Bari, 14/12/2017

Studying Biological Matter with Quantum Field Theory and Path Integrals

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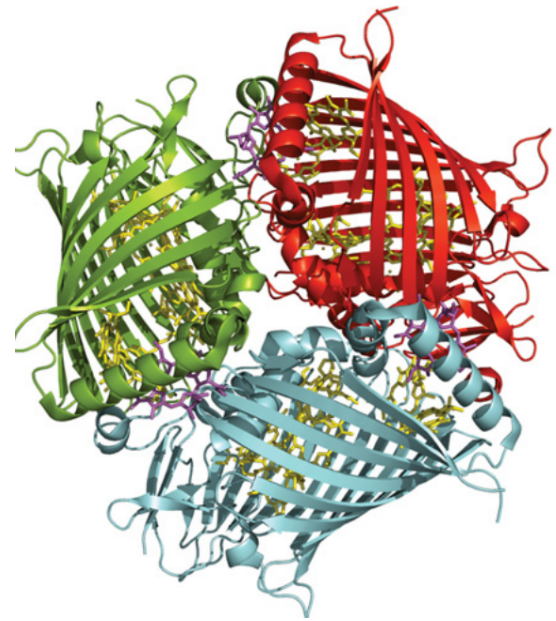
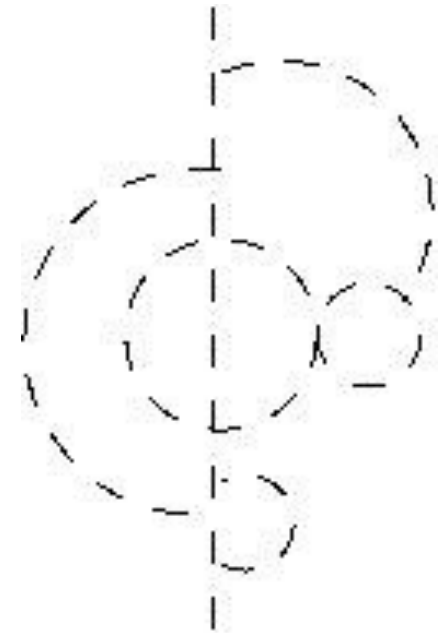
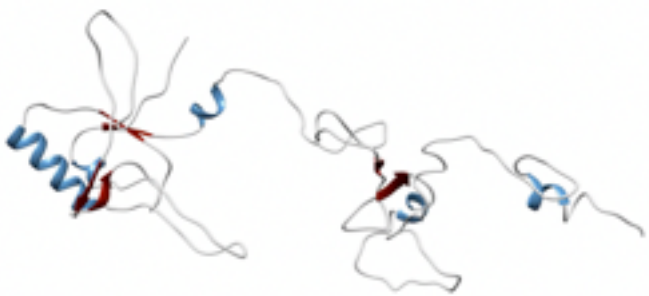
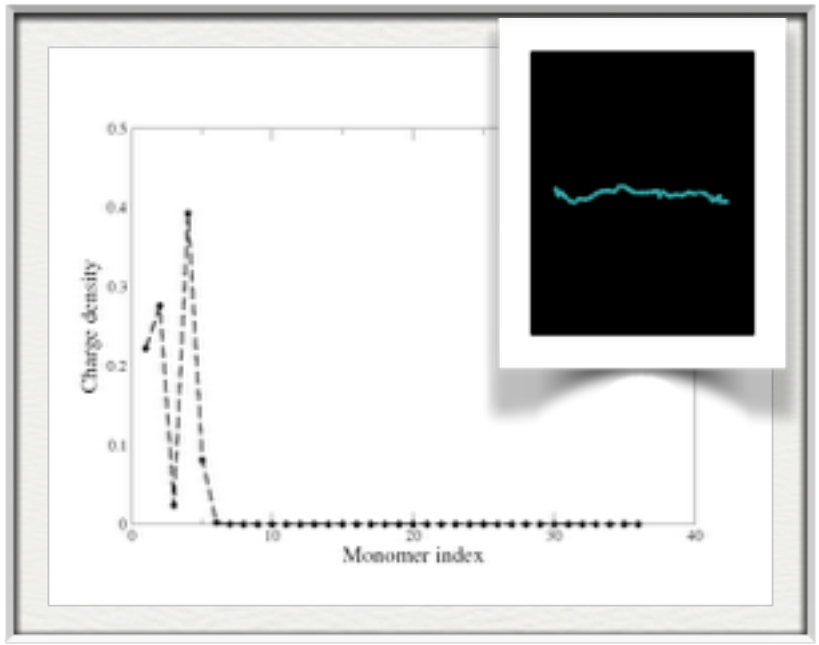




We seek a microscopic approach to model the **dynamics of proteins** (and other biomolecules)

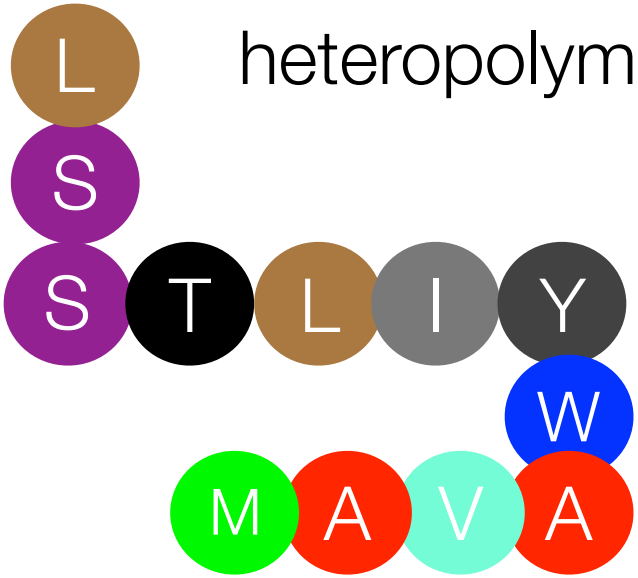


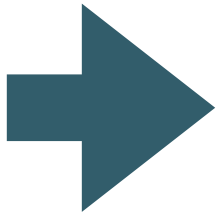


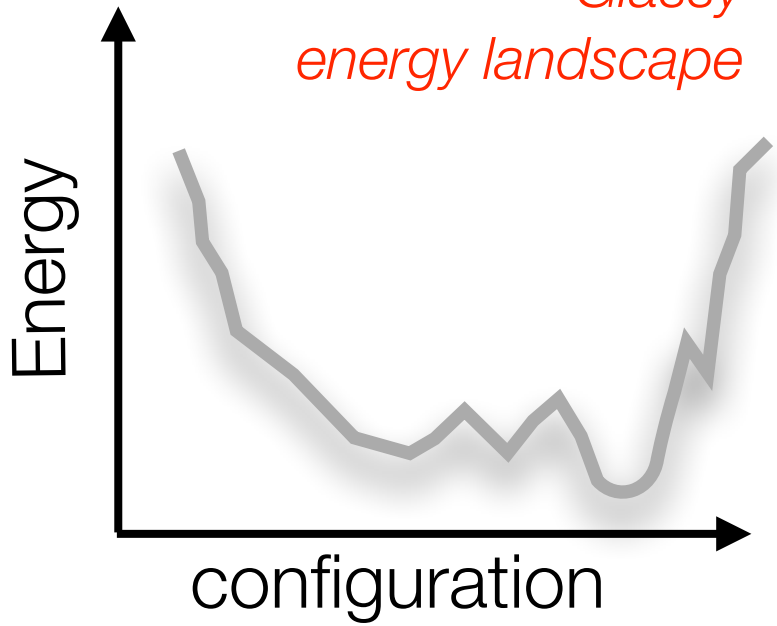
Our footprint: use tools of “high-energy theorists”: Renormalization Group, Path Integrals, Quantum Field Theory, etc..

PROTEIN CONFINEMENT:

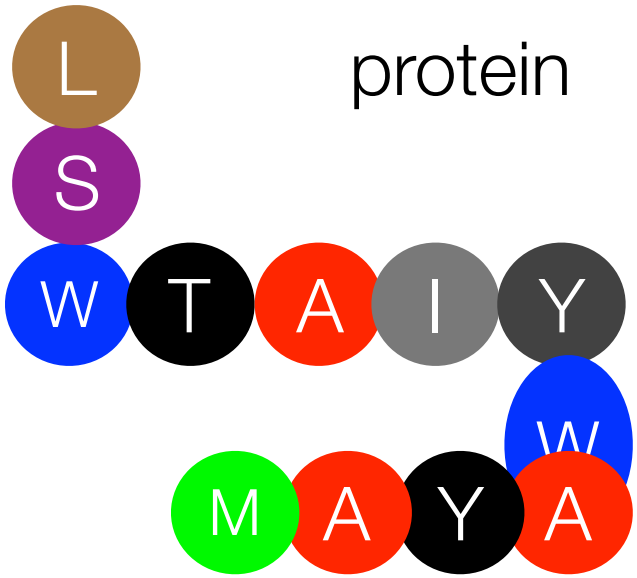
random heteropolymer

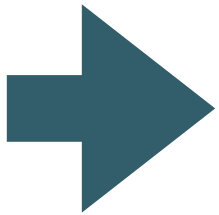


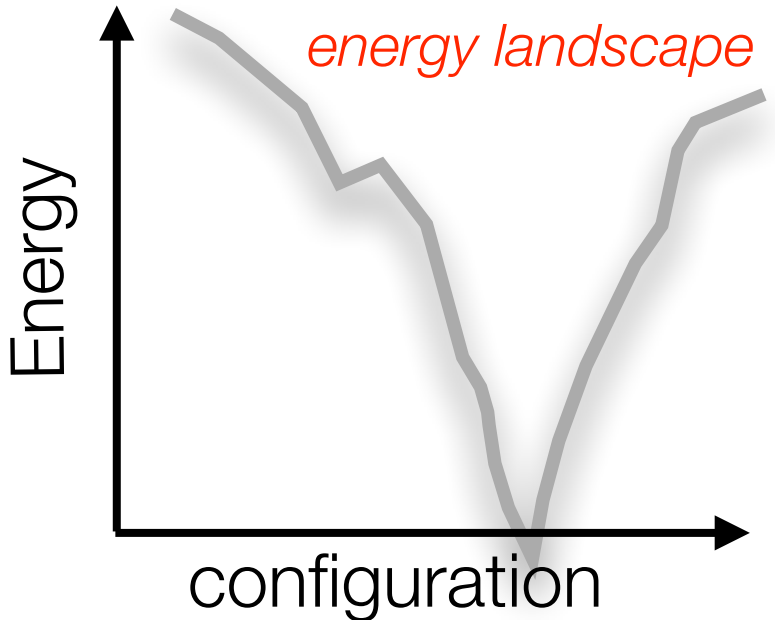




protein





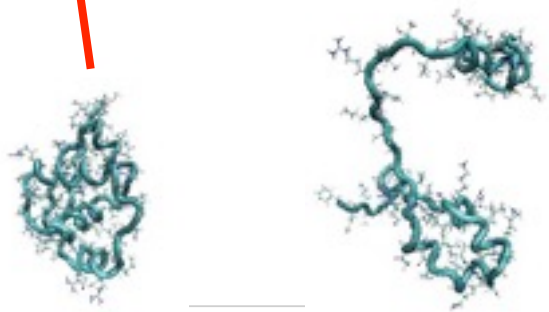


Complete characterisation of the protein dynamics

$$\hat{\rho}(t) = e^{\frac{i}{\hbar}\hat{H}t}\ \hat{\rho}(0)\ e^{-\frac{i}{\hbar}\hat{H}t}$$

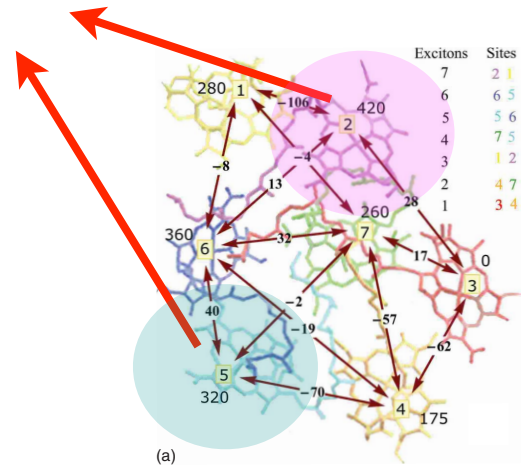
Conformational dynamics:

$$P(Q_f, t|Q_i) = \frac{\mathrm{Tr}[|Q_f\rangle\langle Q_f|\hat{\rho}(t)]}{\mathrm{Tr}\hat{\rho}(0)}$$



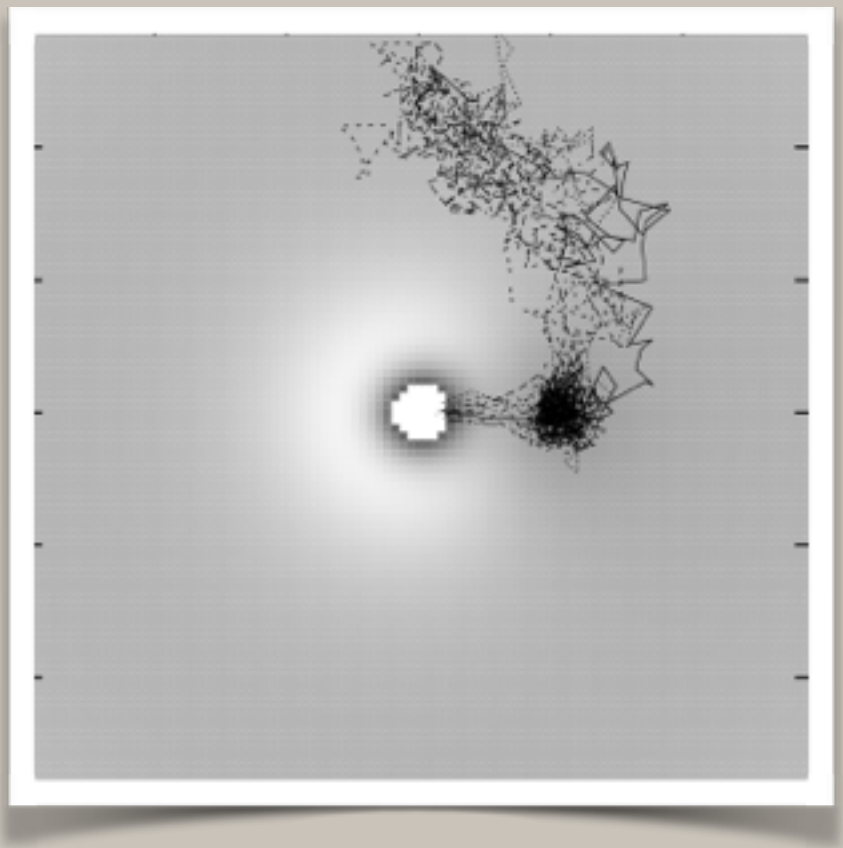
Electronic excitations dynamics:

$$P(k_f, t|k_i) = \frac{\mathrm{Tr}\ [\ |k_f\rangle\langle k_f|\hat{\rho}(t)\ ]}{\mathrm{Tr}\ \hat{\rho}(0)}$$

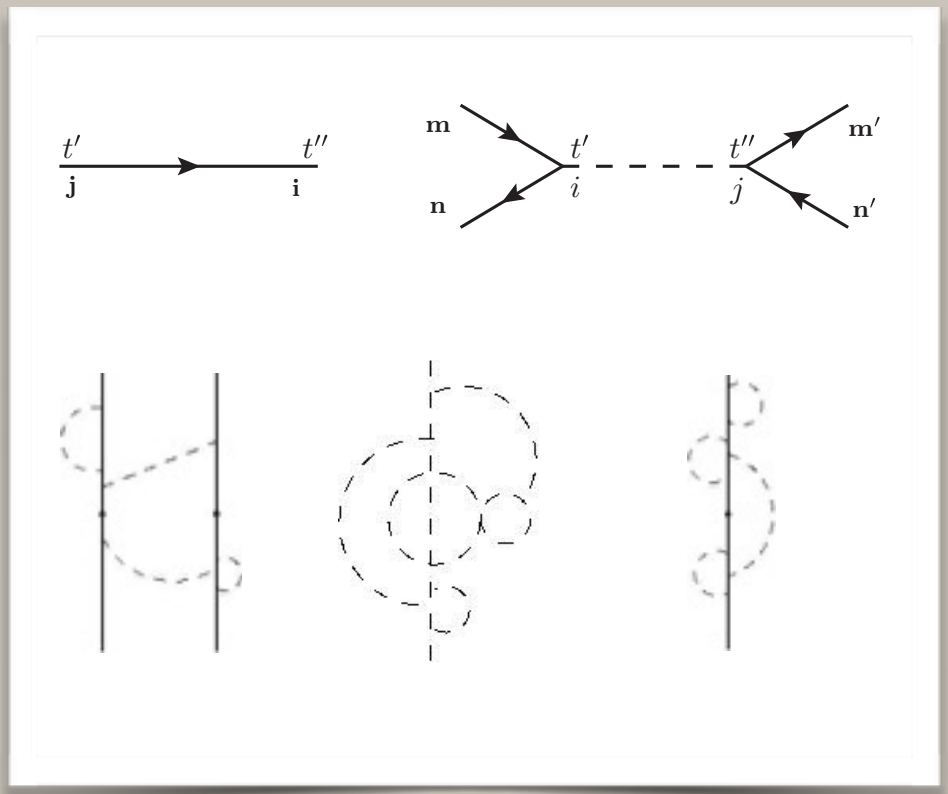


A microscopic calculation of ρ(t) can be achieved using:

* PATH INTEGRALS



* QUANTUM FIELD THEORY



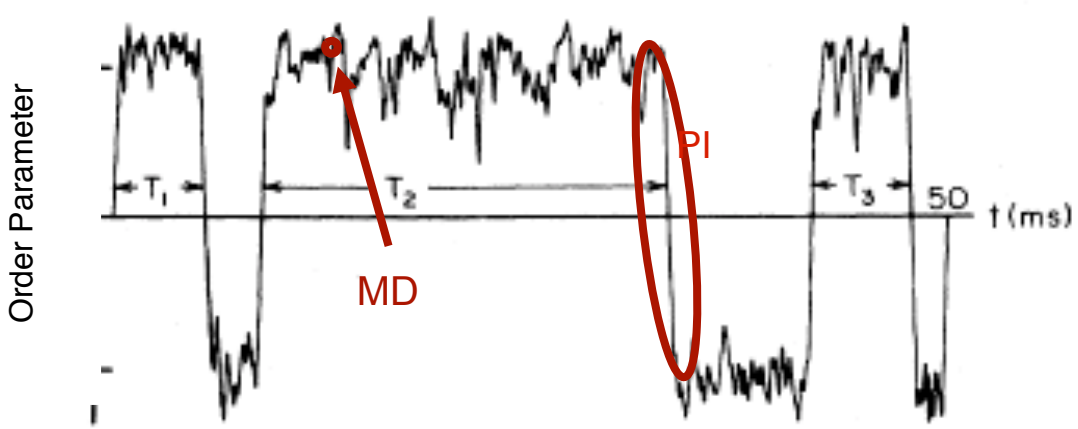
Why using path integrals?

Theoretical convenience:

1) easy to take the classical limit of a subset of d.o.f's (atomic nuclei)

2) easy to trace out (Gaussian) d.o.f.'s

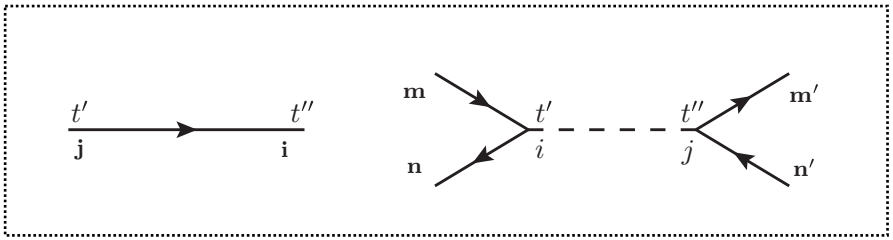
- Computational Convenience:



- Focus on the reactive part of the dynamics

- Exploit approximation methods for functional integrals

Why using Quantum Field Theory?



Quantum evolution:

$$\hat{\rho}(t) = e^{iHt}|Q_0\rangle\langle Q_0|e^{-iHt}$$

The quantum version of the Liuvillian operator is a **superoperator** => Extremely difficult to deal of dynamics of open quantum systems!

Our IDEA: Introduce (bosonic) “spinors”

$$\hat{\rho}(t) = e^{-\frac{i}{\hbar}\hat{H}t}|\text{ket}\rangle\langle\text{bra}|e^{+\frac{i}{\hbar}\hat{H}t}$$

$\phi''(\mathbf{x}, t)$
evolving backwards in time

$\phi'(\mathbf{x}, t)$
evolving forward in time

$$\psi = \begin{pmatrix} \phi' \\ \phi'' \end{pmatrix}$$

“Bra” is (almost) the antiparticle of “Ket”

Molecular Quantum Field Theory

E .Schneider and PF

classical atomic nucl.

quantum electr. excitations

$$\hat{\rho}(t) \propto \int \mathcal{D}R \int \mathcal{D}\bar{\psi}\mathcal{D}\psi e^{iS_e^0[\bar{\psi},\psi]} \times e^{iS_{MD}[R]} \times e^{iI[\bar{\psi},\psi,R]}$$

QED:

$$Z_{QED} \propto \int \mathcal{D}A_\mu \int \mathcal{D}\bar{\psi}\mathcal{D}\psi e^{iS_e^0[\bar{\psi},\psi]} \times e^{iS_{EM}[A_\mu]} \times e^{iI[\bar{\psi},\psi,A_\mu]}$$

Electronic excitations:

$$S_{\mathbf{0}}[\bar{\psi},\psi] = \sum_{nm} \int_0^t dt' \; \bar{\psi}_{\mathbf{m}} \left(i\hbar\,\partial_{t'}\delta_{\mathbf{mn}} - f^0_{\mathbf{mn}}\right) \psi_{\mathbf{n}}$$

QED:

$$S_e^0[\bar{\psi},\psi] = \int dx \int dt\, \bar{\psi}_x (i\partial_\mu\gamma_\mu - m)\psi_x$$

Atomic nuclei:

$$S_{MD}[R] = \frac{i}{4k_BT}\gamma^{-1} \int_0^t \left(\partial_t R + \frac{1}{\gamma}\nabla U(R)\right)$$

QED:

$$S_{EM}[A_\mu] = \int dtdx \, (\partial_\mu A_\nu - \partial_\nu A_\mu)^2$$

An arsenal of approximation techniques

generating functional for the density matrix

$Z[J, \bar{J}]$

Neglecting electronic excitations and

Sampling conformational dynamics

PRL 2006, PRL 2007, PNAS 2012, PRL 2015

JCP 2017

Perturbative diagrammatic techniques

PRB 2012, PRB 2013, PRB 2016

Exact Monte Carlo

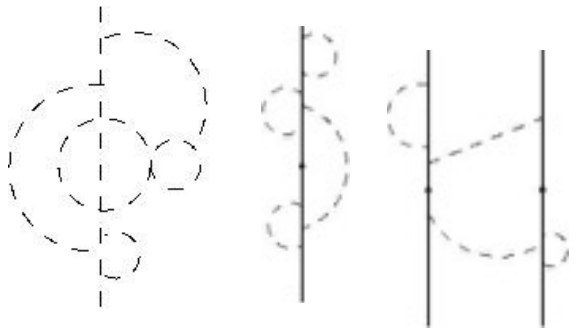
PRB 2016

Renorm. Group and EFT

PRB 2013, JCP 2016

Different sectors of the density matrix for different physics …

$$\rho = \left(\begin{array}{c|ccc|ccc} \rho_{gg} & \rho_{ge_1} & \cdots & \rho_{ge_N} & \rho_{g\alpha_1} & \cdots & \rho_{g\alpha_{N_2}} \\ \hline \rho_{e_1 g} & \rho_{e_1 e_1} & \cdots & \rho_{e_1 e_N} & \rho_{e_1 \alpha_1} & \cdots & \rho_{e_1 \alpha_{N_2}} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ \rho_{e_N g} & \rho_{e_N e_1} & \cdots & \rho_{e_N e_N} & \rho_{e_N \alpha_1} & \cdots & \rho_{e_N \alpha_{N_2}} \\ \hline \rho_{\alpha_1 g} & \rho_{\alpha_1 e_1} & \cdots & \rho_{\alpha_1 e_N} & \rho_{\alpha_1 \alpha_1} & \cdots & \rho_{\alpha_1 \alpha_{N_2}} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ \rho_{\alpha_{N_2} g} & \rho_{\alpha_{N_2} e_1} & \cdots & \rho_{\alpha_{N_2} e_N} & \rho_{\alpha_{N_2} \alpha_1} & \cdots & \rho_{\alpha_{N_2} \alpha_{N_2}} \end{array}\right)$$



conformational dynamics $\rho_{gg} \propto \int DR e^{-S_{OM}[R]} \times \int \mathcal{D}\psi\ \bar{\psi} e^{iS_{exc.}}$

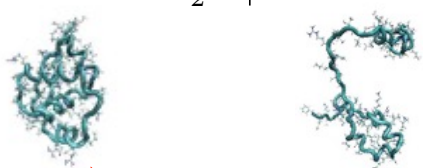
exciton/hole mobility $\rho_{e_k e_l}(t) \propto \int \mathcal{D}\delta R \int \mathcal{D}\psi \mathcal{D}\bar{\psi}\ e^{iS_{tot}}\ \bar{\psi}(e_l,t)\gamma_-\gamma_5\psi(e_k,t)\ \bar{\psi}(e_n,0)\gamma_+\gamma_5\psi(e_m,0)$

Linear Spectroscopy $\rho_{e_k g}(t) \propto \int \mathcal{D}\delta R \int \mathcal{D}\psi \mathcal{D}\bar{\psi}\ e^{iS_{tot}}\ \psi(e_l,t)\ \bar{\psi}(e_n,0)$

2D echo Spectroscopy . . .

conformational dynamics $\rho_{gg} \rightarrow P(x,t|x_i)$

$$\rho = \left(\begin{array}{c|ccc|ccc} \rho_{gg} & \rho_{ge_1} & \cdots & \rho_{ge_N} & \rho_{g\alpha_1} & \cdots & \rho_{g\alpha_{N_2}} \\ \hline \rho_{e_1 g} & \rho_{e_1 e_1} & \cdots & \rho_{e_1 e_N} & \rho_{e_1 \alpha_1} & \cdots & \rho_{e_1 \alpha_{N_2}} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ \rho_{e_N g} & \rho_{e_N e_1} & \cdots & \rho_{e_N e_N} & \rho_{e_N \alpha_1} & \cdots & \rho_{e_N \alpha_{N_2}} \\ \hline \rho_{\alpha_1 g} & \rho_{\alpha_1 e_1} & \cdots & \rho_{\alpha_1 e_N} & \rho_{\alpha_1 \alpha_1} & \cdots & \rho_{\alpha_1 \alpha_{N_2}} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ \rho_{\alpha_{N_2} g} & \rho_{\alpha_{N_2} e_1} & \cdots & \rho_{\alpha_{N_2} e_N} & \rho_{\alpha_{N_2} \alpha_1} & \cdots & \rho_{\alpha_{N_2} \alpha_{N_2}} \end{array}\right)$$

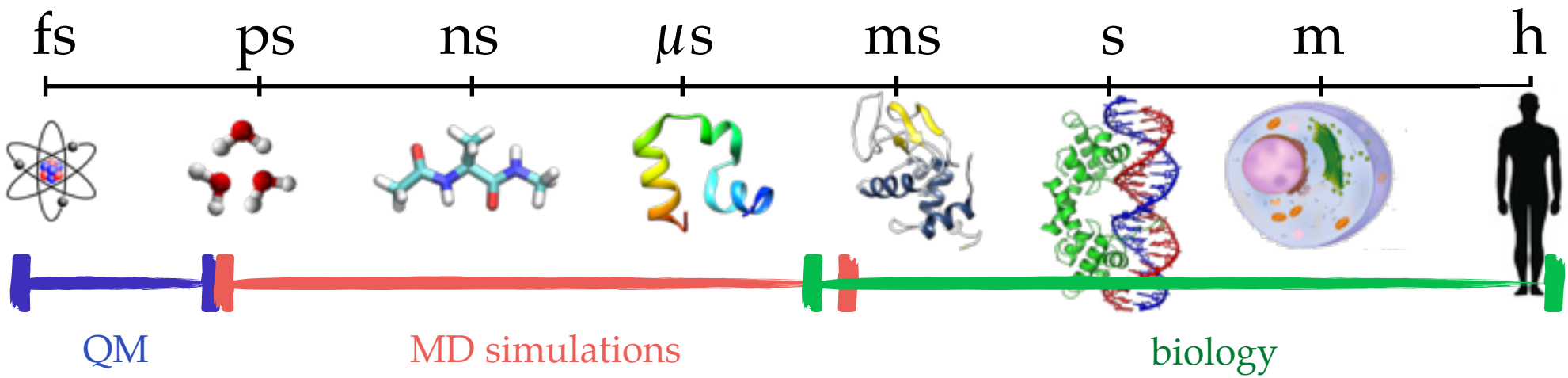


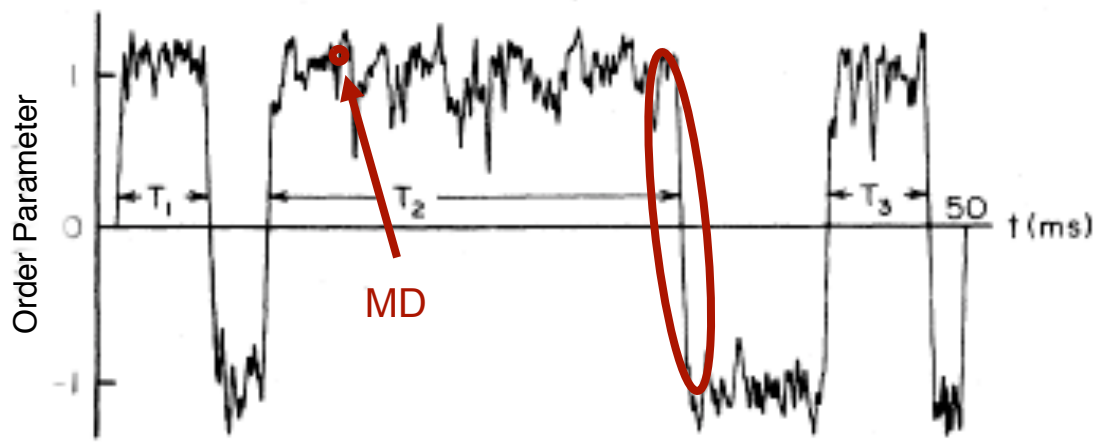
$$P(x,t|x_i) = \int \mathcal{D}R \; e^{-\frac{\beta}{4m\gamma}\int_0^t d\tau (m\ddot{R} + m\gamma\dot{R} + \nabla U)^2}$$

We recovered the path integral representation of Langevin dynamics

NB the same path integral can be obtained starting directly from the classical Langevin equation (Onsager-Machlup):

Useful conformational transitions (e.g. **protein folding**)





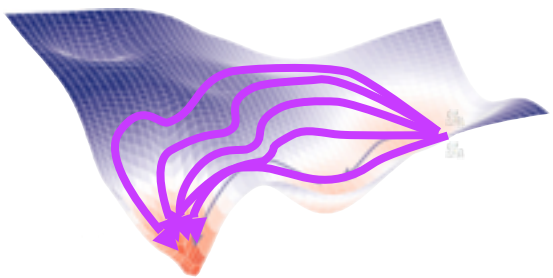
Bias Functional approach

PRL 114, 098103 (2015) PHYSICAL REVIEW LETTERS week ending 6 MARCH 2015

Variational Scheme to Compute Protein Reaction Pathways Using Atomistic Force Fields with Explicit Solvent

S. a Beccara,[1,3] L. Fant,[2] and P. Faccioli[2,3,*]

1) From each initial condition, generate *many* trial reactive pathways using some "smart" biased dynamics

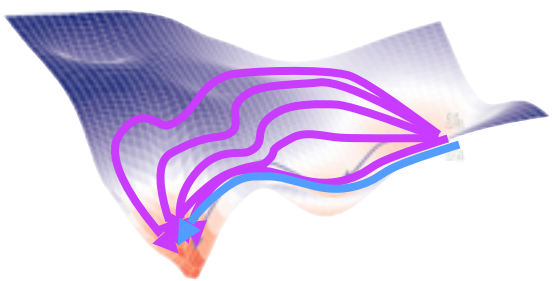


2) Select the trial path with the highest probability to be realised in the *unbiased* dynamics

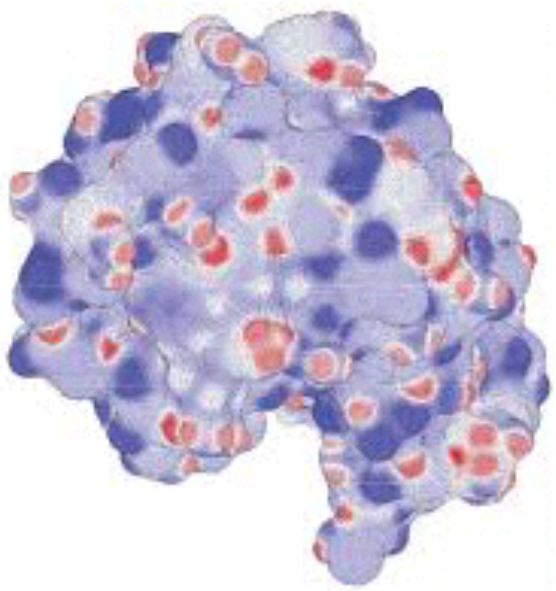
$$P(x_f,t|x_i)=\int_{x_i}^{x_f}\mathcal{D}X e^{-\frac{\beta}{4m\gamma}\int_0^t d\tau(m\ddot{x}+m\gamma+\nabla U(x))^2}$$

$$\frac{\delta}{\delta\bar{X}}\int_0^t d\tau|\nabla U_{bias}[\bar{X}]|^2=0$$

(bias functional)



Analogy with Density Functional Theory



1) Based on a rigorous **variational theorem**

2) Useless without a **smart guess** (or perhaps lucky one) - prior knowledge-

….but if one does find a good guess, then a whole new scale of problems opens up

Similarly, the BF is useless without a scheme to generate reasonable trial paths to choose from

Problem 1: the choice of biasing collective coordinate is arbitrary and introduces uncontrolled systematic errors

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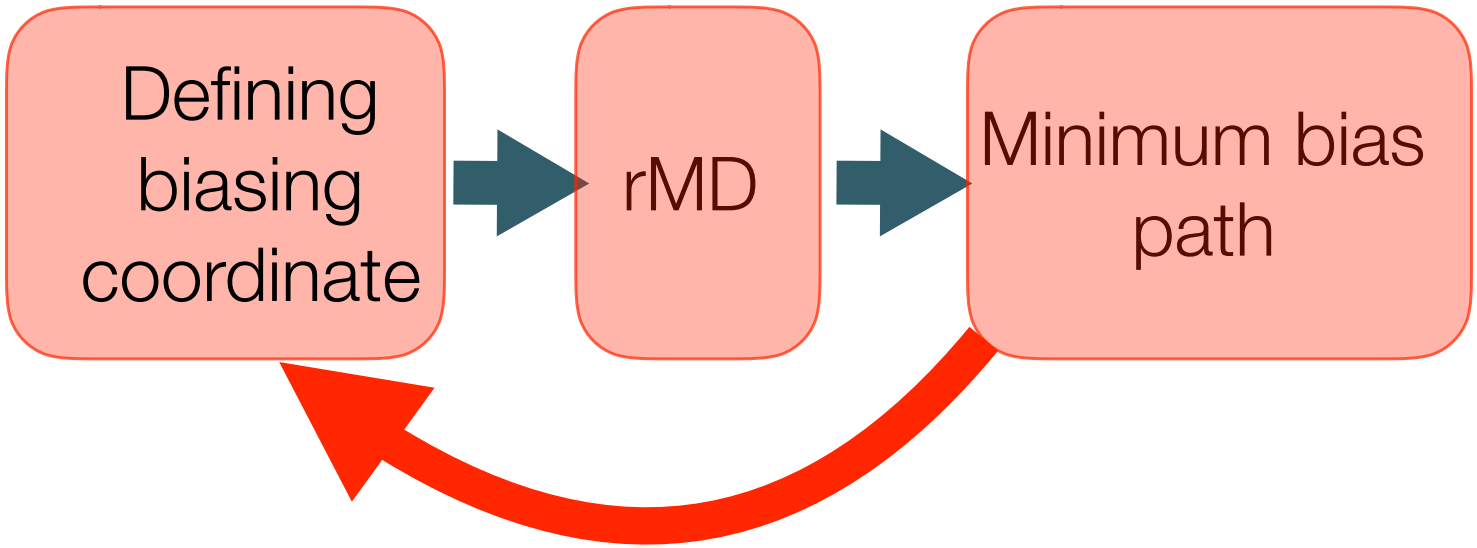
Self-consistent path sampling (2017):

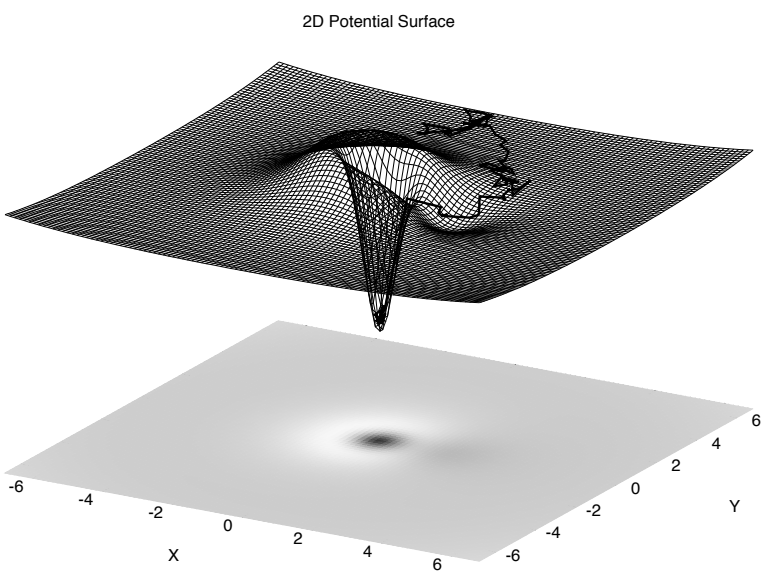


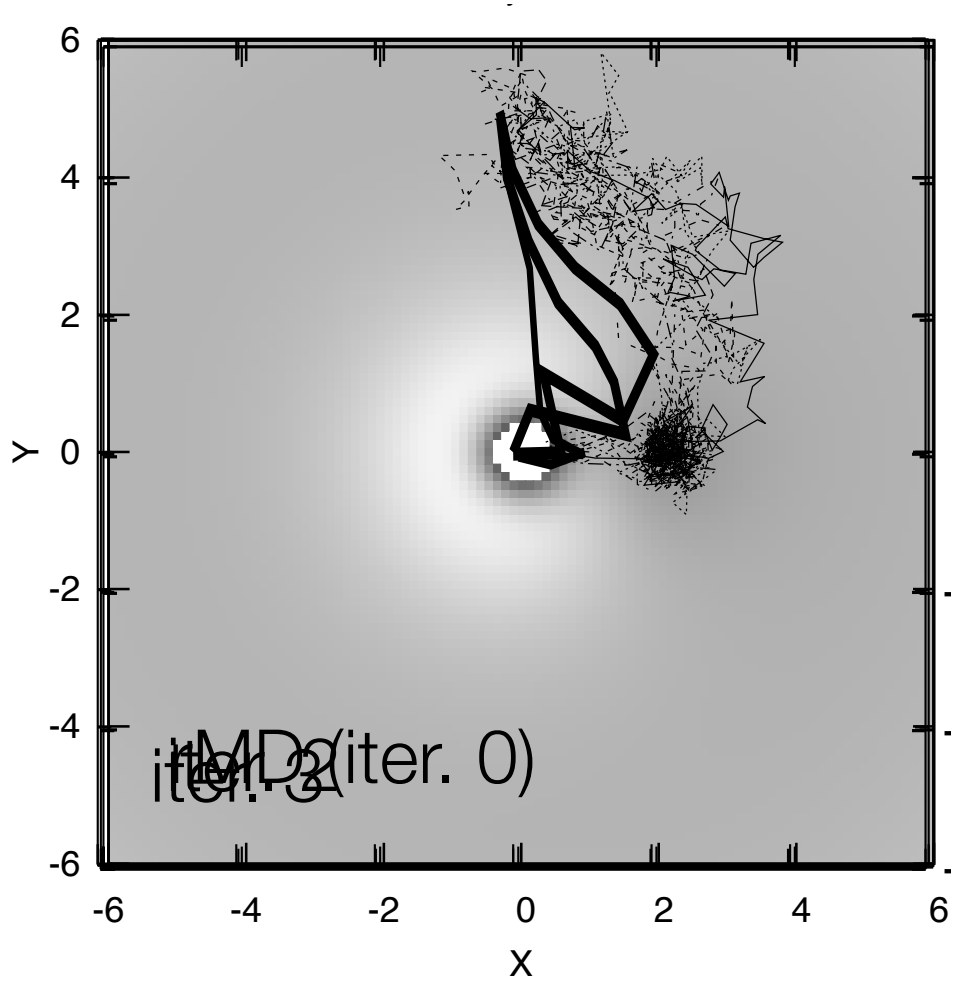
THE JOURNAL OF CHEMICAL PHYSICS **147**, 064108 (2017)

Self-consistent calculation of protein folding pathways

S. Orioli, S. a Beccara, and P. Faccioli[a)]

An illustrative example





Problem 2: Detailed balance is lost. We need to post process in order to recover thermodynamics and kinetics

Method to use the BF result to obtain a computationally efficient calculation scheme for free-energy profile (potential of mean-force)

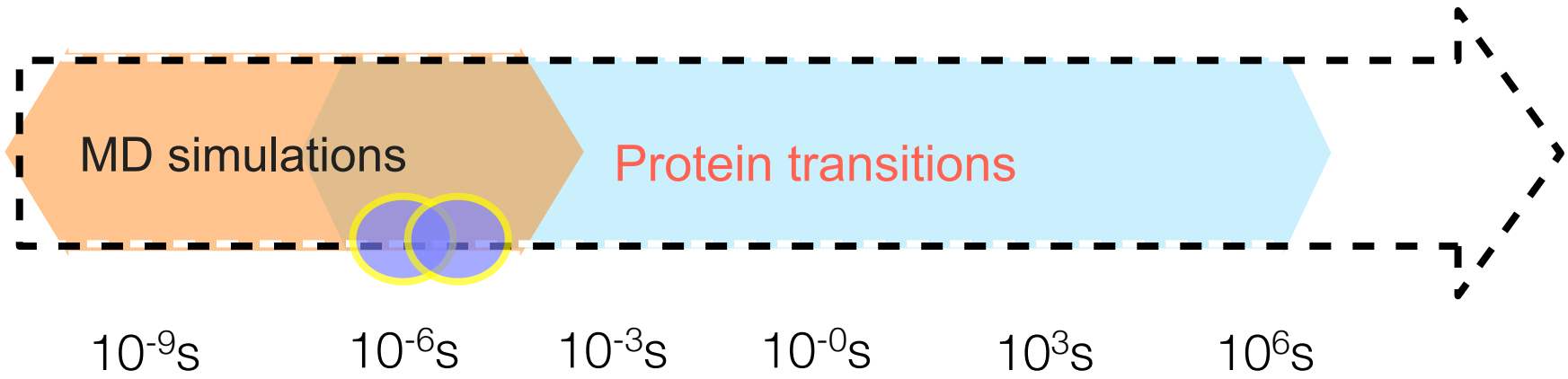
THE JOURNAL OF CHEMICAL PHYSICS **147**, 152724 (2017)

All-atom calculation of protein free-energy profiles

S. Orioli,[1,2] A. Ianeselli,[1,3] G. Spagnolli,[1,3] and P. Faccioli[1,2,a)]

Applications

Validation and beyond:



PNAS

Dominant folding pathways of a WW domain

Silvio a Beccara[a,b], Tatjana Škrbić[a,c], Roberto Covino[a,b], and Pietro Faccioli[a,b,1]

[a]Dipartimento di Fisica, Università degli Studi di Trento, Via Sommarive 14, I-38123 Povo (Trento), Italy; [b]INFN Istituto Nazionale di Fisica Nucleare (National Institute for Nuclear Physics), Gruppo Collegato di Trento, Via Sommarive 14, I-38123 Povo (Trento) Italy; and [c]European Centre for Theoretical Studies in Nuclear Physics and Related Areas, Strada delle Tabarelle 286, I-38123 Villazzano (Trento), Italy

Edited by William A. Eaton, National Institutes of Health -NIDDK, Bethesda, MD, and approved December 19, 2011 (received for review July 27, 2011)

We investigate the folding mechanism of the WW domain Fip35 using a realistic atomistic force field by applying the Dominant Reaction Pathways approach. We find evidence for the existence of two folding pathways, which differ by the order of formation of the two hairpins. This result is consistent with the analysis of the experimental data on the folding kinetics of WW domains and with the results obtained from large-scale molecular dynamics

Noé, et al. performed a Markov state model analysis of a large number of short (≲200 ns) nonequilibrium MD trajectories (11) performed on the WW domain of human Pin 1 protein. In their paper the authors reported a complex network of transition pathways, which differ by the specific order in which the different local meta-stable states were visited. On the other hand, in all pathways the formation of hairpins takes place in a definite sequence (see

THE JOURNAL OF CHEMICAL PHYSICS **147**, 064108 (2017)

Self-consistent calculation of protein folding pathways

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PRL **114,** 098103 (2015) PHYSICAL REVIEW LETTERS week ending 6 MARCH 2015

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S. a Beccara,[1,3] L. Fant,[2] and P. Faccioli[2,3,*]

[1]*European Centre for Theoretical Nuclear Physics and Related Areas (ECT*-FBK),*

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All-atom calculation of protein free-energy profiles

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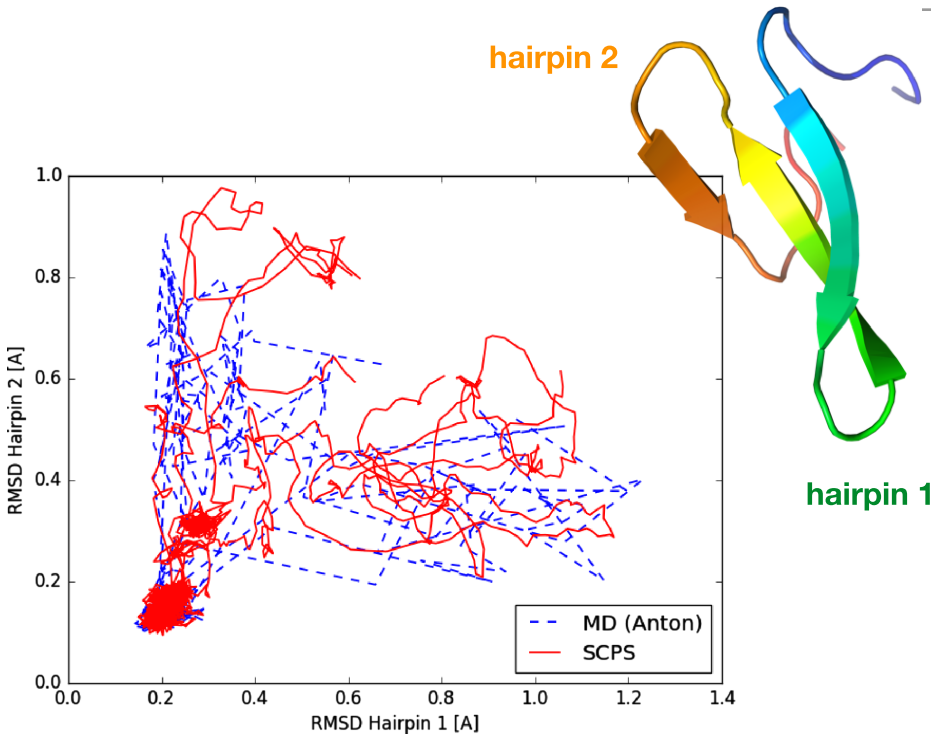
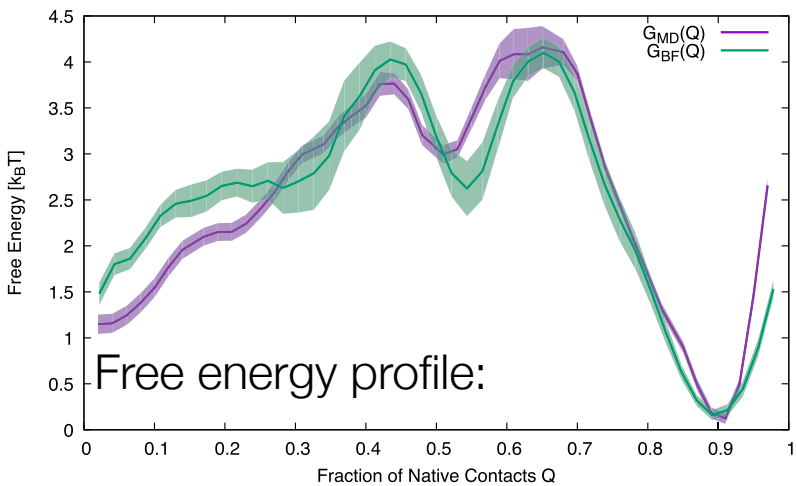
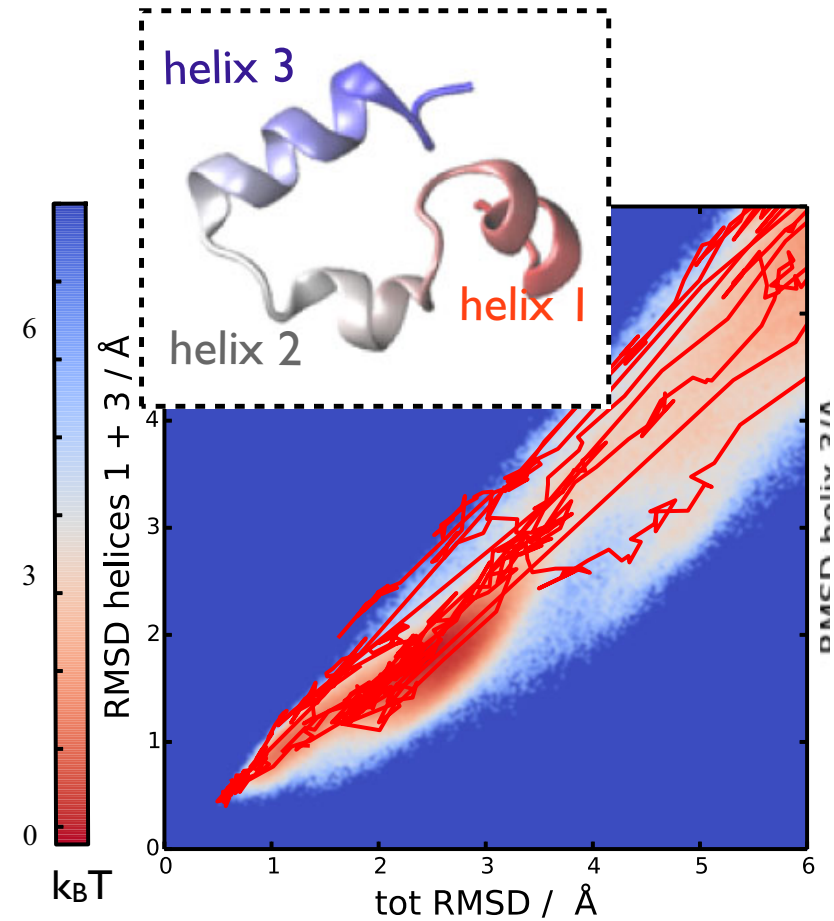
Some benchmark results:

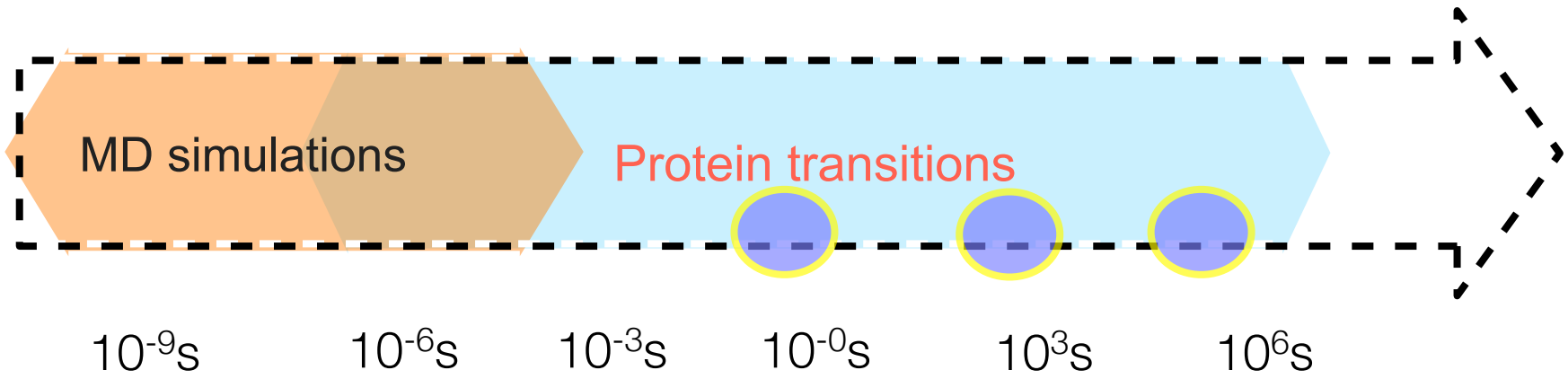






Applications

Validation and beyond:



THE JOURNAL OF PHYSICAL CHEMISTRY B
Article
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Folding Mechanism of Proteins Im7 and Im9: Insight from All-Atom Simulations in Implicit and Explicit Solvent

F. Wang,[†] G. Cazzolli,[‡] P. Wintrode,*[,†] and P. Faccioli*[,‡]

All-atom simulations predict how single point mutations promote misfolding of a serpin protein

Fang Wang[1,†], Simone Orioli[2,3,†], Alan Ianeselli[4], Giovanni Spagnolli[4], Silvio a Beccara[4,5], Anne Gershenson[6*], Pietro Faccioli[2,3*], Patrick L. Wintrode[1*]

Folding Mechanism of Proteins Im7 and Im9: Insight from All-Atom Simulations in Implicit and Explicit Solvent

F. Wang[†], G. Cazzolli[‡], P. Wintrode*[†], and P. Faccioli*[‡]

The atomic detail of protein folding revealed by an ab initio reappraisal of circular dichroism

Alan Ianeselli,[†] Simone Orioli,[‡,§] Giovanni Spagnolli,[†] Pietro Faccioli,*[,‡,§] Lorenzo Cupellini,[¶] Sandro Jurinovich,[¶] and Benedetta Mennucci*[,¶]

PNAS

Serpin latency transition at atomic resolution

Giorgia Cazzolli[a,b], Fang Wang[c], Silvio a Beccara[b,d], Anne Gershenson[e], Pietro Faccioli[a,b,1], and Patrick L. Wintrode[c,1]

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Edited by David E. Shaw, D. E. Shaw Research, New York, NY, and approved September 12, 2014 (received for review April 24, 2014)

Protease inhibition by serpins requires a large conformational transition from an active, metastable state to an inactive, stable state. Similar reactions can also occur in the absence of proteases, and these latency transitions take hours, making their time scales

for polypeptide chains consisting of nearly 100 amino acids (6), which are considerably smaller than PAI-1. Additionally, the PAI-1 active state has a $t_{1/2}$ of 1–2 h at 37 °C (3), a time scale clearly beyond the reach of any present or foreseen conventional

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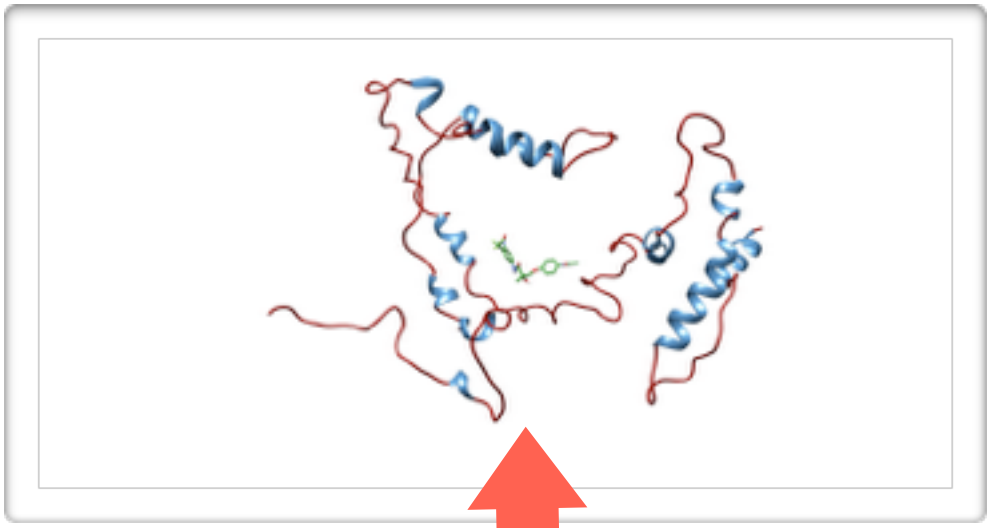
Folding Pathways of a Knotted Protein with a Realistic Atomistic Force Field

Silvio a Beccara[1], Tatjana Škrbić[2], Roberto Covino[3,4], Cristian Micheletti[5], Pietro Faccioli[3,4]*

1 LISC, Bruno Kessler Foundation, Trento, Italy, 2 ECT*, Bruno Kessler Foundation, Trento, Italy, 3 Physics Department, University of Trento, Trento, Italy, 4 INFN, Gruppo Collegato di Trento, Trento, Italy, 5 SISSA and CNR-IOM Democritos, Trieste, Italy

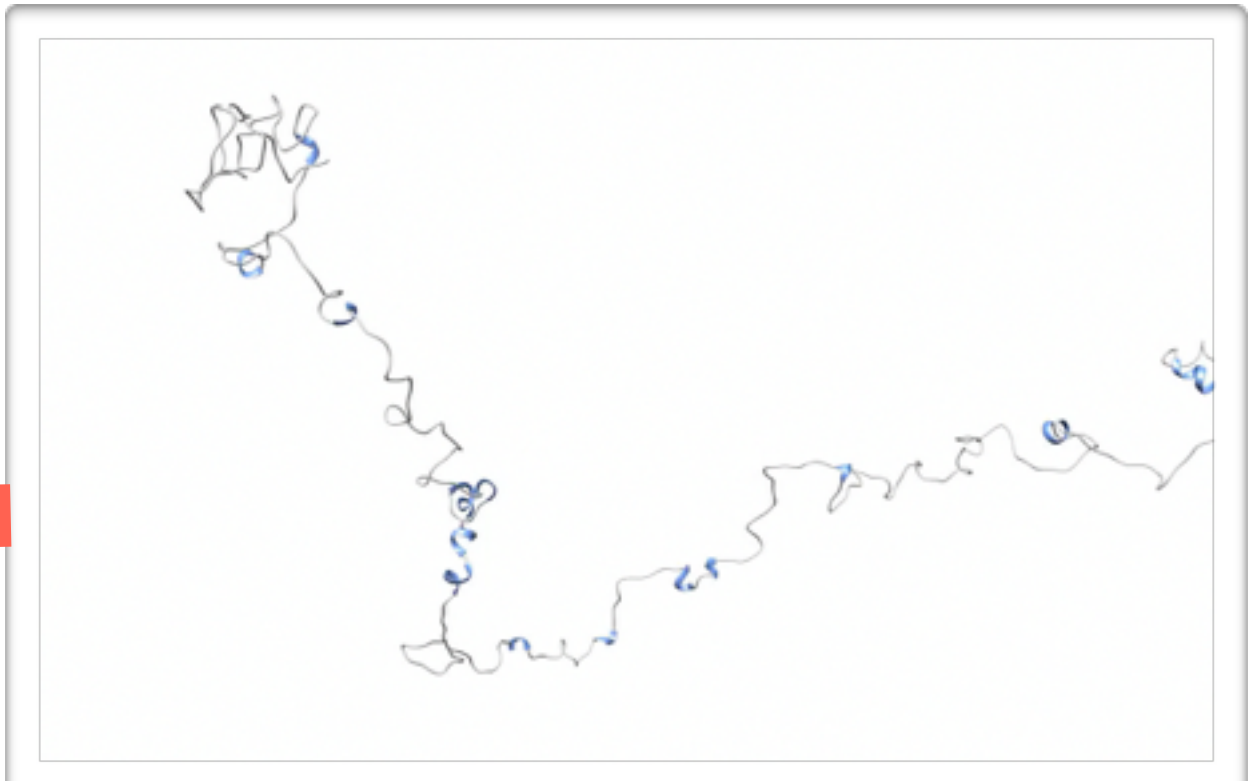
Project with molecular biologists/biophysicists



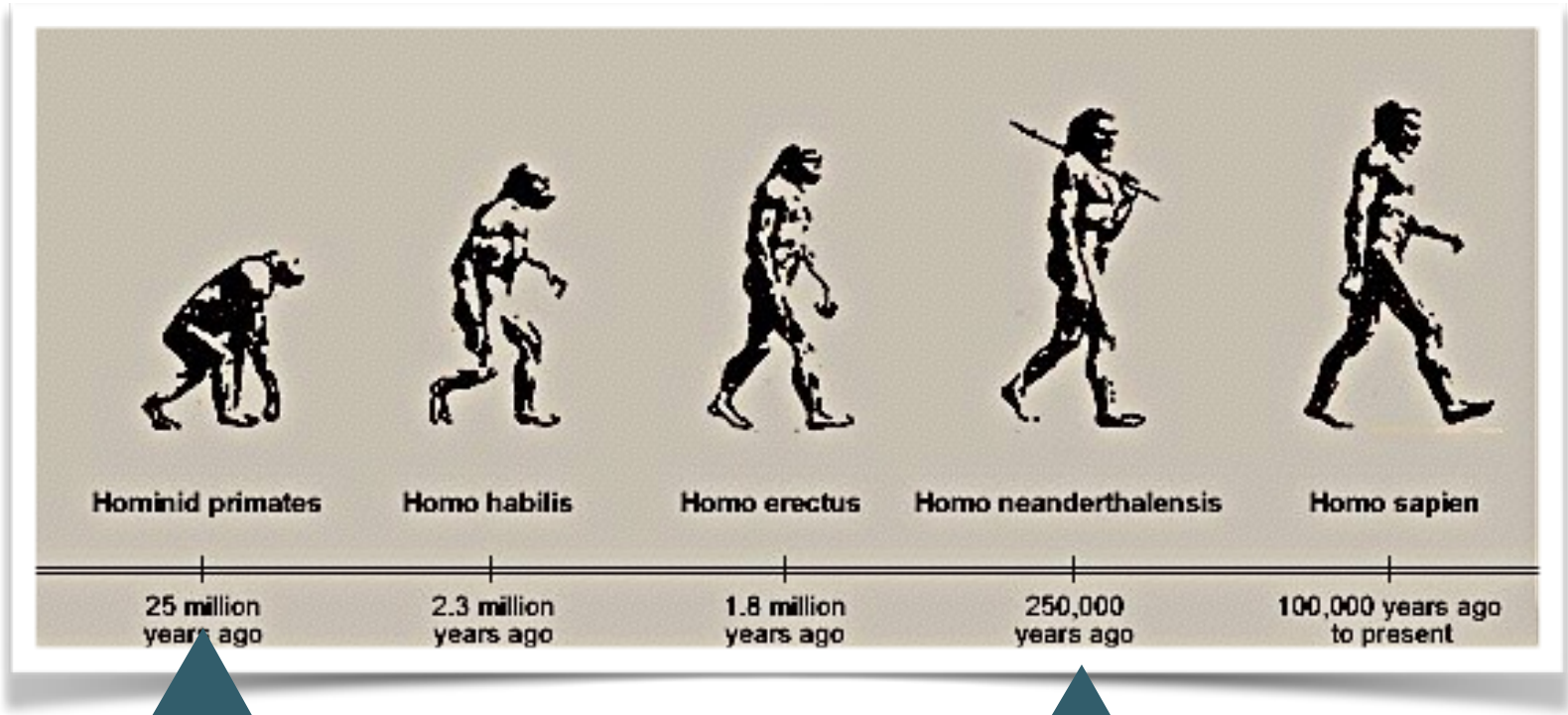
Androgen receptor regulatory mechanism
(disorder-to-order transition)

serpin
confromational
transitions
(mean-first-passage
times: hours to
days.)

folding &
misfolding
of serpin proteins
(~400 a.a.)



Question: When did we need to start a MD simulation in order to have just 1 folding event by today?



Using top-class all-purpose supercomputers

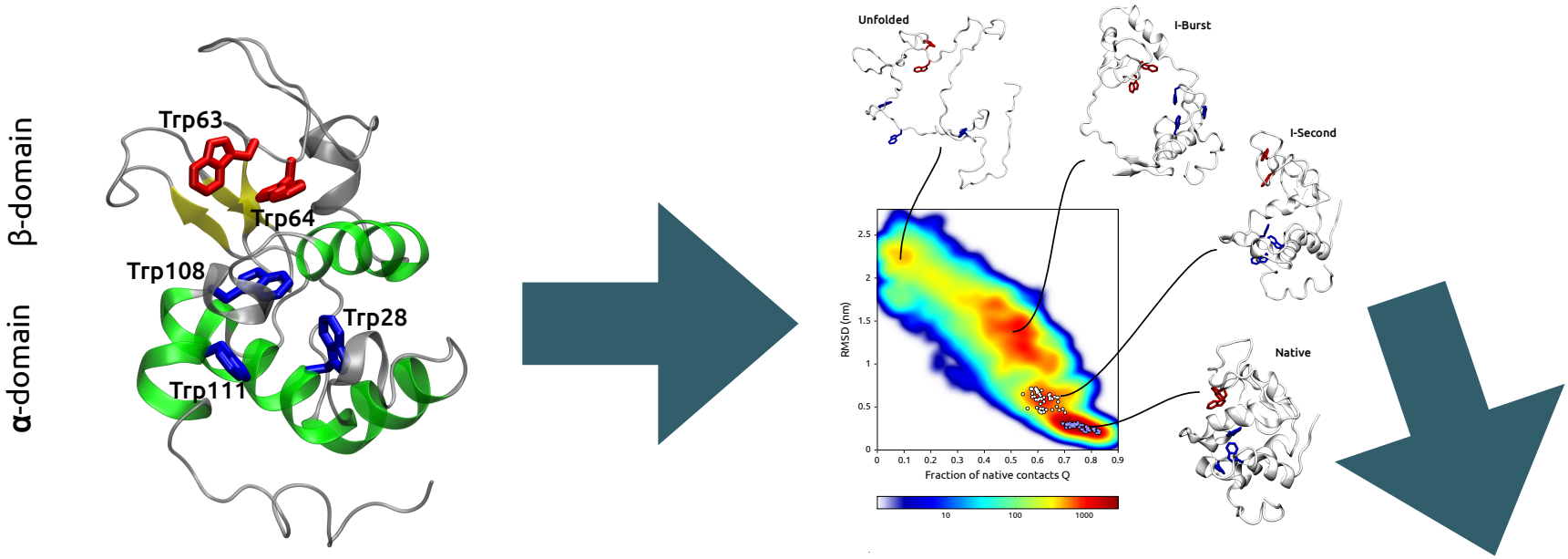
Using a special purpose supercomputer (Anton)

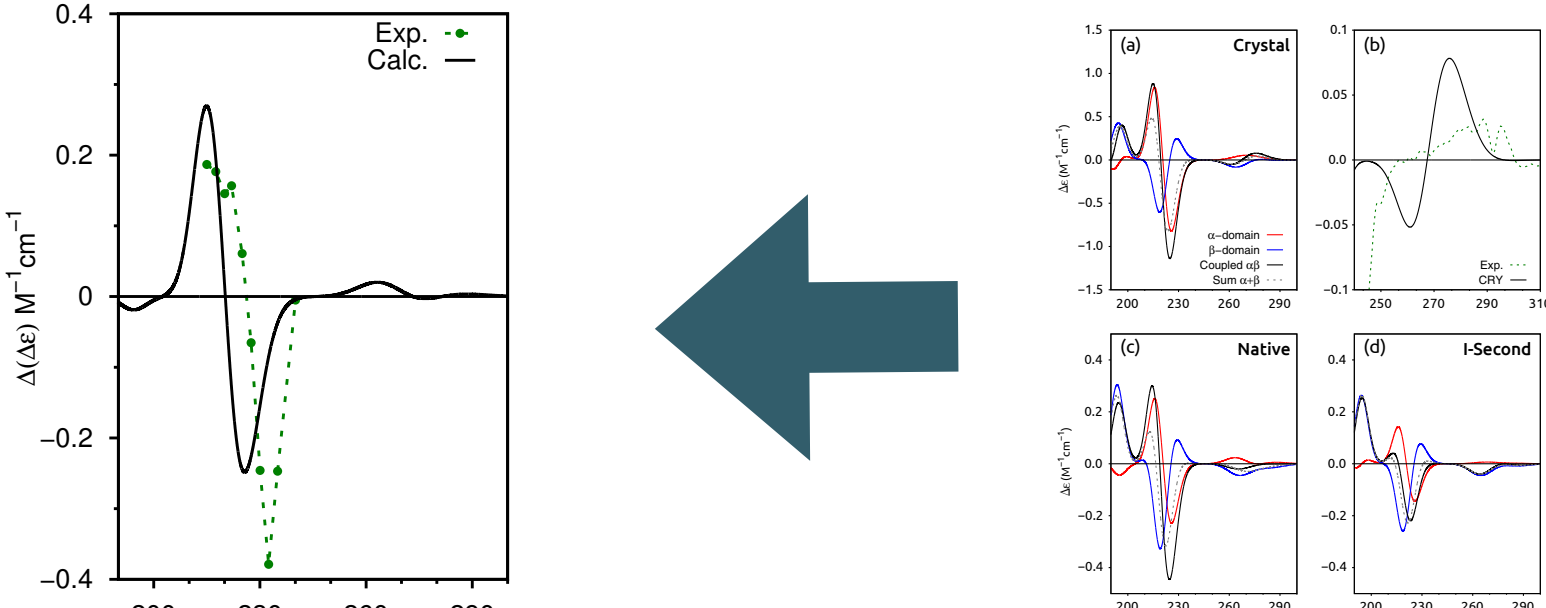
Applications to linear optics

$$\rho = \left(\begin{array}{c|ccc|ccc} \rho_{gg} & \rho_{ge_1} & \cdots & \rho_{ge_N} & \rho_{g\alpha_1} & \cdots & \rho_{g\alpha_{N_2}} \\ \hline \rho_{e_1 g} & \rho_{e_1 e_1} & \cdots & \rho_{e_1 e_N} & \rho_{e_1 \alpha_1} & \cdots & \rho_{e_1 \alpha_{N_2}} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ \rho_{e_N g} & \rho_{e_N e_1} & \cdots & \rho_{e_N e_N} & \rho_{e_N \alpha_1} & \cdots & \rho_{e_N \alpha_{N_2}} \\ \hline \rho_{\alpha_1 g} & \rho_{\alpha_1 e_1} & \cdots & \rho_{\alpha_1 e_N} & \rho_{\alpha_1 \alpha_1} & \cdots & \rho_{\alpha_1 \alpha_{N_2}} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ \rho_{\alpha_{N_2} g} & \rho_{\alpha_{N_2} e_1} & \cdots & \rho_{\alpha_{N_2} e_N} & \rho_{\alpha_{N_2} \alpha_1} & \cdots & \rho_{\alpha_{N_2} \alpha_{N_2}} \end{array}\right)$$

Linear Spectroscopy $\rho_{e_k g}(t) \propto \int \mathcal{D}\delta R \int \mathcal{D}\psi \mathcal{D}\bar{\psi}\; e^{iS_{tot}}\; \psi(e_l, t)\; \bar{\psi}(e_n, 0)$

Extracting detailed structural kinetic information from near UV CD spectra (with B. Mennucci's team)





Conclusions

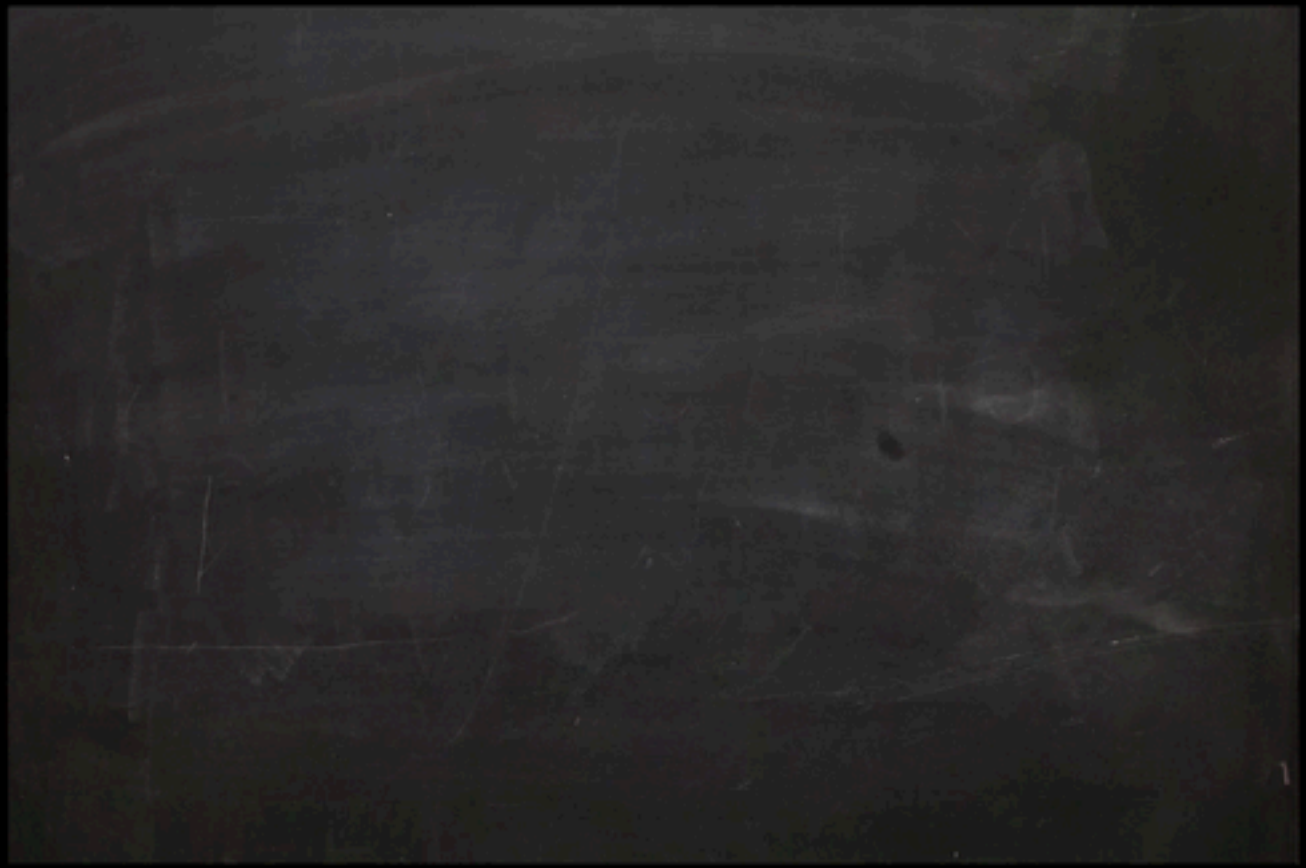
- Theoretical nuclear- high-energy physics is useful beyond its natural cultural perimeter
- Great challenges awaits at the interface between different disciplines
- More general: it's fun go swimming muddy turbulent waters

Technological Transfer (drug discovery research)

SIBYLLA BIOTECH
www.sibyllabiotech.it

- Applying for recognition as INFN spinoff

Our team research themes:



Current Team members:

PhD:
Simone Orioli

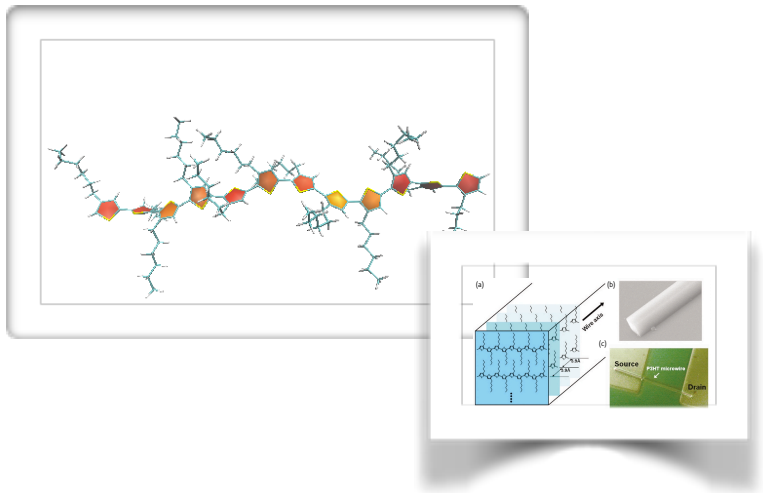
MS:
Giacomo Bartolucci
(stat. mech.)
Daniel Nagel
(algorithms)

Former postdocs
S. A Beccara (all-round)
T. Skrbic (proteins)

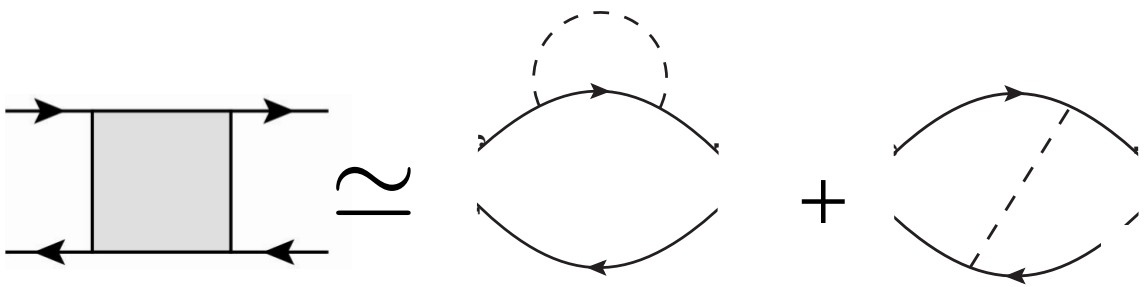
Former PhD students:
E. Schneider (quantum dynamics, now at NYU),
R. Covino (proteins, now at Max Planck)

Thank you for your attention!

Solution strategies: fast exciton propagation limit



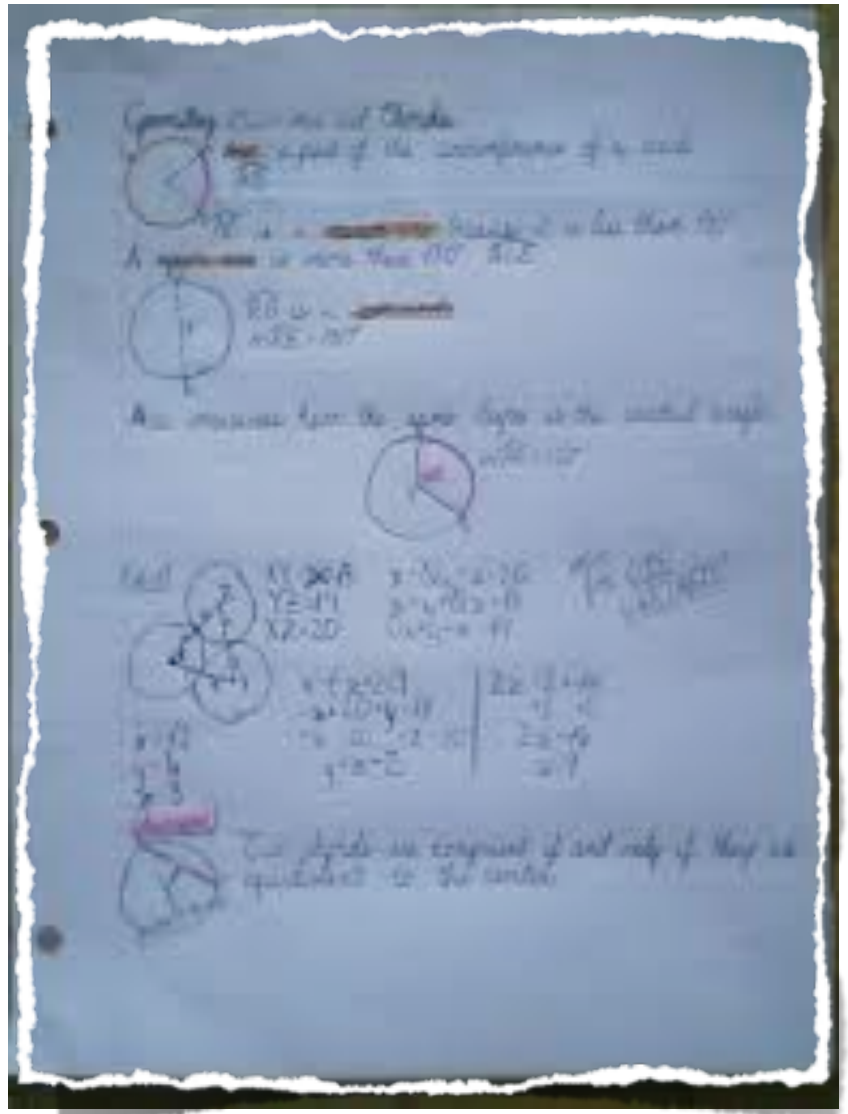
E.g. exciton transfer in a conjugate polymer



Results are simple analytic formulas!

MICROSCOPIC RESULTS WITHOUT NUMERICS!

Technical “intermezzo”: Self Consistent Path Sampling



Unbiasing the BF approach: Self-Consistent Reaction Path Sampling

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Self-consistent calculation of protein folding pathways

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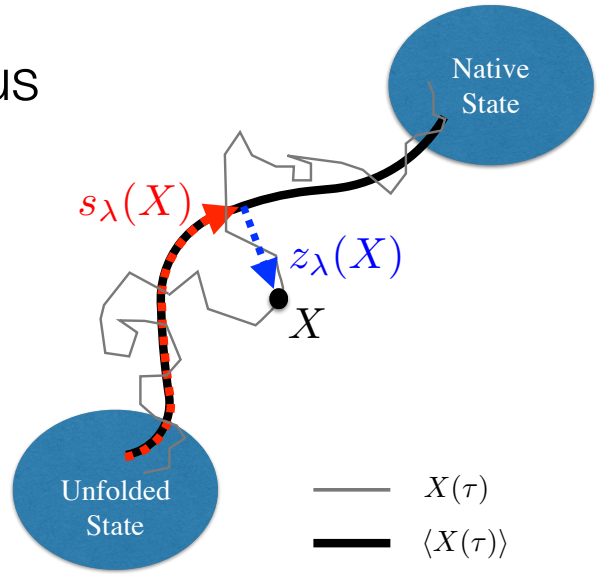
(Received 10 May 2017; accepted 21 July 2017; published online 10 August 2017)

Basic idea: bias along "tube-variables" (Branduardi-Gervasio-Parrinello (BGP)) determined from a previous iteration



Step 1: introduce two auxiliary variables into the stochastic path integral:

$$p(X_f, t|X_i) = \int_{X_i}^{X_f} \mathcal{D}X \cdot e^{-S_{OM}[X]}$$

$$\equiv \int_{X_i}^{X_f} \mathcal{D}X \int_{s(0)} \mathcal{D}s_m \int_{z(0)} \mathcal{D}z_m e^{-S_{OM}[X]} \delta\left[\dot{z}_m - \dot{z}\theta(z_m - z(\tau))\right] \delta\left[\dot{s}_m - \dot{s}\theta(s_m - s(\tau))\right]$$

fixed functions:

$$z(\tau) = z_0 \qquad s(\tau) = 1 - \frac{\tau}{t}$$

Self-Consistent Reaction Path Sampling

Step 2: With a mere mathematical trick, we re-write the external functions in a fancy way

$$s(\tau) = \lim_{\lambda\to\infty} s_\lambda[X,\tau] \equiv \lim_{\lambda\to\infty} \left(1 - \frac{\frac{1}{t}\int_0^t dt' t' e^{-\lambda\ ||C_{ij}[X(\tau)]-C_{ij}[X(t')]||^2}}{\int_0^t dt' e^{-\lambda||C_{ij}(X)-C_{ij}[X(t')]||^2}}\right)$$

$$z(\tau) = \lim_{\lambda\to\infty} z_\lambda[X,\tau] \equiv \lim_{\lambda\to\infty} \left(-\frac{1}{\lambda}\log\int_0^t dt' e^{-\lambda||C_{ij}[X(\tau)]-C_{ij}[X(t')]||^2}\right)$$

NB: X(t) is an arbitrary path in configuration space. In the large λ limit:

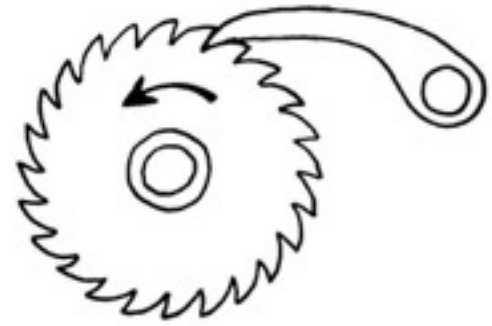
$$s_\lambda[X,\tau] \to 1 - \frac{\tau}{t} \qquad \& \qquad z_\lambda[X,\tau] \to \text{const.}$$

Thus the specific choice of X(t) is irrelevant

Self-Consistent Reaction Path Sampling

Step 3: re-write the OM functional in a fancy way:

$$S_{OM}[X] = \lim_{\lambda \to \infty} S_\lambda[X]$$



Ratchet-and -Pawl (rMD)

$$S_\lambda[X] \equiv \frac{\beta/4}{\gamma m} \int_0^t d\tau \, [m\ddot{\mathbf{x}} + m\gamma\dot{\mathbf{x}} + \nabla_i U(X)$$

$$+k_z \nabla z_\lambda[X,\tau](z_m(\tau) - z_\lambda[X,\tau])\theta(z_m(\tau) - z_\lambda[X,\tau])$$

$$+k_s \nabla s_\lambda[X,\tau](s_m(\tau) - s_\lambda[X,\tau])\theta(s_m(\tau) - s_\lambda[X,\tau])]^2$$

These terms look like rMD biasing forces…but in fact they are identically null!

Self-Consistent Reaction Path Sampling

Thus so far, no approximations have been introduced and the original stochastic path integral is **exactly re-written** as

$$p(X_f, t|X_i) = \lim_{\lambda \to \infty} p_\lambda(X_f, t|X_i)$$

$$p_\lambda(X_f, t|X_i) \equiv \int_{X_i}^{X_f} \mathcal{D}X \int \mathcal{D}s_m \int \mathcal{D}z_m e^{-S_\lambda[X]}$$

$$\delta\left[\dot{z}_m - \dot{z}_\lambda \theta(z_m - z_\lambda)\right] \delta\left[\dot{s}_m - \dot{s}_\lambda \theta(s_m - s_\lambda)\right]$$

Self-Consistent Reaction Path Sampling

Step 4: We now introduce our **only approximation**

$$s_\lambda[X,\tau] \simeq 1 - \frac{\frac{1}{t}\int_0^t dt' t' e^{-\lambda\ ||C_{ij}[X(\tau)] - \langle C_{ij}(t')\rangle_\lambda||^2}}{\int_0^t dt' e^{-\lambda||C_{ij}[X(\tau)] - \langle C_{ij}(t')\rangle_\lambda||^2}}$$

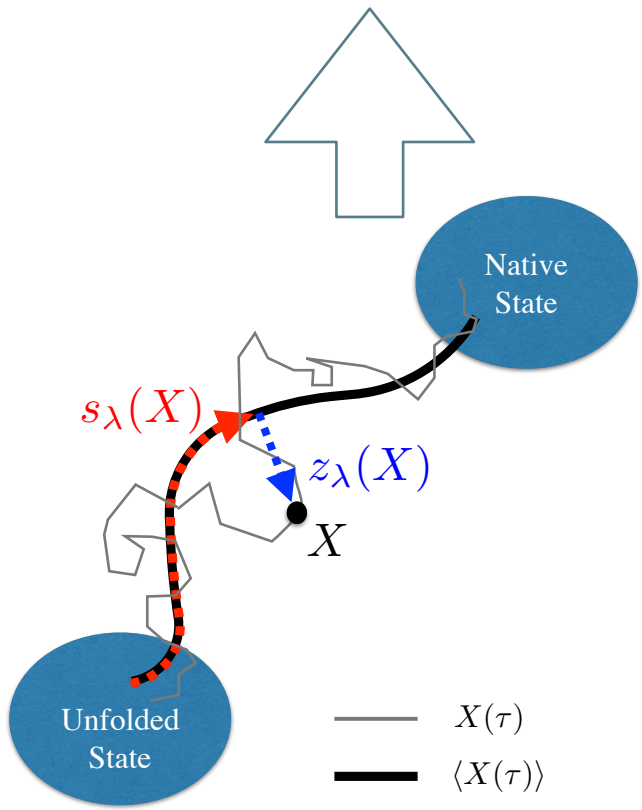
$$z_\lambda[X,\tau] \simeq -\log \int_0^t dt' e^{-\lambda||C_{ij}[X(\tau)] - \langle C_{ij}(t')]\rangle_\lambda||^2}$$

where:

$$\langle C_{ij}(\tau)\rangle_\lambda = \frac{\int_{X_i}^{X_f} \mathcal{D}X e^{-S_\lambda[X]} C_{ij}[X(\tau)]}{\int_{X_i}^{X_f} \mathcal{D}X e^{-S_\lambda[X]}}$$

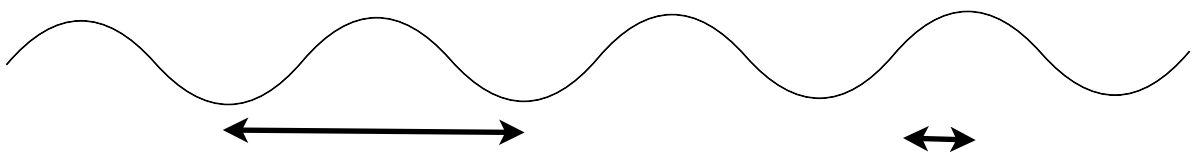
Then s_λ and z_λ become Parrinello's path variables with respect to the average trajectories **in contact map space**

rMD biasing forces along s & *z* switch on!



Solution strategy: long-time, large-distance limit

Use Renormalization Group formalism to perform coarse-graining and lower the time & spatial-resolution power. Obtain an effective theory which yields the same results in the long-time long-distance limit:



λ (cut-off)

λ_B (De Broglie's thermal wavelentgh)

from the microscopic theory we get

$$P(\mathbf{y},t|\mathbf{x},0) \simeq \int_{\mathbf{x}}^{\mathbf{y}} \mathcal{D}\mathbf{R}\; e^{-\int_0^t dT\left[\frac{1}{4D_2^b}\dot{\mathbf{R}}^2+\left(\frac{\lambda_B}{\lambda}\right)^2 C_4^b\;\dot{\mathbf{R}}^4+\ldots\right]}$$

$$\ldots = \mathcal{O}\left(\frac{\lambda_B}{\lambda}\right)^2$$

quantum correction terms

where $\mathbf{A}\cdot\mathbf{B} = \sum_{ij} g_{ij}\; A_i B_j$

Diffusion of a quantum excitation:

The analytic solution (after renormalization):

diffusion of quantum excitation

$$\bar{P}(\mathbf{y},t|\mathbf{x},0) \simeq P_0(\mathbf{y},t|\mathbf{x},0;D_{ren}) \times \left[1 - C_{ren}\left(\frac{(\mathbf{y}-\mathbf{x})^4}{t^3 D_{ren}} - 20\frac{(\mathbf{y}-\mathbf{x})^2}{t^2} + \frac{60 D_{ren}}{t}\right)\right].$$

quantum correction terms

Renormalized constants, to be determined from experiments or micr. sim.s

Illustrative application: hole diffusion on DNA wires

PHYSICAL REVIEW B **89**, 134305 (2014)

Long-distance quantum transport dynamics in macromolecules

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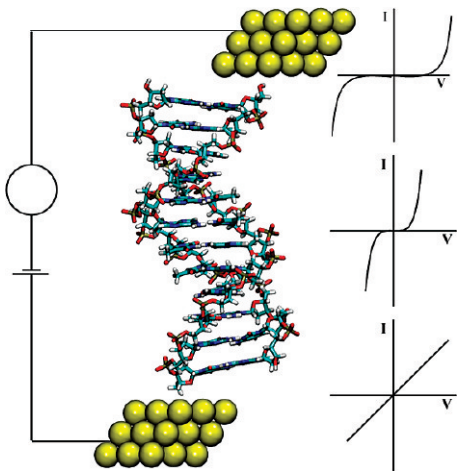
and Trento Institute for Fundamental Physics and Applications (TIFPA), Via Sommarive 14, Povo Trento, Italy
(Received 6 December 2013; revised manuscript received 18 March 2014; published 9 April 2014)

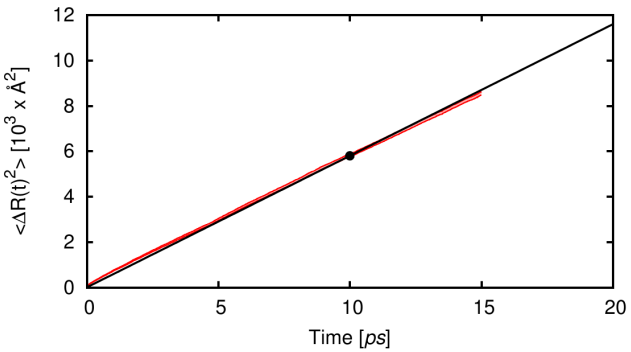
Using renormalization group methods, we develop a rigorous coarse-grained representation of the dissipative dynamics of quantum excitations propagating inside open macromolecular systems. We show that, at very low spatial resolution, this quantum transport theory reduces to a modified Brownian process, in which quantum

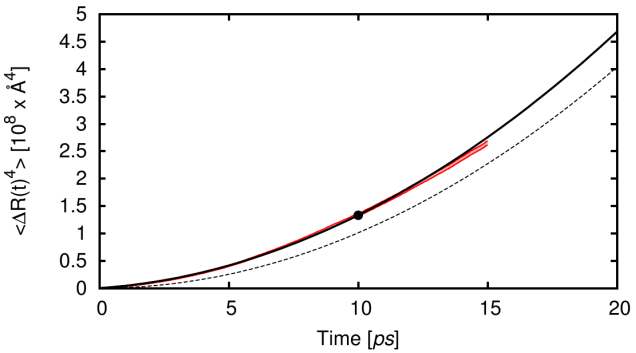


First match with microscopic calculations (renormalization)

Then use the EFT to obtain predictions at long times!

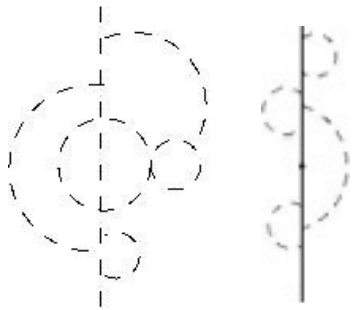
t^* $[ps]$	1
D_{ren} $[\mathring{A}^2/ps] \times 10^2$	3,6 $\pm$ 0.2
C_{ren} $[\mathring{A}^4/ps] \times 10^6$	-1.3 $\pm$ 0.1





Applications to linear optics

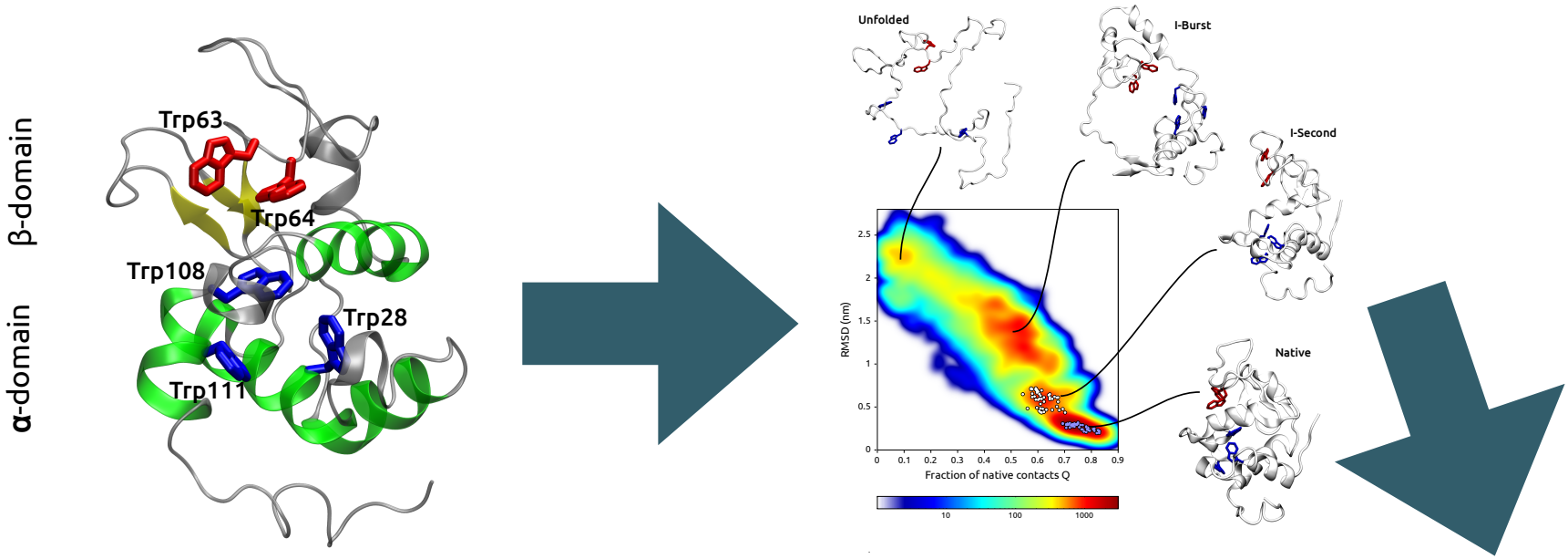
$$\rho = \left(\begin{array}{c|ccc|ccc} \rho_{gg} & \rho_{ge_1} & \cdots & \rho_{ge_N} & \rho_{g\alpha_1} & \cdots & \rho_{g\alpha_{N_2}} \\ \hline \rho_{e_1 g} & \rho_{e_1 e_1} & \cdots & \rho_{e_1 e_N} & \rho_{e_1 \alpha_1} & \cdots & \rho_{e_1 \alpha_{N_2}} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ \rho_{e_N g} & \rho_{e_N e_1} & \cdots & \rho_{e_N e_N} & \rho_{e_N \alpha_1} & \cdots & \rho_{e_N \alpha_{N_2}} \\ \hline \rho_{\alpha_1 g} & \rho_{\alpha_1 e_1} & \cdots & \rho_{\alpha_1 e_N} & \rho_{\alpha_1 \alpha_1} & \cdots & \rho_{\alpha_1 \alpha_{N_2}} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ \rho_{\alpha_{N_2} g} & \rho_{\alpha_{N_2} e_1} & \cdots & \rho_{\alpha_{N_2} e_N} & \rho_{\alpha_{N_2} \alpha_1} & \cdots & \rho_{\alpha_{N_2} \alpha_{N_2}} \end{array}\right)$$

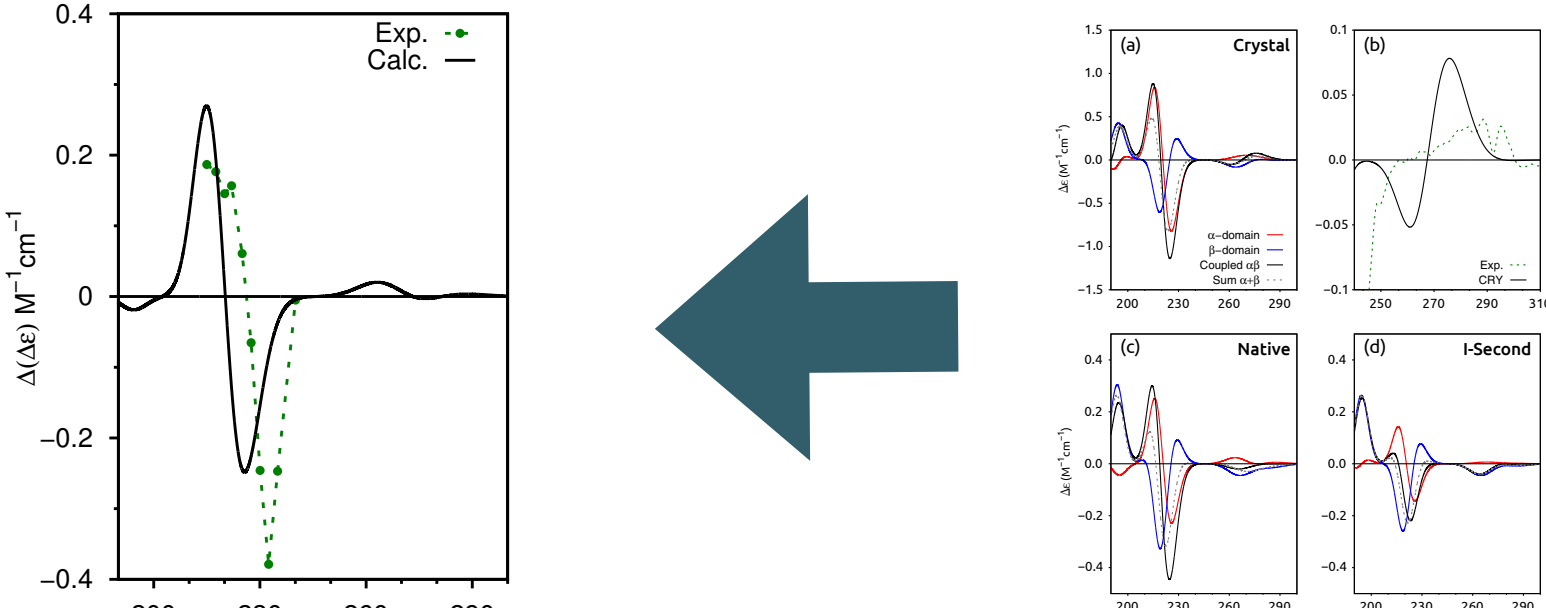


conformational dynamics $\rho_{gg}(t) \propto \int \mathcal{D}\, R \int \mathcal{D}\psi \mathcal{D}\bar{\psi}\; e^{iS_{tot}}$

Linear Spectroscopy $\rho_{e_k g}(t) \propto \int \mathcal{D}\delta R \int \mathcal{D}\psi \mathcal{D}\bar{\psi}\; e^{iS_{tot}}\; \psi(e_l, t)\; \bar{\psi}(e_n, 0)$

Extracting detailed structural kinetic information from near UV CD spectra (with B. Mennucci's team)

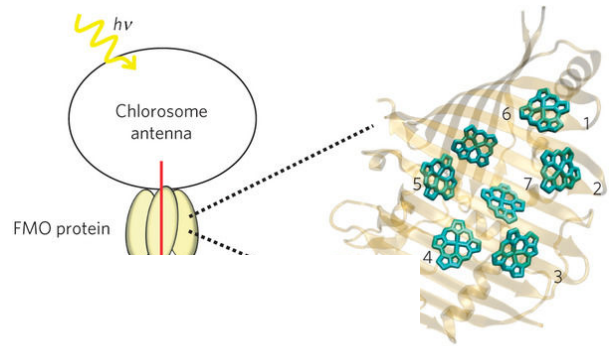




Linear Absorption in Fenna Matthews Olson complex

Test System: Fenna-Matthews-Olson complex

FMO pigment-protein complex is sensible choice



We need:

site energies f^0_{nn}
Literature
hoppings f^0_{nm}
Literature
vibrations R_l
Elastic Network
Interaction of vibrations and excitations $[f^1_{nm}]^l$
Straightforward parametrization

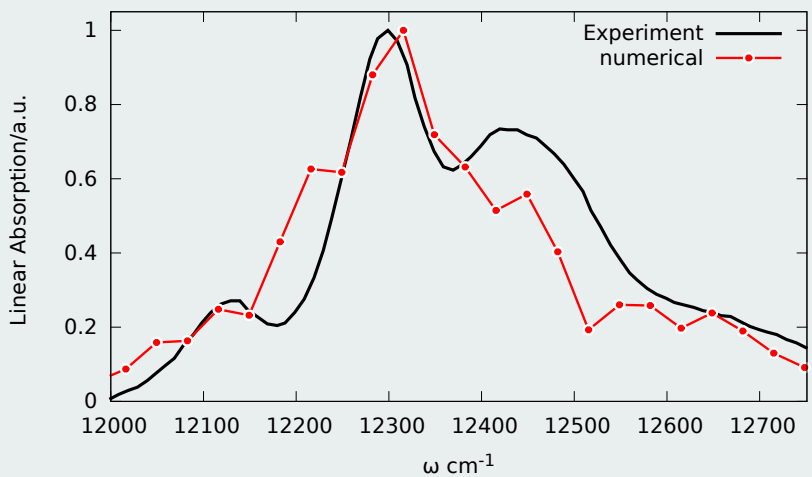
Note: $f_{nm}[R] \to_{cl} f^0_{nm} + [f^1_{nm}]^l R_l + \dots$

Results

The absorption coefficient

$$\kappa_A(\omega) \propto \omega \, \mathrm{Im}\left(\mathscr{F}\left(\mathrm{Tr}\left[\hat{\rho}(t)\hat{\mu}\right]\right)\right)$$

$\hat{\mu}$ dipole operator interacting with Optical Field



Looks Promising!

Results are obtained with a **Monte Carlo** code

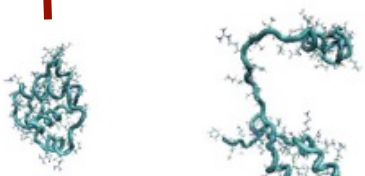
Summary

microscopic model
for bio-molecular dynamics

$$\frac{\mathrm{Tr}[|i\rangle\langle f|\hat{\rho}(t)]}{\mathrm{Tr}[\rho[0]} = \int \mathcal{D}[\dots]$$

Conformational dynamics

$$P(Q_f, t|Q_i) = \frac{\mathrm{Tr}[|Q_f\rangle\langle Q_f|\hat{\rho}(t)]}{\mathrm{Tr}\hat{\rho}(0)}$$

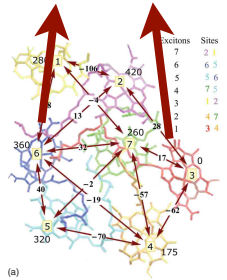


Advantage:
computational efficiency
for rare transitions

Application to:
Protein folding & conformational transitions, chemical reactions

Quantum transport dynamics

$$P(k_f, t|k_i) = \frac{\mathrm{Tr}[\ |k_f\rangle\langle k_i|\ \hat{\rho}(t)\ ]}{\mathrm{Tr}\ \hat{\rho}(0)}$$



Advantages:
derivation of couplings
rigorous approximations

short time:
pert. theory

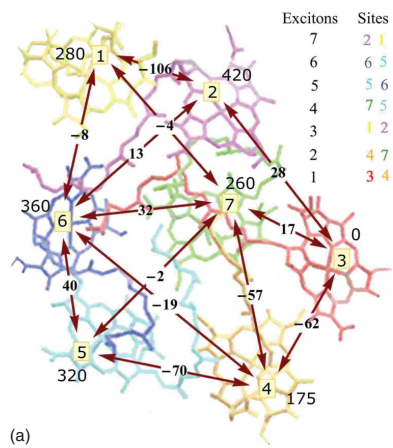
long time:
diffusive approach

Potential applications: charge transfer, exciton de-coherence, etc...

On-going applications:

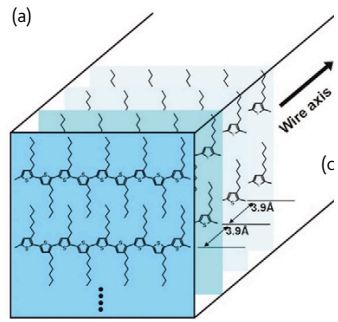
Phenomenology of exciton transfer in biomolecules (quantum biology) and conjugate

2D echo spectroscopy

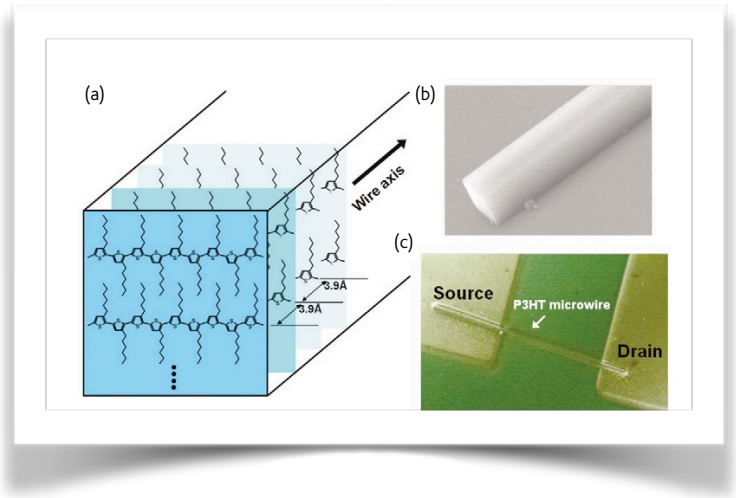


Charge propagation in organic transistors

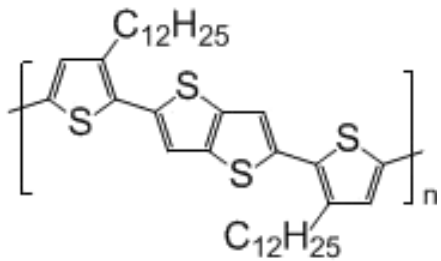
(compounds of conjugate polymers)

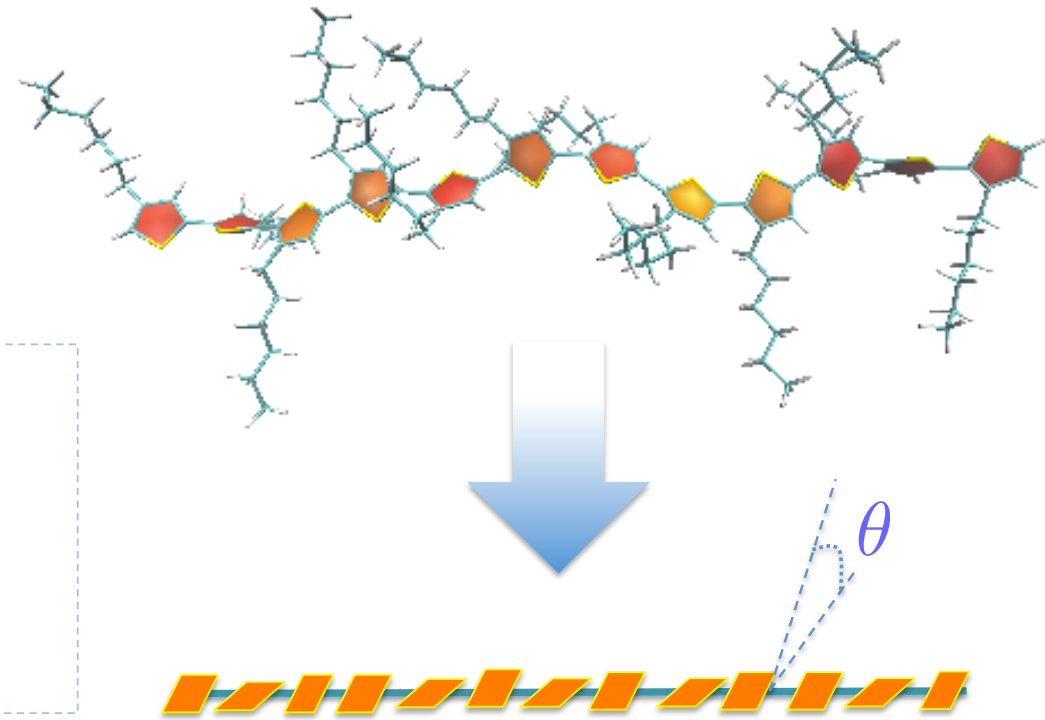


Coarse-Graining the representation of the polymer dynamics:



(organic transitors)

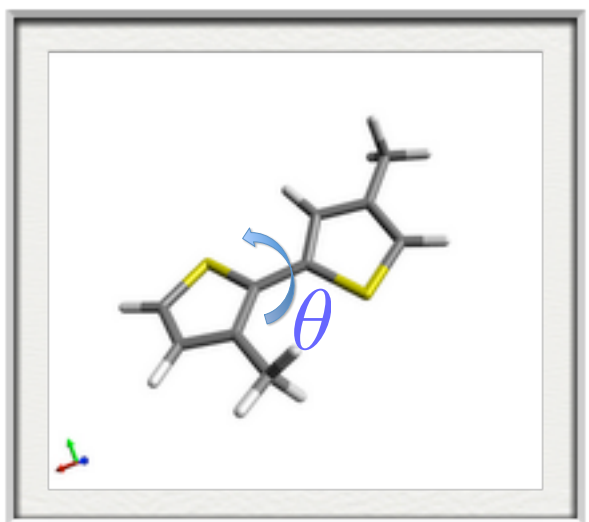




$(\theta_1, \theta_2, \ldots, \theta_N)$ (chain configuration)

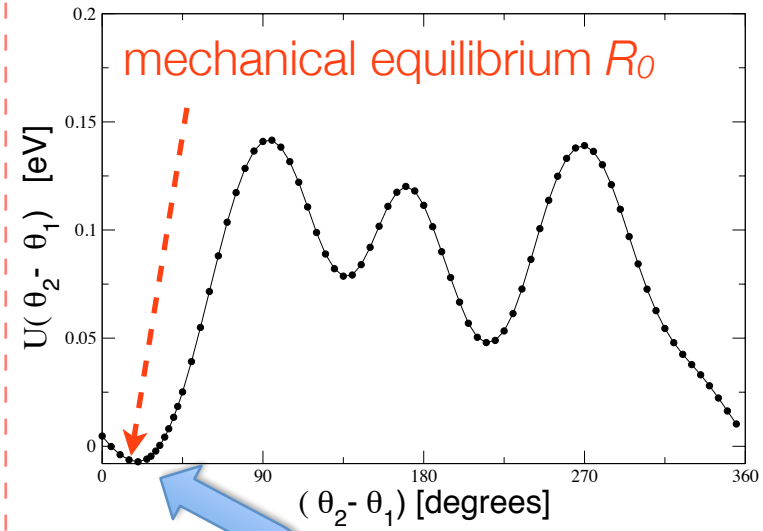
$\rho_{lm}(t) \qquad (l, m = 1, \ldots, N)$ (charge density matrix)

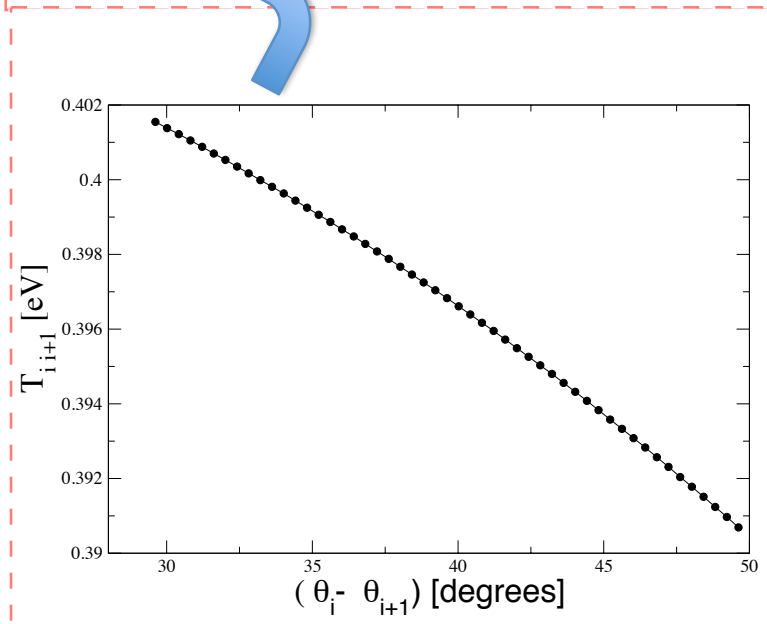
Ingredients from quantum chemistry calculations



DFT-B

density functional theory





Compare to a non-perturbative approach:

- **Saddle-point** level for the coherent fields $(i.e.\ \phi' = \phi'')$
- **One-loop** level for atomic coordinates $(\ i.e.\ \mathcal{O}(Q' - Q'')^2\ )$

Resulting equations of motions:

Generalized **quantum force**

$$\begin{cases} M\ddot{Q}_i = -\gamma\dot{Q}_i - \nabla_i(\ U(Q) + \mathrm{Tr}[\rho f(Q)]\ ) + \eta_i(t) \\ \dfrac{d}{dt}\rho_{lm}(t) = -\dfrac{i}{\hbar}[f(Q), \rho]_{lm} \end{cases}$$

$\rho_{lm} = |l\rangle\langle m|$

- (density matrix)

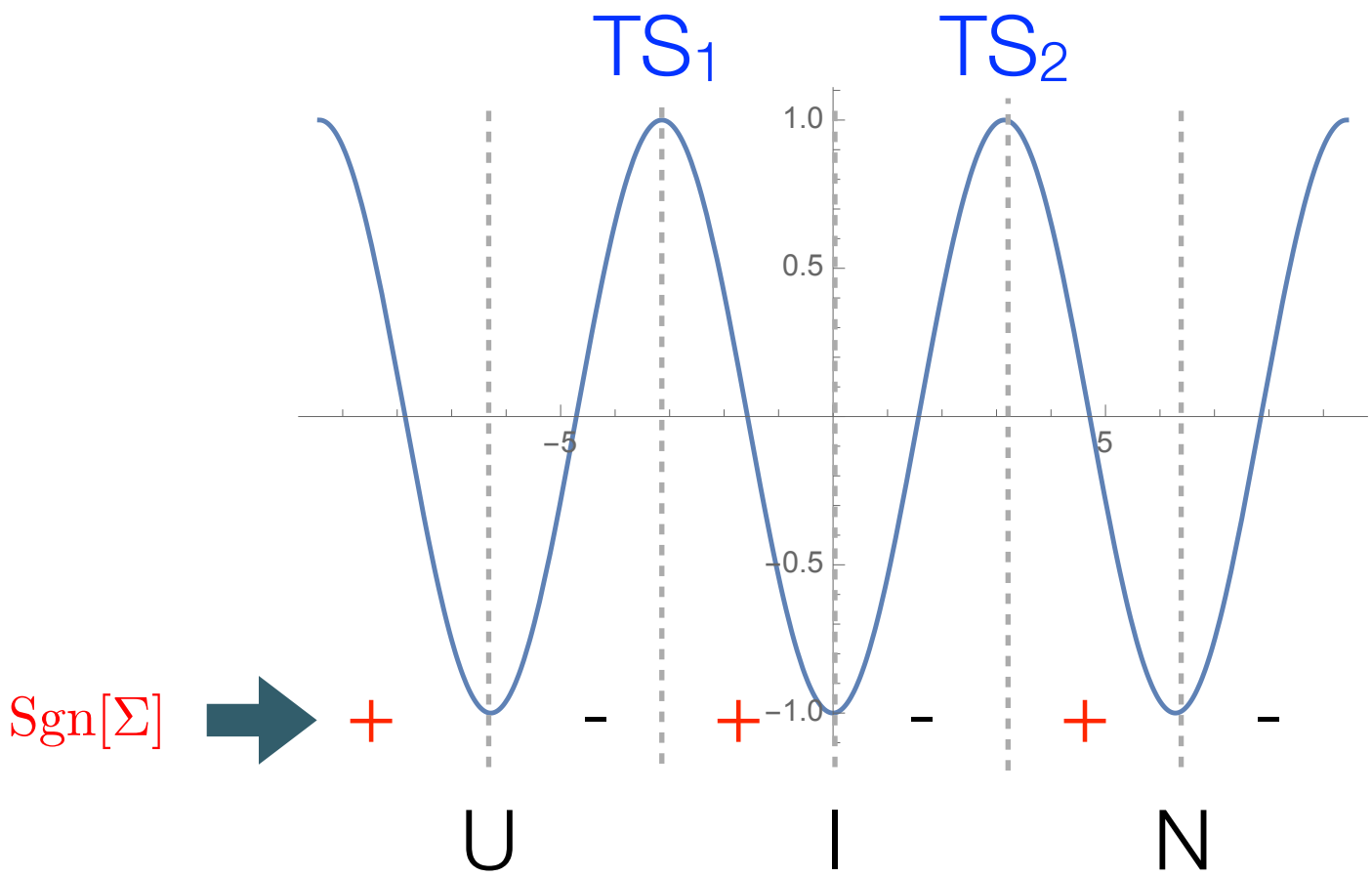
$f_{lm}(Q) = \langle\phi_l(Q)|\hat{H}_{DFT}|\phi_m(Q)\rangle$

- (hopping matrix elements)

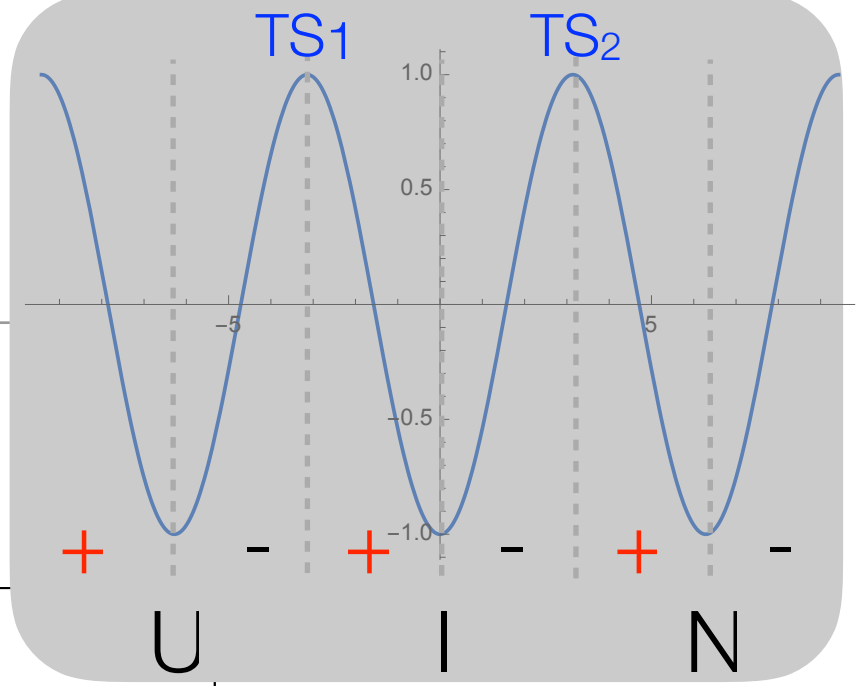
Slope function:

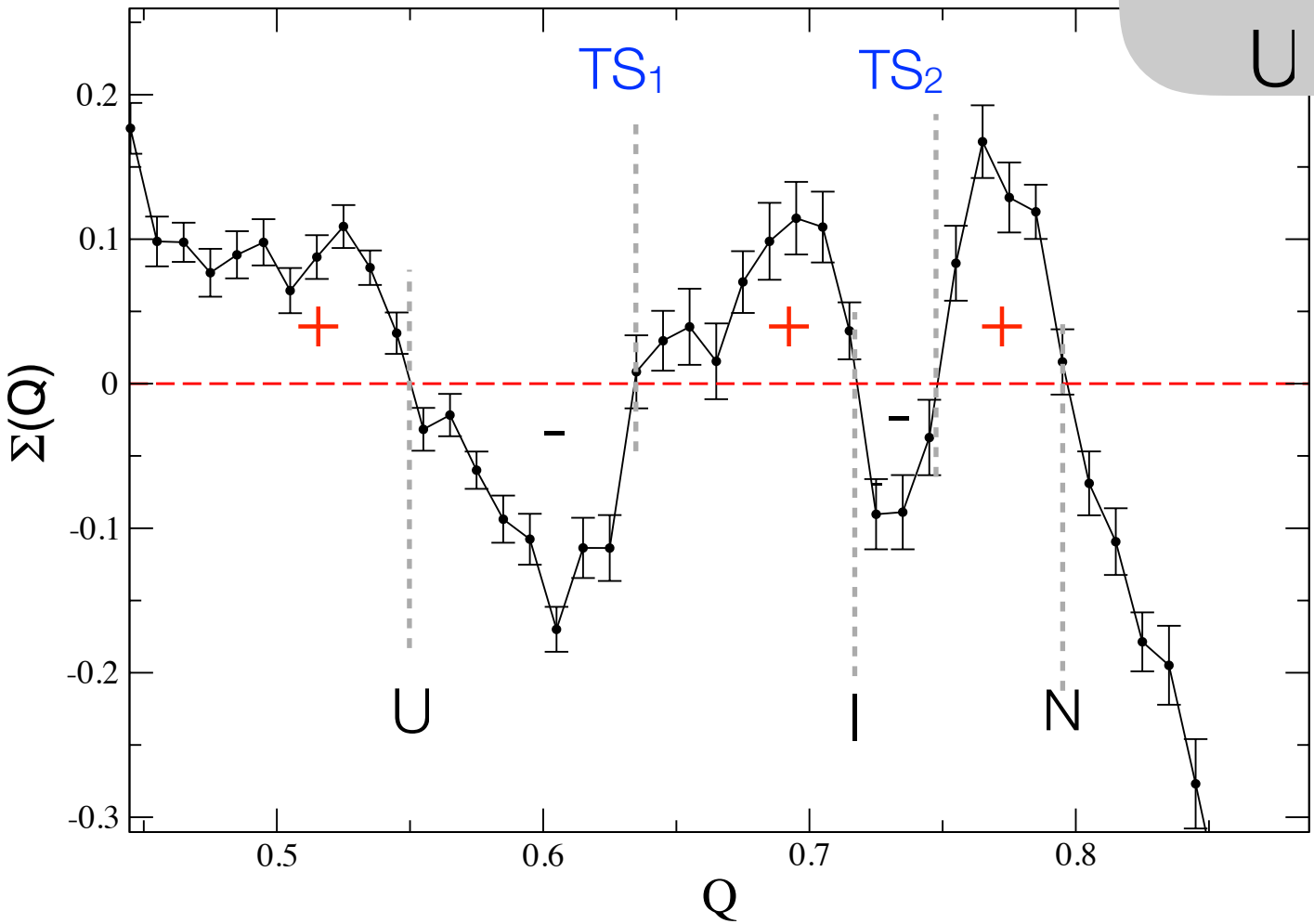
$$\Sigma(Q) = P_f(Q) - P_b(Q) = -\sqrt{\frac{D\Delta t}{\pi}}\frac{G'(Q)}{k_B T} + \dots$$

Prediction:



In realistic rMD simulations



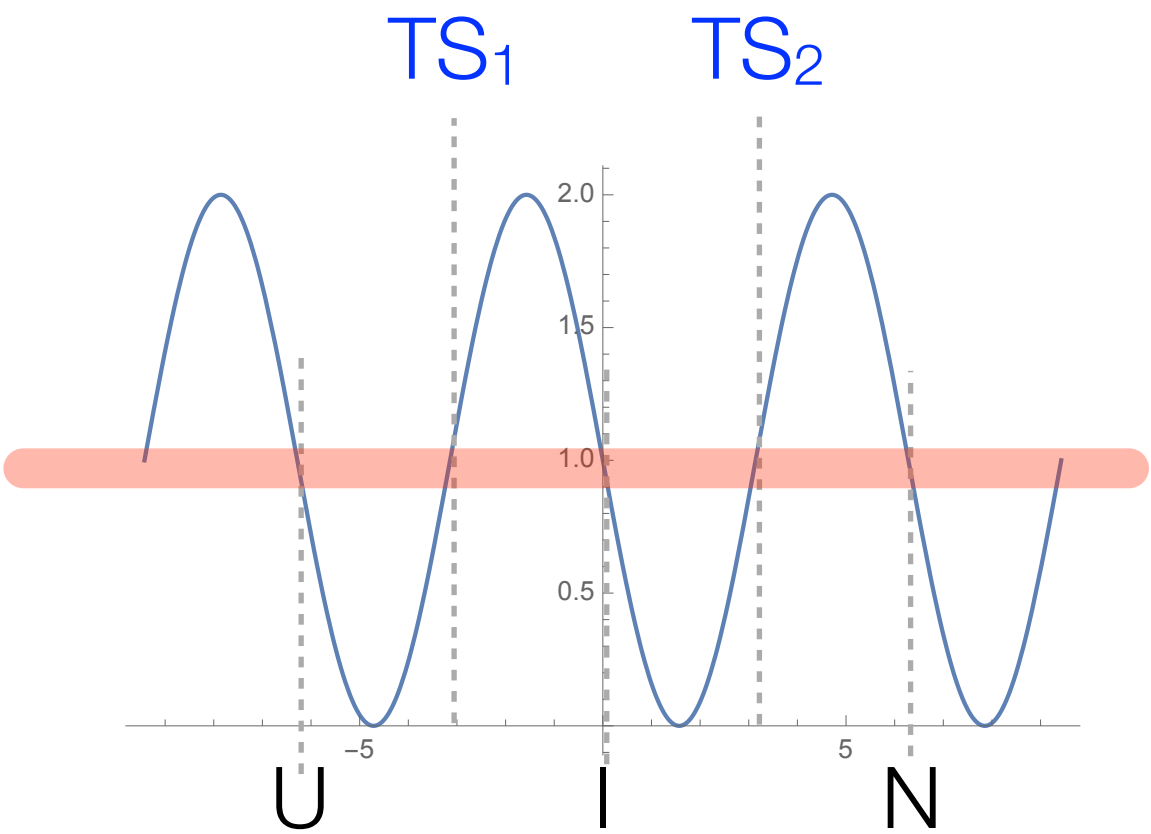


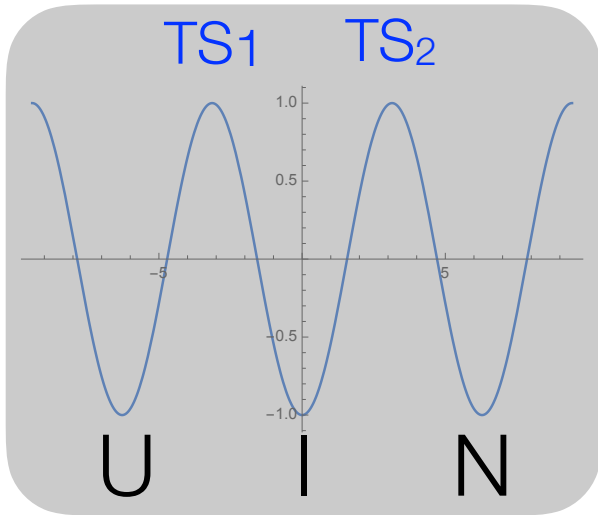
Q_U=0.54
Q_{TS1}=0.64
Q_I=0.71
Q_{TS2}=0.74
N=0.8

First Moment

$$\langle \Delta Q(Q) \rangle_{rMD} = +\sqrt{\frac{D\Delta t}{\pi}}\frac{\xi - 1}{\xi} - \frac{\xi + 1}{2\xi}\frac{G'(z)}{k_B T}(\Delta t D)^{3/2} + \dots$$

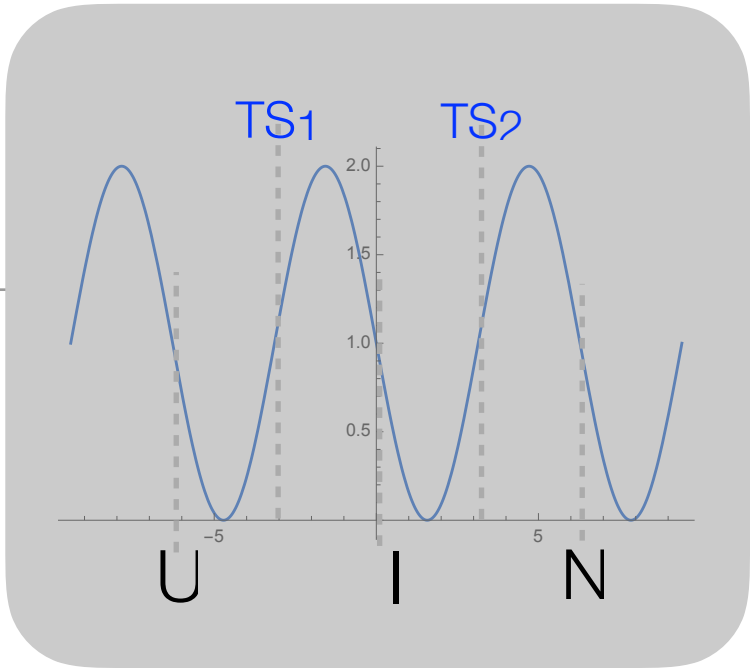
Prediction:

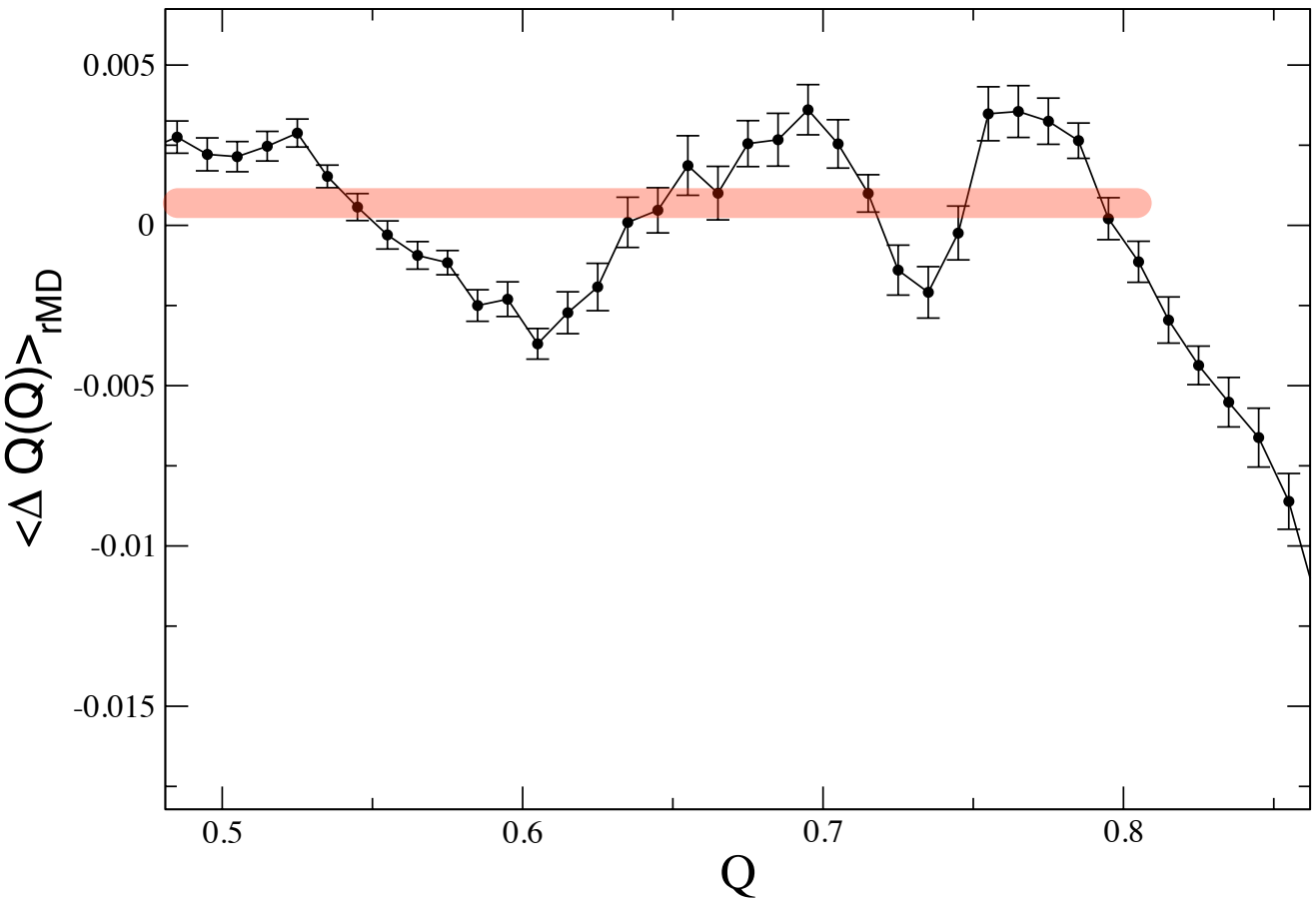




$$\langle \Delta Q(Q_U) \rangle_{rMD} \simeq \langle \Delta Q(Q_{TS_i}) \rangle_{rMD} \simeq \langle \Delta Q(Q_N) \rangle_{rMD} = \sqrt{\frac{D\Delta t}{\pi}}\frac{\xi - 1}{\xi}$$

In realistic rMD simulations





Q_U=0.54

Q_{TS1}=0.64

Q_I=0.71

Q_{TS2}=0.74

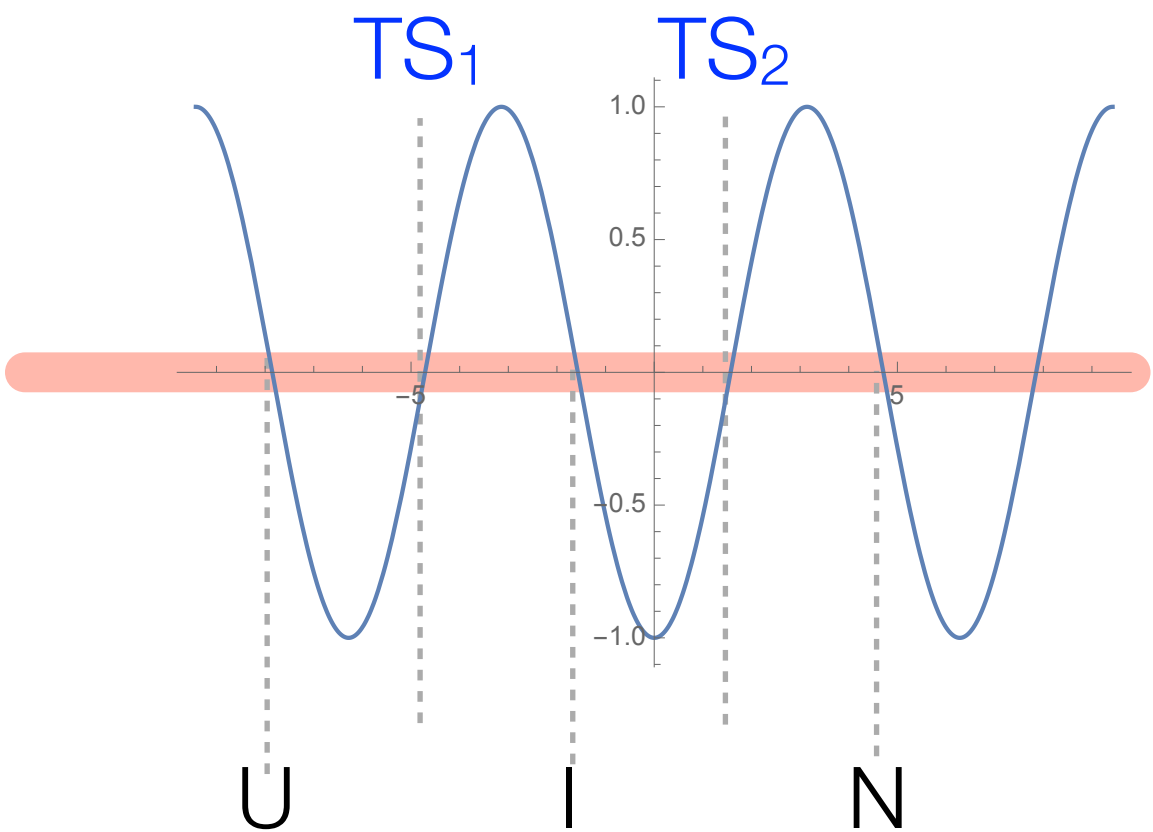
N=0.8

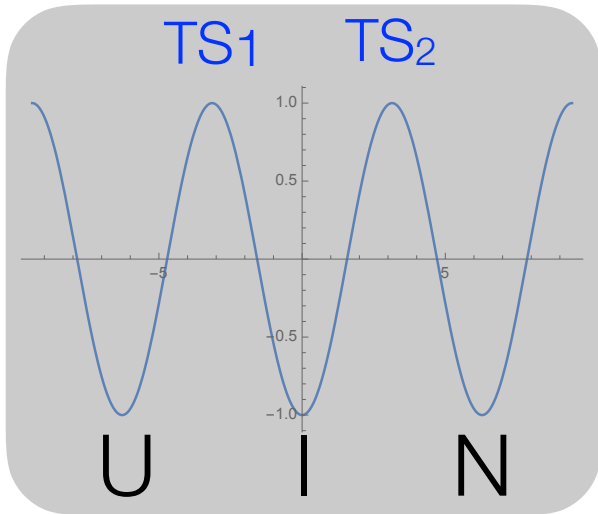
$$\langle \Delta Q(Q_U) \rangle_{rMD} \simeq \langle \Delta Q(Q_{TS_i}) \rangle_{rMD} \simeq \langle \Delta Q(Q_N) \rangle_{rMD} = \sqrt{\frac{D\Delta t}{\pi}} \frac{\xi - 1}{\xi} = 0.0009$$

Second Moment

$$\langle \Delta Q^2(Q) \rangle_{rMD} = D\Delta t \left(1 + \frac{1}{\xi^2}\right) - \frac{2(\xi^2 - 1)}{\sqrt{\pi}\xi^2} \frac{G'(Q)}{k_B T} (D\Delta t)^{3/2} + \dots$$

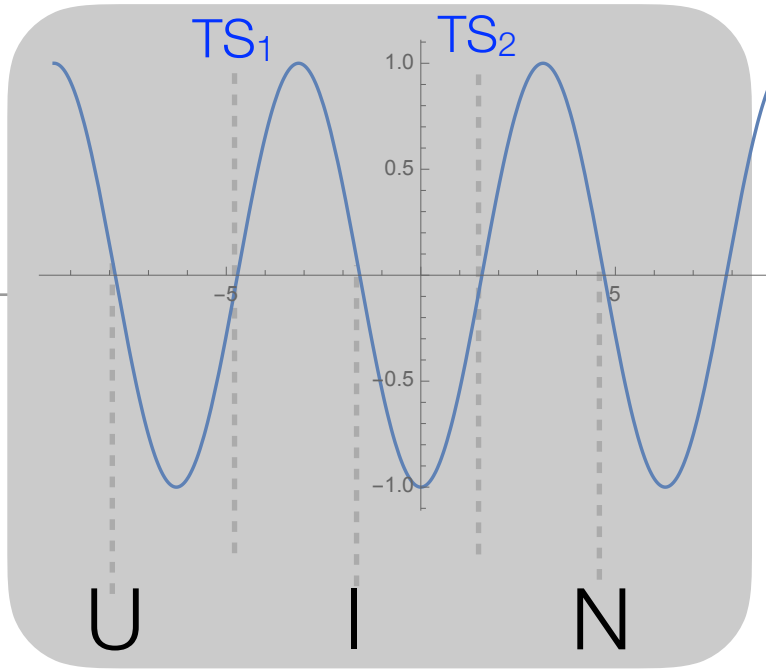
Prediction:

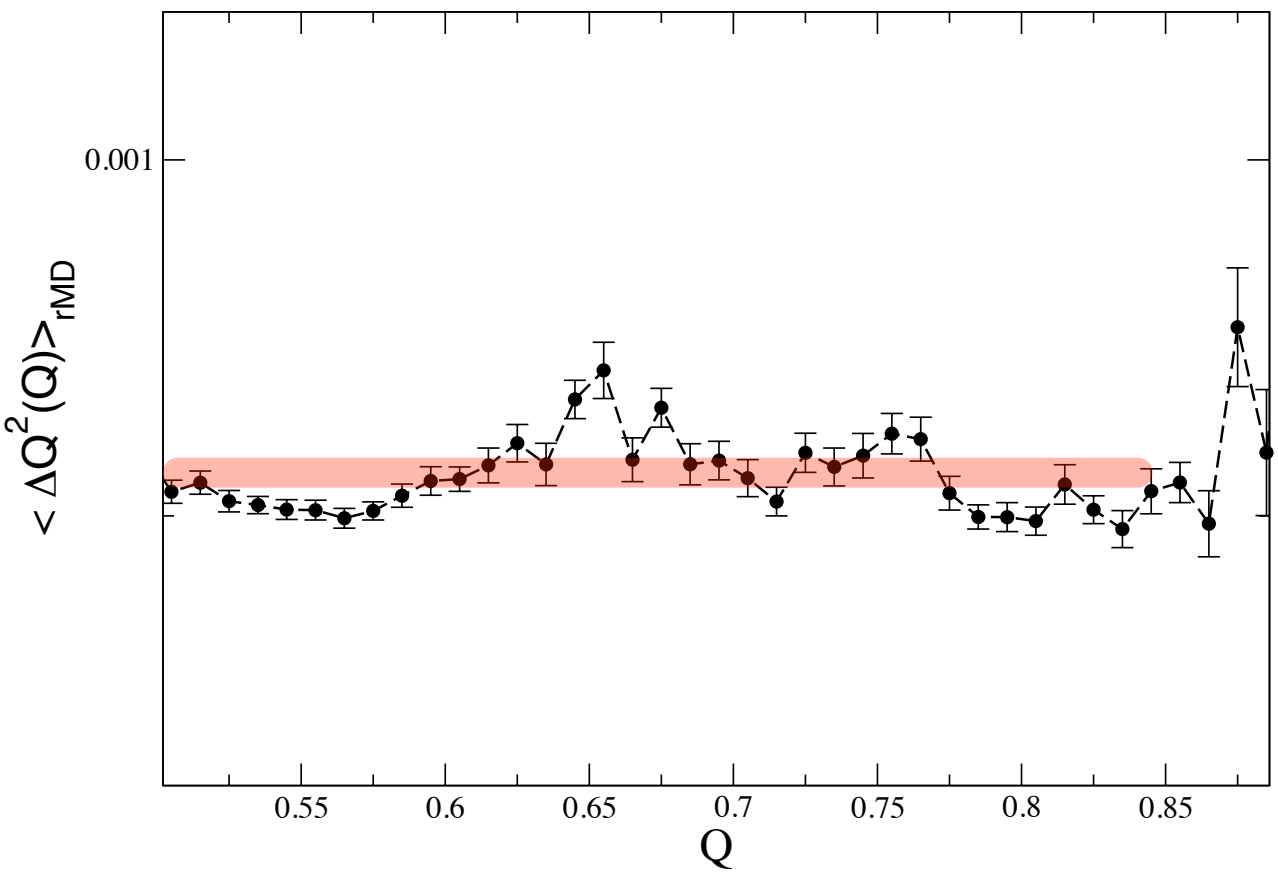




$$\langle \Delta Q^2(Q_U) \rangle_{rMD} \simeq \langle \Delta Q^2(Q_{TS_i}) \rangle_{rMD} \simeq \langle \Delta Q^2(Q_N) \rangle_{rMD} = D\Delta t \frac{\xi^2 + 1}{\xi^2}$$

In realistic rMD simulations





Q_U=0.54

Q_{TS1}=0.64

Q_I=0.71

Q_{TS2}=0.74

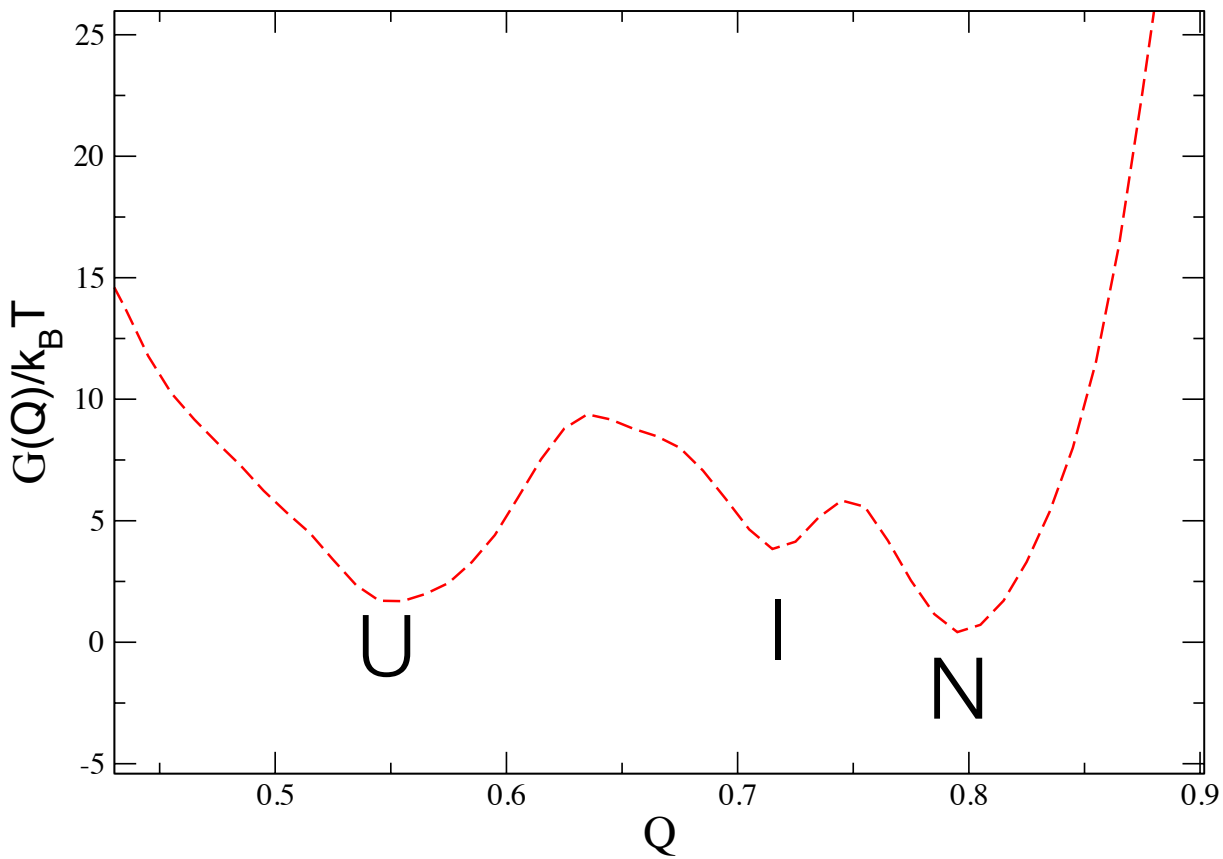
N=0.8

$$\langle \Delta Q^2(Q_U) \rangle_{rMD} \simeq \langle \Delta Q^2(Q_{TS_i}) \rangle_{rMD} \simeq \langle \Delta Q^2(Q_N) \rangle_{rMD} = D\Delta t \frac{\xi^2+1}{\xi^2} = 0.00054$$

Combining the results

Q_U=0.54
Q_{TS1}=0.64
Q_I=0.71
Q_{TS2}=0.74
N=0.8

$$\xi = 1.10$$
$$D\Delta t = 0.0003$$



Implementation in practice: Trotter decomposition

$$1 = \int dQ \int dX \int \left(\prod_{k,s=1,2} \frac{d\phi_{k,s} d\phi^*_{k,s}}{2\pi i} \right) e^{-\sum_{s=1,2} \sum_{l=1} \phi_{1,s} \phi^*_{1,s}} |Q, X, \Phi\rangle \langle Q, X, \Phi|$$

Atomic nuclei, heat-bath variables
in first quantization
(i.e. use coordinates)

Hopping quantum excitation
in second quantization
(i.e. use coherent fields)

Structure of the path integral (PI)

$$\rho_{k_i k_j}(t) = \int \mathcal{D}\phi'^{*}\mathcal{D}\phi' \mathcal{D}Q' \mathcal{D}X' \int \mathcal{D}\phi''^{*}\mathcal{D}\phi'' \mathcal{D}Q'' \mathcal{D}X'' \int \mathcal{D}\tilde{Q}\mathcal{D}\tilde{X}(\ldots)$$

quantum excitation

atomic nuclei

heat-bath variables

quantum excitation

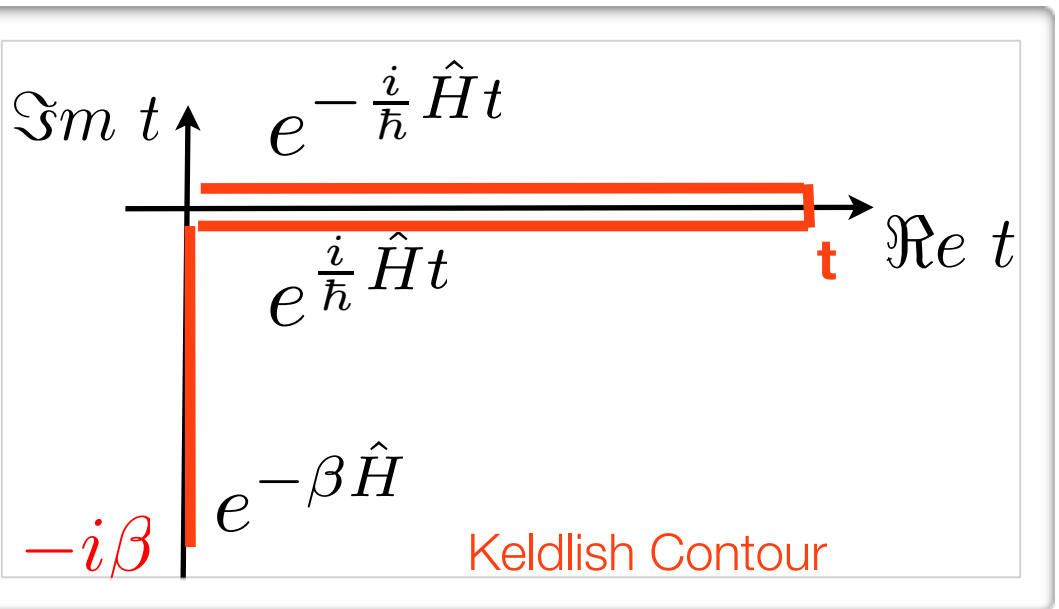
atomic nuclei

heat-bath variables

atomic nuclei

heat-bath variables

Can be carried out analytically (eliminated from the PI)



Explicit form (exact)

The path integral:

$$\rho_{k_i k_j}(t) = \frac{1}{2Z_M(\beta)} \int dQ_f \oint \mathcal{D}\tilde{Q}\, e^{-\beta S_E[\tilde{Q}]} \int_{\tilde{Q}(0)}^{Q_f} \mathcal{D}Q' \int_{Q_f}^{\tilde{Q}(\beta)=\tilde{Q}(0)} \mathcal{D}Q'' \int \mathcal{D}\phi' \mathcal{D}\phi'^* \int \mathcal{D}\phi'' \mathcal{D}\phi''^*$$
$$\times\ e^{-\sum_m \phi'^*_m(0)\phi'_m(0)}\ e^{-\sum_m \phi''^*_m(t)\phi''_m(t)}\ (\phi'_{k_f}(t)\phi'^*_{k_i}(0)\ \phi''^*_{k_f}(t)\phi''_{k_i}(0))\ e^{-\Phi[Q',Q'']}$$
$$\times\ e^{\frac{i}{\hbar}S_{MC}[Q',\phi',\phi'^*]-\frac{i}{\hbar}S_{MC}[Q'',\phi'',\phi''^*]},$$

The functionals:

$$S_E[\tilde{Q}] = \int_0^\beta d\tau\, \frac{M}{2}\dot{\tilde{Q}}^2(\tau) + \int_0^\beta d\tau V[\tilde{Q}(\tau)]$$

$$S_{MC}[Q,\phi,\phi^*] = \int_0^t dt' \frac{M}{2}\dot{Q}^2(t') - \int_0^t dt' \left\{ V[Q(t')] + \sum_m \phi^*_m(t') \left(i\hbar\frac{\partial}{\partial t'}\delta_{mn} - f_{mn}[Q(t')] \right) \phi_m(t') \right\}.$$

$$\Phi[Q',Q''] = \frac{1}{\hbar}\int_0^t dt' \int_{t'}^t dt'' \{(Q'(t') - Q''(t')) \cdot [\mathcal{B}(t'-t'')Q'(t'') - \mathcal{B}^*(t'-t'')Q''(t'')]\}$$
$$+\ i\frac{\bar{\mu}}{2\hbar}\int_0^t dt' \left[Q'^2(t') - Q''^2(t')\right], \qquad \left(\bar{\mu} = \sum_j \frac{c_j^2}{m_j\omega_j^2}\right).$$

coupled evolution of the atomic nuclei and quantum excitations, under the effect of the heat-bath.

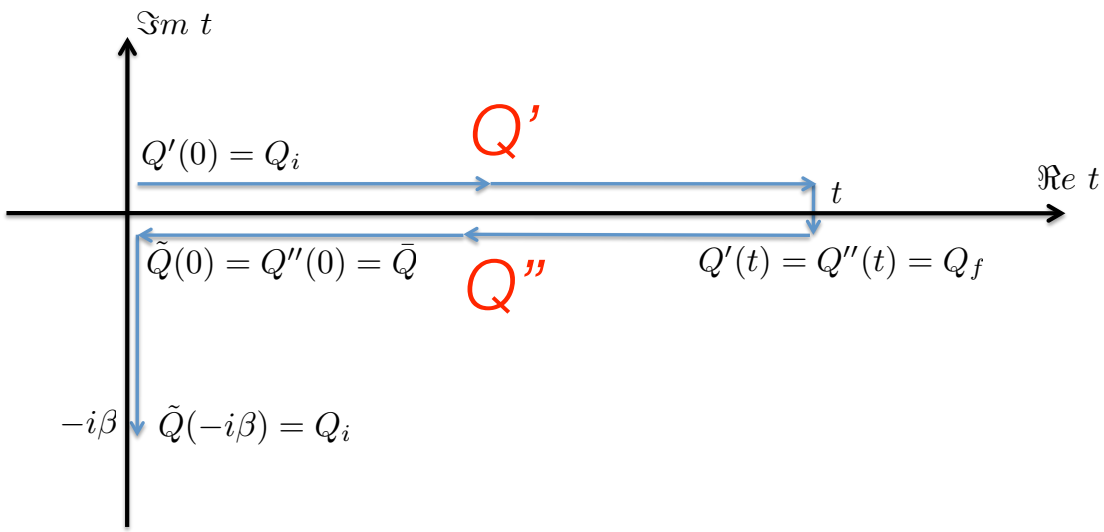
Heat bath Green's function:

$$\mathcal{B}(t) = \sum_j \frac{c_j^2}{m_j\omega_j} \left[\coth\left(\frac{\hbar\omega_j}{2k_BT}\right) \cos(\omega_j t) - i\,\sin(\omega_j t) \right]$$

"memory" effects in the interaction with heat-bath

Now make two approximations:

1. The dynamics of the atomic nuclei is classical:



$$R \equiv \frac{1}{2}\left(Q^{'} + Q^{''}\right)$$
$$y \equiv Q^{'} - Q^{''}$$

classical limit

$$R(t) \gg y(t)$$

expand to order $o(y^2)$

perform $\int \mathcal{D}y$

$$P(Q_f, k_f, t|Q_i, k_i) = \int_{Q_i}^{Q_f} \mathcal{D}R \int \mathcal{D}\phi^{'*}\mathcal{D}\phi^{'} \int \mathcal{D}\phi^{''*}\mathcal{D}\phi^{''} \left(\ldots\right)$$

Now make two approximations:

2. The heat-bath quickly looses its “memory”

delta-correlated white noise

$$\mathcal{B}(t) \to \mathcal{B}^{ohm}(t) = \frac{2k_B T M\gamma}{\hbar}\delta(t) + \frac{i\ M\gamma}{2}\ \frac{d}{dt}\delta(t),$$

fluctuation-dissipation relationship

The molecule ultimately attains thermal equilibrium

Molecular dynamics of atomic nuclei => Langevin dynamics

The goal of our work:

To develop a rigorous **microscopic** approach in which the conformational and quantum transport dynamics are consistently obtained "botton-up" from the same **quantum density matrix**

payoffs

- It is possible to derive analytic approaches to quantum transport (Feynman diagrams)

- it is possible to derive a very accurate variational approximation for rare event problems

- The Renormalization Group (RG) offers the rigorous framework for varying the model resolutions

OBSERVATION: the path integral is very general!

$$\int \mathcal{D}R \int \mathcal{D}\bar{\psi}\mathcal{D}\psi \; e^{iS_0[\bar{\psi},\psi]} \times e^{-S_{OM}[R,\bar{\psi},\psi]} \times e^{iI[R,\bar{\psi},\psi]}$$

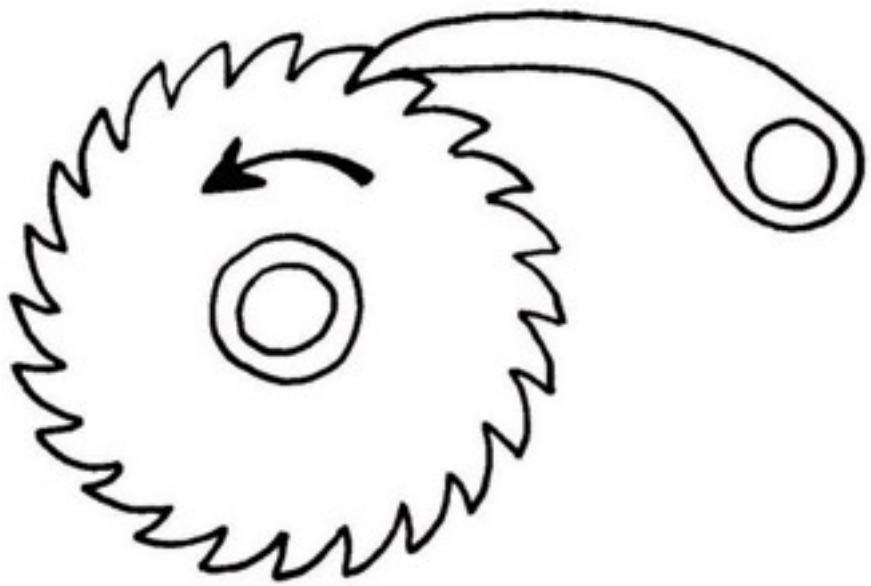
For $R = R_0 + \delta r$ it describes a exciton-phonon system

Electrons in ground-state it describes MD

NB: All coupling constants can be microscopically determined from quantum chemistry calculations (overlap integrals)

GENERATION OF THE FOLDING PATHWAYS

- *ratchet-and-pawl* MD



Camilloni et al., 2011

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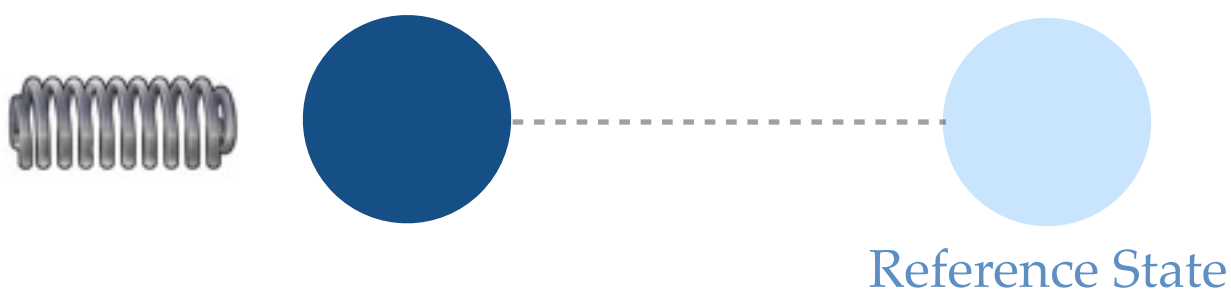

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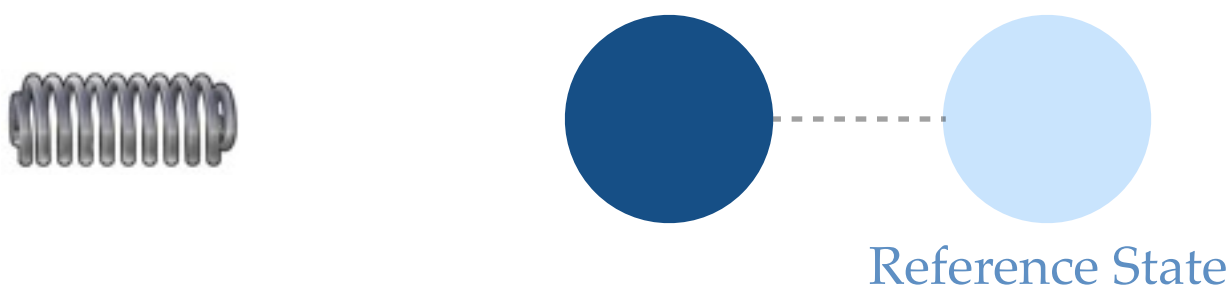


Camilloni et al., 2011

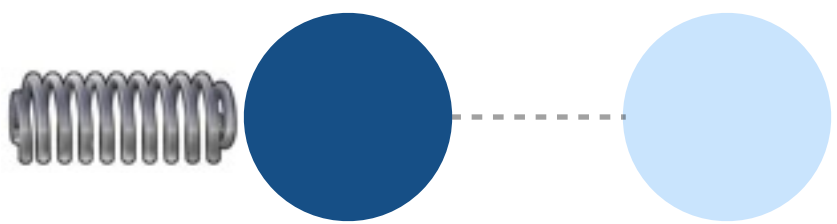
GENERATION OF THE FOLDING PATHWAYS

- *ratchet-and-pawl* MD

$$\text{Bias potential} = k_r(Z - Z_m)^2$$

Z_m = Minimum value obtained by Z up to time

k_r = ratchet spring constant



Reference State

Camilloni et al., 2011

GENERATION OF THE FOLDING PATHWAYS

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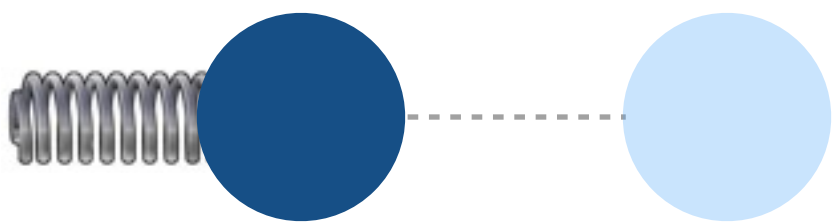
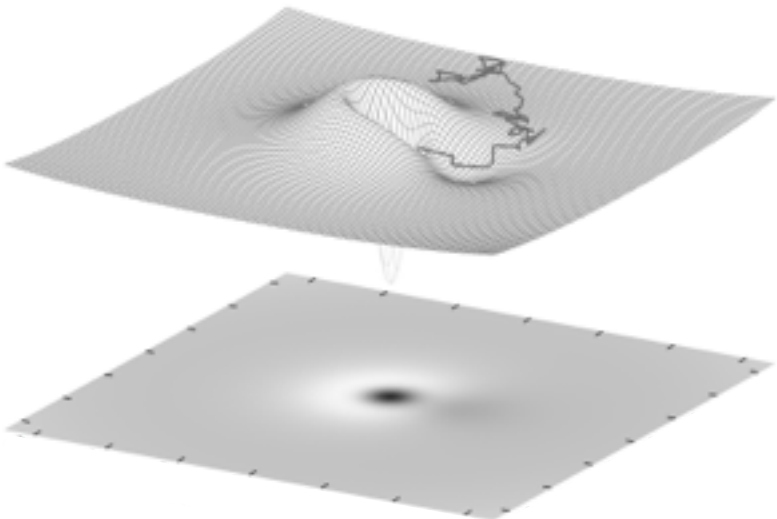


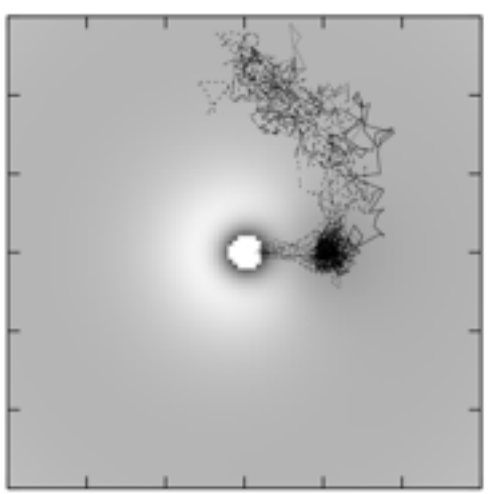
Camilloni et al., 2011

CAN WE TRUST THE *BIAS FUNCTIONAL*?

Validation on a toy model

S a Beccara *et al.*, 2015





Unbiased MD

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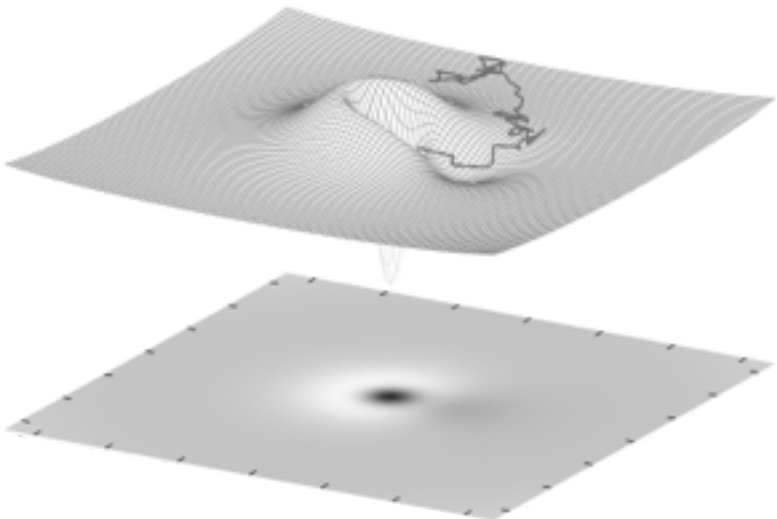
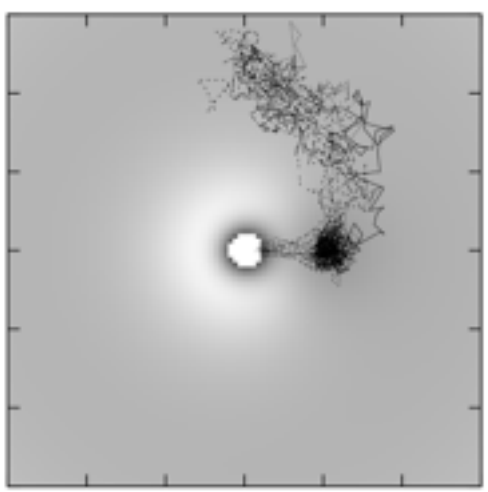
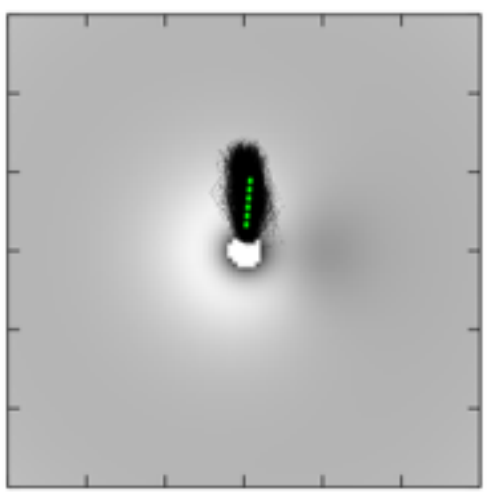




Unbiased MD



Steered MD

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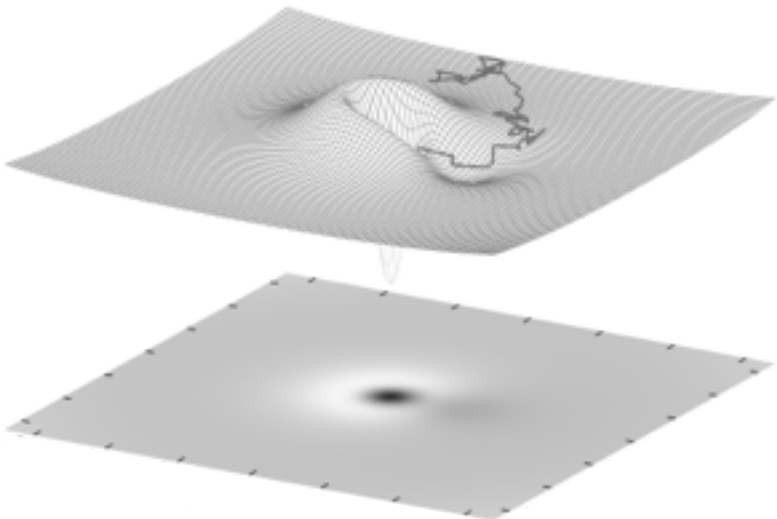

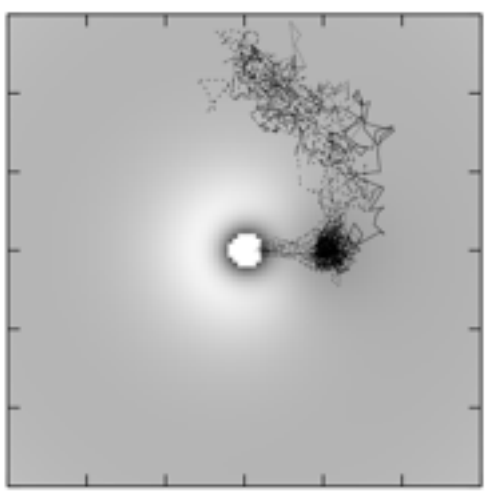

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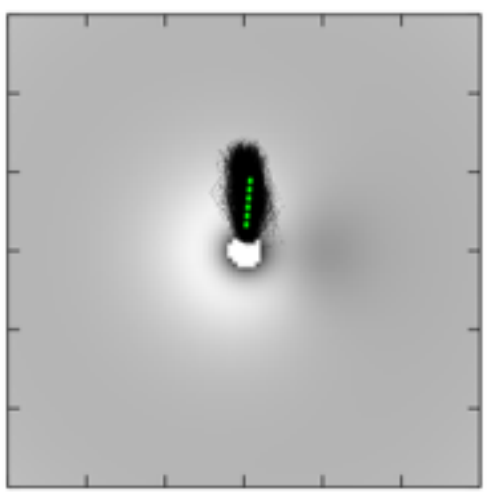
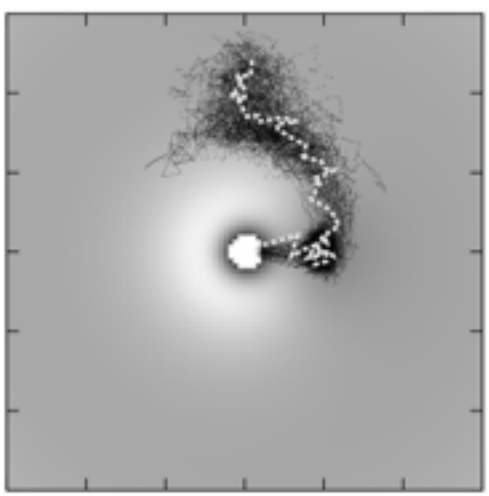


Steered MD



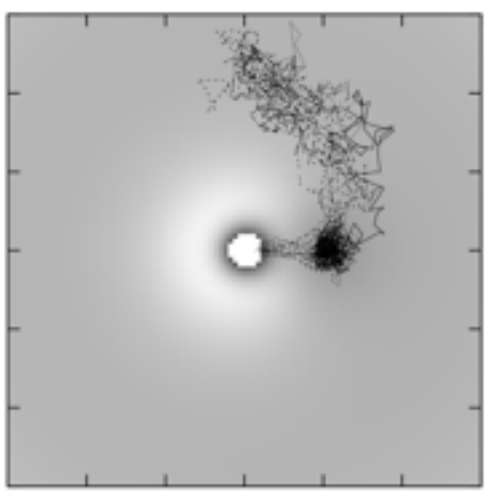
Bias Functional

CAN WE TRUST THE *BIAS FUNCTIONAL*?

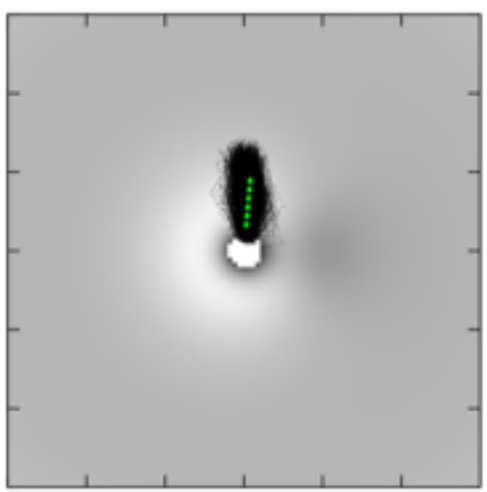
Validation on a toy model

S a Beccara *et al.*, 2015

- *Bias Functional* is consistent on a toy model



Unbiased MD



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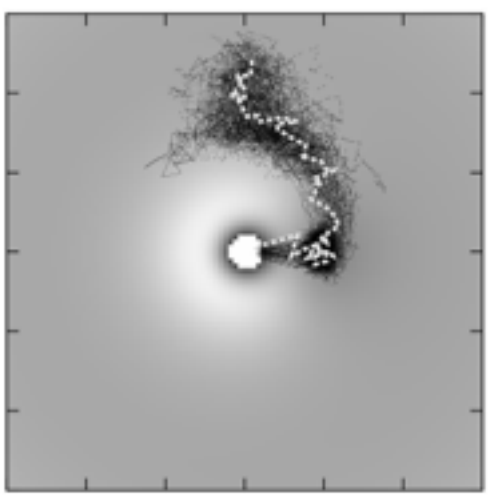
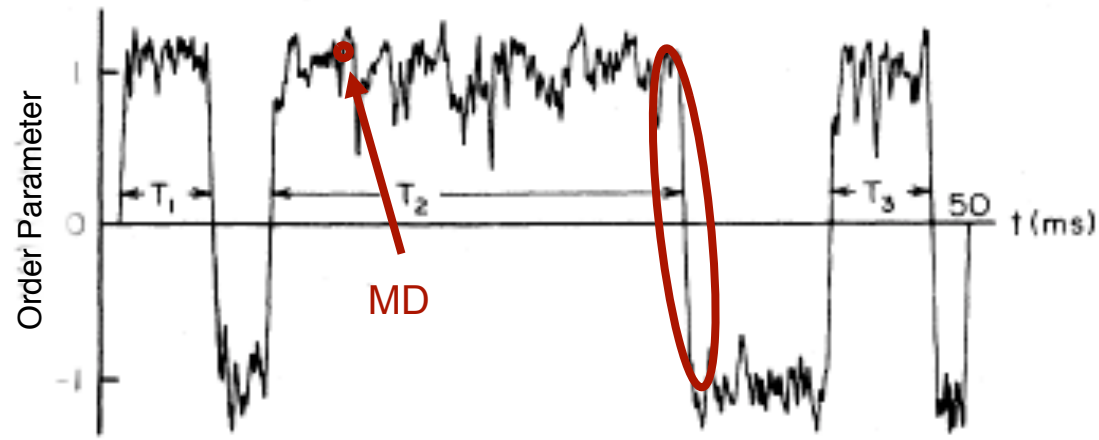


Bias Functional

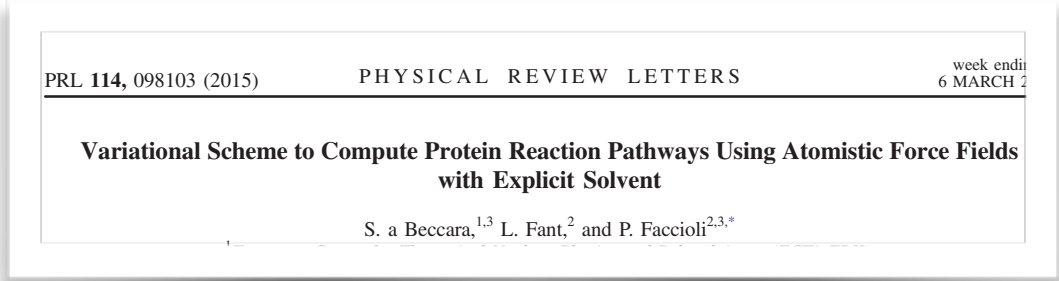
PI enable to focus on the reactive part!



Main difference with respect to instantons in QCD:
here the real challenge is finding the instantons.
Naive “cooling” is not useful: insufficient exploration of the path space

Variational Scheme to the Stochastic Path Integral

(similar to 84's Dyakonov and Petrov's paper)


PRL 114, 098103 (2015) PHYSICAL REVIEW LETTERS week endi 6 MARCH 2

Variational Scheme to Compute Protein Reaction Pathways Using Atomistic Force Fields with Explicit Solvent

S. a Beccara,[1,3] L. Fant,[2] and P. Faccioli[2,3,*]

Step 1: define a new biased stoch. dynamics -> new trial path integral

$$m_i\ddot{\mathbf{x}}_i = -m_i\gamma_i\dot{\mathbf{x}}_i - \nabla_i U + \eta_i(t) + \mathbf{F}_B(x,t) \qquad P_{trial}[\bar{X}] = \mathcal{N}\ e^{-S_{trial}[\bar{X}]}$$

(biased stochastic dynamics which encourages to reach the target)

Step 2: Use reweighting and Feynmann-Kac inequality:

$$P_{R\to P}(t) = P^{trial}_{R\to P}[\bar{X};t]\ \langle e^{-(S_{OM}-S_{trial})}\rangle_{trial} \geq P^{trial}_{R\to P}[\bar{X},t]\ e^{-\langle S_{OM}-S_{trial}\rangle_{trial}}$$

Step 3: Find the most probable trial path

$$\frac{\delta}{\delta \bar{X}} P_{R\to P}[\bar{X};t] = 0 \quad \Longrightarrow \quad 0 = \frac{\delta}{\delta \bar{X}} \left(P^{trial}_{R\to P}[\bar{X},t] \, \langle e^{-(S_{eff}-S_{trial})} \rangle_{trial} \right)$$

$$\frac{\delta}{\delta \bar{X}} \int_0^t |\mathbf{F}_{bias}[\bar{X},t]|^2$$

Bias Functional

optimal trial paths: highest probability to occur without a bias

Variational Scheme to the Stochastic Path Integral

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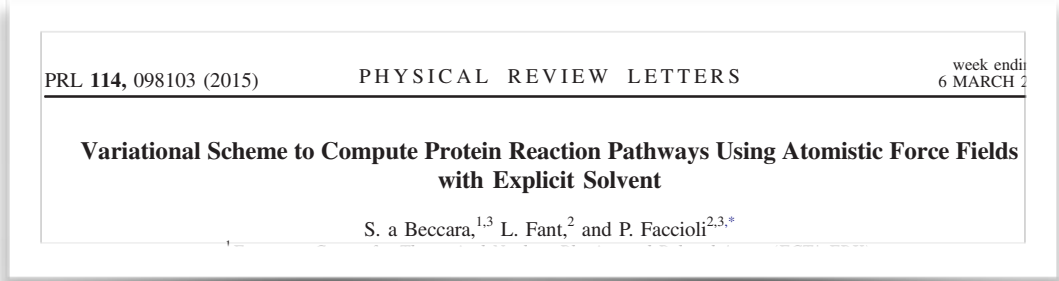
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Bias Functional

optimal trial paths: highest probability to occur without a bias