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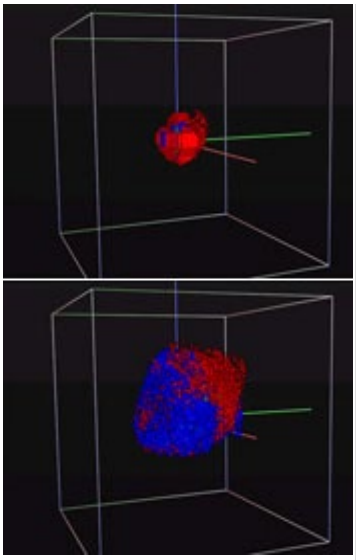
Computational Modeling Paints a Picture of the Future



Researchers at the Harvard-MIT Complex Biosystems Modeling Laboratory (Massachusetts General Hospital), which is supported by NCI's Integrative Cancer Biology Program, have developed a virtual model that predicts the growth of brain tumors over time (shown here at time step 52 and 110), taking into consideration *EGFR* gene-protein interactions and the effect of glucose and oxygen concentrations on cell movement and division. Models such as this one can be used to integrate data and generate hypotheses for tumorigenesis, cancer detection and treatment. (Image courtesy of Dr. Thomas Deisboeck, learn more at http://biosystems.mit.edu and https://www.cvit.org)

In silico research (better known as computational modeling or mathematical modeling) uses complex algorithms requiring high-powered computers to predict unknown properties or outcomes of disease.

Modeling is a familiar tool in the cancer research arsenal, explained Dr. Daniel Gallahan, director of NCI's Integrative Cancer Biology Program (ICBP): "After all, the mouse is a model system. It's a very complex system—we don't know all the components that go into making a mouse—but it's a sophisticated model in that it mimics a lot of the cellular and molecular processes that are ongoing in human cancer."

The ICBP's computational models aim to mimic the most fundamental elements of cancer, "for example, looking at chemical interactions, or molecules that interact within a cell and cause malignant transformation," said Dr. Gallahan. "It can be very efficient to run a computational program as opposed to setting up a series of biological experiments."

Any model's predictions must be validated in a biological system, but modeling can provide substantial time and cost savings to researchers by highlighting the most promising avenues for future research. Nine centers funded by the ICBP are currently building predictive models of a wide

range of biological processes related to carcinogenesis and cancer treatment, including cell signaling pathways, epigenetic changes, and response to targeted therapies.

On the opposite end of the cancer research continuum, NCI's Cancer Intervention and Surveillance Modeling Network (CISNET) uses computational modeling to understand how cancer control interventions influence the disease at the population level. "We observe trends in the national cancer rate, and then try to understand why they're occurring," explained Dr. Eric Feuer, program director of CISNET.

The complex factors that influence national cancer trends are virtually impossible to study in a controlled fashion in the real world. "What modeling does is let us build a sort of virtual world that allows us to decompose the real world into the components that influence these trends," said Dr. Feuer.

For example, after many randomized controlled trials and meta-analyses of mammography, there was still controversy about whether or not mammography reduces mortality from breast cancer. In 2005, using seven independent mathematical models, CISNET investigators were able to show that declines in U.S. breast cancer mortality observed from 1975 to 2000 would be very difficult to explain without a substantial contribution from mammography.

The ICBP and CISNET have recently begun pilot collaborations to model several cancer types all the way from their cellular biology to population-level effects, with the ultimate goal of being able to accurately simulate the results of clinical treatment trials.

“I think the 'holy grail' of modeling, or even understanding cancer, is to have a unified theory—to be able to measure what's going on within a cell at the molecular level, then predict all the way through to what would occur in a population," explained Dr. Gallahan. "It's daunting, but if you look at the specific aspects of it, we're not trying to conquer the world in one fell swoop; we're simply trying to tease it apart, and that's the power and possibility of modeling.”