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Citation: J. Chem. Phys. **137**, 164101 (2012); doi: 10.1063/1.4758458
View online: http://dx.doi.org/10.1063/1.4758458
View Table of Contents: http://jcp.aip.org/resource/1/JCPSA6/v137/i16
Published by the American Institute of Physics.

Stochastic mapping of first order reaction networks: A systematic comparison of the stochastic and deterministic kinetic approaches

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(Received 23 July 2012; accepted 27 September 2012; published online 22 October 2012)

Stochastic maps are developed and used for first order reaction networks to decide whether the deterministic kinetic approach is appropriate for a certain evaluation problem or the use of the computationally more demanding stochastic approach is inevitable. On these maps, the decision between the two approaches is based on the standard deviation of the expectation of detected variables: when the relative standard deviation is larger than 1%, the use of the stochastic method is necessary. Four different systems are considered as examples: the irreversible first order reaction, the reversible first order reaction, two consecutive irreversible first order reactions, and the unidirectional triangle reaction. Experimental examples are used to illustrate the practical use of the theoretical results. It is shown that the maps do not only depend on particle numbers, but the influence of parameters such as time, rate constants, and the identity of the detected target variable is also an important factor. [http://dx.doi.org/10.1063/1.4758458]

INTRODUCTION

Both experimental results and theoretical considerations show that the traditional deterministic approach to chemical kinetics should be replaced by stochastic models when dealing with relatively low numbers of individual molecules or ions.[1–6] The continuous time discrete state (CDS) stochastic approach[2,5] recognizes the fact that chemical reactions occur as a sequence of individual molecular events rather than changes in a continuous concentration-time function and provides a consistent description of natural fluctuations, which are inherent in every chemical system. It is now understood that the application of the CDS approach may be necessary even when the number of involved particles is quite large, e.g., autocatalysis[7,8] or chiral amplification[5,6,9–11] gives rise to macroscopic fluctuations under certain conditions. In many cases, it is an important question to decide whether a particular kinetic problem can be solved by the computationally much less intensive deterministic approach, or the use of mathematically often more demanding stochastic models is inevitable.

Stochastic mapping, which was used in essence in at least three recent articles[8,12,13] but was only named so in the last one,[13] attempts to answer this question by identifying the parameter range of a given kinetic scheme in which only the stochastic approach is viable. These earlier papers were concerned with chiral amplification,[12] extinction phenomena in autocatalysis,[8] and the Michaelis-Menten mechanism.[13] The stochastic region of a given scheme was defined in them as the set of parameter values for which the stochastic approach shows that the relative standard error of the target variable is larger than a pre-set critical value (usually 1%). Kurtz's theorem[14] ensures that the stochastic description of any reactive system converges to the deterministic solution when the volume approaches infinity. Consequently, a sufficiently small standard deviation of the expectation of a variable calculated based on the stochastic approach guarantees that the stochastic expectation is sufficiently close to the deterministic solution. Recently, a different sequence of thought further re-affirmed these conclusions.[15]

The stochastic description of chemically first order (or monomolecular) reaction networks has been the subject of a surprisingly large number of studies at various levels of sophistication.[16–29] From a theoretical point of view, these reaction schemes offer conceptual clarity and simplicity in mathematical formalism, which often facilitates the recognition of known probability distributions in the results. Practical interest is also increasing in these processes due to improvements in single molecule detection.[30–35] Therefore, the objective of this article is to develop stochastic maps for first order reaction networks. General strategies toward building these maps will be illustrated by a number of specific examples involving particularly important reaction schemes. The use of these maps will also be demonstrated using some published experimental data. The main text of the article will only state relevant equations, the derivations are deposited in the supplementary material.[36]

RESULTS AND DISCUSSION

A general first order reaction sequence

A general network of first order reactions involves n different chemical species (A_1, A_2, …, A_n), every one of which can convert to any other, i.e., chemical reactions are possible for all pairs of species present

$$A_i \xrightarrow{k_{i,j}} A_j. \tag{1}$$

Therefore, $k_{i,j}$ is the rate constant characteristic of the first order chemical process converting species A_i into species A_j

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and has the unit s^{-1}. It is practical to complete these series of rate constants with identity constants $k_{i,i} = 0$. The network thus features a maximum of $n(n-1)$ different rate constants, some of which may still be zero. It is also notable that these constants are usually not fully independent of each other because chemical considerations, most often of thermodynamic nature, can set certain relationships between them. Nevertheless, the general treatment presented in this article is valid for any values of the rate constants and does not depend on the mentioned relationships. The rate constants are conveniently given in a form of a matrix, which is denoted $\underline{\underline{k}}$ here

$$\underline{\underline{k}} = \begin{pmatrix} 0 & k_{1,2} & \cdots & k_{1,n} \\ k_{2,1} & 0 & \cdots & k_{2,n} \\ \vdots & \vdots & \ddots & \vdots \\ k_{n,1} & k_{n,2} & \cdots & 0 \end{pmatrix}. \tag{2}$$

Equation (1) is written with a set 1:1 stoichiometry for each process in the reaction network. In this case, conservation of matter ensures that the sum of concentrations is always the same. In deterministic calculations, where concentrations are used, the mathematical description can often be simplified by introducing dimensionless concentrations. For the present problem, dimensionless concentrations (Π_i) are introduced by dividing the concentration of species A_i with the constant (i.e., time-independent) sum of concentrations of all species

$$\Pi_i = \frac{[A_i]}{\sum_{j=1}^{n} [A_j]_0}. \tag{3}$$

If the reactions in Eq. (1) do not all show 1:1 stoichiometry, this should be reflected appropriately in the definition of dimensionless concentrations.

The deterministic description of the reaction network

Although this work aims to give a stochastic description of the chosen model, it is quite useful to describe the deterministic approach and its solution because they will be shown to be notably significant in the stochastic solutions as well. The differential equations for the dimensionless concentrations are as follows:

$$\frac{d\Pi_i}{dt} = -\left(\sum_{j=1}^{n} k_{i,j}\right)\Pi_i + \sum_{j=1}^{n} k_{j,i}\Pi_j. \tag{4}$$

This is a system of ordinary, linear, first order, homogeneous differential equations, the solution of which is well known from mathematics. One way to state this solution uses matrix notations. For this purpose, matrix $\underline{\underline{k}}$ must be transposed ($\underline{\underline{k}}^{\mathrm{T}}$) and completed by adding diagonal elements. The resulting matrix is denoted $\underline{\underline{k'}}$ and has the following composition:

$$\underline{\underline{k'}} = \underline{\underline{k}}^{\mathrm{T}} + \begin{pmatrix} -\sum_{i=1}^{n} k_{i,1} & 0 & \cdots & 0 \\ 0 & -\sum_{i=1}^{n} k_{i,2} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & -\sum_{i=1}^{n} k_{i,n} \end{pmatrix}. \tag{5}$$

This matrix simplifies stating Eq. (4) if the dimensionless concentrations are used in the form of a vector ($\underline{\Pi}$)

$$\frac{d\underline{\Pi}}{dt} = \underline{\underline{k'}}\,\underline{\Pi}. \tag{6}$$

The solution of this equation is most conveniently given using the matrix exponential function[5] (expm):

$$\underline{\Pi}(t) = \mathrm{expm}(\underline{\underline{k'}}t)\underline{\Pi}(0). \tag{7}$$

$\underline{\Pi}(0)$ represents the initial conditions, i.e., the values of dimensionless concentration at $t = 0$. The individual Π_i functions can be given using the eigenvalues of matrix $\underline{\underline{k'}}$. Let m be the number of different eigenvalues of matrix $\underline{\underline{k'}}$, $\lambda_1, \lambda_2, \ldots, \lambda_m$ the eigenvalues themselves, $l_1, l_2, \ldots, l_m$ the multiplicities of these eigenvalues, in order. The following equation holds for the multiplicities:

$$n = \sum_{i=1}^{m} l_i. \tag{8}$$

The sums of all columns in matrix $\underline{\underline{k'}}$ are zero, therefore the matrix itself is singular and at least one of its eigenvalues is zero. The solution given in Eq. (7) can also be given without using the matrix exponential function

$$\Pi_i(t) = \sum_{j=1}^{m} \sum_{h=1}^{l_i} C_{i,j,h} t^{h-1} e^{\lambda_j t}. \tag{9}$$

Complex numbers may arise as eigenvalues, but as all the elements of matrix $\underline{\underline{k'}}$ are real, they can only appear in conjugate pairs. In this case, it is always possible to re-formulate the solution using the real sine and cosine functions only, thus eliminating the need for using the complex exponential function. The values of constants $C_{i,j,h}$ can be given based on the initial conditions.

The stochastic description of the reaction network

As explained earlier, the CDS method will be used here to create stochastic maps of first order reaction networks. The CDS solution of this problem was the subject of several earlier articles[16–29] and will only be covered here to the extent that understanding of the stochastic maps requires. First, it is necessary to identify all possible states of the system. In a given state, let a_i mean the number of molecules for species A_i and N_0 the overall number of particles (these could be both ions and molecules, later discussion will usually call them

molecules for simplicity). Conservation of mass ensures that the sum of all a_i values will be N_0

$$N_0 = \sum_{i=1}^{n} a_i. \tag{10}$$

The number of states can be given by a combinatorial line of thought: it is identical to the number of different non-negative integer solutions of Diophantine Eq. (10). The mathematics of problems like this was discussed earlier Dahmen and Micchelli,[37] and the number of states can be given by a binomial coefficient

$$M = \binom{N_0 + n - 1}{n - 1} = \frac{(N_0 + n - 1)!}{(n-1)!N_0!}. \tag{11}$$

As pointed out in the earlier literature of the CDS method,[5] an enumerating function is often useful in solving stochastic kinetics problems. The enumerating function identifies each possible state with a unique positive integer. An enumerating function for the reaction network defined in Eq. (1) is given as follows:

$$f(a_1, a_2, \ldots, a_n) = 1 + \sum_{i=2}^{n} \sum_{j=1}^{a_i} \binom{N_0 - j + i - 1 - \sum_{h=i+1}^{n} a_h}{i - 2}. \tag{12}$$

The CDS master equation of the first order reaction network is given as follows:

$$\frac{dP(a_1, a_2, \ldots, a_n)}{dt} = -\left(\sum_{j=1}^{n}\sum_{i=1}^{n} a_i k_{i,j}\right) P(a_1, a_2, \ldots, a_n) + \left(\sum_{j=1}^{n}\sum_{i=1}^{n} (a_i + 1)k_{i,j} \times P(a_1, a_2, \ldots, a_i + 1, \ldots, a_j - 1, \ldots, a_n)\right). \tag{13}$$

This master equation, similarly to Eq. (4), is a system of ordinary linear, first order, homogeneous differential equations. It can also be stated in a matrix form using the enumerating function.[4] In this case, the matrix (denoted $\underline{\underline{\Omega}}$) is often called the infinitesimal transition probability matrix or evolution matrix. For a single molecule in the system ($N_0 = 1$), which is understood to have important implications in chiral systems,[38–40] master Eq. (13) is in essence identical to Eq. (4) and $\underline{\underline{\Omega}} = \underline{\underline{k'}}$. This observation makes the connection between the deterministic and stochastic approaches evident.

In the CDS approach, the time-dependent probabilities $P(a_1, a_2, \ldots, a_n)$ carry all the information about the system. Nevertheless, it is extremely useful to define time-dependent descriptors of the system, which have chemical meaning. One such descriptor is the expectation for the numbers of molecules A_i. Its definition is

$$\langle a_i \rangle = \sum_{all\ M\ states} a_i P(a_1, a_2, \ldots, a_n). \tag{14}$$

The expectation for the square of the numbers of molecules A_i is given as

$$s_{i,i} = \sum_{all\ M\ states} a_i^2 P(a_1, a_2, \ldots, a_n). \tag{15}$$

Using the values of $s_{i,i}$, the standard deviation for the $\langle a_i \rangle$ can be calculated

$$\sigma_i = \sqrt{s_{i,i} - \langle a_i \rangle^2}. \tag{16}$$

Next, the probability of having exactly a certain number (N) of A_i molecules is defined by summing the probabilities of all states with $a_i = N$

$$P_i(N) = \sum_{all\ a_i = N\ states} P(a_1, a_2, \ldots, a_i = N, \ldots, a_n). \tag{17}$$

For many problems, it is sufficient to find the values of the descriptors defined in Eqs. (14)–(17) rather than the entire set of $P(a_1, a_2, \ldots, a_n)$ functions. It can be shown that the expectation for molecule numbers can be obtained using the deterministic solution in a quite straightforward way

$$\langle a_i \rangle = \Pi_i N_0. \tag{18}$$

To determine the standard error, an additional quantity needs to be defined, which is characteristic of the expectation for the product of a pair of molecule numbers

$$s_{i,j} = s_{j,i} = \sum_{all\ M\ states} a_i a_j P(a_1, a_2, \ldots, a_n). \tag{19}$$

Differential equations for $s_{i,i}$ and $s_{i,j}$ follow from Eq. (13):

$$\frac{ds_{i,i}}{dt} = (-2s_{i,i} + N_0\Pi_i)\sum_{j=1}^{n} k_{i,j} + \sum_{j=1}^{n} (2s_{i,j} + N_0\Pi_j)k_{j,i}, \tag{20}$$

$$\frac{ds_{i,j}}{dt} = -s_{i,j}\sum_{h=1}^{n}(k_{j,h} + k_{i,h}) - N_0\Pi_i k_{i,j} - N_0\Pi_j k_{j,i} + s_{i,i}k_{i,j} + s_{j,j}k_{j,i} + \sum_{h=1, h\neq j, h\neq i}^{n} (s_{i,h}k_{h,j} + s_{j,h}k_{h,i}). \tag{21}$$

Through differential Eqs. (20) and (21), the time dependences of $s_{i,i}$ and $s_{i,j}$ can be given without solving Eq. (13). Therefore, the standard deviation of $\langle a_i \rangle$ can be calculated.

In the case of first order reaction networks, there is a particularly useful line of thought, which can simplify some considerations. This could be termed the method of independent molecules, which can be employed because — as a consequence of first order processes only — there are no interactions between molecules and the state of each individual molecule can be described without knowing about the states of the rest of the molecules in the system. This line of thought is particularly easily used under conditions when the initial state of the system contains only one type of molecules,

which is not uncommon in practice. If this holds, even $P(a_1, a_2, \ldots, a_n)$ functions can be given in a simple way using Π_i functions

$$P(a_1, a_2, \ldots, a_n) = \frac{N_0!}{\prod_{i=1}^{n} a_i!} \prod_{i=1}^{n} \Pi_i^{a_i}. \quad (22)$$

Probability $P_i(N)$, originally defined in Eq. (17) also has a simple form for this case

$$P_i(N) = \binom{N_0}{N} \Pi_i^N (1 - \Pi_i)^{N_0 - N}. \quad (23)$$

The probability distribution for A_i molecules is therefore described by a binomial distribution. This is in agreement with Eq. (18), and also opens a much simplified way to give the standard deviation of $\langle a_i \rangle$

$$\sigma_i = \sqrt{\Pi_i(1 - \Pi_i)N_0}. \quad (24)$$

Interferences form detection efficiency

In actual measurements when the system is analyzed for one of the components, the detection method cannot normally identify all molecules individually. Therefore, the measurement method is characterized by a detection efficiency (p), which is the probability that a given individual molecule will influence the signal, or, in a slightly different way of thought, the fraction of detected molecules. If any sampling occurs during analysis (i.e., only a fraction of the entire volume is analyzed), this can be also incorporated into the value of p. Under these conditions, the probability of detecting exactly N molecules of A_i is given as

$$D_i(N) = \sum_{j=N}^{N_0} \binom{j}{N} p^N (1 - p)^{j-N} P_i(N). \quad (25)$$

For the case when only one type of molecule is present initially, this formula is simplified into one describing a binomial distribution

$$D_i(N) = \binom{N_0}{N} p^N \Pi_i^N (1 - p\Pi_i)^{N_0 - N}. \quad (26)$$

The expectation and standard error of D_i is simply obtained using Eqs. (18) and (24) with $p\Pi_i$ instead of Π_i

$$\langle D_i \rangle = p\Pi_i N_0, \quad (27)$$

$$\sigma_{D_i} = \sqrt{p\Pi_i(1 - p\Pi_i)N_0}. \quad (28)$$

Irreversible first order decay

Irreversible first order decay is the case when $n = 2$, $k_{1,2} > 0$, and $k_{2,1} = 0$. This is the classical example of first order processes invariably present in all introductory chemical kinetics textbooks. In many cases, chemical reactions are simplified to this mathematical description by the method flooding (i.e., using all the reactants in large excess except the limiting reagent).[41] The stochastic nature of irreversible first order decay is described in some depth and used quite routinely in radioactive decay.[42,43]

In general, stochastic mapping identifies the region of the parameter space in which using stochastic kinetics is inevitable. This also depends on the property that is examined (target variable). Therefore, even for one given scheme, several different maps can be used depending on what the experimentally detectable variable is.

For an irreversible first order reaction, the stochastic region as defined by the time-dependent number of product molecules (A_2) is identified by the following expression:

$$0.01 \leq \sqrt{\frac{e^{-k_{1,2}t}}{(1 - e^{-k_{1,2}t})N_0}}. \quad (29)$$

A graphical representation of the stochastic map is given in Fig. 1. It is quite convenient to use the dimensionless composite variable $k_{1,2}t$ rather than the two parameters individually. This gives a simpler map without any loss of information, as the map only depends on the product of these parameters but not in any other way. The stochastic region in Fig. 1 is located in the lower left-hand corner, whereas the deterministic region lies above it. The map shows experimental data points as well. Point A represents the conditions under which the half-life of the radioactive isotope bismuth-209 was determined.[43] This is probably the isotope with the longest half-life (1.9×10^{19} year) for which the decay constant was determined by real-time monitoring of alpha decay events (41 events in 100 h in a sample of 45,7 g $Bi_4Ge_3O_{12}$). Point A lies firmly in the stochastic region of the map: indeed, the authors of the article used a stochastic method of evaluation,[43] which is standard for extremely slow radioactive decay. The key experimental achievement in that work was the 100% detection efficiency.

Point B in the same map shows the experiments through which the half-life of the isotope tellurium-130 was determined.[42] In this case, a particular piece of Bi_2Te_3 mineral was dated to be 93 million years old by an independent

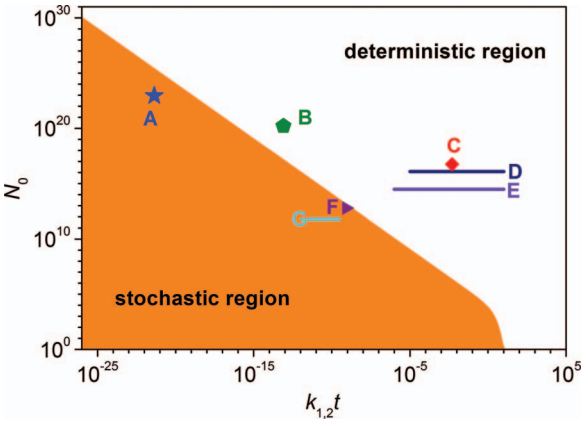

FIG. 1. Stochastic map for the irreversible first order reaction using the number of product molecules as the target variable. A: Conditions for the determination of the half-life of bismuth-209.[43] B: Conditions for the determination of the half-life of tellurium-130.[42] C: Conditions for the $^{40}Ar/^{39}Ar$ dating of jarosite.[44] D: Typical pseudo-first order stopped-flow measurements. E: Typical pseudo-first order laser flash photolysis measurements. F: Single-enzyme kinetics.[45] G: Single-enzyme kinetics.[46]

method and then the decay constant of tellurium-130 was estimated by measuring the excess amount of its daughter isotope xenon-130 enclosed in the crystals. The results showed that the radioactive half-live of tellurium-130 is 7.9×10^{20} years. Although this is longer than for bismuth-209, point B lies in the deterministic region of the map because of the much longer decay time elapsed (93 million years instead of 100 h).

A further experimental point from radiochemistry is defined in Fig. 1 by a study reporting $^{40}Ar/^{39}Ar$ dating of jarosite samples (point C).[44] As already pointed out, kinetic observations can often be simplified to first order mathematics by applying suitably chosen conditions.[41] The range of typical pseudo-first order experiments by the stopped-flow (D) and laser flash photolysis (E) techniques is shown by lines in Fig. 1. Furthermore, the Michaelis-Menten mechanism for enzyme kinetics is also simplified into a pseudo-first order scheme under the limit of low substrate concentration.[13] Two such experiments are shown in Fig. 1: point F describes single enzyme activity studies using Lipase B from *Candida Antarctica*,[45] whereas line G represents similar experimental studies with a β-galactosidase enzyme.[46] Fig. S1 in the supplementary material[36] gives a different, three-dimensional view of the map shown in Fig. 1.

An alternative, somewhat limited version of this map is shown in Fig. 2 for $N_0 = 10^5$. In this graph, the x axis is the same as in Fig. 1, but the y axis shows the expectation of product molecule numbers. The standard error ($\pm\sigma$) of the expectation is also displayed by a pair of blue dotted lines around the expectation. In addition, two independent runs of stochastic simulation for irreversible first order decay carried out by the Gillespie algorithm[47] are also shown. It is clearly seen that the deterministic region lies at reaction times where the standard error line is indistinguishable from the expectation line. The markers in the graph show that the Monte Carlo simulations of the Gillespie method are in excellent agreement with the analytically derived probability data.

Another quite common experimental problem is finding a the value of $k_{1,2}t$ from known values of N and N_0. A stochastic map based on this target variable is shown in Fig. 3. In

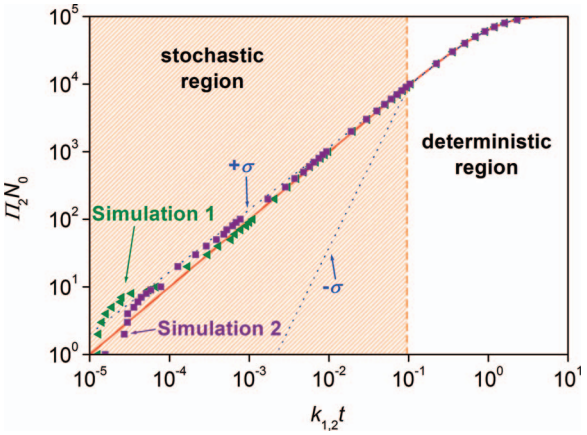

FIG. 2. Expectation of the number of product molecules in the irreversible first order reaction using as a function of dimensionless time. Red solid line: expectation values. Blue dotted lines: standard errors ($\pm\sigma$) of the expectation. Green and purple markers: two runs of simulation using the Gillespie algorithm.

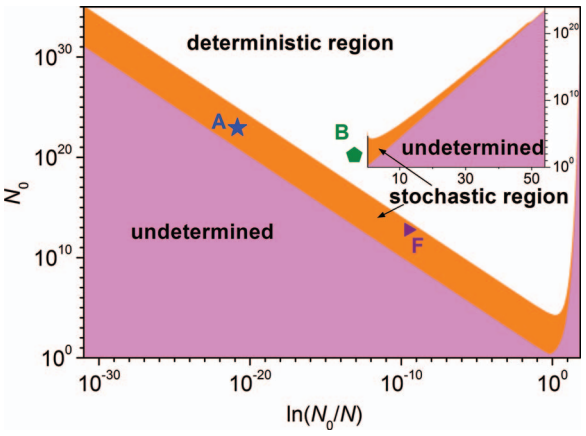

FIG. 3. Stochastic map for the irreversible first order reaction using the product of decay constant and time as the target variable. A: Conditions for the determination of the half-life of bismuth-209.[43] B: Conditions for the determination of the half-life of tellurium-130.[42] F: Single-enzyme kinetics.[45]

practice, this could mean either the determination of the age of a sample using a known rate constant, or determining the rate constant of a process for which the time of experiment is known. If N particles remain in an experiment out of an initial number of N_0, the expectation for $k_{1,2}t$ can be given as follows:

$$\langle k_{1,2}t \rangle = \ln \frac{N_0 + 1}{N + 1}. \tag{30}$$

The standard deviation can be calculated by the following equation:

$$\sigma_{k_{1,2}t} = \ln \left(1 + \sqrt{\frac{N_0 - N}{(N+1)(N_0+2)}} \right). \tag{31}$$

The previous examples from the radioactive decay of the bismuth-209 and tellurium-130 isotopes[42,43] are shown in Fig. 3 as points A and B, whereas results from one of the enzymatic studies with the lipase[45] are represented by point F. The part labeled "undetermined" in Fig. 3 is the part where $N = N_0$ or $N = 0$, in which case no estimate for the value of $k_{1,2}t$ can be given, only lower or upper limits.

Reversible first order reaction

A reversible first order reaction is the case $n = 2$, $k_{1,2} > 0$, and $k_{2,1} > 0$. Only the case $k_{21} = k_{12} > 0$ will be dealt with here as it has experimentally studied relevance in the field of racemization reactions. For the number of product molecules (A_2), the stochastic region is determined as follows:

$$0.01 \leq \sqrt{\frac{1 + e^{-2k_{1,2}t}}{(1 - e^{-2k_{1,2}t})N_0}}. \tag{32}$$

The stochastic map drawn based on Eq. (32) is shown in Fig. 4 (a three-dimensional view is given as Fig. S2 in the supplementary material[36]). Similarly to Figs. 1 and 3, some experimental data are shown on this map. These experimental data were generated using the principle of the amino acid clock,[48,49] which is based on the natural racemization tendency of amino acids. Apart from a few bacterial systems,

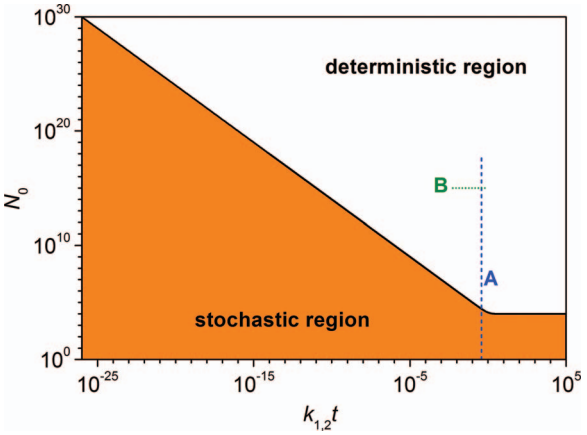

FIG. 4. Stochastic map for the reversible first order reaction using the number of product molecules as the target variable. A: Conditions for Ostrich egg shell dating by amino acid racemization.[48] B: Conditions for silk dating by amino acid racemization.[49]

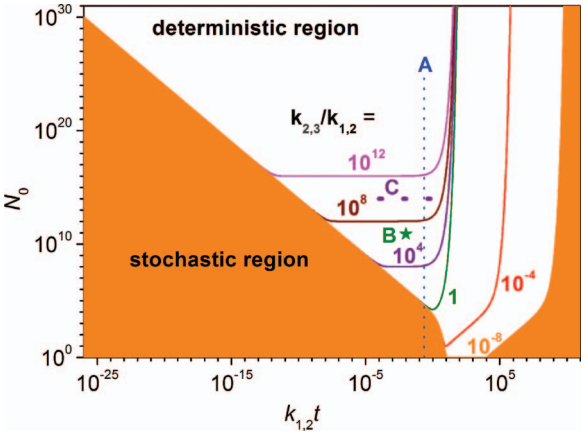

FIG. 5. Stochastic map for the two consecutive first order reactions using the number of intermediate molecules as the target variable. A: Line representing the first two steps of the uranium-238 radioactive decay series with the estimated age of the Universe as reaction time. B: Conditions for ^{230}Th/^{234}U dating of mollusk shells.[50] C: Conditions from a typical double exponential stopped-flow study.[51]

amino acids only occur in life as L enantiomers. As time progresses, D amino acids gradually appear in the remains of organisms because of a natural racemization process. This effect can be used for dating samples when the external temperature is known with reasonable accuracy, although some geochemical technical problems might arise in practice. Vertical line A in Fig. 4 shows results form a study that dated 750 000-year old ostrich eggshells found in the Kalahari desert.[48] These measurements were originally designed to resolve the contradiction in the results obtained in two radiocarbon-based determinations. Unfortunately, the original article does not give information about the sample sizes measured; therefore, a vertical line is used to show the location of the experiments on the map. This line shows that the deterministic description can be used in this case if the number of detected molecules exceeds 10^5 (about 0.2 amol). Silk samples aged 20-2400 years have also been dated based on the same principles.[49] In this case, the line is horizontal because of the overall two orders of magnitude variation in sample ages. All determinations in that study[49] fell into the deterministic region of the model.

Two consecutive irreversible first order reactions

Two consecutive irreversible first order reactions can be described by $n = 3$, $k_{1,2} > 0$, $k_{2,3} > 0$, and $k_{1,3} = k_{2,1} = k_{3,1} = k_{3,2} = 0$ in the general scheme of first order reaction networks. The most commonly used example of these systems is a two-step radioactive decay series. The stochastic map shown in Fig. 5 is based on the number of intermediate (A_2) molecules. The stochastic region can be given by the following expression:

$$0.01 \leq \sqrt{\frac{k_{2,3} - k_{1,2} - k_{1,2}e^{-k_{1,2}t} + k_{1,2}e^{-k_{2,3}t}}{(k_{1,2}e^{-k_{1,2}t} - k_{1,2}e^{-k_{2,3}t})N_0}}. \qquad (33)$$

A special case is $k_{1,2} = k_{2,3}$, which would lead to a somewhat different formula. In the map shown as Fig. 5 (a three-dimensional view is given as Fig. S3 in the supplementary material[36]), the x axis shows $k_{1,2}t$ and the y axis shows N_0 similarly to Figs. 1 and 4. However, the map is also dependent on a parameter other than those displayed on the two axes, this is the ratio of rate constants $k_{2,3}$ and $k_{1,2}$. In Fig. 5, the boundaries between the stochastic and deterministic regions are indicated for six possible ratios between 10^{-8} and 10^{12} by separate lines. Vertical line A is drawn for the $^{238}\text{U} \rightarrow {}^{234}\text{Th} \rightarrow {}^{234}\text{Pa}$ radioactive decays series, where $k_{2,3}/k_{1,2} = 6.7 \times 10^{10}$ and the sample is assumed to be as old as the Universe (1.3×10^{10} years). Another radiochemical example is provided by line B, which represents ^{230}Th/^{234}U dating of mollusk shells.[50] It is also possible to simplify a chemical system to a series of two consecutive irreversible first order reactions by the method of flooding.[41] An example in Fig. 5 is provided by line C, which uses the conditions of a typical double exponential stopped-flow study.[51] An alternative representation similar to Fig. 2 is given in Fig. S4 in the supplementary material.[36] It should be noted that this map can also be used for the first intermediate of a longer series of consecutive first order reactions, as the mathematical description does not depend on the processes appearing later in the system.

The triangle reaction

The unidirectional triangle reaction is obtained by setting $n = 3$, $k_{1,2} > 0$, $k_{2,3} > 0$, $k_{3,1} > 0$, and $k_{2,1} = k_{3,2} = k_{1,3} = 0$ in the general scheme. This scheme has been the notable subject of significant theoretical considerations.[52–57] Only the case $k_{1,2} = k_{2,3} = k_{3,1}$ will be analyzed here, as this is a very special scheme that does not adhere to detailed balance (or microscopic reversibility) yet it does not violate the second law of thermodynamics.[57] It can be shown that sine and cosine functions appear in the solutions in this case from an initial state where only A_1 is present

$$\Pi_1 = \frac{1}{3} + \frac{2}{3}e^{-\frac{3}{2}k_{1,2}t}\cos\left(\frac{\sqrt{3}}{2}k_{1,2}t\right), \qquad (34)$$

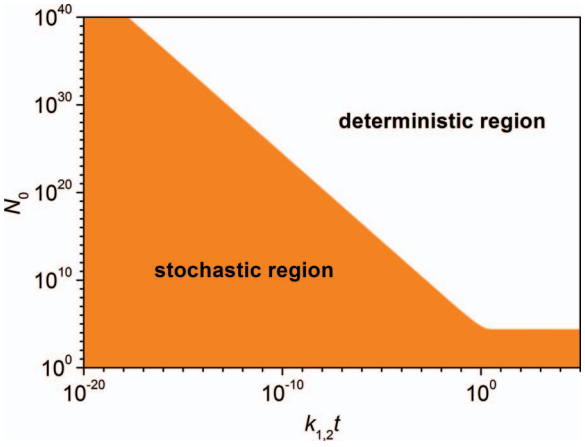

FIG. 6. Stochastic map for the unidirectional triangle reaction using the number of the second product molecule as the target variable.

$$\Pi_2 = \frac{1}{3} - \frac{1}{3}e^{-\frac{3}{2}k_{1,2}t}\cos\left(\frac{\sqrt{3}}{2}k_{1,2}t\right) + \frac{\sqrt{3}}{3}e^{-\frac{3}{2}k_{1,2}t}\sin\left(\frac{\sqrt{3}}{2}k_{1,2}t\right), \quad (35)$$

$$\Pi_3 = \frac{1}{3} - \frac{1}{3}e^{-\frac{3}{2}k_{1,2}t}\cos\left(\frac{\sqrt{3}}{2}k_{1,2}t\right) - \frac{\sqrt{3}}{3}e^{-\frac{3}{2}k_{1,2}t}\sin\left(\frac{\sqrt{3}}{2}k_{1,2}t\right). \quad (36)$$

The stochastic map shown in Fig. 6 can be obtained after some numerical calculations for the number of A_3 molecules as the target variable. Although the scheme itself does not adhere to detailed balance, the map actually looks quite normal. In fact, there is a high amount of similarity with the map of the reversible first order reaction shown in Fig. 4.

Conclusion

This work has shown that the appropriate kinetic approach (stochastic or the deterministic) for any evaluation problem in the field of chemically first order reaction networks can be decided based on stochastic maps. These maps do not only depend on particle numbers, the influence of parameters such as time, rate constants and the identity of the detected target variable is also an important factor. Combinations of parameters (for example, the product of time with a first order rate constant) are often more conveniently used in the construction of stochastic maps than individually considered parameters.

ACKNOWLEDGMENTS

This work was supported by the TÁMOP 4.2.1/B-09/1/KONV-2010-0007 and TÁMOP-4.2.2/B-10/1-2010-0024 projects, which are co-financed by the European Union and the European Social Fund.

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