FINAL REPORT FOR DEPT OF ENERGY GRANT DE-SC0005094

PROJECT TITLE: COMPUTATIONAL MODELING OF DRUG-RESISTANT BACTERIA

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Total Award Amount: $889,380.
Award Period: 09/15/2010 – 05/31/2011. No-cost extension until 03/14/2013

Proposal summary: The evolution of antibiotic-resistant mutants among bacteria (superbugs) is a persistent and growing threat to public health. In many ways, we are engaged in a "war" with these microorganisms, where the corresponding arms race involves chemical weapons and biological targets. Just as advances in microelectronics, imaging technology and feature recognition software have turned conventional munitions into "smart bombs", the long-term objectives of this proposal are to develop highly effective antibiotics using next-generation biomolecular modeling capabilities in tandem with novel subatomic feature detection software. Using model compounds and targets, our design methodology will be validated with correspondingly ultra-high resolution structure-determination methods at premier DOE facilities (single-crystal X-ray diffraction at Argonne National Laboratory, and neutron diffraction at Oak Ridge National Laboratory).

OBJECTIVES AND ACCOMPLISHMENTS

Objective 1: Development of new intermolecular force-fields with physically meaningful energy expansion terms. The increased accuracy of this biomolecular modeling approach is due to the use of a large and unique databank of aspherical and highly transferable atomic charge densities.

Objective 2: Development of fleshed-out pharmacophores with subatomic resolution that will enable high-throughput docking based on local, non-classical interactions. This novel approach to visualization and docking will be empowered by recent volume-rendering advances in computer graphics technology. Visual data-mining will be done efficiently and in parallel via the adaptation of hyperwall technology recently developed by NASA Ames.

Objective 3: Discovered design concepts and drug candidates will be experimentally validated with ultra-high resolution structure-determination methods. Single-crystal X-ray diffraction, in conjunction with neutron diffraction, is capable of determining the total charge density distributions of biomolecules, even near hydrogen atoms. This enables the validation of the physical underpinnings of both the force-field modifications and the pharmacophore enhancements.

Proposal accomplishments and Objectives met:

The 3D-Hyperwall at MTSU is the first of its kind – in the world! (As far as we know, and in the opinion of NASA's Chris Henze, co-inventor of Hyperwall technology.) Because we used off-the-shelf components and assembled the nCPUs, nodes, racks and wall-mounting, the MTSU 3D-Hyperwall (pictured below) was constructed under-budget. We used the savings to expand the Hyperwall from a 3x4 matrix to a 4x4 matrix. The 3D-Hyperwall at MTSU has been the attraction for press releases, public outreach events (such as multiple offerings of the Drug Design Workshops during the Expanding Your Horizons (EYH) conferences for high-school girls pictured below). The Department of Energy sponsorship is always acknowledged and the DOE's logo is shown on the bottom-left of the "home screen" of the Hyperwall (shown below). The

3D-Hyperwall has also been a primary and essential resource for subsequent NSF grant applications by both Drs. MacDougall and Volkov, and will continue to be quite useful in that regard for the foreseeable future. These and similar activities have been described in an article written by Dr. MacDougall (STI number DOE-MTSU-5094-9 for this grant).

The Educational Impact of the grant has also been substantial. Two post-doctoral fellows were hired, and employed for an additional year because an offer to a 3rd postdoc was rejected at the last minute. Drs. Moscovitz and Yang gave multiple presentations on their research (such as STI numbers DOE-MTSU-5094-2 and DOE-MTSU-5094-3), and submitted an article to *Soft Matter* that is in press (STI number DOE-MTSU-5094-1). Two PhD students in MTSU's then brand new doctoral program in Computational Science were supported by this grant. One has graduated and is now

employed as Director of High-Performance Computing at St Jude Research Hospital in Memphis, Tennessee. Dr. Robert Michael's dissertation has been submitted as STI number DOE-MTSU-5094-6. Mr. Kiran Donthula is nearing completion of his dissertation on Using Charge Density Analysis and Machine Learning for Drug Design. Both students presented multiple poster presentations acknowledging their financial support from the DOE. Multiple undergraduates have conducted research using the Hyperwall (see below, pictured with Dr. Volkov), including one who was selected as a Goldwater Scholar and another who went on to teach middle school science. As mentioned above, dozens of high school girls have been exposed to computational science and drug design (pictured below). One young girl wrote the following in the EYH participant evaluation: "I've heard that organic chemistry is hard, but after this workshop, I can't wait to study it!"

Objective 1 (Development of new intermolecular force-fields with physically meaningful energy expansion terms) This objective has been partially met. The large and unique databank of aspherical and highly transferable atomic charge densities has been expanded and applied to accurately model the charge density in 11-mer peptides as well as the active site of the drug target bacterial gyrase (related to topoisomerase IV in humans). The database research was already underway when the grant began, but

the chapter describing the research has been included in the supporting documents for this report (STI DOE-MTSU-5094-8) because it was submitted after the grant began, and was crucial to advancing the project. Before the new force-fields can be developed, some higher-order spherical harmonics for the fitting functions used in the database needed to be determined, and normalized. This work was completed after the grant ended, but was in the planning stage during the grant. It was an oversight on the PI's part not to have the acknowledgment included in this article that has just now been accepted for publication in Acta Crystallographica A (STI number DOE-MTSU-5094-10).

Objective 2 (Development of fleshed-out pharmacophores with subatomic resolution that will enable high-throughput docking based on local, non-classical interactions) This objective was partially met for the active site in gyrase-B, a bacterial target for a new class of antibiotics. The charge density for this active site has been computed, and rapidly synthesized with the database in Objective 1. The Laplacian has been computed and we are in the process of creating the pharmacophore using descriptors obtained by machine learning methods still being developed by PhD student Kiran Donthula. The completed work has been presented at international conferences on molecular modeling and drug design (STI numbers DOE-MTSU-5094-3, DOE-MTSU-5094-4 and DOE-MTSU-5094-5), with acknowledgment of DOE support. When ongoing and future research is published, when the work has employed this pharmacophore, DOE support will again be acknowledged.

Objective 3 (Discovered design concepts and drug candidates will be experimentally validated with ultra-high resolution structure-determination methods) This objective has always been a long-term objective, and was meant to be the foundation of a renewal proposal. Since continued funding was not likely, a renewal proposal was never submitted. In the opinion of the PI, Objective 3 remains a very promising means of developing a truly physics-based drug design platform, which has the potential of being both rapid and accurate.