

Searching for the Laws of Life

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We expect that life originated in a steady, reliable environment that was relatively rich with simple but energetic molecules...

Separating Chance from Necessity

The noted contemporary paleontologist and natural historian Steven Jay Gould has said of the history of life that "...any replay of the tape would lead evolution down a pathway radically different from the road actually taken." [1] Should one make such a strong statement about all aspects of life, though? Gould studied the body plans of the major groups of animals that suddenly appeared in the fossil record 570 million years ago, in a period called the "Cambrian explosion." Indeed it seems largely accidental that just this combination should have come to make up the entire animal world, creating a large-scale taxonomy of which only a subpart has survived to this day.

But what about the chemical composition of those organisms, or the way they capture energy to maintain and replace themselves, which we also share? Could that really have taken a different form than the one we see attested today? What about the great events when biological innovations changed the surface chemistry of the earth, like the

emergence of photosynthesis that loaded our atmosphere with molecular oxygen, after two billion years in which it had had very little? What of endosymbiosis, when one group of bacteria-like unicells began living as organelles within another? How much of chance is there in these stages of our shared structure and history, and how much of necessity?

For five weeks in the summer of 2003, a diverse group led by Science Board member Harold Morowitz, Postdoctoral Fellow Jennifer Dunne, and Research Professor D. Eric Smith met to examine some of the universal structures and patterns in living systems, from biochemistry to ecology, and to ask which might have arisen from the action of underlying "laws of life." The goal was a set of rules or principles that select living forms from chemistry and geophysics, the way simple rules such as the Pauli exclusion principle generate the periodic table of the elements, and all of chemistry, from a few properties of the proton, neutron, and electron.

The discussion ranged from narrow technical details of core biochemistry, to broad philosophical questions of what should be meant by "laws" in biology. It is clear that, while biology is a natural science whose observations can be quite precise and often quantitative, the biological notion of understanding assigns less importance to predictions about the specific course of the future than is given in chemistry or physics. The roles of accident, individuality, and uniqueness are correspondingly greater in biology, and with these it becomes less clear how to interpret those features of life that we do observe as universal.

While the deeper questions about the ontological role of laws were largely left unresolved, a serious attempt was made to account for the specific universal features of life that are simplest and most primitive, for which the predictive power of biological laws should most resemble that in physics and chemistry. For these very old features, universal occurrence is more likely to indicate that few solutions to biological "function" were possible, and that this is why we have the forms we do. Understanding these structures is also likely to be critical as we try to piece together the origin of living from nonliving matter.

Such a focus on early core chemistry leaves many aspects of biological law unexplored, and even leaves us unable to say anything new about a host of regularities that the group examined, such as the beautiful web-like cell wall that encrusts all bacteria like a Fabergé egg, or the ubiquitous scaling laws in ecology. However,

with chemical universals as starting points, the group was able to embed biology in the larger geochemical world, and also to look for the first place where uniquely biological forms of necessity differ from those in physics and chemistry.

A New View of Life's History

A lot has been learned about the earth's early geochemistry and the metabolic history of organisms since the early "chicken soup" models of the emergence of life. In the 1950s, Stanley Miller and Harold Urey showed that a

broth of surprisingly complex molecules could be produced from the action of lightning in an atmosphere of ammonia, methane, and water, and this spawned a whole generation of models for the first emergence of proteins, DNA and RNA, and how these might have assembled into the machinery of cells [2].

The investigations were truly revolutionary, because they turned questions about the origin of life into laboratory science, and many of the experiments uncovered valuable pathways for synthesis of

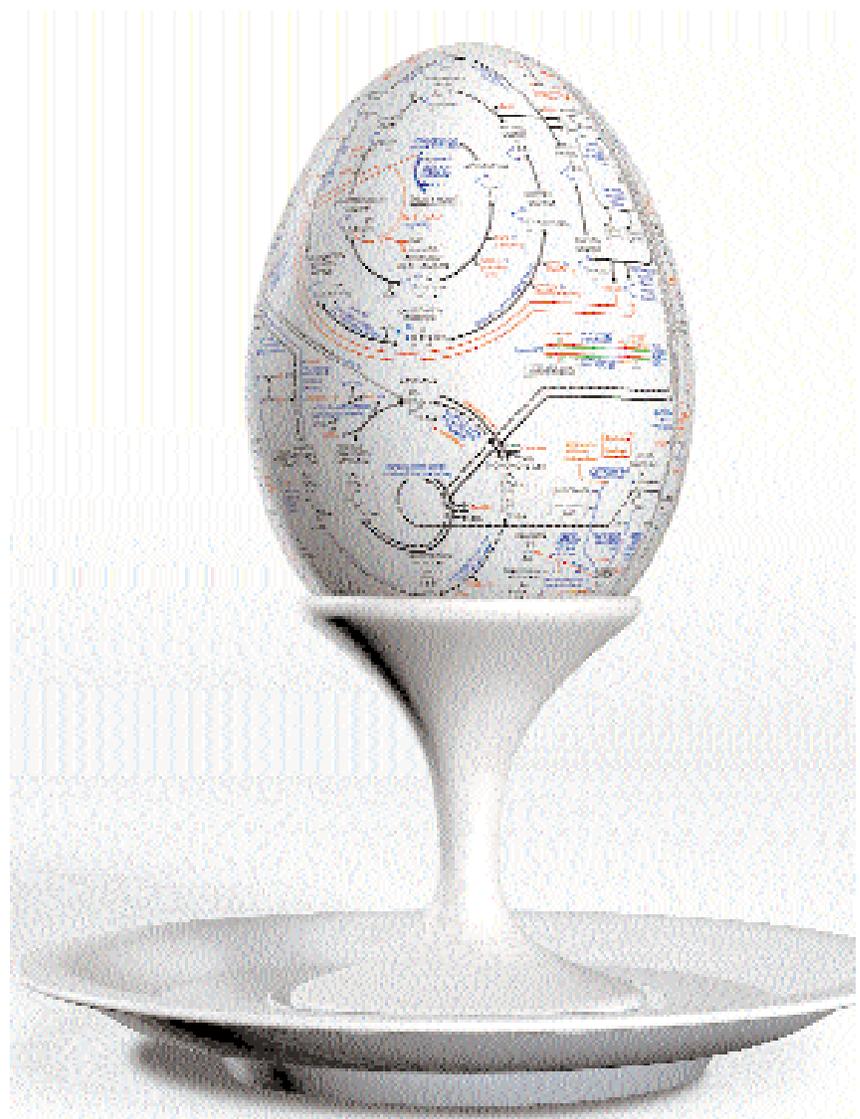


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these important classes of molecules. At the same time, the enterprise fundamentally lacked structure, and no convincing overall origin stories ever came of it. It tried to account for the detailed combinations of molecules we see today, but could give no deep reasons for why those molecules were important. Was containment in cells necessary to run the metabolism that traps energy to build the cells? Were template molecules like RNA or proteins needed to select the reactions that would then build more RNA or protein? Each of these questions led to a version of the uniquely biological conundrum: “Which came first, the chicken or the egg?”

We are finding now that the four-billion-year history of life is divided chemically into two great periods, each about two billion years long. In the first, while sunlight was prevalent as it is today, living things appear not to have used it the way modern plants or blue-green algae do, and perhaps not at all. They may have drawn all of their power and material from energy-rich molecules bubbling up from volcanoes beneath the oceans. The molecules are simple and familiar—carbon dioxide, molecular hydrogen, carbonic acid (tonic water), hydrogen sulfide (rotten-egg gas), acetic acid (vinegar), or ammonia—but the realization that it is possible to live on those has only followed the discovery of families of modern deep-ocean bacteria that do just that. These remarkable organisms need nothing to eat besides such small molecules and inorganic mineral salts, and can build all of their complex biomass, literally “from the ground up.”

Molecules bubbling up from

magma are a limited resource, though, and it appears that photosynthesis emerged as a way to trap light to increase this resource pool, as certain purple bacteria do today. Only as a byproduct of storing energy from light in sugars did bacteria first produce oxygen, which could be used later to burn the same sugars to extract the stored energy. The large-scale adoption of this process converted earth’s atmosphere to the oxygen-rich form we know today, and introduced a whole new way of life, powered by eating sugars, and metabolizing them with atmospheric oxygen. This was the second great period, in which life expanded to fill every niche on the earth’s surface. We have traditionally viewed life inappropriately as if this were its only stage, simply because oxygen renders the older way of life impossible in the surface world where we live.

Life Through the Looking Glass

When things happen in a particular order in history, it is often because the later stages build on the accomplishments of the earlier ones. The very fact that the early origin stories repeatedly run aground on chicken-and-egg paradoxes, where none of the steps seems possible before the others, suggests that we should take the two-stage history of life as an important clue. Can it be that the history of life is also a key to the emergence of the complexity of life?

The results of many different streams of work presented in the “Laws of Life” meetings suggest

that this is indeed the case. For the last 20 years, Morowitz has been steadily rearranging the metabolic chart of all modern organisms[3], showing that the chemoautotrophic¹ reactions creating all the major classes of biomolecules originate somewhere on a single reaction cycle through 10 compounds, known as the Citric acid cycle, or Krebs cycle. This observation in itself is compelling, because it shows that the Krebs cycle is a kind of core of synthesis for all of biomass. However, that observation only goes part of the way toward simplifying our view of modern organisms, because for them the Krebs cycle is simply a way to digest sugars with oxygen, to produce energy. The energy digested is not used with the cycle compounds in any direct way to make biomass, and there is no obvious reason the chemicals in that particular cycle should be the starting compounds from which the rest of life is built.

Even more puzzling, the sugars digested by the Krebs cycle are now produced in plants by a separate complicated photosynthetic pathway, involving chlorophyll and many complex structures for managing energy and carbon flow. The molecules that perform photosynthesis perform no direct steps in their own replacement; that all comes from the Krebs cycle. No subset of this complex network of reactions can persist in isolation, because the whole network is required to supply any one of its compounds. At the molecular level, we again encounter chickens and their eggs.

The Krebs cycle, though, contains a telltale clue that modern organisms are not the place to look for

its explanation. It is a cycle that takes two three-carbon sugar fragments, digests one of them to carbon dioxide to make energetic hydrogen ions, and returns the other through a so-called anaplerotic² reaction chain as a seed to begin the cycle again. Since the sugar is provided externally, this two-into-one cyclicity is not needed to supply materials. Further, from the perspective of SFI science, it is the ultimate paradox. The business of life is to build more life; why is the core engine of synthesis of all life a cycle that turns two copies of a complex molecule into only one? For many decades, a staple in abstract models of the emergence of complexity has been a self-catalyzed reaction that takes in one

complex object, and spits out two. The simplest such reaction, of course, is a cycle. The Krebs cycle has all the topology of such a so-called autocatalytic pathway[4], only the reactions run around the cycle in the wrong direction.

The two-stage history of life resolves this deep puzzle, because in the earlier stage, the core biochemistry was a sort of mirror image of what we find in the later stage. We now know that the Krebs cycle is also present in the self-sufficient organisms of the first phase, and is an engine of synthesis in them, just as in us. This is certainly true for the deep-ocean bacteria found today, and we suspect it is has been a property of organisms back to the first cells. In these organisms, though,

it runs in the right direction for autocatalysis. In other words, this reverse-direction Krebs cycle regenerates itself from nothing more than environmental small molecules, and then serves as a foundation from which all the rest of biomass is formed. Only after a complex life evolved to use and share sugars was an alternate pathway found to use sunlight for their formation. Then, the same Krebs cycle that had once built them was the most natural pathway to run in reverse, to break them down.

The centrality of the Citric acid cycle in the metabolic chart suddenly makes sense, and in the autocatalytic direction, it no longer requires complex external pathways for the production of complex "food" molecules. Since the cycle itself is simple, involving only 10 small compounds of carbon, hydrogen, and oxygen, it is also plausible as a primordial structure. This view is strengthened when one studies the internal chemistry of the Krebs cycle reactions, because it actually requires only three types of reactions involving C, H, O, and helper molecules like pyrophosphoric acid and hydrogen-sulfur molecules that may be available in some deep-ocean environments. The rest of the cycle, chemically speaking, comes for free. The important experiments that will be needed, to see how the cycle relates to the origin of life, involve how the reactions proceed without enzymes. Because modern organisms are highly optimized, and use enzymes to fine-tune every internal reaction, there is no easy reconstruction of pre-enzymatic history from them.

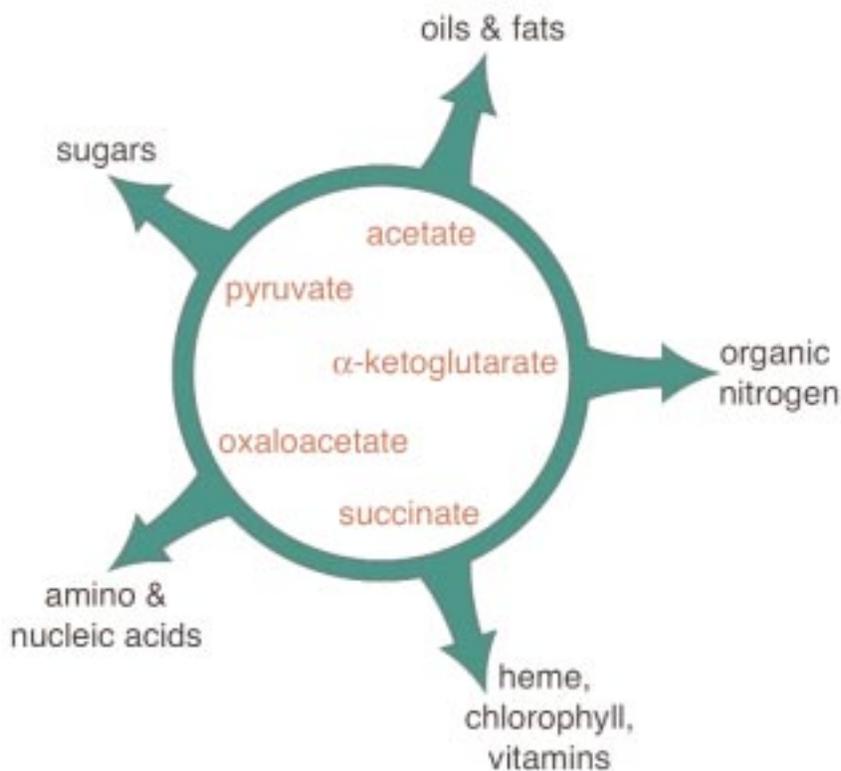


Figure 1: The Citric acid cycle is a core of synthesis for all major classes of biomolecules. Key compounds of the cycle (all organic acids) are shown in red letters, and the types of molecules they generate are shown in black. Other compounds in the cycle that are not direct precursors of biomass are not shown.

Rewriting Origin Stories

These observations about the history of life and the structure of metabolism suggest a new family of scenarios for the origin of life, which is both structured and clearly law-like, in comparison with the chicken soup scenarios. We envision that the earliest life was more like the self-sufficient deep ocean bacteria, than like anything else we know today. It formed around whatever chemical reaction cycles could convert the energy-rich but simple carbon- and hydrogen-containing molecules into structures that would seed their further consumption. The simplest such structure was the reversed Krebs cycle, whose emergence and stability were driven by this metabolic capacity.

For any chemical mixture not tightly regulated by catalysis, the physics and chemistry of finite temperatures ensure that there is a cloud of surrounding reactions, breaking down the chemicals toward lowest energy forms. When the starting chemicals are the intermediates of the Citric acid cycle, these surrounding reactions contain the basic building blocks of sugars, fats, and amino acids that create proteins, and nucleic acids that create DNA and RNA. They also contain the fundamental plate-like molecules that are assembled to make chlorophyll, heme (which is wrapped in different proteins to make myoglobin and hemoglobin), and most of the metal-containing vitamins.

The story is completely reversed from the early scenarios of Miller and Urey. Rather than depend on relatively low concentrations of

complex, atmospherically produced molecules, we expect that life originated in a steady, reliable environment that was relatively rich with simple but energetic molecules, as has been suggested by John Corliss[5] and Günter

Wächtershäuser [6]. The stability of their chemistry slowly led to a simple but stable non-background chemistry, in which carbon cycling in reverse through the Citric acid compounds carried energy from the small-molecule

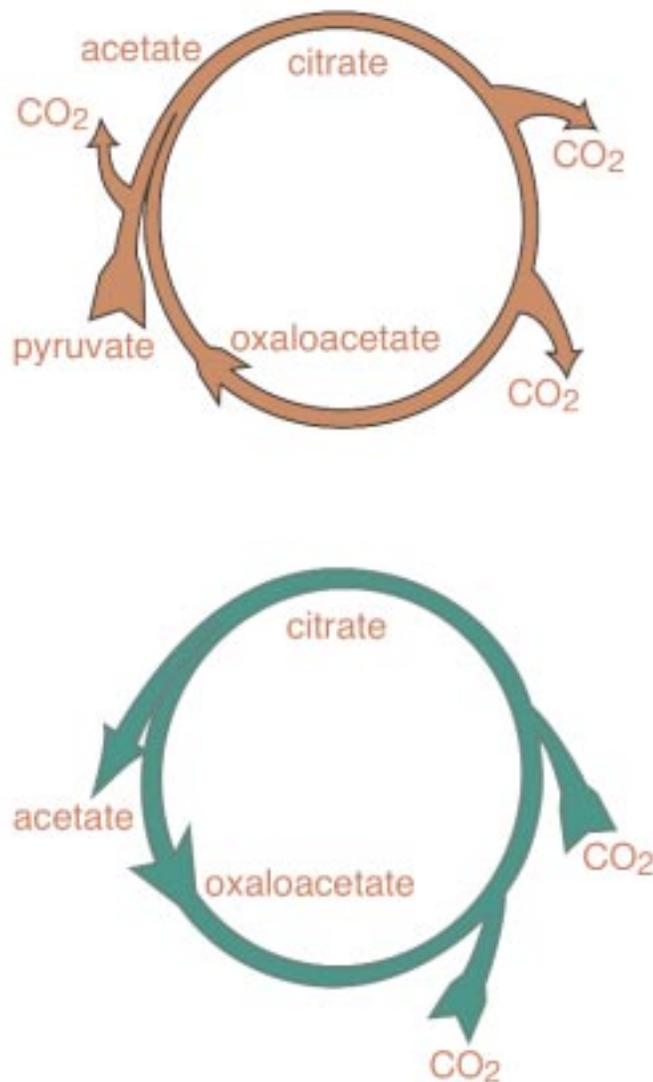


Figure 2: The Citric acid cycle can run in two directions. Top (red) is the oxidizing direction found in modern, sugar-burning organisms. Bottom (green) is the auto-catalytic direction that we believe was primordial, and is still found in some deep-ocean bacteria. Pyruvate, a 3-carbon organic acid produced from sugars, loses a carbon to form acetic acid before entering the cycle. Oxaloacetate is a recycled 4-carbon organic acid that seeds the cycle in both directions. Only carbon entry or exit from the cycle is shown; entry or exit of hydrogen and water are suppressed to simplify the figure.

“food” to equally simple, small-molecule “waste,” accumulating excesses of the building blocks of biomass as a byproduct. Stability of this rudimentary metabolism was the foundation for long trial and error, in which there was time for the discovery of those useful byproducts that could feed back to enhance the core metabolism, like the polar lipids (partly water-soluble, partly oily molecules) that made cell membranes or the protein-like molecules that are the simplest catalysts. These late-stage successes were not required to support the first metabolism, or to provide the supply that allowed the experimentation to go on.

The thing that makes this origin story law-like, however crudely, is its reliance on the ability to sample over and over again from a chemically “ordinary” environment. Rather than rely on chance reactions among rare molecules, it describes an emergent sequence in which each new level was available to be found, discarded, and found again, in samples from a stable level of structure directly beneath it. Metabolism selected from small-molecule chemistry. Biomass synthesized from a chemically stable metabolism. At each stage, the feature that emerged was the most stable, or most probable, that could be built on the foundation directly beneath it. The ability to identify structures as preferred, even in this probabilistic sense, embeds the lowest levels of biology in chemistry and physics.

What About the Genome?

One of the striking sociological features of biology today is the extraordinary importance placed on the sequencing and interpretation of DNA. The search for chemical regularity in the working group’s discussions hearkens back to an older, even pre-Darwinian view of cause for the order of life. The older view says that living things have the shapes they have because, in some absolute sense, those shapes are good for something.

The early theories of visible characteristics³ were often motivated by social, religious, or political idealisms, and gradually took on an aura of disrepute as scientific argument became more mechanistic, and (some) political ideals more egalitarian. During this transition, Darwin articulated the idea that inheritance with random variation determines what is possible, and competition then selects among the choices it is offered. Where the older arguments for “good shapes” seemed reasonable, Darwin’s natural selection offered a way to converge on them, but the original notion of efficient design as a driving force toward good shape was lost in this transition.

In the century since Darwin, the first simple models of fitness with respect to an unchanging environment have given way to more subtle models, recognizing that species create each other’s environments and so co-evolve, and mathematical treatments have also made us more aware of how few of the possible forms and ecologies can ever be discovered

The modern biological perspective is much more like one in which, to the genome, “everything is permitted,” and the history of life is simply the history of accidents in the absurd races among genes in ecologies.

at random. The idea of efficient design has thus been weakened even further—good solutions to problems can easily go undiscovered, and “Red-Queen” dynamics of co-evolution can cause all the species in an ecology to change in order to keep up with each other, while none of them actually “improves” in any obvious sense of its relation to the environment. The modern biological perspective is much more like one in which, to the genome, “everything is permitted,” and the history of life is simply the history of accidents in the absurd races among genes in ecologies.

What does the historical record of the genome say about a metabolism-centric view of life, and about the role of design more generally? When only the genetic history of ribosomes (tiny bodies within cells that build proteins using information transcribed from DNA) had been reconstructed, there appeared to be a clear picture of the family tree of all life. Three major lineages lead to all of the modern organisms, of which two are types of bacteria. The third lineage contains everything else from yeasts to plants and animals. The cleanness of this description led biologists to expect that when a different genealogy from the DNA of nuclei was reconstructed, it would reinforce this ribosomal family tree, and add detail to its earliest divisions.

What happened was rather different[7]. The DNA record muddies the early branches of the family tree, by showing that the early single-celled organisms tried many different strategies for regulating their core biochemistry, and exchanged the DNA that encoded

these strategies rather freely across the early family boundaries. The three families still make sense, as identified by strategies for making structural walls and membranes of different types. Moreover, they seem to have all shared the core metabolism discussed above. These chemical features seem more stable, though, than the DNA that determined their regulatory machinery, as if chemistry determined the “right answers” to the cells’ problems of metabolism and gross structure, and the DNA largely reified those right answers.

It appears as if the chemical “configuration” of the cells determined these earliest levels of structure, more specifically than the genome did. If this is true, it suggests a change in the emphasis of biology, where absolute preferences for configuration interact with the mutation and selection of the genome, to determine which forms of life can emerge and persist, and which cannot. We are not overturning Darwin’s arguments about variation with selection, or returning to the Victorian notions of efficient design. However, we are learning to recognize that genes need not be rigid commitments, for good or ill, and that there may be aspects of life whose form is uniquely determined by the same sorts of thorough sampling that enable us to make specific predictions in physics or chemistry, an expectation that biology seems largely to have lost.

Physical Self-Organization and Biological Law

The group’s investigation of primordial metabolism is very much in the spirit of studies of self-organization that have been traditional at SFI. Indeed, the emergence of an autocatalytic metabolism before there were enzymes, if it can be demonstrated, is as much a problem in pure physical chemistry as in biology. Yet clearly cellular life is more than pre-enzymatic metabolism, and biology obeys rules of order beyond those studied in physics. What light, if any, does our study of origin stories shed on these?

A focus on an emergent and self-sustaining core, from which living matter is constructed, alters our view of the many layers of complexity that surround that core in all modern organisms. We see that enzymes for core reactions “pay their way,” in improving the efficiency of the metabolic cycles that built them. Photosynthesis enabled primitive, volcanic metabolism to expand and fill the world, by wrapping that metabolism in a chemical “space suit,” which could generate food molecules from light. This freed organisms to leave the immediate neighborhoods of hydrothermal vents where they had evolved. Since the photosynthesizing molecules were themselves built from chemicals in the core metabolism, in augmenting it they provided for their own reconstruction.

At all levels of complexity in life, we see a hierarchical structure in which higher, regulatory structures sharpen or direct lower-level constructive processes. When

they serve to enhance the processes by which they are created, either individually or cooperatively, they are favored by selection, and become the stable innovations of evolution. Ultimately, every structure experiences some positive or negative bias from its impact on the energy and material extractable from core metabolism. This principle of construction may have no counterpart in physics, and yet may remain law-like and predictive in the biological realm. It is like a feedback between components in a system, except that it operates between levels in a hierarchy. One could call this reciprocity between construction and regulation a "feed-down" relation.

It is tempting to see feed-down as an input to selection all around us, even at the levels of economy and society. In the economy, many activities lead to production, but those that generate capital enable us to change our means of production. For this catalytic effect, we actively work to protect those ways of life that generate and use capital. Similarly, many early states have their origins in piracy, when the pirates realized that they could extract more from local populations by living among them and instituting cooperative public-works projects. Theft became taxation, and the pirates became rulers, but only when their rule led to innovations such as cooperative irrigation, fisheries management, or reduction in internal conflict. We use such criteria today to distinguish legitimate states from other forms, though we still understand only poorly how to encourage legitimacy. An intriguing problem for the future is to see how much of anatomy, ecology, and

sociology can be accounted for in terms of feed-down reciprocity (perhaps including some properties of Gould's phyla), and what it can predict about future innovations and change.

The authors wish to thank our co-organizer Jennifer Dunne for reminding us that the laws of life are hierarchical, and must look upward to ecology as well as downward to physics and chemistry.

D. Eric Smith is a Research Professor at SFI, and Harold Morowitz is a member of SFI's Science Board.

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¹ "Autotrophs" are the self-starters of the food chain. The chemoautotrophs are organisms that require no intake of either organic matter or light in order to live. They self-sufficiently generate all of their biomass from inorganic small molecules.

² Anaplerotic is a term coined to refer specifically to the pathways that direct carbon in the modern Citric acid cycle into compounds other than fully-degraded carbon dioxide. These include the pathways that return it through oxaloacetate, an organic acid, to seed the next round of the cycle.

³ Called Phenetics, from Greek *phainein*, to show. 52 (1988) 452-484.