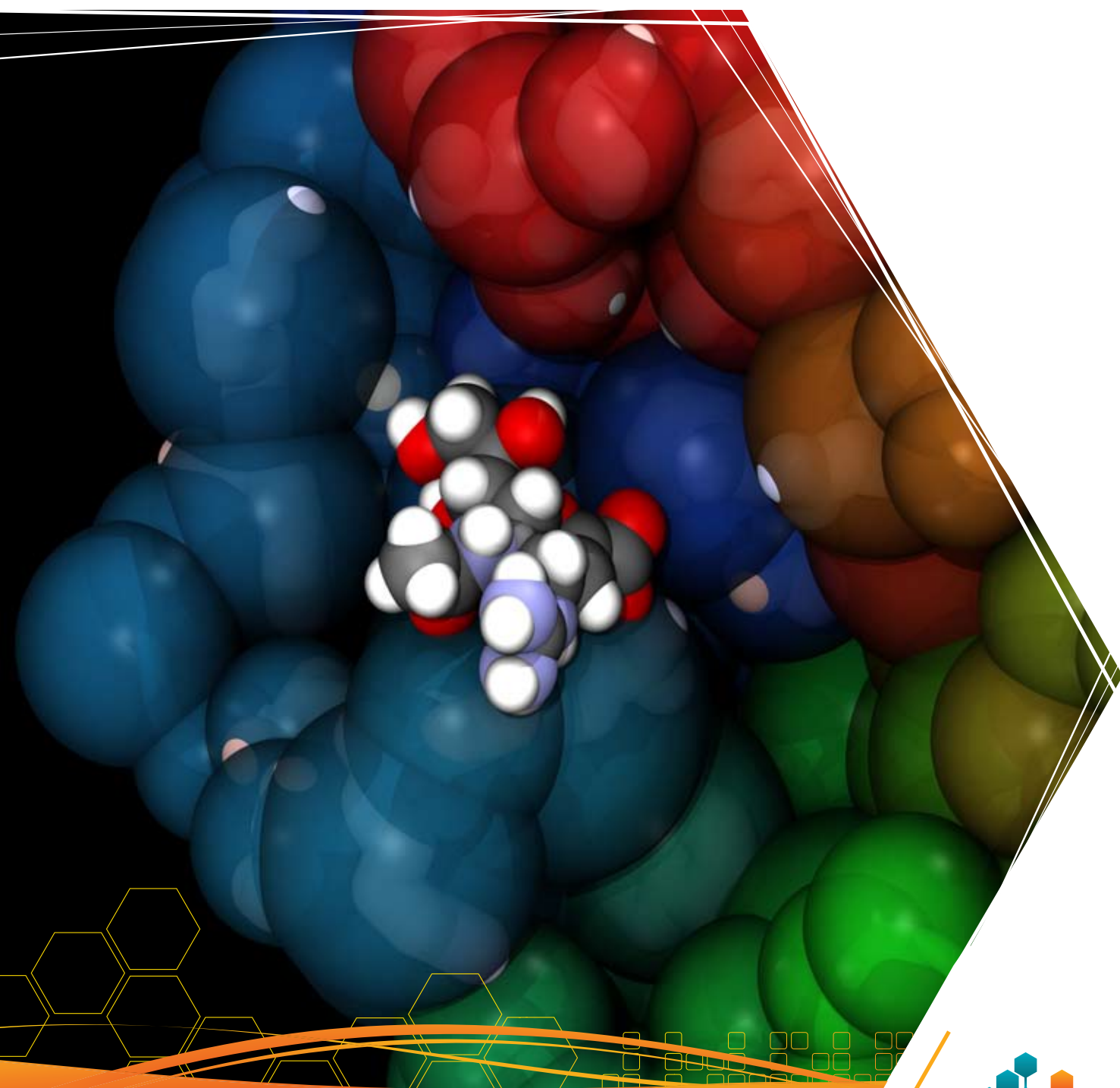


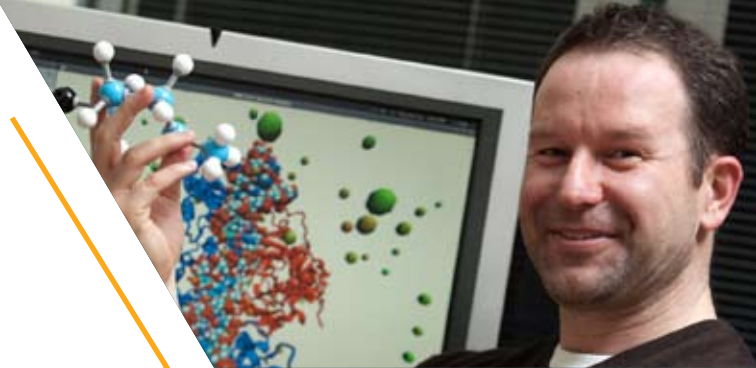
HOW DO DRUGS WORK IN REAL LIFE?

A Melbourne researcher is revealing in detail how drugs dock with their target molecules. His supercomputer simulations could help refine the new generation of designed drugs such as Relenza.

Tim Thwaites, Science Writer



“We’re no longer sacrificing accuracy for speed...”



Mike Kuiper. Image credit: David Paul

The small molecule seems to wander on an erratic path around the much larger one until it settles in the pocket in which it is finally cradled. Even then, it does not remain still. It jiggles about, rather than being firmly held. This realistic simulation of drug docking, put together by Dr Mike Kuiper of the Victorian Partnership for Advanced Computing (VPAC), can teach us many things we did not know about protein interactions. But it was only possible with the aid of a supercomputer.

Mike is a molecular modeller. He has been using parallel or cluster computing – the progenitor of supercomputing – for many years. He joined VPAC seven years ago after a post doc in Canada – and quips that his job is a “missionary position”. What he means is that he spends a lot of his time working with molecular biologists demonstrating how supercomputing can be applied to their work. So he ends up contributing to many projects – a lot of papers credit his assistance – but his own interests revolve around two areas: drug docking and protein dynamics.

“I create models to help people visualise and explain what’s going on at the molecular level,” Mike says. “If you validate such modelling with experimental results, it can provide useful insights. With bigger and more powerful computing resources, you need to make fewer simplifying assumptions, so the models become more realistic.”

Using supercomputers, such as the IBM Blue Gene computer at the Victorian Life Sciences Computation Initiative (VLSCI), Mike has set about breaking the shackles of Newtonian mechanics. Until now, he says, we have typically generated molecular simulations as if atoms were balls bonded by springs, even though we know from quantum mechanics

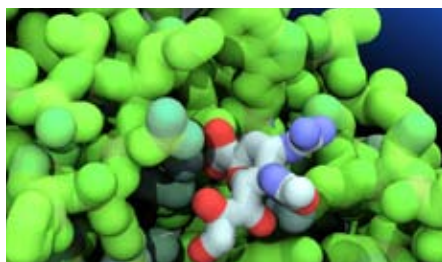
that what we are dealing with is more like a fuzz of moving mass and energy. “Quantum mechanics is counterintuitive and we make compromises, such as using Newtonian mechanics in our simulations, to deal with them on a practical time scale,” Mike explains.

That’s the context he has in mind as he studies how a couple of model drugs – aspirin and Relenza – interact with their protein targets. “Most drug docking programs were written 20 years ago when computers were less powerful and they made assumptions, for instance, that drugs and receptors don’t move around much.

“They also left out water molecules, because water just got in the way. But water is a crucial part of the mechanism. It takes an active part in the drug binding process. Including water molecules, however, demands more computer power, and slows the simulation down. Now, we’re no longer sacrificing accuracy for speed.”

Enhanced computer resources also mean that Mike can run his simulations over longer periods of time. They are dynamic. And the molecules and their components jiggle and move with respect to one another.

“When I started postgraduate research, I would be running what happened in a few hundred picoseconds (trillionths of a second),



The drug Zanamivir (trade name: Relenza) binding into a pocket of the Influenza neuraminidase. Image credit: Mike Kuiper

and I thought that was giving us a pretty good indication of what was going on. A couple of years ago I would have told you that 10 nanoseconds (billionths of a second) was a long simulation, and that was the benchmark then. Now I’m thinking more in terms of 500 nanoseconds to a few microseconds (millionths of a second).” The point is that the longer the simulation, the more time you have to work out what is occurring and what is significant.

In his simulation of the anti-flu drug Relenza, for instance, Mike has not yet reached the point at which the drug has docked into its protein target, neuraminidase. But already he has zeroed in on a part of the molecule near the receptor which appears to usher Relenza into the docking area. And that has stimulated him to think that a mutation changing the structure of this part of the target molecule may be what confers resistance to Relenza’s action.

At all times Mike is aware that he is working with a model on a computer, not a real molecule—which means that, while what’s happening on the screen in front of him may give an indication of the behaviour of a molecule, it may simply reflect the ideas of the modeller or the constraints of the software and hardware with which he or she is working.

That goes for machines too. “The Blue Gene is not necessarily always best suited for a particular job. That’s because of its architecture. For smaller jobs, he says, more conventional cluster machines may be more suitable. But, when these systems are scaled up, you run into all sorts of problems to do with heat, power and plumbing arrangements. The Blue Gene design can provide a better economy of scale.”

For further information about this research contact Mike Kuiper at mike@vpac.org

To contact VLSCI, go to www.vlsci.org.au