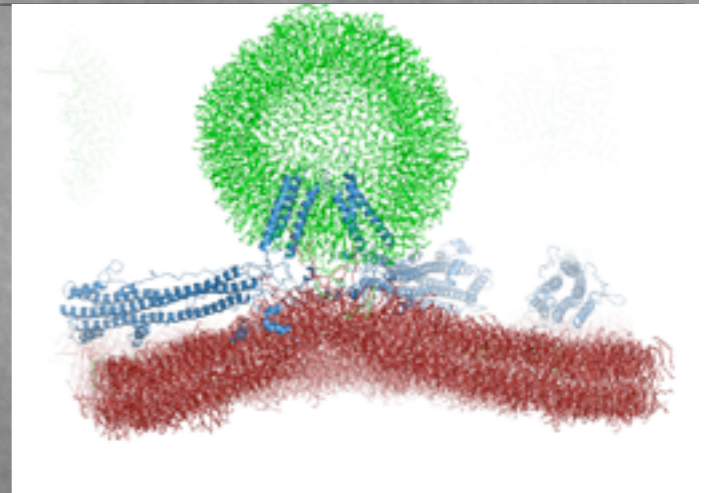
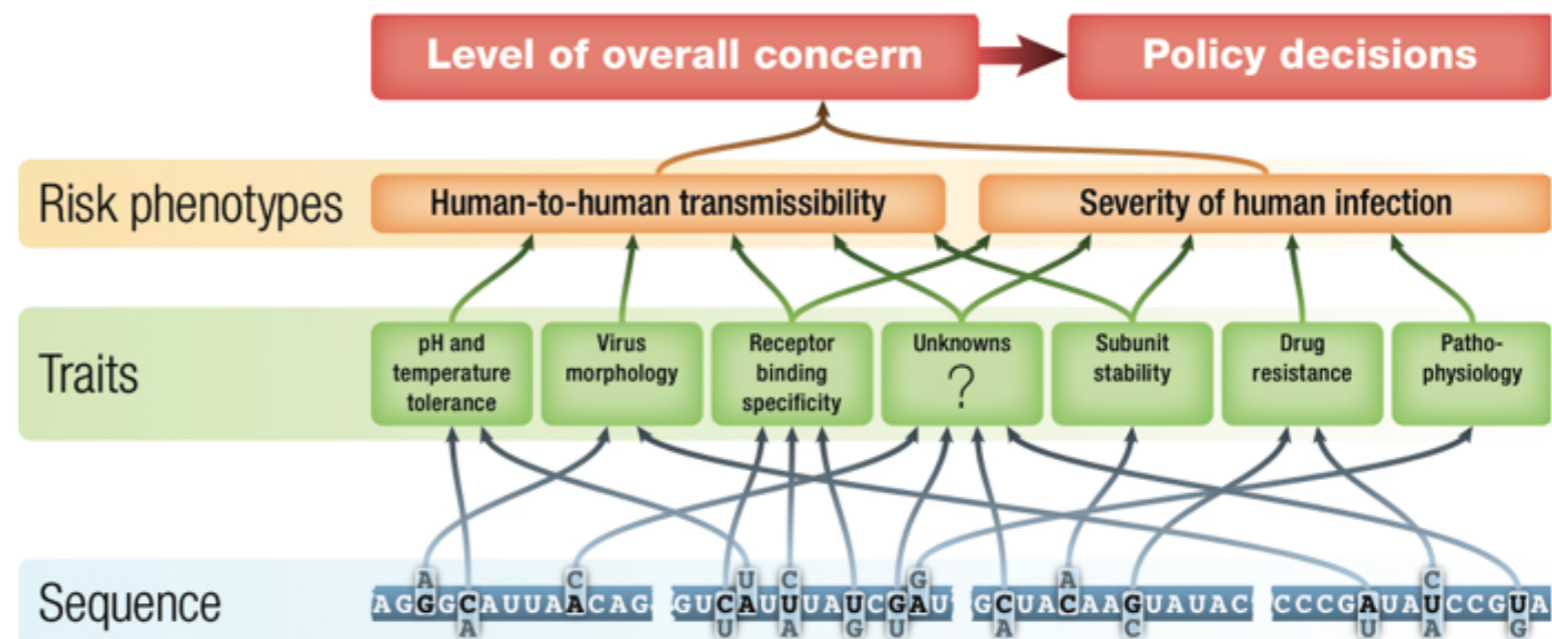
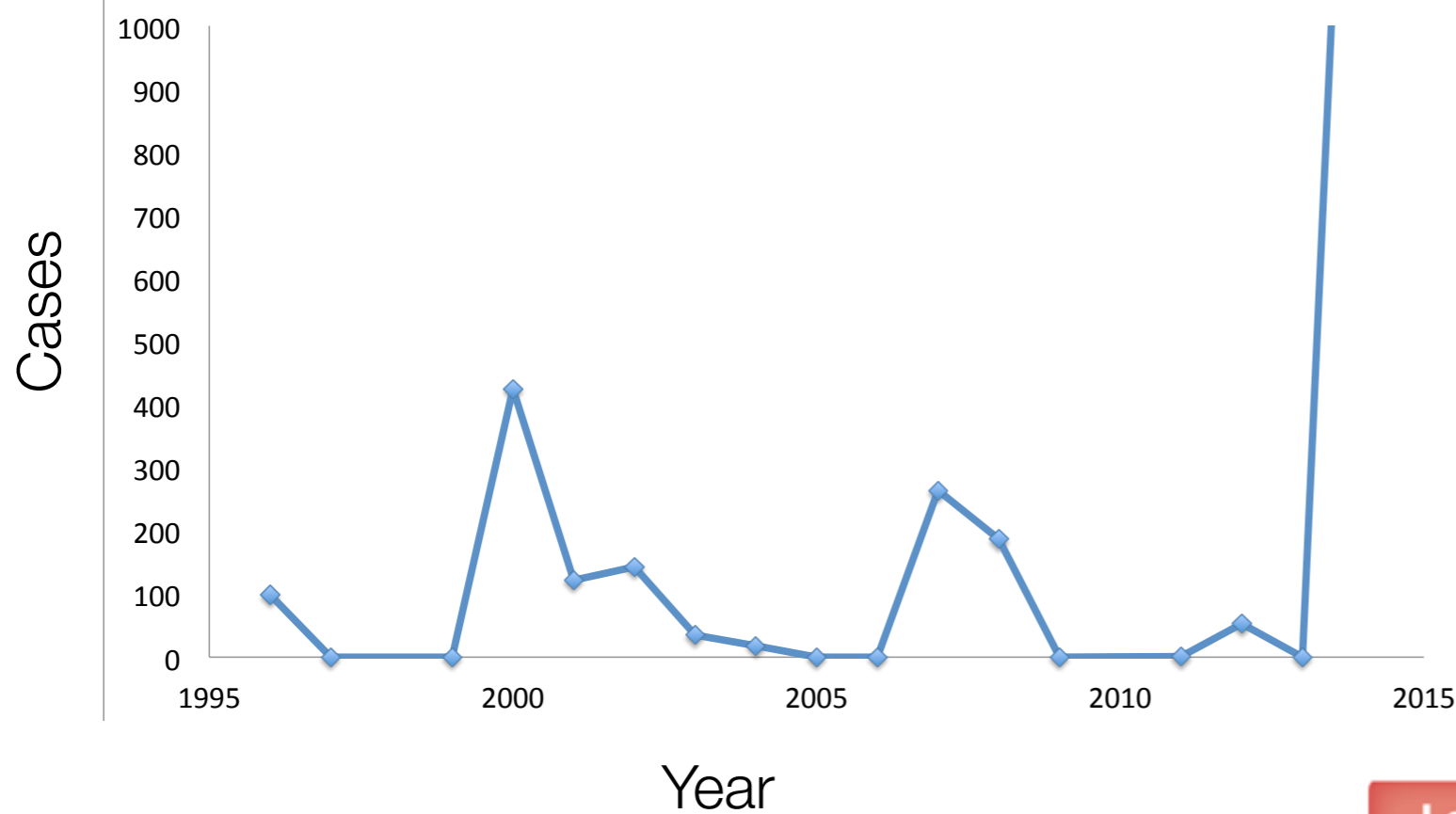


Protein-lipid interactions in influenza virus entry

Peter Kasson
Departments of Molecular Physiology
and Biomedical Engineering
University of Virginia

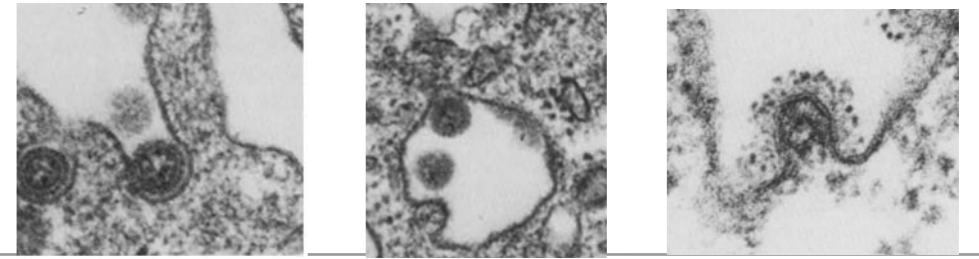


Why is it hard to predict pandemics

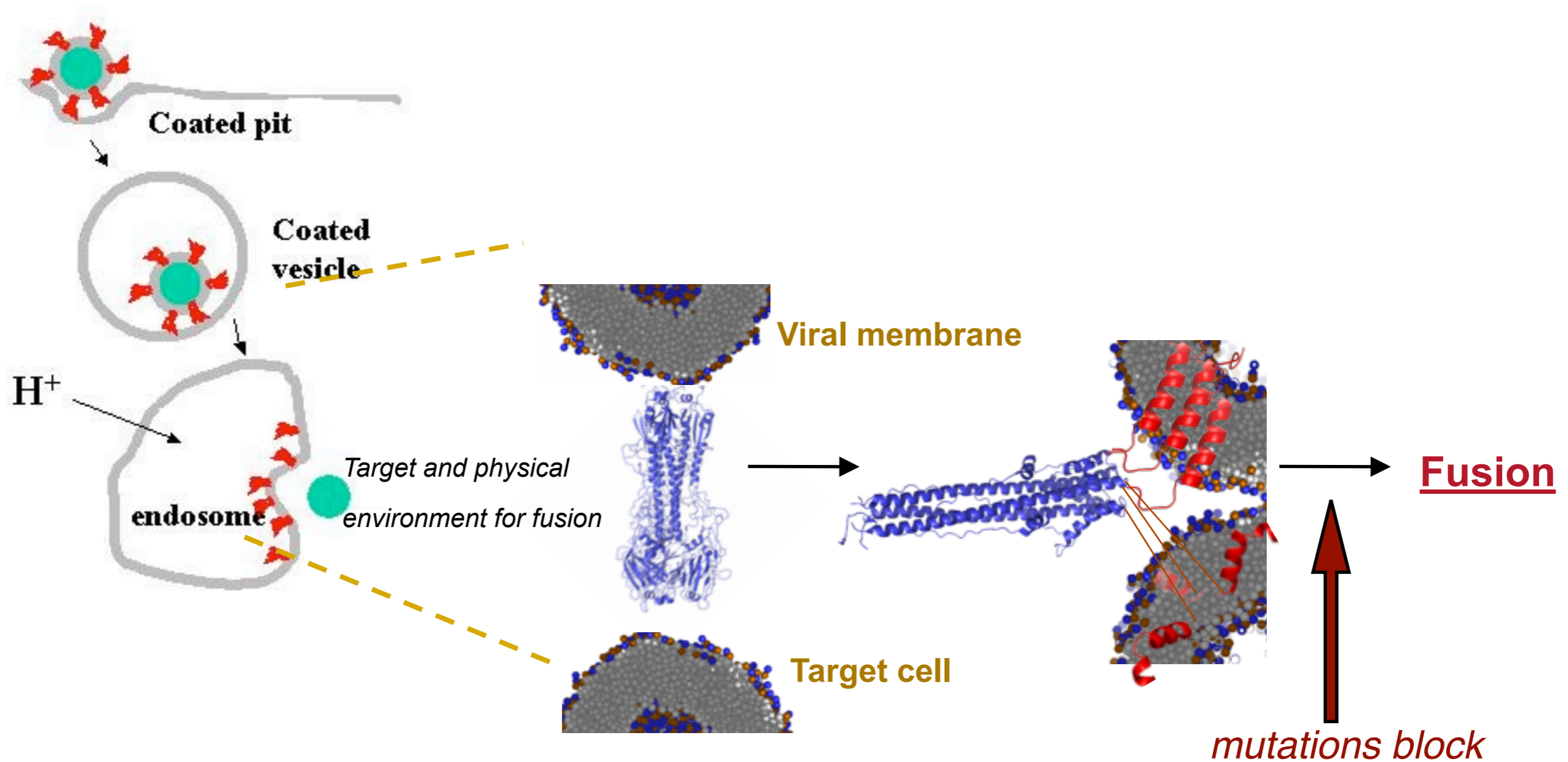


Sources: US CDC;
Russell, Kasson et al., 2014

Cell entry by influenza



Matlin et al., 1981

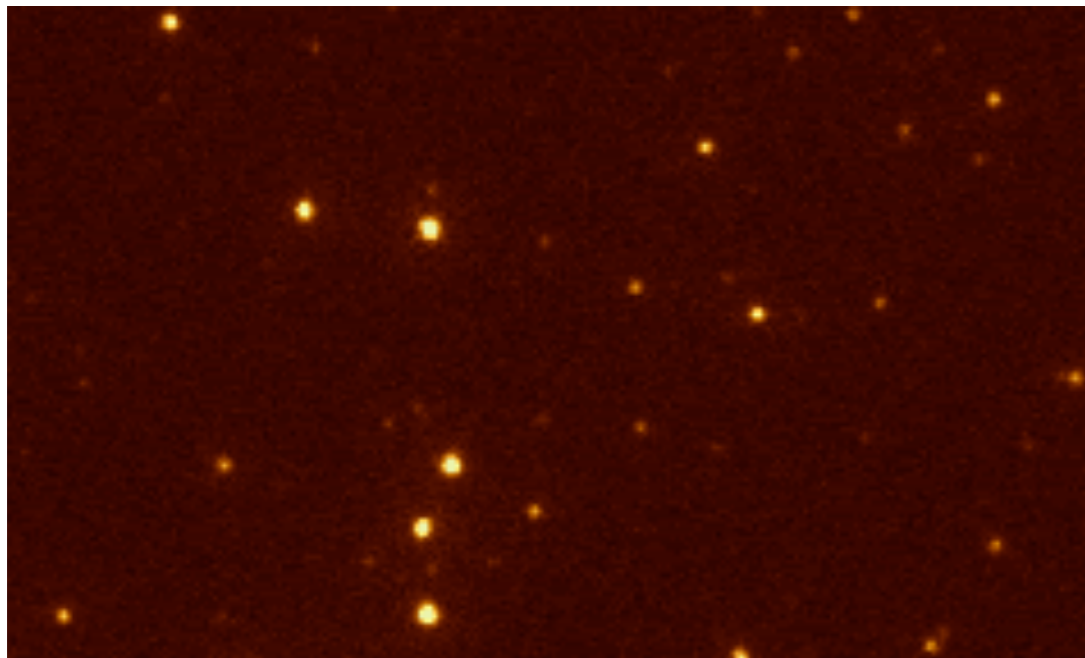


Influenza fusion is heterogeneous on a single-virus level

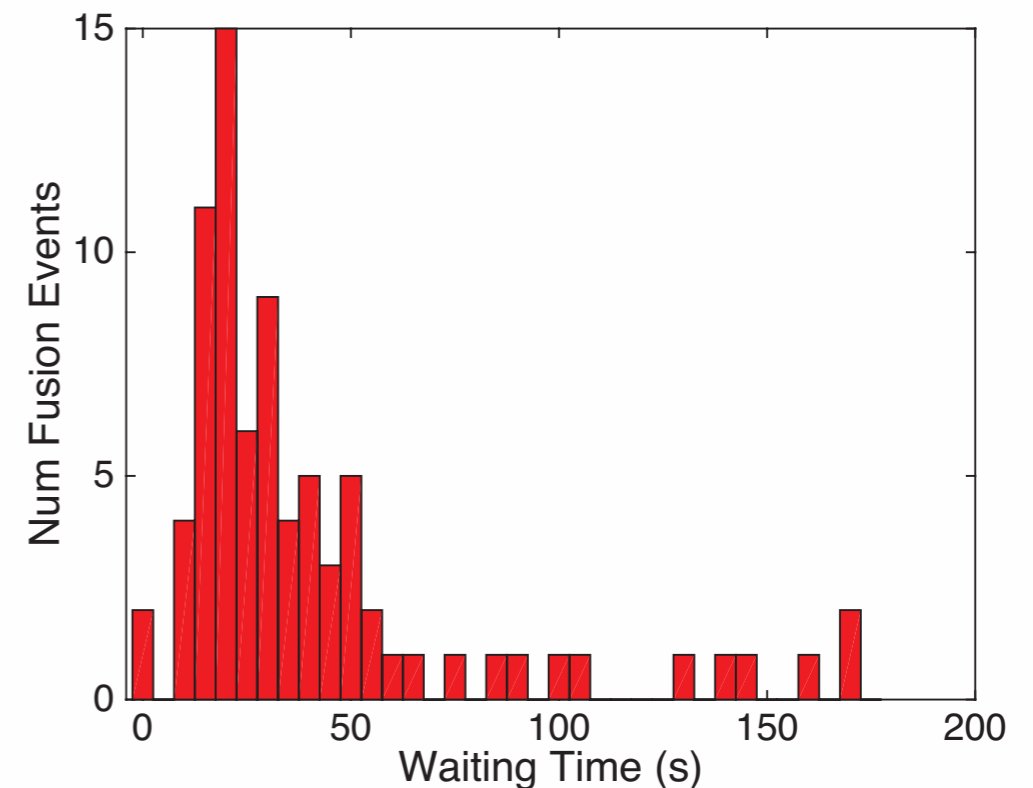
fusion efficiency 10-40% depending on conditions

in-cell fusion efficiency ~10%

even if we could simulate relevant timescales, a single movie wouldn't do it



*Single fusion events detected via
fluorescence dequenching*



Bad combination

Heterogeneous outcomes -> need *many* simulations for statistics

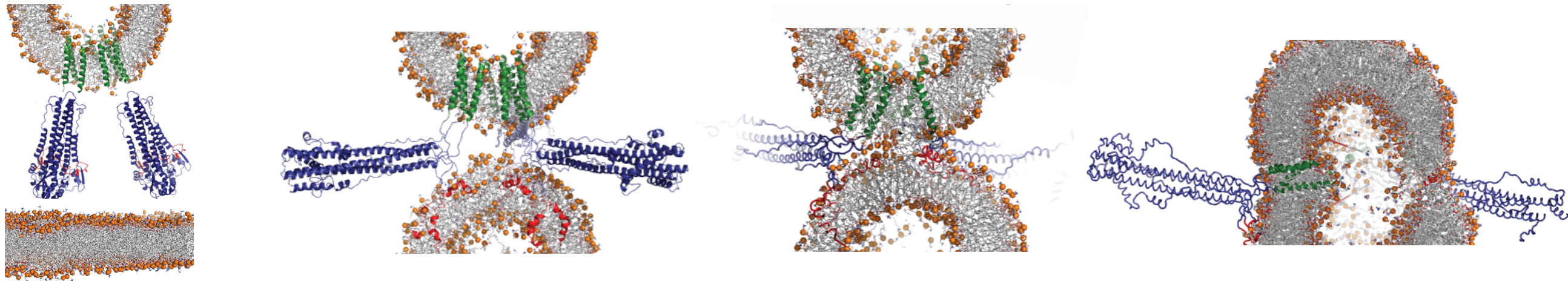
Slow decorrelation times -> need *long* simulations

Simplest full-scale systems $\gg 1$ M particles -> need *large* simulations

Biological system sensitive to fine details -> need *high-fidelity* simulations



Unraveling virus-membrane interactions surrounding fusion

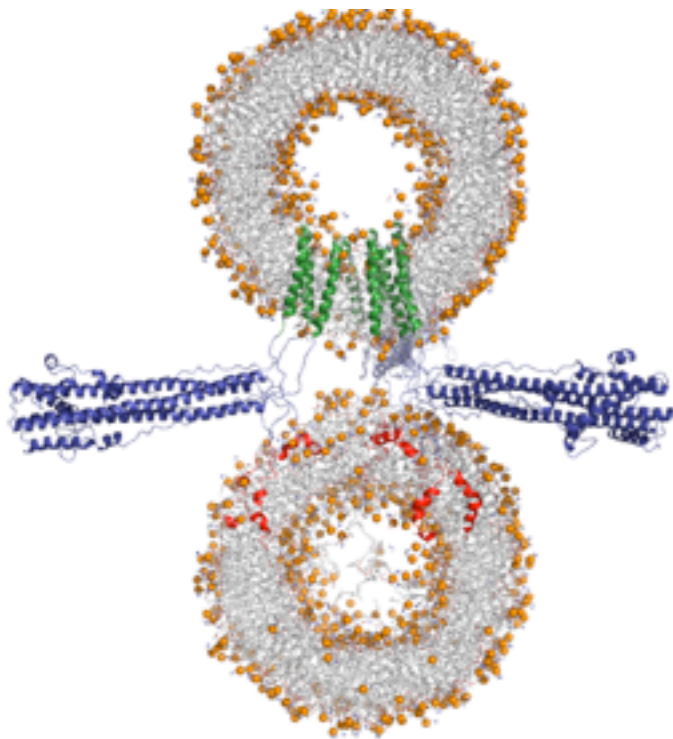


What are the relevant physical interactions controlling influenza viral fusion?
Building an integrated understanding from simulations and biophysical experiments.

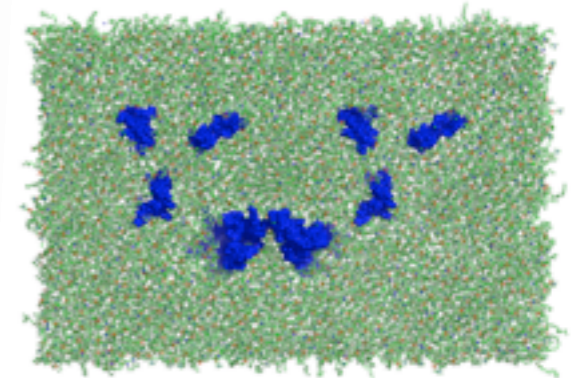
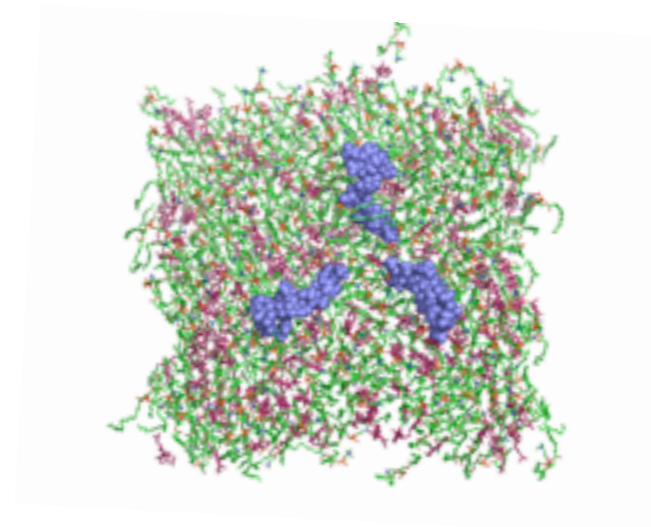
Today: membrane interfaces preceding fusion, membrane-protein interactions.

Multi-pronged approach

Building integrated understanding via statistical models at multiple levels



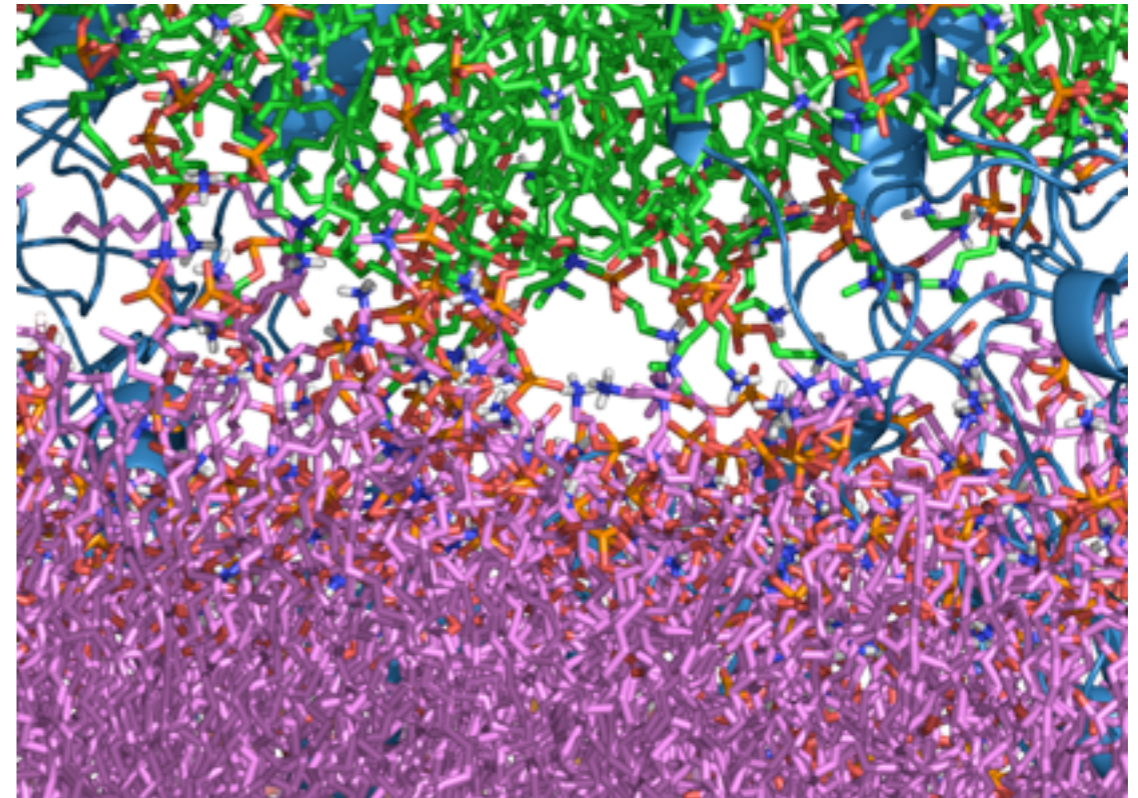
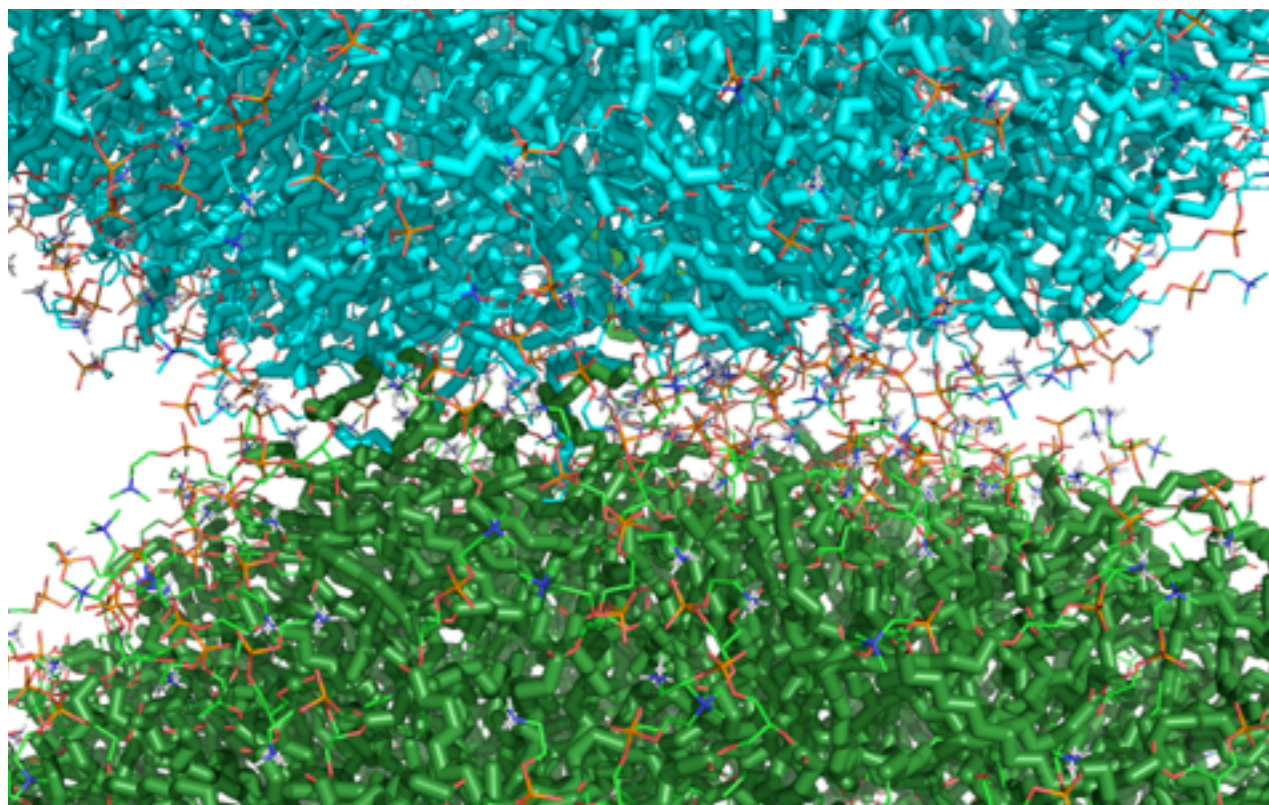
“mid-scale” systems
~1-3M atoms



isolated components
150K-800K atoms

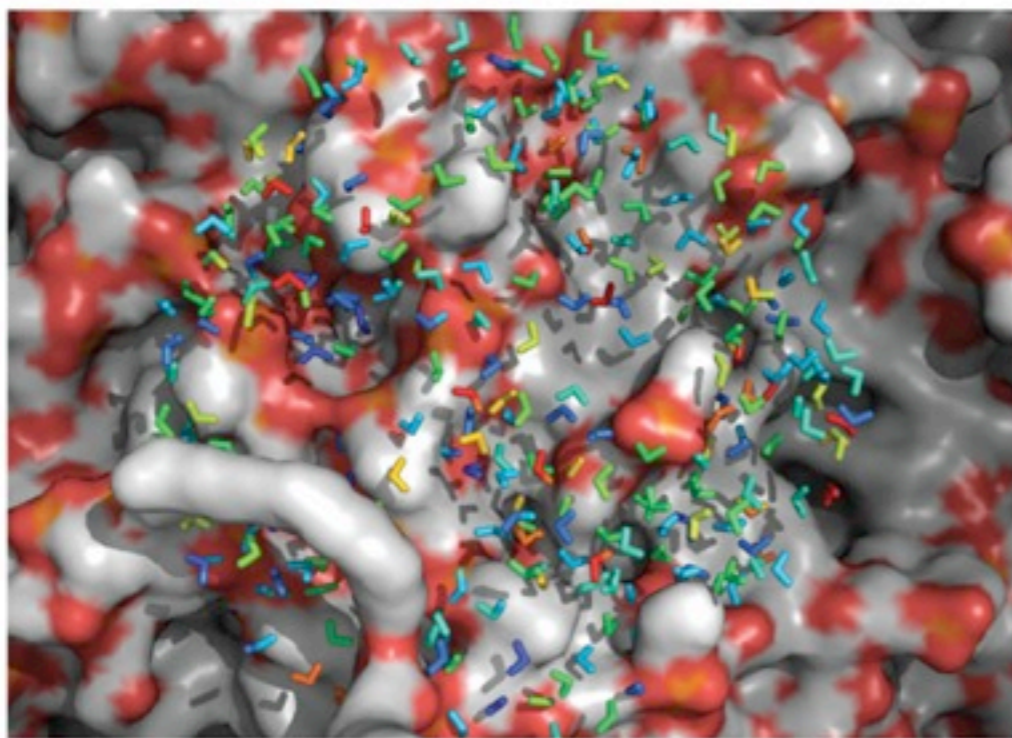
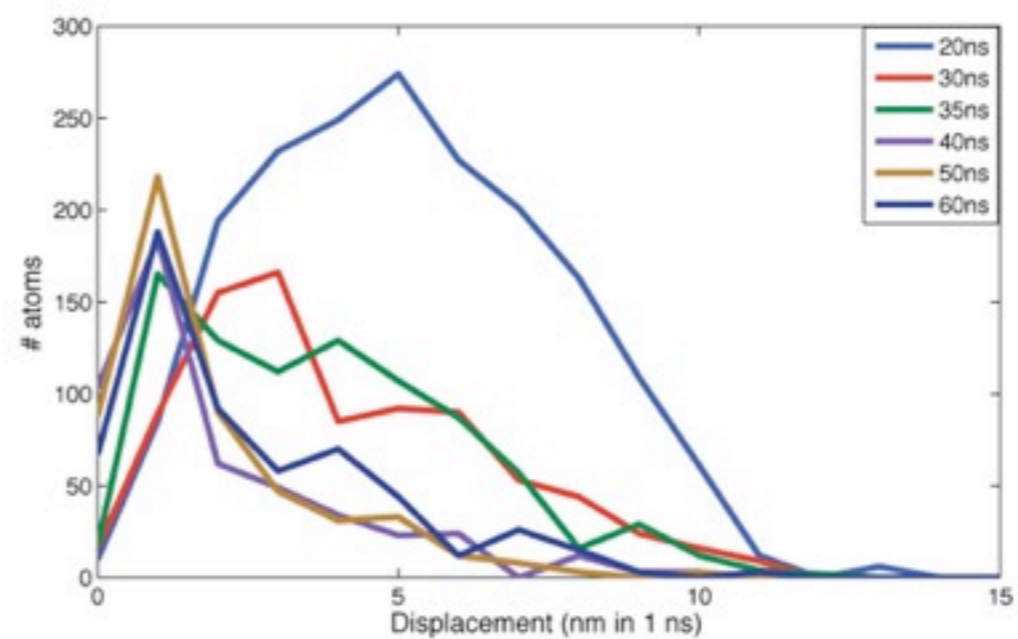
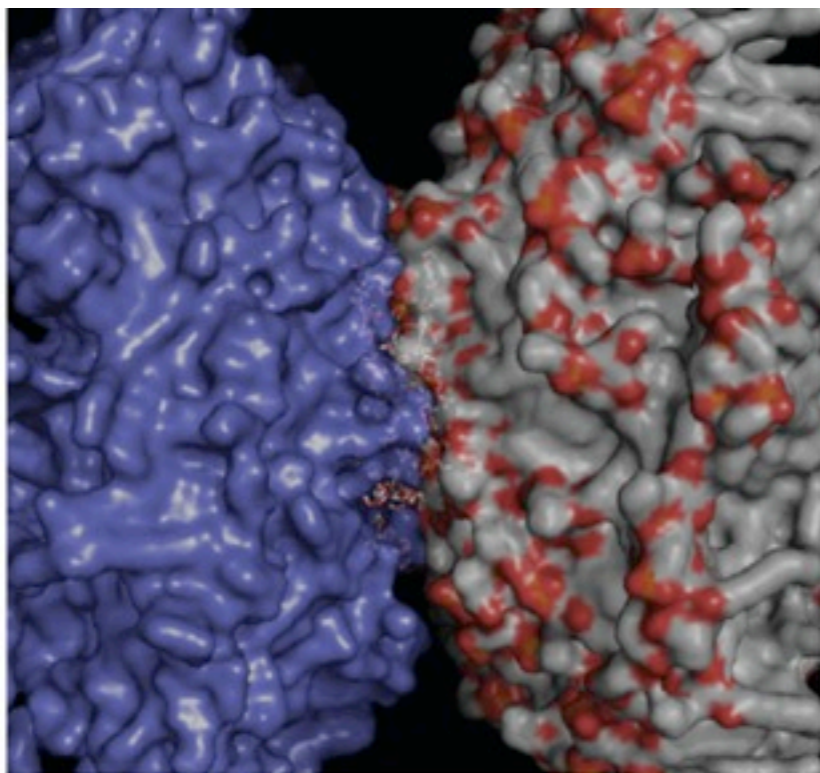
Membranes form stable interfaces prior to fusion

Depending on the system, these can be 10's of ns to $\sim 10 \mu\text{s}$

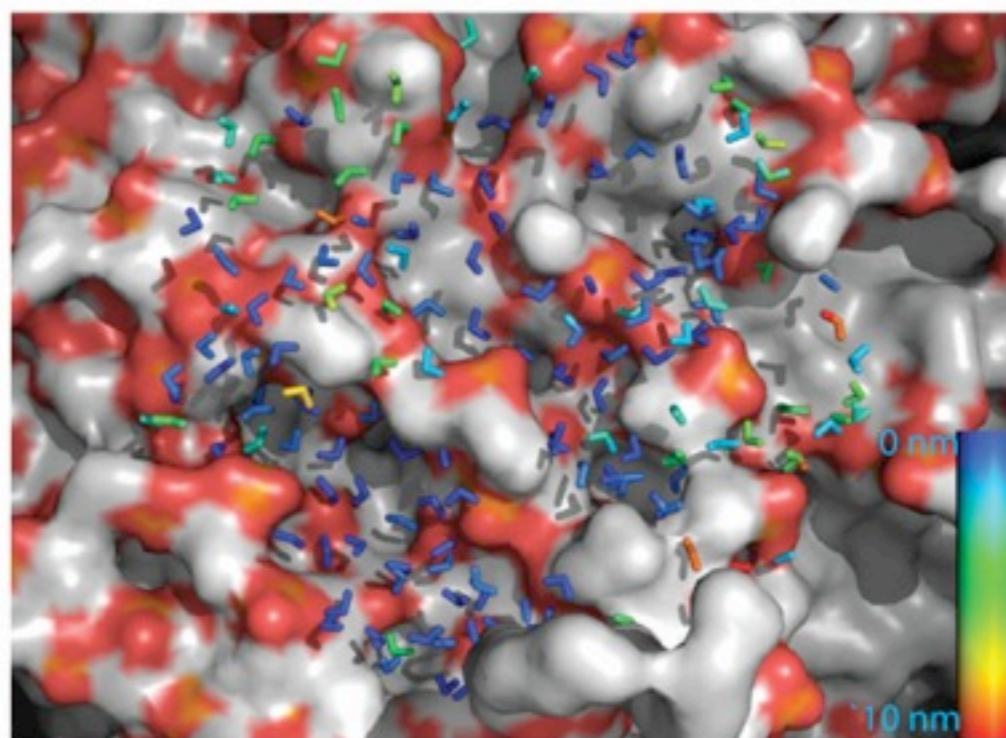


Unexpected! Now good indirect experimental evidence!

Decreased water mobility at vesicle interface

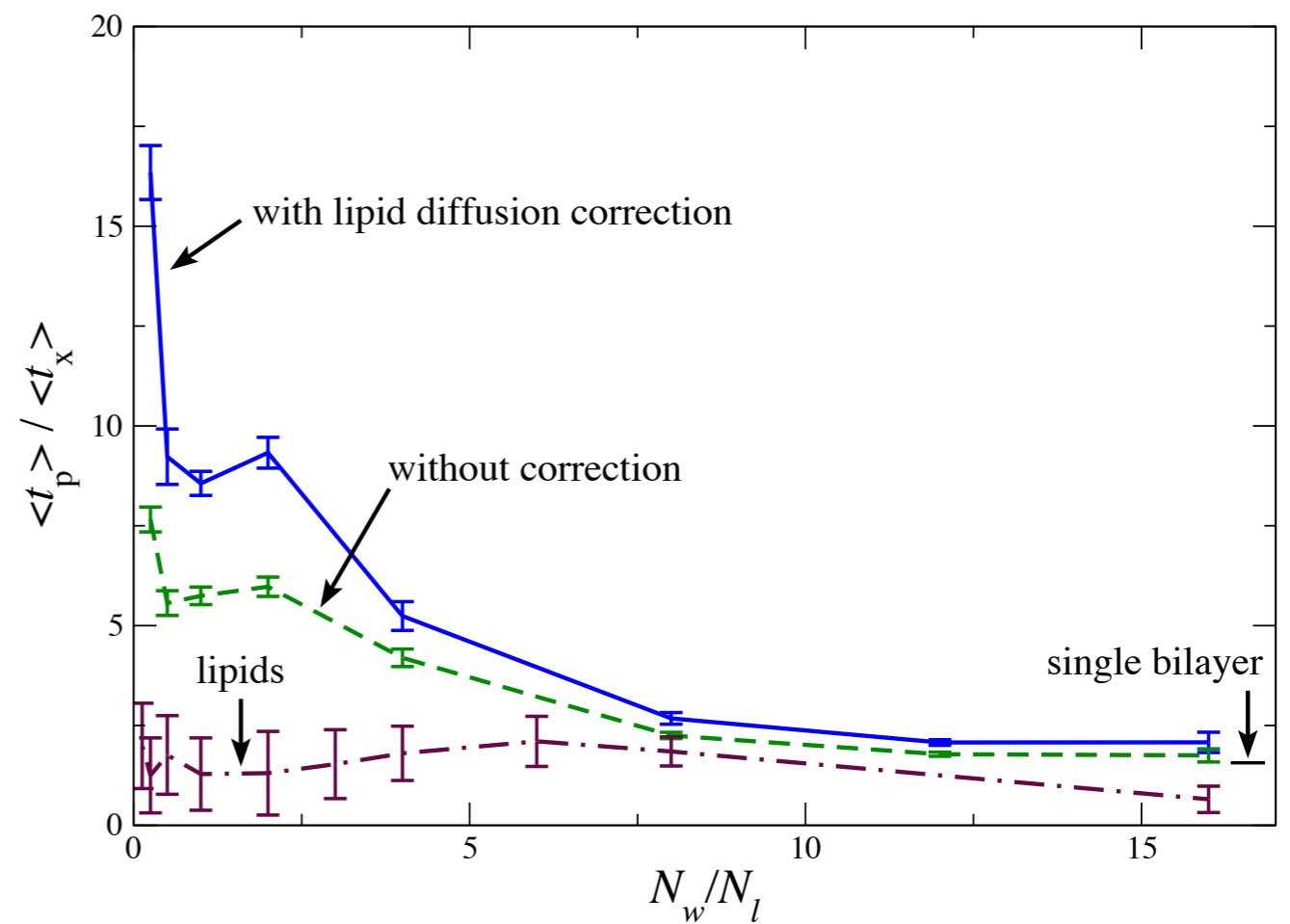
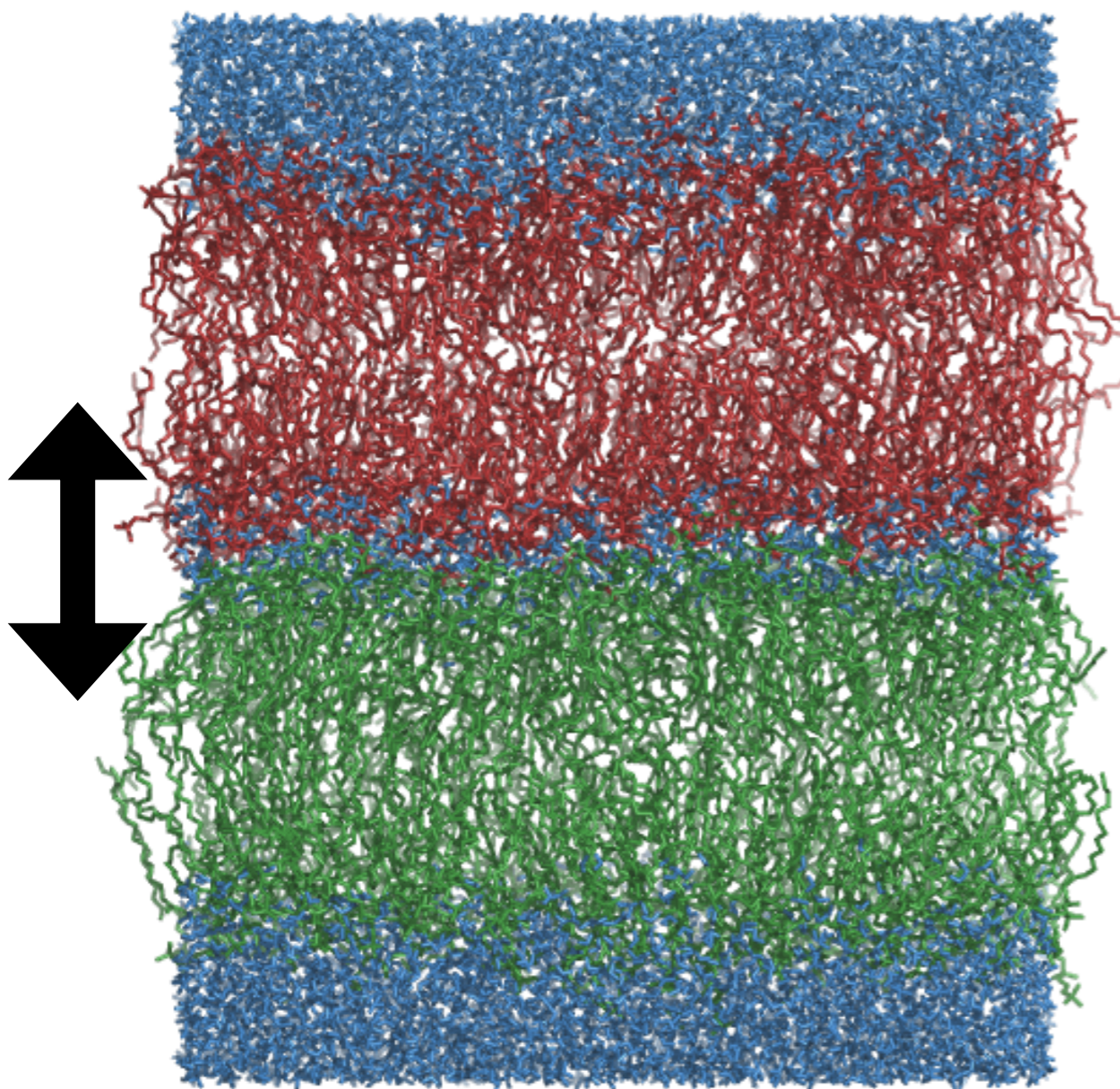


Vesicle interface at 30ns



Vesicle interface at 40ns

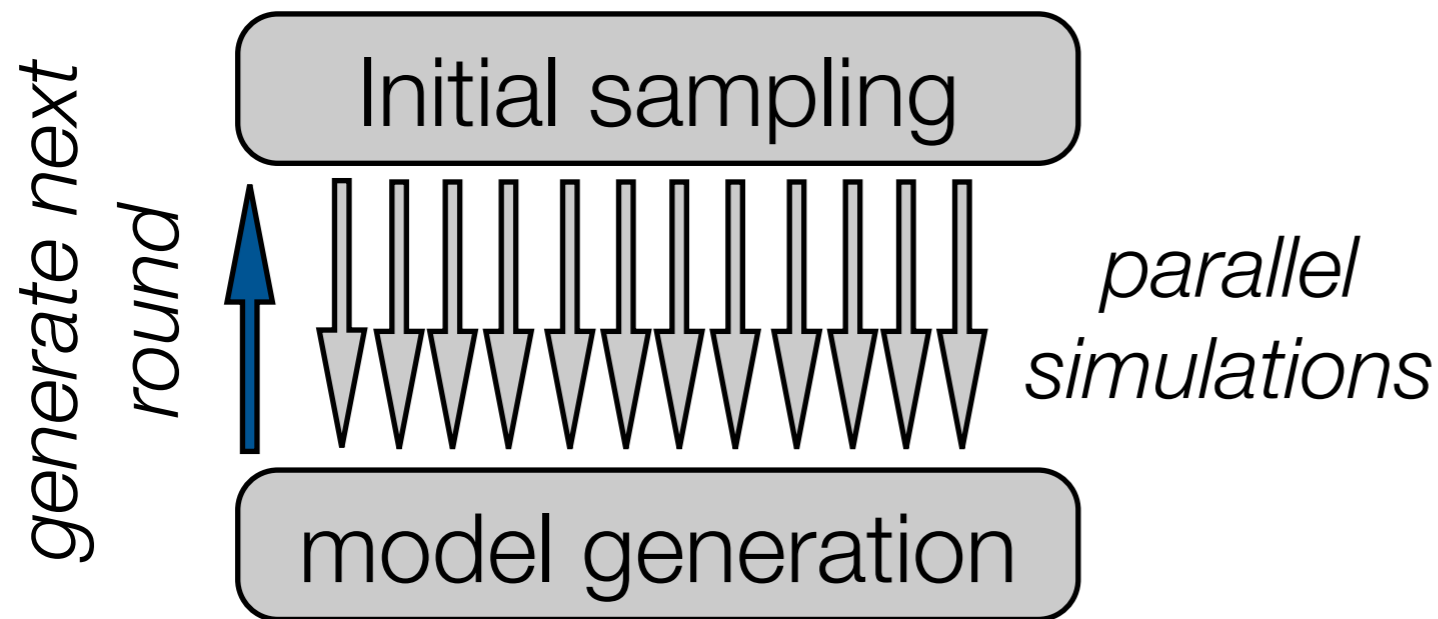
Glassy dynamics of water between two lipid membranes



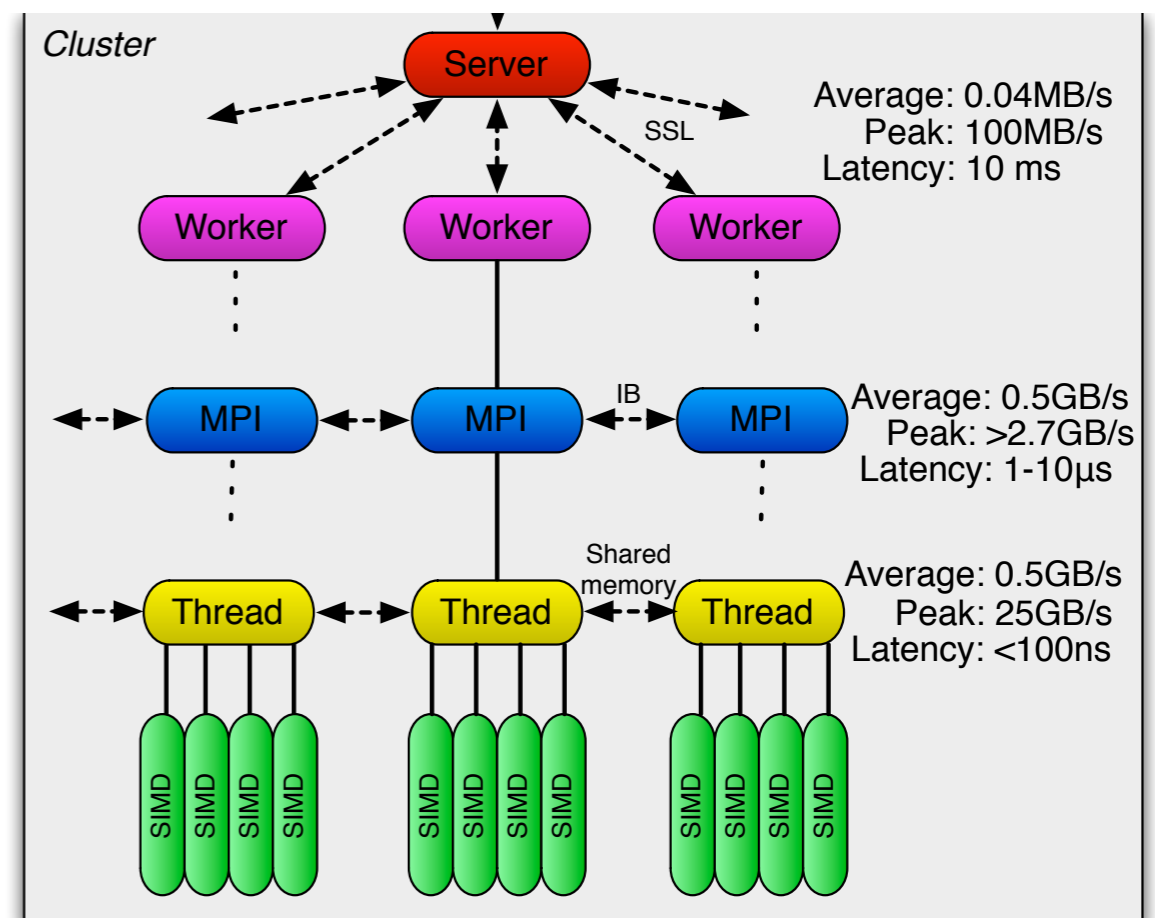
Implications for simulating fusion dynamics--can get stuck!

Multi-level parallelism

Need both parallelism at the individual “partition” level (MD scaling over N cores/GPU’s) and parallelism between partitions in solving the overall statistical problem



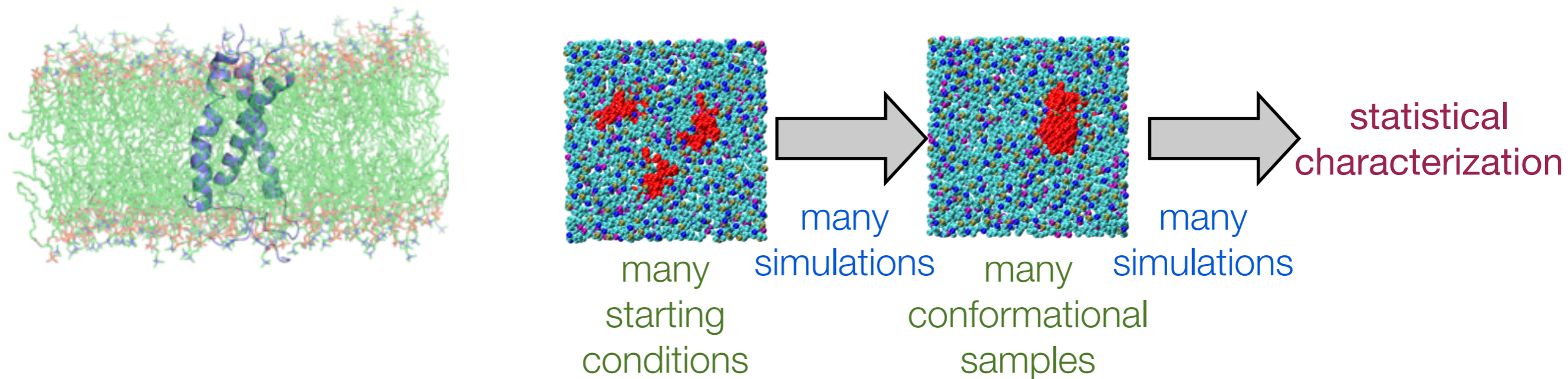
Currently doing this ad-hoc on BW
Copernicus: DAG engine to
coordinate this



Pronk et al., 2011; Pronk et al., 2015

Hemagglutinin transmembrane domains

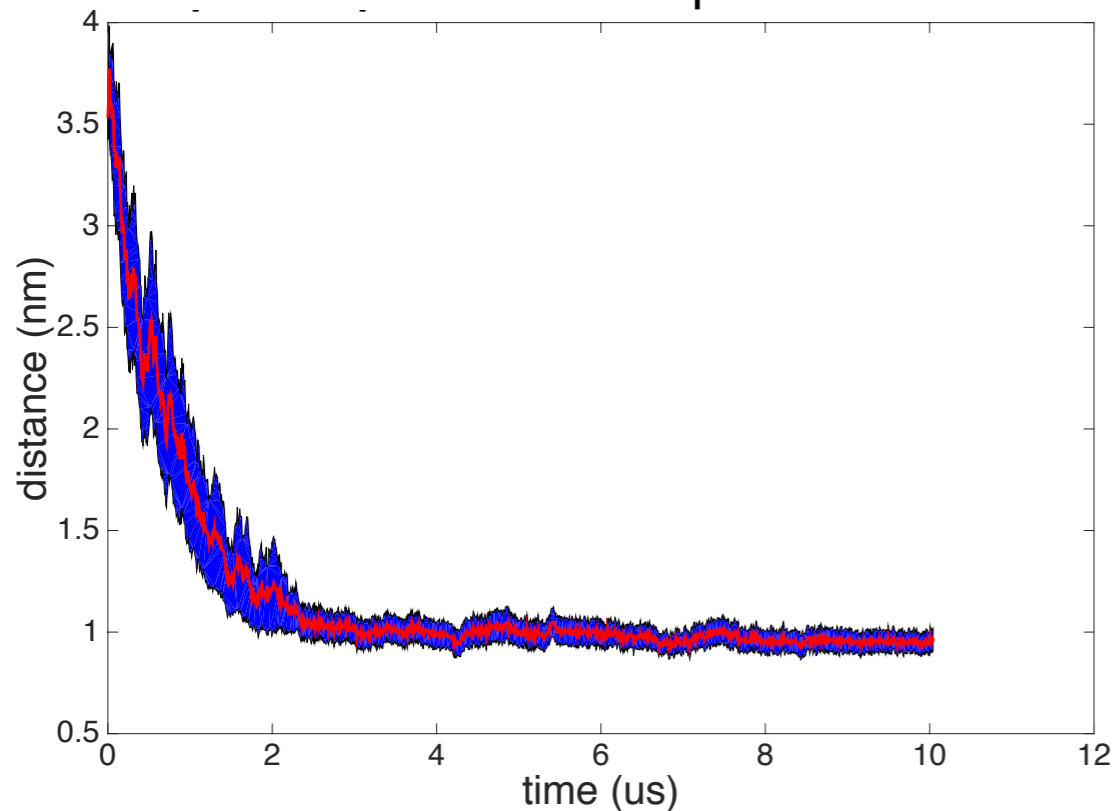
- Hemagglutinin is trimeric; multiple trimers likely act together in fusion
- Truncations to the TM domain can arrest fusion
- Could TM-TM interactions play a role in fusion?



- Multi-resolution approach to characterize TM interactions
- Use coarse graining to sample diffusional processes, atomistic simulations to sample conformational equilibria

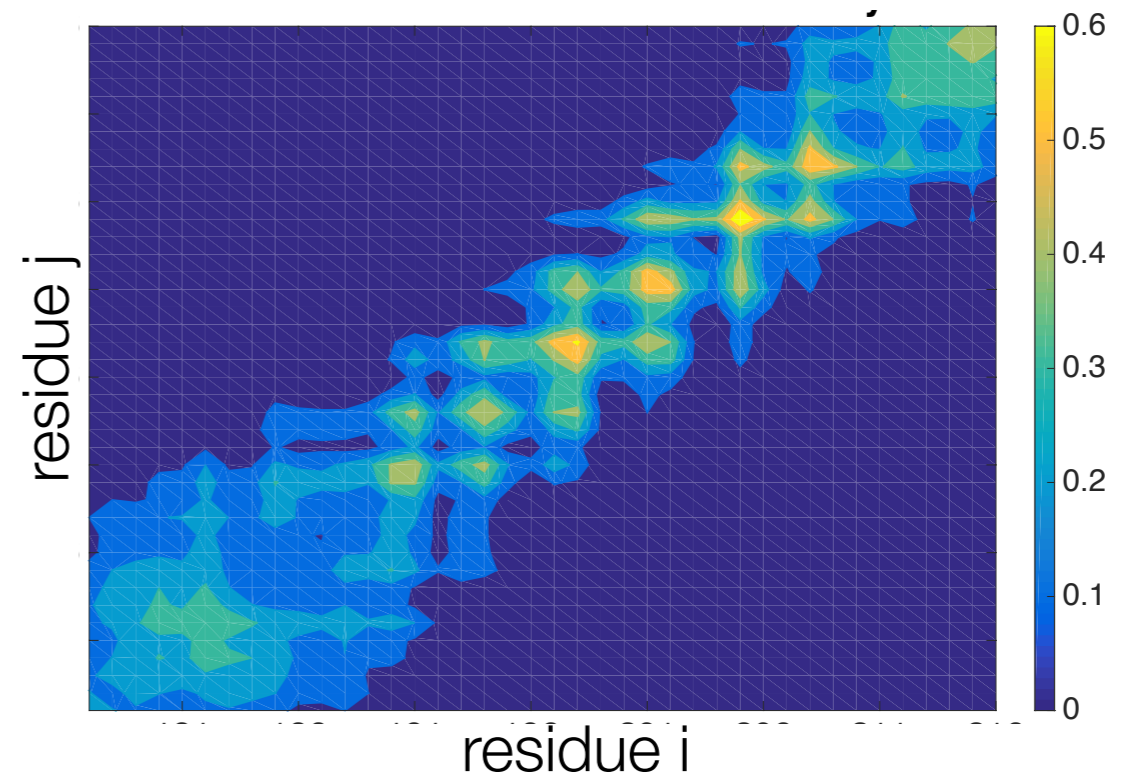
Reproducible, stable trimerization by TM domains

Coarse-grained simulations form TM trimers on the $\sim 2 \mu\text{s}$ timescale



All 24 simulations formed trimers

Probability map of inter-monomer contacts from 50 atomic-resolution simulations



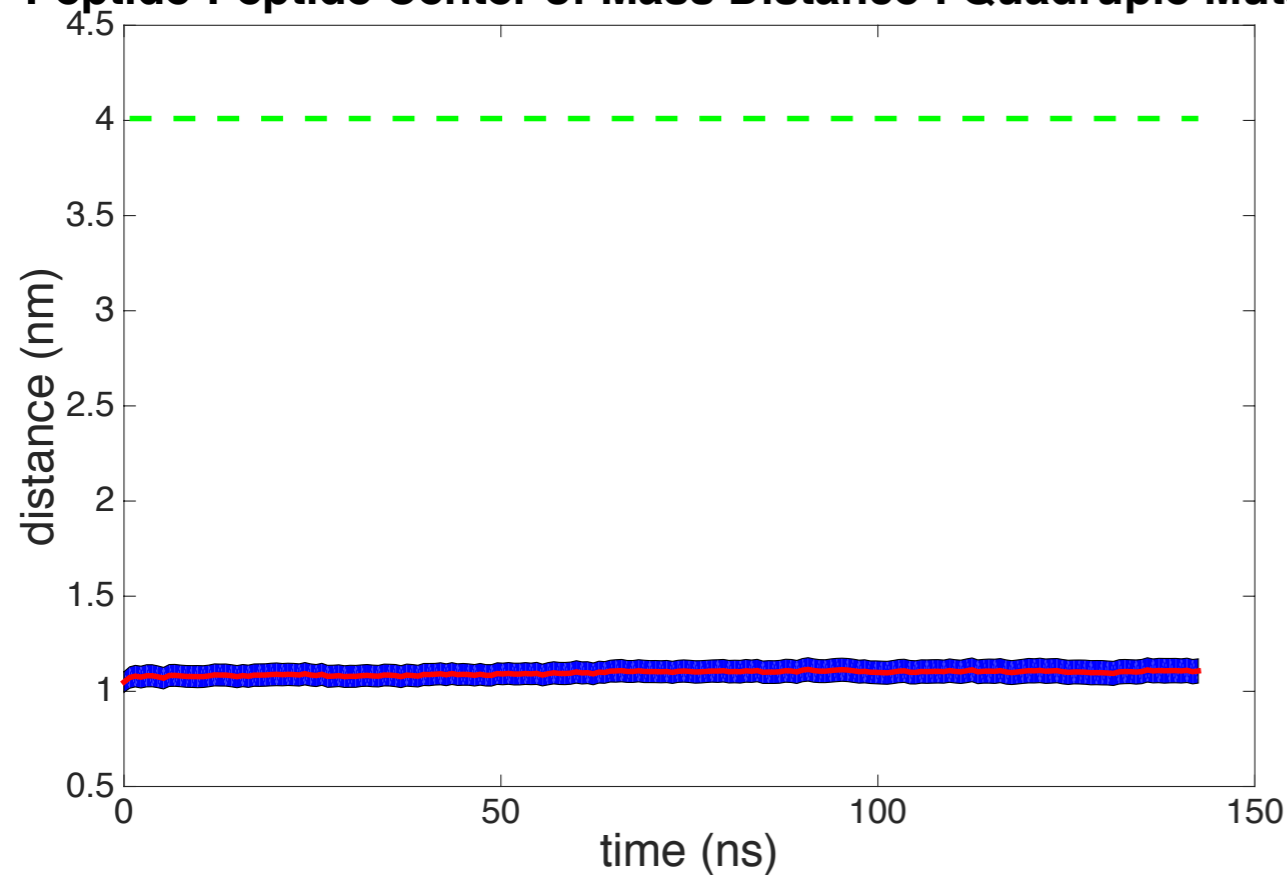
Contacts primarily "in register"

TM domain trimers are robust to mutation

Mutating the top 4 contacts abrogates those contacts but does not disrupt trimer.

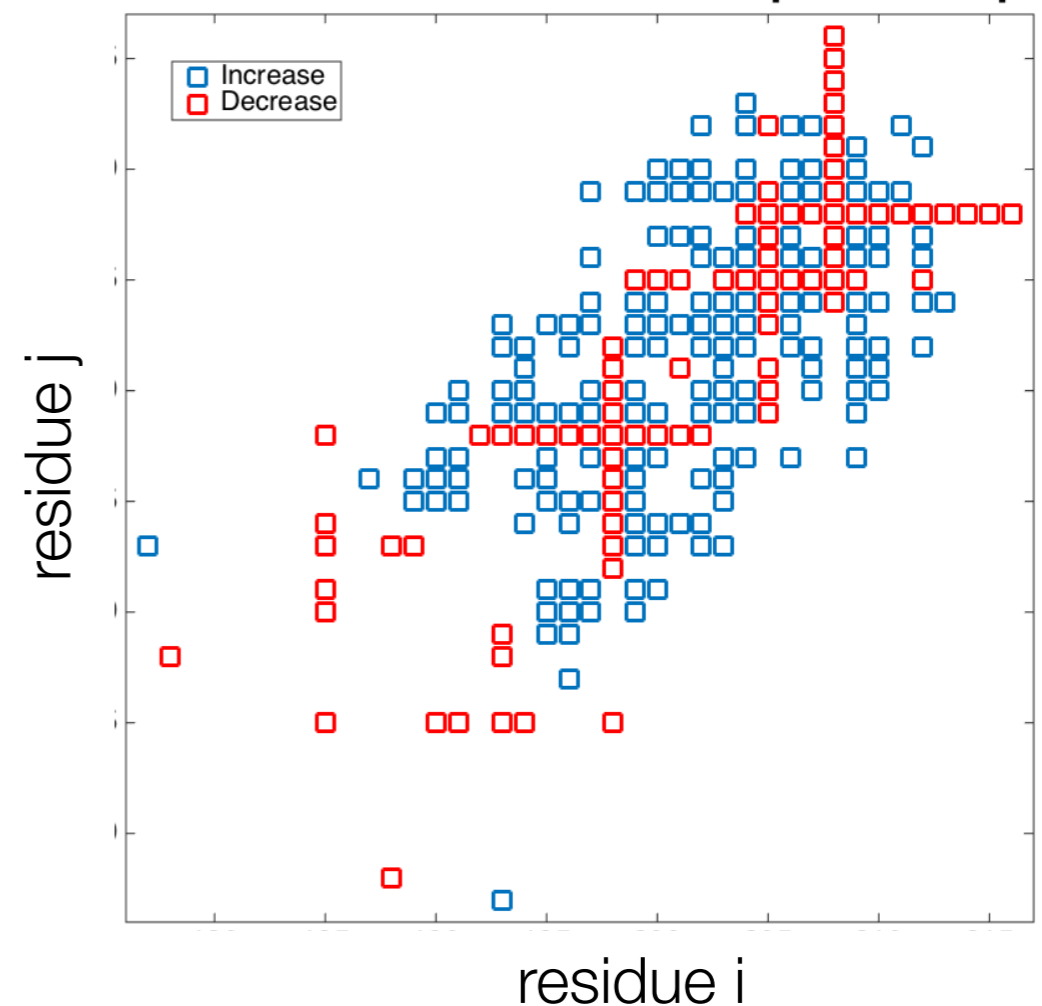
This is consistent with experimental mutational data

Peptide-Peptide Center of Mass Distance : Quadruple Mutant



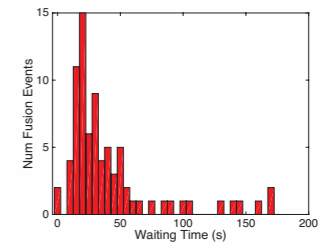
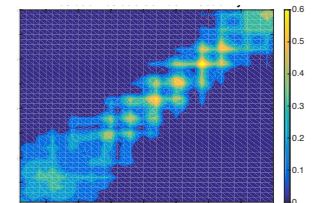
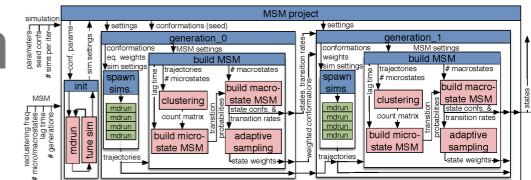
average over 50 simulations

change in inter-monomer contacts



Building integrated understanding...

- Methods: integrate statistical models into high-level parallelism
- Statistical models of protein-membrane dynamics for different interactions involved in influenza viral entry
- Statistical models of influenza-mediated membrane fusion
- Integrating with biophysical experiments



Ultimately, all of this is a single large sampling and statistical learning problem. Hard because we don't know the relevant reaction coordinates.

Acknowledgements

Group members

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BLUE WATERS

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