Investigating the Influence of Various Receptor Organizations on Filamentous Influenza A Motility Under the Presence of Antibodies

Authors: Marusia Shevchuk and Yuan Gao, Supervisor: Liam Yih
University of British Columbia, Department of Mathematics

Background

- Influenza A (IAV) has two glycan-binding surface proteins, hemagglutinin (HA) and neuraminidase (NA).
- HA binds to the sialic acid (SA) on the cell surface. These bonds form and break randomly leading to virus motility [1].
- NA cleaves SA. This creates self-avoiding, random walks on the cell surface [1].
- Together with the consequential SA gradient, this enhances the mobility of IAV and thus, provides an advantage in crossing the mucus barrier and infecting non-ciliated cells [2].

Goal

Through the use of antibodies, simulating an HA/NA inhibitor, this study aims to examine the effect of deactivated sites on virus motility for IAV with different receptor organizations.

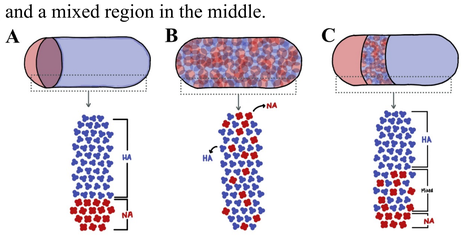
The Model

- This 2D model is developed in Julia and the mathematical parameters and equations are derived from the paper by Vahey and Fletcher [3].
- This is a Monte-Carlo simulation and is driven by random number draws.
- The filamentous IAV is 300 nm long with 100 proteins setup in three cases:

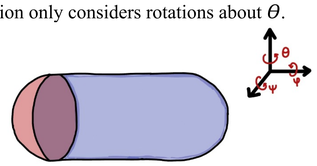
A) Polarized: NA concentrated to one end.

B) Random: a random mixture of HA/NA.

C) Mixed: HAs concentrated to one end, NAs concentrated to the other, and a mixed region in the middle.

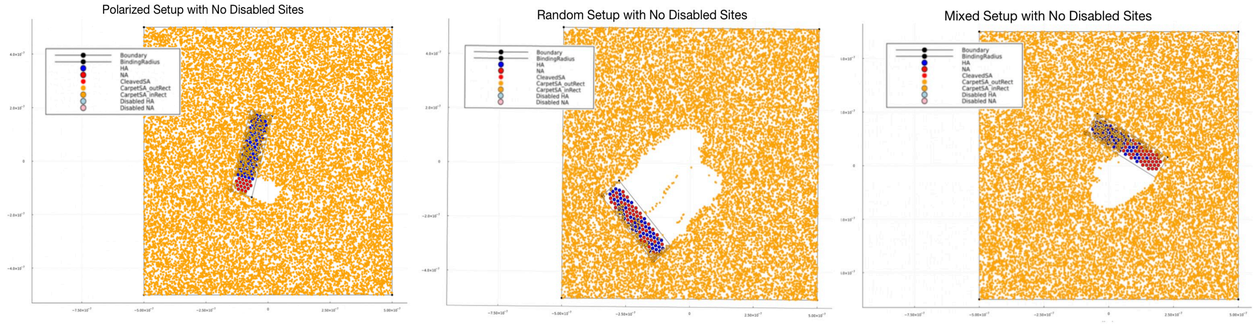


- The simulation only considers rotations about θ.

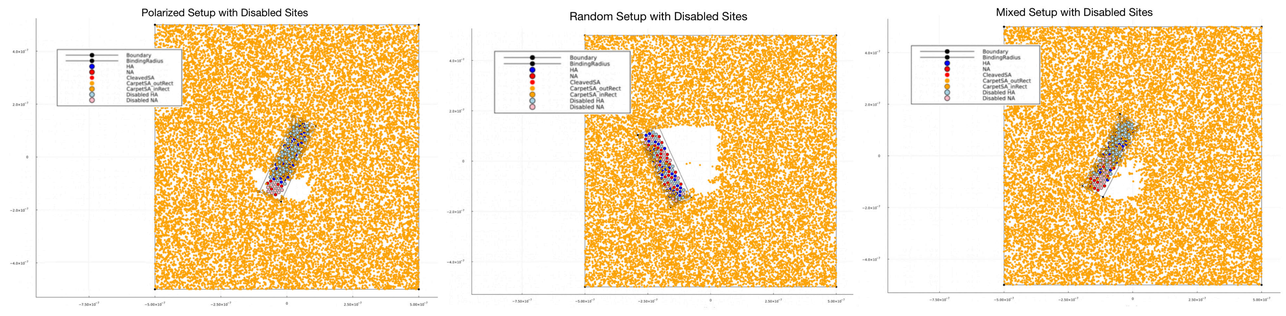


- The environment is modeled with a ‘carpet’ of immobile SA on the cell surface and free-floating antibodies.
- Antibodies can target both HA and NA.
- If an antibody is chosen to bind with an HA or NA, the binding site is disabled and the protein is blocked from further binding for the remainder of the simulation.

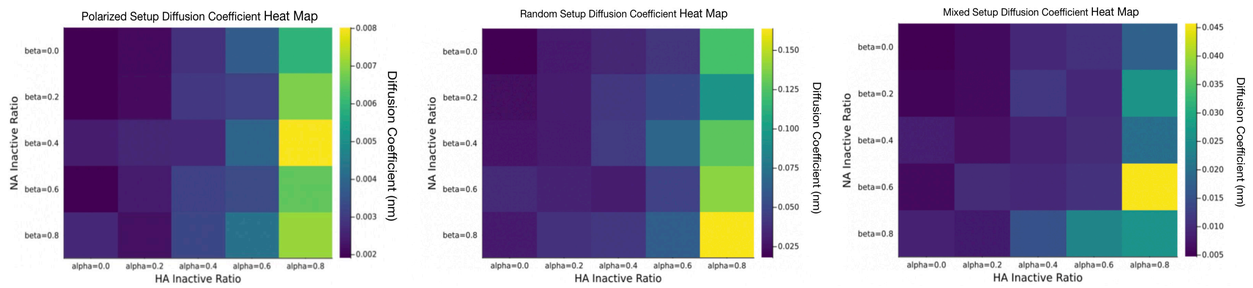
Results



- The polarized NA setup exhibits persistent directional motion away from its NA pole. This matches the results of Vahey and Fletcher [3].
- The random set up exhibits movement perpendicular to its short axis where the initial direction is chosen by stochastic fluctuations [4].
- The mixed setup exhibits a rotating motion. The direction is also likely chosen by stochastic fluctuations.



- For all figures 60% of HA is disabled and 60% of NA is disabled.
- The polarized NA set up exhibits weaker directional motion with some drifting likely due to stochastic motion.
- The random setup displays weaker motion but overall, disabled sites have less effect on the motion of this set up.
- The mixed setup exhibits weaker motion but follows a similar path as without disabled sites.



- All graphs display a clear horizontal gradient; as more HA are disabled, the diffusion coefficient of the virus increases.
- This is due to the restrictive nature of simulation, fewer bonds means less restrictions and thus, more free movement instead of the virus dissociating from cell membrane as expected.
- Disabled NA do not have a large impact on the diffusion coefficient indicating NA-inhibition possibly affects direction rather than speed.

Conclusions

- The virion exhibits the strongest persistent directional motion in the polarized NA setup. This best allows the virus to pass through the mucus barrier and infect non-ciliated cells [2]. This matches current literature [3].
- Disabling HA and NA sites results in weaker directional motion. This implies potential treatment of IAV through HA/NA inhibitors.
- Disabled NA potentially affect direction while disabled HA affect speed.
- Due to the simulation’s restrictions, more disabled HA means a higher diffusion coefficient which contradicts the expectation of viral dissociation.

Limitations

- The restrictive nature of the simulation does not account for viral dissociation from the cell membrane.
- Simulation neglects rotations in φ and ψ therefore ignoring aspects of its real motion.
- Simulation neglects any dragging effects which likely occur in nature.
- Low number of simulations and simulation steps due to computational limit likely affect accuracy of results.

Future Work

- Model could be improved to reflect a 3D setup including rolling and dragging effects to better represent the total motion of the virus.
- This model could be used to more thoroughly investigate directional movement and contribute to a better understanding of the potential benefits of an NA targeting vaccine.

References

[1] N. J. Overeem, E. van der Vries, and J. Huskens, “A dynamic, supramolecular view on the multivalent interaction between influenza virus and host cell,” *Small*, vol. 17, no. 13, Mar. 2021. doi:10.1002/smll.202007214

[2] L. Byrd-Leotis, R. D. Cummings, and D. A. Steinhauer, “The interplay between the host receptor and influenza virus hemagglutinin and neuraminidase,” *International Journal of Molecular Sciences*, vol. 18, no. 7, p. 1541, Jul. 2017. doi:10.3390/ijms18071541

[3] M. D. Vahey and D. A. Fletcher, “Influenza A virus surface proteins are organized to help penetrate host mucus,” *eLife*, vol. 8, 2019. doi:10.7554/elife.43764

[4] L. Stevens, S. de Buyl, and B. M. Mognetti, “The sliding motility of the bacilliform virions of influenza A viruses,” *Soft Matter*, vol. 19, no. 24, pp. 4491–4501, 2023. doi:10.1039/d3sm00371j