Biophysical Chemistry 16 (1982) 173–179
Elsevier Biomedical Press

ANALYTICAL SOLUTION OF COUPLED NONLINEAR RATE EQUATIONS

I. MICHAELIS-MENTEN KINETICS

Paul E. PHILLIPSON *

Max Planck Institut für Biophysikalische Chemie, Postfach 968, D-3400 Göttingen, F.R.G.

Received 21st January 1982
Accepted 9th June 1982

Key words: Enzyme kinetics; Michaelis-Menten rate equations; Chemical kinetics equation theory; Nonlinear rate process

An approximate analytic solution to the Michaelis-Menten kinetic equations is developed which is free of the traditional steady-state hypothesis and is of a simpler form than previous perturbation approaches, so that the relaxation process can be traced in detail. The method involves coordinate transformation of the rate equations and subsequent solution of an integral equation which displays evolution of the system in time as the unfolding of a memory function whose value at any instant is contingent upon the past history of the system. A memory function of the type described here is not present in linear kinetics, so that it can serve to define the distinctly nonlinear features of a kinetic process. The scheme can be enlarged for development of approximate analytical solutions to nonlinear rate equations descriptive of open systems which can evolve into limit cycles or show chaotic behavior.

1. Michaelis-Menten kinetics and the steady-state approximation

The simplest and classic example of an enzyme mechanism is that of Michaelis and Menten [1] which describes the irreversible conversion of a substrate S into product P through formation of an enzyme-substrate complex C

$$\mathrm{S}+\mathrm{E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C} \xrightarrow{k_2} \mathrm{P}+\mathrm{E} \tag{1}$$

The kinetics predicted by this mechanism rest upon solution of the following rate equations, expressed in dimensionless form [2]

$$\frac{\mathrm{d}x}{\mathrm{d}\tau} = -x+(\kappa-\lambda)y+xy \tag{2a}$$

$$\epsilon\frac{\mathrm{d}y}{\mathrm{d}\tau} = x-\kappa y-xy \tag{2b}$$

$$x(0)=1, \quad y(0)=0 \tag{2c}$$

where these quantities are related to the chemical concentrations, rate constants and real time t by

$$x(\tau)=\frac{S(\tau)}{S(0)}, \quad y(\tau)=\frac{C(\tau)}{E(0)}, \quad \tau=k_1E(0)t$$

$$\epsilon=\frac{E(0)}{S(0)}, \quad \lambda=\frac{k_2}{k_1S(0)}, \quad \kappa=\frac{(k_{-1}+k_2)}{k_1S(0)} \tag{3}$$

$$E(t)=E(0)-C(t), \quad \frac{\mathrm{d}P}{\mathrm{d}t}=k_2C(t), \quad C(0)=0$$

In many biological and laboratory situations the ratio of the initial enzyme to substrate concentration is small, $\epsilon \ll 1$, which suggested the steady-state approximation of setting the left side of eq. 2b equal to zero. This produces a simple algebraic equation for y which, when substituted into eq. 2a permits the determination of x as a function of time, formally solving the kinetics problem in this approximation. This approxima-

---

* Permanent address: Department of Physics, University of Colorado, Boulder, CO 80309, U.S.A.

0301-4622/82/0000-0000/$02.75

tion must fail, however, for times of the order of $\epsilon\tau$, since this procedure reduces the order of the system such that the boundary conditions of eq. 2c can no longer be satisfied in a consistent manner. An analytical correction to this defect of the steady-state approximation, in successful agreement with exact computer solution of eqs. 2, has been made by Heineken et al. [3] using singular perturbation theory [4]. This technique involves construction at successive orders of approximation of two solutions – an inner solution appropriate to short times (singular domain) and an outer solution appropriate to long times (steady-state domain) – and matching solutions such that the long-time behavior of the former joins smoothly the short-time behavior of the latter. In zero order to solution is

$$x+\kappa \ln x = 1-\lambda\tau, \quad y=\frac{x}{\kappa+x}-\frac{1}{\kappa+1}\exp-\left[\frac{(1+\kappa)\tau}{\epsilon}\right] \tag{4}$$

This result has the feature that the zero-order solution for x is a transcendental equation. As a consequence, all higher order solutions must in principle be based upon this transcendental equation. The first-order correction, then, is complicated and difficult to interpret other than that it represents a quantitative improvement to eq. 4. More importantly and aside from the matter of complication is that since the transcendental feature is a consequence of the steady-state approximation at the outset, it is not de facto an intrinsic analytic feature of solution to the rate equations. In fact, this structure is at variance to an exact solution found by Miller and Alberty [5] to eq. 1 under the reversible condition which includes a back rate k_{-2} from product to complex provided $k_{-2}=k_1$. The solution in this case is not transcendental, but involves the ratio of exponential terms characteristic of a nonlinear process. The departure from balanced rates was then treated as a perturbation on these solutions, resulting in a complicated linear combination of exponentials without, however, any implicit transcendental time dependence. Two analytically different points of departure lead in this case to similar results. The two methods in principle should agree in infinite order (constituting exact solution), but even the next corrections are complicated and difficult to interpret.

The aim of the present work is to introduce by example an alternative, and indeed opposite, approach to development of approximate analytical solutions to autonomous coupled nonlinear rate equations which occur in both chemical and biochemical kinetics of either closed systems, such as the one here, or open systems which can evolve into limit cycles or perhaps even evince chaotic behavior [6]. The idea is to replace the differential equations in the chemical coordinates (here x and y) by coupled integral equations in coordinates which bear the same relation to x and y that curvilinear coordinates bear to Cartesian coordinates. This coordinate transformation facilitates replacement of a perturbation method by an iteration of a guessed initial trial solution based upon the long-time behavior of the system. The iteration subsequently tracks the solutions backward in time and as a consequence, evolution of the system forward at any instant depends upon memory of its entire past history leading up to this instant. The time evolution of the system is thus interpreted as an unfolding at any present instant based upon the past, the equations themselves serving to drive the system into the future. The present example will illustrate that such unfolding of memory is not present in a linear process but is a distinct feature of a nonlinear process. The criterion for the guess is that the first iteration be sufficient to produce a satisfactory analytical solution to the rate equations, otherwise a repeated iteration to make up for a bad guess would result in the same nightmare of many terms as perturbation theory carried beyond lowest order. The goal of such a program is not to achieve ultimate numerical accuracy, for computers take care of that. Rather, computer results are used as a check to see if the guess is a good one. If it is, the resulting expressions prove to be a simpler form and more analyzable than perturbative solutions: one can get a picture of the dynamics of the process described by the rate equations to supplement rigorous quantitative information supplied by numerical computation. The development here will be confined to the particular Michaelis-Menten system of eq. 1, while section 4 will give a qualitative overview of the implications of this approach. A more general analytic treatment applicable to the broader class of systems mentioned will be treated elsewhere [7].

2. Development of solution

The first step is to investigate the behavior of the relaxation process in the approximation that neglects the nonlinear quadratic xy term in eqs. 2a and 2b. Solution of the linearized equations indicates that the eigenvalues p are

$$p_{\pm}=\mu\pm\Omega$$

$$\mu=-\frac{\kappa}{2\epsilon}\left(1+\frac{\epsilon}{\kappa}\right),\quad \Omega=\frac{\kappa}{2\epsilon}\left[1+\frac{2\epsilon}{\kappa}\left(1-\frac{2\lambda}{\kappa}\right)+\frac{\epsilon^2}{\kappa^2}\right]^{1/2} \tag{5}$$

Since interest here is in the limit that ϵ is small, or more precisely that $\epsilon/\kappa \ll 1$, then

$$\lim_{\frac{\epsilon}{\kappa}\to 0} p_{\pm}=-\begin{bmatrix}\dfrac{\lambda}{\kappa}\\[2mm] \dfrac{\kappa}{\epsilon}\end{bmatrix} \tag{6}$$

Since x and y would evolve in time according to a linear combination of exponentials $\exp(p_{\pm}\tau)$, the limit that ϵ/κ is small implies that for times long compared to $\epsilon\tau$ the solutions should behave as $\exp-(\lambda\tau/\kappa)$. This result, of course, has already been noted in earlier work, although from a different point of view and arising as a consequence of critique of the steady-state approximation [3]. The problem, then, becomes to return to the exact equations and develop solutions which, for $\epsilon/\kappa \ll 1$, evolve according to the small eigenvalue for long times. That the exact solutions must do so follows from the fact that x and y must approach zero for long times characteristic of equilibrium. Since the nonlinear terms involve products of small terms for long times, the long-time behavior must be dominated by the linear terms. We introduce the following linear transformation to polar coordinates characterized by a real radial coordinate R and an imaginary angle coordinate σ

$$x(\tau)=R(\tau)[\alpha_{11}\cosh\sigma(\tau)+\alpha_{12}\sinh\sigma(\tau)]$$
$$y(\tau)=R(\tau)[\alpha_{21}\cosh\sigma(\tau)+\alpha_{22}\sinh\sigma(\tau)]$$

$$\alpha_{11}=1,\quad \alpha_{12}=\frac{\left(\frac{\kappa}{\epsilon}-1\right)}{2\Omega},\quad \alpha_{21}=0,\quad \alpha_{22}=\frac{1}{\epsilon\Omega}$$
$$R(0)=1,\quad \sigma(0)=0 \tag{7}$$

Substitution of this transformation into eqs. 2a and 2b results in the following equations

$$\frac{\mathrm{d}R}{\mathrm{d}\tau}+R\frac{\mathrm{d}\sigma}{\mathrm{d}\tau}=p_{-}R+A(\sigma)R^2 \tag{8a}$$

$$R\frac{\mathrm{d}\sigma}{\mathrm{d}\tau}=\Omega R+B(\sigma)R^2 \tag{8b}$$

$$\begin{bmatrix}A(\sigma)\\ B(\sigma)\end{bmatrix}=\pm\frac{1}{\epsilon}\left\{\left[\cosh\sigma+\frac{\left(\frac{\kappa}{\epsilon}-1\right)}{2\Omega}\sinh\sigma\right]\right. \\ \times\left[\begin{matrix}\left[\dfrac{\left(\frac{\kappa}{\epsilon}+1\right)}{2\Omega}-1\right]\exp-(\sigma)\\ \left[\cosh\sigma+\dfrac{\left(\frac{\kappa}{\epsilon}+1\right)}{2\Omega}\sinh\sigma\right]\end{matrix}\right]\sinh\sigma \tag{8c}$$

The coefficients α_{ij} in the transformation of eq. 7 are chosen such that the quantities multiplying the linear R term in eq. 8 are constants independent of time, and in fact for the radial equation this constant is precisely the small eigenvalue which dominates long-time behavior; the initial conditions on R and σ are fixed by the initial conditions on x and y of eq. 2c. The linear approximation corresponds to neglect of the R^2 terms, in which case $R=\exp(\mu\tau)$, $\sigma=\Omega\tau$ which, when substituted into eq. 7 and the hyperbolic functions expressed as exponentials, reveals the normal mode solution of the linear problem. Eq. 8a has the following formal solution as an integral equation,

$$R(\tau)=\frac{R(0)\exp[p_{+}\tau-\sigma(\tau)]}{1+M(\tau)} \tag{9}$$

$$M(\tau)=-R(0)\int_0^{\tau}\exp[p_{+}\tau'-\sigma(\tau')]A[\sigma(\tau')]\,\mathrm{d}\tau'$$

as can be verified by substitution into eq. 8a. The integral M reflects propagation of the system forward in time through past times τ' up to instant τ, the integrand serving as the propagator. Since the propagator is a function of σ evaluated at all earlier times, which is determined by eq. 8b, the kinetic equations themselves serve to drive the system into the future. In the present formalism, solution of the rate equations at any instant of time depends explicitly upon the behavior of the system for its entire previous history. Thus, we can regard M as the 'memory function' which, importantly, is absent in a linear process as for instance the normal mode solution of the linearized rate equation. Thus, its existence is inextricably connected with nonlinearity of the kinetic mechanism. From this point of view, since M is absent in a linear process, we can define a unimolecular process as one in which the instantaneous state of the system is independent of its previous history, and a pseudo-unimolecular process as one in which memory effects are neglected. We will make the initial guess that the process is pseudo unimolecular so that the initial trial function is just eq. 9 with neglect of M. This starts the process of iteration, from which we proceed to work backward in time. The other approximation is that A and B of eq. 8c are approximated by the lead term for small ϵ/κ: the hyperbolic functions then sum to $\exp(\sigma)$ and $p_+ \approx -\lambda/\kappa$ so that

$$R \approx \exp-\left[\frac{\lambda\tau}{\kappa}+\sigma(\tau)\right] \tag{10}$$

$$A=\frac{2\lambda}{\kappa^2}\sinh\sigma, \quad B=-\frac{1}{\epsilon}\sinh\sigma\exp(2\sigma)$$

and eqs. 8b and 9 become

$$\frac{\mathrm{d}\sigma}{\mathrm{d}\tau}=\frac{1}{2\epsilon}\left[\kappa+\exp-\left(\frac{\lambda\tau}{\kappa}\right)\right]-\frac{1}{2\epsilon}\left[\exp-\left(\frac{\lambda\tau}{\kappa}\right)\right]\exp(2\sigma) \tag{11a}$$

$$R(\tau)\exp(\sigma)=\frac{\exp-\left(\frac{\lambda\tau}{\kappa}\right)}{1+M} \tag{11b}$$

$$M=\frac{\lambda}{\kappa^2}\int_0^{\tau}\exp-\left(\frac{\lambda\tau'}{\kappa}\right)[\exp-(2\sigma(\tau'))-1]\,\mathrm{d}\tau' \tag{11c}$$

The procedure is to solve eq. 11a for σ and then insert it into the memory function M of eq. 11c to obtain the first iterated solution for R. In principle, the next step would be to substitute this iterated solution back into eq. 8b to compute an improved σ and so on. We discuss a concrete example in the next section.

3. Analysis of solution

Solution of eq. 11a and subsequently eq. 11b gives the result, derived in the Appendix, that

$$\exp-(2\sigma)=\frac{1}{\kappa+1}\left[\frac{(\kappa+1)\exp-\left(\frac{\lambda\tau}{\kappa}\right)}{\kappa+\exp-\left(\frac{\lambda\tau}{\kappa}\right)}+\kappa\exp-(N\phi(\tau))\right] \tag{12a}$$

$$R\exp(\sigma)=\frac{\exp-\left(\frac{\lambda\tau}{\kappa}\right)}{1+M}, \quad M=\ln\left[\frac{\kappa+\exp-\left(\frac{\lambda\tau}{\kappa}\right)}{\kappa+1}\right] \tag{12b}$$

$$N=\frac{k}{\epsilon\lambda}, \quad \phi(\tau)=\lambda\tau+\left[1-\exp-\left(\frac{\lambda\tau}{\kappa}\right)\right]$$

Substitution of this result into eq. 7 written in exponential form

$$x=\frac{R\exp(\sigma)}{2}[(1+\alpha_{12})+(1-\alpha_{12})\exp-(2\sigma)]$$

$$y=\frac{\alpha_{22}R\exp(\sigma)}{2}[1-\exp-(2\sigma)] \tag{13}$$

constitutes the approximate analytical solution to eqs. 2 of the present work. Features of the relaxation process can be traced by noting that the parameter N, involving the reciprocal of ϵ/κ, is large, which implies that during short times for which $\kappa\tau/\epsilon \approx 1$, then $\lambda\tau/\kappa \approx 1/\kappa N \ll 1$, so that expanding the exponential in $\phi(\tau)$ for short times we obtain

$$\exp-(N\phi)\quad\begin{array}{l}\xrightarrow{\frac{\lambda\tau}{\kappa}\ll 1}\ \exp-\frac{(\kappa+1)\tau}{\epsilon}\\[2ex] \xrightarrow{\frac{\lambda\tau}{\kappa}\approx 1}\ 0 \text{ as } \exp-\left(\frac{\kappa\tau}{\epsilon}\right)\end{array} \tag{14}$$

The short time period characterizes the fast-decay stage for substrate and the fast-ascent stage for complex, dictated by the same time dependence as the singular domain of perturbation theory (cf. eq. 4). For longer times such that $\lambda\tau/\kappa \approx 1$, corresponding roughly to the steady-state domain of perturbation theory, the process proceeds first through a transition region which leads asymptotically to a final linear region. This transition region is characterized by evolution of the memory term, which in the present case grows logarithmically, and by ratios involving an exponential whose time dependence is controlled by the small eigenvalue of the linear analysis.

$$\exp-(2\sigma)\xrightarrow{\frac{\lambda\tau}{\kappa}\approx 1}\frac{1}{\kappa+1}\left[\frac{(\kappa+1)\exp-\left(\frac{\lambda\tau}{\kappa}\right)}{\kappa+\exp-\left(\frac{\lambda\tau}{\kappa}\right)}\right]$$

$$\xrightarrow{\frac{\lambda\tau}{\kappa}\gg 1}\frac{1}{\kappa}\exp-\left(\frac{\lambda\tau}{\kappa}\right)$$

$$R\exp(\sigma)=\underset{\substack{\uparrow\\ \text{Transition region}}}{\frac{\exp-\left(\frac{\lambda\tau}{\kappa}\right)}{1+M}}\xrightarrow{\frac{\lambda\tau}{\kappa}\gg 1}\underset{\substack{\uparrow\\ \text{Linear region}}}{\frac{\exp-\left(\frac{\lambda\tau}{\kappa}\right)}{1-\ln\left(\frac{\kappa+1}{\kappa}\right)}}\qquad(15)$$

The transition region is the most interesting period during which the complex concentration builds up to a maximum before making its relatively slow descent to zero as product accumulates. Finally, passage to time such that the exponential is small leads asymptotically into the linear region dictated by a single exponential, characteristic of linearity in the final stage of the relaxation process. It is to be noted that the memory function grows in time such that it reaches an asymptotic value of $[-\ln\{(\kappa+1)/\kappa\}]$, which implies that in the linear regime, although the functional time dependence is characteristically linear, concentrations are larger by a factor of approx. $[-\ln\{(\kappa+1)/\kappa\}]^{-1}$ than what they would be if the process were truly unimolecular. This result is a consequence of the nonlinearity of the process reflected even at long times by what might be called a persistence of memory, which must only increase in time, since as time goes on 'there is more to remember'. The long-time quantitative importance of M, however, in a relaxation process to equilibrium such as that described here is offset by the multiplication of its effect by an exponentially decreasing term. From the point of view of formal structure, the present analysis reflects, in sum, the behavior of explicit exponential time dependences, as in the model of Miller and Alberty [5], and is free of the steady-state approximation with the boundary condition problem and transcendental time dependence which it implies.

It remains to be seen how reliable the present approach to kinetics is for the case at hand in relation to exact numerical computation and the results of perturbation theory [3]. The initial substrate concentration is identified with the Michae-

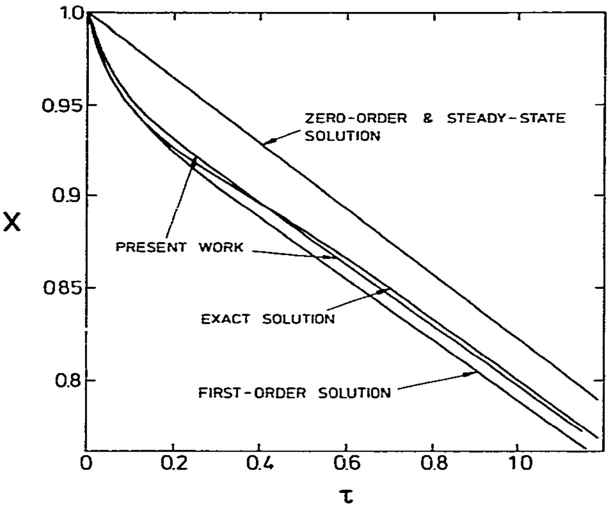

Fig. 1 $x(\tau)$ of present work eqs. 12 and 13 compared to perturbation solutions and exact computer solution by Heineken et al. [3].

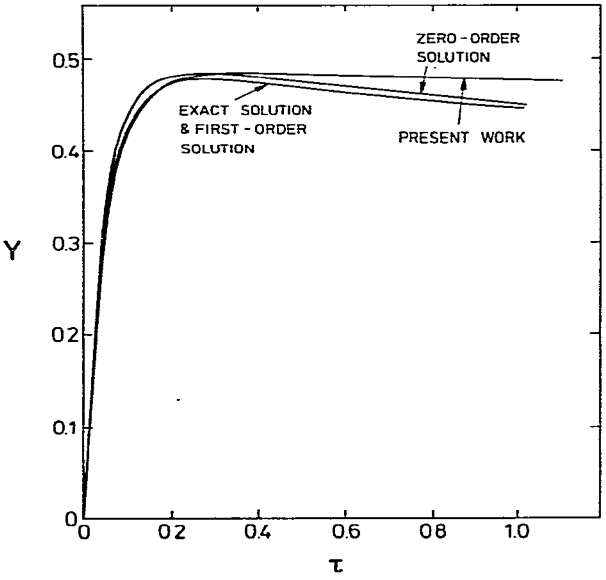

Fig. 2. $y(\tau)$ of present work eqs. 12 and 13 compared to perturbation solutions and exact computer solution by Heineken et al. [3].

lis constant, $S(0) = k_1/k_{-1} + k_2$ which fixes κ to be unity (cf. eq. 3). Data from the hydrolysis of benzoyl-L-arginine ethyl ester catalyzed by trypsin give $\lambda = 0.375$, and the initial enzyme to substrate concentration ratio was chosen to be $\epsilon = 0.1$, from which $N = 26.7$. Comparison of the present study with exact solution and that of zero- and first-order perturbation theory is shown in figs. 1 and 2. It is seen that the time region extends to approx. $\tau = 1$ or $\lambda\tau = 0.375$, corresponding to the transition region. The memory function starting at zero initially reaches a value of -0.17 at $\tau = 1$, to be contrasted with its asymptotic value for time in the linear region of $-\ln 2 = -0.693$ (this value was fixed by $\kappa = 1$, which was fixed by the Michaelis constant). Quantitatively the present result for x in comparison with exact solution is better than that of first-order perturbation theory, but not as good for the case of y. The reason can be seen from eq. 13. Since ϵ is small, α_{12} is almost unity, so that x has a considerably weaker dependence on $\exp-(2\sigma)$. But this term was not corrected iteratively by substitution of eq. 12b into eq. 8b such that it reflects the influence of memory. This, then, would be the next correction to the present results. Agreement here, however, is within 7% of numerical computation, so that this refinement would add little quantitatively or qualitatively to the above argument.

4. Discussion

The present work aims at development of an analytical formulation which goes beyond simple analysis yet yields solutions to coupled nonlinear rate equations which are not so complicated that one can trace the process of evolution in time implied by them. The procedure involves two steps. The first is a transformation to polar coordinates. The second is iterative solution to any desired degree of refinement to coupled integral equations expressed in these coordinates.

The basis of the polar coordinate transformation is that the radial coordinate on the right side of the rate equations is always multiplied by a constant, for example p_+ and Ω in eqs. 8a and 8b. This enormously simplifies the analytical problem, and it can be shown quite generally that these constants are simply related to the eigenvalues of the linear problem. If the rate equations are such that Ω is imaginary, then σ becomes imaginary and the transformation involves the usual polar coordinates. The procedure here is a generalization of phase plane analysis, useful in studies of nonlinear oscillating systems [8]. In that case, there is typically the transformation $x = R\cos\theta$, $y = R\sin\theta$ while here each coordinate would depend on both sine and cosine. The present approach gives the added flexibility to simplify the term linear in the radial coordinate, which is not achieved by the simpler phase plane coordinate representation. If, further, the rate equations are such that in addition μ is positive, then the present formalism is applicable to the kinetics of open systems which can evolve into limit cycles, an example being the 'Brusselator' autocatalytic model [9]. Here, there is motivation to enlarge the scope to include three variables x, y and z, say. This would be a natural requirement for consideration of more realistic open-system kinetics such as embodied by modelling of the Zhabotinskii reaction [6] or the chaotic behavior predicted by the equations of Lorenz [10]. Such extension would lift the limitation of the present simple scheme itself to include the findings of modern relaxation techniques which clearly discern intermediates [11]. In all these cases, the appropriate transformation would be to cylindrical coordinates [7].

The development of approximate analytic solution through construction of an integral equation leads to a memory function whose presence pinpoints traceably the nonlinear features of time evolution. These memory functions open interesting possibilities for interpretation. As the present case suggests, the approach to equilibrium exhibits the unfolding of a memory which accumulates in time until death characteristic of equilibrium overtakes it. But what about an instability evolving into a limit cycle? Here, memory of transition to the limit cycle is 'lost' once the system is in the cycle, yet the cycle itself, being of a periodic nature, must reflect a repetitive pattern, where the repeat frequency is that of the limit cycle. One can only speculate on memory associated with deterministic equations which computer-wise exhibit chaotic behavior [10]. One possibility is that the memory function is stable for a period of time and then itself evolves into a different analytic pattern, but that the transition between the patterns is nonanalytic.

Appendix

The substitution $f = \exp - (\sigma)$ transforms eq. (11a) to

$$\frac{\mathrm{d}f}{\mathrm{d}\tau} = -\alpha f + \beta \tag{A1}$$

$$\alpha = \frac{1}{\epsilon}\left[k + \exp - \left(\frac{\lambda\tau}{\kappa}\right)\right]$$

$$\beta = \frac{1}{\epsilon}\exp - \left(\frac{\lambda\tau}{\kappa}\right)$$

which integrates to

$$f(\tau) = \exp - \left[\int_0^{\tau} \alpha(\tau')\,\mathrm{d}\tau'\right]\left\{1 + \int_0^{\tau} \mathrm{d}\tau' \beta(\tau') \exp\int_0^{\tau'} \alpha(\tau'')\,\mathrm{d}\tau''\right\}$$

$$= \exp - (N\phi)\left\{1 + \int_0^{N[1-\exp-(\frac{\lambda\tau}{\kappa})]} \frac{\exp(x)}{\left[1 - \frac{x}{N}\right]^{N\kappa}}\,\mathrm{d}x\right\} \tag{A2}$$

$$N = \frac{\kappa}{\epsilon\lambda}, \quad \phi = \lambda\tau + \left[1 - \exp - \left(\frac{\lambda\tau}{\kappa}\right)\right]$$

$\epsilon \ll 1$ implies that we are interested in the asymptotic value of the integral for large N. A change of integration and successive integration by parts shows that

$$\lim_{N\to\infty} \int_0^{N[1-\exp-(\frac{\lambda\tau}{\kappa})]} \frac{\exp(x)\,\mathrm{d}x}{\left[1 - \frac{x}{N}\right]^{N\kappa}}$$

$$= \lim_{N\to\infty} N \int_{\exp-(\frac{\lambda\tau}{\kappa})}^{1} \frac{\exp N(1-Z)}{Z^{N\kappa}}\,\mathrm{d}Z$$

$$= \lim_{N\to\infty} \frac{\exp N(1-Z)}{Z^{N\kappa}}$$

$$\times \left[\frac{NZ}{N\kappa - 1} - \frac{(NZ)^2}{(N\kappa-1)(N\kappa-2)}\right.$$

$$\left. + \frac{(NZ)^3}{(N\kappa-1)(N\kappa-2)(N\kappa-3)} - \dots + \dots\right] \Bigg|_{\exp-(\frac{\lambda\tau}{\kappa})}^{1}$$

$$= \frac{\exp N(1-Z)}{Z^{N\kappa}}\left(\frac{Z}{\kappa}\right)\left[1 - \left(\frac{Z}{\kappa}\right) + \left(\frac{Z}{\kappa}\right)^2 - + \dots\right]$$

$$= \frac{\exp N(1-Z)}{Z^{N\kappa}}\left(\frac{Z}{\kappa}\right)\frac{1}{1 + \left(\frac{Z}{\kappa}\right)} \Bigg|_{\exp-(\frac{\lambda\tau}{\kappa})}^{1} \tag{A3}$$

where the last sum is just the geometric series. Substitution of eq. A3 into eq. A2 produces eq. 12a, which in turn, upon insertion into eq. 11c determines the memory function. In principle, the $\exp - (N\phi)$ portion of eq. 12a contributes to the memory function. However, its contribution is of the order of $1/N \approx \epsilon$ and hence is ignored. The other portion of eq. 12a integrates to produce the logarithmic memory function of eq. 12b.

References

1 L. Michaelis and M.I. Menten, Biochem. Z. 49 (1931) 333.
2 J.D. Murray, Lectures on nonlinear-differential-equation models in biology (Clarendon Press, Oxford, 1977).
3 F.G. Heineken, H.M. Tsuchiya and R. Aris, Math. Biosci. 1 (1967) 95.
4 C.C. Lin and L.A. Segal, Mathematics applied to deterministic problems in the natural sciences (Macmillan, New York, 1974).
5 W.G. Miller and R.A. Alberty, J. Am. Chem. Soc. 80 (1958) 5146.
6 H. Eyring and D. Henderson, Theoretical chemistry: periodicities in chemistry and biology (Academic Press, New York, 1978).
7 P.E. Phillipson, in preparation.
8 N. Minorsky, Nonlinear oscillations (Krieger, New York, 1974).
9 G. Nicolis, and I. Prigogine, Self-organisation in nonequilibrium systems: from dissipative structures to order through fluctuations (Wiley Interscience, New York, 1977).
10 E.N. Lorenz, J. Atmos. Sci. 20 (1963) 130.
11 M. Eigen, Q. Rev. Biophys. 1 (1968) 3.