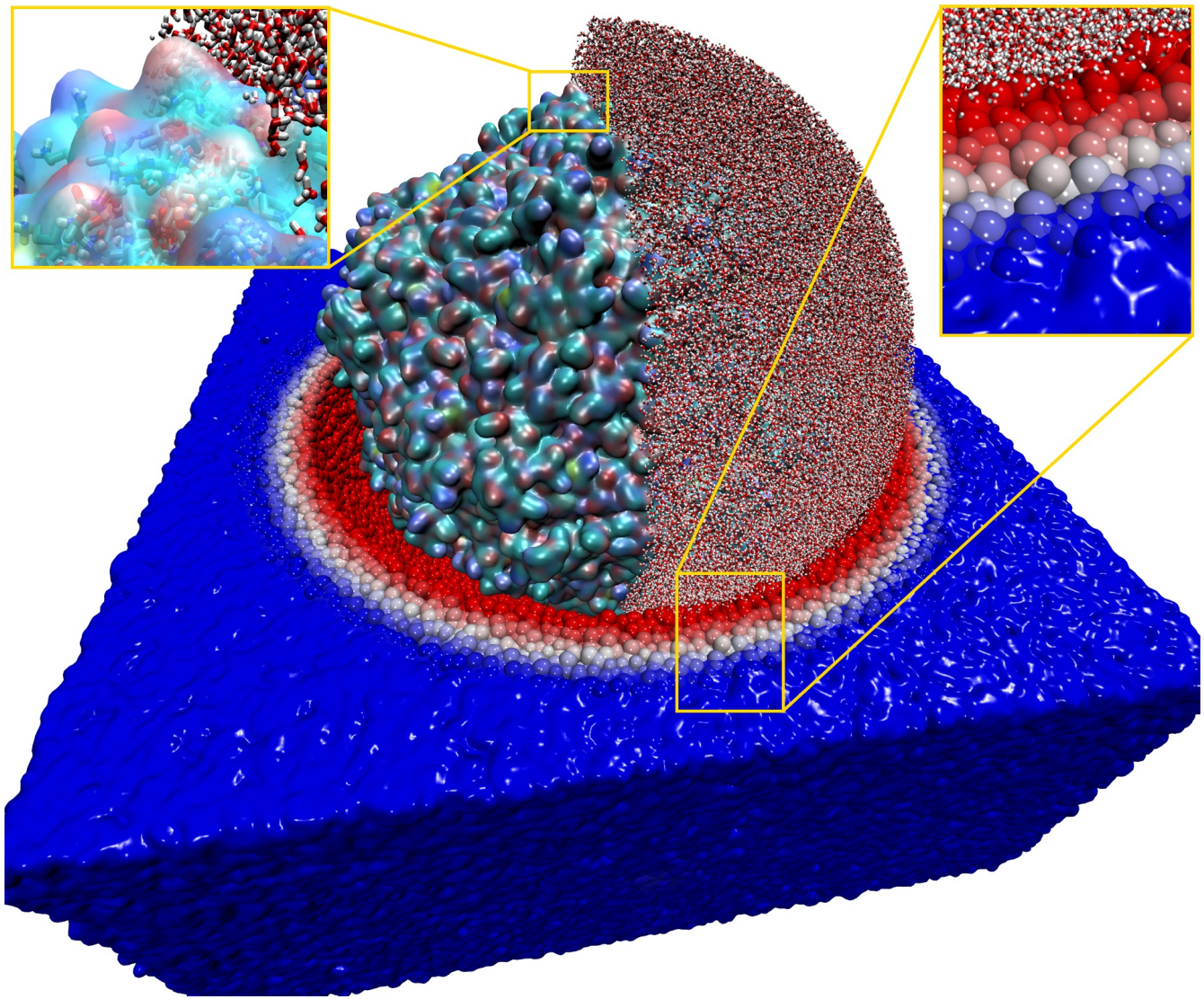
Aston University
Birmingham

hybrid MD/hydrodynamics modelling



Hybrid Molecular Dynamics/hydrodynamics modelling of liquid solutions of complex molecular systems: whole virus at atomistic resolution

Dmitry Nerukh, Sergey Karabasov, Elvira Tarasova, Ivan Korotkin, Vladimir Farafonov

Aston University, UK,
Queen Mary University of London, UK,
Baltic Federal University, Russia
Kharkov National University, Ukraine

EMLG 2016

Acknowledgements

EMLG

G8, EPSRC, Royal Academy of Engineering, Sasakawa foundation

Aston University
Birmingham

Talk outline

I. Our hybrid MD/hydrodynamics approach

II. Whole virus simulations

III. Conceptual points about multiscale description of liquids

Aston University
Birmingham

Talk outline

I. **Our hybrid MD/hydrodynamics approach**

II. Whole virus simulations

III. Conceptual points about multiscale description of liquids

Motivation

JOURNAL OF VIROLOGY, Aug. 2011, p. 7856–7862 Vol. 85, No. 15
0022-538X/11/$12.00 doi:10.1128/JVI.00737-11

The 2.3-Angstrom Structure of Porcine Circovirus 2[▽]

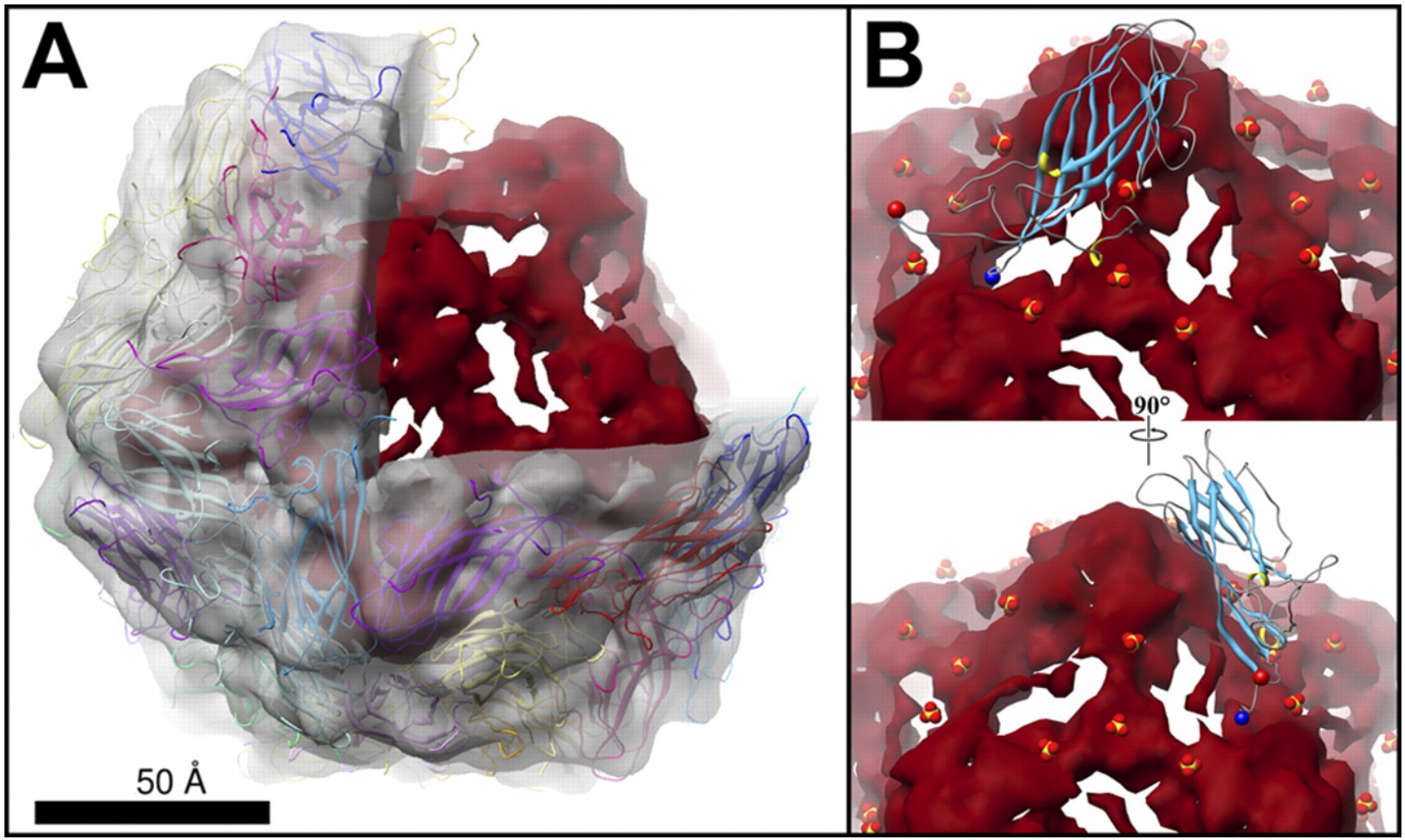
Reza Khayat,[1]* Nicholas Brunn,[1]† Jeffrey A. Speir,[1] John M. Hardham,[2] Robert G. Ankenbauer,[2] Anette Schneemann,[1] and John E. Johnson[1]*

Department of Molecular Biology, The Scripps Research Institute, La Jolla, California 92037,[1] and Veterinary Medicine Research & Development, Pfizer, Inc., 333 Portage Road, Kalamazoo, Michigan 49007[2]

Received 12 April 2011/Accepted 18 May 2011

Porcine circovirus 2 (PCV2) is a T=1 nonenveloped icosahedral virus that has had severe impact on the swine industry. Here we report the crystal structure of an N-terminally truncated PCV2 virus-like particle at 2.3-Å resolution, and the cryo-electron microscopy (cryo-EM) image reconstruction of a full-length PCV2 virus-like particle at 9.6-Å resolution. This is the first atomic structure of a circovirus. The crystal structure revealed that the capsid protein fold is a canonical viral jelly roll. The loops connecting the strands of the jelly roll define the limited features of the surface. Sulfate ions interacting with the surface and electrostatic potential calculations strongly suggest a heparan sulfate binding site that allows PCV2 to gain entry into the cell. The crystal structure also allowed previously determined epitopes of the capsid to be visualized. The cryo-EM image reconstruction showed that the location of the N terminus, absent in the crystal structure, is inside the capsid. As the N terminus was previously shown to be antigenic, it may externalize through viral "breathing."

Motivation



Motivation

- Other large organnels are measured: human ribosome [A. Ben-Shem, Science (2011)], photosystem complex [Y. Umena, Nature (2011)], another virus [P. Plevka, Science (2012)].

- HIV whole virus capsid has been MD simulated [Klaus Schulten, accepted to Nature Comm.].

- Why virus?: the ability of surviving in isolation is exciting.

Do we need multiscale?

Technical limitations of plain MD:

- water molecules come and go;

Do we need multiscale?

Technical limitations of plain MD:

- water molecules come and go;
- many processes in virus are slow, hydrodynamics should "talk" to atoms;

Do we need multiscale?

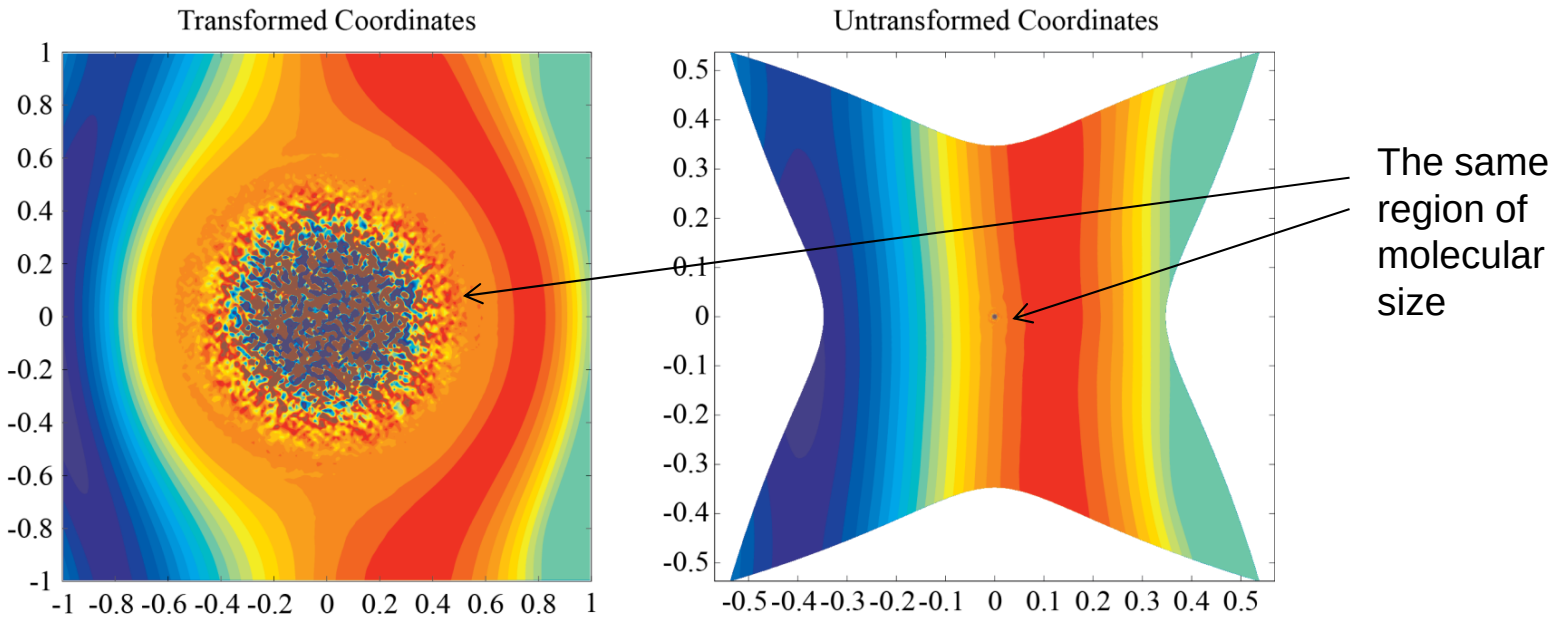
Technical limitations of plain MD:

- water molecules come and go;
- many processes in virus are slow, hydrodynamics should "talk" to atoms;
- regions with atomistic resolution should change in time.

Multiphysics/Multiscale

Transformed (zoomed-in) space & time

Physical (uniform) space & time

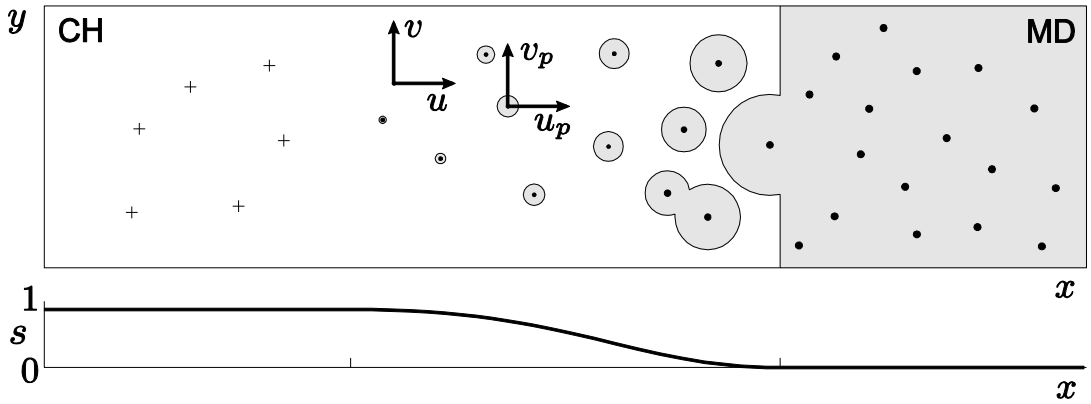


AP Markesteijn and SA Karabasov, *J. Comput. Phys.*, **258**, 137 (2014)

The idea

- We mix the atomistic and hydrodynamic representations of the same liquid.
- For hydrodynamics we use Landau-Lifshitz Fluctuating Hydrodynamics (LL-FH) equations that are a generalisation of the Navier-Stokes (NS) equations.
- For atomistic we use standard MD.
- The representations are connected such that the fundamental conservation laws (mass, momentum, energy) are satisfied locally at hydrodynamic scale.

The model



- 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.

Mass conservation

For HD phase:

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

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.

Restricted dynamics

The deviations of

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

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

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

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

Restricted dynamics

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

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

The sources J and J_2

From these constrains the source J can be found:

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

Modified MD equations

For known source J (and J_2 for the momentum) MD equations are modified to preserve macroscopic conservation laws:

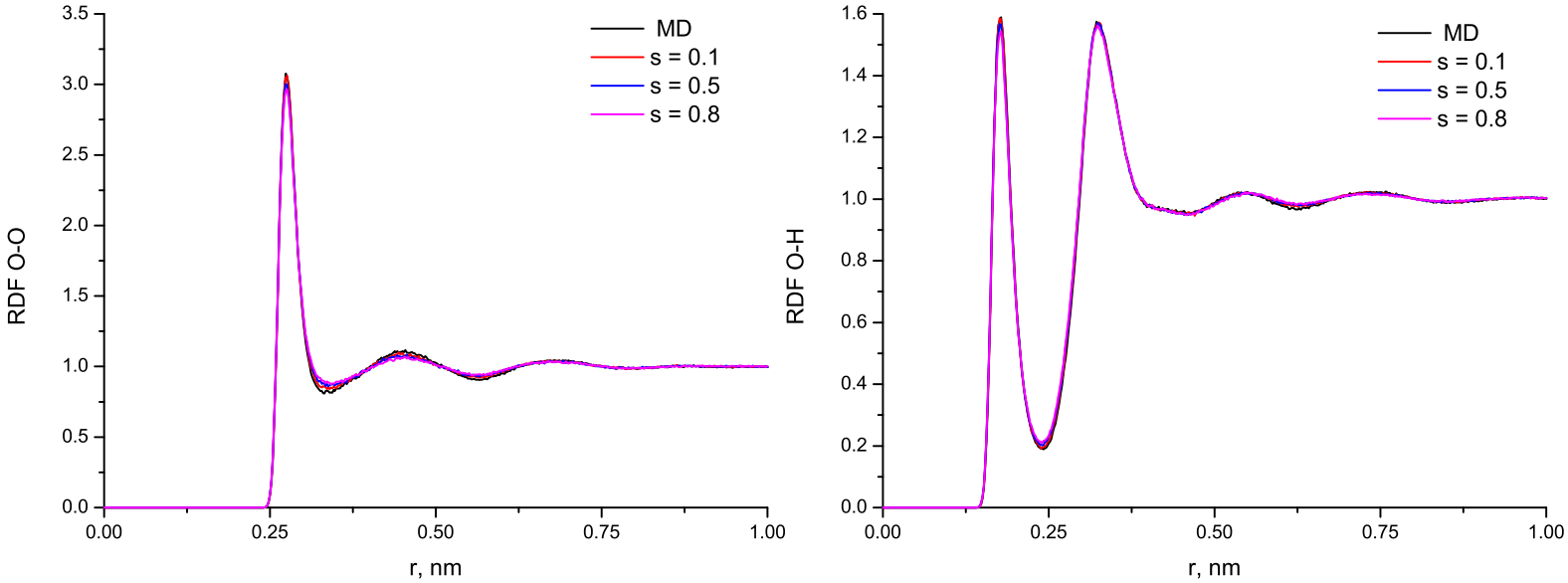
$$\frac{dx_{ip}}{dt} = u_{ip} + s(u_i - u_{ip}) + s(1-s)\alpha \frac{\partial}{\partial x_i}\left(\tilde{\rho} - \sum_{p=1,N(t)} \rho_p\right) \frac{1}{\rho_p N(t)},$$

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

Results: a peptide in water

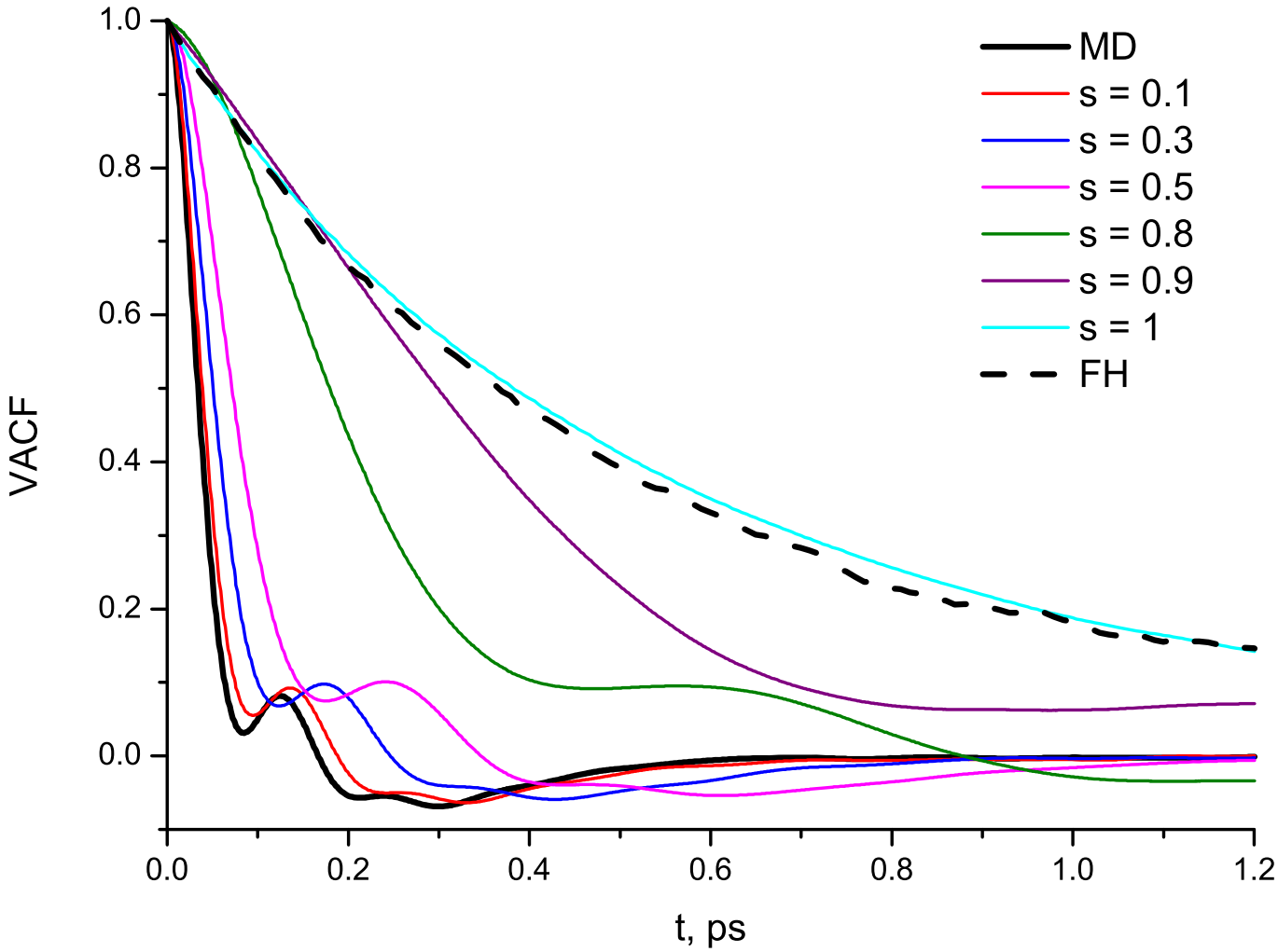
Variable coupling: atomistic core and continuum bulk
Video for dialanine

Results: structure of water



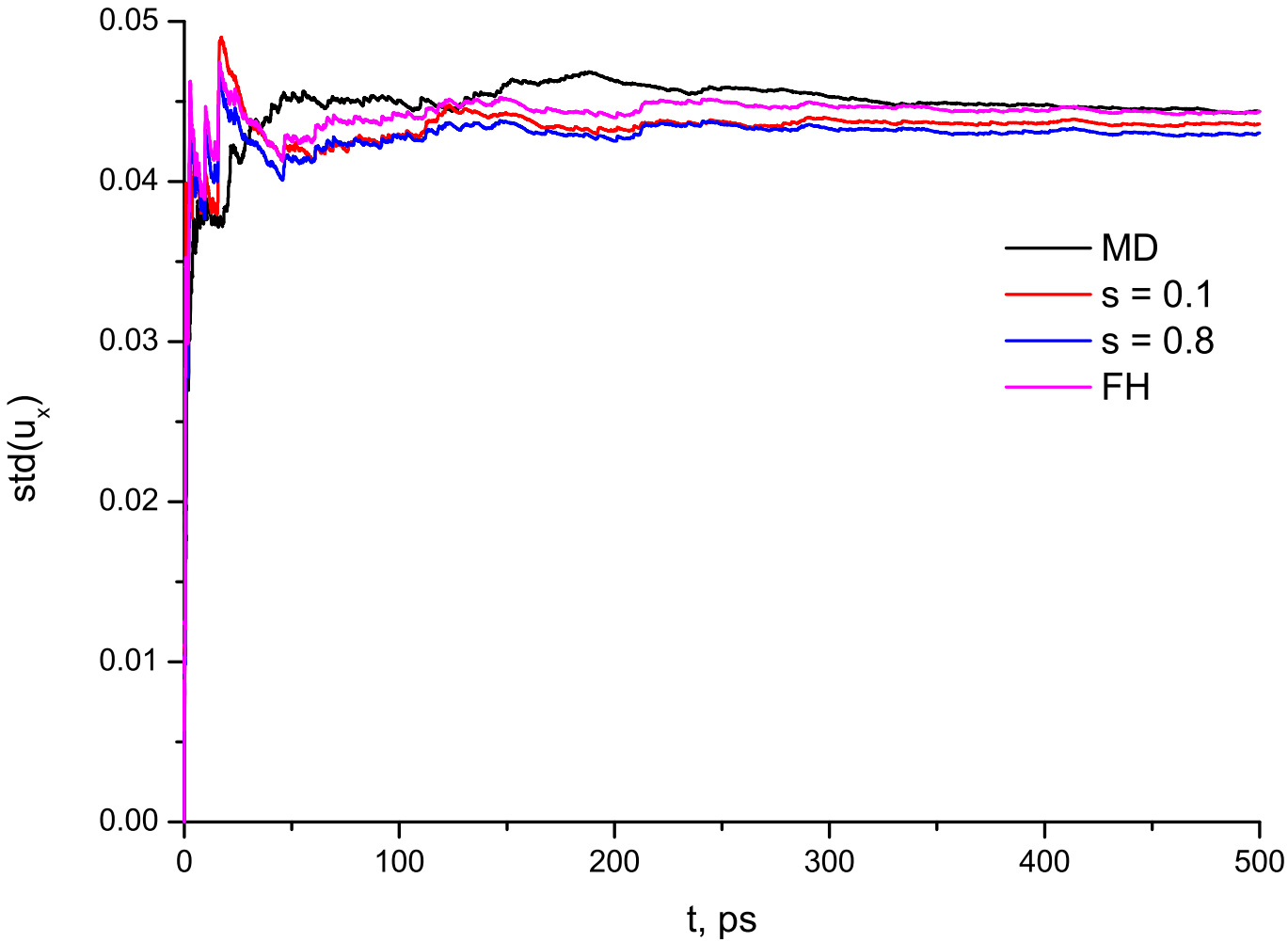
Radial distribution functions of SPC/E water model

Results: dynamics water



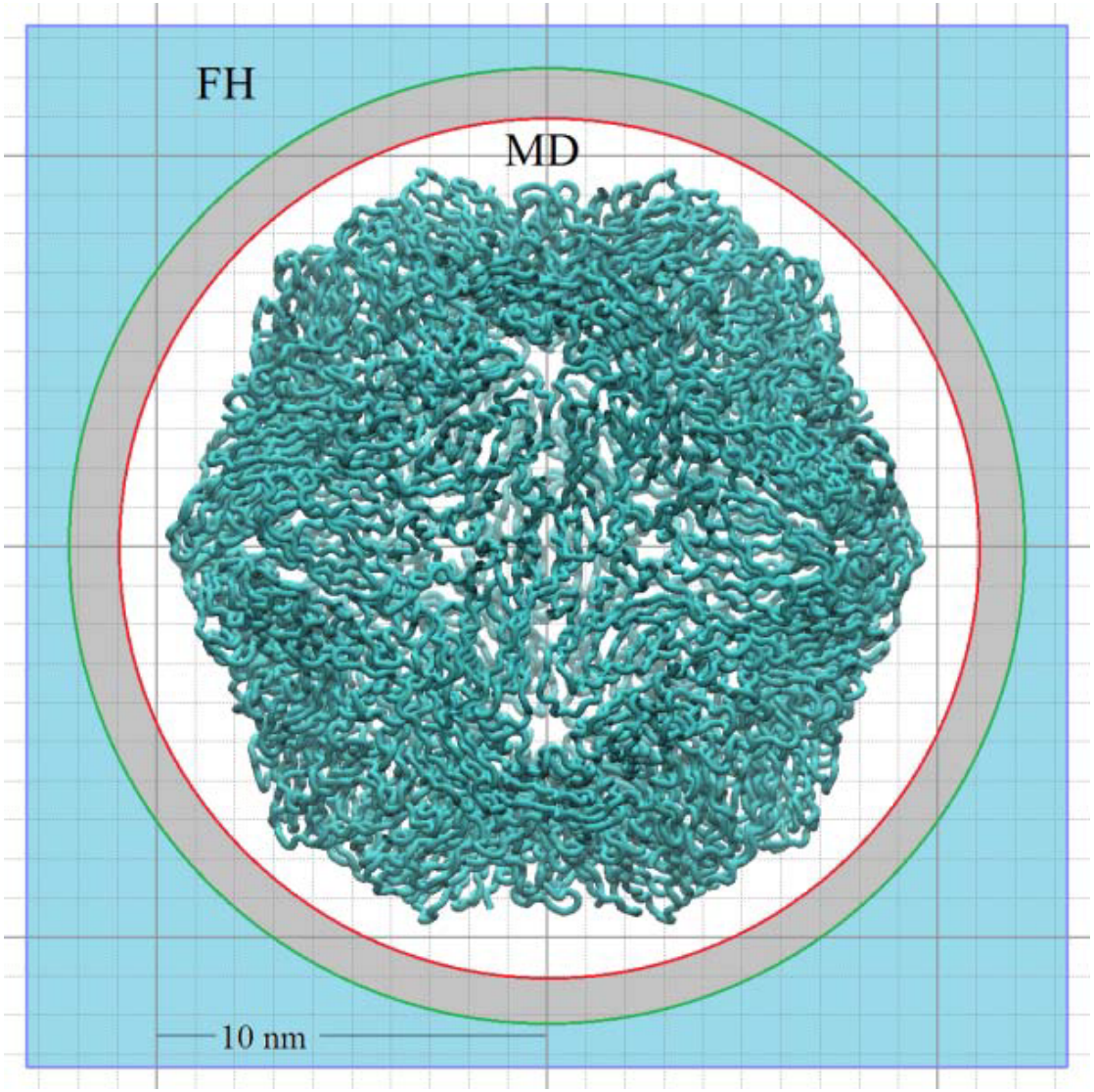
Velocity autocorrelation function of the SPC/E water

Results: fluctuations in water

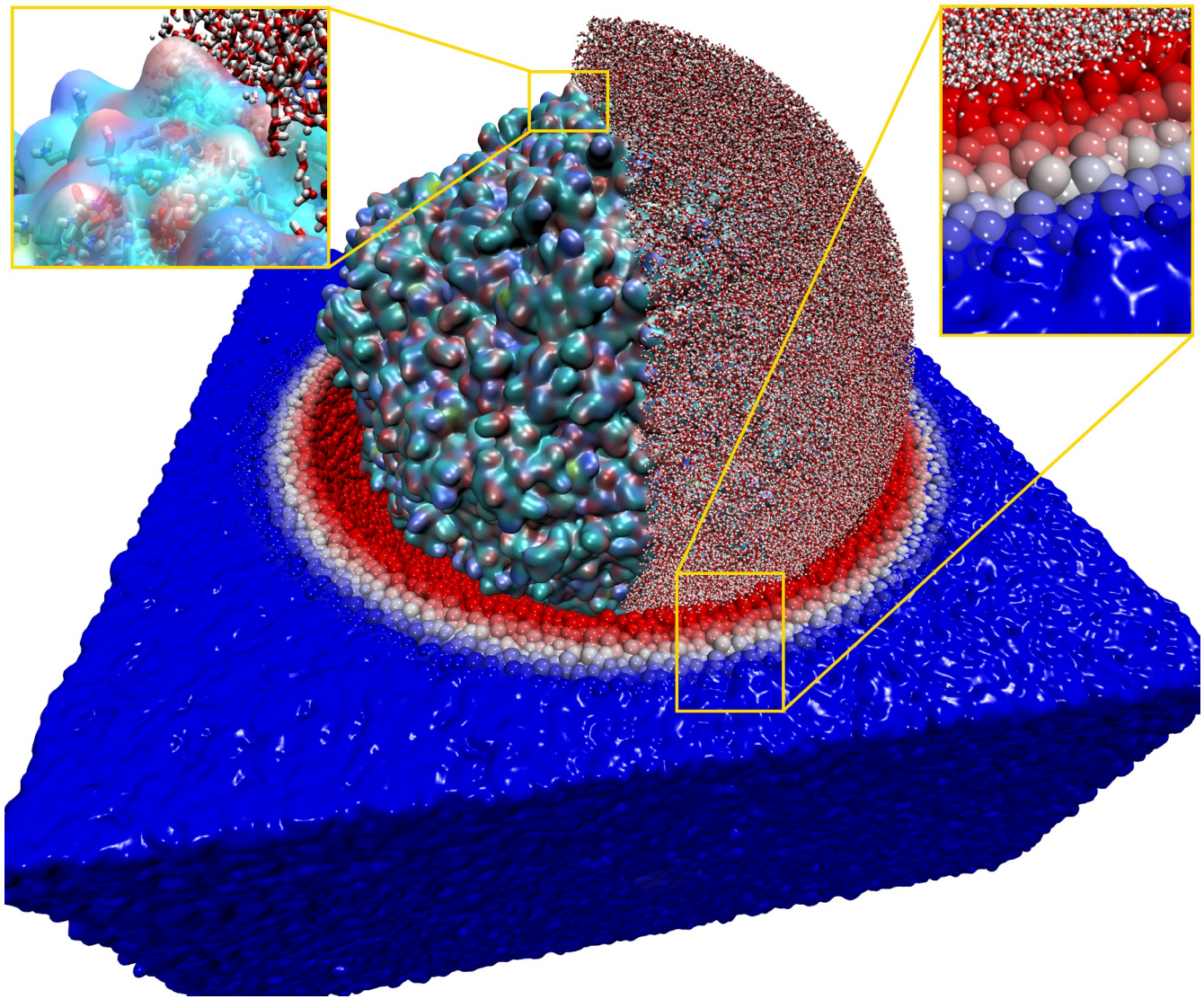


Standard deviations of the velocity x component for SPC/E water

Results: whole virus in water



Results: whole virus in water



Aston University
Birmingham

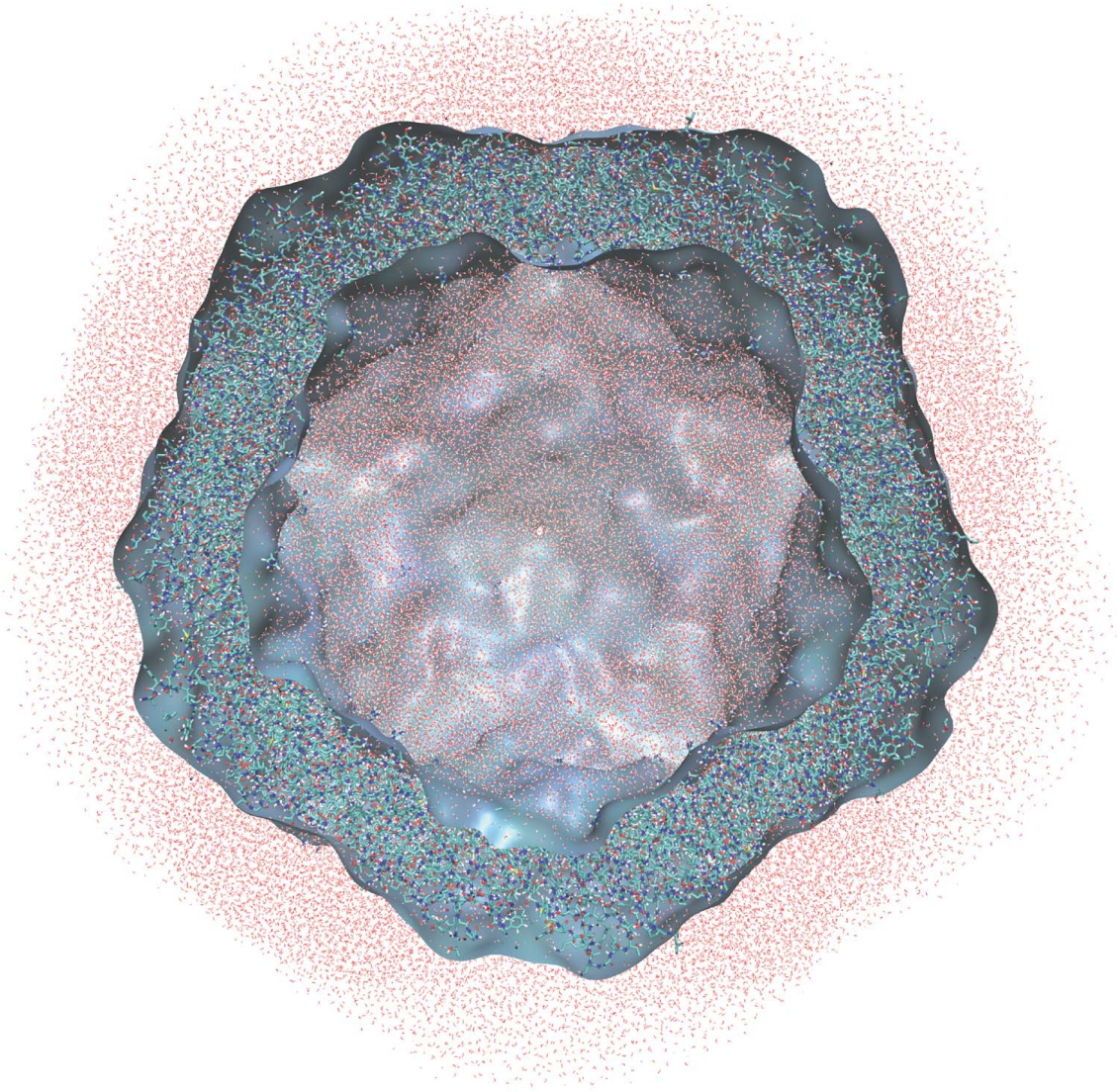
Talk outline

I. Our hybrid MD/hydrodynamics approach

II. **Whole virus simulations**

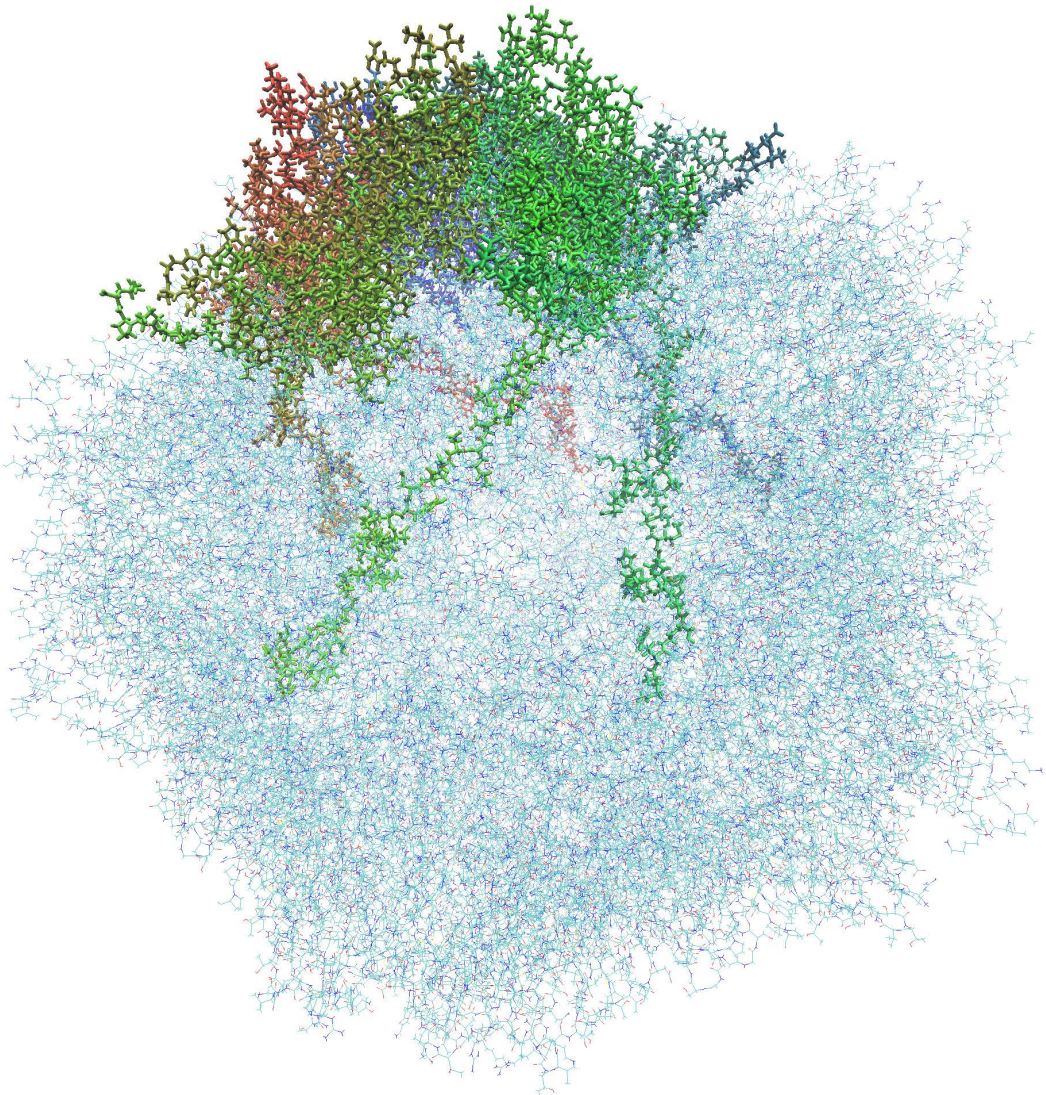
III. Conceptual points about multiscale description of liquids

PCV2 at full atom resolution



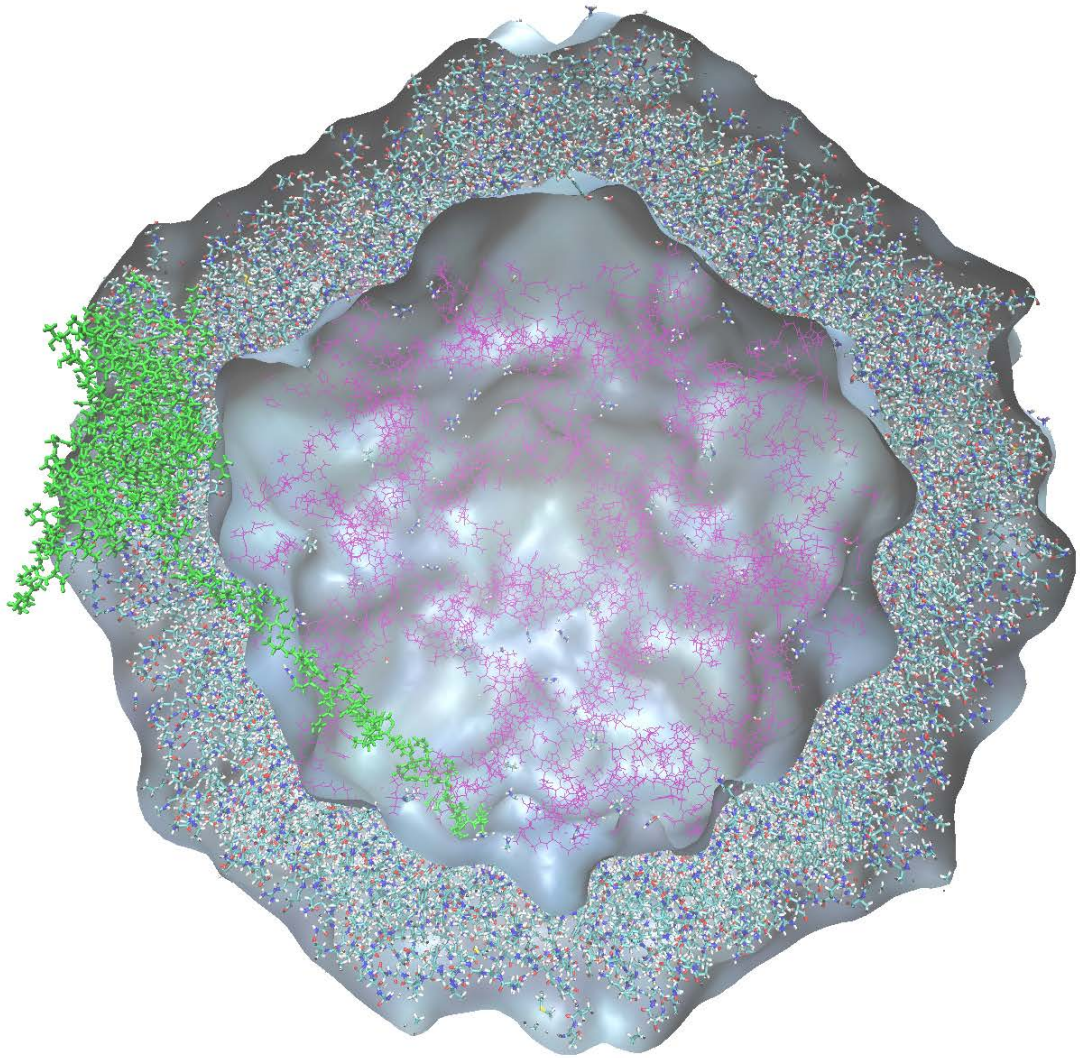
Aston University
Birmingham

PCV2: invisible ‘tails’

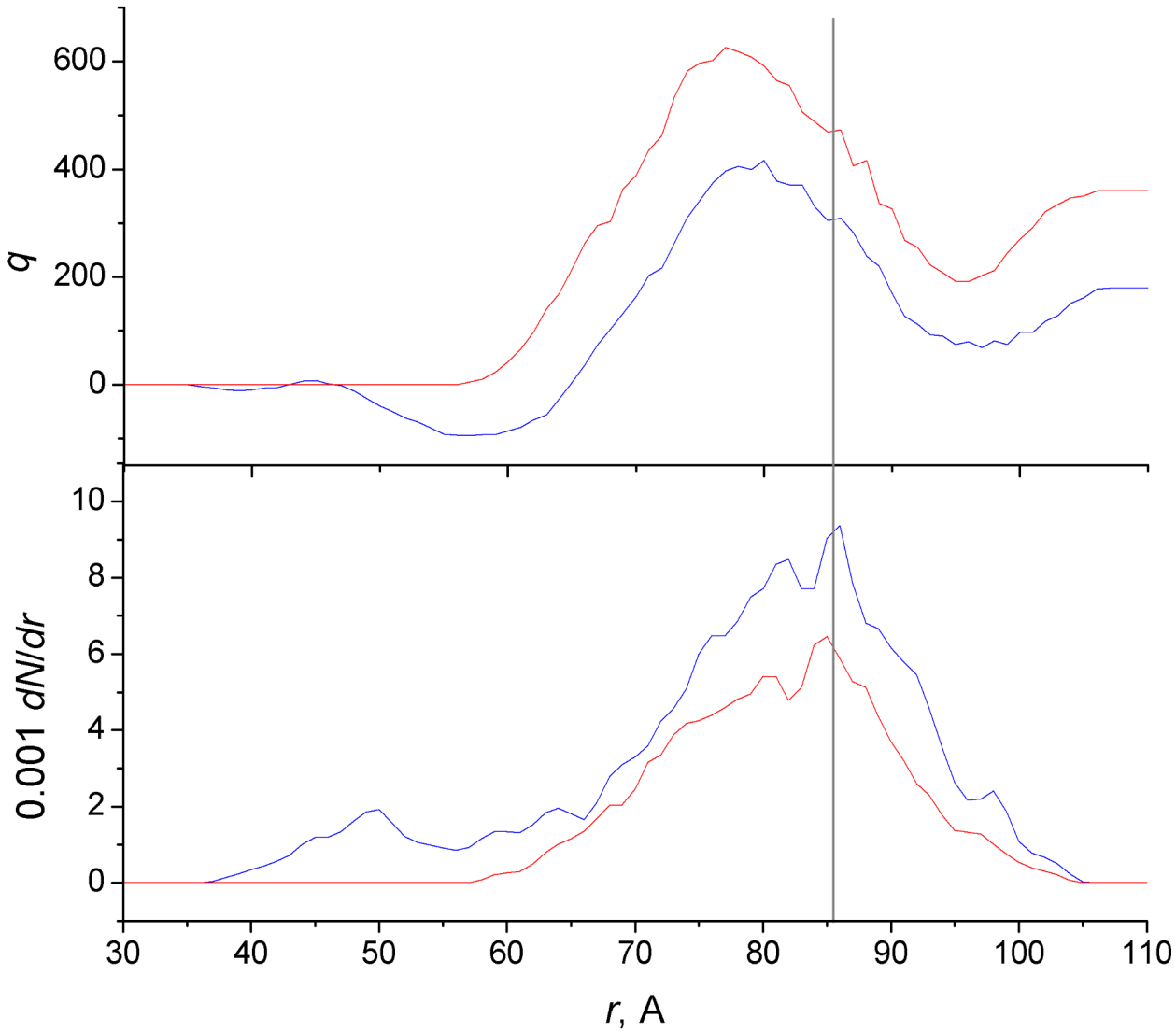


Aston University
Birmingham

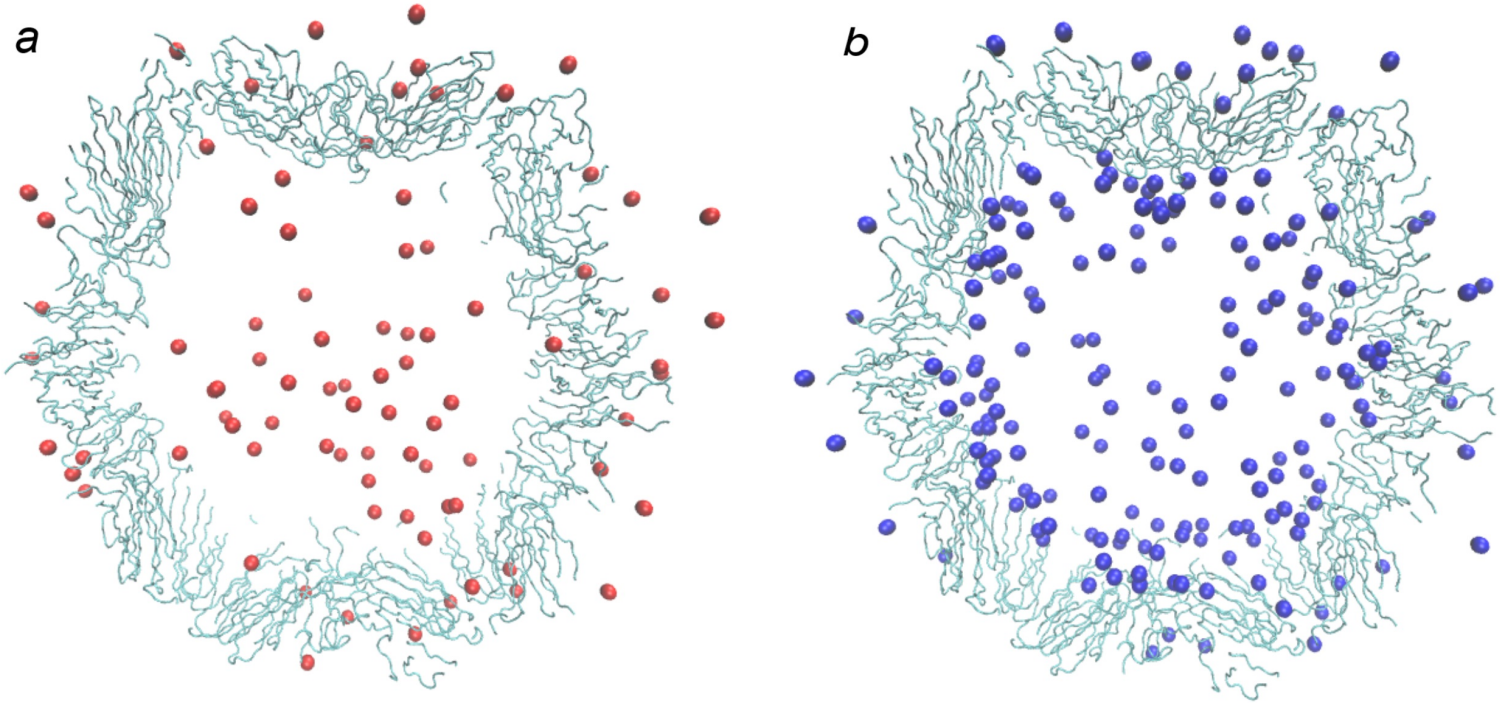
PCV2: invisible ‘tails’



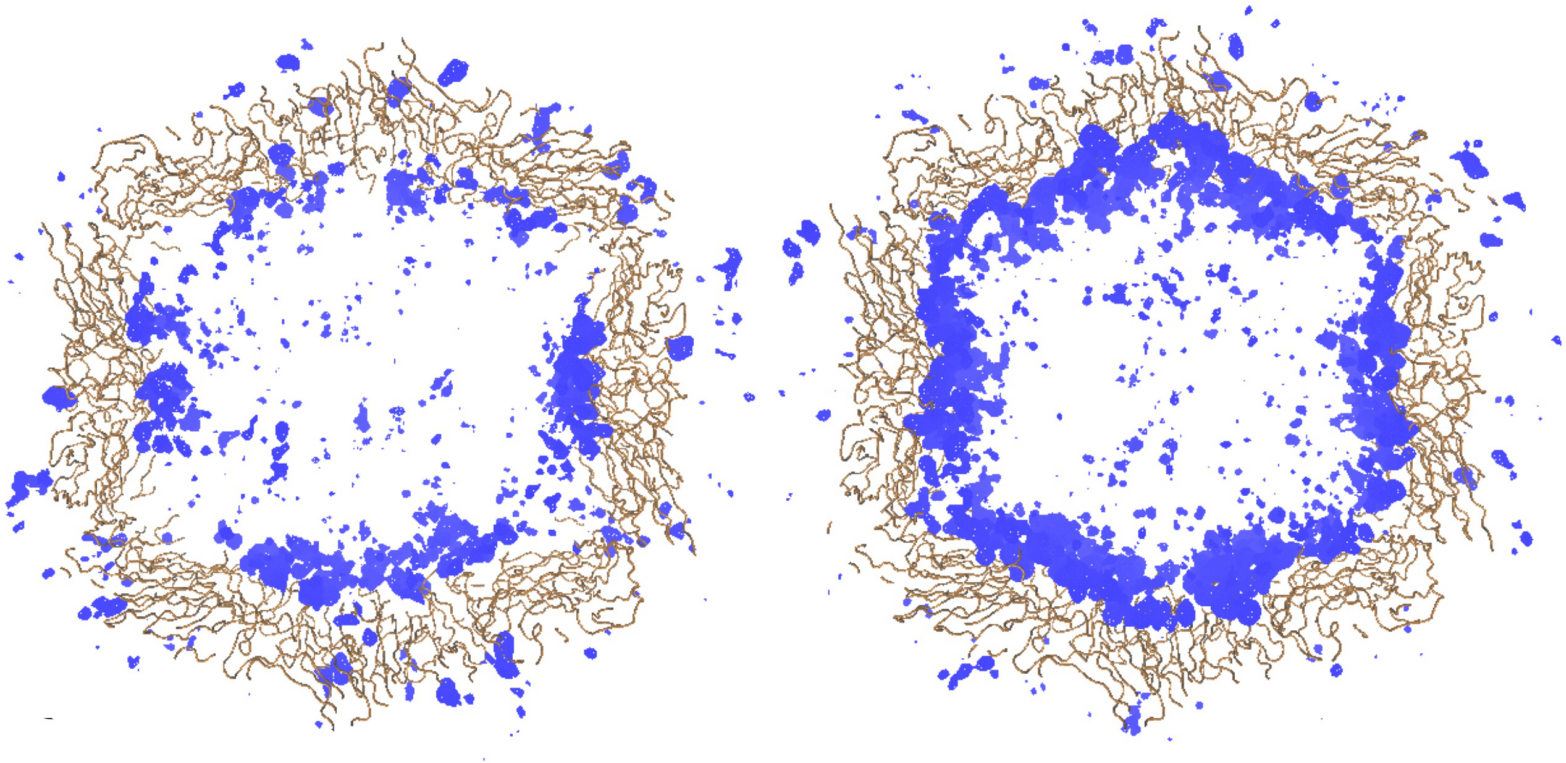
PCV2: ions



PCV2: ions



PCV2: ions



Talk outline

I. Our hybrid MD/hydrodynamics approach

II. Whole virus simulations

III. **Conceptual points about multiscale description of liquids**

Conceptual issues of multiscale/multiphysics

Why is connecting atomistic and macroscopic difficult?

The fundamentals: hydrodynamics and atomistic dynamics

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**:

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

Atomistic representation

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

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

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: the scales

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: the scales

That is for MD→H D connection, what about HD→MD connection?

Navier-Stokes equations

$$\frac{\partial \rho}{\partial t} = -\nabla(\rho \mathbf{u}),$$
$$\frac{\partial \rho \mathbf{u}}{\partial t} = -\nabla P - \nabla \cdot \rho \mathbf{u}\mathbf{u} - \nabla \cdot \sigma.$$

$$\sigma(\zeta, \eta, \mathbf{u}).$$

Voronoi Fluid Particles & Tessellation Fluid Dynamics

Pep Español and Mar Serrano

Departamento de Física Fundamental, UNED, Aptdo. 28080 Madrid, Spain.
{pep,mar}@fisfun.uned.es

Summary. We formalize the concept of fluid particle that it is heuristically introduced in textbooks of fluid mechanics. Fluid particles are regarded as portions of fluid that move along the flow field and they have an extension. A natural way of assigning an extension to a set of points is through a tessellation. With a minimum of physical input information a well-defined discrete fluid particle model emerges. In the process, discrete differential operators based on the volume associated to the fluid particles appear. We identify a set of basic properties that the volume of the fluid particle should satisfy in order for these discrete operators to be exact when applied to linear fields, for arbitrary arrangements of the particles. The Voronoi volume and the Smoothed Particle Hydrodynamic volume are investigated, and a further option based on the volume of the "Delaunay cell" is proposed. We show how the Voronoi fluid particle model can be used to study features of turbulence, and suggests its usefulness for the modeling of complex fluids.

Discrete hydrodynamics

- Navier-Stokes equations are rewritten in Lagrangian form ('go with the flow').
- Fluid particles of mass M_i and volume V_i with coordinates $\mathbf{R}_i$ move with the velocity $\mathbf{U}_i$, their momentum is $\mathbf{P}_i = M_i \mathbf{U}_i$.
- It is postulated that the scales can not be smaller than macroscopic, that is the particle volumes V_i are macroscopically large.

Discrete hydrodynamics

$$\frac{dM_i}{dt} = 0,$$
$$\frac{d\mathbf{R}_i}{dt} = \mathbf{U}_i,$$
$$\frac{d\mathbf{P}_i}{dt} = \sum_j \frac{\partial V_j}{\partial \mathbf{R}_i} P_j + \sum_j \frac{\partial V_j}{\partial \mathbf{R}_i} \cdot \sigma_i.$$

$$\sigma(\zeta, \eta, \sum_j \frac{\partial V_i}{\partial \mathbf{R}_j} \mathbf{U}_j).$$

Discrete hydrodynamics: Hamiltonian dynamics

$$\frac{dM_i}{dt} = 0,$$
$$\frac{d\mathbf{R}_i}{dt} = \mathbf{U}_i,$$
$$\frac{d\mathbf{P}_i}{dt} = \sum_j \frac{\partial V_j}{\partial \mathbf{R}_i} P_j.$$

$$\sum_j \frac{\partial V_j}{\partial \mathbf{R}_i} P_j = -\frac{\partial E_T}{\partial \mathbf{R}_i},$$
$$E_T = \sum_j E_j$$

Describing fluctuations of the continuum

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

In addition to the usual hydrodynamic stress σ, a random stress is added:

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

The conceptual problem in multiscale atomistic/continuous description

– going from hydrodynamics down scale fluctuations should eventually become atoms;

The conceptual problem in multiscale atomistic/continuous description

- going from hydrodynamics down scale fluctuations should eventually become atoms;
- going from atoms up scale averages clearly show strong collective behaviour;

The conceptual problem in multiscale atomistic/continuous description

- going from hydrodynamics down scale fluctuations should eventually become atoms;
- going from atoms up scale averages clearly show strong collective behaviour;
- what is "in between" the atomistic and hydrodynamic scales?: atoms? fields?

The conceptual problem in multiscale atomistic/continuous description

- going from hydrodynamics down scale fluctuations should eventually become atoms;
- going from atoms up scale averages clearly show strong collective behaviour;
- what is "in between" the atomistic and hydrodynamic scales?: atoms? fields?

  a manifestation of this conceptual problem: hydrodynamic 'particles' can overlap, atoms - can't

The conceptual problem in multiscale atomistic/continuous description

- going from hydrodynamics down scale fluctuations should eventually become atoms;
- going from atoms up scale averages clearly show strong collective behaviour;
- what is “in between” the atomistic and hydrodynamic scales?: atoms? fields?

  a manifestation of this conceptual problem: hydrodynamic ‘particles’ can overlap, atoms - can’t

- new concept of the matter is needed.

Thank you.