Homochirality - The problem of left handed amino acids

By

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The origin of homochirality[1] is usually believed to be closely connected with the origin of life (see Bada 1995 for an overview). It may even have been a *prerequisite* for life in that the structural stability provided by chiral polymers may have been essential for the assembly of the first replicating molecule. If this is so, it would probably mean that the origin of homochirality had to be a physical one. Possible candidates for a physical origin of homochirality include the presence of polarized light from a nearby neutron star (Bailey, 2001) magnetic fields, or mechanisms involving the electroweak force (e.g., Hegstrom, 1984). Another perhaps more likely possibility is that homochirality developed rather as a *consequence* of life. This would mean that some primitive form of life should have been possible without chirality having played any role in this.

In connection with the origin of life one used to discuss the hypothesis of a relatively simple self-replicating molecule (e.g. Frank 1953). This picture ignores the possible importance of compartmentalisation which led

[1]Chrirality - means handedness in Greek - and is used to describe an object which is non-superimposable on its mirror image. Homochirality is used to refer to the group of molecules that possess the chirality used by living organisms.

to the concept of a very early lipid world that would have preceded the often discussed RNA world. Some insight into these type of ideas can be gained by looking at recent attempts to build life from scratch invoking a series of steps and chemical processes that are thermodynamically possible (Rasmussen et al. 2003). Interestingly enough, their approach involves peptide nucleic acids (PNA) solely because of its charge carrying properties. Its potential as gene carrier was not utilized at this stage, although it may undoubtly become a candidate for carrying genetic information at later evolutionary stages.

Central to the question of the origin of life is the polymerization of the first complex molecules that can have catalytic properties and that would eventually carry genetic information. It is widely accepted that our current life form involving DNA carrying the genetic code and RNA producing the proteins that, in turn, catalyze the production of nucleotides, must have been preceded by a simpler life form called the RNA world (Woese, 1967; Crick, 1968; Orgel, 1968; see also Wattis & Coveney 1999). Here, the RNA has multiple functionality, it carries genetic code and it is also able to catalyze the production of new nucleotides.

The RNA of all terrestrial life forms involves a backbone of dextrorotatory (right-handed) ribose sugars. Theoretically, life could have been equally well based on levorotatory (left-handed) sugars. Unless this selection was somehow externally imposed, e.g. via circularly polarized light (Bailey, 2001), magnetic fields (Thiemann 1984), or via effects involving the parity-breaking electroweak force (e.g., Hegstrom, 1984), this must have been the result of some bifurcation process. Indeed, the homochirality of left-handed amino acids and of right-handed sugars in living cells can be explained as the result of two combined effects, auto-catalytic production of similar nucleotides during their first polymerization events and a competition between left- and right-handed nucleotides. The general idea goes back to early work of Frank (1953), and has been developed further by Kondepudi & Nelson (1984), Goldanskii & Kuzmin (1989), Avetisov & Goldanskii (1993) and more recently by Saito & Hyuga (2004). Of particular interest here is the recently proposed detailed polymerization model of Sandars (2003). The main point of Sandars' model is the assumption that the polymerization of monomers of opposite handedness

terminates further growth on the corresponding end of the polymer. This is referred to as enantiomeric cross-inhibition. Such inhibition makes it generally quite hard for any polymer to grow successfully. However, once a polymer has become successful in reaching an appreciable length, it will have catalytic properties promoting the production of monomers of the same chirality as that of the catalyzing polymer.

We have developed a polymerization model which include the possibility of polymers breaking at an arbitrary location (Brandenburg et al. 2005a; 2005b; Multamäki & Brandenburg 2005). Without this process polymers would, in the homochiral case, grow to infinite length which is clearly unrealistic.

The polymerization model

In our polymerization model Brandenburg et al. (2005a, 2005b) large polymers are generated by joining successive monomers into long chains. Monomers can be both left, L_1, and right, R_1, handed, and longer chains are formed according to the following set of reaction equations:

$$L_n + L_1 \xrightarrow{2k_S} L_{n+1}, \tag{1}$$

$$L_n + R_1 \xrightarrow{2k_I} L_n R_1, \tag{2}$$

$$L_1 + L_n R_1 \xrightarrow{k_S} L_{n+1} R_1, \tag{3}$$

$$R_1 + L_n R_1 \xrightarrow{k_I} R_1 L_n R_1, \tag{4}$$

where k_S and k_I are the reaction coefficients for monomers to a polymer of the same or of the opposite handedness, respectively. For all four equations we also have the complementary reactions obtained by exchanging $L \rightleftharpoons R$. Note that chains are 'spoiled' if a monomer of opposite chirality is attached to the end of a longer chain, in which case the chain can only grow at the other end. This is in essence what is meant by enantiomeric cross-inhibition. As a results, polymers such as $R_1 L_2 R_1$ and $L_1 R_1$ can no longer grow. This rule is motivated by the experiments of Joyce et al. (1984), who found that in non-enzymatic template-directed polymerization of RNA strands, only a homochiral supply of mononucleotides that

are complementary to the template can polymerize to a typical length of 20 nucleotides. Even a small amount of mononucleotides of opposite chirality prevents the formation of longer polymers, as is seen in high performance color chromatograms. Similar experiments have subsequently also been carried out by Schmidt et al. (1997) and Kozlov et al. (1998).

The monomers are initially generated from a substrate S according to

$$S \stackrel{k_C C_R}{\longrightarrow} R_1, \quad S \stackrel{k_C C_L}{\longrightarrow} L_1, \tag{5}$$

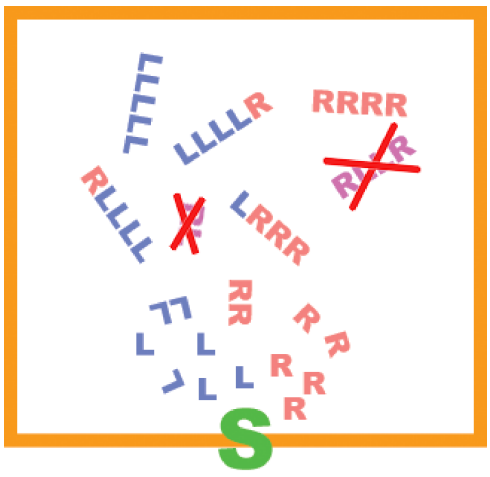
where k_C is proportional to the regeneration rate of monomers, and C_R and C_L determine the enzymatic enhancement of right and left handed monomers. The dependence of $C_{L,R}$ on the existing amount of polymer chains is essential to chirality selection as then an existing excess of either chirality can be amplified. The exact form of C is not crucial and here we follow the choice $C_A = \sum n\, A_n,\ A = L, R$ (Brandenburg et al. 2005a). For alternative prescriptions of C_A we refer to the papers by Sandars (2003) and Wattis & Coveney (2005). The substrate itself is being replenished by a constant source term Q. The polymerization process is represented pictorially in Fig. 1, where one can see how monomers begin to grow into longer chains and can then be contaminated by a monomer of opposing chirality. The crossed out chains represent polymers that can no longer grow. The feedback mechanism built into the polymerization model leads to an unstable system that, depending on the fidelity f of the enzymatic reactions, when perturbed from the initial racemic[2] state can reach a homochiral state. The prescription for C_A discussed above assumes $f = 1$. If $f < 1$, there is some 'cross-talk' between L and R where f determines the relative mixing between the two chiralities.

The chirality of a particular state is conveniently parameterized by a parameter called the *enantiomeric excess*:

$$\eta \equiv \frac{E_R - E_L}{E_R + E_L}, \tag{6}$$

where $E_A = \sum n\, A_n$ with $A = L, R$. For f larger than a critical value (see Brandenburg et al. (2005a) for details), the racemic state ($\eta = 0$)

[2]Racemic describes a mixture of equal amounts of left- and right-handed stereisomers of a chiral molecule. Because the two isomers rotate plane-polarised light in opposite directions, a racemic mixture does not rotate plane-polarised light.



Figur 1: Polymerization process. In addition to a number of monomers, L and R, there are several isotactic dimers, LL and RR, as well as longer polymers. Semi-spoiled polymers such as LLLLR and LRRR can still polymerize on the unspoiled end. Polymers such as LR and RLLR are dead and cannot polymerize further. Figure from Brandenburg & Multamäki (2005).

is unstable with respect to small perturbations. Only for $f = 1$, the end state is fully homochiral ($\eta = \pm 1$).

The model is governed by the total number of left and right handed homochiral building blocks, the reaction rates for polymerization with the same and the opposite chirality, and the corresponding dissociation rates. These numbers can be combined into a single non-dimensional number that characterizes the behavior of the system. At the moment we have no clear idea about its value, but laboratory experiments should be able to determine not only this coefficient, but they should also allow us to test various aspects and predictions of the model.

In order to draw conclusions about the time scale on which homochirality can be achieved, it is important to consider the spatial extent of the system (Saito & Hyuga 2004b). Homochirality may develop rapidly at one point in space, but the handedness may be different at different locations. The relevant time scale for achieving global homochirality is therefore much longer and is given either by the diffusion time scale, which is very long, or by a turbulent turnover time which can be much shorter if turbulent flows are present (Brandenburg & Multamäki 2005).

Emergence and spreading of life on the early Earth

The homochiralization process considered here and, indeed, in much of the theoretical literature on the subject (e.g., Frank 1953, Wei-Min 1982, Goldanskii & Kuzmin 1989, Avetisov & Goldanskii 1993, Sandars 2003, Saito & Hyuga 2004a) has been uniform in space. Relaxing this restriction can, in principle, lead to completely new chirality selection mechanisms that have no analogue in models without spatial extend. In our models we begin with a state that is homochiral everywhere, but that there are minute imbalances in space, i.e.infinitesimally small perturbations. These perturbations grow locally, leading to patches with enantiomeric excess of either handedness. It is then natural to ask how a localized homochiral state spreads to a racemic surroundings and, moreover, can regions of different chirality coexist? This question is not restricted to the model considered here and needs to be addressed in all models where chirality is selected locally by a random process.

The critical ingredients necessary to answer these questions are the presence of different relevant time scales. If the appearance of a homochiral region is a rare process, say with a period of $\tau_{\rm life}$, and the global homochiralization time scale, $\tau_{\rm global}$, is short compared to that, i.e. $\tau_{\rm global} \ll \tau_{\rm life}$, then one would not expect coexisting regions of different chirality. In other words, if the emergence of life is a rare event, then life forms with different handedness did probably not coexist. In the other extreme case, homochiral regions appear frequently compared to the speed at which they can dominate the early Earth, leading to coexisting regions of opposite chirality. Even though here we are mainly concerned with chirality, such arguments can be applied more generally to the emergence and spreading of life as well. For a discussion of the possibility of finding a second sample of life on Earth see the recent paper by Davies & Lineweaver (2005).

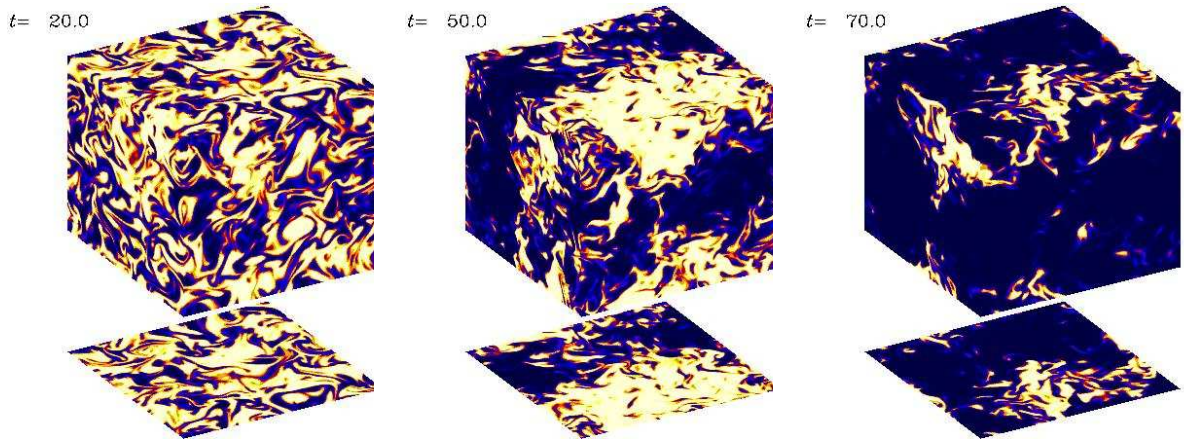
When a reduced polymerization model with spatial extent is considered analytically and by numerical simulations we find that in $1+1$ dimensions (one space and one time dimension) there is no further evolution and one

can view the process as spontaneous symmetry breaking leading to stable, non-propagating domain walls. In more than one spatial dimension, the homochiralization process progresses further. If no advection is present, only diffusion can drive the homochiralization process. Analytical arguments can be utilized to show that a bubble surrounded by a region of opposite chirality tends to shrink. Since the equations are local, the local curvature of the front is the deciding property in determining which way a front will move.

The initial state in the simulation was a racemic state with small fluctuations so that one quickly arrives at a state where there are many left and right handed regions in the box. In $2+1$ dimensions the mixing process is greatly enhanced and the global homochiral state is reached much more rapidly. The actual time scale depends strongly on the strength of the flow, e.g. for root mean square flow of 1 cm/s, the time scale of global homochiralization is of the order of 30 years. If the model captures the relevant features of chirality selection on the early Earth, then the effective mixing of early oceans was vital. As the mixing is affected by many factors such as the existence of continents and salinity of sea water, it is not difficult to speculate that in some secluded parts of the early oceans, life forms of different chirality could have coexisted.

The two horizontal directions is relevant to the Earth's surface where the vertical dynamics may be eliminated by vertical averaging. However in three-dimensional models relevant for processes in the ocean's we find that the speed of homochiralization is enhanced (by about 30%) relative to the two-dimensional case.

In our study of the spreading of homochiral domains on the early Earth, enters a certain set of assumptions. Firstly, we have assumed that the initial state is globally racemic. This implies that the conditions were life could have emerged are uniform and favorable everywhere and, furthermore, that a homochiral region can spread and fill the whole domain. Secondly, we have assumed that the emergence of life is a common event and that it is possible everywhere on Earth, and that there are no mass extinctions. These assumptions may not necessarily be realistic, and one should consider what new effects can possibly arise from relaxing these assumptions.



Figur 2: The spreading of homochiral regions in $3+1$ dimensions. The dark (light) regions correspond to left (right) handed regions. The time $t = 50$ corresponds here to $t/\tau_{\rm turb} \approx 2$. By the time $t = 100$ corresponds here to $t/\tau_{\rm turb} \approx 4$, the right handed life form went extinct. Figure from Brandenburg & Multamäki (2005).

Considering the possibility of mass extinctions and that the emergence of life can be a rare event, it is clear that a new time scale, $\tau_{\rm ext}$, is inserted into the process. Assuming that mass extinctions are local events (i.e. not all life is destroyed in which case the process can start again), the relative lengths of the different time scales determine the qualitative dynamics of the system. If $\tau_{\rm global} \ll \tau_{\rm life} \ll \tau_{\rm ext}$, life appears somewhere and takes over the whole system before life of opposite chirality can emerge. Any later mass extinction events will be insignificant as the dominant chirality will quickly win over the achiral region. If $\tau_{\rm life} \ll \tau_{\rm global} \ll \tau_{\rm ext}$ regions of different chirality compete. If mass extinctions are common, $\tau_{\rm ext} \ll (\tau_{\rm life}, \tau_{\rm global})$, and so any emergent life will quickly be wiped out – at least locally. Again, if $\tau_{\rm global} \ll \tau_{\rm life}$, it is unlikely that life will re-emerge spontaneously in the affected areas, and these areas will more likely be re-populated by the spreading of the homochiral regions surrounding the now racemic area. Thus, in this case homochirality is preserved. On the other hand, if $\tau_{\rm life} \ll \tau_{\rm global}$, the possibility of mass extinctions allows for new life forms to emerge which, in turn, may prolong the time during which life forms of opposite chirality can have coexisted.

Litteratur

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