Joint Press Release

EMBL

NKI-AVL
The Netherlands Cancer Institute
Antoni van Leeuwenhoek Hospital

Mapping the protein world

A software package called ARP/wARP is helping to expose the hidden world of biological molecules

The inventors of ARP/wARP: Victor Lamzin (left) and Anastassis Perrakis (right).

Hamburg/Amsterdam, 11 July 2006 - In the early days of X-ray crystallography obtaining a three-dimensional model of a protein required wire models, screws, bolts and years of tedious calculations by hand. Today macromolecular models are built by computers – thanks to sophisticated software and in particular a package called ARP/wARP. Developed by Victor Lamzin at the Hamburg Outstation of the European Molecular Biology Laboratory (EMBL) and Anastassis Perrakis at the Netherlands Cancer Institute (NKI) in Amsterdam, ARP/wARP is currently used by over 2,000 researchers throughout the world. The capabilities of this software will now expand even further - thanks to a grant of over 800,000 US Dollars from the U.S. National Institutes of Health (NIH).

The grant, which will run over four years, comes at a perfect time. "More than 1,000 research laboratories from over 50 countries are holding ARP/wARP licenses and by June this year our paper that described the key innovative feature of ARP/wARP in Nature Structural Biology in 1999 has reached the magic number of 1,000 citations in the scientific literature. This has created an incredible drive for further scientific development," Lamzin says. "The new funding gives us a push to advance the software's ability to recognise and distinguish different types of macromolecular objects, for example DNA, and to improve the automated generation of structural models. ARP/wARP has made the life of structural biologists worldwide a lot easier and will do even more so once the new features planned under the NIH grant have been implemented."

ARP/wARP transforms 'electron density maps', produced in experiments that bombard protein crystals with X-rays, into 3-dimensional structures. "X-ray experiments result in 'diffraction patterns' that can't be interpreted using our eyes," Lamzin says. "These have to be reconstructed into a three-dimensional image through mathematics and models. This was a very tedious, time-consuming, and subjective process."

ARP/wARP was the first, and for a while the only, software that could generate models to fit experimental data automatically and very accurately. It has cut down the time necessary to create structural models from weeks to minutes.

This grant will allow the scientists to explore new concepts of model-building and enlarge the scope of data that the software can handle. ARP/wARP deals very well with high-resolution data that allows to distinguish individual atoms, but much of the data that scientists have to deal with is of lower quality. The software has steadily been improved to work with lower-resolution data, and Lamzin and Perrakis know how to stretch it even further.

"The high-throughput revolution in Structural Biology allows us to work on more and more complex problems relevant to human health," Perrakis says. "Knowing the structures of molecules that play crucial roles in cancer, cardiovascular and neurodegenerative diseases and molecules from pathogenic bacteria or viruses will contribute to design new revolutionary therapeutic strategies."

To meet this objective the scientists intend to study crystals of proteins bound to diverse drug candidates or containing different types of large molecules.

"ARP/wARP needs to meet a two fold challenge: firstly, it needs to be able to work with structural information at lower resolution, within the range of 3.0 to 3.5 Ångstroms, and secondly, the models produced have to be complete and validated. The new NIH grant will help us to approach these aims. In the future researchers will be able to focus on structure analysis rather than just building the structure and, who knows, by combining ARP/wARP with new cell imaging techniques we might be able to model the molecules of a complete cell," Perrakis concludes. ●

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About EMBL

The European Molecular Biology Laboratory is a basic research institute funded by public research monies from 19 member states (Austria, Belgium, Croatia, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom). Research at EMBL is conducted by approximately 80 independent groups covering the spectrum of molecular biology. The Laboratory has five units: the main Laboratory in Heidelberg, and Outstations in Hinxton (the European Bioinformatics Institute), Grenoble, Hamburg, and Monterotondo near Rome. The cornerstones of EMBL's mission are: to perform basic research in molecular biology; to train scientists, students and visitors at all levels; to offer vital services to scientists in the member states; to develop new instruments and methods in the life sciences and to actively engage in technology transfer activities. EMBL's International PhD Programme has a student body of about 170. The Laboratory also sponsors an active Science and Society programme. Visitors from the press and public are welcome.

About EMBL Hamburg

EMBL Hamburg is situated on the campus of the German Synchrotron Research Center (DESY) in Hamburg-Bahrenfeld, Germany. DESY hosts leading facilities for synchrotron radiation (DORIS-III, in operation, PETRA-III, under construction, user operation planned for 2009) and electron lasers (VUV-FEL, commissioned; X-FEL, planned). EMBL Hamburg operates seven experimental stations with applications in structural biology, using synchrotron radiation from the DORIS III ring. In addition, it runs a biochemistry laboratory hosting a pipeline for sample preparation and characterisation. It also includes facilities for high cell density fermentation, semi-automated protein purification and mass spectrometry. Start of operation of new state-of-the-art beamlines at the storage ring PETRA-3 is planned for 2009-2010. Research at EMBL Hamburg is tightly associated with the available synchrotron experiment stations for applications in life sciences. Several projects are aimed at developing novel technologies to advance methods in structural biology in terms of automation and user friendliness. In addition, faculty members from EMBL Hamburg lead a number of research projects to meet great challenges in structural biology. EMBL Hamburg provides a unique research environment for advanced training by hosting visits and offering specialised courses and workshops.

About the NKI

In the Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital, research takes place on cancer related subjects. Fundamental research at the molecular level (biochemistry, structural biology, molecular biology, cell biology, immunology) is aimed at understanding the processes involved in cancer development. The more clinically related studies (e.g. radiotherapy, clinical trials, epidemiology) are aimed at improving treatment and prevention as well as understanding the epidemiogy and hereditary aspects of cancer. The combination of hospital and research institute makes it possible to do efficient translational research, where findings at the molecular level are used to develop improved clinical practice and fundamental studies are iniated to answer clinical questions. Research at the NKI/AvLhas many educational aspects. Many staff-members have (part-time) positions as professors at local universities. Frequently undergraduate students come to do a rotation (NKI/AvLUndergraduate School), which includes a lecture course in Molecular Oncology. Graduate students take part in the course program Oncology Graduate School Amsterdam (OOA) as well as a special Seminar Series. An international population of post-doctoral fellows helps to maintain the high level of the research within the institute.