FOLLOW THE MONEY:
Big Grants in Biomedical Computing

By Kristin Sainani, PhD

In the current economic climate, every research dollar counts. Fortunately, when it comes to biomedical computing, not everyone has been left counting change. Several big-dollar initiatives received NIH funding in late 2010, including efforts to: map all the connections in the human brain, fight diarrheal diseases with modeling, provide state-of-the-art tools for network biologists, and understand and rewire cellular stress pathways. The projects have implications for a range of human diseases from autism to cancer.

Mapping Brain Connections

In September of 2010, the NIH awarded $40 million dollars for the Human Connectome Project. The effort will create a detailed, searchable map of the neural wiring in the human brain, which is believed to include hundreds of trillions of connections.

"The overarching goal is to use cutting-edge technology to decipher as much as we can about the wiring of the brain in healthy adult humans and to probe the differences in connectivity across a large number of individuals," says **David Van Essen**, **PhD**, professor of anatomy and neurobiology at Washington University in St. Louis.

Van Essen is one of two principal investigators for a nine-institution consortium led by Washington University and the University of Minnesota that will acquire, analyze, and distribute the data. A smaller consortium led by Massachusetts General Hospital and the University of California, Los Angeles, will focus on alternative ways to advance the technology for imaging brain connections.

The WashU/UMinn consortium will scan the brains of 1200 healthy adults (twins and their non-twin siblings) using two types of imaging. MRI diffusion imaging traces the bundles of fibers that structurally link different regions of the brain; and functional MRI (fMRI) reveals which brain areas are linked based on functional interactions. The team will also collect extensive data on genetics and cognitive function.

"We will obtain an enormous amount of data, estimated to be about a petabyte worth," Van Essen says. (A petabyte is one quadrillion, or 10^{15}, bytes.) The data will be made publicly available, along with analysis and visualization tools.

Brain Wiring: Scientists from the human connectome project are using MRI diffusion imaging to visualize the structural connections in the human brain. Image courtesy, www.humanconnectomeproject.org, © 2011 Laboratory of Neuro Imaging at UCLA.

Users will be able to explore average brain connectivity, variation in brain connectivity, and the links between connectivity, cognitive function, and genetics, Van Essen says.

Eventually, they hope that future projects will enable mapping the brains of people with diseases such as autism and schizophrenia, where brain wiring goes awry, he adds.

Modeling Gut Immunity

In October of 2010, Virginia Tech and its collaborators received a $10.6 million grant from the National Institute of Allergy and Infectious Diseases to create and disseminate user-friendly software for modeling gut infections. The models could help scientists develop new drugs and vaccines for diarrheal diseases, a major global health problem.

"The mission of the Center for Modeling Immunity to Enteric Pathogens (MIEP) is to understand the mechanisms of action underlying immune responses to enteric [intestinal] pathogens," says principal investigator **Josep Bassaganya-Riera**, **PhD**, an associate professor at the Virginia Bioinformatics Institute and director of the Nutritional Immunology and Molecular Medicine Laboratory.

MIEP will design and freely distribute models and modeling tools that can be used by immunologists and infectious disease experts with minimal training, Bassaganya-Riera says. "We do not want to design models that will only be utilized by computer scientists. I think that would be a failure." The tools, COPASI (Complex Pathway Simulator) and ENISI (ENteric Immunity SImulator), will simulate specific immune responses in the gut mucosa as well as basic immunological processes, such as T cell differentiation.

Once developed, Bassaganya-Riera's team will run *in silico* experiments—such as infecting a virtual gut with diarrhea-causing *Escherichia coli* and testing various therapeutic agents. Gut pathogens

cause the immune system to overreact, leading to excessive inflammation; so Bassaganya-Riera's group is looking for drugs that can help calm this response.

The tools could eventually be extended to model chronic diseases that also involve inflammation, including obesity, diabetes, cancer, and cardiovascular disease, he says.

Supporting Network Biology

In October of 2010, The University of California, San Diego (UCSD), received a $6.5 million grant for a new resource center for network biologists. Genes and proteins work together in circuits and pathways; and it's

their popular open-source package for network biology—in a variety of novel ways. For example, they are developing a module that allows Cytoscape to hunt for bio-

Rewiring Stress Pathways

The NIH also awarded a pair of $15.4 million grants to create two new National Centers for Systems Biology, one at UCSD

> "There are quite a few centers supporting things like proteomics and genomics," Ideker says. "But, until now, there were no centers that supported network biology."

markers in patient data. "Unlike other efforts we're not going to treat biomarkers as individual proteins or genes. We're treating biomarkers as networks," Ideker

and one at UCSF. UCSD researchers will explore the signaling pathways that cells use to respond and adapt to stress, such as DNA damage; and UCSF researchers will try to rewire these signaling pathways to engineer custom cells for use in medicine and biotechnology.

"Mapping out stress responses is important because there's a growing realization in biology and medicine that so many different aspects of disease and aging are interlinked by how the cell responds to stress," says Ideker, who is involved in the UCSD effort, led by principal investigator **Alexander Hoffman**, **PhD**. "We need a global model that links all these disease pathways together."

Cytoscape and other network biology tools developed by UCSD's National Resource for Network Biology center will play a critical role in helping the team to work out these stress pathways, Ideker says.

Once scientists understand the circuits that the cell uses to respond to stress, then they might be able to manipulate these circuits to "soup up" the cell's response. This is where researchers at the UCSF center, led by principal investigator **Wendell A. Lim**, **PhD**, step in. They hope to engineer synthetic circuits for therapeutic uses. For example, it might be possible to design a cell to detect and precisely kill cancer cells. □
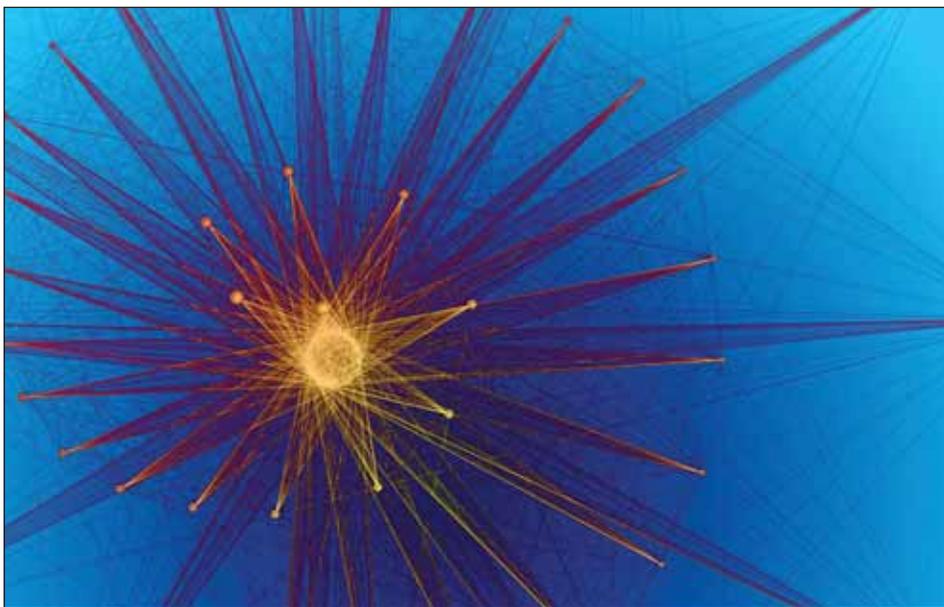
Network Biology in Action: *Picture generated by Cytoscape, a tool that network biologists can use to visualize complex molecular circuits and pathways. Courtesy of: Vuk Pavlovic and Benjamin Elliott, the University of Toronto.*

these pathways that are perturbed in complex diseases, says principal investigator **Trey G. Ideker**, **PhD**.

"Lots and lots of data are now being produced mapping networks inside of cells," says Ideker, professor of medicine and bioengineering and chief of the division of genetics in the School of Medicine. The new center, funded by the National Center for Research Resources, will create tools for NIH-funded scientists to analyze and visualize these data. "There are quite a few centers supporting things like proteomics and genomics. But, until now, there were no centers that supported network biology. So that's our goal," he says.

Ideker's team will expand Cytoscape—

says. "The diagnostic of the future is going to say that some circuit or pathway module has gone awry."

Links to the projects:

- The Human Connectome Project: http://www.humanconnectomeproject.org/

- The Research Center for Modeling Immunity to Enteric Pathogens (MEIP): http://modelingimmunity.vbi.vt.edu/

- National Resource for Network Biology: http://www.nrnb.org/

- National Centers for Systems Biology: http://www.systemscenters.org/

- UCSF Center: http://systemsbiology.ucsf.edu/

- UCSD Center: http://sdcsb.org/