Dialogue

The following section is a Platonic dialogue between Uranya and Reynard. The dialogue format allows a more manifestly *skeptical* account of an issue to be given. The issue here is origins, origin of life, origin of molecular genetics, origin of chirality,... The account is purely speculative. Experiments of many kinds are suggested. However, the purpose here is to build a mechanism using the *molecular algebra* implicit in all that has been presented earlier in *Mysterium Tremendum*.

A Dialog between Uranya and Reynard

Uranya: You think that pure chirality is required for DNA's and RNA's to be effective in evolution?

Reynard: Replication and transcription are feasible only when *a pure* chirality is used. The racemic processes involving RNA's are prone to rapid breakdowns. A single chiral variant in a ploymer chain could jam the mechanism.

U: Thus, before polynucleotides were involved, the (UV-iron-thioester-pyrophosphate)-proteinoid-microsphere system functioned, and even replicated itself, as a racemic system. To get polynucleotides involved the replication/transcription mechanism uses one chiral type exclusively.
Pure chirality !
Chirality and polynucleotides co-evolved ?

R: That is correct.

U: That will be tough to prove.
By the way, does racemic mean "of variable chirality"?

R: Yes, you need homo-chirality for the transcription and replication mechanisms to work quickly enough to keep pace with the cellular membrane growth and division.

Before we go further into the mechanism, there is a new axiom to be recognized and made explicit. It is

the axiom of felicity.

When choices among many different sequences of monomers exist, it is taken for granted that some of the choices will prove *felicitous*. An advantage will accrue. Without this axiom, there is no point to selection, and no evolution.

U: Define *felicitous* !

R: Right from the Merriam-Webster's unabridged: "very well suited or expressed" Or simply: "well-suited for the occasion, as an action, manner, or expression; apt; appropriate" (Dictionary.com)

U: Isn't this just *fitness*, slightly cloaked?

R: When *fitness* is associated with a *struggle for survival* type of thinking then it is different from *felicity*. But any change that increases *felicity* also makes things more *fit, apt, appropriate*… The change increases fitness, and without a *struggle*.

U: So a racemic, energy driven process can give rise to propagating proteinoid microspheres. They grow membrane and they divide. For molecular genetics to get started, polynucleotides are added as an innately chiral process. But to get this nucleic acid system to work, certain basic catalysts are needed such as proto-replicases and proto-ligases. By the *axiom of felicity* some of the available sequences do confer the needed crude catalytic action. Thus strings of order 20 homo-chiral nucleotides can and are made (trimers of hexa/hepta-mers). Is this long enough for building a minimal system ?

R: It has to be ! Thermodynamics and kinetic constraints restrict matters greatly when it comes to making polymers. The minimal system has to be implicit in the geophysical chemical milieu of the primitive Earth. This means short polymers. Proto-ligases are required to get long polymers in the early stages of this system.

U: What couples amino acids with polynucleotides, when there are not yet tRNA's, rRNA's, mRNA's and aaRS's ? What is the minimal mechanism ? How will this mechanism be able to evolve into the complex contemporary system with its tRNA's, rRNA's, mRNA's and aaRS's ?

R: Pure logic will lead many to conclude that a direct interaction chemically is required. The natural choice is, for example, transfer of an amino acid from its carboxyl phosphate activated state to a ribose-carboxyl linked amino acid

activated state. I need to show you the model in detail, like it appears in Fox's *Energy and the Evolution of Life*.

I learned about this model from Ron Fox who heard it from Art Weber around 1970. Art had discussed the idea with Jim Lacey. Ron lectured about it at the Rockefeller University in 1973 and at the University of Colorado in 1974. He made CPK models and tried to answer basic chirality questions:

> Did D-ribose in the RNA fit better with L-amino acids then with D ?
> Is L-amino acid, D-ribose merely relative chirality and not absolute i.e. either LD or DL ?
> Is the three base spacing for the code stereochemically rigorous in the model ?
> Is the 5'-3' polarity colinear with the N-C polarity of the polypeptide ?
> How many contemporary properties are already implicit in the model?

U: *Maybe* we should try to use modern graphics software to visualize these structures and processes.

R: Definitely ! But I need adept *liveware** for that. In the meantime, I can describe the minimal mechanism and discuss its potential evolution into the contemporary mechanism.

* *The Devouring Fungus: Tales from the Computer Age*: by Karla Jennings (Norton Press, New York 1990) ISBN 0-393-30732-8, p.222.

U: Before you describe the mechanism, can we briefly review the context ?

R: Good idea. Why don't you tell me ?

U: The geophysical world is rich in UV energy. Natural processes transduce this energy into:

1) excited electron energy by oxidizing Fe from ferrous to ferric
2) thioester energy using ferric iron
3) pyrophosphate energy using thioester activated phosphate

The geophysical world is also rich in heat. Natural processes transduce this energy into:

1) thioester energy
2) dehydration condensates, e.g. proto-coenzymes and racemic polypeptides

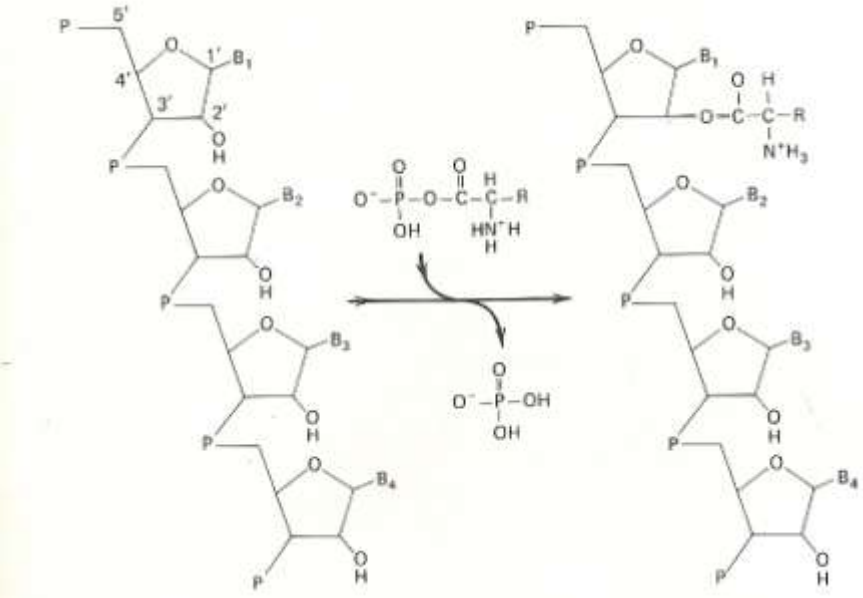
This stage of development is racemic. Thermodynamically and kinetically, only short polymers arise. However, all possible sequences are physically available for selection because the sequences are short enough and the microspheres are large enough. The axiom of felicity implies that some of the available sequences will be beneficial to membrane growth and division, thereby increasing the proportion of those types of proto-cells having these benefits. The polypeptides produced self-assemble into membranes and proto-cells that grow more membrane and divide or bud. While permeable to many small molecules, these microspheres are impermeable to short polymers. In this environment nucleotides could arise and polymerize to a limited degree, say to chains 6 or 7 monomer units long. Without feedback to the membrane microsphere system, no advantage accrues. The details about the structure of the feedback are our focus for now.

R: Not too bad. In this milieu there are also amino acids and activated amino acids in the form of carboxyl phosphates. These amino acyl phosphates are a precursor to modern adenylates and it is the phosphate part that matters. It is this carboxyl-phosphate ester that confers an energy rich state to these molecules, just like the 3' terminal tRNA amino acid attachment in the modern system. Without the polynucleotides, the activated amino aicds might interact and polymerize into short, albeit racemic, polypeptides. Instead, they would interact preferentially with RNA molecules if RNA is available. Existence of this preference is another instance of *felicity*. This putative interaction is the core of the model.

Chirality redux: For j types of monomers, the number of sequences of length i combinatorially is j^i, whereas the number of chiral variants is 2^i. The number of hexamers for j = 4 is 4,096 and the number of chiral variants is only 64. Many replicas of each chiral variety could be present. For j = 7, the numbers are 16,384 and 128. Selection for pure chirality, such as in DNA replication, is natural and feasible for short sequences. This state of affairs is *felicitous*.

The basic model uses two steps, amino acyl activation of RNA molecules and polymerization of polypeptides from such intermediates. A comformation change drives the alternation of the state of the RNA between *charging* with aa's and *polymerizing* aa's. In the figure below, an activated amino acid, a carboxyl phosphate, esterifies an RNA by forming the ribose carboxyl ester at the 2'-OH

group of ribose. As shown this takes place between the first and second bases. Only the first two bases interact with the incoming amino acyl phosphate.



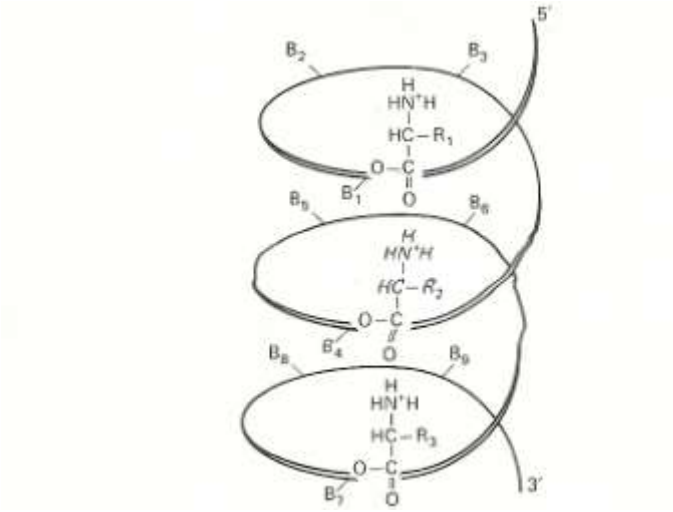
A redistribution of charge, including ions, results in a conformational change to the structure of the RNA strand. The RNA conformation changes from random coil before charging to tight *right*-handed helix (*L*-aa's and *D*-ribose) just after charging. The carboxyl-ribose esters are as energy rich and of the same form as the terminal 3' amino acyl tRNA's used by living cells today. Let that sink in ! In the helix conformation, the amino acid carboxyl groups and amino groups are aligned for easy peptide formation, but only if the amino acids are of pure chirality. The RNA is functioning as a ribozyme (Ron Fox recognized this in two talks mentioned earlier). Moreover, CPK modeling suggests that the 5'-3' polarity of the polynucleotide is colinear with the N-C polarity of the polypeptide. In addition, the relative chiraity of L-aa and D-ribose is also potentially explained. The amino acid alignment shown in the figure below works best if each amino acid is of the same chirality. Thus pure chirality in the replicability of RNA's gives rises to pure chirality in the polypeptides that are translated by this mechanism.

U: Do you mean that if the RNA has exclusively D-ribose, then L-aa's produce a faster replicator cell than do D-aa's ? How do you prove that with mere CPK models ?

R: CPK models prove little. It is probable that the recognition process is kinetic in nature rather than static. Chemistry must be done rather than modeling. In the

mean time, we can conceptualize and learn something, such as the possible origin of pure chirality in both polynucleotides and in polypeptides.

CPK models strongly support the inference that the three base spacing of the code is explained by this model as a stereochemical necessity. Nevertheless, the code is the *first-two-base* code. The third base plays no role in the recognition step. Note also that the three base code requires an RNA strand of order 20 monomer unit long in order to code for a mere polypeptide hexamer. This means that ligase activity for polynucleotides was an early acquisition



Especially interesting are sequences containing lots of CGN's, and their products, poly-arginines. Arginine is part of nitrogen metabolism, featured prominently in the urea cycle. Polyarginine is an excellent candidate for a molecule that will interact strongly with polynucleotides. This is the natural attraction between plus charge and minus charge. CGN codes for arginine. Strings of 5'N(CGN)n, where each instance of N means any base, are self-complementary so that the strings complement is also its replica, and n donotes the number of iterations. A kinetic advantage accrues from this *palindromic* sequence (instead of having to make a complement of the complement to make a replica, the complement is the replica). Polyarginine could lead to proto-replicases and proto-ligases. Thus, an increase in reproductive rate as well as propagation of a particular polynucleotide sequence are coupled. The alternative, 5'N(GCN)n, also a palindrome, and codes for poly-alanine.

The RNA in this mechanism is both the *gene* and the *messenger*, mRNA. Its replication preserves the sequence, and its translation provides feedback. If the feedback is *felicitous* then the gene will become prominent in the population of

spheres. This is the rudimentary genetics potentially possessed by the microspheres. This mechanism will be called the *primitive RNA translator*.

U: Does this system have sufficient evolutionary capacity ? Can it evolve, in a natural manner, the complex apparatus of ribosomes, tRNA's, rRNA's and aaRS's ?

R: That question is perhaps the *mysterium tremendum*.