INDUSTRIAL PILOT PROJECT

Implementing synchrotron serial crystallography as data collection tool at SARomics Biostructures

THE INDUSTRIAL CHALLENGE

SARomics Biostructures is a CRO offering structural biology services in the field of early stage drug discovery. One of our main methods is protein X-ray crystallography, in which crystals of proteins and their complexes with ligands (e.g. inhibitors) are exposed to intense synchrotron X-rays. The quality of data that we obtain is dependent to some extent on the size of the crystals we can produce. Some of the systems that we work with, such as membrane proteins, produce only very small crystals. To get a full picture of such proteins we may have to collect data from a large number of these.

WHY USE A LARGE-SCALE FACILITY?

The relatively new method of serial crystallography involves collecting very small amounts of data from tens of thousands of tiny protein microcrystals, then assembling these using advanced computer methods. This would be impossible using a laboratory X-ray source or older generation synchrotrons. The method was first developed at X-ray free electron laser facilities such as those at Stanford University (SLAC) and in Hamburg (European XFEL). These are, however, relatively inaccessible, especially to commercial entities, due to high running costs and the high competition for beam time. Thus, the implementation of very similar methods at newer synchrotrons gives new possibilities for companies such as SARomics to tackle difficult projects with large systems that only give small crystals, such as membrane proteins, which are the targets for at least 50% of marketed drugs.

HOW THE WORK WAS DONE

The ultimate ambition is to apply the method to a membrane protein, but the small carbohydrate binding protein galectin-3C was used as an initial model system. We grew microcrystals on a novel kind of thin film support (XtalSupport) that could be directly mounted in the X-ray beam. We also tried other kinds of support for the crystals, such as silicon nitride membranes, to evaluate which would give the best data. Serial crystallography data were then collected at the BioMAX beamline of the MAX IV Laboratory in Lund whose staff were also supporting experts in the project. We learned new techniques and software for merging large numbers of partial datasets from individual crystals (tens of thousands).

THE RESULTS AND EXPECTED IMPACT

Two crystal structures of galectin-3C in complex with its natural ligand lactose were solved, one with data from the XtalSupport and the other from crystals transferred to a silicon nitride membrane. The electron density from both structures was of comparable quality to existing structures collected using conventional methods (see the figure below). The experiments showed the ready applicability of the serial crystallography methods being implemented at BioMAX to an industrial project.

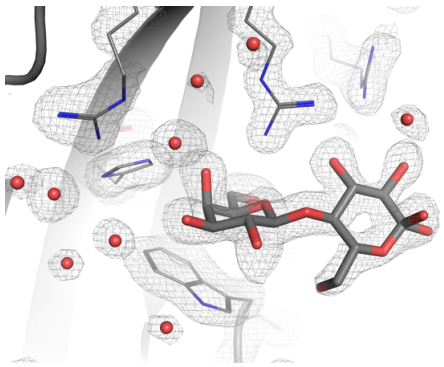

Figure. The binding of lactose to the carbohydrate recognition site of galectin-3C.

The electron density was calculated from data collected from 15 555 crystals at room temperature rather than one crystal cooled to 100K, as is customary.

The main benefit of this pilot project for SARomics was that our staff learned new data collection methods that will extend the range of techniques we can offer, enhancing our attractiveness in a competitive market.

"After this fruitful collaboration with MAX IV we are now poised to exploit the next generation of data collection techniques."
/Derek Logan, SARomics Biostructures

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