

# A (Very) Brief Tutorial on Multiscale Modeling

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## Multi-scale, multi-physics modeling

### Basic ideas:

- use microscopic models to bypass *ad hoc* constitutive relations in macroscopic laws (type B problems);
- use microscopic models in regions when the microscopic laws are invalid (e.g. crack tip, dislocation, boundaries, contact line, etc.) (type A problems)

Note that for type B problems, it is assumed that the general form (but not the details) of the macroscopic law is known.

Many applications, including:

- complex fluids;
- material science;
- *molecular dynamics* – used as illustration here.

## Molecular Dynamics

*Main objective:* understand the structure and function of molecules by simulating the dynamics of their nuclei within Born-Oppenheimer approximation.

Requires a force-field between the nuclei which accounts for the effects of the electrons.

Force-field can be obtained by fitting (e.g. precomputing)

– this is what is used in AMBER, CHARMM, NAMD, etc.

or

Can be computed on-the-fly

– *Car-Parrinello Molecular Dynamics (CPMD)*

## Car-Parrinello Molecular Dynamics (CPMD)

Position of the nuclei:  $R_1, \dots, R_N$ ;

Orbitals of the electrons:  $\phi_1(x), \dots, \phi_M(x)$ .

*In principle:* Force-field obtained by computing the ground state of the electrons given the position of the nuclei (Born-Oppenheimer).

*In practice:* Done on-the-fly using MD with extended Lagrangian:

$$L(R_n, \phi_m, \dot{R}_n, \dot{\phi}_m) = \frac{1}{2} \sum_{n=1}^N M_n |\dot{R}_n|^2 + \frac{1}{2} \sum_{m=1}^M \mu \int_{\Omega} |\dot{\phi}_m(x)|^2 dx \\ - E_{\text{KS}}(R_n, \phi_m) - \sum_{n \neq n'} \frac{Z_n Z_{n'}}{|R_n - R_{n'}|}$$

where  $E_{\text{KS}}$  is the energy of the orbitals in Kohn-Sham density functional theory (DFT).

**What is  $\mu$ ?** *Artificial mass of the electrons.*

Taken much larger than their physical mass to improve efficiency, yet much smaller than the masses of the nuclei to ensure that the electrons remain in their ground state, adiabatically slaved to the nuclei (consistent with Born-Oppenheimer approximation).

## Two key ingredients in CPMD:

1. uses the “microscopic model” (here DFT) to obtain the “constitutive relations” (here the force-field between the nuclei) in the “macroscopic law” (here classical mechanics [ $F = ma$ ] for the dynamics of the nuclei).
2. uses a clever computational trick (the extended Lagrangian with artificial mass) to compute the force field on-the-fly by relying on scale separation and averaging theorems for systems with multiple time-scale.

*Averaging theorem?* (Khasminskii, Kurtz, Papanicolaou, ...)

Consider

$$\begin{cases} \dot{X} = f(X, Y), \\ dY = \varepsilon^{-1}g(X, Y)dt + \varepsilon^{-1/2}\sigma(X, Y)dW(t), \end{cases} \quad (\star)$$

Assume that: (i) the evolution of  $Y$  at every fixed  $X = x$  is ergodic with respect to the probability distribution

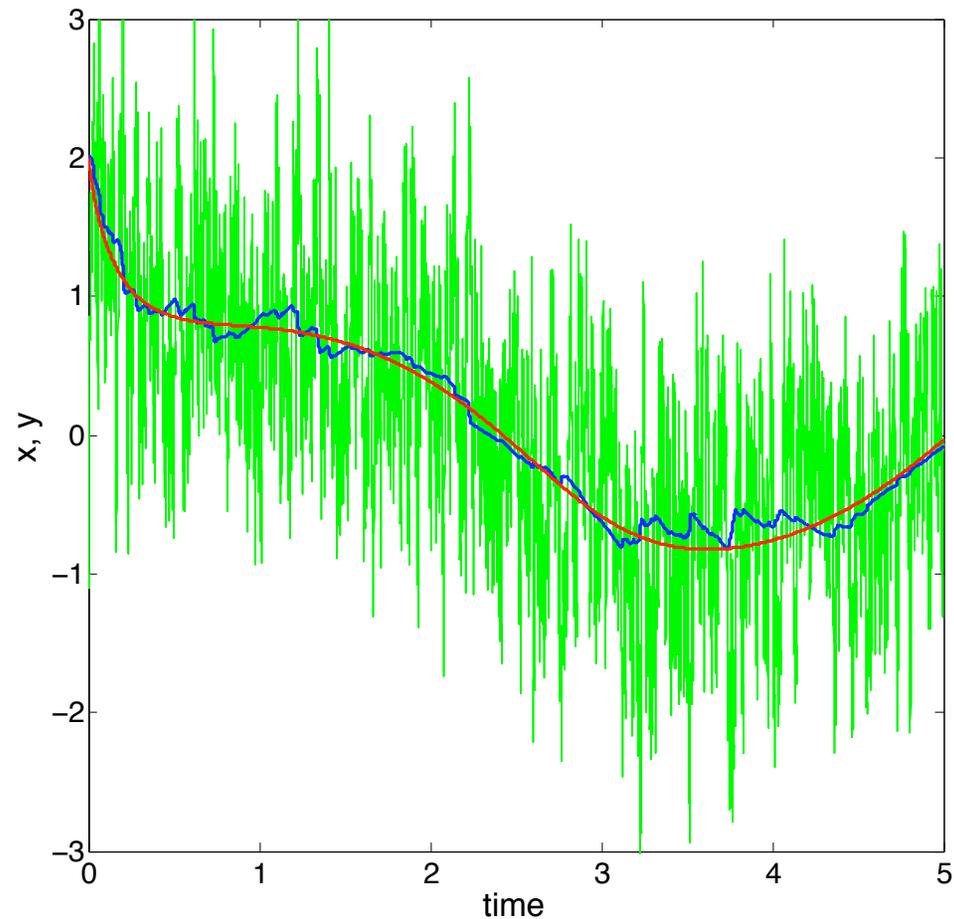
$$d\mu_x(y)$$

and (ii)

$$F(x) = \int_{\mathbb{R}^m} f(x, y)d\mu_x(y) \quad \text{exists}$$

Then in the limit as  $\varepsilon \rightarrow 0$  the evolution for  $X$  solution of  $(\star)$  is governed by

$$\dot{X} = F(X)$$



The solution of

$$\begin{cases} \dot{X} = -Y^3 + \cos(t) + \sin(\sqrt{2}t) \\ dY = -\varepsilon^{-1}(Y - X)dt + \varepsilon^{-1/2}dW \end{cases}$$

when  $\varepsilon = 0.01$  and  $X(0) = 2, Y(0) = -1$ .  $X$  is shown in blue, and  $Y$  in green. Also shown in red is the solution of the limiting equation

$$\dot{X} = -X^3 + X + \cos(t) + \sin(\sqrt{2}t)$$

Notice how noisy  $Y$  is.

## Temperature accelerated technique for free energy calculation and phase-space exploration

**Definition:** Consider a random variable  $X \in \Omega \subset \mathbb{R}^n$  with the *Boltzmann-Gibbs probability distribution*;

$$d\mu(x) = Z^{-1} e^{-\beta V(x)} dx \quad Z = \int_{\Omega} e^{-\beta V(x)} dx$$

where  $V(x)$  is the potential,  $\beta > 0$  is the inverse temperature.

Let  $\theta : \Omega \mapsto \mathbb{R}^N$  be a set of *collective variables* (aka vectorial reaction coordinates).

The *free energy* associated with  $\theta$  is the function  $G : \mathbb{R}^N \mapsto \mathbb{R}$  such that:

*$e^{-\beta G(z)} dz$  is the probability distribution of  $Z = \theta(X)$ .*

In formula:

$$\begin{aligned} G(z) &= -\beta^{-1} \log Z^{-1} \int_{\Omega} e^{-\beta V(x)} \delta(\theta(x) - z) dx \\ &= -\beta^{-1} \log Z^{-1} \int_{\Sigma(z)} e^{-\beta V(x)} J(x) d\sigma_{\Sigma(z)}(x) \end{aligned}$$

where  $\Sigma(z) = \{x : \theta(x) = z\}$ ,  $J(x) = |\det M(x)|^{1/2}$ ,  $M_{\alpha\beta}(x) = \nabla\theta_{\alpha}(x) \cdot \nabla\theta_{\beta}(x)$ .

## Relevance of free energy $G(z)$ ?

Consider e.g. an MD system governed by Langevin equation

$$m\ddot{X}(t) = -\nabla V(X(t)) - \gamma\dot{X}(t) + \sqrt{2\gamma\beta^{-1}}\eta(t),$$

where  $m$  is the mass,  $\gamma$  is the friction and  $\eta(t) = \dot{W}(t)$  is a white-noise.

This system is ergodic with respect to the Boltzmann-Gibbs distribution, i.e.:

$$\frac{1}{T} \int_0^T f(x(t)) dt \rightarrow Z^{-1} \int_{\Omega} f(x) e^{-\beta V(x)} dx \quad \text{almost surely as } T \rightarrow \infty$$

for any suitable  $f : \Omega \mapsto \mathbb{R}$

In particular, letting  $f = F \circ \theta$  for some  $F : \mathbb{R}^N \mapsto \mathbb{R}$ :

$$\frac{1}{T} \int_0^T F(\theta(X(t))) dt \rightarrow \int_{\mathbb{R}^N} F(z) e^{-\beta G(z)} dz \quad \text{a.s. as } T \rightarrow \infty$$

*The free energy permits to organize the data in terms of some relevant observables  $\theta$ .*

Sampling of free energy  $G(z)$ ?

Use:

$$\ddot{Z}(t) = -\nabla G(Z(t)) - \bar{\gamma}\dot{Z}(t) + \sqrt{2\bar{\gamma}\bar{\beta}^{-1}}\bar{\eta}(t)$$

*Problem:* We can only do this directly if we know  $\nabla G(z)$  which is (pretty much) what we are looking for.

Temperature accelerated sampling method: (Maragliano & V.-E.)

Use extended system on state-space  $(x, z) \in \mathbb{R}^n \times \mathbb{R}^N$  with potential

$$U_\kappa(x, z) = V(x) + \frac{1}{2}\kappa \sum_{\alpha=1}^N (\theta_\alpha(x) - z_\alpha)^2$$

$$\begin{cases} \varepsilon^2 \ddot{X}(t) = -\nabla V(X(t)) - \kappa \sum_{\alpha=1}^N (\theta_\alpha(X(t)) - Z_\alpha(t)) \nabla \theta_\alpha(X(t)) - \varepsilon \gamma \dot{X}(t) + \sqrt{2\varepsilon\gamma\beta^{-1}} \eta(t) \\ \ddot{Z}_\alpha(t) = \kappa(\theta_\alpha(X(t)) - Z(t)) - \bar{\gamma} \dot{Z}_\alpha(t) + \sqrt{2\bar{\gamma}\bar{\beta}^{-1}} \bar{\eta}_\alpha(t) \end{cases}$$

*Limit thm:* As  $\varepsilon \rightarrow 0$ , the dynamics for  $Z(t)$  is approximately

$$\ddot{Z}(t) = -\nabla G_\kappa(Z(t)) - \bar{\gamma} \dot{Z}(t) + \sqrt{2\bar{\gamma}\bar{\beta}^{-1}} \bar{\eta}(t)$$

where

$$G_\kappa(z) = -\beta^{-1} \log Z_\kappa^{-1} \int_{\mathbb{R}^n} \exp\left(-\beta V(x) - \frac{1}{2}\beta\kappa \sum_{\alpha} (\theta_\alpha(x) - z_\alpha)^2\right) dx \rightarrow G(z) \quad \text{as } \kappa \rightarrow \infty$$

So: Simulate the system above with  $\varepsilon$  small,  $\kappa$  large and  $\bar{\beta} < \beta$ , and sample (i.e. bin)  $Z(t)$  to retrieve  $G(z)$  or (better) use thermodynamic integration along trajectory.

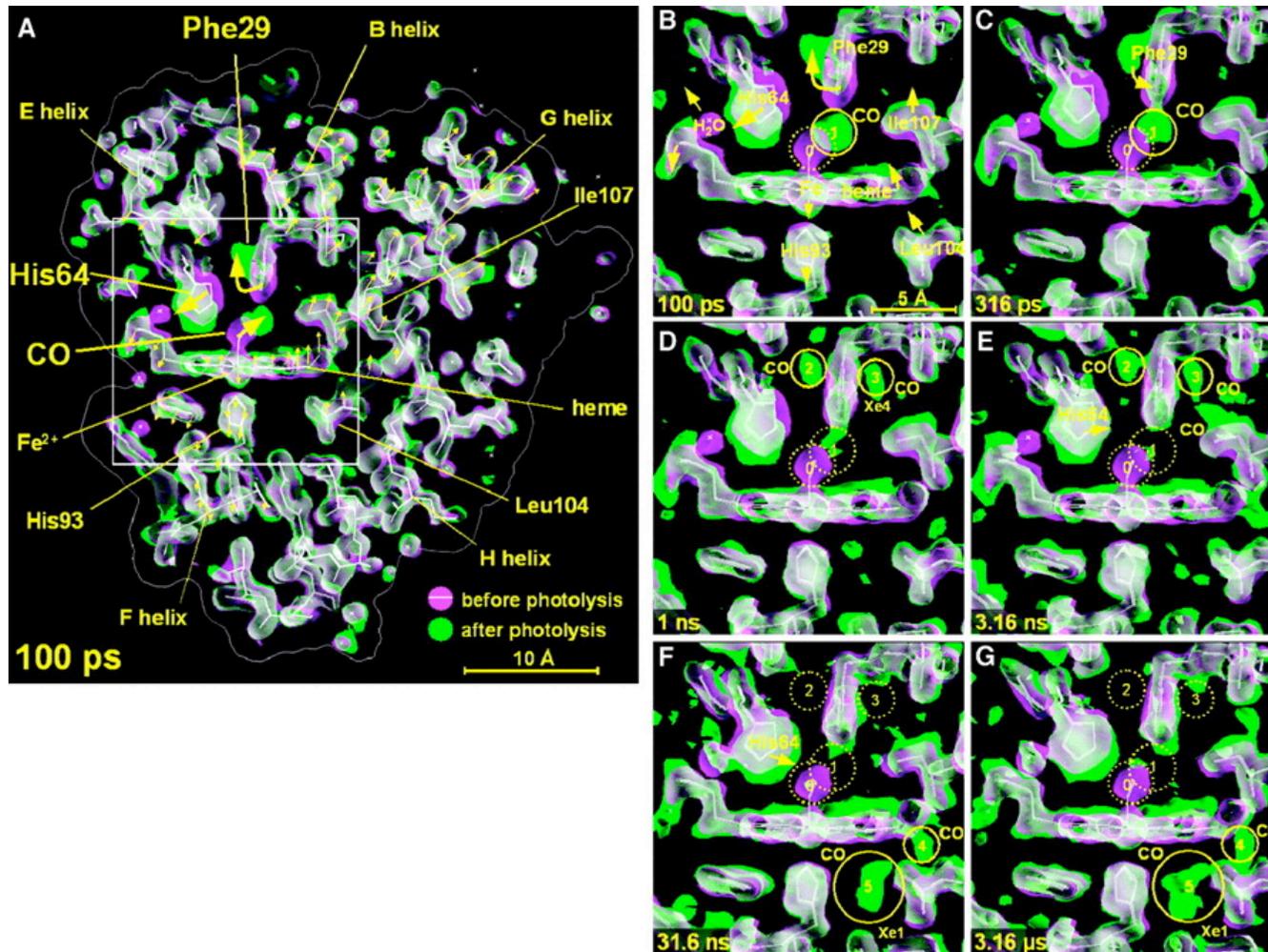
*Remark:* Use constraints instead of restraints to eliminate error in  $\kappa$  (i.e. take  $\kappa \rightarrow \infty$  exactly).

## Example: CO diffusion in Myoglobin



Crystal structure of Carbon-monoxide (CO) - bound Myoglobin (MB), as deposited in the Protein Data Bank archive. The backbone chain is represented in "ribbons" style so to show the alpha-helices structure of MB. The heme is represented as sticks and the Iron atom in the middle as a yellow sphere. The red and green ball-and-stick dumbbell is the CO molecule, bound to the Iron atom.

## Experiment using time-resolved X-ray crystallography

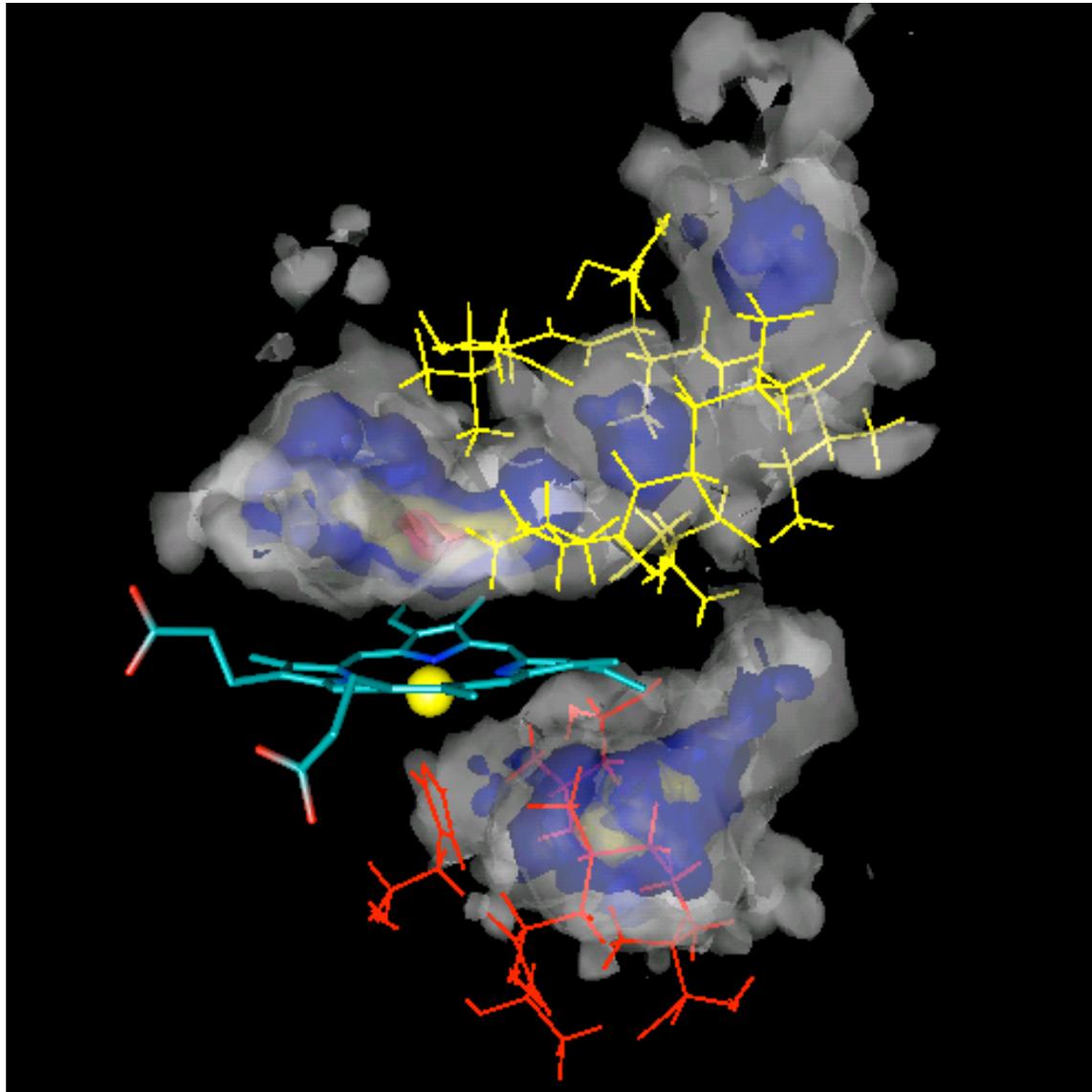


Time-resolved X-ray diffraction on photolyzed MB.

Given the crystal with the bound CO, a laser flash breaks the bond FE-CO. Diffraction patterns from a time-delayed X-ray pulse on the crystal (picosecond Laue crystallography) are then used to follow the CO. Magenta is the pre-photolysis structure (CO-bound), and green are the structures at delayed times. When these are similar to pre-photolysis crystal structures, they are colored white.

From F.Schotte *et al.* Science **300**: 1944–1947 (2003).

## Free energy map of CO relative to binding site (Iron)



Sampling by one-sweep with 5 different trajectories. Shown in red and yellows are the residues used to define the Xe1 and Xe4 cavities. The length of the simulation is 100 picosecond;  $k_B\bar{T} = 7k_B T$ .

This was just a tiny glimpse of multi-scale, multi-physics modeling!

Many other successful examples in applied science (QM-MM, QC method, CGMD, etc.)

But:

Can one make it a respectable branch of applied mathematics?

Can one put it under a unified and constructive framework?

- **Heterogeneous Multiscale Methods (HMM)** (E, Engquist, Ren, Li, Lu, V.-E., ... )

Assumes that the general form (but not the details) of macroscopic laws is known;

Use microscopic models to compute on-the-fly the unknown coefficients in these laws (type B problems).

- **Equation Free Philosophy** (Kevrekidis, ... )

No assumption on the macroscopic law.

Two main building blocks: projective integrators (extrapolation in time) and gap-tooth scheme (extrapolation in space)

More ambitious than HMM (but more limited at the end  
– no free lunch!)

## **CPMD:**

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