Hybrid Molecular Dynamics - Hydrodynamics Modelling of Liquid Solutions:

Whole Virus at Atomistic Resolution

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Motivation

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

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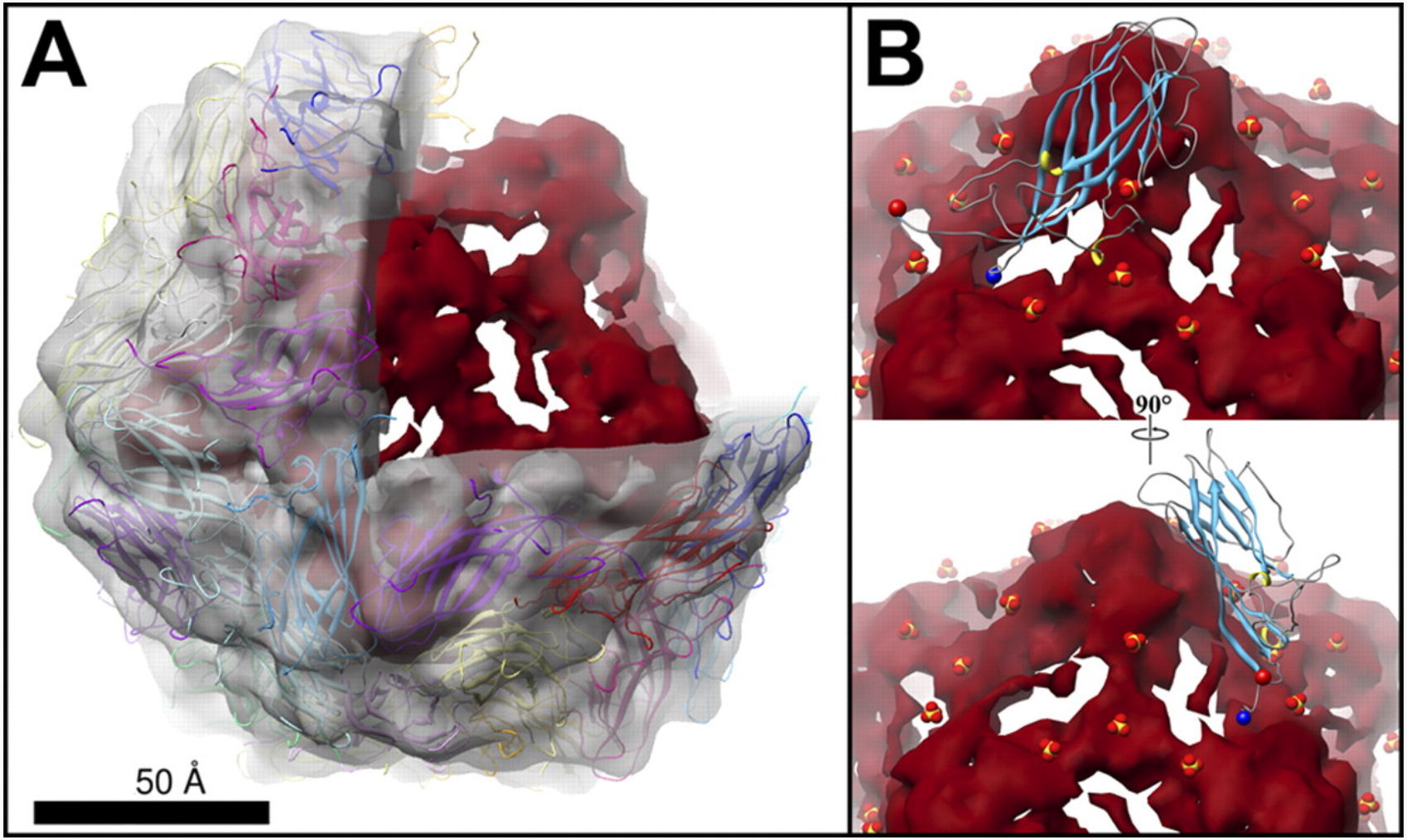
Porcine circovirus 2 (PCV2) is a T=1 nonenveloped icosahedral virus that has had severe impact on the swine industry. Here we report the crystal structure of an N-terminally truncated PCV2 virus-like particle at 2.3-Å resolution, and the cryo-electron microscopy (cryo-EM) image reconstruction of a full-length 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



[R. Khayat, *J. Vir.* (2011)]

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 [J. Perilla, *Nature Comm.* (2017)].

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

Do we need multiscale?

Technical limitations of plain MD:

- water molecules come and go;

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

Hybrid MD/HD

The idea

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- For hydrodynamics we use Landau-Lifshitz Fluctuating Hydrodynamics (LL-FH) equations that are 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

- In the hybrid domain the fluid consists of two “phases”:

  HD phase is continuum liquid with volume fraction $s = \frac{V_1}{V}$,

  MD phase is atomistic liquid, its volume fraction is $(1 - s)$.

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  HD phase is continuum liquid with volume fraction $s = \frac{V_1}{V}$,

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- The parameter $s = s(x)$ is the function of space coordinates, such that $s = 1$ in purely HD domain, $s = 0$ in purely 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 $\sum_{p=1,N(t)} \rho_p$:

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

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

Modified MD equations

From these constrains the source J (and J_2 for the momentum) can be found and MD equations are modified:

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

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

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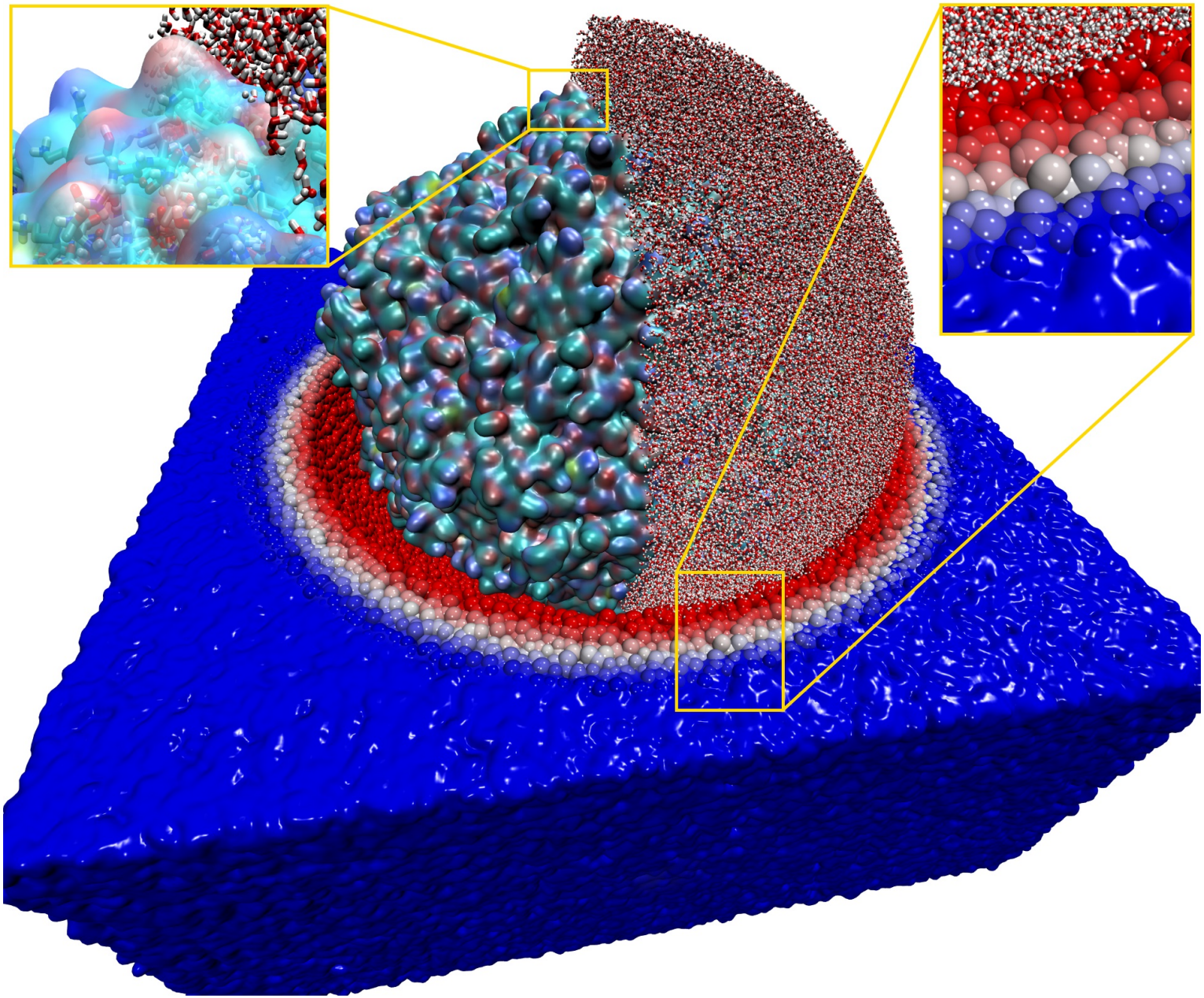
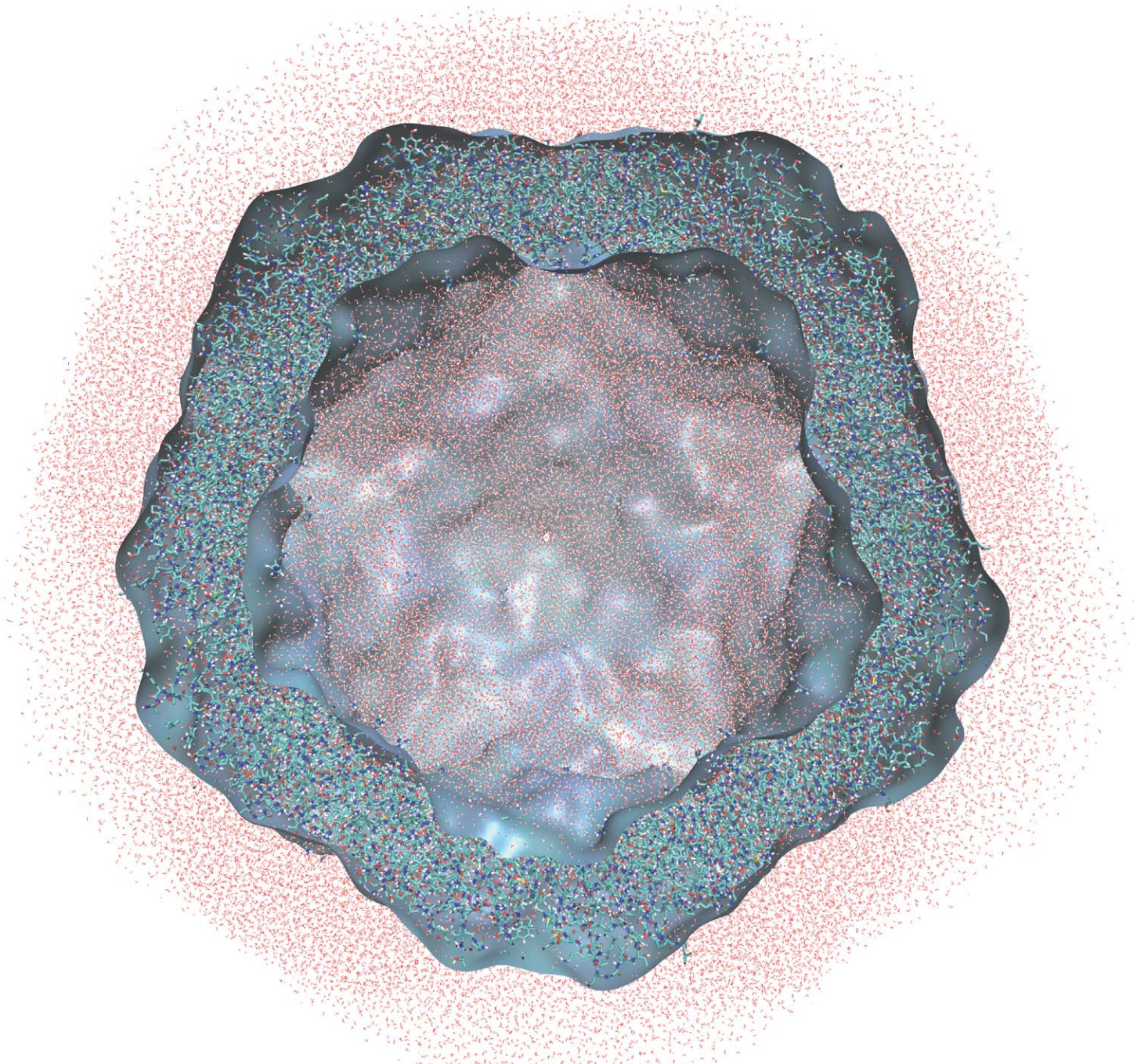


Hybrid dynamics

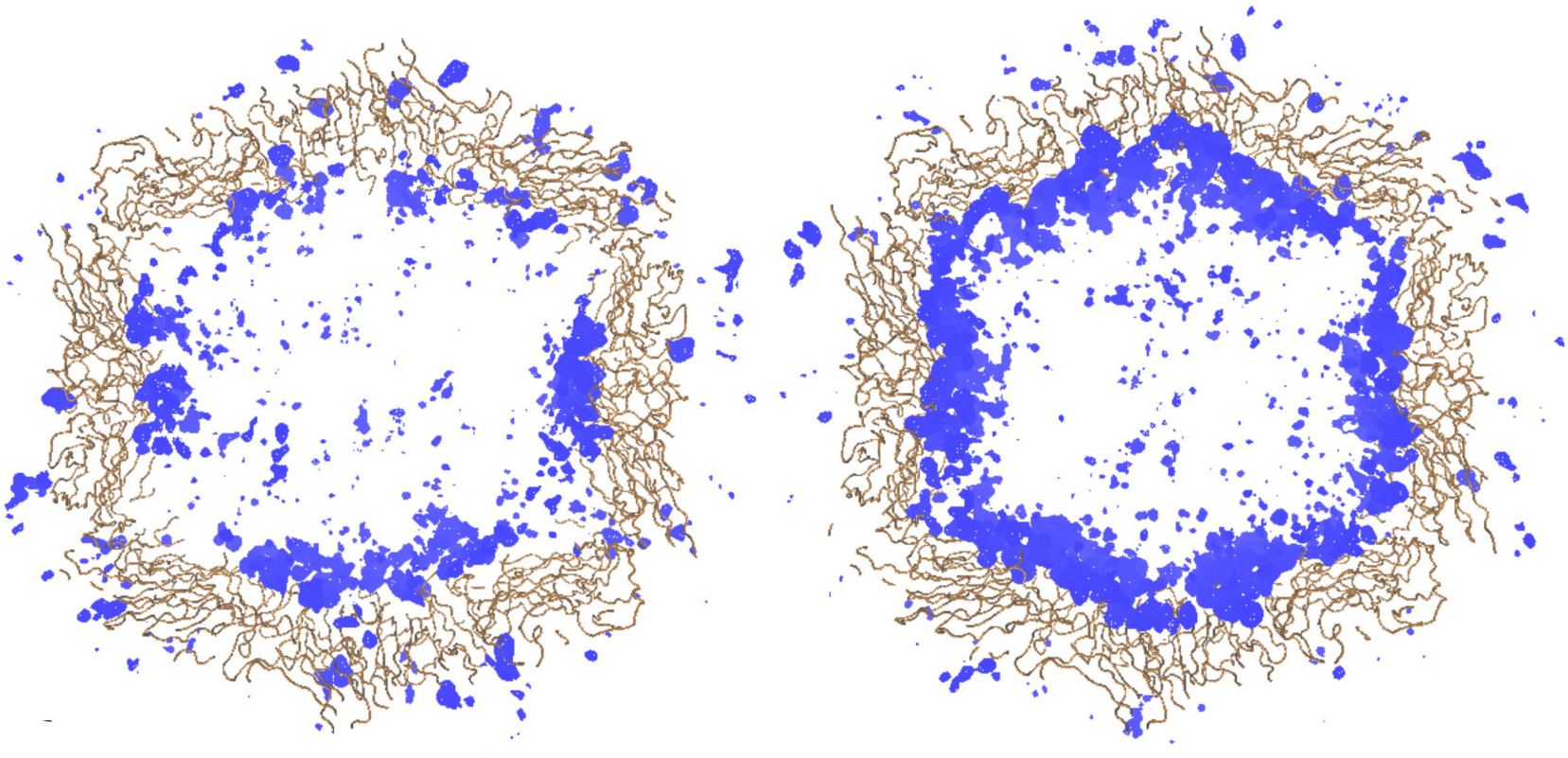
What happens to water molecules in transition from MD to HD domains

All-atom MD of viruses

PCV2 at full atom resolution



Ions are crucial for capsid stability



[E. Tarasova, *J. Phys. Chem. Lett.* (2017)]

“Between” the scales

Voronoi Fluid Particles & Tessellation Fluid Dynamics

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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

$$\frac{dM_i}{dt} = 0,$$
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$$\sum_j \frac{\partial V_j}{\partial \mathbf{R}_i} P_j = -\frac{\partial E_T}{\partial \mathbf{R}_i}, \qquad E_T = \sum_j E_j$$

Fractional derivatives

Caputo fractional derivative:

$$(D^{\alpha} f)(x) = \frac{1}{\Gamma(n-\alpha)} \int_0^x \frac{f^{(n)}(t)}{(x-t)^{\alpha+1-n}}\, dt.$$

Using this definition, the properties of the operator

$$V^{\alpha} f = f^{\alpha-1} D^{\alpha} f$$

are

$$\lim_{\alpha \to 0} V^{\alpha} f = 1,$$
$$\lim_{\alpha \to 1} V^{\alpha} f = D^1 f.$$

Continuous transition between atoms and hydrodynamics

For any α between 0 and 1:

$$\dot{\mathbf{P}}_i = \sum_j \left[\mathcal{V}_j^{\alpha-1} \frac{\partial^\alpha \mathcal{V}_j}{\partial \mathbf{R}_i^\alpha} P_j^\alpha \quad \frac{\partial^{1-\alpha} \phi_{ij}}{\partial \mathbf{R}_i^{1-\alpha}} \phi_{ij}^{1-\alpha} \right] +$$
$$\zeta \sum_j \left[\frac{\partial^\alpha \mathcal{V}_i}{\partial \mathbf{R}_j^\alpha} - (1-\alpha)\, \mathbf{R}_j^{-\alpha} \mathcal{V}_i \right] \mathcal{V}_i^{-1} \frac{\partial^{1-\alpha} \mathcal{V}_i}{\partial \mathbf{R}_j^{1-\alpha}} \cdot \mathbf{V}_j +$$
$$2\eta \left(\overline{\sum_j \left[\frac{\partial^\alpha \mathcal{V}_i}{\partial \mathbf{R}_j^\alpha} - (1-\alpha)\, \mathbf{R}_j^{-\alpha} \mathcal{V}_i \right] \mathcal{V}_i^{-1} \frac{\partial^{1-\alpha} \mathcal{V}_i}{\partial \mathbf{R}_j^{1-\alpha}} \mathbf{V}_j} \right)$$

In the limits, Newtonian dynamics and NS hydrodynamics are recovered.

Conclusions

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

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

- new concept of the matter is needed.

Thank you.