Modelling solutions of biomolecules at atomistic and continuum representation at the same time: hybrid MD/hydrodynamics framework

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Multiscale Modelling of
Condensed Phase and Biological Systems, 8 Jan 2014

The project

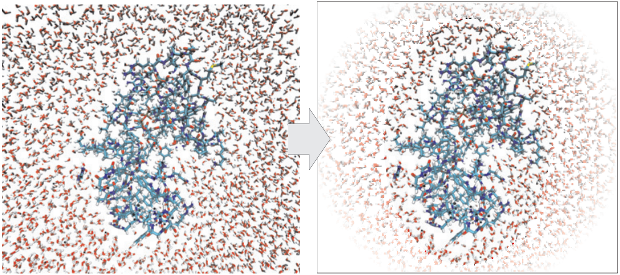
Title: ‘Using next generation computers and algorithms for modelling the dynamics of large biomolecular systems’

Consortium: 5 groups (Japan, UK, Russia)

Funding: G8 Research Councils Initiative on Multilateral Research Funding - Exascale Computing

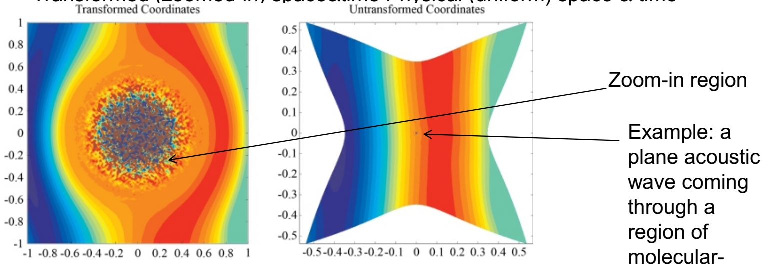
Hybrid MD/HD: motivation

- **Motivation**: multiphysics/multiscale (speed up and data reduction)
- **Examples**:
  - bridging atomistic times and microfluidic mixer times (9 orders of magnitude difference),
  - the effects of viscosity and hydrodynamic shear on protein folding.



multiphysics/multiscale

Transformed (zoomed-in) space&time Physical (uniform) space & time

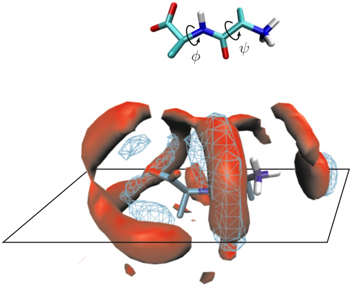


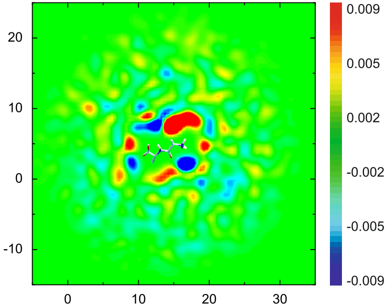
Example: a plane acoustic wave coming through a region of molecular-scale fluctuations

AP Markesteijn and SA Karabasov, *J. Comput. Phys.*, **258**, 137 (2014)

Fluctuations in biomolecular systems

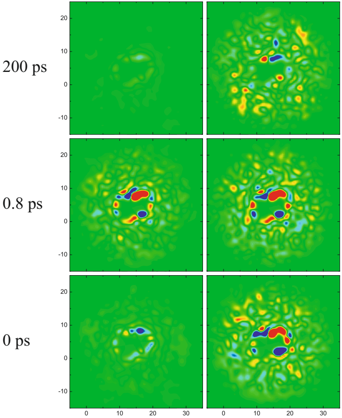
Water density around dialanine zwitterion





Question: to what extend the dynamics of water density (fluctuations) is connected with the dynamics of the peptide (quantified by its dihedral angles ϕ and ψ)?

Water density correlation with the peptide motion



Answer: not only connected but strongly correlated at very specific periods, when the conformational transitions occur

D Nerukh and S Karabasov, *J. Phys. Chem. Lett.*, **4**, 815 (2013)

The fundamentals: hydrodynamics

Continuous representation (hydrodynamics)

- All started with macroscopic thermodynamical quantities: the properties of the system **as a whole**, the largest possible scale.
- Describing the system at smaller scales: the properties become **fields** changing in **time**:

$$\rho(\mathbf{x}, t), \mathbf{u}(\mathbf{x}, t), T(\mathbf{x}, t).$$

- $\mathbf{x}$ is the Euclidean 3D space.
- The equations of motion are the FD equations.
- The solution is the values of the fields at each location in space at every instant of time: $\rho(\mathbf{x}, t), \mathbf{u}(\mathbf{x}, t), T(\mathbf{x}, t)$.

The fundamentals: atomistic

Atomistic representation

- The variables are the positions and momenta of the point masses, the atoms:

$$\{\mathbf{q}_1, \ldots, \mathbf{q}_N, \mathbf{p}_1, \ldots, \mathbf{p}_N\}$$

- The space is the $6N$-dimentional phase space.
- The atoms interact through empirically (in MD) defined Hamiltonian $H(\mathbf{q}, \mathbf{p})$
- The equations of motion describing $\mathbf{q}(t), \mathbf{p}(t)$ are the Hamilton equations

$$\frac{\mathrm{d}q_i(t)}{\mathrm{d}t} = \frac{\partial H(\mathbf{q}, \mathbf{p})}{\partial p_i}, \frac{\mathrm{d}p_i(t)}{\mathrm{d}t} = -\frac{\partial H(\mathbf{q}, \mathbf{p})}{\partial q_i}.$$

- The solution is the molecular trajectory: the values of the coordinates and momenta at every moment of time:

$$\mathbf{q}(t), \mathbf{p}(t).$$

Connecting the representations

Calculating the continuous density:

$$\rho_q(\mathbf{q};\mathbf{x},t) = \sum_{j=1}^{N} m\delta(\mathbf{q}_i(t) - \mathbf{x})$$

It is a *function of the molecular coordinates* (phase space variable), which also parametrically depends on $\mathbf{x}$ and t.

Connecting the representations

How the measurement is done: a probe of volume Δx is placed at the point $\mathbf{x}$ for a period of time Δt at time t.

The 'true' (measured) value of $\rho(\mathbf{x}, t)$ is obtained by overaging $\rho_q(\mathbf{q}; \mathbf{x}, t)$ over Δx and Δt.

$$\rho(\mathbf{x}, t) = \langle \rho_q(\mathbf{q}; \mathbf{x}, t) \rangle_{\Delta x, \Delta t}$$

Connecting the representations

This is MD→HD transformation.

HD→MD - ???

Describing fluctuations of the continuum

The Landau-Lifshitz Fluctuating Hydrodynamics (LL-FH) equations are a generalisation of the deterministic Navier-Stokes (NS) equations:

$$\frac{\partial \rho}{\partial t} + \nabla(\rho \mathbf{u}) = 0,$$
$$\frac{\partial \rho u_i}{\partial t} + \nabla(\rho u_i \mathbf{u}) = \nabla_j \left(\Pi_{ij} + \tilde{\Pi}_{ij}\right),$$
$$\frac{\partial \rho E}{\partial t} + \nabla(\rho E \mathbf{u}) = \nabla_j \left[\left(\Pi_{ij} + \tilde{\Pi}_{ij}\right) \cdot u_i\right] + \nabla(\mathbf{q} + \tilde{\mathbf{q}}).$$

Describing fluctuations of the continuum

The stress tensor consists of a deterministic part

$$\Pi_{ij} = -\left(p - \eta_V \nabla \mathbf{u}\right)\delta_{ij} + \eta\left(\partial_i u_j + \partial_j u_i - 2D^{-1}\nabla\mathbf{u}\cdot\delta_{ij}\right)$$

and a stochastic part, a random Gaussian matrix with zero mean and the covariance

$$\langle \tilde{\Pi}_{ij}(r_1,t_1)\cdot\tilde{\Pi}_{kl}(r_2,t_2)\rangle = 2k_BT\left[\eta\left(\delta_{ij}\delta_{ik} + \delta_{ik}\delta_{jl}\right) + \left(\eta_V - \frac{2}{3}\eta\right)\delta_{ij}\delta_{jk}\right]\delta(r_1 - r_2)\delta(t_1 - t_2).$$

This form of correlations follows from the fluctuation-dissipation theorem, which relates the thermal fluctuations to temperature.

Describing fluctuations of the continuum

The heat flow is also a sum of the averaged flow

$$q_i = \kappa \cdot \partial_i T$$

and a stochastic component with zero mean and the covariance

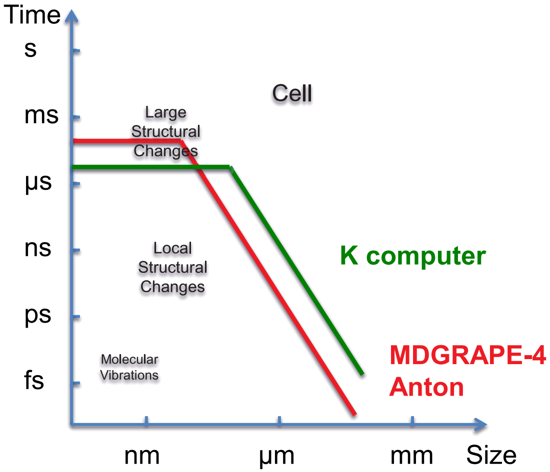
$$\langle \tilde{q}_i(r_1, t_1) \cdot \tilde{q}_j(r_2, t_2) \rangle = 2k_B \kappa T^2 \delta_{ij} \delta(r_1 - r_2) \delta(t_1 - t_2)$$

Describing fluctuations of the continuum

$$\tilde{\Pi}_{ij} = \sqrt{\frac{2k_B T}{\Delta x \Delta t}} \left(\sqrt{2\eta} \cdot \mathbf{G}^s_{ij} + \sqrt{D\eta_V} \frac{tr[\mathbf{G}]}{D} \mathbf{E}_{ij} \right)$$

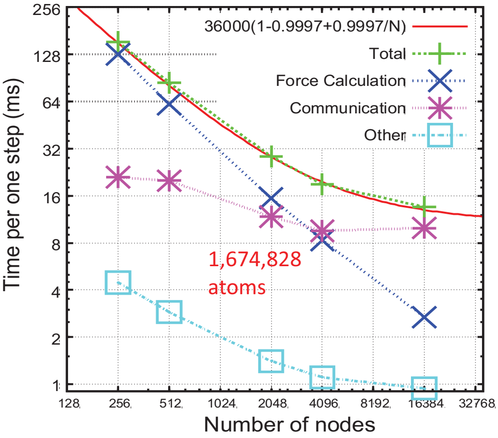
$$\tilde{q}_i = \sqrt{\frac{2k_B \kappa T^2}{\Delta x \Delta t}} \mathbf{G}_i$$

Biomolecular scales



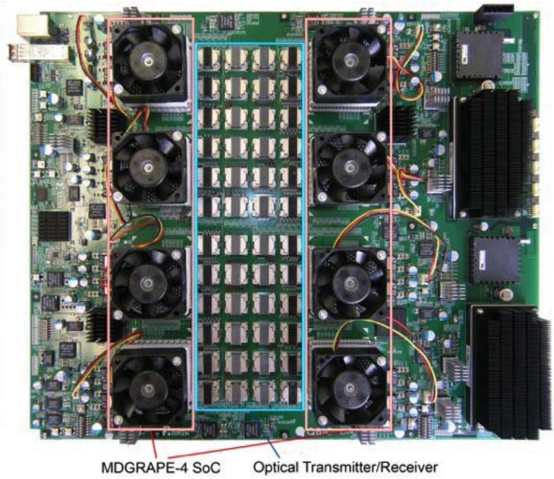
Quick digression: hardware

RIKEN **K-computer**: 10Pflops, 640000 nodes
scaling:

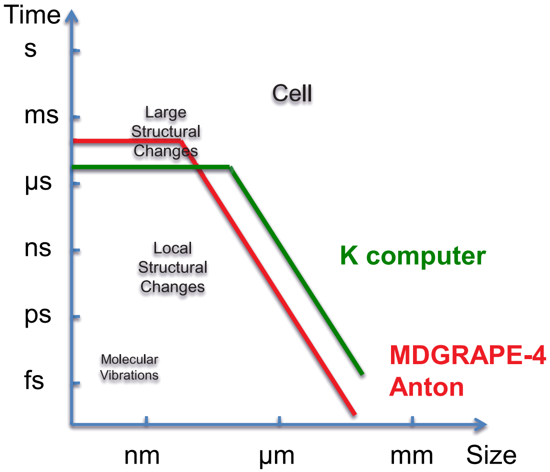


Hardware

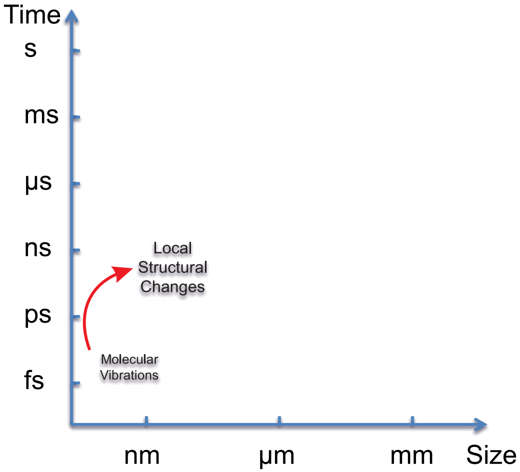
MDGRAPE-4: 100 ps per day for a 100K atoms system



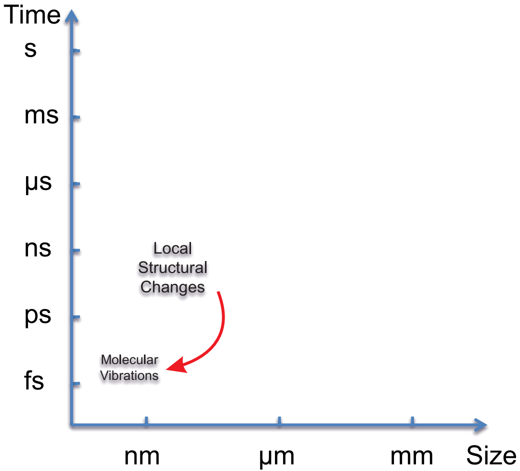
Biomolecular scales



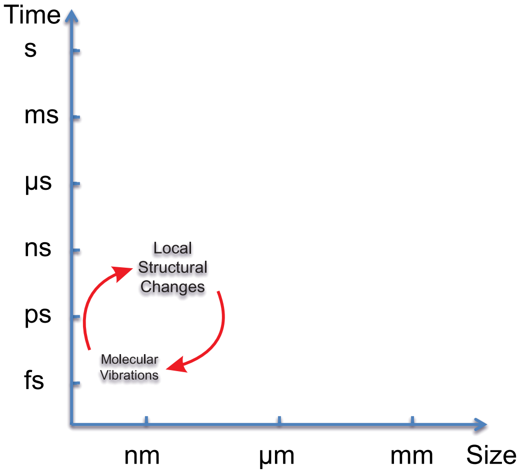
Scales coupling: acyclic 'bottom-up'



Scales coupling: acyclic ‘top-down’



Scales coupling: cyclic



An example of acyclic ‘top-down’ approach

O’Connell Thompson (1995):

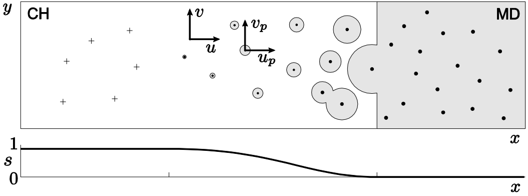
$$\frac{dx_{ip}}{dt} = u_{ip} + s\left(\frac{\sum_N m_{ip}}{M_{CFD}} u_i - \frac{\sum_N m_{ip} u_{ip}}{\sum_N m_{ip}}\right),$$

$$\frac{d}{dt} u_{ip}^{Newton} = \frac{F_{ip}}{m}$$

- CFD = Deterministic N-S model
- Application of repulsive barrier to retain particles
- Not necessarily conserves macroscopic momentum balance
- Not fully coupled (no feedback from MD to CFD)

see our poster for our version of ‘top-down’ coupling

Our framework



- The end domains HD and MD are described by purely hydrodynamic and purely Newtonian equations of motion respectively.
- In the hybrid domain the fluid consists of two "phases":
  - HD phase is a continuum water with volume fraction $s = \frac{V_1}{V}$,
  - MD phase is a phase that incorporates atoms, its volume fraction is $(1 - s)$.
- The parameter $s = s(x)$ is the function of space coordinates, such that $s = 1$ in the HD domain, $s = 0$ in the MD domain.

A Markesteijn, S Karabasov, A Scukins, D Nerukh, V Glotov, and V Goloviznin, submitted to *Phil. Trans. R. Soc. A*

Mass conservation

For HD phase:

$$\frac{\partial}{\partial t}(s\rho) + \frac{\partial}{\partial x_i}(u_i s\rho) = J,$$

For MD phase:

$$\frac{\partial}{\partial t}\left((1-s)\sum_{p=1,N(t)}\rho_p\right) + \frac{\partial}{\partial x_i}\left((1-s)\sum_{p=1,N(t)}\rho_p u_{ip}\right) = -J,$$

where $\rho_p = m_p/V$ is the density of MD particles and J is the birth/death rate due to the coupling between the phases.

$\tilde{\rho} = s\rho + (1-s)\sum_{p=1,N(t)}\rho_p$

Conservation of momentum

For HD phase:

$$\frac{\partial}{\partial t}(s u_i \rho) + \frac{\partial}{\partial x_j}(u_j u_i s \rho) = s F_i + J_2,$$

where J_2 is the HD-MD interaction force and F_i is the hydrodynamic force.

For MD phase:

$$\frac{\partial}{\partial t}\left((1-s)\sum_{p=1,N(t)} u_{i,p}\rho_p\right) + \frac{\partial}{\partial x_j}\left((1-s)\sum_{p=1,N(t)} \rho_p u_{i,p} u_{j,p}\right) = (1-s)\sum_{p=1,N(t)} F_{i,p} - J_2$$

$$\tilde{\rho}\tilde{u}_j = \left[s\rho u_j + (1-s)\sum_{p=1,N(t)} \rho_p u_{jp}\right]$$

Restricted dynamics

The deviations of $\tilde{\rho}$ are driven towards the correct value $\sum_{p=1,N(t)} \rho_p$:

$$\frac{D}{Dt_0}\left(\tilde{\rho} - \sum_{p=1,N(t)} \rho_p\right) = L^{(\rho)} \cdot \left(\tilde{\rho} - \sum_{p=1,N(t)} \rho_p\right),$$

where $\frac{D}{Dt_0} \cdot = \frac{\partial}{\partial t} \cdot + \nabla(\mathbf{u} \cdot)$,

and similarly for $\tilde{u}_j \tilde{\rho}$:

$$\frac{D}{Dt_0}\left(\tilde{u}_j \tilde{\rho} - \sum_{p=1,N(t)} u_{jp}\rho_p\right) = L^{(u)} \cdot \left(\tilde{u}_j \tilde{\rho} - \sum_{p=1,N(t)} u_{jp}\rho_p\right) + s\nabla_j\left(\Pi_{ij} + \tilde{\Pi}_{ij}\right).$$

Restricted dynamics

$\tilde{\rho}$ is diffused towards $\sum_{p=1,N(t)} \rho_p$:

$$L^{(\rho)}.\left(\tilde{\rho} - \sum_{p=1,N(t)} \rho_p\right) = \frac{\partial}{\partial x_i}\left(s(1-s)\alpha\frac{\partial}{\partial x_i}\left(\tilde{\rho} - \sum_{p=1,N(t)} \rho_p\right)\right).$$

$\tilde{u}_j\tilde{\rho}$ is diffused towards $\sum_{p=1,N(t)} u_{jp}\rho_p$:

$$L^{(u)}.\left(\tilde{u}_j\tilde{\rho} - \sum_{p=1,N(t)} u_{jp}\rho_p\right) =$$

$$\frac{\partial}{\partial x_i}\left(s(1-s)\beta\frac{\partial}{\partial x_i}\left(\tilde{u}_j\tilde{\rho} - \sum_{p=1,N(t)} u_{jp}\rho_p\right)\right).$$

The sources J and J_2

From these constrains the sources J and J_2 can be found:

$$J = s\frac{\partial}{\partial t}\sum_{p=1,N(t)}\rho_p + \frac{\partial}{\partial x_i}\left(su_i\sum_{p=1,N(t)}\rho_p\right) + \frac{\partial}{\partial x_i}\left(s(1-s)\alpha\frac{\partial}{\partial x_i}\left(\tilde{\rho}-\sum_{p=1,N(t)}\rho_p\right)\right),$$

$$J_2 = s\frac{\partial}{\partial t}\sum_{p=1,N(t)}\rho_p u_{jp} + \frac{\partial}{\partial x_i}\left(su_i\sum_{p=1,N(t)}\rho_p u_{jp}\right) - sF_j + \frac{\partial}{\partial x_i}\left(s(1-s)\beta\frac{\partial}{\partial x_i}\left(\tilde{u}_j\tilde{\rho}-\sum_{p=1,N(t)}u_{jp}\rho_p\right)\right),$$

Modified MD equations

For known J and J_2 MD equations are modified to preserve macroscopic conservation laws:

$$\frac{dx_{ip}}{dt} = u_{ip} + s(u_i - u_{ip}) + s(1-s)\alpha \frac{\partial}{\partial x_i}\left(\tilde{\rho} - \sum_{p=1,N(t)} \rho_p\right)\frac{1}{\rho_p N(t)},$$

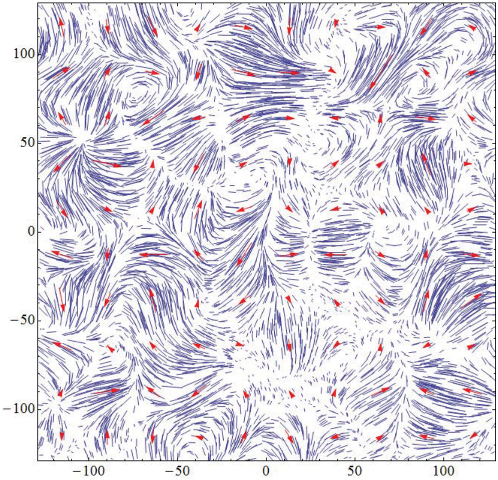
$$\frac{du_{jp}}{dt} = (1-s)F_{jp}/\rho_p + sF_j/\rho_p/N(t)$$

$$+ \frac{\partial}{\partial x_i}\left(s(1-s)\alpha \sum_{p=1,N(t)} u_{jp}/N(t)\frac{\partial}{\partial x_i}\left(\tilde{\rho} - \sum_{p=1,N(t)} \rho_p\right)\right)\frac{1}{\rho_p N(t)}$$

$$- \frac{\partial}{\partial x_i}\left(s(1-s)\beta \frac{\partial}{\partial x_i}\left(\tilde{u}_j\tilde{\rho} - \sum_{p=1,N(t)} u_{jp}\rho_p\right)\right)\frac{1}{\rho_p N(t)},$$

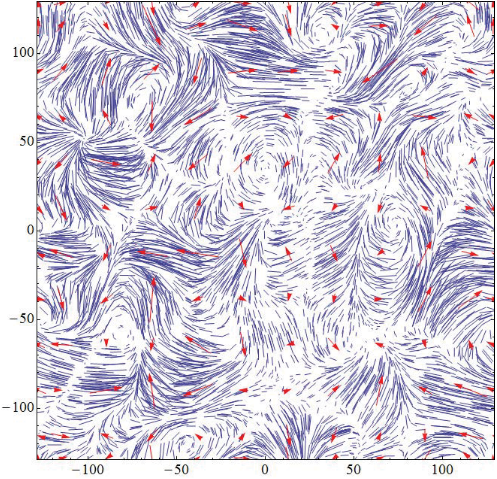
Results: 2D Lennard-Jones liquid

strong coupling: $s = 0.8$

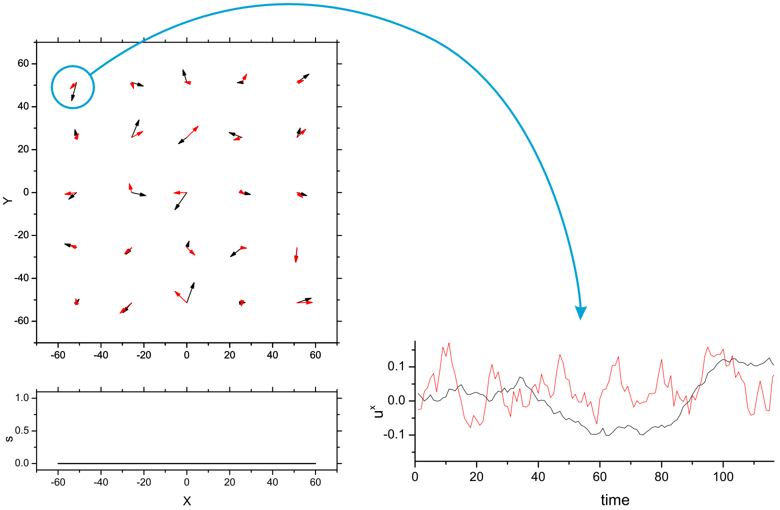


Results: 2D Lennard-Jones liquid

weaker coupling: $s = 0.6$



Velocities at various s



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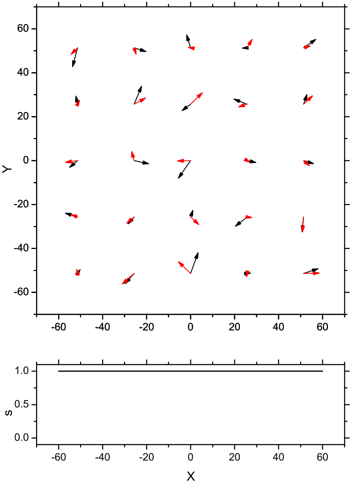
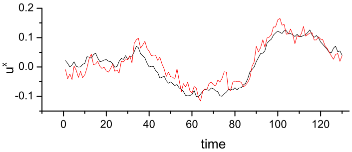
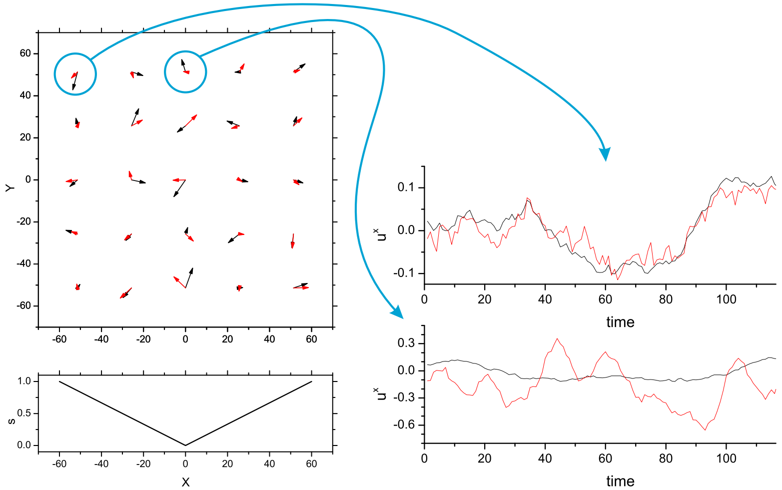


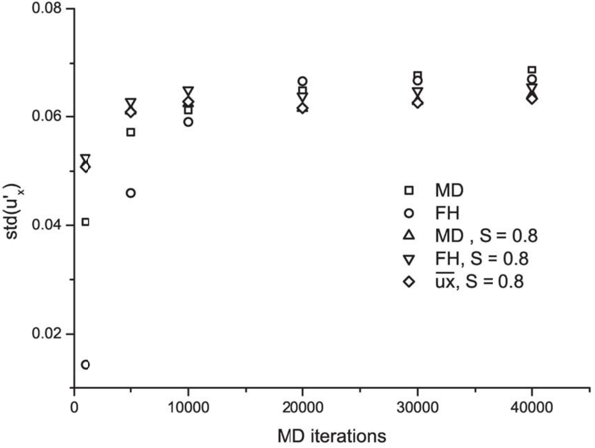


Velocities at various s



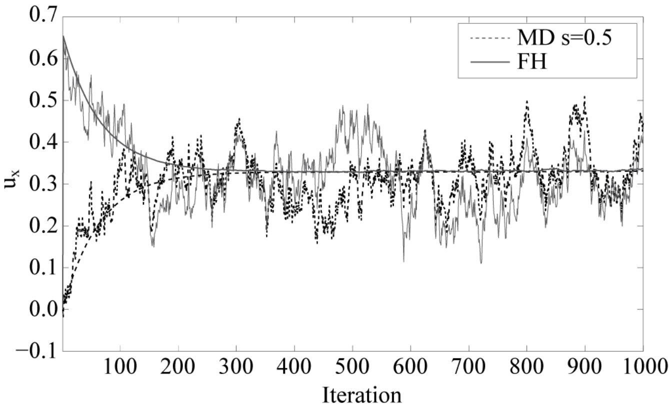
Results: 3D Lennard-Jones liquid

Convergence of fluctuations towards the same limit



Results: 3D Lennard-Jones liquid

Convergence of fluctuations towards the same limit



Conclusions

- Atomistic and continuum representations of liquid can be connected without artificial barriers or ad hoc correction forces in space and time.
- The domains of each representation can be defined arbitrarily in space and time.
- Challenges: *multiphysics* (non-stationary MD + hydrodynamics), multiscale *computing* (efficient multi space-time algorithms in parallel environment).

Thoughts for the future

The need to organize activities in multiscale modelling:

- a database of existing well documented algorithms and codes in multiscale modelling;
- optimising existing algorithms for computational efficiency (GPU, parallel scalability, distributed computing, etc);
- a database of benchmark cases (from the simplest molecular models to realistic biomolecular systems);
- training: hands-on workshops, schools on existing software.