Supercomputing the p53 protein as a promising anticancer therapy

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The Stampede supercomputer at the Texas Advanced Computing Center (TACC) in Austin. Credit: TACC

Even though it's almost impossible to see, computational biophysicist Rommie Amaro is using the Stampede supercomputer at the Texas

Advanced Computing Center at The University of Texas at Austin to model the largest atomic level system of the tumor suppression protein p53 to date—over 1.5 million atoms. The simulations identify new "pockets" to reactivate p53 which would be a tremendous boost for future anti-cancer drug discovery.

Amaro is a professor in the Department of Chemistry and Biochemistry at the University of California, San Diego. She has been studying this important molecule for years trying to understand how it works. Amaro is motivated by the fact that the p53 protein somehow helps prevent the formation of cancerous cells.

"P53 is a major tumor suppressor that is mutated and inactivated in approximately 50 percent of all human cancers. Thus, reactivation of mutant p53 using small molecules has been a long-sought-after anticancer therapeutic strategy," Amaro said.

Amaro calls p53 the 'guardian of the genome.' P53 is at the core of the tumor suppression mechanism and an important protein for regulating cell life, according to a paper she co-authored in the September 2016 edition of the journal *Oncogene*. Study scientists found that when there is damage to a normally functioning cell, p53 senses the damage and engages the elements in other molecules that control things like cell death or cell cycle arrest. This stops the damage where it is in the cell cycle.

Most of the cancer mutations studied change single amino acids in p53. The altered guardian protein cannot bind to DNA, preventing it from effectively regulating cell growth and division. As a result, DNA damage accumulates in cells, which can allow them to grow and divide in an uncontrolled way to form a cancerous tumor.

"If you have a damaged cell, you don't want it to replicate," Amaro said.

Amaro and her colleagues' new work is based on the full length p53, which is challenging because of its complex architecture and multiple highly flexible regions. "We went from studying a relatively small protein of 50,000 atoms in a water box to the full length p53, which included the single binding domain, additional domains, in tetramer form, and in complex with different segments of DNA," Amaro said. "In doing so, there was a huge increase in terms of the complexity of the system and the number of atoms simulated."

"That's why Stampede was so terrific," Amaro explained. "Stampede has many processors and amazing scalability—we were able to run this 1.5 million atom system for nearly a microsecond and actually begin to say things about the dynamics at a completely different scale than what was known previously.

Amaro said that she and her colleagues use these methods like a 'computational microscope.'

Credit: University of California, San Diego

"The science challenge represents a level of complexity that's very difficult if not impossible to experimentally test," she said. In response, the researchers built atomic-level models 'in silico,' and interrogated the system in unique ways. For the first time, for example, the researchers built a large complex of the p53 molecule with three different sequences of DNA: two were recognition sequences (P21 and Puma) and the third strand was a negative control. "We could see how when we the full-length p53 was bound to a DNA sequence that was a recognition sequence, the tetramer clamps down and grips onto the DNA - which was unexpected," Amaro said. In contrast, with the negative control DNA p53 stays more open. "It actually relaxes," she said. "It suggested a

mechanism by which this molecule could actually change its dynamics depending on the exact sequence of DNA."

The supercomputer simulations of the full length p53 system showed some 'firsts':

- First time to see the direct interactions between one region of the p53 molecule, which is called the c-terminal domain, with DNA. The researchers saw this region of p53 actually come down to interact with the DNA.
- First time to suggest an atomic level mechanism by which p53 changes its grip on the DNA depending on the actual DNA sequence.
- First time researchers are getting insight into how the full-length p53 interacts with the DNA.

These firsts were accomplished using atomic level simulations. "We have all of the atoms and the proteins," Amaro said. "We try to replicate the environment of the cell, so we have water molecules and ions, and then we had an actual segment of DNA so we could explore the response of 'full length p53' in terms of its dynamics, depending on what sequence of the DNA was there."

The researchers set up three different systems and ran three different copies of each system to test variability in the data for a total of nine different simulations for nearly a microsecond of aggregated dynamics. "The simulations were very computationally intensive. And then to be able to do something new about the biology that wasn't known before - that's the really exciting part and that's what we showed," Amaro said.

"As the systems get bigger, much more computational time is required. Previously the simulations were run for a few nanoseconds. Now we have microseconds of dynamical data, which is 1,000x more. In this case

we were looking at over a dozen domains and in complex with the DNA. It gives us a much more complete picture of what is actually happening. It's a few steps closer to reality than anything we've been able to accomplish yet," she explained.

Said Amaro: "Computing is getting to the point now where it can have an impact on developing new therapies. It gives us a better understanding of cancer mechanisms and ways to develop possible novel therapeutic avenues. When most people think about cancer research they probably don't think about computers, but these models are getting to the point where they have a great impact on the science." Amaro is hoping these discoveries will translate into new cancer therapies.

"The ideal situation is that cancers of the breast and prostate could possibly be rescued or eliminated if we were able to develop a compound that reactivated p53. You don't have to wait until the cancer is advanced. The sensing of mutation and then shuttling the cell to die is something that happens through the early stages of cancer. It could be detected and fixed before the cancer develops," Amaro concluded.

Provided by University of Texas at Austin