Dynamics of Large Fluctuations: from Chaotic Attractors to Ion Channels

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- **The Concept of Optimal Path**
- **Types of Chaos and the Structural Stability (roughness) of models**
- **Large Fluctuations, Optimal Force and Control**
- **Ion Transport**
- **Conclusions**

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Optimal Path

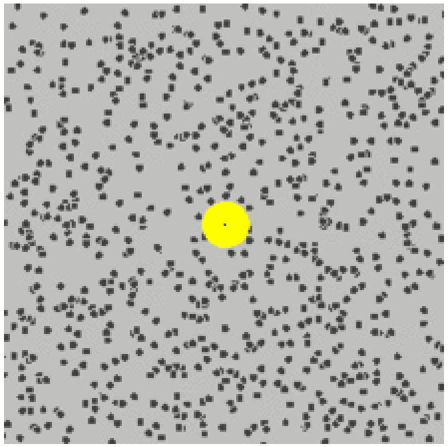
Brownian Motion

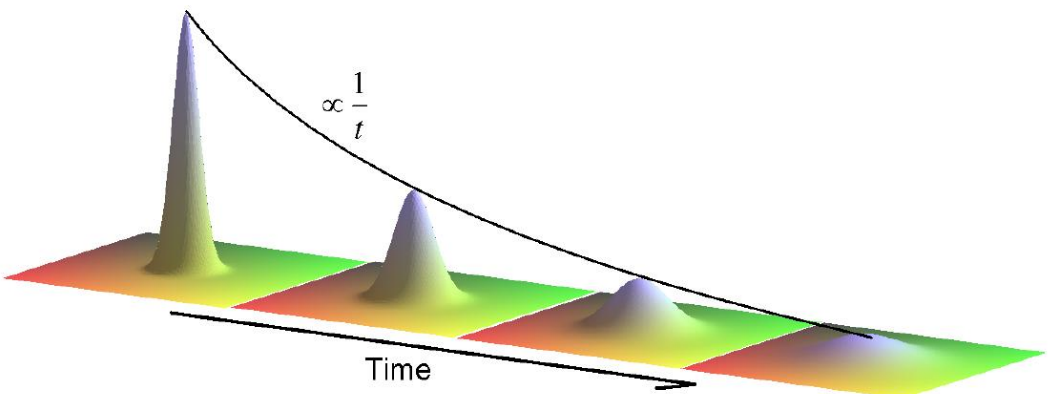
Free Diffusion

$$\rho(r,t) = Z^{-1}\frac{e^{\left(\frac{-r^2}{4Dt}\right)}}{4\pi D t}$$

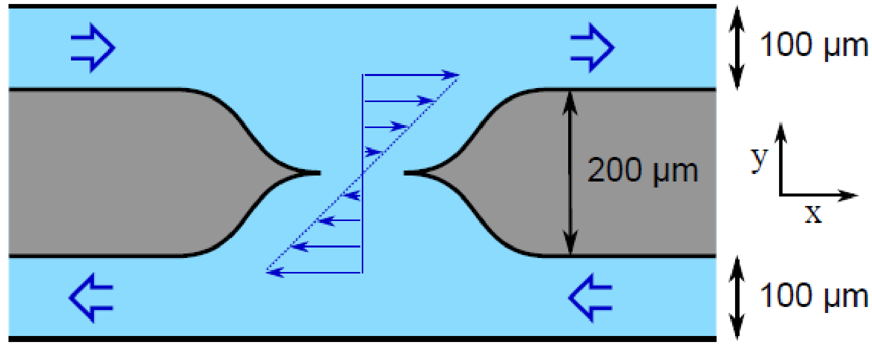
$$D = \frac{k_B T}{6\pi\eta R}$$

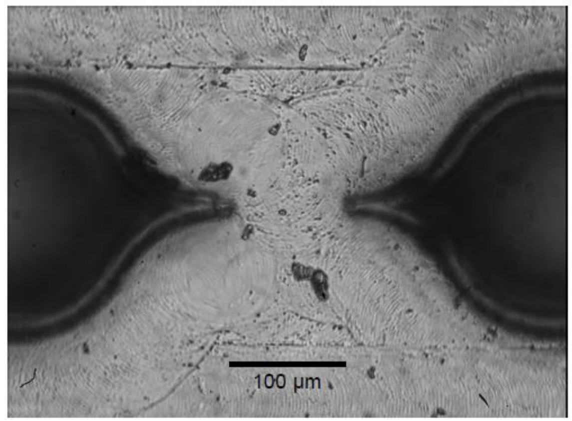
2-Dimensional





Diffusion Under Constraints (interactions)





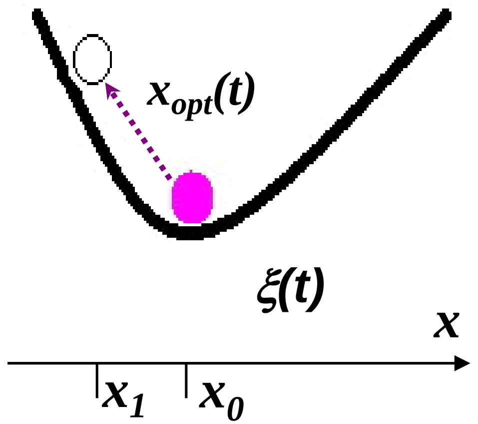
$$\rho(r,t) = Z^{-1} e^{-\frac{U(r)}{k_B T}}$$

The microfluidic cell with two counter-propagating flows that create a shear-flow with zero mean velocity in the central region.

The concept of optimal paths

L Boltzmann (1904),
L Onsager and S Machlup (1953)

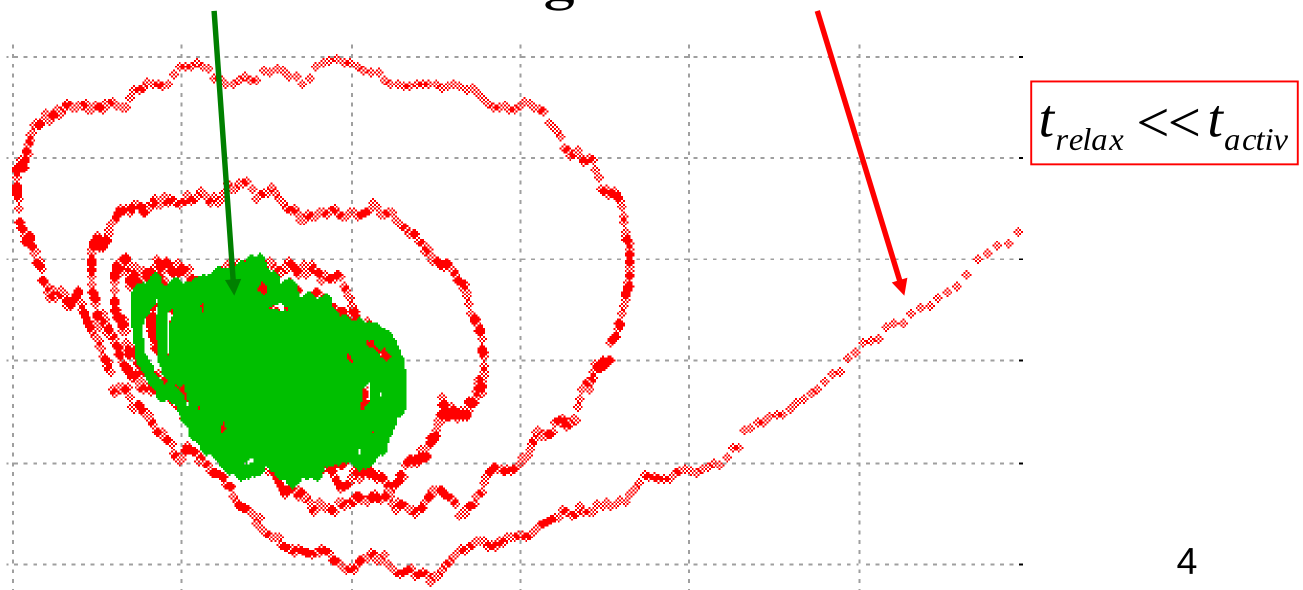
The concept can be applied to *non-equilibrium multi-dimensional* systems



$U(x,t)$ – potential
$\xi(t)$ – fluctuations

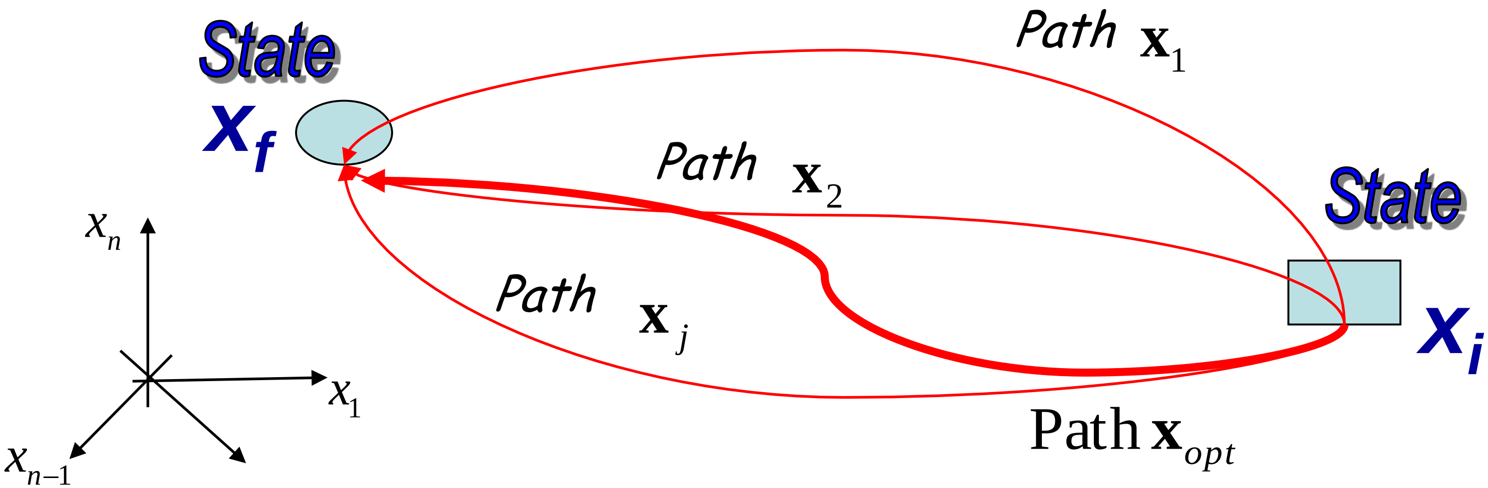
Different manifestations of fluctuations:

diffusion and large fluctuations



Optimal Path

Fluctuational paths in the state (phase) space



The states $\mathbf{x}_i$ and $\mathbf{x}_f$ are attractors

Transition probability

$$\rho(\mathbf{x}_f, t_f \mid \mathbf{x}_i, t_i) = \sum_j \rho[\mathbf{x}(t)_j] \approx \rho[\mathbf{x}(t)_{opt}]$$

The most probable (optimal) path via the principle of the least action

Optimal Path is a *deterministic* trajectory

Assume Langevin Description with White Gaussian Noise

$$\dot{\mathbf{x}} = \mathbf{K}(\mathbf{x},t) + \boldsymbol{\xi}(t), \langle \xi_\alpha \rangle = 0, \langle \xi_\alpha(t)\xi_\beta(s) \rangle = D\mathbf{Q}\delta(t-s)$$

The probability of fluctuational path $\rho[\mathbf{x}(t)_j]$ *is related to the probability* $\rho[\boldsymbol{\xi}(t)_j]$ *of random force to have a realization* $\boldsymbol{\xi}(t)_j$

For Gaussian noise: $\rho[\boldsymbol{\xi}(t)_j] = C\exp\left(-\frac{1}{2}\int_{t_i}^{t_f} \boldsymbol{\xi}(t)_j^{\,2}\,dt\right) = C\exp\left(-\frac{1}{2}S\right)$

***Since the exponential form, the most probable path has a minimal** $S=S_{min}$*

Changing to dynamical variables:

Action $S = S[\boldsymbol{\xi}(t)] \xrightarrow[\boldsymbol{\xi}(t) = \dot{\mathbf{x}} - \mathbf{K}(\mathbf{x},t)]{\dot{\mathbf{x}} = \mathbf{K}(\mathbf{x},t) + \boldsymbol{\xi}(t)} S = [x(t)]$

In the limit $D \to 0$, $\rho(\mathbf{x}_f;\mathbf{x}_i) = \rho\left(\mathbf{x}(t)_{opt}\right) = Const \times \exp\left(-\frac{S[\mathbf{x}(t)_{opt}]}{D}\right)$

$$S_{\min} = S[x_{opt}(t)] = \min \int dt\left(\dot{\mathbf{x}} - \mathbf{K}(\mathbf{x},t)\right)^2$$

Deterministic minimization problem

Optimal Path

Wentzell-Freidlin (1970) small noise picture $D \to 0$

$$\partial_t S = H\left(p \equiv \partial_x S, x, t\right)$$

Least-action paths are defined by the Hamiltonian

$$H = \frac{1}{2}\mathbf{pQp} + \mathbf{pK}(\mathbf{x}, t);$$

$$\dot{\mathbf{x}} = \frac{\partial H}{\partial \mathbf{p}}, \quad \dot{\mathbf{p}} = -\frac{\partial H}{\partial \mathbf{x}},$$

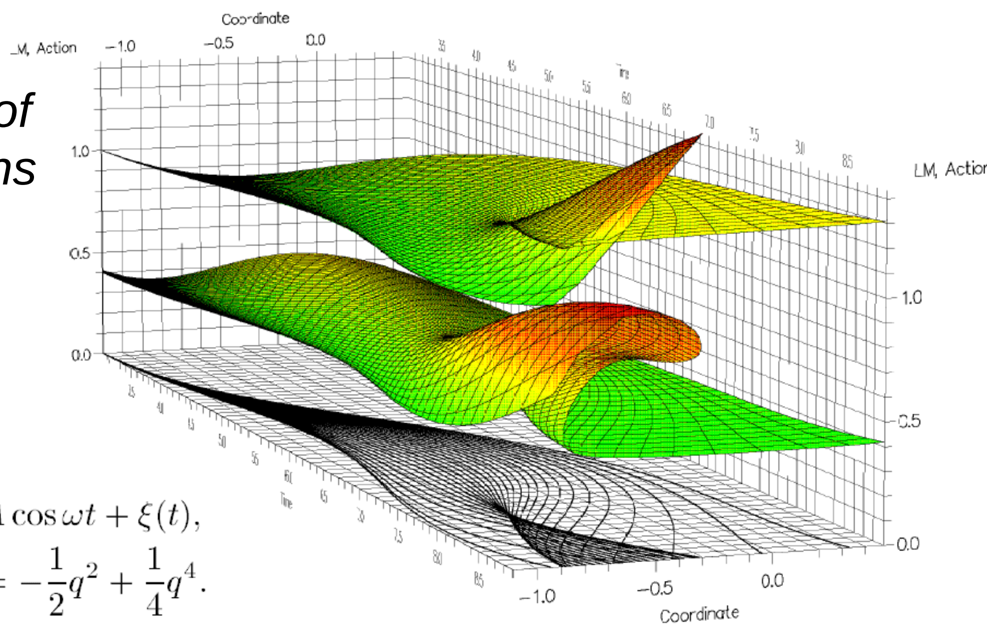
$$\mathbf{p} \equiv \frac{\partial S}{\partial \mathbf{x}}$$

with the boundary conditions, that the action is constant, that is the momenta are zero on sets (invariants) of a dynamical system:

$$Initial\ \ state: \quad \mathbf{x}(t_i) = \mathbf{x}_i, \mathbf{p}(t_i) = 0,$$

$$Final\ \ state: \quad \mathbf{x}(t_f) = \mathbf{x}_f, \mathbf{p}(t_f) = 0.$$

The pattern of extreme paths



$$\dot{q} = -U'(q) + A\cos\omega t + \xi(t),$$

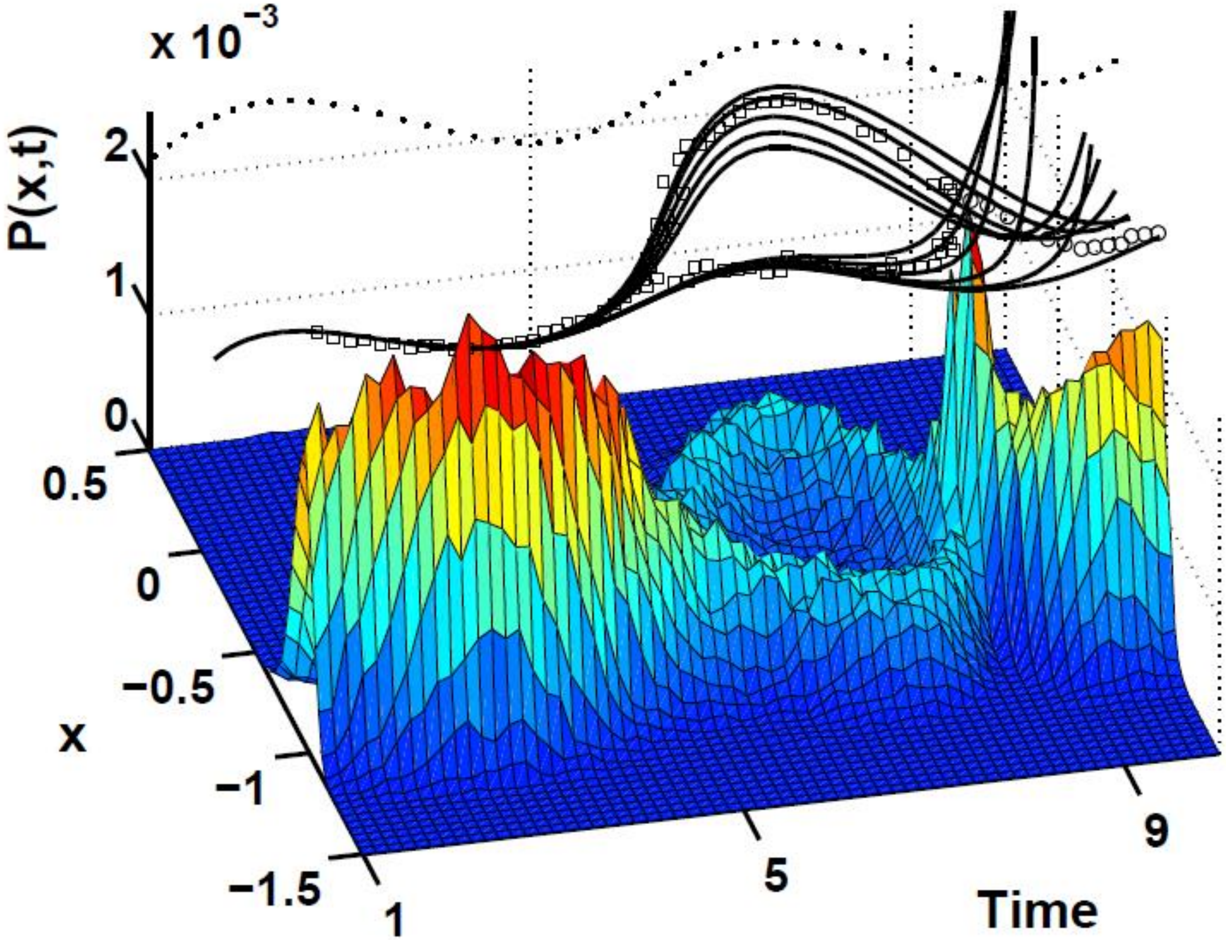
$$U(q) = -\frac{1}{2}q^2 + \frac{1}{4}q^4.$$

Hamiltonian gives an infinite number of extreme trajectories, the optimal path (if it exists) has a minimal action

Double optimization

Extreme Paths

Wentzell-Freidlin (1970) small noise picture $D \to 0$



Fluctuational behaviour measured and calculated for an electronic model of the non-equilibrium system

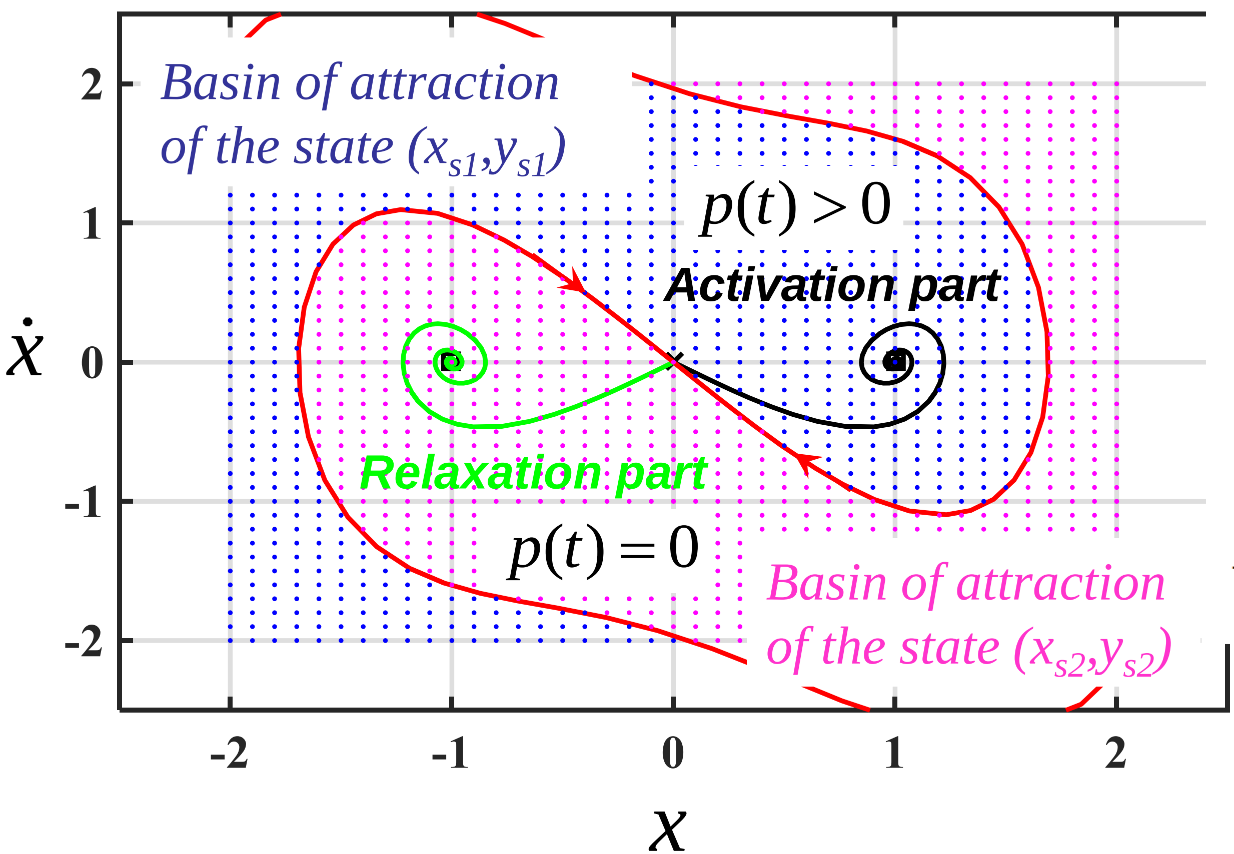
$$\dot{q} = -U'(q) + A\cos\omega t + \xi(t),$$
$$U(q) = -\frac{1}{2}q^2 + \frac{1}{4}q^4.$$

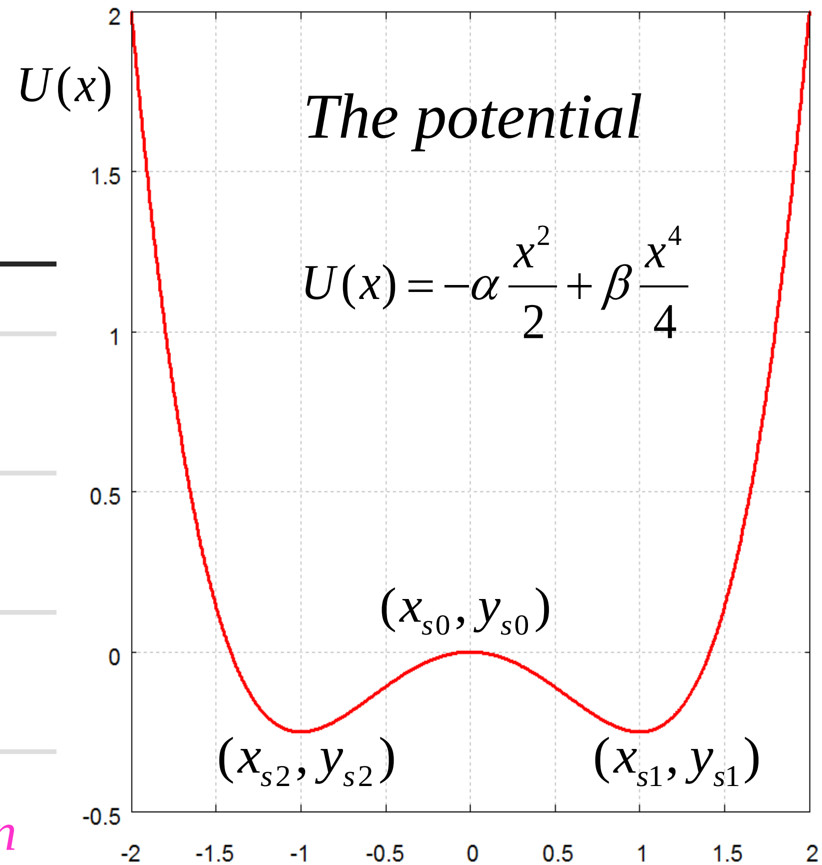
Optimal path

Wentzell-Freidlin (1970) small noise picture $D \to 0$

Noise-induced escape in Duffing oscillator $\ddot{x} + b\dot{x} - \alpha x + \beta x^3 = \sqrt{D}\xi(t)$

*The **optimal path** connects the stable state and the saddle (boundary) state*





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Structural Stability (roughness) of models. An example

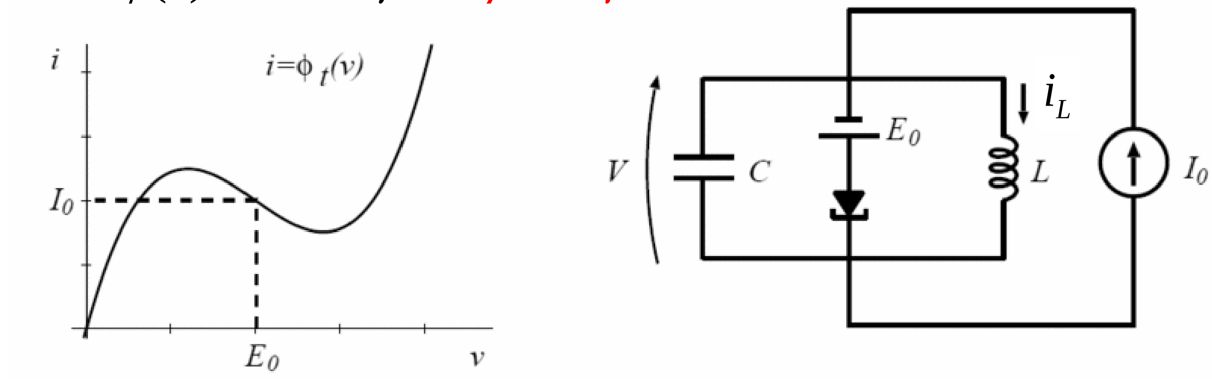
Mathematical Model is an idealization and a simplification

A lumped model of the circuit is

$$i = \phi(v) = -\alpha v + \gamma v^3 + \beta v^4 + \mu v^5 + \ldots$$

$$\left. \begin{aligned} i &= \phi(v - E_0) + I_0 \\ \dot{V} &= \frac{1}{C}\left(-\phi(v) - i_L\right) \\ i_L &= \frac{V}{L} \end{aligned} \right\} \Rightarrow$$

$$\ddot{V} - \frac{1}{C}\left(\alpha - 3\gamma V^2\right)\dot{V} + \frac{1}{LC}V = 0$$



An electrical circuit with a tunnel diode.
(see http://www.scholarpedia.org/article/Van_der_Pol_oscillator)

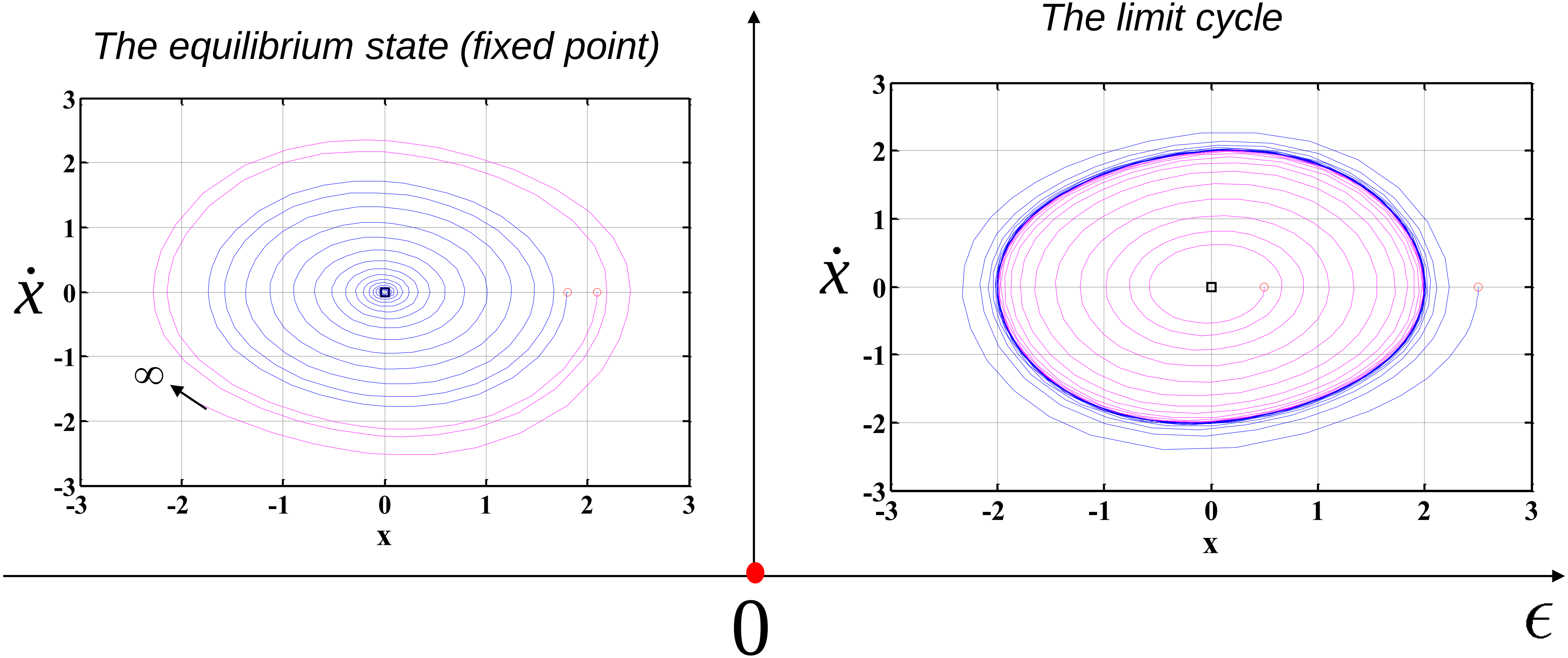
Introduce $x = \sqrt{\frac{3\gamma}{\alpha V}}; t' = \frac{t}{\sqrt{LC}}; \epsilon = \sqrt{\frac{L}{C\alpha}} \Rightarrow$

Van der Pol equation $\ddot{x} - \epsilon(1 - x^2)\dot{x} + x = 0$

<u>Roughness:</u> Small change (uncertainties) in parameters and in nonlinearities cause small change in the state space

Structural Stability (roughness) of models. An example

Van der Pol oscillator. State (bifurcational) diagram $\ddot{x} - \epsilon(1 - x^2)\dot{x} + x = 0$



$\epsilon = 0$ *Corresponds to the Andronov-Hopf bifurcation*

The roughness is observed outside of a vicinity of the bifurcation

2-Dimensioal models are rough (structurally stable)

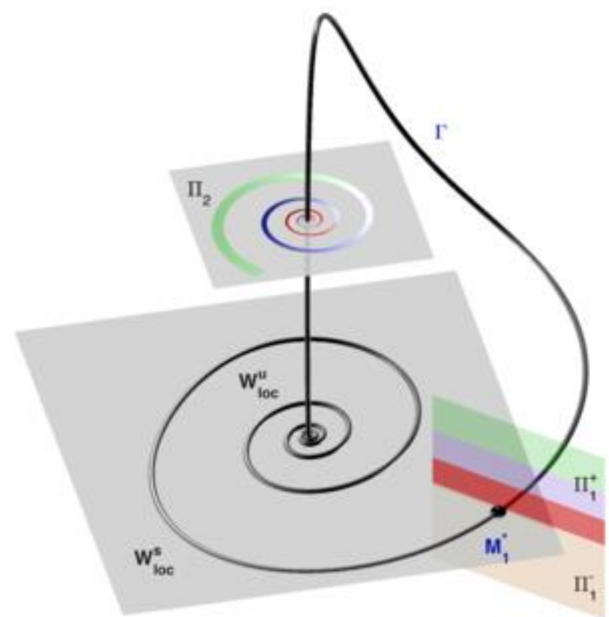
Structural Stability (roughness)

"Mathematical" conclusion (so far, see for example Shilnikov L.P. et al Methods of Qualitative Theory in Nonlinear Dynamics. Part II. World Sci. 2001)

Multi-dimensional rough systems are ***Morse-Smale systems*** *which have the limiting sets in the form of equilibrium states and (quasi)periodic orbits (cycles, tori); such models may only have a finite number of them.*

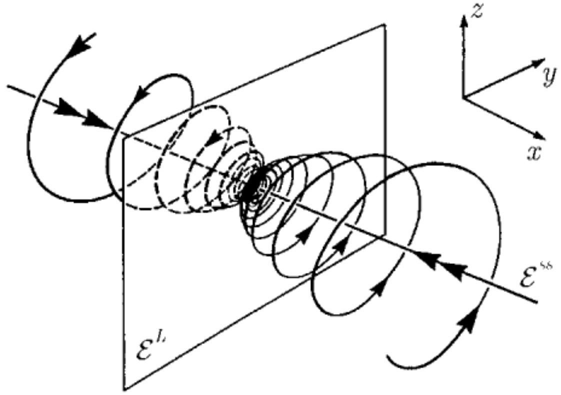
Smale (1963) : Rough systems with dimension of the state space greater than two are not dense in the space of dynamical systems.

Morse-Smale systems do NOT admit ***homo (hetero)-clinic trajectories (tangencies of manifolds)*** *of saddle sets*

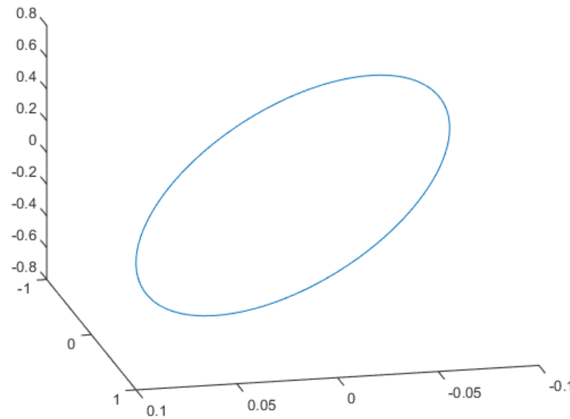


Homoclinic loop of a saddle-focus

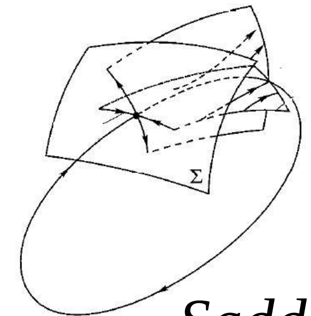
Sets of a Morse-Smale System



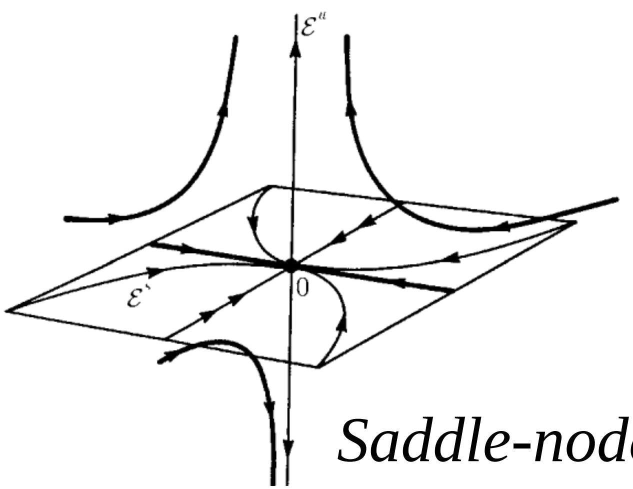
Stable focus



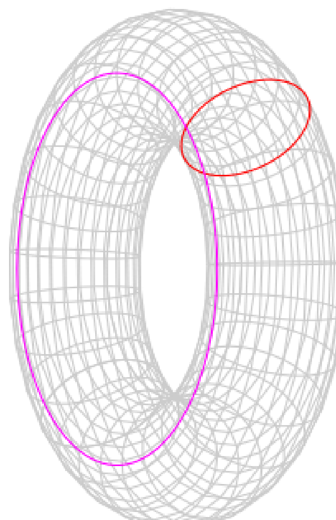
Cycle



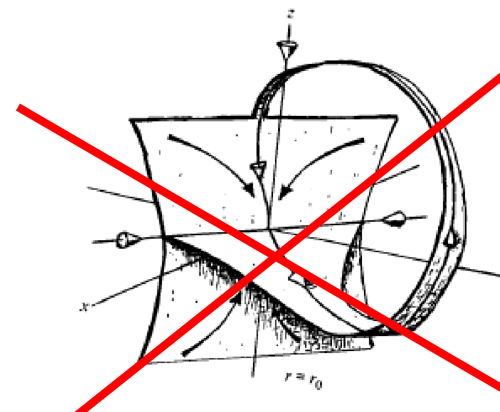
Saddle Cycle



Saddle-node



Torus



Homoclinic Loop

Chaotic systems

http://www.scholarpedia.org/: Chaos. There is currently no text in this page.

http://mathworld.wolfram.com/: "Chaos" is a tricky thing to define…

The complicated **aperiodic** trajectory of **low-dimensional** (3-dimensional and higher) dynamical systems

http://en.wikipedia.org: Dynamical systems that are highly sensitive to initial conditions

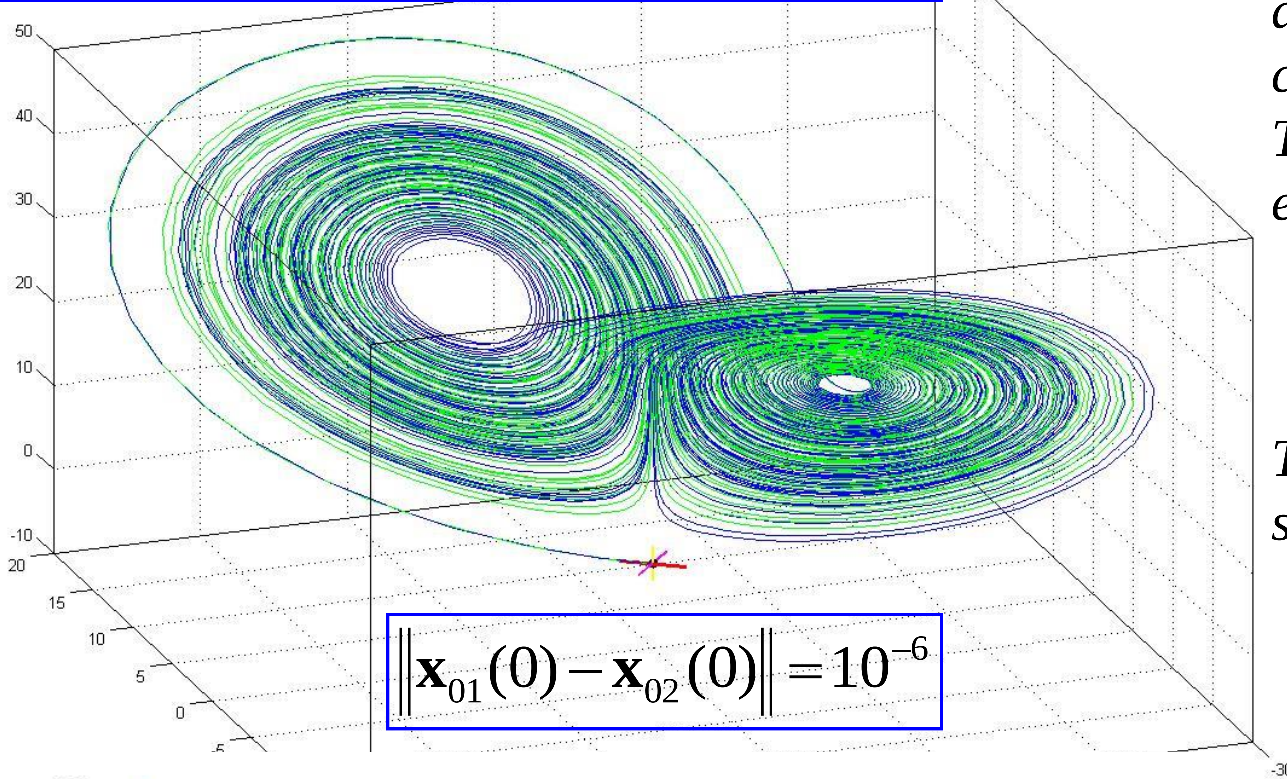
Edward Lorenz: *When the present determines the future, but the approximate present does not approximately determine the future.*

Positive Lyapunov exponents

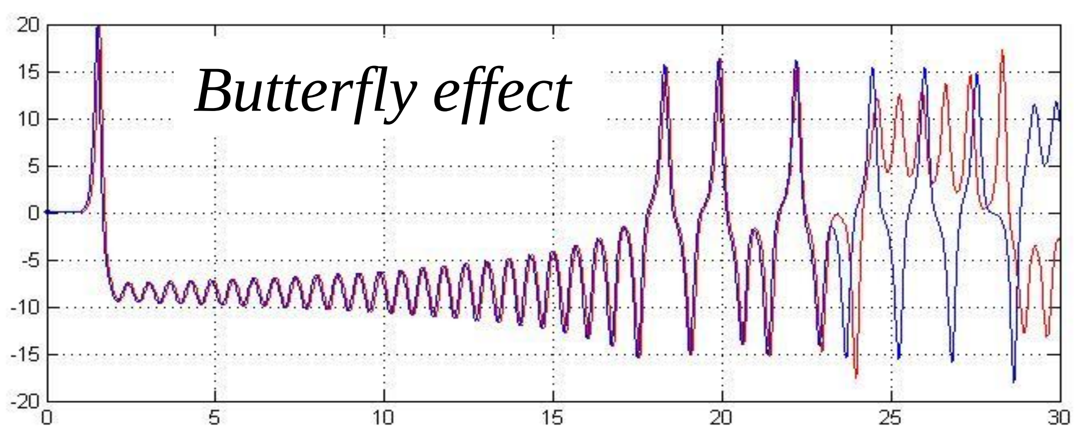
The Chaotic Lorenz attractor

$$\dot{x}=\sigma(y-x) \quad \dot{y}=rx-y-xz \quad \dot{z}=xy-bz$$

$$\sigma=10 \quad b=8/3 \quad r=28$$



$$\left\|\mathbf{x}_{01}(0)-\mathbf{x}_{02}(0)\right\|=10^{-6}$$



The Lorenz attractor demonstrates a sensitive dependence on initial conditions

The largest Lyapunov exponent is positive

$$\Lambda_1=0.897$$

$$\Lambda_2=0 \quad \Lambda_2=-14.56$$

The attractor has no any stable set (points, cycles)

Often assumed:

$$\|\mathbf{x}(t)\| \propto \exp(\Lambda_1 t)$$

The attractor is fractal

$$D_F \approx 2.05$$

The Chaotic Lorenz attractor

Lorenz system: 100 initial points in small sphere

$$\|\mathbf{x}(t)\| \propto \exp(\Lambda_1 t)$$

$$\sigma = 10 \qquad \dot{x} = \sigma(y - x)$$

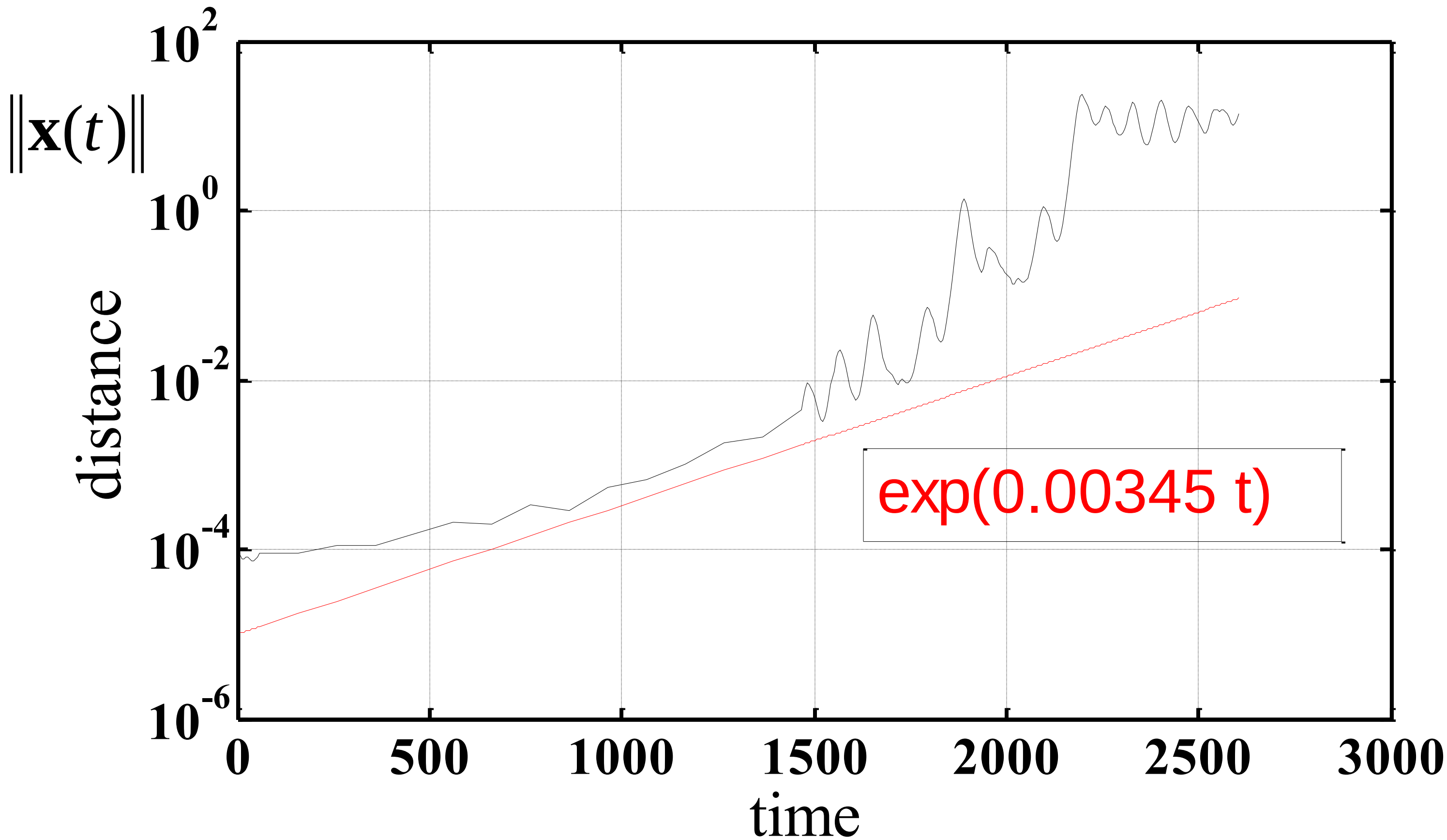
$$r = 28 \qquad \dot{y} = rx - y - xz$$

$$b = 8/3 \qquad \dot{z} = xy - bz$$

$$\Lambda_1 = 0.8971$$

$$\Lambda_2 = -0.0155$$

$$\Lambda_3 = -14.5446$$



Chaos and Noise

How investigate systems with noise?

One possible programme of investigation was suggested by
L. Pontryagin, A. Andronov, and A. Vitt, Zh. Exp. Teor. Fiz. ***3****, 165 (1933)*

The (slightly modified) *programme*

1. ***Classification all sets of dynamical systems and the bifurcations of the sets (without fluctuations)***

2. ***Checking set's stability (robustness) in respect of fluctuations.*** **Consider noise-induced deviations**

The results (so far) of the first step of the programme

The observation of new (in comparison with 2D case) sets: e.g. ***Smale Horseshoe*** *and new regime:* ***Deterministic chaos****;* ***Statistical description*** *of low-dimensional dynamics etc*
Still open problems*: Complete Description of sets and their bifurcations.*

Shilnikov's group results:
"…A complete description of dynamics and bifurcations of systems with homoclinic tangencies is impossible in principle."

S. Gonchenko, D. Turaev and L. Shilnikov, Nonlinearity (2007) ***20****, 241-275*

Types of Chaos

Chaotic Attractors

☺ ***Hyperbolic*** *The distinct feature are*
phase space is locally spanned by the same fixed number of stable and unstable directions in each points of the set;
the existence of SRB probability measure;
the structural stability of the set and shadowing of trajectories.

😐 ***Quasi-hyperbolic*** *There is a localized non-hyperbolicity ("bad set"), away from this set the system is hyperbolic and trajectory spends most of the time on a hyperbolic part*

☹ ***Non-hyperbolic*** *Tangencies of manifolds and dimension variability of manifolds are dominated in phase space; the co-existence of a large number (often infinite) of different sets; quasi-attractor*

Types of Chaos

Types of chaotic systems in "real life"

☹ ***Hyperbolic***

There are not typical, in fact there is no (strictly proven) any example of hyperbolic chaotic system described by ODE

😐 ***Quasi-hyperbolic***

There are rare, but real; the famous example is the Lorenz System

☺ ***Non-hyperbolic***

The majority of systems are non-hyperbolic

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Chaos and Noise

Our Aim: Dynamics of Large Fluctuations versus types of chaotic attractors

Approach: *starting with noise-free dynamics to noisy dynamics,*
is problematic, since we have no complete description of attractors.

Another approach *is based on simplification of initial task:*

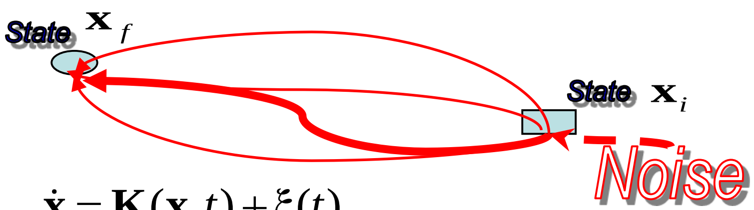
We consider noise-induced ***significant changes*** *in dynamics only;*

we analyse ***Large Fluctuations*** *(deviation) from chaotic attractor;*

The noise-induced deviations must exceed diffusion along trajectories

The optimal path concept (formalism) allows to solve an optimal control problem, since it defines both the optimal path and the optimal fluctuational force.

Large Fluctuations and Optimal Control



$$S_{\min} = S\left[x_{opt}(t)\right] = \min \int dt \left(\dot{\mathbf{x}} - \mathbf{K}(\mathbf{x},t)\right)^2$$

$$\dot{\mathbf{x}} = \mathbf{K}(\mathbf{x},t) + \xi(t),$$

$$\langle \xi_\alpha \rangle = 0, \langle \xi_\alpha(t)\xi_\beta(s)\rangle = D\mathbf{Q}\delta(t-s)$$

Formally the deterministic minimization problem can be formulated in the Hamiltonian form:

$$H = \frac{1}{2}\mathbf{pQp} + \mathbf{pK}(\mathbf{q},t);$$

$$\dot{\mathbf{q}} = \frac{\partial H}{\partial \mathbf{p}}, \quad \dot{\mathbf{p}} = -\frac{\partial H}{\partial \mathbf{q}},$$

$$Initial\ state: \quad \mathbf{q}(t_i) = \mathbf{x}_i, \mathbf{p}(t_i) = 0, \quad t_i \to -\infty;$$

$$Final\ state: \quad \mathbf{q}(t_f) = \mathbf{x}_f, \mathbf{p}(t_f) = 0, \quad t_f \to \infty.$$

This form coincides with Hamiltonian formulation of deterministic optimal (energy-minimal) control problem:

$$J = \inf_{f \in F} \frac{1}{2} \int_{t_1}^{t_2} f^2(x,t)dt$$

The variable $\mathbf{q}(t)$ *corresponds to the optimal paths* $\mathbf{x}(t)_{opt}$,
The variable $\mathbf{p}(t)$ *defines the optimal fluctuational force* $\xi(t)_{opt}$ *and the energy-minimal function* $\mathbf{f}(\mathbf{x},t)$.

New way to solve the deterministic control problem via analysis of large fluctuations and vice versa.

Quasi-hyperbolic attractor

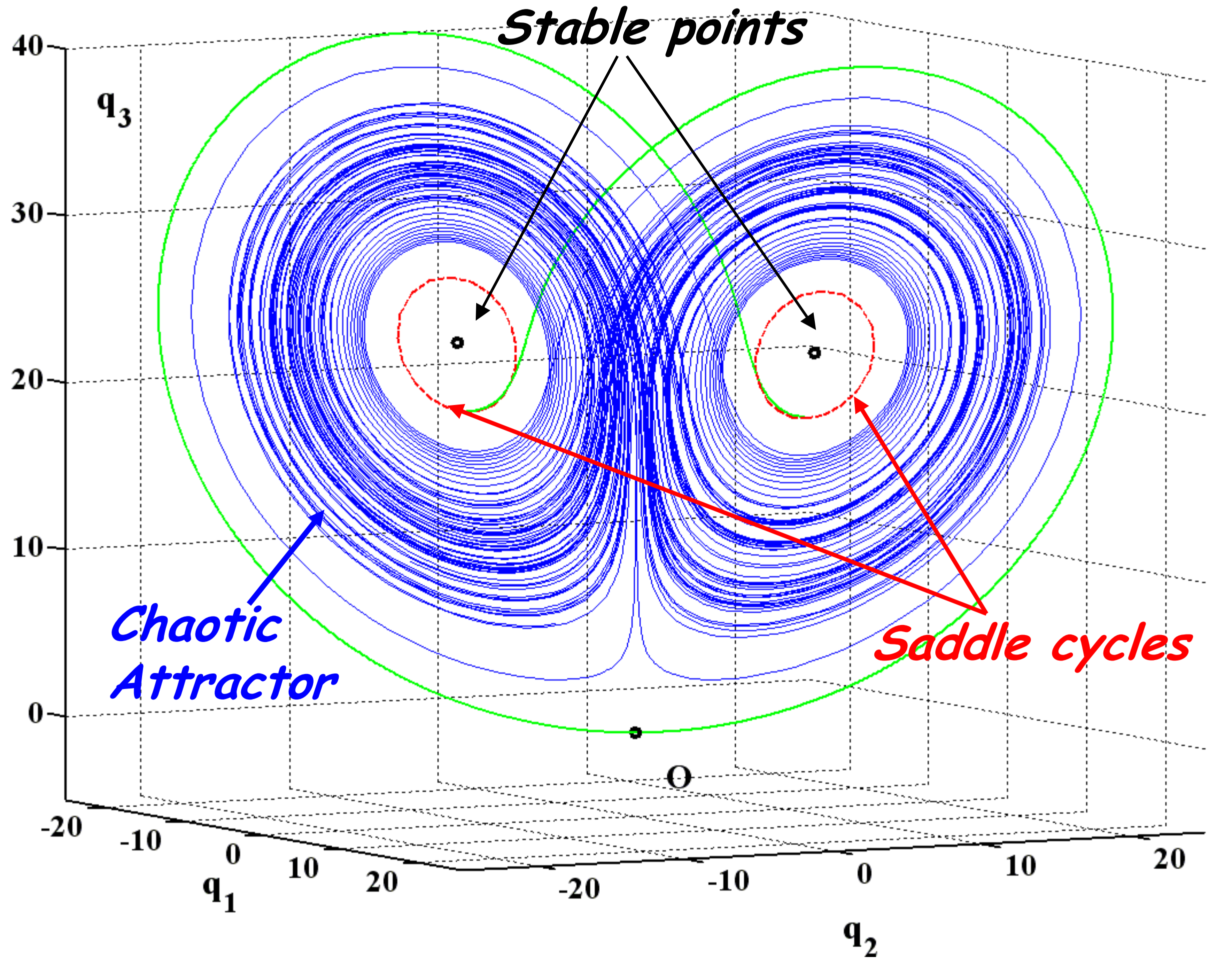
Lorenz system

$$\sigma = 10, \quad b = 8/3, \quad r = 24.08$$

$$\dot{q}_1 = \sigma(q_2 - q_1)$$
$$\dot{q}_2 = rq_1 - q_2 - q_1 q_3$$
$$\dot{q}_3 = q_1 q_2 - bq_3 + \sqrt{2D}\,\xi(t)$$

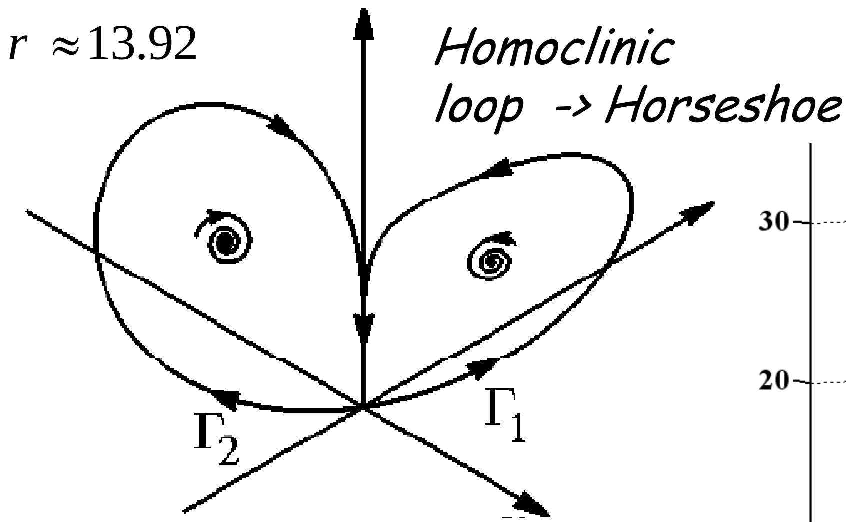
Consider noise-induced escape from the chaotic attractor to the stable point in the limit $D \to 0$

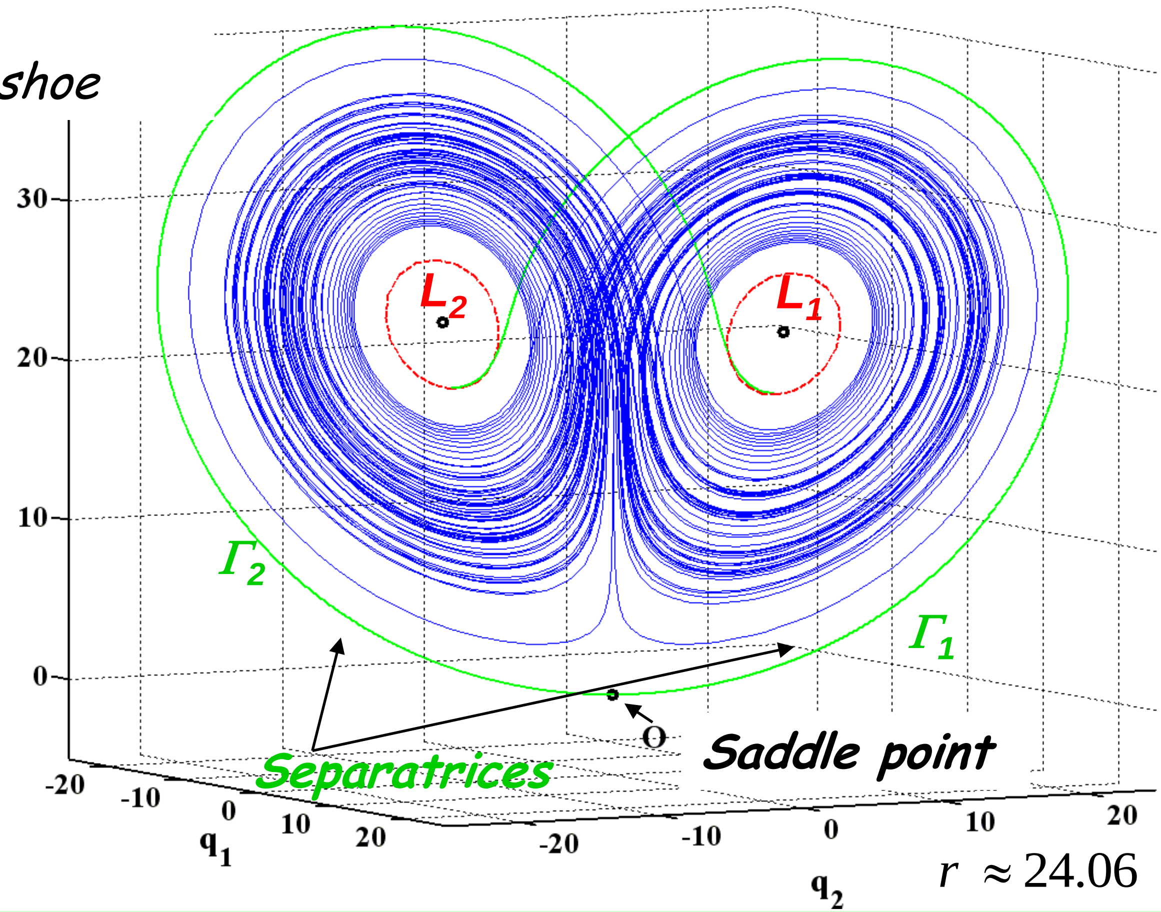
The task is to determine the most probable (optimal) escape path



Quasi-hyperbolic attractor

Lorenz Attractor





The saddle point and its separatrices belong to chaotic attractor and form "bad set" or non-hyperbolic part of the attractor

Loops between separatrices Γ_1 and Γ_2 and stable manifolds of cycles L_1 and L_2 generate
The Lorenz attractor – quasi-hyperbolic attractor

Large Fluctuations in Chaotic Systems

Hamilton formalism of Large Fluctuations: The problem of initial conditions

$$\dot{\mathbf{x}} = \mathbf{K}(\mathbf{x},t) + \boldsymbol{\xi}(t),$$

$$\langle \xi_\alpha \rangle = 0, \langle \xi_\alpha(t)\xi_\beta(s) \rangle = D\mathbf{Q}\delta(t-s)$$

$$H = \frac{1}{2}\mathbf{pQp} + \mathbf{pK}(\mathbf{q},t);$$

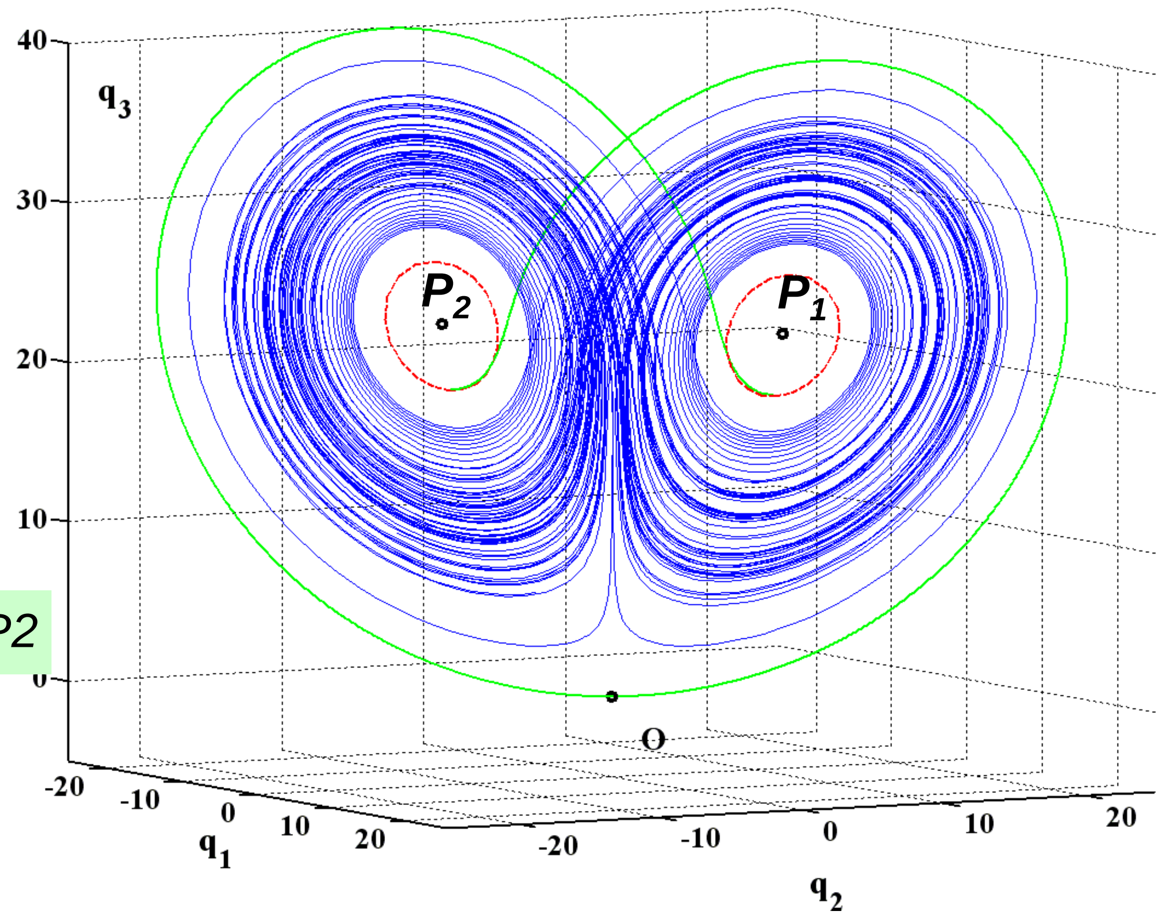
$$\dot{\mathbf{q}} = \frac{\partial H}{\partial \mathbf{p}}, \quad \dot{\mathbf{p}} = -\frac{\partial H}{\partial \mathbf{q}},$$

Initial state : **?**

$$\mathbf{q}(t_i) = \mathbf{x}_i, \mathbf{p}(t_i) = 0, \quad t_i \to -\infty;$$

Final state : *The points P1 and P2*

$$\mathbf{q}(t_f) = \mathbf{x}_f, \mathbf{p}(t_f) = 0, \quad t_f \to \infty.$$



The solution of the problem is the use of prehistory approach, i.e. analysis of real escape trajectories

Prehistory approach

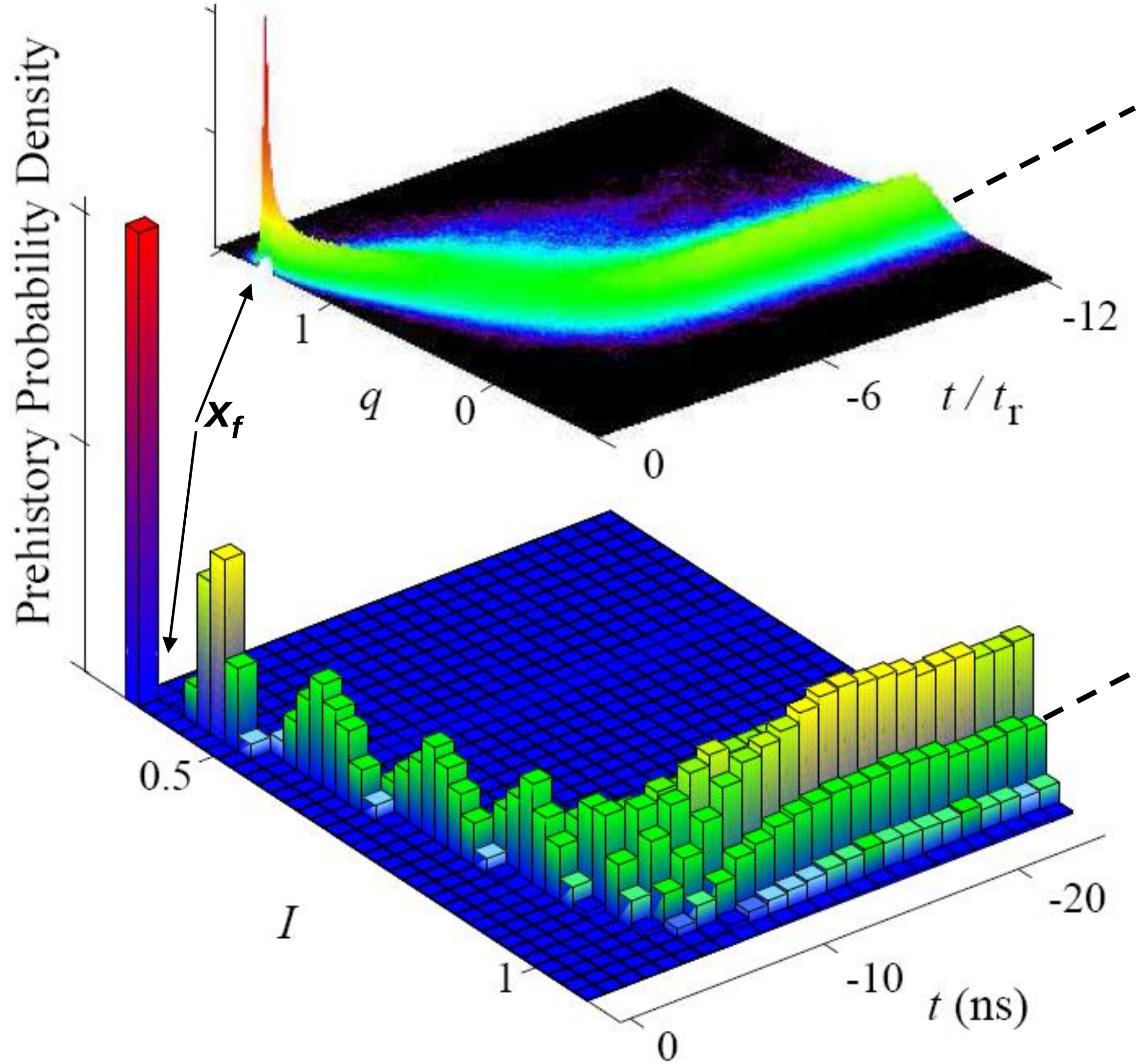
$$\dot{\mathbf{x}} = \mathbf{K}(\mathbf{x},t) + \xi(t),$$

$$\langle \xi_\alpha \rangle = 0, \langle \xi_\alpha(t)\xi_\beta(s) \rangle = D\mathbf{Q}\delta(t-s)$$

1. Select the regime $D \to 0$
i.e. rare large fluctuations

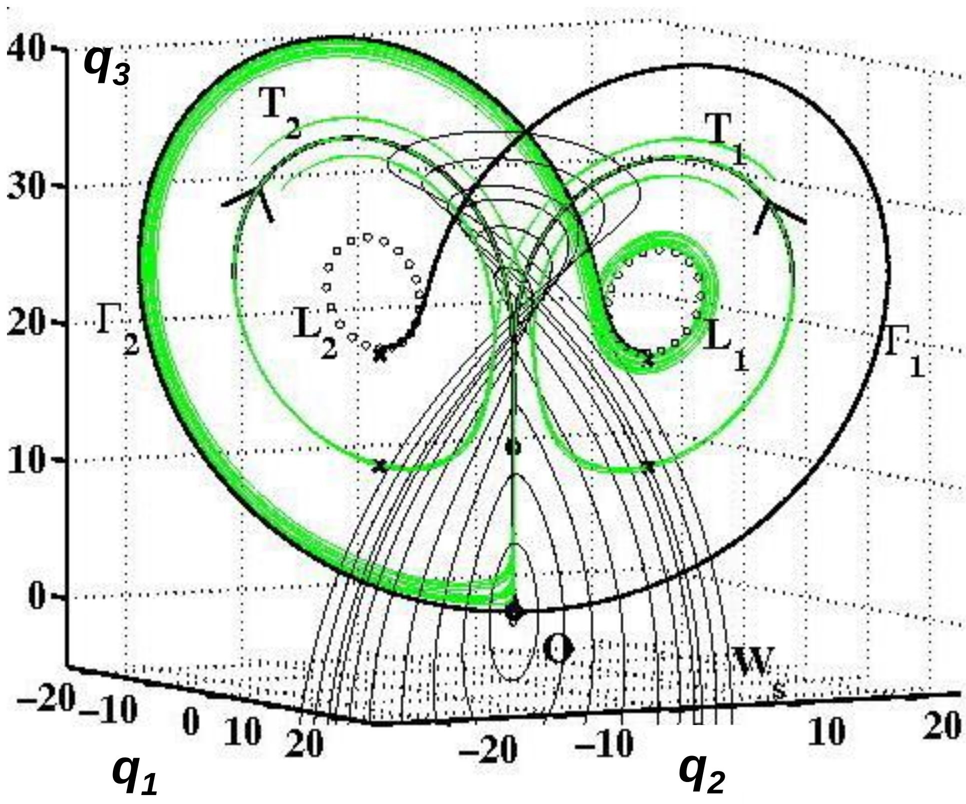
$$t_{relax} << t_{activ}$$

2. Record all trajectories $x_j(t)$ arrived to the final state and build the prehistory probability density $p_h(x,t)$
The maximum of the density corresponds to the most probable (optimal) path
3. Simultaneously noise realizations ξ(t) are collected and give us the optimal fluctuational force



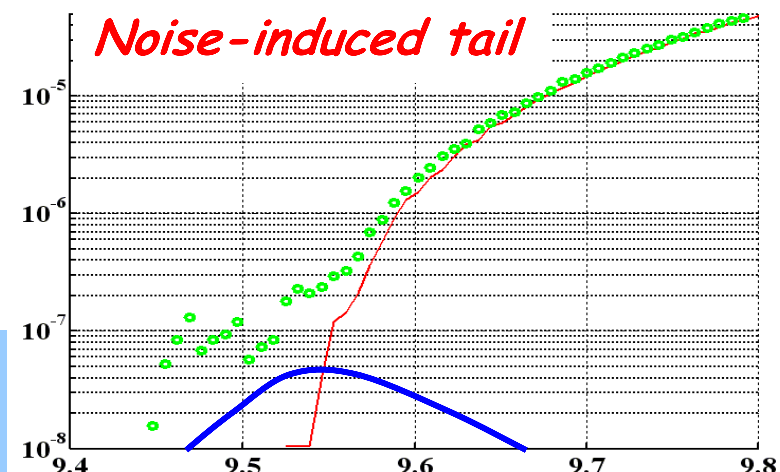
There is no any explicit initial states in the approach

Escape from quasi-hyperbolic attractor



Escape trajectories

***W**$_S$* *is the stable manifold and*
Γ_1 and Γ_2 are separatrices of the saddle point ***O***
***L**$_1$ and **L**$_2$ are saddle cycles*
***T**$_1$ and **T**$_2$ are trajectories which are tangent to* ***W**$_S$*



The escape process is connected with the non-hyperbolic structure of attractor: stable and unstable manifolds of the saddle point

The distribution of escape trajectories (exit distribution)

Non-hyperbolic attractor

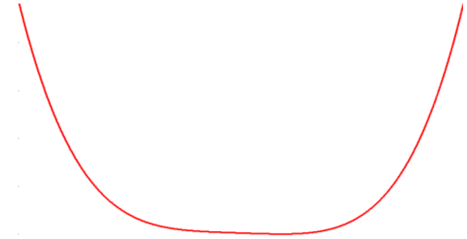
Non-autonomous nonlinear oscillator

$$\ddot{q} + \Gamma \dot{q} + \frac{\partial U(q,t)}{\partial q} = \sqrt{2D}\xi(t)$$

$$U(q,t) = \frac{\omega_0^2}{2} q^2 + \frac{\beta}{3} q^3 + \frac{\gamma}{4} q^4 + q\, h \sin \Omega t$$

$$\Gamma = 0.05 \quad \omega_0 = 0.597 \quad \beta = \gamma = 1 \quad h = 0.13 \;\; \Omega = 0.95$$

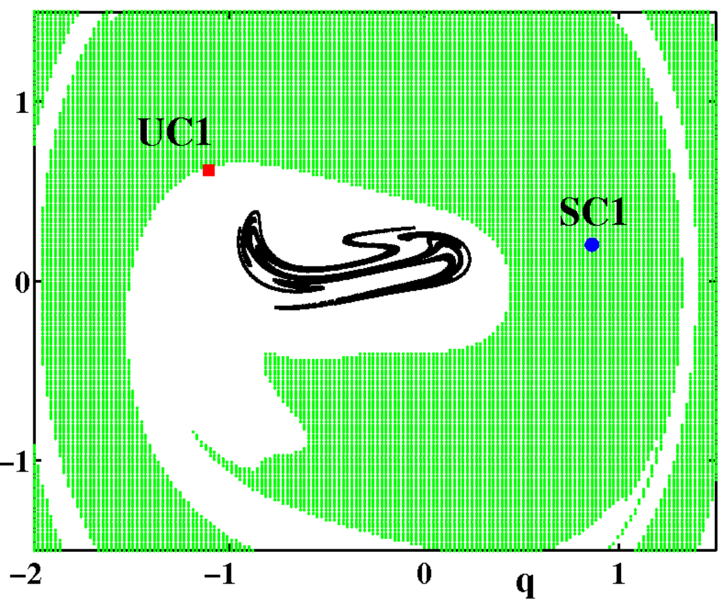
The potential $U(q)$ is monostable



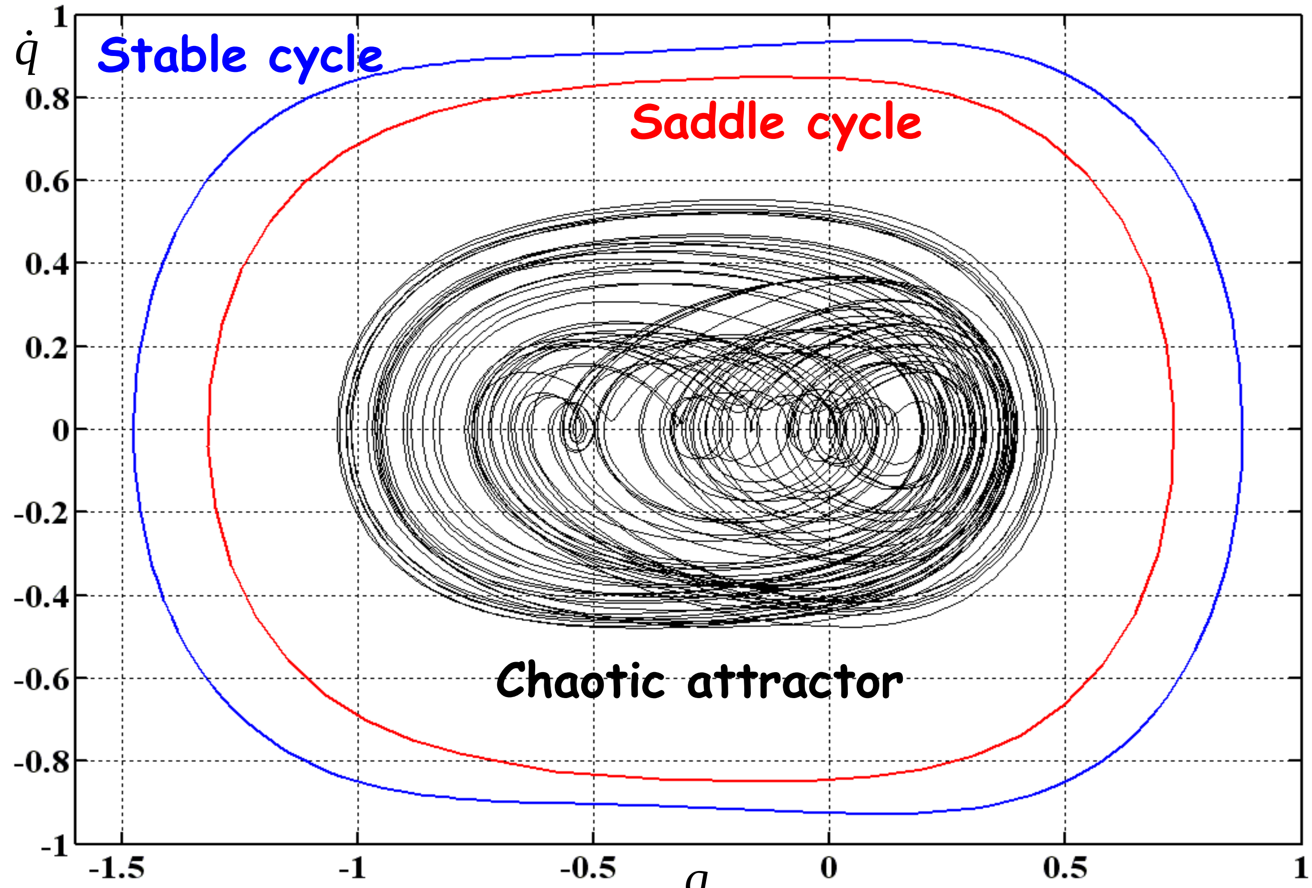
The motion is underdamped

Model of particle in the cooling beam

Poincare section



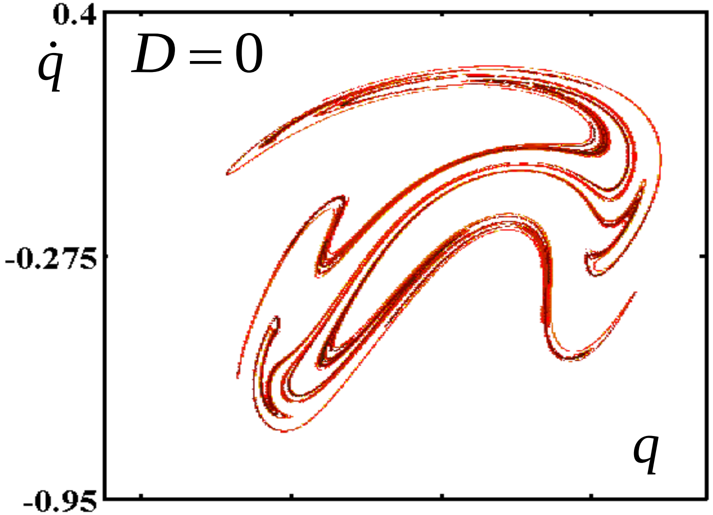
Initial conditions are on the chaotic attractor



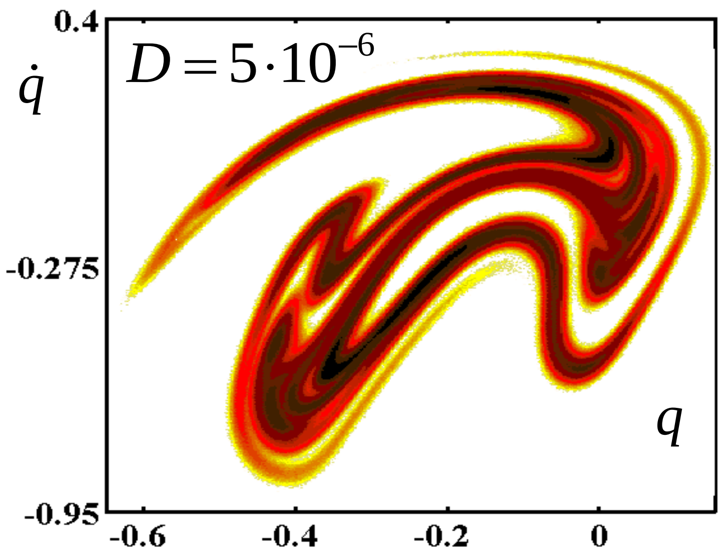
Deterministic pattern of noise-induced escape from a chaotic attractor

Noise significantly changes (deforms) the probability density of the attractor

Fractal structure

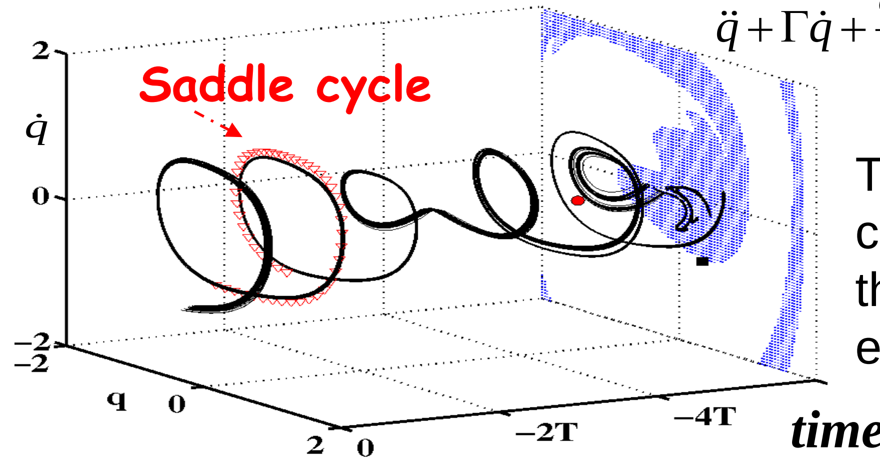


Smooth structure

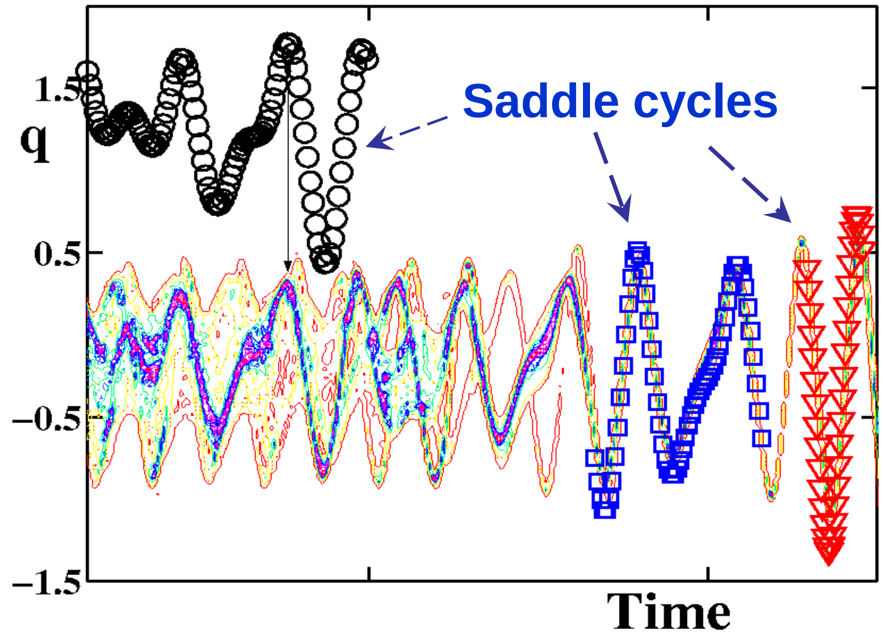


The escape corresponds to the noise-induced jumps between saddle cycles of chaotic sets

$$\ddot{q} + \Gamma \dot{q} + \frac{\partial U(q,t)}{\partial q} = \sqrt{2D}\xi(t)$$



Trajectories corresponding to the noise-induced escape



Prehistory probability of trajectories

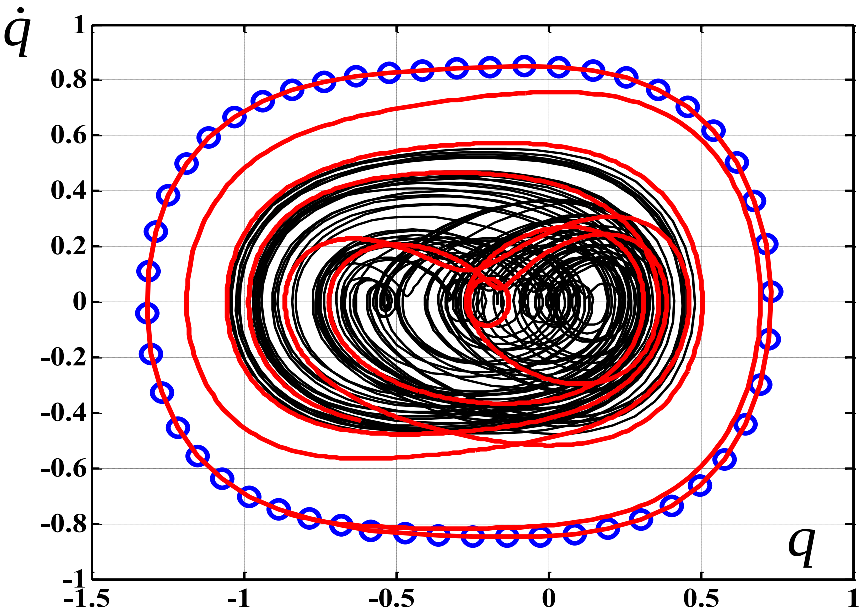
Via Large Fluctuation to Energy-minimal Deterministic Control: Migration between states

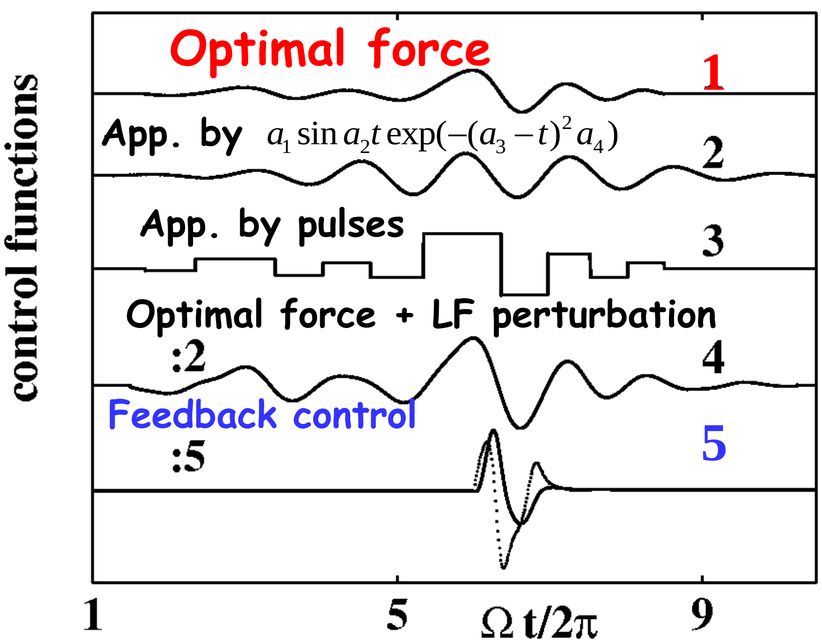
$$\ddot{q} + \Gamma \dot{q} + \frac{\partial U(q,t)}{\partial q} = f(t)$$

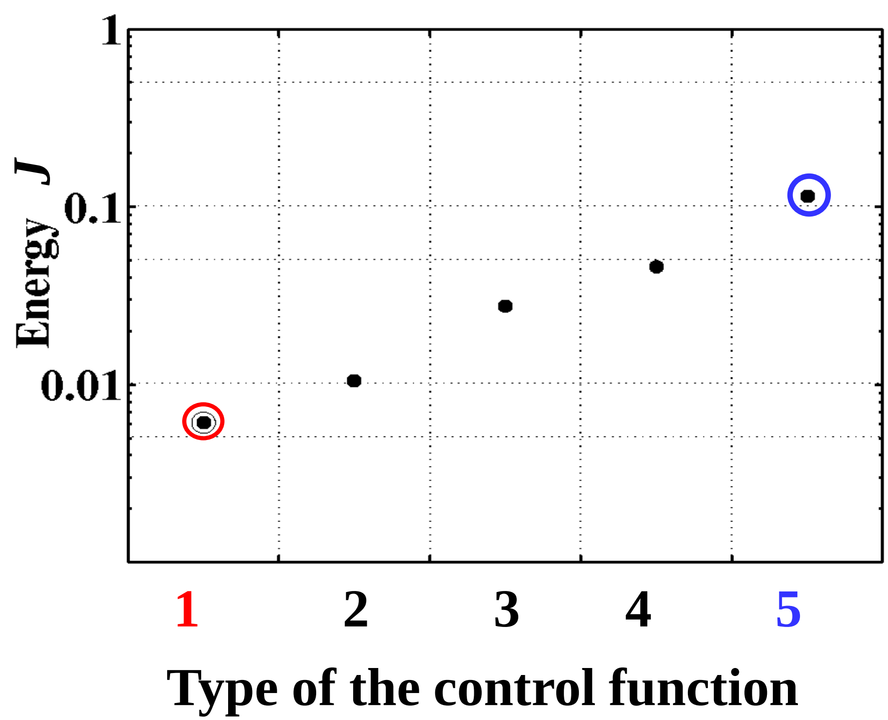
f (t) is a control function corresponding to the optimal fluctuational force $\xi_{opt}(t)$

The cost (energy) of control

$$J = \frac{1}{2} \inf_{f \in F} \int f^2(t) dt$$

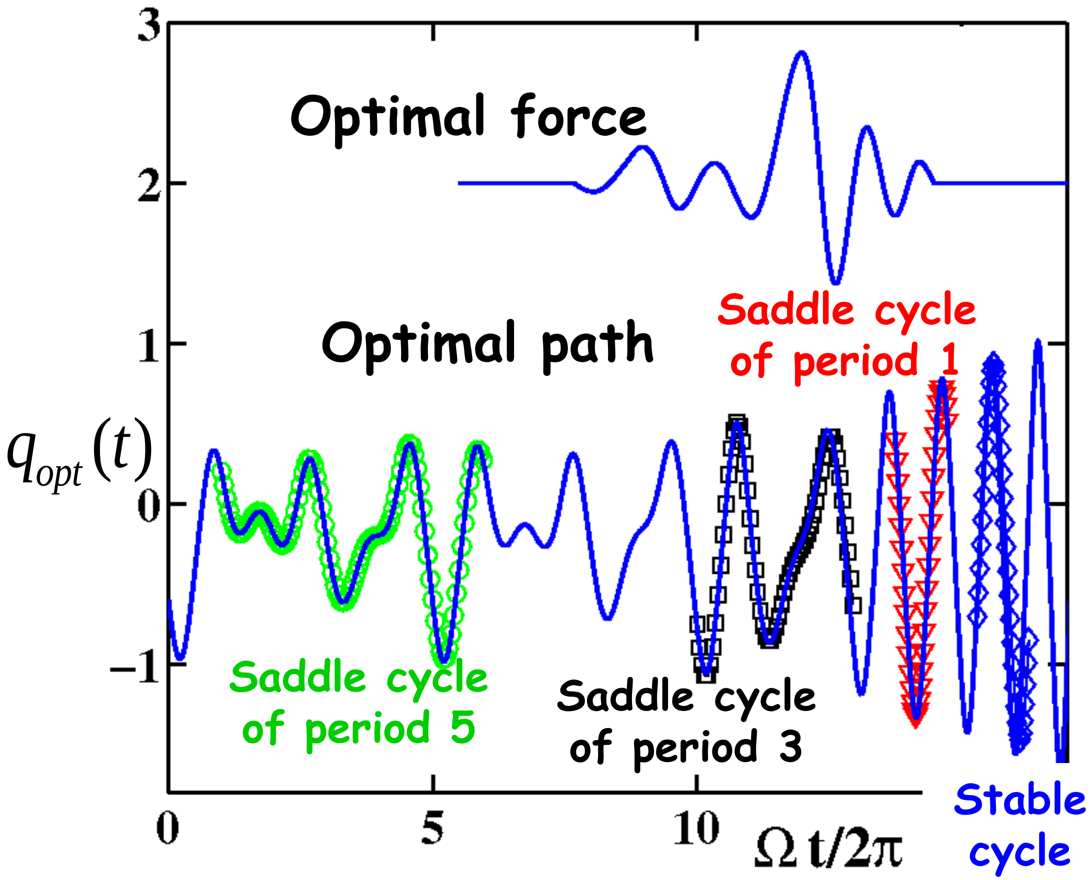






Suppression of the noise-induced escape

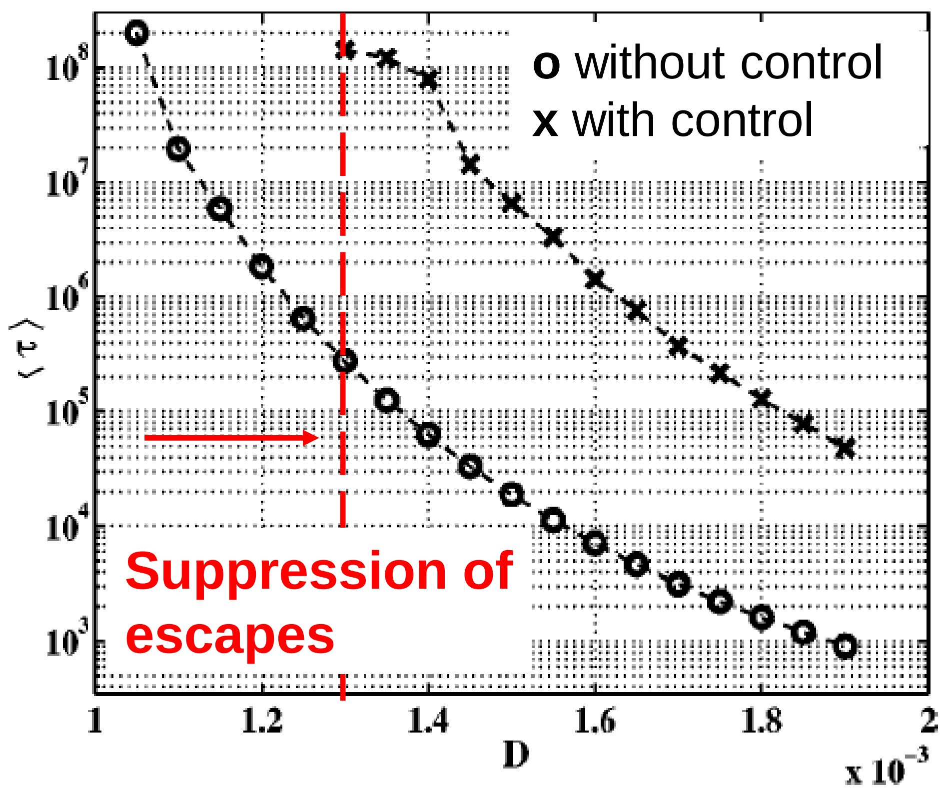
The optimal force and paths are used for suppressing the escape



$\xi_{opt}(t) \equiv f(t)$

0

Mean time between escapes as a function of noise intensity



Control force as an ***inverse optimal*** fluctuational force in a particular time moment

$$\ddot{q} + \Gamma\dot{q} + \frac{\partial U(q,t)}{\partial q} = \sqrt{2D}\xi(t) - \xi_{opt}(t)\delta\left(t - t_c\right)$$

Large Fluctuations and Types of Chaos. Control problem

Summary

For a quasi-hyperbolic attractor, its non-hyperbolic part plays an essential role in the escape process. The saddle point and its manifolds form the non-hyperbolic part. The fluctuations lead escape trajectory along stable and unstable manifolds.

For a non-hyperbolic attractor, saddle cycles embedded in the attractor and basin of attraction are important. Escape from a non-hyperbolic attractor occurs in a sequence of jumps between saddle cycles.

The analysis of large fluctuation provides an alternative way to solve a non-linear control problem. The optimal path and optimal fluctuational force, determined by using large fluctuations approach, corresponds to the solution of deterministic energy-minimal control problem.

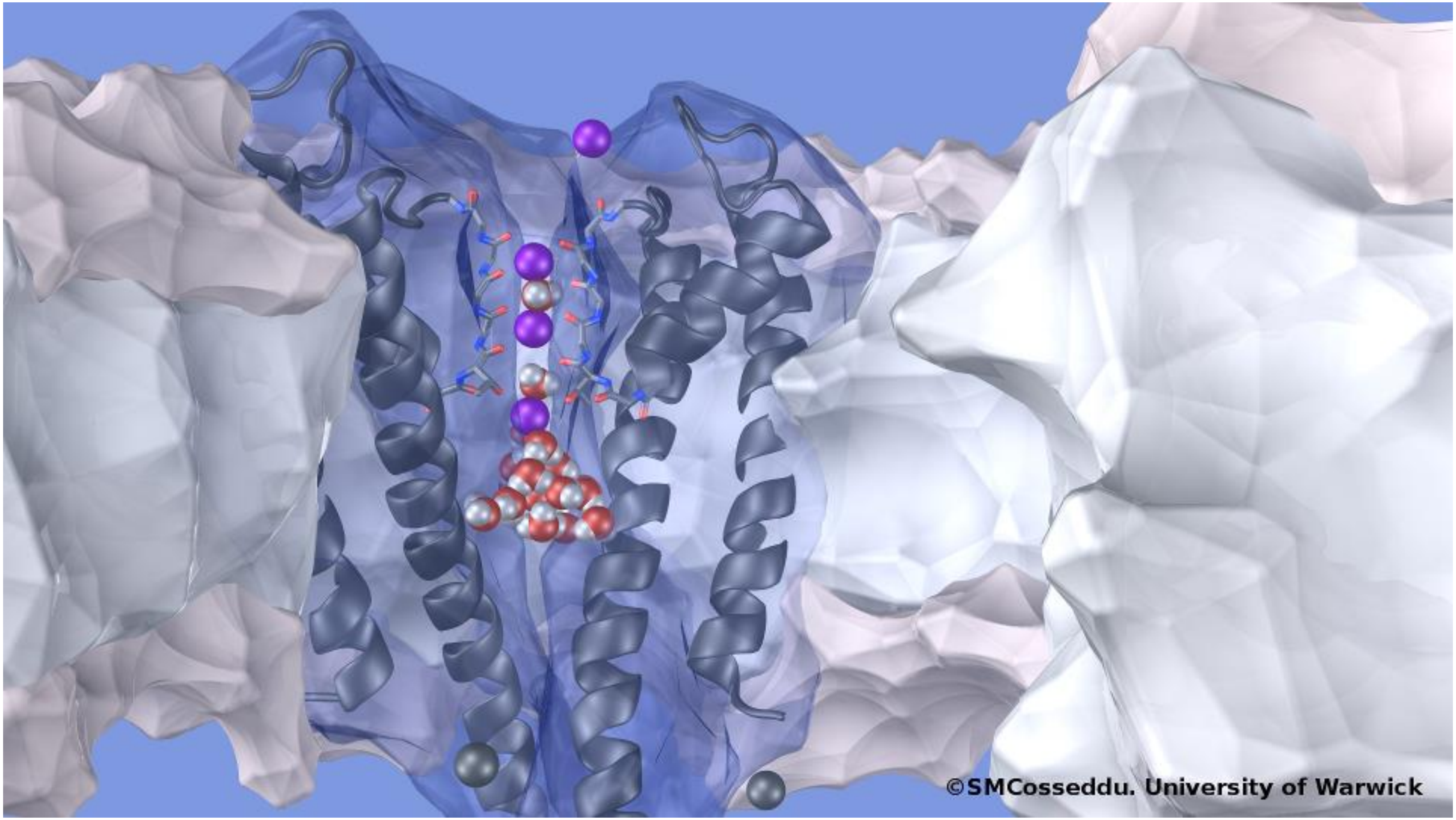
Dynamics of Large Fluctuations:
from Chaotic Attractors to Ion Channels

Igor Khovanov

University of Warwick

- The Concept of Optimal Path
- Types of Chaos and the Structural Stability (roughness) of models
- Large Fluctuations, Optimal Force and Control
- **Ion Transport**
- Conclusions

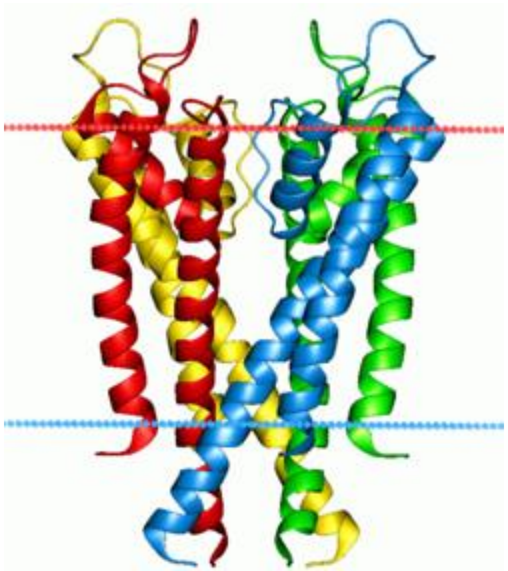
Potassium channel KcsA



MD simulations of KcsA

Main steps in line with the tutorial: http://www.ks.uiuc.edu/Research/smd_imd/kcsa/

1. Building the full protein using the information available from the x-ray structure from MacKinnon group, 2.0 A resolution, Y. Zhou, J. H. Morais-Cabral, A. Kaufman, and R. MacKinnon, "Chemistry of ion coordination and hydration revealed by a K+ channel-Fab complex at 2.0 A resolution," Nature, vol. 414, pp. 43–48, Nov. 2001.



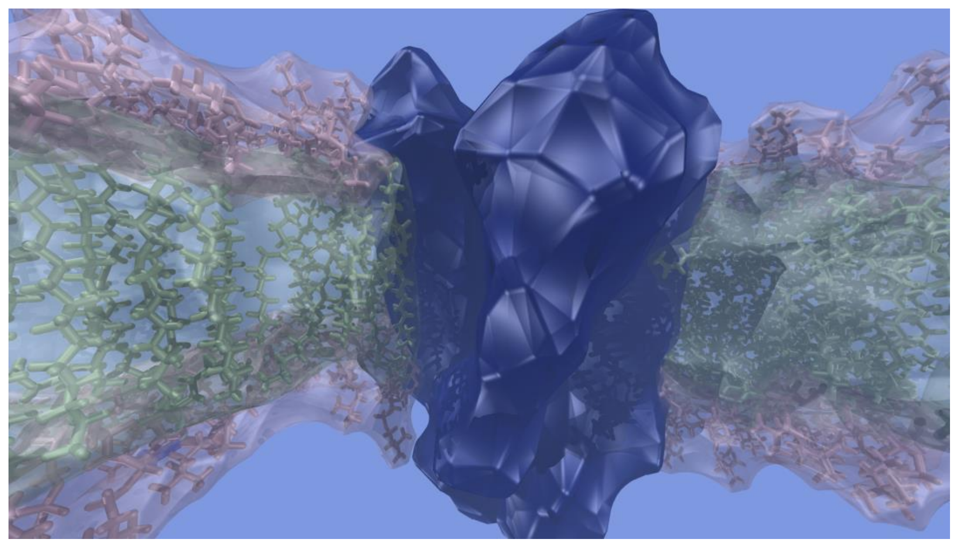
2. Building a phospholipid bilayer;

3. Inserting the protein in the membrane;

4. Solvating of the entire system.

5. Relaxing the membrane to envelop the protein and to let it assume a natural conformation.

KcsA is a tetramer composed of four identical subunits



MD simulations of KcsA

Molecular Dynamics is the *solution* of the classical (Newtonian) equations of motion for a set of molecules.

Within the Born-Opphenheimer approximation, the Hamiltonian of a system can be expressed as a function of the nuclear coordinates $\mathbf{q}_i$ and momenta $\mathbf{p}_i$.

For Cartesian coordinates:

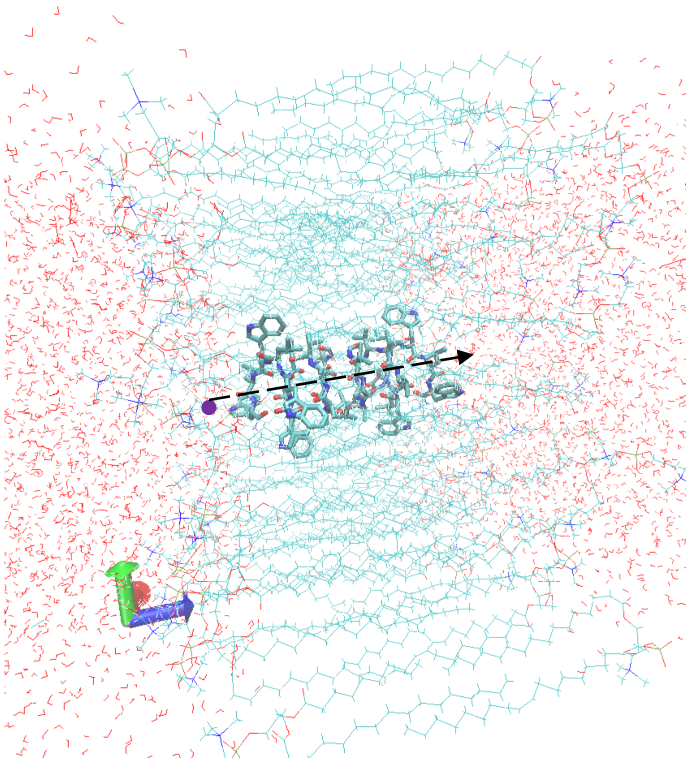
$$\dot{\mathbf{r}}_i = \mathbf{p}_i / m_i$$
$$\dot{\mathbf{p}}_i = -\nabla \mathcal{V}_i(\mathbf{r}_i)$$

Is it a Morse-Smale System?

Empirical *CHARMM Force Field,* ***VMD, NMAD***

$$V(r) = \sum_{bonds} K_b (b - b_0)^2 + \sum_{angles} K_\theta (\theta - \theta_0) + \sum_{dihedrals} K_\phi [1 + cos(n\phi - \phi_0)] + \sum_{impropers} k_\psi (\psi - \psi_0)^2$$
$$+ \sum_{i,j} 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] + \sum_{Urey-Bradley} K_u (u - u_0)^2 + \sum_{i,j} \frac{q_i q_j}{\epsilon_D r_{ij}}$$

From MD to Experiments via BD



All-Atom Molecular Dynamics (MD)

Hamiltonian Equation:

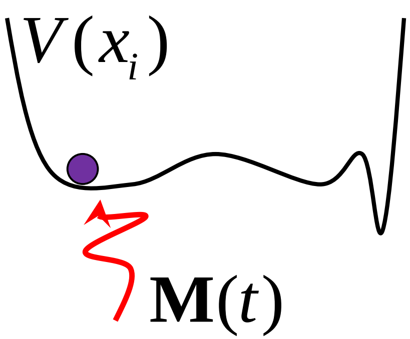
$$H = \sum_{k=1}^{N} \frac{\mathbf{p}_k \cdot \mathbf{p}_k}{2m_k} + U(\mathbf{r}_1, \mathbf{r}_2, \ldots \mathbf{r}_N)$$

$$\frac{d\mathbf{r}_i}{dt} = \frac{\partial H}{\partial \mathbf{p}_i} \equiv \frac{\mathbf{p}_i}{m_i}, \qquad \frac{d\mathbf{p}_i}{dt} = -\frac{\partial H}{\partial \mathbf{r}_i} \equiv -\nabla_{\mathbf{r_i}} U$$

$$N \sim 10^6 - 10^7$$

One-Atom Brownian Dynamics (BD).

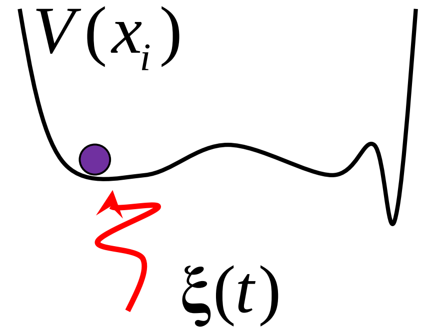
Generalized Langevin Equation:



$$m_i \dot{\mathbf{v}}_i(t) = -\frac{\partial V(\mathbf{r}_i)}{\partial \mathbf{r}_i} - \int_0^t \mathbf{M}(t-\tau)\mathbf{v}_i(\tau)d\tau + \mathbf{R}(t)$$

$$\mathbf{M}(t) = \frac{1}{k_B T}\langle \mathbf{R}(0)\mathbf{R}(t)\rangle$$

Overdamped Equilibrium Dynamics



One-Atom Brownian Dynamics (BD).

Typical assumption *(See B. Roux, M. Karplus, J. of Chem. Phys., Vol 95, 4856, 1991)*

Overdapmed Markovian *diffusion:*

$$\dot{\mathbf{r}}_i(t) = -\frac{1}{m_i\gamma(\mathbf{r}_i)}\frac{\partial V(\mathbf{r}_i)}{\partial \mathbf{r}_i} + \sqrt{\frac{2k_BT}{m_i\gamma(\mathbf{r}_i)}}\boldsymbol{\xi}(t)$$

$\gamma(\mathbf{r}_i)$ damping coefficient

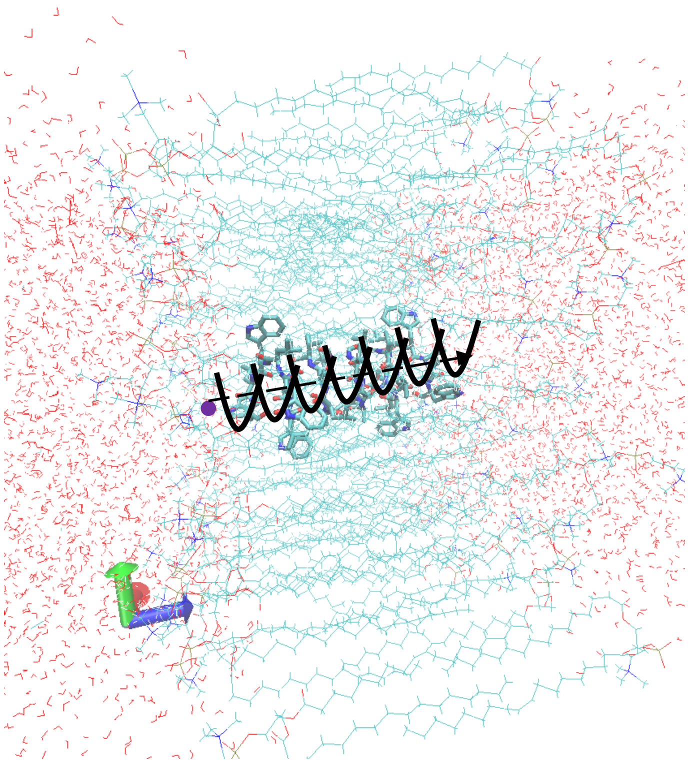
$\boldsymbol{\xi}(t)$ white Gaussian noise

Potential of mean force (PMF)

Biased simulations (*Umbrella Sampling*)

$$H_b(\mathbf{r},\mathbf{p}) = H_0(\mathbf{r},\mathbf{p}) + U(\mathbf{z}) \quad \Rightarrow \quad V(\mathbf{z})$$

Biased Hamiltonian — *Initial Hamiltonian* — *Biasing Potential* — *Resulting PMF*



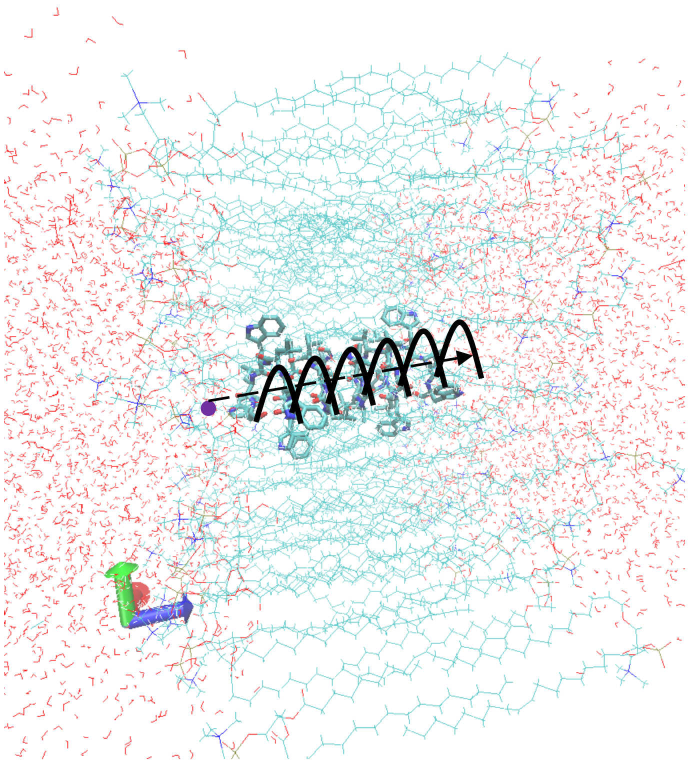
- *Will the resulting PMF be a potential we are looking for?*

Potential of mean force (PMF)

Biased simulations (*Meta-Dynamics*)

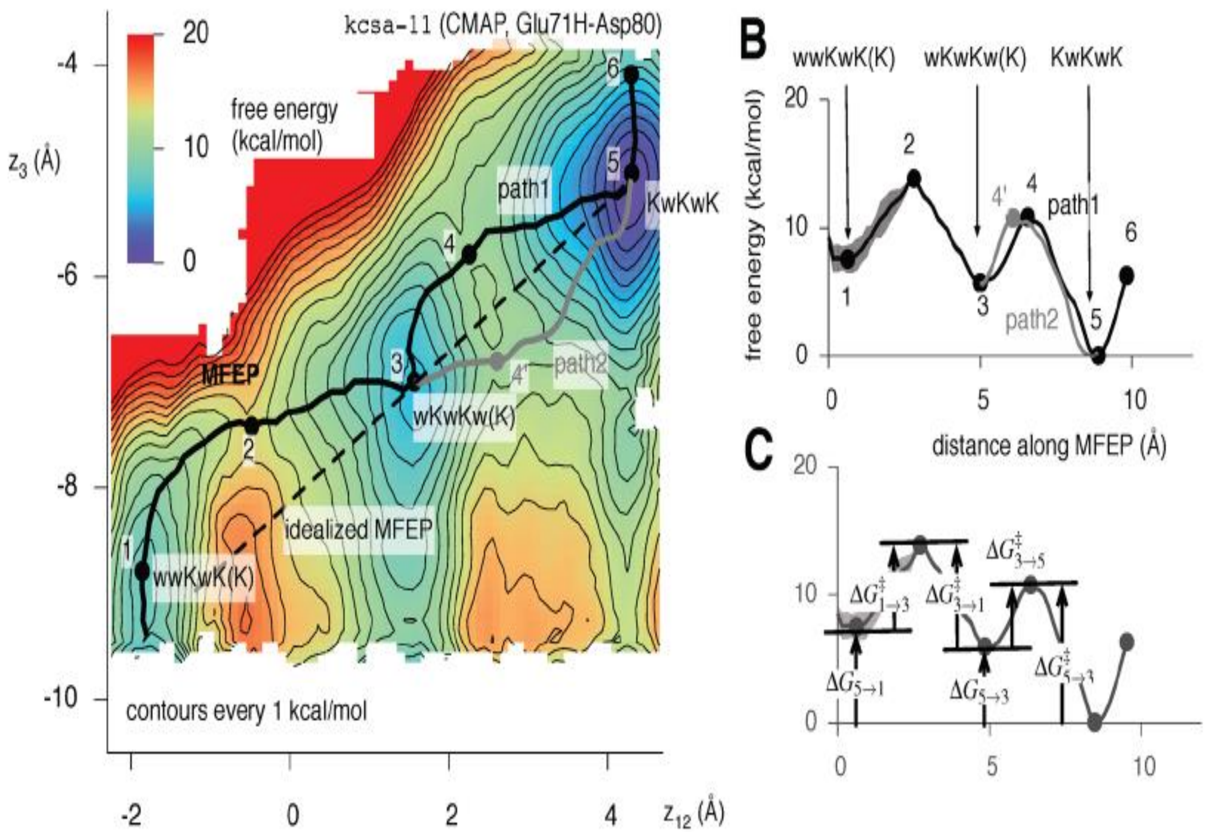
$$H_b(\mathbf{r},\mathbf{p}) = H_0(\mathbf{r},\mathbf{p}) + U(\mathbf{z}) \quad \Rightarrow \quad V(\mathbf{z})$$

Biased Hamiltonian	Initial Hamiltonian	Biasing Potential	Resulting PMF



- *Will the resulting PMF be a potential we are looking for?*

Ion permeation and PMF

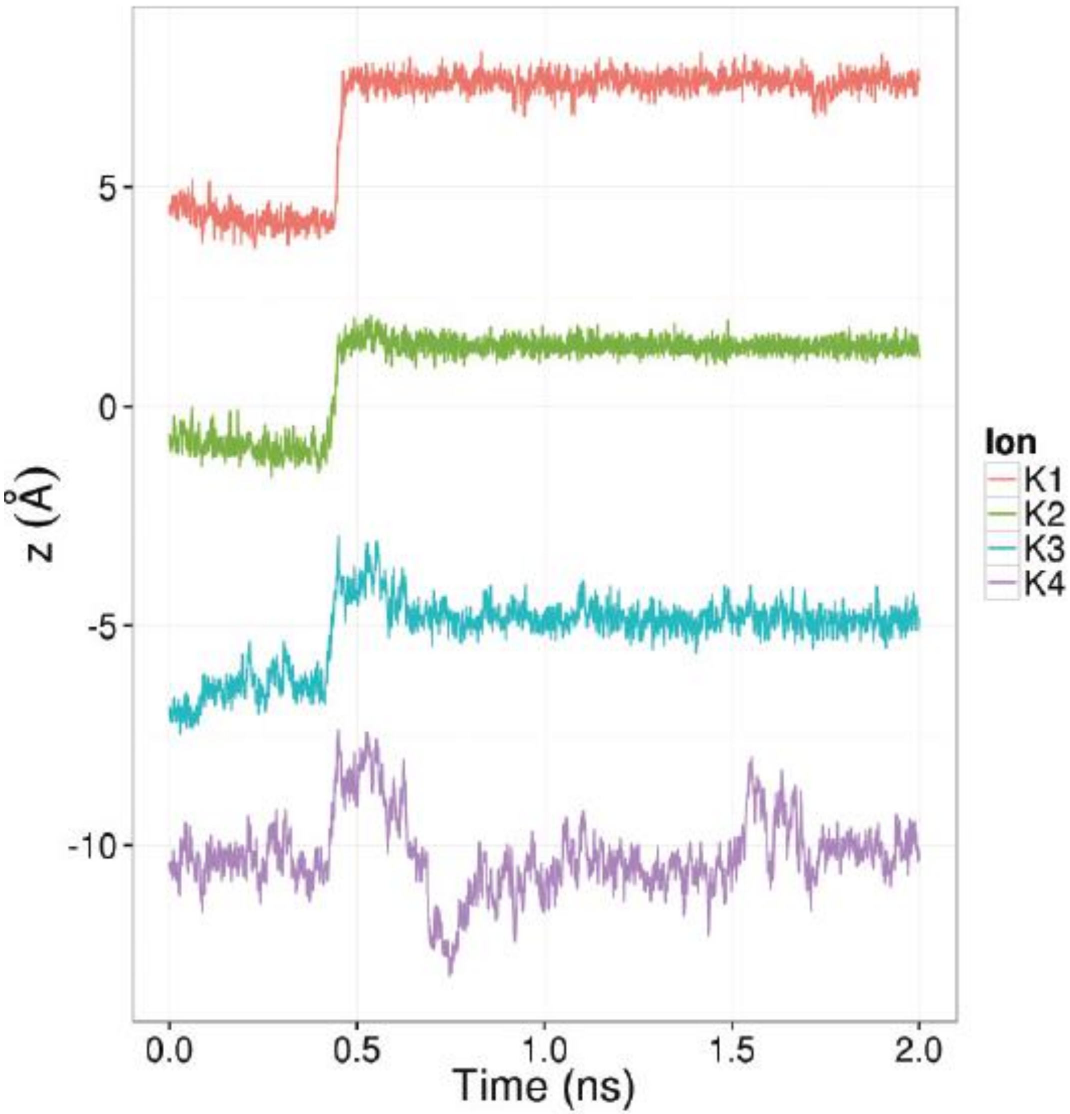


From
P.W. Fowler et al
J Chem Theory Comput
2013, 9, 5176-5189.

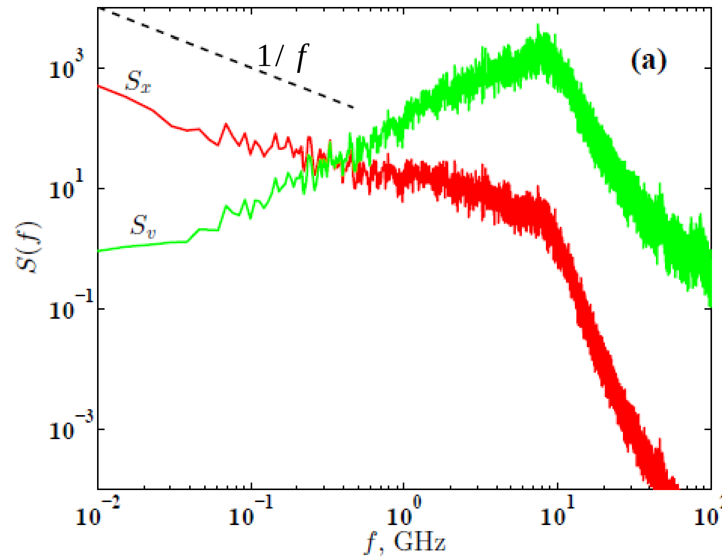
Abstract. "… the heights of the kinetic barriers for potassium ions to move through the selectivity filter are, in nearly all cases, too high to predict conductances in line with experiment. This implies it is not currently feasible to predict the conductance of potassium ion channels, but other simpler channels may be more tractable."

Ions activation dynamics

Ions trajectories

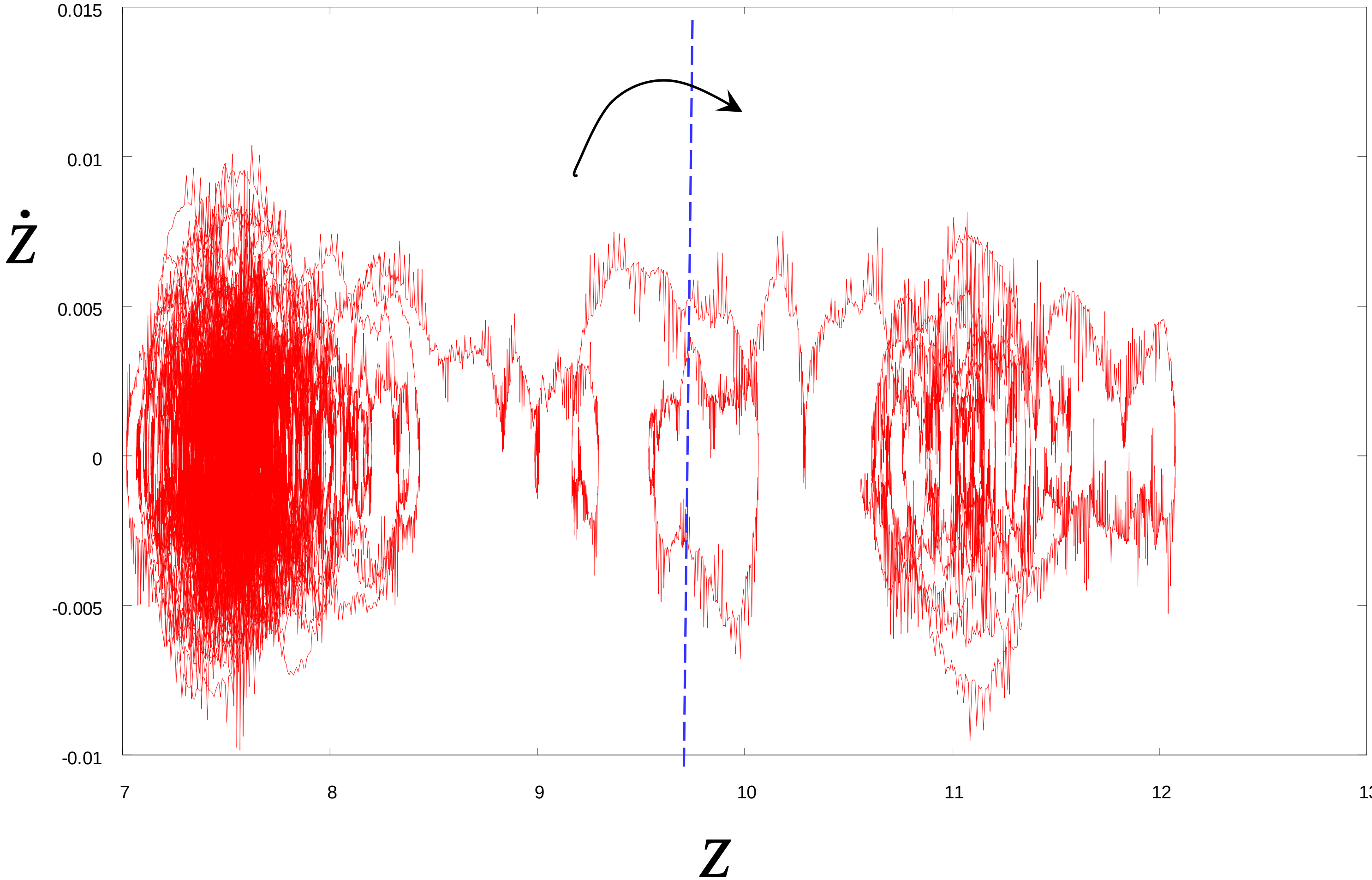


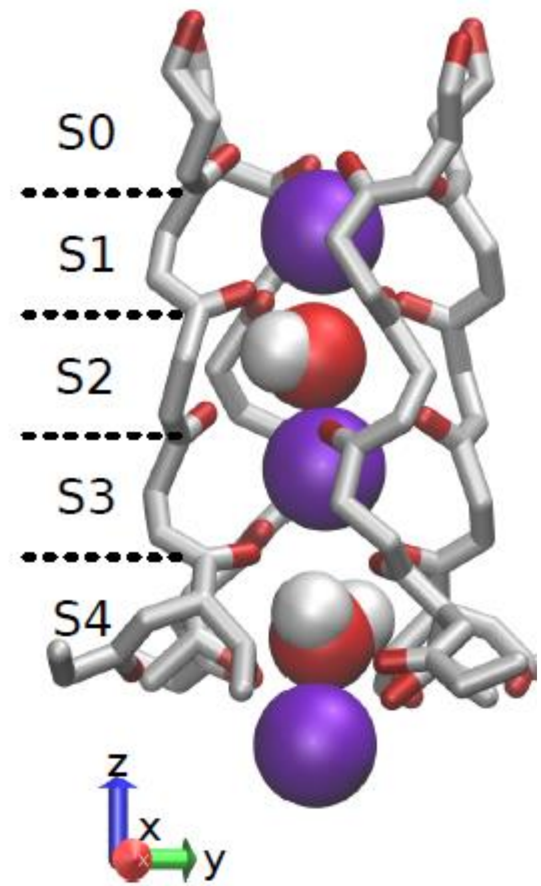
Power spectrum



Ions activation dynamics

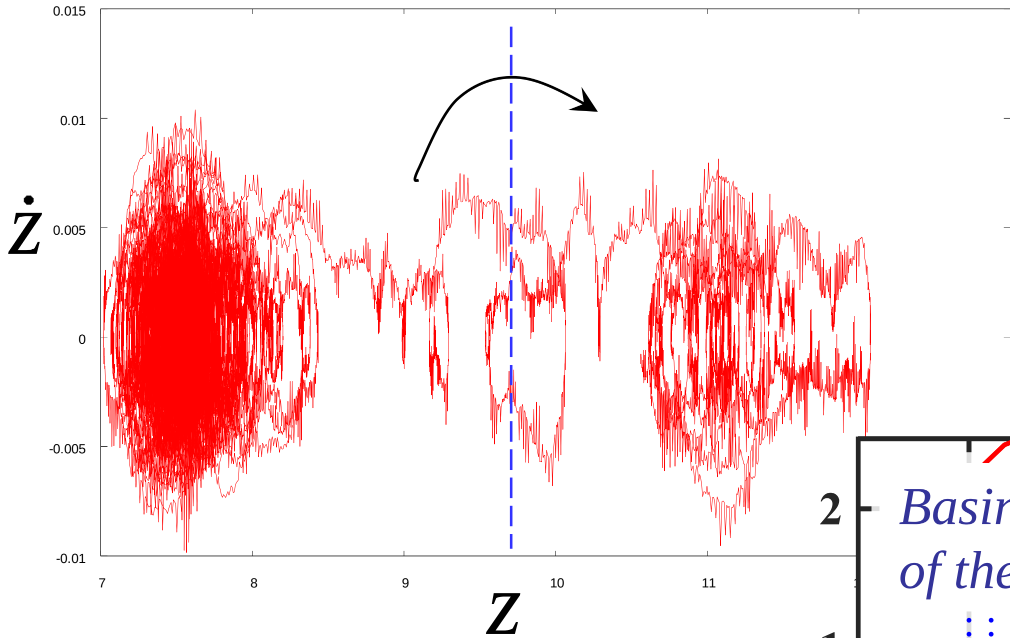
Transition from site to site





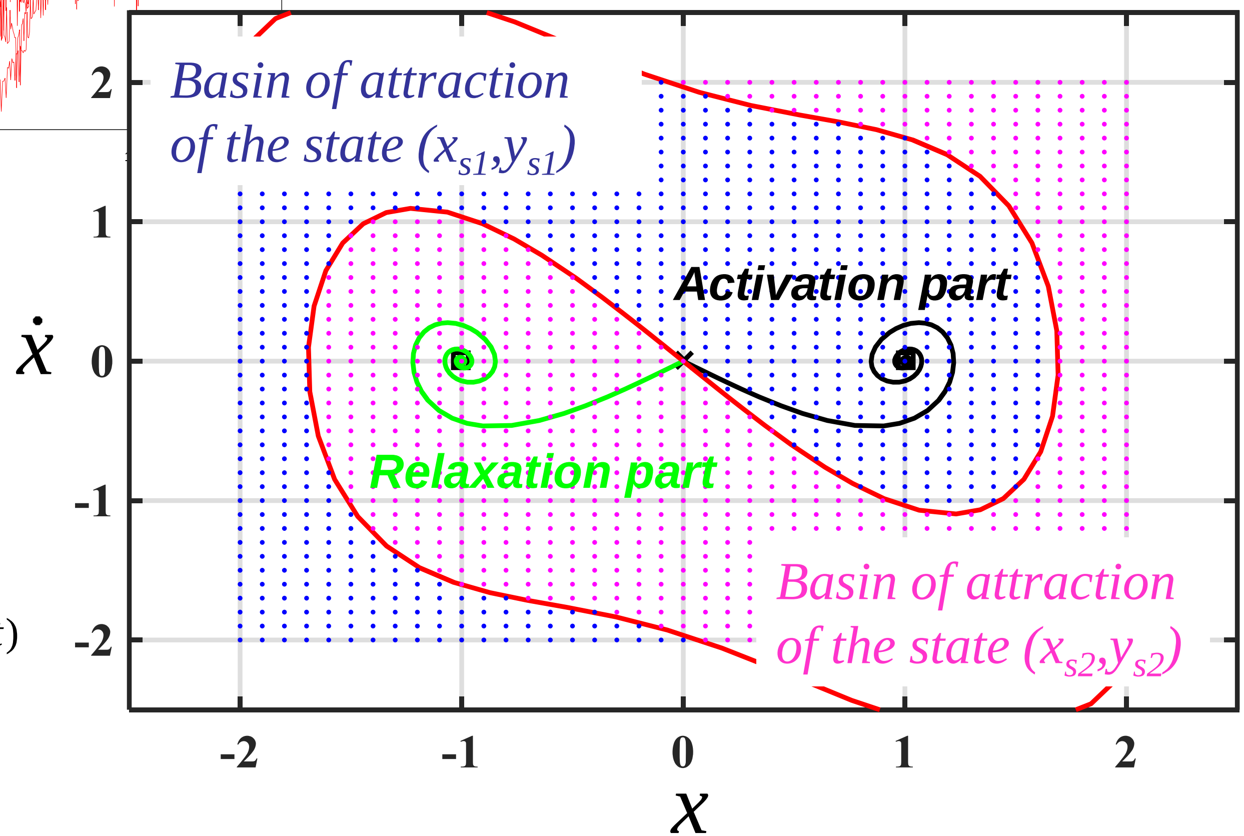
Selectivity filter

Ions activation dynamics



$$\ddot{x} + b\dot{x} - \alpha x + \beta x^3 = \sqrt{D}\xi(t)$$

Noise-induced escape in Duffing oscillator



Conclusion:

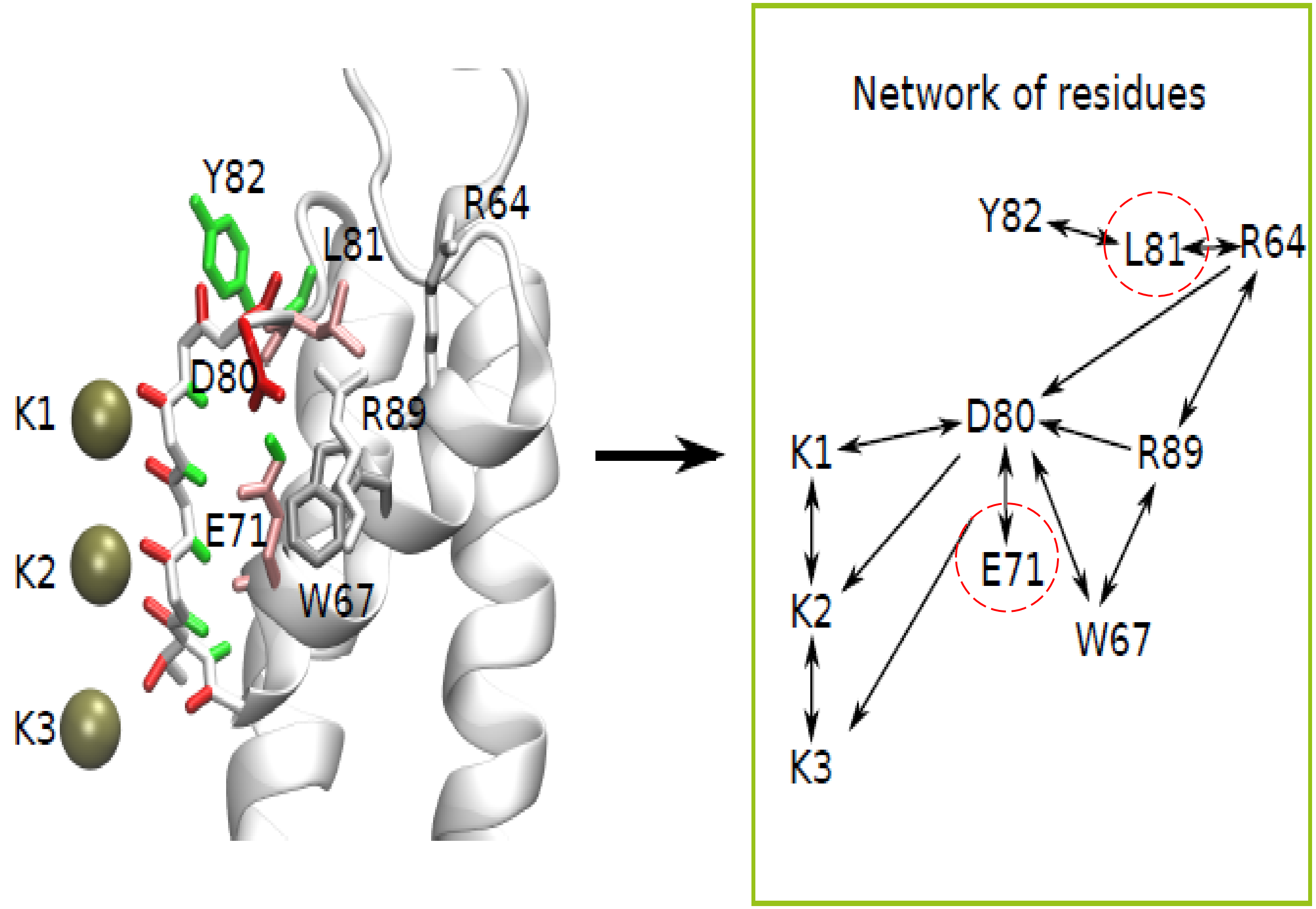
Ion dynamics is underdamped and non-Markovian

$$m_i \dot{\mathbf{v}}_i(t) = -\frac{\partial V(\mathbf{r}_i)}{\partial \mathbf{r}_i} - \int_0^t \mathbf{M}(t-\tau)\mathbf{v}_i(\tau)d\tau + \mathbf{R}(t)$$

$$\mathbf{M}(t) = \frac{1}{k_B T}\langle \mathbf{R}(0)\mathbf{R}(t) \rangle$$

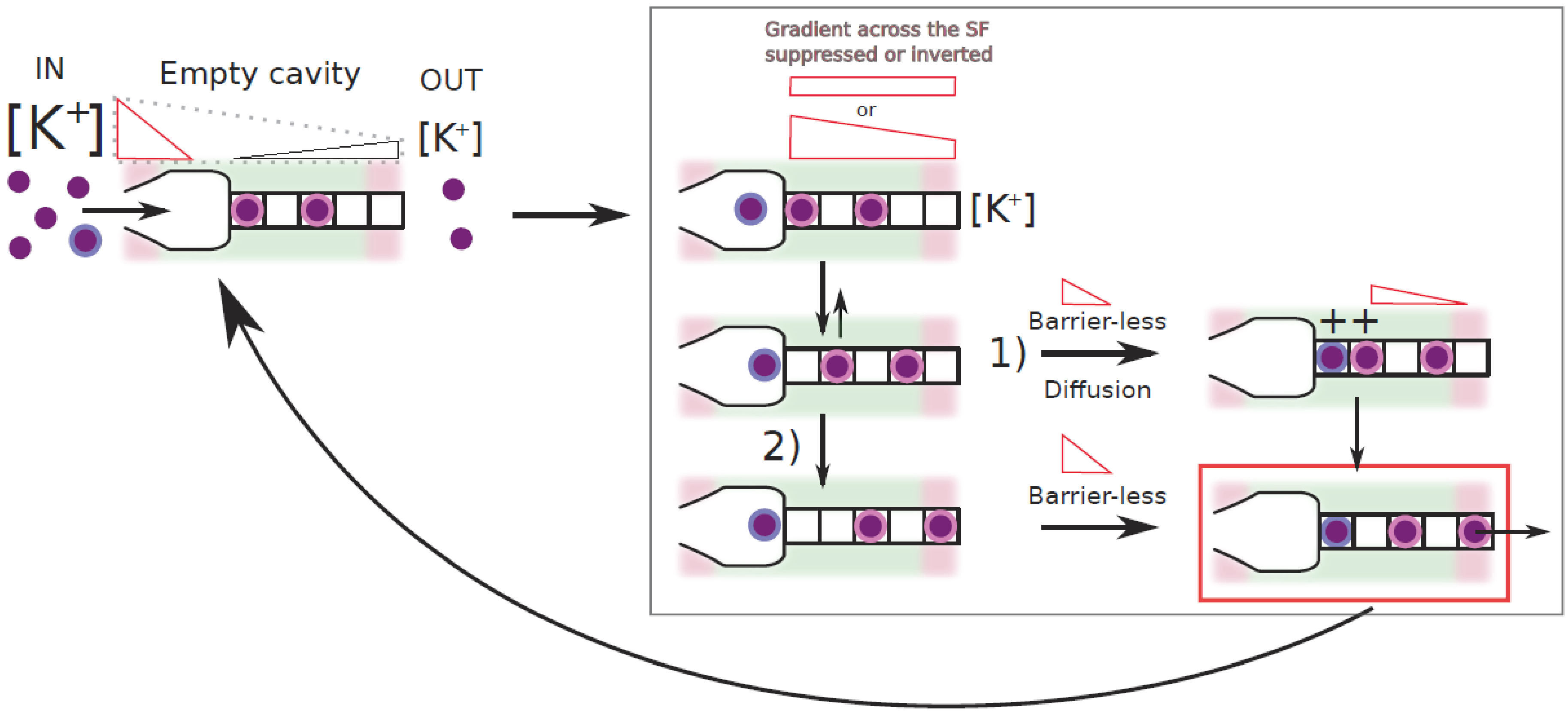
Ion permeation

Network of residues control the permeation



Ion permeation

There is a conductive conformation.



Lessons of KcsA channel

Advantage of MD technique

provide a bridge from the structure to functions

Pitfalls of MD technique

high degree of uncertainty in each step of the technique

"standard" approaches are not (always) reliable

require "experience" in the use of MD