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From Pasteur's molecular dissymmetry to homochirality: a brief overview

Abstract
Since the discovery of chirality in organic molecules by Pasteur in the 19th century, the emergence of homochirality in biological molecules such as DNA and proteins has puzzled generations of scientists. Although the origin of such an asymmetry is still unknown, many researchers tried to understand the mechanism behind this symmetry breaking process through experiments and theoretical approaches. This article aims at providing a brief overview of the main experimental and theoretical contributions to this research field. In addition, the author's contributions in the framework of his master thesis as well as the investigations planned in the context of his PhD thesis are presented. This article does not claim to be exhaustive and specific but rather aims at providing an introduction to this rapidly growing research field.

Key Words
Chirality, Stochasticity, Deracemization, Hydrodynamic, Numerical Simulations

Figure 1. Louis Pasteur (1822-1895), a famous french biologist and chemist. During his lifetime, he greatly contributed to the development of microbiology. He is particularly known for his discoveries on chirality as well as his pioneering work on vaccines and Pasteurization.

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1. Introduction

Our aim here is to provide the reader with a brief introduction on the fascinating question of the origins of homochirality, i.e. the property of a system composed of objects that exhibit the same chirality. First, a brief introduction about the discovery of chirality and the enigma of homochirality is presented in Sections 1.1 and 1.2. Second, the main theoretical and experimental works related to the emergence of homochirality are succinctly reviewed in Section 2. The author's contribution to this research field in the framework of his master thesis is summarized in Section 3. Finally, future works and a conclusion are featured in Sections 4 and 5.

1.1. Chirality – a breakthrough discovery of chemistry

In the 19th century, Louis Pasteur highlighted one of the most interesting features in nature known today as chirality. Since then, chirality has been a central pillar of modern chemistry and is established as an essential property that every chemist and micro-biologist should take into account.

Capitalizing on the works by Fresnel and Biot on polarized light, Pasteur deduced in 1842 the existence of a "molecular dissymmetry" from a cautious study of tartaric acid crystals exhibiting an optical activity [1]. In 1874, this optical activity was connected to the tetrahedral arrangement of the atoms bound to carbon by van 't Hoff and Le Bel [2, 3]. However, the term "chirality" was only introduced by the end of the 19th century by Kelvin [4]. At the time, he proposed the following definition:

> "*I call any geometrical figure, or group of points, "chiral", and say that it has chirality if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself.*"

In other words, an object is considered chiral when it cannot be superimposed on its image in a mirror. There are a multitude of chiral objects including molecules and galaxies, not to mention our hands. When a molecule is chiral, it will be able to exist in two different forms called enantiomers. Over time, multiple nomenclatures have been introduced to characterize chirality, causing occasionally some confusion among scientists. The original description was based on the deviation of the plane of polarization of polarized light (*d*-dextrogyre and *l*-levogyre). Another one has been proposed regarding the absolute configuration or the spatial arrangement of the compound compared to a certain reference (D/L). This later nomenclature is still commonly used by biologist to characterize sugars and amino acids. Nowadays, the most common nomenclature used by chemists is the one proposed by Cahn, Ingold and Prelog, also known as the "priority rule" or "CIP" system [5] (Rectus and Sinister).

Two enantiomers share the same chemical formula but do not have the same geometric structure. In addition, they will have different biological properties. More precisely, a cellular receptor, which is itself chiral, can discriminate between two enantiomeric molecules by interacting with the molecule of appropriate symmetry. The simplest example to understand this is to consider a pair of gloves. A right glove is suitable for a right hand, but not for a left hand.

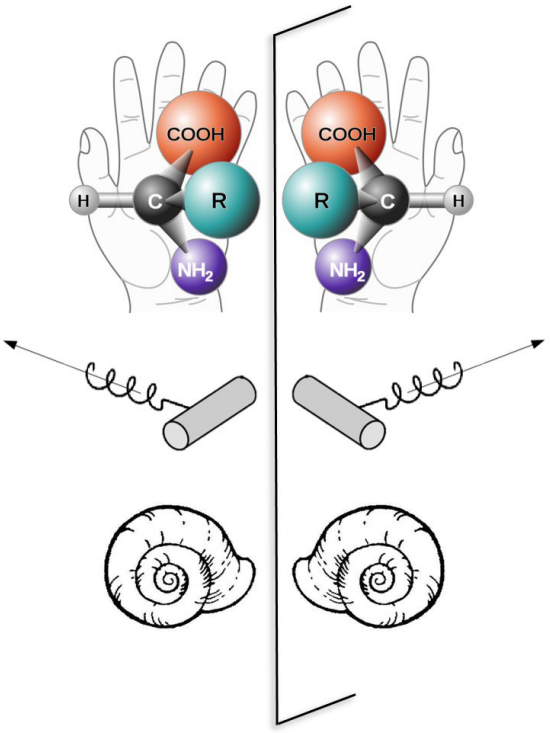

Figure 2. Illustration of various examples of chirality.

1.2. Homochirality – the new enigma of life

This preponderant role of chirality in the biological world goes back to the origins of life on earth. Indeed, nineteen of the twenty natural amino acids composing all the proteins of living things are homochiral, that is to say that they are found in a single enantiomeric form, namely, the left-handed form (Homo- from Greek "same" and -chirality derived from Kheir or "hand"). A homochiral composition is the opposite of a so-called racemic composition, in which we will find an equal distribution of the enantiomers.

Proteins are not the only macromolecules to present homochirality. Aside from its fabulous capacity of information storage, DNA exhibits the particularity to be composed almost exclusively of sugars in the right-handed form. From a chemical perspective, DNA can be considered as a polymer chain assembled from monomeric units that contain all the genetic information. Some theoretical models have been proposed to understand its growth using a stochastic approach of the underlying co-polymerisation processes. However, little attention has been paid to the chiral asymmetry and its origin.

While the focus of this research field has been initially on questions regarding the origin of homochirality in DNA and proteins, the interest has widened to numerous chemical systems. Since then, many applications have already been found such as the deracemization of organic compounds and more are expected to come in a wide variety of fields, such as polymer chemistry and self-assembled materials [6].

2. Emergence of homochirality – an asymmetric stor

Since Pasteur's works on chirality the origin of single-handedness in the biological world has remained an intriguing question. Numerous researchers tried to understand the emergence of such an asymmetry by building theoretical models. The main goal was to introduce a model presenting the amplification of a chiral state at the expense of the mirror state, leading to a homochiral system. If research was essentially theoretical at the beginning, experimental demonstrations appeared quickly, thus motivating the understanding of the underlying mechanisms.

2.1. Theoretical models for homochirality

The construction of theoretical models exhibiting the appearance of homochiral states dates back to 1953 with the description of a minimal system containing all the necessary components by Frank [7]. Frank's original model is based on an autocatalytic production and a mutual antagonism between enantiomers.

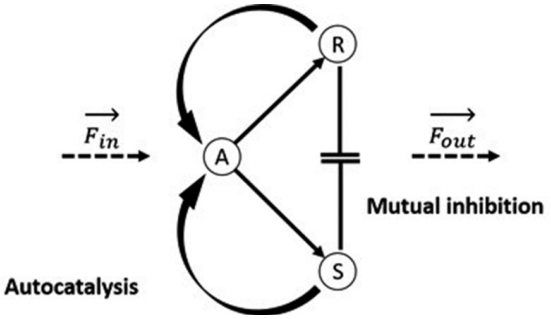

Figure 3. A relatively simple model coupling the autocatalysis with mutual antagonism between enantiomers, allowing the amplification of an enantiomeric excess until reaching a homochiral state.

This model was the first to propose a coupling between autocatalysis and symmetry breaking. By maintaining the system far from equilibrium under flow conditions, Frank's model allows a transition from a racemic state to a stable symmetry-breaking state where one or the other enantiomer is dominating beyond a certain threshold value of the matter flow parameter. Many extensions of this model have been derived, by considering, for example, a fast racemization process [8], the reversibility of reactions [9] or modifications to the mass flows [10–13].

One of the most significant modifications to Frank's model has been proposed by Kondepudi and Nelson [9]. The two main modifications were the addition of a spontaneous production of chiral products from achiral reactants and the reversibility of the production processes.

With these modifications, they demonstrated that chiral symmetry breaking may occur when the concentration of achiral reactant exceeds a certain critical concentration, resulting in the amplification of a small initial chiral bias towards homochirality.

They proposed a general equation for this symmetry breaking process which describes the evolution in time of the enantiomeric excess, α, a measure of the excess of one enantiomer compared to the other:

$$\frac{d\alpha}{dt} = -A\,\alpha^3 + B\,(\lambda - \lambda_c)\,\alpha + C\,g$$

in which A, B, C *and* λ are coefficients determined by the kinetic parameters, and g is the parameter measuring the chiral bias.

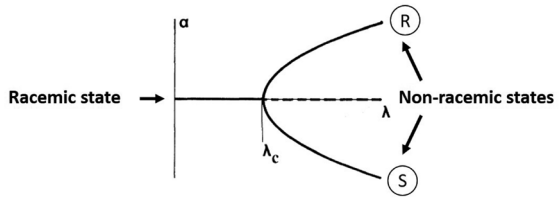

Figure 4. Chiral symmetry breaking illustrated by pitchfork-type bifurcation. Maintained out-of-equilibrium, Kondepudi's model shows a bifurcation beyond a certain critical parameter value, where the system can evolve from one racemic state to two homochiral states.

Polymers have always attracted a lot of attention due to their broad range of properties and applications. Moreover, numerous molecules essential to life are natural polymers such as DNA or proteins. It is interesting to note that the chiral properties of these biomolecules are still puzzling generations of scientist. When the possibility of chiral induction during polymerisation processes arose [14], several researchers started to study the possibility to extend the ideas from Frank's work to polymerisation reactions. To build the bridge to polymerisation processes, Sandars proposed a variation of Frank's model including polymerisation reactions [15]. Incoming reactants provide a continuous flow of chiral monomers that can be integrated in a growing chain, which leads to heterochiral chains. The larger polymers are flushed out to maintain the system open. Later, Saito proposed a similar model including the reversibility of all the steps, except for the open flow processes [16]. In Saito's model, the reverse reactions act as a correction mechanism for the growing polymer chain.

2.2. Emergence of homochirality in experimental system

The first experimental demonstrations of the emergence of homochirality were published in the early 90s. Kondepudi and Soai reported the observation of spontaneous chiral symmetry breaking in crystallization [17] and in asymmetric autocatalysis in organic chemistry [18], respectively.

In Kondepudi's experiment, stirring a solution of $NaClO_3$ under crystallization conditions resulted in spontaneous chiral symmetry breaking. $NaClO_3$ precipitates as an enantiomeric conglomerate composed of 4 sub-units and the chirality of the resulting crystals can be detected optically. It was then assumed that the effect of stirring was central, because it would make crystallization autocatalytic and thus lead to a spontaneous chiral symmetry breaking [19]. It was suggested that a secondary nucleation process was the driving mechanism behind

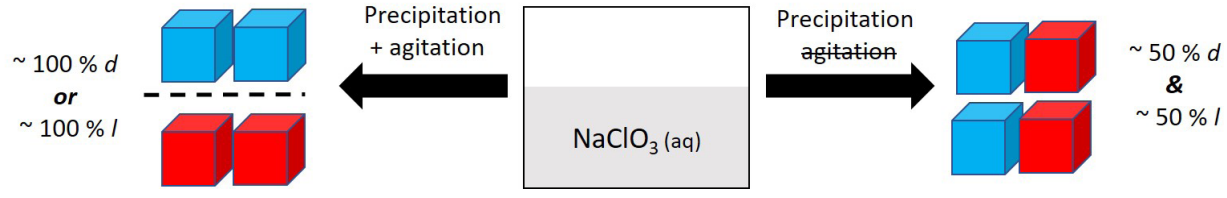

Figure 5. Illustration of Kondepudi's experimental work. When a saturated solution of Sodium Chlorate undergoes crystallisation under constant stirring, a symmetry breaking is observed in the resulting crystals. This symmetry breaking is no longer observed when the system is no longer agitated.

these results. The selection of the amplified enantiomer is arbitrary, depending on the randomly generated primary crystal.

The Soai reaction is another experimental demonstration that inspired many researchers and still attracts a lot of attention. The Soai reaction is an alkylation of aldehydes where the initial reactants A and B are achiral but the final product C is chiral. To prepare the reaction, the reactants A and B are dissolved in a solvent with a small chiral bias introduced in order to create a small imbalance. When the reaction proceeds, it manages to amplify the initial chiral bias into a non-negligible enantiomeric excess [18]. By iterating the process several times, large enantiomeric excesses close to homochirality can be obtained. One the most impressive features of this reaction is its extreme sensitivity. Indeed, Soai managed to selectively amplify one the enantiomers by using polarised light, chiral organic and mineral crystals but also, he demonstrated that chiral isotopic isomers, i.e. species having the same number of each isotope of each element but differing in their spatial arrangement, could act as chiral triggers of asymmetric autocatalysis [20].

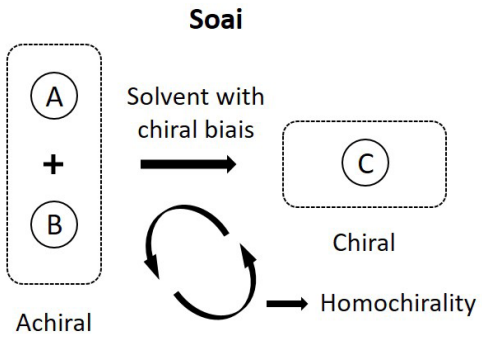

Figure 6. Starting from achiral precursors to form a chiral final product, Soai's reaction is able, after a few iterations, to amplify a small enantiomeric excess toward a homochiral composition.

Fifteen years later, Viedma was able to achieve complete deracemization of a racemic mixture of *l*- and *d*-$NaClO_3$ crystals using abrasive glass balls while stirring [21–23]. Based on these results, Viedma suggested that secondary nucleation is not the main reason behind deracemization. He suggested instead that glass balls lead to grinding, which continuously crushes the growing crystals (a phenomenon often referred to as attrition). This causes a nonlinear autocatalytic-recycling process responsible for the deracemization, which can be summarized as follows: 1) Racemization in solution (not necessary for achiral molecule crystallizing as enantiomeric clusters), 2) Ostwald ripening – the growth of large crystals at the expense of smaller ones, 3) Enantioselective incorporation of chiral clusters into larger crystals, 4) Enhancement of the Ostwald ripening by attrition.

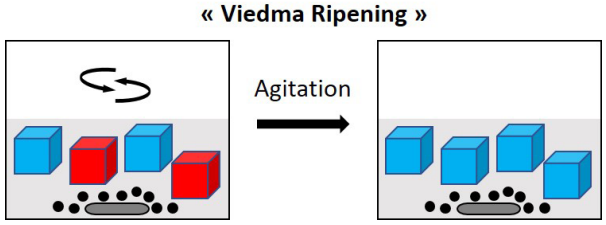

Figure 7. Illustration of the "Viedma Ripening". Glass beads (black dots) coupled to agitation continuously crush the growing crystals leading to a complete deracemization.

This so-called "Viedma ripening", was a big step for the implementation of a reliable resolution method for crystals and a true proof of concept for the special role played by nonlinearity in chiral symmetry breaking.

A few years later, Viedma *et al.* extended this procedure to intrinsically chiral molecules with the observation of a significant increase of the enantiomeric excess for a proteinogenic amino acid. More generally, the Viedma ripening has found many applications [23] such as the complete deracemization of pharmaceutical molecules [23–25], the total resolution of metal complexes [26, 27] or the enantioenrichement in organic chemistry reactions from chiral or achiral compounds [28–33].

To investigate the effect of grinding, Uwaha and Katsuno proposed a theoretical model which evaluates the influence of the size distribution of the chiral clusters [34]. They showed that in absence of grinding, for an appropriate size distribution, the chirality conversion can be obtained through a slow Ostwald ripening. With grinding, the initial asymmetric distribution of

chiral clusters can be rapidly amplified, leading to a homochiral state [35].

Grinding and stirring are not the only ways to achieve deracemization. Indeed, El-Hachemi *et al.* demonstrated that a temperature gradient can be sufficient to induce a strong enantiomeric excess [36]. A supersaturated solution of $NaClO_3$ was boiled following a distillation process where water was constantly removed. The reflux system was supposed to be determinant during the nucleation process.

In 2011, Viedma and Cintas pushed forward the effect of temperature gradients by reporting a complete deracemization from a boiled racemic mixture of *l*- and *d*-$NaClO_3$ crystals [37]. To obtain complete deracemization, the solution is simply heated with a hot plate at the bottom of the flask. A random distribution of the final chirality is obtained through repeated experiments, showing again the arbitrary character of the selection process. In the same study, it was also shown that the effect of the temperature gradient can be cancelled by stirring the solution.

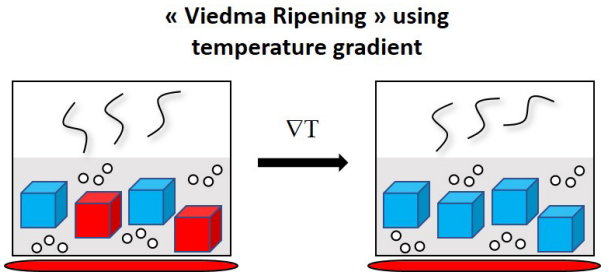

Figure 8. Illustration the "Viedma Ripening", using a vertical temperature gradient.

Coquerel *et al*. extended this concept using heating cycles to better understand the results from Viedma and Cintas [38]. In addition to an experimental demonstration, they conducted mathematical modelling, which suggests that a difference in the crystal growth kinetics can cause chiral symmetry breaking [39]. The bubbling and the hydrodynamic flows generated by the temperature gradient were suspected to be involved in the deracemization process, but no definitive conclusion has been reached yet.

2.3. Microscopic description of homochirality

The large number of works regarding the emergence of homochirality has been succinctly reviewed in the previous paragraphs. Among these contributions, many theoretical models have been proposed to study the emergence of homochirality. Most of them rely on a so-called "macroscopic" approach. Such an approach consists in developing deterministic evolution equations that allow the prediction over time of the evolution of the collective quantities of a system such as, for example, the concentrations of different chemical species.

From a completely different perspective, "microscopic" theoretical models have been proposed to understand the growth of homochiral molecules. Unlike a macroscopic approach, a microscopic approach will try to integrate the role of processes involving individual molecules. Since these processes take place at random (they are stochastic processes), this type of approach can be qualified as probabilistic, in opposition to the determinism of macroscopic theories.

In this framework, Kondepudi and Nelson wanted to apply this probabilistic description to the chiral symmetry breaking processes. During their study on the influence of weak neutral currents on the chiral symmetry breaking process [40], they also proposed a mesoscopic approach of the transition that occurs between a racemic state and a homochiral state. Indeed, the general equation used is a Langevin equation which takes into account the stochastic character of the system's dynamics.

More specifically, they were interested in predicting the probability with which the system evolves toward one of the two homochiral states when the value of a control parameter λ exceeds a certain threshold λ_c. To do so, they started from a Fokker-Planck equation in order to describe the evolution of the probability to have a certain chiral asymmetry α:

$$\frac{\partial}{\partial t}P(\alpha,t) = -\frac{\partial}{\partial t}[-A\,\alpha^3 + B\,(\lambda(t)-\lambda_c)\,\alpha + C\,g\,]P(\alpha,t) + \left(\frac{\epsilon}{2}\right)\frac{\partial^2}{\partial t^2}P(\alpha,t)$$

where $P(\alpha,t)$ is a probability density function quantifying the probability that the chiral asymmetry takes the value alpha at time t. Using this equation, they derived an expression for the selection probability to have a certain homochiral state which depends on the initial distribution of α.

From a different perspective, Gaspard has been working on a stochastic description of co-polymerisation processes [41, 42]. These pioneering studies paved the road toward a new approach to co-polymerisation. Indeed, previous studies were considering fully irreversible growth regimes where a monomer is attached to the end of the growing co-polymer but its detachment was neglected [43, 44]. Moreover, these works were essentially following a macroscopic description of the co-polymerisation. His first paper on the subject was mainly motivated by the understanding of the influence of a detachment rate comparable to the attachment rate on the growth of a co-polymer [41]. The central assumption of his study was to consider that these rates only depend on the last monomeric unit present at the tip of the chain. Using this assumption and from the ensuing kinetics, he demonstrated that a co-polymer chain undergoing such a growth mechanism was exactly following the behaviour of a first-order Markov chain, thus allowing him to derive some thermodynamic features like the entropy production or the affinity associated to the growth process. Since it has been shown that the growth of DNA can be associated to the same kind of attachment-detachment process [45]. Afterwards, he extended his study to another particular case where the rates do not depend on the last monomeric unit. A co-polymer undergoing such a growth mechanism is called a Bernoulli chain. Later, he pushed forward his study by generalising the growth to a k^{th}-order Markov chain where the k last monomeric units influence the attachment-detachment rates [42].

3. Stochastic behaviour of copolymerisation processes

As described in the previous section of this overview, numerous theoretical models have been proposed to investigate the emergence of homochirality in various chemical systems among different research fields such as crystallization processes, organic chemistry, and polymerisation reactions.

However, the connection between the microscopic growth mechanisms of chiral macromolecules (such as DNA) and the corresponding macroscopic properties has not yet been elucidated. Motivated by this unresolved question, the author's master thesis aimed to clarify this link by proposing a new approach to chiral copolymerisation processes. To do this, a new model has been proposed involving different growth mechanisms of a chiral chain from achiral monomers.

3.1. A new model for co-polymerisation processes

The model can be briefly summarized as follows: (i) An achiral monomer A is adsorbed on an activated site and adopts a certain conformation R or S as a result of the adsorption process, (ii) this species becomes an initiator site with which a new achiral monomer A will be able to react. Similar to the initial adsorption, the newly attached monomers become chiral as a consequence of the addition reactions. The combination of these two processes leads to the gradual growth of the polymer chain with different enantiomeric compositions. All the processes involved are considered fully reversible.

Inspired by Gaspard's works, two distinct growth mechanisms have been investigated: 1) A first mechanism in which the addition of a monomer is totally arbitrary, referred to as "Bernoulli's growth" and 2), a second mechanism where the activated chiral monomer at the growing tip of the polymer chain favors the addition of a monomer with the same chirality, referred to as "Markov's growth".

During the master thesis, the corresponding macroscopic behaviors have been studied through the construction and numerical integration of evolution equations describing the evolution in

time of the enantiomeric composition. Then, a more microscopic description has been used to evaluate the distribution of probability associated to each growth mechanism. Finally, stochastic simulations have been performed using Gillespie's algorithm to compare the results with the prediction from the previous analysis.

3.2. Importance of the description scale

First, it has been shown that the macroscopic description, which remains the most common approach for these kinds of problems, can provide misleading information about the chirality of the resulting polymers. Our microscopic description has made it possible to demonstrate that certain mechanisms lead to a population of racemic chains (50% of R monomers and 50% of S monomers in each chain), while others give rise to two equivalent populations of homochiral polymers. (100% of R or 100% of S in each chain). The macroscopic approach, which only concerns the average of the population, does not make it possible to distinguish these two cases which are intrinsically different in terms of chirality. It is therefore not, in this sense, a relevant tool for detecting the emergence of homochirality.

3.3. Fluctuation-driven growth

The microscopic approach revealed that polymers can grow even when the macroscopic approach predicts that they cannot. This growth is due to the presence of fluctuations in the rates of the processes, which are a signature of the deeply probabilistic character of the dynamics of the system. It is observed for all the mechanisms considered and is probably universal. Such growth would be possible thanks to the free energy associated with the gain of configurations accessible by a growing chain. Indeed, the entropy associated to the variability of the chains' composition might contribute to the driving force (the *affinity*) of the growth process. This has already been suggested during the analysis of general fluctuating co-

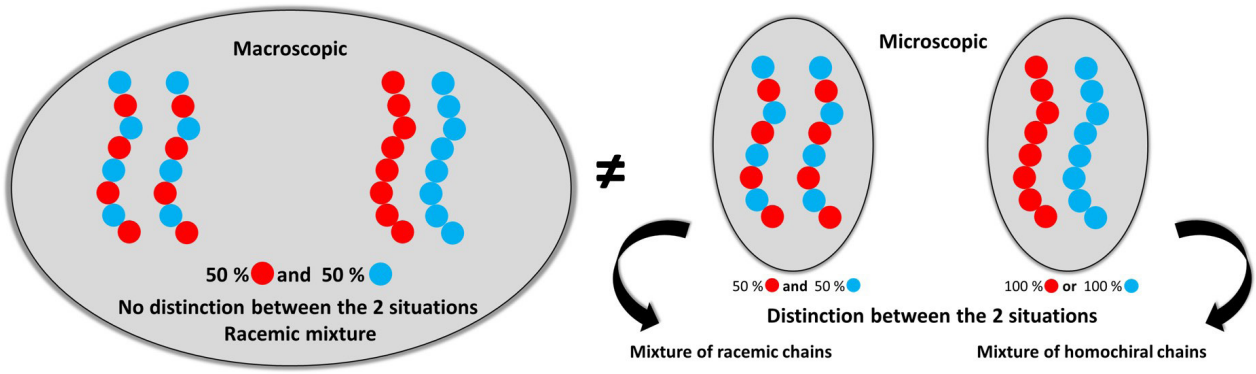

Figure 9. Schematic representation of the importance of description scale.

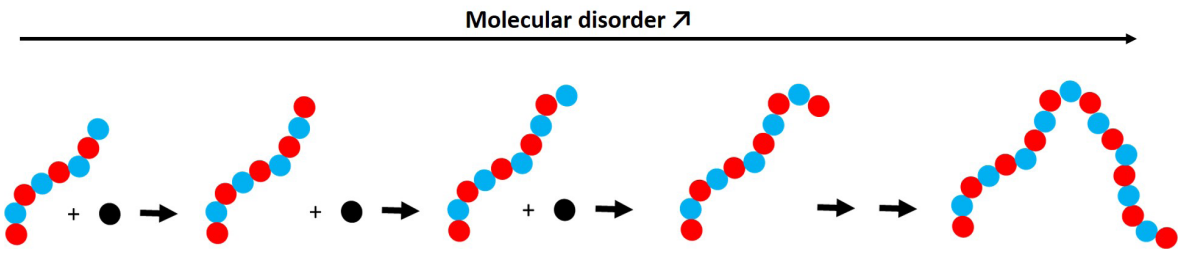

Figure 10. The gradual addition of monomers increases the number of possible configurations of the chain and thus, its entropy.

polymerisation processes [46]. In their study, Andrieux and Gaspard showed that the rate of entropy production during for the growth of a co-polymer obeys the relation:

$$\frac{1}{k_b}\frac{d_i S}{dt} = v\mathcal{A} = v\,(\varepsilon + D) \geq 0$$

where v is the mean velocity, ε is the free-energy parameter per monomer and D, the Shannon parameter, which measures the disorder in the chain due to its growth. Thus, it would seem that the quest for "disorder" is an engine for the growth of such polymer chains.

3.4. Formation of homochiral oligomers

A new path towards the formation of small homochiral polymers has been demonstrated by our stochastic approach. Certain growth mechanisms give rise to polymers which are racemic, but composed of long homochiral segments. The recombination of such segments could give rise to long homochiral polymers, such as those observed in the living world. These results may open new horizons for understanding the emergence of homochiral molecules essential to life, such as DNA or proteins.

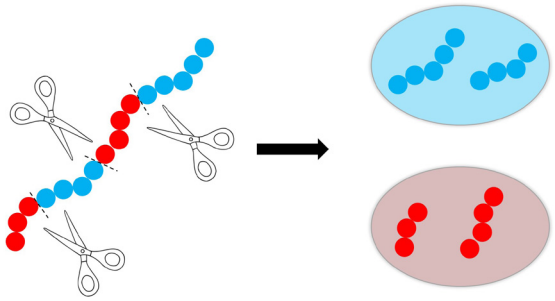

Figure 11. Homochiral segments can be isolated as homochiral oligomers.

4. Hydrodynamics & homochirality – a new pathway to chiral amplification?

Inspired by the experiments mentioned in this overview, numerous theoretical models have been developed to understand the underlying mechanisms but none of these explicitly considers the effect of transport phenomena such as diffusion or natural convection. However, as highlighted by Viedma's work, it is fair to suspect that these processes are involved in the amplification mechanism.

Thanks to a F.R.S-FNRS funding, the author has the opportunity to explore this last hypothesis during his thesis under the supervision of Pr. Laurence Rongy and Pr. Yannick De Decker, from the Université libre de Bruxelles.

The main aim of this recently started thesis is to investigate the effect of transport phenomena on the amplification of an enantiomeric excess toward homochirality. More precisely, the influence of diffusion, advection and hydrodynamic instabilities on the selection and the amplification of a chiral state will be investigated. Kinetic reaction-diffusion-convection simulations will be performed in order to (i) assess the importance of different transport phenomena on the amplification of an enantiomeric excess, and (ii) reproduce key experimental results of the literature and provide new experimental perspectives for the deracemization of chiral compounds. The effect of temperature and heat of reaction, as well as the role of transport phenomena on the attrition-decomposition of chiral clusters, will also be investigated.

In such a way, chemical processes of high interest such as the emergence of homochirality near submarine hot springs in the early instants of life on earth, enantioselection during organic synthesis or homochiral self-assembled materials could be studied with a realistic theoretical approach that includes transport phenomena. From another perspective, microscopic extensions could be considered regarding the possible stochastic behaviours behind the symmetry breaking process.

5. Conclusion

As illustrated in this overview, chirality and homochirality have not revealed all their secrets yet. The emergence of single-handedness in nature is still an enigma which continues to puzzle many scientists. This research field shows once more that interdisciplinary scientific collaboration is the key to move forward.

Theoretical works along experimental evidences feed each other to provide insights regarding the unsolved questions surrounding us.

The interested reader can find additional information in some of the most recent reviews on the subject [6, 13, 47].

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