

## Monomer to Polymer Transition

While Fritz Lipmann once stated

“*coupling of redox energy to phosphate energy may have been first step on the road to life*”,

I argued above that

“*the transition from no life to life is essentially the transition from monomeric matter to polymeric matter.*”

Without energy inputs, the equilibrium thermodynamics for the mixture of molecular species on the primitive Earth leads to many biologically relevant small molecules but does not yield polymers. The primitive geophysical world does not give rise to macromolecules of the type seen now in genetically directed protein biosynthesis enzyme (and ribozyme) complexes until energy is allowed to flow through this matter. UV, redox energy, reducing potential, thioesters and pyrophosphate are natural products of geophysically natural processes. This is the coupling Lipmann speaks about. Banded iron formations are a lasting signature of this naturalness. As argued above, this creates a world in which dehydrations can be promoted, in spite of the preponderance of water. Heat is also available to support production of dehydration bonds. So multimers, oligomers, small polypeptides, proto-coenzymes, and even mononucleotides can be expected in this developing primitive environment. *Not* polynucleotides and *not* even modestly big proteins! There are several aspects to this puzzle: 1) ribose and nucleic acid bases need to be accounted for, 2) the ribophosphate backbone of polynucleotides needs to be considered, and 3) limitations on numbers of polymers of any length.

Of course, having to make all the dehydration linkages inhibits polymer synthesis unless energy of activation is present. Pyrophosphate is a candidate for the precursor to ATP, the ubiquitous carrier today (again see Lipmann). Thioesters may well have preceded pyrophosphate in this role. In **Harnessing energy** above, the argument has been made that prior to protein synthesis, energy processing became quite advanced and was conducive to polymer synthesis. Large polymers raise the issue of sequences and the number of different sequences for a fixed length.

As an example, consider E.Coli, a bacterium about 2 cubic microns in size. One source lists 4377 genes, of which 4290 are for proteins and 87 are for RNA's. A typical protein, say an enzyme, may have 300 residues, just to use a round number. There are 20 regular amino acid choices for each position in the sequence. Thus  $20^{300}$  different sequences are *conceivable*. Note the *italics*. This number of sequences is not *realizable* because the number is too enormous. One says some quantity is “*astronomically large*” when one wishes to express the idea that a quantity

is really enormous. But both the number of nucleons in the Universe and the distances between galaxies given in units of meters, do not exceed a number like  $10^{80}$ . However,  $20^{300}$  is  $2^{300} \times 10^{300} = 10^{390}$ . This is so much bigger than “*astronomical*” we must say it is “*combinatorially large*”. If one tries to realize this number of polymers with *real* molecules the total nucleon mass ( $\sim 10^{371}$ ) would be more than the total nucleon mass of the Universe ( $\sim 10^{56}$  gm) by many many orders of magnitude, at least that part given by protons and neutrons. For comparison, the Earth’s mass is  $\sim 6 \times 10^{27}$  gm and the Sun’s mass is order 330,000 Earth masses. If the Earth and the Sun are “typical” then this is the equivalent of  $10^{11}$  Suns per galaxy and maybe  $10^{11}$  galaxies, or  $2 \times 10^{55}$  gm. This is the whole Universe and it is nothing compared to the combinatorial number  $10^{371}$  in  $10^{371}$  gm.

*The E. Coli needs just 4290 particular amino acid sequences, out of the  $10^{390}$  possible.*

Clearly, the evolution of polymers did not start by selecting from *all* the possibilities, at least not with their present lengths and with their present number of different amino acid types. Only a very small, vanishingly small, proportion of sequences of this size can be generated as real molecules. On the other hand, *those generated have to do all the needed jobs*. Such considerations become easier if we suppose that the earliest proteins (and earliest RNA’s) were small, of short sequence, and a more primitive set of amino acids was smaller in number of types. If sequences of length 8 from 12 types of monomer, say, are considered then the total number of sequences is  $12^8 = 4.3 \times 10^8$ , and this would have a mass of about  $1.4 \times 10^{-21}$  gm per polymer, or  $\sim 6 \times 10^{-13}$  gm for one real copy of each sequence. An E. Coli mass is about the same. Thus copies of all possibilities for enough *shorter* (length 6 or 7) polymers, of 12 types of monomer, could easily fit inside an E. Coli volume. Another way to look at this issue is to consider RNA sequences from *four types* of monomer, or polypeptides from *four types* of amino acid: *positive, negative, neutral polar* and *neutral non-polar*, without regard for type more specifically than that (see p.10 of [[lipids, membranes and chemiosmosis](#)]). Now a polymer of length 14 comes in  $4^{14} = 2.7 \times 10^8$  varieties. Each has a greater mass (length 14) than before (length 8), about  $2.5 \times 10^{-21}$  gm for the proteins and 3 times that for the polynucleotides (average amino acid molecular weight, MW, is 136, and average mononucleotidylphosphate MW is 380). Just enough for one copy of each possibility to fill an E. Coli volume.

Two issues are intertwined here. **Compartmentalization** and **selection from all possibilities**. The size of the compartment is crucial. If one objects that a cubic micron is too small and we should use, say, a cubic meter instead, then that increases the volume by  $10^{18}$  but that in no way overcomes the needs, given  $10^{390}$ . If Darwinian selection is to work from the beginning of the origin of life (as is often assumed if only tacitly) at the energy driven prebiotic chemistry stage of development, then sequence variety cannot be too great, and this means sequence lengths must be small enough initially. How small depends on the size of the compartments. For a volume of order 1 cubic micron,  $10^{-12}$  cm<sup>3</sup>, sequences of length 12, say,

from 4 types of monomer permit selection from all possibilities, even in multiple copies. Recall that even polymer lengths of only 12 are greatly inhibited thermodynamically without coupling to activation energy, such that none would be present in thermodynamic equilibrium. Their hydrolysis products, the monomers, would predominate instead.

There is an even more subtle inhibition to the production of polymers of any significant length even when activation energy is readily available. This inhibition is of kinetic origin rather than thermodynamic. Let us suppose that activation energy robustly activates available monomers and that activated monomers react with each other to produce polymer. To simplify matters somewhat, suppose that an activated monomer can combine with any polymer already formed by adding to one end. This is like the situation in contemporary synthesis of proteins, polynucleotides and polysaccharides. For the time being, the possibility of ligase activity wherein polymers are added to polymers, usually polynucleotides, will be ignored. This possibility will be considered later. So for now, activation of monomers is robust and activated monomers can add to one end of a growing polymer (there is always an asymmetry between the ends of polymers [e.g. amino group or carboxyl group in the case of proteins] and growth usually occurs only at one end). Further suppose that hydrolysis is so slow that it can be ignored. This assumption favors polymer growth over monomer population preservation. It also prevents long polymers from hydrolyzing into shorter segments as would naturally occur otherwise. Start with  $M_0$  monomers (only one type will be assumed, again for simplicity), and assume that the polymerization step occurs at a rate independent of the length of the polymer to which an activated monomer is added. A system of equations can be written down that describes this kinetic model (variations of the model have been studied by Will Mather and confirm the robustness of the qualitative features of the simple model treated here). The basic question is: what happens after a long time? Sub-questions that answer this question are: 1) What is the average length of a polymer at steady state? 2) What is the distribution of polymer lengths at steady state? The answers to these questions are surprising.

Let  $N_i$  denote the steady state number of polymers of length  $i$  in steady state.  $N_1$  denotes the number of polymers of length 1, that is the number of monomers at the end of the reactions. This number was initially  $M_0$  but at steady state it is 0, i.e. all monomers get activated and polymerized. The steady state occurs when all reactions have run to completion. This is as expected in the absence of hydrolysis. Now for the surprise. The average length of polymers in steady state, denoted by  $\langle i \rangle$ , is  $e$ , Napier's  $e$ ! Somewhat less than an average length of 3 ( $e = 2.718,281,828 \dots$ ). This is independent of  $M_0$ . It is amazingly short. Let it sink in for a while. An examination of the details will explain this surprising result. The formula for the steady state number of polymers of length  $i \geq 2$  is (for large  $M_0$ )\*

$$N_i = \frac{M_0}{e} \frac{1}{(i-2)! i}$$

The total number of polymers of any length is

$$\sum_{i=2}^{M_0} N_i = \frac{M_0}{e} \sum_{i=2}^{M_0} \frac{1}{(i-2)! i} = \frac{M_0}{e}$$

because

$$\begin{aligned} \sum_{i=2}^{M_0} \frac{1}{(i-2)! i} &= \sum_{i=2}^{M_0} \frac{i-1}{i!} = \sum_{i=2}^{M_0} \frac{1}{(i-1)!} - \sum_{i=2}^{M_0} \frac{1}{i!} \\ &= (e-1) - (e-1-1) = 1 \end{aligned}$$

The  $N_i$ 's account for all of the original monomers:

$$\sum_{i=2}^{M_0} i N_i = \frac{M_0}{e} \sum_{i=2}^{M_0} \frac{1}{(i-2)!} = M_0$$

These results permit computation of the average polymer length from

$$\langle i \rangle = \frac{\sum_{i=2}^{M_0} i N_i}{\sum_{i=2}^{M_0} N_i} = e$$

Even though this very small number is the average length, lengths as large as 7, say, do occur if  $M_0$  is much larger, say 10,000. In this case,  $N_7 = \frac{10,000}{e} \frac{1}{5!7} = 4.3795 \dots > 4$ . It is estimated (James Watson) that an E. Coli cell during rapid division contains  $3 \times 10^7$  amino acids not already in proteins, and another  $3 \times 10^8$  already in proteins. This amounts to about 16% of the total cell weight. Assuming  $M_0 = 3 \times 10^8$  the number of polymers of length 7 is now  $N_7 = \frac{300,000,000}{e} \frac{1}{5!7} = 131,385.5 \dots > 131,385$ . This is the number to be expected if we ignore sequence details. The number of different sequences using the modern number for amino acid types, 20, is  $20^7 = 1.28 \times 10^9$ , much larger than 131,385. If we assume a number of types that is more primitive, such as 12, then the number of different sequences is  $12^7 = 35,831,808$ , also much bigger than 131,385. If however, we assume a number of types such as 4, as explained above earlier, then we get for the number of different sequences  $4^7 = 16,384$ , which is much less than 131,385. Now many copies of each sequence are possible in a volume of an E. Coli.

The lesson learned from this excursion into kinetics is that if the number of monomers inside a compartment initially is  $M_0$  and there are  $j$  types of monomers, then polymers of length  $i$  will occur in the amount  $\frac{M_0}{e} \frac{1}{(i-2)!}$  and with  $j^i$  different sequences. As long as  $j^i < \frac{M_0}{e} \frac{1}{(i-2)!}$  all possible polymer sequences can be tried inside a single compartment. Darwinian selection remains possible. The left side of this inequality grows with  $i$  whereas the right hand side decreases. If initially  $M_0$  is much larger than  $j$  then as  $i$  increases from 1 the two sides eventually become equal for some value of  $i$ . These constraints imply that rather short sequences ( $< 8$ ) played the dominant role initially. One immediate consequence of this reasoning is that if initially three nucleic acid bases determined one amino acid, as they do now, and if this connection is thought necessary from the start, then the short polynucleotides potentially available in an E. Coli volume would code for polypeptide dimers mostly, with perhaps some trimers. This would not be a very auspicious start for protein synthesis that was gene directed. Proto-tRNA models usually require lengths of at least 18 nucleotides, the size of a hairpin RNA, about  $\frac{1}{4}$  the size of a contemporary tRNA. A proto-mRNA that replaced the pre-genetic production of polypeptides of length 6 or so would also need to be at least 18 nucleotides long. Some sort of proto-ligase for polynucleotides would seem to have been required. The only sources are thermal proteinoids or condensates from energy activated monomers (activation by thiols or phosphates). We will return to this issue later.

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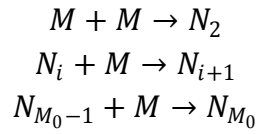
### Simple polymerization model

The basis for these models is that activation of monomers is essential. Only activated monomers can react with activated polymers to form longer polymers. Deactivation of activated monomers and polymers competes with polymerization. Activated monomers are asymmetric and polymerization occurs by adding a monomer to only one end of a growing polymer, just as in contemporary synthesis of proteins and polynucleotides. The basic components of the model are listed in the table:

Reaction	Rate	Description
$\gamma + 2P \rightarrow P_2$	$RP(P - 1)$	Light driven pyrophosphate production
$P_2 \rightarrow 2P$	$hP_2$	Pyrophosphate hydrolysis
$M + P_2 \rightarrow M^* + P$	$BMP_2$	Monomer activation
$M^* + M^* \rightarrow N_2^* + P$	$KM^*(M^* - 1)$	Dimerization
$N_i^* + M^* \rightarrow N_{i+1}^* + P$	$GM^*N_i^*$	Elongation $i$ to $i + 1$
$N_i^* \rightarrow N_i + P$	$hN_i^*$	Activated polymer deactivation
$M^* \rightarrow M + P$	$hM^*$	Activated monomer deactivation
$N_i^* \rightarrow N_j + N_{i-j}^*$	$C(i - 1)N_i^*$	Cleavage of activated polymer
$N_i \rightarrow N_j + N_{i-j}$	$C(i - 1)N_i$	Cleavage of deactivated polymer

This scheme leads to coupled non-linear differential equations. No analytic solutions are available and numerical integration is required.

To get some insight into how large the polymers generated by this scheme can be, a simpler version of the table is studied. We ignore all deactivation steps and all cleavage steps as much slower than the polymerization steps. We also assume that formation of and activation by pyrophosphate is very fast so that all monomers are in the activated form. This should yield the maximal length results for polymers formed. To simplify notation in the following the asterisk denoting activation will be omitted. If we start with  $M_0$  monomers, the reaction scheme becomes:



The first step is dimer formation. The second is generalized elongation, and the third is the last possible polymerization step for finite  $M_0$ . We further assume that the dimerization rate and the elongation rate are the same,  $G$ . The rate equations are:

$$\begin{aligned} \frac{d}{dt}M &= -2GM^2 - GM \sum_{i=2}^{M_0-1} N_i \\ \frac{d}{dt}N_2 &= GM^2 - GMN_2 \end{aligned}$$

$$\frac{d}{dt}N_i = GMN_{i-1} - GMN_i \quad 2 \leq i \leq M_0 - 1$$

$$\frac{d}{dt}N_{M_0} = GMN_{M_0-1}$$

These appear to be coupled nonlinear equations. However, a rescaling of time linearizes them. Let

$$F(t) = G \int_0^t ds M(s)$$

We can change from the time derivative to an  $F$  derivative by the formula

$$\frac{d}{dF} = \frac{d}{GMdt}$$

Now the four  $t$  derivative equations become the four linear  $F$  derivative equations:

$$\frac{d}{dF} M = -2M - \sum_{i=2}^{M_0-1} N_i$$

$$\frac{d}{dF} N_2 = M - N_2$$

$$\frac{d}{dF} N_i = N_{i-1} - N_i \quad 2 \leq i \leq M_0 - 1$$

$$\frac{d}{dF} N_{M_0} = N_{M_0-1}$$

The monomers can be accounted for by looking at the quantity

$$Y = M + \sum_{i=2}^{M_0} iN_i$$

This should be a constant for all times and if it's  $F$  derivative is computed using the  $F$ -rate equations above, the result is zero. Thus the monomers are distributed among the polymers except possibly for those that remain unpolymerized.

Now consider the total number of polymers of any length:

$$X = \sum_{i=2}^{M_0} N_i$$

Again using the  $F$  derivative equations it is easy to show that

$$\frac{d}{dF} X = \frac{d}{dF} N_2 + \sum_{i=3}^{M_0-1} \frac{d}{dF} N_i + \frac{d}{dF} N_{M_0} = M - N_2 + \sum_{i=3}^{M_0-1} (N_{i-1} - N_i) + N_{M_0-1} = M$$

Therefore, the dynamics reduces to two coupled equations

$$\frac{d}{dF} M = -2M - (X - N_{M_0})$$

$$\frac{d}{dF}X = M$$

Now let  $M_0 \gg 1$  and ignore the term  $N_{M_0} \sim 0$ . This last assumption is justified *a fortiori* (see below). It is straight-forward to integrate these equations analytically to obtain

$$M = e^{-F}M_0(1 - F)$$

From its definition,  $F$  is monotone increasing so that when it reaches 1 the dynamics stops and  $M$  vanishes, i.e. all monomers are incorporated into polymers. Look at the quantity  $Z = M + X$ . In the  $M_0 \gg 1$  approximation

$$\frac{d}{dF}Z = -Z$$

and

$$Z = e^{-F}Z_0 = e^{-F}M_0$$

The average length of a polymer at long times ( $t \rightarrow \infty$  and  $F \rightarrow 1$ ),  $\langle i \rangle$ , is given by

$$\langle i \rangle \equiv \frac{Y}{Z} = \frac{M_0}{Z(t = \infty)} = \frac{M_0}{e^{-1}M_0} = e$$

This is a great surprise !! The average length of a polymer is less than 3. By solving the  $N_i$  equations in succession it is straight-forward to show that at long times ( $t \rightarrow \infty$  and  $F \rightarrow 1$ )

$$N_i = \frac{M_0}{e} \frac{i-1}{i!}$$

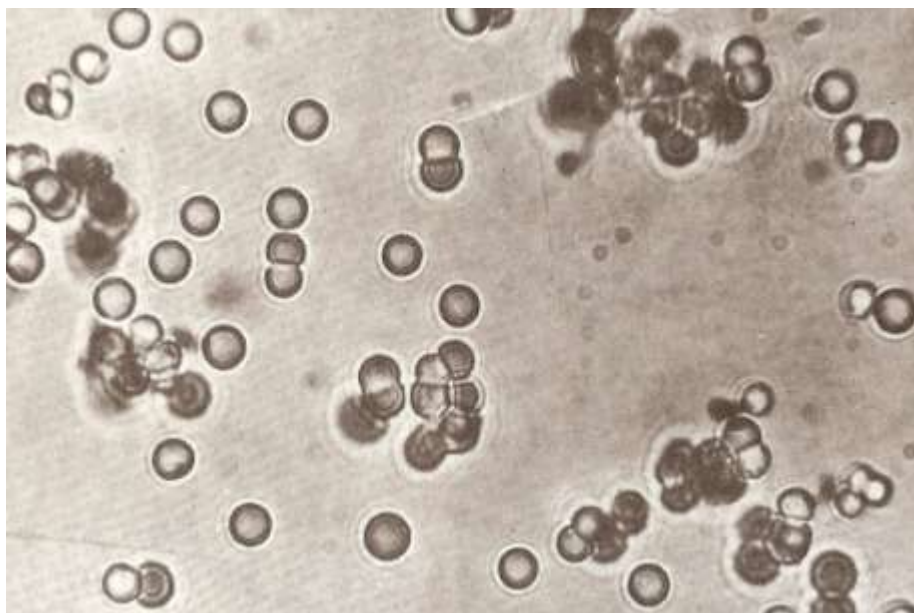
for all  $i \geq 2$ . With this result all previous results for  $M, Y, X, Z$  and  $\langle i \rangle$  can be explicitly verified. Clearly there are polymers of great length, just not enough of them to make  $\langle i \rangle$  bigger than  $e$ .

### Compartmentalization

A digression is called for at this juncture. My views regarding origins have been influenced by my father, [[Sidney W. Fox](#)], and his proteinoid microsphere model. *Proteinoid* is a word coined for thermally synthesized polypeptides prepared from mixtures of amino acids. 150

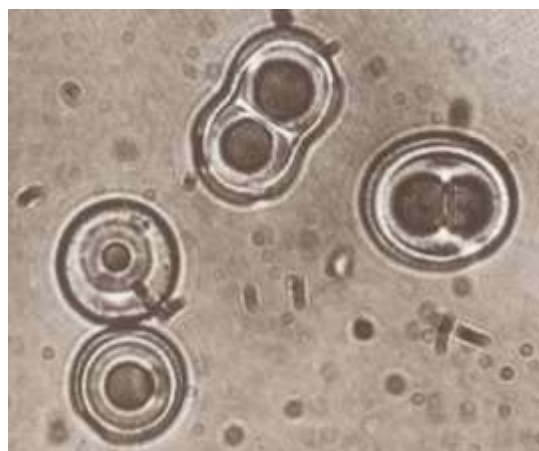
hours of heating at 120 C yields proteinoids, polymers of amino acids (the temperature can be significantly lowered to 60 C if 2-3 parts phosphoric acid or polyphosphoric acid is added). The primary linkage is the amide bond (although there is some imide as well) between the  $\alpha$ -amino and the  $\alpha$ -carboxyl groups. Secondary linkages can also occur between  $\delta$ -carboxyl,  $\gamma$ -carboxyl, and  $\alpha$ -amino (aspartate, glutamate), or  $\epsilon$ -amino (lysine) and  $\gamma$ -carboxyl groups (glutamate). Starting with pure enantiomorphs, either L or D amino acids, much racemization occurs. Thus, typically mixtures of DL amino acids are used to make proteinoids. The reason for the contemporary pure enantiomorphic state (chirality) of living matter (L amino acids and D ribose) is an open question. Many suggestions have been made, some more plausible than others. We will return to this issue later. For now we do not assume a pure state of chirality, L amino acid and D ribose. It may pay to wait for this selection to occur when it does so naturally. Note that almost surely a pure chiral state would function faster than a racemic state. The basis for LD versus DL however seems random. The mirror chirality no doubt exists elsewhere in the Universe. And finally, is LD absolute, or could it be LL (DD) instead?

Proteinoids are remarkable for several reasons. 1) They are easily generated from amino acid mixtures. 2) They show limited heterogeneity in sequence which means some selectivity between nearest neighbors in a chain is manifested during polymerization. Thus, a starting mixture of amino acids that is one part aspartic acid, one part glutamic acid and one part equimolar in all the other amino acids yields a polymer with a composition significantly different than this (S.W. Fox liked to say that these pre-genetic polymers were partially *self-informed*). The product can be fractionated and the fractions can be analyzed by an amino acid analyzer. The results show this limited heterogeneity and are robustly reproducible. 3) When the dry polymer product is mixed with water, the polymer self-assembles into 1-5 micron diameter microspheres.



For a given reaction composition and protocol for proteinoid generation by heating, the diameter of the microspheres produced, upon mixing with water, is very uniform within the preparation's population. The range 1-5 microns stated above is for a variety of different compositions and protocols. Each choice generates a very sharp distribution of radii. Lipid vesicles, on the contrary, produce a great variety of shapes and diameters (for the spheroids) that are easily perturbed. Monoglyceride lipids form micelles whereas diglyceride lipids (e.g. lecithin) can form lipid bilayer vesicles. The proteinoid microspheres are similar to the bilayer in that they have two membranes like the bilayers. The presence of hydrophobic residues in proteinoids may be partially responsible for these similarities with lipids. The microsphere membranes are not tightly attached to each other as are the two surfaces in lipid bilayers.

The membranes of proteinoid microspheres are not as impermeable as are lipid bilayer vesicles. Indeed, proteinoid membranes are relatively "porous," although they do show shrinking or swelling upon transfer to relatively hypertonic or hypotonic solutions (sometimes the inner membrane swells or shrinks disproportionately to the swelling and shrinking of the outer membrane). Experiments have shown that preparation of microspheres in sugar solutions results in microspheres that retain the polysaccharides but not the monosaccharides. This feature, retention of polymers but not monomers) will be drawn upon later as perhaps crucial to the emergence of life. The uniformity in size of the microspheres suggests that opposing physical forces are at work. Some sort of optimization is achieved that is manifested as a sharp distribution in size. Surface tension, curvature, osmotic pressure and electrostatic (capacitive) properties of the membrane may be involved. To date this is an unresolved issue. As some of the dissolved proteinoid self-assembles into microspheres, other proteinoid molecules remain in solution. As more of these polymers are incorporated into the membranes and the membranes grow, the opposing forces that control size drive microsphere division instead. This way the microspheres do not grow larger than the physical forces permit. The inner membrane divides first, then the outer membrane and then the daughter spheres separate as all of these steps are jostled by Brownian motion.



One could argue that contemporary cell division has its ultimate origin in a natural physical process, the fission of proteinoid microspheres.

The early Earth is thought to have more volcanic activity than today. Many geophysical niches that would be able to promote heating and then washing with water can be imagined. Tidal basins around volcanoes, thermal pools, shallow oceanic thermal vents, tidal beaches absorbing sunlight, are just a few. A diurnal cycle may have been involved rather than, say, uniform heating for a week (making proteinoids for 150 hours could be 15 hours a day for 10 days). A periodic *high* tide might wash the polymerized material after many days and produce a tidal pool of microspheres. One gram of proteinoid produces  $10^8$ - $10^9$  microspheres. Each sphere contains on order  $10^{10}$  proteinoid molecules.

Many questions remain to be answered regarding the microspheres. There are enough hydrophobic residues in proteinoids for them to self-assemble into microspheres with a favorable (a decrease) change in Gibbs free energy. The bilayer structure is stable and spherical and uniform in size. Which physical factors contribute? What determines the radius magnitude and sharpness of the radius distribution? Why would they divide rather than just getting bigger? How do area and radius contribute?

Alternative models for lipid vesicles early in evolution based on proto-lipids are also attractive. Very likely, the lipids identified by David Deamer from carbonaceous meteoritic amphiphiles, together with the proteinoid microspheres make an even more vibrant setting for proto-life. However, I will argue that initially the lipids were absent and the proteinoid's hydrophobic characteristics dictate the outcome of the selection in a lipid-like way. Once "cells" were functioning at the biochemical level sufficiently well, the utility of incorporating lipids would be recruited. The modern amphiphilic lipids are well mimicked by the proteinoids with their charged residues and hydrophobic residues. There is a favorable Gibbs free energy change when the proteinoid molecules self-assemble into vesicle membranes, no doubt sequestering the hydrophobic residues away from water while leaving the charged residues to interact directly with the water.

The permeability of the proteinoid microspheres to small molecules and monomers is an advantage, not a liability. The primitive Earth's state is rich in energized chemical transformations yielding ample amounts of thioesters, and where geophysically possible, pyrophosphate. One can envisage shallow acidic sulfurous seas containing iron and in some places also apatite. The energy driven mix of chemicals in these shallow seas is the "primordial soup." This soup bathes the microspheres. As the microspheres grow by self-assembly of more proteinoid molecules into their membranes, the membranes grow in radius and eventually divide. The soup inside is divided too, equally into each of the daughter cells. This soup experiences a

very robust Brownian motion at the molecular level and the mixing of contents inside vesicles is thorough. Moreover the soup is free to cross the microsphere membrane before and after division. Now suppose that monomers are activated and short polymers are grown. As argued earlier, hexamers, heptamers and octamers predominate; the shorter sequences (dimers, trimers, tetramers and pentamers) are not retained by the “porous” membrane whereas hexamers and longer are !! The length that determines the difference in retention is arbitrarily set at 5-6 in this narrative but something this short is probably correct. It is possible to imagine feedback effects from the hexamers (or longer polymers) on what happens chemically inside the cells. Two feedbacks are *catalytic* action and *structural* function. Hexapeptides or a bit longer fit with E. Trifonov’s finding of such sized modular components in modern proteins using massive sequence data banks. (A wonderful example is that of a proteinoid made to mimic melanocyte-stimulating hormone, MSH. When the real hormone is fragmented, a hexapeptide fragment has an activity of  $10^4$ - $10^5$  units per gram compared to the intact hormone’s rate,  $10^9$ - $10^{10}$  units per gram. A proteinoid made from the amino acids in this active fragment (thus containing glutamic acid, glycine, histidine, arginine, phenylalanine and tryptophan), contains the same active sequence [activity  $10^3$ - $10^5$  units per gram] in a disproportionately large portion of the total product (*limited heterogeneity* or *non-randomness*). This indicates some self-selection for the active sequence (*self-informed*) and the importance of even mere hexameric lengths.) What if these activated monomer condensates self-assembled into the membrane as well. How short can a polypeptide be and still have microsphere membrane generating ability?