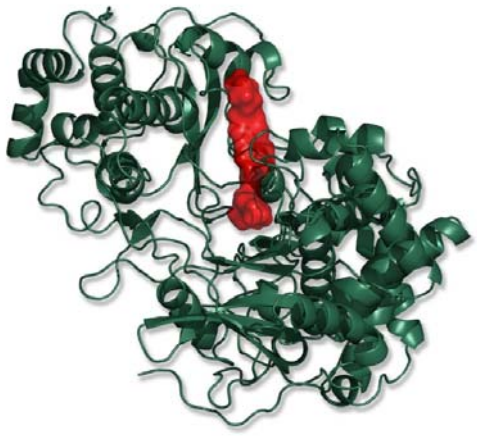
ANTAREX 4ZIKA

The Zika virus

In 2016, the Zika virus spread rapidly from south America to north America affecting also some islands in the Pacific and the southeast Asia, so WHO declared Zika a pandemic issue. Zika virus is a flavivirus transmitted by mosquitoes, mainly aedes aegypti and also albopictus. The virus determines mild symptoms as fever, rash, conjunctivitis, muscle and joint pain, malaise or headache, but Zika virus infection during pregnancy can spread from the mother to the baby and can cause severe defects to the fetuses. Infants often born with microcephaly and other congenital malformations and developmental problems. Additionally, an increased risk of neurologic complications is associated with Zika virus infection in adults and children, including Guillain-Barré syndrome, neuropathy and myelitis.



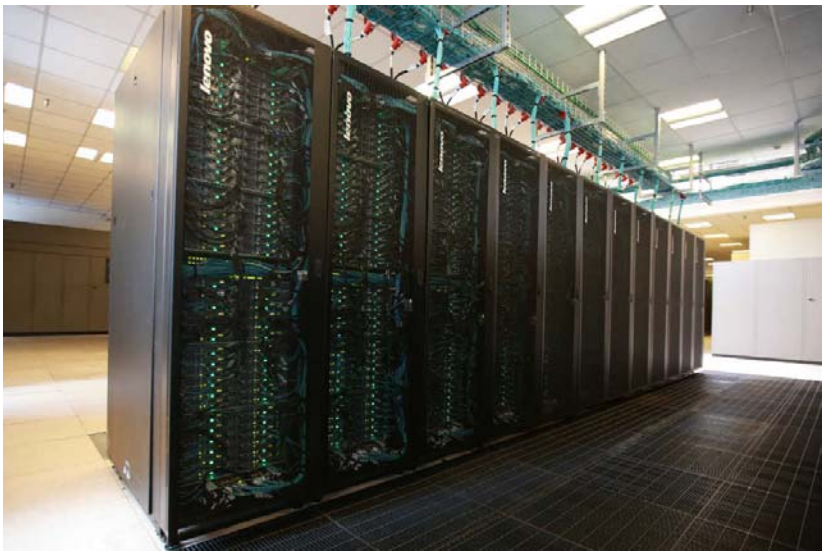
Computer-aided drug design

Computer-aided drug design (CADD) techniques are used to speedup the early-stage drug development allowing the selection of new active compounds. Through virtual screening, large virtual chemical libraries can be screened to find active molecules for query targets. Virtual screening techniques can be divided in ligand-based and structure-based if they use the structure of an active molecule to find similar compounds or they use the structure of the target to identify putative ligands, respectively. In the last years, the growing availability of protein structures, resolved by structural biologists, progressively raised the possibility to deploy structure-based drug design. Key for the success of the structure-based drug design is the evaluation of a chemical space big enough to allow the identification of chemical structures having the best complementary pattern of interactions with the biological target under investigation along with other phys-chem characteristics as well as novelty and synthesis feasibility.

The ANTAREX project

The ANTAREX research project has been granted in the H2020 Future and Emerging Technologies program on High Performance Computing. The project involves CINECA, the Italian Tier-0 Supercomputing Centre and IT4Innovations, the Czech Tier-1 Supercomputing Center. ANTAREX project was coordinated by Politecnico di Milano and concluded successfully on November 30, 2018. Final results have been presented at the Final Review Meeting held at the European Commission in Luxembourg on January 31, 2019. The main goal of the ANTAREX project is to provide a breakthrough approach to map, runtime manage and autotune applications for green and heterogeneous HPC (High Performance Computing) systems up to the exascale level. The ANTAREX project is driven by two use cases chosen to address the self-adaptivity and scalability characteristics of two important scenarios in HPC, chosen for their major scientific and social impact. Here we present the application scenario linked to a biopharmaceutical HPC application for accelerating drug discovery deployed on the 10 PetaFLOPS MARCONI supercomputer at CINECA (#19 in TOP500 most powerful supercomputers).

The simulation



To demonstrate the benefits of code optimization and scalability, we selected the Zika pandemic crisis to support and promote the identification of novel drugs able to address the unmet medical need in terms of effective therapies. We selected 26 binding sites identified from the already resolved crystal structures of 5 Zika proteins: NS5, NS1, NS2B/NS3, NS3 and the envelope protein. For this experiment, the biopharmaceutical company Dompé Farmaceutici SpA has created a virtual chemical space of 1.2 billion small molecular-weight molecules. The evaluation of such a huge chemical space was possible thanks to the outcome of the ANTAREX project and the almost 1 million computational threads available at CINECA. The focus was on molecular docking, an increasingly important application for HPC-accelerated drug discovery. We started by analysing the most computationally intensive kernels of the LiGen molecular docking application used by Dompé. In ANTAREX, the research team at Politecnico di Milano developed a runtime tuneable version of the molecular docking application for use in virtual screening experiments. This application was deployed and scaled out to the full size of the 10 PetaFLOPS Marconi supercomputer at CINECA to screen the 1.2 billion ligand database (including all investigational and marketed drugs) targeting the Zika virus. This represents the largest virtual screening experiment ever launched in terms of computational threads (up to one million) and size of the compound database (one billion molecules).

The outcome

Intention of the ANTAREX partners is to make available to the research community the outcome of the simulation to support and speedup the discovery of novel treatments to fight the Zika pandemic. Participating in ANTAREX allowed Dompé to take advantage of HPC-accelerated and tuneable solutions, thus illuminating new development paths not viable using conventional computing. Exploiting ANTAREX's HPC technologies supporting autotuning, scalability and energy efficiency, Dompé is now able to optimize molecular docking to reduce the virtual screening process for the identification of new active compounds by two orders of magnitude. The lesson learnt from the point of view of the drug industry (but for the scientific research as well) this perspective opens up the possibility to shorten the path from the discovery of a health threat, like the case of a sudden pandemic virus, to the prompt availability of candidate drugs.

For more info: https://www.antarex4zika.eu/

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