Jeff's view
My other genomes

The hunt for the complete sequence of our nuclear DNA is now a heroic tale. But heroic tales invite hyperbole. I am tired of hearing that the 23 chromosomes in my cells' nucleus hold the *complete blueprint* of what is, or could be, me. There is more to me than that. The sequence of my nuclear DNA is not *my complete genome*. If a genome is an *integrated set* of biological information that is passed on from one generation to the next, then I have not one genome, but at least three. Maybe more.

Hardly anybody mentions these other genomes, as if they were slightly illegitimate. In fact, that is what they probably are. They are the fruits of illicit trysts whose story goes back a long way.

To start with, there is my mitochondrial genome. I should really say 'genomes', because each of my body cells has hundreds or even thousands of them. Each is a small ring of double-stranded DNA that encodes 13 water-insoluble subunits of the oxidative phosphorylation system in the mitochondrial inner membrane. My mitochondrial genome only has 16 569 letters and talks a strange lingo. For example, when it says 'TGA' it does not mean 'stop' like everybody else, but 'tryptophan'. For 'stop', it says AGA, by which a well-spoken DNA would specify 'arginine'. Yet this small genome is nothing to sneeze at. I need every single one of its 13 protein products to stay alive. My mitochondrial genome does not say much, but what it does say counts. It detests small talk.

My mitochondrial genome is also bizarre in many other ways. For example, it is hard to see why it exists at all. To replicate it and to express its 13 protein products, my cells must set aside at least 100 proteins, all of them encoded by nuclear DNA and made outside the mitochondria. You do not have to be Swiss to wonder why cells put up with such an investment. I once thought that the proteins encoded by mitochondrial DNA are so water-insoluble that they must be made right where they are used – inside the mitochondria. This idea is now less attractive to me, because three of my colleagues have recently engineered yeast cells that can make some of these 13 proteins outside the mitochondria and transport them back in. When everything is said and done, there is no logical reason for the existence of mitochondrial DNA. The reason is historical. About 1500 million years ago, some mysterious ancestor cells engulfed respiring Gram-negative purple bacteria and this symbiosis turned out to be a success. The engulfed bacteria gave their host ATP by oxidative phosphorylation, and the host offered a protective environment, or perhaps a more efficient system for safeguarding and replicating the endosymbionts' DNA. DNA is an easy prey for oxygen radicals coming from the respiratory chain in the cell membrane, and the bacterial endosymbionts may have been eager to put a safe distance between that membrane and their DNA. Who wants to store precious family records near the fireplace? This DNA transfer may still go on, or may have stopped once the domesticated endosymbionts had modified their genetic code. These endosymbionts are now my mitochondria, and what is left of their genome is my mitochondrial DNA.

That makes two DNA genomes for me. Yet even the two together do not know all it takes to make one of my cells. This feat also requires information that is not written down in DNA, but in membranes.

My mitochondria arise by growth and division, just as their free-living bacterial ancestors did 1500 million years ago. Most of the mitochondrial building blocks are specified by my nuclear DNA and made in the cytosol, but many of them can only be put together correctly on a mitochondrion that is already there. Each mitochondrion is a matrix, or template, that tells new building blocks where to go. Mitochondria, unlike multi-enzyme complexes, bacterial ribosomes, or simple viruses, cannot form spontaneously when their parts are randomly mixed together. They are too complex for that. They have been enslaved long ago, yet cling to what is left of their former independence. They know how to keep up appearances. If a cell were to lose its last mitochondrion, most of the mitochondrial proteins would still be made, but they would wander around aimlessly and be degraded. Mitochondria contain at least a dozen 'usher proteins' that are essential for other mitochondrial proteins to find their proper place and become functional inside the mitochondria. These usher proteins include receptors on the mitochondrion's surface, subunits of channels across the outer or inner membrane, chaperone proteins, and proteases. Import and proper function of an usher protein often requires that the very same usher protein be already in place and ready to work; in other words, many usher proteins import and activate themselves. If any of them is inactivated by mutation, the mitochondrion's template function is lost, mitochondrial biogenesis fails, and the cell dies. Once the last template is gone, the lights go out forever.

My cells appear to have a few other membranes that can neither self-assemble nor arise by transformation of other structures. The endoplasmic reticulum is one of them. Hydrogenosomes and peroxisomes may be others. And in plants, it is the chloroplasts, of course. Each of these membrane-bound organelles appears to be descended from a free-living organism that entered symbiosis with another cell, and then became one of its integral parts. Hydrogenosomes are particularly intriguing. One finds them in mitochondria-less organisms that eke out a living in oxygen-deficient biological slums. Hydrogenosomes have a striking resemblance to mitochondria: they have about the same size, are bound by two membranes, and make ATP by converting pyruvate to acetyl-coenzyme A. Many of their enzymes have very similar amino acid sequences as the corresponding mitochondrial enzymes and the signals that target proteins from the cytosol into hydrogenosomes show an uncanny resemblance to those that target proteins into mitochondria. Yet unlike mitochondria, hydrogenosomes lack DNA, and some of the primitive eukaryotes in which they exist diverged from the main line of eukaryotes well before typical mitochondria saw the light of the day. Most likely, hydrogenosomes and mitochondria arose from a common ancestor and then went their separate ways. Hydrogenosomes did not need most of the proteins made by

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present-day mitochondria and may have managed to jettison their DNA completely before this DNA had a chance to adopt its own dialect. Peroxisomes, too, may have arisen from a respiring endosymbiont, even though they lack DNA and are in many ways quite different from mitochondria. I wonder how many such licentious encounters are going on at this very moment, spawning future organelles.

The Golgi apparatus, lysosomes, endosomes, exocytotic vesicles, the vacuole of yeast and plant cells, even the plasma membrane – they all are formed by modifying the endoplasmic reticulum. If one mistreats cells with drugs, conditional mutations, or other insults, they may lose their Golgi apparatus, their exocytotic vesicles, or their vacuole without dying, and will reform them from the endoplasmic reticulum if the air is again clear. The same is apparently true for the other derivative organelles. With mitochondria, and probably also with hydrogenosomes, the endoplasmic reticulum, and peroxisomes, there is no way that this can happen. They must be passed on from one cell to the next. They are part of my biological heritage – my other genomes, as it were. My two DNA genomes will tell you everything about the molecules in my mitochondria, and quite a bit about how these molecules are assembled into multi-protein complexes. But they will be silent about the existence of an inner and an outer membrane, or how these membranes are put together the right way.

That a particular arrangement of molecules can be heritable biological information has been known for almost half a century. The cilia on the surface of the protozoan *Paramecium aurelia* are arranged in characteristic rows such that all cilia of a given row point in the same direction. During sexual reproduction, two *Paramecium* cells attach themselves to each other and form a cytoplasmic bridge through which they exchange their genetic material. In most cases, the two partners then separate precisely so that each gets back its normal surface structure. But even *Paramecium* can get carried away by passion and occasionally the separation is faulty so that one partner retains a snippet of the other's surface. This surface abnormality is reproduced for many generations in the offspring when these divide non-sexually. DNA does not seem to be involved, because one can get a similar result by surgically grafting a piece of surface the wrong way and letting the disfigured cell divide asexually. This surface change behaves like a DNA-linked mutation, but is less stable. It injects a little Lamarckian heresy into the Darwinistic dogma and reminds us that evolution is inherently irreverent. The most plausible explanation is that the surface of *Paramecium* is a template for building new surface. Reading the DNA of a given *Paramecium* cell could perhaps tell us that there are different *possible* surface structures, but not which of them is actually present.

How much information is there in my cell structures? I do not know. But I do know that this information is inherited and that it is just as essential as the one that is written down in my two DNA genomes. I could never redraw the borders of Europe's countries by reading textbooks on law or geography, because these borders were shaped by chance skirmishes, clever treaties, or propitious marriages. They are a record of Europe's long and convoluted history. In the same way, I could never reconstruct my cells' membrane borders by reading my two DNA genomes, because these membrane borders are a record of life's dramatic history. It is this history that makes everything about them fall into place.

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