

## *Mysterium Tremendum*

The origin and evolution of the Universe is surely *the* age old problem that for millennia has fascinated thinking persons. That life could arise and develop to the point of thinking, reasoning creatures is an aspect of the larger problem that has caused special fascination. This means that the Universe has reached the stage where it contemplates itself. It also means it is able to fashion machines that can leave this Earth and land on the Moon, and then return, all the while carrying a few of these living, thinking creatures. How splendidly amazing this circumstance is!

In the following paragraphs, I will focus on that aspect of the broader problem we call life. Specifically, I will focus on the origin and evolution of molecular genetics, i.e. the genetic code and its associated protein biosynthesis machinery. This topic is especially interesting because mankind has learned a very great deal about it during the last hundred years and because certain conceptual issues remain unresolved in spite of this great progress. These issues constitute what I mean by the *Mysterium Tremendum*. My purpose will be to enunciate as clearly as possible what the unresolved issues are. To do this, a review of what is already known is necessary. This review will cover many different features of the problem because so much depends upon the context for the discussion. I hope to be able to eventually point the reader down the correct path to a potentially final resolution, although, for now, that resolution will surely remain out of grasp.

This account requires a special structure that the modern age of electronic word processing makes possible. While the main text continues linearly from this point onwards, many side issues are presented as needed and where needed in clickable excursions [*links*]. The reader can choose to take those excursions as he/she sees fit. Often the content of an excursion will be used in the main text, so the excursions are not really optional.

Since this topic is often associated with religious thinking, it is necessary for me to clearly express my personal position. Obviously, a literal believer in the Judeo-Christian-Islamic old testament Book of Genesis already has answers to the origin of life question (as do adherents of many other religions), if not to the more detailed issues of the genetic code and protein biosynthesis. I believe that mankind's religions have an evolutionary origin that parallels the rise of thinking, wondering creatures whose questions far outstrip their ability to answer them. In my view religions and Gods are constructs of evolving brains in relatively highly evolved thinking organisms. These religious belief structures can make daily existence less difficult and may bring some social order to the society of humans. I believe that such creatures with such highly evolved brains populate the Universe in large numbers. These beliefs are related to the question of [[Universality](#)]. (By clicking on the preceding *Italic* [[Universality](#)] you will be taken on the

first excursion of this text. Other excursions will appear as clickable bracketed *Italic* words or phrases.)

It is important to immediately address one issue that will otherwise create unwanted confusion. That issue is [[Irreducible Complexity](#)]. The Creationist movement has evolved into the Intelligent Design (ID) movement. One conceptual construct used by the ID movement that is useful in the present text is that of Irreducible Complexity (IC). IC is an idea *much older* than ID and it is useful in the present context of origins and evolution *independently of ID*.

I will use IC in the following way. Looking at the contemporary molecular mechanism of gene directed protein biosynthesis one sees a complex macromolecular apparatus made up of a great many component molecules (ATP, replicase, transcriptase, ribosomes (rRNA, rProteins), mRNA, tRNA, aaRS...). It is clear from study of this system that it did not evolve full blown but instead developed and evolved with increasing complexity over a very long time (probably millions of years). Nevertheless, it is difficult to imagine removing any of its various parts and have remaining a functioning system. Thus, the question arises: at what stage, *if at any*, is there IC? At what stage can the mechanism contemplated for the genetic code and its associated protein biosynthesis machinery no longer be reduced to a simpler mechanism from which it evolved? If there is a stage of IC, could it have arisen *naturally*? By *naturally* I mean by the laws and rules of physics and chemistry. These questions are at the heart of the matter when we address the origin and evolution of the genetic code and its associated protein biosynthesis machinery. I will attempt to argue for a progressive development of the contemporary protein synthesis system from relative simplicity to relative complexity by natural means. At no stage do I imagine there is IC. Believers in IC require a Deity (the Designer) to create the first putatively IC stage of genetic molecular mechanisms. Moreover IC is unavoidable according to followers of such thinking. I repeat: At no stage do I imagine there is IC.

Some readers may decide that based on my declarations regarding Gods, religions and IC, there is no need to continue reading this presentation. I write this for those readers with enough curiosity to confront the issues to be developed and I welcome their feedback. Perhaps one of you can help me to take a few more steps down the path towards a potentially final resolution.

### **The Elements of Life**

Life is made from the materials that are available. This simplistic sounding remark is too often ignored. Living matter is built from the elements that are readily available in planetary systems in the Universe. Our present knowledge of stellar nucleosynthesis [[elements of life](#)] is quite advanced and explains why certain nuclei are more common than others. Our understanding of chemistry also explains why certain small elements give rise to myriads of

molecules containing single and double bonds, and why other elements do not. It is especially noteworthy that carbon (C) is a principle constituent of living matter whereas silicon (Si), with the same tetra-valency, is not. Carbon makes huge varieties of small molecules in combination with oxygen (O), nitrogen (N) and hydrogen (H) whereas Si combines primarily with O<sub>2</sub> to yield silicates. This can be understood from the respective positions of C and Si in the second and third periods of the periodic table. A detailed discussion of these facts is in [[elements of life](#)].

The table of free energies of formation in [[elements of life](#)] contains many biologically relevant molecules. The reader should study this table. Molecular life as we know it is made from *available molecules and ions*. All those substances with negative free energies of formation per gram in the 2's and 3's are especially noteworthy: calcium (aq), hydronium and hydroxyl ions, magnesium ion, hydrogen phosphate and dihydrogen phosphate, phosphoenolpyruvate, quartz, sodium ion, and water. Calcium and phosphate combine to make the mineral apatite (calcium hydrogen phosphate in the table). Fundamentally, a salt water (dissolved ions) solution of apatite is a natural setting for a system of life based on both a phosphate energy economy and on bone. Adding in the molecules with negative free energies of formation between 1 and 2 provides sugars, amino acids, formaldehyde, nucleic acid bases, glyoxylate and many others. From the perspective of small molecules, life as we know it is made in large part from those types of molecules that were naturally available, e.g. sugars and amino acids. While it is true that contemporary metabolism produces many molecules of exotic types, many of the molecules present in the core metabolic pathways are also naturally occurring before there was life. In addition, there are molecules with positive free energies of formation that occur naturally anyway as a result of various energy fluxes (solar wind, high energy light, heat, electrical discharge, shock waves...) through molecular matter. Hydrogen cyanide is one such molecule and the nucleic acid base adenine is a cyanide pentamer. Thus energy flow through molecular matter can create a richer variety of molecules than free energy of formation considerations alone would suggest. A representative sample of molecules seen in interstellar space is given in the table below:

Interstellar molecules

Chemical formula	Common name
H <sub>2</sub>	hydrogen molecule
HCOOCH <sub>3</sub>	methyl formate
C <sub>2</sub> H <sub>4</sub>	ethylene
CH <sub>3</sub> CN	acetonitrile
HCN	hydrogen cyanide
CH <sub>3</sub> OH	methanol
CH <sub>4</sub>	methane
CO	carbon monoxide
HNCO	isocyanate

NCOOH	formate
NH <sub>2</sub> CHO	formamide
H <sub>2</sub> O	water
H <sub>2</sub> S	hydrogen sulfide
H <sub>2</sub> CO	formaldehyde
MgCN	magnesium cyanide
NaCN	sodium cyanide
H <sub>3</sub> O <sup>+</sup>	hydronium ion
NH <sub>3</sub>	ammonia
N <sub>2</sub> O	nitrous oxide
SO <sub>2</sub>	sulfur dioxide
SiO	silicon monoxide
CO <sub>2</sub>	carbon dioxide
CS	carbon monosulfide
PN	phosphorus mononitride

### The Physico-Chemical Context for Life

Several contributions make up the context for the development of life by natural means. Each appears to be essential. We have already addressed the issue of building materials. A tentative list is as follows:

- (1) building blocks (small molecules)
- (2) energy transductions
- (3) compartmentalization
- (4) transition from monomers to polymers

In the following presentation, energy fluxes will play a key role. This is largely a result of the fundamental transition from monomeric matter to polymeric matter that requires an input of energy to be achieved. In fact one could argue that in the natural sequence of events *the transition from no life to life is essentially the transition from monomeric matter to polymeric matter*, at least as long as one is speaking about biological polymers.

One of the locally universal (i.e. universal here on Earth) observations that has been made during the last hundred years is that those molecules that we recognize as biological are primarily polymers: proteins, polynucleotides and polysaccharides. The common feature each of these polymers shares is that they are dehydration condensates [[polymer biosynthesis](#)]. This means several things. Each type of polymer is metastable and is subject to hydrolysis in an environment rich in water, such as the inside of a cell. Synthesis of the linkage of monomers to make polymers requires an input of metabolic free energy. Hydrolysis is catalyzed by relatively simple hydrolases and requires no energy and is spontaneous. Synthesis requires energy and

complex synthesis complexes of proteins, of proteins and coenzymes or of proteins and polynucleotides. The main inhibitor of synthesis is the release of a water molecule during linkage of a monomer to the growing polymer chain, in an environment rich in water. The input of energy is also universal and involves phospho groups.

A study of cellular metabolism in all organisms will show that the central metabolic pathways are designed around the harvesting of chemical energy [[energy metabolism](#)] (aside from those photosynthetic pathways dedicated to creating chemical energy from light). The ultimate source of biological energy is sunlight. In photosynthetic organisms, whether algae, bacteria or plants, sunlight is used to create four major products: carbohydrates, ATP (*adenosinetriphosphate*), reducing potential in NADPH (*nicotinamide adenine dinucleotide phosphate*) and O<sub>2</sub>. In non-photosynthetic organisms, carbohydrates are oxidized to produce energy water and carbon dioxide, completing the cycle. There are specialized organisms that do their energy processing by other means, but these are exceptional and may or may not provide insight into origins. It is often stated that the ecologies surrounding thermal vents along the mid-oceanic ridges represent a primitive alternative based on hydrogen sulfide chemistry providing energy through chemosynthesis. However, these ecologies are actually driven by oxygen rich ocean currents and the hydrogen sulfide is in fact oxidized. The giant tube worms found in these sites attest to this oxygen based chemistry with their brilliantly red, heme containing tissues in which the thermophilic bacteria use the oxygen to react it with the sulfide [[Hydrothermal Vents](#)]. So even in these vents we have a modern ecology, not a primitive one. Nevertheless, such sites might still have been ideal for the origin of life on the primitive Earth before the advent of atmospheric O<sub>2</sub>. Returning to metabolism, we find that the basic energy pathway is glycolysis. This relatively simple pathway partially oxidizes carbohydrate, glucose, and generates two forms of chemical energy: ATP and reduced NADH (*nicotinamide adenine dinucleotide*). Pyruvate is also a byproduct and shows that an incomplete oxidation of glucose has occurred. Pyruvate is converted to acetyl-CoA in many organisms and this chemical feeds the citric acid cycle in which more oxidation occurs. Three byproducts of the citric acid cycle are GTP (*guanosine triphosphate*), NADH and FADH<sub>2</sub> (reduced *flavine adenine dinucleotide*). In true aerobes, the reduced products, NADH and FADH<sub>2</sub>, feed their energy rich electrons to the electron transport chains in the membranes of mitochondria where they ultimately end up combining with O<sub>2</sub> and protons yielding water. At the same time, an energized state of the mitochondrial membrane is created that supports an electrical potential and a pH gradient. These physical properties of the membrane are able to drive protons across the membrane through ATPases and generate the vast bulk of the ATP aerobes produce [[lipids, membranes and chemiosmosis](#)]. Pathways emanating from these central core energy pathways yield various carbohydrates, amino acids, nucleotide bases, lipids and other chemical species.

A more precise statement of the *Mysterium Tremendum* (MT) is now possible. The transition from monomers to polymers requires energy of activation. Today this energy is

supplied by energy pathways that are catalyzed by enzymes and these enzymes are made by a genetic apparatus rich in other enzymes, various types of polynucleotides including some ribozymes, and the molecular machinery needed to make polynucleotides and proteins. The synthesis of polynucleotides requires activation energy. Each of the types of energy activation of monomers needed to make polymers involves phosphates in one way or another. Thus, the first issue for origins is:

*how did energy activation begin before there were energy pathways, enzymes and the genetic apparatus to make both the enzymes and the polynucleotide components?*

There must have been precursor energy generating mechanisms and they must have functioned initially without the rare component, phosphate. Fritz Lipmann once stated “ coupling of redox energy to phosphate energy may have been first step on the road to life”. This coupling may have involved sulfur in the form of *thioesters*. Christian De Duve is a strong proponent of this early in evolution version of energy activation and transduction. In the following we will present a detailed scenario for these events. We will show a transition from redox energy through thioesters and finally into *pyrophosphate*, the precursor to ATP. So the first issue to be addressed regarding MT is energy metabolism. This stage is NOT a stage of IC since we will dispense with the contemporary energy pathways altogether, and still be able to activate monomers and make polymer, using a source of energy that is plentiful, sunlight and redox potential. Indeed, UV rays activate ferrous iron electrons, yielding ferric iron and energized electrons. The mixtures of ferrous and ferric iron formed in the primitive seas precipitate out magnetite and hematite that make up (along with layers of shale and chert) the world wide banded iron formations that date from 3+ billion years ago until about 1.5-2.0 billion years ago, when atmospheric oxygen became concentrated enough for ozone formation and UV shielding. By 1.5-2.0 billion years ago life as we know it was already fully developed at the cellular and molecular level. It is possible to be non-IC with energy pathways and couplings. UV, iron and sulfur make possible a vigorous energy metabolism without proteins and polynucleotides. At the heart of this stage of energy metabolism evolution is the *thioester*. Thioester driven chemistry is bountiful and spontaneous. The *Thioester World* can support development of a pyrophosphate based energetics as it evolves.

The second issue for MT is to make a detailed list of the contemporary components of the genetic apparatus and its protein biosynthesis machinery. Here the issue of IC is much more difficult. Many of these components were listed above in the sixth paragraph from the beginning. Here more detail is given below [[polymer biosynthesis](#)]. The contemporary system requires:

*ATP*, for monomer activation

*DNA replicase*, a protein complex that replicates DNA

*DNA transcriptase*, a protein complex that makes mRNA from genes for proteins  
as well as various RNA's

*Ribosomes*, containing r-proteins (52 in E. Coli) and rRNA's (3 in E. Coli)  
*mRNA*, the transcript of DNA genes that is the template for protein synthesis  
*tRNA*, the adaptor molecules that carry amino acids to the ribosomes for protein synthesis  
*aaRS's*, the *amino-acyl-tRNA synthetases* that attach an amino acid to its cognate tRNA

as well as many other protein factors that help coordinate and facilitate the many reactions involved. This is an impressive list of components, all the more impressive when seen in operation, as part of a living cell. Clearly, this molecular machinery did not simply appear full blown, so to speak. There had to be a long evolution and development of the parts seen today compared to a primitive earlier form. What form did that primitive, earlier form take? How did it work so that it would one day evolve into the contemporary form? What is the natural simple, non-IC mechanism for this?

This broad question includes many facets, such as e.g. the origin of the genetic code. Why these codons? "Physico-chemical" reason or "frozen accident?" Another facet of the general question is the origin of the aaRS's, the *translators*. This set of enzymes energetically and physically connects amino acids with cognate anticodonic tRNA's. Modern synthesis involves 20 (22) aaRS's, one for each amino acid identity. Without them, the genetic code would not work.

*The sequence of nucleotides in an informational macromolecule becomes a sequence of amino acids in proteins (enzyme, structural element, regulator, rotary arm,..). Translation of one language into another, polynucleotide to protein, is the mechanism. How did it evolve?*

How does this piece of the mechanism fit into the context of evolution? Where did all those aaRS's come from, all at once? Even all 20 at once defies reason. In our model, there is 1 special protein, followed by 20 new ones, one at a time, not all at once. What that 1 protein does will be explained. Thus, an apparent [\[IC\]](#) really isn't !