SPECIAL ESSAY:

The Seven Pillars of Life

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What is the definition of life? I remember a conference of the scientific elite that sought to answer that question. Is an enzyme alive? Is a virus alive? Is a cell alive? After many hours of launching promising balloons that defined life in a sentence, followed by equally conclusive punctures of these balloons, a solution seemed at hand: "The ability to reproduce--that is the essential characteristic of life," said one statesman of science. Everyone nodded in agreement that the essential of a life was the ability to reproduce, until one small voice was heard. "Then one rabbit is dead. Two rabbits--a male and female--are alive but either one alone is dead." At that point, we all became convinced that although everyone knows what life is there is no simple definition of life.

If I were forced to rush in where angels fear to tread, I would offer "a living organism is an organized unit, which can carry out metabolic reactions, defend itself against injury, respond to stimuli, and has the capacity to be at least a partner in reproduction." But I'm not happy with such a brief definition. When allowed more extensive reflection, however, I think the fundamental pillars on which life as we know it is based can be defined. By "pillars" I mean the essential principles--thermodynamic and kinetic--by which a living system operates. Current interest in discovering life in other galaxies and in recreating life in artificial systems indicates that it would be desirable to elucidate those pillars, their operation, and why they are essential to life. In this essay, I will refer to the particular mechanisms by which those principles are implemented in life on Earth, while reserving the right to suggest that there may be other mechanisms to implement the principles. If I were in ancient Greece, I would create a goddess of life whom I would call PICERAS, for reasons that will become clear.

The first pillar of life is a **Program**. By program I mean an organized plan that describes both the ingredients themselves and the kinetics of the interactions among ingredients as the living system persists through time. For the living systems we observe on Earth, this program is implemented by the DNA that encodes the genes of Earth's organisms and that is replicated from generation to generation, with small changes but always with the overall plan intact. The genes in turn encode for chemicals--the proteins, nucleic acids, etc.--that carry out the reactions in living systems. It is in the DNA that the program is summarized and maintained for life on Earth.

The second pillar of life is **IMPROVISATION**. Because a living system will inevitably be a small fraction of the larger universe in which it lives, it will not be able to control all the changes and vicissitudes of its environment, so it must have some way to change its program. If, for example, a warm period changes to an ice age so that the program is less effective, the system will need to change its program to survive. In our current living systems, such changes can be achieved by a process of mutation plus selection that allows programs to be optimized for new environmental challenges that are to be faced.

The third of the pillars of life is **COMPARTMENTALIZATION**. All the organisms that we consider living are confined to a limited volume, surrounded by a surface that we call a membrane or skin that keeps the ingredients in a defined volume and keeps deleterious chemicals--toxic or diluting--on the outside. Moreover, as organisms become large, they are divided into smaller compartments, which we call cells (or organs, that is, groups of cells), in order to centralize and specialize certain functions within the larger organism. The reason for compartmentalization is that life depends on the reaction kinetics of its ingredients, the substrates and catalysts (enzymes) of the living system. Those kinetics depend on the concentrations of the ingredients. Simple dilution of the contents of a cell kills it because of the decrease in concentration of the contents, even though all the chemicals remain as active as before dilution. So a container is essential to maintain the concentrations and arrangement of the interior of the living organism and to provide protection from the outside.

The fourth pillar of life is **ENERGY**. Life as we know it involves movement--of chemicals, of the body, of components of the body--and a system with net movement cannot be in equilibrium. It must be an open and, in this case, metabolizing system. Many chemical reactions are going on inside the cell, and molecules are coming in from the outer environment--O_2, CO_2, metals, etc. The organism's system is parsimonious; many of the chemicals are recycled multiple times in an organism's lifetime (CO_2, for example, is consumed in photosynthesis and then produced by oxidation in the system), but originally they enter the living system from the outside, so thermodynamicists call this an open system. Because of the many reactions and the fact that there is some gain of entropy (the mechanical analogy would be friction), there must be a compensation to keep the system going and that compensation requires a continuous source of energy. The major source of energy in Earth's biosphere is the Sun--although life on Earth gets a little energy from other sources such as the internal heat of the Earth--so the system can continue indefinitely by cleverly recycling chemicals as long as it has the added energy of the Sun to compensate for its entropy changes.

The fifth pillar is **REGENERATION**. Because a metabolizing system composed of catalysts (enzymes) and chemicals (metabolites) in a container is constantly reacting, it will inevitably be associated with some thermodynamic losses. Because those losses will eventually change the kinetics of the program adversely, there must be a plan to compensate for those losses, that is, a regeneration system. One such regeneration system is the diffusion or active transport of chemicals into the living organism. For example, CO_2 and its products replace the losses inevitable in chemical reactions. Another system for regeneration is the constant resynthesis of the constituents of the living system that are subject to wear and tear. For example, the heart muscle of a normal human beats 60 times a minute--3600 times an hour, 1,314,000 times a year, 91,980,000 times a lifetime. No man-made material has been found that would not fatigue and collapse under such use, which is why artificial hearts have such a short utilization span. The living system, however, continually resynthesizes and replaces its heart muscle proteins as they suffer degradation; the body does the same for other constituents--its lung sacs, kidney proteins, brain synapses, etc.

This is not the only way the living system regenerates. The constant resynthesis of its proteins and body constituents is not quite perfect, so the small loss for each regeneration in the short run becomes a larger loss overall for all the processes in the long run, adding up to what we call aging. So living systems, at least the ones we know, use a clever trick to perfect the regeneration process--that is, they start over. Starting over can be a cell dividing, in the case of *Escherichia coli*, or the birth of an infant for *Homo sapiens.* By beginning a new generation, the infant starts from scratch, and all the chemical ingredients, programs, and other constituents go back to the beginning to correct the inevitable decline of a continuously functioning metabolizing system.

The sixth pillar is **ADAPTABILITY**. Improvisation is a form of adaptability, but is too slow for many of the environmental hazards that a living organism must face. For example, a human that puts a hand into a fire has a painful experience that might be selected against in evolution--but the individual needs to withdraw his hand from the fire immediately to live appropriately thereafter. That behavioral response to pain is essential to survival and is a fundamental response of living systems that we call feedback. Our bodies respond to depletion of nutrients (energy supplies) with hunger, which causes us to seek new food, and our feedback then prevents our eating to an excess of nutrients (that is, beyond satiety) by losing appetite and eating less. Walking long distances on bare feet leads to calluses on one's feet or the acquisition of shoes to protect them. These behavioral manifestations of adaptability are a development of feedback and feedforward responses at the molecular level and are responses of living systems that allow survival in quickly changing environments. Adaptability could arguably include improvisation (pillar number 2), but improvisation is a mechanism to change the fundamental program, whereas adaptability (pillar number 6) is a behavioral response that is part of the program. Just as these two necessities are handled by different mechanisms in our Earth-bound system, I believe they will be different concepts handled by different mechanisms in any newly devised or newly discovered system.

Finally, and far from the least, is the seventh pillar, **SECLUSION**. By seclusion, in this context, I mean something rather like privacy in the social world of our universe. It is essential for a metabolizing system with many reactions going on at the same time, to prevent the chemicals in pathway 1 (A→B→C→D for example) from being metabolized by the catalysts of pathway 2 (R→S→T→U). Our living system does this by a crucial property of life--the specificity of enzymes that work only on the molecules for which they were designed and are not confused by collisions with miscellaneous molecules from other pathways. In a sense this property is like insulating an electrically conducting wire so it isn't short-circuited by contact with another wire. The seclusion of the biological system is not absolute. It can be interrupted by feedback and feedforward messages, but only messages that have specifically arranged conduits can be received. There is also specificity in DNA and RNA interactions. It is this seclusion of pathways that allows thousands of reactions to occur with high efficiency in the tiny volumes of a living cell, while simultaneously receiving selective signals that ensure an appropriate response to environmental changes.

These seven pillars of life--**P**(rogram), **I**(mprovisation), **C**(ompartmentalization), **E**(nergy), **R**(egeneration), **A**(daptability), **S**(eclusion), PICERAS, for short--are the fundamental principles on which a living system is based. Further examination makes it clear how life on Earth has implemented these principles. But these mechanisms may not be perfect and might be improved. For example, the regeneration system used by life on Earth is imperfect for any particular individual and hence requires a "starting over." That mechanism in turn requires a device for heredity to maintain continuity in the program for the next generation. Suppose the proteins, hormones, and cells had a better feedback system so that the gradual decay with age was constantly being corrected by feedback. Then, the need to start over would disappear. That would eliminate the death and hereditary needs of the current system. It would also mean that a single individual could live forever without aging. There would be a problem, however, because the starting over (death and a new birth) provide an opportunity for improvisations (mutations in the DNA), and that pillar would need to be replaced by a new mechanism to achieve the same advantage. Such dilemmas make us confront another reality. At the present time the way in which mutation and selection (survival of the fittest) has worked over evolutionary time no longer seems to apply to *Homo sapiens*. We have become more compassionate, less demanding. Perhaps a newer approach--longer life and deliberate changes in the program by a supreme council of wise Solomons--could be substituted for the cruder survival-of-the-fittest scenario. I do not necessarily advocate such a drastic change in the current mechanism of improvisation, which has served us well over the centuries, but am only pointing out that there is the possibility to change particular mechanisms as long as we maintain the pillars.
This listing of the seven foundations of life allows us to think differently about the goals and therapeutic approaches of current research. The adaptability concept, for example, is certainly one in which better mechanisms could be devised, probably by adjusting existing mechanisms to allow these to work more effectively in real living systems. For example, the eye can adapt to outside light levels that range over 10 orders of magnitude (10^{10}), whereas the other organs of the human body have much smaller ranges. Perhaps other organs such as the lungs, kidneys, or spleen could be improved so that they would function over larger concentrations of regulators and aging would be less harmful to them.

Thus, the PICERAS principles seem to be necessary for the operation of a living system. Mechanisms to achieve such a system can be varied as long as they satisfy the thermodynamic and kinetic requirements. We have one example, life on Earth, showing how it can be done. It will be interesting to see whether a different, self-consistent set of mechanisms could yield a model with life as an outcome.

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Artificial Life Likely in 3 to 10 Years

AP Associated Press

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By SETH BORENSTEIN
AP Science Writer

WASHINGTON (AP) - Around the world, a handful of scientists are trying to create life from scratch and they're getting closer.

Experts expect an announcement within three to 10 years from someone in the now little-known field of "wet artificial life."

"It's going to be a big deal and everybody's going to know about it," said Mark Bedau, chief operating officer of ProtoLife of Venice, Italy, one of those in the race. "We're talking about a technology that could change our world in pretty fundamental ways—in fact, in ways that are impossible to predict."

That first cell of synthetic life—made from the basic chemicals in DNA—may not seem like much to non-scientists. For one thing, you'll have to look in a microscope to see it.

"Creating protocells has the potential to shed new light on our place in the universe," Bedau said. "This will remove one of the few fundamental mysteries about creation in the universe and our role."

And several scientists believe man-made life forms will one day offer the potential for solving a variety of problems, from fighting diseases to locking up greenhouse gases to eating toxic waste.

Bedau figures there are three major hurdles to creating synthetic life:

—A container, or membrane, for the cell to keep bad molecules out, allow good ones, and the ability to multiply.

—A genetic system that controls the functions of the cell, enabling it to reproduce and mutate in response to environmental changes.

—A metabolism that extracts raw materials from the environment as food and then changes it into energy.

One of the leaders in the field, Jack Szostak at Harvard Medical School, predicts that within the next six months, scientists will report evidence that the first step—creating a cell membrane—is "not a big problem." Scientists are using fatty acids in that effort.

Szostak is also optimistic about the next step—getting nucleotides, the building blocks of DNA, to form a working genetic system.

His idea is that once the container is made, if scientists add nucleotides in the right proportions, then Darwinian evolution could simply take over.

"We aren't smart enough to design things, we just let evolution do the hard work and then we figure out what happened," Szostak said.

In Gainesville, Fla., Steve Benner, a biological chemist at the Foundation for Applied Molecular Evolution is attacking that problem by going outside of natural genetics. Normal DNA consists of four bases—adenine, cytosine, guanine and thymine (known as A,C,G,T)—molecules that spell out the genetic code in pairs. Benner is trying to add eight new bases to the genetic alphabet.

Bedau said there are legitimate worries about creating life that could "run amok," but there are ways of addressing it, and it will be a very long time before that is a problem.

"When these things are created, they're going to be so weak, it'll be a huge achievement if you can keep them alive for an hour in the lab," he said. "But them getting out and taking over, never in our imagination could this happen."

(This version CORRECTS Bedau quote to "shed new light")