Defects within the HIV-1 immature lattice support dynamic remodeling and protease dimerization

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Abstract

For the dangerous HIV virions to become infectious, the immature lattice of Gag polyproteins must remodel into the mature core, which is initiated with the homo-dimerization of Gag-Pol carrying proteases. However, only 5% of the proteins in the lattice are Gag-Pol, and the mechanism of Gag-Pol dimerization is unknown. Here, we use the reaction-diffusion model and simulations to study the dynamics of the immature lattice, which show that the immature lattice is stable enough to assembly but can still allow unbinding and rebinding along the edge to promote the Gag-Pol dimerization because of the defects and imperfect edge.

Immature and mature HIV lattice

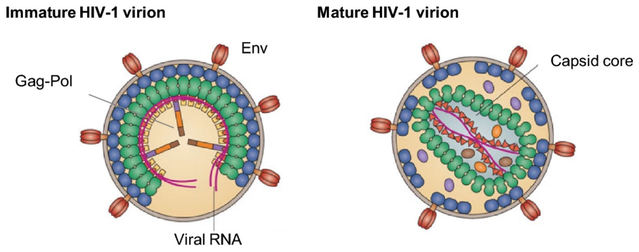

Fig 1. Structure of HIV-1 virion. The figure is copied from Ref 1.

The reaction-diffusion model for Gag assembly

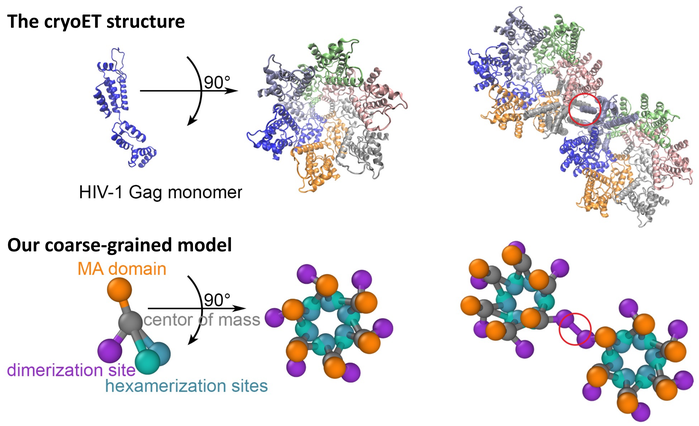

Fig 2. Our coarse-grained model is derived from the cryoET structure taken from 5L93.pdb.

Initial Gag immature lattices within the membrane are assembled via simulation

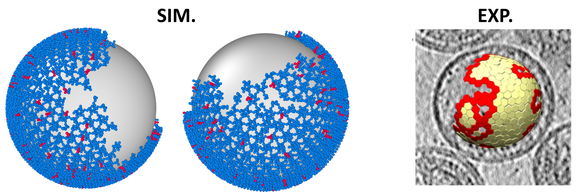

Fig 3. The starting Gag immature lattices are assembled. ~5% of the monomers are Gag-Pols shown in red. Formation of the lattice produces defects that are like those present in cryoET structures.

Remodeling dynamic simulation

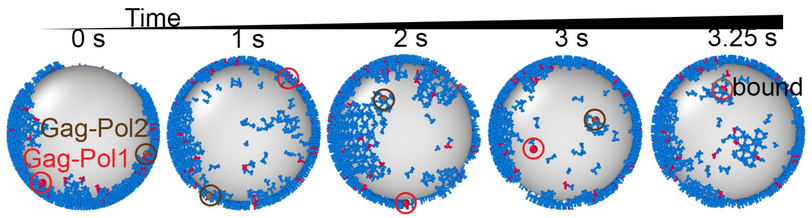

Fig 4. An example from a simulation of how two Gag-Pols found each other through detach, diffuse, and reattach.

First-passage times for protease dimerization

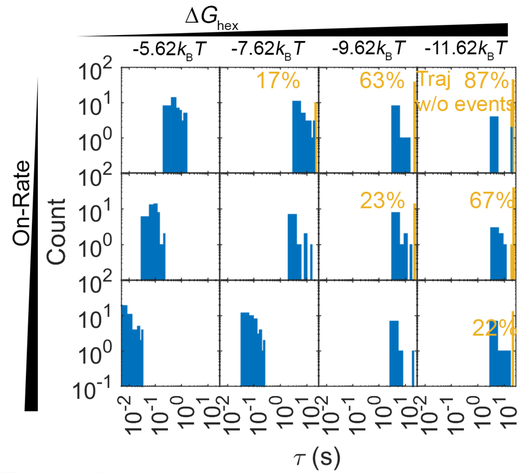

Fig 5. The distributions of the first passage times at different reaction rates and hexamer free energy. The yellow bars and yellow numbers report the percent of traces without any Gag-Pol dimerization event over the time simulated.

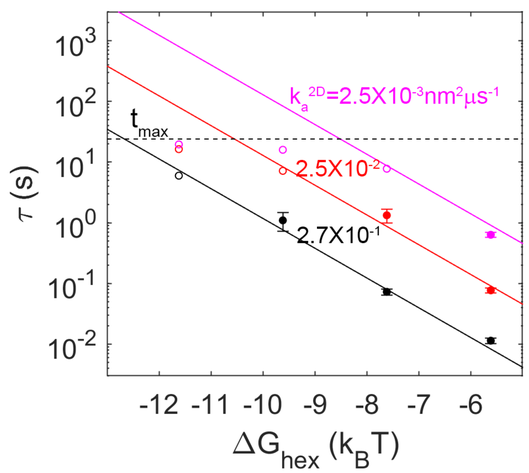

Fig 6. Mean first-passage times can be well-approximated and predicted as a function (lines).

$$\tau_{MFPT} = 7 \times 10^{-5}(k_a^{2D}/(4\pi R^2))^{-1}\exp(-1.13\Delta G_{\mathrm{hex}}/k_B T)$$

Biochemical measurements of Gag mobility

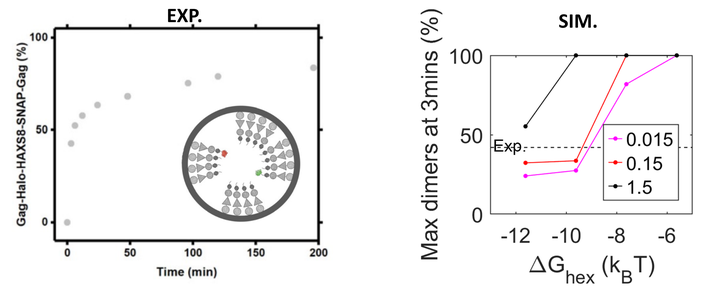

Fig 7. Biochemical measurements of Gag mobility in VLPs [3] agree with our moderately stable lattices.

Large-scale and heterogeneous lattice dynamics

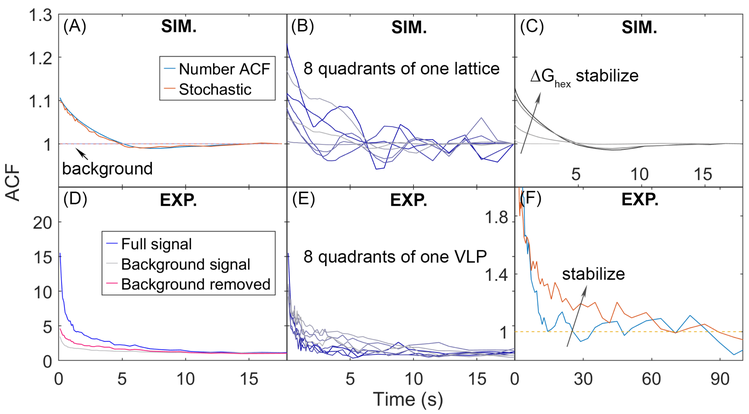

Fig 8. Auto-correlation functions of lattice dynamics from simulation and experiment [4] show qualitatively similar trends.

Summary

1. We develop a model of Gag proteins that assemble into the spherical HIV-1 lattice;

2. We validate our models against recent experimental measures of Gag lattice dynamics;

3. Our models show that the lattice is stable enough to assembly but can still allow unbinding and rebinding because of the defects and imperfect edge to promote the Gag-Pol dimerization.

References

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