# Control of a Model of DNA Division via Parametric Resonance

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## Overview

- Study
  - internal resonance,
  - energy transfer,
  - activation mechanism, and
  - control

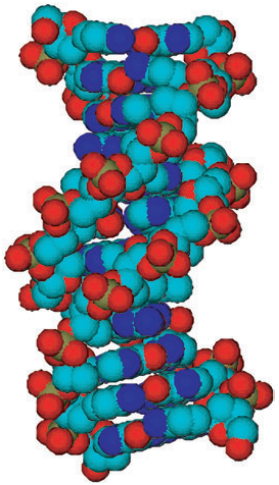
  of a model of DNA division
  via parametric resonance.
- It may provide a method
  for controlling real DNA division by EM fields,
- suggest how enzymes initiate DNA opening dynamics.

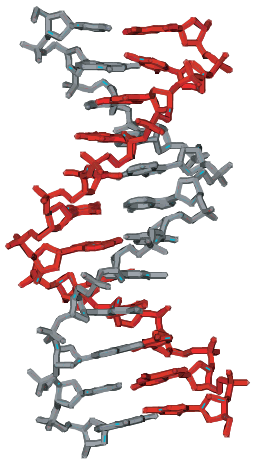
- Koon, Owhadi, Tao, and Yanao, Control of a model of DNA division via parametric resonance, *Chaos* **23**, [2013].

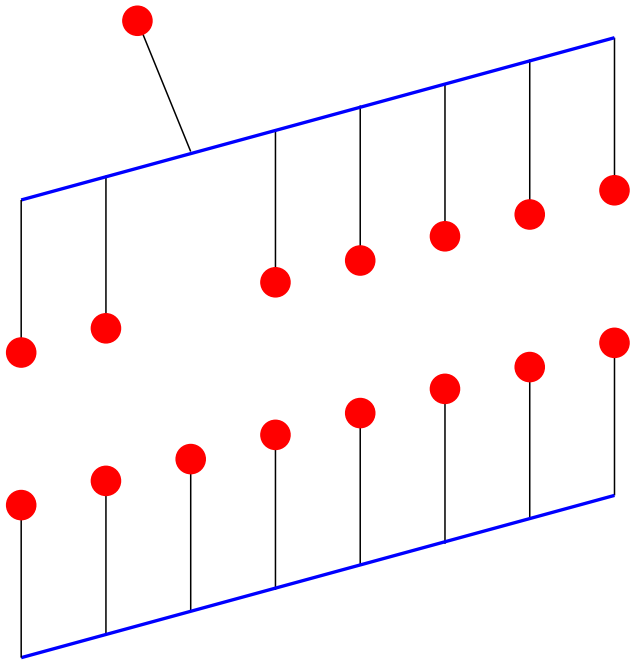
## The Model (Mezic [2006])

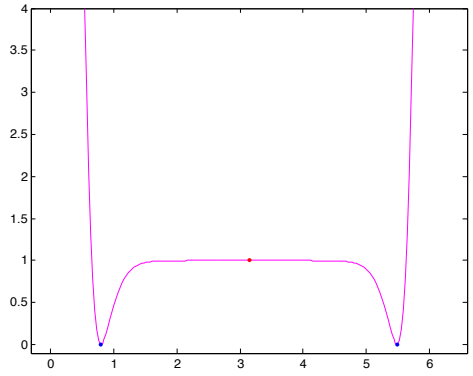
- A chain of pendula that rotate about axis of a fixed backbone ($\theta_k$).
  - Pendula interact with nearest neighbors along backbone through harmonic torsional coupling,
  - with pendula on immobilized strand via Morse potential.
- Non-dimensional Hamiltonian for these $n$ coupled pendula

$$H(\theta, p_\theta) = \sum_{k=1}^{n} \left[ \frac{1}{2} p_{\theta k}^2 + \frac{1}{2}(\theta_k - \theta_{k-1})^2 + \epsilon \left( e^{-a(1+\cos\theta_k - d_0)} - 1 \right)^2 \right]$$



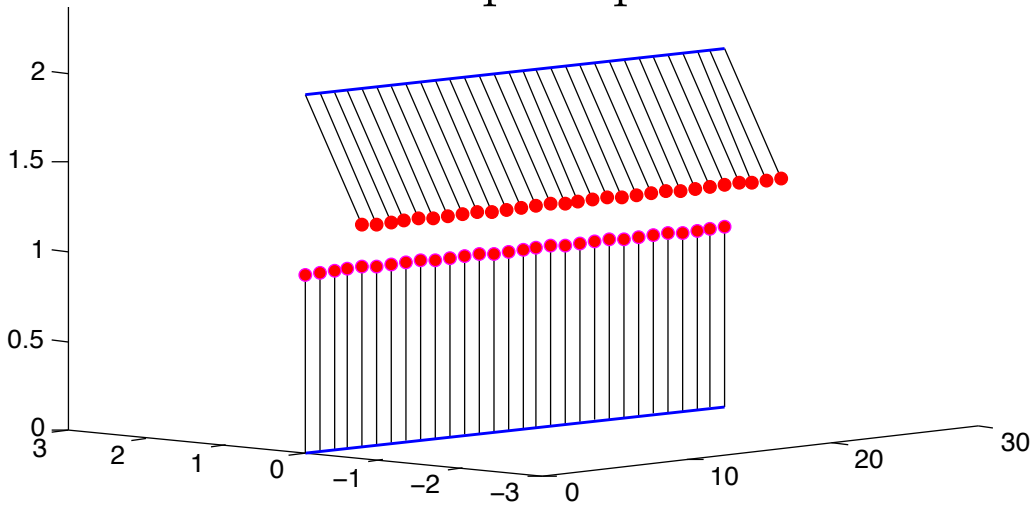


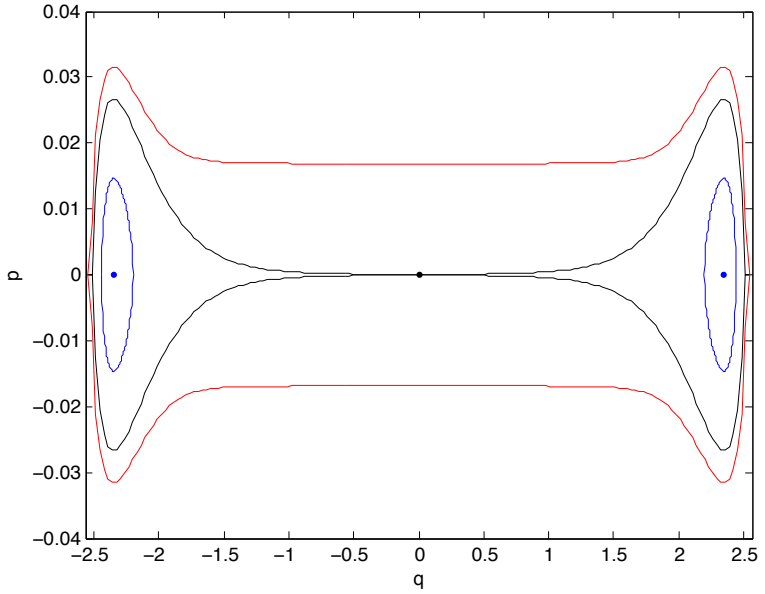




# The Model

- Instructive to look at phase space of a single pendulum:
  - 2 stable equilibria at $(\pm\theta_e, 0)$, 1 saddle at $(0, 0)$.
  - **Separatrix**, oscillation near equilibria, flipping across saddle.
- $n$-coupled pendula has similar but much complicated behaviors.
- 2 stable equilibria when $\theta_k = \pm\theta_e$, 1 rank one saddle when $\theta_k = 0$.
  - For small energy, liberate near stable equilibria (global minima).
  - For large enough energy, move collectively from one energy basin to the other and flip across a rank 1 saddle.
- Model of 30 coupled pendula:

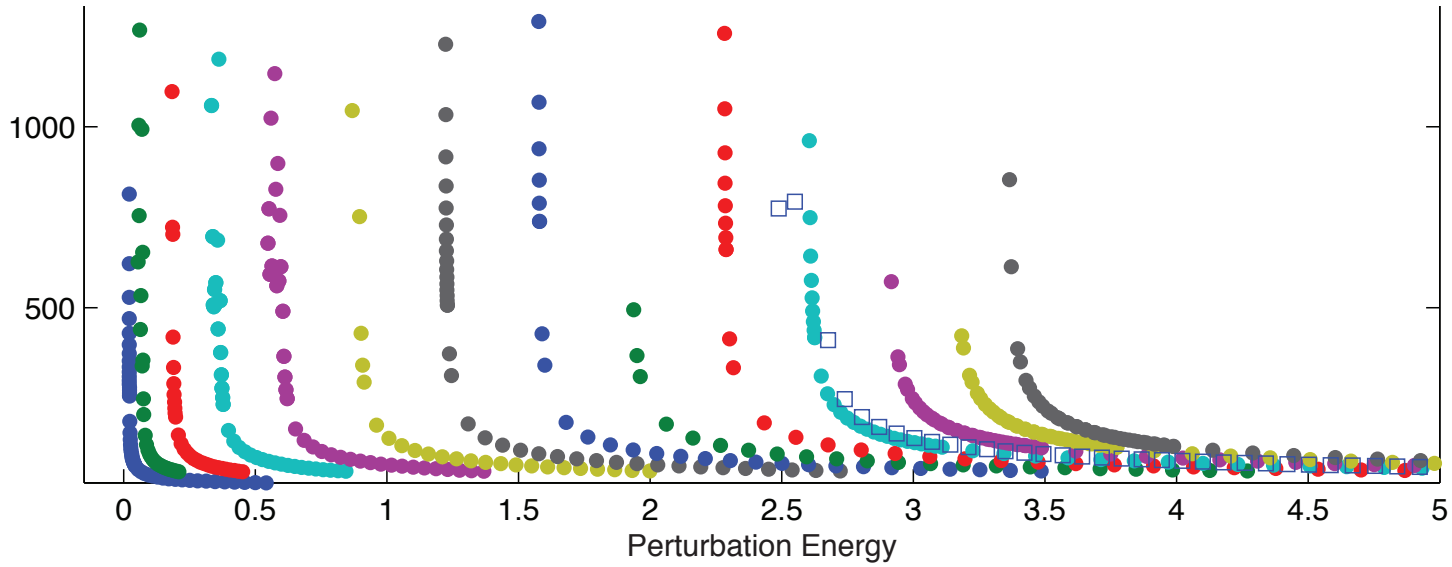


## Structured Activations

- Previous studies, mainly numerical, showed that this model exhibits an intriguing phenomenon of structured activations:
  - While the system is **robust to noise**, it is sensitive to certain specific fine scale modes that can trigger the division.
- To appreciate figure, Eisenhower [2009], Fourier modal coordinates is needed to diagonalize coupling terms/rewrite Hamiltonian as:

$$H(q,p) = \sum_{\alpha=0}^{n-1} \left( \tfrac{1}{2} p_\alpha^2 + \tfrac{1}{2} \omega_\alpha^2 q_\alpha^2 \right) + \epsilon \sum_{k=1}^{n} U\Big( \sum_{\beta=0}^{n-1} T_{k\beta} q_\beta \Big)$$



## Structured Activations

- Hamiltonian

$$H(q,p) = \sum_{\alpha=0}^{n-1} \left( \tfrac{1}{2} p_\alpha^2 + \tfrac{1}{2} \omega_\alpha^2 q_\alpha^2 \right) + \epsilon \sum_{k=1}^{n} U\Big( \sum_{\beta=0}^{n-1} T_{k\beta} q_\beta \Big)$$

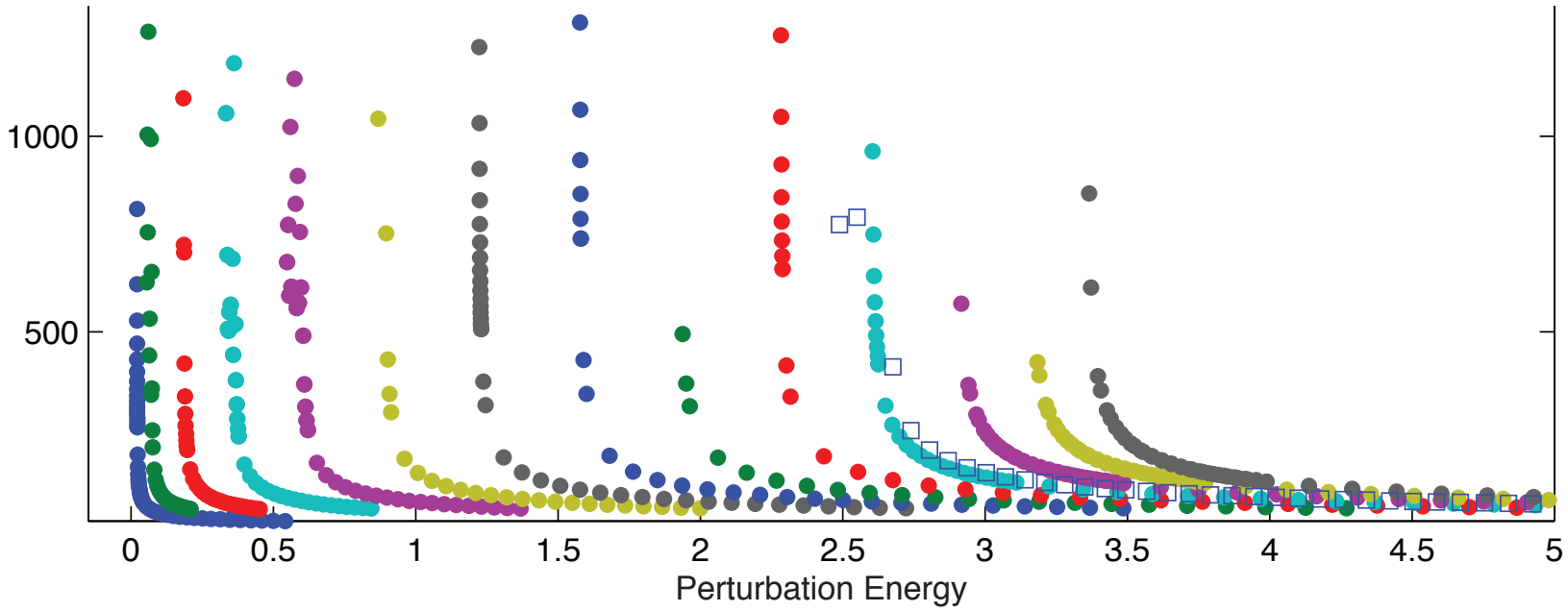
- **Now**, the model can be seen as a small perturbation of $n$ oscillators with frequencies $\omega_\alpha$ : $\omega_\alpha^2 = 2 - 2\,cos\,(2\pi\alpha/n)$, $\alpha = 0, ..., n-1$.
- The coordinate of 0th (Fourier) mode, $q_0$, given as follows

$$q_0 = \frac{1}{\sqrt{n}} \sum_{k=1}^{n} \theta_k = \sqrt{n}\bar{\theta}$$

  is the average angle $\bar{\theta}$ of pendula (except a factor of $\sqrt{n}$).
- It plays the special and important role as the collective variable, reaction coordinate, and slow variable.
- Other $(n-1)$ modal coordinates $q_\alpha$ are the bath coordinates, and the fast variables.

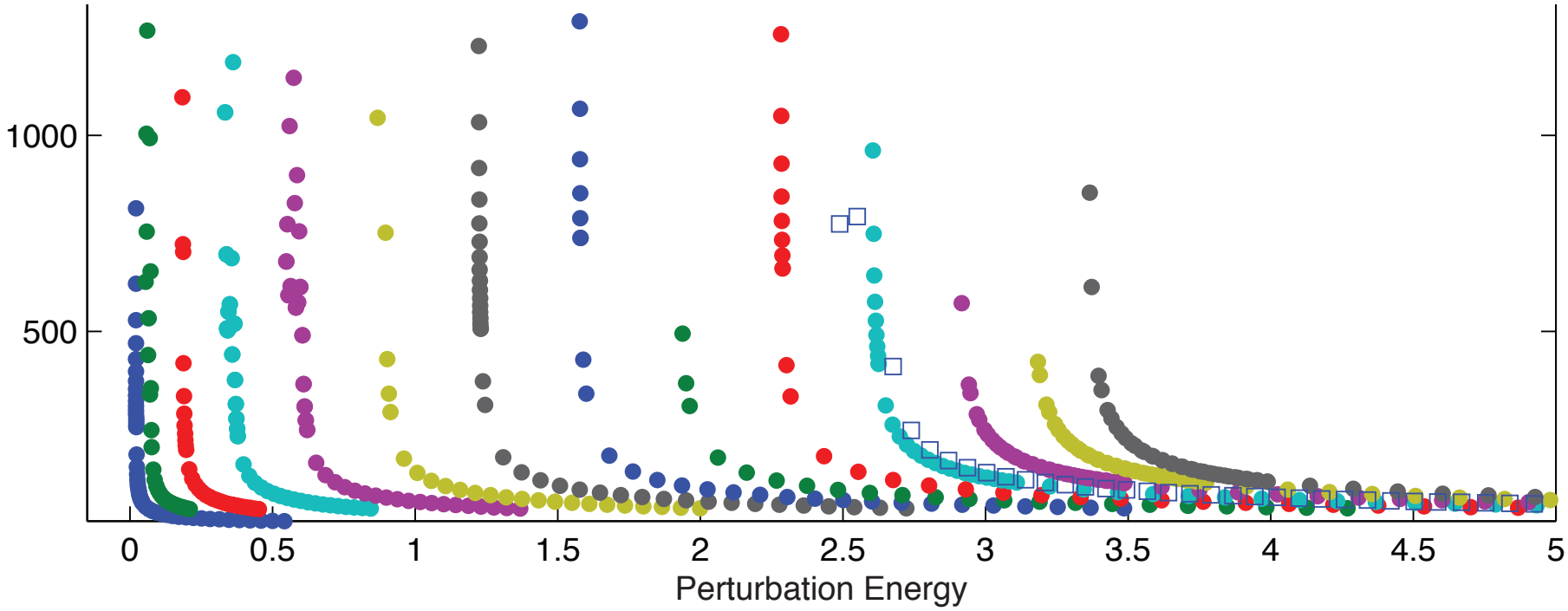
## Structured Activations

- Initial activation is chosen as a single Fourier mode, with certain amount of energy.
- Time to division determined when average angle $q_0$ cross $q_0 = 0$.
- A curve is obtained that shows amount of activation energy vs time to division for each Fourier mode.
- Each has asymptote at low energy limit (min. activation energy).
- White "□"s show the data for **random noise**.



## Structured Activations

- Minimum activation energy (MAE) depends on the way this energy is injected into the system.
- While the system is **robust to noise**, it is sensitive to certain specific fine scale modes that can trigger the division.
- Want to develop analytical method to reveal activation mechanism and to compute MAEs.
- Want to develop methods for controlling DNA division via EM fields and to reveal how enzymes initiate DNA open state dynamics.



## Analytical Study

- Recall EOM

$$\begin{aligned} \ddot{q}_0 &= -\epsilon M_0(q_0, q_1, ..., q_{n-1}) \\ \ddot{q}_\alpha + \omega_\alpha^2 q_\alpha &= -\epsilon M_\alpha(q_0, q_1, ..., q_{n-1}) \end{aligned}$$

  can be seen as a **nonlinear perturbation** of n oscillators ($\omega_\alpha$ varies from 0.2091 to 2).

- The reactive mode (0th mode) forms a nearly $0:1$ **resonance** with any other mode, each of which has an $O(1)$ frequency

$$m\omega_0 + 0\omega_\alpha = 0, \qquad \text{with } m = 1.$$

- This fact leads to **small denominators** and **coupling terms** in corresponding **averaged equations** or **normal form**.

- Other modal frequencies, are not rationally commensurate and do not have significant time scale separation.
  We do not expect strong resonance among them.

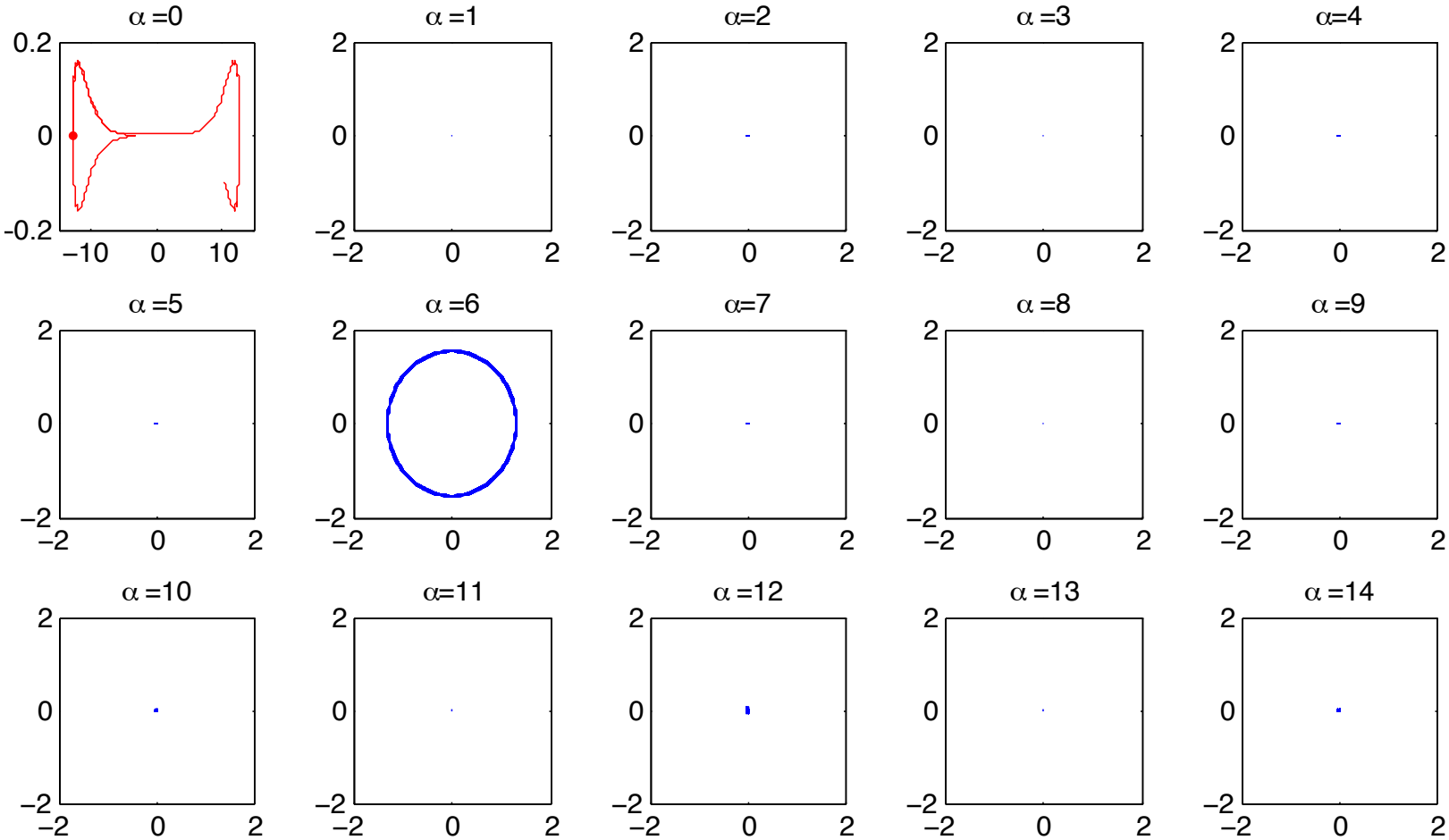
- Nearly $0:1$ **resonance** will be main focus of our study.

## Nearly $0:1$ Resonance and Partial Averaging

- Nayfeh and Chin [1995] and Haller [1999] has studied such degenerate resonance:
  - they applied a modified averaging method to 2 mode truncation of a mechanical system having this type of resonance.
- While Eisenhower & Mezic did not mentioned $0:1$ resonance,
  - they employed Arnold's method of partial averaging to a truncated Hamiltonian in the study of a chain of Duffing oscillators.
- The work of these researchers, our extensive numerical simulations, and a rigorous error estimate have convinced us
  - 2 mode truncation is adequate for our analytical study of structured activations,
  - we can apply partial averaging to these reduced models.

# Numerical Simulations

- Projections of a sample trajectory on phase spaces of first 15 modes. Initial activation chosen to be single 6th mode $(q_0^e, ..., p_6(0), ...)$.
  - energy transfer over-whelmingly from excited to reactive mode,
  - only an extremely small amount of energy transfers from the excited mode to 1 or 2 other modes via near resonances.



## Partial Averaging of Truncated Hamiltonian

- First, **expand** Morse potential $U$ (exponential function) as a polynomial of 26 degrees.

$$H_2^{\gamma}(q,p) = \sum_{\alpha=\{0,\gamma\}} \left(\tfrac{1}{2}p_\alpha^2 + \tfrac{1}{2}\omega_\alpha^2 q_\alpha^2\right) + \epsilon \sum_{k=1}^{n}\sum_{j=0}^{26} a_j \Big(\sum_{\beta=\{0,\gamma\}} T_{k\beta} q_\beta\Big)^j$$

- Then, **use** action angle coordinates

$$q_\gamma = \sqrt{2I_\gamma/\omega_\gamma}\sin\phi_\gamma, \qquad p_\gamma = \sqrt{2I_\gamma\omega_\gamma}\cos\phi_\gamma.$$

  and **rewrite** reduced Hamiltonian as $H_2^{\gamma}(q_0, p_0, I_\gamma, \phi_\gamma)$.

- Notice: Besides $q_0, p_0$, action $I_\gamma$ is also a slow variable.

- The **average reduced Hamiltonian** can be obtained by **averaging** the only fast variable $\phi_\gamma$

$$\bar{H}_2^{\gamma}(\bar{q}_0, \bar{p}_0, \bar{I}_\gamma) = \frac{1}{2\pi}\int_0^{2\pi} H_2^{\gamma}(q_0, p_0, I_\gamma, \phi_\gamma)d\phi_\gamma$$

## Averaged Reduced Hamiltonian

- After renaming variables, **average reduced Hamiltonian** is

$$\bar{H}_2 = \frac{1}{2}y^2 + \omega I + \epsilon \left( n a_0 + \sum_{k=0}^{13} c_{2k}(I) x^{2k} \right)$$

  - $x = \bar{q}_0, y = \bar{p}_0$ are Cartesian coordinates of 0th mode;
  - $I = \bar{I}, \omega = \omega_\gamma$ are action and frequency of the other mode;
  - $c_{2k}(I)$, polynomials in $I$; $\epsilon n a_0 = 0.0214$: energy value at saddle.

- **Average reduced Hamiltonian equations** are

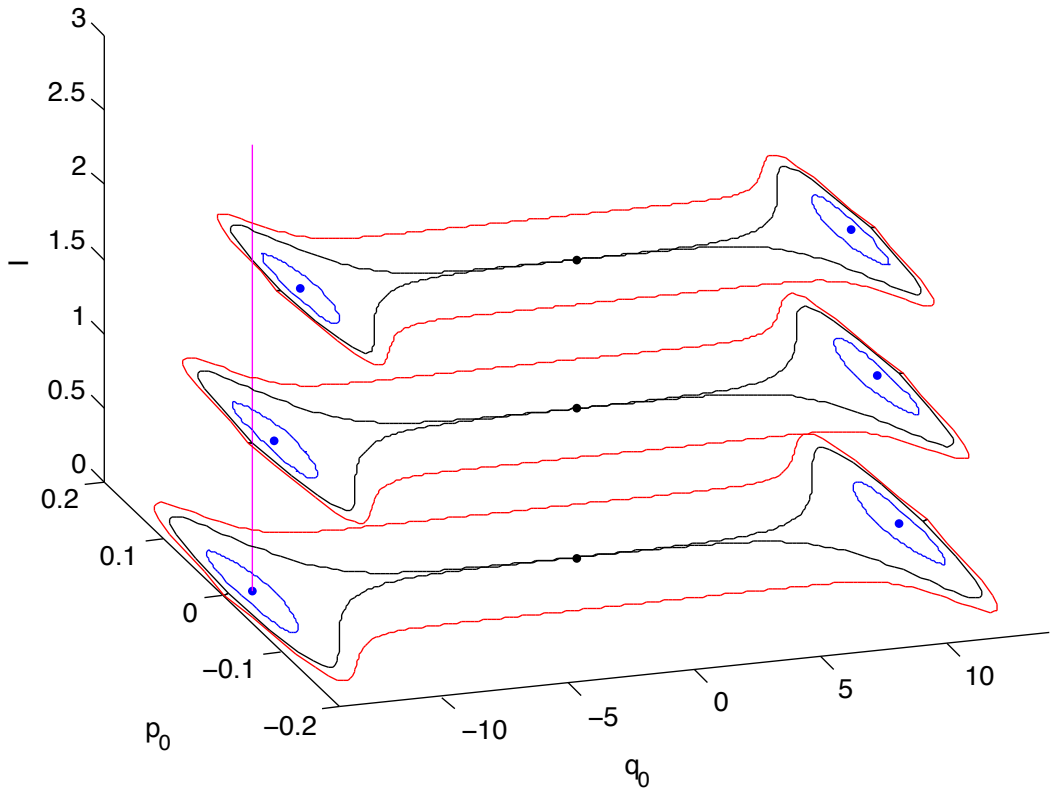
$$\dot{x} = y, \qquad \dot{I} = 0$$

$$\dot{y} = -\epsilon \left( \sum_{k=1}^{13} 2k c_{2k}(I) x^{2k-2} \right) x; \qquad \dot{\phi} = \omega + \epsilon \left( \sum_{k=0}^{13} \frac{dc_{2k}}{dI} x^{2k} \right)$$

$I$ is a constant of motion. Averaged equations and averaged phase space structures of the reactive mode are parametrized by $I$.

# Phase Space of Averaged Reduced Equations

- Show contour plots for average reduced Hamiltonian which is phase space for average reduced equations.
  - **Separatrix**: Liberation and Flipping.

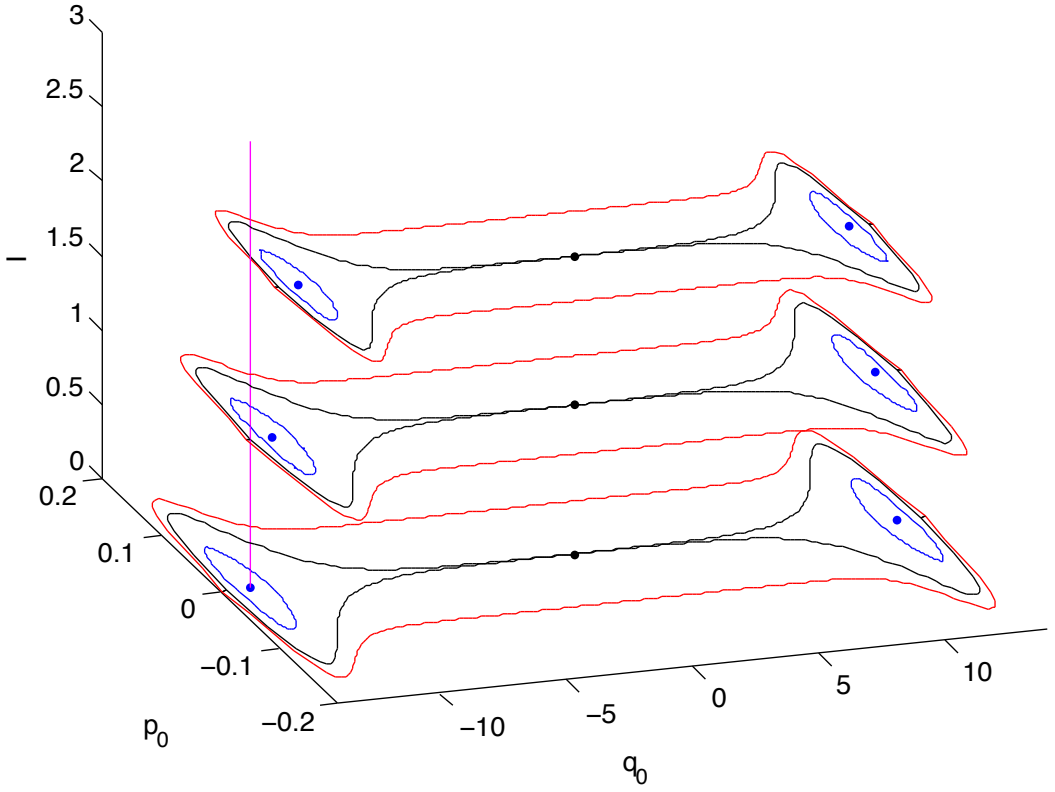



- **Separatrix** "shrinks" towards saddle as $E_{act}=\omega I$ increases. Together, ("**homoclinic** set") can be used to study MAEs.

# Analytical Study of MAE

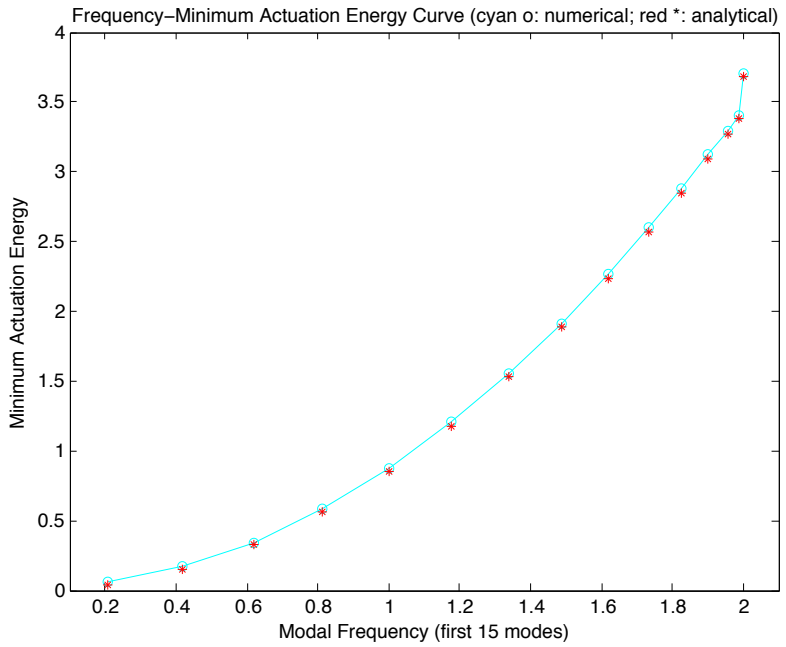
- MAE can be found by the **condition** that point $(x_e, 0, I_m)$ is on **separatrix** passing through saddle $(0, 0, I_m)$.
- For smaller $I$, $(x_e, 0, I)$ is inside of "**homoclinic** set".
  For larger $I$, $(x_e, 0, I)$ is outside of "**homoclinic** set".
- MAE can be found by solving for $I_m$ from the **condition**

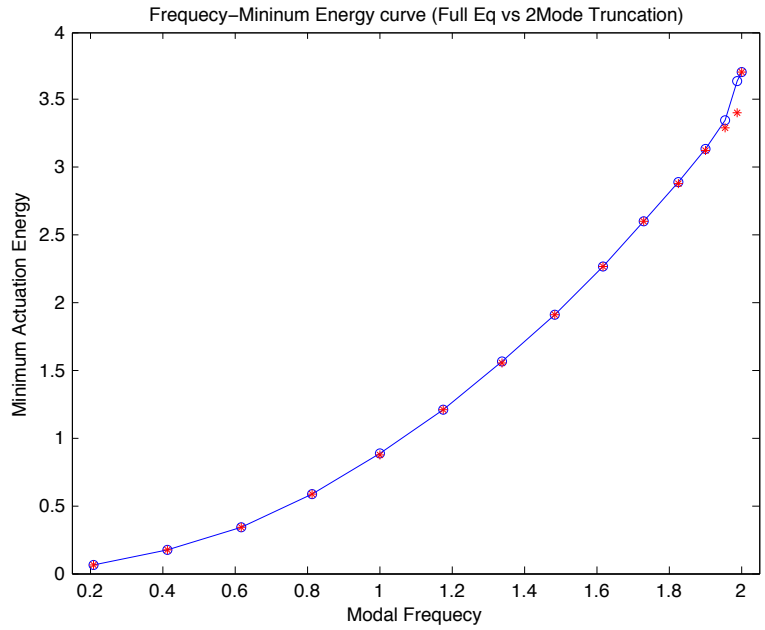
$$\bar{H}_2(x_e, 0, I_m) = \bar{H}_2(0, 0, I_m).$$



# Analytical Study of MAE

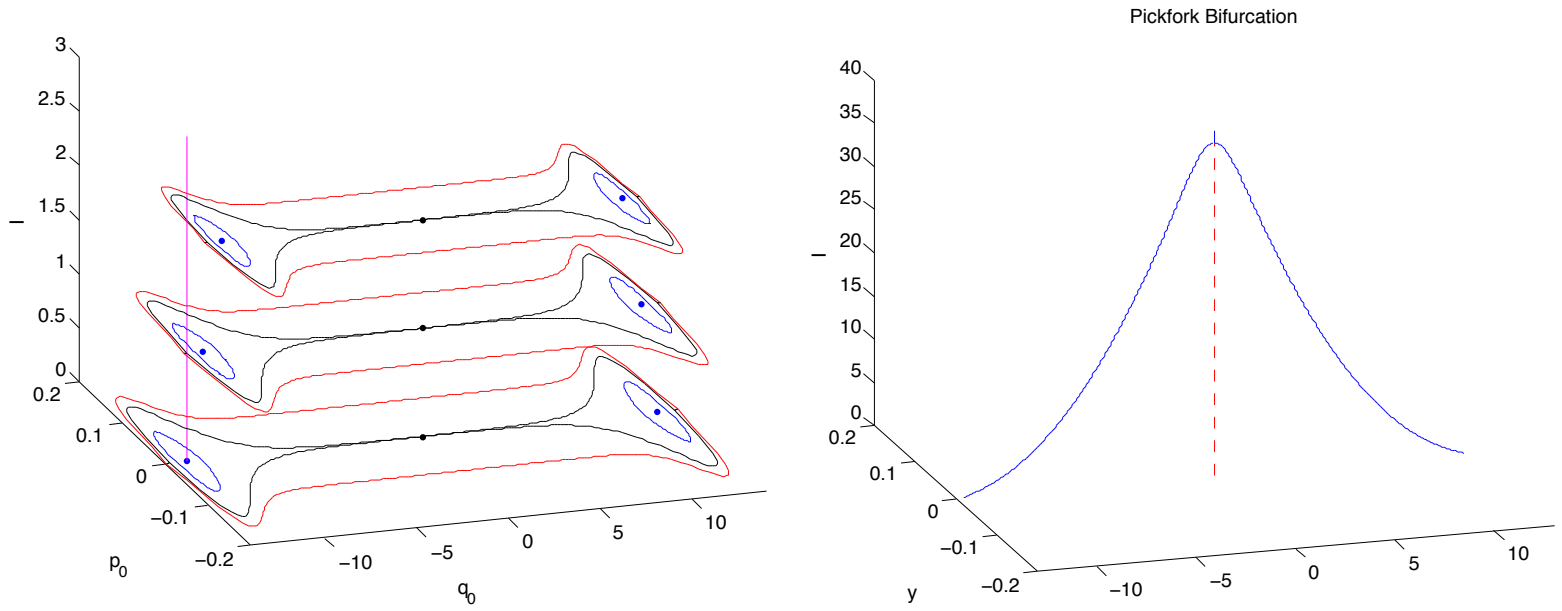
- Data for cyan "o"s are from simulations (2 Mode Truncation).
  Data for magenta "*"s are from analytical computations.
  Data from simulations/analytical computations match very well.
- Blue "o"s are data from simulations of full equations (30 modes).
  Red "*" are from simulations of 2Mode truncations.
- For the study of MAEs,
  analytical computation provides **accurate prediction**
  not only for the reduced models, but also for the full system.



# Control via Parametric Excitation (PE)

- Building on understanding of internal dynamics, want to control division via PE, in resonance with internal trigger modes.
- Guided by 2 observations/conjectures:
  - Averaged Red. Eqs has a pitchfork bifurcation at $I_b \approx 38$: (curve of stable equilibria; dashed line of saddles; for $I > I_b$, $(0, 0, I)$ is stable, chain remain at open state.)
  - PR is an efficient way for energy transfer from external source.
- Conjectures: EM/Enzyme use PR to pump energy into trigger modes and keep DNA at open state.



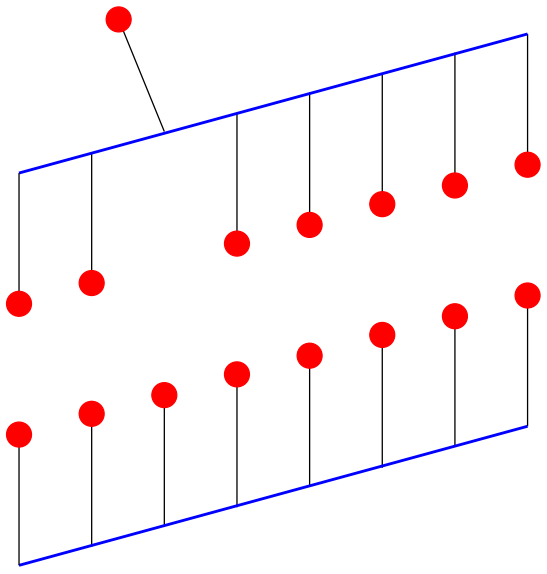
## EOM of Full Model with PE

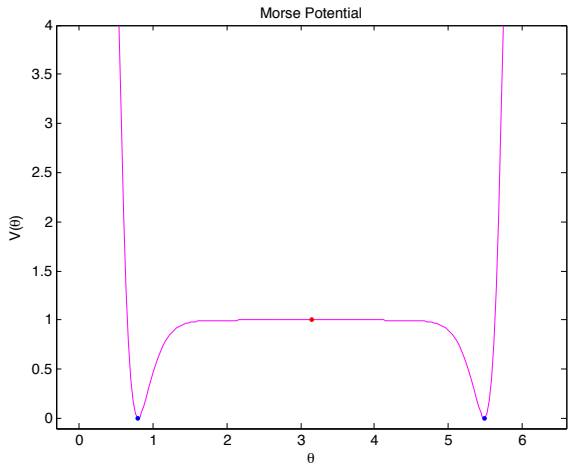
- EOM of full model with PE and frictions can be written as

$$\ddot{\theta}_k - (\theta_{k+1} - 2\theta_k + \theta_{k-1}) - \epsilon U'(\theta_k) = \epsilon\theta_k f \cos\Omega t - \epsilon\mu\dot{\theta}_k$$

where $k = 1, ..., n; \theta_0 = \theta_n;$

- LHS is original EOM (without PE or frictions);
- $f, \Omega$ are amplitude/frequency (dipole moment of bases/EM); $\Omega$ in nearly 1:2 resonance with frequency $\omega_\gamma$ of an internal mode.
- $\mu$ is frictional coefficient (energy loss caused by interaction with surrounding molecules; thermal energy gain is ignored for now).





## EOM of Averaged Reduced Model with PE

- After using FMC and applying partial averaging, we obtain **Averaged Reduced EOM**

$$\dot{x} = y, \qquad \dot{\beta} = \epsilon(\bar{M}_I - \sigma/2\omega + f\cos 2\beta/4\omega),$$
$$\dot{y} = -\epsilon(\bar{M}_x + \mu y), \qquad \dot{I} = \epsilon I(f\sin 2\beta/2\omega - \mu).$$

where $I, \beta$, action/phase of trigger mode $(q_\gamma, p_\gamma)$;
$\sigma$ is a detuning parameter, defined by $\Omega^2/4 = \omega^2 + \epsilon\sigma$.

- The Averaged Reduced System (without friction) has an **effective Hamiltonian**

$$H_{PR} = \frac{1}{2}y^2 + \epsilon\bar{M} - \epsilon\frac{\sigma}{2\omega}I + \epsilon f\frac{I\cos 2\beta}{4\omega}$$

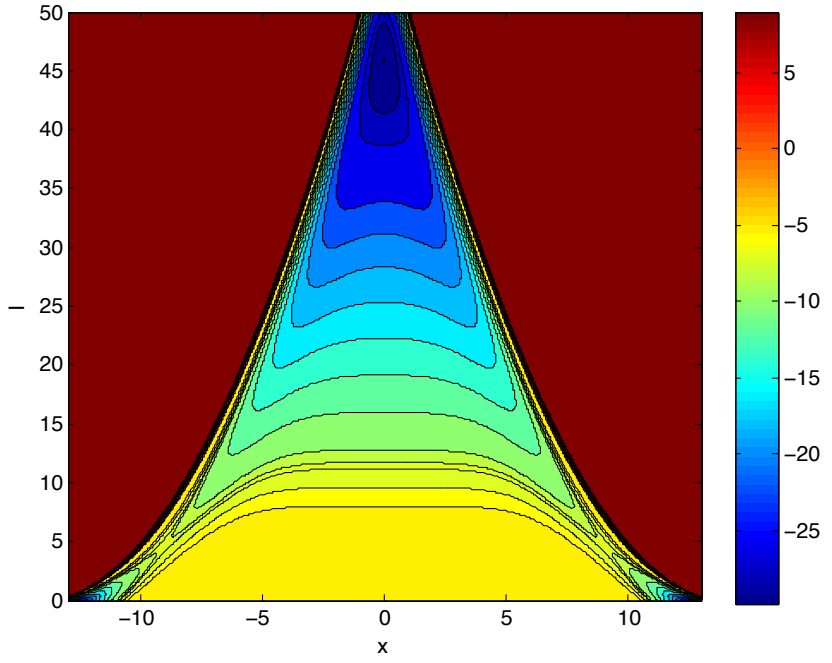
that can provide insights on global phase space structures of this average reduced model.

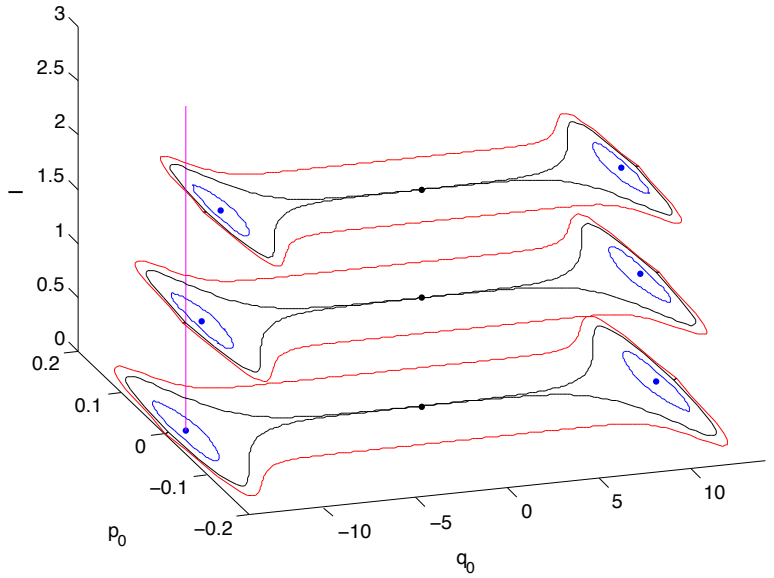
- **Bifurcation analysis** can be used to reveal **ranges of** $\sigma$, $f$, and $\mu$, where **desired dynamics** may be available.

# Global Geometry of Effective Hamiltonian

- Effective Hamiltonian is needed to give a clear and global picture.
- Energy contours of effective potential show how
  **3 types of fixed points** fit together
  within global geometry of effective Hamiltonian
  - PE turns $(x, J) = (0, J_e)$ which marks DNA division into a sink;
  - creates 2 rank 1 saddles close to 2 stable equilibria $(\pm 12.6, 0)$.

  Addition of PE allows trajectory with a little energy to move from an almost equilibrium state over the saddle and reach the sink.

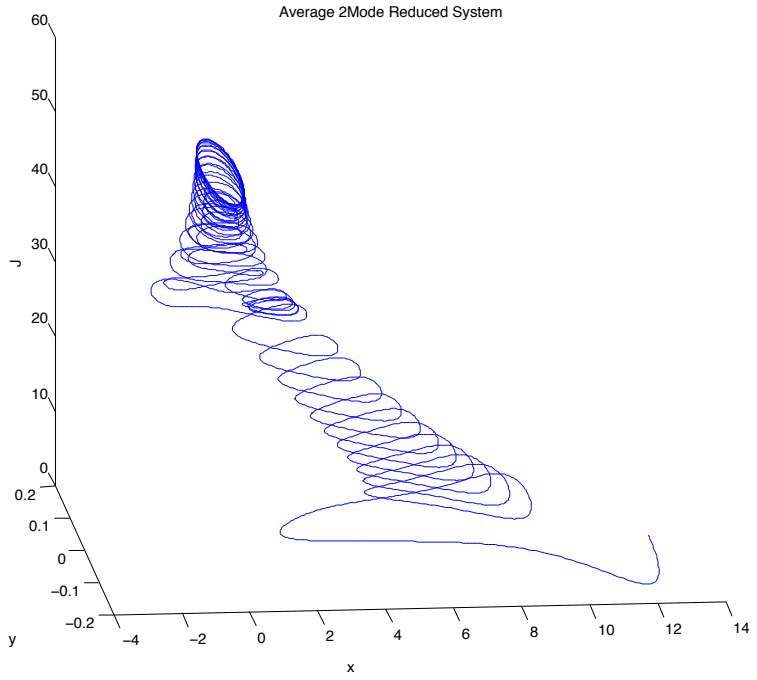


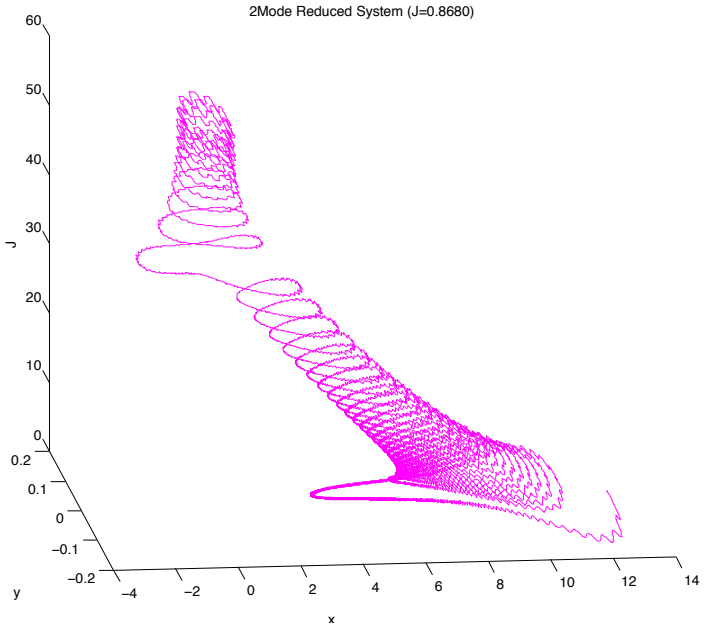



# Identify a Class of Characteristic Trajectories

- This insight enable to generate trajectories that show how PR drive averaged reduced system from its almost equilibrium state to its open state.
- Right: a corresponding trajectory for reduced model:

$$\dot{q}_0 = p_0 \qquad \dot{p}_0 = -\epsilon M_0 - \epsilon\mu p_0 + \epsilon f q_0 \cos\Omega t.$$
$$\dot{q}_\gamma = p_\gamma \qquad \dot{p}_\gamma = -\omega_\gamma^2 q_\gamma - \epsilon M_\gamma - \epsilon\mu p_\gamma + \epsilon f q_\gamma \cos\Omega t.$$



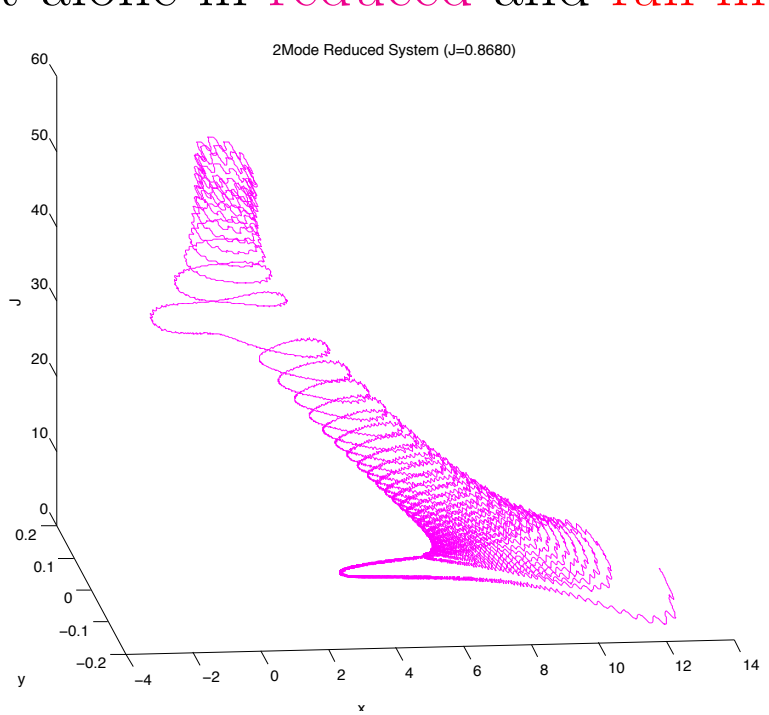



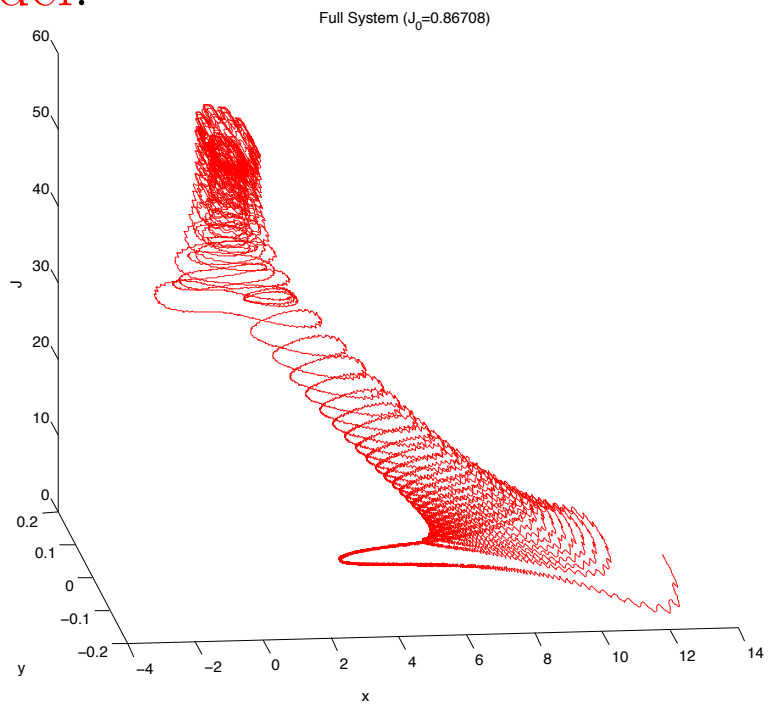
# Extend Results to Full Model

- A corresponding trajectory for the full model:

$$\ddot{\theta}_k - (\theta_{k+1} - 2\theta_k + \theta_{k-1}) - \epsilon U'(\theta_k) = \epsilon\theta_k f \cos\Omega t - \epsilon\mu\dot{\theta}_k$$

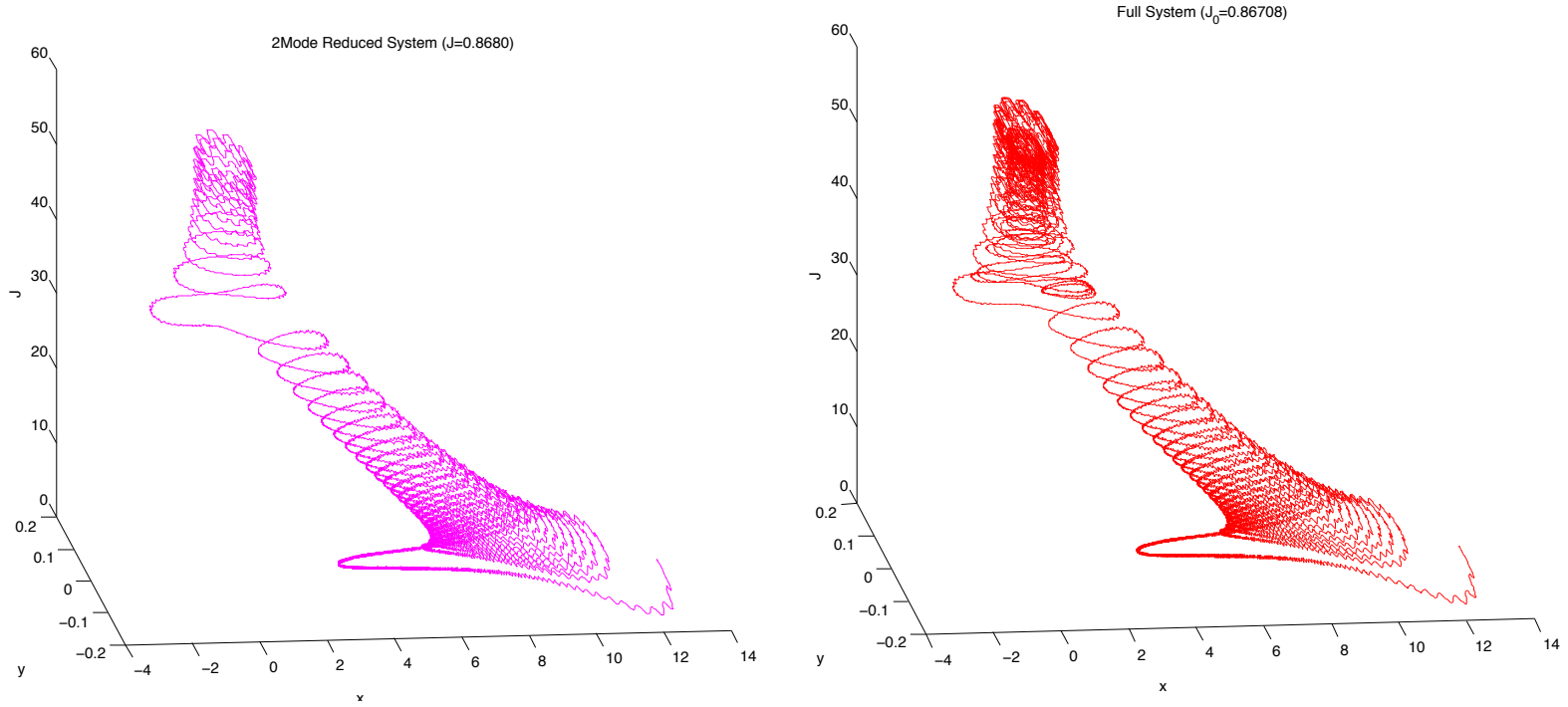
- Despite its simplicity, averaged reduced model is surprisingly accurate by the fact that 3 trajectories are very similar.
- Without a careful study of averaged reduced equations, difficult to guess such trajectories exist in averaged reduced model, let alone in reduced and full model.



# Remarks on the Characteristic Trajectories

- Trajectory starts at equilibrium with a little energy in trigger mode. Without **PE**, liberates near equilibrium state if no friction, or dies down if friction exists.
- With **PE**, **PR** inject energy into trigger mode, increase $I$, make trajectory reach region that marks DNA division ($x = 0$), but with large energy in trigger mode.
- DNA chain is near open state (upright with 0 average angle) but with a periodic swing.



# Evolution of DNA Chain Near Its Open State

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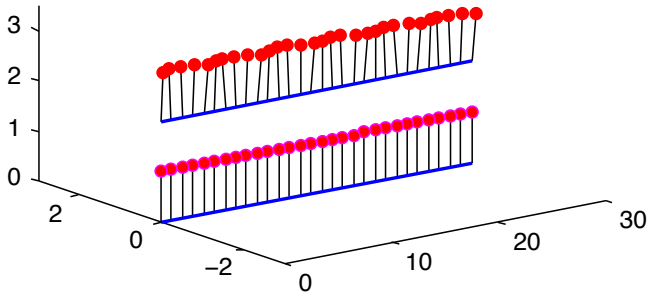


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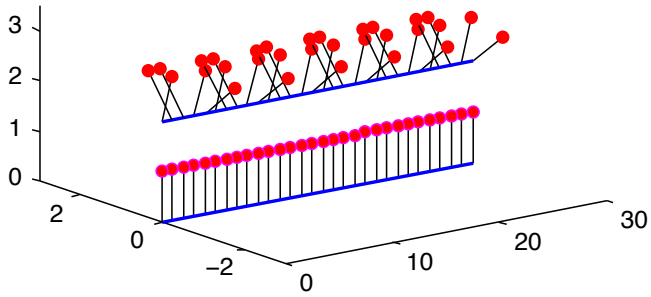


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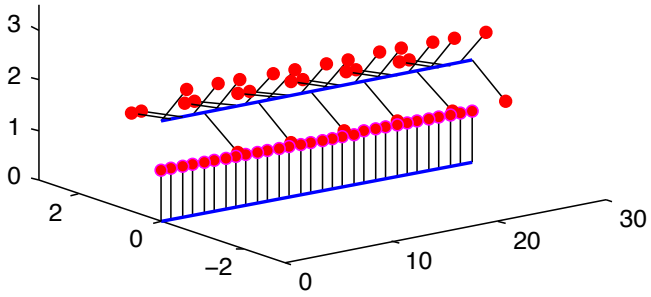


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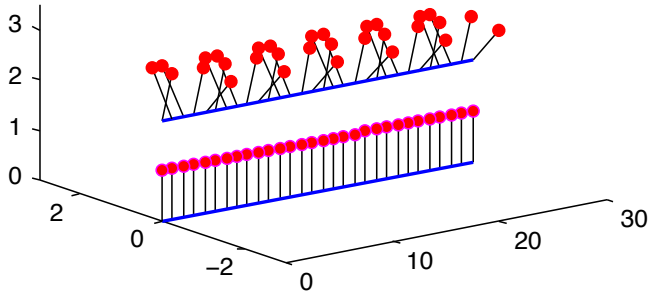


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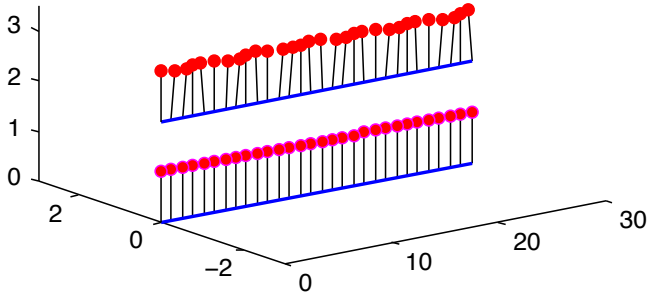

## Summary and Future Work

- Study internal resonance, energy transfer, activation mechanism, and control of a model of DNA division via PR.
- Future work: add effects of **inhomogeneity** and **helicity**.
- Methodology forged in this study which merges
  - geometric reduction, partial averaging, chaotic transport,
  - control via parametric resonance

  should be applicable to many molecular and biomolecular systems that involve **multiple-scales**.