in a haploid organism directly leads to an altered phenotype, making forward and reverse genetic approaches more straightforward in haploid moss than in diploid seed plants.

A major additional asset of mosses came from the discovery that, in the moss *Physcomitrella patens*, recombination occurs between DNA introduced into cells by transfection and homologous sequences in its nuclear DNA. This occurs as efficiently as in yeast — five orders of magnitude (!) more efficiently than in any other plant species that has been tested. Since then, this technique has been used to study gene–function relationships in single gene knockout mosses. Additionally, homologous recombination has been used to generate tagged, saturated *Physcomitrella* mutant collections as the basis for genome-wide studies of plant gene functions.

A special offer from moss? The last common ancestor of mosses and seed plants lived about 450 million years ago. Mosses have not changed much since then, and, consequently, they offer the chance to learn more about plant evolution and diversity. Are there differences between gametophytic and sporophytic gene regulation? How do single cells decide to differentiate into new tissues? Are basic mechanisms of regulatory networks and cross-talk conserved between mosses and seed plants? Can novel genes or metabolites be identified from moss?

Mosses offer a variety of metabolites that are not known from seed plants. Some of them, like very long-chain polyunsaturated fatty acids, are of significant commercial value in improving the human diet and consequently the relevant moss genes are being transferred into seed plants to alter their fatty acid composition into a moss-like one. Moss can be grown efficiently in large-scale bioreactors to produce foreign proteins, including human proteins. Inactivating, by homologous recombination, the genes for the enzymes that mediate plant-specific protein glycosylation alters the modification patterns of moss proteins to a human-like pattern; a milestone in the production of biopharmaceuticals in plants.

The best has yet to come... Sequence information from the *Physcomitrella* transcriptome is rapidly increasing and presently covers more than 95% of the estimated 25,000 protein-encoding moss genes. Mosses have conserved, ancient biochemical pathways; unlike seed plants they show no real codon-bias; on average, they have fewer representative members per protein family; and they have more than 5,000 genes with no clear homolog in seed plants. This impressive set of novel genes is attracting more and more scientists.

However, to fully understand — and exploit — land plant diversity, the full genome sequence of *Physcomitrella* is needed. The genome size is 511 Mb on 27 chromosomes, so sequencing the complete genome is not too daunting a mission these days. An international sequencing consortium will be launched at the next international moss meeting in Freiburg, Germany (www.plant-biotech.net/moss2004). Support from the broader community, however, is greatly appreciated.

Where can I find out more?

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Useful moss links:
http://www.moss.leeds.ac.uk
http://moss.nibb.ac.jp/
http://www.biology.wustl.edu/faculty/quatrano.html
http://www2.unil.ch/lpc/docs/pp.htm
http://www.plant-biotech.net
http://www.cosmoss.org

[1]Plant Biotechnology, University of Freiburg, Schaenzlestr. 1, 79104 Freiburg, Germany.
[2]Centre for Plant Sciences, University of Leeds, Leeds LS2 9JT, UK.

Theory in Biology

A precarious balance

John J. Tyson

Many areas of modern science and engineering owe their strength and vitality to a rich interplay of experiment, theory and computation. For example, quantum chemistry, aerodynamics, meteorology and membrane electrophysiology are all firmly based on extensive quantitative observations, sound theoretical formalisms and accurate, predictive calculations. Molecular cell biology, on the other hand, is still, for the most part, proudly and precariously balanced on one leg — experimental observations — and its staunchest defenders believe that theoretical and computational approaches have little or nothing to contribute to our understanding of cell physiology (see Peter Lawrence's recent essay in these pages *Theoretical embryology: a route to extinction?* [1]).

This view is surely wrong. A living cell is an intrinsically dynamical system, ceaselessly adapting in space, time and internal state to environmental challenges. Catalogs of genes and static diagrams of the structural and functional relationships of proteins, though necessary for full understanding, can never adequately account for the dynamism of organelles and cells. Take, for example, cilia: these beautiful tiny whips, attached to many cells, lash back and forth in wondrous synchrony, propelling cells through liquids or liquids past cells. Without cilia you wouldn't have been born (they transport eggs from ovary to uterus) and you couldn't breathe (they continually sweep mucus and debris from the lungs and airways). How do these elegant little machines accomplish their essential tasks?

Open any modern textbook of cell biology and you will find an attempt to answer this fundamental question. What you will see is a parts list of a typical

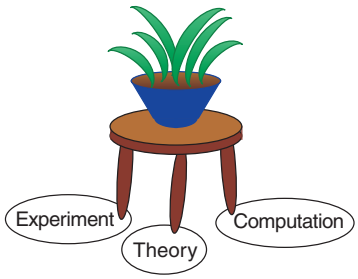
cilium — dynein, tubulin, nexin, and so on — and a pseudo-color, artist's rendition of how the parts seem to be connected. Then a few words about how dynein molecules can pull on microtubules, causing then to slide past each other. End of story.

This explanation leaves me unsatisfied. How am I to understand the dynamic function of a cilium from this static textbook picture? The essence of a cilium is to move in space and time. What principles organize the tiny pulls of each dynein motor into the 'power stroke' that sweeps along the cilium from base to tip? What forces drive the recovery stroke along a trajectory so different from the power stroke? What invisible choreographer synchronizes the movements of vast fields of cilia to carry the egg to its destination?

These sorts of questions cannot be answered by cataloging parts, defining their connections, and drawing schematic diagrams. The problem demands a movie. "Well then, if you want a movie, go to the electronic version of the textbook and click on the icon for the quick time movie of a beating cilium." What you will see is either a living cilium observed through a microscope or an animated cartoon of how the author imagines a cilium to move. But animation is not scientific explanation; it is likely to be as entertaining and as fundamentally mistaken as a Road Runner cartoon.

What we desire is a realistic computation of the coordinated motion of a field of cilia, based on solid principles of biochemistry and biophysics, including the forces exerted by motor proteins on the stiff and elastic components of the axoneme, and the forces exerted by cilia on the viscoelastic liquid in which they are immersed. Although much interesting work has been done on this problem [2–6], a full and satisfying solution remains for the future.

Every aspect of molecular cell biology faces the same challenge. How do cells move, feed, grow, divide, secrete, anticipate sunrise, find mates and avoid dangers? In the 1960s and 70s, some brave souls speculated about the



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dynamical systems underlying these behaviors before knowing anything about the molecular components inside the black box. For example, René Thom and Christopher Zeeman (much maligned by Lawrence) were basically correct in their contention that cells should be thought of as dynamical systems governed, in a deep sense, by the generic bifurcations of vector fields. Unfortunately, they picked the wrong sort of vector field: a gradient of potential, a good model in many areas of physics, but a bad assumption in biology. Nonetheless, in recent years it has been shown that the same sorts of bifurcations envisioned by Thom and Zeeman arise from realistic models of gene–protein networks and explain a great deal about the qualitative dynamical behavior of cells [7].

Another early practitioner of topological reasoning in biology was Arthur Winfree, whose stunning revelation of a 'timeless' point for the circadian oscillator was based on elegant theoretical ideas and unconventional experimental designs [8]. Winfree later used high performance computing to uncover the timeless points in heart muscle that are the organizing centers of lethal cardiac arrythmias.

Over the last ten years, an appreciation of dynamics has appeared in some areas of cell biology. People are tracing cell behavior back to elementary parts lists by means of realistic computational models based on sound equations of biophysics and biochemistry. My favorite examples include Bray *et al.* [9] on bacterial chemotaxis, Arkin *et al.* [10] on lambda phage infections, and Teusink *et al.* [11] on glycolysis. In all cases, the models provide accurate simulations — not just imaginative animations — of some aspect of cell physiology. From these models and simulations come insights and predictions that cannot be reached by intuition alone. It seems that a new generation of cell biologists is ready to stand on all three feet.

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Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061, USA. E-mail: Tyson@vt.edu