Prof. Stephen Quake

Lecture Title: *Precision Measurements in Biology: Transforming biology to a truly quantitative and mathematical science.*

Is biology a quantitative science like physics? I will discuss the role of precision measurement in both physics and biology, and argue that in fact both fields can be tied together by the use and consequences of precision measurement.

The elementary quanta of biology are twofold: the macromolecule and the cell. Cells are the fundamental unit of life, and macromolecules are the fundamental elements of the cell. I will describe how precision measurements have been used to explore the basic properties of these quanta, and more generally how the quest for higher precision almost inevitably leads to the development of new technologies, which in turn catalyze further scientific discovery. In the 21st century, there are no remaining experimental barriers to biology becoming a truly quantitative and mathematical science.

Scientific achievements

Stephen Quake invented the biological equivalent of the integrated circuit. He and his students developed the first microfluidic large scale integration (LSI) by fabricating chips with thousands of mechanical valves. This technology paved the way for large scale automation of biology at the nanoliter scale, and in recent years Quake and his collaborators have used it for applications as diverse as discovering a new drug for hepatitis C, mapping the genomes of unculturable environmental microbes, and measuring gene expression in individual cancer stem cells.

Quake's group was the first to apply microfluidic technology to the determination of protein structure through x-ray crystallography. By showing that the unique fluid physics of nanoliter scale reactors allow one to control and manipulate the kinetics of protein growth in ways that are impossible at the macroscale, they developed a chip to screen protein crystal growth conditions that outperforms conventional methods by an impressive margin. This chip has been commercialized and is used in structural biology labs in industry and academia around the world.

Quake used microfluidic plumbing to create combinatoric arrays of assays that give unique economies of scale in labor and reagent consumption; these dynamic arrays have also been commercialized and are used by major pharmaceutical companies and research organizations for applications ranging from managing salmon fisheries to studying cancer.

Quake also demonstrated the first successful single molecule DNA sequencing technology, which has been commercially developed and is a leading candidate to deliver the first $1,000 genome. In 2009 he and two co-workers sequenced his genome using the commercial version of the single molecule sequencing technology that he developed, an event that was widely reported in the popular press. He is one of the first half dozen people to have their entire genome sequenced and the only one to also have invented the sequencer used to obtain their genome.

His contributions to genomics also include the development of the first non-invasive prenatal test for Down syndrome, which was enabled by next generation sequencing technologies, and the first measurement of the immune repertoire of an organism.

Selected Publications

1-15

1. Ashley EA, Butte AJ, Wheeler MT, Chen R, Klein TE, Dewey FE, Dudley JT, Ormond KE, Pavlovic A, Morgan AA, Pushkarev D, Neff NF, Hudgins L, Gong L, Hodges LM, Berlin DS, Thorn CF, Sangkuhl K, Hebert JM, Woon M, Sagreiya H, Whaley R, Knowles JW, Chou MF, Thakuria JV, Rosenbaum AM, Zaranek AW, Church GM, Greely HT, Quake SR, Altman RB. Clinical assessment incorporating a personal genome. *Lancet.*375(9725):1525-1535.
2. Maerkl SJ, Quake SR. Experimental determination of the evolvability of a transcription factor. *Proc Natl Acad Sci U S A.* 2009;106(44):18650-18655.
3. Pushkarev D, Neff NF, Quake SR. Single-molecule sequencing of an individual human genome. *Nat Biotechnol.* 2009;27(9):847-852.
4. Weinstein JA, Jiang N, White RA, 3rd, Fisher DS, Quake SR. High-throughput sequencing of the zebrafish antibody repertoire. *Science.* 2009;324(5928):807-810.
5. Wu AR, Hiatt JB, Lu R, Attema JL, Lobo NA, Weissman IL, Clarke MF, Quake SR. Automated microfluidic chromatin immunoprecipitation from 2,000 cells. *Lab Chip.* 2009;9(10):1365-1370.
6. Fan HC, Blumenfeld YJ, El-Sayed YY, Chueh J, Quake SR. Microfluidic digital PCR enables rapid prenatal diagnosis of fetal aneuploidy. *Am J Obstet Gynecol.* 2009;200(5):543 e541-547.
7. Diehn M, Cho RW, Lobo NA, Kalisky T, Dorie MJ, Kulp AN, Qian D, Lam JS, Ailles LE, Wong M, Joshua B, Kaplan MJ, Wapnir I, Dirbas FM, Somlo G, Garberoglio C, Paz B, Shen J, Lau SK, Quake SR, Brown JM, Weissman IL, Clarke MF. Association of reactive oxygen species levels and radioresistance in cancer stem cells. *Nature.* 2009;458(7239):780-783.
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10. Harris TD, Buzby PR, Babcock H, Beer E, Bowers J, Braslavsky I, Causey M, Colonell J, Dimeo J, Efcavitch JW, Giladi E, Gill J, Healy J, Jarosz M, Lapen D, Moulton K, Quake SR, Steinmann K, Thayer E, Tyurina A, Ward R, Weiss H, Xie Z. Single-molecule DNA sequencing of a viral genome. *Science.* 2008;320(5872):106-109.
11. Zhong JF, Chen Y, Marcus JS, Scherer A, Quake SR, Taylor CR, Weiner LP. A microfluidic processor for gene expression profiling of single human embryonic stem cells. *Lab Chip.* 2008;8(1):68-74.
12. Marcy Y, Ouverney C, Bik EM, Losekann T, Ivanova N, Martin HG, Szeto E, Platt D, Hugenholtz P, Relman DA, Quake SR. Dissecting biological "dark matter" with single-cell genetic analysis of rare and uncultivated TM7 microbes from the human mouth. *Proc Natl Acad Sci U S A.* 2007;104(29):11889-11894.
13. Ottesen EA, Hong JW, Quake SR, Leadbetter JR. Microfluidic digital PCR enables multigene analysis of individual environmental bacteria. *Science.* 2006;314(5804):1464-1467.
14. Lee CC, Sui G, Elizarov A, Shu CJ, Shin YS, Dooley AN, Huang J, Daridon A, Wyatt P, Stout D, Kolb HC, Witte ON, Satyamurthy N, Heath JR, Phelps ME, Quake SR, Tseng HR. Multistep synthesis of a radiolabeled imaging probe using integrated microfluidics. *Science.* 2005;310(5755):1793-1796.
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