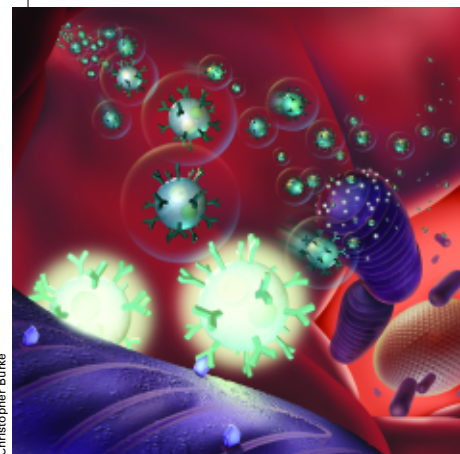


Researchers Launch Ambitious Exploration of Inner Space

A collaborative effort of University of Michigan researchers will attempt to capture never-before-seen views of the chemical activity inside living cells in real time and 3-D. The three-year project brings together public health, engineering, chemistry, biology, physics, and statistics faculty with support from a \$1.5 million grant from the W.M. Keck Foundation in Los Angeles and \$500,000 from UM.



Christopher Burke

“The applications for this kind of technology are going to be as wild as the imagination of the people we are training in our labs,” says Martin Philbert, associate professor of toxicology in the School of Public Health, and project co-leader.

The UM team will be using synthetic nanoprobes small enough to fit inside a cell without interrupting its normal functions to measure the activity of metal ions like zinc and copper as the cell works. Sophisticated statistical modeling programs will be used to interpret data that looks something like a swarm of fast-moving fruit flies zinging around a bowl of fruit.

Trafficking metal ions in and out of the cell is crucial to basic functions like muscle contraction and the nervous system. But science has

been unable to measure this dynamic process in real time.

The study will look for patterns in the motion of ions to determine when and how individual molecules in swarms might trigger the cell to act in a certain way at a particular time. Biochemists in the group will provide proteins that bind specifically to zinc and copper ions to help the nanoprobes do their work.

“Simulations are being used to figure how and where to deliver the probes to the cell,” says Ann Marie Sastry, project co-leader, and associate professor of mechanical and biomedical engineering. “A supercomputer crunches through millions of different scenarios to help the scientists later determine which actions were random, and which had meaning. If we don’t do this we have no way of interpreting the richness of data provided by the probes.”

“In this project, the biochemists are the device guys and we engineers are the hypothesis-testers,” Sastry adds. “It’s usually the other way around.”

“We’re creating a seamless connection between analytical chemistry,

Biologists have long known that ions like calcium, zinc, sodium, potassium, and copper are critical to cell function, but they’ve never been able to see the individual buying and selling of ions that each cell does.

experimental cell biology, and these mathematical models,” Philbert explains. “For the first time, we have a real shot at looking at the function of the low-abundance metal ions that we know are so critical for cell function.”

Biologists have long known that ions like calcium, zinc, sodium, potassium, and copper are critical to cell function, but they’ve never been able to see the individual buying and

selling of ions that each cell does, nor where those ions go inside the cell. In fact, an enormous amount of the literature on cell function concerns the mere presence or absence of an ion, or its average abundance. But that’s like a two-dimensional snapshot in time, not the dynamic, three-dimensional process that actually occurs.

Zinc ions are one of the targets of this study because they are known to be important players in many neurological diseases and conditions, including Alzheimer’s and brain injuries, but they are notoriously difficult to measure.

The nanoprobes that will help make these measurements were developed by Philbert and Raoul Kopelman, the Kasimir Fajans Collegiate Professor of Chemistry, Physics and Applied Physics. They can be made from a variety of synthetic materials, including plastics, and tailored for a variety of uses, including exploding on cue as a smart-bomb against individual cancer



PHILBERT

cells. Kopelman and Philbert call them PEBBLEs, or Probes Encapsulated By Biologically Localized Embedding. The probes—which are as small as 20 nanometers—can be made to emit light when an ion, such as zinc, binds to a specific site within the sensor.

To get some sense of how small these probes are, if the cell were the size of a football stadium, the

PEBBLE would be about the size of an offensive lineman. So it and thousands of its colleagues are able to move around without disturbing the cell too much.

Each of the technologies being applied to this project has developed a pretty good track record on its own. But by bringing them together in a new way, this approach to cell-by-cell diagnostics should be able to see healthy and diseased cells in action and determine how they operate differently from one another.

“Only by combining several fields of science can this exploration even be attempted,” says UM President Mary Sue Coleman. “This is an innovative, cross-cutting, collaborative project that represents the best of what the University of Michigan has to offer.” She notes that four deans—engineering, public health, medicine, and literature, science, and the art—and the provost’s office provided support for the Keck Foundation grant.

The W. M. Keck Foundation was established in 1954 by William Myron Keck, founder of The Superior Oil Company. The foundation’s grant-making is focused primarily on the areas of science, engineering, medical research and higher education. ■