Stochastic Fluctuations and Chiral Symmetry Breaking: Exact Solution of Lente Model†

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The stochastic description for the autocatalytic process has been proposed by Lente (*J. Phys. Chem. A* **2004**, *108*, 9475) to demonstrate chiral symmetry breaking. He assumed that the number of reacting molecules is macroscopic and that no products are present initially. The Lente model consisting of a finite number of molecules that may include the product molecules as chiral seeds is explored and the characteristics of stochastic distributions of the product are examined. It is shown that the presence of racemic product in the substrate reduces the possibility of chiral symmetry breaking while a few more molecules of a specific enantiomer added can yield chiral dominance for strong autocatalysis. Besides, small reactive volumes or dense reactant concentrations have a preference for chiral symmetric breaking.

The origin of biological homochirality has been a challenging problem since Pasteur observed that life is driven by asymmetry 160 years ago.[1] There are two kinds of tentative answers to this question. One is deterministic, and the other is of accidental interpretation. The advocates of a deterministic explanation believe that the chirality of biomolecules are prescribed with the known physical laws. Actually, the parity violation effect (PVE) causes energy difference and stability thereof between the two enantiomers of one chiral molecule.[2] Although the effect is very weak, it might be amplified through certain physical mechanisms in a long time evolution.[3] The other viewpoint is that the chirality the biomolecules possess is a result of random selection. An immediate problem then is how such a selection or the mirror symmetry breaking would take place. Once the handedness is generated, its preserving and propagating to form the biological homochirality is of course another problem.

Many theoretical and experimental investigations have been carried out to understand the biological homochirality.[2−4] More than 50 years ago, Frank proposed a kinetic model in which both autocatalysis and mutual antagonism are two essential properties to yield spontaneous asymmetric synthesis.[5] About 30 years later, Kondepudi and co-workers explored the possibility of chiral symmetry breaking in nonequilibrium systems and analyzed how the weak PVE can be amplified.[3] An important observation in experiments was also made by Kondupudi and co-workers who found that stirring a supersaturated sodium chlorate solution or a supercooled melted binaphthyl results in crystals with a dominant enantiomorph in almost each experiment.[6] Although these and other experiments clearly show the mirror symmetry breaking, they are not genuine chemical processes because there is neither formation nor cleavage of chemical bonds. A breakthrough was not made until Soai and co-workers discovered the so-called Soai reaction that is an asymmetric autocatalytic reaction in which the chiral product pyrimide alkanol is obtained from the reaction between pyrimidine carbaldehyde and diisopropylzine.[7] It was observed that a few thousands molecules are sufficient to control the enantiomeric outcome of the reaction.[8]

Several kinetic models were suggested for chiral symmetry breaking in crystallization and Soai reaction,[6,9] but the proposed mechanisms are far from conclusive. Recognizing the particulate feature of molecules, Lente put forward a stochastic model to explain the chiral symmetry breaking in autocatalytic reactions.[10] He considered the case where no chiral product exists at the beginning of the reaction and used the cumulative distribution function as the quantity for experimental verification. In fact, when the number of molecules becomes small, the deterministic theory of chemical kinetics is no longer valid, and the stochastic theory characterizing the indeterministic behavior for the individual molecules should be used to describe the dynamical processes. An extreme example is a prochiral reaction with one reactant molecule in the container. Without any chiral influences, the very one molecule produced must randomly choose a specific configuration between its two enantiomers. One may think that as the number of molecules becomes macroscopic, the racemic product is most dominant. This, as shown in ref 10 is only true when the autocatalysis is very weak and asymmetric outcomes are the most probable for sufficiently strong autocatalysis.

The stochastic model needs to be further explored. In particular, because it is the particulate feature of molecules that makes the chemical reactions intrinsically stochastic, to reveal the interplay between the number of molecules the presence of chiral product and the symmetry breaking, which has not been examined in ref 10, is desired. To this end, we define direct statistical measures for experiments and analyze how the initial product molecules control the chiral yields. We start with the prochiral reaction with autocatalysis, which is well described by the following steps[10]

$$A \xrightarrow{k_1} \frac{1}{2} B_R + \frac{1}{2} B_S \tag{1a}$$

$$A + B_R \xrightarrow{k_2} 2B_R \tag{1b}$$

$$A + B_S \xrightarrow{k_2} 2B_S \tag{1c}$$

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Here the change of concentrations of the three reacting components $[A]$, $[B_R]$, and $[B_S]$ obeys the conventional kinetic equations, namely $d[A]/dt = -k_1[A] - k_2[A]([B_R] + [B_S])$ and $d[B_{R,S}]/dt = 0.5k_1[A] + k_2[A][B_{R,S}]$. Solving the differential equations with the initial conditions $[A]_0$, $[B_R]_0$, and $[B_S]_0$, one readily obtains the enantiomeric excess (ee)

$$\mathrm{ee} = \lim_{t\to\infty} \frac{[B_R] - [B_S]}{[B_R] + [B_S]} = \frac{[B_R]_0 - [B_S]_0}{[B]_0} \frac{1 + k'/[C]_0}{1 + k'/[B]_0}$$

where $k' = k_1/k_2$, $[B]_0 = [B_R]_0 + [B_S]_0$ is the initial concentration of the product and $[C]_0 = [A]_0 + [B_R]_0 + [B_S]_0$ is the total concentration of all three components, a conserved quantity in the reaction. Obviously, when $[B_R]_0 = [B_S]_0$, the product is racemic. It is also clear that the final product always has a smaller ee value than that of the initially added product.[11] What will happen if the reactions take place in a stochastic rather than deterministic manner?

As discussed by many researchers, it is advantageous to regard chemical reactions as stochastic processes for the number of reacting molecules.[12] To be specific, the basic quantity of interest is now the probability that one component possesses a certain number of molecules instead of the concentration. In this way the traditional kinetic equation are "converted" to the corresponding master equation,[10,12] namely

$$\frac{1}{\kappa_1}\frac{dP(r,s,t)}{dt} = -a[1+\alpha(r+s)]P(r,s,t) + (a+1)\{[0.5+\alpha(r-1)]P(r-1,s,t) + [0.5+\alpha(s-1)]P(r,s-1,t)\} \quad (2)$$

where $P(r, s, t)$ denotes the probability that there are r molecules of B_R and s molecules of B_S at time t, a is the number of A molecules, and $\alpha = \kappa_2/\kappa_1$ is the parameter characterizing the autocatalysis. Note that the total number of all molecules $n = a + r + s$ is a constant during the reaction. Here the parameters κ_1 and κ_2 are related to the rate constants k_1 and k_2 through $\kappa_1 = k_1$ and $\kappa_2 = k_2/(N_A V)$ where N_A is the Avogadro's constant and V is the volume of the container. In the stochastic picture, the probability that more than one reaction takes place in an infinitesimal time is assumed to be negligible. The master equation can readily be solved by invoking the Laplace transform $\mathscr{P}(r, s, \omega) = \mathscr{L}\{P(r, s, t)\}$ and the result is

$$\mathscr{P}(r,s,\omega) = \frac{a+1}{\frac{\omega}{\kappa_1} + a[1+\alpha(r+s)]} \times \{[0.5+\alpha(r-1)]\mathscr{P}(r-1,s,\omega) + [0.5+\alpha(s-1)\mathscr{P}(r,s-1,\omega)]\} \quad (3)$$

Let the reaction start with r_0 molecules of B_R, s_0 molecules of B_S, and a_0 molecules of A. Thus, there are $P(r_0, s_0, 0) = 1$ and $P(r, s, 0) = 0$ for $r \neq r_0$ or $s \neq s_0$. Note that $P(r, s, t) = 0$ for $r < r_0$ or $s < s_0$. One obtains from eq 2 $P(r_0, s_0, t) = e^{-a_0\kappa_1[1+\alpha(r_0+s_0)]t}$ and $\mathscr{P}(r, s, \omega) = 1/\{\omega + a_0\kappa_1[1 + \alpha(r_0 + s_0)]$. This condition allows us to work out the explicit form of $\mathscr{P}(r, s, \omega)$, that is,

$$\mathscr{P}(r,s,\omega) = \frac{a_0!(\bar{r}+\bar{s})!}{a!\bar{r}!\bar{s}!} \frac{\prod_{j=r_0}^{r-1}(0.5+\alpha j)\prod_{k=s_0}^{s-1}(0.5+\alpha k)}{\kappa_1\prod_{j=r_0+s_0}^{r+s}\left[\frac{\omega}{\kappa_1} + (1+\alpha j)(n-j)\right]} \quad (4)$$

where $\bar{r} = r - r_0$ and $\bar{s} = s - s_0$ are the number of produced B_R and B_S molecules, respectively. This expression can readily be transformed back to $P(r, s, t)$ by using Heaviside's formula. Because we are interested in the final distribution of the product, we only need to calculate $\tilde{P}(r, s) \equiv \lim_{t\to\infty} P(r, s, t)$. In this case, all molecules of A are used up to produce either B_R or B_S, that is, $n = r + s$, which yields

$$\tilde{P}(r,s) = \binom{n-r_0-s_0}{r-r_0} \frac{\prod_{j=r_0}^{r-1}(0.5+\alpha j)\prod_{k=s_0}^{s-1}(0.5+\alpha k)}{\prod_{j=r_0+s_0}^{n-1}(1+\alpha j)} \quad (5)$$

where $\binom{n-r_0-s_0}{r-r_0} = (n - r_0 - s_0)!/(r - r_0)!(n - r - s_0)!$ is the binomial coefficient. By virtue of Euler's formula for the gamma function and the definition of beta function, we may recast the final probability distribution as

$$\tilde{P}(r, n-r) = \binom{n-r_0-s_0}{r-r_0} \frac{B(r+\delta, n-r+\delta)}{B(r_0+\delta, s_0+\delta)} \quad (6)$$

where $B(p,q)$ denotes the beta function and $\delta = 0.5/\alpha$ measures the propensity of no autocatalysis. This can be viewed as a discrete beta distribution. For an autocatalysis-free reaction $\alpha = 0$ or $\delta \to \infty$, there yields $\tilde{P}(r, s) = \binom{n-r_0-s_0}{r-r_0} 0.5^{r-r_0} 0.5^{n-r-s_0}$, a binomial distribution that the probability of producing a B_R or B_S molecule from an A molecule is equal (50%) as it should be.

Now the number r of B_R molecules or $(2r - n)/n$, the ee value defined by the concentration difference of the two enantiomers, can be regarded as a random number. Therefore, the quantities of experimental relevance are the average $\langle \mathrm{ee} \rangle = 2\langle r \rangle/n - 1$ and the standard deviation $D_{ee} = \sqrt{\langle \mathrm{ee}^2 \rangle - \langle \mathrm{ee} \rangle^2}$. A tedious yet straightforward algebra gives

$$\langle \mathrm{ee} \rangle = \frac{2}{n}\sum_{r=r_0}^{n-s_0} r\tilde{P}(r, n-r) - 1 = \frac{1}{n}\frac{(n+2\delta)(r_0-s_0)}{(r_0+s_0+2\delta)} \quad (7)$$

and

$$D_{ee} = \frac{2}{n}\sqrt{\langle r^2 \rangle - \langle r \rangle^2} = \frac{2}{n(r_0+s_0+2\delta)} \times \left[\frac{(n+2\delta)(n-r_0-s_0)(r_0+\delta)(s_0+\delta)}{r_0+s_0+2\delta+1}\right]^{1/2} \quad (8)$$

Obviously, D_{ee} measures the difference in ee of an individual experiment trial from the average. We first consider the possibility of spontaneous symmetry breaking (SSB). In this case, no net chiral seeds are available at the beginning of the reaction, which means $r_0 = s_0$. Equation 7 gives a zero mean of the ee value. In other words, the total outcome of the product

for many tests is racemic. Now, from eq 8 the standard deviation of the ee reads

$$D_{ee} = \frac{1}{n}\left[\frac{(n+2\delta)(n-2r_0)}{2r_0+2\delta+1}\right]^{1/2} \tag{9}$$

It is clear that D_{ee} is never vanishing for $n > 2r_0$. As a consequence, it seems that SSB is a rule rather than an exception. Of course, a genuine SSB corresponds to $D_{ee} = 1$, the maximum of the standard deviation. In this case, each experiment will produce a pure enantiomer.[13] D_{ee} is in general a monotonically decreasing function of r_0 and δ (for $n > 2r_0 + 1$). For the autocatalysis-free reactions ($\delta \to \infty$), one obtains $D_{ee} = \sqrt{n-2r_0}/n$ or $1/\sqrt{n}$ for $n \gg r_0$, which is negligible for macroscopic systems. This may be the reason why SSB is in general not a common phenomenon. For extremely autocatalytic reactions ($\delta = 0$), however, eq 9 becomes

$$D_{ee} = \left[1 - \frac{2r_0}{2r_0+1}\left(1+\frac{1}{n}\right)\right]^{1/2}$$

which becomes unity for $r_0 = 0$, corresponding to SSB in each experiment. Note that D_{ee} drops rapidly to a small value as r_0 increases. In other words, the presence of a racemic product initially with the substrate is very detrimental to the realization of SSB.

For $r_0 = 0$ and $n \to \infty$, which may be thought of as the general conditions for reactions, the standard deviation is $D_{ee} = (2\delta + 1)^{-1/2} = k_2^{1/2}(k_1 N_A V + k_2)^{-1/2}$. This simple relation between the standard deviation D_{ee} and the size V of the dynamical system can be used in the analysis of experimental data to verify if the mechanism described by eq 1a−c operates in the dynamics. It is not surprising that SSB is more easily found as the size of the system becomes smaller. The experimental results available[6,14,15] in literature are consistent with this observation.

For induced symmetry breaking requiring $r_0 \neq s_0$, the mean of the ee value in eq 7 can be recast as

$$\langle ee \rangle = \Delta_0\left(\frac{1}{2\delta}+\frac{1}{n}\right)\frac{ee_0}{\frac{\Delta_0}{2\delta}+ee_0}$$

where $\Delta_0 = r_0 - s_0$ is the difference in number of the enantiomers and $ee_0 = (r_0 - s_0)/(r_0 + s_0)$ is the initial ee value. It should be stressed that this result is similar to that from the deterministic kinetic equation. As there is no nonlinear effect, one rigorously obtains $ee < ee_0$, that is, chiral amplification is impossible. In real reactions, $n \gg 1$, which allows us to approximately have $\langle ee \rangle = ee_0/(1 + 2\delta ee_0/\Delta_0)$. When the autocatalysis is strong, therefore, a few more molecules of a specific enantiomer was added, namely, a large Δ_0, results in $\langle ee \rangle \approx ee_0$.

To summarize, we have studied the Lente model in a general case and have derived the exact expression for the mean and standard deviation of the ee value for the chiral product. It is observed that racemic product added in the reaction is detrimental to chiral symmetry breaking while the presence of chiral seeds helps enantioselectivity. The relationship between the standard deviation D_{ee} of the ee value and the size of the system V, namely, $D_{ee} = (2\delta + 1)^{-1/2} = k_2^{1/2}(k_1 N_A V + k_2)^{-1/2}$, is also worked out, which is consistent with intuition and might be readily tested by experiments.

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$$\lim_{t\to\infty}\frac{[B_R]-[B_S]}{[B_R]+[B_S]}\frac{[C]_0}{[B_R]_0-[B_S]_0} = 1+\frac{[A]_0}{[B]_0+k'}$$

for $[B_R]_0 \neq [B_S]_0$, which is unity when there is no autocatalysis or $k_2 = 0$.

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