

SIMPLE on a chip – real-time electron microscopy (EM) feedback

A team of researchers at Monash University have developed a novel image processing algorithm that can potentially revolutionise the discovery of 3D molecular structures by providing real-time image quality assessments to electron microscopists. The team is exploring implementing the algorithm on a combination of GPU and FPGA chips to realise a dramatic improvement over the current state-of-the-art technology.

Benefits over existing technologies:

- Potential to develop 'First in Class' solution to revolutionise EM;
- Real-time EM feedback, which represents an improvement of more than an order of magnitude compared with current state-of-the-art; and
- Portable and flexible architecture which allows applicability to a wide range of instruments and platforms.

Background

The three dimensional (3D) atomic arrangements of molecules determines their chemical and physical properties, which are exploitable for applications in medicine, biology, materials science and more. EM, and more specifically Transmission Electron Microscopy (TEM), is one of the key techniques used to characterise the 3D structure of molecules.

However, typically molecules or particles imaged in a TEM undergo dynamic phenomena as a consequence of radiation damage, movements due to instabilities in the sample holder, or electron beam-induced motion. In order to determine the structure of the molecules being analysed, complex image processing is carried out after thousands of raw images have been collected.

The current state-of-the-art algorithms¹⁻³ typically require weeks to months of supercomputing cluster time to evaluate whether the images obtained were of sufficient quality. This is a tremendous bottleneck for researchers attempting to determine whether their EM experiments were successful, and to EM facilities worldwide because these microscopes typically cost several hundred dollars per hour to run.

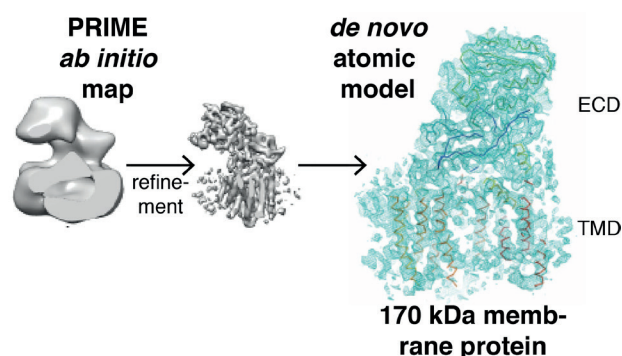
The opportunity

Our team has developed image processing algorithms that can be compartmentalised into initial image analysis steps, which are required to assess image quality, and subsequent image processing steps, which are required for more detailed analysis and 3D reconstructions.

Implementing the initial image analysis steps on a FPGA chip has the potential to dramatically increase the speed of the calculations, enabling real-time feedback to be provided to the electron microscopist regarding the quality of their sample.

A large part of the code base involves standard image processing operations such as Fourier transformations, linear image transformations, Fourier filters, convolutions and correlations, all of which can be readily implemented using FPGAs.

The team is currently working with nVidia to implement portions of the algorithms on GPU chips to enhance performance. The Centre for Advanced Molecular Imaging and Monash University are seeking partners who can help us drive the implementation of our image processing algorithm onto FPGA chips towards realising a real-time feedback device for EM. Our team of researchers have deep expertise in programming in various languages, have an intimate understanding of electron microscopy techniques and standard workflows, and have published numerous studies on image processing algorithms for EM.



How the gamma-secretase structure was solved (Ref. 4). The PRIME algorithm, which was developed by CI Elmlund and colleagues and is implemented in the SIMPLE software package, was used to generate a map ab initio. The refined map allowed building of an atomic model de novo. The extracellular domain (ECD) and transmembrane domain (TMD) is indicated.

1. Elmlund, H. et al. (2013) PRIME: probabilistic initial 3D model generation for single particle cryo-electron microscopy. *Structure* 21, 1299-1306.
2. Grigorieff, N. et al. (2007) FREALIGN: High-resolution refinement of single particle structures. *J. Struct. Biol.* 157, 117-125.
3. Scheres, S. H. et al. (2012) RELION: implementation of a Bayesian approach to cryo-EM structure determination. *J. Struct. Biol.* 180, 519-530.
4. Lu, P. et al. (2014) Three-dimensional structure of human gamma-secretase. *Nature* 512, 166-170.

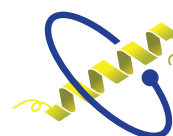
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