Proton Transport in Influenza A M2 Channel

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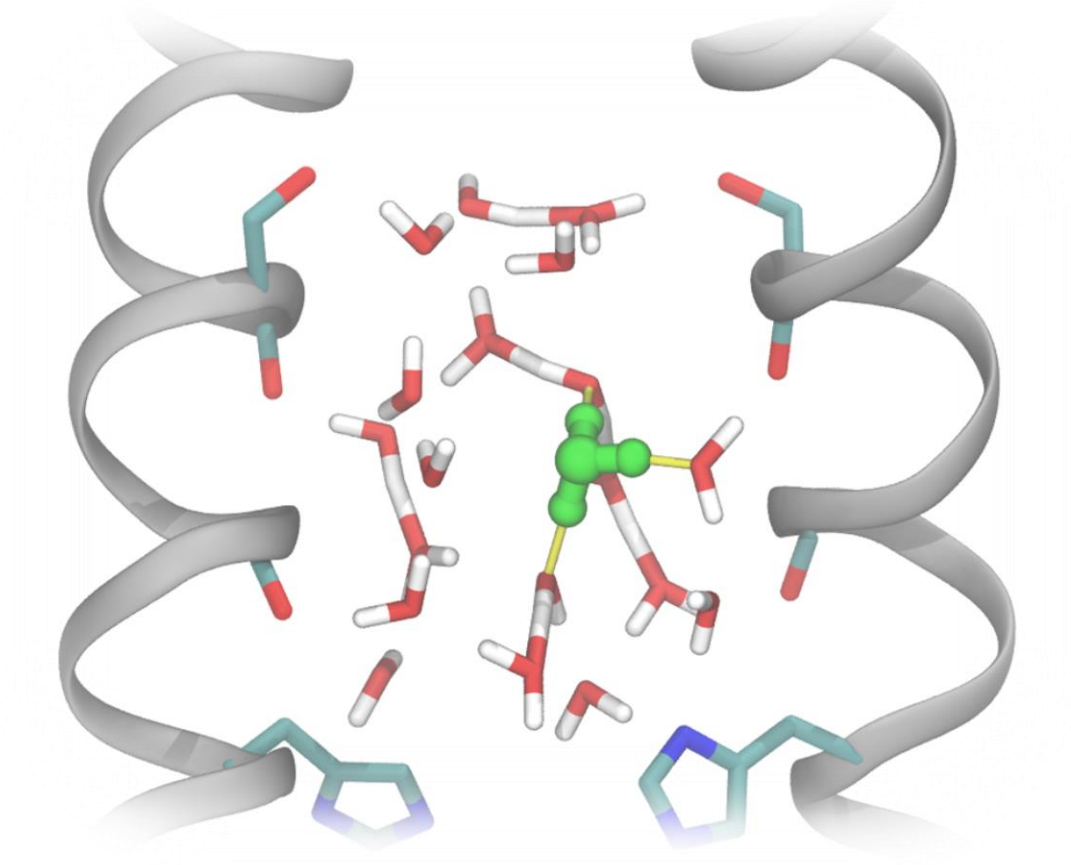
DOE CSGF Virtual Program Review

July 2020

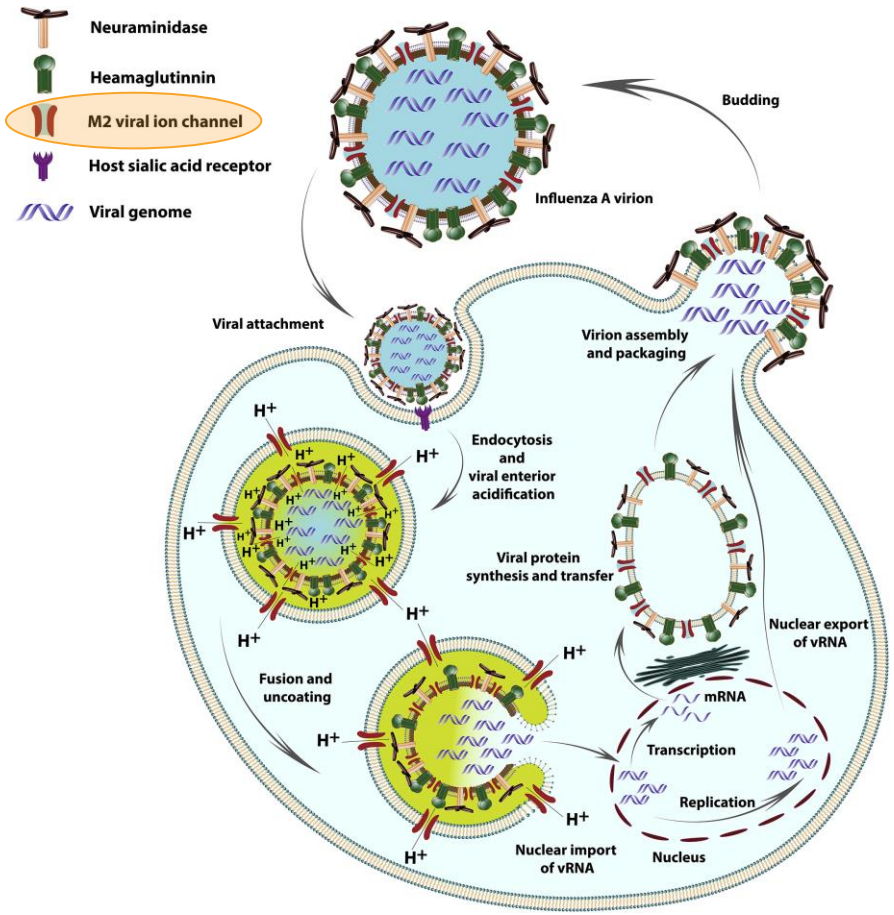


THE UNIVERSITY OF CHICAGO

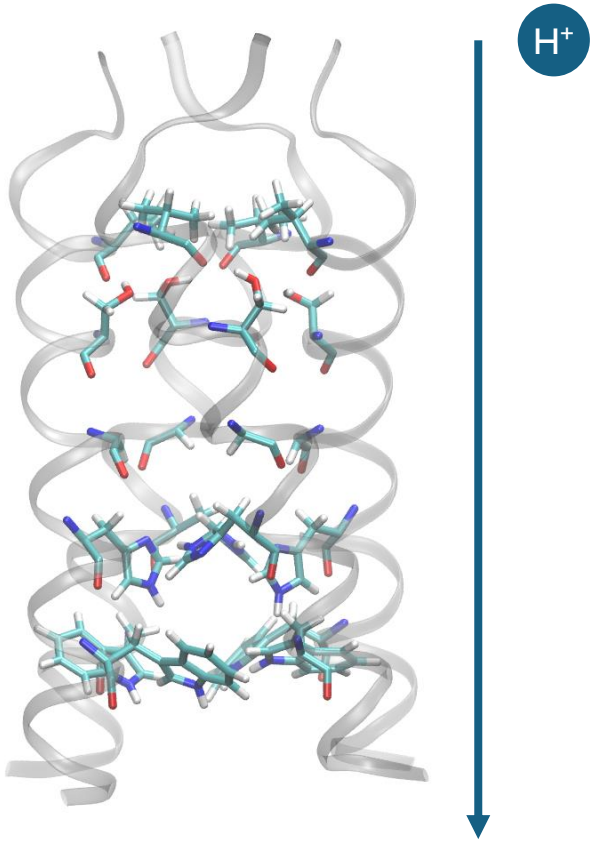
DOE CSGF

Influenza A M2: Critical Drug Target in Influenza Virus

Influenza A Lifecycle

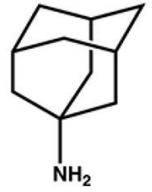


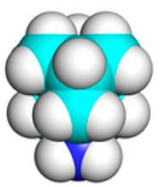
M2 Proton Channel



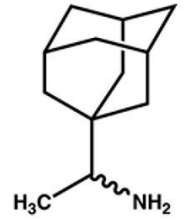
Inhibitors (now ineffective)

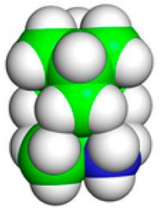
Amantadine





Rimantadine

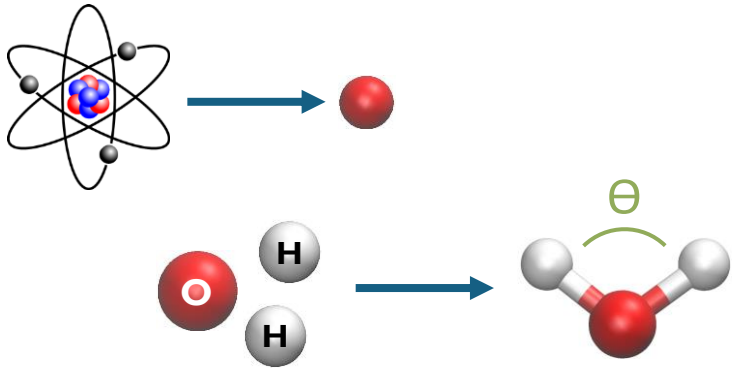


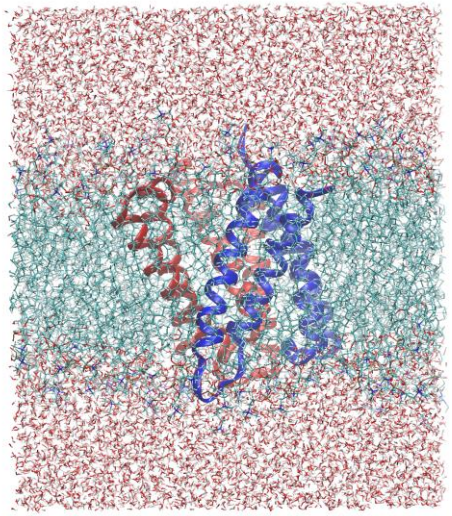


Jalily *et al.* Antiviral Research. 2020 Jun;178:104780. Thomaston JL, *et al.* (2015). Proc Natl Acad Sci USA 112(46):14260–14265.
Thomaston JL, *et al. J. Am. Chem. Soc.* 2018, 140, 45, 15219-15226

Proton Transport Requires Reactive Simulation Method

Classical Molecular Dynamics





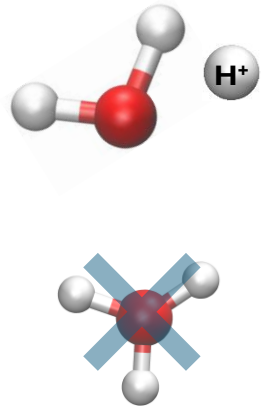
$$U(\boldsymbol{x}) = E_{bond} + E_{angle} + E_{dihedral} + E_{nonbonded}$$

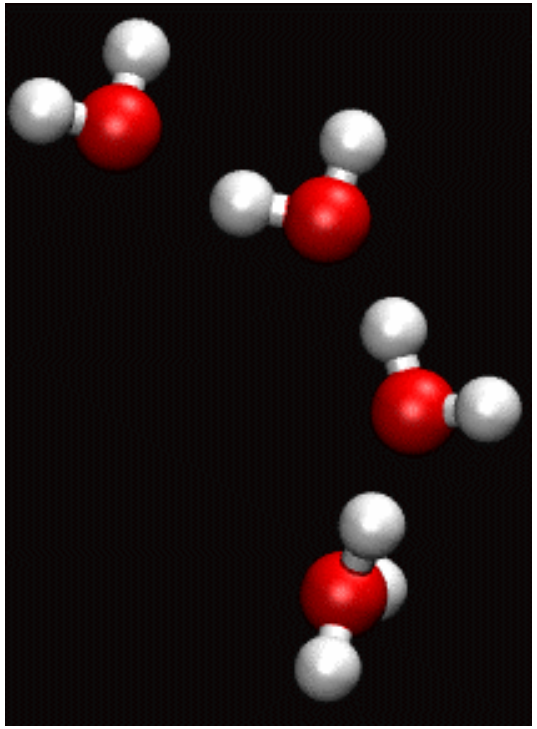
$$\boldsymbol{F} = m\boldsymbol{a}$$

$$F(\boldsymbol{x}) = -\nabla U(\boldsymbol{x})$$

Proton Hopping Mechanism

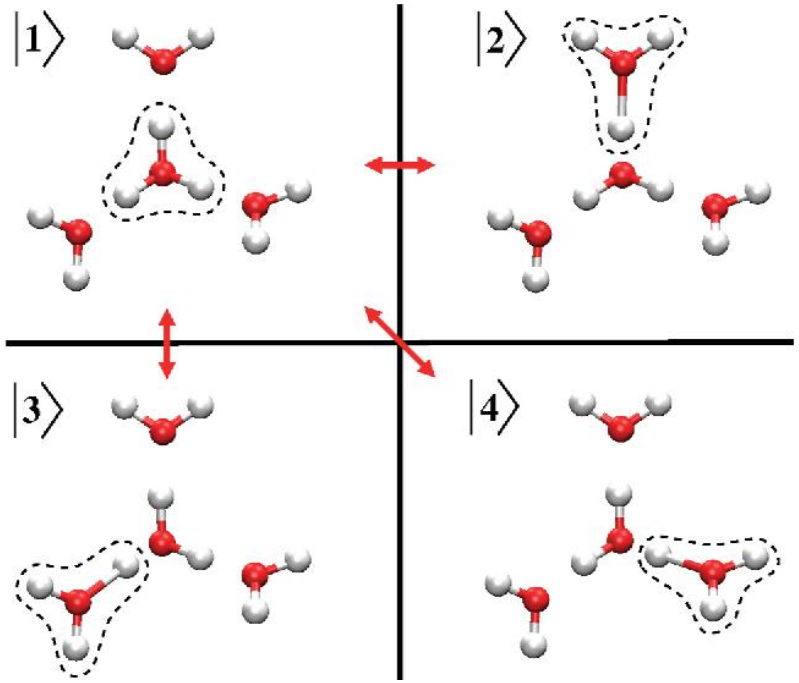
$$2\ H_2O \rightleftharpoons OH^- + H_3O^+$$





Proton Transport Requires Reactive Simulation Method

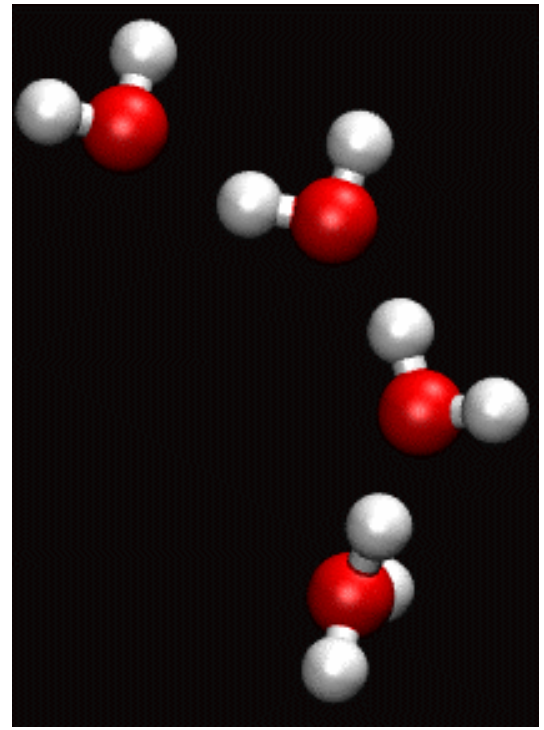
Multiscale Reactive Molecular Dynamics



MD with an **explicit, reactive** excess proton
Allows bonds to break and form

Proton Hopping Mechanism

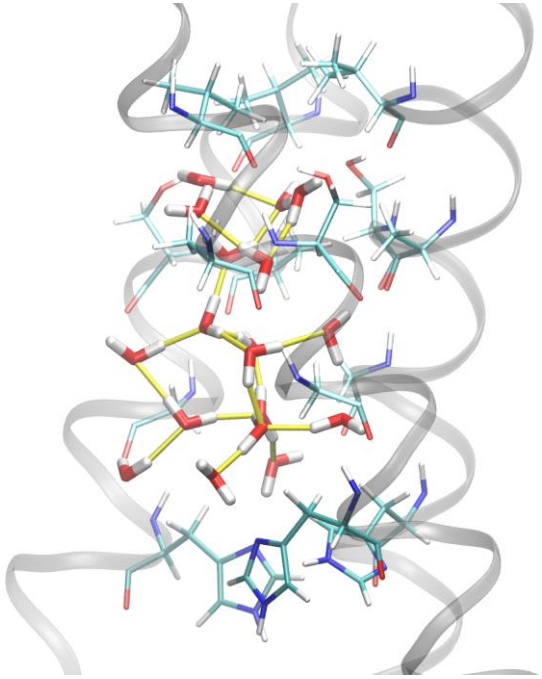
$$2\ H_2O \rightleftharpoons OH^- + H_3O^+$$



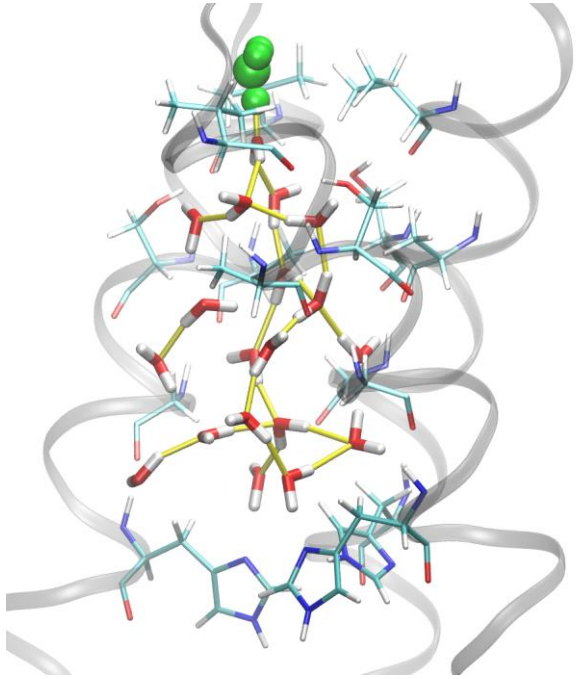
Matt K. Petersen, http://en.wikipedia.org/wiki/Grotthuss_mechanism. Knight, C., *et al. J. Chem. Phys.* **137,** (2012)

Excess Proton Reorients Hydrogen Bond Network

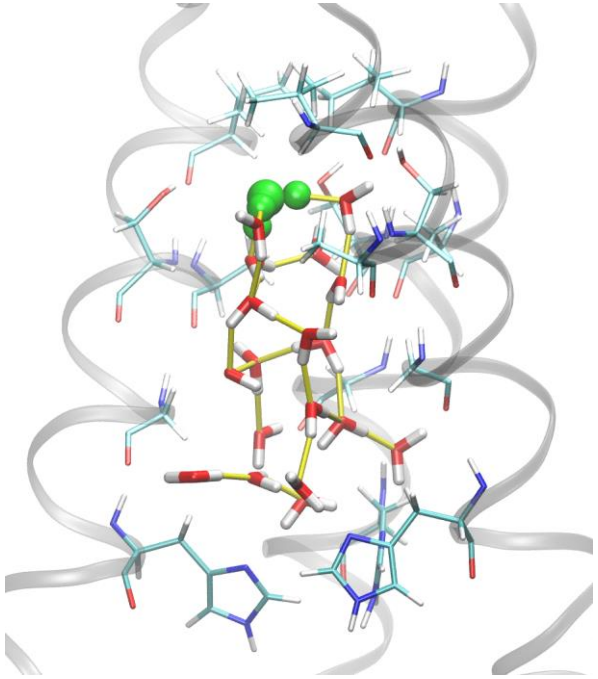
Proton outside of channel:



Proton near:



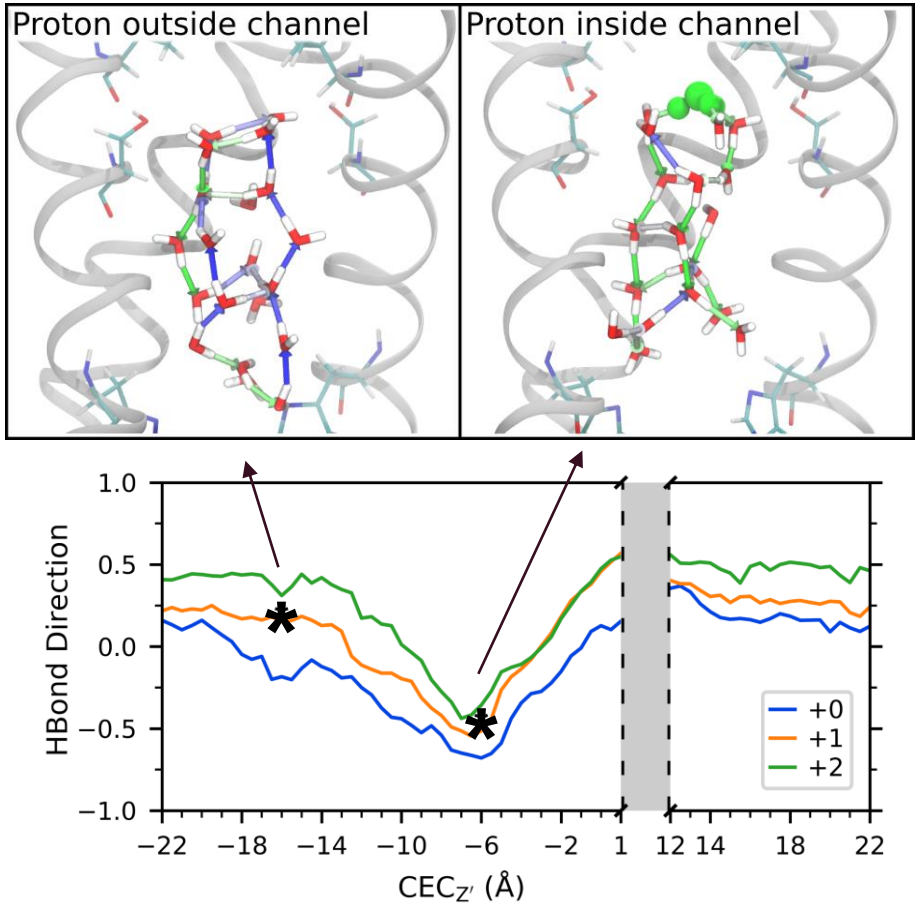
Proton directly above:



Green = most hydronium-like water
Yellow = hydrogen bonds

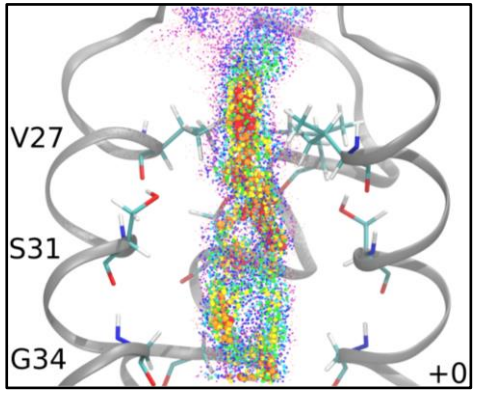
Excess Proton Interacts with Water and Channel

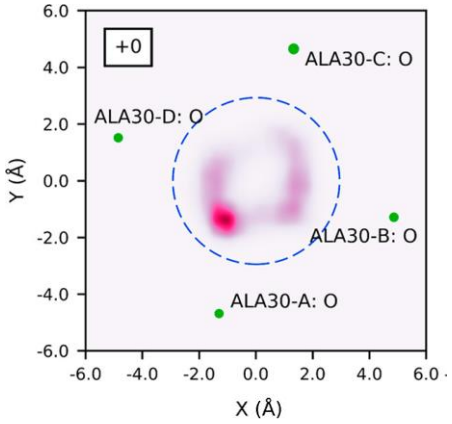
Proton reorients hydrogen bond network



CEC = Center of excess charge

Proton path and channel asymmetry



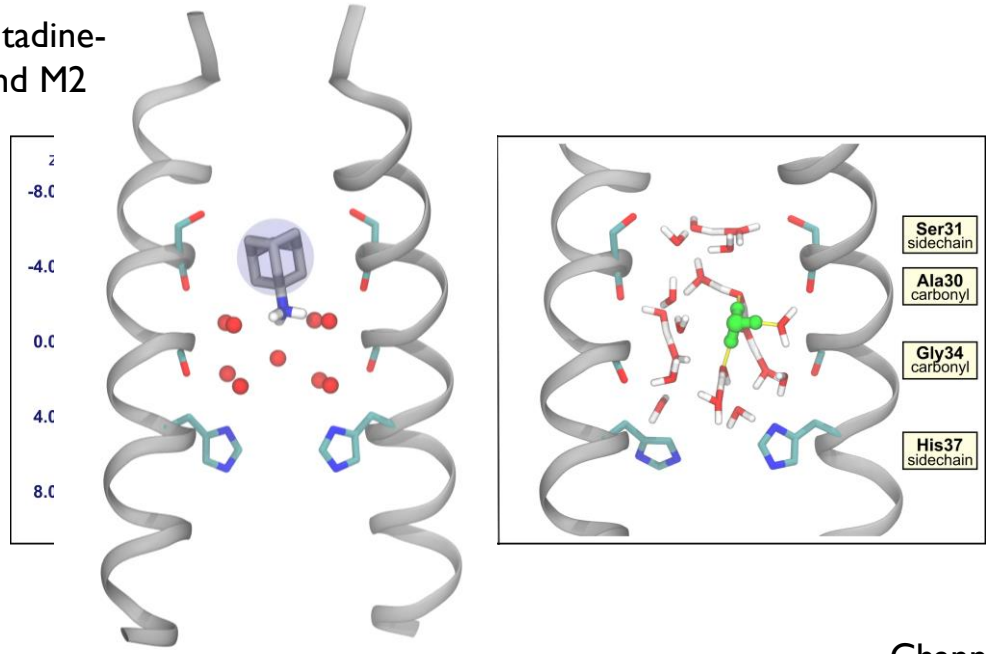


Important feature for drug design

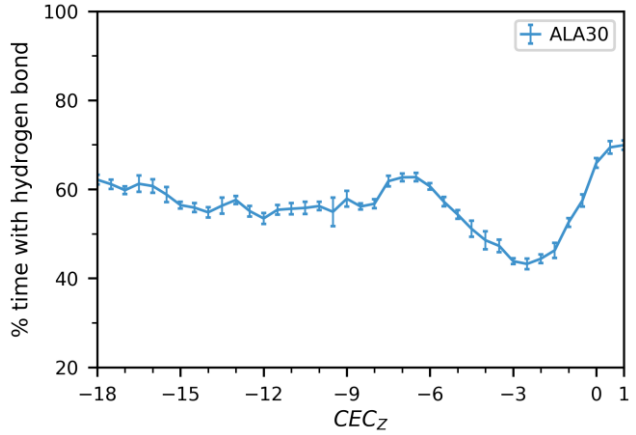
Static structures from crystallography are not the full story

Inhibitors Take Advantage of Channel's PT Mechanism

Amantadine-bound M2

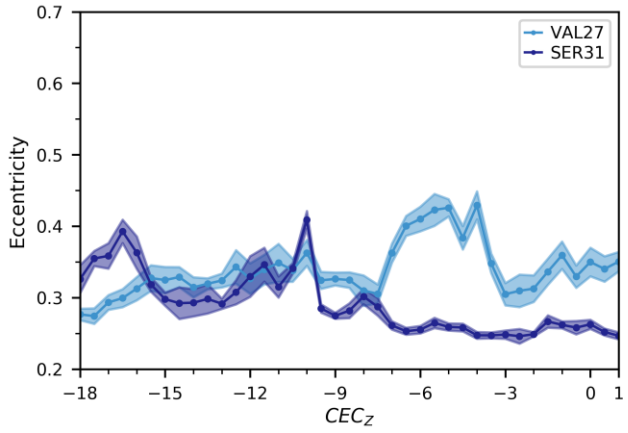


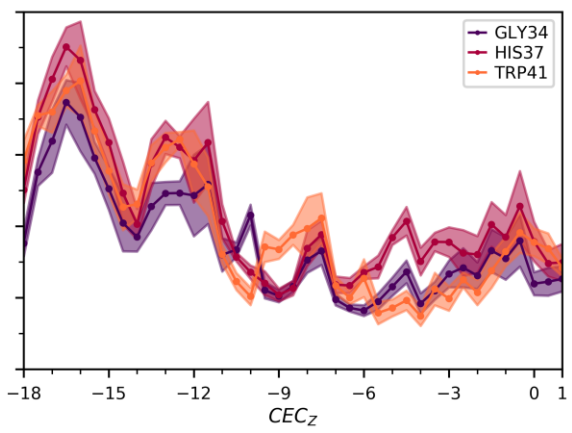
Flexible hydrogen bonds stabilize excess charge

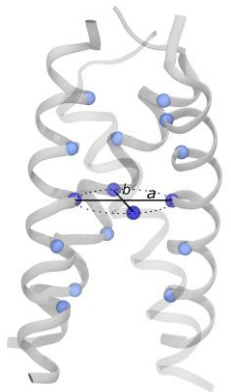


Channel is most stable and spherical where drug binds

$$e = \sqrt{1 - \frac{b^2}{a^2}}$$



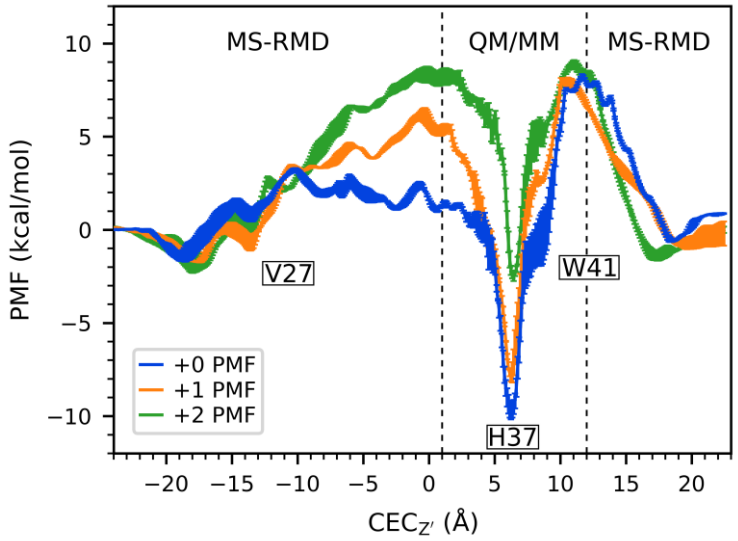




Thomaston JL, *et al. J. Am. Chem. Soc.* 2018, 140, 45, 15219-15226
Watkins, LC, *et al.* bioRxiv 2020.06.19.162248

M2 Conclusions and Other Results

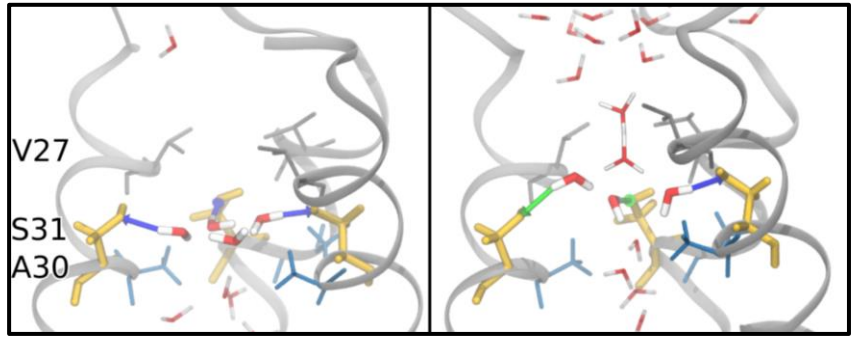
Proton Transport Mechanism in M2 Mutant



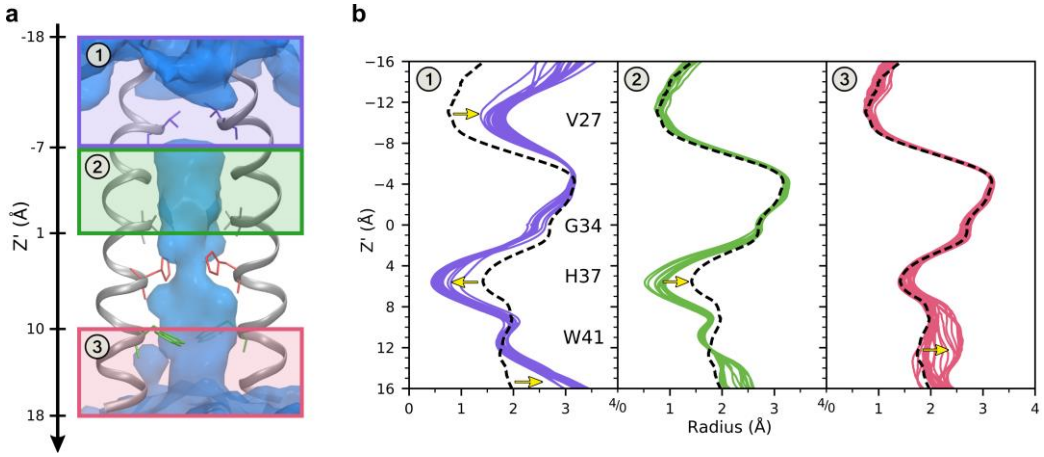
Proton transport is incredibly dynamic!

An excess proton can "pave its own path"

Protein creates scaffold for proton transport



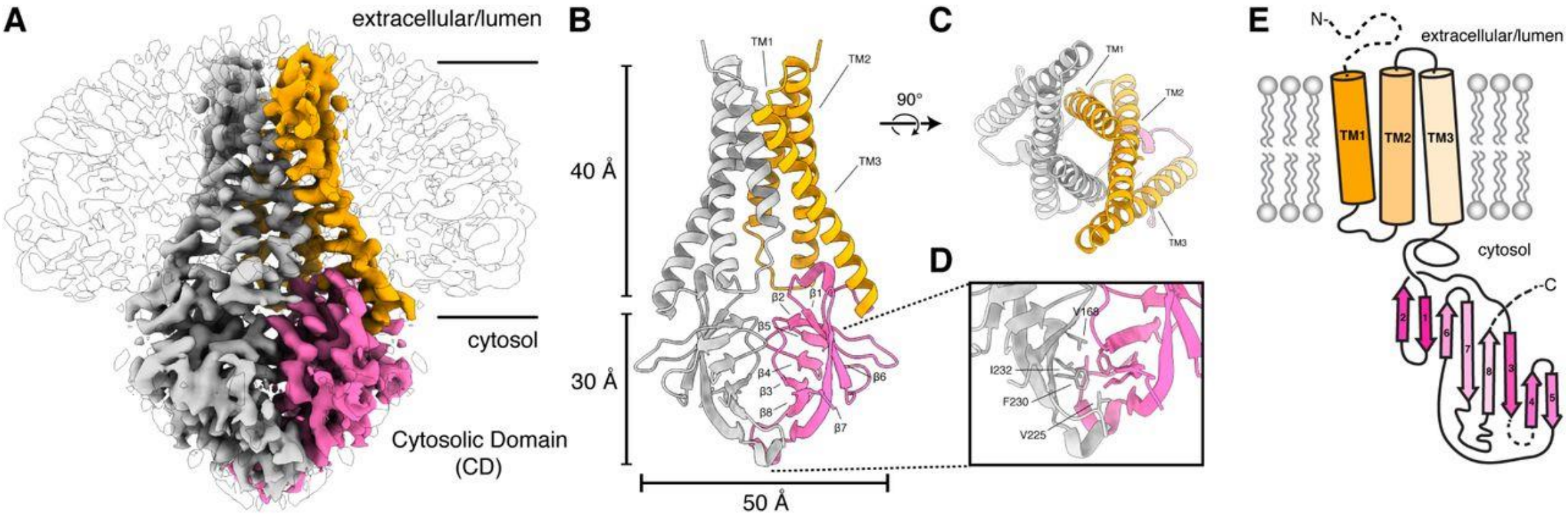
Proton Dynamically Alters Protein Structure



Liang, R. *et al. Proc. Natl. Acad. Sci* **113,** E6955-E6964 (2016). Watkins, LC *et al. J. Am. Chem. Soc.* 2019, 141, 29, 11667-11676

This looks like biology, what about COVID-19??

Just published structure of protein p3 from SARS-CoV-2



Acknowledgements

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Voth group members

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