Molecular dynamics
by applied mathematicians

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Presentation of the institutions at play

- **CERMICS: Applied mathematics laboratory of Ecole des Ponts**
  - 20 permanent members (14 HdR)
  - about 30 PhD students and 10 postdocs
  - research directions:
    - applied probability
    - modeling, analysis and simulation
    - optimization and operations research

- **MATHERIALS: project-team of Inria Paris**
  - 8 permanent researchers
  - strong overlap with CERMICS
  - analysis and development of simulation methods for multiscale models (incl. stochastic homogenization) and molecular simulations (quantum/classical)
What can (and cannot) applied mathematics do?

We, applied mathematicians...

- work on simplified models (one dimensional reaction coordinates, overdamped Langevin dynamics, etc) → this make us look like fools...
- exaggerate sources of errors (for instance by considering situations which rarely happen in practice) → this makes us insufferable

...but the aim is to

- rigorously understand why some methods work and some don’t (mathematical proofs)
- devise new numerical strategies based on this theoretical understanding
- validate them on toy examples
- transfer the knowledge to practitionners by helping them to implement the methods into their own codes
Computational Statistical Physics

- *Predict macroscopic properties of materials from their microscopic description*

- **Microstate**
  - positions $q = (q_1, \ldots, q_N)$ and momenta $p = (p_1, \ldots, p_N)$
  - energy of the system $H(q, p) = V(q) + \sum_{i=1}^{N} \frac{p_i^2}{2m_i}$
  - (almost) all the physics is in the choice of $V$...

- **Macrostate**
  - described by a probability measure $\mu$
  - constraints fixed exactly or in average (number of particles, volume, energy)

- **Properties:** static (equation of state, heat capacities, etc) and dynamical (transport coefficient, transition pathway, etc)
Examples of molecular systems (1)

Ubiquitin (protein): structure? conformational changes?
→ In silico drug design
Examples of molecular systems (2)

What is the **melting temperature** of Argon?

(a) Solid Argon (low temperature)  
(b) Liquid Argon (high temperature)
Examples of molecular systems (3)

Equation of state of Argon: density as a function of pressure, $T = 300$ K (comparison with data of National Institute of Standards and Technology)

Explore extreme conditions of matter...
Some orders of magnitude...

- **Physical quantities**
  - distances $\sim 1 \, \text{Å} = 10^{-10} \, \text{m}$
  - energy per particle $\sim k_B T \sim 4 \times 10^{-21} \, \text{J at 300 K}$
  - atomic masses $\sim 10^{-26} \, \text{kg}$
  - typical times $\sim 10^{-15} \, \text{s}$
  - number of particles $\sim N_A = 6.02 \times 10^{23}$

- **“Standard” simulations**
  - $10^6$ particles [“heroic”: $10^9$ particles and more]
  - total time: (fraction of) ns [“heroic”: (fraction of) µs]

- **Analogy** to understand what such large numbers represent...
  - about $10^{22}$ moles of water on Earth
  - $10^6$ moles of water $\sim 1 \, \text{m}^3$
Aims of computational statistical physics

- “Numerical microscope”
  - gaining some insight into physical mechanisms at the atomic scale
  - From the press release for the Nobel prize in Chemistry 2013 (Karplus/Levitt/Warshel)

  *Today the computer is just as important a tool for chemists as the test tube. Simulations are so realistic that they predict the outcome of traditional experiments.*

- Computation of average properties (static)

  $$\langle A \rangle = \int_{\mathcal{E}} A(q, p) \, \mu(dq \, dp)$$

  Computation of high dimensional integrals
  - $\mu$ is a probability measure
  - $A$ is the observable
Outline

• Computation of average properties (free energy, error estimation)
• Computation of transport coefficients
• Sampling reactive trajectories

Main message

A careful construction of the numerical method can reduce both systematic and statistical errors

Note: takes a lot of time to understand hence improve numerical methods in molecular dynamics [and the impetus comes from various channels...]

Computation of average properties
Free energy computations (1)

- Canonical distribution \( \mu(dq \, dp) = Z^{-1} e^{-\beta H(q,p)} \, dq \, dp \)

- For a given reaction coordinate \( \xi(q) \), compute the function

\[
F(z) = \int_{\xi^{-1}\{z\}} e^{-\beta H(q,p)} \delta_{\xi(q) = z}(dq)
\]

Thermodynamic integration, free energy perturbation, nonequilibrium techniques, adaptive methods (ABF, *-metadynamics, ...)

- ABF in the simplest case \( \xi(q) = q_1 \)

\[
\begin{cases}
dq_t = -\nabla \left( V - F_t \circ \xi \right)(q_t) \, dt + \sqrt{2\beta^{-1}} \, dW_t, \\
F'_t(z) = \mathbb{E} \left( f(q_t) \bigg| \xi(q_t) = z \right)
\end{cases}
\]
Free energy computations (2)

- **Our contributions for ABF include:**
  - a theoretical understanding of the improved convergence rate compared to unbiased dynamics (entropy methods)
  - improvements of the simulation methods: use of *replicas* and *selection* (implemented in NAMD)
  - multidimensional reaction coordinate case: projecting the current estimated mean force onto a gradient

- **Other results for adaptive dynamics:**
  - convergence of *Wang-Landau* type dynamics (including Self-Healing Umbrella Sampling and Well-Tempered metadynamics)
  - suggestion of modifications in the methods to improve convergence rates (e.g. allow for larger steps in the free energy update for WTM)

- **Also results for other types of dynamics/methods:**
  - constraints (overdamped/underdamped, TI, Jarzynski–Crooks, etc)
  - temperature accelerated molecular dynamics
Finding good reaction coordinates

• Reaction coordinates are often chosen based on chemical intuition

• Use **machine learning techniques** to automatically find RC?
  - supervised techniques (known metastable conformations)
  - unsupervised techniques (autoencoders, tICA/EDMD, etc)

PhD thesis started in November in collaboration with Sanofi
Errors on average properties (1)

- Errors due to **timestep discretization**?

- Positions \( q \in \mathcal{D} = (LT)^d \) or \( \mathbb{R}^d \) and momenta \( p \in \mathbb{R}^d \)
  \( \rightarrow \) phase-space \( \mathcal{E} = \mathcal{D} \times \mathbb{R}^d \)

- **Hamiltonian** (more general kinetic energies \( U(p) \) can be considered\(^1\))

\[
H(q, p) = V(q) + \frac{1}{2} p^T M^{-1} p
\]

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Stochastic perturbation of the Hamiltonian dynamics

\[
\begin{align*}
    dq_t &= M^{-1} p_t \, dt \\
    dp_t &= -\nabla V(q_t) \, dt - \gamma M^{-1} p_t \, dt + \sqrt{\frac{2\gamma}{\beta}} \, dW_t
\end{align*}
\]

- **Friction** \( \gamma > 0 \) and inverse temperature \( \beta = \frac{1}{k_B T} \)

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Errors on average properties (2)

• Decompose the dynamics in three parts as

\[
\begin{align*}
(A) & \quad \begin{cases} 
 dq_t = M^{-1}p_t \, dt, \\
 dp_t = 0, 
\end{cases} \\
(B) & \quad \begin{cases} 
 dq_t = 0, \\
 dp_t = -\nabla V(q_t) \, dt, 
\end{cases} \\
(C) & \quad \begin{cases} 
 dq_t = 0, \\
 dp_t = -M^{-1}p_t \, dt + \sqrt{\frac{2}{\beta}} \, dW_t.
\end{cases}
\end{align*}
\]

• First order splitting schemes: Trotter splitting

\[
P_{\Delta t}^{ZYX} = e^{\Delta tZ} e^{\Delta tY} e^{\Delta tX} \approx e^{\Delta t(A+B+\gamma C)}
\]

• Second order schemes: Strang splitting

\[
P_{\Delta t}^{ZYXYZ} = e^{\Delta tZ/2} e^{\Delta tY/2} e^{\Delta tX} e^{\Delta tY/2} e^{\Delta tZ/2}
\]

• Other category: Geometric Langevin algorithms, e.g. \( P_{\Delta t}^{\gamma C,A,B,A} \)
Errors on average properties (3)

- $P_{\Delta t}^{B,A,\gamma C}$ corresponds to

\[
\begin{align*}
\bar{p}_{n+1}^{} &= p_{n}^{} - \nabla V(q_{n}^{}) \Delta t, \\
q_{n+1}^{} &= q_{n}^{} + \Delta t \, M^{-1} \bar{p}_{n+1}^{}, \\
p_{n+1}^{} &= \alpha_{\Delta t} \bar{p}_{n+1}^{} + \sqrt{\frac{1 - \alpha_{\Delta t}^2}{\beta}} \, M \, G_{n}^{}
\end{align*}
\]

where $G_{n}^{}$ are i.i.d. Gaussian and $\alpha_{\Delta t} = \exp(-\gamma M^{-1} \Delta t)$

- $P_{\Delta t}^{\gamma C,B_{n},A,B_{n},\gamma C}$ for

\[
\begin{align*}
\bar{p}_{n+1/2}^{} &= \alpha_{\Delta t/2} p_{n}^{} + \sqrt{\frac{1 - \alpha_{\Delta t}}{\beta}} \, M \, G_{n}^{}, \\
p_{n+1/2}^{} &= \bar{p}_{n+1/2}^{} - \frac{\Delta t}{2} \nabla V(q_{n}^{}), \\
q_{n+1}^{} &= q_{n}^{} + \Delta t \, M^{-1} \, p_{n+1/2}^{}, \\
\bar{p}_{n+1}^{} &= p_{n+1/2}^{} - \frac{\Delta t}{2} \nabla V(q_{n+1}^{}), \\
p_{n+1}^{} &= \alpha_{\Delta t/2} \bar{p}_{n+1}^{} + \sqrt{\frac{1 - \alpha_{\Delta t}}{\beta}} \, M \, G_{n+1/2}^{}.
\end{align*}
\]
Errors on average properties (4)

- **Invariant measure** $\mu_{\gamma, \Delta t}$ different from $\mu$

Error estimates on the bias

\[ \int_{\mathcal{E}} \varphi \, d\mu_{\gamma, \Delta t} = \int_{\mathcal{E}} \varphi \left( 1 + \Delta t^p f_\gamma \right) d\mu + O(\Delta t^{p+1}) \]

with

- $p = 1$ for Trotter splitting
- $p = 2$ for Strang splitting and GLA

- **Various asymptotic results** in the Hamiltonian limit $\gamma \to 0$ or in the overdamped limit $\gamma \to +\infty$
- e.g. understanding why the BAOAB scheme is much better than other discretizations of Brownian dynamics

Computation of transport coefficients
Computation of transport coefficients

- Thermal conductivity, shear viscosity, etc: takes a lot of time to estimate (possibly several months)

- **Green-Kubo formulas**: integrated correlation functions

### Effective diffusion at equilibrium

Unperiodized displacement $Q_t - Q_0 = \int_0^t M^{-1} p_s \, ds$

$$D = \lim_{t \to +\infty} \frac{\mathbb{E} \left[ (Q_t - Q_0) \otimes (Q_t - Q_0) \right]}{2t} = \int_0^{+\infty} \mathbb{E}_0 \left[ M^{-1} p_t \otimes M^{-1} p_0 \right] \, dt$$

- Alternatively: linear response of steady-state nonequilibrium dynamics

### Issues/questions:
- **bias** due to discretization in time
- **variance** reduction (in progress)
Results in 1D for $\varphi = \psi = V'$ and cosine potential
Sampling
reactive trajectories
Sampling reactive trajectories (1)

- **Motivation:** Unbinding of a ligand from a protein

- **Challenge:** bridge the gap between timescales
  - Elementary time-step for the molecular dynamics $= 10^{-15}$ s
  - Dissociation time $\simeq 0.02$ s
Sampling reactive trajectories (2)

- **Mathematical setting: rare event computation**
  - Stochastic process \((X_t)_{t \geq 0}\), stopping times \(\tau_A\) and \(\tau_B\)
  - Aim: simulate and compute the very small probability \(\mathbb{P}(\tau_B < \tau_A)\)
  - Here sets \(A\) and \(B\) defined as metastable states (bound/unbound)

- **Splitting technique:** find intermediate events easier to simulate

\[
\{\tau_{z_1} < \tau_A\} \supset \{\tau_{z_2} < \tau_A\} \supset \ldots \supset \{\tau_{z_{\text{max}}} < \tau_A\} \supset \{\tau_B < \tau_A\}
\]

and simulate the successive **conditional events:** for \(k = 1, 2, \ldots\),

\[
\{\tau_{z_q} < \tau_A\} \quad \text{knowing that} \quad \{\tau_{z_{q-1}} < \tau_A\}
\]

where \(\tau_z = \inf\{t, \xi(X_t) > z\}\) for good importance function \(\xi \in \mathbb{R}\).

- **Adaptive feature:** build the intermediate levels \((z_i)_{i \geq 1}\) on the fly \(\rightarrow\) Adaptive Multilevel Splitting algorithm (C´erou/Guyader, 2007)
Schematic illustration of the AMS Algorithm
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Sampling reactive trajectories (3)

- In collaboration with the group of K. Schulten (C. Mayne and I. Teo), AMS is currently implemented in the NAMD code.

- **Unbinding event of benzamidine from trypsin:**
  - MD setup: about 70,000 atoms, CHARMM36 force field, NPT conditions (298 K)
  - Estimated dissociation rate: $k_{\text{off}} = (260 \pm 240) \text{s}^{-1}$ which is in the same order of magnitude as the experimental rate $(600 \pm 300) \text{s}^{-1}$
  - Overall simulation time: 2.3 $\mu$s which is 4 orders of magnitude shorter than the estimated dissociation time