Technological Innovation Leads to Fundamental Understanding in Cell Biology

David Botstein

The science of cell biology began in the seventeenth century with the discovery of cells by Hooke and van Leuwenhoek. This discovery came shortly after, and indeed it required, one of the most important single technological innovations in seventeenth century physical science, namely, the development of practical vision-enhancing instruments based on the refractive properties of glass. The development of telescopes drove discovery and understanding in astronomy; it is significant that Galileo was an active developer of telescopes as well as an astronomer. Similarly the development of microscopes drove, somewhat later in the same century, the discovery of cells; Hooke and van Leuwenhoek, like Galileo, were hands-on developers of their instruments. Thus, the studies that resulted in the secure understanding, first clearly set forth by Schwann in the early nineteenth century, that cells are the basic units of all life, began with a reduction to practice of some early ideas about physical optics.

It is my thesis that, like the discovery of cells, most major subsequent developments in cell biology continue to be driven by technological innovations and improvements whose origins lie in diverse and intellectually distant areas of science. This continuing relationship between technology and discovery means that cell biologists in the next 50 years will have to be conversant with the fundamental concepts over a broad intellectual landscape ranging from physics through chemistry to genetics, but especially with the mathematical and computational ideas and methods that are dominating technology development. This is a particular challenge for education because the quantitative skills of most of our current students are underdeveloped, leaving them ill-equipped to deal with the technologies that will drive innovation in their scientific lifetimes.

A few twentieth century examples should suffice to illustrate how closely progress in cell biology continues to be tied to technological development of discoveries and ideas quite far afield.

- Visualization of cellular and subcellular structure followed in the path of the development of optical microscopy (compound lenses, phase contrast, differential interference contrast, and fluorescence imaging). The invention and development of electron microscopy (based on electronics rather than physical optics) provided orders of magnitude increases in resolution and unprecedented resolution of membranes and viruses.

- Elucidation of the chemical composition of cellular components followed the introduction and development of the new sciences of biochemistry and molecular biology. Subcellular localization of these components followed, mainly through the technologies associated with production of specific antibodies that could be made visible with dyes, radioactive tracers, and fluorescent tags.

- Imaging of specific proteins in living cells, tissues, and even intact model organisms followed the advent of molecular genetics, from which emerged mature technologies for manipulating the genes and genomes. Protein engineering of green fluorescent protein (GFP) provides a wide spectrum of different emission colors that are the foundations of modern cellular imaging.

These fantastic advances were made with analog technologies resulting in images that were recorded as photographic images and analyzed mainly by inspection. Increasingly, technology advances in chemistry, imaging, biochemistry, genetics, and indeed in cell biology rely on quantitative and computational methods and analysis. Many, if not quite all, of the great advances and opportunities in the future will involve a mixture of advances in hardware and software, with more and more of the effort in the latter category. A few examples illustrate these trends: Digital image capture and computation methods introduced already ≥20 years ago have made possible reconstruction of cellular structures in three dimensions from stacks of images obtained from optical and electron microscopes. Also, the diffraction limit of optical resolution by light microscopy has...
been exceeded by diverse but related methods that use fast digital image capture and computation to localize fluorescent molecules to a resolution of ca. 10 nm in three dimensions (Betzig et al., 2006; Rust et al., 2006; Baddeley et al., 2007).

Single-molecule and single-cell imaging has been made practical with the result that the variability among apparently identical cells can be studied in situ. Such studies have already resulted in discoveries about the role of noise in gene expression (Elowitz et al., 2002).

The introduction of laser technology not only for illumination but also for measuring forces has allowed the study of very basic issues in cell biology, such as the nature and magnitude of forces during muscle contraction (reviewed in Tyska and Warshaw, 2002).

Close adjacency of molecules in vivo can be detected and measured by fluorescence resonance energy transfer among suitable engineered GFP variants (reviewed in Pollok and Heim, 1999).

Genome-scale technologies (DNA microarrays, comparative genome hybridization, genome-wide gene knockouts, or RNA interference knockdowns, morphometrics) require sophisticated statistical analysis for thorough and rigorous interpretation.

Quantitative and computational analysis is no longer optional for cell biologists: obtaining insight by simply looking at images is becoming less and less common. As resolution becomes better, signals tend to become weaker relative to the noise, often requiring considerable statistical and quantitative analysis even when the measurements can be made in commercially available instruments. It is unlikely that the cell biologists of the future can function effectively with just the 1 year of undergraduate physics and 1 year of undergraduate calculus required of Ph.D. candidates in most cell biology graduate programs. If major progress in the future is not to be limited to just a few of our students, we should act now to expect more quantitative thinking, and to provide more quantitative and computational content in our curricula.

REFERENCES


