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Non-racemic mixture model: a computational approach

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The behavior of a slight chiral bias in favor of L-amino acids over D-amino acids was studied in an evolutionary mathematical model generating mixed chiral peptide hexamers. The simulations aimed to reproduce a very generalized prebiotic scenario involving a specified couple of amino acid enantiomers and a possible asymmetric amplification through autocatalytic peptide self-replication while forming small multimers of a defined length. Our simplified model allowed the observation of a small ascending but not conclusive tendency in the L-amino acid over the D-amino acid profile for the resulting mixed chiral hexamers in computer simulations of 100 peptide generations. This simulation was carried out by changing the chiral bias from 1% to 3%, in three stages of 15, 50 and 100 generations to observe any alteration that could mean a drastic change in behavior. So far, our simulations lead to the assumption that under the exposure of very slight non-racemic conditions, a significant bias between L- and D-amino acids, as present in our biosphere, was unlikely generated under prebiotic conditions if autocatalytic peptide self-replication was the main or the only driving force of chiral auto-amplification.

Key words: origin of homochirality, prebiotic peptide formation, chiral asymmetry, amino acids

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Abbreviations: D-amino acids; L6; L5D1; L4D2; L3D3; L2D4; L1D5; D6; NCA-amino acid

INTRODUCTION

A feasible scenario related to the chirally asymmetric profile of constitutive amino acids in the organic matter of the early Earth could be conceptualized by the delivery of simple organic molecules to Earth by comets or meteorites (Alicea & Gordon, 2014; Muñoz-Caro *et al*., 2002; Wainwrigh*t et al*., 2014). From the 90 amino acids found in the Murchison meteorite in 1969 (Cronin & Pizzarello, 1997), 19 of them were present on Earth. Supposed the Earth was bombarded with a non-racemic amino acid mixture of 1% left orientation, i.e. of L-amino acids, for 7 billion years; could this bias be sufficient to pave the way for the present homochirality of Earth's biosphere consisting almost exclusively of L-amino acids?

Our simulations were inspired by experimental results from Hitz & Luisi (2004) on the spontaneous onset of homochiral oligopeptide sequences during the polymerization of hydrophobic NCA-amino acid racemates in aqueous solution. We tried to rationalize these experimental results in general terms of a formerly developed toy model orientated to the Miller-Urey experiment (Polanco *et al*., 2013) of prebiotic amino acid generation and the subsequent prebiotic peptide evolution by focusing on the possible role of relative amino acid abundances (Polanco *et al*., 2013). Our present computational approach intended to re-create the prebiotic scenario from a discrete Markovian system, including the chiral implications of peptide formation. The modeling allowed the implementation of multiple variables without adding excessive complexity to the algorithm due to its Markovian property (Isaacson & Madsen, 1976). From this model, it was possible to observe an increasing but not sustained trend in the formation of L-amino acid sequences over D-amino acid sequences in the polymerization process.

In order to identify any drastic change of behavior in the graph, the modeling was run up to 100 generations in groups of 15, 50 and 100, varying the chiral bias in the first generation from 1% to 3%.

MATERIAL AND METHODS

We considered for the model, the polymerization of one single amino acid with a random bias of 1% in favor of the L-enantiomer over the D-enantiomer for each new peptide generation. The simulations produced mixed chiral peptide hexamers consisting of L- and D-amino acid sequences. We introduced an autocatalytic evolving process through peptide self-replication (Issac *et al*., 2001) where peptides and peptide fragments coexisted in the same medium. These species were used in repetitive simulation steps to project the future trend of the peptide over the first 100 generations on a cumulative basis. For this purpose, the chiral bias of 1% and 3% was applied to the first generation of the three modeling stages mentioned above, in order to detect any meaningful changes in the graph pointing to a different behavior.

Then the percentage disparity of the peptides was calculated for each generation and its geometric representation was used to visualize the future trend of the formed peptides based on their chiral sequences.

Non-racemic model. In reminiscence of our former toy model (Polanco *et al.,* 2013), the non-racemic model included the splitting of the hexamers and the merging of peptide fragments as well as template-directed peptide self-replication. These processes acted jointly to recreate the evolutionary aspect of the model. The peptide splitting produced the random division of the peptide hexamers into trimer segments, enabling each segment to interact with other peptides being formed. Thus, the polymerization process consisted of two ways to form a peptide: the step-wise addition of amino acid monomers to the growing peptide by the polymerization process

and the addition of amino acid fragments present in the simulated medium.

The process of peptide self-replication mimicked the evolutionary process and introduced the essential autocatalytic element for asymmetric amplification, creating new peptides from segments of the already formed peptides, extending the process up to 100 generations in the three stages of 15, 50 and 100 generations with chiral bias of 1% and 3% in the first generation, totaling six modelling processes. In summary, the non-racemic model simulated the peptide building considering segments of other peptides located in the medium, new amino acids during the polymerization process and inherited segments used as templates to form new peptides.

Amino acid polymerization. The peptide building started with the two first amino acids either L–D, L–L or D–D with the constantly implemented bias of 1% in favor of L. New amino acids were added to one side of the growing peptide in a combined and ordered process with equal polarity conditions.

Peptide splitting and merging. This reversible process provided the dynamic aspect to the model. The mixed chiral peptide hexamers were divided into two trimers when a peptide adopted an L6, L5D1, L4D2, L3D3, L2D4, L1D5, or D6 sequence distribution with an arbitrarily chosen splitting probability in the order of L6 = D6 < L1D5 = D1L5 < L4D2 = D4L2 < L3D3 = D3L3. This means that if a peptide shows an **LDLLLL** sequence, it is divided into **LDL** and **LLL** fragments giving higher priority to **LLDDDD** over **LLD** and **DDD**. This reasoning was based on the assumption that hexamers with a higher degree of homochirality exhibit higher structural stability and, therefore, show a lower probability of fragmentation; all peptides were generated with this constraint. Once the peptide was divided, the non-racemic model kept arbitrarily the right-hand side trimer, and sent the remaining trimer back to the medium, keeping an accumulative file of all segments divided in such a way called cutting record.

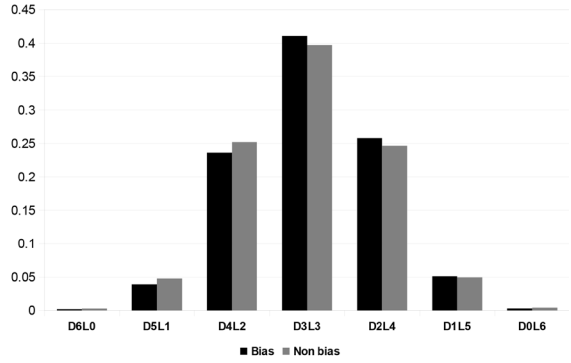

Figure 1. Percentage distribution of L- and D-enantiomers in the peptide hexamers after the simulation of 100 peptide generations.

All peptides were likely to be affected by this division anytime during the execution of the process. For instance, if the simulation constructs an **LLLDDL** hexamer, the **LLL** fragment is sent to the medium and the building protein becomes **DDL**.

Self-replication. This process introduced the evolving and nonlinear dynamics into the model and demanded most memory and processing computational resources. It produced copies ("clones") of the trimer peptide segments and inherited them to new generations to create new peptides, i.e. parents inherited some of their features to offspring. These copies were always generated at random, see for details as described elsewhere (Polanco *et al*., 2013). For instance, if the non-racemic model constructs a **DDDLDL** peptide, the **LDL** copy segment is transferred as a seed to a similar program called non-racemic model_1. Then in the non-racemic model_1 the peptide building mechanism that started with two amino acids is substituted by the starting **LDL** seed that was submitted by the non-racemic model.

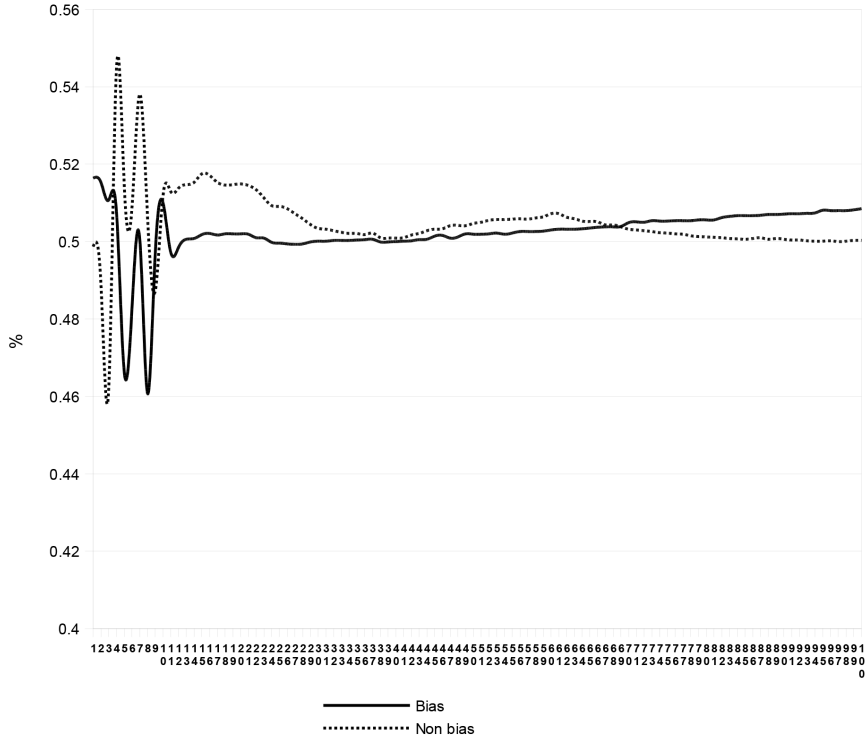

Figure 2. Evolution of the enantiomeric excess during 100 peptide generations. Dotted line: no bias applied; solid line: constant asymmetric bias of 1%.

Trial test. To evaluate the robustness of the model, a number of variations in the initial conditions and parameter values were conducted. The chiral percentage bias of 1% and 3% was applied to: (i) only the first generation, (ii) generations 15, 50 and 100 and (iii) all generations i.e. mimicking a single asymmetric event or the presence of a constant asymmetric force, respectively.

RESULTS AND DISCUSSION

Our simulations show that during the sequential generation of new peptide hexamer generations, the peptides with preferential L distributions increasingly outnumber the amino acids with D

distributions (see D3L3, D2L4, and D1L5 distributions; Fig. 1). But this trend is asymptotically approaching to 0.5100 (1% bias), not exceeding this value. Similar results are observed in all the other trial test simulations as detailed above. The same process executed with and without any chiral bias over 100 generations, i.e. under racemic conditions (Fig. 2), show that in the absence of a chiral bias in favor of any of the two amino acid enantiomeric excess no asymmetric amplification takes place while in the presence of the 1% bias there is an increasing but not conclusive tendency of an ascending chiral asymmetry.

The different models affected with chiral bias of 1% and 3%, accumulated in the three stages (15, 50, and 100 generations), show that the behavior of the model is similar to the chiral bias of 1% over 100 generations. This leads to the assumption of the lack of drastic changes in the behavior of this prebiotic experiment, regardless of the number of generations involved. It is worth mentioning that although this is a stochastic modeling, the models replicate a deterministic process (Poincaré, 1952). If the model had been deterministic since the beginning, it could have been automated using a differential model with eight variables (polarity, abundance, amino acids, among others). However, its complexity would have increased considerably as the solution space would have been the total combination of all the possibilities. Such a large figure, would have led to limit the possible values for each variable whereas stochastic models, due to their nature, allowed the addition of variables without increasing the complexity of the model.

The results found with the non-racemic model indicate that it is unlikely that a continuous asymmetric bias of 1%, applied generation after generation, is sufficient to change the original proportion of L and D amino acids from 51:49% to significantly higher proportions as e.g. 99:1% in the ideal case. In the early stages of the simulations (Fig. 1), there is a notoriously ascending asymmetric trend that, however, is not sustained for the higher generations.

Our approach could lead to the modeling of a prebiotic scenario with greater granularity since it is possible to prioritize the involved biases to influence the number of amino acids, their relative abundances and their polarities (Polanco *et al.*, 2013). Computer simulations in this direction are already under progress because the mathematical profile of this type of model allows taking into account several biases without increasing the computational complexity of the program.

CONCLUSIONS

We observed that in a highly simplified scenario of peptide building, where only one enantiomer couple of one amino acid is present and in which asymmetric amplification is assumed to originate exclusively from peptide self-replication, most probably no significant enantiomeric excess can be generated through chiral autoamplification. In reference to the experiments by Hitz & Luisi (2004), additional factors as for instance structural aspects of mixed-chiral vs. homochiral hexamers, as well as the presence of enantiomeric cross-inhibition as established in the seminal Frank model (Frank 1953), should be additionally taken into account to rationalize these interesting findings.

SOFTWARE RESOURCES

The program was written in FORTRAN 77 and executed on a Fedora 14 Unix-type platform (GNU). We run the program from 1 to 100 generations in an HP Workstation Z210-CMT-4x Intel Xeon E3-1270/3.4 GHz (Quad-Core)-RAM 8GB-SSD 1x 160GB-DVD SuperMulti - Quadro 2000 - Gigabit LAN, Linux Fedora 14, 64-bits. Cache Memory 8 MB. Cache Per Processor 8 MB. RAM 8 GB.

Conflict of Interests

We declare that we do not have any financial and personal interest with other people or organizations that could inappropriately influence (bias) our work.

Author Contributions

Theoretical conception and design: CP and TB. Computational performance: CP. Data analysis: CP and TB. Results discussion: CP and TB.

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