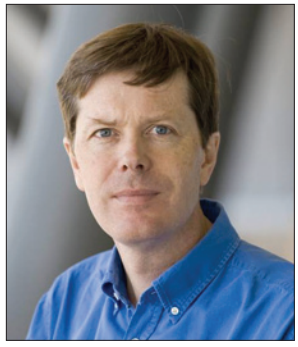
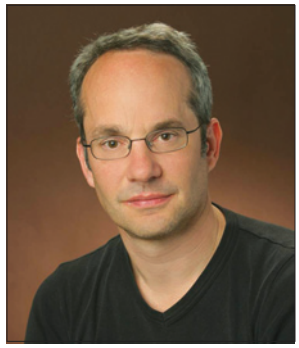
Automating Cell Biology: Genomics as Industrial Revolution

Genetic approaches have long been a driver of progress in cell biology. Genetic screens in the last quarter of the 20th century demonstrated the power of genetics to elucidate biological problems as diverse as cell cycle control, secretion, *Drosophila* development, apoptosis, and cell polarity. Much of the progress came from traditional genetic screens that have been termed "forward genetics." First a set of identical organisms or cells are mutagenized then altered phenotypes are identified within the mutagenized population. Next the altered phenotype must be correlated with the altered genotype. This means trying to find out which genes have been mutated in individuals showing any altered phenotype.



Richard Durbin



Anthony A. Hyman

Doing this is akin to finding the proverbial "needle in a haystack." Typically for chemical mutagenesis, one altered base pair must be found among 100 million. In single cell organisms such as yeast this can be done relatively rapidly, and thus genetic analysis has proceeded quickly in these organisms. However, for multicellular organisms, even in the best cases it is hard to identify the mutated gene in under a year. Next generation sequencing will make mutation finding very fast for organisms with small genomes like yeast, but it will likely take longer to apply this approach directly to larger genomes. Furthermore, because different laboratories use diverse methods and qualitative scoring techniques, it is hard to establish standardized phenotyping methods.

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Lab "Guilds"

Laborious exchange of strains between labs is required to sort this out. The whole process of linking genotype to phenotype using forward genetics is a small-scale activity. Individual students work in diverse locations, with the speed determined by individual skill and dedication of the scientist, with a large dose of luck required. This can be likened to a medieval guild. The PI as the master craftsman, postdocs as journeymen, graduate students as apprentices, all organized into departments akin to guilds.

A similar situation persisted for the production of goods into the late 18th century. Most manufacturing was performed in cottages; hence the term "cottage industries." The quality and beauty of the goods depended on the skill of the manufacturer. If the artisan died, the quality of the product might die with them (e.g., Stradivarius violins). In the late 18th century the Industrial Revolution arrived in Britain. Production was moved into factories and standardized. The standardization of production methods and quality control led to a great increase in reliability, average quality, and economy. For instance, when one buys a car one expects it to run 50,000 miles without any problems. The continued development of the microprocessor would have been impossible without industrial production standards. However, many of the items we treasure most as a society have been made using pre-industrial techniques, or even came from the pre-industrial era.

Genome Phonebooks

With the introduction of genomics-based techniques we are witnessing an industrial revolution of genetics. This revolution was stimulated by the successful sequencing of whole genomes. A whole genome sequence can be likened to a "yellow pages" in which there are the names of 30,000 businesses, but without any mention of the services they provide. Similarly a genome sequence is a set of genes looking for function. The development of rapid techniques for evaluating gene function has made it possible to fill in the "genome phonebook" for any process that can easily be assayed. These procedures are called reverse genetics and differ from conventional genetics in the following way: A known gene is first targeted and the phenotype is then assessed. Among these reverse genetics techniques are RNA interference, which reduces the expression of genes, and

gene targeting, which mutates the gene itself. Further examples include genome-wide tagging screens to measure protein levels or document localization patterns.

Taken together the two processes, genome sequencing and rapid reverse genetics, allow standardization of the process by which genotype is linked to phenotype, and thus completely change the scale of genetics. As in industrial production where different functions such as welding or painting are done by different people, different aspects of genomics will also be done by different people. By focusing on a component of the process such as DNA sequencing, an individual or group can concentrate on process engineering. Thus, increase in scale will bring enormous increase in accuracy, as has already been seen for DNA sequencing.

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The Size of the Puzzle

As the techniques get better and better, the screens will become more and more complete, or saturating. Completeness has a general advantage in studying a biological problem: Whereas forward genetics gives you pieces of the puzzle, genomics can also give you the size of the puzzle. To realize how important this is, imagine a child's jigsaw puzzle. If you are given 10 pieces of the puzzle and the puzzle is 50 pieces, you are on your way. But if the puzzle is 500 pieces, it may not be possible to begin. Knowing the size of the puzzle allows the design of appropriate experiments to understand how your process works. A further advantage of industrialization is that, because the phenotype of all of the genes can be screened in one location, one person can look at all the phenotypes and thus provide a global picture of the process under study. This ability to accurately measure often subtle phenotypes on a genome scale will also drive the future of systems biology.

Initially industrialization was confined to a few genomics centers, but as the technology becomes cheap and standard, it is rapidly spreading among the scientific community, just as industrial production spread from Britain all over the world. However, the Industrial Revolution had many downsides. Among these was a reduction in identifiable individual contributions and creativity, as factories standardized production. Movements such as Arts and Crafts with William Morris in the UK, and Art Nouveau in France, were among the reactions to this problem. One of the most damaging aspects of the Industrial Revolution was that while it increased the standard of living, it created a huge shift in the structure of society. Among the problems were alienation of workers, by divorcing the worker from the creative process, and concentration of power and money in the hands of a few people. In the long term, industrialization led to proliferations of design and ideas, freeing production from tradition. In time we have come to recognize the value of handmade products, while appreciating the precision and functionality of modern industrial design.

Cultural Shifts

How will the culture of biomedical research handle this shift? As the collection of data becomes more standardized, and the opinions of the individual become less important, there is a danger that fewer creative people will be interested in going into biomedical research as a career. Furthermore, the concentration of power and money could mean that fewer and fewer new ideas will be tested. It is therefore essential that biomedical research continue to fund small individual research programs, and even talented individuals working on their own, searching out new and undescribed problems, while at the same time funding large, industrialized projects. One possible way forward is to look at the development of the chemical and physical sciences. While departments of chemistry focus on basic research in chemistry, departments of chemical engineering focus more on the process engineering necessary for scaling up syntheses in large scale. Genomics is in essence process engineering of lab-based protocols so that they can be performed on an industrial scale. Perhaps establishing departments based on engineering biological experiments would be beneficial for the future of biomedical research, by allowing separate concentration on small-scale research groups and large-scale process engineering.

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In the Western world, we have moved into a postindustrial era in which service economy now dominates. In a service economy, production has been so standardized as to become a commodity. Instead, information gathering and processing is the driving force. Perhaps biomedical research will eventually end up with a similar service model, with analysis of information lying at the heart of discovery. We are far from this stage right now, as automation of cell biology is still in its infancy. However, the current acceleration of industrialization of all techniques in cell biology, from mass spectrometry to microscopy, suggests that such a future is a real possibility. ■

—Richard Durbin, Wellcome Trust Sanger Institute, and Anthony A. Hyman, Max Planck Institute of Molecular Cell Biology and Genetics

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MEMBERS in the News

Bonnie L. Bassler, of Princeton University, an ASCB member since 2003, is the recipient of the National Academy of Sciences' Richard Lounsbery Award. The award recognizes extraordinary scientific achievement by French and American scientists in biology and medicine.

Photo: Elizabeth Armstrong

Gary Borisy, of the Marine Biological Laboratory, an ASCB member since 1970 and 2002 ASCB president, was recently appointed Head of Faculty for Cell Biology at Faculty of 1000.

Bruce A. Jackson, of Massachusetts Bay Community College, who first became an ASCB member in 1992, is one of the recipients of the Presidential Award for Excellence in Science Mentoring.