Towards more efficient molecular simulations

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Presentation of the institutions at play

- **CERMICS: Applied mathematics laboratory of Ecole des Ponts**
  - 18 permanent members (16 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) $\rightarrow$ this make us look like fools...
- exaggerate sources of errors (for instance by considering situations which rarely happen in practice) $\rightarrow$ 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

Free energy computations (1)

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

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

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

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

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

$$\left\{\begin{array}{c} dq_t = -\nabla\Big(V - F_t \circ \xi\Big)(q_t)\,dt + \sqrt{2\beta^{-1}}\,dW_t, \\ F_t'(z) = \mathbb{E}\left(f(q_t)\,\middle|\,\xi(q_t) = z\right) \end{array}\right\}$$

Free energy computations (2)

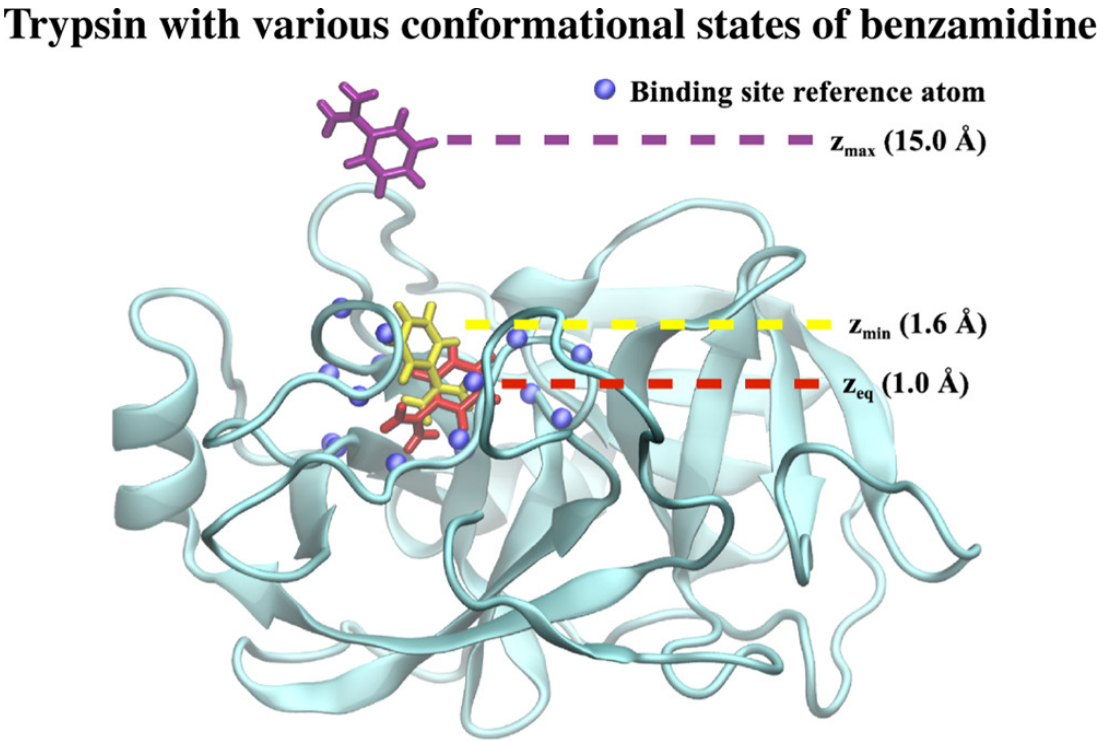
- **Our contributions for ABF include:**
  - a theoretical understanding of the improved convergence rate compared to unbiased dynamics (entropy methods)
  - improvements of the simulation methods: use of replicas and selection (implemented in NAMD)
  - multidimensional reaction coordinate case: projecting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

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 $= 10^{-15}\,\mathrm{s}$
  - Dissociation time $\simeq 0.02\,\mathrm{s}$

Sampling reactive trajectories (2)

- **Mathematical setting: rare event computation**
  - Stochastic process $(X_t)_{t\geq 0}$, stopping times τ_A and τ_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

$$\{\tau_{z_1} < \tau_A\} \supset \{\tau_{z_2} < \tau_A\} \supset \ldots \supset \{\tau_{z_{\max}} < \tau_A\} \supset \{\tau_B < \tau_A\}$$

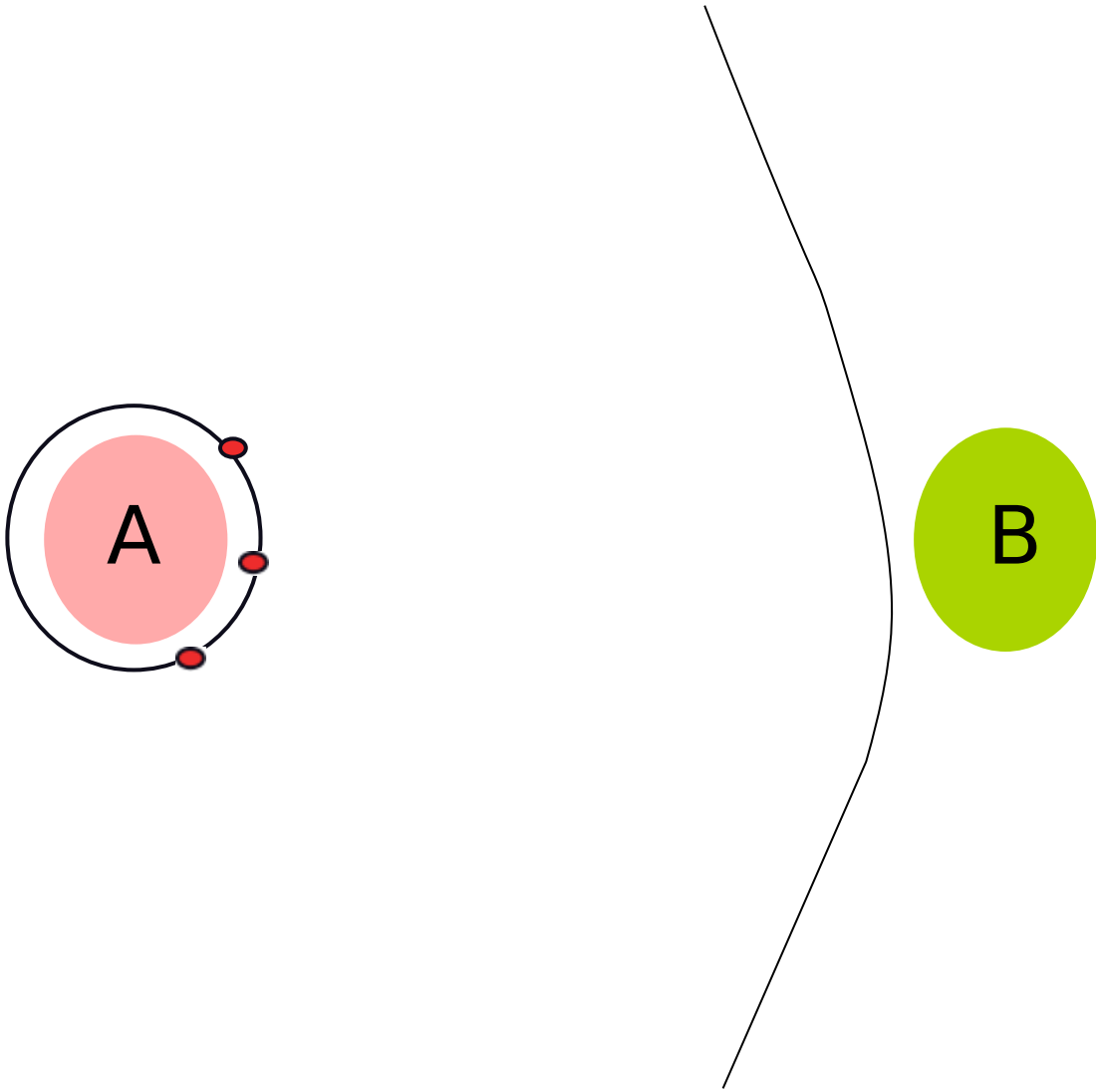
and simulate the successive conditional events: for $k = 1, 2, \ldots,$

$$\{\tau_{z_q} < \tau_A\} \text{ knowing that } \{\tau_{z_{q-1}} < \tau_A\}$$

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 (Cérou/Guyader, 2007)

Schematic illusration of the AMS Algorithm



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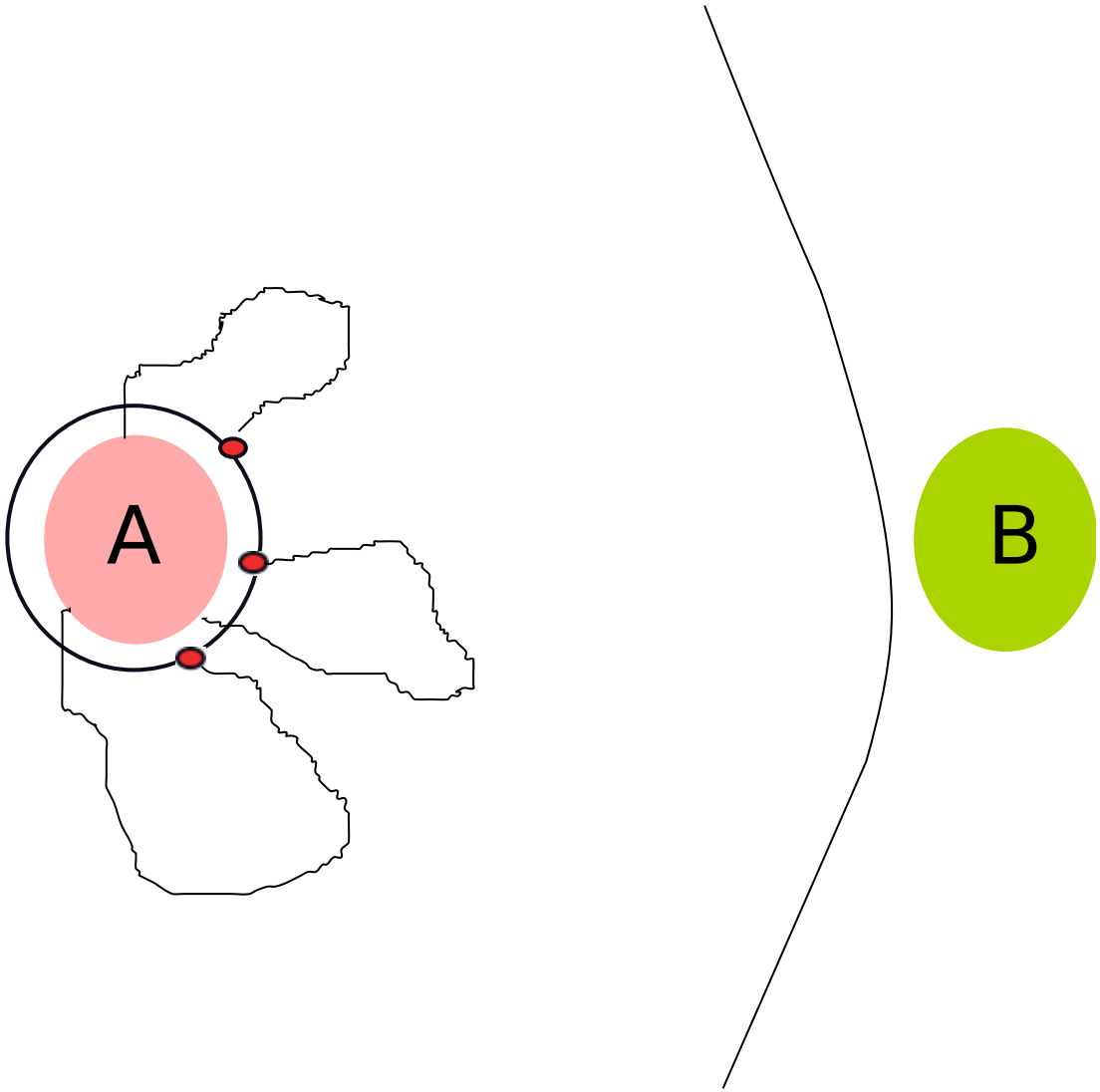

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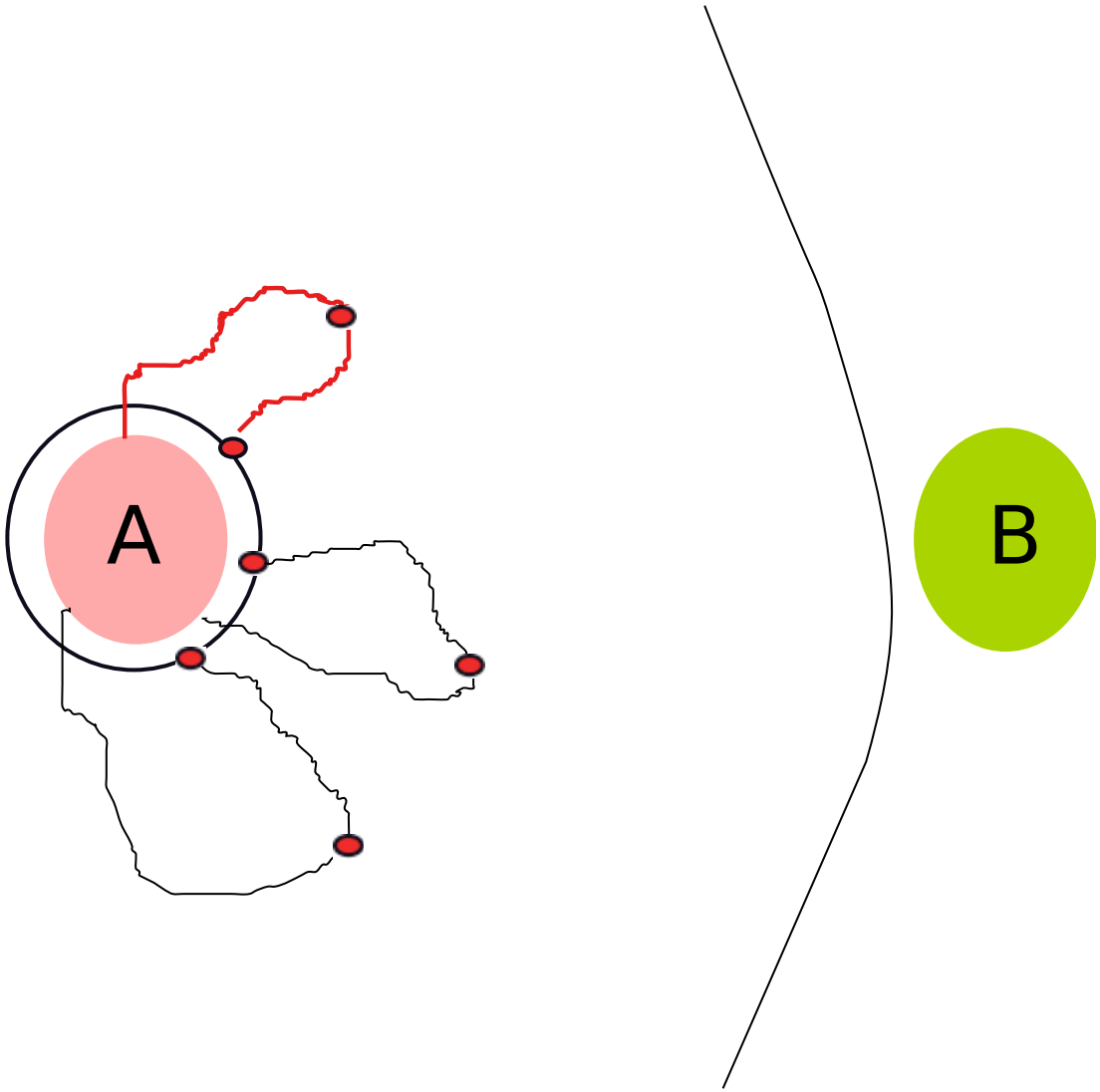

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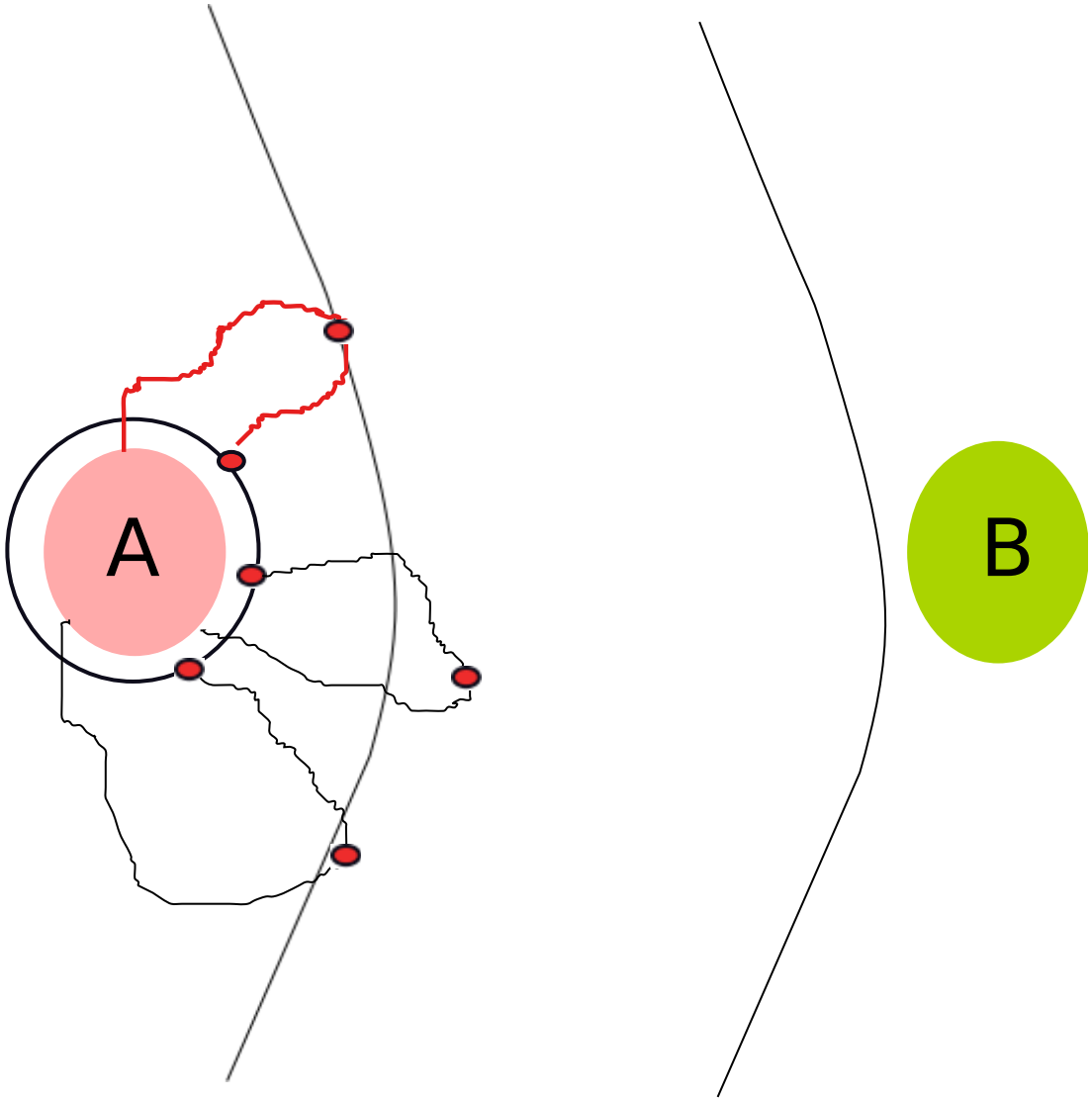

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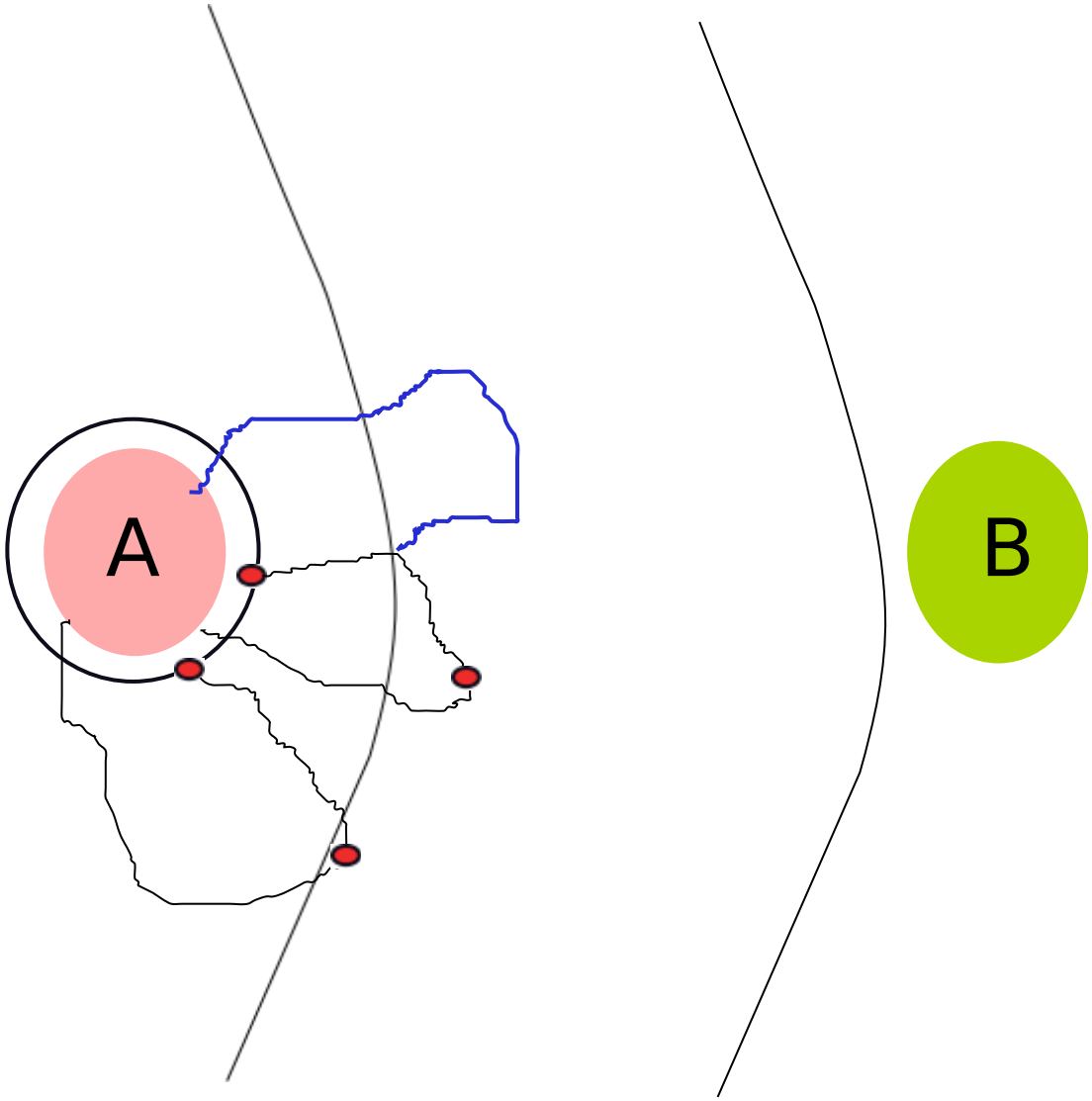

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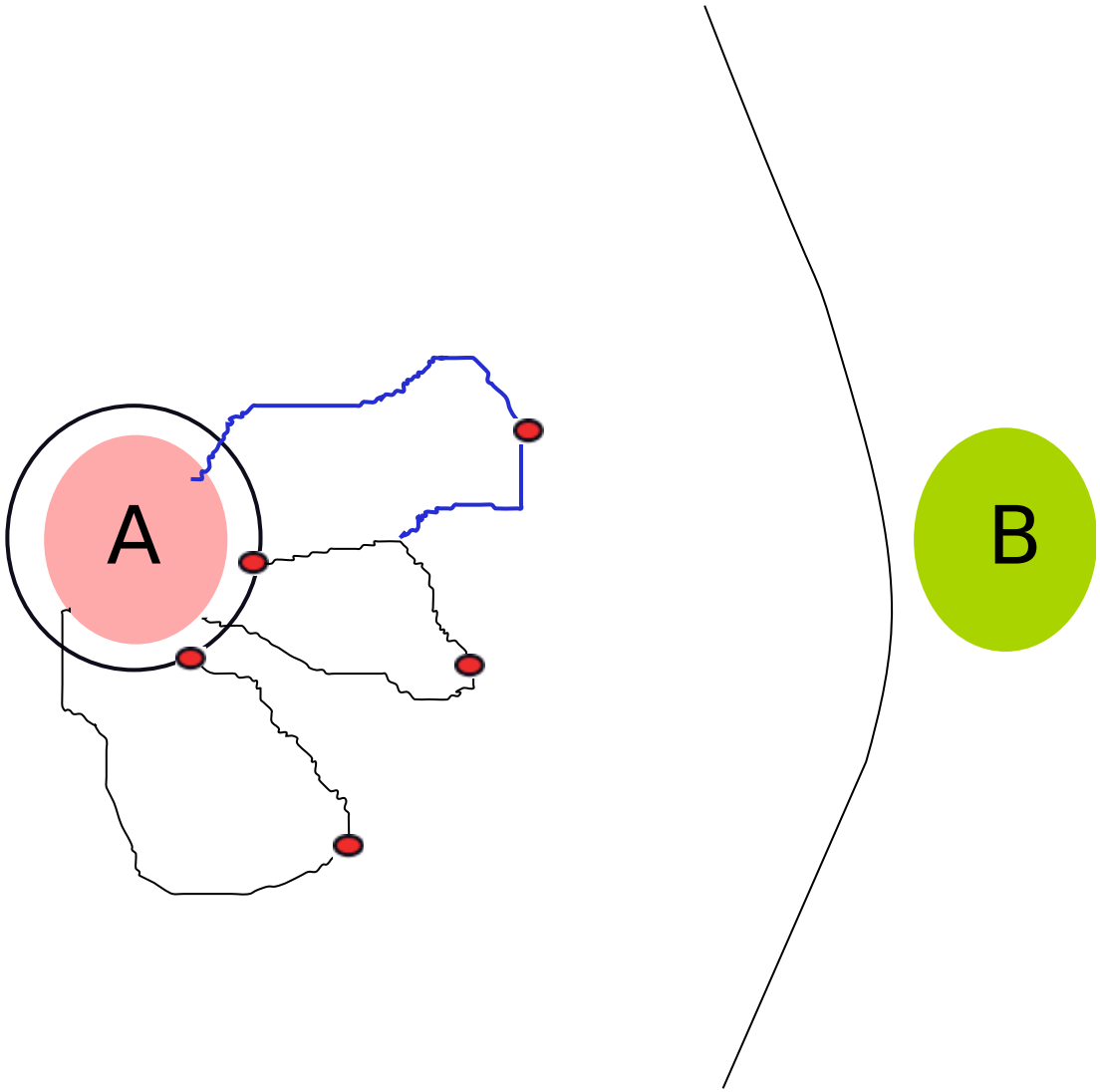

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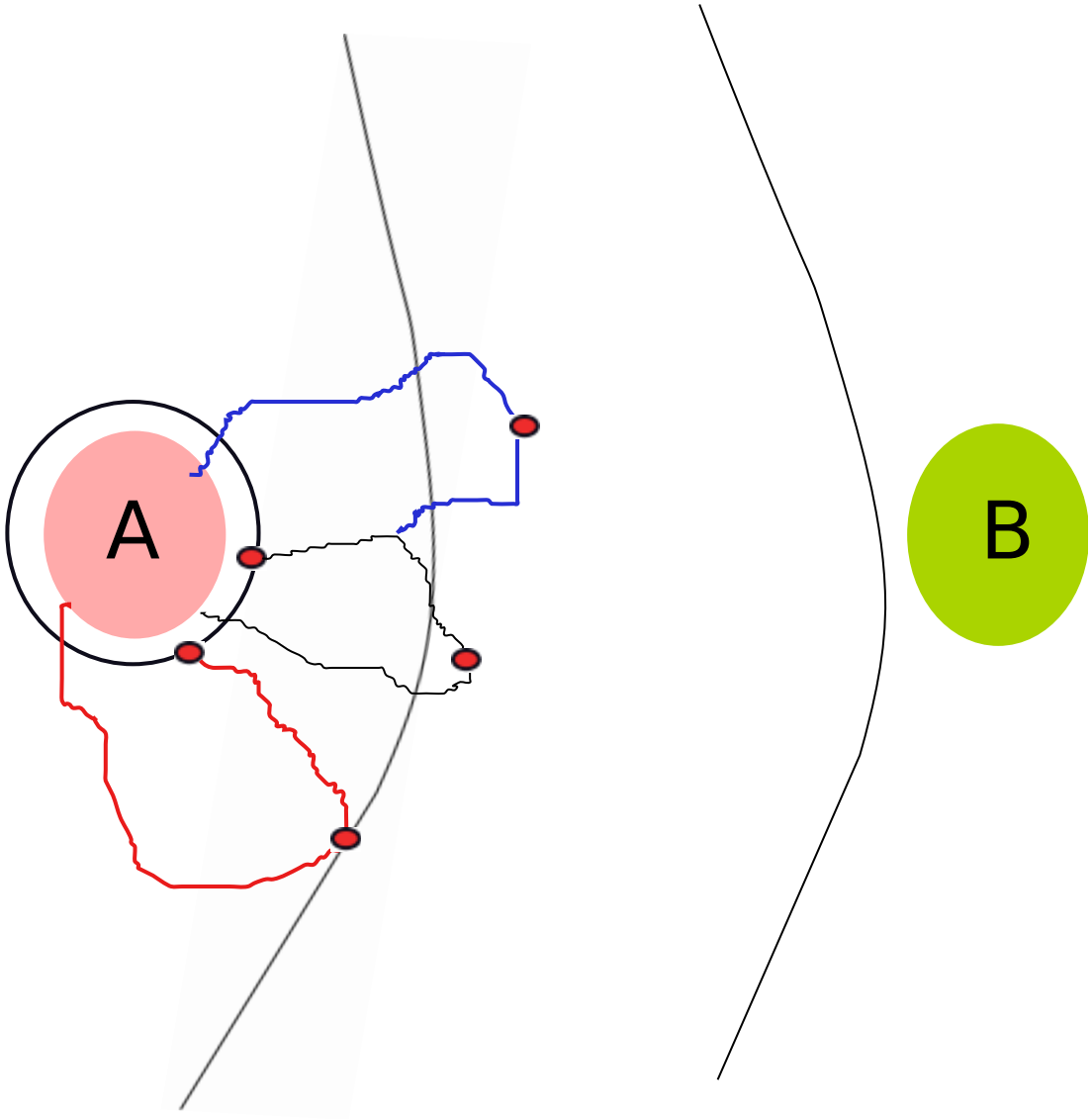

Sampling reactive trajectories (3)

- 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: $k_{\text{off}} = (260 \pm 240) s^{-1}$ which is in the same order of magnitude as the experimental rate $(600 \pm 300) s^{-1}$
  - Overall simulation time: $2.3\ \mu s$ which is 4 orders of magnitude shorter than than the estimated dissociation time

Computation of transport coefficients

- **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

$$\int_0^{+\infty} \mathbb{E}\Big(\psi(x_t)\varphi(x_0)\Big) dt = \Delta t \sum_{n=0}^{+\infty} \mathbb{E}_{\Delta t} \left(\widetilde{\psi}_{\Delta t, \alpha}\left(x^n\right) \varphi\left(x^0\right)\right) + \mathrm{O}(\Delta t^\alpha)$$

  - variance reduction (in progress)

Results in 1D for $\varphi = \psi = V'$ and cosine potential