Think Pieces

GENOMES, GOULD, AND EMERGENCE

by Ursula Goodenough

Abstract. The publication of the human genome has elicited commentary to the effect that, since fewer genes were identified than anticipated, it follows that genes are less important to human biology than anticipated. The flaws in this syllogism are explained in the context of a treatise on how genomes operate and evolve and how genes function to produce embryos and brains. Most of our most cherished human traits are the result of the emergence of new properties from preexisting genetically scripted ideas, offering countless opportunities to celebrate the evolutionary process.

Keywords: embryology; emergence; Stephen J. Gould; human genome; neurogenesis.

THE INCREDIBLE SHRINKING GENOME

I remember when I first heard about it a few months ago, the rumor that they weren't finding the 100,000 genes they were expecting for humans, that it was going to be more like 40,000 (the first rumors). And I smiled to myself. "Uh-oh," I thought, "this is going to freak people out."

So now it's down to more like 30,000, and now everybody knows what we already knew, which is that there are 20,000 genes in a roundworm and 25,000 genes in a tiny mustard plant. For many persons this has meant the final death knell for those scientific imperialists who keep telling us that "genes are everything"—as in this offering from Robin McKie, science editor for the *London Observer* (11 February 2001):

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> Scientists have made a radical breakthrough in our understanding of human behaviour with the discovery that we possess far fewer genes than previously thought. The discovery of our meager gene numbers—by two major groups of international scientists—reveals that environmental influences are vastly more powerful in shaping the way humans act. Their analysis of the first human genetic map—known as the genome—shows that we have as few as 30,000 genes, the blueprints for brain and body cells. This is a far lower total than expected, and dramatically undermines claims that human beings are prisoners of their genes. . . .
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> We are more free, it seems, than we had realized. The discovery that humans have far fewer genes than previously thought . . . has led scientists to reignite a debate that has split philosophers, educationalists and social reformers for millennia. There simply aren't enough genes, researchers now suggest, to have one each for all the characteristics that have been associated with them, from alcoholism to criminality to intelligence. The finding is a setback for those who believe we are largely preprogrammed, and a fillip to those who insist we are formed by our experiences. Nurture, the scientists now suggest, is far more important than nature.

The gene stock fell from 100 to 30 in a single round of journalism.

In this essay I describe what the genome projects, and the parallel breakthroughs in our understanding of embryology, cellular differentiation, and neurogenesis, are in fact telling us about how we came to be and who we are. After this I offer a short homily on the concept of emergence.

How Embryos Happen

The first common ancestral genomes encoded the core ideas found in the genomes of all living organisms, organisms that are now members of three superlineages—the prokaryotes (bacteria), the archea (hot springs inhabitants), and the eukaryotes (ourselves and most of the creatures we knowingly encounter). These core ideas include (1) encoding biological instructions in DNA, copying these instructions, and transmitting them to the next generation; (2) manifesting these instructions functionally in the shapes of proteins, proteins that interact with and modify one another; (3) encoding regulatory proteins that modulate the expression of target genes by recognizing shapes in DNA sequences that lie "upstream" of the genes themselves; and (4) running metabolic pathways and DNA replication/repair systems using the same time-tested sets of "housekeeping" enzymes. After the great three-way split, each superlineage utilized these core ideas to pursue its own styles of niche acquisition, with the eukaryotes coming up with some permutations that undergird their particular life cycles and patterns of radiation.

For the eukaryotes, gene numbers did increase: while the bacterium *E. coli* has 4,200 genes, yeast has 6,000, flies 14,000, worms 20,000, and mustard 25,000. But the numbers don't get us very far psychologically—why should a tiny plant that just sits there have 11,000 more genes than a fly that makes brain-based decisions? Nor do they tell the tale. The real trick was not an increase in gene number. The trick was the invention of

multicellular embryology, with a separate germ line to deal with the transmission of instructions to the next generation. In embryos, somatic cell types differentiate from one another and then influence the subsequent differentiation of other cell types to form the final niche-negotiating organism (or organisms if the life cycle includes larval stages). And embryos use genes and their regulatory modules with great economy and stunning ingenuity.

A gene carries the instructions for making a particular protein shape, but a protein rarely generates a phenotype on its own. Instead, it combines with other proteins, and the resultant protein complex interacts with other protein complexes, and so on. Once there is embryology, a particular cell type will express one set of genes and differentiate along one pathway, while a second cell type will express a second set of genes and differentiate along a second pathway. Should a given gene be expressed in the first cell type at a particular stage of development, its protein product will encounter a particular set of partner proteins to interact with, whereas should it be expressed in the second cell type, where a second set of genes is being expressed, many of the partner proteins on offer will be quite different.

Thus, a protein expressed in an embryonic neural lineage may participate in constructing the brain, but this same protein when expressed with different partners in an embryonic gut lineage may participate in constructing the pancreas. That is, the process is deeply combinatorial, and as we know, combinatorial systems can generate large numbers of variants with a small number of initial units—and 30,000 is hardly a small number. Moreover, embryos are set up to keep the combinatorial process going: certain protein complexes in a given cell type have the necessary configuration to switch on the next set of genes, whose protein products then make the next set of protein-partner choices, paving the way for the next round of cell-type differentiation. And finally, the cells themselves influence the expression of one another's genes as they make contact with one another during embryonic development.

Proteins engage in dazzling informational feats of their own. Consider the "idea" of the protein kinase, an idea that has arisen independently in several evolutionary lineages. Just as there are enzymes that catalyze housekeeping activities, so also are there enzymes that can modify one another, the most popular modification being to attach phosphate groups at targeted amino acid positions. Enzymes with this activity are called protein kinases. When a kinase recognizes the shape of its target protein and adds a phosphate group to it, the presence of the phosphate induces the target protein to adopt one of its two shape possibilities, the other possibility being the shape it adopts when the phosphate is absent (a kind of toggle-switch arrangement). The phosphate-induced conformational change will in turn allow the target protein to bind to its downstream partners, and so

on, resulting in a cascade of consequences. Particularly elegant are protein kinase cascades, where in one case a protein kinase kinase kinase phosphorylates a protein kinase kinase that can then phosphorylate a protein kinase that can then phosphorylate its target protein. And what gets this cascade started? The presence of a growth-stimulating hormone. And what is the final target protein? A protein that, when phosphorylated, induces the expression of genes necessary for undergoing growth and cell division. Cascades such as these undergird numerous cellular responses to their circumstances and numerous cell-cell interactions during embryogenesis.

But the real wild cards in embryology are the so-called "upstream" modules, the DNA sequences that govern whether, and when, their "downstream" genes will be expressed. These modules are not constrained to code for functional protein shapes; their only constraint is that they carry sequences that protein shapes recognize. Thus, an upstream sequence ATAGGCTAT will adopt one DNA-helical shape, and ATAGGTTAT another, and a regulatory protein (also called a transcription factor) can discriminate between the two, bind to one or the other, and influence whether the adjacent gene expresses its encoded protein—as in the following example.

Imagine a gene with a single upstream module and a transcription factor that, when it binds to that module, allows the gene to be expressed. The analogy can be to a lamp (the gene) with a single on-off switch: the gene is "on" when the transcription factor binds to the module and "not on" when it doesn't. Imagine now that this gene carries a second upstream module with the capacity to bind a second transcription factor, where the binding of the second protein interferes with the binding of the first and hence nullifies its "on" activity. If the second protein is present in cell type B but not cell type A, the result will be that our gene is off in cell type B and on in cell type A: the regulation of the gene's expression has become cell type specific. Cell type C, derived from B, builds on this arrangement, expressing a protein kinase with the capacity to phosphorylate the second and modulate its shape and hence its off activity: the more phosphorylation, the less the second protein can exert its off influence, and the more the gene is on. The switch has acquired a "dimmer" unit. Moreover, if levels of this kinase display a gradient along an animal embryonic axis such that cells destined to give rise to an organism's head contain much more of it than cells destined to give rise to the tail, our original gene will be on in the head lineage, off in the tail lineage, and intermediate in the thorax, with cascading consequences for each pathway.

Genes important for cell type determination in embryos in fact carry long strings of such upstream modules that display highly diverse regulatory-protein binding patterns in different cell lineages. Lamps with on-off switches have evolved into jet-age lighting systems, and most of this is

accomplished with combinatorial algorithms. Moreover, much of animal and plant evolution is driven by mutational changes in these upstream modules such that genes are expressed at different times and/or in different cell types during embryonic development. (For readers not familiar with our spectacular recent understandings of how embryos work, I warmly recommend Enrico Coen's *The Art of Genes: How Organisms Make Themselves* [1999] and Eric Davidson's *Genomic Regulatory Systems in Development and Evolution* [2001]).

How Brains Happen

The human organ that we are most interested in, our sentient brain, starts out as we have just described, with cell types differentiating into particular neural lineages. But complex brains like ours then go on to develop in a robustly epigenetic fashion, where *epi-* means building *on* the genes and not *beyond* the genes, as some seem to misunderstand the term. During brain development, key genes are expressed ab initio, and key genes are expressed along the way, but most of what happens is the consequence of cell-cell interactions and local cell-hormone interactions that are carried out by the proteins. The information encoded in the protein shapes mediates countless interactions between the vast network of neuronal cells. They contact and stimulate and inhibit one another in a combinatorial fashion reminiscent of the genetic regulatory circuits that set up embryos, and hence neurogenesis, in the first place. They migrate past one another, responding to mutually elaborated directional cues, and trigger phosphorylation cascades in one another. They compete with one another for access to growth hormones and electrical connections. Many survive, and many others die off. Nurture is involved in the sense that poor maternal health or nutrition can adversely affect the outcome, but otherwise the outcome has a life of its own: genetically instructed, epigenetically realized.

Genes set all this up, and in this sense human brains are preprogrammed —no genes, no brain—but they don't directly participate in most of the "decisions" made as the brain develops: we left behind some time ago the notion that there is a gene for this neuronal connection or that one. Indeed, given the trillions of neural connections in the brain at birth, not to mention those that form as a consequence of experience, 100,000 genes are no more up to the task than 30,000.

To be sure, faulty versions of key genes can compromise the project. Usually the failures occur early in neurogenesis, and the embryo fails to survive; but certain genes, for example, may influence the course of neurogenesis in such a way that the final outcome is a brain that may go on to develop schizophrenia. In this sense schizophrenia is heritable, and the faulty genes that participate in this outcome may come to be dubbed the "schizophrenia genes." But this is shorthand, a shorthand that has, regrettably, led to much of the confusion about the 30,000 number. Whatever

the schizophrenia genes turn out to be, they will almost certainly prove to be team players.

The Emperor's New Clothes

So now we can step back and contemplate our genome with fresh perspective. Consider, for example, the genome project announcement that there are "only" three hundred genes in the human that are not also found in the mouse. Three hundred now starts to look like a large number. If one of these new genes were to be expressed early in the lineages giving rise to neurons of the prefrontal cortex, quite different patterns of precortical wiring might result: effect A, generated by the new gene, might influence outcome B, which would modulate outcome C. Another of the new gene products might alter the configuration of a gene-regulating protein complex such that a gene expressed at day 12 in mouse neurogenesis would not be expressed until the analogous day 15 in the human, again with multiple consequences. Such changes in the timing of embryonic gene expression are called heterochronic, and heterochrony accounts for much of the diversity among embryos. Indeed, when we learn, as we will, that we share almost all of our genes with the chimpanzee, heterochrony will emerge as the most likely explanation for most of our differences.

A second observation to come from the human genome project is that, if our DNA genome can be said to be six feet in length, then our 30,000 genes occupy less than one inch of the total (Rick Weiss, *Washington Post*, 11 February 2001). Most of the rest is an apparent wasteland of dead genes and pieces of "selfish" DNA that hitchhike along for the ride, the replicating enzymes being blind as to what they copy. Different lineages vary enormously in how much of this stuff they carry along: yeast has very little of it, presumably because of selection for streamlined genomes in rapidly dividing organisms, while salamanders have much more of it than we do. Some news reports have attempted to put a positive spin on this, proposing that the nongenic DNA may be DNA-in-waiting, poised to contribute to evolutionary change. Others have even suggested that this DNA contributes to mysterious properties such as spirituality (suggesting that the salamander is more spiritual than we are?). But most of these proposals seem both strained and to miss the point. The point is that, whenever you have a memory system in which the copying function is not stringently edited, "junk" will accumulate. The wonder is that we and other creatures forge ahead despite this major design flaw.

And indeed, design, at least in the way we humans use the term, seems to have little to do with what we encounter in genomes. Rather, they record a history of tinkering. With the sequence of a human gene in hand, we can go to computer databases and ask whether a similar gene has been found in other organisms, such similar genes being called homologues. The answer is that approximately 50 percent of human genes have homo-

logues in yeast, and approximately 75 percent of human genes have homologues in worms. The evolutionary explanation for this finding is that when a gene arises that encodes a "good idea"—a protein domain that is particularly adept at phosphorylation, or binding to iron or to DNA or to another cell—that idea gets used again and again as other genes arise. Indeed, new genes are rarely created from scratch. Instead, a gene duplicates and the second copy accumulates new mutations, or else pieces of several old genes splice together to form a new hybrid gene such that several good ideas show up in the same protein product, much as a car might be fabricated using a Rolls engine and a Chevy chassis. The overwhelming evidence for tinkering as the core evolutionary process is, to my mind, the most important intellectual insight to emerge from genomics.

The Gould Response

This essay must now be put in a temporal context. The morning after I wrote the preceding paragraphs, there appeared an op-ed in the *New York Times* (19 February 2001) by Stephen Jay Gould, which I quote in near–full length. The echoes of Robin McKie of the *London Observer* should be apparent.

> The fruit fly *Drosophila*, the staple of laboratory genetics, possesses between 13,000 and 14,000 genes. The roundworm *C. elegans*, the staple of laboratory studies in development, contains only 959 cells, looks like a tiny formless squib with virtually no complex anatomy beyond its genitalia, and possesses just over 19,000 genes.
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> The general estimate for *Homo sapiens*—sufficiently large to account for the vastly greater complexity of humans under conventional views—had stood at well over 100,000, with a more precise figure of 142,634 widely advertised and considered well within the range of reasonable expectation. *Homo sapiens* possesses between 30,000 and 40,000 genes, with the final tally almost sure to lie nearer the lower figure. In other words, our bodies develop under the directing influence of only half again as many genes as the tiny roundworm needs to manufacture its utter, if elegant, outward simplicity.
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> Human complexity cannot be generated by 30,000 genes under the old view of life embodied in what geneticists literally called (admittedly with a sense of whimsy) their "central dogma": DNA makes RNA makes protein—in other words, one direction of causal flow from code to message to assembly of substance, with one item of code (a gene) ultimately making one item of substance (a protein), and the congeries of proteins making a body.
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> We may envision several kinds of solutions for generating many times more messages (and proteins) than genes, and future research will target this issue. In the most reasonable and widely discussed mechanism, a single gene can make several messages because genes of multicellular organisms are not discrete strings, but composed of coding segments (exons) separated by noncoding regions (introns). The resulting signal that eventually assembles the protein consists only of exons spliced together after elimination of introns. If some exons are omitted, or if the order of splicing changes, then several distinct messages can be generated by each gene. [This mechanism is called alternative splicing—Au]

The implications of this finding cascade across several realms. The commercial effects will be obvious, as so much biotechnology, including the rush to patent genes, has assumed the old view that "fixing" an aberrant gene would cure a specific human ailment. The social meaning may finally liberate us from the simplistic and harmful idea, false for many other reasons as well, that each aspect of our being, either physical or behavioral, may be ascribed to the action of a particular gene "for" the trait in question.

But the deepest ramifications will be scientific or philosophical in the largest sense. From its late 17th century inception in modern form, science has strongly privileged the reductionist mode of thought that breaks overt complexity into constituent parts and then tries to explain the totality by the properties of these parts and simple interactions fully predictable from the parts. ("Analysis" literally means to dissolve into basic parts). The reductionist method works triumphantly for simple systems—predicting eclipses or the motion of planets (but not the histories of their complex surfaces), for example. But once again—and when will we ever learn?—we fell victim to hubris, as we imagined that, in discovering how to unlock some systems, we had found the key for the conquest of all natural phenomena. Will Parsifal ever learn that only humility (and a plurality of strategies for explanation) can locate the Holy Grail?

The collapse of the doctrine of one gene for one protein, and one direction of causal flow from basic codes to elaborate totality, marks the failure of reductionism for the complex system that we call biology—and for two major reasons.

First, the key to complexity is not more genes, but more combinations and interactions generated by fewer units of code—and many of these interactions (as emergent properties, to use the technical jargon) must be explained at the level of their appearance, for they cannot be predicted from the separate underlying parts alone. So organisms must be explained as organisms, and not as a summation of genes.

Second, the unique contingencies of history, not the laws of physics, set many properties of complex biological systems. Our 30,000 genes make up only 1 percent or so of our total genome. The rest—including bacterial immigrants and other pieces that can replicate and move—originate more as accidents of history than as predictable necessities of physical laws. Moreover, these noncoding regions, disrespectfully called "junk DNA," also build a pool of potential for future use that, more than any other factor, may establish any lineage's capacity for further evolutionary increase in complexity.

The deflation of hubris is blessedly positive, not cynically disabling. The failure of reductionism doesn't mark the failure of science, but only the replacement of an ultimately unworkable set of assumptions by more appropriate styles of explanation that study complexity at its own level and respect the influences of unique histories. Yes, the task will be much harder than reductionistic science imagined. But our 30,000 genes—in the glorious ramifications of their irreducible interactions—have made us sufficiently complex and at least potentially adequate for the task ahead.

We may best succeed in this effort if we can heed some memorable words spoken by that other great historical figure born on Feb. 12—on the very same day as Darwin, in 1809. Abraham Lincoln, in his first Inaugural Address, urged us to heal division and seek unity by marshaling the "better angels of our nature"—yet another irreducible and emergent property of our historically unique mentality, but inherent and invokable all the same, even though not resident within, say, gene 26 on chromosome number 12.

Let me begin by commenting on alternative splicing, a mechanism I omitted from my earlier account. By invoking alternative splicing (and flies and worms do alternative splicing as well), the human numbers can be pushed back up to something closer to 100,000 if each gene is assumed, on average, to be alternatively spliced three different ways: you basically get three proteins for the price of one gene. I omitted alternative splicing from my account because my core argument is that it is not the number of genes that is important but their combinatorial properties. Increasing the protein number to 100,000 does not explain how animal, and particularly mammalian, genomes achieve their results. In fact, alternative splicing is yet another elegant example of gene-controlled regulation. A gene is spliced in a particular fashion to yield a particular protein depending on its cell-type context: gene *a* is spliced to yield protein A1 in one cell type and spliced to yield protein A2 in a second cell type. The splicing enzymes are responding to gene-driven cues. It is still genes all the way down.

If my paragraphs preceding the Gould op-ed have succeeded, my reader should be able to recognize some of the flawed premises and conclusions that he offers. Nothing is awry with the "central dogma," and the doctrine of one gene for one protein (or three proteins) has in no way collapsed. The notion of "one direction of causal flow from basic codes to elaborate totality" has not been the doctrine of biology for the past fifty years: the studies of Jacob and Monod on bacteria in the 1950s offered elegant evidence that many genes generate proteins that bind to the upstream modules of other genes and influence their expression, generating anything but a unidirectional causal flow. And yes, it can be said that organisms are indeed "a summation of their genes," once it is grasped that this means that "organisms are a combinatorial summation of their gene products and regulatory sequences." Humans may well have "better angels," and these will indeed not be encoded by gene 26 on chromosome 12. Instead, we now understand that a wondrous collaboration of genetics and epigenetics creates human brains with their "historically unique mentality."

There is a passage where Gould says things along these lines: "The key to complexity is not more genes, but more combinations and interactions generated by fewer units of code." But he then goes on to state that "many of these interactions . . . must be explained at the level of their appearance, for they cannot be predicted from the separate underlying parts alone." This is correct, but those participating in genome projects never thought otherwise. The sequence of a genome, and hence the sequences of its encoded proteins, does not indicate how an organism works. Having a genome sequence is analogous to a linguist having a list of the words (proteins) used by a particular culture. With the list in hand, she can go to databases and in many cases trace the etymology of particular words, often thereby obtaining clues as to what concept they might encode. And then, list in hand, the next project is to understand how these words fit together,

in grammar and syntax and context, to generate the language, and hence the understandings, of the culture.

Now that we have in hand the list of human proteins and have some clues as to what some of them may be doing from the study of simpler organisms, the next project does not entail *predicting* their interactions with DNA and with one another but rather *studying* these interactions, using the same methodological reductionism as before. A whole array of technologies is available to analyze the expression, coexpression, interactions, and function of genes and proteins. Indeed, these techniques have been under intensive development during the past decade by biotechnologists who have been anticipating this next and most intriguing postgenomics level of analysis. Gould predicts that an "ultimately unworkable set of assumptions" (reductionism) will be replaced by "more appropriate styles of explanation" that study "complexity at its own level," but it is not apparent how he envisions this study of complexity at its own level to take place with reductionism disallowed.

Meanwhile, from my bottom-up perspective, I predict that organisms will indeed eventually be explainable as a summation of their gene products, with the sums mind-boggling but not irreducible. Reductionism has not "failed for the complex system that we call biology." It has only just gotten started. How far we want to take the resultant understandings along the path of technological application, and in which directions, are urgent questions that plead for informed dialogue, but these difficult issues are independent of the discovery process itself.

As for humility, I myself prefer the testimonial of Robert Waterston, Director of the Washington University Genome Center. It is a humbling perspective, Waterston told Weiss of the *Washington Post* (11 February 2001). A person who gazes upon the human genome, he said, is likely to walk away feeling a little bit less the center of attention, less certain about being the sole purpose of it all. "You can't study the genome for very long before you start feeling that you're just a transient vehicle for making more DNA."

But I was heading toward the concept of emergence, and I will take Gould and McKie along with me.

Emergence

Just as there was the great three-way split in the evolution of organisms, so do I observe a trifurcation, with many intergradations, in theistic responses to the scientific worldview. One path rejects science, usually in favor of something more familiar and presumably more meaningful. The second path posits that God designed/planned the universe and life—photons and DNA and all—with something in mind that we can come to discern. And the third is to posit that God *is* the process, the unfolding, the manifestation. Those of us who are awkward with God-talk can nonetheless join in consecrating the process of becoming. And to do so is to declare the sa-

credness of all these genomes, flawed and junk-filled and jerry-rigged as they may be. Genomes are absurd. They really are. Small islands of meaningful genes and their regulatory modules floating in seas of meaningless sequences, each gene some crazyquilt of former ideas. Their very absurdity calls us yet again to acknowledge, in Gordon Kaufman's wonderful phrase, the serendipitous creativity of Nature (Kaufman 1995). And in biology, serendipitous creativity is all about emergence.

I have offered an explanation of emergence in a previous issue of this journal (Goodenough 2001) and will only summarize here. Granted that biological traits (and hence their summation as an organism) are constructed from protein-protein and protein-gene interactions, it is also the case that these interactions repeatedly generate emergent properties, "something more from nothing but." For example, the ability of a neuron to stimulate or suppress the firing of another neuron is nothing but the summation of hormonal neurotransmitters, ion fluxes, and the electrical excitability of membranes, all of which can be reduced to their component parts. But it generates something more: neural communication. The communication is an emergent property, one that is then acted on by natural selection: In a population of animals, those with neurons that communicate well are more likely to survive and produce viable offspring than those with neurons that communicate less well. In selecting for communication, what is in fact being selected are the genetic programs that give rise to brains with communicative properties. The genes, the nothing-buts, don't go away, but the emergent traits emerge as life's mode of creativity.

Gould states that the "better angels of our nature" are yet another "irreducible and emergent" property of our mentality, but "inherent and invokable all the same." I would respond that it is not coherent to state that an emergent property is irreducible; if something is emergent, then it emerged from that to which it can be reduced. Our historically unique mentality, I would say, is reducible, and robustly emergent, *and* (not *but*) inherent and invokable. Our mentality takes off from the capacities inherent in our gene-instructed epigenetically crafted brain, and our brains are fashioned to be eminently invokable and to be instructed and deeply complexified by nurture and environment and experience.

We are not prisoners of our genes. Rather, we are beholden to them for producing bodies that work and brains that allow us to be human.

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