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Complete virus capsid at all-atom resolution: Simulations using molecular dynamics and hybrid molecular dynamics/hydrodynamics methods reveal semipermeable membrane function

Elvira Tarasova [a], Ivan Korotkin [b,d], Vladimir Farafonov [c], Sergey Karabasov [d], Dmitry Nerukh [e,*]

[a] Immanuel Kant Baltic Federal University, A. Nevskogo str. 14, Kaliningrad 236041, Russian Federation
[b] Nuclear Safety Institute of Russian Academy of Sciences, Bolshaya Tulskaya 52, Moscow 115191, Russian Federation
[c] Department of Physical Chemistry, V.N. Karazin Kharkiv National University, Svobody Square 4, Kharkiv 61022, Ukraine
[d] School of Engineering and Materials Science, Queen Mary University of London, Mile End, London E1 4NS, UK
[e] Systems Analytics Research Institute, Aston University, Birmingham B4 7ET, UK

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ABSTRACT

Simulations of complete virus capsid at atomistic details have been performed using standard molecular dynamics as well as original hybrid molecular dynamics/hydrodynamics methodologies. The results show that the capsid is stable in water solution at room temperature and ions composition similar to physiological conditions. Detailed analysis of the flow of water molecules and ions through the capsid's wall is performed. It demonstrates that ions do not cross the capsid shell, while water exhibits substantial flows in both directions. This behaviour can be classified as a semipermeable membrane and may play a role in mechanical properties of the virus particle.

1. Introduction

Modern experimental techniques have reached resolution high enough to measure the structure of entire viruses at atomistic level [1–5]. This provides a unique opportunity to model them using classical molecular dynamics (MD) approaches producing very important biomolecular information on the details of virus functioning, which, in turn, can be used for designing methods of manipulating and deactivating viruses.

Unfortunately, the experiments are usually restricted to detect only static and symmetric parts of the structure, while the dynamics of viral structures is important for representing specific interactions between viral parts, the solution, and cell membrane. Also, the experimental data is performed at low temperature and does not reflect the influence of physiological solution on the sample. However, it is known that water is important for the dynamics of the protein when molecules of water guide the protein adjustment and movements [6].

The solution of this problem is provided by theoretic and computational modelling that have been developed dramatically during recent years [5–12]. Fortunately, the development of new approaches coincide with the development of new powerful computer clusters, including specialised ones [13,14], that allow to perform very large scale simulations with millions of atoms for significant time. Therefore, now there is a great opportunity to investigate atomistic and molecular properties of the viral particles and suggest directions of further experimental developments. This approach will help us to understand the logic of some viral processes that are hidden in the dynamics, interactions with the solution that take place at short times. This complementary experimental and theoretical approach will help us to save time and resources for experimental research and suggest ways of developing effective treatment of virus infections.

In this paper we present the investigation of some processes that could be detected with all-atom molecular dynamics simulation. We show that MD simulation predicts experimental structure of the virus. In addition, it allows us to investigate molecular processes currently undetectable by experiments. In particular, we report the analysis of water and ion flows through the virus capsid and arrive at interesting conclusions that may be important biologically.

Atomistic MD modelling of the whole viral capsid is very resource demanding, it needs to contain all atoms of the system in the calculation, including all water molecules. The fact that the systems usually consist of millions of atoms, where most are water molecules, makes the simulation computationally expensive.

For this reason, we apply our new approach, a hybrid MD/hydrodynamics method that is created with the idea to reduce the simulation cost. The method allows us to represent the system at fully atomistic resolution in the parts where all atoms are necessary, and at much cheaper continuous resolutions in the rest of the system. We have tested our approach on smaller systems [15,16] and now we report its

* Corresponding author.
E-mail address: d.nerukh@aston.ac.uk (D. Nerukh).

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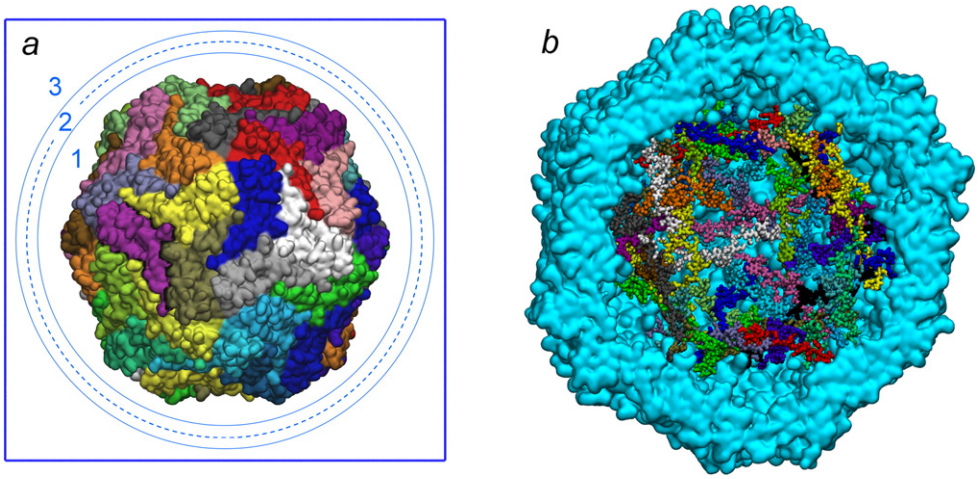

Fig. 1. The initial structure of the capsid: a) the overview with the boundaries of the simulation box and the division of the system onto regions: 1 — pure MD region, 2 — hybrid region, 3 — pure hydrodynamics region; the dashed line shows the subdivision of the hybrid region for thermostating; b) the cross-cut showing the "tails" (system B); the individual proteins (a) or tails (b) are shown in different colour.

application to a virus simulation. The realisation of the hybrid MD/hydrodynamics method for the viral capsid will allow to significantly increase the simulation time. Here we show that our method can successfully simulate the virus preserving its atomistic structure and producing similar dynamical behaviour.

For our study we have chosen the capsid of the porcine circovirus type 2 (PCV2), because PCV2 is the smallest virus with the diameter of about 20 nm and with circular DNA inside [17]. The capsid of PCV2 is stable without the genome and its atomistic structure is defined from X-ray crystallography [1]. However, the N-termini of the capsid have not been detected in the experiment, probably, because of their flexible or disordered structure. The combination of these facts makes this viral capsid a convenient model for all-atom MD simulations.

We have simulated two cases of the whole viral capsid at atomistic resolution: with N-termini (we call them "tails") and without them. Both structures are stable in physiological environments and they have good agreement with experimental data. We have demonstrated in our previous paper [18] the small value of the RMSD for the structures compared to the X-ray structure.

In this report we focus on the detailed analysis of the flow of water molecules and ions in and out the capsid. This is an important process that defines several biological properties of the virus, for example, its mechanical strength under the influence of pressure changes. We show that water exhibits substantial rate of exchange across the capsid's wall, while ions essentially do not permeate the wall. This makes the capsid shell to function as a semipermeable membrane, the behaviour also demonstrated for other viruses [9].

2. Materials and methods

2.1. System preparation

All-atom MD simulation has been performed with explicit model of solvent using GROMACS. For the simulations we used X-ray structure [1] that is deposited in Protein Data Bank (3R0R), and the sequence of N-terminus, which is not detected with X-ray, probably because of their flexible or disordered structure. Therefore, we have reconstructed the structure of the missing N-termini with homology modelling approach in MODELLER [19] and, then, we have assembled the 60 proteins into the whole capsid using Viperdb [20].

We have prepared two initial structures of the capsid: the first one was without the N-termini (Fig.1a) and the second one with the N-termini (Fig.1b), (we will call them "A" and "B" systems respectively).

The capsid is charged highly positively (360 e), while the tails are charged negatively (−3 e per tail). The system is divided by the capsid in two parts: the cavity and the outer solution, which raises the problem of correct neutralization of the system's charge. To solve it we estimated the radial distribution of the capsid's charge by splitting the capsid into a number of concentric spherical layers with the centres located at the capsid centre of mass (COM). The incremental charge of layers was plotted depending on the radius of the largest layer, Fig. 2. It could be seen that the integral capsid charge increases with distance up to ≈7.8 nm and then decreases. This fact indicates that the capsid is highly polarized with the inner surface having a large positive charge, and the negatively charged outer surface. Therefore, to correctly neutralize the capsid we neutralized each surface separately. The number of Cl^- ions equal to the height of the peak on the charge plot, were placed inside the capsid, while to the outer solution, Na^+ ions were added in the amount equal to the difference between the total capsid charge and the charge of the inner surface. These values are listed in Table 1. Finally, additional 1720 Na^+ and Cl^- ions were randomly distributed across the cell, which corresponded to physiological solution concentration (0.9 wt% NaCl). We stress that the total charge of both simulation cells was zero.

Pure MD simulation has been performed using AMBER03 force field with TIP3P water model. The total number of atoms in the system was 1,898,573 for system A and 1,897,998 for system B. The simulated systems had only protein capsid, water, and ions without nucleic acids.

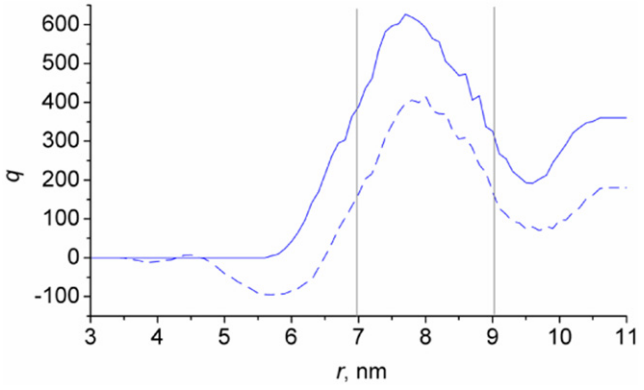

Fig. 2. The dependence of the integral charge of the capsid layers on the radius of the largest layer; the solid curve corresponds to system A, the dashed curve corresponds to system B; vertical lines indicate the approximate boundaries of the capsid wall.