



Molecular simulation to accelerate vaccine development

A large three-year project (BacAbs) involving pharmaceutical and bio-informatics companies and Universities has exploited the DEISA resources to render vaccine development simpler, faster and therefore less expensive for pharmaceutical companies and eventually to the end-users being treated. The goal of the project is to develop tools that help predict which antigens will be suitable for vaccine development at an initial stage of the development process. The molecular dynamics simulations run on DEISA were finalized at the end of 2007, and the final results of the whole European Union's FP6 funded BacAbs project will be available in 2009.

"In the process of vaccine development, the early stages until the immunogenic testing can take a couple of years: If we'd be able to reduce the number of proteins expressed – say by half – this would be a huge gain, since the

initial steps are heavy consisting of hundreds of proteins", tells Xavier Daura, who works at Universitat Autònoma de Barcelona.

Daura's group evaluates the structural requirements for viable bactericidal vaccine candidates through a novel multidisciplinary approach and develops bioinformatics tools to predict compliance with such structural requirements.

"Many bacterial proteins actually do elicit production of antibodies when injected into a model animal, but only a small fraction of them are good antigens in the sense that together with the antibody it will produce a bactericidal response which will lead to immunity", says Daura. He explains that there are many complexes between an antigen and an antibody that do not lead to the killing of the pathogen. "For the cure the antigen and the antibody must bind to one another effectively, and this antigen and antibody complex must be recognized by the so-called complement system. There is a particular protein, C1q, which binds first. We will also try to study this type of interaction".

To this end, a systematic analysis of sequence, structure, dynamics and interactions of potential antigens are analysed systematically using as model system serogroup-B *Neisseria meningitidis*, a pathogen causing septicemia and meningitis, and for which no effective vaccine exists. This analysis involves the application of several computational techniques, some of which posing extreme demands on computing time, to the study of complex biomolecular systems.

"We are interested in both global dynamics and in the dynamics of specific regions" says Daura. "One effort in our consortium is to map the regions that interact with monoclonal antibodies. This is called Epitope Mapping. Epitope is a small part of a



Fig. 2. Xavier Daura presented the initial results of his simulations at the 5th DEISA training.

macromolecule that is recognized by the immune system, in this case by antibodies." He adds that there are basically two types of recognition by antibodies. The one is purely by sequence and the other one is by structure. This means that if the antibody is able to recognize a peptide independently of its shape, it will indicate that it is identified by the sequence and not by the structure. In some cases the antibody will only recognize a specific peptide if it is in a specific structure. Connected to that, one possibility is that epitopes which adapt to a specific structure are recognized by it.

Continues Daura: "We have hypothesized that epitopes may have similar structural properties when isolated in solution. This is why we do all these studies on epitopes, their sequences separated from the proteins. There is something intrinsic in the structure of the peptide that makes it recognizable by an antibody independently of the protein."

Need of Supercomputers

"Our research is very challenging since there are a lot of degrees of freedom, many interactions between the proteins and such system sizes that must be simplified to be run with currently available resources, says Daura and explains that at the moment it is possible to do a simulation in the range of nanoseconds to microseconds. "However, this is far from the length of any biological process, which nor-

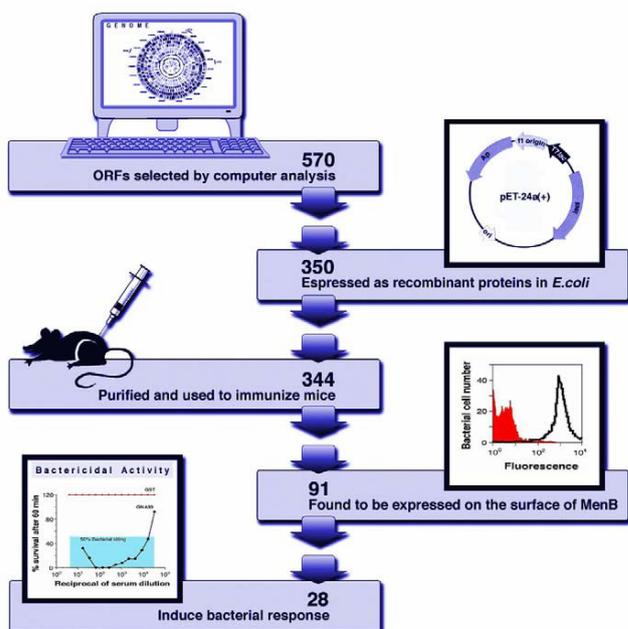


Fig 1. Initial steps in a vaccine development process, from research at Novartis Vaccines & Diagnostics (partner to this project) on group-B *N. meningitidis*.

mally is in the time frame from milliseconds to seconds. It is likely to take decades before supercomputers will be powerful enough to simulate a whole biological process", points out Daura.

Opportunity to learn to use the DEISA infrastructure

Xavier Daura presented the initial results of his simulations at the 5th DEISA Training Event that was held at the CINECA – Supercomputing Centre, in Bologna, Italy the end of October, 2007. The purpose of the training sessions is to enable fast development of user skills and know-how needed for the efficient utilisation of the DEISA infrastructure.

The next opportunity to take part in the training will be in March, when the 6th DEISA Training Event will be organized in Stuttgart by HLRS. The first part of the training will give a global description and introduction to the usage of the DEISA infrastructure, followed by presentations of the DEISA Life Sciences Portal and the Globus Toolkit. On the third day of the training Use Cases will be presented.

For more information:

www.bacabs.org/

www.deisa.org/applications/projects2006-2007/BacAbsMS.php

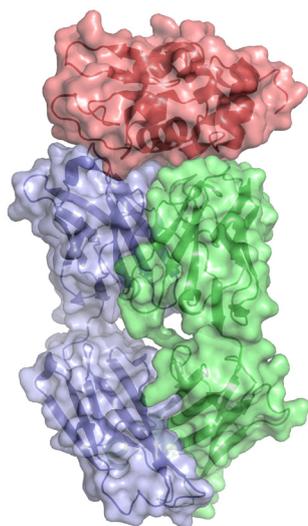


Fig 3. Protein antigen bound to the Fab (antigen-binding) domain of an antibody in ribbons and molecular surface representation. Coordinates taken from PDB entry 1NDG.

CAMP: Catalysis by Ab-initio Metadynamics in Parallel

Michele Parrinello, *ETH Zurich, Switzerland in partnership with Chemical Research Centre of the Hungarian Academy of Sciences (Institute of Chemistry), Hungary*

There is an ongoing discussion concerning the processes that have contributed significantly to the formation of life on early Earth. Several possible scenarios and theories have been suggested. Their proof, however, often requires performing experiments under extreme conditions, where many complex reactions are simultaneously taking place. These are conditions that exist under the deep-sea, in volcanoes or at the interfaces of extremely hot, pressurized water and iron-sulfur minerals.

This is where high-performance computing and modeling come in: since the laws of physics are the same now as they were on Earth four billion years ago, it is possible to study the early conditions by simulating different scenarios and testing hypothesis with computer modeling.

Ammonia for prebiotic life

When considering the formation of a reducing environment favorable for the production of the organic precursors to life, an essential step is the formation of ammonia. Particularly pyrite (FeS_2) has been suggested to act as

the key catalyst in the synthesis of prebiotic molecules in the early history of Earth, since there is experimental evidence that pyrite exhibits high catalytic activity under hydrothermal conditions similar to those present in the prebiotic world, i.e., under the deep-sea, near volcanoes, and at the interfaces between extremely hot, pressurized water and iron-sulfur minerals. Experimental evidence shows, that pyrite catalysis could have provided a significant amount of the required ammonia to the early life forms in the prebiotic world.

Focus on pyrite surface chemistry

The goal of the project was to achieve a better understanding of the pyrite surface and its chemistry by means of ab initio calculations. We modeled a defective pyrite surface by a periodic orthorhombic supercell containing a pyrite slab made of 18 atomic layers, each containing eight iron or eight sulfur surface atoms. The calculations were performed with the efficiently parallelized CPMD program package.

We created a surface sulfur vacancy by removing an originally three-coordinated surface sulfur atom, which was subsequently bonded

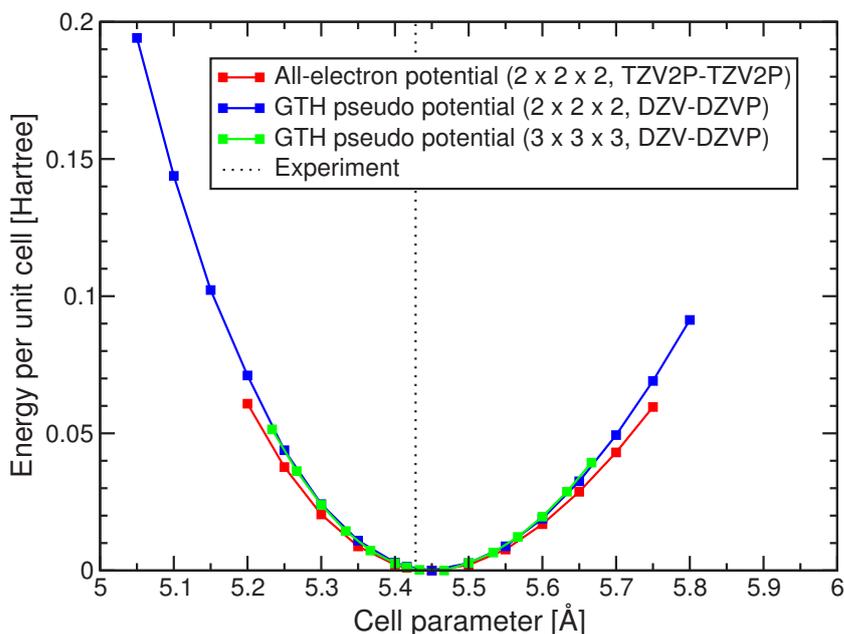


Fig 1. The results of the all-electron and pseudopotential calculations for bulk pyrite using different Gaussian basis sets.

to a surface iron atom. This results in two defects, which could be also obtained by a heterolytic breaking of the surface sulfur dimers as it would occur during pyrite fracturing. For such a defective surface structure, also open shell spin states have to be considered as the possible ground state and consequently a series of possible multiplicities was investigated.

Finally, a spin triplet state turned out to be the ground state for this defect system. This state was also stable against the wetting of the surface. A triplet state implies the presence of two unpaired electrons. Such biradicals are known to be very reactive, i.e., they are able to lower the activation barriers of chemical reactions significantly. In this way, the presence of such radical species presumably facilitates the redox reactions needed for the reduction of nitrate anions to ammonia. This would explain the high concentration of ammonia found in the experiments and thus the availability of ammonia to early life forms in the prebiotic world under similar conditions.

Moreover, the formation of the sulfur defect site was accompanied by a change in the oxidation state of the iron from Fe(II) to Fe(IV). This observation is confirmed by a good agreement between the calculated sulfur core level shifts of different sulfur species and the experimental photoemission spectra.

Surface calculations from two simulations programs

Parallel to the investigation of the defective pyrite surface using Car-Parrinello molecular dynamics simulations, we started the investigation of the same surface employing the QUICKSTEP module of the CP2K program package. QUICKSTEP can perform all-electron calculations, which means that all-electron calculations for bulk pyrite model structures of different sizes could be performed as a reference for the pseudopotential calculations employing large and, thus, accurate all-electron basis sets, which were optimized for the use with QUICKSTEP.

The accuracy of the pseudopotential calculations employing relatively small Gaussian basis sets are excellent compared to the all-electron reference calculations and the experimental data. Encouraged by these results, we started the simulation of the nitrate reduction using an enlarged model system compared to

the Car-Parrinello molecular dynamics simulations. However, these simulations are not yet finished.

Results of the project

The short time scale of ab initio simulations is often a serious problem. Therefore a new method was developed, which combines Car-Parrinello and Born-Oppenheimer molecular dynamics in order to accelerate the density functional theory based ab initio simulations. This means that simulations as long as tens or even hundreds of picoseconds can be routinely performed, thus making completely new phenomena accessible to ab initio simulations.

The computing resources provided by DEISA were used for the evaluation of the new method. We could demonstrate that the dynamics are correctly reproduced and that high accuracy can be maintained throughout for systems ranging from insulators to semiconductors and even to metals in condensed phases. This development considerably extends the scope of ab initio simulations. The new method has been implemented into the QUICKSTEP code.

Finally, a web application plug-in for the CP2K program package has been implemented in collaboration with the RZ Garching, which will facilitate the use of CP2K within the DEISA computing infrastructure.

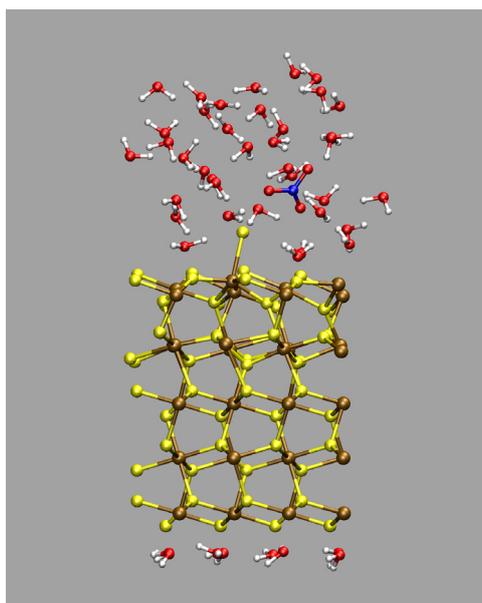


Fig 2. Simulation of the nitrate reduction using an enlarged model system.

DEISA events



DEISA Symposium 2008

April 28 – 28, Edinburgh, UK
Advancing HPC in Europe

This year, the DEISA Symposium is in two parts. The first day will feature talks from key players in the field of HPC e-Infrastructures, including a DEISA status report. The second day will contain presentations from DEISA users, focusing on both the science they achieved and their experience of using the DEISA infrastructure.

As per tradition, the Symposium will start with lunch on the first day, Monday 28 April, and end with lunch on the second day, Tuesday 29 April.

Please visit www.deisa.eu/symposium, which will be updated regularly. Attendees can register for the Symposium at this website. Registration is free and closes on Monday, April 21. Attendees will have to arrange their own travel and accommodation. Note that some hotel rooms have been reserved at a reduced rate.

We look forward to welcoming you to Edinburgh in April!

DEISA Training

March 5 – 7, Stuttgart, Germany
HLRS – High Performance Computing Center Stuttgart

Scientists from all European countries and members of industrial organizations involved in high performance computing are invited to attend to the 6th DEISA Training Event at HLRS – High Performance Computing Center Stuttgart.

The training enables fast development of user skills and know-how needed for the efficient utilisation of the DEISA infrastructure.

The attendance is limited to 30 participants. Upon request, DEISA will take charge of the travel and living expenses of up to 15 participants arriving from outside of Germany.

Register for this event at www.deisa.org/training