International Journal of Astrobiology 4 (3 & 4): 233–239 (2005) Printed in the United Kingdom
doi:10.1017/S1473550405002752 First published online 3 January 2006

Unidirectional polymerization leading to homochirality in the RNA world

M. Nilsson[1,2], A. Brandenburg[1], A. C. Andersen[1] and S. Höfner[1,3]

[1]*Nordita, Blegdamsvej 17, DK-2100 Copenhagen Ø, Denmark*
e-mail: mnilsson@nordita.dk
[2]*Department of Physical Resource Theory, Chalmers University of Technology, SE-412 96 Göteborg, Sweden*
[3]*Department of Astronomy & Space Physics, Uppsala University, Box 515, SE-751 20 Uppsala, Sweden*

Abstract: The differences between unidirectional and bidirectional polymerization are considered. The unidirectional case is discussed in the framework of the RNA world. Similar to earlier models of this type, where polymerization was assumed to proceed in a bidirectional fashion (presumed to be relevant to peptide nucleic acids), left- and right-handed monomers are produced via an autocatalysis from an achiral substrate. The details of the bifurcation from a racemic solution to a homochiral state of either handedness is shown to be remarkably independent of whether the polymerization is unidirectional or bidirectional. Slightly larger differences are seen when dissociation is allowed and the dissociation fragments are recycled into the achiral substrate.

Received 5 October 2005, accepted 1 November 2005

Key words: enantiomeric cross-inhibition, origin of homochirality, RNA and DNA polymerization.

Introduction

The origin of homochirality is usually believed to be closely connected to the origin of life (see Bada 1995 for an overview). It may have even 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 (Rubenstein *et al*. 1983), magnetic fields (Thiemann 1984; Rikken & Raupach 2000), or mechanisms involving the electroweak force (e.g. Hegstrom 1984). However, Bailey *et al*. (1998) and Bailey (2001) showed later that supernova remnants have not actually displayed circularly polarized light. 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 compartmentalization that may be required to achieve the concentrations necessary for the chemical reactions to take place and to allow for different chemistries to take place inside and outside the proto-cells (Deamer *et al*. 2002). In addition, complex compartmentalized reactions can be carried out under conditions in which polymeric products are protected from degradation by hydrolytic enzymes present in the external medium (Monnard & Deamer 2001). This led to the concept of a very early lipid world (Segré *et al*. 2001; Deamer *et al*. 2002) that would have preceded the often discussed RNA world. Some insight into these ideas can be gained by looking at recent theoretical attempts to build life from scratch invoking a series of steps and chemical processes that are thermodynamically possible (Rasmussen *et al*. 2003). Interestingly enough, this approach involves peptide nucleic acid (PNA) because of its charge carrying properties and the hydrophobic backbone of the molecule. Its potential as contemporary genome, which would for example require a machinery for protein synthesis, was not utilized at this stage, although it may undoubtedly become a candidate for carrying genetic information at later evolutionary stages.

Although this is speculation and details are unknown, the idea of a combined PNA/lipid world provides an attractive scenario to discuss the origin of homochirality in the context of genetic evolution (Nelson *et al*. 2000; Pooga *et al*. 2001). We picture here a situation where PNA has developed to having autocatalytic properties, just like RNA in the RNA world (Woese 1967; Gilbert 1986). Although glycine-based PNA monomers are achiral, PNA polymers tend to curl up and form either a random coil or a double helix. However, this would still only produce a racemic mixture of equally many right- and left-handed helices. In such a combined PNA/lipid world a simple form of metabolism might have developed (Rasmussen *et al*. 2003). Subsequently, PNA molecules derived from other amino acids, e.g. from lysine (e.g. Ray & Nordén 2000), might have been incorporated. The corresponding PNA monomers would then be chiral in such a way that the handedness of the PNA helix depends

on the chirality of the monomers. An assembly of mixed L and D PNA poly-nucleotides is unlikely, just as it is unlikely in the corresponding case of DNA polymerization (Joyce *et al.* 1984). Moreover, the addition of a nucleotide of opposite handedness is known to 'spoil' further polymerization (also known as 'enantiomeric cross-inhibition'). This makes it increasingly unlikely to generate L and D polymers of any appreciable length greater than just a few.

The main difference between PNA and DNA polymerization is that DNA can only attach new monomers on the 3′ end of the ribose sugar (e.g. Turner *et al.* 2000), so polymerization is unidirectional, i.e. it can only proceed in one direction. In contrast, PNA does not have this restriction and can polymerize in a bidirectional fashion, i.e. in either direction. The latter case has been addressed in a number of recent studies starting with Sandars (2003), but the former case is more readily amenable to laboratory verification, as is shown by recent experiments confirming the process of enantiomeric cross-inhibition (Schmidt *et al.* 1997; Kozlov *et al.* 1998). Given that the differences between unidirectional and bidirectional polymerization have not yet been explored, we must first extend the formalism of Sandars (2003) to the unidirectional case and then focus on the comparison between the two.

Following common convention, we use the term polymerization somewhat loosely. Strictly speaking the formation of PNA and DNA polymers is a polycondensation that involves the elimination of another molecule (e.g. water in the case of the peptide bond). However, for simplicity we continue to use the term polymerization.

Although enantiomeric cross-inhibition seems to be an important ingredient in homochirality, this can only work if the production of new monomers is somehow biased toward the enantiomeric excess of the already existing polymers – even if this bias is extremely tiny. This is the second important ingredient in homochirality and is known as *autocatalysis*. This mechanism provides the main 'driving force' of the system. Certain chemical reactions are indeed known to have such properties (Soai *et al.* 1995; Sato *et al.* 2003; Mathew *et al.* 2004). It is important to point out that these reactions are only based on dimerization, but they are nevertheless quite valuable in establishing the basic elements of homochiralization in chemical systems (Kitamura *et al.* 1998; Plasson *et al.* 2004), and can lead to quantitative predictions that have been tested by measuring the reaction rate using accurate calorimetry (Blackmond *et al.* 2001; Buono & Blackmond 2003). For recent reviews see the papers by Mislow (2003) and Blackmond (2005).

The importance of the combined action of enantiomeric cross-inhibition on the one hand and autocatalysis on the other has been well known since the very early work of Strong (1898) and a seminal paper by Frank (1953), who first proposed a simple mathematical model consisting of only two variables representing the relative numbers of left- and right-handed building blocks. His paper was tremendously insightful in that he understood not only the two basic ingredients needed for homochirality, but he was also aware that there are two rather different scenarios through which homochirality can be achieved, depending basically on how frequent the creation of a potential life bearing molecule is. If the creation of life was sufficiently frequent, life may have emerged at different locations on the Earth's surface (including the oceans), giving rise to the interesting possibility of having different life forms of opposite handedness simultaneously. This is the case studied recently by Brandenburg & Multamäki (2004), who estimated that left- and right-handed life forms could have coexisted for not more than the first 500 million years. This is because the different populations will have spread over the Earth's surface and will have eventually come into contact, extinguishing one of the two life forms. The other possibility is that the creation of life was an infrequent event, in which case there was ever only one life form, which was then the one that led eventually to the global population over the Earth's surface. Regardless of which of the two scenarios applies, the final outcome would have been the same.

In his paper, Frank (1953) only analysed the second alternative in detail. This is also the scenario discussed in most of the approaches since then, which all discuss homochirality as the result of a bifurcation process (see also Saito & Hyuga 2004a for a recent classification of different possibilities). This also forms the basis for the model discussed in the present paper, where we present a modification of a detailed polymerization model recently proposed by Sandars (2003). In this model the enantiomeric excess grows exponentially in time. However, if the creation of life is a frequent event such that left- and right-handed life forms may have been established independently at different locations, the process toward *global* homochirality could only occur approximately linearly in time (Brandenburg & Multamäki 2004; see also Saito & Hyuga 2004b for related work). Thus, in that case the global enantiomeric excess can no longer grow exponentially in time, but only linearly. The possibility of finding a second (independent) sample of life has recently also been discussed by Davies & Lineweaver (2005).

In the model by Sandars (2003), autocatalysis is incorporated by assuming that the rate of monomer production of given handedness is proportional to the concentration of polymers of the same handedness. As noted above, this effect alone, i.e. without the additional effect of enantiomeric cross-inhibition, cannot lead to complete homochirality, because the initial enantiomeric excess is not (or only weakly) amplified. In order to model this quantitatively, Sandars (2003) assumed that polymerization can, at a certain rate, also occur with monomers of opposite handedness. This reaction produces chemically inactive products and it acts thus as a means of removing oppositely oriented building blocks (that are already in the minority) from the system. This model has been studied further by Wattis & Coveney (2005) and by Brandenburg *et al.* (2005a; hereafter referred to as BAHN) who showed that, for a large enough fidelity of the catalyst, the departure from a racemic state occurs exponentially fast at a growth rate that depends on the fidelity and the rate of enantiomeric cross-inhibition. They also discussed a

model consisting only of primers and dimers, which can be reduced to a set of two ordinary differential equations that are similar to those of Frank (1953). An important difference to Frank's model is the form of the cross-inhibition term. As discussed by Blackmond (2004), the feedback term in his model corresponds to the formation of inactive dimers with one left- and one right-handed building block. This is unrealistic, because dimers with two left- or two right-handed building blocks should also form. This led to the conclusion that the dimers must act as catalysts. So far, only autocatalytic dimer reactions have been possible to demonstrate experimentally, but it plausible that for longer polymers autocatalytic behaviour should be even stronger. However, while various different assumptions about the autocatalytic behaviour lead to noticeably different quantitative outcomes, the very fact that homochirality is the result of a bifurcation still remains true (BAHN; Wattis & Coveney 2005).

We have emphasized that Sandars' original model assumed that polymerization can occur on either end of the polymer. While this may be a reasonable assumption in general (and probably also for PNA), it is not realistic for RNA polymerization where polymerization can usually only proceed in a unidirectional fashion. Since unidirectional polymerization leads to a simpler model, and since the derivation of the bidirectional polymerization model has already been discussed elsewhere (see, e.g., BAHN), the unidirectional case is ideal for introducing the basic ingredients of the model. Following the mathematical description of the unidirectional model, we present numerical solutions that show that the main conclusions obtained from the earlier bidirectional polymerization models carry over to the unidirectional case. This addresses the possible objections that the Sandars model is not applicable to RNA and DNA polymerization, which is more easily amenable to detailed laboratory verification.

Polymerization model

The starting point of the model is a basic polymerization process

$$L_n + L_1 \overset{k_S}{\rightarrow} L_{n+1}, \tag{1}$$

where L_n denotes left-handed polymers of length n and k_S the reaction rate. The corresponding model of the polymerization process reads

$$\frac{\mathrm{d}}{\mathrm{d}t}[L_n] = -k_S[L_1]([L_n] - L_{n-1}), \tag{2}$$

where $[L_n]$ is the concentration of L_n. New building blocks are continuously added to the model, e.g. by the inclusion of a substrate that provides a source Q_L of new monomers, i.e.

$$\frac{\mathrm{d}}{\mathrm{d}t}[L_1] = Q_L - \sum_{n=1}^{N} k_S[L_1][L_n]. \tag{3}$$

The solution of (2) and (3) is simply a wave travelling toward longer polymers at velocity $k_S[L_1]$ (see Fig. 1), as can also be seen by considering the continuous limit of this

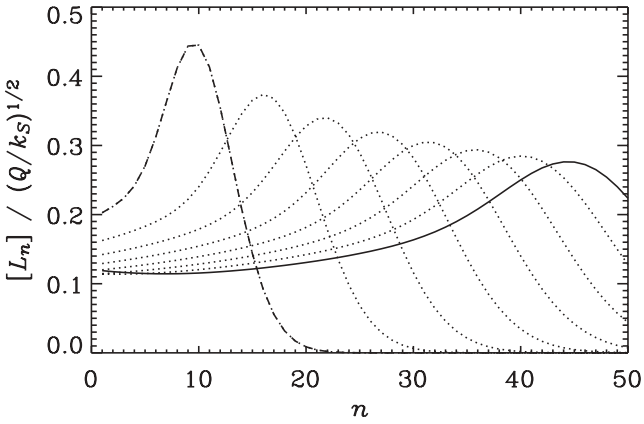

Fig. 1. Wave-like propagation of a finite amplitude perturbation in the unidirectional polymerization model. The initial profile is a Gaussian. Note the undisturbed outward propagation of the wave at $n = N$. The time difference between the different curves is $20/(k_S Q)^{1/2}$. The first and last times are shown as dashed and solid lines, respectively, and all other times as dotted lines. The parameters are $N = 50$ and $k_C/k_S = 1$. Note that, unlike the bidirectional bifurcation model discussed in BAHN, the dependence here of $[L_n]$ on n is continuous at $n = 1$.

equation, $\partial[L_n]/\partial t = -k_S[L_1]\partial[L_n]/\partial n$. Note that, in contrast to a similar result for bidirectional polymerization (see BAHN, their fig. 1), the functional form of $[L_n]$ is continuous between $n = 1$ and 2. In the bidirectional case $[L_1]$ is about twice as large as $[L_2]$.

The model becomes more interesting when the right-handed polymers, R_n, are also included. The interaction between the mirrored strands is assumed to occur through two separate phenomena: enantiomeric cross-inhibition and enzymatic autocatalysis. The autocatalysis makes the left-handed, (respectively right-handed) polymers catalyse the production of left-handed (respectively right-handed) building blocks. The source terms Q_L and Q_R are proportional to the concentration of the achiral substrate $[S]$ and a corresponding reaction coefficient k_C. In the case of perfect fidelity, $f = 1$, the source terms are written as

$$Q_L = k_C[S]C_L, \quad Q_R = k_C[S]C_R, \tag{4}$$

where C_L and C_R are some measures of the catalytic effect of the already existing left- and right-handed polymers. There should be a monotonically increasing function of the overall concentration of the left-handed polymers. The exact functional form of these expressions are not known. In fact, different authors have chosen different prescriptions for C_L and C_R. The qualitative results of the models do not, however, seem affected by this choice. We find it natural to assume that

$$C_L = \sum_{n=1}^{N} n[L_n], \tag{5}$$

$$C_R = \sum_{n=1}^{N} n[R_n]. \tag{6}$$

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In the more general case of finite fidelity of the assumed autocatalysis, i.e. for $0<f<1$, we assume there will be 'cross-talk' between the two handednesses, so we write

$$Q_L = k_C[S]\left\{\frac{1}{2}(1+f)\mathrm{C_L} + \frac{1}{2}(1-f)C_R + C_{0L}\right\}, \tag{7}$$

$$Q_R = k_C[S]\left\{\frac{1}{2}(1+f)C_R + \frac{1}{2}(1-f)C_L + C_{0R}\right\}. \tag{8}$$

Here the terms C_{0L} and C_{0R} allow for the possibility of non-catalytic production of left- and right-handed monomers. However, in the following we assume that $C_{0L}=C_{0R}=0$. (The inclusion of C_{0L} and C_{0R} terms leads to so-called imperfect bifurcations; see fig. 6 of BAHN).

The enantiomeric cross-inhibition occurs when a building block attaches to a polymer of opposite handedness. The resulting polymer cannot continue to grow at the affected end and can therefore be considered spoiled. This phenomenon has been observed in experiments by (Joyce *et al.* 1984) who studied template-directed polymerization. When cross-inhibition is included, the set of reactions in the model is (for $n\geqslant 2$)

$$L_n + L_1 \xrightarrow{k_S} L_{n+1}, \tag{9}$$

$$L_n + R_1 \xrightarrow{k_I} L_n R_1, \tag{10}$$

and for all four equations we have the complementary reactions obtained by exchanging L and R. The new parameter k_I measures the rate at which the cross-inhibition occurs. The rate equations now read (for $n\geqslant 2$)

$$\frac{\mathrm{d}[L_n]}{\mathrm{d}t} = k_S[L_1]([L_{n-1}]-[L_n]) - k_I[L_n][R_1], \tag{11}$$

$$\frac{\mathrm{d}[R_n]}{\mathrm{d}t} = k_S[R_1]([R_{n-1}]-[R_n]) - k_I[R_n][L_1]. \tag{12}$$

The evolution of the spoiled polymers, L_nR_1 and R_nL_1, can be discarded, because, in contrast to bidirectional polymerization, their concentrations do not enter the unidirectional model.

In comparison with bidirectional polymerization we note that here for $n=2$ there is no extra $\frac{1}{2}$ factor in front of the $[L_1]^2$ and $[R_1]^2$ terms in (11) and (12). This is because with polymerization from either end the total reaction rate would be twice as large. However, when two monomers interact, the corresponding reaction equation is the same for both unidirectional and bidirectional polymerization, because the two reacting monomers are indistinguishable. Thus, whether the first binds to the second or the second to the first monomer does not make a difference. This is then equivalent to saying that for two monomers polymerization can occur both on the 3′ and on the 5′ end of the ribose sugar. In effect, this removes an awkward $\frac{1}{2}$ factor for the $n=2$ equations in the model of Sandars (2003); see also (7) of BAHN.

The reactions (9) and (10) imply the presence of additional loss terms in the evolution equations of monomers, so instead of (3) we now have

$$\frac{\mathrm{d}}{\mathrm{d}t}[L_1] = Q_L - \lambda_L[L_1], \tag{13}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[R_1] = Q_R - \lambda_R[R_1], \tag{14}$$

where we have defined decay rates

$$\lambda_L = k_S\left([L_1] + \sum_{n=1}^{N}[L_n]\right) + k_I\sum_{n=1}^{N}[R_n], \tag{15}$$

$$\lambda_R = k_S\left([R_1] + \sum_{n=1}^{N}[R_n]\right) + k_I\sum_{n=1}^{N}[I_n]. \tag{16}$$

Comparing again with the bidirectional model, the present model has an extra $[L_1]$ (or $[R_1]$) term, but there is no factor of 2 in front of the k_S and k_I terms and the sums over the concentrations of semi-spoiled polymers are also absent.

From symmetry considerations it follows that a racemic steady state ($[R_n]=[L_n]$) of the rate equations always exists. In fact, we can show that a steady state is given by (for $n\geqslant 2$)

$$[L_n] = \left(1+\frac{k_I}{k_S}\right)^{-(n-1)}[L_1] \quad \text{(racemic)}. \tag{17}$$

In particular, if $k_I=k_S$, then $[L_n]=[L_1]/2^{n-1}$, i.e. $[L_n]$ drops by a factor of 2 from one n to the next. This is also true between $[L_1]$ and $[L_2]$, while in the bidirectional model their ratio is 4.

While the existence of a racemic solution is trivial, the interesting question is whether other fixed points of the equations exist, and in this case which of these fixed points are stable under certain conditions. As was shown in BAHN the model typically goes through a pitchfork bifurcation from a single stable fixed point (the racemic solution) to a state with two homochiral stable fixed points where the racemic solution corresponds to an unstable fixed point. The order parameter controlling the bifurcation is the fidelity f of the autocatalysis. In Fig. 2 we show the enantiomeric excess, defined here as

$$\eta = \frac{C_R - C_L}{C_R + C_L}, \tag{18}$$

for $k_I/k_S=1$ and $k_I/k_S=0.1$. We also compare with the corresponding result from the bidirectional polymerization model. The difference between the two cases is however surprisingly small.

Polymer dissociation

The model described in the last section provides a possible explanation of homochirality, without appealing to external mechanisms for symmetry breaking. One may also argue that the model is rather realistic in that it explicitly considers the polymerization process. Less satisfactory are some of the details in the description of the polymerization process. Perhaps most importantly, the polymerization process is

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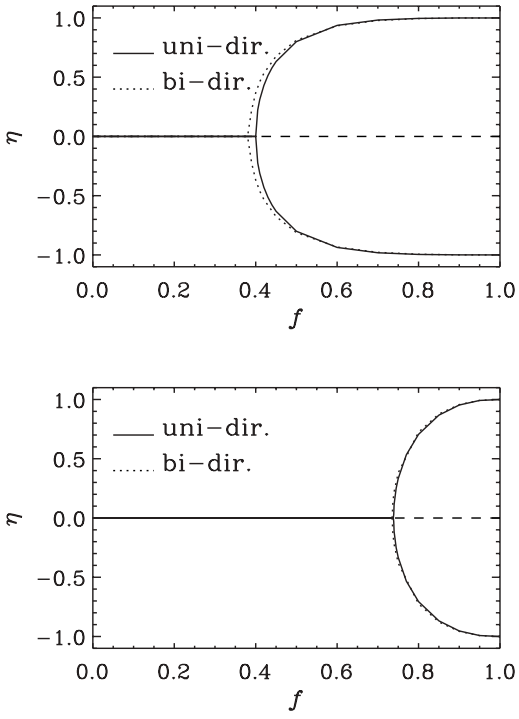

Fig. 2. Comparison of the bifurcation diagram for unidirectional and bidirectional polymerization (solid and dotted lines, respectively) for two different values of k_I/k_S (1 in the upper panel and 0.1 in the lower panel). The data for the bidirectional case are taken from the BAN paper. Note the close similarity between the two cases (dotted and solid lines). The transition from a racemic to a homochiral state occurs for $f \approx 0.4$ when $k_I/k_S = 1$ and for $f \approx 0.75$ when $k_I/k_S = 0.1$. For weak enantiomeric cross-inhibition ($k_I/k_S = 0.1$ in the lower panel) the range of permissible values of the fidelity parameter is decreased, demonstrating the importance of enantiomeric cross-inhibition.

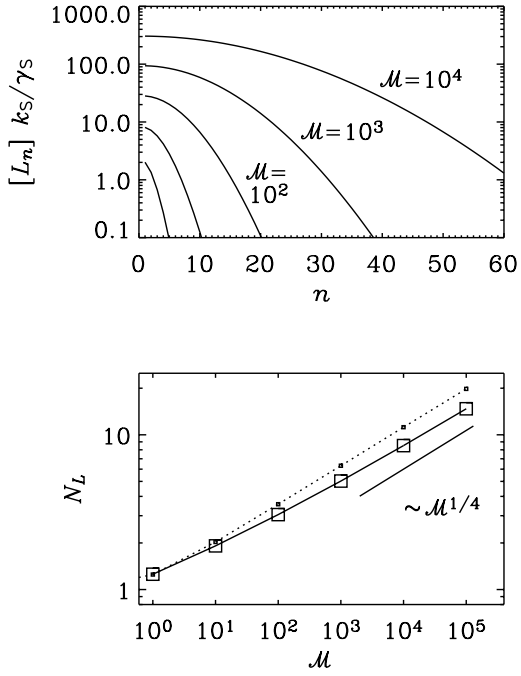

Fig. 3. Isotactic equilibrium states with polymerization, dissociation, and recycling of fragments into the substrate, for different values of $\mathcal{M}$ (upper panel), and the mean polymer length N_L (lower panel, solid line), compared with the bidirectional polymerization model of BAHN (dotted line).

irreversible, no chain-breaking (i.e. dissociation) is included in the model. As we have already pointed out in an earlier paper (Brandenburg *et al.* 2005b; hereafter referred to as BAN), this is unrealistic because for a large enough fidelity the polymer length always tends to diverge. Also, the model cannot be self-contained as there is no feedback from the polymers back to the substrate.

Before discussing the differences between unidirectional and bidirectional polymerization in the presence of dissociation in more detail, let us first recall the main aspects of the polymerization model with dissociation, as developed recently by BAN. The dissociation process is described by the reaction

$$L_n \xrightarrow{\gamma_S} L_m + L_{n-m},$$

and the corresponding reaction for the right-handed polymers. It turns out that there are a number of subtleties that need consideration when constructing the detailed model for chain breaking. For example, if we assume that the fragments can continue to polymerize, the result is a catastrophic over-abundance of the short chains. The reason for this is that all building blocks (L_1 and R_1) are used to produce longer polymers whereas polymers of length two or more cannot (according to the reactions above) agglomerate into longer polymers. One way to remedy this would, of course, be to include the agglomeration in the model, but the disadvantage of this is that the model then becomes significantly more complex due to the higher degree of non-linearity. These issues are discussed in further detail in BAN, where a number of possible alternatives of the model are also considered. We focus here on the model where the polymerization fragments are recycled back into the achiral substrate. In the rest of this paper we discuss the modifications necessary to incorporate dissociation in a unidirectional polymerization model.

In the presence of dissociation, the new system of equations is

$$\frac{\mathrm{d}}{\mathrm{d}t}[L_n] = p_n^{(L)} - (n-1)\gamma_S[L_n],$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[R_n] = p_n^{(R)} - (n-1)\gamma_S[R_n],$$

where $p_n^{(L)}$ and $p_n^{(R)}$ indicate the terms due to polymerization described above. The source term in the substrate is given by

$$Q = W_L + W_R + W_{LR} + W_{RL}, \tag{19}$$

where

$$W_L = \sum_{n=1}^{N} n w_n^{(L)}, \quad W_R = \sum_{n=1}^{N} n w_n^{(R)}, \tag{20}$$

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is the total number of recycled building blocks (both left and right handed), and

$$W_{LR} = \sum_{n=1}^{N} (n+1) w_n^{(LR)}, \quad W_{RL} = \sum_{n=1}^{N} (n+1) w_n^{(RL)} \tag{21}$$

are the corresponding contributions from fragmented (inactive) polymers.

As in the bidirectional case, the average polymer length scales with a quarter power of the parameter $\mathcal{M} = (k_S/\gamma_S) \times \sum_{n=1}^{N} n([L_n]+[R_n])$. Thus, in order to achieve appreciable polymer length, the normalized total mass must be sufficiently large.

Histograms of the chain distribution and the dependence of the chain length on the total normalized mass are given in Fig. 3 and compared with the bidirectional case. For small chain mass ($\mathcal{M} \leqslant 10$) the chains tend to be very short ($N_L \approx 1, \ldots, 2$), which is common to both bidirectional and unidirectional cases. For larger total masses, however, the two cases begin to depart from each other such that for the same total mass the chains are slightly shorter in the unidirectional case.

Conclusions

In the present paper we have modified the polymerization model of Sandars (2003) such that polymerization is only possible on one of the two ends of the polymer. Although PNA polymerization is probably still bidirectional, this is normally not the case for RNA polymerization. The significance of considering RNA polymerization is that it is readily amenable to direct experimental verification (e.g. Joyce *et al*. 1984). Perhaps, one of the most curious properties of the model is the wave-like evolution of the polymer length after the initialization of the polymerization process. This prediction could possibly be tested experimentally by setting up a range of different polymerization experiments that are stopped at different times. A subsequent analysis, as is done for DNA sequencing, might then reveal a structure as seen in Fig. 1.

We emphasize that homochirality appears spontaneously when two separate mechanisms are present in the polymerization process: autocatalysis and enantiomeric cross-inhibition. The accuracy of the autocatalysis is parametrized by a fidelity factor. At low fidelity the polymerization leads to a racemic solution whereas at higher fidelity a homochiral state is reached from an initially (almost) racemic solution. The corresponding bifurcation diagram displays a classic pitchfork bifurcation and the autocatalytic fidelity acts as a control parameter. The differences between unidirectional and bidirectional polymerization are however surprisingly small.

In the second part of this paper we have extended the model to include dissociation within the framework of unidirectional polymerization. As in the case of bidirectional polymerization, the model becomes chemically more realistic in that longer chains are now possible. Moreover, the model is constructed to be self-contained in that the need for external replenishing of the substrate is now replaced by the recycling of dissociation fragments. This aspect of the model should also be amenable to experimental verification. However, with respect to chirality, the qualitative behaviour of the model is shown to persist the inclusion of dissociation. We therefore conclude that the existence of a transition between a racemic and homochiral state, as a function of the autocatalytic fidelity, is a robust phenomenon within the class of models under consideration.

Acknowledgements

We thank Peter Egil Nielsen for discussions about PNA and the anonymous referees for making useful suggestions that have led to several improvements in the presentation.

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