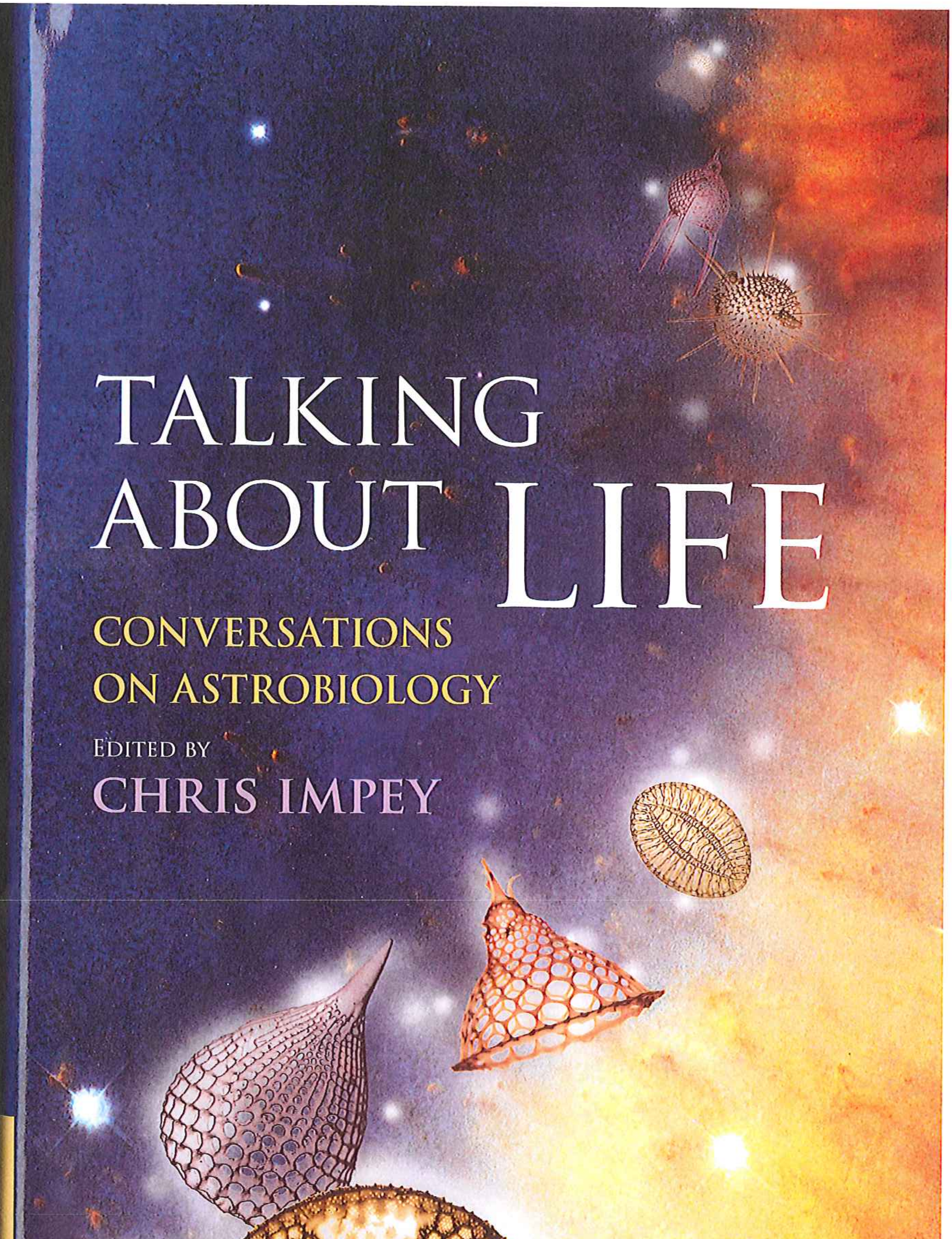


# TALKING ABOUT LIFE

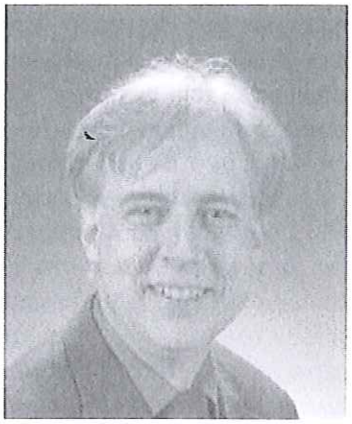
## CONVERSATIONS ON ASTROBIOLOGY

EDITED BY

CHRIS IMPEY

## 7

# Steven Benner



To Steven Benner, questioning the fundamentals is as essential as pursuing the unknown. He began his quest with Bachelor's and Master's degrees in molecular biophysics and biochemistry from Yale University, and a PhD in chemistry from Harvard. The recipient of numerous honors and fellowships, Benner has been a professor at the Swiss Federal Institute of Technology, Harvard University, and the University of Florida. He established several companies and organizations to ask the big questions about genetics and biology at the molecular level, including FfAME (The Foundation for Applied Molecular Evolution), EraGen Biosciences, FireBird Biomolecular, and most recently, TWIST (The Westheimer Institute of Science and Technology). Benner has done pioneering experiments that alter the basic toolkit of biochemistry to see what the effects might be on life processes. This lets him speak with authority on the plausibility and possibility of alternative biochemistries elsewhere in the universe.

CI Tell me about the paradox in the question of life.

SB The paradox is a matter of origins, because the chemistry is not enough. When you take organic molecules and cook them normally, or put energy into them, you don't get organized matter or life emerging – you get tar or asphalt. People say, "Stanley Miller did an experiment, and from that we've concluded that life is the intrinsic outcome of organic chemicals reacting as they do," but it's not. Stanley Miller showed that if you sparked energy through organic material, you got asphalt or tar, from which you could extract compounds or components that were biologically interesting, but otherwise it was just tar.

CI If we try to do a "life in a bottle" experiment, we don't get too far. How much of an obstacle to our understanding of the nature of life is the fact that we can't connect the dots between simple chemical ingredients and cells?

SB There are two different origins questions. We can ask: what are the exact steps through which life arose? That's difficult to answer. The other side of the question is: how do we reconcile the chemical structure and molecular physiology of the life that we know with what we know about organic reactivity not occurring subject to Darwinian mechanisms?

We're trying to answer that second question. People complained that the NSF was funding incremental research and not creative, forward-looking research. So I called Jack Szostak and said, "Is artificial life a big enough problem for these people?" Jack said, "Sure," so we have Harvard, Florida, and Scripps with Jerry Joyce and his group as the partners in an NSF Center. We have people in the laboratory trying to get self-replicating systems, and self-replicating systems that replicate imperfectly, and then systems where the imperfections are themselves heritable. That's what we need chemically to get a Darwinian process going. We encounter many difficulties when we try to do it, because normal chemicals do not behave this way. DNA is very special and RNA is even more special, and if we change the structures of either of them only modestly, we destroy their ability to do rule-based templating and rule-based molecular recognition, which is the basis of evolution.

The central issue is that everything that we know about organic chemistry in the laboratory going back two hundred years shows that we don't get Darwinian behavior out of chemical systems spontaneously, or even when we try. It's not as simple as saying that because we've got the general outline and life is the intrinsic outcome of chemical reactivity, that we're just left with a historical question and we shouldn't be all that worried if we don't solve the intermediate steps. We're up against a couple of problems. Take the "RNA World" hypothesis, which is based on rather strong evidence that there was an episode of life on Earth that used RNA as the only genetically encoded component of biological catalysis. Maybe that was the first form of life, but to get that, we need to get RNA to appear out of a nonbiological environment. If there's water around, it's very difficult.

CI What do you make of fine-tuning or anthropic arguments about biology?

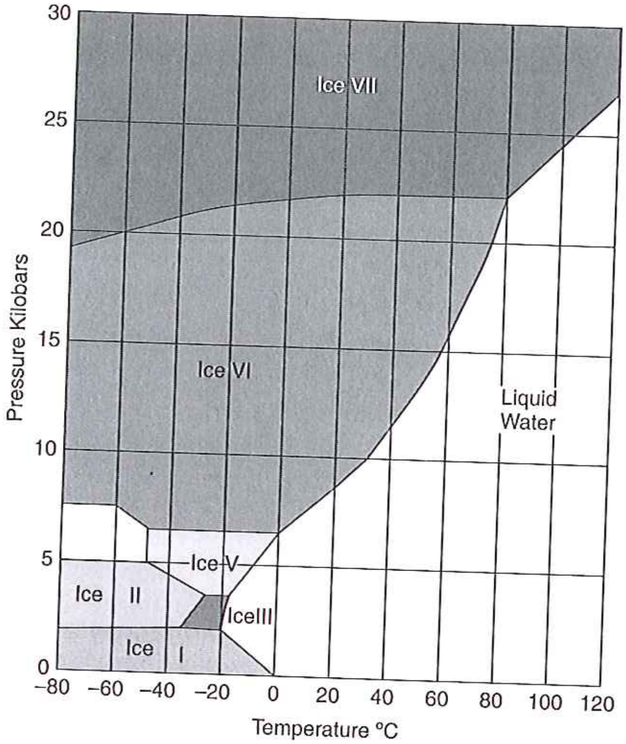
SB There is one anthropic principle that is indisputable. If the universe had physical laws that made life impossible, we would not be here talking about it. Water is a good example. People are confusing the notion that life is adapted to water with the anthropic idea that water is adapted to life. We cannot get from one to the other. Life is clearly adapting to its environment; we see a signature of adaptation that's extremely strong. We can't expect to see a strong signal underneath that says it's the other way around.

For another example, we have a prebiotic way of making ribose and RNA, and this is the major breakthrough that was published in *Science* in 2004. We're showing that minerals containing boron magically stabilize ribose. Previously, we've shown that ribose is pretty much the only sugar that supports genetics and the general structural constraints of DNA. For some accidental reason, the sugar that's stabilized by boric-containing minerals happens to be the very sugar that best supports DNA structures and genetics. One might say, "My God, that's an argument for design." On the other hand, if we look at the solar nuclear synthesis of boron, it's one of the elements that doesn't do very well based on fundamental physical laws. With the neutron cross-section capture for boron, you shouldn't get neutrons anywhere near boron if you want to keep it around. The Solar System abundance of boron is quite low, down near scandium. We can start talking about these counterfactuals. We can marvel at how wonderful water is, because it's what supports the life we know, but the minute you put any level of thought into this problem, you can see how you or I might have done it a lot better if we had been in charge.

Then there's the problem of ice floating. When water freezes, it floats. That is an unusual property of a liquid, and people have written books about how that shows that water is ideally suited for life. However, looking at the history of the Earth for the last 50 million years, when ice floats, it's white. White reflects light, and because of ice floating, it doesn't damp perturbations in the energy input to the Earth – it amplifies them. One of our big problems right now is that the Earth has ice ages, and no one has a clear idea how it gets out of the cycle of ice ages. Antarctica started to frost over about 30 million years ago, and consequently the albedo of the Earth went up, so it frosted more. Frankly, I would rather not have ice float, or perhaps have water ice be black.

CI Water expanding when it freezes doesn't help cells, because they burst.

SB Exactly. We can combine all of the counterfactuals. We ask, "What do you mean, ice floats?" What we mean is that familiar, terrestrial ice floats, but ice at lower temperatures and at higher pressures is denser. On a rocky planet five times the mass of Earth, the most likely ice to form would not float. People talk about how wonderful water is because of its large liquid range. But that only means we have a large liquid range on Earth at atmospheric temperature and pressure. Water does not have any liquid range on Mars at the equator; it's like carbon dioxide on Earth. We don't consider carbon dioxide having a large liquid



It has been argued that the special properties of water – the fact that it floats when frozen and is a good solvent – are favorable for life. But in general, as this phase diagram shows, ice has a number of crystalline forms (called polymorphs) at high pressure, and only the familiar Ice I is less dense than water. The high-pressure forms are presumed to exist in non-terrestrial settings. As far as life is concerned, water has negative aspects because it acts against the formation or stability of a number of important biochemical ingredients (courtesy Steve Dutch, University of Wisconsin-Green Bay).

range on Earth because it doesn't have a liquid state at the temperature and pressure we're used to. On Venus there is supercritical carbon dioxide, which is fluid.

You can't go far into the discussion before becoming totally anthropocentric, terracentric, and biased by what you find normal based on your own experiences. Liquid ammonia actually has a larger temperature range under reasonable pressure. With liquid water and ammonia, there is a terribly large liquid range that goes down to temperatures we expect to find on Titan.

CI I agree with you, anthropic ideas are overplayed. Let me ask you about your own research – you're a hard-core chemist with a lab and you also do bioinformatics and biotechnology. What attracted you to these areas of research?

SB The core paradigm of research has been expended and exhausted. There's not really a lot left to do. The problems that natural chemists worked on in the nineteenth century, and mechanistic organic chemists worked on in the fifties and sixties, are gone – the periodic table being one of them. So chemists moved into researching complex biological systems. They discovered very quickly that there are many interesting mechanistic and structural questions that were not solved as of 1975, but a whole bunch of physical technologies like X-ray crystallography and chemical methods were being brought to bear on these problems. Coming up as a student, I was able to talk about the rate of flipping of rings in proteins at the nanosecond timescale, or the positions of all the atoms to within an angstrom resolution using crystallography. We can measure the rate constants of reactions, and there's a whole field of enzyme kinetics, which I was trained in.

One of the important questions to ask is: what is worth studying when you have this problem of physical technique outpacing the science? You can study a Picasso with an electron microscope, but what you can say about the Picasso is that it's not worth studying with an electron microscope. You may publish papers, but what you're doing is collecting information about the arcane. It has nothing to do with the art or the artist or the conception of the art, and the same principle goes for biological systems.

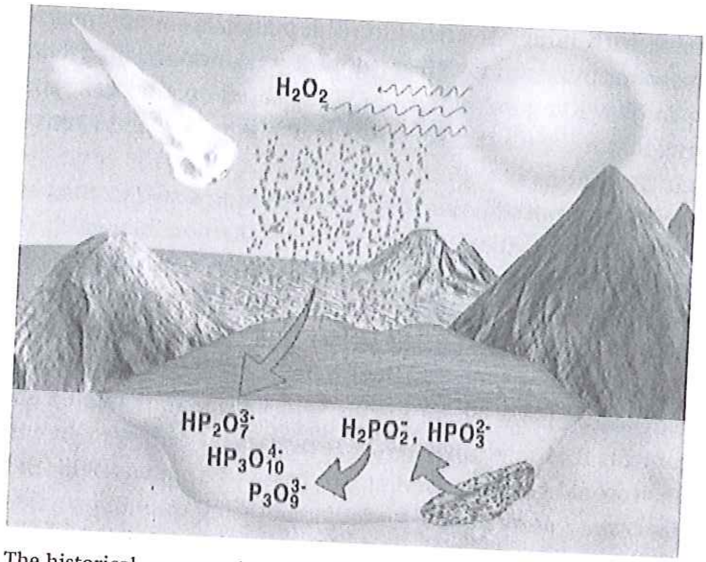
By the eighties, chemistry was sufficiently well advanced that we could study the molecular systems far past the level of function. Here, function is ultimately the ability of the host organism to survive, get married and have children. We became involved in the historical side of chemistry in living systems as a research selection problem. If we understand the history of the biochemical or biomolecular system, we have a chance of knowing what in that system is actually important to biology, and what is not.

In biology, some features of the molecular structures are random, arising from historical accidents or fixed for no good reason. Some of the structure is going to be vestigial and there will be information about past selection pressures that have vanished without changing the physiology of the organism, because it's too hard to keep the system coherent. We need to look at the molecular system and try to decide which features are adaptive and which are detrimental before we commit heavy resources to the analysis. That's how we got started, but once we ask which molecular features are important for fitness, it goes on forever.

CI The interplay between chance and necessity is a large underlying theme of your research. How does that affect your attempts to pin down the various possibilities you just listed?

SB It makes it harder to receive funding. We got funded by collecting more systems biology sequence data. We have collected a lot of fundamental chemical data. The human genome is nothing more than a statement about how carbon, hydrogen, nitrogen, oxygen, and phosphorus atoms are bonded in a genome. We've collected all this *data*, but little has ever emerged that resembles understanding.

I'm not surprised or disappointed. We knew from nineteenth-century chemistry that we could isolate natural products and determine their structure, but



The historical sequence by which simple chemical ingredients formed the first living cells is not known. But one important step was priming the Hadean Earth with condensed phosphates, which are necessary precursors of RNA and DNA. The source of much phosphate material was meteor and comet impacts during the early bombardment of the planet (courtesy NASA/NAI).

that the biological function was not embedded in the structure in a transparent way. So why would we expect it to be transparently embedded if the natural product now happens to be a gene? The history of the genetic sequence is much more transparent in the DNA sequence than the structure of cholesterol is. I can't look at the structure of cholesterol and tell you much, other than that it's soluble in oil and not soluble in water. I really can't tell you the history of cholesterol from it. But if you give me cholesterol synth-base, an enzyme, the sequence, and the families of those, its history is accessible right away. We use that method as we try to interpret function in these biological systems. We resurrect proteins from two- or three-billion-year-old bacteria, which tell us that the protein is optimally active at 65 °C; so it probably lived at that temperature. Much of what we're trying to do is tie the historical narrative to the function.

CI Let me ask about the narrative. If you had a hundred Earths that started with the same chemical conditions and energy input from the Sun, how often would you expect to see the same chemical basis for life? How unique is life's narrative?

SB We go back and forth on this question from year to year. Given an Earth-like planet, given the general instability of the nucleic acids that are necessary for the emergence of life, given that we've tried to make about two hundred alternative versions of these molecules without finding something better than RNA, and given that the RNA seems to fall out of an interaction of organics known in the cosmos with minerals known on the planet in environments that help us solve the water problem, my view is that if we found independent life emerging on planets like "Klingon," it would still be based on ribose. It's interesting that I'm saying that, because that's not necessarily what I would have said a couple of years ago.

CI Does that also apply to the specificity of the amino acids? Or the proteins that are used on Earth as a function of the almost infinite possible set?

SB No, I would not say that about amino acids. If you interact with a Vulcan, I could easily imagine him having different amino acids. I'm perfectly prepared to believe he will have different bases on the nucleotides. I do believe the backbone will be a sugar, like ribose, and that he will have emerged by a similar process on an Earth-like planet where there's water. If we start talking about Titan and the organisms that might live in the supercritical hydrogen–helium mixtures of Neptune, it would be very different. For Earth-like planets of Earth-like mass plus or minus twenty percent, and a similar position around a similar star, I would expect the chemistry to be constrained.

CI How strongly should astrobiologists be guided by the range of extremophiles?

SB None of the extremophiles or extreme environments on Earth is in any sense extreme from the perspective of the cosmos or the Solar System. Let's talk about pH. DNA molecules, the ones we know on Earth, don't really work if we lower the pH from 7 to 5, and they don't work if we raise the pH from 7 to 10. The reason for that is that hydrogen and its positions are very important for how DNA works. If we start changing the pH, we start changing where the hydrogen atoms are.

People talk at length about Rio Tinto, where the pH is 1, and how wonderful it is that the organism has adapted, but the organism hasn't really adapted. The organism has set up a pump so that it furiously pumps the protons out of the cell, and that's how organisms in Rio Tinto survive. That's not a way to get life to emerge. I'm not going to expect life based on DNA to emerge in Rio Tinto with a pump that takes an ambient pH of 1 and decreases the proton concentrations by a factor of a million. That's something we find when an advanced life form, which evolved or emerged at a pH of 7, has moved into the Rio Tinto by accident and had to survive there.

Most extremophiles on Earth aren't actually extreme in the cosmos. We don't ever get to a point where an extremophile lives without water, we never get out of the liquid phase of water, we never go to a high or low pH, and we never have a very high concentration of salt. At the end of the day, I'm absolutely convinced that organisms on Earth are living in environments that are basically normal. Jonathan Lunine speculates about whether or not life is possible in water and ammonia at 112 K, and the answer is probably yes, but that's a real extreme environment where pH is going to be 15 to 20 – way above the pH range we know on Earth. There's no way that studying extremophiles on Earth is going to prepare us to construct a device that would detect life in that sort of environment once we get there.

CI So astronomers should probably have a liberal definition of the habitable zone.

SB Yes. The habitable zone concept is also terribly Earth-centric. Dave Stevenson of Caltech has pointed out that life could live off nuclear energy left over in the form of geothermal energy. It's radioactive decay of radioisotopes that were generated in the last cycle of supernovae. Once you've agreed to live off of that, there's really no constraint on where you live. Stevenson's idea was that in the early formation of planets, many rocky planets were ejected from the Solar System due to gravitational tugs and pulls. There's no reason you need a star to live if you're a microorganism living off of geothermal energy. When you're five miles down in the ocean or even five miles down in the subsurface soil or rock, you don't really care whether there's a star there or not, and you don't really know. It's an interesting problem. The ability of life to live in places where the energy source is quite different from ours on Earth means we could very easily have life scattered throughout the Galaxy on wandering, rogue planets without stars.

CI Let me return to the specificity of life. What is the potential range of information-storing molecules for any biology? Can that be approached experimentally?

SB Absolutely – that has been ten years of my life. We have to ask these "what if" and "why not" questions. When I said ribose is the only sugar that can support genetics in a DNA-like structure, it's because the community has made about two hundred variants of ribose, put them into the backbone, and concluded that almost all of them work *worse*. Most of them don't actually work at all, which is why we say that ribose is essential. This is why I said that if we went to Vulcan we'd expect to have the same kind of chemistry.

You can criticize it by saying, "Steve, you didn't think of the Vulcan. You haven't done everything, or anything close to everything." You can argue that there is a different chemistry we haven't thought of, so we can't draw the hard conclusion that because there is *no* other genetic form that supports the origin of life like ribose, life everywhere in the Galaxy that exists on an Earth-like planet must be built from ribose. But the facts are that there are other structures for genetic backbones and we've made them. One feature we've argued for as a universal is a repeating charge in the backbone, which is something found in natural DNA. Again, we have a good reason to argue that it's universal, because we've tried to make nucleic acids, genetics, and DNA without the charge, and failed.

CI What about mineral or clay-type mechanisms as templates for information?

SB We're trying. The A–T base pair is too weak, so we change the A–T base pair and we send chemists in the laboratory to make a better one, and try to get it to work better. Right now we're exploring the realm of chemical possibilities. We say, "Damn the prebiotic history," because we don't care at this point whether we can actually find evidence that the alternative structure we've thrown together existed naturally at some point in the history of the Earth. We're trying, but it doesn't work. Jack Szostak has a paper in *Science* about making membranes, so parts of the story are available. Mostly, we'd be happy if we could just get life from the standard clays we know about on the Earth, ignoring the question of whether prebiotic Earth actually had these specific clays. We'll worry about that later; right now, we can't get any clay to get RNA to have kids.

CI Where does this leave really "out of the box" ideas about non-carbon life?

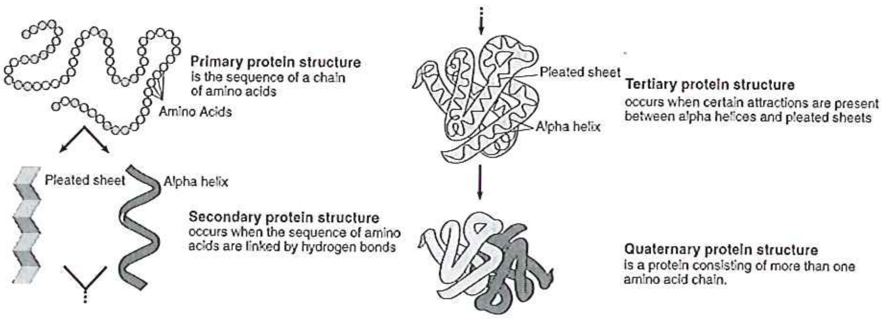
SB I don't know. I published this paper about silicon-based life, and William Baines had an article in 2004 in which he talked about it. It's an interesting question. For example, if our principal solvent were liquid di-nitrogen II, there are some advantages to silicon compounds in that solvent. The disadvantages of silicon compounds in water go away the minute we get rid of water as a solvent. This is the kind of thing we can imagine, and I'm not ruling it out. Once we get past silicon, it's difficult to think of things that will form networks. Anybody can view an episode of *Star Trek* and see a life form that is weird, and you could argue that they can't be ruled out. There's silicon-based life and the Crystalline Entity, which is a mineral-based. There's also the Calamarain, which is a pure energy life form.

When I wrote an article for *Current Opinions* in which I had to define life, I defined it as any self-replicating chemical system that goes through evolution. The restriction to a chemical system is not because we'd rule it out if we were to come across a robotic system that was self-replicating, or a *Star Trek* character like Q, who moves in and out of the cosmos without much of a need for matter or energy. The reason why I don't include those in my definition of life is because I don't believe they exist, and I don't think they're possible. We're constantly viewing these things based on our view of what *is* and *is not*. I don't happen to think that it's possible for an organism to live in the continuum – although I find the premise hilarious – and I think that Q is one of *Star Trek*'s more entertaining organisms. Scientists are not going to suffer their definition of life to include Q.

CI You've talked about the sculpting of life by its larger environment. The Gaia idea implies that life is symbiotic with its global environment. It's always been hard for me to understand how that works at the microscopic level of reactions, and in the Darwinian molding of organisms on the small scale. Does it make sense?

SB Yes, it makes sense. The Gaia hypothesis is maybe two or three steps further. There's no question that life and the planet are intimately connected. We can't talk about one without the other. We're sitting on a planet that had its atmosphere poisoned by the emergence of oxygen. There's no question that geology has been greatly influenced by the emergence of photosynthesis, which generates oxygen – even down to the erosion of iron-containing rocks. We can't ignore that process as we think about the history of life. Conversely, the Earth fought back, and we can't think about life without thinking about how Earth and the cosmos are trying to kill it. Gaia goes further. It's more mystical. It's more of an intimate connection.

CI It implies an equilibrium established at a global level. I don't understand how the small-scale equilibria that life forms establish with their immediate environment play into that, when the range of environments across the planet is so large.



The four levels of protein structure that code for functions of all life on Earth. Terrestrial life uses about 10 000 from an almost infinite set of possible proteins, and computational methods are unable to predict the behavior of any particular structure (courtesy National Human Genome Research Institute).

SB It's worse than that – ecologists don't know how it's possible to avoid the excesses of predator–prey relationships. It's not good for a predator to eat all the prey and drive it to extinction, because that's selfish suicide. But the mechanisms to prevent that are not terribly clear. People assume negative feedback that acts as a damper, but human society is certainly not dampening its effect on the ecosystem. Europeans came into North America, took over, and, as far as we can tell, hunted many of the animals to extinction. A lot of the big game seems to have gone because we overfed on them, and there's no mechanism in biological systems to prevent that from happening.

This is one of the interesting aspects about ecology, which is embedded in astrobiology. People are trying to ask, "Are these mass extinctions cosmogenic? Did we just have a bad day in the Solar System or the Galaxy, or was there an interaction between the life here and the planet that was constrained by chemistry and amplified and caused things to go bad?" Some people would argue that humans are an example of that, and time will tell. The Australian Aborigines burned a relatively lush climate to flush game out and then the whole continent was driven to a desert, which wasn't the right way to do it.

CI How useful is computational chemistry as a tool, for example, the simulation of autocatalytic networks? Does the work need to be done in the wet lab, or are purely computational techniques powerful enough to yield insights?

SB I'll give you the party line, but there are people in the business who don't agree. My view is that we cannot compute in a way that predicts or retrodicts quantities as simple as the freezing point or boiling point of water, the solubility of sodium chloride in water, or the packing of small organic molecules into crystals. No one can do it. The theory is inadequate. Lots of people are trying to predict the three-dimensional structures of proteins by number-crunching methods, and I'd argue it's a ridiculous thing to be trying to do.

CI If you can't do those simple things, then you're overreaching.

SB Of course. For a protein structure, in addition to being an *N*-body problem, we also have to deal with the microscopic elements of interaction, including pluses bonding to minuses, the solubility of salt, the solution in a strong-interacting, high-dielectric solvent like water, the freezing point of water, and the packing of organic molecules into crystals. In my view, we don't have a prayer of ever getting anything serious out of pure number crunching. Now, the minute we're willing to do something creative with computers, we can make progress. We rely on computers in great detail to analyze the evolutionary history of proteins, and I'd hate to have to do it by hand. So as a tool, when we apply it with ideas, I think computation becomes very valuable.

CI The last thing I wanted to ask you about gets straight into astrobiology. I know you're involved in discussing the bio-signatures that future Mars missions might detect. What's the best way to approach that, given that we don't know exactly what we're going to find?

SB I'm a little frustrated, because NASA had a mantra to follow the water – which I think is what we have to do, because we can't expand our knowledge beyond that. Mars is a rocky planet like Earth, and it's not very likely that anything other than water would be the physiological solvent. The Opportunity landing site was ideal. We couldn't have wished for anything better. We expect to see borate minerals there because it's a lot like Death Valley. We expect to see ribose. We expect to see certain compounds associated with the oxidated degeneration, the degradation, of meteoritic stuff that falls in from the cosmos. There are all sorts of things we expect to see.

When I was on a panel for one of these Mars missions, we wanted one instrument. It was a laser Raman Spectrometer, which Steve Squyres had on the payload, and it was approved. One thing I learned about NASA is that you have to be at the last meeting, and if you think you're at the last meeting, they'll schedule another one after it. I had to trek all the way out to Pasadena, so it was a chore. That laser-Raman wasn't on the rover, and their alpha particle element detector couldn't get any elements lighter than chlorine. We had the geologists design instruments to detect iron and bromine. That instrument doesn't detect anything light, which includes hydrogen, carbon, lithium, boron, oxygen, nitrogen, and all the things we want to detect that are relevant to biology.

The bottom line with going to Mars – as it is with any exploratory science – is not to get too creative. We don't need to be thinking about silicon-based life and all that. What we're talking about is just getting back to Opportunity's site with the correct instruments, seeing what's there, and doing it step-by-step.

CI What are your expectations for Europa if we actually send a mission there?

SB It wouldn't surprise me in the slightest if there was life in the oceans under the icepack. There is presumably energy from radioactive decay. We probably don't need a lot, and we probably don't want too much.

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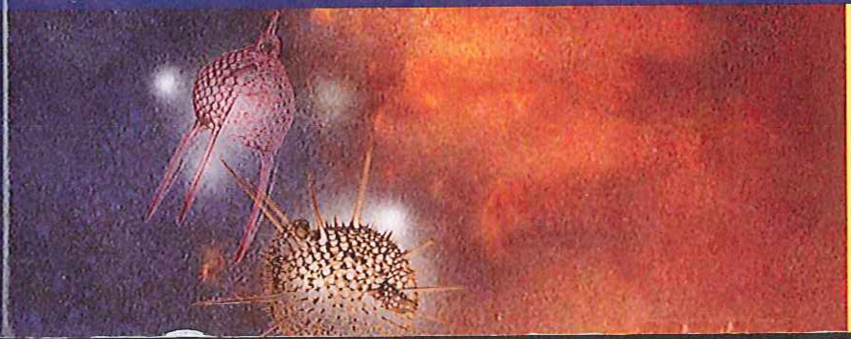
Cover illustration: images of radiolarians (the mineral skeletons of oceanic zooplankton) superimposed on a region of the Helix Nebula (as imaged by the Hubble Space Telescope). Design concept by Jessi Richins and Chris Impey; radiolarian images from Haeckel (1862, Berlin); and nebula image from Space Telescope Science Institute/European Space Agency.



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