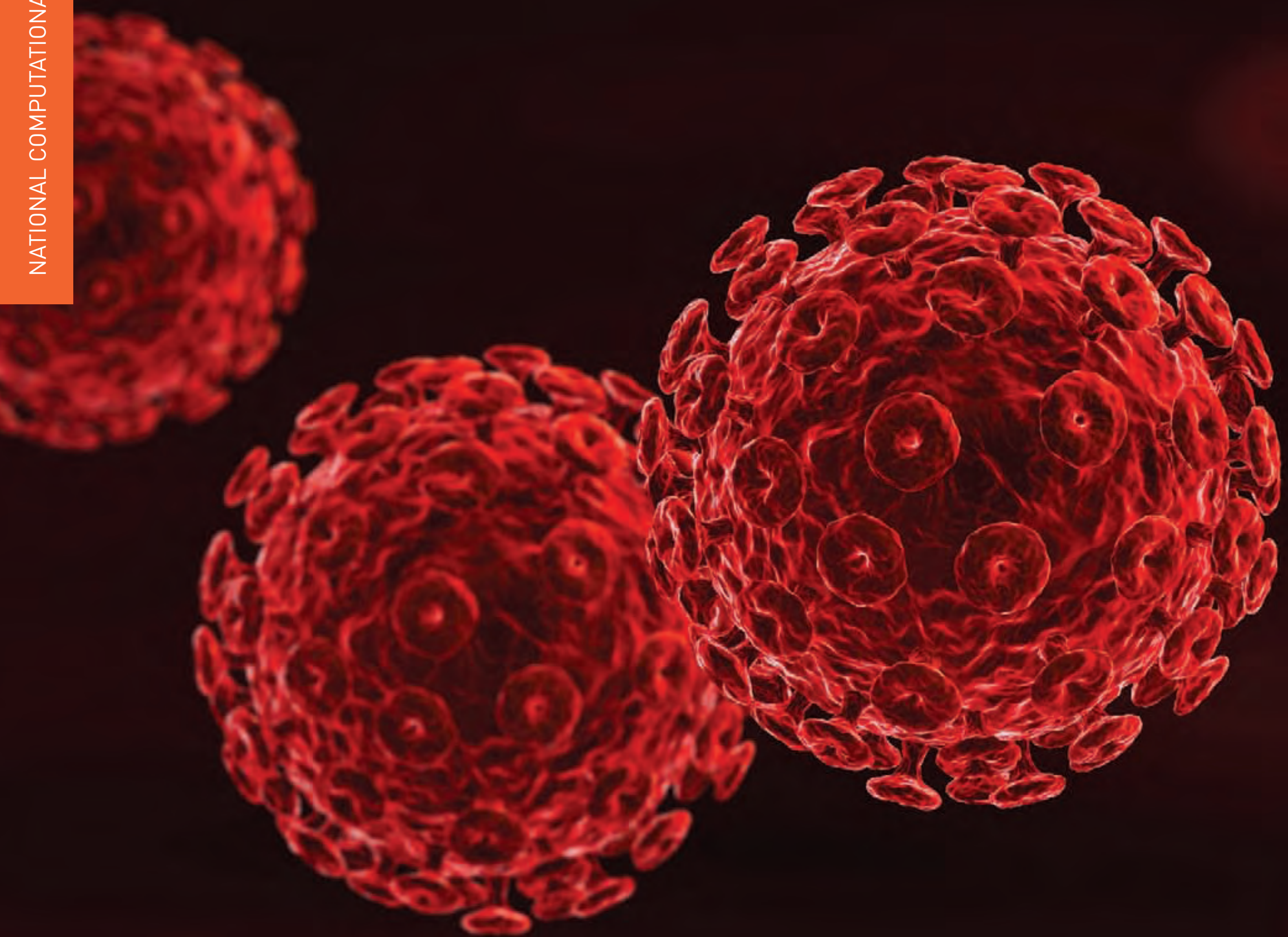
NATIONAL COMPUTATIONAL INFRASTRUCTURE

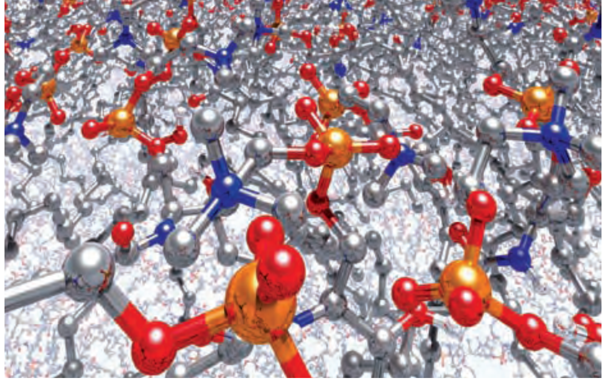


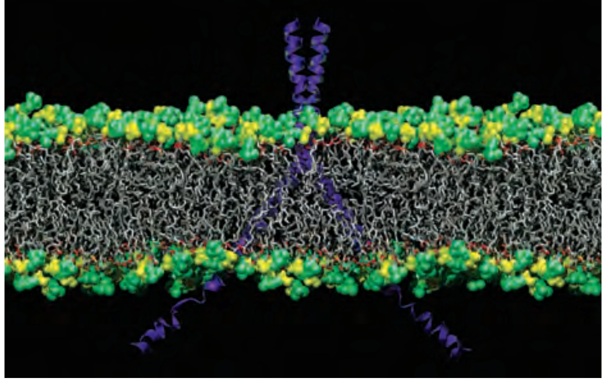
ILLUMINATING THE MACHINERY OF LIFE

ATOM BY ATOM SCIENTISTS PROBE HOW LIFE WORKS, IN ORDER TO DEFEAT DISEASE

NCI

Among life's most profound mysteries is how molecules, of their own accord, assemble themselves into the structures essential for living creatures to exist. Understanding this sheds fresh light on the machinery of life itself. It also promises a new generation of safe, effective treatments for hitherto intractable diseases as well as revolutionary products that construct themselves.





Professor Alan Mark and his team at the University of Queensland are using the NCI supercomputer to model the movements of hundreds of thousands of individual atoms in the proteins, peptides, lipids and sugars which are the building blocks of life itself as they interact to form and reform the structures that decree how everything from a virus to a prime minister works.

"We're essentially using the NCI to make a 'movie' of how biological molecules function in reality," he explains. "Molecular self-assembly is a feature of all living systems. Most proteins fold spontaneously and then further self-organize into functional complexes, effectively biological machines. Understanding how this works lies at the heart of future biology and medicine."

The atoms in the individual molecules that make up cells are too small and their motions too rapid to observe directly as they form and reform themselves into functional biological machines so, to study these processes, Professor Mark and his colleagues develop models and employ immense computational power to simulate each step in the process. "We can look directly at the dynamics of complex molecular systems and watch them evolve in nanoseconds into new structures with different properties."

For example, the team models how antimicrobial peptides can bind to a membrane and assemble into a pore that enables the peptides to enter and kill the microbe. How the binding of a hormone to its receptor on the outside of a cell sends a mechanical signal through the cell wall that triggers a flood of chemical signals inside the cell. How an Ebola virus, stimulated by mild acidity, fuses with a cell as a prelude to invasion and deadly conquest. Or how the toxic amyloid plaques, a feature of Alzheimer's and many degenerative diseases, form from minute clusters of misfolded fragments of certain proteins and grow into complex microscopic fibres—a process still poorly understood.

Self-assembly tends often to occur at boundaries or surfaces, between a liquid and a solid or a gas and the team is probing events in this environment in particular. The formation of amyloid fibrils for example, is enhanced by the presence of tiny bubbles—and insights into their initial formation may one day help to defeat them.

The simulations of these processes are carried out using two programs developed by Professor Mark with colleagues in the Netherlands and Switzerland, GROMOS and GROMACS. Fascinatingly, this state-of-the-art research employs one of science's earliest and greatest advances—Newton's equations of motion, first published in 1687, and now reiterated at blinding speed through the power of NCI's supercomputer.

"The systems we simulate are very, very large: we calculate the interactions between anything up to 250,000 individual atoms, let the atoms move according to the forces acting on one another, then recalculate the interactions based on the new positions they have adopted. We must do this a million times to simulate a system for just a few nanoseconds, so the computations involved are vast. We can eat up as much computer time as we can get."

"The fascination is understanding life at its most basic level," Prof. Mark confides. "The amazing thing is that it always turns out to work differently to what you had expected." Intuitively, one might expect such basic molecular processes to be highly ordered, regular and repetitive: not so, he says. Self-assembly is more like watching a football match in which, under very broad rules, the ball can reach the goal in countless different ways. "It looks chaotic—but the ball arrives, somehow."

Modelling these atomic processes will help to keep Australia at the global forefront of biological and biomedical research. It will assist in the design of novel drugs that disrupt or prevent disease-causing processes. It will lead to the creation of new polymers and industrial materials that build themselves. And it will provide a powerful springboard for sciences such as proteomics and genomics.

"When we began this research we could only model the interactions of 500 atoms or so. Now we model hundreds of thousands, thanks to advances in computational power. If NCI keeps on increasing its speed we may one day be able to model what occurs in specific parts of the cell. It is a phenomenal tool," he concludes.

Research Support:
- ARC Grant: FF0455865, DP0878608, LP0884027, LE0882357, LX0882184 and DP0770375
- NHMRC Grant: 519709
- NCI Grant: M72

Acknowledgement:
Images kindly provided by David Poger

NCI, an initiative of the Australian Government, is hosted by The Australian National University and is jointly funded by the Department of Innovation, Industry, Science and Research under its NCRIS program, CSIRO and ANU.