Some results on interspike interval statistics in conductance-based models for neuron action potentials

Nils Berglund
MAPMO, Université d'Orléans
CNRS, UMR 7349 et Fédération Denis Poisson
www.univ-orleans.fr/mapmo/membres/berglund
nils.berglund@math.cnrs.fr

Collaborators: Barbara Gentz (Bielefeld)
Christian Kuehn (Vienne), Damien Landon (Orléans)

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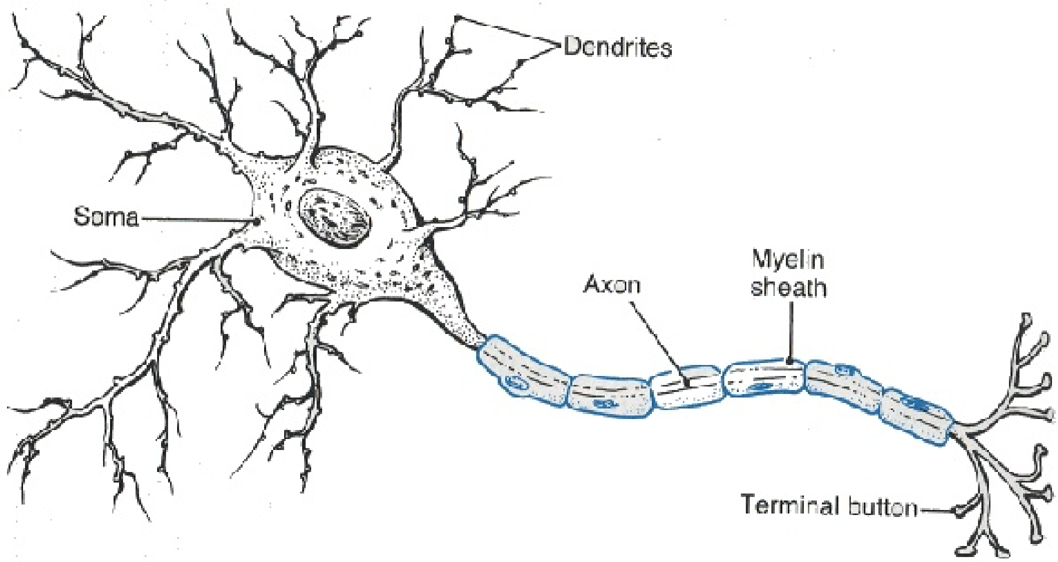
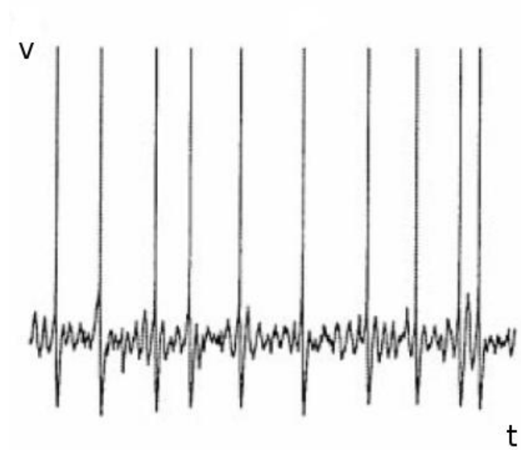
Random Models in Neuroscience
UPMC, Paris, July 5, 2012

The Poisson hypothesis





Action potential [Dickson 00]

▷ Interspike interval (ISI) statistics (under random stimulation)

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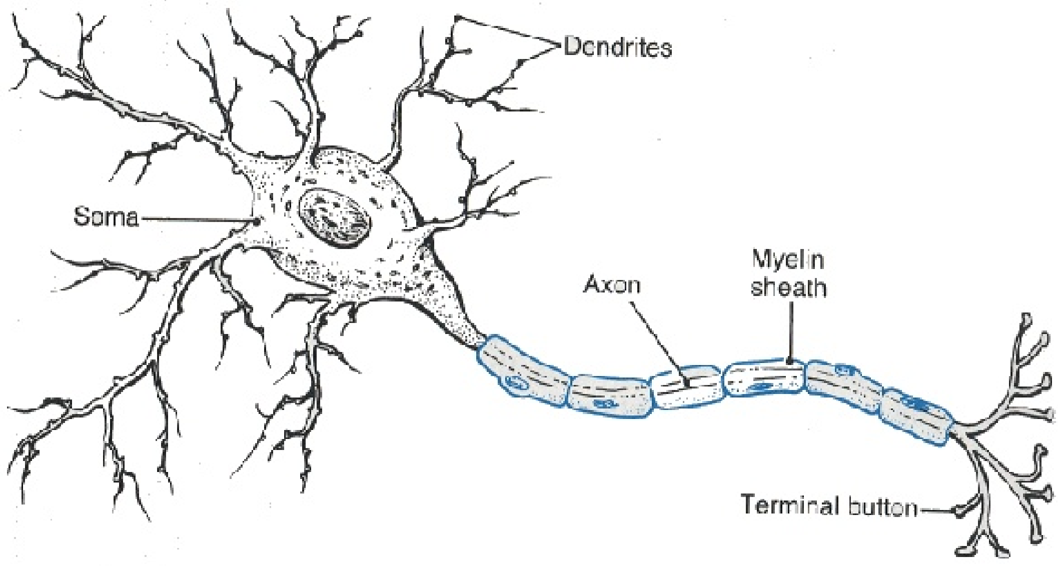

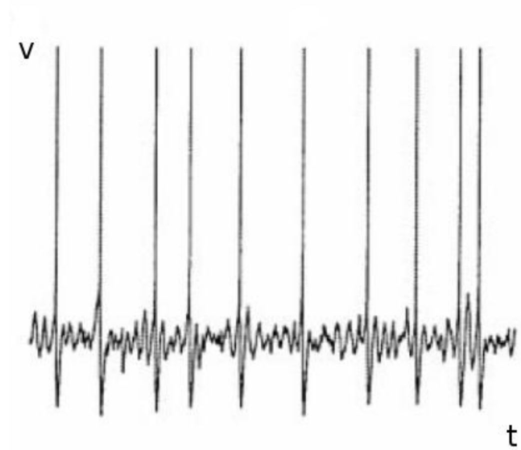

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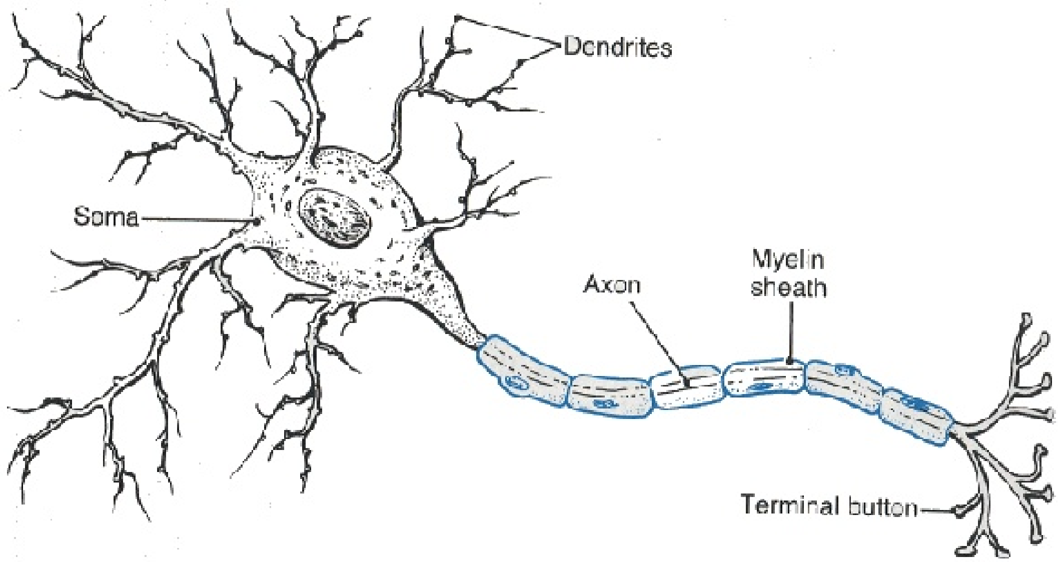
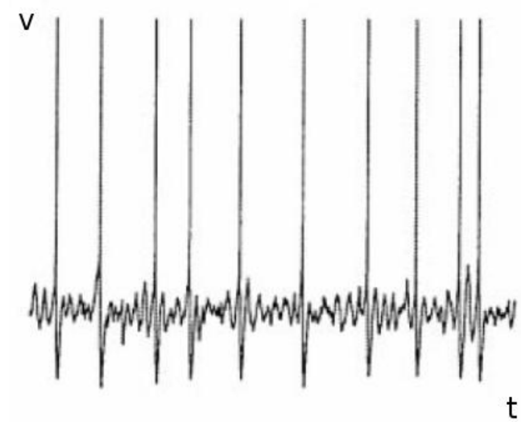




Action potential [Dickson 00]

- ▷ Interspike interval (ISI) statistics (under random stimulation)
- ▷ Poisson hypothesis: ISI has exponential distribution
  Consequence: Markov property
- ▷ For which models is it a good approximation?
  What ISI can we expect for other (stochastic, conductance-based) models?

The stochastic exit problem

Stochastic differential equation (SDE)

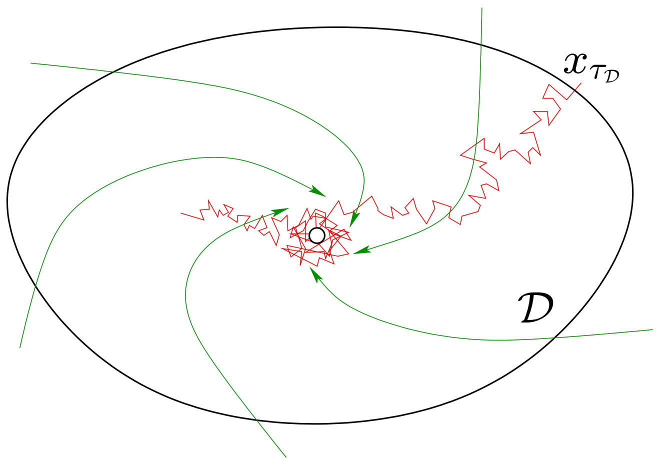
$$\mathrm{d}x_t = f(x_t)\,\mathrm{d}t + \sigma g(x_t)\,\mathrm{d}W_t \qquad x \in \mathbb{R}^n$$

Exit problem:

Given $\mathcal{D} \subset \mathbb{R}^n$, characterise

First-exit time (and location)

$\tau_{\mathcal{D}} = \inf\{t > 0 \colon x_t \notin \mathcal{D}\}$



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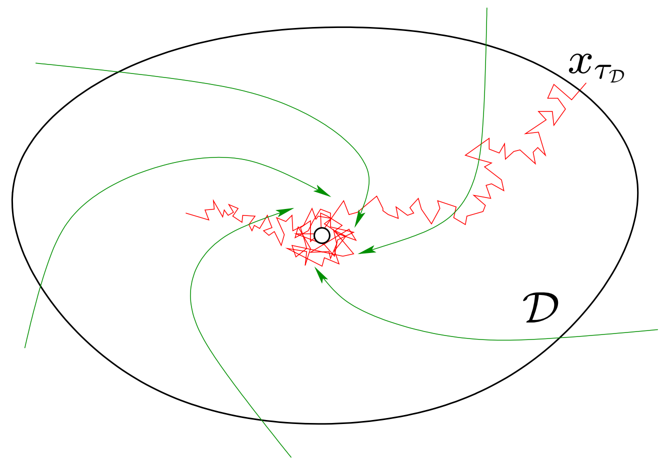

When do we have $\lim_{\sigma\to 0} \mathbb{P}\Bigl\{\tau_{\mathcal{D}} > s\mathbb{E}[\tau_{\mathcal{D}}]\Bigr\} = \mathrm{e}^{-s}$?

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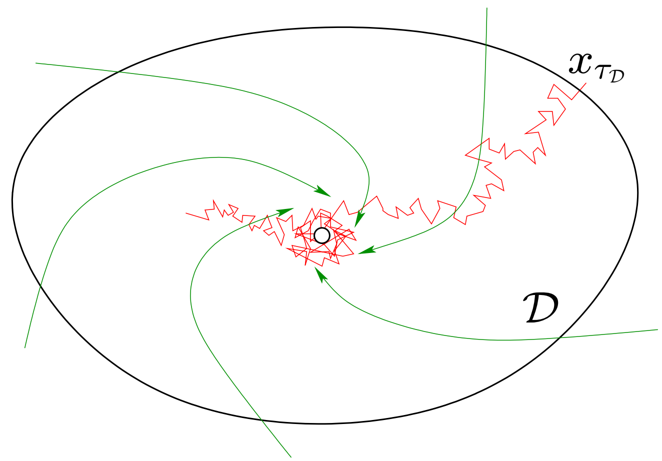

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- ▷ True if $n = 1$ ⇒ true for integrate-and-fire models
- ▷ True if $\mathcal{D} \subset$ basin of attraction [Day '83]
- ▷ True if $f(x) = -\nabla U(x)$ and $g(x) = \mathbb{1}$ [Bovier et al '04]

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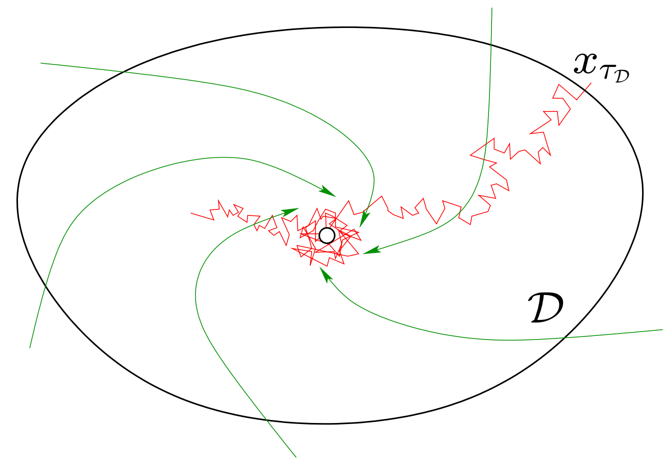

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- ▷ True if $f(x) = -\nabla U(x)$ and $g(x) = \mathbb{1}$ [Bovier et al '04]
- ▷ Not necessarily true if $n \geqslant 2$, $\operatorname{curl} f \neq 0$ and $\partial\mathcal{D} \supset$ det orbit

Deterministic FitzHugh–Nagumo (FHN) equations

Consider the FHN equations in the form

$$\varepsilon \dot{x} = x - x^3 + y$$
$$\dot{y} = a - x - by$$

- ▷ $x \propto$ membrane potential of neuron
- ▷ $y \propto$ proportion of open ion channels (recovery variable)
- ▷ $\varepsilon \ll 1 \Rightarrow$ fast–slow system
- ▷ $b = 0$ in the following for simplicity

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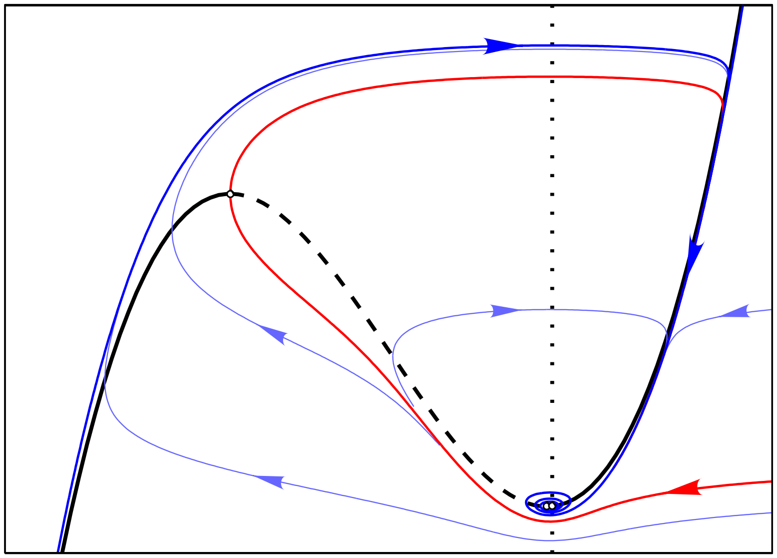
Stationary point $P = (a, a^3 - a)$
Linearisation has eigenvalues $\frac{-\delta \pm \sqrt{\delta^2 - \varepsilon}}{\varepsilon}$ where $\delta = \frac{3a^2 - 1}{2}$

- ▷ $\delta > 0$: stable node ($\delta > \sqrt{\varepsilon}$) or focus ($0 < \delta < \sqrt{\varepsilon}$)
- ▷ $\delta = 0$: singular Hopf bifurcation [Erneux & Mandel '86]
- ▷ $\delta < 0$: unstable focus ($-\sqrt{\varepsilon} < \delta < 0$) or node ($\delta < -\sqrt{\varepsilon}$)

Deterministic FitzHugh–Nagumo (FHN) equations

$\delta > 0$:

- ▷ P is asymptotically stable
- ▷ the system is excitable
- ▷ one can define a separatrix



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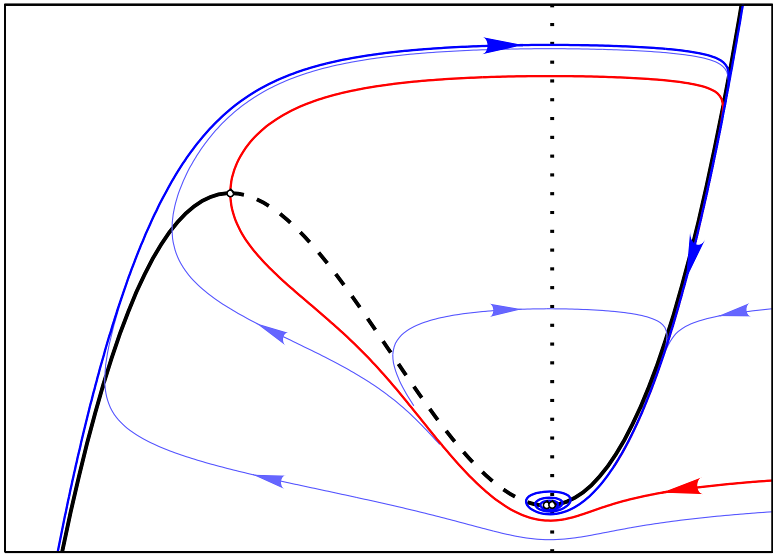

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- ▷ P is unstable
- ▷ ∃ asympt. stable periodic orbit
- ▷ sensitive dependence on δ:
  canard (duck) phenomenon
  [Callot, Diener, Diener '78,
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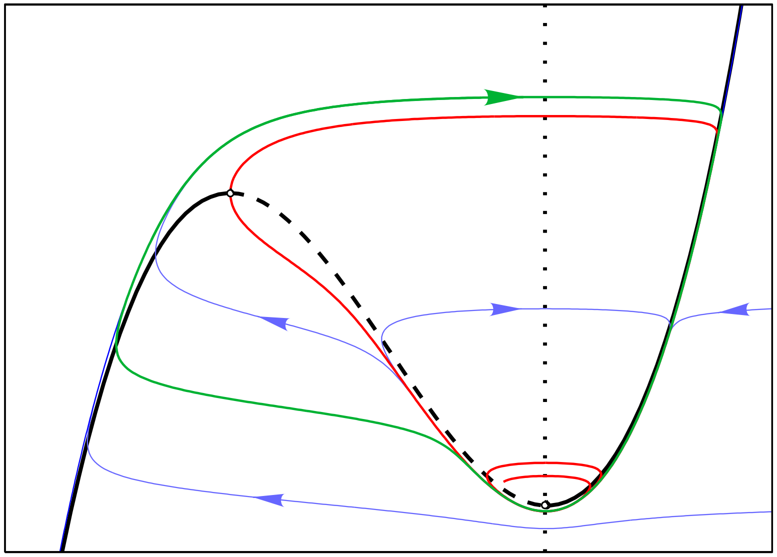

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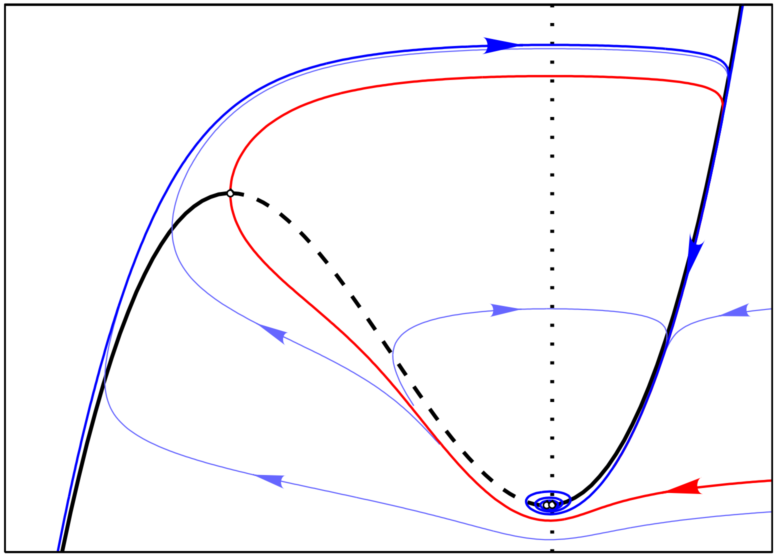

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Stochastic FHN equations

$$\mathrm{d}x_t = \frac{1}{\varepsilon}[x_t - x_t^3 + y_t]\,\mathrm{d}t + \frac{\sigma_1}{\sqrt{\varepsilon}}\,\mathrm{d}W_t^{(1)}$$
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▷ $W_t^{(1)}, W_t^{(2)}$: independent Wiener processes

▷ $0 < \sigma_1, \sigma_2 \ll 1$, $\sigma = \sqrt{\sigma_1^2 + \sigma_2^2}$

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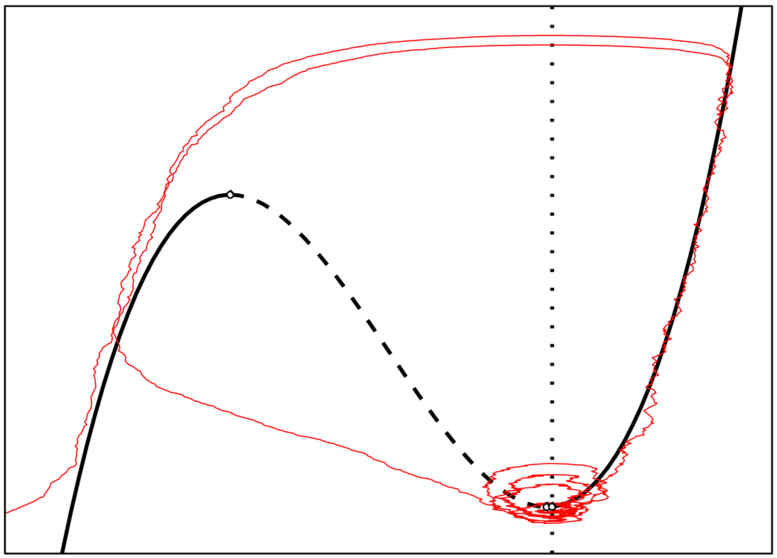

$\varepsilon = 0.1$
$\delta = 0.02$
$\sigma_1 = \sigma_2 = 0.03$

Some previous work

- ▷ Numerical: Kosmidis & Pakdaman '03, . . . , Borowski et al '11
- ▷ Moment methods: Tanabe & Pakdaman '01
- ▷ Approx. of Fokker–Planck equ: Lindner et al '99, Simpson & Kuske '11
- ▷ Large deviations: Muratov & Vanden Eijnden '05, Doss & Thieullen '09
- ▷ Sample paths near canards: Sowers '08

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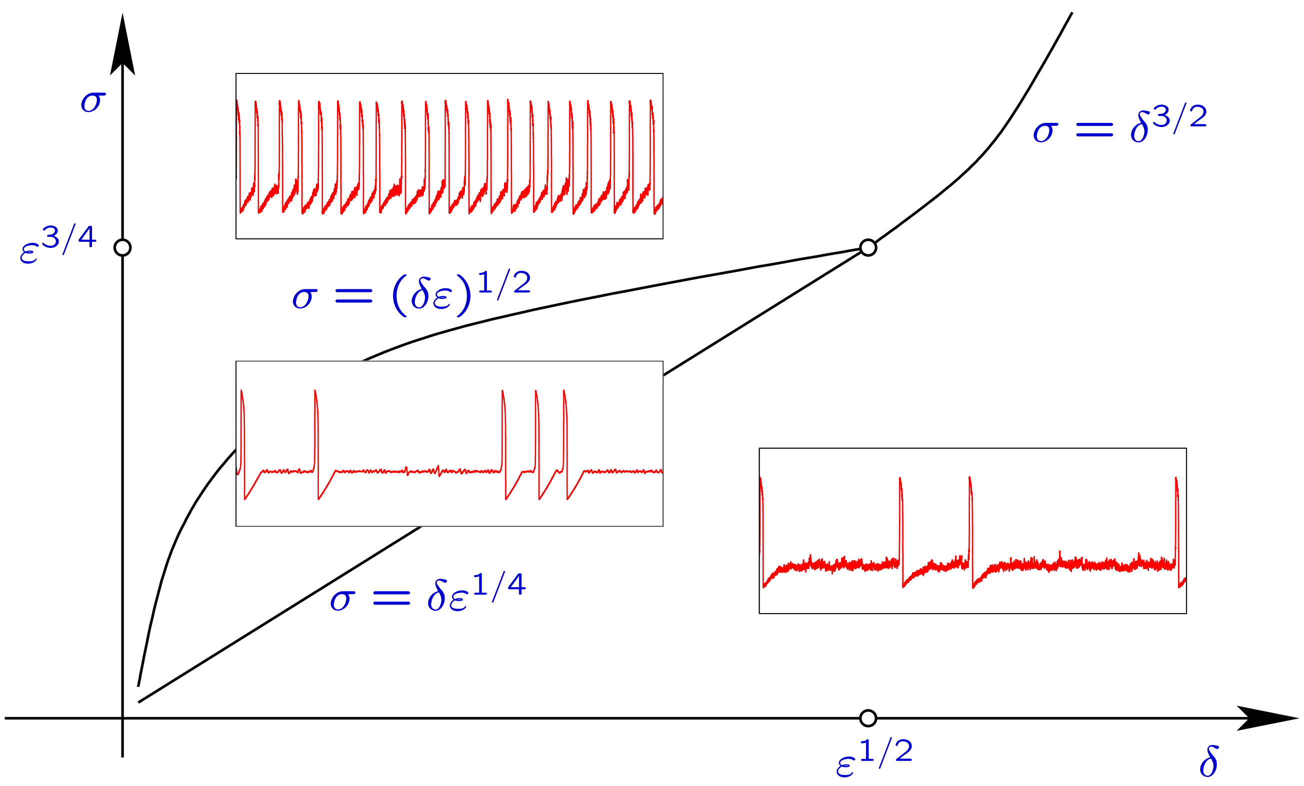
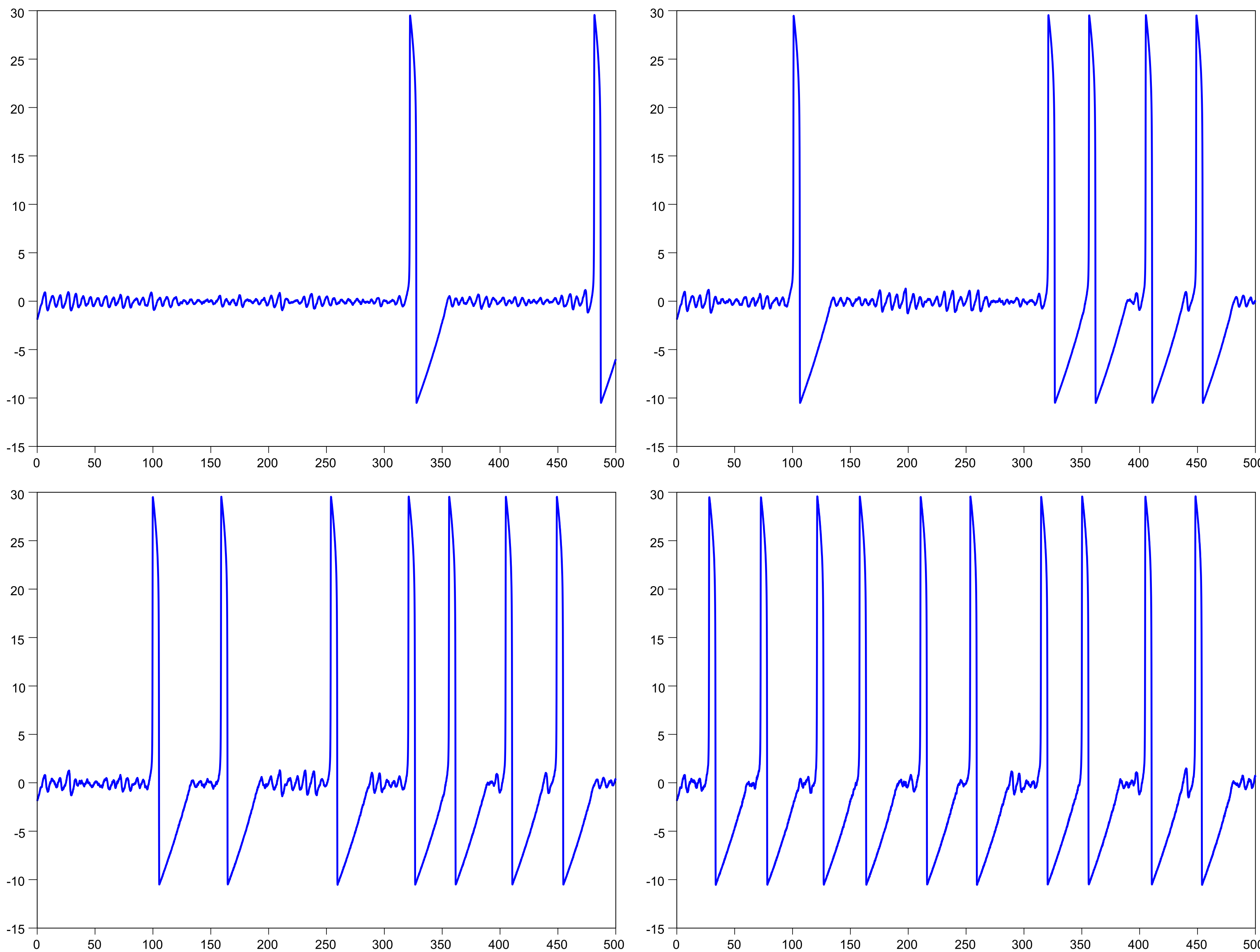
Proposed "phase diagram" [Muratov & Vanden Eijnden '08]

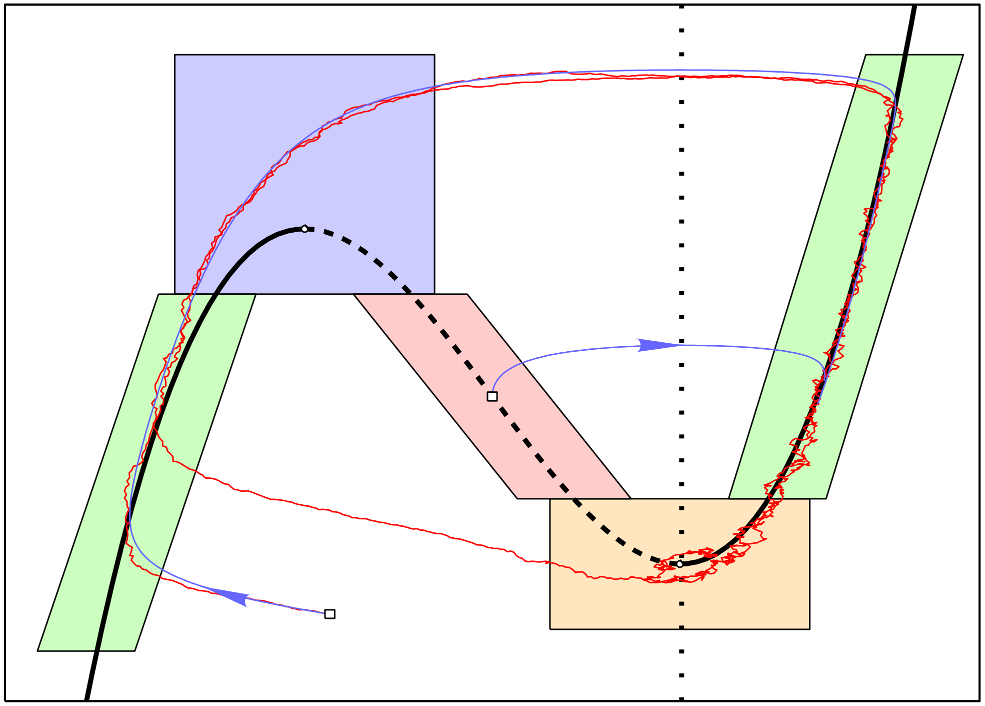


Intermediate regime: mixed-mode oscillations (MMOs)



Time series $t \mapsto -x_t$ for $\varepsilon = 0.01$, $\delta = 3 \cdot 10^{-3}$, $\sigma = 1.46 \cdot 10^{-4}, \dots, 3.65 \cdot 10^{-4}$

Precise analysis of sample paths



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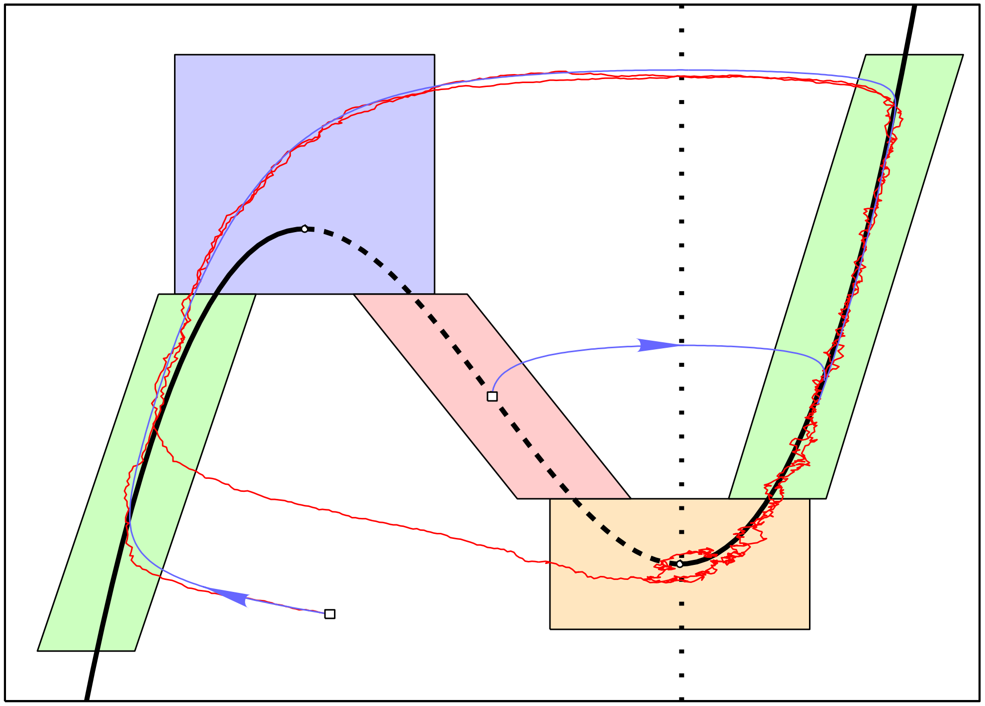
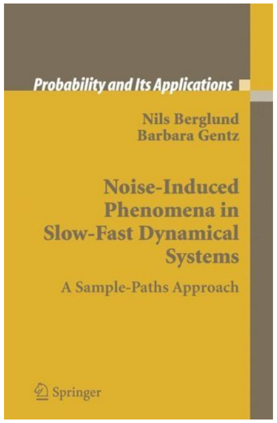


▷ Dynamics near stable branch, unstable branch and saddle–node bifurcation: already done in [B & Gentz '05]



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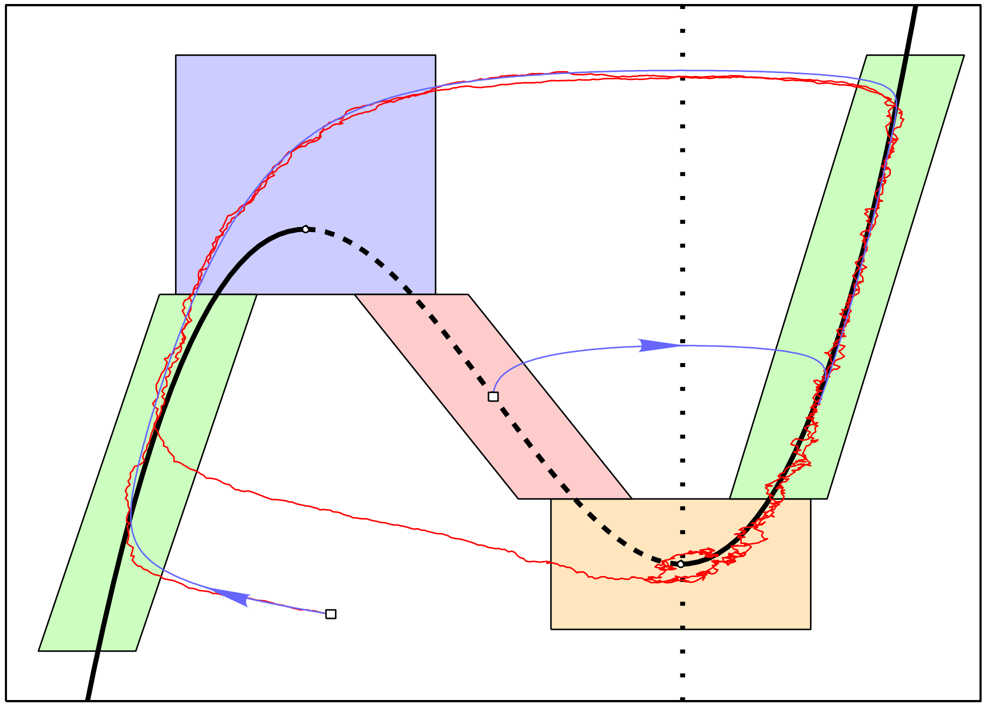
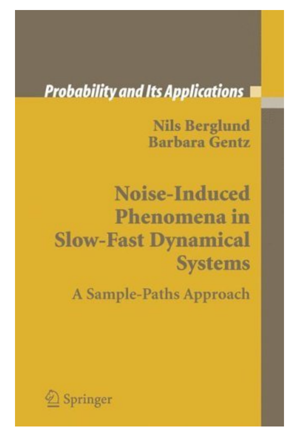
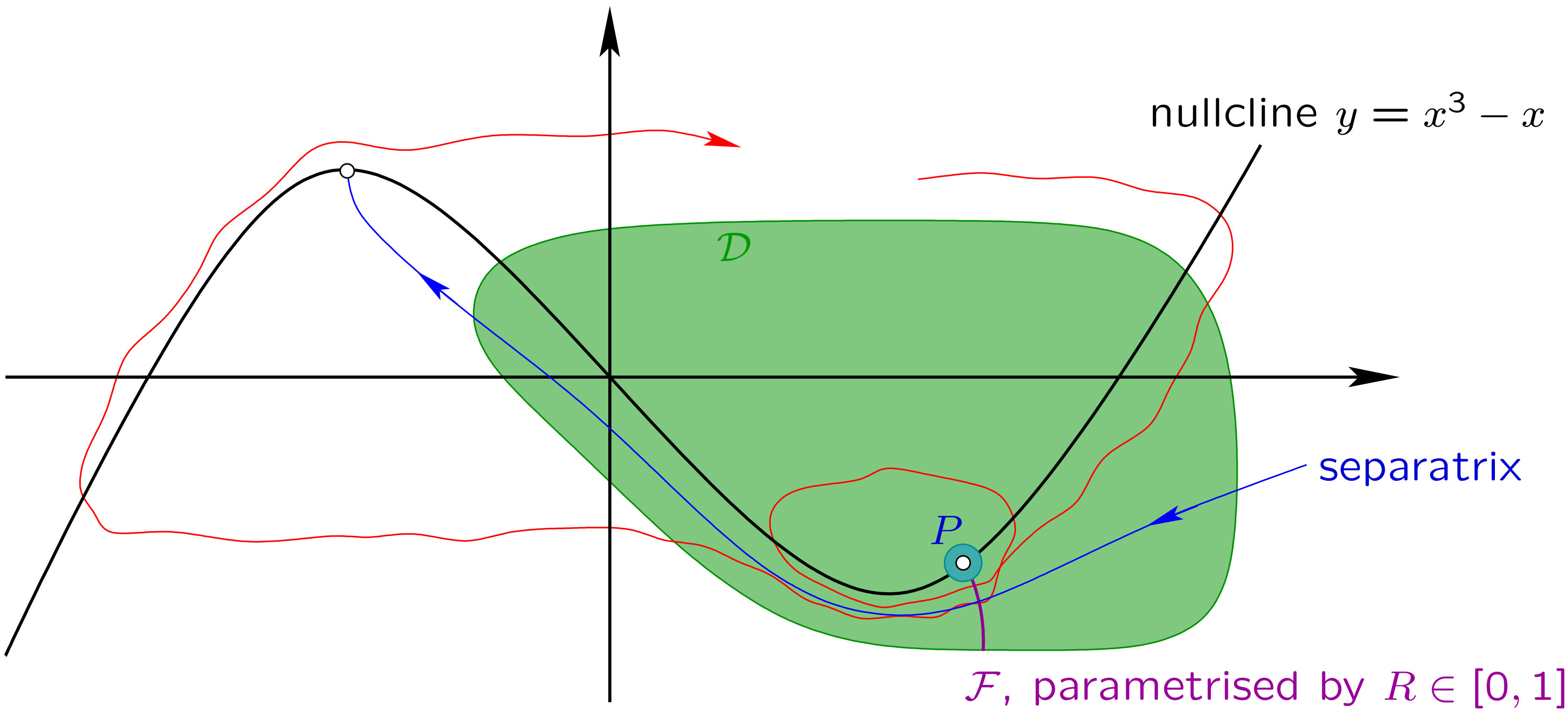


- ▷ Dynamics near stable branch, unstable branch and saddle–node bifurcation: already done in [B & Gentz '05]
- ▷ Dynamics near singular Hopf bifurcation: To do



Small-amplitude oscillations (SAOs)

Definition of random number of SAOs N:



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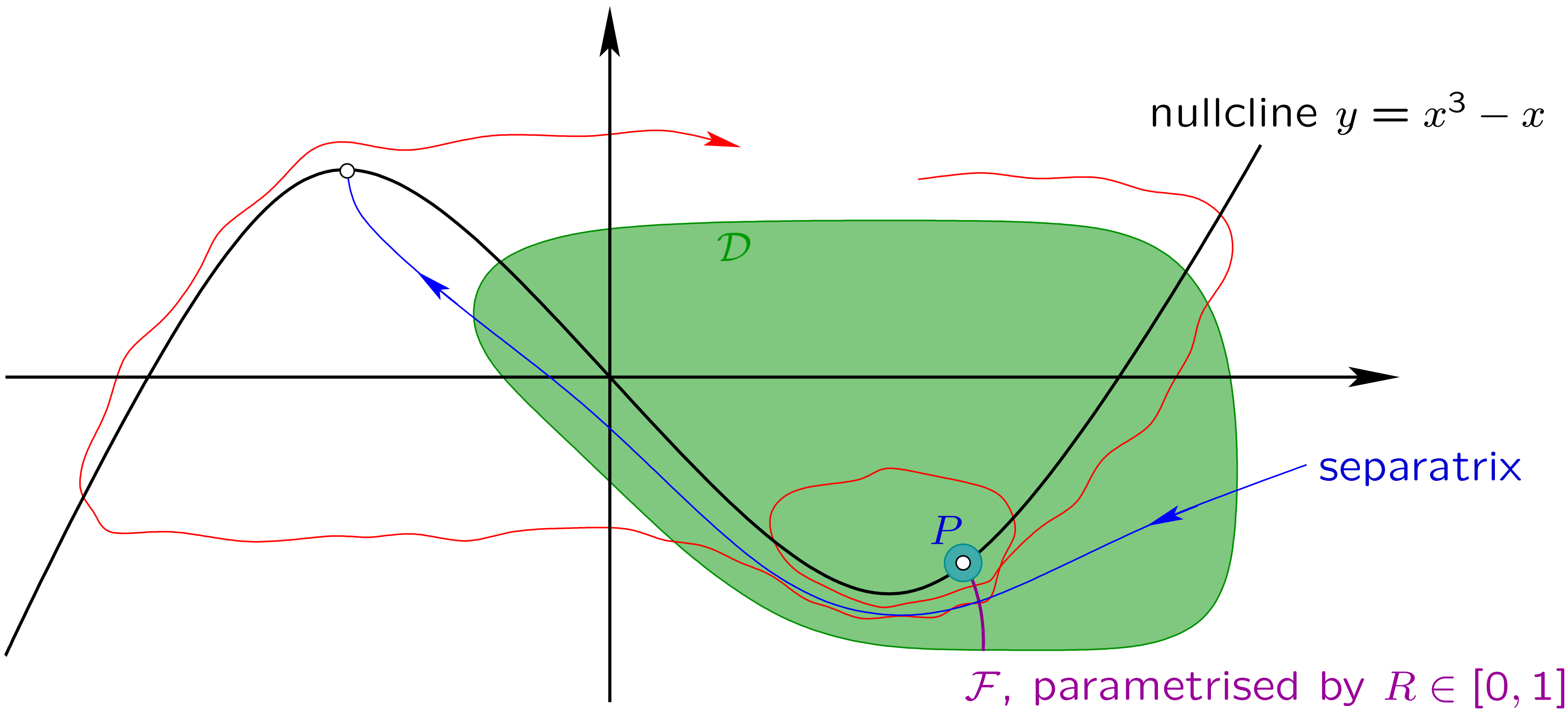

$(R_0, R_1, \dots, R_{N-1})$ substochastic Markov chain with kernel

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

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

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

General results on distribution of SAOs

General theory of continuous-space Markov chains: [Orey '71, Nummelin '84]

Principal eigenvalue: eigenvalue λ_0 of K of largest module. $\lambda_0 \in \mathbb{R}$
Quasistationary distribution: prob. measure π_0 s.t. $\pi_0 K = \lambda_0 \pi_0$

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Theorem 1: [B & Landon, 2011] Assume $\sigma_1, \sigma_2 > 0$

- ▷ $\lambda_0 < 1$
- ▷ K admits quasistationary distribution π_0
- ▷ N is almost surely finite
- ▷ N is asymptotically geometric:

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

- ▷ $\mathbb{E}[r^N] < \infty$ for $r < 1/\lambda_0$, so all moments of N are finite

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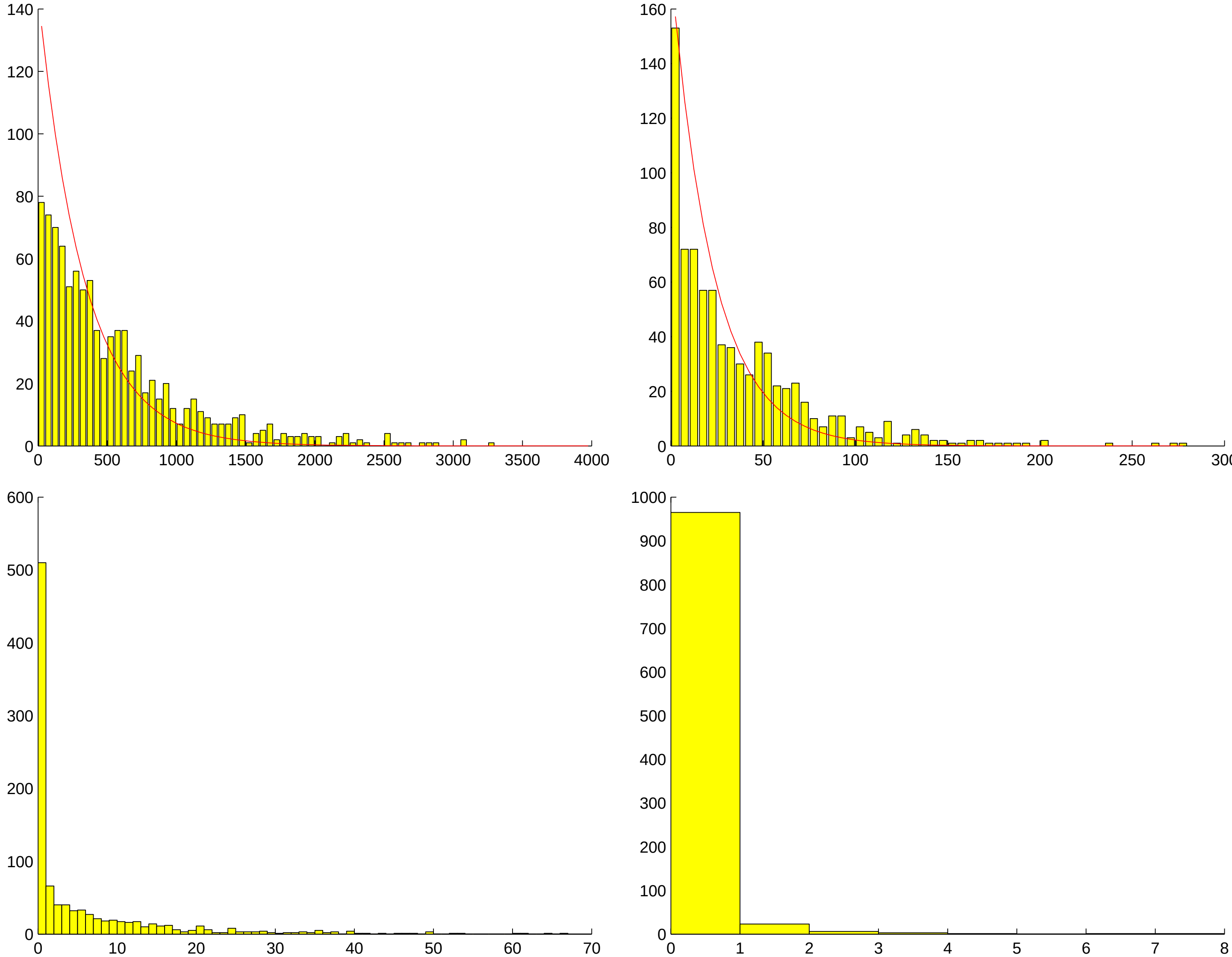
Proof:

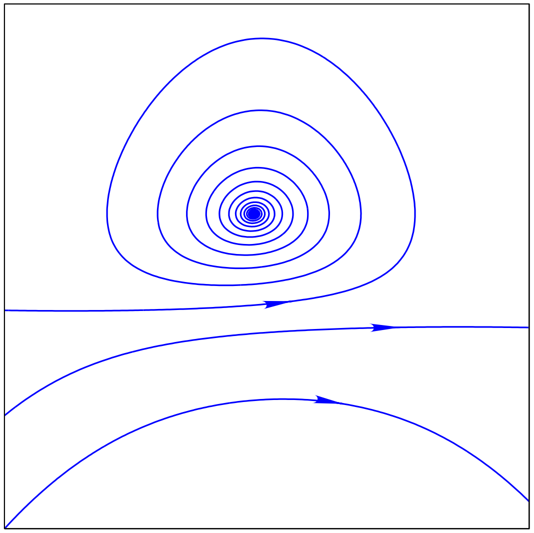
- ▷ uses Frobenius–Perron–Jentzsch–Krein–Rutman–Birkhoff theorem
- ▷ [Ben Arous, Kusuoka, Stroock '84] implies uniform positivity of K
- ▷ which implies spectral gap

Histograms of distribution of SAO number N (1000 spikes)

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



Dynamics near the separatrix



Change of variables:

- ▷ Translate to Hopf bif. point
- ▷ Scale space and time
- ▷ Straighten nullcline $\dot{x} = 0$

$\Rightarrow$ variables (ξ, z) where nullcline: $\{z = \frac{1}{2}\}$

$$\mathrm{d}\xi_t = \left(\frac{1}{2} - z_t - \frac{\sqrt{\varepsilon}}{3}\xi_t^3\right)\mathrm{d}t$$

$$\mathrm{d}z_t = \left(\tilde{\mu} + 2\xi_t z_t + \frac{2\sqrt{\varepsilon}}{3}\xi_t^4\right)\mathrm{d}t$$

where

$$\tilde{\mu} = \frac{\delta}{\sqrt{\varepsilon}}$$

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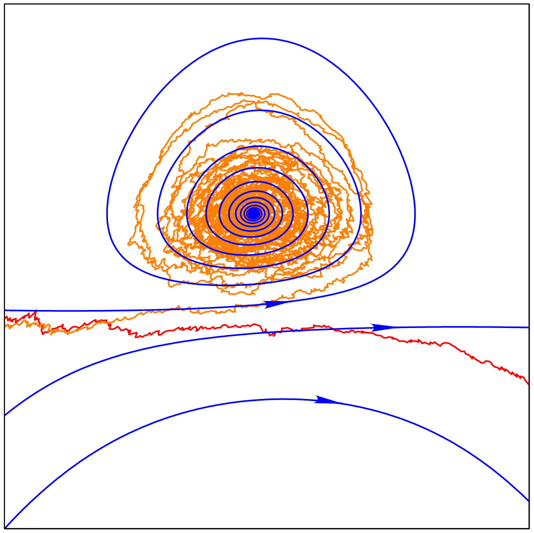

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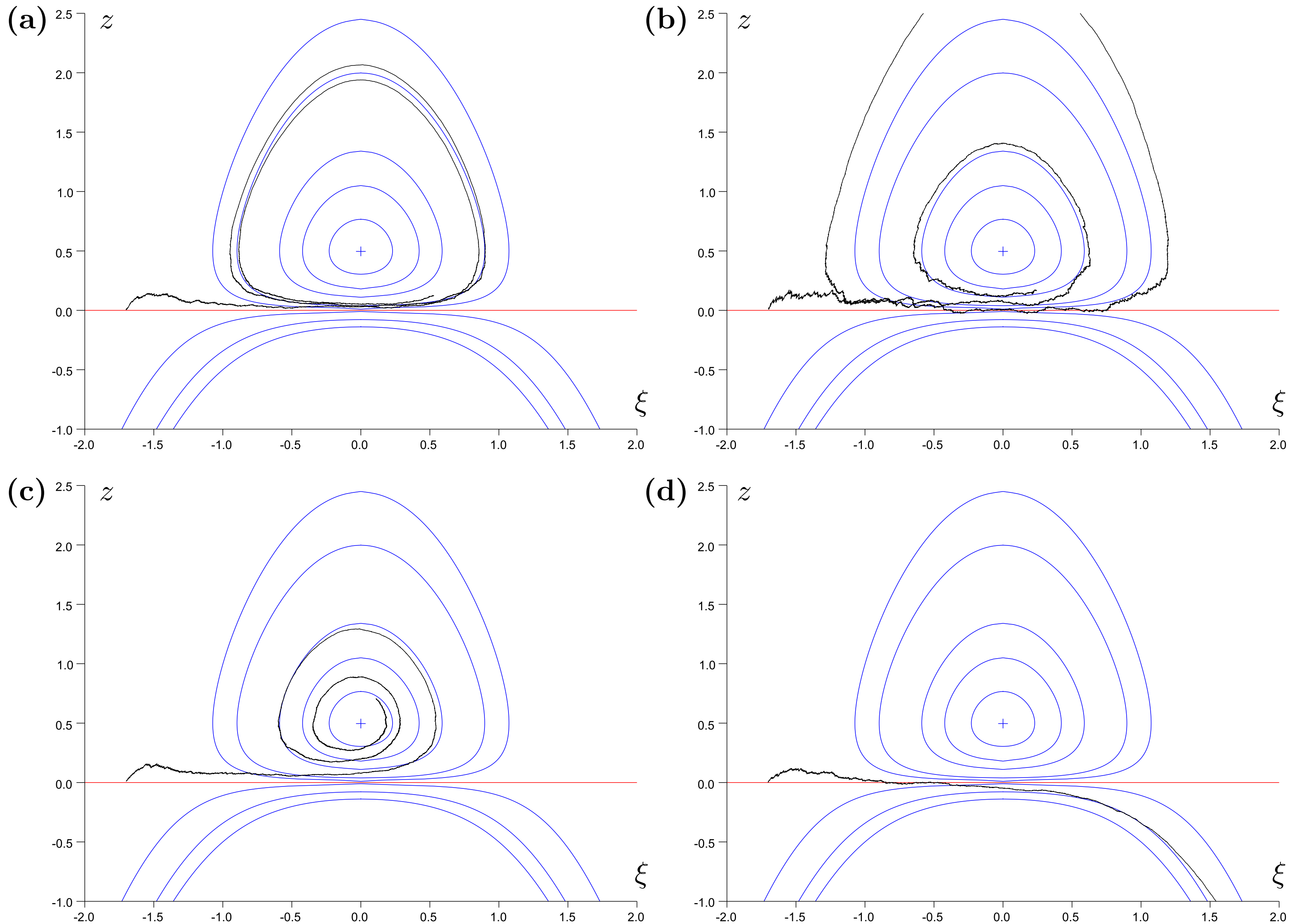
where

$$\tilde{\mu} = \frac{\delta}{\sqrt{\varepsilon}} - \tilde{\sigma}_1^2 \qquad \tilde{\sigma}_1 = -\sqrt{3}\frac{\sigma_1}{\varepsilon^{3/4}} \qquad \tilde{\sigma}_2 = \sqrt{3}\frac{\sigma_2}{\varepsilon^{3/4}}$$

Upward drift dominates if $\tilde{\mu}^2 \gg \tilde{\sigma}_1^2 + \tilde{\sigma}_2^2 \Rightarrow (\varepsilon^{1/4}\delta)^2 \gg \sigma_1^2 + \sigma_2^2$

Rotation around P: use that $2z\,\mathrm{e}^{-2z-2\xi^2+1}$ is constant for $\tilde{\mu} = \varepsilon = 0$

Dynamics near the separatrix



Transition from weak to strong noise

Linear approximation:

$$\mathrm{d}z_t^0 = \left(\tilde{\mu} + t z_t^0\right)\mathrm{d}t - \tilde{\sigma}_1 t\,\mathrm{d}W_t^{(1)} + \tilde{\sigma}_2\,\mathrm{d}W_t^{(2)}$$

$$\Rightarrow \quad \mathbb{P}\{\text{no SAO}\} \simeq \Phi\left(-\pi^{1/4}\frac{\tilde{\mu}}{\sqrt{\tilde{\sigma}_1^2+\tilde{\sigma}_2^2}}\right) \qquad \Phi(x) = \int_{-\infty}^{x} \frac{\mathrm{e}^{-y^2/2}}{\sqrt{2\pi}}\,\mathrm{d}y$$

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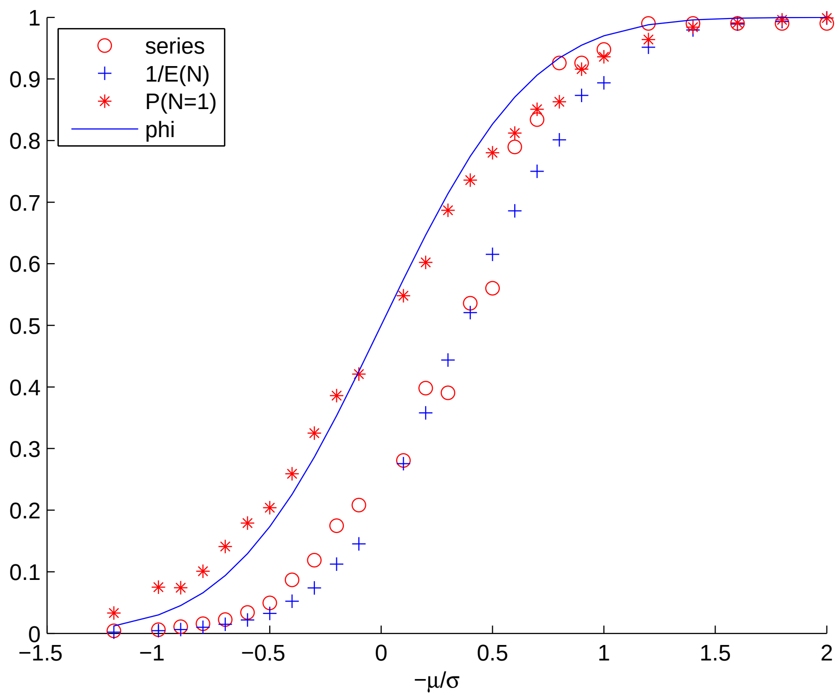

$*$: $\mathbb{P}\{\text{no SAO}\}$

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

$\circ$: $1 - \lambda_0$

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

$$x = -\frac{\tilde\mu}{\sqrt{\tilde\sigma_1^2 + \tilde\sigma_2^2}} = -\frac{\varepsilon^{1/4}(\delta - \sigma_1^2/\varepsilon)}{\sqrt{\sigma_1^2 + \sigma_2^2}}$$

The weak-noise regime

Theorem 2: [B & Landon 2011]

Assume ε and $\delta/\sqrt{\varepsilon}$ sufficiently small

There exists $\kappa > 0$ s.t. for $\sigma^2 \leqslant (\varepsilon^{1/4}\delta)^2/\log(\sqrt{\varepsilon}/\delta)$

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▷ Principal eigenvalue:

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

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▷ Expected number of SAOs:

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

where $C(\mu_0)$ = probability of starting on $\mathcal{F}$ above separatrix

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

▷ Expected number of SAOs:

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

where $C(\mu_0)$ = probability of starting on $\mathcal{F}$ above separatrix

Proof:

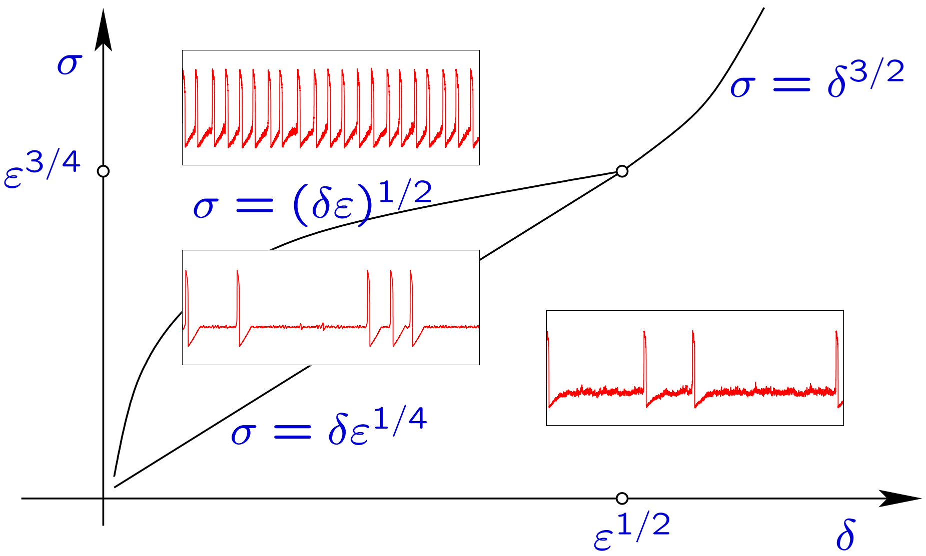
▷ Construct $A \subset \mathcal{F}$ such that $K(x, A)$ exponentially close to 1 for all $x \in A$

▷ Use two different sets of coordinates to approximate K:
Near separatrix, and during SAO

The story so far

Three regimes for $\delta < \sqrt{\varepsilon}$:

- ▷ $\sigma \ll \varepsilon^{1/4}\delta$: rare isolated spikes
  interval $\simeq \mathcal{E}xp(\sqrt{\varepsilon}\, \mathrm{e}^{-(\varepsilon^{1/4}\delta)^2/\sigma^2})$
- ▷ $\varepsilon^{1/4}\delta \ll \sigma \ll \varepsilon^{3/4}$: transition
  asympt geometric nb of SAOs
  $\sigma = (\delta\varepsilon)^{1/2}$: geometric($1/2$)
- ▷ $\sigma \gg \varepsilon^{3/4}$: repeated spikes



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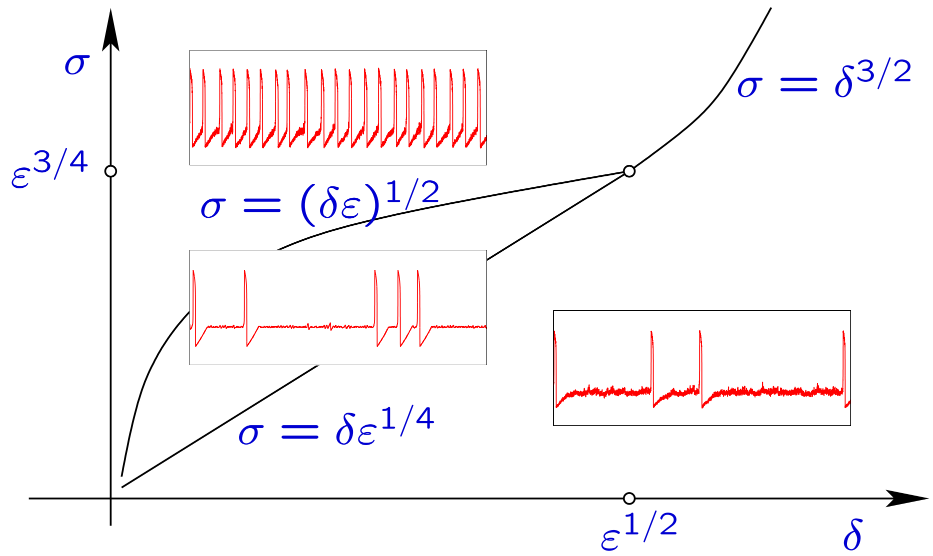
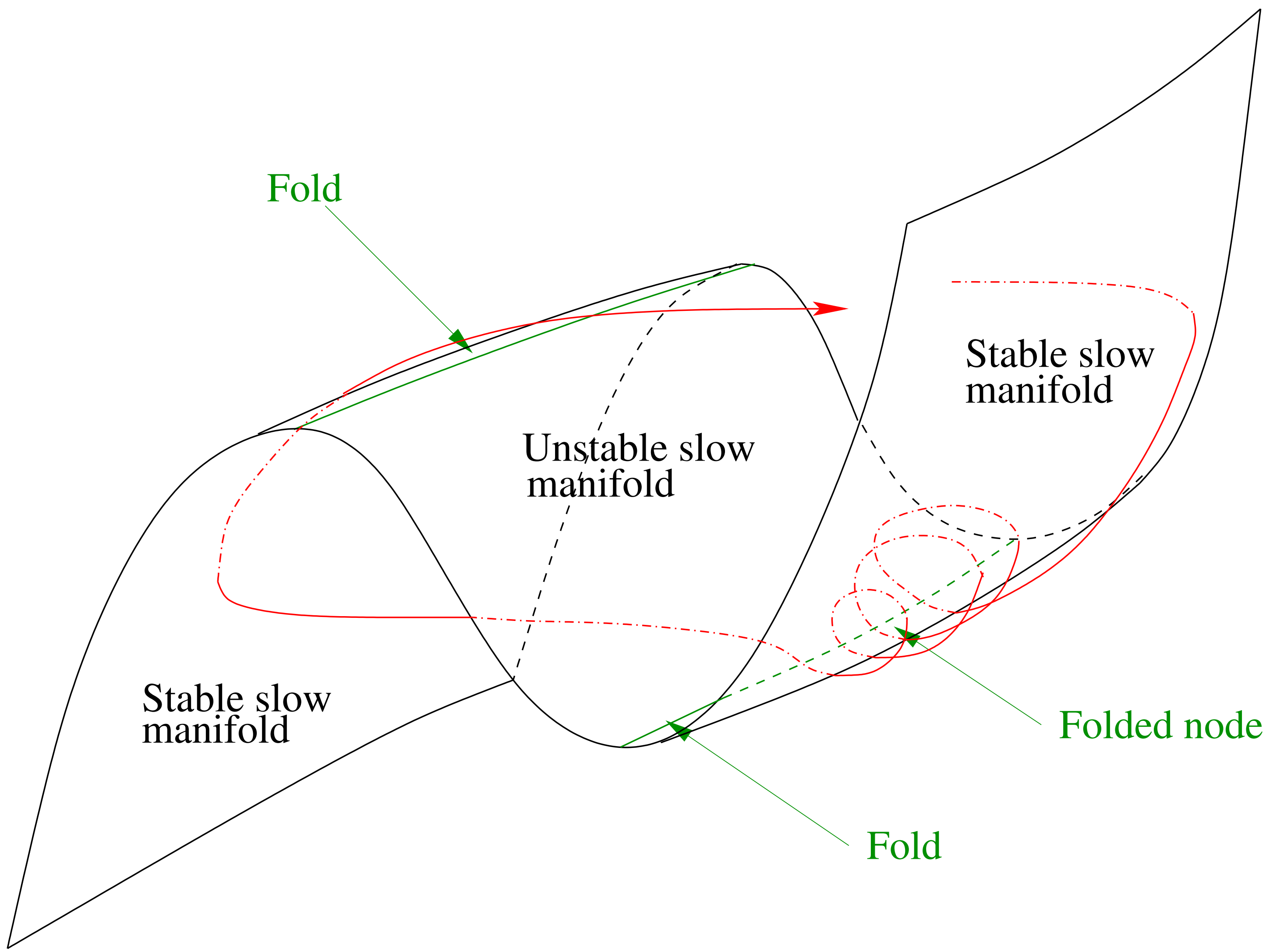


Perspectives

- ▷ interspike interval distribution $\simeq$ periodically modulated exponential – how is it modulated?
- ▷ transient effects are important - bias towards $N = 1$
  relation between $\mathbb{P}\{\text{no SAO}\}$, $1/\mathbb{E}[N]$ and $1 - \lambda_0$
- ▷ consequences of postspike distribution $\mu_0 \neq \pi_0$
- ▷ sharper bounds on λ_0 (and π_0)

Higher dimensions

Systems with one fast and two slow variables



Folded node singularity

Normal form [Benoît, Lobry '82, Szmolyan, Wechselberger '01]:

$$\begin{aligned} \epsilon\dot{x} &= y - x^2 \\ \dot{y} &= -(\mu+1)x - z \qquad\qquad \text{(+ higher-order terms)} \\ \dot{z} &= \frac{\mu}{2} \end{aligned}$$

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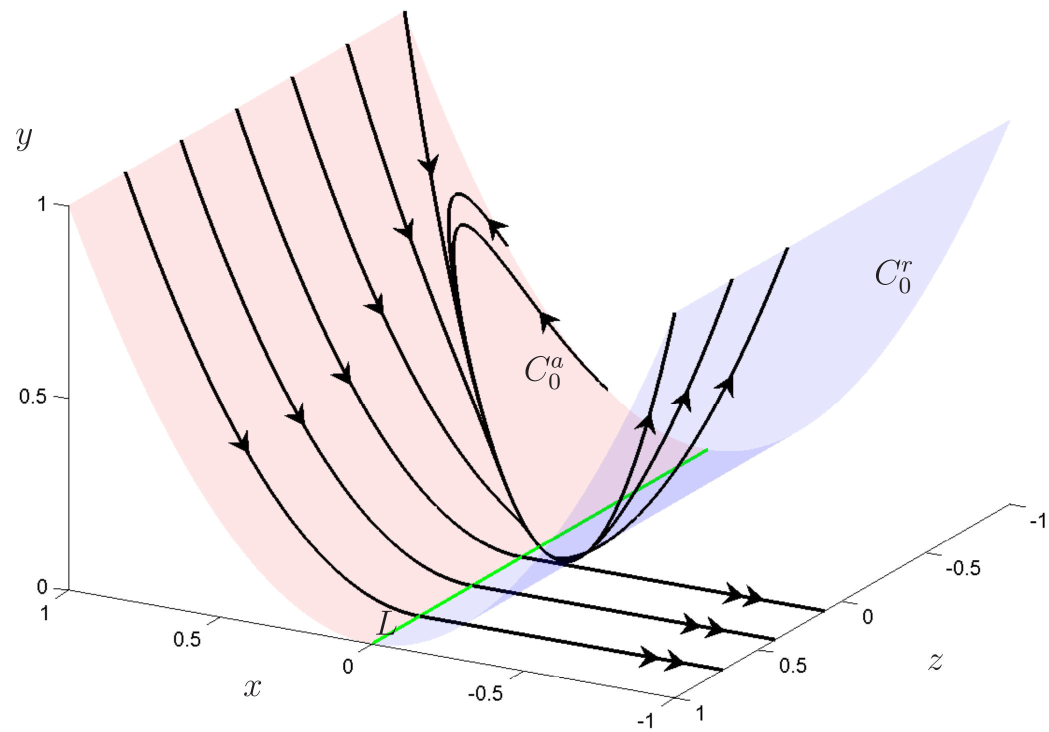
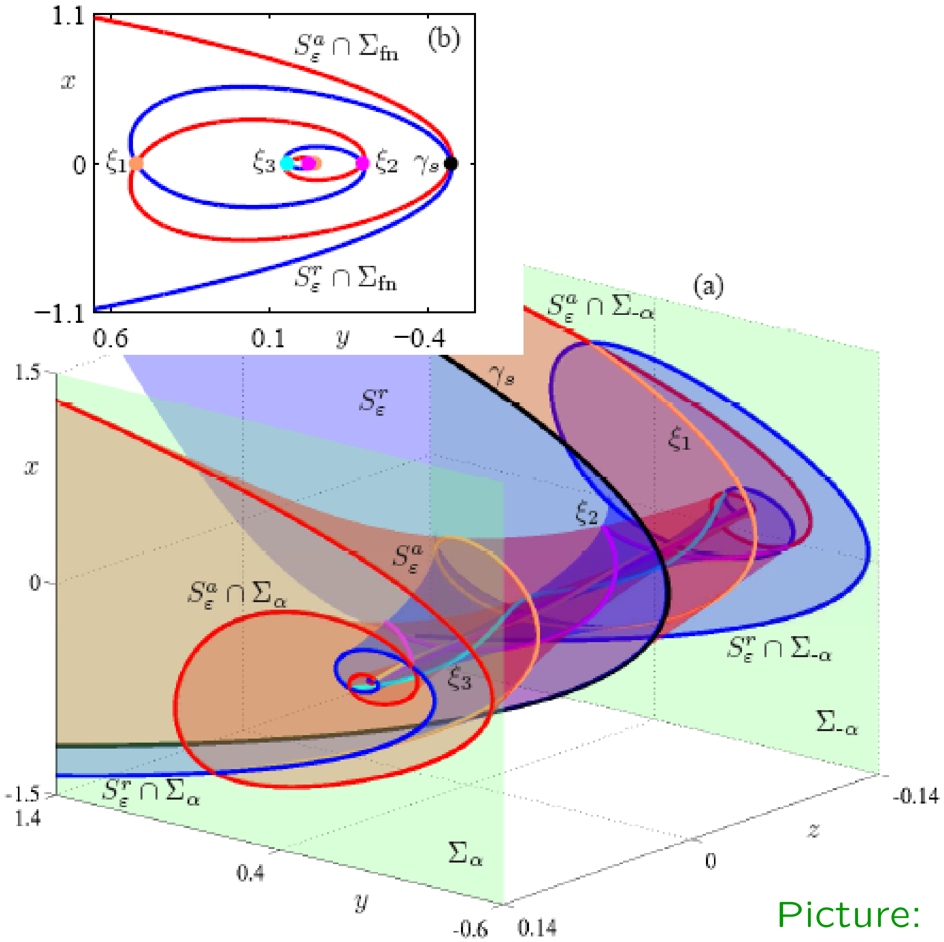
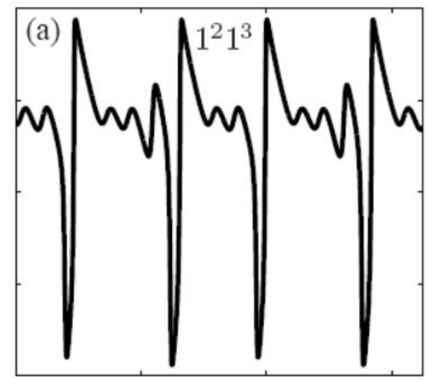


Folded node singularity

Theorem [Benoît, Lobry '82, Szmolyan, Wechselberger '01]:
For $2k + 1 < \mu^{-1} < 2k + 3$, the system admits k canard solutions
The j^{th} canard makes $(2j + 1)/2$ oscillations



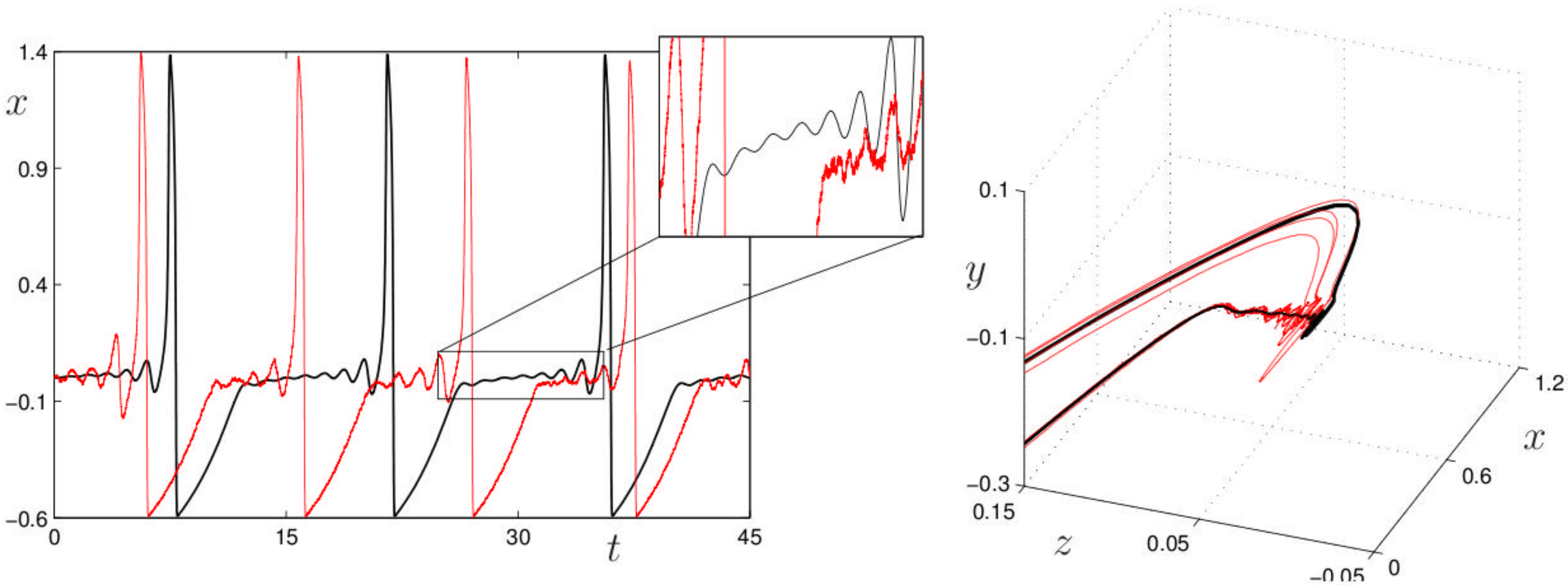


Mixed-mode oscillations (MMOs)

Picture: Mathieu Desroches

Effect of noise

$$
\begin{aligned}
\mathrm{d}x_t &= \frac{1}{\varepsilon}(y_t - x_t^2)\,\mathrm{d}t + \frac{\sigma}{\sqrt{\varepsilon}}\,\mathrm{d}W_t^{(1)} \\
\mathrm{d}y_t &= [-(\mu+1)x_t - z_t]\,\mathrm{d}t + \sigma\,\mathrm{d}W_t^{(2)} \qquad\qquad + \text{h.o.t.} \\
\mathrm{d}z_t &= \frac{\mu}{2}\,\mathrm{d}t
\end{aligned}
$$

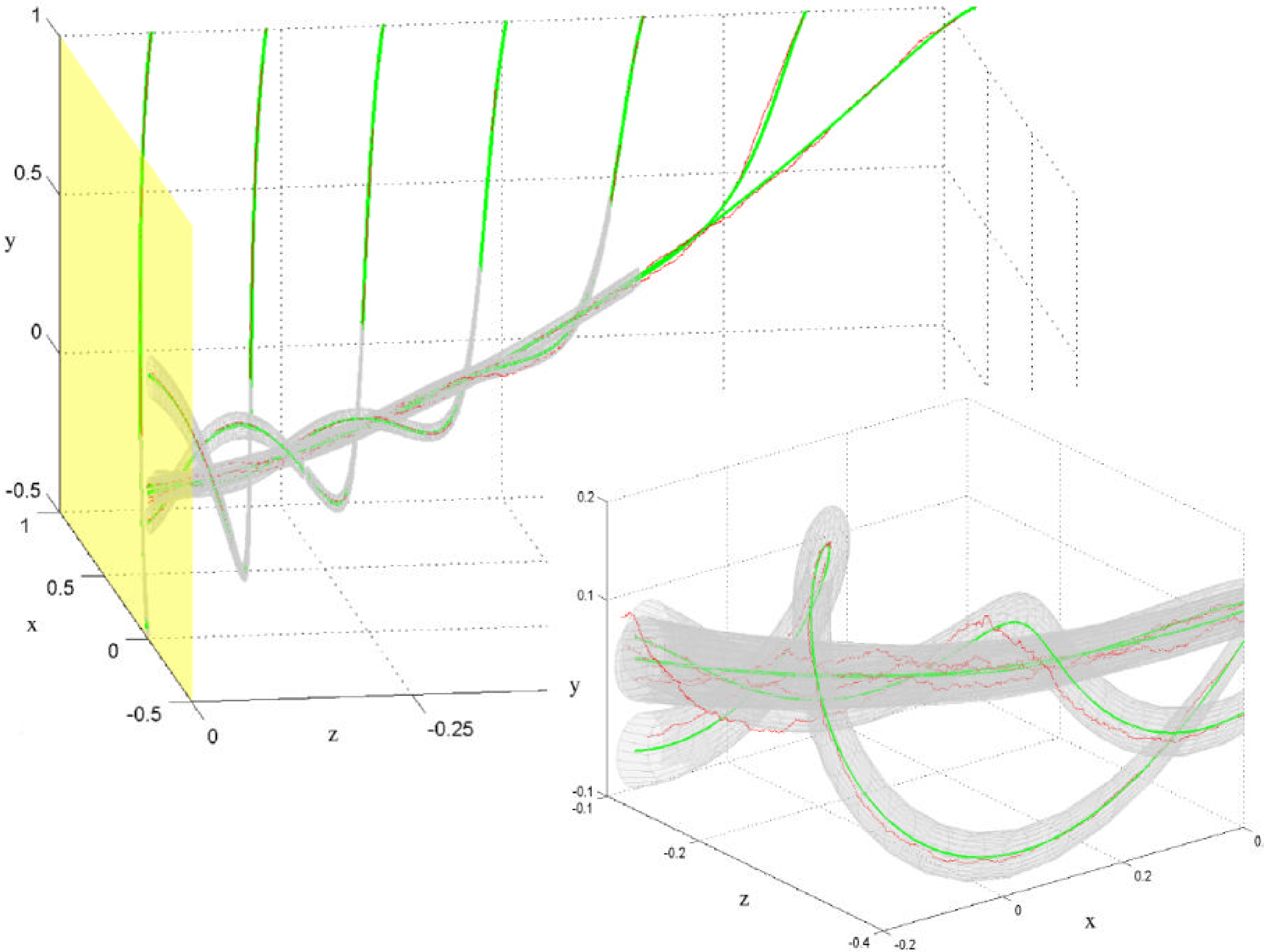


- Noise smears out small amplitude oscillations
- Early transitions modify the mixed-mode pattern

Main results

Theorem 3: [B, Gentz, Kuehn 2010]

- ▷ For $z \leqslant 0$, paths stay with high probability in covariance tubes
- ▷ For $z = 0$, section of tube is close to circular with radius $\mu^{-1/4}\sigma$
- ▷ Distance between k^{th} and $k+1^{\text{st}}$ canard $\sim \mathrm{e}^{-(2k+1)^2\mu}$



20-a

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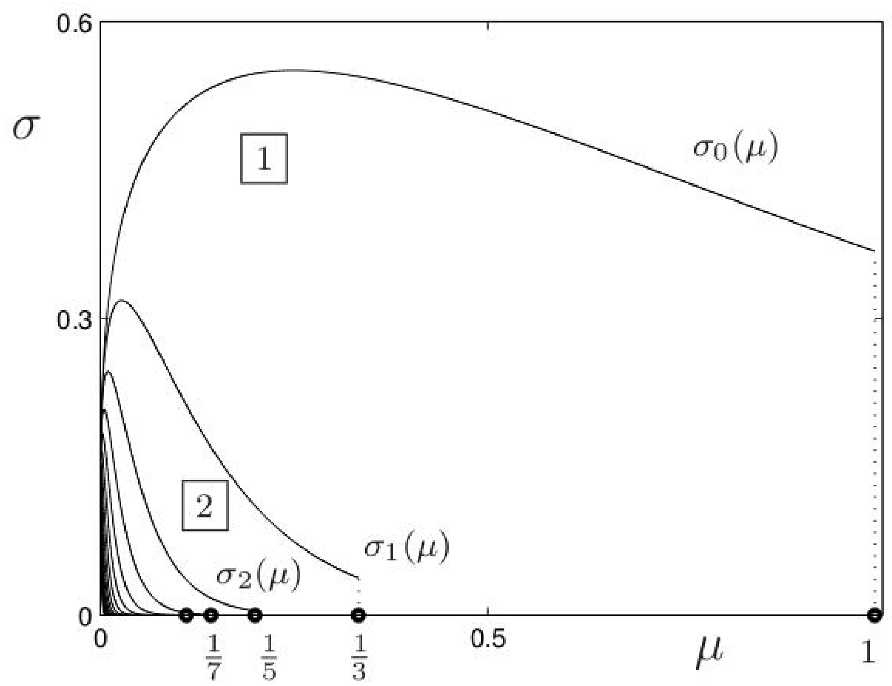
Corollary:

Let

$\sigma_k(\mu) = \mu^{1/4}\,\mathrm{e}^{-(2k+1)^2\mu}$

Canards with $\frac{2k+1}{4}$ oscillations become indistinguishable from noisy fluctuations for $\sigma > \sigma_k(\mu)$



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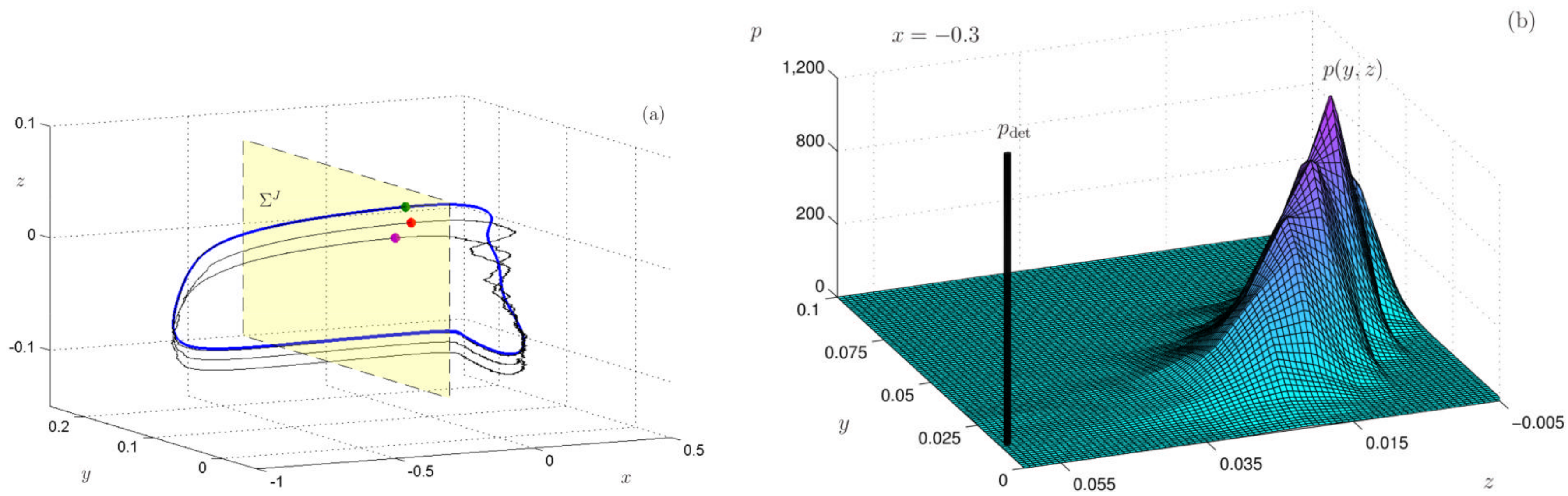
Theorem 4: [B, Gentz, Kuehn 2010]

For $z > 0$, paths are likely to escape after time of order $\sqrt{\mu|\log\sigma|}$



What's next?

- ▷ Estimate global return map for stochastic system
- ▷ Analyse possible mixed-mode patterns

  Possible scenario:

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- ▷ Comparison with real data

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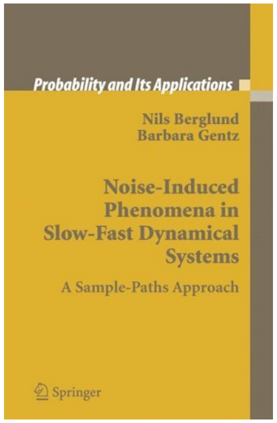
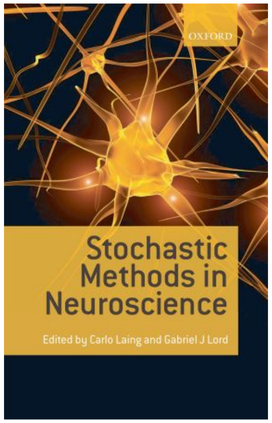
Summary

- ▷ ISI distributions are not always exponential
- ▷ Transient effects are important (QSD, metastability)
- ▷ Precise sample path analysis is possible, useful tools exist (in some cases): singular perturbation theory, large deviations, martingales, substochastic Markov processes, . . .
- ▷ Still many open problems: other bifurcations, better approximation of QSD, higher dimensions, other types of noise, . . .

Further reading





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N.B. and Damien Landon, *Mixed-mode oscillations and interspike interval statistics in the stochastic FitzHugh–Nagumo model*, Nonlinearity, at press (2012). `arXiv:1105.1278`

`www.univ-orleans.fr/mapmo/membres/berglund`

Additional material

Covariance tubes

Linearized stochastic equation around a canard $(x_t^{\text{det}}, y_t^{\text{det}}, z_t^{\text{det}})$

$$\mathrm{d}\zeta_t = A(t)\zeta_t \,\mathrm{d}t + \sigma \,\mathrm{d}W_t \qquad A(t) = \begin{pmatrix} -2x_t^{\text{det}} & 1 \\ -(1+\mu) & 0 \end{pmatrix}$$

$$\zeta_t = U(t)\zeta_0 + \sigma \int_0^t U(t,s)\,\mathrm{d}W_s$$ ($U(t,s)$: principal solution of $\dot{U} = AU$)

Gaussian process with covariance matrix

$$\mathrm{Cov}(\zeta_t) = \sigma^2 V(t) \qquad V(t) = U(t)V(0)U(t)^{-1} + \int_0^t U(t,s)U(t,s)^T \,\mathrm{d}s$$

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Covariance tube :

$$\mathcal{B}(h) = \Big\{\langle (x,y) - (x_t^{\text{det}}, y_t^{\text{det}}), V(t)^{-1}[(x,y) - (x_t^{\text{det}}, y_t^{\text{det}})]\rangle < h^2\Big\}$$

Theorem 3: [B, Gentz, Kuehn 2010]
Probability of leaving covariance tube before time t (with $z_t \leqslant 0$) :

$$\mathbb{P}\Big\{\tau_{\mathcal{B}(h)} < t\Big\} \leqslant C(t)\,\mathrm{e}^{-\kappa h^2/2\sigma^2}$$

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Sketch of proof :

▷ (Sub)martingale : $\{M_t\}_{t\geqslant 0}$, $\mathbb{E}\{M_t|M_s\} = (\geqslant) M_s$ for $t \geqslant s \geqslant 0$

▷ Doob's submartingale inequality : $\mathbb{P}\Big\{\sup_{0\leqslant t\leqslant T} M_t \geqslant L\Big\} \leqslant \frac{1}{L}\mathbb{E}[M_T]$

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- ▷ Linear equation : $\zeta_t = \sigma \int_0^t U(t,s)\,\mathrm{d}W_s$ is no martingale
  but can be approximated by martingale on small time intervals
- ▷ $\exp\{\gamma\langle\zeta_t, V(t)^{-1}\zeta_t\rangle\}$ approximated by submartingale
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- ▷ Nonlinear equation : $\mathrm{d}\zeta_t = A(t)\zeta_t\,\mathrm{d}t + b(\zeta_t,t)\,\mathrm{d}t + \sigma\,\mathrm{d}W_t$

$$\zeta_t = \sigma \int_0^t U(t,s)\,\mathrm{d}W_s + \int_0^t U(t,s) b(\zeta_s,s)\,\mathrm{d}s$$

Second integral can be treated as small perturbation for $t \leqslant \tau_{\mathcal{B}(h)}$

Early transitions

Let $\mathcal{D}$ be neighbourhood of size $\sqrt{z}$ of a canard for $z > 0$ (unstable)

Theorem 4: [B, Gentz, Kuehn 2010]
$\exists \kappa, C, \gamma_1, \gamma_2 > 0$ such that for $\sigma |\log \sigma|^{\gamma_1} \leqslant \mu^{3/4}$ probability of leaving $\mathcal{D}$ after $z_t = z$ satisfies

$$\mathbb{P}\Bigl\{ z_{\tau_{\mathcal{D}}} > z \Bigr\} \leqslant C |\log \sigma|^{\gamma_2} \, \mathrm{e}^{-\kappa(z^2 - \mu)/(\mu |\log \sigma|)}$$

Small for $z \gg \sqrt{\mu |\log \sigma| / \kappa}$

Sketch of proof :

- ▷ Escape from neighbourhood of size $\sigma|\log \sigma|/\sqrt{z}$:
  compare with linearized equation on small time intervals + Markov property
- ▷ Escape from annulus $\sigma|\log \sigma|/\sqrt{z} \leqslant \|\zeta\| \leqslant \sqrt{z}$:
  use polar coordinates and averaging
- ▷ To combine the two regimes : use Laplace transforms