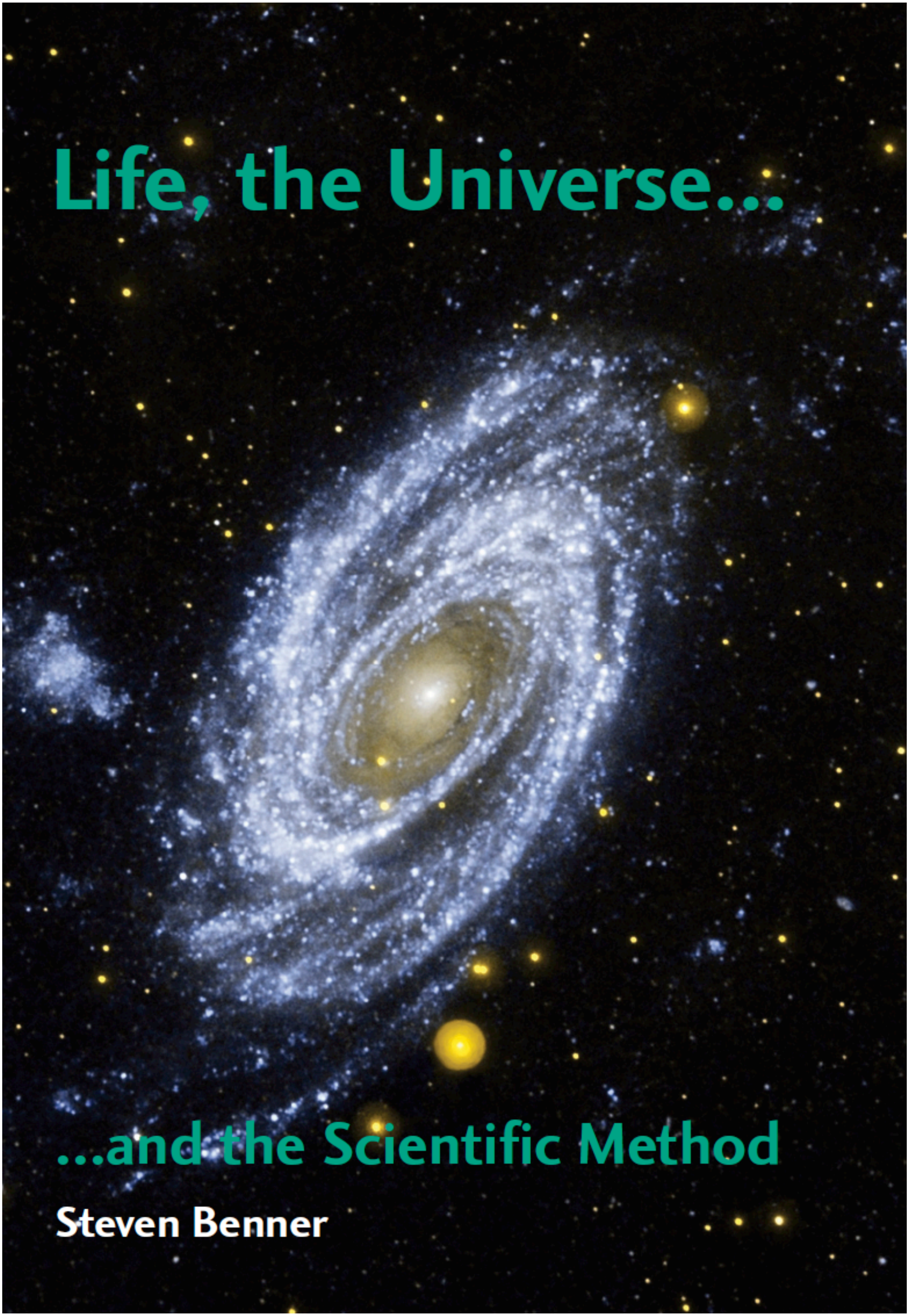
Life, the Universe...



...and the Scientific Method

Steven Benner

What is science? And how should students be taught to practice it? Steven Benner describes many kinds of science that relate to life as a universal concept. Biology, chemistry, physics, geology, astrobiology, and informatics are woven together in ways that reflect the contribution of Dr. Benner and his laboratory to each of these areas. As a founder and developer of synthetic biology, paleogenetics, and evolutionary bioinformatics, Benner helps the reader understand science as it is actually done, with all of its imperfections. He then shows how those imperfections are managed to make progress towards solving "big" questions. How did life begin? How did ancient life adapt? How might alien life appear? Can we make artificial life in the laboratory? Benner covers some philosophical ground: What makes a good scientific theory? What strategies can be used to study something we cannot observe? What disciplines help scientists avoid their biggest challenge: the propensity to deceive themselves? The book can be read by any viewer of Public Television, but also by professionals in each of these fields who want to understand how scientists in neighboring fields do what they do. With cartoons by Jake Fuller, this book combines humor and seriousness to make a most entertaining read.

"This book combines science, philosophy, education, and entertainment in an original and attractive way that should appeal to the new generations of students and enlighten them at the same time."
Christian de Duve, cell biologist, author, and Nobel laureate.

"This book is truly wonderful. Steve Benner is an example of a research scientist who can also explain science to the public".
Eric Gaucher, Professor, Georgia Institute of Technology

"Benner's 'Darwinian evolution in a test tube' encapsulated the thrill of the [2009] AAAS meeting at its best. American science's best orators provided insights … to a rapt audience, gleefully playing on the fundamental questions of what makes life, who we are, and where we're headed."
Rob Mitchum, Seed Magazine

ISBN Bar Code

Life, the Universe
and the Scientific Method

Steven A. Benner

Foundation for Applied Molecular Evolution
The Westheimer Institute for Science and Technology
Gainesville FL 32601

Steven Benner is a Distinguished Fellow at the Foundation for Applied Molecular Evolution and The Westheimer Institute for Science and Technology. His research seeks to combine two broad traditions in science, the first from natural history, the second from the physical sciences. Towards this goal, his group works in fields such as organic chemistry, biophysics, molecular evolution, bioinformatics, geobiology, and planetary science. He contributed to the founding of several new fields, including synthetic biology, paleogenetics, and computational bioinformatics. He co-chaired with John Baross the National Research Council's 2007 panel on the "Limits to Organic Life in the Solar System", advised the design of missions to Mars, and invented technology that improves the medical care of some 400,000 patients each year suffering from infectious diseases and cancers.

The Foundation for Applied Molecular Evolution (www.ffame.org) and The Westheimer Institute for Science and Technology (www.westheimerinstitute.org) are non-profit research organizations that use private donations and peer-reviewed grants from government and private sources to pursue research that crosses boundaries to address "big questions" in science and technology. Current activities seek to apply human genomics to manage diseases such as cancer, hypertension, and alcoholism, as well as to ask: How did life originate? How did we come to be? Are we alone in the universe? The FfAME is currently a member of the NASA Astrobiology Institute, as well as the team sponsored by the National Human Genome Research Institute to lower the cost of acquiring human genomic information for the purpose of personalizing patient care.

Cover: An ultraviolet image of the M81 spiral galaxy (center) taken by GALEX, NASA's Galaxy Evolution Explorer. GALEX uses ultraviolet wavelengths to measure the history of star formation 80 percent of the way back to the Big Bang. The large fluffy bluish-white material to the left of M81 is a neighboring galaxy called Holmberg IX. Image credit: NASA/JPL-Caltech.

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Chapter 1
Life and the Scientific Method

The movie *The Puppet Masters* introduced America to a field of science known as *exobiology*. Adapted from a novel of the same name by Robert Heinlein (spoiler to follow), the movie featured an especially nasty species of aliens who glued themselves to the backs of their human victims, sent tentacles into their brains, and controlled them like, well, puppets. Julie Warner played Mary Sefton, a NASA exobiologist called to the spacecraft's landing site. Sam Nivens, a government operative played by Eric Thal, asked Sefton about exobiology. The exchange went like this:

The Puppet Masters *(1994, Hollywood Pictures) describes a contest between the best minds on Earth (such as the planetary protection expert Andrew Nivens, played by Donald Sutherland (above) and a vicious species of aliens (napping below) in a battle that required the science of exobiology to win.*

Nivens: So tell me Mary. What exactly do you do for NASA?
Sefton: My specialty is exobiology.
Nivens: Exobiology?
Sefton: Uh-huh. It's a study of what alien life forms might be like.
Nivens: You actually make a living at that? Seems like it would be mostly guesswork.
Sefton: Well, we had a little joke in school. Ours is the only science that didn't have a subject matter.

To the American middle school student trained in the "scientific method", this would be the end of the story about extraterrestrials, at least the part belonging in a science class. There, "the scientific method" is a prescription that begins with neutral observations of the world. Objective hypotheses then follow from those observations. Scientists test these hypotheses by deftly constructing experiments, preferably experiments that distinguish between alternative hypotheses.

This prescription pretty much rules out exobiology as a science. If no alien life is available to observe, how can we construct objective hypotheses about aliens by observing them? Even if we manage to construct hypotheses, how can we test them? Without observations, hypotheses, or tests, we have no scientific method. Therefore, no science of exobiology is possible. Only "guesswork".

Yet the public is interested in the questions like: Are we alone in the universe? As I write this, the NASA Phoenix laboratory is on the surface of Mars. The *absence* of reported results for just one week in June 2008 sent the internet into a real life episode of *The X-files*. Was NASA concealing Martian life that it had found, the bloggosphere asked. "What do the Martians being concealed by NASA look like?" It went downhill from there.

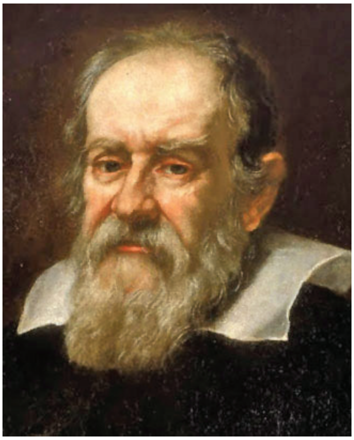
In part, our fascination with aliens comes from our interest in other "big questions". What is 'life"? How did it arise? What is the future of *our* life in the cosmos?

What activity other than science might effectively address such questions? Philosophers have made less satisfactory progress addressing many of these questions without a scientific method than four centuries of science having a method.

Thus, the public believes that "scientific" opinion is better than "non-scientific" opinion. A popular book by Thomas Kida subtitled "The six basic mistakes we make in thinking" exhorts us to "think like a scientist". OK. Seems good. But how?

Understanding life as a "universal" (or, as philosophers like Carol Cleland at the University of Colorado say, as a "natural kind") is a goal of research in my own laboratory. Accordingly, one goal of this book is to explain how that research is making progress towards answering these and other big questions.

A second goal is to show how "the scientific method" as taught in middle school is different from what real scientists actually do. Science *often* concerns things that are not observed. Observations are rarely neutral. Hypotheses are rarely objective. Proof is impossible for almost any interesting proposition. *Dis*proof is also not easy. Experiments rarely distinguish alternative hypotheses.



Galileo Galilei (1564-1642) by Giusto Sustermans.

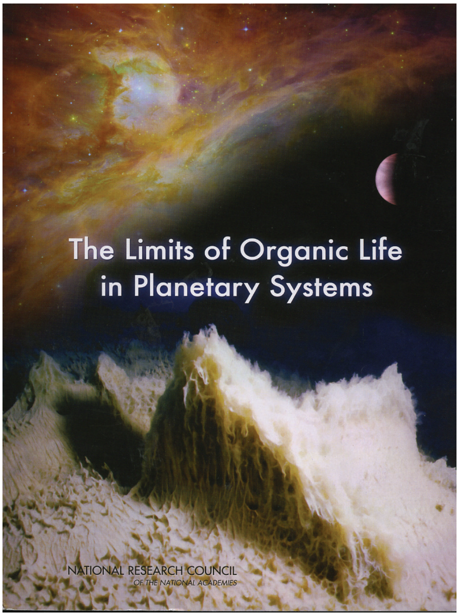
Thus, the real practice of science is very human, with weaknesses intrinsic to humans. In general, humans *want* to believe something. They then select from many observations only those that support that want. Like dead people that Cole sees in the movie *The Sixth Sense* (1999, Hollywood Pictures), humans see only what they want to see.

The third goal of this book is to teach how scientists make progress despite this aspect of their humanity. Successful scientists develop within themselves an intellectual discipline that

Chapter 2
A Definition-Theory of Life

In 2002, I got a call from David Smith, a physicist who works for the National Academy of Sciences.

"Steve", David asked, "the National Research Council has been commissioned by NASA to write a report on what alien life would look like. John Baross [a microbiologist at the University of Washington] said he would chair the committee but only if you agreed to co-chair".



The book produced by the National Research Council committee co-chaired by John Baross and Steven Benner. The book is an excellent place to go for a deeper understanding of many topics covered here, but especially where in the Solar System weird life might exist. Courtesy National Academy Press.

Five years later, after defections, disease and delay, many hours on airplanes, and a separate trip to Washington D.C. to sit with David to rewrite the entire draft, the report finally appeared in the summer of 2007. Entitled *The Limits of Organic Life in Planetary Systems* and published by the National Academy Press, the report provided an in-depth discussion of some of the topics presented in the chapters to follow in this book. Readers interested in a more technical discussion of exobiology than what is presented here are referred to the National Research Council report.

One thing will not be found in the National Research Council report, however: A definition of life. This is no accident. Early in the committee's deliberations, a conscious decision was made *not* to include a definition of "life" in the book. Perhaps this reflected cowardice. It may, however, be better viewed as an expedient based on wise experience. Nearly every member of the panel had spent hours in other committee meetings discussing that definition with little productive outcome. We did not want to spend any more hours doing the same.

Chapter 3

Four Approaches to Understanding Life

Life as a universal presents a quandary similar to that faced by Galileo

Throughout this book, we will use the definition-theory that considers life to be a self-sustaining chemical system capable of Darwinian evolution. Unfortunately, this definition-theory creates a quandary analogous to the one faced by Galileo. We are worried about life as a universal, a "natural kind" of thing. But this includes life that we have not observed, that we may not observe for some time, and for most life in the universe, that we will never observe. How can we be certain that we have chosen the correct definition-theory for life or even one that is useful? Can our definition-theory be used to recognize alien life should we encounter it, even if it does not plaster itself to our backs to control us like puppets?

First, don't panic. Science often concerns what it cannot directly observe.

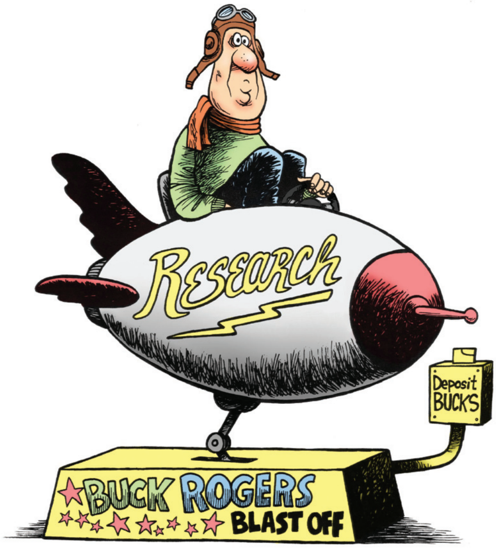
Next, we need to identify experimental approaches that serve the same role for exobiology as the rolling balls did for Galileo's studies of the solar system. Since we cannot observe life universally, we must do experiments here on Earth to help us decide whether we have chosen a good definition-theory for life with the potential for universality. The next chapters outline some of these experiments and methods, and tell the stories of how their pursuit created (and continues to create) new scientific methods.

No bucks, no Buck Rogers

First, a comment about one factor that determines the course of science. That comment comes from Tom Wolfe's book *The Right Stuff*, which includes the following exchange between test pilots in the 1940's:

Operative: You know what really makes your rocket ships go up?
Pilot: The aerodynamics alone are so complicated …
Operative: Funding. That's what makes your ships go up. No bucks, no Buck Rogers. Whoever gets the funding gets the technology. Whoever gets the technology, stays on top.

One factor driving science *not* taught in middle school are decisions that direct resources to fund science. Different organizations offer such resources in



different ways. Some government agencies and private foundations have specific missions and direct resources to meet those missions. Other organizations claim to seek individual innovators, hoping to find individuals worthy of "pioneer awards" or "genius prizes". Some grant prizes after specific goals are met, such as Lindbergh's crossing the Atlantic or the *Ansari X Prize* for putting a rocket into space.

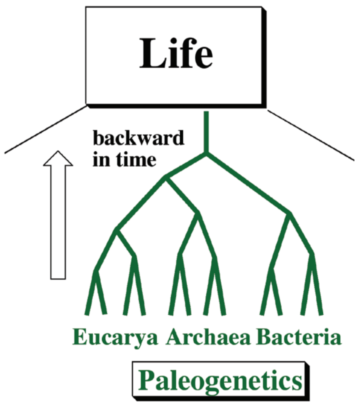
Some organizations seek community input to determine what the mission should be, how it would best be met, or what goals are worthy of prizes. Others decide this on their own. Some evaluate proposals from applicants; others do not accept proposals. Some evaluate proposals internally, while others distribute them to individuals in the community and base funding decisions on peer review.

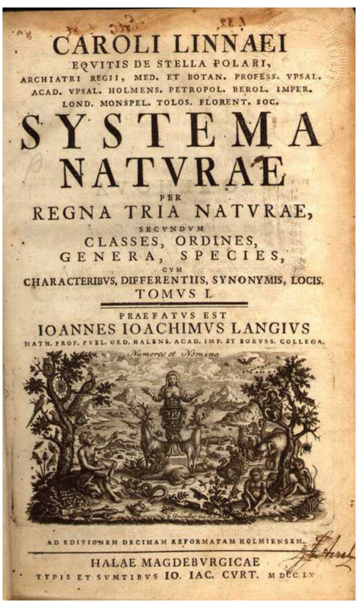
The sociology associated with science funding needs volumes to describe. We will not address this topic here with any generality, mentioning the topic only when funding decisions drove the science that we interests us. As a general rule, however, community-guided efforts do not fund "big questions" or breakthrough research. Nor are they expected to. Galileo was not funded by the Pope, and certainly not after the Pope understood what Galileo was up to.

In part our disregard of this important topic comes from the difficulty of obtaining the unbiased data that is needed to examine it "scientifically". Many examples exist, of course, where a grant of bucks has had remarkable impact in science. However, the *absence* of funding for a project generally means that it will not get done. This in turn means that we will never know that this breakthrough science had the chance of existing. Not knowing of projects that *might have been*, we cannot begin to evaluate how much better the global outcome would have been had a rejected project been funded and a funded project been rejected.

This is a common problem in history. We know well of Martin Luther and his Protestant Reformation. We know little about Jan Hus and his protestant reformation. Why is this so? Most simply, the political environment surrounding Luther allowed him to survive the Inquisition, just as Galileo's fame allowed him to survive. No analogous political environment surrounded the unfortunate Hus. He

Chapter 4
Working Backwards in Time from Life on Earth Today





CAROLI LINNAEI
EQVITIS DE STELLA POLARI,
ARCHIATRI REGII, MED. ET BOTAN. PROFESS. VPSAL.
ACAD. VPSAL. HOLMENS. PETROPOL. BEROL. IMPER.
LOND. MONSPEL. TOLOS. FLORENT. SOC.
SYSTEMA
NATVRAE
PER
REGNA TRIA NATVRAE,
SECVNDVM
CLASSES, ORDINES,
GENERA, SPECIES,
CVM
CHARACTERIBVS, DIFFERENTIIS, SYNONYMIS, LOCIS.
TOMVS I.
PRAEFATVS EST
IOANNES IOACHIMVS LANGIVS
MATH. PROF. PVBL. ORD. HALENS. ACAD. IMP. ET BORVSS. COLLEGA.
Numero et Nomina
AD EDITIONEM DECIMAM REFORMATAM HOLMIENSEM.
HALAE MAGDEBVRGICAE
TYPIS ET SVMTIBVS IO. IAC. CVRT. MDCCLX

Title page of Systema Naturae (1816) by Charles Linnaeus. This introduced the animal-vegetable-mineral trichotomy.

As humans, we have a special advantage as we seek to understand life as a universal: Unlike Galileo, who had to enter celestial mechanics with no knowledge of the subject, all children begin their study of biology knowing that life exists. Further, we humans instinctively distinguish the living from the non-living. We begin doing so as children long before we know intellectually how challenging it is to formalize a definition-theory that makes this distinction rigorously.

Thus, biology *is* a science with a subject matter. Therefore, if we want to understand life as a universal, at least we have a place to start: the life that surrounds us on Earth.

Many books offer information describing what is known about terran life. These are written at many levels, from picture books for young children to textbooks designed to train the next generation of biologists. We will not summarize their contents here. Our discussion of life as a universal relies on only a few features of terran biology; we will explain these as we go along.

Classification as a method in biology

We start with a simple scientific method: *classification*. As Heinlein wrote in his book *Have Space Suit, Will Travel* (1958), library science is basic to all science. Much science begins as an attempt by humans as librarians to classify what humankind has already observed.

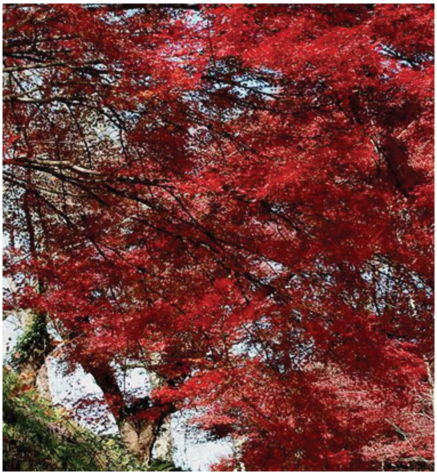
Humans are instinctive classifiers. Unfortunately, different instincts give different classifications. Therefore, classification systems and the language they use often tell us more about the classifier than about the classified. We will see many examples of this in this chapter.

The "animal-vegetable-mineral" classification system is one that we learn early in school. It is associated with Charles Linnaeus, the Enlightenment scientist who based his *General and Universal System of Natural History* on this three-way division. Leaving aside his exaggerated use of the word "universal" (Linnaeus had no access to extraterrestrials), this classification distinguishes the non-living from the living. It then divides the living into two classes, animal and vegetable.

In practice, this division of life is done by inspecting *characters*, attributes of the entity being classified. As with green emeralds, a character can be color. Or the ability to walk. For example, to make the animal-versus-vegetable classification, we ask: Is the living entity green, and can it move around? If the entity is *not* green and *can* move, it is animal. If it *is* green and *cannot* move, it is vegetable.

It might be argued that "able to move" is a better character for classifying terran life than "green in color". A frog is green, but can move. Since we instinctively believe that a frog is better classified as an animal, mobility must trump greenness. A Japanese maple tree is red, but the tree cannot move. We instinctively believe that the maple is a plant. Immobility apparently trumps non-greenness in our classification scheme.

This frog is green but can hop. The frog is "therefore" an animal. Leaves of the Japanese maple tree are red but the tree cannot hop. The tree is "therefore" a plant.

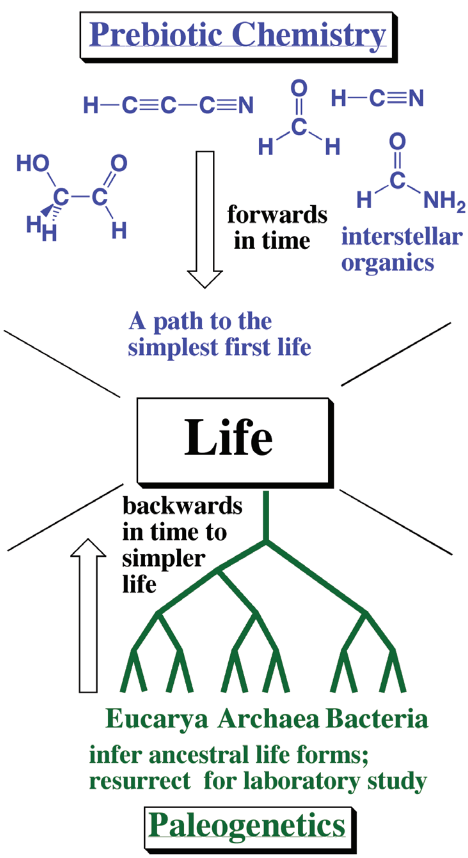


If anthropologists tried to infer our constructive beliefs about classification by examining our behavior, they would note that the ease with which we discard classification characters when they fail to deliver a desired classification. This suggests that we *constructively* believe that "animal" and "plant" are more fundamental concepts than characters themselves. This is metaphysical progress, as it suggests that "animal" and "vegetable" are the *natural kinds*, at least to us.

The characters are useful nevertheless because they provide a way to determine

Chapter 5
Forward in Time: From Chemicals to the Origin of Life

In Chapter 3, we used a graphic to illustrate four ways to indirectly explore life as a universal concept. Part of that graphic is reproduced below. Chapter 4 focused on the bottom wedge of the graphic, which represented a backwards-in-time approach to understanding life. Here, the sequences of ancient genes and proteins are inferred from the sequences of descendent genes and proteins. Biotechnology is then used to bring these ancient biomolecules back to life for study in the laboratory. This allows experimental methods to be brought to bear on historical hypotheses involving parts of living systems.



In the two decades since paleogenetics was introduced as an experimental science, several dozen studies have developed its methods. Many more paleogenetics studies will become possible as sequences emerge from whole organism DNA sequencing. A new field of science has been created. A scientific community has emerged with its own culture and standards-of-proof. Paleogenetics is now "normal science".

But what has paleogenetics said about life as a universal? The backwards-in-time approach has helped broaden our view of what life might be by providing broad support for the RNA-world hypothesis. This hypothesis proposes that an earlier episode of life on Earth used RNA as its only encoded biopolymer. According to this life form, no proteins were encoded. This, in turn, suggests that life based on just one biopolymer is possible, even though such life has never actually been observed. As we shall see later, single biopolymer life might be the most likely to be encountered as we explore the Solar System.

Unfortunately, the realities of natural history on Earth mean that working backwards in time from the life that we observe today on Earth makes it unlikely that we will be able to model forms of life at the beginning of the RNA world. The various lineages of terran life apparently separated well after terran life invented proteins. Until we find a lineage of life that diverged within the RNA world, we will not be able to triangulate our way back to build models for any RNA life, and certainly not at the beginning of RNA life.

This is a shame. It may be that RNA life was the first form of life on Earth. This would mean that RNA life began just after chemistry gained access to Darwinian evolution. As the closest thing to non-biology this side of the frontier between non-biology and biology, such life would reflect most the "essence" of life as a universal. To model this most basic life form, we must look elsewhere.

Working forwards in time from chemistry

Fortunately, the graphic in Chapter 3 suggests where else we might look. Complementing the lower wedge is an upper wedge that represents research that works forwards in time. This research starts with a list of organic molecules that might have been present on Earth before life formed. It then tries to build a model for how Darwinian systems might have emerged from those molecules.

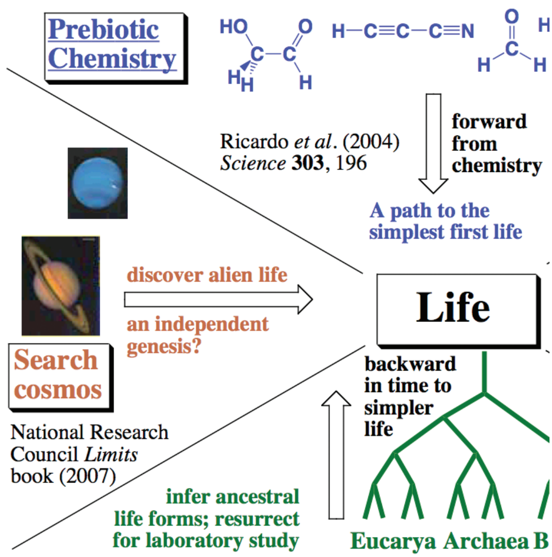
This is a "carbonaceous chondrite", a meteorite whose dark color comes from the organic compounds that it contains.

How can we possibly know what organic molecules were present on Earth four billion years ago? Is this not just another science without a subject matter?

To address this question, we rely again on our favorite aphorism from geology: The present is the key to the past. To apply this aphorism, we begin by identifying organic compounds that arrive *today* from the cosmos to the Earth on meteorites. Sandra Pizzarello, George Cooper, and many others have extracted and identified organic

Chapter 6

Exploration to Expand Our View of Life



In the past two chapters, we have gone as far as we could to explore life as a universal concept based on what we know about the present. We exploited two complementary strategies. First, we described an approach based on natural history that begins with the life that we know today and works backwards in time, inferring structures of ancient genes and proteins and resurrecting them for study in the laboratory. This permitted experiments to explore and constrain historical hypotheses that connect chemistry to Darwinian processes. We observed a success in science, the development of a new field with its own methods and standards-of-proof and the emergence of a new kind of "normal science".

The complementary approach begins with organic compounds likely to have been present on early Earth and works forwards in time in an effort to obtain chemistry that supports Darwinian evolution from chemistry that does not. Here, progress is less evident. The community has developed no accepted standards-of-proof for evaluating the relevance of a prebiotic experiment to the problem of origins, let alone a set of methods for doing so. Nevertheless, progress has been made. Paradoxes central to origins have been recognized. Research focused on these paradoxes has identified solvents and minerals that offer at least a few approaches mitigate the intrinsic tendency of organic molecules to form tar rather than life.

Although these approaches have placed new constraints on our view of life as a universal, these constraints are not very tight. The first has suggested that simpler forms of life based on just one biopolymer (RNA) might be possible, even though no such RNA on Earth is known. However, because of the realities of natural history, it is difficult to triangulate from today's biosphere back in time to a form of life deep within the "RNA world" that is simple enough to capture life's essentials. Known life on Earth evidently all diverged from an ancestor that arose after terran life gained access to proteins, and that carried baggage from accidents and contingency associate with perhaps a billion years of history on Earth. This baggage obscures the "essence" of truly primitive life even for that part of the RNA world that we might infer by extrapolation back in time from life found on Earth today.

The forwards-from-chemistry approach is not similarly defeated by natural history. Nevertheless, we still do not have a convincing model to get RNA from plausible prebiotic organic molecules. Further, even if we find ways to get pools of RNA spontaneously on early Earth, we have no estimate of the likelihood that those pools contained RNA molecules able to ignite Darwinian evolution. As a consequence, the culture lacks constructive belief in the possibility of an RNA-first scenario for the origin of life. Therefore, two essential ingredients for success in science (funding and enthusiasm) are not in hand.

We need some new ideas

This is no reason for despondency. Every science worthy of the name has had similar issues at some point in its history. Nevertheless, one thought comes easily to readers of Chapters 4 and 5: We need some new ideas.

Chapters 4 and 5 have provided examples (if examples are needed) of the value of new ideas, even as we as anthropologists observe the human propensity to reject these. The idea of resurrecting ancient proteins brought experimental methods to bear on historical hypotheses, something that many had thought was impossible. The idea that borate minerals might stabilize ribose as it is synthesized under prebiotic conditions revitalized thinking about the RNA-first hypothesis. The idea of formamide as a solvent to manage the intrinsic destructive power of water mitigates some of the problems with water as a solvent for originating life.

JODIE FOSTER LEARNS THAT SHE WAS RIGHT ABOUT SETI ALL ALONG...

But a prescription to get a new idea is more easily written than filled. The human brain does not easily create new ideas. This is perhaps a

Chapter 7
Synthetic Biology: If We Make It, Then We Understand It

So far, we have emphasized how different communities of scientists differ in their application of scientific methods. Let us now do the opposite by focusing on research strategies that different fields of science share. To the extent that different fields must interact to understand life, the similarities that connect scientific fields and their various methods will be important.

For example, *observation* is done in essentially every scientific field. Auto mechanics, symphony conductors, and others who do not call themselves scientists also observe. Indeed, it is difficult to conceive of a human activity that does *not* involve observation of some kind.

Of course, scientists in different fields observe in different ways. Moose in Montana are observed using binoculars. Moons around Jupiter are observed with telescopes. Molecules of methane in interstellar clouds are observed by microwave spectroscopy.

Nevertheless, observation in all of these disciplines shares one thing: it does not alter the observed system. Neither the moose, the moons, nor the methane behave differently because they are being observed.

Perturbation is another strategy that is used in nearly every science, as well as by mechanics, conductors, and others who do not call themselves scientists. Here, the system of interest is probed. Observation follows to see how the system responds to the probe. The conductor might poke a first violinist and see if he plays faster. The auto mechanic might oil an axle and see if squeaking stops. The scientist might drop hay near a moose and see if he eats it.

Scars (dark regions in the upper hemisphere) were formed where pieces of Comet Shoemaker-Levy 9 crashed into Jupiter. The cometary probe revealed behaviors of Jupiter's atmosphere in ways that simple observation could not.

Useful perturbations may also come naturally. For example, when fragments of the Shoemaker-Levy 9 comet hit Jupiter in 1994, the Jovian atmosphere was perturbed. Even though planetary scientists did not deliberately throw the comet at Jupiter as a probe, they certainly used observations of the planet after Jupiter was naturally probed to test their models for the Jovian atmosphere.

Analysis generates lists of parts

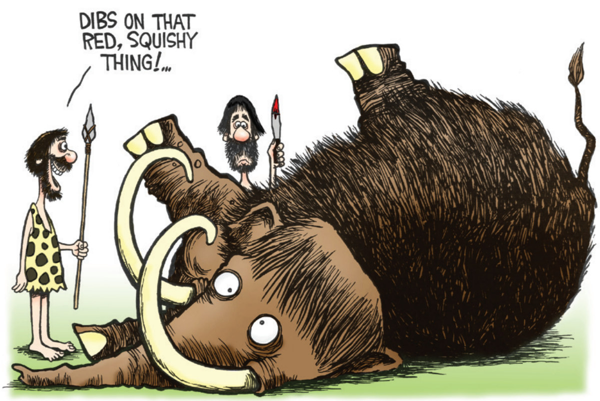
Analysis is yet another research strategy. Analysis begins by taking a system apart, dissecting it to give pieces. These are then named and put on a *parts list*. Such a list cannot generally be obtained by simple observation or by observation that follows perturbation. It requires in most cases that the system under study be destroyed.

Analysis is found throughout science. In geology, for example, analysis was used to discover that green emeralds, green peridots, and green rocks from Solomon's mine contain the elements beryllium, magnesium, and copper (respectively). In chemistry, analysis showed that methane is built from one carbon atom and four hydrogen atoms (CH_4), ammonia is built from one nitrogen atom and three hydrogen atoms (NH_3), and water is built from one oxygen atom and two hydrogen atoms (OH_2).

In biology as classically done, analysis begins by killing the system. Then, the life-that-was is physically dissected and the parts encountered are listed. Classically, these lists include the names of the organs, bones and tissues, names that middle school science students are forced to memorize.

Only technology limits what ends up in a parts list. When applied to living systems with a low-tech optical microscope, for example, analysis generates lists of cell types such as the types of neurons in the brain or the types of cells in the blood. If supported by electron microscopy, analysis generated lists of sub-cellular structures such as the nucleus, the ribosome and the mitochondrion.

The value of such analysis in biology is indisputable. Indeed, progress in biology over the last century has been measured in what analysis has produced. Christian de Duve, whom we met in Chapter 5 discussing the origin of life, won his Nobel Prize for his work analyzing structures within cells. Peter Mitchell, whom we met in Chapter 3, won his Nobel Prize for his work analyzing mitochondria.



THE BEGINNINGS OF ANALYSIS IN BIOLOGY

Chapter 8
Weird Life. Life as We Do Not Know It

Congratulations. We have survived seven chapters of heavy lifting together. We began with a discussion of the differences between "the scientific method" taught in middle school and the actual practice of science in different scientific communities. We considered ways in which different communities construct arguments, do experiments, and decide when experiments should end. We have encountered science that functions as science should; we have encountered science best characterized as dysfunctional. This is heavy stuff.

We also discussed how scientists might consider one specific non-observable: life as a "universal", also known as a "natural kind". We first worked backwards in time from observations of modern organisms on Earth to infer the structures of the genes, proteins and metabolisms used by ancient organisms. Developing the field of paleogenetics, we learned to resurrect ancient proteins for study in the laboratory. This brought experimental methods to bear on historical hypotheses, helping them become more than just-so stories.

This backwards-in-time approach helped us infer the habitat of bacteria living two or three billion years ago (it was hot). It provided the outlines of a form of life that did not have any encoded proteins, but instead used RNA for both genetics and metabolism. This, in turn, adumbrated a simpler form of life than is known on Earth today. It expanded our view of what kinds of life are possible.

Unfortunately, this approach did not allow us to infer the structures of the *simplest* past forms of life on Earth, including the life that *first* gained access to the power of Darwinian evolution on Earth (assuming life began here). Having a model for such a life form would further constrain views of the essence of life.

We therefore examined an alternative approach to understand life that works forwards in time. This approach started with organic compounds that were almost certainly present on early Earth. Relying on chemical theory, we looked for ways that RNA might spontaneously emerge under conditions on early Earth. Progress has been made, especially concerning hypotheses for prebiotic synthesis of pieces of RNA. In particular, we have come to appreciate the power of minerals to control the intrinsic propensity of organic molecules to become tar.

The forwards-in-time approach encountered serious methods issues, however. Different participants in the community do not agree on the types of experiments relevant to address questions surrounding life's origins. Indeed, many practitioners do not understand that the absence of community-shared standards *is* a problem that needs to be addressed. Chairs are thrown and invectives are traded.

So we turned to exploration to provide a jolt of discovery that comes most easily when one leaves home. Here, we encountered two new problems. First, *any* search for life in the cosmos is expensive, and the bucks for a systematic search are simply not available. Also, we learned that our understanding of biosignatures is inadequate to interpret data from the partial searches that are now fundable. The result has been contradictory certitude from competing experts. Some community members argue that life is absent elsewhere in the Solar System. On Mars, for example, water is absent or frozen or too salty. Opposing this are members like Gil Levin who argue that life on Mars may have already been detected.

This notwithstanding, constructive hope remains to find life on Mars, Titan, and Europa (for starters), life that would be recognizable under theories that tie our definition-theory of life to molecular structures having a potential to support Darwinian evolution. The polyelectrolyte theory of the gene and the repeating dipole theory of metabolic catalysts are two. However, the number of places where Darwinian molecules are possible is far larger than the bucks available to look.

Therefore, we considered a fourth approach to get our hands on a life form that is not just an evolutionary cousin of the life that we already know: Synthetic biology. Synthetic biology allows scientists to be proactive; they are challenged to design *new* chemical systems capable of Darwinian evolution in the laboratory. If we understand life and its parts, we should be able to synthesize some life of our own. If our theory empowers a successful synthesis, we can say we understand.

Several synthetic protein enzymes and synthetic genetic systems have been produced to meet challenges in synthetic biology set with increasingly higher bars. Through these, we can say that we understand the first factor of 10,000 in biological catalysis produced by proteins. We can say that we understand essentially all of the discriminatory power of natural genetic systems. The empowering theory is simple, requiring no numerical simulations. Indeed, numerical simulations do not empower further.

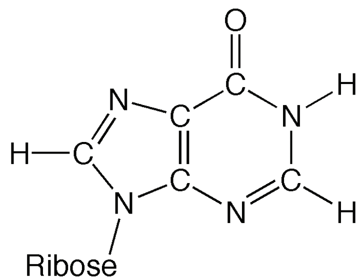
Moving the bar higher, we have now synthesized chemical systems capable of Darwinian evolution, allowing us to say that we constructively understand something about what structural features support Darwinian evolution. Synthetic biologists are contemplating the next grand challenge: to make *self-sustaining* Darwinian chemical systems based on chemistry still more different from that found in natural terran biology. As with any grand challenge, this will drag us across uncharted territory where we must solve unscripted problems in ways where failure cannot be overlooked, driving discovery and paradigm change. But we will need bucks to do it.

The art of scientific speculation

Even with this heavy lifting, our four approaches have still not taken us very far from the life that we already know. Our synthetic proteins still look like proteins. Our synthetic genes still look more or less like DNA. Are more exotic forms of life possible? If so, what would they look like? How would we recognize them as "life"? These were the questions raised by NASA when it set up the committee of the National Research Council that I co-chaired with John Baross, a distinguished microbiologist at the University of Washington.

Some questions are best answered by a simple: "We don't know". As we have noted, we have direct knowledge of only terran life forms, all of which appear to be related by common ancestry. We have no method to decide whether the similarities that they share reflect common ancestry or the needs of life as a universal. But if we retreat to a position of defensible agnosticism, we have no fun. Accordingly, we close with a chapter on what science offers by way of method that supports entertainment: Constrained speculation.

The best science fiction writers also use scientific constraints. For example, Steven Spielberg's ET has the same number of nucleotides in its DNA (six) as the number of nucleotides in some of the Darwin-ready synthetic genetic systems that we made in our laboratory. As ET lay dying, one hears chatter that the extra letters are "inosine and a pyrimidine that we cannot identify". Inosine has the structure below. Return to Chapter 7. Play Watson-Crick. What can that pyrimidine be? There are only a few possibilities, making us wonder why the people wanting to dissect this cute alien could not identify it. Remember, ET: Shoot or hide. Forget phoning home.



Inosine

Scientific speculation balances the known with the possible

The modifier "constrained" is what allows speculation to be given the coveted title "scientific". Fiction writers can propose anything. Scientific speculation, however, must be constrained by what we know (or think we know) about the real world. We are *not* allowed to say that water is H_3O as we speculate on the form of alien life. On the other hand, the challenge in scientific speculation is not to be *too* constrained. We want to stray as far as possible under physical law, but not farther.

So far, we have not strayed a great distance from what is known. For example, even though the synthetic genetic systems described in Chapter 7 have six letters

Chapter 9
Concluding Remarks: Think Like a Scientist

Michael Crichton, author of *Jurassic Park*, *The Andromeda Strain*, and other parables of modern times, was always prepared to show the human side of science. His appreciation of this aspect of science method came from his training in medicine, where he had ample opportunity to observe the medical arts as they are actually practiced. Crichton was nevertheless mostly an observer, an anthropologist of science who had no professional stake in the science that he described.

I have also tried to show science as it is practiced. However, I have professional views about most of the topics presented here, excepting those that were controversial only in centuries past. I worried about the possibility that this involvement would create a lack of objectivity, but set it aside. Frankly, I could not see how the practice of science could be described from anyone other than an insider. An outsider simply would not know enough about the details to have informed opinions.

What is remarkable about the science that we have discussed is how flexible its methods are. This sentiment has been expressed by non-scientists, notably in the idea that "anything goes" as elaborated by Paul Feyerabend, my colleague at the E.T.H. in Switzerland. One certainly has no difficulty finding examples in science where stamp collecting was informative, disproof was best ignored, mathematical formalisms impeded progress, data were selected to support a desired theory as opposing data were ignored, peer review was wrong, and publication was forbidden. Upon re-reading these 300 pages, I was surprised to see so many examples of this in its narratives.

Which brings me to a question that arises often in curriculum committee meetings: What do we teach the students? This question is not as conspiratorial as it might sound to a student reading this book; your teachers are actually interested in seeing you have successful careers in science. But if Feyerabend is right, if new theories are accepted not because they comply with a scientific method but because their supporters made use of "any trick, rational, rhetorical or ribald" necessary to advance their cause, we need to enrich our science curriculum with more courses on the rhetorical arts.

I share Feyerabend's understanding of the appalling implications of his conclusion. He wrote: "'Anything goes' is not a 'principle' I hold … but the terrified exclamation of a rationalist who takes a closer look at history" (*Against Method*, 1975). Nevertheless, I suspect that Paul is not entirely correct. If advocacy without method is all that scientists do, we would not expect to see the progress that science has produced. There must be something more to science as it is practiced and there is evidence for something more.

First, progress does not appear to be random, and does not exclusively come from scientists who were in the right place at the right time (although being so undoubtedly helps). We have mentioned a few scientists who repeatedly contributed to progress in many fields. Linus Pauling was a prominent example, but Frank Westheimer, Joseph Kirschvink, Christian de Duve and Freeman Dyson have appeared at more than one place in this book in different contexts. One sees in their science a focus on method, an understanding of the need to avoid self-deception, and a willingness to construct for each problem a set of rules appropriate to that problem.

Above all, we want to teach students to recognize that scientists need a discipline, largely self-imposed, that helps them avoid traps that are set by Nature, circumstance, colleagues, community, culture and their own minds. We rarely write out syllogisms; life would be unbearably slow if we did so frequently. Yet we must always be prepared to do so. We rarely consider crackpot assaults on deeply held beliefs; our lives would be hopelessly distracted if we did so routinely. Yet we must occasionally do so. Our constructive beliefs come in part from learning by authority and were shaped by accidents in our training and professional lives; it cannot be any other way. But from time to time, we must ask ourselves whether we constructively believe what we say we believe, why we believe it, and whether we really should not believe something else. In doing so, we must be prepared to know and revisit primary data that are behind our beliefs.

With this heavy stuff out of the way, we can return to science for its intellectual and entertainment values. Given tools described in Chapter 4 that allow the discipline of experimental science to be applied to historical models for biology, we see the opportunity to create a "grand unification" that joins the chemistry of proteins, genes, metabolisms and pathways by way of cells and organisms to the ecosystem, the planet, and the cosmos. Based on the profusion of genome sequence data now becoming available, there seems to be no barrier to prevent this unification and its application to human biology, including disease.

With only slightly less enthusiasm, we anticipate the imminent emergence of more coherent models for the origin of life. These will be written in the language of chemistry, the language that we developed in Chapter 5. There remain problems, and not just in the sociology behind the conflict between those who disagree on what experiments are relevant to the origins problem. A real potential exists that current theory will *never* solve the problem at hand, keeping open the possibility for a true revolution in the related and surrounding sciences.

The potential for discovery through exploration is also considerable. The pace of NASA and ESA missions is slow, a reflection of their cost as well as the difficulty of knowing just where and how to look for an alien life that has unknown form. Nevertheless, various considerations of universal chemistry and (possibly) universal biology suggests that we have a chance of finding evidence for an alien life by looking for specific kinds of organic molecules in Martian rocks and Titan's methane oceans. If we find alien life, this will change the game, perhaps not from theory, but certainly the data available from which to construct theory. This would be big.

The only thing bigger, and this because it is more likely to happen sooner, would be to construct an artificial chemical system capable of Darwinian evolution in the laboratory. Having in hand our own artificial form of life would set in motion a century of new biology, one that builds from the bottom up rather than dissects from the top down. Just one example would open doors. Within the well-controlled confines of artificial life, we would first attempt to build a synthetic metabolism. In doing so, we will learn more about metabolism, natural and synthetic. Once synthetic metabolisms are in hand, we would use the artificial Darwinian system as a platform to engineer regulation. Again, this activity could not help but teach us about regulation, natural and synthetic.

Most important about this "grand challenge" is that it is risky; it may fail. Of course, we need to give it a serious try and would need the bucks to do so. But if a laboratory Darwinian chemical system could *not* reproduce the behaviors that we have come to demand from life, then something might be wrong with our definition-theory of life. The synthetic challenge is already dragging scientists across uncharted territory to address unscripted problems in ways where failure is obvious. This effort will drive discovery and paradigm change like almost nothing else in science. All that is needed to pursue this understanding is funding; no bucks, no Buck Rogers.

Finally, what are our prospects of encountering truly weird life? Something that does not live in water, uses different sets of chemical elements, or has two dimensional genetic information systems, for example? We simply do not know, but it appears small for the immediate future, unless we are lucky enough to stumble on an RNA-world organism left over from our ancestry. The certainty of many that this will not happen is balanced by the certainty that if such weird life were beneath our feet, the tools that we are using to search for life on Earth today would not find it.

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