THE EVOLUTION OF THE GENETIC CODE

Life is impossible without the genetic code. The code determines when and where chemical reactions will occur in living organisms.

A code needs code carriers. The code carriers of the genetic code are DNA and RNA.

Without these code carriers life will be impossible.

Where did the code carriers come from. ? Are they the connection between non-living and living matter? Did they precede the code?

This is an attempt to give a summary of all the information collected since the middle of the 19th century.

An excellent article about the history of the science behind the early quests to solve the mystery of life, can be find here :

http://www.americanscientist.org/issues/pub/winter-1859

(July-August 2010 edition)(Vol 98 No 4 Page 286)

The reader are advised to read this article , it will give an excellent summary of the human desire to solve the mystery of **LIFE**. No biologic background is necessaryThe article to follow and understand it, .

The article doesn't discussed the building block of life , it only mentions that life's chemistry was preceded by non living chemistry

The elements oxygen, carbon , hydrogen, nitrogen, sulphur and phosphorus were necessary It is accepted that of these elements were present in sufficient quantities on the primordial earth to support the the beginning of life. These elements had to combine and form molecules of which the important ones were ribose , deoxy-ribose, amin-acids. phosphates , and sulphates (phosphates and sulphates are molecules containing phosphorus and sulphur) All these molecules had to form at a sustainable rate to allow for life to originated. It doesn't matter if life was a random event or an event caused by an other entity, the mentioned building blocks were necessary what ever the spark. Life cannot exists without them.

The big question was " how did these molecules originate in the primordial earth?" In the current biologic environment the majority of them are the products living cells. An example being the production of carbohydrates in chlorophyll containing cells..

A solution appeared, during 1953 ,

Stanley Miller,

Miller designed the famous Miller_-Urey experiments that produce some of these building blocks, especially amino acids. Millar stared his experiments during 1952 but the first results were published on the 15th of May 1953. Miller's experiments indicated that t was probable for the building blocks of life to originate in the primordial atmosphere of earth. Follow up experiments using the same

methods were also able to produce simple carbohydrates (sugars) and purines and pyrimidines . (other important building blocks)

http://science.sciencemag.org/content/117/3046/528/
Science Vol 117 Issue 3046 page 528 Aprir 25, 1953
[unfortunately no "open"article available"

Watson and Crick' entered the scene a little while earlier. The famous article about DNA's structure was published on the 25th of Aplril in Nature. It opened the way to discover that the sequence of purine and pyrimidine bases constitute a code .

www.**nature**.com/**nature**/dna50/archive.html
Nature April 25, 1953 No 4356 page 737

Amazing, the possible origin of some the building blocks of life and the discovery of structure of DNA, made known to the scientific world within a time period of less than two weeks.

The understanding of the double helix and the manner in which the purines and pyrimidines (organic bases) kept the two strings together, quickly led to the realisation that the sequences of the bases are very important . The sequences contains all the information necessary to build specific cells and organisms. The morphology (form and appearance) and physiology (function) of every living thing are determined by the information contained in this sequence. This sequence became known as the genetic code. The DNA molecule is not a code, the sequence of the organic bases constitute a code. The DNA molecule is just a code carrier.

The the following ten years (Francis Crick still playing a major role) the code was deciphered and the role of the different RNAs (m, t and r) molecules understand,. The DNA → mRNA→Protein pathway was discovered and the role played by . tRNA and ribosomes .(and later by rRNA and ribozymes)

The code was discovered , but the code carriers were still problematic.

The genetic code was discovered, we had a better understanding about the origin of the building blocks of the code carriers ,but how did the code developed? The code itself needed a stable and large enough code carrier to be able to store an ever increasing amount of data. The code carriers also had to be stable for extended periods . Decay of parts of the carrier will lead to memory loss and even code disappearance . A decaying code carrier will be counter productive and not be able to allow the development of a code capable to sustain life.

Did the code developed spontaneously over time in a RNA WORLD?

Was a " RNA World" where RNA replication and RNA controlled chemical reactions, at the root of the origin of life " and the origin of the code. Can a RNA molecule be large and stable enough to provide enough stable storage memory for the development of the

genetic code as [postulated by Higgs and Lehman

Nature Reviews Genetics | AOP, published online 11 November 2014; doi:10.1038/nrg3841

http://physwww.mcmaster.ca/~higgsp/756/HiggsLehman2014.pdf

Let us go back to Stanley Miller for a better historical insight. Miller was co-author of the following papers displaying his superb understanding of the chemistry and problems involved in research regarding the origin of life and the genetic code.

www.pnas.org/content/92/18/8158.full.pdf
Rates of decomposition of ribose and other sugars – PNAS
May 30, 1995 - (RNA world/pre-RNA world/ribose stability). ROSA LARRALDE*, MICHAEL P. ROBERTSONt, AND STANLEY L. MILLER

http://www.cell.com/cell/abstract/S0092-8674(00)81263-5?_returnURL=http%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867400812635%3Fshowall%3Dtrue

(click full text)

It is advisable to read these papers intensively to understand the influences of stability, racemic mixtures, enantiomeres, enantionetric cross inhibition, chirality etc. on the development of the code carriers and the code itself..

Lindahl is another researcher who did very important research on the stability of the code carriers , supporting the intrinsic instability of the code carriers observed by Miller. (Lindahl -one of the Noble laureates -Chemistry 2015)

http://n.ethz.ch/~nbennett/download/Reading_NEW/DNA%20Damage%20and%20Repair/Lindahl.pdf

A quarter of century later, we are still struggling with the problems Miller and Lindahl recognized.

Miller postulated that the code originated on a code carrier that preceded the RNA and DNA worlds.

After reading these articles it will become clear that the origin and evolution of the code carriers are complicated . Understanding these articles also explain why research in trying to solve the mystery of the genetic code and its code carriers origin is an ongoing process .

Many researchers were and are still trying to find ways around Miller and Lindahl's concerns , but their efforts are hampered by the effects of enantiomrtic cross inhibition , chirality and homochirality .
recognized.

Back to the RNA world and current research efforts to circumvent Miller's concerns.

Their are many researchers struggling to solve these concerns. I will refer to two recent papers to illustrate how we are still struggling to get a final answer the question how did the code carriers originate?

Two recent research papers discussed research around possible solutions to the mystery of biological homochirality (D-sugars , d RNA and d-DNA and L am acids)

One is by Donna G Blackmond, one of the prominent resercehrs who trying to solve this mystery, In a recent article she discussed and proposed mechanisms of how homochirality developd in biology. Unfortunately she also use the " lucky break" terminology under the heading " *Homochirality: Chance Aided by Luck*"

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2857173

Gerald Joyce is another of the prominent researchers who is trying to solve this mystery. In recent paper (Joyce a co-author) the possibility that a d-RNA polymerase as a solution,, is discussed.. . Joyce's laboratory managed to developed and synthesize a possible RNA -polymerase candidate.,

http://www.nature.com/nature/journal/v515/n7527/full/nature13900.html

https://www.quantamagazine.org/20141126-why-rna-is-right-handed/

Let us assume that researchers as Blackmond and Joyce will be able to solve the chirality and code carrier stability mysteries , the mystery of the origin of the code still remains.

Let us now move on to the genetic code and its origin.

Kroopnin and Novozhilov discussed the problems surrounding the development of the genetic code , extensively in an excellent review article.. They concluded "*Our consolation is that we cannot think of a more fundamental problem in biology*."

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3293468/

G Caetano-Anollés et al proposed a mechanism for the development of the code that involved the simultaneous evolvement of protein (polypeptide) molecules and tRNA . Their model postulated the incorporation of only l-amino acids in the peptide chain , causing homochirality of the polypeptides. Their research also indicated the possibility that the genetic code is tightly coupled to the history of amminoacyl-tRNA synthetase enzymes and their interactions with tRNA.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0072225

It is however unclear if the code carriers they proposed will be stable enough allow the long term stability to allow a stable and large enough code carrier to evolve.

What are the the minimum known requirements necessary to sustain cellular life as we known it?

The 2015 Nobel Prize for Chemistry refers to a very important requirement. The requirement is that there must be a method or methods in place that protect the code carrier against decay, safeguarding the integrity of the genetic code.

Read the press release of the Swedish Royal Academy of the Sciences that announce the 2015 Chemistry Prize laureates here :

https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2015/press.html

The most important code carrier (DNA) is prone errors and crashes but for the presence of effective stabilizers.

The J Craig Venter Institutes team made a very surprising and far reaching discovery. In highly favourable conditions in a laboratory a cell needs at least 474 “genes” to flourish. The big surprise was however that the function of a third of these genes are currently unknown. If it wasn't a well controlled study, these unknown genes would probably be regarded as junk.

http://science.sciencemag.org/content/351/6280/aad6253

Important aspects that many researchers bypassed or not discuss in their efforts to “solve” the chirality and code origin problems.

On the primordial earth the only source of life's building blocks were racemic mixtures of the building blocks. Abiotic production of building blocks.production manufactured

Any process that select a particular enantiomer to be part of a larger molecule will decrease the concentration of this specific in the primordial soup and actually select for the opposite enantiomer.. The concentration of the opposite enantiomer will increase in the mixture. The more effective the formation of lager molecule , the quicker the concentration of the opposite enantiomer will increase.

REMEMBER EVOLUTION IS A SLOW PROCESS AND IT WILL TAKE AGES OF THE NECESSARY ENZYMES TO EVOLVE THAT ARE ABLE TO PRODUCE BIOTIC BUILDING BLOCKS.

If l-amino acids are effectively incorporated in polypeptides , the concentration of the d-amino acids will increase and block the effectiveness of l-polypeptides production. Effective enzymes takes time to developed and needs a vast quantity of l-amino acids before they can effectively support and sustain an RNA world. Enzymes are necessary to catalyse production of life the necessary supporting nutrients.

The **abiotic** sources of the building blocks will continue to supply racemic mixures of the building blocks at a more variable rate. Effective d-sugar and l-amino-acid selectors will

quickly deplete the primordial soup of d-sugars and l-amino acids. To support an RNA world on the early earth (or early sustainable life) vast quantities of ribose (d-ribose) and amino acids (l- amino acids) would have to be present.

This concern apply to to all the postulations proposed by Blackmond, Joyce and Caetano-Anollés. Another concern is that all their possible possible precursors was developed in an ideal controlled laboratory environment guided by human intelligence.

It seems there is only two possibilities to obtain complete homochirality in the promordial soup:

1 A system that recognised and destroyed l-sugars and d-amino acids.

Or

2 A system that very quickly evolved into minimal cell systems that were able to produce their own d-ribose and l- amino acids , thus bypassing the necessity of abiotic building blocks. . This will lead to the eventual disappearance of their opposite enantiomers

What is the most probable scenario taking in account all the mentioned problems

1 A slow molecular evolution

2 A very fast molecular evolution

3. A pre-existing code containing all the information necessary to produce minimal cells.

All are possible, but which is the most probable ?

The probability of a genetic code that precede life ?

Is Pasteur's dictum still holding? Shouln't it change to only intelligence beget life, only intelligence begets intelligence.

The following quote is correct except that it doen't allow for the sustainability of the building blocks.

Quote from

https://www.quantamagazine.org/20141126-why-rna-is-right-handed/

“

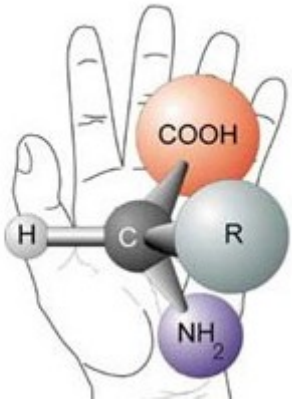
A reaction that selectively plucked right-handed building blocks from the primordial soup would quickly start to create only right-handed molecules, just as a machine that selects only red or only blue Lego blocks from a mixed box would create single-colored towers. “

My comment : “…. But if the red block selecting machine doesn't develop a way to produce its own red blocks, it will quickly run out of building material,”

The next drawing give an idea what will happen if a highly effective l- polypeptide catalysing ribozyme is let loose in the primordial soup.

Basic structure of amino acids:

l – amino acid's basic stucture

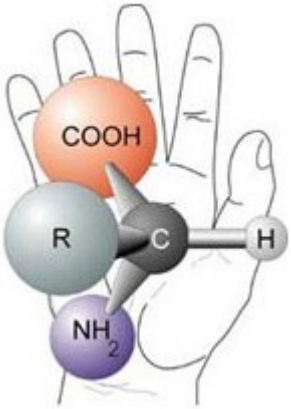


Turn vertical polarized light counter-clockwise or left
Also called levorotation rotation

Abbreviated l-

l-amino acids

d-amino acid's basic structure



Turn vertical polarized light clockwise
Also called dextrorotation or right

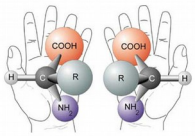
Abbreviated d-

d-aminoacids

Refer to the following page to observe the effect of l-aminoacid selection in the absence of biotic produced l- amino acids.

L-amino -acid depletion is the result

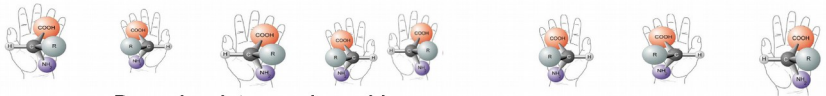
And, rather than emerging from an electrified primordial soup, amino acids emerge from biosynthetic enzymatic reactions (otherwise no sustainable source of l-amino acids)



R = SIDE CHAIN

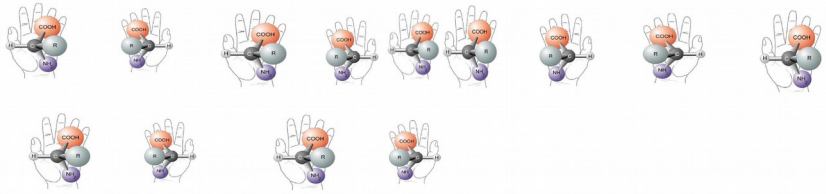
Basic Amino Acid Structure

(http://www.astrochem.org/sci/Amino_Acids.php)



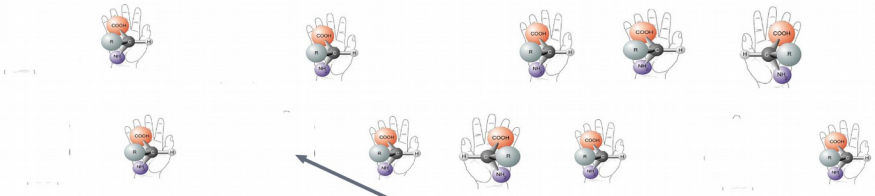
Racemic mixture amino acids.

Assumption primordial earth's atmosphere produce 4 amino acids per time span " t "

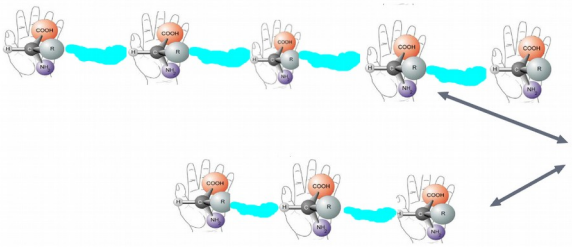


End t1

Assumption during t1 ribosome
enzymes able to form polypeptides
tRNA combining with amino acids
Ability to combine 41-amino acids during
t2. becoming more effective with every passing t



Abionic source of l-amino acids deplete and polipeltide synthesis interupted



Ribozymes catalyzing two polypeptide chains

END t2

how did the code come to be ?????

Nucleotide excision repair

Still prob;em multihandedness.

NATURE CHEMISTRY **| ARTICLE**

Common origins of RNA, protein and lipid precursors in a cyanosulfidic protometabolism

•**Bhavesh H. Patel, ET AL** *Nature Chemistry* **7**, 301–307 (2015)
doi:10.1038/nchem.2202

(The reader is advised to “google” stanley- Urey experiment to obtain more background information)