

Steady State of Stiff Linear Kinetic Systems by a Markov Matrix Method

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The absence of detailed balance in systems containing pseudo-first-order reactions can cause the evaluation of steady-state concentrations to be a difficult computational problem. If the rate constants differ by many orders of magnitude, direct solution for these concentrations from the matrix of rate constants is not practical. The embedded Markov chain generated by the state-changes of one molecule has a transition matrix whose better separation of eigenvalues makes it more suitable for analysis than the matrix of rate constants. Solution for an eigenvector of this matrix by the method of inverse iteration provides an efficient means for obtaining steady-state concentrations.

INTRODUCTION

We [1] have been interested in economically computing the steady state of large numbers of models of the early physicochemical processes of photosynthesis. The models use "first-order kinetics," meaning that they are described by a linear first-order system of differential equations with constant coefficients. The model systems can have 40 or more components, and involve reaction times ranging from 10^{-14} s (for exciton migration) to over 10^9 s (for reverse electron transfers).

When different components of a physical system decay with greatly differing time constants, the differential equations describing the system are said to be "stiff," and great ingenuity may be required to obtain an economical and accurate solution [2-5]. If one wishes only to evaluate the condition of the system at infinite time, the steady state, then the problem is far simpler, but potentially still difficult.

When all of the processes in a linear kinetic system correspond to passive physical or chemical changes, then the principle of detailed balance permits a trivial evaluation of the steady state [6]. However, if one is interested in an open system where not all processes obey detailed balance, then this method of solution is not available.

The conventional numerical techniques fail when faced with a 40×40 coefficient matrix having nonzero elements ranging over 20 orders of magnitude, and they are very expensive when used for somewhat more modest systems. These problems have spurred us to develop a new method which is particularly suitable for the extremely stiff systems we have encountered.

This paper discusses existing techniques for evaluating the steady state of linear systems, and introduces the computational use of an embedded discrete Markov process where a very large dynamic range of rate constants creates a numerical situation which cannot be solved by more conventional techniques.

CONVENTIONAL METHODS

The behavior of a three-state linear kinetic system [7] is described by the following set of equations.

$$\begin{aligned}\frac{dc_1}{dt} &= -(k_{21} + k_{31})c_1 + k_{12}c_2 + k_{13}c_3, \\ \frac{dc_2}{dt} &= k_{21}c_1 - (k_{12} + k_{32})c_2 + k_{23}c_3, \\ \frac{dc_3}{dt} &= k_{31}c_1 + k_{32}c_2 - (k_{13} + k_{23})c_3.\end{aligned}\tag{1}$$

For a general system, this set of equations may be written as

$$\frac{d\mathbf{c}}{dt} = \mathbf{Kc}\tag{2}$$

where

$$k_{jj} = -\sum_{i \neq j} k_{ij}.\tag{3}$$

In chemical kinetics, c_j is the amount or concentration of species j , and k_{ij} is the rate constant for the reaction of species j to form species i . Physiologists interested in interconnected pools of biochemicals might refer to c_j as the amount of a radioactive tracer in compartment j , and k_{ij} as the rate constant for transfer between compartments. A physicist might refer to c_j as the number of atoms in quantum state j , and k_{ij} as the rate constant for transfer between quantum states. An electrical engineer might refer to c_j as the electrical charge on capacitive element j , and k_{ij} as a conductance. We will refer to the c_j as the *concentration of molecules in state j* .

Equation (3) is a consequence of assuming that the system conserves the material whose amount in different states is described by the c_j . A nonconservative N -state system can be handled by adding a $(N + 1)$ st state, with $k_{(N+1)j}$ being the rate constant at which material in state j is lost from the physical system.

In the steady state, the system of Eqs. (2) reduces to

$$\mathbf{Kc} = 0,\tag{4}$$

with auxiliary normalization requirement that

$$\sum_i c_i = 1\tag{5}$$

identifying the c_i as relative concentrations or amounts.

If the rate constants satisfy detailed balance, then the steady-state c_i are determined simply by the equations

$$c_i/c_j = k_{ij}/k_{ji}.\tag{6}$$

For the remainder of this paper, we assume that this simple solution is not available because a number of the rate processes considered are pseudo-first-order, and do not obey detailed balance.

Graph theory, known in chemical kinetics as the King-Altman method, can be used to get an analytic solution for small systems [8, 9]. Unfortunately, the complexity of this approach increases rapidly with the size of the system. A sample system of eight states has a total of 2300 algebraic terms [10].

The set of Eqs. (4) and (5) may not be solved numerically by simply calling on a stock computer program which solves sets of linear equations, because the matrix \mathbf{K} is singular. It is useful to rewrite Eq. (4) as

$$\mathbf{Kc} = 0\mathbf{c}, \quad (7)$$

which makes it clear that what is desired is the eigenvector of \mathbf{K} corresponding to an eigenvalue of zero.

If money is no object, and the rate constants in the system are not too widely divergent, then there are several ways to solve for the steady-state concentrations. However, increased sophistication on the part of the user is repaid with both a substantially more efficient calculation, and the ability to handle problems which are intractable when attacked with simpler methods.

The easiest method, for the user, is to feed the matrix \mathbf{K} to a package of computer programs written to handle general eigensystem problems [11]. The user need only feed in the matrix, and take as his solution the eigenvector corresponding to an eigenvalue of zero. However, the matrix is nonsymmetric: Computer programs written to handle general eigenproblems arising from such matrices perform an arduous transformation on the matrix in order to evaluate all of the eigenvalues [12, 13].

This transformation is expensive, far more so than that required to solve the Hermitian matrices familiar to most physical scientists. In addition, it may be less accurate than more appropriate methods because of the accumulation of roundoff errors during the lengthy computations. In our case, however, the transformation is unnecessary, because much is known about the properties of a rate matrix such as \mathbf{K} .

Gerschgorin's theorem [12, 14] states that every eigenvalue of an n by n matrix \mathbf{A} lies in at least one of the n circular disks in the complex plane which have centers at a_{ii} and radii of $\sum_{j \neq i} a_{ij}$. For the transpose of the matrix \mathbf{K} , these disks are centered at $-\sum_i k_{ij}$ and have radii of $\sum_i k_{ij}$. All of the disks are contained within the largest, which has its center at

$$-\max_j \sum_{i \neq j} k_{ij} \quad (8)$$

and a radius of the same magnitude. See Fig. 1a.

If any state can eventually be reached from any other state, then there is but one eigenvalue of zero, which is a mathematical confirmation that the steady state is unique [7]. Gerschgorin's theorem shows that all of the other eigenvalues have negative real parts [6, 15]. If the principle of detailed balance were obeyed for all closed paths of state changes, then all of the eigenvalues would be strictly real [6, 16, 17].

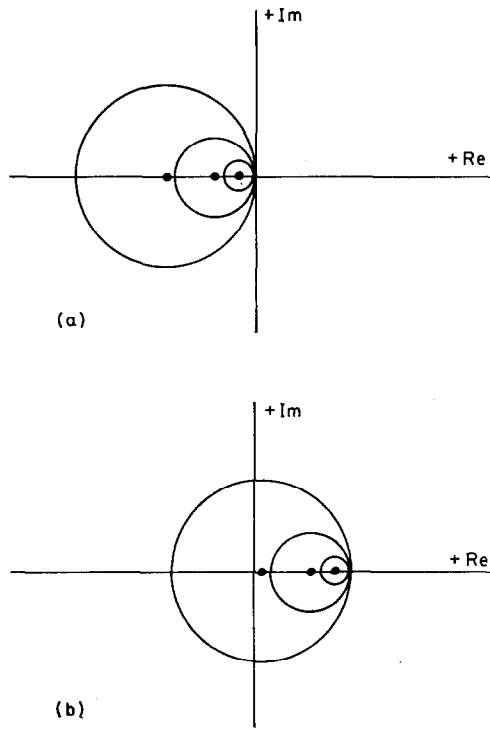


FIG. 1. (a) Gerschgorin disks for the transpose of the rate matrix \mathbf{K} . All eigenvalues lie within the union of the disks, and hence within the largest disk. The desired eigenvalue is at the origin; (b) Gerschgorin disks for the transpose of $\mathbf{K} + s\mathbf{I}$, where $s = 1.1$ times the radius of the largest disk. The desired eigenvalue is now s , and is guaranteed to be larger in absolute value than any other.

Our eigenvalue of interest, zero, is an extremal eigenvalue, at one edge of the disk described in Eq. (8). The most common technique for evaluating an extremal eigenvalue is the power method, also called the matrix iteration method. This technique relies on the fact that

$$\lim_{n \rightarrow \infty} \mathbf{A}^n \mathbf{b} = \lambda_m^n \mathbf{v}_m \tag{9}$$

where \mathbf{b} is an arbitrary vector, λ_m is the eigenvalue of \mathbf{A} which is largest in absolute values, and \mathbf{v}_m is the corresponding eigenvector.

To apply the power method to determine the eigenvector of \mathbf{K} with eigenvalue zero, we must consider the modified matrix $\mathbf{M} = \mathbf{K} + s\mathbf{I}$, where \mathbf{I} is the identity matrix. The eigenvectors of \mathbf{M} are the same as those of \mathbf{K} , but the corresponding eigenvalues are shifted by s . If s is set equal to 1.1 times the maximum sum defined in Eq. (8), then the eigenvector of interest, whose components reflect the relative concentrations of different states, now corresponds to the largest eigenvalue, s . See Fig. 1b. Application of the power method to this modified matrix will, in theory, yield this eigenvector.

The power method is the one discussed by Wei and Prater [18] for use in chemical kinetics, discussed in Wilson, Decius, and Cross [19] for use in the analysis of molecular vibrations, and by Robinson [20] for use in evaluating exciton migration. Unfortunately, the rate of convergence of the power method depends on the ratio of the largest eigenvalue to the next largest. As Wei and Prater noted, this ratio is very close to one in characteristically stiff kinetic systems, so that convergence can be extremely slow.

In our case, however, reliance on the power method is unnecessary, because the eigenvalue of interest, namely zero, is known with complete accuracy. When one knows the eigenvalue of interest, and other eigenvalues are nearby, the numerical method of choice is one known as inverse iteration, which corresponds in essence to applying the power method to the inverse of the original matrix [12, 13]. The algorithm is based on solution of the linear equation system

$$(\mathbf{A} - s\mathbf{I}) \mathbf{x} = \mathbf{b}, \quad (10)$$

where \mathbf{A} is the matrix of interest, and \mathbf{b} is an arbitrary vector, such as $(1, 1, \dots, 1)$. The solution vector \mathbf{x} will approximate the eigenvector whose eigenvalue is closest to s . If \mathbf{b} is replaced by \mathbf{x} and the process repeated, then \mathbf{x} will converge to this eigenvector. When s lies much closer to the desired eigenvalue than to any other eigenvalue, the rate of convergence is quite high. The bulk of the computer program for this technique may be composed of commonly available routines for the solution of a system of linear equations by Gaussian elimination [21].

For most situations, inverse iteration to find the zero eigenvector of the rate matrix \mathbf{K} is a highly accurate and efficient method for evaluating the c_i . However, when the rate constants for the system vary over an extremely wide range, so that the system of equations is very stiff, the matrix \mathbf{K} may become badly ill-conditioned. The requirements of the inverse iteration method are modest, but it is necessary that the precision of the computer use (for example, 10^7 when computations are carried to seven decimal digits) be greater than the ratio

$$\frac{\lambda_n - \lambda_1}{\lambda_2 - \lambda_1} \quad (11)$$

where λ_1 is the eigenvalue whose eigenvector is desired, λ_2 is the eigenvalue nearest to λ_1 , and λ_n is the eigenvalue furthest from λ_1 .

Because of our interest in problems in which this ratio for the \mathbf{K} matrix is prohibitively large, we have been motivated to examine the properties of the discrete Markov process which is mathematically embedded in any linear kinetic system.

THE EMBEDDED PROCESS

In chemical kinetics the c_i of Eqs. (1) through (7) are ordinarily considered to be concentrations. With the normalization requirement stated in Eq. (5), the c_i are relative concentrations.

However, it is possible to give a probabilistic interpretation of these c_i . Instead of focusing on the bulk concentration of molecules in the different states, one can instead concentrate on the fate of an individual molecule as it undergoes conversion into the various states described by Eq. (2). This is known in probability theory as a continuous parameter (time) Markov process [22, 23]. The stochastic equations governing the fate of a particular molecule during the course of time are Eqs. (2), where c_i is now the probability that a particular molecule is in state i , and k_{ij} is the probability per unit time that a molecule in state j will undergo a transition to state i . This stochastic process of course underlies the macroscopic changes in concentration which Eq. (2) is more often used to discuss.

These equations describe the fate of both individual molecules and bulk concentrations because the latter is just a scaled up version of the former. As a consequence of this, any method that we can use to evaluate the stochastic problem more efficiently will be equally applicable to the more general linear kinetics problem.

Until now, we have been treating the problem as a continuous time Markov process. We have been considering the probability that a molecule, being in a particular state, undergoes a change of state in a particular infinitesimal increment of time. The point of view is that of describing a molecule, or an ensemble of molecules, continuously with time.

Let us instead suppose that we describe a molecule only with respect to its changes from one state to another. If the molecule is known to be in state 1, we do not ask *when* it changes to state 2, or to state 3; but only "to which state does it change?" One can then make a list of the states through which a molecule passes, such as 12313213. This series of state changes is a *discrete parameter* Markov process. This discrete process of state changes is said to be *embedded* in the continuous time process. Especially in the queuing literature the embedded process is often examined in preference to the continuous process, frequently because the discrete process is Markovian even when the continuous process is not [22, 23].

When examining our system from this point of view, we no longer ask about the relative probability of being in a particular state at any instant in time, because time is no longer the independent variable. The independent variable is now the integer label describing how many times the molecule has changed states. What we are interested in is the probability that a state change will produce a particular state. We may write a matrix of conditional probabilities \mathbf{P} , whose elements p_{ij} describe the probability that a molecule currently in state i will next be in state j . The matrix \mathbf{P} is known in the probability literature as the one-step transition matrix. Its elements may be constructed quite easily from the rate constants of the system

$$p_{ij} = k_{ji} / \sum_{l \neq i} k_{il} \quad \text{for } i \neq j, \quad (12)$$

$$p_{ii} = 0.$$

The eigenvalues of such a matrix all lie on or within the unit circle on the complex plane, with, for an irreducible chain, as ours is, exactly one eigenvector with eigenvalue

one.¹ The eigenvector of the transpose of \mathbf{P} with eigenvalue 1 is known as the stationary probability vector. Its components describe the relative probability that a change of state of the molecule will produce a particular state. When each component of this vector is multiplied by the lifetime of the corresponding state, the resultant is identical to the steady-state probability vector of the continuous time formalism. Accordingly, the steady-state concentrations of the state of the molecule may be evaluated by a simple transformation of an eigenvector of the matrix \mathbf{P} , as well as by an eigenvector of the matrix \mathbf{K} .

This vector of \mathbf{P} may be determined by either the power method or inverse iteration. As will be demonstrated shortly with examples, application of the power method to \mathbf{P} is usually much more effective than application to \mathbf{K} because of a better separation in eigenvalues. However, since the eigenvalue of interest is known precisely, inverse iteration is also the method of choice in solving for the desired eigenvector of \mathbf{P} .

It should also be noted that the concept of the embedded chain is very useful in designing effective Monte Carlo calculations for the study of time-dependent behavior.

SAMPLE APPLICATIONS

EXAMPLE 1. We begin with the general three-state system, which can readily be solved by hand, and thus display the dependence of the eigenvalues of the matrices \mathbf{K} and \mathbf{P} on the rate constants of the system. The eigenvalues of the rate matrix \mathbf{K} are 0, and $\frac{1}{2}[-B \pm (B^2 - 4C)^{1/2}]$, where

$$B = k_{21} + k_{12} + k_{32} + k_{23} + k_{31} + k_{13},$$

and

$$C = k_{21}k_{23} + k_{21}k_{32} + k_{23}k_{12} + k_{31}k_{12} + k_{31}k_{32} + k_{31}k_{23} + k_{13}k_{21} + k_{13}k_{12} + k_{13}k_{32}.$$

When $4C > B^2$, two eigenvalues will be complex. This will occur, for example [17], when $k_{12} = k_{23} = k_{31} = 0$, $k_{21} = k_{32} = 1$, and $k_{13} = 2$, in which case the eigenvalues are 0 and $-2 \pm i$.

In most cases, however, quite the opposite will be true, with $B^2 \gg C$. This will occur whenever one or both of the rate constants connecting one pair of states (call them a and b) are much greater than the rate constants connecting a and b to the third state. With $C/B^2 \ll 1$, the eigenvalues become 0, $-C/B$, and $-B + C/B$.

If one were to apply the power method to this \mathbf{K} matrix, not knowing the analytic solution, the first step would be to shift the desired eigenvalue into prominence by adding 1.1 times the maximum sum (8) along the diagonal of \mathbf{K} . For this system, the

¹ The chain being irreducible means that any state can eventually be reached from any other state. Application of Gerschgorin's theorem to \mathbf{P} proves that all of the eigenvalues have a modulus less than or equal to one. From the definition of a stochastic matrix it follows that \mathbf{P} has an eigenvalue 1 with eigenvector (1, 1, ..., 1), while Frobenius's theorem states that, for any irreducible nonnegative matrix, all eigenvalues of maximal modulus are distinct. See [24].

maximum sum lies between $B/3$ and B . For $B^2 \gg C$, the ratio of the desired eigenvalue to the next largest is thus approximately $1 + C/B^2$ after shifting. Convergence of the power method is dependent on this ratio being significantly greater than 1, so the use of this method is clearly inappropriate whenever the rate constants connecting one pair of states is many times the rate constants connecting another pair.

With $B^2 \gg C$, the ratio (11) for determining the usefulness of inverse iteration on the \mathbf{K} matrix becomes B^2/C . When this ratio is less than 1% of computer precision, inverse iteration will be very effective. This requirement is far less stringent than that necessary for effective use of the power method, but it can easily be violated when the range of rate constants is sufficiently large.

The transition matrix \mathbf{P} of the embedded chain of state changes has eigenvalues of 1 and $-\frac{1}{2} \pm \frac{1}{2}(1 - 4D/A)^{1/2}$, where

$$A = (k_{21} + k_{31})(k_{12} + k_{32})(k_{13} + k_{23}),$$

and

$$D = k_{21}k_{32}k_{13} + k_{12}k_{23}k_{31}.$$

To illustrate the advantages of using the \mathbf{P} matrix, let us consider the worst possible situation: The separation between the desired eigenvalue, 1, and the other eigenvalues is at a minimum when $D = 0$, in which case the eigenvalues are 1, -1 , and 0.

After adding 0.5 along the diagonal of \mathbf{P} to shift the desired eigenvalue into prominence, the ratio of this eigenvalue to the next largest is 3. This is sufficient to assure fairly rapid convergence with the power method, independent of the actual values of the rate constants.

In this worst possible situation, the ratio (11), which determines the usefulness of inverse iteration, is 2. This is of course far less than the precision of any computer, and guarantees extremely rapid convergence.

EXAMPLE 2. As a second example, we consider a highly simplified version of the problem [1], quantum conversion in photosynthesis, which stimulated this work. This example is too complex to be conveniently handled by analytic techniques, but it remains small enough, and has a sufficiently modest range of rate constants, that numerical solution for all eigenvalues of the \mathbf{K} and \mathbf{P} matrices is possible. This permits comparison of the merits of different numerical methods for determining the steady-state concentration.

Consider a system composed of two molecules, P and A . P is a specialized chlorophyll which, when electronically excited, can transfer an electron to an acceptor A . A then transfers the electron to a secondary acceptor, not considered to be a part of the system, and P is reoxidized by a secondary donor, also not a part of the system.

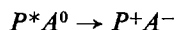
P has three stable conditions: P^0 , ground state; P^* , electronically excited; and P^+ , oxidized. A has two conditions: A^0 , oxidized; and A^- , reduced. The system has a total of six states, corresponding to each possible condition of each molecule.

The allowed reactions are as follows:

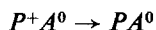
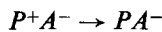
(a) electronic excitation



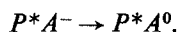
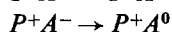
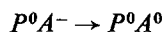
(b) initial electron transfer



(c) P restoration



(d) A restoration



Reasonable rate constants (in s^{-1}) for each of the reactions in these four categories are $+a, 1$; $-a, 10^8$; $+b, 10^{11}$; $-b, 10^5$; $+c, 10^6$; $-c, 10^3$; $+d, 10^4$; $-d, 10^2$.

With these rate constants, the eigenvalues of the rate matrix \mathbf{K} are 0, -1.01×10^4 , -1.00×10^6 , -1.01×10^6 , -1.00×10^8 , and -1.00×10^{11} . The eigenvalues of the transition matrix \mathbf{P} are 1, -1.00000 , ± 0.43 , and ± 0.007 .

Relative to its distance from the furthest eigenvalue, the eigenvalue 0 of the matrix \mathbf{K} is degenerate with the nearest eigenvalue to 1 part in 10^7 . Use of the power method on \mathbf{K} is thus completely out of the question. With 10 or more decimal digits of machine accuracy, one *could* use inverse iteration on \mathbf{K} , but any further spreading of the eigenvalues would cause trouble very quickly.

On the other hand, the eigenvalue 1 of the matrix \mathbf{P} is well separated from the others. One could use the power method: After shifting by 0.5, the ratio of the desired eigenvalue to the next largest would be 1.7. However, in our computing experience with comparable but somewhat larger systems, the eigenvalue 1 is often degenerate with its nearest neighbor to within 1 part in 100. Even though convergence can be obtained with the power method, it is with computing charges 10 to 100 times those for the more efficient inverse iteration method.

CONCLUSIONS

After reviewing methods available for determining the steady state of a linear kinetic system, we have considered the stochastic processes that underlie any such system. Because of the homology between linear kinetic processes and Markov processes, any numerical method suitable for a Markov process is also applicable to linear kinetic systems.

Two matrices can be constructed from the rate constants for state-to-state transitions. One is the rate matrix of the kinetic system and of the underlying continuous time Markov process. The other is the one-step transition matrix of the embedded discrete-parameter Markov chain of state changes. Of the two, the transition matrix almost always has a much better relative separation of the desired eigenvalue, making determination of the corresponding eigenvector easier.

Each of the two matrices can be subjected to two different techniques to get the eigenvector desired: the power method, and inverse iteration. Inverse iteration is by far the more powerful, but it is somewhat more difficult to program than the power method.

Of all the techniques available, inverse iteration on the transition matrix is by far the best for the stiff equations characteristic of many kinetic systems. Inverse iteration on the rate matrix is quite satisfactory whenever the range of rate constants is much less than the precision of the computer used, but seems to present no advantages over use of the transition matrix.

Use of the power method on the transition matrix is not as efficient as use of inverse iteration, but the computation is usually quite fast for small systems. Simplicity of programming makes it attractive for the casual user.

The power method on the rate matrix almost always gives quite slow convergence, and should be avoided.

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