gies that steer the system toward a state with an improved signal-to-noise ratio (*5*). The experiments of Saba *et al.* (*1*) should inspire a new generation of work on the quantum mechanics of phase and atom number (*6*, *7*).

Since their discovery in 1995, gas-phase Bose-Einstein condensates have offered fascinating insights into basic physics, but in the words of a quip about lasers from the 1960s, they are a solution looking for a problem. Some of the first applications are likely to be in interferometric measurement devices. The advance reported by Saba *et al.* (*1*) is an important step in this direction.

References and Notes

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CELL BIOLOGY

Whither Model Organism Research?

Stanley Fields and Mark Johnston

Almost everything we know about the fundamental properties of living cells—how they grow and divide, how they express their genetic information, and how they use and store energy—has come from the study of model organisms. These simple creatures traditionally include the bacterium *Escherichia coli* and its bacteriophage viruses, bakers' yeast *Saccharomyces cerevisiae*, the nematode worm *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster*, and the mouse *Mus musculus*, each a representative of the diversity of life. Our colleague Gerry Fink has likened this handful of organisms to the Security Council of the United Nations because, among the world's multitude of organisms, they garner most of the attention of researchers and dictate the distribution of most of the biomedical research funds that are not targeted to specific diseases. A few other organisms—the fission yeast *Schizosaccharomyces pombe*, the mustard plant *Arabidopsis thaliana*, the zebrafish *Danio rerio*, and the frog *Xenopus laevis*—may qualify for seats on the council, but membership is limited. But has the very success of experimental approaches using model organisms made them (and the scientists who study them) endangered? Now may be an opportune time to ask: What more can model organisms tell us about fundamental biological processes?

Three daunting issues confront biologists who devote their careers to studying model organisms. First, some of the most crucial questions have been answered, at least in part. Thus, we know a lot about the mechanisms that underlie the cell cycle; the cellular components that synthesize, modify, repair, and degrade nucleic acids and proteins; the signaling pathways that allow cells to communicate; and the mechanisms that lead to the selective expression of subsets of genes. Remarkably, the operating principles of these cellular processes have been conserved throughout the tree of life. Second, problems of human biology and human disease are becoming increasingly seductive. Given that the flow of information and molecules around individual cells is established, at least in outline, many biologists find more excitement in, for example, discovering how organ systems develop and function, how learning and memory operate, and how innate and adaptive immunity coordinate their responses. We want to understand how people get old, why they get sick, and what we can do about it. The intrinsic appeal of these topics is bolstered by encouragement from the National Institutes of Health and other funding agencies to conduct "translational research," studies that directly address the prevention or treatment of disease. Third, the tools and resources that made uncomplicated model organisms so attractive to begin with can be applied increasingly well to much more complex creatures including mice and humans. Thus, we now have essentially complete mammalian genome sequences, an expanding resource of purified genes and proteins, DNA chips to measure gene expression, and vast numbers of DNA sequence polymorphisms to map traits such as susceptibility to disease. Perhaps most disquieting for the model organism researcher is the recent acquisition by mammalian biologists of a method that was once the sole province of those working on simpler creatures: facile elimination of gene function. The new method of RNA interference has leveled this playing field.

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So what does the future hold for model organism research? In the case of *S. cerevisiae*, the eukaryotic model organism with the smallest number of genes, we contend that it will be "solved" within the next 20 to 30 years. Of course, not every facet of yeast biology will be known: Precise biochemical functions will not be available for every gene product, the level of every metabolite will not have been measured under all possible environmental stresses, and the subtle effects of mutations on protein folding, stability, or modification will not be wholly predictable. But no basic molecular process in yeast will remain obscure. This is a remarkable accomplishment that should be celebrated. And if we expect to essentially "solve" over the next few decades a cell constructed from 6000 genes, how much longer can it be before we "solve" the fruit fly with only twice as many genes, or the roundworm with only about three times as many genes?

The benefits that we will realize from these successes include a working blueprint first of a cell, then of multicellular organisms, that will enable researchers to decipher ever more complex biological processes such as tissue development, the immune response, and neurobiology. Because of the spectacular progress of model organism research, we can expect to reach a thorough understanding of the molecular basis of life. This Security Council, unlike its political counterpart, is proving to be a resounding success.

That said, are we playing a dirge to model organism research or singing a paean to its reinvention? We are singing, because we believe that the hegemony of model organisms in biological research will persist. We see at least five reasons why.

1) Over the coming few decades, model organisms will continue to provide insights into replication, transcription, translation, protein secretion, metabolism, and many other aspects of cell biology, biochemistry, and physiology, because they offer the keenest methods of analysis. In fact, the value of model organisms will only increase, because the human geneticist who identifies a disease gene implicated in a conserved cellular process will turn to these models to provide deeper insights into the function of that gene. And that researcher will discover a rich

encyclopedia of knowledge that can be drawn upon for formulating incisive experiments to illuminate the disease process.

2) Model organisms will increasingly be used for the direct investigation of medical problems that seemingly have little to do with them. For example, the misfolding or aggregation of proteins implicated in the process of neurodegeneration in disorders like Alzheimer's disease, Parkinson's disease, and Huntington's disease, can be recapitulated in yeast, worms, and flies. In addition, other components discovered in these organisms may be important in the disease process. Analysis of aging in simple models is turning up genes that play analogous roles in more complex organisms. Model organisms will provide further insights into the cell cycle and cancer, glucose metabolism and diabetes, chromosome segregation and mental retardation, protein glycosylation and lysosomal storage diseases, mechanisms of drug action and resistance, and much more. Studies of *S. cerevisiae* will help us to unravel the workings of its pathogenic cousins such as *Candida albicans*; studies of *D. melanogaster* will reveal secrets of the *Anopheles* mosquito.

3) Model organisms will remain at the forefront for the foreseeable future in efforts to sort out biological complexity and achieve a more quantitative understanding of life processes, which is needed to unravel the network of molecular interactions that constitute an organism as complicated as a human. For example, it is with yeast that biologists first will elucidate how DNA binding proteins, DNA sequence elements, components of the transcriptional machinery, chromatin structure, and signaling pathways combine in the circuitry of gene regulation. The resulting comprehension of biological networks that will result will bestow upon biologists the predictive powers and design capabilities long held by physicists and engineers. Such insights will require the application of multiple technologies, the confluence of individual investigator's experiments and genomewide data sets, and the intense collaboration of experimentalists and computational biologists. Learning how to carry off this ambitious project is itself a lofty goal of model organism research.

4) Model organisms offer the best hope for coming to grips with the breadth of genetic diversity and the depth of its consequences. Most of the variance among individuals of a species is due to small differences in multiple genes, and it is with model organisms that we will first learn how to analyze and understand complex quantitative traits. Such an understanding will provide the principles and procedures for predicting disease susceptibilities in humans and tailoring optimal methods for prevention and treatment. Genetic diversity is the grist for the mill of natural selection that produced the remarkable diversity of life on Earth, and model organisms should continue to teach us about the origin of the species.

5) Model organisms will remain the proving ground for developing new technologies, which typically spread quickly throughout the research community. For example, our skills in isolating and manipulating genes were won while studying bacteria and bacteriophages. Many other technologies got their start or achieved their apogee in yeast, including two-hybrid analysis, high-throughput protein purification and localization, genomewide epistasis analysis (synthetic lethality), gene expression profiling, protein arrays, and genomewide chromatin immunoprecipitation (ChIP). Worms and flies have been the test beds for large-scale RNA interference screens. We don't see these developments abating. Indeed, the more the fund of knowledge of simple organisms grows, the more useful they become for subsequent technological innovation.

But will an organism like yeast be able to maintain its seat on the Security Council? Not indefinitely. And just as yeast has led the way in many areas of research, we expect that its fate as an experimental organism will foreshadow that of the rest of the council. Does this mean that the end of biology is near? Hardly. We will still be a long way from a comparably deep-seated understanding of humans and our afflictions. How do cells and organs regenerate after damage? How do eukaryotic parasites, which are so different from model organisms, wreak havoc with fatal diseases like malaria, African sleeping sickness, and Chagas' disease? How do strange bacteria and viruses elude our immune systems and stymie our best efforts at drug therapy? How do genes and the environment interact in behavioral diseases like schizophrenia or autism? What is the basis of memory and consciousness?

The reductionist approach of biologists has enabled remarkable achievements by causing us to focus on just a few experimentally tractable organisms, but it also has tended to restrict our vision. There is much to learn about the many organisms that populate our planet, most in ways we can't yet begin to fathom. How do creatures survive in extreme environments? How do some manage to metabolize bizarre substrates? How do individuals organize themselves into incredibly complex communities? This list of questions seems endless (as seemed the list of genes in model organisms not so long ago). Providing adequate answers to these and many other questions is certain to occupy us for a long time. And the knowledge and sophisticated analytical tools that model organism research has laid at our feet bring the entire General Assembly of organisms within our reach, enabling us eventually to answer a question that has framed our enterprise from its beginning: What is life?

References and Notes

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MOLECULAR BIOLOGY

Signal Processing in Single Cells

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Consider a high-tech version of the "telephone game" in which you and a group of your friends attempt to transmit a message via your cell phones. One person in the chain has a phone from the 1990s, which is very noisy. Another person is standing in the middle of Times Square in New York City. It would not be surprising if the message received by the person at the end of the chain, or cascade, were corrupted as a result of noise intrinsic to the old phone and the noise arising from the Times Square environment. In this issue, Rosenfeld *et al.* on page 1962 (*1*) and Pedraza and van Oudenaarden on page 1965 (*2*) investigate a living-cell version of this game by exploring how signals are transmitted through gene cascades in noisy cellular environments.

Cell phones consist of multiple, interacting components. Engineers characterize the performance of such devices by determining quantitatively the input-output relationships, or transfer functions, of the respective components. Rosenfeld *et al.* present a new method for calculating the transfer function for the expression of a single gene. Specifically, they investigate the relationship between the concentration of active transcription factor (input) and the rate at which target protein is produced (output) in

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