Selfish Metabolism

Evolutionary biology has traditionally made much of the concept of selfishness. Charles Darwin reduced adaptation (and to a less satisfying degree, speciation) to the heritable variation and competition among individuals. As understanding of the genetic control of heredity and morphogenesis has become more sophisticated, Richard Dawkins has advocated displacing selfishness somewhat, from the organism to its genes. This perspective makes many mathematical aspects of the population genetics of kin selection, viral infection, and genomic imprinting intuitive and natural; though it perhaps underemphasizes the difficulty of apportioning evolutionary credit among genes that act in concert during development. Certain proposals for the RNA world as a first chemical stage of life have even gone so far as to attempt to keep the self while possibly doing away with the cell. Tiny, selfish RNAs in solution or on surfaces are imagined to have competed with one another for replicating potential and raw materials from a transient primordial mixture of organics, much as modern viruses compete with a cell's host genome for consumption of the cell's metabolic resources.

In all these scenarios, selfishness brings together two very different notions. One is a kind of greediness, in which existing states of order compete to increase their own instantiation at the expense of others. The other is a notion of individuality, whether of the organism, gene, or self-replicating RNA molecule. In Darwin's theory of evolution, and for many practical applications to modern life, the two are indeed tightly coupled. However, this need not always be so (even today), as evolutionary theorists are coming to recognize whenever viral and host genes define two co-present and incommensurable notions of self, or when they consider that the parentally imprinted haplotype in a diploid organism is both genetically incomplete to make a cell, and yet has an identity that spans multiple generations of organisms.

Moreover, certain areas of biology do not seem adequately captured in this selfish paradigm at all. Ecology concerns robust and richly ordered networks of relations, which are not properties of any of the individuals or taxa per se. And it doesn't help to try to envision ecosystems (Gaia notwithstanding) as super-organisms, because ecosystems don't obey the mathematics of simple Mendelian heredity and they don't compete; they pass through sequential forms of relatednesses in a sort of noisy succession. The greedy but non-individualistic nature of ecosystems becomes especially salient if we try to understand the origin of life, because many of the most universal and robust properties of life are more easily visible at the ecosystem level of aggregation than at the level of individual organisms.

Perhaps the most striking such universal is the network of reactions that we call core metabolism. As with many familiar concepts in biology, our understanding of what metabolism is continues to change. For most of the past 60 years metabolism has been understood in biochemistry to refer to the metabolic pathways chart first developed by Donald Nicholson in 1955 and constantly updated since that time. Much of the original chart was based on the physiology of humans and

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other complex heterotrophic organisms. Stanley Miller has even proposed that metabolism be defined as that network of reactions in a cell catalyzed by proteinaceous enzymes which in turn are encoded in the cell's genes. Such a definition ties metabolism to the individuality of the cellular compartment and the genome, and gives little prominence to the small molecules (called core metabolites) which are the substrates; they are in this view merely followers of the selfish genes.

Many are coming to believe, however, that there is more to metabolism than can be captured in the selfishness of genes or compartments: that metabolism is in many respects a property of ecosystems, and that the metabolic character of life is a planetary phenomenon, no less than the atmosphere, hydrosphere, or geosphere, and may predate individuality. For one thing, it is extraordinary that the metabolism of every species, perhaps as many as thirty million, maps in whole or in part onto a single chart. The phylogenetic root chart appears to correspond well with the extant metabolisms of many reductive chemo-autotrophs which, like ecosystems unto themselves, synthesize the entire organism from inputs of simple inorganic molecules and ions and one-carbon compounds. The notion of a canonical ancestral chart, together with the phenotypic conservativeness of the reductive chemo-autotrophs, may suggest that the core can be traced to the last universal common ancestor, and that it has been considerably more insensitive to evolutionary change than other features of the biological hierarchy. That is, the genes and proteins seem to adapt themselves to preserving the integrity of the metabolic chart, even as the conditions of life and the complexity of developmental and ecological organization have repeatedly undergone major innovations.

If we want to think of metabolism as more than a follower of genes—and in many respects, we will want to think of it as a leader—we need a different conceptualization. The construct "Metabolism" should be one that sensibly applies to prebiotic, cellular, organismic, or ecological entities. To match the instances we know, it must refer to the ingestion of carbon, hydrogen, nitrogen, oxygen, sulfur, phosphorous, and a few other assorted atoms, and the synthesis of a small set of molecules, perhaps less than 300, which may further react to form a hierarchy of more complex molecules. The latter include chimeromers, multimers, polymers, and the larger aggregates that make up cells. (Chimeromers are a subclass of multimers consisting of two or more types of monomers; several cofactors are examples.)

A metabolism capable of serving as such a bridge, between inorganic chemistry and biochemical complexity, could not have been just any old network of organic chemical reactions. It would need to have been: (1) sparse within the network of possible reactions (so that most of the chemical material flows through a few pathways); (2) particular (the pathways observed should be necessary and predictable, not accidents which would depend on later memory mechanisms such as genes to be preserved), and (3) robust (the observed pathways should be stable under stochastic fluctuations of the components, if there were to have been any possibility that more complex molecular systems should have emerged using core metabolites as foundations).

Metabolism endowed with these properties at a network level could be greedy for order without being individual, and it would thus require us to separate these two aspects of selfishness. Such a metabolism would also naturally entrain the order of the structures built on it, in that whenever a molecule or structure arises at a higher level and enhances core metabolism, it is recruited via a feedback loop or loops to remain part of the developing complexity of the evolving structure. In extant life, this feedback dependency can be seen at the biochemical, cellular, organismic, and ecological levels. Darwinian competition among organisms emerges with the advent of individuality, from a deeper molecular competitive exclusion that statistically selects the inputs from which all of life must be assembled. The appeal to metabolism for ultimate validation can be seen as much when a cofactor develops to enhance reactions that incorporate ammonia into amino acids, as when a Lake Turkana crocodile develops a jaw structure enabling it to catch and eat Nile perch.

The commonness of the metabolic core for all biota leads to trophic ecology, for the eaten is always reduced to the core by the eater—but it typically is not reduced further. The ecosystem, like the reductive chemo-autotrophic cell, takes in CO_2, H_2 (or other reductants), NH_3, H_2S, and H_3PO_4, to create this core which consists of twenty amino acids, four ribonucleotides, four deoxyribonucleotides, and a few sugars, polar lipids, and cofactors. The rest of biomolecular complexity, and most of the distinction among individuals and species, is defined by combinatorial assembly of building blocks from this core.

As we look at biochemistry, we can see that some parts were sensitive to the emergence of individuality, while others largely were not. The catalytically active cofactors are often produced only by bacteria or archaea and then exchanged via trophic networks through whole ecosystems. The ecology does not really care which organisms carry the genes to make cofactors, as long as they are present in the collective (a prioritization reflected in J. Craig Venter's Global Ocean Sampling metagenome). To varying degrees, the same is true for sugars, amino acids, lipids, and nucleotides. In contrast, at the polymer-sequence

level, we do not share. Humans cannot incorporate bovine hemoglobin, and while many people are fortunately able to use the small polymer swine insulin, we are reminded of that good fortune by the significant minority who cannot.

Acknowledging the selfishness of metabolism does not undermine ideas we have come to value from evolutionary theory, but it may require more complexity in the ways we use them. The observed canonical metabolic core contains about 300 compounds, and of these 30–40 outputs go into higher structures. The network of these compounds appears to be universal, but we do not know if it was the only one possible. Indeed, one of the major queries in looking at biochemistry from the bottom up is asking why this particular sparse set and why these outputs from it. Is it unique today because it was most successful for individuals in the post-Darwinian world? Or was it unique as a chemical part of the geosphere, so that the Darwinian age never had the chance to emerge on a foundation that was much different? The second alternative would suggest that there is a grand unified theory for at least the core of metabolism, which links ecology, biochemistry, and the Darwinian world into a whole larger than any one of them.