Developing a hybrid atomistic-continuum simulation method for biological macromolecules

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Equilibrium sampling of biological macromolecules

Need a robust, atomistic approach

- Heterogeneous, nanoscale structures w/ partial charges
- (Ionic) solvent-solute interactions
- Full mechanistic picture requires high spatiotemporal resolution

Molecular mechanics (classical MD)

$$\dot{\mathbf{x}}_i = \mathbf{v}_i(t) \qquad m_i\dot{\mathbf{v}}_i = -\boldsymbol{\nabla}_{\mathbf{x}_i} U\left(\mathbf{x}(t)\right) \qquad U \text{ (all-atom force field)}$$

Sampling cost†

$$\sim \frac{\text{cost}}{\text{step}} \times (\#\text{ steps needed})$$

$$\sim \text{ (cost of energy call)} \times \text{(potential landscape roughness)}$$

† D. M. Zuckerman. (2011) *Annu. Rev. Biophys.* **40**

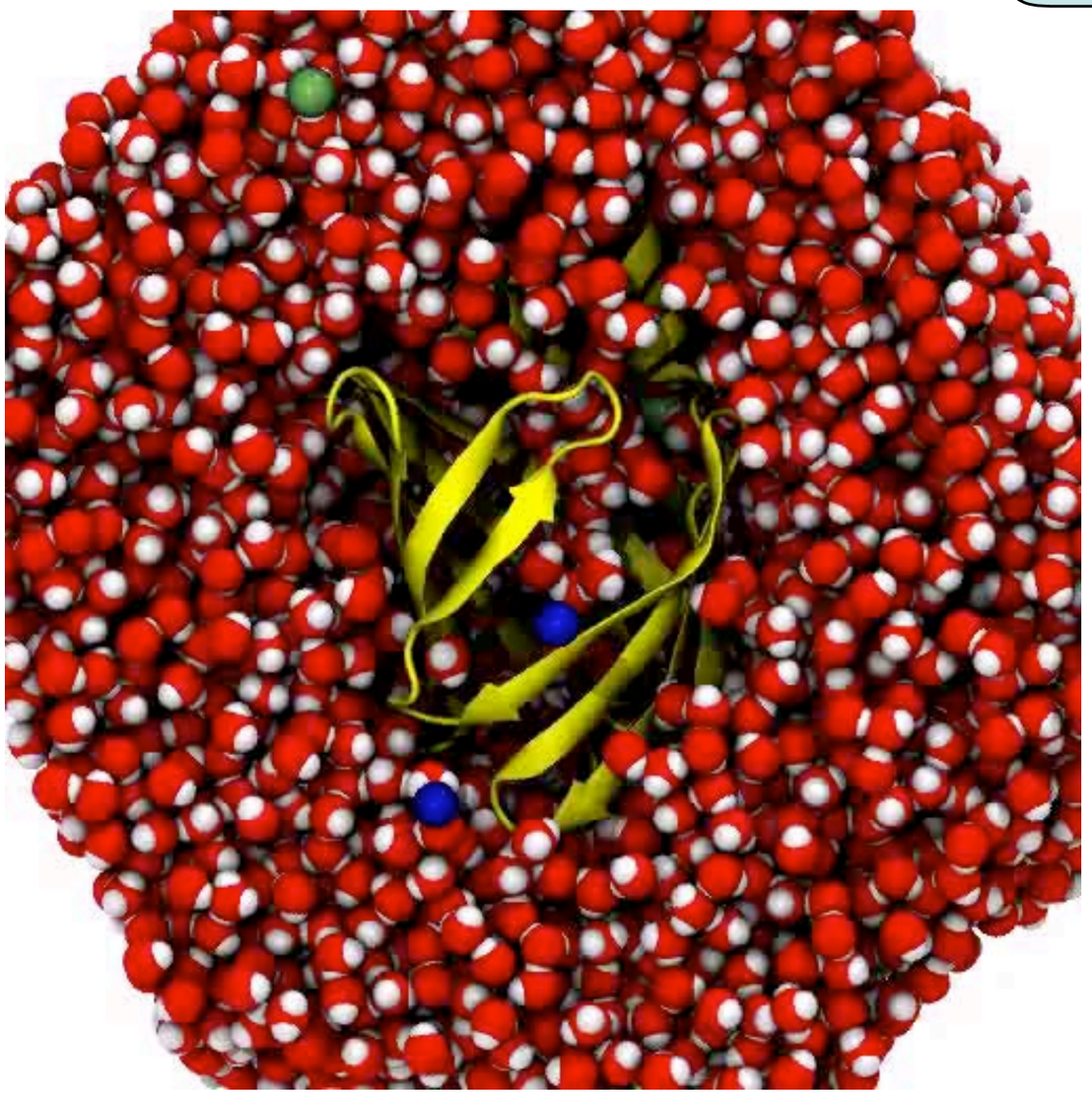
Timesteps:
femtoseconds

Billions to trillions of steps

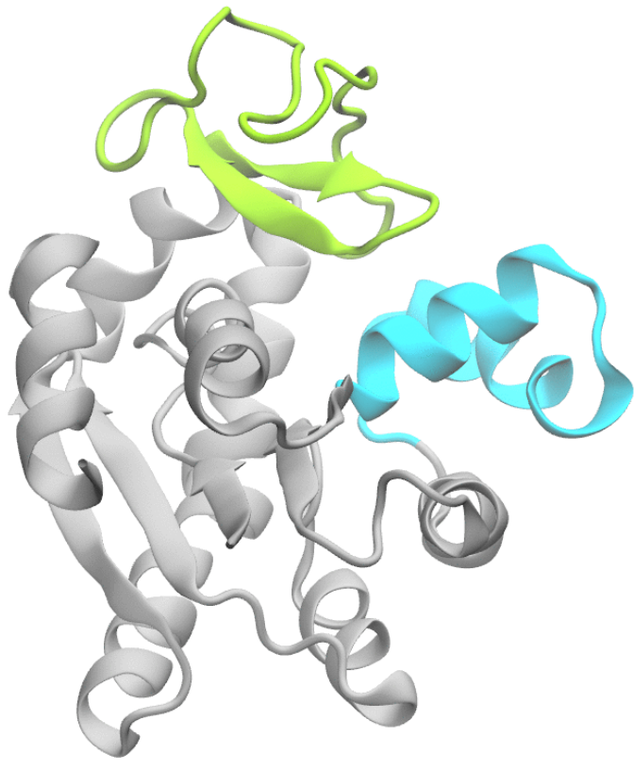
Timescales of interest:
micro- to milliseconds+

- **Explicit solvent** (water)

➡ solvent buffers against electrostatic self-interaction



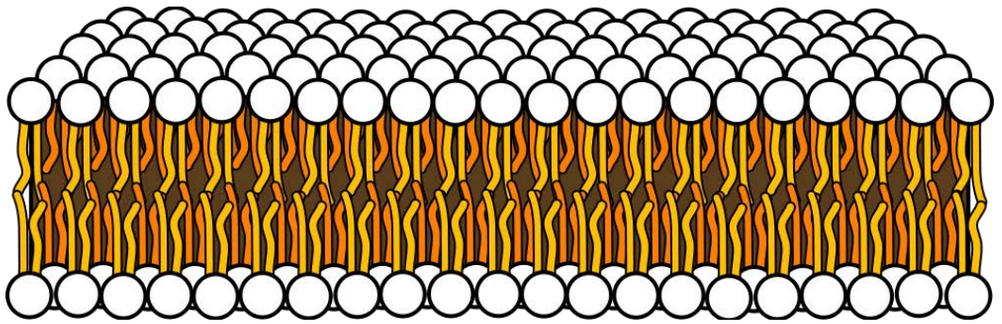
Conformational transitions
- membrane transporters
- ion channel gating
- enzyme/binding kinetics



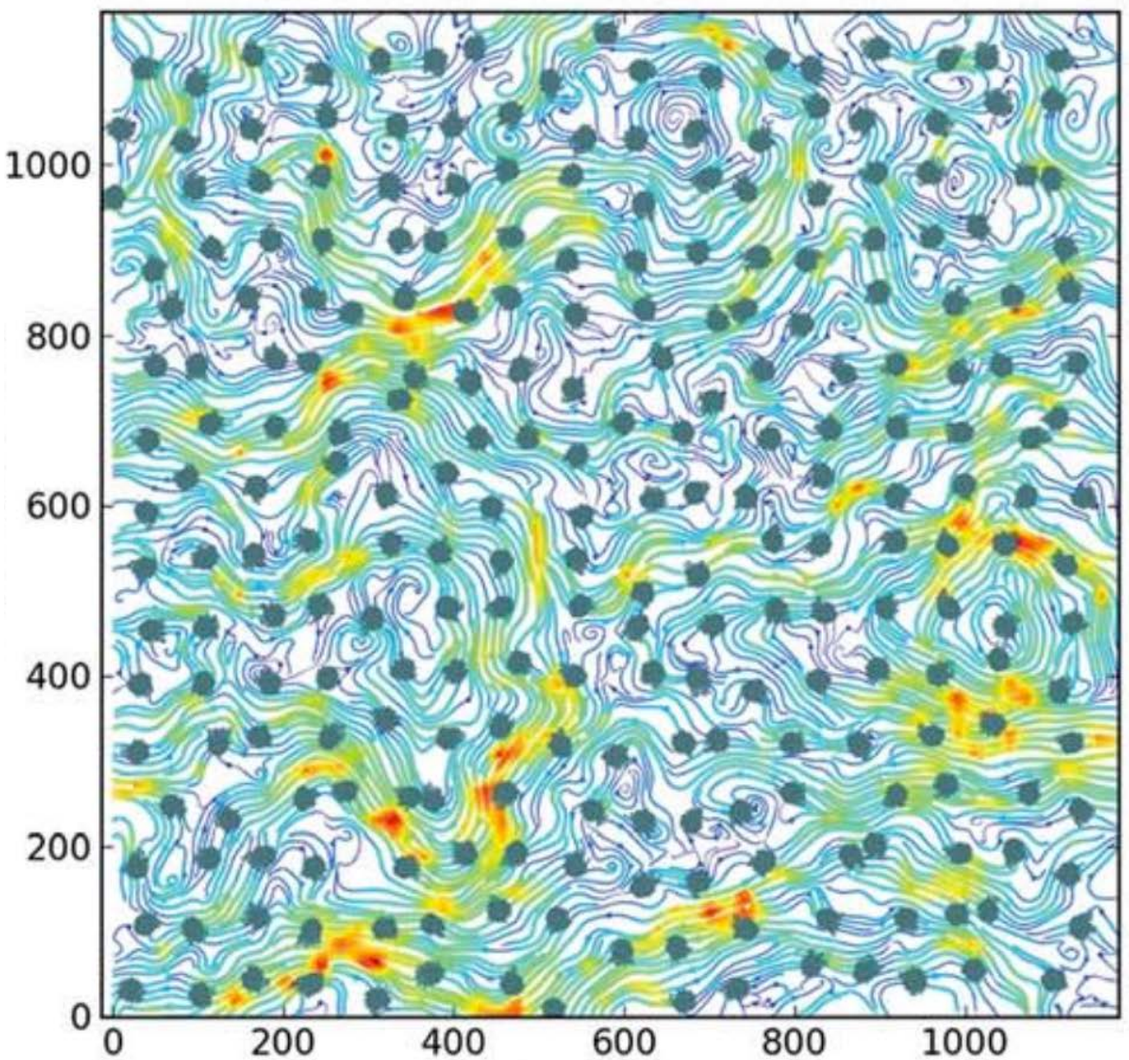
- **Enhanced sampling** (*e.g., targeted MD, metadynamics, replica exchange, …*)

- **Coarse-graining** (*elastic network models, structure-based potentials, …*)
- **Implicit solvation** (*up to 10-100 times cheaper*)

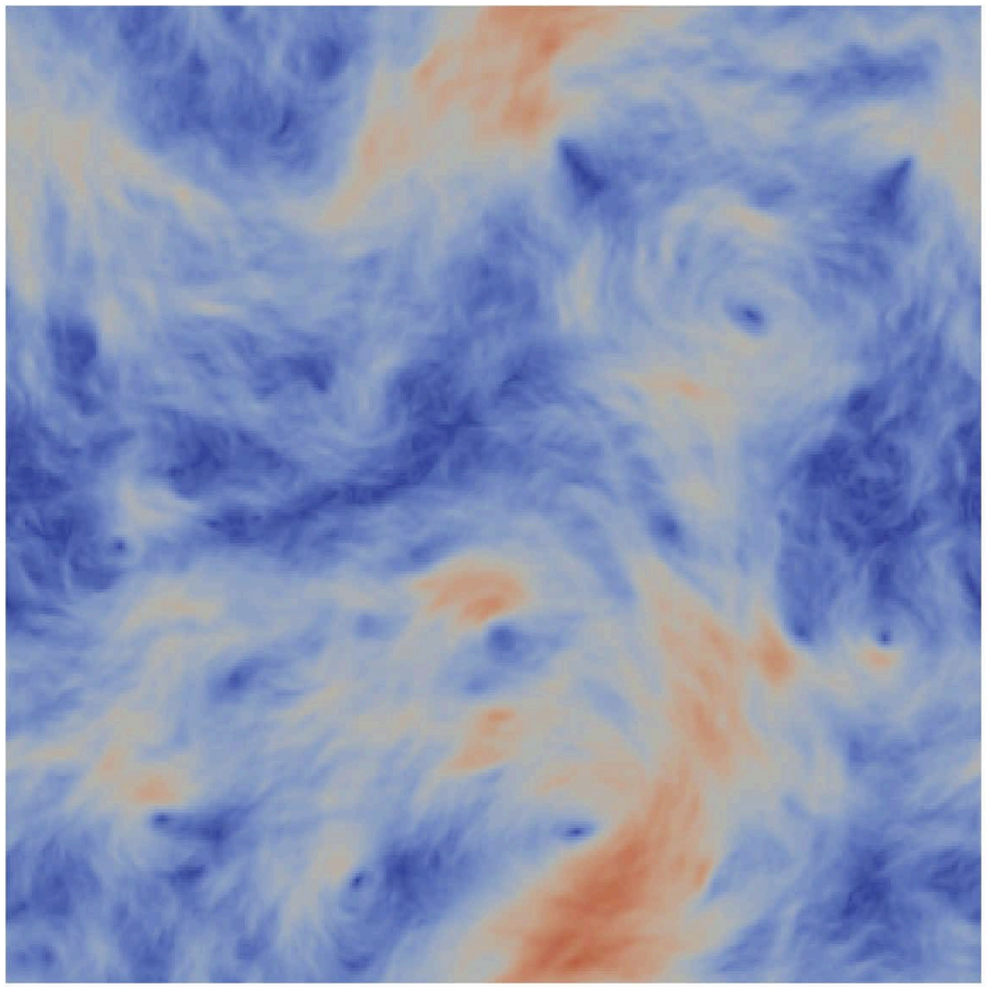
Hydrodynamics in lipid bilayers



Streamlines (velocity field) of a planar lipid



Velocity field (magnitude) for 2D turbulent system



†M. Chavent et al. *Faraday Discussions* **169**, 455 (2014)

Hybrid atomistic-continuum model

Multiscale approach to preserve atomistic detail

- All-atom **MD** in *restricted subdomain*…
- efficient continuum **hydrodynamic** model for *surrounding solvent*

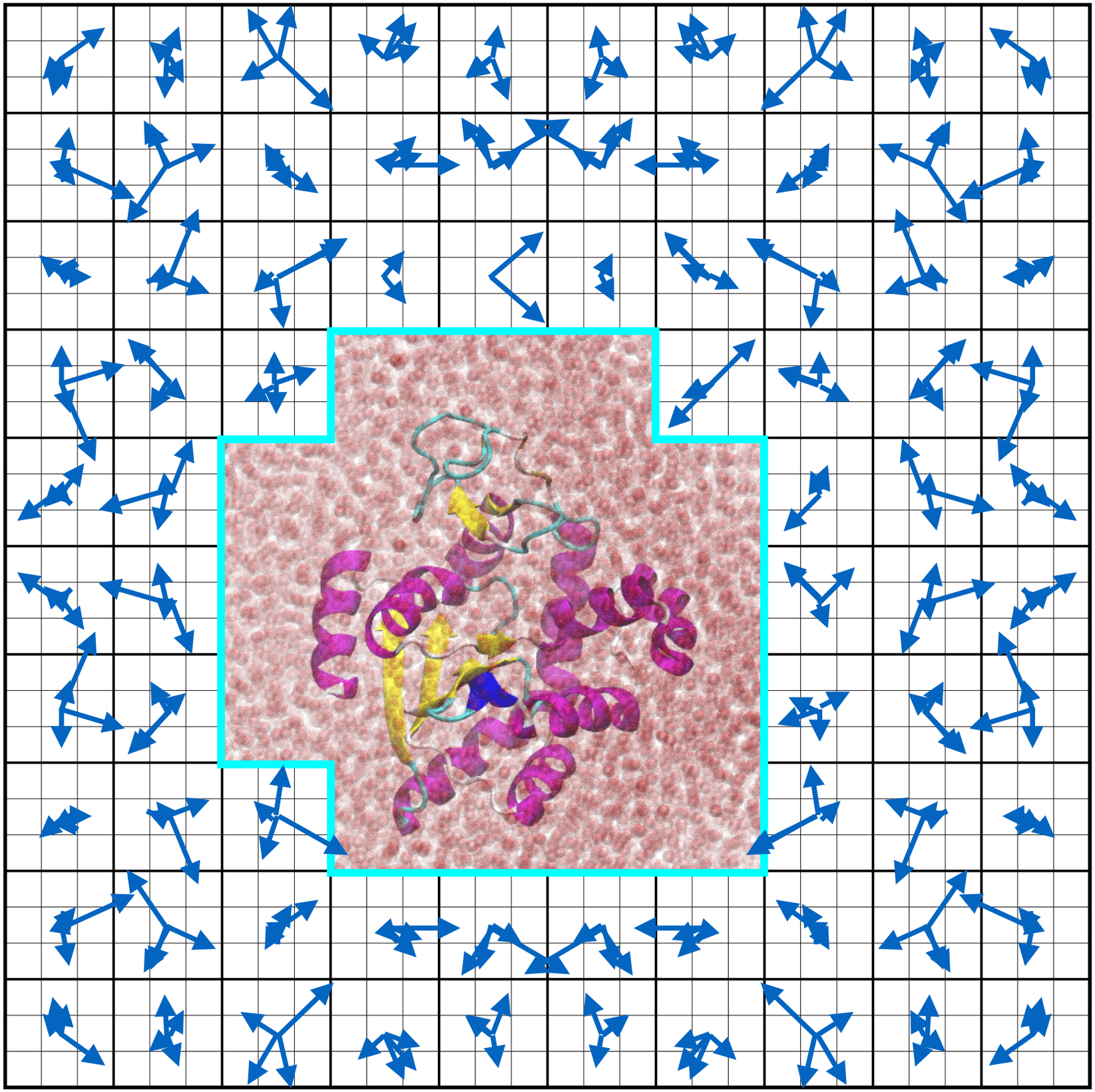
Direct (continuum-solute) coupling

Continuum-solvent coupling

Hybrid approaches are *general*

- E.g.,
  - **DSMC** (vs MD)
  - **Lattice Boltzmann** (vs Navier-Stokes)

The basic idea: less explicit solvent



Basic components

Standard MD codes

- Need: MD engine that supports *biomolecular force fields*
  - open-source
  - interface (**Python**) for communicating w/ external code
- Choice: LAMMPS*‡

3D fluctuating hydrodynamics code

- Need: 3D FVM-like hydro solver for compressible, dense fluids
- Choice: custom discontinuous Galerkin (DG) code†
  - open-source
  - interface (**Python**) for communicating w/ external code

Umbrella (driver) code

- **Python**

† X. Zhao, Y. Yang, & C. E. Seyler. (2014) *J. Comput. Phys.* **278**

* S-H. Ko, et al. (2014) *J. Mech. Sci. Technol.* **28**

‡ F. E. Mackay, et al. (2013) *Comput. Phys. Commun.* **184**

Hydrodynamic equation in conservation form

$$\partial_t \phi + \boldsymbol{\nabla} \cdot (\phi \mathbf{u}) = S(\phi)$$

Mass

$$\partial_t \rho + \boldsymbol{\nabla} \cdot (\rho \mathbf{u}) = 0$$

Account for *thermal fluctuations* in **stress** and heat flux (not shown)†

Momentum

$$\partial_t (\rho \mathbf{u}) + \boldsymbol{\nabla} \cdot \left(\rho \mathbf{u}\mathbf{u} + p\vec{\vec{I}} + \vec{\vec{\sigma}} + \cancel{\vec{\vec{S}}} \right) = 0$$

Energy

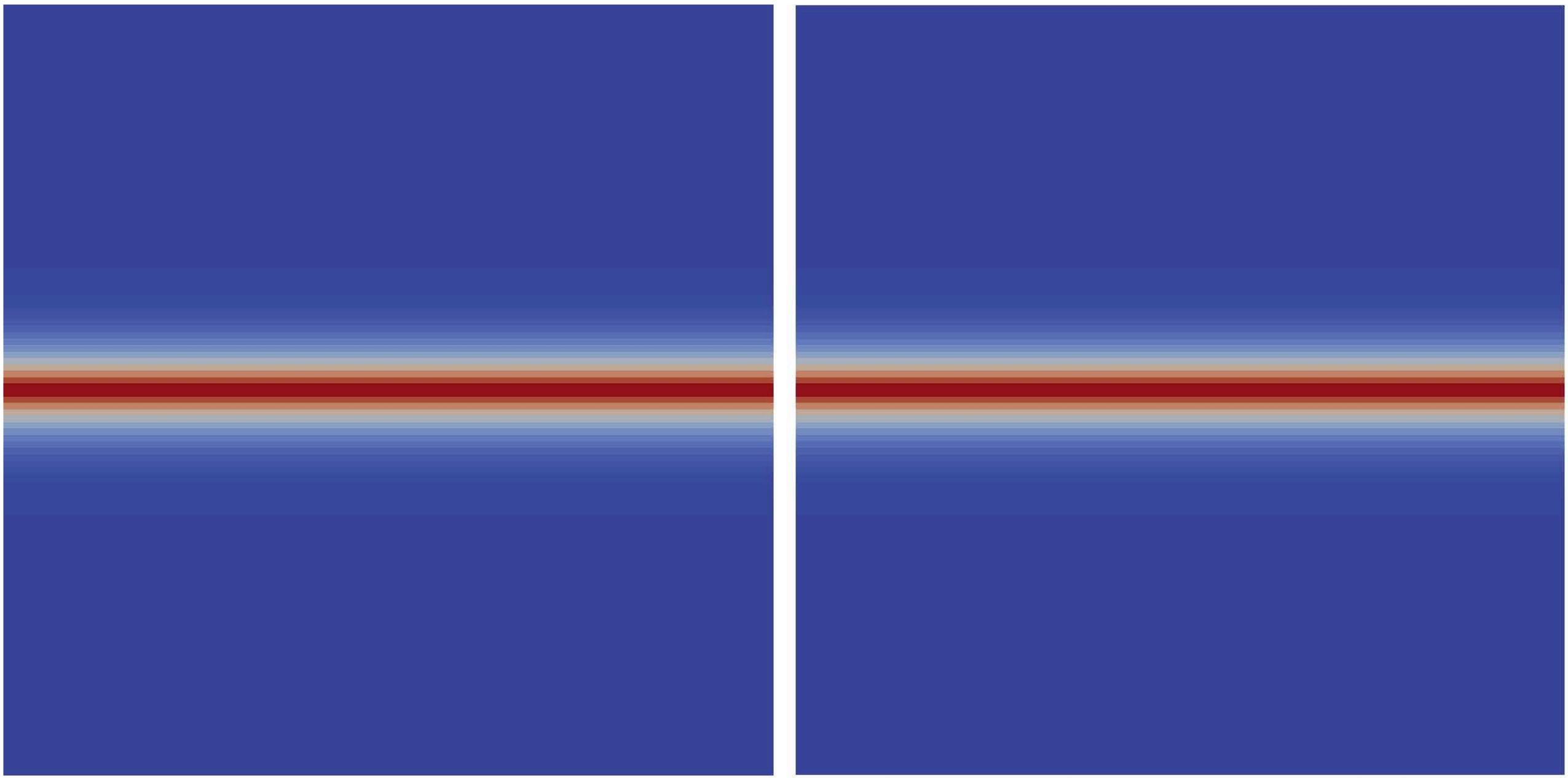
$$\partial_t \mathcal{E} + \boldsymbol{\nabla} \cdot \left[\mathbf{u}(\mathcal{E} + p) + \mathbf{u} \cdot \left(\vec{\vec{\sigma}} + \cancel{\vec{\mathcal{S}}} \right) \right] = 0$$

~~Stress tensor = Navier-Stokes~~ Linearized 10-moment equations

$$\partial_t \vec{\vec{\sigma}} + p_0 \left(\left[\boldsymbol{\nabla}\mathbf{u} + (\boldsymbol{\nabla}\mathbf{u})^\mathsf{T} - \frac{2}{3}(\boldsymbol{\nabla} \cdot \mathbf{u})\vec{\vec{I}} \right] \right) = -\nu \left(\vec{\vec{\sigma}} + \vec{\mathcal{S}} \right)$$

† L. D. Landau & E. M. Lifschitz. (1959) *Fluid Mechanics.* **6**
‡ H. Grad. (1949) *Comm. Pure Appl. Math.* **2**, 331–407

2D nanojet: with and without fluctuations

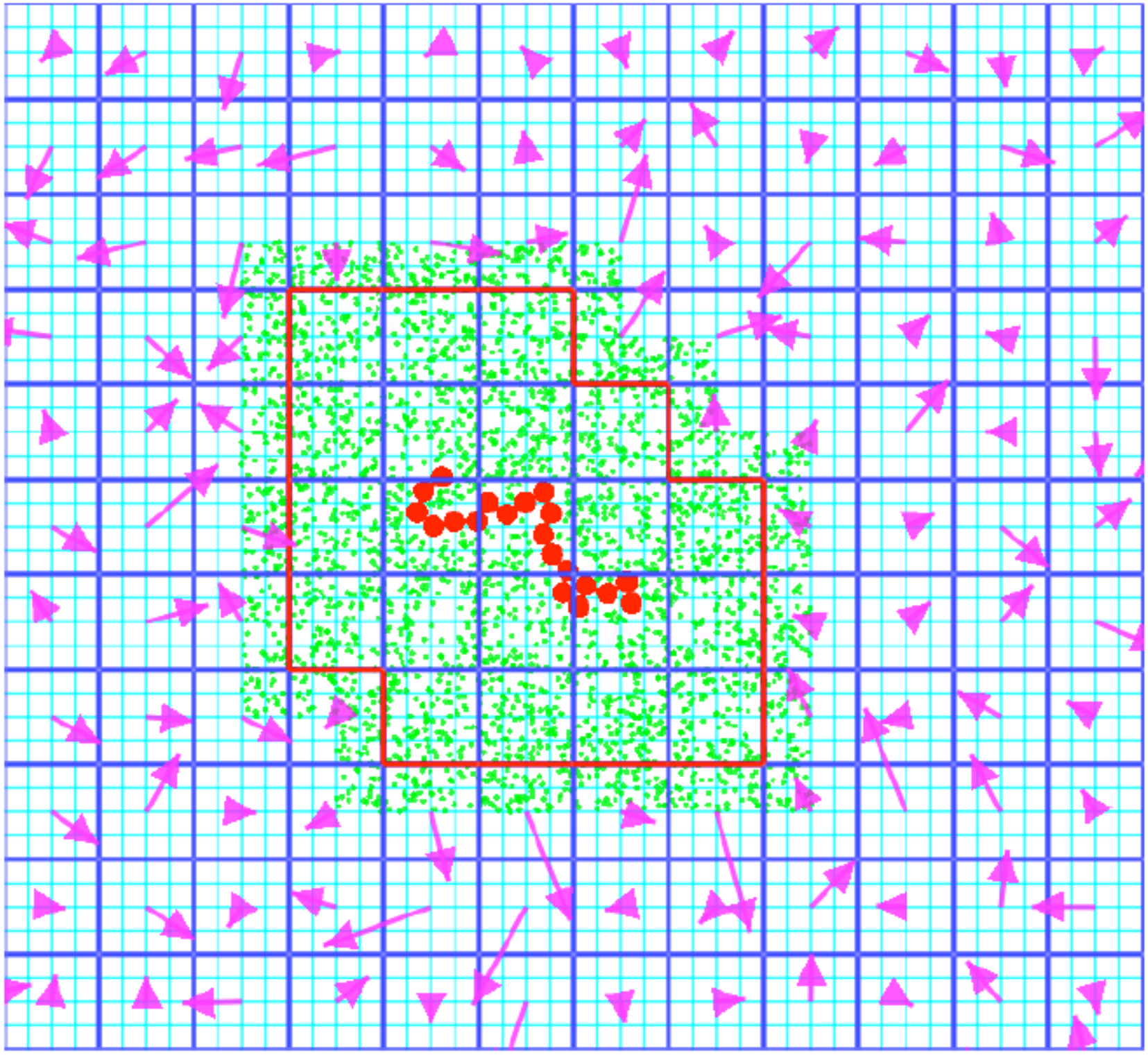


Navier-Stokes

fluctuating hydrodynamics

jet velocity

Coupling via reservoir/buffer region



A. Donev et al. *J. Multiscale Model. Simul.* **8** (2010)

Putting the pieces together

Dynamical coupling

- Communication via “reservoir” particles in overlap region

State variables

$$\rho/\mathbf{x}_i \quad \mathbf{u}/\mathbf{p}_i \quad \mathcal{E}/P/T$$

Fluxes

$$\rho\mathbf{u} \qquad \rho\mathbf{u}\mathbf{u} + p\vec{\vec{I}} + \vec{\vec{\sigma}}$$

$$\mathbf{u}(\mathcal{E} + p) + \mathbf{u} \cdot \vec{\vec{\sigma}}$$

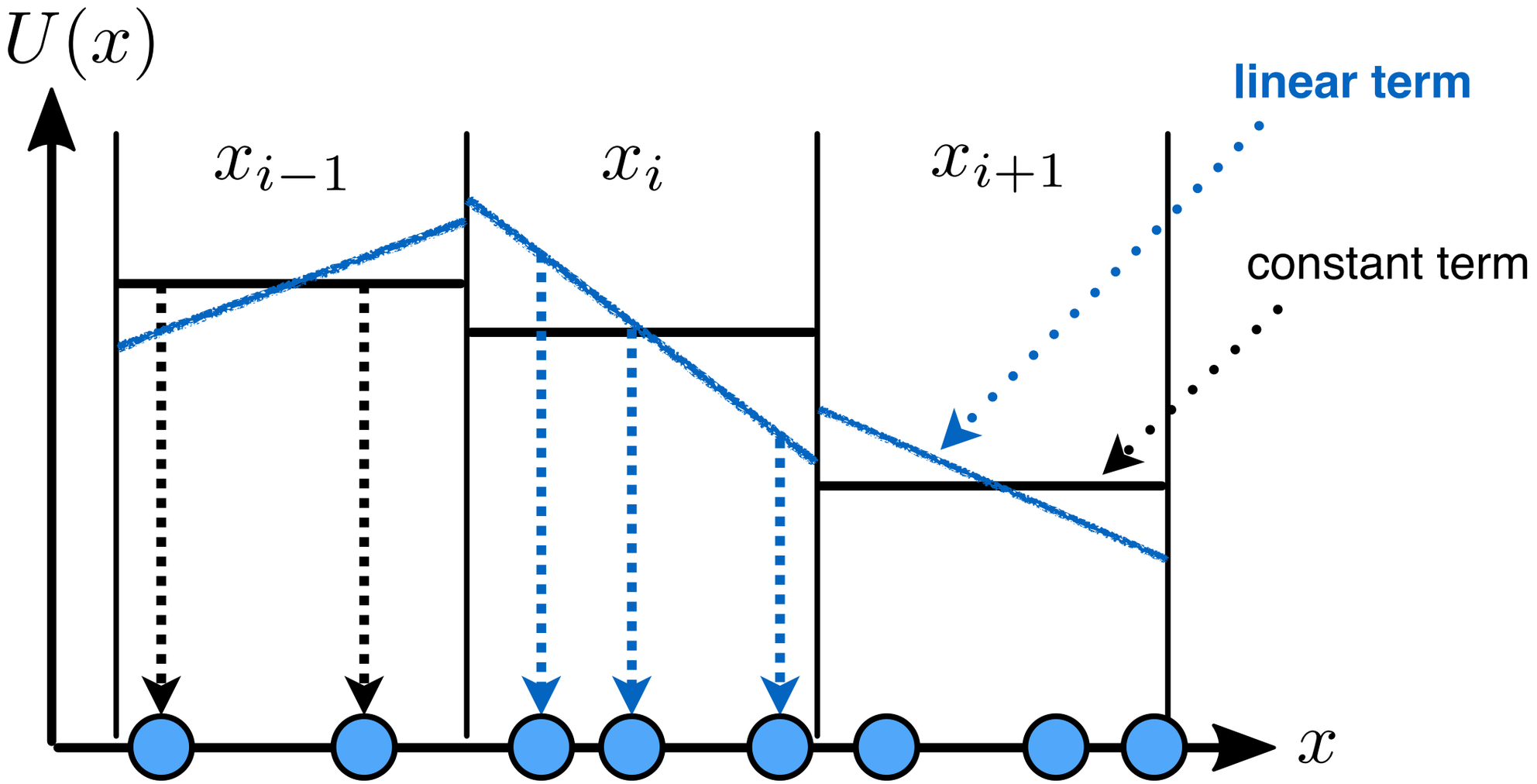
Inter-domain boundary conditions

$\Omega_A \rightarrow \Omega_C$ Simple. Take averages over microscopic variables

$\Omega_C \rightarrow \Omega_A$ Complex. Need mapping from fields variables to atomic coordinates

K. M. Mohamed & A. A. Mohamad. (2010) *Nanofluidics* **8**

Hybrid simulation with DG FHD



- With DG:
  - ➡ natural interpolation from fields to particles
  - ➡ spatial resolution decoupled from fluctuations
- In numerical FHD, grid cell size choice:
  - ➡ sets effective observation scale
  - ➡ determines size of fluctuations

MD

Build topology
Set ICs
Equilibrate

Start HAC simulation

Build mesh
Set fluid properties
Set ICs

FHD

Compute total energies/forces on atoms

Integrate by dt_{MD}

Apply BCs

No

$n = N_{MD}$?

Yes

Get atom data from *reservoir*: (e.g., **x**, **v**, **F**)

End

Yes

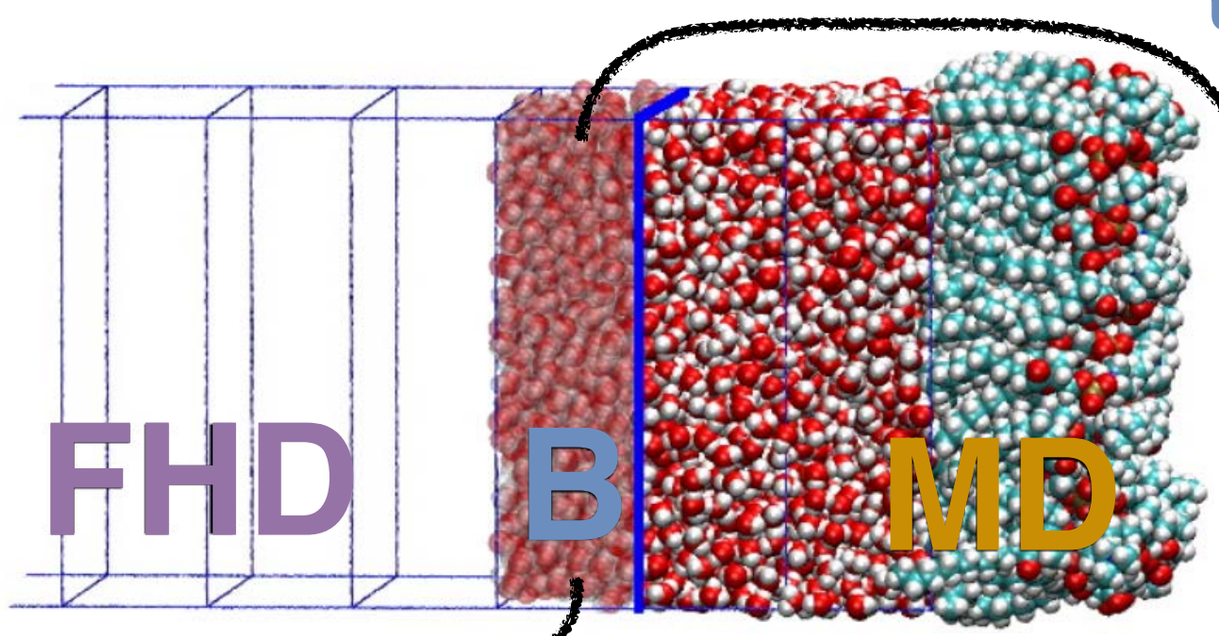
$t > t_{final}$?

No

Apply BCs

Compute fluxes/sources

Integrate by dt_{FHD}



Get fluid data from *reservoir*: (e.g., ρ, **u**, T, p/σ)

To MD

Compute forces on *fluid* due to *atoms*

Compute forces on *atoms* due to *fluid*

To FHD

G. De Fabritiis, et al. (2006) *PRL* **97**

Project status

HERMESHD

- Hyperbolic Equations and Relaxation Model for Extended Systems of HydroDynamics
- Modular code, callable as library via **Python**
- Open source on GitHub (soon)!

Hybrid simulation

- LAMMPS: called as a library using a Python wrapper
- Driver **calls** HERMES/LAMMPS via **Python** interface, **manages** communication

Why Blue Waters?

- HAC simulation test problems $\Longrightarrow$ comparison with pure MD/FHD
- Get physics of coupling right (e.g., EOS from MD for various water models[‡])

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```python
from mpi4py import MPI
import numpy as np
from hermeshd import hermeshd

nx, ny, nz = 80, 80, 1  # 80 x 80 x 1 grid
nq, nB = 11, 8          # 11 eqns (10-moment), 8 basis funcs
t  = np.array(0.00, dtype=float)    # current time
dt = np.array(0.01, dtype=float)    # time step
tf = np.array(10.0, dtype=float)    # final time
dtout = np.array(0.0, dtype=float)  # output frequency

# data arrays for fluid variables: Qio is primary array
Qio = np.empty((nx,ny,nz,nQ,nB), order='F', dtype=np.float32)
Q1  = np.empty_like(Qio)  # temp array
Q2  = np.empty_like(Qio)  # temp array

hermeshd.setup(Qio, t, dt, dtout, MPI.COMM_WORLD.py2f())
while ( t < tf ):
    hermeshd.step(Qio, Q1, Q2, t, dt)
    hermeshd.output(Qio, t, dt, dtout)
hermeshd.cleanup()
```

Run from command line: `mpirun -n 16 python test.py`

f90wrap. http://www.jrkermode.co.uk/f90wrap
P. Peterson. (2009) *Int. J. Comput. Sci. Eng.* **4**, 296–305.

The Ten Moment Equations (Grad's Approach)

$$\partial_t \rho + \partial_{x_k}(\rho u_k) = 0$$

Continuity equation

$$\partial_t(\rho u_i) + \partial_{x_k}\mathcal{E}_{ik} = 0$$

Momentum equation

$$\partial_t \mathcal{E}_{ij} + \partial_{x_k}(\rho u_i u_j u_k + u_i P_{jk} + u_j P_{ki} + u_k P_{ij}) = -\nu S_{ij}$$

Energy equation

$$\mathcal{E}_{ij} = \rho u_i u_j + P_{ij}$$

Total energy tensor

$$P_{ij} = \delta_{ij} p + S_{ij}$$

Pressure tensor

scalar pressure

deviatoric stress tensor

Collision frequency → $\nu = p/\mu$ ← dynamic viscosity

Ten Moment Equations

$$\partial_t \rho + \partial_{x_k}(\rho u_k) = 0 \qquad \partial_t(\rho u_i) + \partial_{x_k}\mathcal{E}_{ik} = 0$$

$$\partial_t \mathcal{E}_{ij} + \partial_{x_k}(\rho u_i u_j u_k + u_i P_{jk} + u_j P_{ki} + u_k P_{ij}) = -\nu S_{ij}$$

$$\mathcal{E}_{ij} = \rho u_i u_j + P_{ij} \qquad P_{ij} = \delta_{ij} p + S_{ij}$$

Component form

$$\partial_t \rho + \nabla \cdot (\rho \mathbf{u}) = 0 \qquad \partial_t(\rho \mathbf{u}) + \nabla \cdot \vec{\vec{\mathcal{E}}} = 0$$

$$\partial_t \vec{\vec{\mathcal{E}}} + \nabla \cdot \left(\rho \mathbf{uuu} + 3\,\mathbf{Sym}\{\mathbf{u}\vec{\vec{P}}\} \right) = -\nu \vec{\vec{S}}$$

$$\vec{\vec{\mathcal{E}}} = \rho \mathbf{uu} + \vec{\vec{P}} \qquad \vec{\vec{P}} = \vec{\vec{I}}\, p + \vec{\vec{S}}$$

Vector Form

Navier-Stokes equations (neglecting heat flow)

$$\partial_t \rho + \partial_{x_k}(\rho u_k) = 0$$

$$\partial_t(\rho u_i) + \partial_{x_k}\left(\rho u_i u_k + \delta_{ik} p + S_{ik}\right) = 0$$

$$\partial_t \mathcal{E} + \partial_{x_k}\left[u_k\left(\mathcal{E} + p\right)\right] = 0$$

$$S_{ij} = -\mu\left(\partial_{x_i} u_j + \partial_{x_j} u_i - \frac{2}{3}\delta_{ij}\partial_{x_k} u_k\right)$$

$$\partial_t \rho + \nabla \cdot (\rho \mathbf{u}) = 0$$

$$\partial_t(\rho \mathbf{u}) + \nabla \cdot \left(\rho \mathbf{u}\mathbf{u} + \vec{\vec{I}} p + \vec{\vec{S}}\right) = 0$$

$$\partial_t \mathcal{E} + \nabla \cdot \left[\mathbf{u}\left(\mathcal{E} + p\right)\right] = 0$$

$$\vec{\vec{S}} = -\mu\left(2\,\mathbf{Sym}\{\nabla \mathbf{u}\} - \frac{2}{3}\vec{\vec{I}}\nabla \cdot \mathbf{u}\right)$$

Component form

Vector form

$$\mathcal{E} = \frac{p}{\gamma - 1} + \frac{1}{2}\rho u^2$$

Equation for pressure