrm{e}^{u\tau_B}\, \theta(X_{\tau_B})]$ where $\theta(x) = \sum_j [h(x) - h_j] 1_{\{x \in B_j\}}$

To show that $h(x) - h_j$ is small in B_j: use Harnack inequalities

Conclusions

- ▷ Reduction to an N-state process in the sense that

$$\mathbb{P}^x\{X_n \in B_i\} = \sum_{j=1}^{N} \lambda_j^n h_j(x) h_j^*(B_i) + \mathcal{O}(|\lambda_{N+1}|^n)$$

- ▷ Residence times are approx exponential (provided system can relax to QSD)
- ▷ Generically, eigenvalues λ_j are determined by "metastable hierarchy" of periodic orbits

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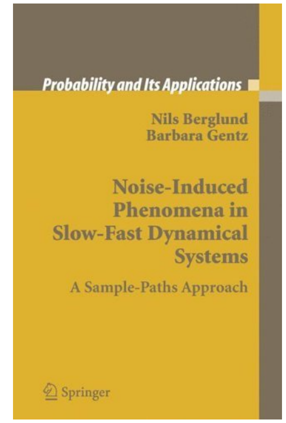
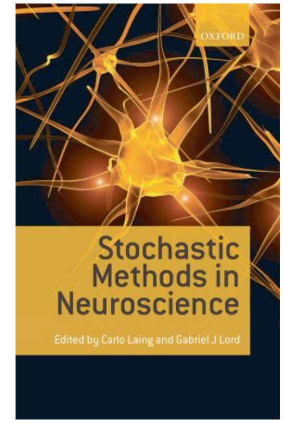
Open questions/outlook

▷ How to determine efficiently the M_{ij} or $P_{ij} = \mathbb{P}^{x_i}\{\tau_B = \tau_{B_j}\}$? Large deviations – but not easy to implement and not very precise

▷ Chaotic orbits?

Further reading





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