Computer simulations of biotic chiral selection scenarios

Savino Longo1,2, Carmela Mundo3 and Gaia Micca Longo1,2

1Dipartimento di Chimica, Università degli Studi di Bari Aldo Moro, Via Orabona 4–70125, Bari, Italy
2Istituto per la Scienza e Tecnologia dei Plasmi – Consiglio Nazionale delle Ricerche, Bari Section – Via Amendola 122/D – 70125, Bari, Italy
3Dipartimento di Bioscienze Biotecnologie e Biofarmaceutica, Università degli Studi di Bari Aldo Moro, Via Orabona 4–70125, Bari, Italy

Author for correspondence: Savino Longo, E-mail: savino.longo@uniba.it

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Abstract
The biotic scenario of the selection of biological homochirality is one of the most interesting applications of computer modelling to astrobiology. These scenarios have been studied for more than 70 years, yet there are plenty of studies to better assess them, in particular in the development of models of the selective extinction process. In this paper, we review former studies performed by biology-grounded models of this process and present a new class of computer programs: they further demonstrate the complexity of the selective extinction dynamics and the role played into it by non-trivial chemical-physical concepts. Indeed, the results display large and persistent differences between the populations of the two different chiral types, made possible by the freedom of individual populations to fluctuate wildly while the total population is stabilized by the limited availability of chemical energy. Such strong differences ultimately lead to the selective extinction of one of the two types. This way, computer simulations provide increasing evidence in favour of the biotic scenario.

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Introduction
Most of the computer models employed in the context of astrobiology describe phenomena either on an atomic scale (in the order of nanometres) or on a geochemical scale (in the order of hundreds of kilometres). Our group has been working for some years on astrobiological simulations, on a scale that has so far been little considered: the order of tens or hundreds of microns (Micca Longo and Longo, 2017; Micca Longo and Longo, 2018; Micca Longo et al., 2019). At this scale, the phenomena described might be accessible to a microscope. Some of these phenomena are of extreme interest in the understanding of the origin of life.

In this respect, one of the most important issues in origin-of-life studies is the explanation of the predominance of biological molecules, as well as whole organisms, with a well-defined chirality. Chirality is a geometric property of a molecule, according to which the mirror transformation of an object is a non-identity operation, i.e. the molecule and its mirror image are non-superimposable by any translation or rotation.
In particular, amino acids are identified by an L configuration and a D configuration, but only the L version, with very sporadic exceptions, is used in the construction of proteins on Earth (Ageno, 1971). This peculiarity is called ‘biological homochirality’.

Biological homochirality is one of the deepest mysteries in the evolution of life, since the two chiral variants (enantiomers) have the same chemical stability and should be found in biological systems with the same frequency, quite the opposite of what is actually detected (Babinec and Krempasky, 1994; Plasson, et al., 2007; Kafri, et al., 2010; Quack, 2012; Ruiz-Mirazo, et al., 2014; Quack, 2015; Ribó and Hochberg, 2019).

Amino acids in meteorites do not show homochirality, except by a very small extent (Pizzarello, et al., 2003; Meierhenrich, 2008). Therefore, the ‘chirogenesis’, that is the origin of homochirality, took place on Earth shortly before or in conjunction with the development of the first life forms (Bergstrom and Reimchen, 2003; Loehr, et al., 2012).

The numerous explanations of the predominance of a single chirality in biomolecules include many possible external causes that might have favoured the formation of a specific enantiomer by a process of chirality induction, or inheritance, or alternatively a ‘deracemization’ of an initially racemic state, a state where both enantiomers are equally present (Kondepudi and Nelson, 1985; Epstein, 1995; Crusats, et al., 2010; Elango, et al., 2010; Aquilanti, et al., 2011; Szurgot, 2012). The classic Ageno’s book on the origin of life (Ageno, 1971) provides an exhaustive historical exposition. The chirality of the crystalline surfaces on which the biomolecules were produced for the first time, and the selective destruction of the molecules by polarized light are among the possible chirogenesis causes.

A complete recent review concerning the autocatalytic models of the emergence of biological homochirality can be found in (Blackmond, 2019). Experimental examples of such an amplifying autocatalytic reaction are the Soai reaction (Soai, et al., 1995), in which the amplification of a small difference in enantiomeric excess in the autocatalytic reaction product can lead asymptotically to a homochiral population, and the Viedma deracemization (Viedma, 2005), that proceeds through an autocatalytic feedback mechanism that exponentially deracemizes an initially racemic solid state to an enantiopure end state.

However, most of these theories show specific problems when they are deeply analysed. For example, the pre-existent homochiral environments need to be explained, so the solution of a problem is just moved elsewhere, e.g. to mineralogy. At the same time, chemical autocatalytic processes need to be formulated without the comfort of any direct evidence.

A way out from this problem is to use, as an autocatalytic process, one that for sure was and is constantly realized: the reproduction of living organisms.

**Biotic selection and ‘games of life’**

In 1957, G. Wald proposed a strictly biological model to explain the selection of chirality (Wald, 1957). In his paper, he provides extended evidence according to which in the alpha-helix, an essential secondary structure in all proteins, amino acids must all have the same chirality for the helix to wind efficiently and be synthesized promptly (Fig. 1 and related comment).

Therefore, according to Wald’s first hypothesis, on primordial Earth, two primitive varieties of life used proteins and enzymes, either L or D configuration. They simply coexisted in an environment that did not favour any of the two.

Wald’s second hypothesis states that one of the two life varieties became extinct relatively quickly: this means that symmetry broke during an extreme primordial era, within the most elementary forms of life. It is a biotic, not a prebiotic, mechanism.

The advantage of Wald’s biological hypothesis, over chemistry-based prebiotic selection mechanisms, lies on a peculiarity of life: the reproduction. This is a great advantage, because many mechanisms proposed by chemists for the self-reproduction of molecules involve reagents and reactions that hardly could have played that role on primitive Earth.
On the other hand, his second hypothesis is more problematic: the two forms of life were completely equivalent from the point of view of the ability to survive. If this was not the case, the cause of homochirality would be sought again from the environment and we would thus be brought back to the previously mentioned theories.

A few years ago, our research group formulated the idea that the presence of a single chiral variant of proteins and enzymes in current life forms can be caused by large random fluctuation, that helps the selective extinction (Longo and Coppola, 2013; Longo, et al., 2020).

There is a chemical-physical assumption behind this idea: the so-called ‘breakdown of the law of large numbers’ (Prigogine, 1981, in particular Chapter VI). It means that one of the fundamental laws of statistics, according to which with large numbers one gets closer and closer to the average, may not work in certain chemical reactions. In the biological case, the breakdown of the law of large numbers means that the populations of the variants do not converge to the average, but can deviate without limit, leading to the extinction of one of the two types very quickly.

Therefore, the idea in (Longo, et al., 2020) was to create a probability model that allows several replicator types (bringing L or D amino acid depending on the type) to colonize space, by taking into account both the use of chemical energy in their metabolism and the distribution of chemical energy in the environment.

The history of the first life forms is so reduced to a game with some element of randomness, that is ‘played’ by a computer with a specially created program.

The idea of studying biology as a game is not new: Manfred Eigen argued that dynamic and constructive principles of life can be simulated as board games, as long as dice are used occasionally and appropriate rules are formulated [Eigen and Winkler, 1993 (original German version, 1975)].
Therefore, on this basis, one can speak of a paradigm in the formulation of new research in biology based on the ‘games of life’ (Dewdney, 1989; Longo, 2009).

The first analysis in this direction was presented in Longo and Coppola (2013). The model was a probabilistic analysis of a classic simulation of artificial life called ‘Palmiter protozoa’. This simulation includes actors that are able to move on the game board with random changes of direction, similar to current microscopic motile life forms. They use chemical energy in a simulated metabolism and are endowed with a virtual genome, that produces different forms of life, with different behaviours. Variations of this genome are randomly introduced during cellular reproduction.

Under certain conditions, two possible types of microorganisms with opposite chirality (clockwise and counterclockwise, which is a chiral feature in a two-dimensional world) predominate. For sufficiently long simulations, only one of the two chiral types survived, the surviving one being outright random (Fig. 2): this represented a first observation of stochastic chiral selection in a life simulation with different chiral types, a description of feeding, metabolism, even genetic code and a mutation-selection mechanism.

It is important to underline that a simulation of the origin of chirality on a biological basis must be placed in the biological world: the simulation must allow variants to colonize their environment, must show that the overall population of living types remains stable, and that this happens for a sound biological reason. Only after that, it must show that one of the two types become extinct. In this way, the computer, thanks to programs based on the idea of a game, explores primordial life scenarios and allows us to gain insights into the chiral selection processes.

In the last 2 years, our research group has created several simulation programs in order to study selective extinction scenarios on the ground of population kinetics in a simulated space. These models include the description of reproduction and diffusion of these primordial replicators and, in a very simplified way, of their metabolism: the need and use of chemical energy present in the environment (Longo et al., 2020). These earliest forms of life were much probably heterotrophic (Ageno, 1971), that is, they had to feed with chemically active molecules generated by prebiotic processes, powered by solar or geochemical energy, such as sulphides, or very simple sugars.

The details of our model can be found in our previous work (Longo et al., 2020): each replicator produces a copy of itself in an adjacent position on the game board, as long as the adjacent position is empty and as long as there is sufficient energy available in the starting position; it also risks to die randomly at any time. These rules do not imply direct aggression of the two types against each other, but they compete for space and energy resources.

In the same work, the results of simulations by means of programs in Fortran language were described. These first models show that, while the total population of replicators is effectively stabilized

Fig. 2. The evolutionary Palmiter model as a model of the genesis of homochirality: one of the two chiral types colonize the source of nutrition at the centre; the other type become extinct. On the right, the interpretation of the phenomenon as instability, which randomly chooses one of the two types. Figure from (Longo and Coppola, 2013).
by the limited availability of chemical energy, selective extinction of one of the two types of the population is achieved in a short time. These preliminary studies also suggest that the spatial distribution of groupings formed by replicators of different chirality and the correlation between energy availability and populations play an important role in the selection mechanism.

Therefore, we have quantitative proof of the possibility of the selective extinction in the Wald model.

**Space and time dynamics of replicator populations**

We recently developed a set of new programs in Python: although being much slower, they allow to get in real time, during the simulation, much more detailed information in a graphical form.

These computational programs are based on the same algorithm of the Fortran programs (Longo et al., 2020). Basically, any replicator can produce a copy of itself in an adjacent position, if enough energy is available in its own square. Additionally, any replicator can die, e.g. disappear from its circle. Either events may occur randomly at any time: death is an essential process to obtain the selective event and is interpreted as an effect due to a chemical attack by species present in the environment. A ‘biological time unit’ (the unit of x-axis in Fig. 3) implies a complete scan of the game board. Chemical energy is provided randomly in form of virtual ‘monomers’, with a rate of 0.05 per square per time unit, until a maximum of three per square is reached: this energy is used by replicators in the reproduction events. The energetic cost of replication is one monomer. Replicator death may happen only if less than two monomers of chemical energy are individually available: this simulates the presence of self-repair mechanisms which lose effectiveness when nutrients are lacking. The probability of reproduction, if allowed, is 0.2 per time unit, while the probability of death is 0.075 per time unit. As already mentioned in our previous papers, these numerical values are arbitrary, but hardly editable, as the stability margin is quite narrow when just one numeric value is changed.

The more recent programs assume the closest eight positions (Moore neighbourhood) to define ‘adjacent position’, while in (Longo et al., 2020) four closest squares where assumed.
Furthermore, differently from the previous Fortran versions, the system has side boundaries, meaning that it is not periodic; the two replicator types are initially ‘seeded’ in two opposite corners of the game board and not mixed. All these aspects can be promptly changed, if necessary.

These new programs allow a comfortable observation of the dynamics of replicator populations and chemical energy in time and space: in this way, we get closer to an actual biological computer experiment, allowing the researcher to look at the evolution of the colonization of the simulated space. The perspective here is to allow the biology-oriented researcher to study the morphology and dynamics of a cell group in these biotic scenarios, without the need to understand the implementation details of the code, at least not for most of it. Several parameters, that are easily changed, provide further room for future experiments. In some cases, the limits of the available computer resources may hinder systematic investigations; however, the 1.6-thousands time units runs performed on a 20 × 20 game board, shown in the following, required just a few minutes each on good quality laptops. For statistical analysis, when the number of individual experiments is by necessity high, new Fortran implementations may become of interest, because of the higher speed obtainable.

Results are produced by snapshots of the images that the program produces on the screen. As an example, Figs. 3 and 4 show results produced by a typical run of the last version of our simulation programs, on a 20 × 20 game board, as just mentioned.

In Fig. 3, the populations of the two replicator variants engage an initial, chaotic dynamics, later they slowly diverge until one of the two types disappears. During the whole process, except in the very first phases, the total population, that is the average of the two curves, remains constant. The role played by chemical energy in stabilizing the total population is showed in the lower panel of the same figure: the chemical energy collapses during the first stages of the simulation, when the replicator number increases. Then, it stabilizes for the entire simulation, thus equilibrating the global population. This scenario is compatible with Wald’s one.

The differences between the populations of the two types of replicators are on the whole extremely persistent, even if reversal events may occur during the simulation (Fig. 3): these differences ultimately lead to selective extinction.

Fig. 4. Two stages of the simulation are shown in Fig. 3. The central circle in any square of the boards represents one of the two types (cyan or deep blue), or an empty square (white). The periphery of each square displays the available chemical energy: purple corresponds to the lowest level, green to the highest level (abundance of nutrients).
Figure 4 shows an example of the complexity of the colonization of the available space by the two, equivalent types: actually, it is a group of replicators that wins the competition, not the single replicator. This certainly does not imply that the surviving type has a ‘better strategy’, since both types play individually according to simple rules; but there is no doubt that the game played on the virtual game board leads to emerging complex patterns and trends.

The type that retains a prolonged population advantage is actually the one that occupies the game board more stably with its groups of replicators. This suggests that the spatial distribution of replicators plays an essential role. In particular, it seems that, after a threshold of population difference is exceeded, selective extinction of the minority type cannot be avoided, even if the final stage lasts for a long time (see again Fig. 3).

The complex group dynamics we observe may hardly be captured by the numerous, homogeneous, previous selection models. It would be very interesting to understand how the statistical mechanisms that leads to random selection in several homogeneous models may be ultimately related to those unfolded in two-dimensional (and possibly three-dimensional), spatially structured models, like the one employed in this paper, and in prebiotic models based on compartmentalized systems, for example with different phases in contact. One interesting perspective is that some zero-dimensional stochastic models in the literature may be considered as metamodels, or model interpretations while the object model, that is the model to which the meta-modelling is applied, is a multidimensional, relatively complex simulation of the kind presented here.

This meta-modelling operation was performed explicitly already in (Longo and Coppola, 2013): on the one hand, there was the Palmiter model of artificial life, with dozens of life forms acting in a structured environment; on the other hand, a stochastic interpretative model based on a Master Equation for local populations was used to understand the arising of anomalous fluctuations in the model.

Even if, in our research, following Wald’s work, we stick to a point of view that is as phenomenological as possible and directly linked to biology, what we observe is the result of well-characterized phenomena in the field of non-equilibrium kinetics. In particular, it is evident that autocatalysis plays a fundamental role in producing the phenomena featured by the simulations. The violation of the law of large numbers has autocatalysis in non-equilibrium phenomena as its key to interpretation.

The Wald’s hypothesis may be seen an application of Occam’s razor: the very first forms of life, however primitive, are capable of reproduction, that is a very advanced form of autocatalysis. Therefore, in the lack of any direct observational evidence of the very early phenomena, it is advantageous to place the role of autocatalysis at the level of the first forms of life, as we are certain of the existence of this type of autocatalysis on the primordial Earth.

Of course, kinetics similar to the one we show might have occurred at the pre-biotic level in the presence of autocatalysis and chemical attack.

Our simulations, demonstrating the efficiency of the Wald’s mechanism, show that if homochirality had not already established itself in a prebiotic phase, it would have been at the level of the first forms of life. Currently, we are unable to establish a detailed history of the events.

The fact that the death of a replicator occurs randomly, as well as the selection of the reproduction event and the exact location of the new replicator, makes the simulation irreversible in the thermodynamic sense. This means that it is possible to define a formal entropy that constantly increases during the evolution of the system. This increase in entropy can be a further key in understanding the observed phenomenology.

In the future, it may be fruitful to establish a relationship between different kinds of models and metamodels, that can also create a synergy between much of the literature produced on this topic.

Conclusions

The biotic-type biological chirality selection scenarios presented in this paper are very promising: they are supported by various biochemical considerations, by the substantial racemic composition of organic
molecules of extraterrestrial origin, and by the fact that they do not require a pre-existing homochiral environment or a homochiral physical effect.

In our opinion, a better comprehension of the selective extinction mechanism, that plays an essential role in these scenarios, must go through the formulation of computer simulations that try to grasp the biological aspects in wide detail.

This approach can complement research studies based on reducing the process to a physical-theoretical or mechanical-statistical mechanism inspired by relatively simple systems.

In this light, understanding the consequences of the unfolding of biological activity and the use of resources is essential. Our latest computational programs show the importance of group formation. Future studies should pursue this path, by allowing replicators, similar in morphology and function, to aggregate to form tissues. Another future topic may be to account for the chirality of organic matter released after cell death: an L type, after death, releases organic matter which may only feed another L type. This suggestion was already present in Wald’s publication.

Increasingly detailed modelling of the biological aspects of the selection mechanism can help us better understand these scenarios, in order to be able to evaluate them on a soundness basis, looking forward to experimental data, possibly provided in the future by new discoveries in paleobiology, or by the biochemistry of extraterrestrial life, even past, if finally detected.

Conflict of interest. All authors have contributed to the realization of the present paper, including computer software development, computer simulation, paper writing.

References


