Simbios: Bringing Biomedical Simulation to Your Fingertips
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University of Pittsburgh Medical Center. Luna suggests that the method could next be applied to study subjects engaged in specific activities. BJ Casev, PhD, a neuroscientist at the Weil Medical College of Cornell University in Ithaca, New York, finds the study to be “a very novel characterization of neural system development” ideally suited to study developmental disorders such as autism. “It’s going to drive a lot of research,” she says.

—By Chandra Shekhar, PhD

**Chromatin Fiber: Zigzag or Solenoid?**  

Try packing a two-meter-long stretch of DNA into a cell nucleus just a few millionths of a meter thick—with key coding segments readily accessible. It’s a seemingly impossible feat that eukaryotic cells routinely pull off by building a highly compact, fibrous mix of DNA and proteins called chromatin. Now a new study uses a combination of novel lab experiments and computer simulations to provide long-sought details about the structure of chromatin fibers.

“Our study appears to resolve a 30-year-old controversy about the structure of chromatin fiber,” says Gaurav Arya, PhD, assistant professor of nanoengineering at the University of California, San Diego. The findings, published in the August 11 issue of Proceedings of the National Academy of Sciences, could improve our understanding of cell growth, differentiation, and cancer.

This much is generally accepted: Chromatin starts off as a series of nucleosomes—protein spindles wrapped with about a turn and a half of DNA—connected by stretches of linker DNA; this “beads on a string” structure then folds itself into stiff, compact fibers. What is debated is the interaction and arrangement of nucleosomes within this fiber.

One school of thought favors a spiral arrangement, or solenoid, in which successive nucleosomes interact and are connected with bent DNA linkers. Another school argues that DNA is too stiff to bend easily, and proposes instead a zigzag structure with straight linkers in which alternate nucleosomes interact. Until now, this issue could not be resolved because the available experimental techniques required the chromatin fiber to be unwrapped before it could be studied.

In the new work, researchers first used formaldehyde to create permanent cross-links between interacting nucleosomes. These interactions give rise to loops in the fiber when it is unwrapped under various conditions. Studying these loops under an electron microscope, the researchers found evidence to support the existence of the zigzag structure in the absence of divalent ions such as magnesium; in the presence of such ions, however, a fraction of nucleosomes switch to the solenoid motif.

The researchers then used a computational model developed by New York University researcher Tamar Schlick, PhD, to simulate the structure of chromatin fiber. The model confirmed the experimental results and added additional details: Without divalent ions present, the zigzag fiber packs about 7 nucleosomes per 11nm stretch; with divalent ions, about 20 percent of the linkers in the fiber bend, solenoid-style, and this helps the fiber accommodate about 8 nucleosomes per 11nm.

“Our study appears to resolve a 30-year-old controversy about the structure of chromatin fiber,” says Gaurav Arya.

chromatin fiber structure is.” It’s also a major advance experimentally, she says, because it captures nucleosome interactions under physiological conditions. Further, no other group has been able to come up with a computational model that fits the native structure of chromatin so well, she says.

—By Chandra Shekhar, PhD

**Predicting Cancer Treatment Success**

No two cancer patients respond identically to treatment. Some will be cured while others will see their cancer return, and physicians are at a loss to explain why. Now, using MRI imaging researchers have developed a mathematical model of tumor growth that identifies two factors that are predictive of cervical cancer treatment success: responsiveness to radiation and the ability to clear dead cells.

“This work gives us strategies to find out early on if the tumor does not respond to cancer therapy … and to adjust treatment to increase the chance of cure,” says Nina Mayr, MD, radiation oncologist at Ohio State University and principal investigator of the study. The work was presented at the annual meeting of the American Association of Physicists in Medicine.

Currently, “little is known about the underlying biological mechanisms that govern the tumor response to radiation therapy,” says Zhibin Huang, PhD, a postdoctoral researcher at Ohio State University and lead author of the study. “We wanted to see if this imaging technology could find some early indications of the outcome.”

The research group, headed by Jian Z. Wang, PhD, medical physicist and the director of the Radiation Response Modeling Program at the Ohio State University, followed 80 women with various stages of cervical cancer—with tumors ranging from the size of a cherry to the size of a grapefruit. All of the patients received MRI scans before, during and after radiation therapy—the standard treatment for cervical cancer. With these scans, the researchers could measure the change in tumor volume over the course of the cancer therapy.

The team developed a mathematical model to fit the tumor volume data from the MRI scans and, using this model, identified two factors that correlated with the likelihood of a patient’s cancer returning. The first is the patient’s radiation sensitivity—essentially, the percentage of the cells that survived the radiation dose. The higher this number, the worse the outcome. More specifically,

“This work gives us strategies to find out early on if the tumor does not respond to cancer therapy … and to adjust treatment to increase the chance of cure,” says Nina Mayr.

Ohio State University researchers used magnetic resonance imaging and a mathematical model to predict cancer recurrence. These images show decreasing tumor volume over a 5 week radiation course in a patient who was alive and cancer free 9 years later. Photo Credit: Dr. William Yuh and Dr. Nina Mayr.