Modeling and Simulation of the Shape and Interior Pressure of Enveloped Viruses:

Motivated by Orthopoxviruses and Coronaviruses

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Introduction

Viral infections have been major public health issues and have attracted intense interest in scientific research. Both Orthopoxviruses and Coronaviruses, such as Monkeypox and Covid-19, are classified as enveloped viruses with lipid membranes that enclose and protect their genetic material. Nevertheless, Orthopoxviruses exhibit a rectangular prism shape, whereas Coronaviruses are spherical.

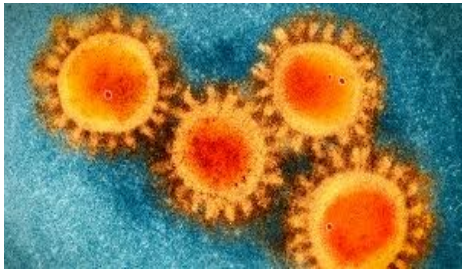


Figure 1 Coronaviruses Illustration

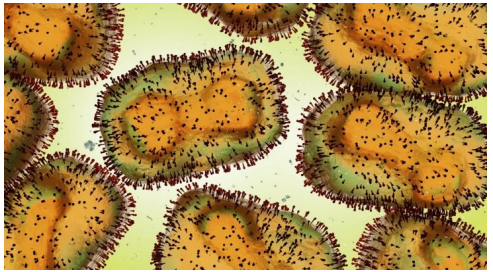


Figure 2 Orthopoxviruses Illustration

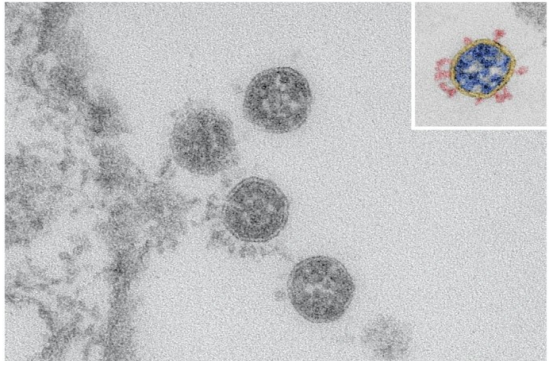


Figure 3. Four SARS-CoV-2 particles imaged by transmission electron microscopy at 135,000x magnification, positioned near the Vero cell surface on the left. The inset displays a color-coded particle with spikes in red, the viral membrane in yellow, and the ribonucleoprotein in blue. Scale bar = 100 nm.[22]

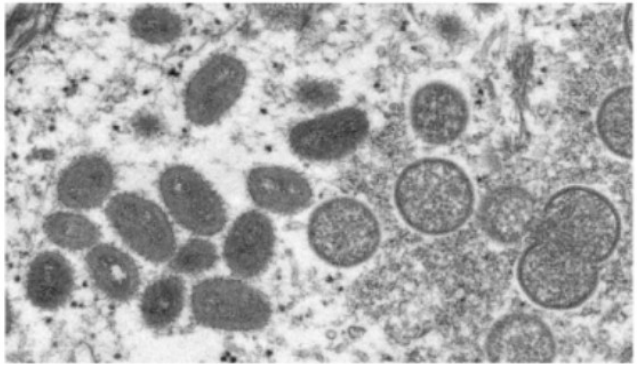


Figure 4. Electron microscopic (EM) image for Monkeypox virus particles. Oval-shaped virus particles are mature, and spherical particles are immature virions.[6]

Introduction

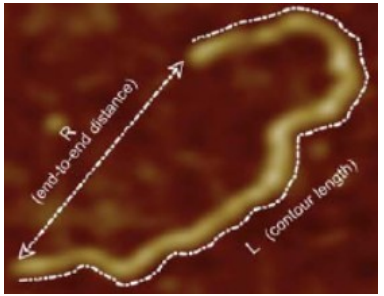


Figure 5 Determination of the contour length and the end-to-end distance for an isolated DNA. [23]

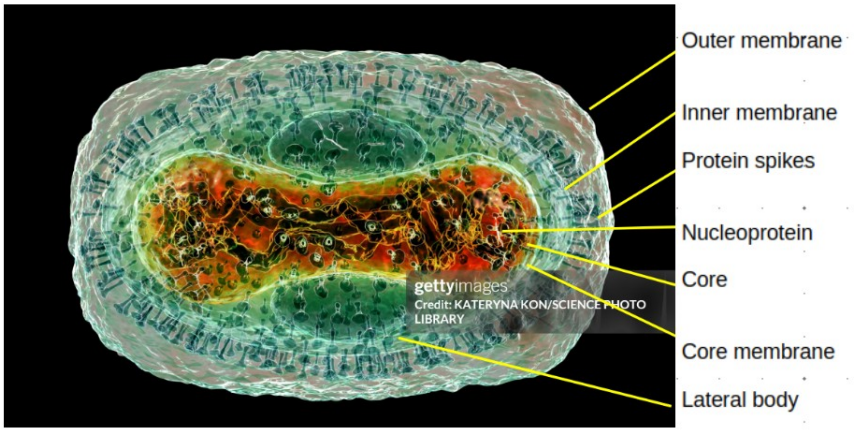


Figure 6 Monkeypox virus particle, Illustration

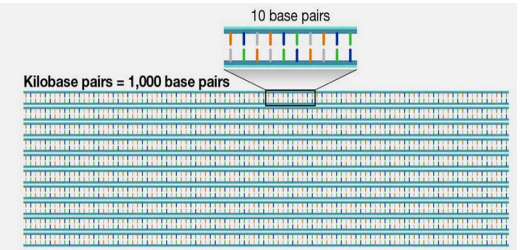


Figure 7. A kilobase (abbreviated kb) is a unit of measurement used to help designate the length of DNA or RNA. One kilobase is equal to 1,000 bases.

In terms of genomes, Orthopoxviruses are DNA viruses containing about 200 kilobase pairs of double-stranded DNA on average, forming a rigid, elongated dumbbell morphology with a contour size of about 250 nm in length and 200 nm in width. Coronaviruses,by contrast, are single-stranded RNA viruses with around 30 kilobase pairs and an average contour size of 50–140 nm. A general feature among these viruses is that their genomes are highly confined and crowded insidethe capsid. As a result, they may exhibit internal pressures ranging between 10–60 atm to facilitate genome injection into the host cell's nucleus.

Introduction

Motivated by these viruses, we developed a simple liquid-state model with minimal parameters to explore the basic physicochemical effects underlying viral shape and internal pressure. The model consists of sticky hard spheres and/or rods confined in fluctuating simulation boxes in all dimensions, studied using NPT Monte Carlo simulations under fixed pressure and rigid walls. Our preliminary results showed that rods induced elongated cuboid simulation boxes at equilibrium—mimicking the shape of Orthopoxviruses—with internal pressures comparable to those of real viruses. More systematic studies are being conducted, such as how viruses prevent crystallization of their genome material.

Host cells have organelles, but viruses do not. Host cells are complex, living cells with various specialized structures (organelles) like mitochondria and ribosomes. In contrast, viruses are much simpler, acellular entities consisting only of genetic material (DNA or RNA) wrapped in a protein coat. Viruses lack the metabolic machinery to reproduce on their own and must infect a host cell to hijack its organelles and other components to make more viruses.

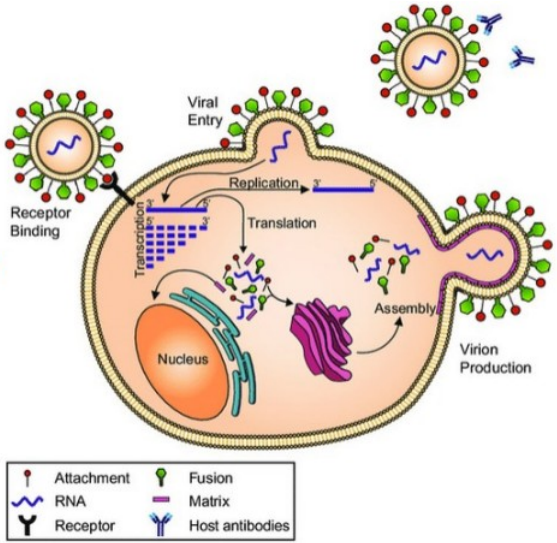


Figure 8 Diagram of the viral life cycle. Virions bind to host cell receptors (black), facilitating viral entry into the cell. Once within the cell, transcription and replication occur.

Monte Carlo Simulations

The Metropolis acceptance probability P is defined as:

$$P = \begin{cases} 1 & \text{if } \Delta E \leq 0 \\ e^{-\Delta E/(k_B T)} & \text{if } \Delta E > 0 \end{cases}$$

Metropolis rule:

$$P = \min\left(1, e^{-\beta \Delta E}\right)$$

This is a key expression in the Metropolis algorithm, often used in Monte Carlo simulations, to determine the acceptance probability of a proposed move in a system. P : Probability of accepting the proposed move; if accepted, positions update, otherwise the move is reverted. ΔE: Energy change from the move ($E_{new} - E_{old}$). β: Inverse temperature factor, $\beta = 1/(k_B T)$, from the Boltzmann distribution. If $\Delta E \leq 0$, the move is always accepted (P = 1) since it means a lower-energy, more favorable state.

Techniques

Coarse-Grained Models (CGM):

It simplifies complex systems by grouping atoms or molecules into larger particles called beads. This allows for large-scale simulations at low computational cost and supports the identification of minimal-parameter models.

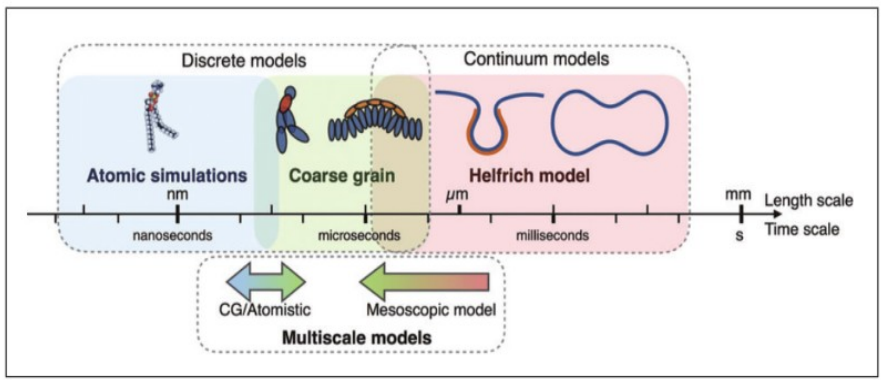


Figure 9 Different computational methods developed to study membrane and genome are valid in different length and time scales.

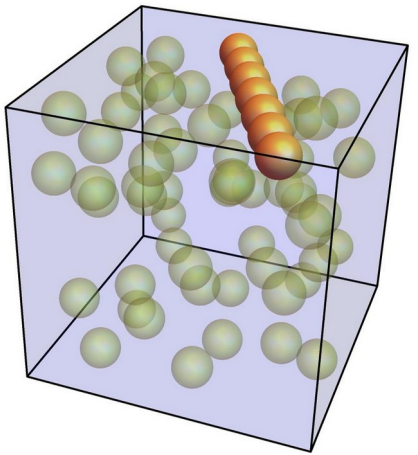
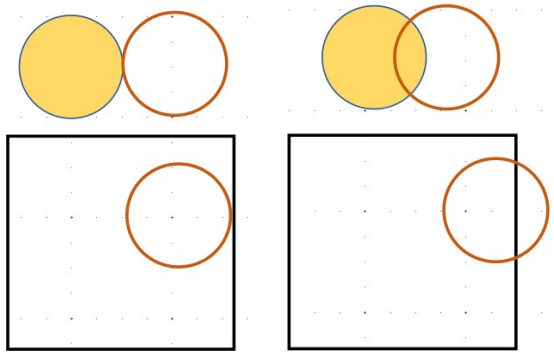


Figure 10 Model of DNA/RNA (Orange Rod) and Organelles (Green Spheres) Confined in a Membrane (Rectangular Prism)

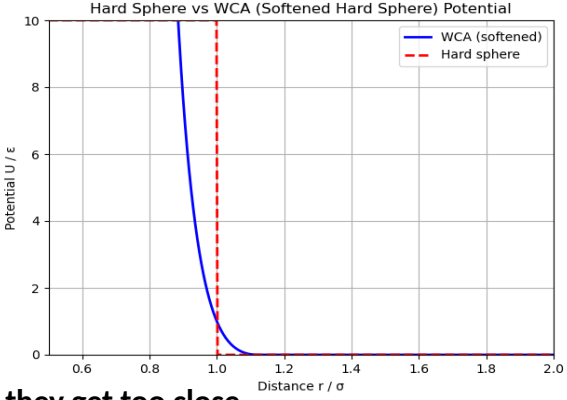
Excluded Volume with Lennard-Jones Potential

Excluded volume is a key component of coarse-grained (CG) modeling, ensuring that two particles cannot occupy the same space. Without it, particles may overlap or penetrate each other, causing unphysical behavior. To incorporate excluded volume effects,we use repulsive interaction potentials—such as the Lennard-Jones potential. This equation represents an excluded volume interaction using the Weeks–Chandler–Andersen (WCA) potential. WCA is a softened version of the hard sphere potential,which is derived from the Lennard–Jones potential but truncated and shifted at its minimum ($r_c=2^{1/6}\sigma$).It is commonly used in coarse-grained simulations (like polymers or DNA beads).



Allowed Not allowed

$$U_{\mathrm{WCA}}(r) = \begin{cases} 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] + \varepsilon, & \text{if } r \le 2^{1/6}\sigma \\ 0, & \text{if } r > 2^{1/6}\sigma \end{cases}$$



r is the distance between two particles,
ϵ is the depth of the potential well (sets energy scale),
σ is the particle diameter (distance scale),
$r_c = 2^{1/6}\,\sigma$ is the cutoff distance at the potential minimum.
For $r < r_c$, the potential sharply rises to strongly repel particles as they get too close.
For $r > r_c$, the potential is zero — no interaction beyond the cutoff.

1. Excluded Volume (Hard Sphere Condition)

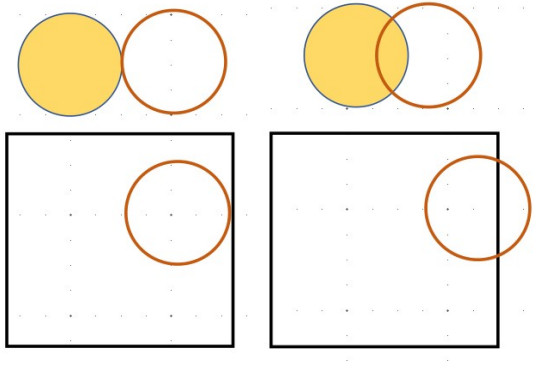
For every pair of particles i,j:

$$r_{ij}^2=(x_i-x_j)^2+(y_i-y_j)^2+(z_i-z_j)^2$$

If

$$r_{ij}^2+10^{-6}<1$$

then the configuration is rejected (this enforces hard spheres of diameter = 1).



2. Pairwise Attractive Energy ($-1/r^6$ term)

The program adds an attractive interaction between particles:

$$E = -\,\mathrm{ASP}\sum_{i<j}\frac{1}{r_{ij}^6}$$

This is the attractive tail of a Lennard-Jones potential, but without the repulsive $1/r^{12}$ part (that role is replaced by the hard-sphere overlap test).

3. Wall Interaction Energy (Soft Repulsion from Boundaries)

For a particle at position (x,y,z)(x,y,z)(x,y,z) inside a box of half-lengths (Hx,Hy,Hz) the code adds:

$$E_{\text{wall}} = -AW\left[\frac{1}{(x-H_x-0.5)^6}+\frac{1}{(x+H_x+0.5)^6}+\frac{1}{(y-H_y-0.5)^6}+\frac{1}{(y+H_y+0.5)^6}+\frac{1}{(z-H_z-0.5)^6}+\frac{1}{(z+H_z+0.5)^6}\right]$$

This mimics weak attraction/repulsion to the walls, scaled by the parameter AW

4. Metropolis Acceptance Criterion

For a trial move (either moving a particle or resizing the box):

$$P_{\text{accept}} = \min\left(1, \exp[-(E_{\text{new}} - E_{\text{old}})]\right)$$

5. Isothermal–Isobaric Ensemble (NPT Monte Carlo)

When the box volume changes, the acceptance probability includes:

and the trial is $\Delta H = P_s(V_{\text{new}} - V_{\text{old}}) - N \ln\left(\frac{V_{\text{new}}}{V_{\text{old}}}\right) + (E_{\text{new}} - E_{\text{old}})$

$$P_{\text{accept}} = \min\left(1, e^{-\Delta H}\right)$$

P_s = external pressure
N = number of particles
V = box volume
This is the standard NPT Metropolis equation

Results

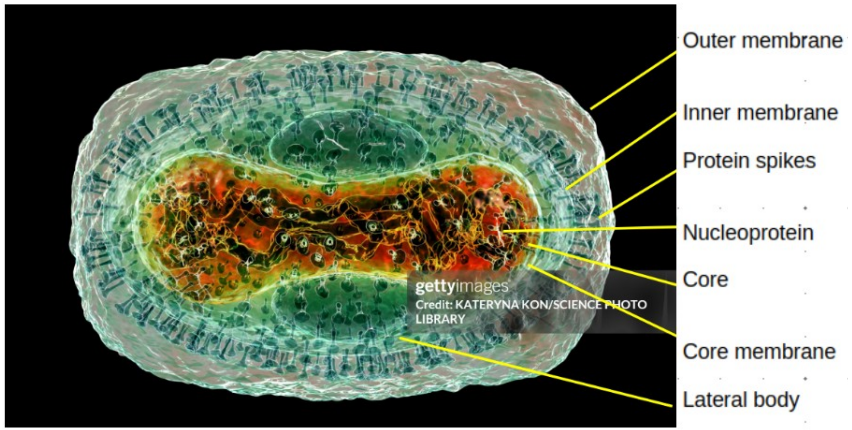
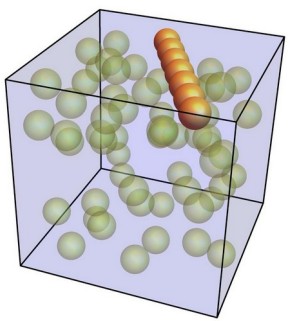


Figure Monkeypox virus particle, illustration

What is the depletion force?

The **depletion force** is an *effective attractive force* that arises in a mixture of large and small particles due to **excluded volume effects**.

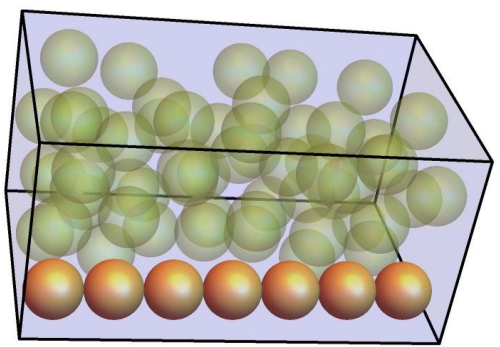
- **Small crowders (green spheres):** They cannot enter the narrow space between the rod and the wall because of their finite size.
- **Excluded volume:** This creates a "depletion zone" where small crowders are absent.
- **Unbalanced pressure:** Outside the rod–wall gap, crowders collide from all directions, exerting an osmotic pressure. Inside the gap, there are fewer collisions (lower pressure).
- **Result:** The rod feels a net push toward the wall — as if there is an attraction between the rod and the wall, even though no direct attractive potential was applied.



$N_c = 57$
$N_B = 7$

$L_x = 7.2$ s
$L_y = 7.2$ s
$L_z = 7.2$ s
σ: diameter of each sphere

Figure Initial configuration before NPT simulation



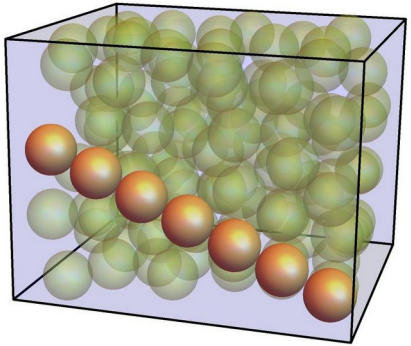
$N_c = 57$
$N_B = 7$

$L_x = 7.239$ s
$L_y = 4.362$ s
$L_z = 3.711$ s

FigureFinal configuration after NPT simulation

Observation: The rod tends to lie next to the wall.
Reason: This is caused by the depletion force—smaller crowders push the larger rod toward the wall to maximize entropy (free volume)

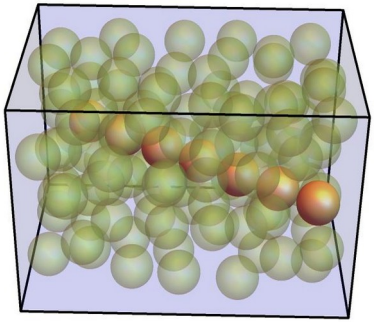
Results



$N_c = 117$
$N_B = 7$

$L_x = 5.546$ s
$L_y = 6.693$ s
$L_z = 5.745$ s

Case 1: only hard repulsion:
The system is relatively compact but anisotropic.

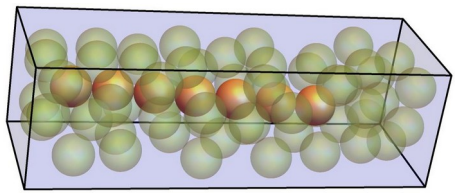


$N_c = 117$
$N_B = 7$

$L_x = 7.569$ s
$L_y = 5.086$ s
$L_z = 5.276$ s

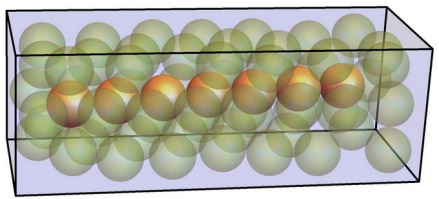
Case 2: plus attraction between rod monomers and crowders ($2k_BT$):
Adding attraction shifts the box dimensions, expanding in x while contracting in y.

Interpretation:
More crowders increase confinement and push the rod around, changing box anisotropy. Adding rod–crowder attraction reorganizes the system, redistributing box dimensions instead of simply compressing.



$N_c = 57$
$N_B = 7$

Reduced pressure: $Ps^3/k_BT = 3$
$L_x = 9.904$ s
$L_y = 3.068$ s
$L_z = 3.253$ s



Reduced pressure: $Ps^3/k_BT = 6$
$L_x = 8.521$ s
$L_y = 3.083$ s
$L_z = 3.041$ s

Interpretation: Increasing pressure compresses the system more isotropically, reducing elongation. This shows how confinement geometry responds differently to applied pressure.

Conclusion and Future work

Conclusion:
Entropy (depletion force) drives rods toward the wall even without explicit attraction.
Attractions reorganize confinement geometry, redistributing box dimensions.
Pressure tunes the balance: higher pressure enforces more isotropic packing.

Explore More Realistic Interactions:
Include electrostatic interactions (Yukawa potentials) to mimic charged DNA/RNA and lipid membranes.
Compare pure WCA repulsion vs. LJ-type attraction, to see how viral genome compaction differs.