Every field of study has its “Holy Grail” — a tantalizing new model or discovery with the potential to revolutionize society. With incremental advances in theory, observation, experimentation and computer simulation, researchers advance towards this goal, pulling science and technology along with them.

In biomedicine, the Holy Grail is patient-specific medical treatment, says Peter Coveney, Professor of Physical Chemistry at University College London (UCL) and Director of the Centre for Computational Science there. Instead of a generalized approach to illness, personalized medicine promises treatments developed just for you and sophisticated diagnostic tools to differentiate your genetic disposition and strain of illness from your neighbor’s.

Coveney is among a handful of scientists leading the charge to develop patient-specific approaches to medicine. His simulations of drug-resistant HIV protease proteins, performed with the resources of the Texas Advanced Computing Center (TACC), push the limits of biomedical research and test methods for the fast and accurate treatment of unique illnesses. The results of Coveney’s research at TACC, performed with Dr. Ileana Stoica and Kashif Sadiq, were published in the prestigious Journal of the American Chemistry Society on January 29, 2008.

“Given that we know so much now about the genetic makeup of individuals and are able to collect data on them as individuals, not just as a ‘generic patient’, the obvious challenge is to develop treatments that address the particular patient and the ailments that they may have,” Coveney explained.

Though this method is relevant to all aspects of health, the need for patient-specific medicine is particularly vital in the treatment of HIV, where the high rate of viral mutation threatens to derail decades of inquiry and billions of dollars in research and development that have led to nine FDA-approved, anti-viral HIV protease drugs.

“Many of these infectious diseases are clever enough to develop strategies to resist the drugs over time,” Coveney said. “The HIV virus is very good at doing this because of the way it copies itself. The error rate in reproduction is so great that its mutations allow it to outwit drugs.” Though Coveney’s research has dealt mainly with HIV, his computational approach could apply equally well to the flu, hepatitis and other mutating diseases.

Stoica, Sadiq and Coveney’s study is the most compute-intensive investigation of the cause of saquinavir resistance in HIV protease mutants, and helps to explain exactly why mutations in the HIV protein, protease, cause medicines to lose their effectiveness. “How can these single point mutations — some of which may be nowhere near the active site in the protein — how can they have such a dramatic effect on whether the drug is inhibited or not? There’s no way of understanding that unless you have a faithful, atomistic molecular representation of the protein and how it interacts with the drug,” Coveney said.

Coveney and his colleagues first developed fine-detailed molecular representations for HIV protease and saquinavir, the first HIV drug to be discovered that inhibits the replication of HIV by binding to the protease molecule. They then used molecular dynamics codes that fully exploit the massively parallel power of TACC’s supercomputers to determine how well the drug binds to the “wild-type” HIV protease and to three drug-resistant mutant...
haven’t done this yet, but we see a way of doing it in the future.”

For Chris Hempel, TACC Associate Director for User Services, the project was a chance to test the flexibility and scheduling capabilities of the 22nd largest supercomputer in the world, proving just how powerful a tool for science it can be. “Projects like this have a fantastic impact,” Hempel said. “Coveney’s research not only helps physicians understand the mechanics of HIV drug-resistance, but it enables the formulation of a future, computationally-based medical treatment. His work is truly ground-breaking.”

To date, Coveney has focused his biomedical research mainly on the HIV protein, protease. However, his future studies will model and predict the binding energies of reverse transcriptase, another molecule involved in HIV replication that is significantly larger than protease. For these simulations, Coveney will likely use Ranger, the world’s largest supercomputer for open science research, which comes online in February 2008 at TACC.

“The huge numbers of processors that are available on Ranger make it an incredible tool. If you’ve got the problems, or you can think of ways of using that scale of machine – and we certainly can – then you can have a field day there,” Coveney said.

At present, the realistic application of patient-specific medicine remains quite a few years away. But by harnessing the power of supercomputers, Coveney is blazing a path to rapid advances in computationally-assisted diagnosis and drug prescription.

“To be able to tailor medical treatment to a person and their ailments, instead of giving them some average course of treatment — we’re only going to get to that level of patient specificity if we use computational science and high performance computing, of that there can be no doubt,” Coveney said. “Computational science is not going away, it’s just going to become increasingly pervasive as time goes on.”