The century beyond the gene

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In an increasing number of biological laboratories, the focus of research is shifting from sequence data to the functional meaning of that data. No longer content with structural mappings, there is a renewed interest abroad in what the United States Department of Energy calls, 'Bringing Genomes to Life'. For many, this means a movement beyond 'reductionism' to a 'systems biology'. The question is, what does this mean?

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1. Introduction

As a historian and philosopher of science, my particular interest is in changes in direction of scientific (and especially biological) research – in how they come about, how they change our questions, our understanding, and our expectations. And since we seem to be living through some of the most cataclysmic changes in biology, it is perhaps inevitable that over the last few years, I have turned my attention to the changes that are happening right now, under our very feet. Of course, one faces all kinds of pitfalls in trying to be a historian of the present. But perhaps the most serious, especially in exciting times such as ours, is that history can happen a lot faster than a scholar (at least a scholar like me) can write.

Thus, almost five years ago, I published a book called *The Century of the Gene* (Keller 2000). This book was an attempt to map a trajectory of the gene concept from the time of the rediscovery of Mendel's laws in 1900 to the sequencing of the human genome in 2000 – a nice neat century. It was both a celebration of productivity of the concept of the gene throughout the century, and, at the same time, a somewhat impassioned argument for the need to move on, into what I called the century beyond the gene. I agreed with William Gelbart, a molecular biologist at Harvard University, who wrote, "[U]nlike chromosomes, genes are not physical objects but are merely concepts that have acquired a great deal of historic baggage over the past decades." [and] "we may well have come to the point where the use of the term 'gene' . . . might in fact be a hindrance to our understanding" (Gelbart 1998). Some molecular biologists read my book as anti-genetics, but this was a mistake. My point was that if the 20th century was the century of the gene, the 21st would in all likelihood be the century of genetics, or rather, of genetic systems. The difference is important, so let me explain: Genetics, I take to be the study of the processing of DNA in the construction of phenotype; genes, I take to refer to the entities historically assumed to be the particulate of inheritance. The former, I take to refer to the biochemical interactions underlying the construction of actual organisms, the latter to a hypothetical conceptual scheme.

The principal historical baggage of the gene concept dates back to the view of genes as the basic units (the atoms) of life. But what is a gene? The fact of the matter is that molecular biologists employ a number of different definitions, and they need all of the variations. On one definition, it is a specified stretch of the DNA, passed on intact from generation to generation. But which stretches of DNA count as genes? Those that code for proteins? Or should we include those corresponding to bits of RNA that are crucial for regulation, but are never translated into proteins? On another definition, a gene is the coding sequence corresponding to a particular protein – a sequence that, for higher organisms exists as such only as mRNA, after it has been processed. Only by splicing together shuffled segments of the original DNA sequences can a molecule corresponding to the protein in question be constructed, a molecule that might be said to have

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existed as a chromosomal entity only in potentia. Yet more problematic are those proteins that are constructed from mRNA transcripts that have been specifically modified at particular developmental stages (e.g. by the insertion of several nucleotides): for these proteins, no corresponding sequence can be found on the DNA even after shuffling and splicing. Furthermore, the nucleotide sequences on the final version of the mRNA molecules are not (at least not directly) transmitted to the next generation. The most recent upset has come from the discovery of small RNA molecules with dramatic regulatory powers. The DNA corresponding to these molecules is scattered throughout the genome, much of it in regions previously discarded as 'junk'. In fact, 98·5% of human DNA consists of non-protein-coding DNA, much of it corresponding to RNA with regulatory functions. And sometimes the term 'gene' refers only to protein coding sequences; at other times, it includes these non-coding regions as well. Many problems arise from such ambiguities. For example, when we ask how many genes are on the human genome, the answer will vary according to which definition one employs, perhaps as much as by 2, 3, or more orders of magnitude.

By contrast to the gene, we do know what DNA is – we can spell out its sequence, and we can observe the remarkable stability of that sequence over the course of generations. But the most important lesson we have learned is that virtually every biologically significant property conventionally attributed to the DNA – including its stability – is in fact a relational property, a consequence of the dynamic interactions between DNA and the many protein processors that converge upon it. The very meaning of any DNA sequence is relational – for the purpose of understanding development or disease, the patterns of genetic expression are what really matters, and these patterns are under the control of a vastly complex regulatory apparatus, and they cannot be predicted from knowledge of the sequence alone.

2. A turning point

I probably should have waited. Five years ago, the number of molecular geneticists willing to give up on their paradigm of genetic reductionism was still relatively small, but biologists seem to be undergoing a paradigm shift right under our noses. Overnight, as it were, biology departments have begun to jump on the bandwagon of 'Systems Biology.' In my book, I gave abundant thanks to the Human Genome Initiative (HGI) for this shift, and it may well be that I was premature. But today, it seems clear that it has, and also, that my thanks were well placed.

A few quotes will make my case. From the Bauer Center at Harvard University, we read: "The completion of the draft sequence of the human genome has marked a turning point in molecular biology and has stimulated a broad movement towards system-wide approaches to biological complexity. The central question has shifted from "who are the actors?" to "what are the scripts?" . . . "How does collective behaviour emerge from the actions of individual actors?". Or, from a lead article of a recent issue of *The Scientist*:

"For 50 years, biologists have focused on reducing life to its constituent parts, first focusing on the cell, then working their way down to the genome itself. However, such achievements created a new challenge – making sense of the huge amounts of data produced. As professor Denis Noble, Oxford University, puts it: 'It took Humpty Dumpty apart but left the challenge of putting him back together again.'" (Hunter 2003).

In a similar vein, at the US Department of Energy (DOE), where the project of sequencing the human genome was first born, a new project has now been organized. It is called "Bringing Genomes to Life Program", and is explained as follows:

"From the foundation of whole-genome sequences, the aspiration of the new biology is to build a new, comprehensive, and profound understanding of complex living systems. . . . The current paradigm in biology – variously described as 'single gene,' 'reductionist,' or 'linear' – is not likely to be successful on its own . . . "Knowing the functions of all genes in the genome, by itself, will not lead to understanding the processes of a living organism." Instead, they continue, the existing research approaches will be augmented by a 'systems' approach . . .. The new paradigm grows out of rapid advances in instrumentation for the biosciences, the vast improvements in computing speeds and modelling capabilities, the growing interest from physical and information scientists in biological problems, and the recognition that new approaches are needed for biology to achieve its full promise [of improving human well-being]." In other words, having helped take the genome apart, the DOE is now embarked not only on putting it back together again, but also, in bringing it to life. Somewhere along the line, people have come to realize that the genome, by itself, is not in fact alive. Somewhere along the line, we seem to have learned that that vitality, as Linus Pauling long ago reminded us, does not reside in the molecules, but in the relations among them. The architects of the new DOE program write, "we need to figure out what these parts do in relationship to each other" In short, they are telling us that what we need is a systems biology.

In much the same spirit, Massachusetts Institute of Technology (MIT) has launched a new Computational and Systems Biology Initiative (CSBI), and its mission is "to lay the foundation for treating biological entities as complex living systems rather than an amalgam of indi-

vidual molecules." In his opening address at the first annual conference of this Initiative, then president of MIT Charles M Vest said: "Until now, biologists have learned more and more about the detailed structure and functions of the molecular components of life, but we have not yet understood how individual components are networked to control physiology. . . . Now we are in a position to begin the search to understand our molecular machines and cell circuitry – how the parts are connected and how they operate. In a third revolutionary transformation, biology will become a systems science." (Vest 2003).

I could go on. Efforts of a similar kind are gathering strength all over the US and Europe. Harvard medical school has opened an entire new department called "Systems Biology." Two questions leap out at us: First, what drives this move to systems biology? Why now? And second, what does it mean? What is systems biology? The first question is relatively easy to answer, the second, a bit more difficult. I therefore start with the first.

3. Why now?

The most important impetus seems clearly the realization of the HGI's first set of goals. As already evident from the quotes I read you, there is a widespread sense that the reductionist phase of genetic research is now over. Steven Benner (2003) speaks for many when he writes, "Sequencing the human genome represents a culmination, of sorts, . . . of chemical reductionism", and now "we need to move on." But also, the completion of the first phase of the HGI brought with it something of a disappointment. The human genome has been sequenced, but it has failed to tell us who we are. As the DOE puts it, "We now have the parts lists for these organisms", and we can see that knowing the parts, and even knowing the function of the parts, is not enough. However, the HGI, and molecular genetics more generally, have given us far more than a parts list over the last decades; perhaps even more importantly, they have also given us tools for going beyond the individual parts – i.e. the tools for probing the complexity of cellular dynamics. And together, the tools and the lists of parts have produced a veritable avalanche of data.

Just a few years ago, Sydney Brenner (1999) wrote, "There seems to be no limit to the amount of information that we can accumulate, and today, at the end of the millennium, we face the question of what is to be done with all this information". It has become evident that the methods of data analysis and interpretation traditionally available to molecular biologists no longer suffice, and that new methods are required, perhaps to be borrowed from other disciplines. And fortunately, technical developments in computer science, together with the recent emergence of an entire discipline of computational analysis for dealing with massive amounts of complex data, have guaranteed that such new methods are available. Furthermore their integration into molecular biology, conjoined with the techniques of molecular analysis (e.g. gene chips), has proven not only necessary, but manifestly productive. In fact, the influx of huge numbers of physicists and engineers into molecular biology today is one of the most conspicuous marks of the new systems biology.

4. But what is systems biology?

In brief, I want to argue that, so far, 'systems biology' is a concept waiting for definition. The term itself evokes the name Von Bertalanffy and his strong advocacy of a systems biology beginning in the 1930's. With somewhat uncharacteristic modesty, Von Bertalanffy wrote, "The notion of a system may be seen as simply a more self-conscious and generic term for the dynamic interrelatedness of components" (Von Bertalanffy 1932). Today, however, advocates for a systems biology have more to work with, and they are accordingly less modest: they want, both literally and figuratively, to put Humpty Dumpty back together again, and they have great hopes for the gains they expect to follow. President Vest at MIT voiced particularly high hopes in his address to the new Computational and Systems Biology Initiative: "The ability to better understand and predict the actions of complex biological systems is expected to lead to advances in drug design, disease diagnosis, biologically inspired computers, environmental health and national defense" (see http://csbi.mit.edu/news/archive/2003/January/20030129000000/story.pdf). We can of course recognize a certain amount of hype here, and of a kind that is precisely Vest's job as president of a large institution like MIT. But Vest is far from alone, and his comments echo the sentiments of many others. Leroy Hood, founder of System Biology Institute (SBI) in Seattle explains: "Unlike traditional biology that has examined single genes or proteins in isolation, systems biology simultaneously studies the complex interaction of many levels of biological information – genomic DNA, mRNA, proteins, functional proteins, informational pathways and informational networks – to understand how they work together" (http://www.systemsbiology.org/Default.aspx?pagename=faqs). And for Hood, as for the vast majority of engineering scientists, understanding how the parts work together is followed by "understanding how to control the system, and how to design the system" (www.symbio.jst. go.jp/symbio/sbgE.htm).

In other words, as the term is now used, systems biology is an exceedingly plastic and multi-faceted concept. It calls on a wide range of skills, and promises an equally wide range of results. It is a siren call to scientists from disciplines far afield from biology – e.g. from engineer-

ing, from computer science, from physics, from mathematics – and researchers from all these areas are pouring in. So far, it is the biologists who are setting the terms of the demand: what they ask of the new recruits is that they help integrate and make functional sense of the data that came from the recent triumphs of the subject. This may change, but for now, at least in most places, the biologists seem to be in the driver's seat.

5. Systems biology and an appropriate theoretical framework

Recognition of the demand for new tools of analysis in molecular biology, created by the deluge of data now pouring in, was not, however, the main point of Sydney Brenner's 1999 paper, cited above. He went on to argue "that the prime intellectual task of the future lies in constructing an appropriate theoretical framework for biology" (Brenner 2003). And this leads us to ask: Will 'Systems Biology' provide us with such a framework? The answer, I think, is no. The simple fact is that there is no common theoretical framework shared by engineers, computer scientists, physicists, and mathematicians. Indeed, the current situation is a bit reminiscent of Pirandello's six characters in search of an author. Furthermore we need to ask, what would an "appropriate theoretical framework" in fact look like?

I have no crystal ball to help me answer this question, but there are some obvious candidates out there, and perhaps I can make use of history to cast some light on the future and offer a few comments about their likely promise. One such candidate (and probably the most obvious candidate) comes from physics, the discipline that, for more than three centuries, has been accepted as the traditional arbiter of theory in the natural sciences. Indeed, for many scientists, and especially for physicists, the words theory and physics are virtually synonymous. Such an assumption was especially in evidence at a recent meeting outside Aspen, Colorado, several dozen theoretical physicists with an interest in biology gathered to celebrate, and here I quote from a report in *Nature*, the "growing feeling that their discipline's mindset will be crucial to reaping the harvest of biology's post-genomic era" (Cook 2002). Everywhere, it seems, physicists and mathematicians have heard the siren call, and they are accordingly looking to the life sciences for new fields to ply their trade, or with what one reporter calls "bio-envy". Some say that physicists are looking for ways to reclaim lost glory, others suggest a more pragmatic goal: that biology is where the money now is. Or one can put it somewhat more high-mindedly, here is where the intellectual and scientific action now is: if the last century belonged to physics, the new century, it is frequently said, belongs to biology.

But many of these physicists bring with them at attitude that comes from the assumption that they are the arbiters of theory. A few quotes from the recent literature will serve to illustrate: "Biology today is where physics was at the beginning of the twentieth century," or, "It is faced with a lot of facts that need an explanation." Or "physics gives us deeper understanding; it can offer biology fundamental explanations" (Cook 2002). Such an attitude, and such assumptions, indicate that the move from physics to biology is not quite so simple. As many have observed, there is a culture gap between the disciplines: biologists and physicists have different goals and traditions, they ask different kinds of questions, and perhaps even look for different kinds of answers. If the cross-fertilization now being attempted is to be productive, that culture gap must be bridged, and for this to happen, some resolution of, or accommodation to, these differences is required.

In fact, this is hardly the first time in history that physicists and mathematicians have turned to biology for new problems, new fields to plow. But the history of such efforts is somewhat dismal (at least from the perspective of building bridges between the two cultures): physicists have shown little interest in entering into the nitty gritty of biologists' experimental life, and biologists have shown little interest in past efforts to mathematize or 'theorize' their discipline; more typically by far, they have shown impatience and even indignation.

Apparently, this is no longer the case – When viewed from the outside, physicists today see collaborations between experimental biologists, physicists and mathematicians everywhere. But crucial changes in attitude have occurred in the involvement of mathematical scientists in these collaborations. Indeed, the place of mathematics in biology now seems to have entered an entirely new phase.

Part of the story is told by the numbers: Over the last few years, both the National Science Foundation (NSF) and the National Institute of Health (NIH) (especially the NSF) have launched a number of large-scale initiatives aimed specifically at realizing the potential of mathematical and computational approaches in biology. Since 1983, the proportion of funding for mathematical and computational research coming from the Biological Division of the NSF has increased about 50-fold. Also contributing to the new resources are a number of private foundations – like the Keck Initiative for exploring new directions for interdisciplinary collaborations.[1] Indeed, the complaint most frequently heard today is one of a

[1]Consider, e.g. the 2004 National Academy of Science conference on "Signals, Decisions and Meaning in Biology, Chemistry, Physics, and Engineering", organized as part of the new Keck *Futures Initiative*.

paucity of applicants, rather than a paucity of funding (Dearden and Akam 2000). This increase in resources is in turn reflected in a corresponding growth both in the rate of publication and in the formation of new programs in mathematical or computational biology. And unlike their precursors, most of these programs are now housed in departments of experimental biology, rather than in Mathematics of Computer Science Departments.

But also, there are qualitative shifts as well. Those coming from the mathematical sciences do not simply collaborate with experimental biologists, they themselves often become practicing biologists. Conversely, biologists no longer need to simply hand over their questions and data to others; thanks in part to the rise in computer literacy and in part to the development of 'user-friendly' computer programs that bring the techniques of mathematical analysis within the grasp of enables those with little or no conventional training in the subject, they can build (either by themselves or as active participants) their own 'mathematical/theoretical' models.[2] The net effect is the beginning of an entirely new culture that is at once theoretical and experimental, giving rise to "a breed of biologist-mathematician as familiar with handling differential equations as with the limitations of messy experimental data" (Dearden and Akam 2000).

If, as a number of people now claim, and as the evidence supports, "a new mathematical biology is emerging," it is because the beginnings of a reconciliation of traditional cultural conflicts is in the air. The new mathematical biology brings with it not only new skills, but also new epistemic values, giving rise to a discipline that bears only passing resemblance to past efforts to do for biology what mathematics had done for physics – to make of biology a theoretical science like that of physics. It promises not so much a vindication of past failures as a transformation of the methods, the aims, and the epistemological grounding of past efforts. Let me briefly sketch what I see as the key features of this transformation.

- First, the most successful efforts at modelling suggest the need to rethink the meaning of words like essential and fundamental: no longer is the essence of a process to be sought in abstract or simple laws, but in the messy specificity of particular adaptations that have come into existence by the haphazard processes of evolution. All too often, it is the accidental particularities of biological structure (like, e.g. that of DNA) that is fundamental – fundamental, i.e. in the sense of having been built in on the ground floor, and hence most deeply entrenched. Thus, if physicists are to be helpful in forging an appropriate theoretical framework, they will need to rethink some of their most basic epistemological assumptions (not to mention, on some of their traditional arrogance). Biology throws a serious monkey wrench into all our traditional assumptions about what ought to count as deep or fundamental, about what counts as explanation, or even about what we will count as progress.
- Biological systems are, as we know, extraordinarily complex, but again because of evolution, they are complex in somewhat different ways than systems in physics are understood to be complex: for one, they are always and inevitably hierarchical. Accordingly, familiar notions of emergence, rooted in the non-linear dynamics of uniform systems (gases, fluids, or lattices), are not adequate to the task. Hiroaki Kitano describes what is different about the reality of biological systems as follows: "Here large numbers of functionally diverse, and frequently multifunctional, sets of elements interact selectively and nonlinearly to produce coherent rather than complex behaviours" (Kitano 2002). The central point is that the inhomogeneities and ordered particularities of biological systems are essential to their functioning and hence cannot be ignored; indeed, to ignore them is to risk exactly the kind of biological irrelevance that has historically been the fate of so many mathematical models in biology.
- Because of the character of biological complexity, useful models of biological systems tend not to be mathematical in the usual sense; more often, they are computational. Nor are these models stepping stones to a final theory, but instead, the models are the theory. Or, to put it somewhat differently, theoretical biology will not be formulated in a few simple differential equations, but rather in a messy complex of algorithms, vast systems of differential equations, statistical analyses, and simulations. Such models can only be

[2]Consider, e.g. Stephen Wolfram's program *Mathematica* (introduced in 1988). Exploiting the power of Cellular Automata to simulate differential equations, Wolfram developed and marketed a "user-friendly" computer program that enables someone who is not literate in conventional mathematics to analyse almost any of the equations he or she would normally encounter. Soon, a number of similar programs appeared on the market [e.g. *Maple*, *Mathcad*, *Scientific Workplace*, and *Theorist* – among mathematical biologists, programs such as *Grind* (de Boer, Utrecht) and *Biograph* (Odell) have been especially popular]. What the availability of such programs has achieved is the effective removal of the most obvious barrier that has historically insulated biologists from mathematics, namely, their lack of training in mathematical techniques. *Mathematica* has proven a phenomenal commercial success – Wolfram's own claim is of a million users to date (personal communication). But even if his estimate were to prove exaggerated, there is little question that programs like *Mathematica* have created a new and significantly expanded market for the use of mathematical models – in biology, in the physical and engineering sciences, and even in the history of science.

successfully formulated in the most intimate back-and-forth relation with experiment. In fact, I sometimes think that the best use of the term model in biology is as a verb.

- Finally, distinctions between pure and applied, between theoretical and practical – distinctions that are so basic to our contemporary view of physics – also have to go, and this is in large part a consequence of the very technology that has enabled the collection of so much data. Techniques of recombinant DNA have made it possible to directly intervene in the internal dynamics of development; they have turned genetic markers into handles for effecting specific kinds of change. In short, the very technology that has paved the way for a theoretical biology has also, and simultaneously, made genetic engineering a reality, and as well, a business. Biology is becoming a practical science in the same move as it turns theoretical – indeed, the two terms have become almost impossible to disentangle.

The second – and in many ways, more promising – candidate for a new theoretical framework to consider comes from computer science, and from our current love affair with the image of the organism as computer, and of biology as a digital science. I say more promising precisely because of the rich practical tools computer science has given us for thinking about interactive systems, in many ways, tools and metaphors that take us far closer to the complexity of biological systems than do the traditional models of theoretical physics. But there is surely a serious error in overemphasizing the digital aspects of genetic processing, and overlooking the fundamentally analog nature of the chemistry that underlies all such processing. Furthermore, here too, there is a lesson to be learned from history. As scientists, our way to think about phenomena we do not understand is, as it has always been, and as it of necessity must be, to liken the unfamiliar to the familiar. Thus, the image of the organism as a machine goes back to ancient theorizing about the nature of life – the only thing that has changed is what we think of as a machine. Building up from pulleys, hydro-pumps, clocks, steam engines, we have displayed extraordinary ingenuity in constructing ever more versatile and more inspiring machines. Likening the organism to each of these machines has been instructive in the past, just as likening the organism to our newest machines is instructive today. But it would hardly be reasonable to suppose that our ingenuity has run out, that we will not yet build even more 'life-like' machines. In fact, our best computer scientists are betting on our ability to do so, and, once again, they are looking to biology for inspiration. So let us embrace the terms and the images of computer science to help us think about the systemic properties of cells and organisms, but we should not forget that these biological systems have a few tricks still to teach our engineers. Many people argue that systems biology would do better by looking to the engineering sciences than to the physical sciences for kinship, and perhaps so. But let us not forget that our engineers have yet to build a system that is both self-designing and self-generating, a system we would be willing to call alive. I am not saying such a task is impossible, only that our current computers, our latest airplanes, and our most sophisticated internet systems are not quite up to the task.

What will it take to bring the genome to life, to formulate an appropriate theoretical framework for understanding living systems? This question I obviously cannot answer, but I might hazard three suggestions: First, if I had to lay odds, I would pay close attention to where the current limits of both engineering design and genomics science are. And I would ask, alongside our most advanced engineering scientists, have we put enough time into enliven these systems? Have we taken sufficient account of the temporal dynamics of our systems? Have we paid enough attention to the time keeping of our regulatory systems? Is it enough to think of genes as turning on and off, or must geneticists, like their colleagues in neuroscience, begin to examine the precise timing of these on-off switches, both relative to each other, and to the temporal dynamics of global processes in the cell? I think I would put my money there for our next leap forward. But even if I am right, attention to temporal dynamics does not in itself constitute an appropriate theoretical framework.

This leads me to my second suggestion, which is to ask, does systems biology in fact need a single, coherent, theoretical framework? Perhaps it can forge an adequate, or at least workable, scaffolding by molding, transforming, and combining elements of the theoretical traditions that have preceded it. In the absence of an available framework that can be imported from an already existing discipline, that may well be how things will proceed and, based on an examination of the kinds of work thus far emerging under the name 'systems biology', clearly seems to be the current modus operandi. But many – even those who disavow the possibility of a single coherent theoretical framework – are unhappy with this state of affairs, wishing for just a bit more coherence than now seems available.

Hence my third and last suggestion: To the extent that our conceptual frameworks are constrained by lexicons fashioned for other kinds of challenges, it may well be worth stepping back and taking a brief look at the linguistic habits that have underline our existing theoretical traditions. Indeed, I suggest that the challenges now posed by our most recent encounter with biological complexity may require some new ways of talking.

6. Toward new ways of talking

Most biologists may now agree on the need to shift their focus to the interaction between and among individual parts, and even to the dynamics of these interactions, but I suggest that, in this effort, they are handicapped by ingrained habits of thought and speech that give ontological priority to those parts. When, e.g. the architects of the new DOE program designed to bring the genome to life write, "we need to figure out what these parts do in relationship to each other," the implicit assumption is that the parts come first, and only later, out of the interactions between and among those parts, do larger entities emerge. However, there are some obvious problems with this assumption, one of which is especially prominent in genetics, where the parts are taken to be genes. The problem here is that genes, by any definition, do not have meaning in isolation. A sequence of nucleotides is constituted as a gene only in the presence of transcriptional and translational system of the kind we find in a living cell. The cell, in other words, is a meaning making system that turns nucleotide sequences into genes (again, however they are defined). How then can it possibly be appropriate to think of the cell as constituted of genes and their products?

What I am suggesting is that, prior to the need to construct an appropriate theoretical framework may well be the need to construct a more appropriate linguistic framework, one that takes us beyond the paradigm of building the whole out of the parts, and begins to accommodate the historical co-construction of parts and wholes that is so central a theme of evolutionary biology. Indeed, one of the greatest benefits of the remarkable technical developments we have seen in recent years is that it has begun to be possible to explore the dynamic interactions that not only bind parts into wholes, but equally, that reveal the ways in which those interactions constitute the parts themselves. The beginnings of a new lexicon is already evident as geneticists seek to forge new ways to think about biological function, looking for the clues to that function not in particular genes, nor in the structure of DNA and its protein products, but rather in the communication networks of which the DNA and the proteins are part. To be sure, DNA sequences remain an absolutely critical resource in these efforts, for the researcher as for the cell, but we are beginning to see a shift in focus in the search for biological function turns to the cellular processes responsible for regulation, and to the cross-talk between and among all the players of the cellular orchestra. Communication has become the new buzz word in biology, and it captures the discovery by traditionally reductionist life scientists of the powers of sociality. This is a definite good, but communication is just one term. The more we learn about how the parts work not only in interaction with each others, but also with the larger entities in which they are embedded, about the extraordinarily complex and versatile systems of gene regulation, about the signals mediating all the different levels of organization, and about the variety of epigenetic mechanisms of inheritance at play and the evolutionary feedback between the different mechanisms, the more compelling the need for an entire new lexicon, one that has the capacity for representing the dynamic interactivity of living systems, and for describing the kinds of inherently relational entities that can emerge from those dynamics. To repeat, time is crucial here: It is the medium in which interactions occur. For too long we have tried to build a biology out of nouns, a science constructed around entities. Perhaps it is time for a biology built out of verbs, a science constructed around processes. Perhaps even gene can be revived for the 21st century by reconceptualizing them as verbs.

I envision, in short, a conceptual framework that rests on a dynamic and relational epistemology. Of course, this is just one observer's guess, and as I say, my crystal ball is pretty cloudy. What is not a guess, however, what is, I believe, incontrovertible, is the need of post-genomics molecular biology both for new methods of analysis, for new conceptual frameworks, and for new language. Call it systems biology if you like, but exactly what that is, the various kinds of scientists now working under the umbrella that term provides will have to figure out as they go.

Postscript

I recently attending a meeting of physicists, engineers, and biologists, organized by the National Academy of Science (NAS), and it might be useful to compare my speculations with what actually transpired there. The conference was part of the NAS' new Keck *Futures Initiative*; and its the aim was to explore the new directions for interdisciplinary collaborations. Its title was: "*Signals, Decisions and Meaning in Biology, Chemistry, Physics, and Engineering*." The list of participants reads like a 'who's who' in the new "Systems Biology." Topics included: the evolution of modularity, of evolvability, temporal organization in living systems, cell-cell communication, quorum-sensing, the management of noise in single cells, strategies for survival in uncertain environments, and so on. It is noteworthy that, while some of these topics are familiar to experimental biologists, others are almost entirely new. The small number of molecules required for many processes suggests the almost ubiquitous presence of noise, and the focus on this issue – on both its uses and disuses; on mechanisms for noise amplification, and for its reduction raises familiar enough questions for engineers, but not ones that have often been asked by biologists. The same can be said for

the management of uncertainty. Also, the new focus on robustness – which appeared in virtually every session – draws deeply from the familiarity of engineers designing reliable systems. Yet, in each of these topics, the researchers drew deeply on both existing experimental data and on data they themselves had collected. Indeed, in many cases, by now standard molecular techniques were put to work in entirely novel kinds of experiments, e.g. using fluorescent markers to measure fluctuations in numbers of molecules. Or, in a somewhat more conventional kind of experiment, using fluorescent markers to track the biochemical response of individual bacteria to the number of other bacteria (of the same or of different kinds) present in its immediate vicinity.

In other sessions, profiles of gene expression at different stages of growth (e.g. bacterial growth) were used to probe organizational dynamics e.g. David Botstein is using gene chips to re-investigate the old chemostat experiments of Novick and Szilard to try to get a handle on what is actually going on inside the cells. Still other projects involve mining the data bases on signal transduction pathways to map the frequency of different kinds of logic circuits employed in biological evolution (recalling the pioneering work of Rene Thomas). Finally, and of particular interest to me, were efforts to probe the temporal dynamics of individual cells and cell populations, and to integrate temporal with spatial sensing in individual cells (chemo-attractant gradients, neuronal activity).

Many physicists were present, but hardly a trace could be found of the kinds of theoretical tools on which physicists usually rely. As is evident from my brief description, far more familiar were the theoretical tools of engineering and computer sciences.

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