Genomics Giant

George Church is a confessed computational science junkie whose sequencing advances have driven the field forward since even before the HGP

By Meredith W. Salisbury

George Church has been fascinated with computers practically since he was old enough to pronounce the word. By the age of 10, he was trying to find ways to link biology to the machines. He even built his own: analog computers, mechanical computers, and some digital circuits.

So it’s no great surprise that by the time Florida-native Church landed at Duke University for his undergraduate years, he was still trying to find a connection between his two passions, science and computing. Sophomore year, he lucked out when he stumbled across Sung-Hou Kim, who was working with crystallography and 3D structural software. “That was probably the first really great [connection],” he recalls.

Church’s familiarity with computers eventually earned him a reputation. David Botstein, now director of the Lewis-Sigler Institute for Integrative Genomics at Princeton University, remembers meeting him for the first time in Wally Gilbert’s Harvard lab. “George was running around with a TRS-80, one of the very first computers that you could carry around, from Radio Shack. He was one of the first completely computer-literate graduates in biology,” says Botstein, who describes Church as “obviously brilliant.”

Tackling that challenge — linking the new computing technology to biology — is characteristic of Church, 48, who now directs the computational genetics center at Harvard Medical School, where he continues to pursue new challenges. A giant in the industry (at 6’5” with a bushy beard, he certainly looks the part), Church was involved in the earliest large-scale sequencing efforts, helped launch the Human Genome Project, and is now stumping for cost reductions so drastic that anyone could get his genome sequenced.

ATTACK ON SEQUENCING

Though crystallography had Church intrigued, it was working with Wally Gilbert that altered the trajectory of his career. Gilbert introduced the concept of sequencing to Church, who thought if it could be automated and truly comprehensive, it would be just what he’d been looking for. “I attacked that like nobody’s business,” he says. Naturally, he turned to computers and “wrote one of the first automated DNA sequencing programs” in 1978. “But everyone said, ‘Why are you doing that? That’s the one part of sequencing that’s fun.’ So I put that on the back burner.”

In the early ’80s, Church invested himself in a multiplexed genome sequencing technology that, while promising, was eventually eclipsed by the automated DNA sequencers that would come from Applied Biosystems a few years later. He still refers to the idea as his “real love” — only now it is coming back into vogue as the basis of the polony technique he developed with Rob Mitra and presented at last year’s Genome Sequencing and Analysis Conference.

Though the sequencing technology stayed on the back burner, Church himself was coming to the forefront of the genomics field. He remembers the scathing letters people wrote to scientific journals at the time criticizing “this new human genome project” that some people were talking about. Their main argument — “that 98 percent of the genome did not code for proteins, and why sequence that?” — didn’t sway Church, who had just finished his thesis work on two introns. The regions, known as “the ultimate in junk DNA,” he says, “were just full of interesting biological functions.” So Church joined the proponents, went to the planning meetings in Alta, Santa Cruz, and Santa Fe, and even wound up with what may be the earliest genome project grant, a 1987 award from the DOE that continues to help fund Church’s lab to this day.

Church went on a speedy postdoc rotating through posts at Biogen, MIT, and the University of California, San Francisco, before settling in at Harvard Med in 1986. His lab pounced on genomics and proteomics work, doing “one of the first large proteomics studies where we used sequence tags,” he says.

Meanwhile, Church’s early expertise in sequencing was being tapped heavily by the nascent genome project as the first 1990 grants were funded. He worked to get genome centers up and running at Stanford, MIT, and the Waltham lab that would become part of Genome Therapeutics. “I knew that I wasn’t ready at that time for my own lab to be a production lab,” he says. “But I was excited about getting them going, it was a blast.”
As it turned out, his lab never became a production lab, making him a respected nonpartisan in the public/private race. "Nature asked me to write a paper comparing the two genome sequences. This was a very delicate thing, and I wasn't too keen on doing it," he says. "I was talking to Eric and Craig leading up to that. I was probably one of the few people talking to both of them on a regular basis," he laughs.

GENOMES FOR ALL

Since its original focus on genomics and proteomics, Church's lab has morphed into computational and systems biology. From the very beginning of the genome movement, Church has seen the target as cheap genome sequences available to everyone.

He has been interested in affecting human health for quite some time and, during college, volunteered to be "a guinea pig in a nutritional study. ... I wanted to learn more about clinical studies," and the best way I could get close to it was to be on the other side of the table." For some three months, Church subsisted on a diet of drinks made of powdered amino acids with virtually no leucine, an effort to study nutrition problems in Sri Lanka. "They paid for my food, which turned out not to be such a gift," he jokes.

For today's healthcare, Church is a firm believer that genome sequencing should become an integral part of any doctor's arsenal. One of his research projects could actually bring that closer to fruition: polonies, or DNA colonies where PCR is done in situ, are a tool that could be used for genotyping, sequencing, haplotyping, and more.

Church mentioned the project to Craig Venter, who asked him to present it at a 2002 GSAC panel optimistically titled "the $1,000 genome." "He was starting to think about personal sequencing, but I had been my dream for years," Church says.

As for the $1,000 price tag, "I don't think that's a pipe dream," says Church, comparing the use of this technology to how rapidly and unexpectedly the Internet caught on. "I think that could be shockingly soon."

But that's not the be-all and end-all of genomics, if you ask Church, who makes a habit of looking further into the future than most people, in part through his capacity to learn from all disciplines. "I can have a detailed conversation about some aspect of electromagnetic waves [with him]," says Mitra, an electrical engineer by training. "It's impossible to tell that he's not an electrical engineer as well. And it's the same with microbiology. His knowledge about every field is so deep."

Functional and comparative genomics will be the first, most powerful uses of the data, Church says, emphasizing the importance of doing studies with, for instance, several primates—despite naysayers' argument that it wouldn't make a cost-effective project. He also predicts that genomics will be critical for environmental surveillance: looking for emerging diseases, introduction of new species, and migration of infectious agents. "It's amazing when winter comes and we all get the sniffles how little we know about that," he says. One day, Church envisions turning on the news and seeing something like a weather map that, using genomic data, tracks the spread of certain colds or other germs.

"I see it as much broader than just getting a personal genome sequence," he says. "If you have a really low-cost genomics platform, you could do all these things."
WASH U SNAGS MITRA AND HIS POLONIES

ROB MITRA calls himself a "card-carrying electrical engineer," so it may seem a tad odd that his work is piquing the interest of genomic scientists. But for Mitra, it's just a natural extension of his engineering days.

Armed with two degrees in electrical engineering, Mitra was working on his PhD in the same subject at MIT. His master's work had entailed "testing steel roller bearings," he says. "While the work went well, I found it pretty unsatisfying at the end of the day." So over the summer, he volunteered at a hospital to make more of an impact in people's lives. Afterward, he decided to take a freshman biology class — and wound up with ERIC LANDER as a professor. "I just really thought biology was going through a revolution," Mitra recalls.

He stuck with engineering, looking for biology advisors. But in the days before microarrays came on the scene, he says, "it wasn't so hip to be an engineer and into biology. I talked to a lot of professors and they didn't want to give me a job because I had never picked up a pipette."

Mitra wound up working for the Palo Alto Institute for Molecular Medicine, a nonprofit lab, for two and a half years before returning to MIT. His thesis committee steered him to GEORGE CHURCH's lab, where he got into PCR colony research. "People would spend a week thinking about it and then they'd quit," Church says of the project he had tried to start before. "When Rob came ... he had the engineering mindset that it didn't have to be fascinating biology right away for it to be interesting."

The PCR colony research became known as polonies, a technology that could be used for genotyping, sequencing, haplotyping, and finding alternate splice variants. Mitra, 32, is still heavily involved in polony work and, to some extent, it dictated his move after MIT. Just a few months ago, Mitra headed to Washington University to start his own lab — soon to become part of the sequencing center there — where polonies will get plenty of attention. He seriously considered taking a job in industry, but figured he would have to give up his polony work if he did so, "I like the independence of academics," he says. "The polony technology is just in its infancy and I think it needs more people and more labs to develop it."

WITH WILLIS IN LEAD, PARALELE COMES OUT OF SILENT MODE

Until last year, the people at ParAllele BioScience worked away with almost no industry attention. But ever since TOM WILLIS's company, a spinout from RON DAVIS's Stanford genome center, won an NHGRI grant to work on the HapMap, its name seems to be everywhere.

Willis comes from a physics background ("We call ourselves recovering physicists," he jokes), and he got drawn into genomics after reading about it in scientific journals. "Genomics and the biology in general was making a transition from really smart people doing very clever experiments with pretty stable technology to a mode in which physics has been for a long time," he says.

Gregory Sullivan, previously medical director of the Longevity Institute, joins Genomics Collaborative as director of business development and sales.

Venture capital firm Tullis-Dickerson announces that Curt LaBelle, who has worked at biotech and pharma companies, joins as senior associate on the healthcare investors team.

Deltagen CEO William Matthews resigns. Chairman Constantine Anagnostopoulos will manage the firm until a replacement can be found.

TGen, Arizona's Translational Genomics Research Institute, goes on a hiring spree: Dietrich Stephan will be director of the neurogenomics program; Edward Suh will be CIO of the computational bioscience center; and Michael Berens will be VP of research for the institute.

Maverick Kary Mullis joins the scientific advisory board for Madison, Wis.-based optical mapping company OpGen.

The National Disease Research Interchange expects to name the Whitehead's Eric Lander as scientist of the year.

Talk about parties: To celebrate the 50th anniversary of the double helix discovery, James Watson and 1,000 of his friends got together for an invitation-only black-tie dinner at New York's Waldorf Astoria hotel.