HPC @ UNM
THE CENTER FOR HIGH PERFORMANCE COMPUTING

December 2005
Issue 8

Fig. 1 : UNM computational chemists Xu and Guo

UNM Researchers Tackle Bacterial Antibiotic Resistance using Computational Chemistry

Since its discovery more than 70 years ago by Alexander Fleming, penicillin and its analogs have been at the forefront of the fight against bacterial infections. These molecules share a common ring motif called β-lactam, thus the name β-lactam antibiotics. They operate by forming a covalent adduct with membrane-bound bacterial transpeptidases, which are also known as penicillin-binding proteins, involved in the biosynthesis of cell walls. These mechanism-based inhibitors prevent the construction of the bacterial cell wall and lead eventually to cell lysis and death.

In the last twenty years, the efficacy of these antibiotics has been overshadowed by the emergence of drug-resistant bacterial strains resulting from their evolutionary responses to widespread overuse and abuse of antibiotics in clinical and agricultural settings. The problem has escalated to a crisis level, posing a serious public-health and economic challenge to modern society.

There are many ways that bacteria adopt to resist the antibiotics. The most common and effective strategy is through a bacterial enzyme called β-lactamase, which inactivates β-lactam antibiotics by breaking the C-N bond in the lactam ring with a water molecule (hydrolysis). Such a reaction is typically very slow in water solution, but can be greatly accelerated by the enzyme. So, the understanding of how β-lactamase catalyzes the hydrolysis of β-lactam antibiotics would help us to design effective drugs to inhibit its activity. In fact, the co-administration of antibiotics and β-lactamase inhibitors is now a common clinical practice.

Assistant Research Professor D. Xu and Professor H. Guo (Fig. 1) in the Department of Chemistry at UNM are using sophisticated computational approaches to understand the catalytic mechanism of a unique class of β-lactamases. The so-called Class B2 β-lactamases possess a zinc ion in its active site, which helps to accelerate the hydrolysis of a β-lactam antibiotic molecule that docks at the active site. Although the Class B2 β-lactamases are still rare in the clinical setting, an alarming trend in recent years points to a rapid spread of these metallo-enzymes in pathogenic micro-organisms by plasmid-mediated gene exchanges. Their broad substrate spectra and the absence of clinically useful inhibitors render them a dangerous threat to the relatively small arsenal of β-lactam antibiotics.

A key step in designing inhibitors is to understand the mode of binding for the antibiotic molecule in the enzyme active site and the structure of the transition state in the slowest step of the catalysis. Unfortunately, the enzyme has so far resisted to yield its secret. This is because the enzyme-catalyzed hydrolysis reaction is so fast that it is not amenable to any existing experimental technique in structure determination. The lack of substrate analogs (inhibitors) for Class B2 β-lactamases renders it very difficult to determine how the antibiotic molecule binds with the enzyme. Computational approaches can thus be very helpful to unravel the structure and reaction kinetics of the a ntibiotic-enzyme complex.

In a recent publication in Journal of Medicinal Chemistry, the two UNM researchers reported a computational study of the antibiotic binding dynamics of a third generation β-lactam antibiotic molecule (biapenem) to a β-lactamase (CphA) from the bacterium *A. hydrophila*. Using a state-of-the-art quantum mechanical/molecular mechanical (QM/MM) method, the UNM study identified a unique binding mode that sheds valuable light on the catalytic mechanism of the β-lactamase. This binding model is unique in that it is consistent with a recently published structure of enzyme-intermediate complex.

As shown in Fig. 2, the antibiotic biapenem is engaged in direct metal binding with the zinc co-factor in the enzyme through its 3-carboxylate oxygen. It is further anchored by several hydrogen bonds between the substrate and active-site residues, particularly those made possible by conformational changes of Asn233. An active-site water is poised to attack the carbonyl carbon in the β-lactam ring of the antibiotic molecule, with the help of either a Histidine or Aspartate residue serving as the general base. Work to elucidate the detailed catalytic mechanism using the QM/MM approach is underway in their laboratory, which is expected to provide helpful guidance to the designing of mechanism-based inhibitors that mimic the transition state structure.

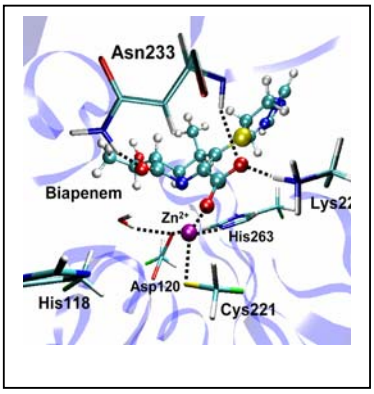
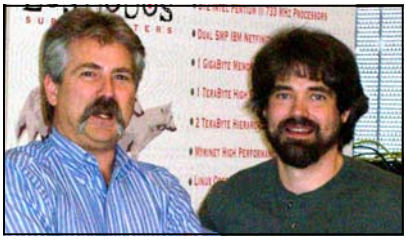


Fig. 2: A snapshot of the active site of the CphA-biapenem complex. Metal-ligand bonds and hydrogen bonds are indicated by dashed lines.

Part of the UNM work was carried out on a recently purchased high performance shared-memory computer (IBM p570) with 16 Power 5 chips and 256 GB of memory. This new addition to UNM's HPC center was made possible by a Major Research Instrumentation grant from the National Science Foundation (NSF). As the Principal Investigator of the NSF grant, Prof. Guo is very excited about the prospect of scientific computing at UNM. Apart from the β-lactamase project, the Guo group is also investigating a number of important enzymatic reactions, such as proton transfer, phosphoryl-transfer, hydrolysis, and arginine modification. The insights provided by these computational studies will help us to understand catalytic principles in general and to design new drugs that block the enzyme catalysis when needed.



HPC Directors, Dr, Barney Maccabe & Dr. Tim Thomas

FROM THE DIRECTORS:

HPC machinery moves into new room

We are very excited to be successfully moved in to our new 1500 square foot, high density capacity machine room facility, sitting atop part of the space previously occupied by a repair bay of the 52 year old Galles building and next to the advanced facilities of the ARTS Lab. (For more details about our new room and/or the ARTS Lab facilities, refer back to our previous newsletter... or better yet, stop by on December 7 for our grand opening event from 3:30 – 5:00 PM.)

We have now officially named the new machine room the "Performance Pit", an idea suggested by Ernie Herrera, former Associate Director of HPCERC. This is a nod to the distinguished, if greasy, 40 year auto repair history of the space.

This facility was designed to professionally house the types of systems the Center expects to procure and operate over the next five years. All of the systems we presently operate - with the exception of Vista and LosLobos - have been moved into the space. We have anticipated that water and other advanced cooling technologies will appear in the near future. The new space can handle upwards of 200 watts/square foot of power density at full capacity. Presently, it is at 25% capacity.

The combined Performance Pit / ARTS Lab Garage build-out has been the most complex "remodel" project ever undertaken by the University's Physical Plant Department. As it has neared completion, we have marveled as the details have all fallen into place... the spaces are coming alive!

Due to the infrastructure complexity of the machine room project by itself, plus the added complications due to its deep interaction with the ARTS Lab Garage project, there were the inevitable delays bringing the space to stable operation. What's more, the diversity of the Center's machinery itself has increased significantly in the past year. We now have more than half a dozen diverse architectures, with as many operating systems and user environments. Never before had the Center performed a relocation of this magnitude on so much installed, operating high performance computing equipment.

The Center was down for most of the week of November 7, but we correctly anticipated the magnitude of various contingencies in our planning, and we brought the Center back on line almost exactly on our projected schedule. The staff deserves to be publicly commended for their smart, hard, and great work transitioning the Center to this shiny new infrastructure.

If you - our customers - identify any problems, please contact the Center right away. We appreciate that most of you prefer person-to-person communications, but we want to emphasize that we really need for you to submit a help ticket in association with any issues that you report: send e-mail to help@hpc.unm.edu. This helps us maintain quality and measure our progress.

Supercomputing in Seattle was huge! This is now the second largest ACM conference with over 9,000 attendees. Once again, we shared a booth with NMT, NMSU and UTEP. The booth was much larger this year and we were able to emphasize the diversity and quality of the computing based research at all of the institutions. Thanks to all who contributed posters. Next year SC will be held in Tampa Bay -- again the week before Thanksgiving. Please think about material for posters and let us know if you are thinking about attending.

If you have been by the center, you have probably noted that Cecilia has returned. She's not quite back to 100%, but she is making steady progress and we're very happy to have her back. If you get a chance, please stop by and welcome her back.

Calendar of Events

December 7, 2005 Grand Opening of the new HPC machine room and the ARTS Lab Garage

December 23, 2005 - January 2, 2006 UNM Winter Break