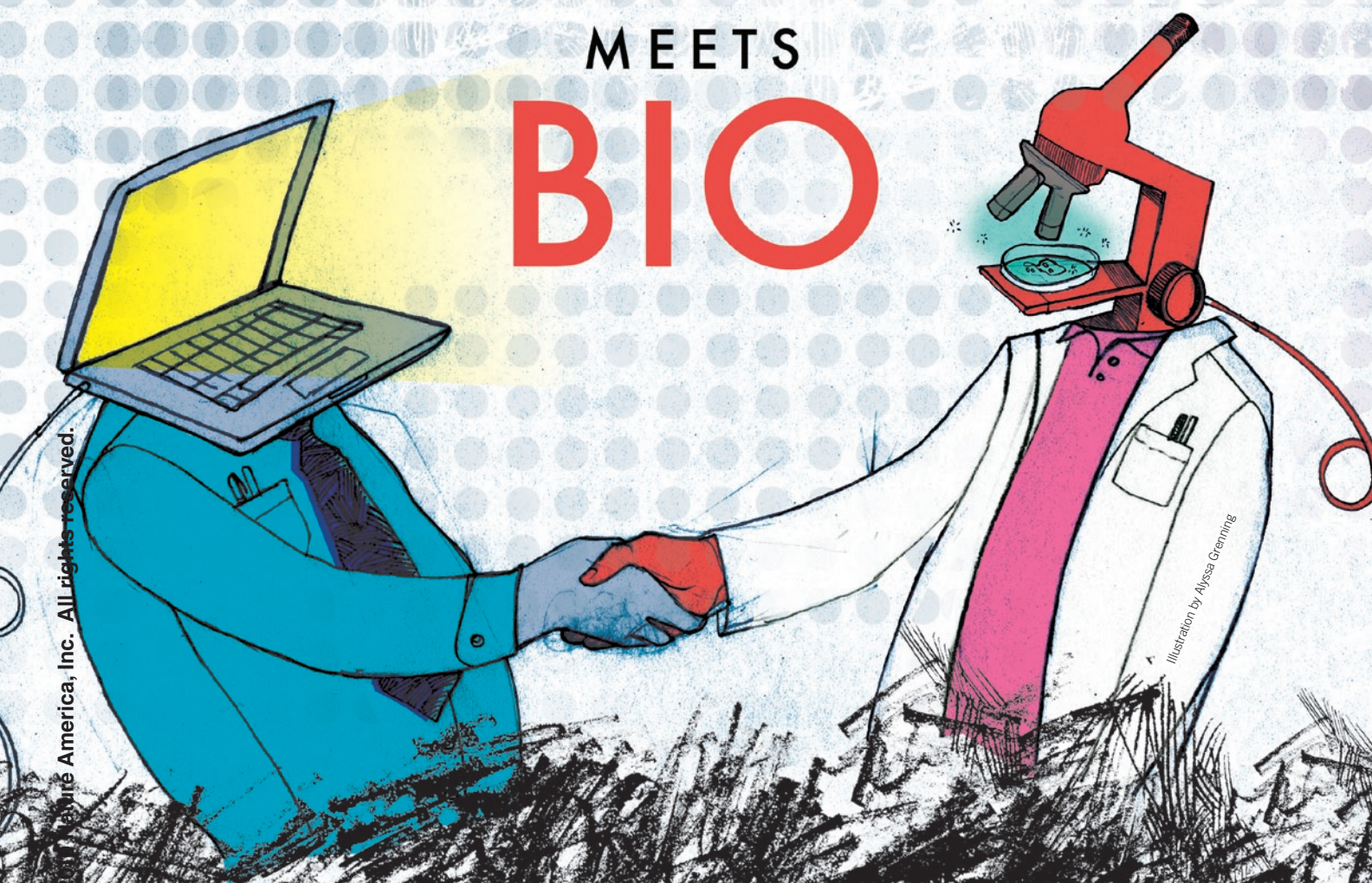


TECH MEETS BIO



IBM computers and Microsoft software have been mainstays of biomedical studies for years. But, in the past decade, software and technology companies have increasingly been taking a more active role in biological research. **Monica Heger** profiles four of the movers and shakers who have been leading the charge.

Roni Zeiger:

Doing medicine, not evil

There's a doctor in the house at Google, but he's not treating sick employees. Roni Zeiger is chief health strategist at the Mountain View, California-based search giant, where he works to improve Google's medical-related search queries and has helped develop Google Health, which stores patients' personal health records, and Google Flu Trends, which models

and estimates current flu activity on the basis of internet searches.

After obtaining his medical degree from California's Stanford University in 1999, completing an internal medicine residency program at the University of California-San Francisco and practicing medicine for two years, Zeiger decided that treating one patient at a time was not making the large impact on global health that he wanted.

Convinced that opportunities abounded at the intersection of computing and health, he earned a master's degree in biomedical informatics from Stanford in 2006. The same year, he began working at Google, just as the company was starting to move into the health field.

As a medical student and resident, Zeiger had developed software for physicians to help

them make more informed, evidence-based decisions about patient care. For example, he used data from the long-running Framingham Heart Study to create a tool called 'Heart to Heart' that assesses people's risk of coronary heart disease (*Prev. Cardiol.* 7, 26-33, 2004). At Google, Zeiger saw opportunities to create similar software to enable patients to be more involved with their own health care. For instance, Google Health keeps track of the medications a person is taking and will alert the user if any drugs are known to adversely interact with each other.

Four years on, Zeiger feels vindicated by his career move. "More [people] ask health questions at Google than any other source. So it's a tremendous responsibility and opportunity to make a big impact," says Zeiger, now 39 years

old, who still sees patients some weekends at a local urgent care clinic.

Yet even for a company like Google, which prides itself on thinking outside the box, branching out from its core business model was no small feat. At first, Google Health faced strong resistance from the company's leadership because the online medical portal was seen as "too conventional," says the initiative's founder Adam Bosworth, who hired Zeiger before leaving Google in 2007 to start Keas, a medical informatics company in San Francisco. But Zeiger "did the right thing," Bosworth says. "He basically moved Google Health toward the interest of the company, which is 'what can we learn from what people do and are looking for?'"

Google Flu Trends is a perfect example of how the company has turned what people are already searching for into a useful tool. By just aggregating flu-related search terms such as 'aches' and 'fever', Google's data has a 92% correlation with corresponding data from the US Centers for Disease Control, and the search giant can produce results up to two weeks faster than the government agency, according to company estimates.

"If you think about how hard public health experts work to track flu and other diseases, it's a pretty sophisticated and complicated science," says Zeiger, who was actually skeptical of the original idea. But the problem turned out to be more of an engineering challenge than an epidemiological one—making it uniquely suited for a company like Google to tackle.

Zeiger also seems to be uniquely suited to Google, according to a former graduate supervisor. "He has a real understanding of the way humans use computer systems and how those systems can be greatly improved to work more closely with the way humans think and interact," says Mary Goldstein, a health services researcher at the VA Palo Alto Health Care System in California. "He has a lot of insight into the needs of real human beings, combined with a knowledge of what computers can do."

Michael Montalto: Imaging at work

In 2002, after finishing a postdoc studying cardiovascular drug discovery at Harvard Medical School in Boston, Michael Montalto



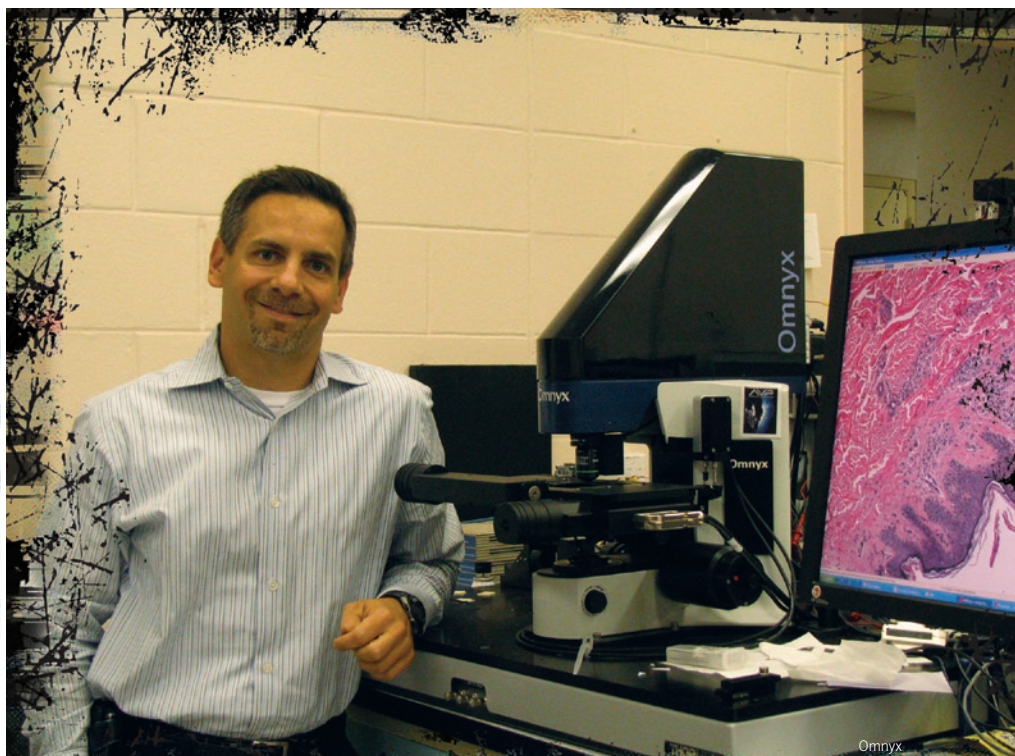
Corrie Connors

was working as an entry-level instructor at the school when he saw a job posting for a biologist at General Electric (GE). He applied and was called in for an interview. "I met with tons of people," he recalls, "and they said they wanted me to get into molecular medicine and biology research." But, that was about all the direction they gave him.

Drawn by the opportunity to build GE's biology research from the ground up (plus the

fact that the job was based out of Niskayuna, his hometown in upstate New York), Montalto took the post. On his first day, Montalto asked to see the labs. Down a mostly deserted corridor, he found an old chemistry lab that looked as if it hadn't been used in years—a relic from another era, it contained a fume hood, but that was essentially it.

Montalto's total budget for outfitting the lab was a mere \$30,000. So, to equip the lab, "we



Omnyx

looked for used centrifuges, used everything,” he says. “We rummaged the whole research center for anything we could find.” It was a humble beginning; yet even with his shoestring budget, many of the programs started by the 39-year-old Montalto continue today.

From the start, Montalto’s overarching goal was to combine GE’s expertise in imaging technology with biomedical research. His first project focused on Alzheimer’s disease, searching for molecules that could bind to beta-amyloid, a protein that builds up in the brains of people with Alzheimer’s and is an early indicator of the disease. In 2005, for example, Montalto and his team developed a proof-of-principle model that used imaging technology to trace the molecule as it responded to treatment (*Mol. Imaging Biol.* 7, 69–77, 2005).

“It was a very difficult project,” says Nadeem Ishaque, an engineer at GE who was responsible for hiring Montalto. But “he was very energized. He could infect people around him with his enthusiasm.”

These kinds of successes helped convince the GE leadership to continue investing in the fledgling biology unit. But Montalto’s main challenge remained convincing other biologists to come work at GE. Summing

“I had to explain to them why biology matters and why proteins matter.”

up the general response he got from recruits, Montalto titled his first entry on the company’s blog, “Biology...at GE?” “In the beginning, it was tough,” he admits. But the situation improved, and GE now boasts 80 scientists in its biosciences division in Niskayuna, with scientists from other divisions, such as the imaging and computing and decision sciences divisions, frequently collaborating on biomedical projects.

These days, Montalto is pushing the envelope in new ways. He helped extend GE into the field of pathology and has used imaging technology to discover biomarkers to predict colon cancer prognosis (*Clin. Cancer Res.* 14, 3814–3822, 2008). Two years ago, he also helped spin off a new company called Omnyx, a joint venture between GE Healthcare and the University of Pittsburgh Medical Center, focused on digitizing pathology products.

With this new startup, Montalto, Omnyx’s head of research and instrument development, has again found himself engaged in a company where biology often takes a back seat to engineering and technology. But, according to Omnyx’s chief executive Gene Cartwright, Montalto has made it work through extensive collaborations with researchers at 13 academic medical centers spread across three continents. “He’s a hard worker, a clear thinker, and he can communicate his ideas well,” Cartwright says.

Ajay Royyuru: International biology machine

Sheer stubbornness is how Ajay Royyuru began his 12-years-and-counting tenure at IBM. Early in his academic career as a molecular biologist—some 20 years ago, well before ‘computational biology’ entered the scientific lexicon—Royyuru began using computation to solve biological questions. At the time, he had no clue that he was on the cusp of a new field of biology. “It was just something I was interested in,” he says. “I was somewhat pigheaded.”

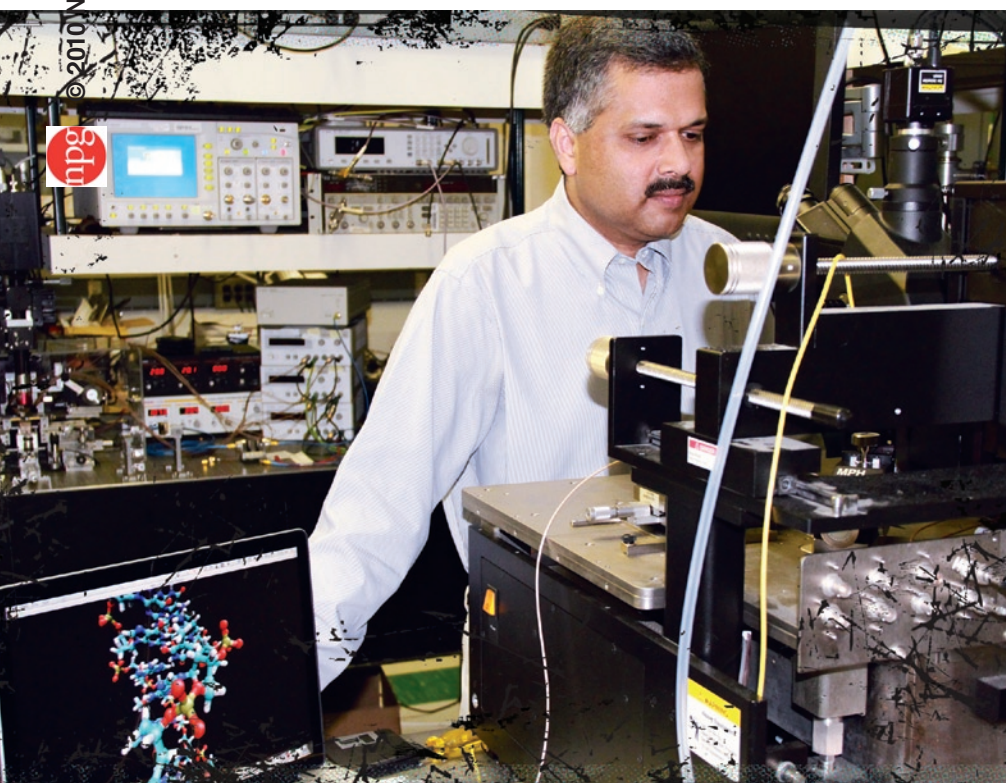
Royyuru, 46, taught himself how to program computers and think algorithmically while earning his PhD in molecular biology from the Tata Institute of Fundamental Research in Mumbai in 1993. He then came to New York’s Memorial Sloan-Kettering Cancer Center to study the structures of antitumor molecules, and in 1998 he joined IBM’s Thomas J. Watson Research Center in Yorktown Heights, New York.

For his first project, Royyuru set out trying to predict how proteins fold. The scale of the problem was enormous. After first building Tinkertoy-like models from blocks and string, Royyuru turned to computers. The only problem was that he needed around a petaflop of computing power, which was about 500 times faster than the most powerful computer of the time.

IBM’s then director of research Paul Horn was an early believer that the problem could be overcome. “The work [Royyuru] was doing was truly leading,” he says. Horn pointed Royyuru to computer engineers at IBM who were building new and improved supercomputers, but it wasn’t an easy sell to convince the engineers that deciphering protein structures was the best use of their resources.

“I had to explain to them why biology matters and why proteins matter,” recalls Royyuru. He told them that being able to predict how proteins fold would have implications for many diseases, including Alzheimer’s and cystic fibrosis, both of which result from misfolded proteins.

Eventually, Royyuru and his colleagues launched the Blue Gene project, which still exists today. Originally a supercomputer



Chuck Treppada

designed to understand protein structure and the dynamics of protein folding, it is now being used in a number of applications such as climate modeling, molecular dynamics and quantum chemistry.

Royyuru, now senior manager of computational biology at the company, continued to bend the mold when he convinced IBM to get involved in the Genographic Project. The project, launched in 2005, involves taking DNA samples from volunteers—something unheard of for IBM—and using the genetic information to reconstruct the history of human migration. In July, Royyuru also helped spearhead a partnership between IBM and the Swiss pharma giant Roche to build a new type of machine to sequence DNA with nano-sized, single molecule-based technology.

Gustavo Stolovitzsky, manager of functional genomics and systems biology at IBM, who started at IBM around the same time as Royyuru, says Royyuru's ability to listen and quickly come up with solutions to problems helps make him so successful at convincing management to back his ideas. "He will rapidly extract the basic elements of the conversation, zoom in on what are the bottlenecks and come to a solution that is intuitive but also out of the box," he says.



him that computational methods were needed to truly understand what the brain actually does. And he thought the same held true for understanding other complex systems.

It took two years for Emmott to double the size of his division by hiring one additional scientist, in 2006. But the lab has taken off since then. Microsoft Research's British offices now employ around 40 computational scientists, with 11 in the biology division conducting research in fields such as immunology and stem cell biology. Another 1,000 scientists—not all of whom are biologists—work for Microsoft Research worldwide.

Emmott's lab is building computational models that aim to better understand how the immune system responds to infection. The group is currently studying the molecule tapasin, which acts as a mediator between two key components of the immune system: the major histocompatibility complex and a protein called transporter associated with antigen processing. Already, in unpublished work, his team has made advances in predicting various immune system responses to HIV.

True to Microsoft's remit, Emmott, 50, likens the human body to an information processing device. "Thinking about it in terms of what the system in every cell computes, rather than just how the parts are associated with each other, is going to be essential," He says. For instance, his team modeled in four-

dimensional detail how the pancreas develops from precursor stem cells (*Proc. Natl. Acad. Sci. USA* **105**, 20374–20379, 2008).

Emmott's view of thinking about biology as a computational problem was not an easy sell at Microsoft. "The culture here is not based on biology," says Andrew Blake, a senior research scientist at Cambridge's Microsoft Research center. "Early on, he faced some skepticism."

Blake is not sure exactly what triggered the company to get on board with Emmott's vision but says it came gradually with the support of a few key people within the company. Craig Mundie, chief research and strategy officer,

was an early proponent of Emmott's ideas, as was Andrew Herbert, the managing director of research at Microsoft's Cambridge office.

Emmott "talked with great passion about how computing was moving from just being a service into having a great impact on fundamental life sciences research," says Herbert, one of the people responsible for hiring Emmott. "I found that a fascinating proposition."

To this day, Emmott continues to call for a radical rethink of the way science is done. "All our advances in stem cell research, cancer and aging will fundamentally rest, I believe, on taking a new view of what biology does," he says.

Monica Heger is a freelance writer based in Brooklyn, New York.

Stephen Emmott: Tech passion, bio potential

At the end of 2003, the executives at the software giant Microsoft phoned up neuroscientist Stephen Emmott and asked him if he wanted to join the company to, in Emmott's words, "figure out what it should do in science." After that initial, if rather vague, proposition, Emmott who had settled into academia at University College London after several years as director of advanced research at the Georgia-based IT company NCR, left to become the first life scientist at Microsoft Research in Cambridge, UK.

Emmott, now head of computational science at Microsoft Research, says he accepted the company's offer because he saw an opportunity to transform the way science is done. In his own research in neuroscience, it became clear to

"All our advances in stem cell research, cancer and aging will fundamentally rest, I believe, on taking a new view of what biology does."