

Stochastic aspects of asymmetric autocatalysis and absolute asymmetric synthesis

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Abstract The main goal of the present review is to collect in a unified framework the deterministic and stochastic models of emergence and amplification of chirality by mechanisms such as asymmetric autocatalysis and absolute asymmetric synthesis. Empirical approach and modeling have recently provided a good insight into these phenomena. Our groups in Italy and Hungary have a wide variety of expertise both in fields of experiments and modeling. In the last decade important results have been achieved, however, more experiments and more detailed deterministic and stochastic models are needed for a better understanding of details and significance of asymmetric autocatalysis and absolute asymmetric synthesis.

Keywords Chirality · Autocatalysis · Stochastic kinetics · Markovian jump process · Multimodality · Deterministic kinetics · Polynomial differential equations

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1 Introduction

Chirality (see 2.1) is an important structural feature of organic molecules. Such molecules form two isomeric forms, called enantiomers. The preparation of pure enantiomers is a highly actual problem of chemistry.

The elaboration of such methods requires a detailed understanding of the relevant reaction mechanisms. One of the most popular and efficient ways for exploring reaction mechanisms is chemical kinetics (the study of concentration changes as function of time in course of the reaction).

In the history of studying this question it turned out that the usual **deterministic** models of chemical reaction kinetics fail to answer all the emerging questions, in many cases essential help is obtained from the **stochastic** description which in its most often used standard form takes into consideration both the inherent randomness of chemical reactions and also the discrete nature of matter.

It is interesting to note that early reaction kinetics started with the analysis of chirality. The first quantitative kinetic measurements were made by Wilhelmy [158], who studied the rate of inversion of cane sugar in presence of acids. He showed conclusively that the rate of change at any moment is directly proportional of the cane sugar present at the time. Later, Guldberg and Waage [52] gave a more precise quantitative meaning to these and similar results.

The structure of our review is as follows. First, we introduce the relevant phenomena, such as chirality, autocatalysis, bistability and bimodality. Then we formulate the deterministic model of reaction kinetics which we shall use throughout as a starting point and as a reference. We apply this model to simple common examples and also to the formal reactions introduced to study chirality. As the stochastic models are much less known we give a very short and terse introduction into the theory of stochastic processes mainly to be able to formulate the stochastic models of reaction kinetics. Here emphasis is laid upon the standard continuous time, discrete state stochastic model: a Markovian pure jump process. Having the tool, we write down the evolution equations for the most often used reactions, such as the Frank model and its modifications. At the end we collect the most important knowledge on the stochastic aspects of asymmetric autocatalysis and absolute asymmetric synthesis, and formulate open problems as well.

2 Phenomena

Let us consider the following formal chemical reaction

$$\sum_{m=1}^M \alpha(m, r) X(m) \longrightarrow \sum_{m=1}^M \beta(m, r) X(m) \quad (r = 1, 2, \dots, R), \quad (1)$$

where $M, R \in \mathbb{N}$; $\alpha, \beta \in \mathbb{N}_0^{M \times R}$, and $\alpha = (\alpha(m, r))$, $\beta = (\beta(m, r))$ are the matrices of **stoichiometric coefficients**. What we are interested in at the most general level is the quantity (concentration or number of molecules) of the species $X(m)$ either as a function of time or in the stationary state, i.e. on the long run. (Concrete examples can be found in Subsection 3.1 and below.)

2.1 Chirality

Chirality is a **geometric** feature of molecular structure: chiral molecules are different from their specular images [105]. This feature can be due to the spatial order of bonding between atoms or in the relative position of groups of atoms in molecules. The former is linked to the **configuration** of molecules (configurational chirality), while the latter is a consequence of the molecular **conformation** (conformational chirality). The two specular forms are called **enantiomers**. Transformation of configurational enantiomers in each other needs the breaking and re-making of chemical bonds (or equivalent processes), while in the case of conformational enantiomers this needs only rotations around some bonds. As a consequence configurational enantiomers are generally more stable than conformational ones.

The fact that enantiomers are differing only in their orientations in 3D space results, that interatomic distances in these species are strictly equal and therefore their energies are also equal with the exception of the contribution of the asymmetry of weak nuclear forces (WNF). According to the present state of our knowledge the WNF contribution is negligible. As a consequence of this situation there is no energy driven priority for the formation of one or other enantiomer if such chiral molecules are prepared from achiral precursors. In mathematical terms one can say, that the **formation probability of enantiomers is strictly equal**. This fundamental feature of chiral molecules is known since more than a century [110].

The energetic equivalence of enantiomers raises two very important problems. One of these is of theoretical nature and is linked to the fact that all terrestrial living organisms are using exclusively or in overwhelming excess only one form of chiral molecules in these organisms (“biological chirality” [67, 107, 108]. The origin of this phenomenon is one of the most prominent challenges of biochemistry today. The other problem is of highly practical nature: in chemical industry (pharma, polymers, etc.) it would be highly desirable to prepare pure enantiomers from achiral precursors. Such syntheses are today realized by using asymmetric physical fields (e.g. circularly polarized light) or chiral additives (“auxiliaries”). For several practical reasons it would be very important to realize these syntheses without these “helping hands”. Such synthesis, called **absolute asymmetric synthesis**, would be the dream of all preparative chemists working on the synthesis of pure enantiomers of chiral molecules. For the moment only two examples of such synthesis are known, the addition of dialkylzinc compounds to *N*-heterocyclic aldehydes, (alkylation of *N*-heterocyclic (pyrimidyl) aldehydes by diisopropyl zinc) the Soai reaction [133–142], and the preparation of a chiral cobalt(III) complex *cis*-[CoBr(NH₃)(en)₂]²⁺, from the reaction of trinuclear mixed valence [Co(H₂O)₂]{(OH)₂Co(en)₂}⁴⁺ with NH₄Br in aqueous solution [6].

It has been shown recently, that absolute asymmetric synthesis by the Soai reaction is inherently linked to the stochastic behavior of the first few molecules in the achiral to chiral transformation leading to high enantiomeric excesses without any chiral additive or application of any asymmetric physical field [9–11].

The stochastic aspects of the Soai synthesis will be discussed in detail later in the present review.

The energy (and formation probability) equivalence of enantiomers leads to the formation of 1:1 mixtures of the two forms in achiral to chiral transformations. These mixtures, called **racemates**, were fairly neglected by chemical literature as “undesired” products. One should realize, however, that racemates are not achiral chemical substances, in the strictest sense of the word, but only (physical) mixtures of two asymmetric molecule kinds. This again leads to important stochastic considerations and requires a re-evaluation of the concept of racemates [21, 109]. The stochastic problems emerging from the modern view of racemates will be also discussed later in this review.

We emphasize that we are interested in the **dynamics** of chirality, even if we speak about the stationary state or stationary distribution of a process, and not in the structural description of static chirality, i.e. not in analyzing the geometric form of the molecules themselves, which is, however, an important topic in itself, see e.g. [79] and also the papers in [95].

2.2 Autocatalysis

There are a lot of definitions of autocatalysis. Bazsa and Beck [15] has collected and presented a few heuristic definitions. According to Blackmond [17] autocatalysis is present if the reaction products serve as catalyst to produce more of themselves.

Supercatalysis: autocatalysis of order higher than 1 [101].

An appropriate definition should not be based on a specific, say, deterministic or standard stochastic model, but on the mechanism of the reaction.

2.3 Multi- and bistability

The deterministic model of the simplest reactions have the property that there is a single stationary state (concentration vector), and no matter how the reaction starts, the concentration vs. time functions finally evolve to this stationary state: one has an asymptotically stable stationary state. In the last decades, more complex phenomena were discovered and investigated, such as oscillation, chaos, spatial patterns, in one word **exotic phenomena** [39, 116]. Of all these interesting phenomena we are here interested in cases where more than one stationary state exists, and depending on the initial concentration one or the other enantiomer can be attained: this is the case of multistability, see e.g. [112, 123].

Hou and Xin [59] show a specific example that internal noise can induce chemical oscillations in a parameter region subthreshold to deterministic oscillatory dynamics. Coupling may enhance the effects. Such systems are highly relevant to the evolution of enantiomeric excess without physical or chemical auxiliary.

2.4 Multimodality

If one has a stochastic model (of any kind) then chirality can be formulated by having a probability distribution or probability density function which has two maxima,

corresponding to each of the enantiomers. Sufficient conditions for multimodality of the stationary distribution in the standard stochastic model has been given by Érdi et al. [40]. The questions are: How such a multimodal (time dependent or stationary) distribution emerges, survives, how can it be characterized etc. A fundamental reference on multimodality is [93].

Definition 1 The distribution $\{p_n\}_{n \in \mathbb{Z}}$ is said to be **unimodal** (at a) if $n \mapsto p_n - p_{n-1}$ becomes negative for the first time at $a + 1$. The point (a, p_a) is the **peak** of the graph of the distribution.

A few conditions to ensure uni- or multimodality in the standard stochastic model of reactions have been given in [58]. Even the definition is not trivial in the multispecies case.

3 Models

3.1 The mass action type deterministic model of homogeneous reaction kinetics

Usually functions $w_r \in C^1(\mathbb{R}^M, \mathbb{R})$ called **kinetics** are given to represent the reaction rate of the r th reaction step. With all these data the induced kinetic differential equation of the reaction (1) is

$$\dot{c}_m(t) = f_m(\mathbf{c}(t)) := \sum_{r=1}^R (\beta(m, r) - \alpha(m, r)) w_r(\mathbf{c}(t)) \quad (m = 1, 2, \dots, M), \quad (2)$$

where $c_m(t)$ is the concentration of $X(m)$ at time t : $c_m(t) := [X(m)](t)$. Sometimes we are also interested in the initial value problem related to this equation. The most important special case is the case of **mass action type kinetics** when we have

$$w_r(\bar{\mathbf{c}}) = k_r \prod_{p=1}^M \bar{c}_p^{\alpha(p,r)} = k_r \bar{\mathbf{c}}^{\alpha(\cdot, r)} \quad (\mathbf{w}(\bar{\mathbf{c}}) = \text{diag}(\mathbf{k}) \bar{\mathbf{c}}^\alpha = \mathbf{k} \otimes \bar{\mathbf{c}}^\alpha) \quad (3)$$

with the positive numbers k_r , ($r = 1, 2, \dots, R$) called **reaction rate coefficients**. (The operation \otimes denotes the product taken by coordinates.)

Example 1 Consider the simple inflow $O \longrightarrow X$. Here $M = R = 1$, $\alpha = 0$, $\beta = 1$, $\mathbf{k} = \lambda$. The mass action type induced kinetic differential equation of this reaction is:

$$\dot{x} = \lambda. \quad (4)$$

Example 2 Consider the first order irreversible autocatalytic reaction $X \longrightarrow 2X$. Here $M = R = 1$, $\alpha = 1$, $\beta = 2$, $\mathbf{k} = (k_1, k_2)$. The mass action type induced kinetic differential equation of this reaction is:

$$\dot{x} = k_1 x - k_2 x. \quad (5)$$

Example 3 Consider the second order (or: quadratic) irreversible autocatalytic reaction $2X \longrightarrow 3X$. Here $M = R = 1$, $\alpha = 2$, $\beta = 3$, $\mathbf{k} = k$. The mass action type induced kinetic differential equation of this reaction is:

$$\dot{x} = kx^2 \quad (6)$$

having the property that the maximal solution blows up in a finite time [32].

Example 4 Consider the well-known Michaelis–Menten reaction $E + S \longleftrightarrow C \longrightarrow P$. Here $M = 4$, $R = 3$, $\mathbf{k} = (k_1, k_{-1}, k_2)$, and

$$\alpha = \begin{bmatrix} 1 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 1 \\ 0 & 0 & 0 \end{bmatrix} \quad \beta = \begin{bmatrix} 0 & 1 & 0 \\ 0 & 1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix}.$$

The mass action type induced kinetic differential equation of this reaction is (see [96], [39] p. 178):

$$\begin{aligned} \dot{e} &= -k_1 es + k_{-1}c & \dot{s} &= -k_1 es + k_{-1}c \\ \dot{c} &= +k_1 es - (k_{-1} + k_2)c & \dot{p} &= +k_2c \end{aligned}$$

Example 5 Consider the Gray model [88] with second order autocatalysis: $A + B \longrightarrow 2B$, $B \longrightarrow 0$, $A \longleftrightarrow 0 \longleftarrow B$. Here $M = 2$, $R = 5$, $\mathbf{k} = (k_1, k_2, v, va_0, v)$, and

$$\alpha = \begin{bmatrix} 1 & 0 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 \end{bmatrix} \quad \beta = \begin{bmatrix} 0 & 0 & 0 & 1 & 0 \\ 2 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

The induced kinetic differential equation of this reaction is:

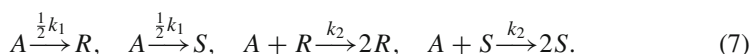
$$\dot{a} = v(a_0 - a) - k_1 ab \quad \dot{b} = k_1 ab - (k_2 + v)b.$$

3.1.1 Bistability in the deterministic model

Usual beliefs on bi- and multistationarity and oscillation in deterministic models are critically analyzed in [150].

3.1.2 Deterministic models of chirality

The simplest model comes from [42], see also [73, 80, 85, 130]. Here we present it in a slightly different way (having in mind the stochastic model):



The induced kinetic differential equation to describe this reaction is

$$a' = -k_1a - k_2a(r + s), \quad r' = \frac{k_1}{2}a + k_2ar, \quad s' = \frac{k_1}{2}a + k_2as \quad (8)$$

with the initial conditions

$$a(0) = a_0, \quad r(0) = r_0, \quad s(0) = s_0. \quad (9)$$

As one has $a(t) + r(t) + s(t) = a_0 + r_0 + s_0$, the system can easily be solved to get

$$\begin{aligned} a(t) &= \frac{a_0k_3}{k_2a_0 + (k_3 - k_2a_0)e^{k_3t}} \\ r(t) &= k_3 \left(\frac{k_1}{2k_2} + r_0 \right) \frac{e^{k_3t}}{k_2a_0 + (k_3 - k_2a_0)e^{k_3t}} - \frac{k_1}{2k_2} \\ s(t) &= k_3 \left(\frac{k_1}{2k_2} + r_0 \right) \frac{e^{k_3t}}{k_2a_0 + (k_3 - k_2a_0)e^{k_3t}} - \frac{k_1}{2k_2} \end{aligned}$$

with $m_0 := a_0 + r_0 + s_0$, $k_3 := k_1 + k_2m_0$. Therefore the stationary enantiomeric excess can be calculated as

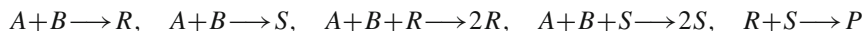
$$\lim_{t \rightarrow +\infty} \frac{r(t) - s(t)}{r(t) + s(t)} = \frac{(r_0 - s_0)(k_2(a_0 + r_0 + s_0) + k_1)}{(a_0 + r_0 + s_0)(k_1 + k_2(r_0 + s_0))} \quad (10)$$

while Shao and Liu [130] gives the result with a slight error:

$$\lim_{t \rightarrow +\infty} \frac{r(t) - s(t)}{r(t) + s(t)} = \frac{(r_0 - s_0)(k_2(a_0 + r_0 + s_0) + k_1)}{(r_0 + s_0)(k_1 + k_2(r_0 + s_0))}. \quad (11)$$

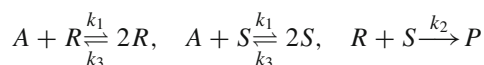
However, their final qualitative conclusion (see also [73, 104]) is correct: the stationary enantiomeric excess is always smaller than the initial one. To put it in another way: autocatalytic reaction (7) is unable to amplify the enantiomeric excess according to the deterministic model Figs. 1, 2.

Kondepudi and Nelson [72] introduces a more complicated model



which is also used by Markó [89]. Markó also states (without explicit calculations) that starting from small equal initial conditions the quantities of the two enantiomers remain the same for very long times. However, starting from larger initial concentrations small differences will be amplified and a stable stationary state with different quantities emerges.

The deterministic model of the seemingly simple reaction [144]



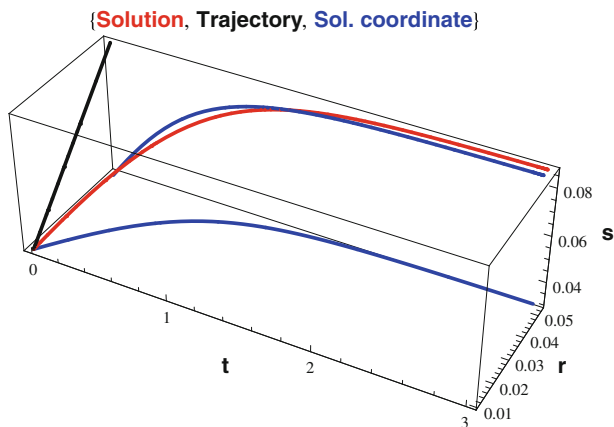
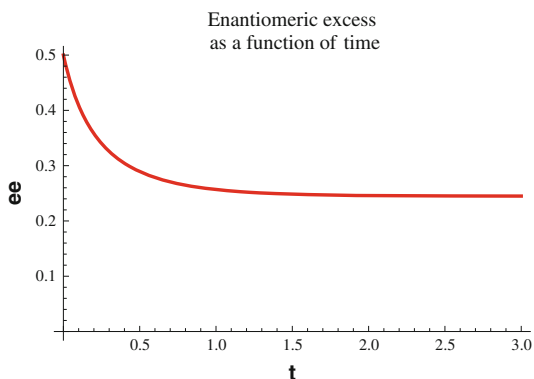


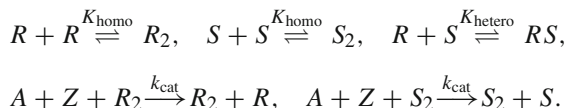
Fig. 1 Solution, coordinate functions and trajectories of the simplest Frank model (7). $k_1 = 1, k_2 = 10, a_0 = 0.1, r_0 = 0.01, s_0 = 0.03$

Fig. 2 Enantiomeric excess in the Frank model (7). Data are the same as in Fig. 1



does not seem to be symbolically solvable. However, as a and $a + r + s$ are monotonously decreasing and bounded from below they have a limit as $t \rightarrow +\infty$. Numerical calculations also suggest that the concentration vs. time curves behave in a similar way as in the model (7), still enantiomeric excess in this reaction might increase. More precisely, as Gutman [53] put it, three distinct time-evolutions of the modified Frank model can occur, one in which both S and R completely disappear from the system, another leading to complete monochirality, and a third resulting in a racemic final state.

The reaction proposed by Blackmond [17, 18] is even more complicated, although much less (neither symbolically, nor numerically, only intuitively, using traditional arguments of **quasistationarity**) analyzed in detail:



She also defines enantiomeric excess in a slightly different way: $ee(t) := \frac{r_2(t) - s_2(t)}{r_2(t) + s_2(t) + rs(t)}$. She emphasizes the importance of catalytic effects of dimers, and obtains quite a good agreement with experimental data. $a(0) = 0.2$, $z(0) = 0.4$, $K_{\text{dimer}} := \frac{K_{\text{hetero}}}{K_{\text{homo}}} = 4$.

Finally we mention here that [98] constructed a simple model to show bistability, and fitted it to the data obtained by the Soai group.

3.2 Stochastic processes

Almost all relevant definitions can be found in Wikipedia, but a relatively easy-to-read classic summary is [60].

3.2.1 Definition of stochastic processes

Definition 2 A **stochastic process** is a collection of random variables $\{X(t), t \in T\}$ defined on the same probability space. The set T is called its **parameter set**, its elements usually represent time, whereas the **state space** \mathbf{S} is the set of possible outcomes of the stochastic process.

Definition 3 The mapping $t \mapsto X(t, \cdot)$ defined on the parameter set T , is called a **realization** or the **sample path** of the process. (The name **trajectory** is also used, but it may cause misunderstanding, because in the case of deterministic models this term is used differently.)

3.2.2 Time and state space

Stochastic processes can be divided into four categories depending on

- whether the values assumed by the time parameter are discrete or continuous.
- whether the values assumed by the random variables are discrete or continuous,

According to these, the categories are as follows:

DDS: Discrete time, discrete state stochastic processes If the values of the time parameter are discrete (i.e. they belong to a finite or to a countable set), and the assumed parameter values t_i , ($i = 1, 2, \dots$) form an increasing sequence, then $\{X(t_i)\}$ is called a **random sequence**. If the process is Markovian (see point 3.2.3) and the state space is discrete, then it is said to be a **Markov chain**.

CDS: Continuous time, discrete state stochastic processes Here $X(t)$ assumes only discrete values as above, and the time parameter assumes a continuous range of values in $(-\infty, +\infty)$. If the process is Markovian, it is called a **continuous time Markov chain**. The standard stochastic model of reactions belongs to this class, with \mathbb{R} as the set of times, and \mathbb{N}^M as the set of states, where M is the number of chemical species.

DCS: Discrete time, continuous state stochastic processes In this case, $X(t)$ assumes a continuous range of values and t assumes discrete values. If the process is Markovian, it is called a **discrete time Markov process**.

CCS: *Continuous time, continuous state stochastic processes* In this process, both $X(t)$ and t assume continuous ranges of values. If the process is Markovian, it is called a **continuous time Markov process**.

3.2.3 Nature of determination

Stationary processes A stochastic process is called a **stationary process** if the joint probability distributions do not change when shifted in time. Formally, let $X(t)$ be a stochastic process and let $F_{X_{t_1}, \dots, X_{t_k}}(x_{t_1}, \dots, x_{t_k})$ represent the cumulative distribution function of the joint distribution of $X(t)$ at times t_1, \dots, t_k . Then, $X(t)$ is said to be stationary if, for all k , τ , and for all t_1, \dots, t_k ,

$$F_{X_{t_1}, \dots, X_{t_k}}(x_{t_1}, \dots, x_{t_k}) = F_{X_{t_1+\tau}, \dots, X_{t_k+\tau}}(x_{t_1}, \dots, x_{t_k}). \quad (12)$$

Weakly stationary processes A weaker form of stationarity is known as **weak sense stationarity**, **wide-sense stationarity** (WSS) or **covariance stationarity**. This only requires that the 1st and 2nd moments do not vary with respect to time. Any strictly stationary process which has a mean and a covariance is also weakly stationary.

Independent processes A discrete space, discrete time stochastic process or a random sequence $\{X_n\}$ is an **independent process** if the joint density function can be written as a product of the density functions of each variable X_n , ($n = 1, 2, \dots$):

$$f_{X_1, \dots, X_n}(x_1, \dots, x_n; t_1, \dots, t_n) = f_{X_1}(x_1; t_1) \cdots f_{X_n}(x_n; t_n). \quad (13)$$

White noise process A random vector \mathbf{X} is said to be a **white random vector** if its mean vector and autocorrelation matrix are the following:

$$\mathbb{E}\{\mathbf{X}\} = \mathbf{0} \quad R_X = \mathbb{E}\{\mathbf{X}\mathbf{X}^\top\} = \sigma^2 \mathbf{I}. \quad (14)$$

That is, it is a zero mean random vector, and its autocorrelation matrix is a multiple of the identity matrix. When the autocorrelation matrix is a multiple of the identity, we say that it has **spherical correlation**. A continuous time random process $\mathbf{X}(t)$ where $t \in \mathbb{R}$ is a **white noise process** if its mean function and autocorrelation function satisfy the following:

$$m_{\mathbf{X}}(t) := \mathbb{E}\{\mathbf{X}(t)\} = \mathbf{0} \quad R_{\mathbf{X}}(t_1, t_2) = \mathbb{E}\{\mathbf{X}(t_1)\mathbf{X}(t_2)^\top\} = \frac{N_0}{2} \delta(t_1 - t_2). \quad (15)$$

i.e. $\mathbf{X}(t)$ is a zero mean process and has infinite power at zero time shift since its autocorrelation function is the Dirac delta function.

Processes with independent increment Let us denote again a continuous time stochastic process by $X(t)$. The increments of such a process are the differences $X(s) - X(t)$ between its values at different times $t < s$. To call the increments of a process independent means that increments $X(s) - X(t)$ and $X(u) - X(v)$ are independent

random variables whenever the two time intervals $[t, s]$ and $[v, u]$ do not overlap and more generally, any finite number of increments assigned to pairwise non-overlapping time intervals are mutually (not just pairwise) independent.

Markov processes We start to discuss the Markov processes with the simplest case: the discrete time, discrete state processes, usually called Markov chains.

DDS Markov chains

Definition 4 The sequence of random variables $X_1, X_2, \dots, X_n, \dots$ form a **Markov chain** if for every n ($n = 1, 2, \dots$) the random variables satisfy the following equation:

$$P(X_n = j | X_1 = i_1, X_2 = i_2, \dots, X_{n-1} = i_{n-1}) = P(X_n = j | X_{n-1} = i_{n-1}). \quad (16)$$

It means that the probability of the state at time n depends only on the state at time $n - 1$ and does not depend directly on the former states: future depends on the past only through present. Usually we say that the Markov chain has no memory. The probabilities $p_{ij} = P(X_n = j | X_{n-1} = i)$ are called the **one step transition probabilities**. These tell us what is the probability of the Markov chain going from the state i into the state j in one step. In the special case when the one step transition probabilities do not depend on n the Markov chain is called **(time-)homogeneous**.

We can define the **m -step transition probabilities** in the homogeneous case as follows:

$${}^n p_{ij}^m = P(X_{n+m} = j | X_n = i). \quad (17)$$

From now on we speak only about homogeneous Markov chains, then we can use the shorter notation p_{ij}^m for the m -step transition probabilities.

One can easily prove from (16) Markov property that

$$p_{ij}^m = \sum_k p_{ik}^{m-l} p_{kj}^l \quad (m = 2, 3, \dots) \quad (18)$$

for any l such that $0 < l < m$. Equation (18) is a special case of the Chapman–Kolmogorov equation, see (22) for the case when time is restricted to change discretely.

Consider a homogeneous Markov chain with a finite state space. The transition probability distribution can be represented by a matrix, called the **transition probability matrix**: $\mathbf{P} = [p_{ij}]$. Since each row of \mathbf{P} sums to one and all elements are non-negative, \mathbf{P} is a **(right) stochastic matrix**. If the Markov chain is time-homogeneous, then the transition matrix is the same after each step, so the k -step transition probability can be calculated as the k -th power of the transition matrix, \mathbf{P}^k .

A probability distribution π is called a **stationary distribution** if it satisfies the equation $\pi = \pi \mathbf{P}$. In other words, the stationary distribution π is a normalized (meaning that the sum of its entries is 1) left eigenvector of the transition matrix associated

with the eigenvalue 1. Alternatively, π can be viewed as a fixed point of the linear (hence continuous) transformation on the unit simplex associated to the matrix \mathbf{P} . As any continuous transformation on the unit simplex has a fixed point, a stationary distribution always exists, but it is not guaranteed to be unique, in general. However, if the Markov chain is irreducible and aperiodic (see page 13), then there is a unique stationary distribution. Additionally, in this case \mathbf{P}^k converges to a rank-one matrix in which each row is the stationary distribution, that is, $\lim_{k \rightarrow +\infty} \mathbf{P}^k = \mathbf{1}\pi$, where $\mathbf{1}$ is the column vector with all entries equal to 1, and a dyadic product can be seen on the right hand side.

State j is said to be **accessible** from state i (written $i \rightarrow j$) if a system started in state i has a non-zero probability of passing into state j at some point. Formally, state j is accessible from state i if there exists an integer $n > 0$ such that $P(X_n = j | X_0 = i) = p_{ij}^n > 0$. A Markov chain is said to be **irreducible** if it is possible to reach any state from any state.

A state i has period k if any return to state i must occur in multiples of k time steps. Formally, the period of a state is defined as $k = \gcd\{n : P(X_n = i | X_0 = i) > 0\}$ (where \gcd is the greatest common divisor). Note that even though a state has period k , it may not be possible to reach the state in k steps. For example, suppose it is possible to return to the state in $\{6, 8, 10, 12, \dots\}$ time steps; then k would be 2, even though 2 does not appear in this list.

If $k = 1$, then the state is said to be **aperiodic**, i.e. it returns to state i can occur at irregular times. Otherwise ($k > 1$), the state is said to be **periodic with period k** . A Markov chain is said to be **aperiodic** if all its states are aperiodic.

A state i is said to be **transient** if, given that we start in state i , there is a non-zero probability that we will never return to i . Formally, let the random variable T_i be the **hitting time**, i.e. the first (earliest) return time to state i : $T_i = \inf\{n \geq 1 : X_n = i | X_0 = i\}$. Then, state i is transient if and only if $P(T_i = +\infty) > 0$. If a state i is not transient (it has a finite hitting time with probability 1), then it is said to be **recurrent** or **persistent**. Even if the hitting time is finite, it needs not have a finite expectation. Let M_i be the expected return time, $M_i := \mathbb{E}\{T_i\}$. Then, state i is **positive recurrent** if M_i is finite; otherwise, state i is **null recurrent** (the terms **non-null persistent** and **null persistent** are also used, respectively).

It can be shown that a state is recurrent if and only if $\sum_{n=0}^{+\infty} p_{ii}^n = +\infty$. An irreducible Markov chain has a stationary distribution if and only if all of its states are positive recurrent. In that case, $\pi := (\pi_1, \pi_2, \dots)$ is unique and is related to the expected return time: $\pi_i = \frac{1}{M_i}$. Further, if the chain is both irreducible and aperiodic, then for any i and j , $\lim_{n \rightarrow +\infty} p_{ij}^n = \frac{1}{M_j}$. Note that there is no assumption on the starting distribution; the chain converges to the stationary distribution regardless of where it begins. Such π is called the **equilibrium distribution** of the chain.

A state i is called **absorbing** if it is impossible to leave this state. Therefore, the state i is absorbing if and only if $p_{ii} = 1$ and $p_{ij} = 0$ for $i \neq j$.

A state i is said to be **ergodic** if it is aperiodic and positive recurrent. If all states in a Markov chain are ergodic, then the chain is said to be **ergodic**. It can be shown that a finite state irreducible Markov chain is ergodic if its states are aperiodic.

Now, we reformulate the definition (16) for continuous time, discrete state Markov processes as follows.

CDS Markov processes

Definition 5 A stochastic process $\{X(t)\}_{t \in \mathbb{R}}$ is a **continuous time Markov process** if for every $t_1 < t_2 < \dots < t_{n+1}$ the equation

$$P(X(t_{n+1}) = j | X(t_1) = i_1, X(t_2) = i_2, \dots, X(t_n) = i_n) \quad (19)$$

$$= P(X(t_{n+1}) = j | X(t_n) = i_n) \quad (20)$$

holds, where n is a positive integer.

One can recognize that Eq. (19) is similar to Eq. (16), thus many properties of the continuous time Markov process is similar to the Markov chain. From now on we restrict our investigations to continuous time, discrete state Markov processes, and we also assume that the states of the processes can only be natural numbers. (This is not so with the applications, however.)

Let τ_i denote the time that the process spent in the state i . According to the Markov property (19) it does not depend on the past of the process, so we can write:

$$P(\tau_i > s + t | \tau_i > s) = h(t) \quad (21)$$

where $h(t)$ only depends on the remaining (present and future) time t and not on the past time s . The only continuous probability distribution which satisfies the Eq. (21) is the exponential distribution. This is called as the **memorylessness property** of the Markov process. (In the discrete time case requirement (21) leads to the geometric distribution.)

Evolution Equations for CDS Markov Processes

Chapman–Kolmogorov Equation We have already defined the probability of m -step transition (17) for a homogenous Markov chain. One can define for non-homogenous Markov chain as follows: $p_{ij}(m, n) = P(X_n = j | X_m = i)$. In a similar way we define the transition probability for the continuous time Markov chain: $p_{ij}(s, t) = P(X(t) = j | X(s) = i)$. It means that the process is in the state $X(t)$ at epoch t and $s \leq t$. From this expression one can derive the **Chapman–Kolmogorov equation**:

$$p_{ij}(s, t) = \sum_k p_{ik}(s, u) p_{kj}(u, t) \quad (i, j = 0, 1, 2, \dots) \quad (22)$$

Let us define the transition probability matrix: $\mathbf{H}(s, t) := [p_{ij}(s, t)]$, and let $\mathbf{H}(t, t) = \mathbf{I}$ be the identity matrix. Using this notation the (22) Chapman–Kolmogorov equation becomes

$$\mathbf{H}(s, t) = \mathbf{H}(s, u) \mathbf{H}(u, t) \quad s \leq u \leq t. \quad (23)$$

If the transition probabilities satisfy some continuity conditions then they also satisfy a certain system of differential equations, of which the first one is the Kolmogorov forward equations.

Kolmogorov Forward Equation We get these equations from the (22) Chapman–Kolmogorov equation if we follow the probability of the trajectory starting from the state i at the epoch s through the state k at the epoch t to the state j at the epoch $t + h$. The continuity conditions are as follows.

1. For every state j there exist functions $t \mapsto c_j(t) \geq 0$ such that

$$\lim_{h \rightarrow 0} \frac{1 - P(t, t + h, j, j)}{h} = c_j(t) \text{ for every } t \geq 0. \quad (24)$$

2. For every pair of states j and k , $j \neq k$ and for all epoch t there exist continuous functions $t \mapsto q_{jk}(t)$ such that

$$\lim_{h \rightarrow 0} \frac{P(t, t + h, j, k)}{h} = c_j(t)q_{jk}(t) \quad (j \neq k), \quad (25)$$

where the functions c_j are the same as in (24). Furthermore,

$$\sum_k q_{jk}(t) = 1 \quad \text{and} \quad q_{jj}(t) = 0 \text{ for every } t \geq 0.$$

3. In the condition (25) convergency is uniform in k for every fixed j and epoch $t \geq 0$.

Theorem 1 (Kolmogorov forward equations) *If the transition probabilities*

$$P(s, t, i, j) := P(X(t) = j | X(s) = i)$$

of the CDS Markov process $X(t)$ $t \geq 0$ with states $1, 2, \dots$ satisfy the three conditions above, then

$$\frac{\partial P(s, t, i, j)}{\partial t} = -c_j(t)P(s, t, i, j) + \sum_k P(s, t, i, k)c_k(t)q_{k,j}(t). \quad (26)$$

Kolmogorov Backward Equation To derive the Kolmogorov backward equations we need two conditions, similar to (24) and (25):

1. For every state j there exist functions $t \mapsto c_j(t) \geq 0$ such that

$$\lim_{h \rightarrow 0} \frac{1 - P(t - h, t, j, j)}{h} = c_j(t) \text{ for every } t \geq 0. \quad (27)$$

2. For every pair of states j and k , $j \neq k$ and for all epoch t there exist continuous functions $t \mapsto q_{jk}(t)$ such that

$$\lim_{h \rightarrow 0} \frac{P(t-h, t, j, k)}{h} = c_j(t)q_{jk}(t) (j \neq k), \quad (28)$$

where the functions c_j are the same as in (27). Furthermore,

$$\sum_k q_{jk}(t) = 1 \text{ and } q_{jj} = 0 \text{ for every } t \geq 0.$$

Notice that here we do not need a third condition.

Theorem 2 (Kolmogorov backward equations) *If the transition probabilities of the CDS Markov process $X(t)$ $t \geq 0$ satisfy the conditions (27)–(28), then*

$$\frac{\partial P(s, t, i, j)}{\partial s} = c_s(t)P(s, t, i, j) - \sum_k P(s, t, k, j)q_{i,k}(s). \quad (29)$$

Master equation Let us introduce the **absolute probabilities** $P_i(t) := P(X(t) = i)$ of a CDS Markov process, i.e. the probabilities for the system to be in the state i . Although these quantities do not describe fully the time evolution of a stochastic process, still these are very often the most preferred characteristics of CDS Markov processes, especially in physical and chemical applications. An easy consequence of the Kolmogorov backward equations follows.

Theorem 3 (Master equation) *Under the conditions (27)–(28) we have*

$$\frac{dP_i(t)}{dt} = \sum_j q_{ij}(t)P_j(t), \quad (30)$$

where the matrix q_{ij} is filled with a grid of transition rates (**infinitesimal transition probabilities**).

Note that because $\sum_i q_{ij}(t) = 0$ (i.e. probability is conserved), therefore the equation may also be written as

$$\frac{dP_i(t)}{dt} = \sum_j (q_{ij}(t)P_j(t) - q_{ji}(t)P_i(t))$$

allowing us to omit the term $j = i$ from the summation. Thus, in the latter form of the master equation there is no need to define the diagonal elements of q .

Let us see a few special cases of Markov processes with continuous time and discrete state space.

Example 6 (Birth-and-Death Process) Let us suppose that a population with size i the probability of one birth approximately $\lambda_i h$ and the probability of one death approximately $\mu_i h$ during a short period of time h . The size of the population is a *birth-and-death process*. More precisely,

Definition 6 A continuous time Markov chain $X(t) \geq 0$ is a **birth-and-death process** with parameters $\lambda_0, \lambda_1, \dots$ and μ_0, μ_1, \dots if the transition probabilities satisfy the following conditions:

$$\begin{aligned} P(t, t+h, i, i+1) &= \lambda_i h + o(h), \\ P(t, t+h, i, i-1) &= \mu_i h + o(h), \\ P(t, t+h, i, i) &= 1 - (\lambda_i + \mu_i)h + o(h), \text{ and} \\ P(t, t+h, i, j) &= o(h), \text{ if } j \neq i, \text{ and } j \neq i \pm 1, \quad h \rightarrow 0. \end{aligned} \quad (31)$$

Because the birth-and-death process is a special CDS Markov process one can get the special form of the master equation. If $P_n(t)$ stands for the probability of the process in the state n at time t then

$$\begin{aligned} P'_0(t) &= -\lambda_0 P_0(t) + \mu_1 P_1(t) \text{ and} \\ P'_n(t) &= -(\lambda_n + \mu_n)P_n(t) + \lambda_{n-1}P_{n-1}(t) + \mu_{n+1}P_{n+1}(t) \text{ if } n \geq 1. \end{aligned} \quad (32)$$

Similarly we can write the Kolmogorov backward equation:

$$P'(t, i, j) = -(\lambda_i + \mu_i)P(t, i, j) + \lambda_i P(t, i+1, j) + \mu_i P(t, i-1, j). \quad (33)$$

Example 7 (Poisson Process) A continuous time discrete state process $N(t)$ is called **Poisson Process** if it satisfies the following three properties:

1. It starts at zero: $N(0) = 0$.
2. It has independent, stationary increments.
3. For every $t > 0$, $N(t)$ is a Poisson random variable with parameter λt :

$$P(N(t) = n) = \frac{(\lambda t)^n}{n!} e^{-\lambda t}, \quad n = 0, 1, 2, \dots \quad (34)$$

First of all it is easy to see that the Poisson process is a pure birth process i.e. if

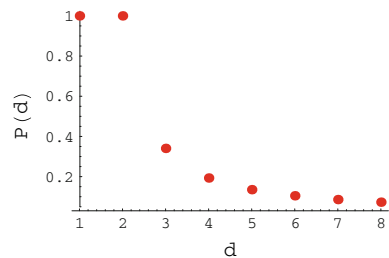
$$\lambda_i = \lambda \text{ and } \mu_i = 0 \text{ for } i = 0, 1, 2, \dots$$

then Eq. (32) reduces to:

$$P'_n(t) = -\lambda(P_n(t) - P_{n-1}(t)). \quad (35)$$

The solution of Eq. (35) is exactly given by (34).

Fig. 3 Return probability of a d -dimensional random walk as a function of d



Example 8 (Random walk) Let us denote by G^d the points of a d -dimensional lattice. Position of a point at time $t = n$ denoted by S_n^d . The point changes its position such that one of its coordinate will be changed by ± 1 with probability $\frac{1}{2d}$ and all the other $d - 1$ coordinates remain unchanged.

If X_k^d stands for the shift in the time interval $(k - 1, k)$ then

$$S_n^d = S_0^d + \sum_{k=1}^n X_k^d.$$

The X_k^d are independent identically distributed random variables hence S_n^d is a Markov process.

Theorem 4 [115] Let $P(d)$ be the probability that a random walk on a d -dimensional lattice returns to the initial position. Then, $P(1) = P(2) = 1$ but $P(d) < 1$ for any $d \geq 3$. Moreover, the probability that a random walk on a d -dimensional lattice infinite many times returns to the initial position equals 1 for $d = 1$ and $d = 2$ but equals 0 for $d \geq 3$.

The following table shows some approximate values of $P(d)$:

Dimension	Probability
3	0.340537
4	0.193206
5	0.135178
6	0.104715
7	0.0858449
8	0.0729126

Example 9 Finally, we mention that of the processes described above independent processes and processes with independent increments are also Markovian processes, both can have discrete and continuous state space, as well Fig. 3

CCS Markov Processes An analogue of the master equation (30) is the **Fokker-Planck equation** which describes the time evolution of the probability density function of the position of a particle undergoing Brownian motion in a fluid.

In one spatial dimension the Fokker–Planck equation for a process with drift $D^1(x, t)$ and diffusion $D^2(x, t)$ is

$$\frac{\partial}{\partial t} f(x, t) = -\frac{\partial}{\partial x} \left[D^1(x, t) f(x, t) \right] + \frac{\partial^2}{\partial x^2} \left[D^2(x, t) f(x, t) \right].$$

More generally, the time-dependent probability distribution may depend on a vector \mathbf{x} of N macrovariables x_i . The general form of the Fokker–Planck equation is then

$$\frac{\partial f(\mathbf{x}, t)}{\partial t} = -\sum_{i=1}^N \frac{\partial}{\partial x_i} \left[D_i^1(\mathbf{x}) f(\mathbf{x}, t) \right] + \sum_{i=1}^N \sum_{j=1}^N \frac{\partial^2}{\partial x_i \partial x_j} \left[D_{ij}^2(\mathbf{x}) f(\mathbf{x}, t) \right], \quad (36)$$

where D^1 is the drift vector and D^2 the diffusion tensor; the latter results from the presence of a random force.

Let us see a few examples of CCS Markov processes.

Example 10 (Wiener process)

Definition 7 A CCS process W_t is called **Wiener process** if it satisfies the following three conditions:

1. $W_0 = 0$,
2. W_t is almost surely continuous,
3. W_t has independent increments with normal (Gaussian) distribution i.e.

$$W_t - W_s \sim N(0, t - s).$$

Here $N(\mu, \sigma^2)$ denotes the normal distribution with expected value μ and variance σ^2 . The Wiener process plays a key role in describing a random movement what is known as **Brownian motion**.

The basic properties of the Wiener process:

1. The expectation is zero: $E(W_t) = 0$.
2. The variance is t : $E(W_t^2) - E^2(W_t) = t$.
3. Its covariance and correlation are:

$$\text{cov}(W_s, W_t) = \min(s, t) \quad \text{corr}(W_s, W_t) = \frac{\min(s, t)}{\sqrt{st}} = \sqrt{\frac{\min(s, t)}{\max(s, t)}}.$$

4. The unconditional probability density function at a fixed time t is: $f_{W_t}(x) = \frac{1}{\sqrt{2\pi t}} e^{-\frac{x^2}{2t}}$.

Example 11 (Langevin Equation) In statistical physics, a Langevin equation is a stochastic differential equation describing Brownian motion of charged particles in a potential.

The first Langevin equations to be studied were those in which the potential is constant, so that the acceleration \mathbf{a} of a Brownian particle of mass \mathbf{m} is expressed

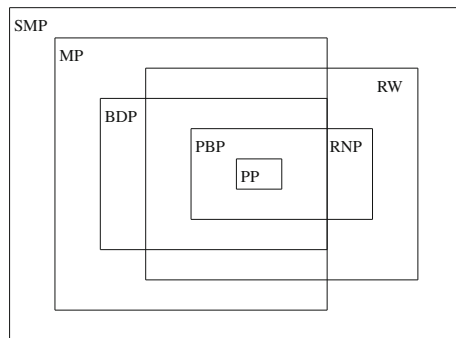


Fig. 4 Classification of stochastic processes. *SMP* Semi-Markov process (p_{ij} arbitrary, F_τ arbitrary); *MP* Markov process (p_{ij} arbitrary, F_τ memoryless); *BDP* birth-and-death process ($p_{ij} = 0$ if $|i - j| > 1$, F_τ memoryless); *PBP* pure birth process ($\mu_i = 0$, F_τ memoryless); *RW* random walk ($p_{ij} = q_{j-i}$, F_τ arbitrary); *RNP* renewal process ($q_1 = 1$, F_τ arbitrary); *PP* Poisson process ($\lambda_i = \lambda F_\tau$ memoryless)

as the sum of a viscous force which is proportional to the particle's velocity \mathbf{v} (by Stokes' law), a noise term $\boldsymbol{\eta}(t)$ (the name given in physical contexts to terms in stochastic differential equations which are stochastic processes) representing the effect of a continuous series of collisions with the atoms of the underlying fluid, and $\mathbf{F}(\mathbf{x})$ which is the systematic interaction force due to the intramolecular and intermolecular interactions:

$$m\mathbf{a}(t) = m \frac{d\mathbf{v}(t)}{dt} = \mathbf{F}(\mathbf{x}(t)) - \beta\mathbf{v}(t) + \boldsymbol{\eta}(t).$$

In the simplest case, the solution is an Ornstein–Uhlenbeck process, see [103], or [60, p. 294].

Semi-Markov Process A semi-Markov process is a process that may change states any time (it is a continuous time process) and the waiting times between the changes are not necessarily exponentially distributed as it happens for the Markov process. A continuous time Markov chain (CTMC) is a special case of a semi-Markov process in which the transition times are exponentially distributed as we have seen in (21).

Renewal processes Let T_1, T_2, \dots ; $T_i > 0$ for $i = 1, 2, \dots$ be a sequence of independent identically distributed random variables. We refer to the random variable T_i as the i th **holding time**. By definition, for each $n > 0$ $J_n := \sum_{i=1}^n T_i$ and $J_0 := 0$ is referred to as the n th **jump time**. The process $N_t := \sup\{n : J_n \leq t\}$ is called a **renewal (counting) process**.

Example 12 If the random variables T_i are exponentially distributed with parameter λ , then N_t is a Poisson process with parameter λ Fig. 4.

Pólya's Urn Model In early twentieth century, Pólya proposed and analyzed the following model known as the Pólya urn model [34]. Suppose we have an urn with r red balls and s smaragdite balls. At each step i , we pick a ball uniformly at random from the urn and replace it with two balls of the same color.

The probability of seeing n_1 red balls and n_2 smaragdite balls after $n = n_1 + n_2$ steps is

$$P(\text{Number of red balls is } n_1) = \frac{n!}{n_1!n_2!} \frac{(r+s-1)!}{(r-1)!(s-1)!} \frac{(r+n_1-1)!(s+n_2-1)!}{(r+s+n-1)!}$$

Let $x := \frac{n_1}{n}$, and take the limit for each term,

$$\begin{aligned} \lim_{n \rightarrow +\infty} \frac{(r+n_1-1)!}{n_1!} &\rightarrow n_1^{r-1}, \\ \lim_{n \rightarrow +\infty} \frac{(s+n_2-1)!}{n_2!} &\rightarrow n_2^{s-1}, \\ \lim_{n \rightarrow +\infty} \frac{(r+s+n-1)!}{n!} &\rightarrow n^{r+s-1}, \end{aligned}$$

then the probability of seeing n_1 red balls converges to

$$\lim_{n \rightarrow +\infty} P(\text{number of red balls is } n_1) = \frac{(r+s-1)!}{(r-1)!(s-1)!} x^{r-1} (1-x)^{s-1}$$

which is a random variable with beta distribution with parameters r and s .

The Pólya urn model can be generalized but at the moment the generalizations do not seem to have immediate chemical applications.

3.3 The standard stochastic model of homogeneous reaction kinetics

The usual deterministic model of homogeneous reaction kinetics with mass action type or other type reaction rates is usually quite appropriate to describe chemical kinetic experiments. However, there are several cases when the both the intrinsic stochasticity of the reactions, and discreteness of the quantities of the species are to be taken into consideration.

These cases are when the system is **small**, i.e. when the number of molecules in the investigated system is not of the order 10^{20} – 10^{23} (milimol to mol) but much smaller. For example this is the case if macromolecules are present in a cell. The number of the molecules in a cell might be a few dozen, or even (DNA) one. If we have such a system then there might be a large difference between the expectations of the stochastic and the deterministic models, and this difference **does not average out** if one has a large number of cells. A model system to describe this situation is the Michaelis–Menten reaction with one enzyme molecule [4, 74, 118, 143], or induction of chirality by only one chiral molecule [23]

Another situation to provide marked differences arises when the system is close to an **unstable stationary point**. Here the effect of fluctuations can be enlarged. Actually, this is the case in some models of chirality [24, 109].

The presence of certain structures such as those within a living cell may also require a stochastic description [153]. In a system confined to a small space it may also happen

that the diffusion is limited due to crowding. On the effect of spatial heterogeneity see also [88].

Another type of the situation is when discretization of the physical space in a stochastic reaction-diffusion model (generalization of the standard stochastic model for the spatially inhomogeneous case) leads to a qualitatively different stationary distribution [146]. Therefore, it is a hard question to decide which model to use to describe spatial inhomogeneities caused by the presence of intracellular structures.

More generally, any kind of exotic phenomena, such as e.g. oscillation [120], blow up [32], multimodality [58] etc., may appear in a qualitatively different way in the deterministic and in the stochastic model, respectively.

Experimental results—to give *raison d'être* to stochastic kinetics—showing inherent stochasticity of reactions have been obtained by Nagypál and Epstein [101, 102]. These results showed that reaction time of the chlorite-thiosulfate reaction displays a striking irreproducibility. These authors have also found fluctuation induced transition. The key contributors to stochasticity are local concentration inhomogeneities resulting from imperfect stirring and the supercatalytic reaction rate. A quantitative description of this process has also been given later.

More detailed treatment of these and related (including thermodynamical) problems can be found in [39, Chapter 5]. See also [16, 46, 123].

We do not want to give a full historical description of stochastic kinetics, still, we should mention a few important names. Delbrück [33] investigated the autocatalytic reaction $A + X \longrightarrow 2X$ which is used to describe the formation of tripsin from tripsinogen. The deterministic and the standard stochastic models are formulated and the binomial distribution of the latter is approximated by a normal distribution. The distribution of the time at which a given number of particles is attained is also determined. In the same year [75] provided a general approximation of CDS models with CCS models.

Rényi [121] was the first to provide a detailed analysis of the standard stochastic model of a higher than first order reaction. He has shown that the expectation of the numbers of molecules in a stochastic model is close to the corresponding quantities in the deterministic model, and the difference is proportional to the reciprocal of the square root of the number of molecules. (see also [12, 100]) Therefore, the relative error is small, if this number is large, otherwise it is large. He also made a series of approximations of the distributions of molecule numbers under different conditions. A direct continuation of his work can be found in [78]. The author carried out the calculations on the standard stochastic model of $A + B \longleftrightarrow C$ in detail using Laplace transforms. His results correspond to the work of Kurtz [76].

The above phenomena only show why it is **necessary** to use stochastic models. It is also **possible** recently, because of the development of measurement techniques, see e.g. [41, 160].

The publication of Feher and Weissman [41] is an early paper on the possibility of measurement of intrinsic stochasticity of reactions. The kinetic parameters of the dissociation reaction of beryllium sulfate were obtained from analysis of the frequency spectrum of the fluctuations in the concentrations of the reactants. In fluctuation spectroscopy, no external perturbation is applied and the system remains in macroscopic chemical equilibrium during the experiment. Results obtained by this method agree

well with those obtained by relaxation methods. Noise originating from a source different from the chemical reaction was also observed and analyzed. The method of fluctuation spectroscopy should be applicable to other problems of physical, chemical, and biological interest, too.

3.3.1 Evolution equations of the time dependent characteristics of reactions

The usual stochastic model of (1) is a CDS Markov process or a Markovian pure jump process \mathbf{X} with the state space \mathbb{N}_0^M and with the transitions

$$\mathbf{n} \longrightarrow \mathbf{n} + \boldsymbol{\beta}(\cdot, r) - \boldsymbol{\alpha}(\cdot, r).$$

The (infinitesimal) probabilities of these transitions in the interval $]t, t + h[$ are as follows: $k_r(\mathbf{n})\boldsymbol{\alpha}(\cdot, r)h + h\varepsilon(h)$, where $(\mathbf{n})\boldsymbol{\alpha}(\cdot, r) := \prod_{m=1}^M n_m(n_m - 1) \dots (n_m - \alpha(m, r) + 1)$, and $\lim_0 \varepsilon = 0$. The above assumptions also mean that the state vector of the process stays constant for an exponentially distributed time (the parameter of this distribution being $\sum_{r=1}^R k_r(\mathbf{n})\boldsymbol{\alpha}(\cdot, r)$) and then it jumps to another state. The probability of choosing state $\mathbf{n} + \boldsymbol{\delta}$ is proportional to

$$\sum_{r: \boldsymbol{\beta}(\cdot, r) - \boldsymbol{\alpha}(\cdot, r) = \boldsymbol{\delta}} k_r(\mathbf{n})\boldsymbol{\alpha}(\cdot, r).$$

One can easily write down the Kolmogorov backward and forward equations for the transition probabilities, and also the master equations for the absolute probabilities $P_{\mathbf{n}}(t) := P(\mathbf{X}(t) = \mathbf{n})$:

$$\dot{P}_{\mathbf{n}} = - \sum_{r=1}^R k_r(\mathbf{n})\boldsymbol{\alpha}(\cdot, r)P_{\mathbf{n}} + \sum_{r=1}^R k_r(\mathbf{n} - \boldsymbol{\beta} + \boldsymbol{\alpha})\boldsymbol{\alpha}(\cdot, r)P_{\mathbf{n} - \boldsymbol{\beta} + \boldsymbol{\alpha}}. \quad (37)$$

Although the absolute probabilities do not determine the behavior of the process in the strict mathematical sense, from the practical points of view it is generally enough to start from these. We can also have the equation for the stationary distribution π .

$$\sum_{r=1}^R k_r(\mathbf{n})\boldsymbol{\alpha}(\cdot, r)\pi_{\mathbf{n}} = \sum_{r=1}^R k_r(\mathbf{n} - \boldsymbol{\beta} + \boldsymbol{\alpha})\boldsymbol{\alpha}(\cdot, r)\pi_{\mathbf{n} - \boldsymbol{\beta} + \boldsymbol{\alpha}}. \quad (38)$$

There is a generally accepted view that the stationary distribution is necessarily Poissonian. However the situation is that it is an exception [149] rather than a rule [151, 159]. Recently, an interesting connection has been discovered between the deterministic and the stochastic models. It turned out that a sufficient condition of the existence of product form stationary distribution is complex balancing, a property also implying the regular behavior of the deterministic model [3].

The equation for the generating function is also very useful: Let $\mathcal{G}(t, \mathbf{z}) := \sum_{\mathbf{n}} P_{\mathbf{n}}(t) \mathbf{z}^{\mathbf{n}}$, then

$$\partial_0 \mathcal{G}(t, \mathbf{z}) = \sum_{r=1}^R k_r (\mathbf{z}^{\beta(\cdot, r)} - \mathbf{z}^{\alpha(\cdot, r)}) \partial_{\alpha(\cdot, r)} \mathcal{G}(t, \mathbf{z}) \quad \mathcal{G}(0, \mathbf{z}) = \mathbf{z}^{\mathbf{D}}, \quad (39)$$

where $\mathbf{D} \in \mathbb{N}^M$ is the initial number of the species. One can deduce easily equations for the moments, we only cite here the differential equation for the first moment both because of its usefulness and simplicity:

$$\frac{d\mathbb{E}\{\mathbf{X}(t)\}}{dt} = \mathbb{E}\{\mathbf{f}^K(\mathbf{X}(t))\}, \quad (40)$$

where \mathbf{f}^K is practically the same as the right hand side of the induced kinetic differential equation. The major difference, however, comes from the fact, that expectation is taken **after** application of \mathbf{f}^K , and not before it. This makes a difference, if the reaction steps are of the order higher than one.

Example 13 The stochastic model of the simple inflow $O \rightarrow X$ with rate λ is the Poisson process. Equation (37) in this case goes into (35), and for the generating function we have

$$\partial_0 G(t, z) = \lambda(z - 1)G(t, z) \quad G(0, z) = 1.$$

Then the equation for the first moment is the same as (4).

Example 14 The stochastic model of the first order autocatalytic reaction $X \rightarrow 2X$ with outflow $X \rightarrow O$ added is the simple linear birth-and-death process, thus the master equation is

$$P'_n(t) = k_1(n - 1)P_{n-1}(t) + k_2(n + 1)P_{n+1}(t) - (k_1 + k_2)n P_n(t).$$

Consequently the equation for the first moment is

$$\frac{d\mathbb{E}\{X(t)\}}{dt} = (k_1 - k_2)\mathbb{E}\{X(t)\},$$

which is the same as (5).

Example 15 The stochastic model of the supercatalytic (second order) autocatalytic reaction $2X \rightarrow 3X$ is the simple quadratic pure birth process, thus the master equation is

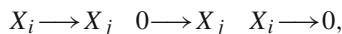
$$P'_n(t) = k(n - 1)(n - 2)P_{n-1}(t) - kn(n - 1)P_n(t).$$

Explicit solution of the equation shows that the stochastic model stays altogether with probability 1 in one of the finite states, therefore the model does not blow up, in contrast to the deterministic one. The equation for the first moment is

$$\begin{aligned}\frac{d\mathbb{E}\{X(t)\}}{dt} &= k\mathbb{E}\{X(t)(X(t) - 1)\} \\ &= k(\mathbb{E}\{X(t)^2\} - \mathbb{E}\{X(t)\}) \\ &= k\left[\mathbb{D}^2\{X(t)\} + \mathbb{E}\{X(t)\}(\mathbb{E}\{X(t)\} - 1)\right]\end{aligned}$$

which is different from (6). It has also the property that it is **not closed** in the sense that the right hand side also contains the second order moment.

Although it is relatively simple to write down the evolution equations for the standard stochastic model of chemical reactions, almost nothing can explicitly be calculated in a symbolic way. The only large class of reactions which can be treated without approximations is the class of compartmental systems:



a special case of first order reactions. The last two steps describe in- and outflow, respectively. (The reaction $X \longrightarrow 2X$ is a first order reaction, although it is not a compartmental system.) The stochastic models of compartmental systems are beyond the scope of the present paper but for the readers who are interested in recommended to see one of the very last papers in this topic: [45], or [39, p. 107].

For other classes approximations and simulation have to be used.

3.3.2 Transient and stationary multimodality in the standard stochastic model of chemical reactions

Érdi and Tóth [39, pp. 140–142] provides a sufficient condition for the stationary distribution to be unimodal. The simple example of the van der Pol oscillator shows that additive noise may cause bimodal stationary distribution, see e.g. [39, pp. 135, 154–156].

Baras et al. [14] have shown on a concrete mechanism of a homogeneous system that the behavior of the standard stochastic model is closer to the deterministic one than the description by the Langevin equation in the case when the deterministic one shows bistability. To read more about this topic see [19] and [43, 44].

A class of reactions, generalization of the three species Ivanova reaction $sO \longleftrightarrow X_i, X_i + X_{i+1} \longrightarrow 2X_{i+1}$ is introduced, and the Langevin equation of the system with four species is simulated to prove that a certain linear combination of the quantities of the species shows transient bimodality with appropriate parameter values [145]. Later, [147] by simulating the standard model discreteness induced first order (as opposed the known second order) transition and found transient bistability without symmetry breaking. The authors make a clear distinction between discreteness and stochasticity, and state that discreteness has not been separately studied. Really, one usually turns from the CCD model to the CDS model in a single step.

3.3.3 Approximations

The early classic work by Delbrück [33] contains an approximation of the CDS model of the simple autocatalytic reaction $X \rightarrow 2X$ using Gaussian distribution. Different approximations are given by Rényi [121]. The most important paper on the relation between the standard deterministic models is [76], again provides an approximation of the CDS model by Gaussian processes. More precisely, Kurtz considered only reversible, detailed balanced mechanisms (the most important class of mechanisms for applications in chemistry), and he has shown that fluctuation of the standard stochastic model around the corresponding quantities in deterministic model is normally distributed with a variance negligible if the number of particles is as large as in ordinary circumstances: 10^{20} – 10^{23} particles, corresponding to milimol to mol per liter. Finally, let us mention that [76] is only a short summary of the results (outlined in a series of papers full with heavy mathematics) for the chemist.

Goutsias [50] proposes (after so many authors again) the closure of the moment equations, as a kind of approximation which is always needed if one also has higher than first order reactions.

Here we mention only two general methods of approximations. One possible approach has been shown by Zheng and Ross [159]. They numerically solved the master equation of the quadratic autocatalytic Schlögl reaction for 20–100 particles. Hellander and Loetstedt [55] combine macroscopic and mesoscopic descriptions to solve the master equation, then apply simulation.

Lente [80] approximates the Polya distribution with a beta distribution.

3.3.4 Simulation

The simulations are based on the structure of the process and on Doob's theorem described above: One has to choose exponentially distributed random variables to calculate the times between reaction steps, then one has to select a reaction step. Such a program has been written by Hanusse [54], and Lindbald and Degn [86] for a very special case, and [38, 132] described a general simulation program for this purpose in the very beginning of the seventies.

Goss and Peccoud [49] provided a general program for simulating stochastic models of biology, including the standard stochastic kinetic model based on the formulation of stochastic Petri nets.

Shibata [131] based on recent theoretical and experimental studies states that gene expression and signal transduction reactions are noisy. In this context one should be aware of the fact, that “biology” is based on networks of chemical reactions [31, 35, 47]. Recently, many authors try to accelerate the simulation of the stochastic models. (see for example [26, 30, 111, 155, 157].)

3.3.5 Stochastic models of chirality

The major questions to be described are as follows.

1. How does a difference between the quantities of enantiomers emerge?

2. Which mechanisms help stabilize and amplify these differences?

Let us consider the standard CDS model of the Frank reaction (7), following [80, 85, 130]. First of all, instead of $P_{a,r,s}(t)$ it is enough to use, say, $P_{r,s}(t)$, because of the linear relationships between the variables. The master equation is now:

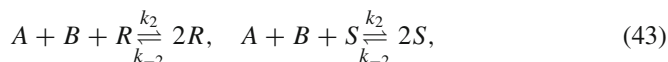
$$\begin{aligned} \dot{P}_{r,s} = & (m_0 - r - s + 1) \left(\left(\frac{1}{2}k_1 + k_2(r-1) \right) P_{r-1,s} + \left(\frac{1}{2}k_1 + k_2(s-1) \right) P_{r,s-1} \right) \\ & - (k_1 + k_2(r+s))(m_0 - r - s)P_{r,s} \end{aligned} \quad (41)$$

with $m_0 := a_0 + r_0 + s_0$ as before. Then, if one defines the stationary enantiomeric excess in the natural way: $ee := \frac{2r-a_0-r_0-s_0}{a_0+r_0+s_0}$, one can obtain for the standard deviation $D(ee)$ of this variable an expression showing that if no autocatalysis is present then $D(ee) \sim \frac{1}{\sqrt{m_0}}$, a quantity negligible for macroscopic systems. However, if efficient autocatalysis is present in the system, then spontaneous symmetry breaking occurs. The limits of sufficient efficiency of autocatalysis was determined by an empirical equation [97]. This effect is enhanced if the volume is small or if the concentrations are high. Lente [80] has also given the stationary distribution introducing an intermediate probability. The stationary distribution is a very special (discrete) beta distribution which can also be approximated by a beta distribution and can be fitted to the data by Asakura et al. [6], and by Soai et al. [137], although in this case the fit is worse.

Barabás et al. [11] analyzed the enantiomeric excesses obtained in absolute enantioselective synthesis by asymmetric autocatalysis (Soai-reaction). Two sets of parallel experiments, which were performed under chemically different conditions, are available. One group contains 37, while the other 84 preparative results. The former group shows some interesting tendencies, but does not give conclusive statistical results. The sample of 84 parallel experiments, providing 39 R- and 45 S-excesses have shown that these data represent two distinct sets with different non-Gaussian distributions. Clear S-preference was found. Possible reasons for this unexpected behavior include the parity violating energy difference between the transition states leading to the two enantiomers ([87]).

Terrestrial biochemistry supports L- α -amino acids and D-sugars [152]. This chiral preference may be a result of very small differences between the energies of enantiomeric molecules. The energy differences are so small that the propagation of homochirality would require a dissymmetry amplification mechanism involving both large quantities of reactants and a long reaction time. Alternative theory: A small parity violating energy difference between the corresponding state energies of a chiral system and its enantiomeric system may preferentially stabilize one with respect to the other. Kinetic mechanisms amplify this dissymmetry to yield homochirality. It may also happen that asymmetrically crystallized achiral clays may serve as a catalyst to amplify this prebiotic-biotic transition. Matsuura and Koshima [92] assert that formation of an asymmetric crystal may help form chirality. A large number of achiral compounds such as benzophenone, phenol, phenantrene, etc. are known to crystallize into chiral crystals from their solutions. It has been proved experimentally that enantiomorphs of such crystals can induce very efficiently excess chirality in one or other direction at asymmetric autocatalysis (e.g. [63] and references cited there). See also [22].

Kondepudi and Nelson [72] uses the reaction



(Let us note that the reaction is kinetically very similar to (7) except that the first four steps are reversible and a kind of sink is also included in the same way as in (12)). In model systems that spontaneously evolve to a state dominated by either the R, or the S enantiomer, parity violation is thought to be too small to have any significance on the emergent chirality [84]. There is a simple and extremely sensitive mechanism by which a minute but systematic chiral interaction can, over a period of cca. 15,000 year determine which enantiomer will dominate. Mason and Tranter, or [91] state that the terrestrially dominant L amino acids are favored by the weak neutral current interaction. The above reaction is investigated using the deterministic model and also by the Fokker–Planck equation. They also derive the Langevin equation: $\dot{\alpha} = \alpha^3 + \dots$ from the model, and calculate distributions as a function of g with the assumptions $k_S = (1 + g)k_R D$.

Barabás et al. [10] analyzed the statistical distribution of enantiomeric excess obtained by two sets of parallel experiments of absolute asymmetric synthesis by asymmetric autocatalysis. They have found that experimental data give an excellent fit to a mixture of two beta distributions, where the components are in a **golden section ratio**. The parameters of this higher order beta distribution were found by computer-simulated Pólya urn model experiments. The urn model experiments indicate that the Soai-autocatalysis might operate by three concerted and cooperating catalytic cycles. These results provide a general model of asymmetric autocatalysis. Actually, the fit is better than the one obtained by Lente [80], who used a (very special) single beta distribution for fitting.

Gridnev et al. [51] in a mostly experimental (NMR, HPLC) paper shows that a symmetric autocatalysis in ZnR_2 alkylation of pyrimidin-5-aldehydes, spontaneous enantiomeric excess, is independent from reaction parameters. Enantiomerically enriched product without initial bias may be due to stochastic effects. They propose the mechanism $A + 2R \longrightarrow 3R$, $A + 2S \longrightarrow 3S$, $A + S \longrightarrow 2S + R$, $A + R \longrightarrow 2S + R$. (We do not see how the principle of mass conservation is obeyed here.) Stochastic modeling here means to use binomial distribution. They also consider the dimer catalyzed model: $R_2 + A + Z \longrightarrow R_2 + RZ$, $S_2 + A + Z \longrightarrow S_2 + SZ$, but make no theoretical statements on it.

A description of a small autocatalytic system using Langevin equation is given by Togashi and Kaneko [145].

ODE model with random parameters Todorović, Gutman and Radulović [144] state that if the reaction (12) was absolutely racemic initially then it will remain forever.

However, with a small initial enantiomeric excess the system evolves into a homochiral state provided $k_3 < k_2$, or into a racemic terminal state, if $k_3 > k_2$, where k_2 and k_3 are rate constants of the second order steps. They give a very detailed analysis based on numerical calculations of an ODE model with random parameters.

Perhaps it would be worth analyzing the standard stochastic model of the same reaction.

Kou et al. [74] uses a semi-Markov process to describe chirality.

Pál [106] studied the stochastic properties of the lifetime of small systems controlled by autocatalytic reaction by using the standard model of reaction kinetics.

4 Conclusion

Let us summarize what we have learned from the dynamic models of chirality. Following [89] (which is more recent and more detailed than [91]): considering that sugars may have more than one asymmetric C atoms, let us concentrate on the simpler case of amino acids. One has three questions to answer.

1. Initialization, or the origin of asymmetry.
2. Amplification of small differences.
3. Why does living Nature have just L-amino acids and D-sugars?

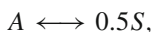
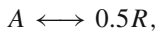
4.1 Possible mechanisms of initialization

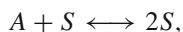
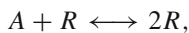
4.1.1 Randomness

According to Barabás et al. [12] **isotopic substitution** in isotopically prochiral groups of otherwise achiral molecules can provide such concentrations of stochastically formed enantiomeric excesses, which are exceeding the sensitivity threshold of sensitive asymmetric autocatalytic (Soai-type) reactions. Caglioti et al. [24,25] have shown that even the chirality of a single molecule can be amplified to macroscopic levels by Soai-type asymmetric autocatalysis. See also the recent papers [64,65].

4.1.2 External asymmetry

Enantioselective decay or catalysis Országh and Beck [104] An early hypothesis of the origin of optical activity comes from [27]: Stereospecific autocatalysis is supposed to be the main reason. Hochstim ([57]) has added some fluctuation analysis, based on the \sqrt{N} rule without chemical analysis. In that paper the author estimates the reaction rate coefficients, and conclude that supercatalysis is needed to understand homochirality. More specifically, [73,80] investigates practically the model by Frank [42]:





and shows that the standard deterministic model of this reaction is not capable of clarifying homochirality whereas the standard CDS model even with first order autocatalysis is able to show considerable enantiomeric excess.

Asymmetric catalysis with chiral crystals Quartz is chiral, but chemically inactive, perhaps adsorption may have a role. There is, although a very small, enantiomeric excess of the two forms of quartz crystals in nature, although this remains within the limits of statistical error.

Photochemical effect of polarized light Polarized light through a solvent with no enantiomeric excess may initiate an enantioselective process. Experimental proof exists (an instance has been found). Polarized light in nature: differences can be found between sunrise and sunset.

Parity violation of β -decay Left-rotating electrons are more abundant. Experimental proof exists, but the effect is very weak.

Parity violation of WNC Between electrons, and between electrons and neutrons. Consequence: atoms are chiral with respect to electromagnetic radiation, such as e.g. light. L and D amino acids have a different energy content. L enantiomers are more stable. Factors corroborating this effect: polymerization, interaction between molecules, larger molecules. Experimental proof exists: [72,69].

Local fluctuations because of diffusion [6,7] says that if the growth in a local concentration due to an autocatalytic process overcomes diffusion, a concentration fluctuation on a small volume will grow. In a chiral autocatalytic system this phenomenon could produce a large variation in enantiomeric effects.

Meteorites, comets, asteroids rich with L-amino acids (Murchison meteorite, [77] and Tagish Lake meteorite, [113]). Proofs: isotope ratios, unknown amino acids. L enantiomeric excess. Enantioselective processes in the space: supernova explosions of type II and circularly polarized radiation.

4.2 Amplification

See the models above. Let us also remark that problems of signal transduction are of very similar nature from the modelling point of view [117,123,131], because in both situations a small, perhaps even microscopic signal is amplified to the macroscopic level with the aid of a kinetic mechanism.

4.3 Why just L-amino acids?

They are a bit more stable than the other enantiomers.

Bada [8] reviews the lectures of a conference saying that the result of physical mechanisms (parity violation in weak interactions) should be amplified via autocatalysis. Racemization of amino acids is also a problem, even in vivo. L-amino acids turn

into a racemic mixture in a period of the order of a few 1000 years (depending also on the chemical structure of the amino acid). Thus, spontaneous racemization should block chiral selection.

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