WHY BLUE WATERS

A first-principles quantum-mechanical calculation of an infinitely extended solid, not to mention liquid, was previously unthinkable. Blue Waters has now **made these calculations a reality** using a combination of computing power and the algorithmic breakthrough (embedded-fragmentation) that exposes scalability with both system and computer sizes.

NEXT GENERATION WORK

We will fully develop a software system that will allow routine applications of predictive *ab initio* all-electron quantum-mechanical methods to a whole range of properties of any molecular solids and molecular liquids on supercomputers. Thanks to Blue Waters, it will no longer be necessary to rely on empirical potentials or density-functional approximations.

PUBLICATIONS AND DATA SETS

Hirata, K. et al., *Ab initio* ice, dry ice, and liquid water. *Fragmentation: Toward Accurate Calculations on Complex Molecular Systems*, Ed by Mark S. Gordon, in review.

Salim, M.A., S. Y. Willow, and S. Hirata, Ice Ih anomalies: Thermal contraction, anomalous volume isotope effect, and pressure-induced amorphization. *J. Chem. Phys.*, 144, (2016), doi: 10.1063/1.4951687

Willow, S.Y., M. A. Salim, K. S. Kim, and S. Hirata, *Ab initio* molecular dynamics of liquid water using embedded-fragment second-order many-body perturbation theory towards its accurate property prediction. *Scientific Reports*, 5 (2015), doi:10.1038/srep14358

Willow, S.Y., et al., Why is MP2-water "cooler" and "denser" than DFT-water? *J. Phys. Chem. Lett.* 7 (2016), p. 680-684, doi: 10.1021/acs.jpclett.5b02430

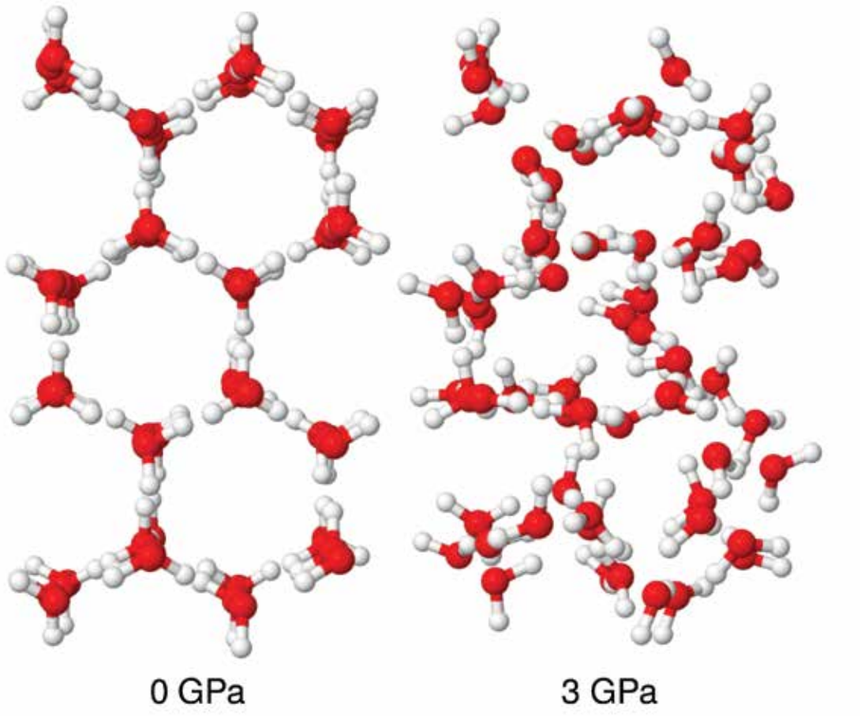
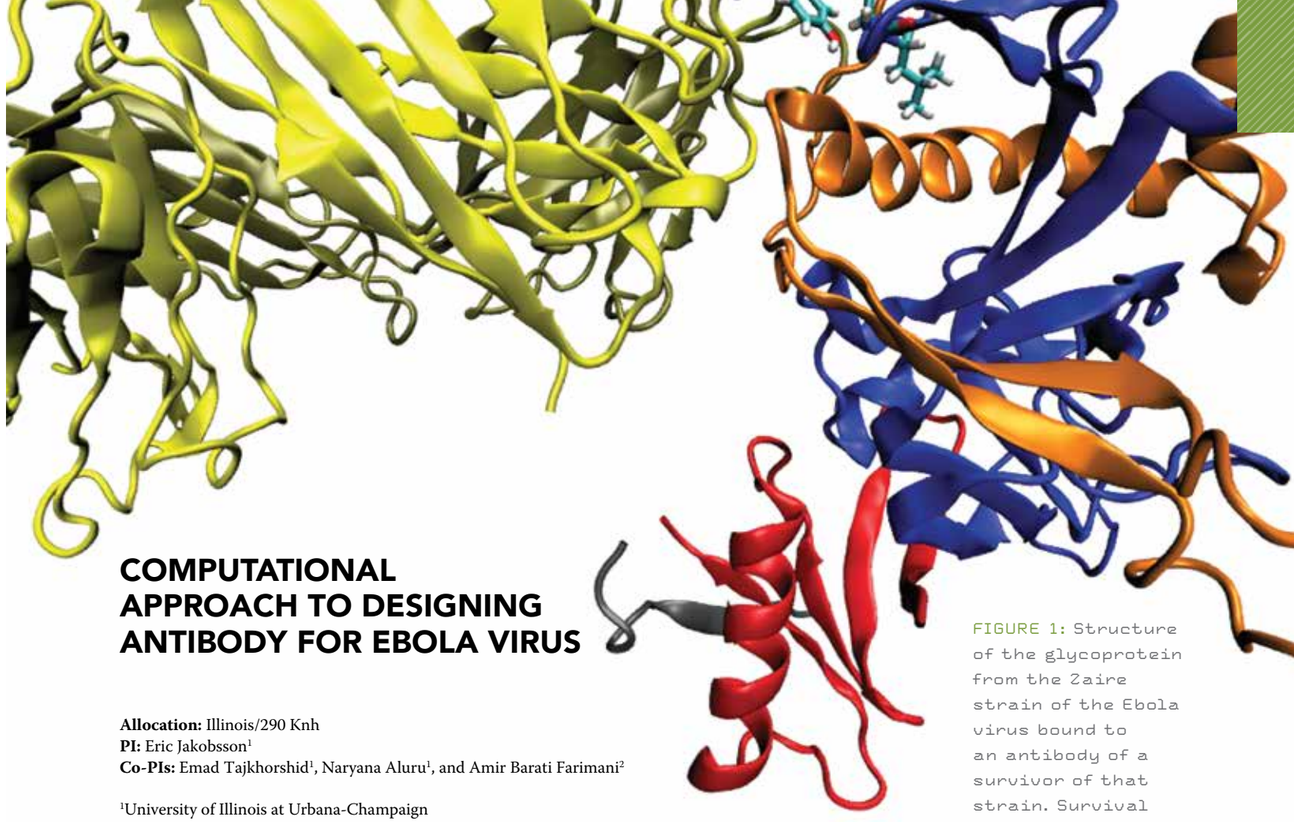


FIGURE 3: Optimized (left) and partially optimized (right) structures of ice-Ih and ice-HDA. Reprinted from [3].



COMPUTATIONAL APPROACH TO DESIGNING ANTIBODY FOR EBOLA VIRUS

FIGURE 1: Structure of the glycoprotein from the Zaire strain of the Ebola virus bound to an antibody of a survivor of that strain. Survival was because of the effective binding of the glycoprotein to the virus pictured. The glycoprotein is essential to the virus' ability to enter the host cell.

Allocation: Illinois/290 Knh
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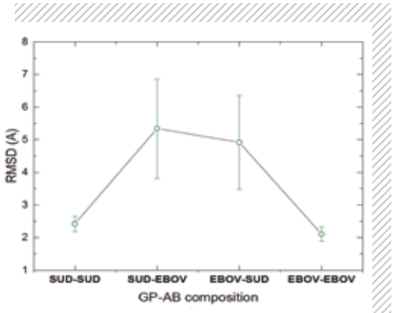
EXECUTIVE SUMMARY

Our work on Blue Waters successfully demonstrated the feasibility of computational design of synthetic antibodies against evolving Ebola infections. We simulated multiple cycles of viral mutation and redesign of a synthetic antibody to counter the mutations successfully and restore high-affinity binding of the antibody to the virus. Viral mutations were selected by random walk theory biased according to the statistical propensity for amino acid substitution. Trial substitutions for redesign were selected according to the statistical propensity for forming favorable interfaces. The success of the redesign was evaluated by using molecular dynamics (MD) to compute viral protein-antibody binding energy. Blue Waters provided the essential computational power to do the many simulations to test the ability to redesign successfully, and we feel this approach should be extendable to other viruses. In combination with experimental sequencing and structure determination, our approach should enable rapid design and redesign of synthetic antibody therapy in response to rapidly evolving viral challenges.

INTRODUCTION

The ability to produce antibodies specific to predefined biomolecular targets was a landmark development in biological research and potential therapy [1]. At the core of this work was engineering at the cellular level, in particular induced cell fusion to produce hybrid cells. A fundamental advance was to extend the engineering to the molecular level, including the engineering of chimaeric antibodies [2]. It should be possible to engineer antibodies against viruses, specifically, the coat glycoprotein that is an essential component of the entry mechanism for Ebola and many viruses into the host cell [3]. Nature has afforded us with a proof-of-concept for such engineering, by providing us with definable sequences and structures for Ebola glycoprotein bound to antibodies that enabled the host to survive the disease [4]. On the other hand, nature makes our task harder by enabling the virus to evolve in such a way as to neutralize the effect of the antibody [5]. Sequences and structures provide an outline of how the evolutionary arms race proceeds between Ebola virus glycoprotein vs. antibodies from the host immune system for multiple glycoprotein-

FIGURE 2: RMSD (magnitude of structural fluctuations, a measure of structural instability) derived from MD simulations when Sudan strain antibody is matched with Sudan virus, when Sudan antibody is matched with Zaire virus, when Zaire strain antibody is matched with Zaire virus, and when Zaire antibody is matched with Sudan virus. This image shows proof-of-concept that molecular dynamics is sufficiently sensitive to distinguish between effective binding (that can overcome the infection by preventing viral entry into cells) and ineffective binding.



antibody complexes [6]. However, this description of the glycoprotein-antibody competition does not in itself lead to a predictive model for how the virus will evolve and what change in the antibody will be effective against the evolved viral protein.

METHODS & RESULTS

We began by considering how to construct a predictive model for how the virus is likely to evolve, and what alterations in the sequence of a binding region of the antibody would most effectively counter the viral mutation(s) and restore the ability of the antibody to bind the glycoprotein. To predict likely mutations, we used existing statistical data on the likelihood of particular substitutions, as embodied in a "substitution matrix" in which each element corresponds to a relative probability of an amino acid substitution [7]. To predict effective responses to viral mutations, we used existing statistical data on amino acids that interact favorably at protein-protein interfaces [8]. Finally, we used MD simulations of the mutated glycoprotein-antibody complex to test the statistical prediction by computing the effects of the postulated mutations [9].

The starting points for the simulations were structures of Ebola glycoprotein complexed with antibody fragments that were known to prevent infection successfully. We then mutated the glycoprotein, which invariably resulted in degradation of binding energy between glycoprotein and antibody. Following that, we used the databases of favorable amino acid interactions to make educated guesses as to mutations on the antibody. In the majority of cases, we were able to re-engineer the antibody to bind the viral protein as well or better than the wild type. In those cases where we did not succeed in doing that, we believe that we would have succeeded if provided with more computertime.

WHY BLUE WATERS

We could not have done the project without the sheer computational power of Blue Waters.

NEXT GENERATION WORK

Our long-term goal is to establish our approach as a standard for the design and redesign of synthetic antibodies against viral infections so that humankind can prevail in the evolutionary arms race against evolving viral pathogens.

PUBLICATIONS AND DATA SETS

Farimani, A.B., et al., Computational approach to designing antibody for Ebola virus. *Biophyss J.*, 110:3 (2016)537a.

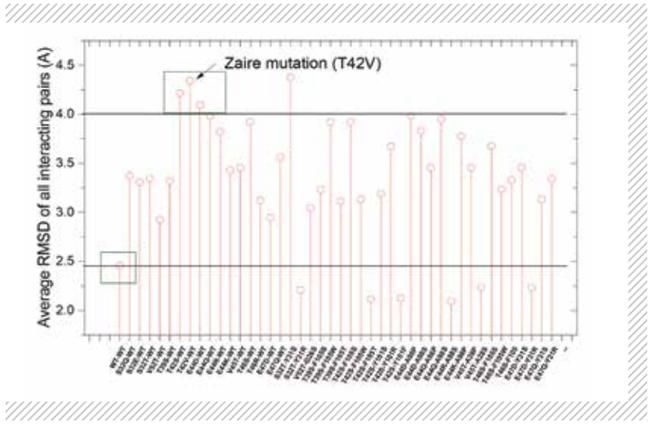


FIGURE 3: RMSD for selected mutants of the Sudan virus and mutated antibodies. The symbols that fall below 2.5 angstroms are actually binding better than wild type. Antibody redesign succeeded by that criterion for approximately half of the mutant glycoproteins.

UNVEILING ALLOSTERIC PATHWAYS IN ION CHANNELS

Allocation: NSF PRAC/5.60 Mnh
PI: Michael L Klein[1]
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EXECUTIVE SUMMARY

Transient receptor potential (TRP) channels are central to environmental sensation in animals, fungi, and unicellular eukaryotes. All known TRP channels are nonselective cation channels that open in response to a wide array of factors. Clarifying how TRP channels convert physical and chemical stimuli from the environment into the allosteric signals underlying channel activation is key to understanding how they control cell excitability in both physiological and pathological conditions. Their relevance in the molecular pathways that mediate pain makes them promising targets for novel classes of analgesics (medicines that relieve pain). Building on the structural information made recently available for transient receptor potential cation channel subfamily V member 1 (TRPV1), thanks to a series of cryo-electron microscopy (CryoEM) experiments, we performed free energy (metadynamics) simulations on models of TRPV1 embedded in a lipid bilayer. Harnessing the computation capabilities of Blue Waters, we explored several pathways of activation and characterized ion channel conductance and selectivity. Our calculations reveal a **novel** mechanism for sensing temperature and osmolality.

INTRODUCTION

A fit cell must perceive and comprehend the conditions of its inner and outer worlds, integrating diverse and transitory physicochemical stimuli into concerted cellular decisions. For this reason, the membranes of even the simplest bacteria are studded with ion channel proteins that detect cellular conditions and translate them into electrochemical information via gated ionic conduction [1].

In eukaryotes, the complexity of cellular life has taken this requirement to its apex. Accordingly, natural selection has elaborated on the ion channel, producing an impressive array of polymodal cellular sensors, the TRP channels [2]. All TRP channels detect multiple physicochemical stimuli, with some overlap among the eight extant TRP subfamilies. However, the response to each stimulus varies substantially from channel to channel, presumably dictated by heterogeneous and subfamily-specific intra- and extracellular domains [3]. Indeed, since their divergence from the voltage-gated potassium (Kv) channel superfamily over a billion years ago, TRP channel proteins have maintained a tetrameric six-transmembrane (6-TM) architecture and little else. The (TRPV1) or vanilloid receptor 1 is a polymodal mammalian nociceptive integrator [4] abundantly expressed in the free nerve endings of primary pain-sensing afferent Aδ and C fibers [5]. Structurally, the TRPV1 channel is a homotetramer, symmetrically organized around a solvent exposed central pore. Each subunit is formed by six transmembrane helices (S1–S6) with the channels' N- and C-termini located in the intracellular medium [6].

TRPV1 is activated by a wide range of proinflammatory and proalgesic mediators [7]; including temperatures above 43°C, external pH, bradykinin, anandamide, arachidonic acid metabolites, jellyfish and spider toxins, vanilloid and others. The scope of the TRPV1 pharmacological spectrum [8-10] is mainly in the area of analgesics: novel painkillers could be either TRPV1 agonists or antagonists. Moving forward toward the rational drug design of TRPV1 modulators requires a basic understanding of how known ligands trigger the closed to open transition in TRPV1.

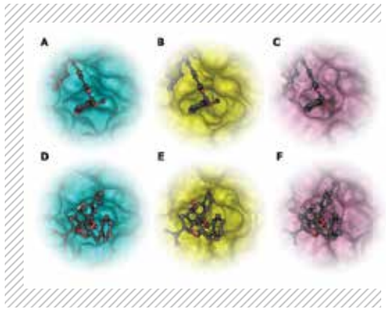

FIGURE 1: Optimal docking poses of capsaicin and resiniferatoxin in the vanilloid binding site of TRPV1. Shown are: A) capsaicin in the apo structure; B) capsaicin in the TRPV1-capsaicin complex; C) capsaicin in TRPV1-resiniferatoxin complex; D) resiniferatoxin in the apo structure; E) resiniferatoxin in the TRPV1-capsaicin complex; F) resiniferatoxin in the TRPV1-resiniferatoxin complex. Adapted from ref. (Elokely, 2015)