A new paradigm for life beyond genetic determinism

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Shocking news from the Human Genome Project

When the highly anticipated sequencing of the human genome was completed in February, a headline in the San Francisco Chronicle announced: "Genome Discovery Shocks Scientists." Only some 30,000 genes were found in the human genome where scientists had expected 100,000; further, we humans have only 300 unique genes distinguishing us from a mouse. Discussion focused on the shock, the surprise, the wonder of it all.

News articles also made much of the fact that genes could work together to produce many proteins-far more than most scientists had previously thought. But none of this should have been shocking, none of these discoveries were really new. We have seen suggestions of 30,000 to 40,000 genes for at least a year; we have known for some time that different species have highly similar genomes-humans and chimps, for example; and scientists have, for years, been investigating the number and range of proteins resulting from gene interactions.

In fact, many biologists have suspected for decades that genetics alone would not be sufficient to explain life's complexity, and something more must be present. For these scientists, myself included, none of this news was a surprise.

Even Craig Venter, president of Celera, the corporate arm of the DNA sequencing effort, commented: "This tells me that genes can't possibly explain all of what makes us what we are." I would go further. I would interpret Venter's comment as suggesting nothing less than the failure of genetic determinism-the biological theory that the complex characteristics of human beings are caused by specific genes.

But after almost a century of life sciences dominated by this theory, and after ten years of the Human Genome Project (HGP) dedicated to finding the genes which cause human diseases, with the human genome finally sequenced and biotechnologists and drug companies standing by-after all that, to announce that the entire project was based on an incomplete and flawed theory would have been much more than "shocking." It would have been a scandal.

So Venter and his colleagues went on to describe how they would develop new technologies that would enable researchers to read the "Book of Life" and thereby describe the most complex diseases and behaviors in terms of causal genes. In other words, the HGP leaders were saying that, in spite of the surprises, genetic explanations would be found as promised.

Most observers commenting on the sequencing of the human genome, after their shock and surprise, fell back to genetic determinism. One exception was the distinguished Harvard biologist Stephen Jay Gould, who wrote in the New York Times: "The collapse of the one gene for one protein, and one direction for causal flow from basic codes to elaborate totality, marks the failure of [genetic] reductionism for the complex system we call cell biology."

So, reading between the lines of the news reports and press conferences with the HGP leadership last February, we may say that the theory behind the technology beginning to be

applied to living cells is flawed. While it does tell us much about our genome, it tells us little about who we are and how we got that way.

Where is the programme for life?

If Gould and Venter are correct in saying that genes alone cannot tell us who we are, then what will tell us? If the programme for life is not in our genes, then where is it? Many of us have been saying for years that there is no programme in the sense of an inherited, pre-existing script waiting to be read. Rather, inside each cell there are regulatory networks of proteins that sense or measure changes in the cellular environment and interpret those signals so that the cell makes an appropriate response.

What, then, is the role of genes? Genes specify information necessary to make proteins, and the genome as a whole provides a collective informational source. However, by itself a genome is passive: DNA, for example cannot make itself, and cannot construct a protein, never mind an actual cellular function. DNA has been called the Book of Life by HGP scientists. But for many other biologists DNA is not a book but simply a random collection of words from which a meaningful story of life may be assembled.

In order to assemble a meaningful story, a living cell uses a second informational system. Let me give an example. Let's say you have 100 genes related to a heart disease or cancer. These genes code for at least 100 proteins, some of which are enzymes, so you have a *dynamic-epigenetic* network, consisting of 100-plus proteins, their many biochemical reactions and reaction products. It is "dynamic" because it regulates changes in products over time, and it is "epigenetic" because it is above genetics in level of organization. And some of these changed products feed back to DNA to regulate gene expression. The key concept here is that these dynamic-epigenetic networks have a life of their own-they have network rules-not specified by DNA. And we do not fully understand these rules.

In short, genetics alone does not tell us who we are, or who we can be. While, as Gould says, the reductionist theory of genetics has collapsed, the dynamic-epigenetic point of view retains genetics as part of a new paradigm for life, one that has striking implications for the future of the life sciences.

The problem is part science and part philosophy

We must now ask two questions. First, where did the Human Genome Project go wrong? That is, where did the mistaken idea originate that complex human diseases could be traced to one or a few major genes? Second, why is the new science of gene management-dynamic-epigenetic biology-not in the news?

In response to the first question, there are indeed some diseases that are traceable to single genes. I worked on one, muscular dystrophy, for 25 years. These monogenetic diseases provided a simple model and a simplified formula: one gene leads to one disease.

But that model is wrong because it has limited application: Muscular dystrophy is one of the few clear cases where it works. In these relatively simple diseases, a single defective gene finds no redundancy, or back-up information, in the cell, and therefore the gene may be said to the be the single cause. But these diseases are rare; in fact they account for only 2 percent of our disease load.

The mistake of the HGP was to use that *simplified* model to attack all diseases, including diseases such as most cancer, heart disease, and bipolar disorder (manic depression). Together, those disease account for over 70 percent of our disease load.

The vast majority of human diseases are multifactorial: They are influenced by many genes interacting with one another and by a vast array of signals within the cellular environment (including nutrient supply, hormones, and electrical signals from other cells), and all of these are in turn influenced by the external world of the organism as a whole. Thus, mutations in specific genes in one human body, given its genetic background (all other interacting genes), might produce a disease; but in any other human body there might be little or no disease because each human being has a genetic background that is unique.

In addition, many diseases will be altered when the conditions of life are altered, especially in early life. For diseases involving many genes, the effect of each gene is small, and loss of function for one may be compensated by gene interaction and by environmental conditions.

Lung cancer is an obvious example of environmental impact: Even for long-term smokers, the impact on life expectancy is vastly improved for those who give up the habit. Even more telling is Spina bifida, one of several potentially fatal neural tube diseases in which there is failure of spinal cord or brain to close or develop.

Long thought to be a multifactorial genetic disease, Spina bifida is now actually known to be due to a deficiency of a vitamin. If the 70 million women capable of becoming pregnant were to take folic acid one month prior to conception, many of the neural tube diseases would disappear.

But HGP scientists thought, and still do, that they could find a small number of genes that are the key to these diseases. However, this strategy is flawed because for most multifactorial diseases affected by many genes, these genes have small, not large, effects. And genes with small effects are very hard to find. Even when found, one would have no way of predicting the disease outcome unless one also knew the "initial conditions" surrounding the developmental history of the individual. In addition, most multifactorial diseases like cancer take many years, even lifetimes, to develop, and one would have to know all the historical details to make predictions.

Finally, the strategy is flawed because it traces all causality back to genes rather than to genes coupled with dynamics, the duration of exposure to changing environments. Here again lung cancer is instructive since the disease is dependent on the dose (number of cigarettes) and the duration (number of years) of exposure.

Our second question is: Why is the alternative to genetics - the dynamic-epigenetic management of complex diseases - not in the news? The answer has as much to do with philosophy and sociology as it does with science.

This new view of life is right now being tested in laboratories around the world, and scientific journals bring weekly news of its progress. However, the full extent of cellular regulatory networks is not understood, nor do we have knowledge of how the cell as a whole integrates the output of these systems to produce an adaptive response to a complex set of ever-changing external signals.

The transition from a genetic determinist paradigm to a new, more complex regulatory paradigm will take much more time. The Human Genome Project has been devoted to a

determinist, gene-based view of life, and spent ten years sequencing the genome. But scientists outside the HGP tested various predictions along the way, and the community of science and technology arrived at a much more complex picture of life and of the genome that it started out with.

Until we have a theory, or a paradigm, of life that is able to assimilate the contradictions generated by the HGP and by the experimental community at large-one that is able to explain what genetics alone cannot-we will have to move ahead with caution and with every effort to put the dynamic regulatory science in place alongside the more familiar genetics. But moving ahead with caution, and with an incomplete theory of life, is not exactly newsworthy in today's atmosphere of certainty and instant rewards.

Nor does the HGP exist solely in the world of science. Over the past ten years, it has developed strong relationships with corporate, social, and economic interests, and has-willingly, I would say-become a tool of those interests. It has given itself over to a propaganda stream of unprecedented dimension and has made promises that play on the health aspirations of people everywhere. In addition, the corporate world of biotechnology has investments of billions of dollars in the pipeline, so withdrawal from the determinist position is extremely difficult. These are all clear facts, confirmed in our daily news.

Where do we go from here?

Along with many other scientists, I conclude that we are in the middle of a biological revolution. We have a failed or, at the least, an incomplete scientific paradigm called genetic determinism. At the same time, we have an alternative paradigm called epigenetic-dynamics, which is extremely interesting but also incomplete. Unfortunately, over the last 50 years our research portfolio has become unbalanced, heavily favouring genetics and ignoring dynamics. It will be difficult to change direction, if for no other reason than it will take a long time to train the next generation of scientists who understand both sides of the equation. And any change away from the genetic-determinist view will also be resisted by corporate forces that have a huge economic investment at stake. This resistance grows stronger as a result of university alliances with the corporate world of biotechnology.

In the long run, the issue of genetic determinism will only be settled when something like dynamic-epigenetics becomes complete enough to challenge the status quo. For now, the important problem before us is the technological problem of genetic engineering of organisms in the light of an imperfect understanding of how the living cell actually works. It must be emphasised that we simply do not understand how living cells respond over time to their manipulation through genetic engineering, and thus the error factor here remains large.

It seems to me that we must move ahead at several levels. The first as at the level of the social organisation of biology, and the second is at the level of biological science itself. By social organisation I mean the construction and imposition of scientific standards that should constrain attempts to genetically engineer or clone ourselves, our children, other animals, and the plants that constitute the basis of our agriculture and much more. If the announcements from the HGP tell us anything, they tell us that we do not now how organisms make themselves. As many developmental biologists have said, we are still in the dark ages about how organisms regulate their genomes to produce adults. While the

scientific inquiry must go on, technological applications must stop-until we are assured that we may proceed without doing any harm.

At the level of science itself, we must now ask what we want our life scientists to do next. They already can measure and show us things far beyond our expectations of only a few years ago. But now we are reminded, once again, that the wider environment as well as complex cellular processes - and not just genes - play important roles in shaping our lives. The work of corporate biotechnology will go on; as the *Wall Street Journal* reminds us, it is inevitable, as is human cloning, as is a future gene-based medicine for the wealthy few who hope to immunise themselves against premature diseases and death. But theirs will be a false hope. Premature disease and death will surely come if we allow a continued degradation of the very environment so necessary for the healthy expression of genes now present in all of us.

Emphasis on gene technology causes us to forget that a technology called public health has already provided a model for the future. Public health technology has given us nearly forty years of increased life expectancy in just the past 100 years-without genetic engineering of any kind, proving that the genomes we all have are already competent to provide us with a life expectancy at birth of 85 years.

The university and national (public) laboratories may now choose to take up the quest for new rules of complex adaptive systems we call life. We can choose to support work that would allow us to discover constraints at the level of multi-cellular organisms, populations, and ecological settings. Violation of these constrains could bring great risk to individual health and to stable ecosystems.

We thought the programme was in the genes, and then in the proteins encoded by genes. But knowing all the individual proteins will not reveal a programme; for that one needs to know the rules of protein networks that are coextensive with the cell itself. The programme location is the cell as a whole, and the cell, through signalling pathways, is connected to larger wholes and to the external world. If we could find the financial and other necessary inspiration, and the will to implement the additional research, we would have a science and a technology-a university-industrial complex-that everyone could invest in. The real questions for all of us are: Who chooses, and who decides the future of life?

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