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A Full Stochastic Description of the Michaelis-Menten Reaction for Small Systems

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A method is presented to solve the Komogorov-equations for the stochastic model of the Michaelis-Menten reaction. The results are given for the case when only one enzyme molecule is involved in the reaction and can be extended to the case when a few enzyme molecules react. The important differences between the results of stochastic and deterministic treatment are emphasized, and their possible biological implications are discussed. Beside the exact solution of the time course of the irreversible reaction also the equilibrium is described for the reversible reaction. The method provides means for studying other biologically important reactions assuming stochastic behaviour. A comperison is made also with the steady state approximation.

Introduction

Since Delbrück (1940) first used the theory of stochastic processes to approach the kinetics of a reaction of autocatalytic type, and of biological interest, there appeared papers from time to time in the literature by different authors attempting to give a stochastic description of a variety of reactions important in biochemistry. The authors had to cope with considerable mathematical difficulties, especially when complex mechanisms involving elementary steps of second order (e.g. the Michaelis-Menten mechanism) were considered. It was inferred in several papers and has become a widely accepted view that the expectation value obtained by the rather cumbersome methods, and – when really computed – distorted by a series of approximations, differs only slightly from the solutions of the differential equations stemming from the deterministic model. Moreover, the coefficient of variation i.e. the relative standard deviation tends to zero as the number of reacting molecules tends to infinity. As in the case of test tube reactions the number of molecules is generally larger than 10^{10}, the condition for the variance to be neglected is fulfilled. It was roughly concluded therefore that it is an unnecessary complication of the biochemists' work to use a stochastic approach (Heyde, Heyde, 1969, 1971), Only few people were against this view, realizing that a small number effect, or heterogeneity effect should be taken into consideration when systems – not too rare in biochemistry – are investigated which comprise only a small number of at least one of the reactants (Stuart, Branscombe, 1971; Smeach, Smith, 1973). This situation can be the consequence of compartmentalization.

One could think for instance of a specific sequence of DNA that may be present only in a single copy in one cell, or of hydrogen ions of which only one or two can be found at the phsiological pH in a subcellular compartment (Friedrich, 1974). An E. coli cell contains on the average about 20 lac repressor protein molecules, but cells with much less of them should exist in a not absolutely homogeneous population (Stuart, Branscombe, 1971). From a functional point of view a membrane unit can be considered independent of the other thousands of units in the same membrane and the kinetics of the enzymes being present in it in a very limited number duly deserve the elaboration of suitable stochastic models. Indeed, for membrane bound enzymes this work has partly been done (Smeach, Smith, 1973; Smeach, Gold, 1975a, b,).

The aim of the present paper is to solve the stochastic model of the frequently examined Michaelis-Menten mechanism not in the complicated general case, but for small systems including one or few enzyme molecules. We wish to emphasize the important deviation from the deterministic model. The position of the equilibrium in the reversible case is also examined.

Time course of the irreversible reaction

a) *The model*

In this section we first specify a stochastic model for the Michaelis-Menten reaction

$$E + S \rightleftharpoons C \rightarrow E + P \qquad (I)$$

where E, S, C and P stand for enzyme, substrate, enzyme-substrate complex and product molecules, respectively. This model does not differ significantly from that given by Bartholomay (1962) and later by Jachimowski et al. (1964). It is even restricted in the sense that it permits only the participation of one enzyme molecule. This crucial simplification, which is, however, justifiable for several biologically important systems, allows us to give an exact solution of the differential equations which will emerge. Furthermore, this solution consists of finite sums of exponential functions. It is by no means complicated, and lends itself easily to comparative studies with the deterministic solution.

The basic assumptions are as follows:

1. We investigate a cell compartment of sufficiently small volume that contains one enzyme molecule, and several substrate molecules. The number of substrate molecules is not limited.

2. At a given moment the enzyme molecule may be free, or complexed with one substrate molecule.

3. The enzyme-substrate complex may dissociate into free enzyme and substrate or enzyme and product molecules.

4. All the substrate molecules act in a stochastically independent and identical manner.

5. The product molecules can neither undergo chemical transformation nor influence the interaction between the enzyme and a substrate molecule.

6. The compartment considered is independent of its environment or the similar compartments inside or outside the cell.

Now we define a stochastic vector process $\{(\xi(t), \zeta(t); 0 \leq t\}$ which is a discrete state, continuous time Markov process with stationary transition probabilities, where the random variable $\xi(t) = 0$, if the enzyme is complexed, and $\xi(t) = 1$ if it is free; the random variable $\zeta(t)$ denotes the number of substrate molecules at a given time, and its value can vary over all the natural numbers from 0 to S_0. The model is completely specified by the infinitesimal transition probabilities (Table 1).

We assume that all the transitions occurring in the interval $(t, t+\Delta t)$, except those given in Table 1, are of probability $o(\Delta t)$. The probability that more than one transition takes place in the interval $(t, t+\Delta t)$ is also $o(\Delta t)$. The probabilities of transitions to state (e, s), where $e < 0$, $e > 1$, $s < 0$ or $s > S_0 - 1 + e$ are zero.

We can easily see that state (1,0) is absorbing. So we defined a finite state Markov process with an absorbing state accessible from any other state. Thus, the process has a unique limiting distribution, namely

$$\lim_{t\to\infty} P(e, s; t) = \begin{cases} 1, & \text{if } e = 1,\ s = 0, \\ 0 & \text{otherwise.} \end{cases}$$

(See the Appendix and Arányi, 1976).

So we obtained the not too astonishing result, that, in the limit, our model gives the same result as the deterministic one: after infinitely long time all the substrate molecules are transformed to product molecules and the enzyme is recovered.

Table 1

Infinitesimal transition probabilities

Reaction	Transition	Probability
$E + S \xrightarrow{k_1} C$	$(e, s) \to (e-1, s-1)$	$k_1 \cdot e \cdot s \cdot \Delta t$
$C \xrightarrow{k_{-1}} E + S$	$(e, s) \to (e+1, s+1)$	$k_{-1}(1-e)\,\Delta t$
$C \xrightarrow{k_2} E + P$	$(e, s) \to (e+1, s)$	$k_2(1-e)\,\Delta t$

b) *The time course of the stochastic process*

The absolute probability functions can be determined from the Kolmogorov-equations (1)

$$\frac{\mathrm{d}\,\mathrm{P}(e,s;t)}{\mathrm{d}t} = k_{-1}(2-e)\,\mathrm{P}(e-1,s-1;t) + k_2(2-e)\,\mathrm{P}(e-1,s;t) + \tag{1}$$
$$+ k_1(e+1)(s+1)\,\mathrm{P}(e+1,s+1;t) - [k_1 e s + (k_{-1}+k_2)(1-e)]\,\mathrm{P}(e,s;t)$$
$$(e = 0,1;\ \mathrm{P}(e,s;t) \equiv 0, \quad \text{if} \quad e<0,\ e>1,\ s<0 \quad \text{or} \quad s > \mathrm{S}_0 - 1 + e)$$

through the generating functions. Since the infinitesimal transition probability corresponding to the reaction

$$\mathrm{E} + \mathrm{S} \rightarrow \mathrm{C}$$

is proportional to the number of enzyme as well as of substrate molecules, the partial differential equation to be solved will contain a second order derivative, and cannot be solved exactly (Bartholomay, 1962).

One can define, however, marginal generating functions (Smeach, Smith, 1973) as follows:

$$G_e(z,t) = \sum_{s=0}^{S_0-1+e} z^s \mathrm{P}(e,s;t) \quad (e = 0,1;\ t \geq 0)$$

Equation (1) can be transformed into a system of partial differential equations for the marginal generating functions by multiplying by z^s and summing over s.

$$\frac{\partial G_e(z,t)}{\partial t} = k_1(e+1)\frac{\partial G_{e+1}(z,t)}{\partial z} - k_1 e z \frac{\partial G_e(z,t)}{\partial z} -$$
$$- (k_{-1}+k_2)(1-e)\,G_e(z,t) + (k_2+k_{-1})\,z(2-e)\,\mathrm{G}_{e-1}(z,t) \quad (e=0,1) \tag{2}$$

A simple substitution reveals that the following pair solves equation (2) for a more detailed treatment of equation (2) (see Arányi, 1976)

$$G_0(z,t) = \bar{\Gamma}\exp\left[-\frac{k_{-1}}{k_1}(z-1)\right]\exp(-k_2 t) + \bar{\bar{\Gamma}}\frac{k_{-1}+k_2}{k_{-1}z+k_2}\exp\left[-(k_1+k_2)t\right] +$$
$$+ \sum_{i=1}^{2}\sum_{n=0}^{\infty}\Gamma_i^{(n)}\left[\frac{k_2-(k_2+\lambda_i^{(n)})\,z}{-\lambda_i^{(n)}}\right]^{q_n} e^{\lambda_i^{(n)}t};$$

$$G_1(z,t) = \Gamma^{(-1)} - \bar{\Gamma}\exp\left[-\frac{k_{-1}}{k_1}(z-1)\right]\exp(-k_2 t) - \bar{\bar{\Gamma}}\exp\left[-(k_{-1}+k_2)t\right] -$$
$$- \sum_{i=1}^{2}\sum_{n=0}^{\infty}\Gamma_i^{(n)}\left[\frac{k_2-(k_2+\lambda_i^{(n)})\,z}{-\lambda_i^{(n)}}\right]^{q_n+1} e^{\lambda_i^{(n)}t} \tag{3}$$

where

$$\lambda_i^{(n)} \neq -k_2, \quad q_n = -\frac{\lambda_i^{(n)2} + (k_{-1}+k_1+k_2)\,\lambda_i^{(n)} + k_1 k_2}{k_1(k_2+\lambda_i^{(n)})}, \quad i = 1,\ 2$$

The constants Γ can be determined from the initial conditions:

$$G_0(1, t) + G_1(1, t) = 1 \qquad \text{(a)}$$

$$G_0(z, 0) \equiv 0 \qquad \text{(4) (b)}$$

$$G_1(z, 0) = z^{S_0} \qquad \text{(c)}$$

The conditions (4) are of a deterministic type.

Assuming that the solutions $G_e(z,t)$ to (2) subject to (4) are true generating functions, i.e. are polynomials of finite degree in z, it can be shown that the summation contains a finite number of terms only, and $\bar{\Gamma} = \bar{\bar{\Gamma}} = 0$, if $k_{-1} \neq 0$. The q's are integers, $0 \leq q_n \leq S_0 - 1$, $(q_n = n)$ and the λ's are the roots of the equations

$$\lambda^2 + [k_{-1} + k_1(n + 1) + k_2]\,\lambda + k_1 k_2(n + 1) = 0 \quad (n = 0, 1, \ldots, S_0 - 1) \qquad (5)$$

All the λ's are different negative real numbers. If we take stochastic initial conditions instead of (4) (b) and (c), i e. $G_0(z,0)$ and $G_1(z,0)$ are polynomials in z of degrees less than $S_0 - 1 + e$, the solution pair still would contain a finite number of terms only, but of course, the Γ's would be different.

The absolute probabilities can be calculated from the generating functions according to equation (6):

$$P(e, s; t) = \frac{1}{s!} \left. \frac{\partial^s G_e(z, t)}{\partial z^s} \right|_{z=0} \qquad (6)$$

Consequently the absolute probabilities themselves are finite sums of exponential functions. They of course, are solutions of the Kolmogorov-equations with the initial conditions

$$P(e, s; 0) = \begin{cases} 1, \text{ if } e = 1, s = S_0 \\ 0 \text{ otherwise.} \end{cases} \qquad (7)$$

The linear algebraic equation system for $\Gamma_j^{(n)}$ obtained from (4) has a unique solution (its determinant is nonvanishing). These parameters, together with $\bar{\Gamma} = \bar{\bar{\Gamma}} = 0$ permit us to calculate $P(e,s;t)$ functions that satisfy the Kolmogorov equation system. As the state space is finite, the latter has a unique solution that can be obtained by means of marginal generating functions.

c) *Comparison with the deterministic model*

The differential equations serving as a deterministic model to reaction (1) – assuming $E_0 = 1$ – are as follows:

$$\begin{aligned} \frac{d[E]}{dt} &= -k_1 [E] [S] + (k_{-1} + k_2)(1 - [E]) \\ \frac{d[S]}{dt} &= -k_1 [E] [S] + k_{-1}(1 - [E]) \end{aligned} \qquad (8)$$

where brackets mean concentrations. For the sake of comparison the fixed reaction volume can be taken unity so that concentrations or molecule numbers are expressed by the same value. The initial conditions are

$$[\mathrm{E}](0) = 1, \quad [\mathrm{S}](0) = \mathrm{S} \tag{9}$$

No exact solution to system (8) subject to conditions (9) can be found. It comes from the nature of the deterministic model that – in contrast to the stochastic one – it does not become simpler when the number of reacting molecules is diminished, say to one molecule each. It can easily be shown, as pointed out by many people, that stochastic means are subject to differential equations very similar to (8) with the initial conditions (9). The only difference is that at the right hand sides $\mathrm{E}(\xi \cdot \zeta)$ occurs instead of $\mathrm{E}(\xi)\,\mathrm{E}(\zeta)$. (Here $\mathrm{E}(\ )$ means expected values. As $|\,\mathrm{E}(\xi \cdot \zeta) - \mathrm{E}(\xi)\mathrm{E}(\zeta)\,| \leq \mathrm{D}(\xi)\mathrm{D}(\zeta)$, $\mathrm{D}(\ )$ means standard deviation, the deterministic solution approaches the stochastic means as $\mathrm{D}(\xi)\mathrm{D}(\zeta)$ tends to zero. The differences between them may become large when the standard deviations are relatively large numbers. The relative difference vanishes as the number of substrate (or in the general case of enzyme) molecules tends to infinity.

Figures 1–4 serve the comparison. The deterministic solutions were obtained by a computer program using the Runge-Kutta approximation. As $S_0 = 1$ was assumed, the marginal generating functions are

$$\begin{aligned} G_0(z,t) &= [k_1/(\lambda_1^{(0)} - \lambda_2^{(0)})]e^{\lambda_2^{(0)}t} - [k_1/(\lambda_1^{(0)} - \lambda_2^{(0)})]\, e^{\lambda_1^{(0)}t} \\ G_1(z,t) &= 1 - [k_1/(\lambda_1^{(0)} - \lambda_2^{(0)})]\,\{[k_2 - (k_2 - \lambda_2^{(0)})\,z]/(-\lambda_2^{(0)})\}\, e^{\lambda_2^{(0)}t} + \\ &+ [k_1/(\lambda_1^{(0)} - \lambda_2^{(0)})]\,[k_2 - (k_2 + \lambda_1^{(0)})\,z]/(-\lambda_1^{(0)})\, e^{\lambda_1^{(0)}t} \end{aligned} \tag{10}$$

where

$$\lambda_{1,2}^{(0)} = -(k_{-1} + k_1 + k_2)\left(1 \pm \sqrt{1 - 4k_1k_2/(k_{-1} + k_1 + k_2)^2}\right)/2$$

The standard deviations are rigorously zero at $t = 0$.

They assume their maxima when $\mathrm{E}(\xi) = 1/2$ or $\mathrm{E}(\zeta) = 1/2$, as they can be given by equation (11)

$$\mathrm{D}(\xi) = [\mathrm{E}(\xi) - \mathrm{E}^2(\xi)]^{1/2}, \quad \mathrm{D}(\zeta) = [\mathrm{E}(\zeta) - \mathrm{E}^2(\zeta)]^{1/2} \tag{11}$$

(Note that ξ and ζ can assume only 0 and 1.)

The standard deviations tend to zero when $t \to \infty$, but the coefficient of variation $\mathrm{D}(\zeta)/\mathrm{E}(\zeta)$ is growing to infinity.

It can be seen that, depending on the actual values of the rate constants k_1, k_{-1}, and k_2, the differences between the stochastic means and the deterministic solution may assume relatively large values for the substrate, even 20–30 per

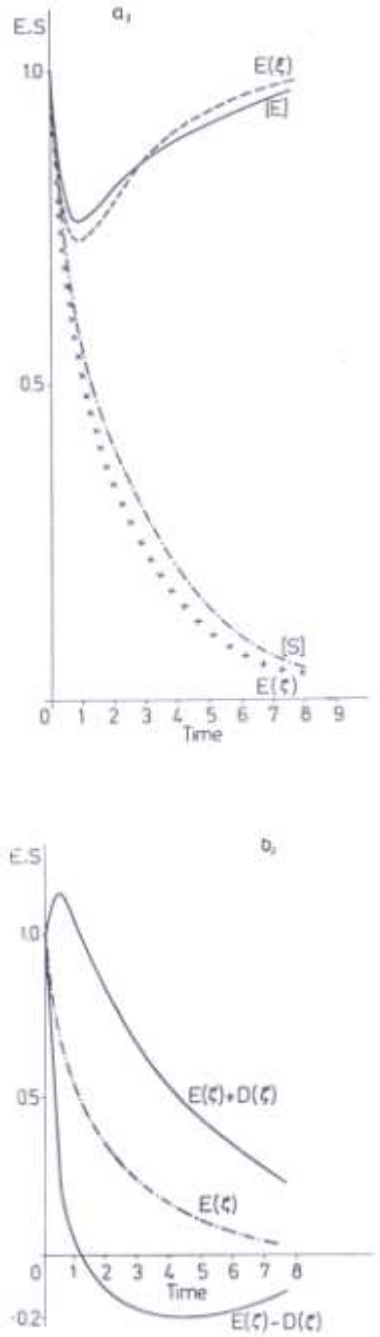

Fig. 1. Time course of the Michaelis-Menten reaction. $k_1 = 1$, $k_{-1} = 1$, $k_2 = 1$. Solutions to equation (8) ([E], [S]) and stochastic expected values [E(ξ), E(ζ)] are compared (a). The stochastic expected value E(ζ) is plotted together with its variance (b).

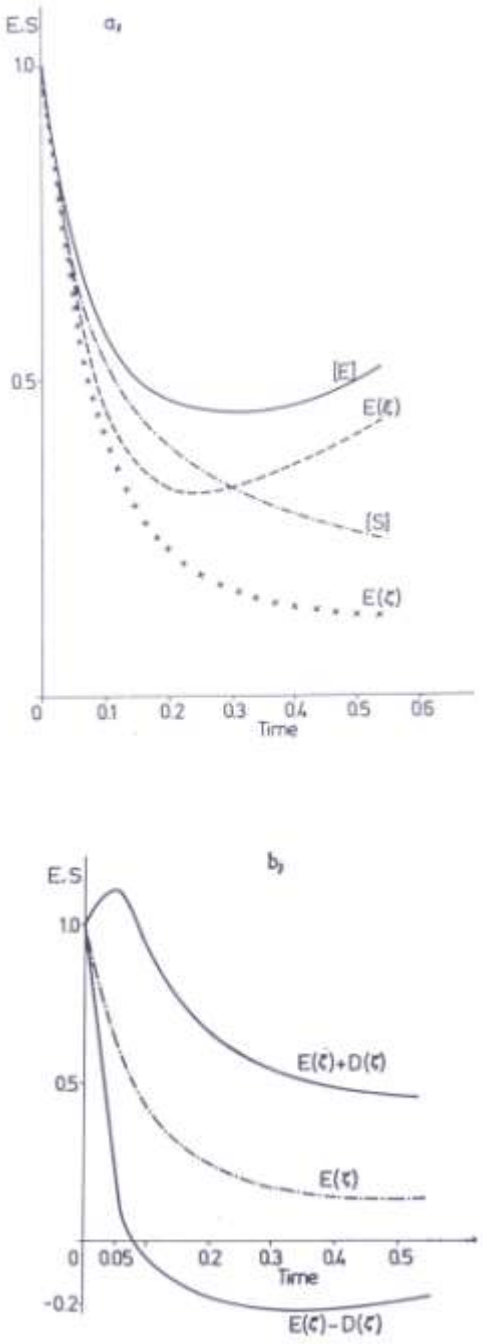

Fig. 2. Time course of the Michaelis-Menten reaction. $k_1 = 10$, $k_{-1} = 2$, $k_2 = 1$. Solutions to equation (8) ([E], [S]) and stochastic expected values [E(ζ), E(ζ)] are compared (a). The stochastic expected value E (ζ) is plotted together with its variance (b).

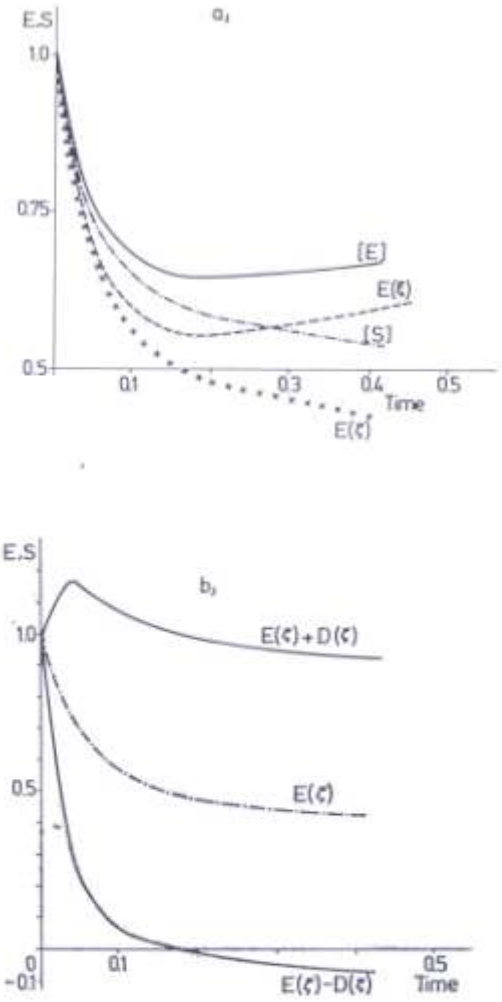

Fig. 3. Time course of the Michaelis-Menten reaction. $k_1 = k_{-1} = 10$, $k_2 = 1$. Solutions to equation (8) ([E], [S]) and stochastic expected values [E(ξ), E(ζ)] are compared (a). The stochastic expexted value E(ζ) is plotted together with its variance (b).

cent of the deterministic functions, which, as a rule, always run higher. This difference can by no means be neglected *a priori*.

Fig. 4.a shows for comparison the function $\tilde{S}(t)$ obtained by assuming a steady state throughout the reaction. Not much to our astonishment at the beginning of the reaction it approximates the deterministic solution to a lesser extent than the stochastic mean. Namely, the latter ones are exactly the same as $t \to 0$ (or $t \to \infty$) due to the initial conditions (4).

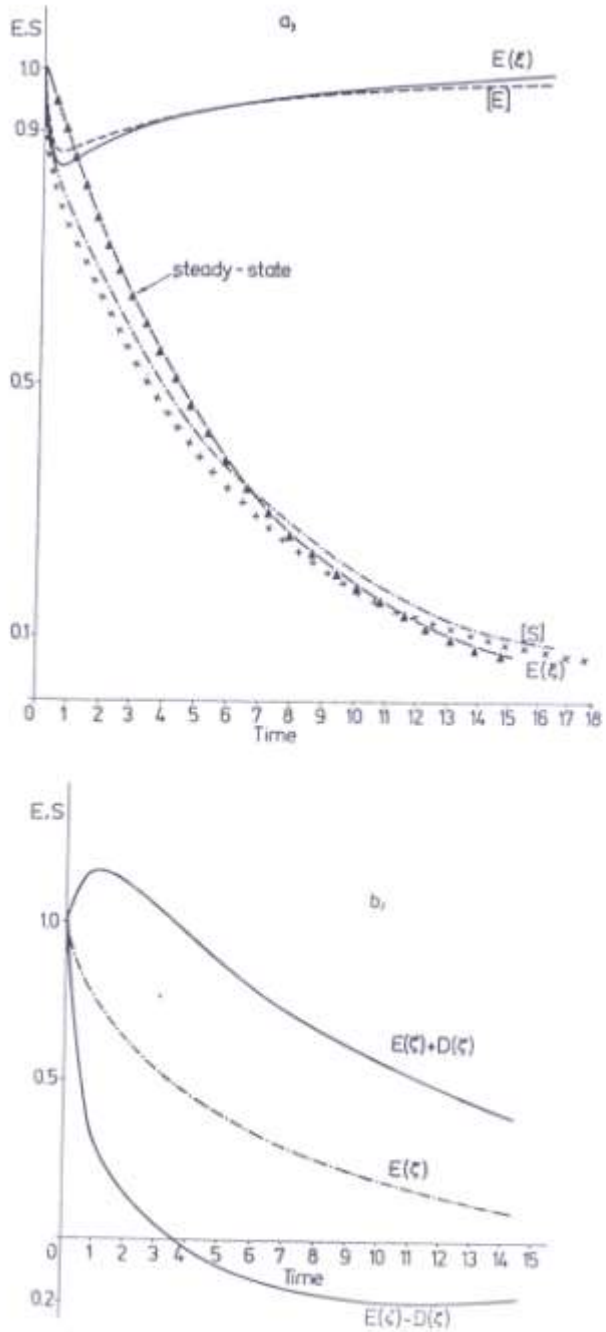

Fig. 4. Time course of the Michaelis-Menten reaction $k_1 = 2\ k_{-1} = 10\ k_2 = 1$. Solutions to equation (8) ([E], [S]) and stochastic expected values [E(ξ), E(ζ)] are compared (a). The stochastic expected value E(ζ) is plotted together with its variance (b). The steady state approximation to the function [S] (t) is also given (a).

The reversible reaction

The basic assumptions on which a stochastic model is based for the reaction

$$E + S \leftrightharpoons C \leftrightharpoons E + P \tag{II}$$

are identical with those itemized in section 2.a, except that product molecules are allowed to interact with the enzyme (cf, assumption 5). Correspondingly, we have to add a reaction to Table 1 of infinitesimal transition probabilities:

$$E + P \xrightarrow{k_{-2}} C$$

This reaction means a transition $(e, s) \to (e-1, s)$ with an infinitesimal transition probability $k_{-2}e\ (S_0-s-1+e)\ \Delta t$.

The absolute probabilities can be determined in the same way as for reaction (I). Here only equilibrium will be considered in detail.

The Markov process defined for reaction (II) is irreducible. Its state space is finite and so it has a unique limit distribution (Rényi, 1954). So the problem of investigating the equilibrium is well set in this sense.

Introducing the following notation

$$F_e(z) = \lim_{t\to\infty} G_e(z, t)$$

we have the following partial differential equations

$$\begin{aligned}(k_{-1} - k_{-2}z)\frac{dF_1(z)}{dz} &= -k_{-2}S_0F_1(z) + (k_{-1} + k_2)F_0(z)\\ (k_{-2} - k_1)z\frac{dF_1(z)}{dz} &= k_{-2}S_0F_1(z) - (k_{-1}z + k_2)F_0(z)\end{aligned} \tag{12}$$

and the condition

$$F_0(1) + F_1(1) = 1 \tag{13}$$

whose solutions are (Arányi, 1976):

$$\begin{aligned}F_0(z) &= [k_1k_{-2}S_0(k_{-1}k_{-2}+k_1k_2+k_1k_{-2}S_0)]\,[(k_{-1}k_{-2}z+k_1k_2)/(k_{-1}k_{-2}+k_1k_2)]^{S_0-1}\\ F_1(z) &= [(k_{-1}k_{-2} + k_1k_2)/(k_{-1}k_{-2} + k_1k_2 + k_1k_{-2}S_0)]\times\\ &\quad\times[(k_{-1}k_{-2}z + k_1k_2)/(k_{-1}k_{-2} + k_1k_2)]^{S_0}\end{aligned} \tag{14}$$

Solution to the general problem when $k_1 = k_{-2}$ was given by Darvey and Staff (1967), and, without restriction by Staff (1970). Again, however, the case of few molecules has not been discussed in detail. The absolute probability functions can be obtained from (14) using equation (6) after taking the limit $t \to \infty$ at both

sides. For comparison with the deterministic model we give an expression for the stochastic mean

$$E(\zeta(\infty)) = \frac{k_1 k_{-1} k_{-2}^2 S_0^2}{(k_{-1}k_{-2}+k_1k_2)(k_{-1}k_{-2}+k_1k_2+k_1k_{-2}S_0)} + \\ + \frac{(k_{-1}k_{-2}+k_1k_2-k_1k_{-2})k_{-1}k_2 S_0}{(k_{-1}k_{-2}+k_1k_2)(k_{-1}k_{-2}+k_1k_2+k_1k_{-2}S_0)} \quad (15)$$

Its deterministic counterpart from the condition $\frac{d[E]}{dt} = \frac{d[S]}{dt} = 0$ is

$$[S](\infty) = \frac{k_{-1}}{2k_1(k_{-1}k_{-2}+k_1k_2)}\{[(S_0-1)k_1k_{-2}-k_1k_2-k_{-1}k_{-2}] + \\ + [(k_1k_{-2}(S_0+1)+k_1k_2+k_{-1}k_{-2})^2 - 4k_1^2k_{-2}^2S_0]\} \quad (16)$$

When S_0 assumes large values, both $E(\zeta(\infty))$ and $[S](\infty)$ approach $S_0 = \frac{k_{-1}k_{-2}}{k_{-1}k_{-2}+k_1k_2}$ i.e. the difference between the stochastic and deterministic equilibria vanishes. In Table 2 numerical values are given for $E(\zeta(\infty))$ and $[S](\infty)$ at different k sets and S_0 values.

Table 2

Comparison of deterministic substrate molecule numbers with stochastic means at equilibrium

S_0	k_{-1}	k_{-2}	k_1	k_2	$E(\zeta(\infty))$	$[S](\infty)$	$\frac{[S](\infty)-E(\zeta(\infty))}{[S](\infty)}$
1	2	1	1	1	0.400	0.457	0.125
1	10	1	1	1	0.476	0.577	0.175
1	100	1	1	1	0.498	0.614	0.189
1	1000	1	1	1	0.500	0.618	0.191
3	10	1	1	1	2.062	2.110	0.023
10	10	1	1	1	8.272	8.280	0.001
1	100	1	120	1	0.008	0.058	0.862
1	15	1	10	1	0.086	0.200	0.570
3	15	1	10	1	1.232	1.245	0.010
10	15	1	10	1	5.410	5.411	0.000
1	1	1	1000	1	0.000500	0.000618	0.191
1	1	1	10	1	0.048	0.058	0.172
3	1	1	10	1	0.206	0.211	0.024
10	1	1	10	1	0.827	0.828	0.001
1	2	10	1	10	0.625	0.627	0.003
3	2	10	1	10	1.889	1.894	0.003
10	2	10	1	10	6.400	6.406	0.001

Conclusions

What inferences can be drawn for real systems from a stochastic model which is based upon the assumption that only one enzyme molecule is present in a reaction vessel?

As the intricate reaction pathways in the living cell are highly compartmentalized for the sake of regulation (or for other reasons) (Friedrich, 1974), it may easily happen that only a single enzyme molecule will be active in one compartment.

We saw that in this case stochastic and deterministic descriptions give significantly different results when means are compared with the solutions of equations (8). Of course, the biochemist observes the average of thousands of millions of such compartments. However, if they function independently, stochastic means sum up, and the difference between the results obtained from the two models does not disappear, although the coefficients of variation tend to zero. That is to say the expected value is of crucial importance from an experimental point of view. If the enzyme catalyzes a process vital for the cell, the consequences of stochastic uncertainty, i.e. variance, would also play an important role.

Indirec ly, one can conclude that systems which contain more than one, but not too many enzyme molecules may display a behaviour that reminds one of the one-enzyme-molecule case rather than that of infinitely many molecules.

The mathematical means introduced here and developed elsewhere (Arányi, 1976) allow us to investigate these systems directly. The extension of systems (1) and (2) to cases when $P(e>1)>0$ is straightforward.

Since in the living cells there exist molecules of vital importance other than enzymes of Michaelis-Menten behaviour (mainly nucleic acids) that are definitively known to be present in a few copies only, it seems to be worth-while to examine time courses or equilibria of their possible reactions in a similar way.

Finally, from a computational point of view we can recommend the use of stochastic mean functions when the situation is clearly closer to deterministic, but the exact solution of equation (8) cannot be obtained, and steady state approximation does not seem to apply.

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Appendix

Proof of ergodicity of finite Markov process with an absorbing state, accessible from any other state. Let state 0 be absorbing.

Then $P_{0j}(t)$ transition probabilities are 0 if $j \neq 0$ or 1 if $j = 0$. Examine separately $\lim_{t\to\infty} P_{i0}(t)$ $(i \neq 0)$ and $\lim_{t\to\infty} P_{ij}(t)$ $(i, j \neq 0)$. As state 0 is accessible from any state, $\min_{l\neq 0} P_{l0}(t_0) = q > 0$ for $t_0 > 0$. Now, if $t = nt_0 + h$ $(0 < h < t_0)$ it is easy to realize that

$$P_{ij}(t) = P_{ij}(nt_0 + h) \leq \sum_{k\neq 0} P_{ik}(nt_0)\, P_{kj}(h) \leq \sum_{k\neq 0} P_{ik}(nt_0) =$$

$$= \sum_{k\neq 0}\sum_{l\neq 0} P_{il}[(n-1)t_0]\, P_{lk}(t_0) \leq (1-q) \sum_{l\neq 0} P_{il}[(n-1)t_0] \leq (1-q)^n$$

As $n \to \infty$ with $t \to \infty$,

$$\lim_{t\to\infty} P_{ij}(t) = 0 \quad (i, j \neq 0),$$

For proving $\lim P_{i0}(t) = 1$ consider that $1 - P_{i0}(t) = \sum_{k\neq 0}^{t\to\infty} P_{ik}(t)$. This sum tends to zero as $t \to \infty$, as it consists of a finite number of terms.