Mixed Feedback: A Paradigm for Regular and Irregular Oscillations

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1. Some Considerations on Biological Organization

One of the many striking features of living systems is their circular organization. Indeed, the essence of this property is captured in the old question: "Which came first, the chicken or the egg?".

Circular organization, or circularities, may be observed in biological systems from the microscopic molecular level to the macroscopic ecological level. At the molecular level, the most famous is the DNA - protein cycle. Thus, through several intermediate steps the DNA molecule produces protein enzymes which are, in turn, used in DNA synthesis. It is also important to note that during this process two DNA molecules may result out of one. Here, the circular organization is of an autocatalytic type which is just the condition that life can continue as a self-maintaining process. The necessity and importance of circularity and autocatalysis for living systems as parts of the self-generating and self-maintaining stream of life has been elaborated explicitly in the work of AN DER HEIDEN et al. /1 /, /2/.

At the cellular level, the circular organization of the cell cycle gives rise to two daughter cells out of a single mother cell.

Circular organization is not necessarily coupled to autocatalysis, e.g. generally there is a complicated circular interdependence between the organs of a multicellular organism. Thus the heart, liver, kidney and lungs are all highly dependent on one another for their individual integrity. Of course the number of organs in mature organisms is not increased.

The production of organisms is again autocatalytic. From one (or, in the case of sexual reproduction, from two) organism two or more additional organisms may result. At this level the autocatalytic principle has been pushed to its extreme. Thus, a single tree may have, in principle, millions of offspring.

Evidently, autocatalytic processes always produce populations (of molecules, cells, organisms etc.). Therefore, population dynamics generally includes autocatalytic feedback effects. Other nearly necessary effects are saturation (caused by environmental or internal, e.g. density, constraints) and destruction, which is unavoidable in any open system. Many types of destruction are known, e.g. mechanical, thermodynamic, chemical, and biological (death).

The interaction of autocatalysis, saturation and destruction is capable of generating dynamics ranging from the most simple to the most complicated. In this paper a simple model is presented which combines these three principles and demonstrates a variety of their effects.

2. A model for the interaction of autocatalysis, saturation, and destruction

Autocatalysis implies a circular dependence of a quantity x_1 (a single variable, a vector or a function of space) on itself. This dependence is not necessarily realized after a single step, but generally involves several intermediate steps which can be viewed diagrammatically as

$$x_1 \to x_2 \to x_3 \to \dots \to x_n \to x_1 \ .$$

The quantities x_i are assumed to be functions of time: $x_i=x_i(t)$. Each step requires a certain time for completion, so the time structure of the cycle is

$$x_1(t) \to x_2(t+d_1) \to x_3(t+d_1+d_2) \to \dots \to x_n(t+d_1+\dots+d_{n-1}) \to$$

$$\to x_1(t+d),$$

where $d = d_1+d_2+\dots+d_n$.

The detailed dynamics in each step may, in fact, be very complicated. A rather general Ansatz is given by

$$x_i(t) = \int_{-\infty}^{t} K_i(t,t',x_{i-1}(t'),x_i(t'))dt' - \int_{-\infty}^{t} G_i(t,t',x_i(t'))dt' \qquad (1)$$

$i = 1,2,\dots,n$

(in the case that $i=1$, set $i-1$ equal to n).

Here the delays d_i are implicit in the kernels K_i. The first integral describes production of the quantity x_i, while the second integral describes its destruction. A mathematical or numerical analysis of system (1) is not yet available.

The advantage of a general description like (1) is that many models in the literature may be recognized as special cases of this general system. In this way a definite relationship between these models may be established. Thus the well-known Goodwin model /3/ for the control of protein synthesis, closely related to early concepts of Jacob and Monod, is a special case of (1). Goodwin's system of equations, with delays introduced by LANDAHL /4/, is

$$dx_1(t)/dt = f(x_n(t-d_n)) - a_1 \ x_1(t) \ ,$$

$$dx_i(t)/dt = g_{i-1} \ x_{i-1}(t-d_{i-1}) - a_i \ x_i(t), \text{ for } i=1,2,\dots,n \ . \qquad (2)$$

Here a_1, $a_2, \ldots$, a_n and g_1, $g_2, \ldots$, g_{n-1} are positive and constant rate factors. Only through the term $f(x_n(t-d_n))$ is nonlinearity introduced. Goodwin, and most other investigators of this system, have assumed the function $f: \mathbb{R}_+ \to \mathbb{R}_+$ to be either monotone increasing or monotone decreasing. In the first case system (2) represents a positive feedback loop, in the second case a negative feedback loop. Generally it is presumed that the function f is bounded (i.e. $f(x) \leq$ const. for all $x \in \mathbb{R}_+$), reflecting the principle of saturation. A review of mathematical results concerning the behavior of solutions to the system (2) in the situation where all delays $d_i = 0$, $i=1,2,\ldots,n$, can be found in TYSON & OTHMER /5/.

In case of negative feedback the essential result is that the system has a unique steady state which may be either (locally asymptotically) stable or unstable. In the first case the steady state is also globally asymptotically stable, meaning that all solutions approach the steady state as $t \to \infty$. If, on the other hand, the steady state is unstable then non-constant periodic solutions do exist (as proved for n=3 by TYSON /6/ and for arbitrary n by HASTINGS, TYSON & WEBSTER /7/).

For $n < 3$ and no delays, according to these results periodic solutions do not exist. Computer simulations suggest that periodic solutions, in cases where they exist, define a unique limit cycle which is attractive with respect to all solutions with the exception of the unstable steady state. However, no proof of this conjecture is available.

In the case of positive feedback there is either a unique globally asymptotically stable steady state or there are several steady states which are either locally asymptotically stable or unstable. Computer simulations suggest that no undamped oscillations do occur, normal hysteresis appears to be common. However, this question is not yet completely settled.

In considering situations with delays, let us return to the situation of negative feedback, i. e. f monotonic decreasing. The restriction $n > 2$ for the existence of periodic oscillations is not necessary when there are delays $d_i > 0$. This was proved by HADELER & TOMIUK /8/ for n=1 (in which case the system (2) reduces to a single differential-difference equation), by AN DER HEIDEN /9/ for n=2, and finally by MAHAFFY /10/ for arbitrary n.

These proofs only demonstrate that the system (2) has periodic solutions without addressing the stability of these solutions. However, in the case of positive delays extensive computer simulations always show stable limit cycles. These cycles are simple in the sense that within one period each of the variables x_i has a single maximum and a single minimum.

For n=1 the system (2) reduces to the single equation

$$dx(t)/dt = f(x(t-d)) - a\,x(t). \qquad (3)$$

Interestingly enough, this equation has been used in a variety of quite different areas. WAZEWSKA & LASOTA /11/, before 1974, used it for modelling the production of red blood cells. MACKEY and his co-workers /12-17/ have used it to explain the origin of a variety of haematological diseases including aplastic anemia and periodic haematopoiesis, COLEMAN & RENNINGER /18/ applied it to periodic excitations of neurons, MAY /19/ to the population dynamics of whales; MACKEY and GLASS /20/ to the respiratory cycle; KING et al. /21/ to psychiatric disorders like schizophrenia and panic attacks, AN DER HEIDEN et al. /22/ for inhibitory neural networks; MACKEY & AN DER HEIDEN /23/ to epileptic disorders; NISBET & GURNEY /24/ to blowflies; ANDERSON & MACKEY /25/ for commodity cycle oscillations. Solutions of equation (3) have also been used to explain the potential applicability of the concept of dynamical diseases /26/, /27/, /16/.

In some of these cases it cannot be claimed that (3) is a very realistic description of the underlying biology. What is important, however, is that a single equation of this type is sufficient to produce nearly all the phenomena observed in these different areas. For many of these phenomena, in particular for complex periodic oscillations (exhibiting more than one maximum per period) and irregular, chaotic-like oscillations, it is essential that the feedback function f is not monotone, i. e. f represents neither strictly positive nor negative feedback. Instead, the graph of f must have at least one "hump" as illustrated in Fig. 1a.

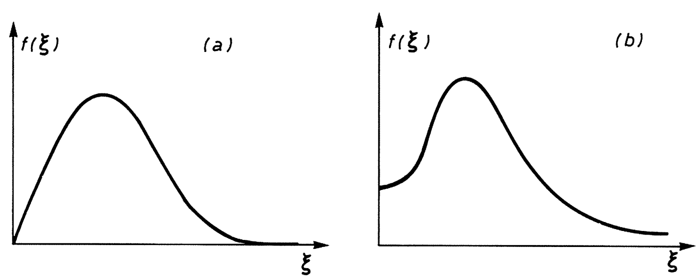

Fig. 1 Feedback nonlinearities of mixed type. It is essential that the functions are neither strictly decreasing (negative feedback) nor strictly increasing (positive feedback), but have at least one "hump"

Such a shape is quite reasonable for systems with autocatalysis and saturation. Since f(x(t-d)) describes the production of the quantity x, autocatalysis requires f(0) = 0: in the absence of x no new x can be produced (think e.g. that x is the concentration of red blood cells or the number of whales in a whale population). On the other hand, saturation implies that for large values of x no additional x is produced, i. e. $f(x) \to 0$ as $x \to \infty$. More generally it can be said that a function like that in Fig. 1 a or b represents positive feedback in its increasing part and negative feedback in its decreasing part. The functions of Figures 1 illustrate mixed feedback.

The fact that transition from single sign feedback to mixed feedback tremendously increases the complexity of the behavior of the system was first discovered by MACKEY & GLASS /20/ and independently by WAZEWSKA & LASOTA /11/. They used computer simulations to study behavior of solutions to (3) and found phenomena like period doubling bifurcations and chaotic oscillations (see e. g. GLASS & MACKEY /26/ for illustrations). AN DER HEIDEN /28/, /29/ showed numerically that system (2) without any delays (i. e. $d_i=0$ for $i=1,2,\ldots,n$) also produces chaotic oscillations if f is assumed to be a humped function.

However, it is extremely difficult to give any mathematical treatment of the phenomena revealed by the computer "solutions". Thus, insight into why these complicated types of behavior occur is restricted. Recently, however, some progress has been made by choosing particularly simple feedback functions (AN DER HEIDEN & WALTHER /30/, AN DER HEIDEN & MACKEY /31/, AN DER HEIDEN /32/). In the following we give a simple approach to illustrate how complicated temporal behavior may arise from simple interactions, incorporating destruction, mixed feedback and delay.

3. A Paradigm for Complexity

In this section we show, step by step, how a complicated time series may arise from a simple limiting case of equation (3). To facilitate the analysis, the feedback function f has the simple humped form illustrated in Fig. 2., i. e.

$$f(x) = \begin{cases} 0 & \text{if} \quad x < b \quad \text{or} \quad x > 1 \\ c & \text{if} \quad b \leqq x \leqq 1 \end{cases} \tag{4}$$

where the (constant) parameters b and c satisfy $0 < b < 1$ and $c > 0$.

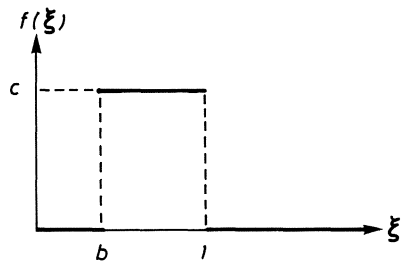

Fig. 2 Extreme case of a mixed feedback nonlinearity with a single hump

Combining equations (3) and (4) gives

$$dx(t)/dt = \begin{cases} -a\,x(t) & \text{if } x(t-1) < b \text{ or } x(t-1) > 1 & \text{(5a)} \\ c - a\,x(t) & \text{if } b \leqq x(t-1) \leqq 1 & \text{(5b)} \end{cases}$$

where we have set the delay, d, equal to 1 by choosing the unit of time t to be d.

The choice of such a step nonlinearity is purely for illustrative purposes. (The form of the nonlinearity suggests a process with two thresholds in production: a lower threshold (at x=b) for the onset of production; and an upper one (at $x=1$) for the cessation of production.) However, the type of behavior demonstrated here is not an artefact of the discontinuity in the function f, and in /30/ a mathematical argument is given why all results for the step function also hold for a class of smooth nonlinearities. The general case of a smooth nonlinearity requires substantially more effort in mathematical analysis, and also obscures understanding with a mountain of technical considerations. By considering the simpler situation we illustrate the principal aspects which may be important for understanding complexity in the applied sciences.

Since f is either 0 or c, Eq.(5) says that any solution $x(t)$ obeys, alternately in successive time intervals, either

$$x(t) = x(\bar{t})\, e^{-a(t-\bar{t})} \qquad \text{if } x(s)>1 \text{ or } x(s)<b \text{ for all } s\varepsilon(\bar{t}-1,t-1) \quad (6a)$$

or

$$x(t) = \gamma - (\gamma - x(\bar{t}))\, e^{-a(t-\bar{t})} \quad \text{if } b \leq x(s) \leq 1 \text{ for all } s \in (\bar{t}-1,t-1) \quad (6b)$$

where $\gamma = c/a$.

Eq.(6a) (exponential decrease to 0) holds if, in the time between $\bar{t}-1$ and $t-1$, the values of x are larger than 1 or smaller than b. Correspondingly x obeys Eq.(6b) (exponential increase to γ) whenever, in the time interval from $\bar{t}-1$ to $t-1$, the values of x are between b and 1. Thus any solution of Eq.(5) is a piecewise and continuous composition of the functions of Eq.(6a) and Eq.(6b). A change between Eq.(6a) and Eq.(6b) takes place at any time t^* if, at time t^*-1, the variable $x(t)$ crosses the level b or 1. Figures 3 through 6 show solutions of Eq.(5), and illustrate this pattern.

For simplicity, we restrict our attention to the case $b = 1/2$ and a fixed ratio $\gamma = 2$. Some remarks for arbitrary parameters are given in the end of this section. In the following, we show that increasing a from low to high values (thereby also increasing c because $\gamma = 2$) leads to a sequence of increasingly more complex oscillations.

The characterization of the temporal evolution of the process commences at time $t_0=0$. Because of the delay an arbitrary initial condition $x(t)$, $-1 \leq t \leq 0$, must be given which uniquely determines $x(t)$ for all $t > 0$. For simplicity start with the initial condition $x(t)=1$ for $-1 \leq t \leq 0$ (later it is shown that the following considerations hold equally well for a broad class of initial conditions). Then in the interval from $t=0$ to $t=1$ Eq.(6b) applies (take $\bar{t}=0$), resulting in

$$x(t) = 2 - \exp(-at) \qquad \text{for } 0 \leq t \leq 1 \qquad (7)$$

and thus, in particular, $x(1) = 2-\exp(-a)$. In Figs. 3 through 6 the time course of $x(t)$ is plotted for various values of a. All of these plots show this initial rise of $x(t)$ described by Eq.(7). In all of these figures the horizontal lines $x=b=1/2$ and $x=1$ are plotted as they prove to be important in understanding the solution: namely whenever they are crossed, then one time unit later an alteration between the equations (6a) and (6a) applies, i. e. an alteration between exponential increase and exponential decrease takes place.

Since $x(t)$ is larger than 1 between $t=0$ and $t=1$, Eq.(6a) applies for t between 1 and 2 (note that now $\bar{t}=1$) and thus

$$x(t) = x(1)\, e^{-a(t-1)} \qquad \text{for } 1 \leq t \leq 2\,. \tag{8}$$

In particular $x(2) = x(1)\exp(-a)$.

The first maximum of $x(t)$ occurs at $t = 1$. Subsequently, $x(t)$ decreases exponentially, as described by (6a), until the level $x(t)=1$ is again reached. Denote the time at which this occurs t_1, so $x(t_1) = 1$ (see Fig. 3). Then because of Eq.(6a) (now with $\bar{t}=t_1$) $x(t)$ will still decrease exponentially until the time $t=t_1+1$, when it has the value $x(t_1+1) = \exp(-a)$. However, according to Eq.(6b) with $\bar{t}=t_1+1$, once this point is reached $x(t)$ rises again, and therefore at t_1+1 a minimum is attained. As long as the parameters satisfy

$$\exp(-a) > b = 1/2 \tag{9}$$

this minimum is above the level b.

Assume inequality (9) to hold (as, e.g., in Fig. 3a for $a = 0.6$). After $t=t_1+1$, the variable $x(t)$ increases according to Eq.(6b) until a time $t=t^*+1$, where t^* is the first time when $x(t)$ crosses the level 1 from below. Clearly the time course of $x(t)$ in the time interval from $t=0$ to $t=1$ and in the interval from $t=t^*$ to $t=t^*+1$ coincide and so we have determined one period of a periodic solution of Eq.(5). Figure 3a shows a periodic solution (with period $\simeq 3.3$) of this type. It is simple in that there is just one minimum within one period.

The situation evolves in a different fashion if the inequality in (9) is reversed, i.e., if $\exp(-a) < b$. Then since $x(t)$ is below the level b for a certain time interval there is a decrease of $x(t)$ in the corresponding interval one time unit later. This decrease can be seen in Fig. 3b (for $a=0.8$) to occur between $t=3$ and $t=4$, and it is due to the undershoot by $x(t)$ of the level $b=1/2$ between $t=2$ and $t=3$. If a is not too large this undershoot lasts for a rather short time and consequently the short decrease of $x(t)$ in the time between $t=3$ and $t=4$ will not lead to a crossing of the level 1 from above. Afterwards $x(t)$ again increases until time $t=t^*+1$, where t^* again denotes the first time where $x(t)$ crosses level 1 from below. This increase is followed by an exponential decrease lasting until $t=t_2+1$, where $t_2=t^*+1$ is the time where $x(t)$ crosses 1 from above again. Obviously $x(t_2+1) = \exp(-a)$. Hence during the interval $t=t_2$ until $t=t_2+1$ the solution x behaves just as in the time interval from $t=t_1$ to t_1+1. Again we obtain one period of a periodic solution, where the period equals t_2-t_1 ($\simeq 3$ for $a=0.8$, see Fig.3b). However, this solution is slightly more complex than found for low values of a, since now there are 2 minima within one period.

If a is further increased beyond 0.8 then the time when $x(t) < b=1/2$ becomes progressively more prolonged (compare Figs. 3b,c et. seq.). As a consequence, for values of a near $a=0.86$ the decrease of $x(t)$ one

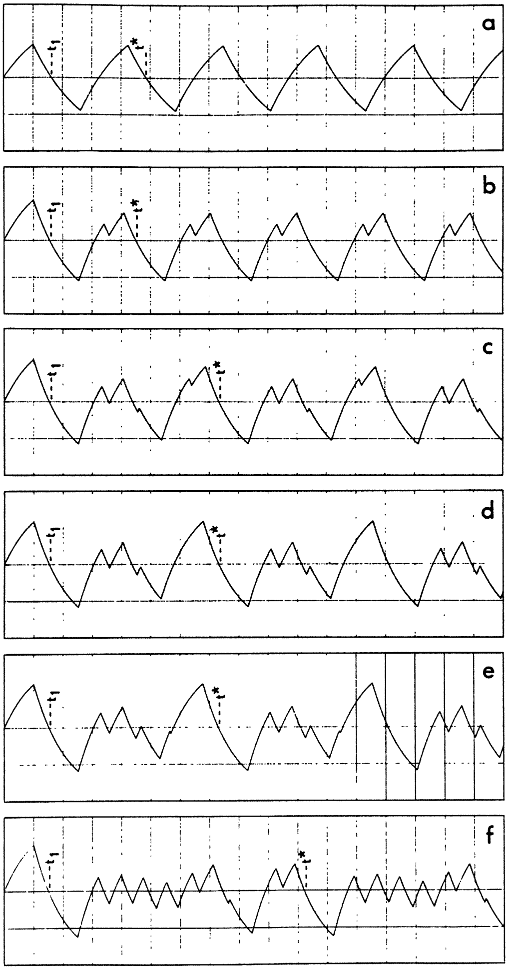

Fig. 3 The analytic solutions to Equation (3) in conjunction with Equation (4), and various values of the decay rate a. b=1/2, γ =c/a=2, x(t)=1 for $-1 \leqq t \leqq 0$, t=0 to 17 and x=0 to 2 throughout. The vertical lines here and in Figs. 4, 5 and 6 are spaced one time unit apart, and the horizontal lines are x=0, 1/2, 1 and 2. (a) a=0.6 (b) a=0.8 (c) a=0.86 (d) a=0.88 (e) a=0.9 (f) a=0.98 (AN DER HEIDEN & MACKEY /31/)

time unit later lasts so long that x(t) crosses the level 1 from above (for a=0.86 this occurs between t=3 and t=4, see Fig. 3c), ultimately giving rise to an additional minimum of x(t) in the interval between t=4 and t=5 (see Fig. 3c). This in turn implies that the duration of the second undershoot of the level 1/2 by x(t) becomes shorter, so short in fact that the decrease between t=6 and t=7 does not go beyond the level 1. Since between t=6 and t=7 the solution x(t) is larger than 1, x(t) afterwards decays exponentially to the value of exp(-a), completing one cycle which started at $t=t_1$ (see Fig. 3c). The important fact to note is that the crossing of 1 between t=3 and t=4 leads to a sudden increase of the period from about 3 at a=0.8 to about 6 at 0.86. A period doubling bifurcation is present at just that value of the parameter a for which the minimal value of x(t) between the times 3 and 4 equals 1. One period now contains 5 minima.

It may happen that a minimum will again disappear if a is increased still further. An example is shown in Fig. 3d, where a=0.88. There, the increase of x(t) between t=4 and t=5 has become so large that the undershoot of the level 1/2 present for a=0.86 between t=5 and t=6 is now missing. This, in turn, obliterates the minimum between t=6 and t=7. However, this change has no drastic influence on the period.

For a=0.9 (see Fig. 3e) the increase of x(t) in the time interval between t=4 and t=5 is so large that an additional minimum is again created between t=5 and t=6, though the periodicity remains unchanged and the period is still near 6 (remember that the time unit is just the delay time).

The next large change of period occurs between a=0.97 and a=0.98. For a=0.98 (see Fig. 3f) the maximum between t=5 and t=6 has become so large that the duration of the overshoot above 1 is sufficient to create a minimum between t=6 and t=7 which is below 1. The second exponential decay from 1 to exp(-a) occurs between t=10 and t=12 because x(t) is above 1 in the interval between t=9 and t=10. The periodic solution obtained has a period of about 8.8 time units and includes 9 minima. In this case the period of the new bifurcating solution is not twice as long as that of the original periodic solution.

As a is increased, progressively more complex solutions arise. The details of these behaviors may be reconstructed as in the above examples, using Eq.(6a) and Eq.(6b). Instead of discussing the details we briefly outline a criterion to demonstrate the existence of a stable periodic solution, which has already been applied several times.

3.1 A Sufficient Criterion for Periodicity

Whenever the solution x(t) exceeds the value 1 during a time interval longer than the delay (remember d=1 here), then afterwards the solution must decay exponentially to the value exp(-a). We have chosen the initial condition such that this decay occurs after one time unit. Therefore, if this occurs later on a second time we have ascertained that the solution between thes two events comprises just one period of a periodic solution, no matter what details the solution shows in between.

It is easily shown that the periodic solutions so far observed all obey this criterion. Its usefulness is seen directly from an example, as in Fig. 4a where a=1.0015. Here x(t) is larger than 1 in the interval from t=0 to t=1 and, for the second time, in the interval from t=12.3 to t=13.6. Therefore, there is a periodic solution between t_1 and t_2 (see Fig. 4a) with period $t_2 - t_1 \simeq 12.2$ (and 13 minima).

It is not a general rule that the length of the period, or the number of minima within one period, will increase when the parameter a is increased. For a=1.0125 (see Fig. 4b) the period is only about 7, a reduction by nearly a factor 2 from the period at a=1.0015 (Fig. 4a). The reduction is due to the fact that the seventh minimum shown in Fig. 4a, which is below 1, has a value above 1 for a=1.0125. Thus our criterion for periodic solutions applies in the interval between t=7 and t=8.

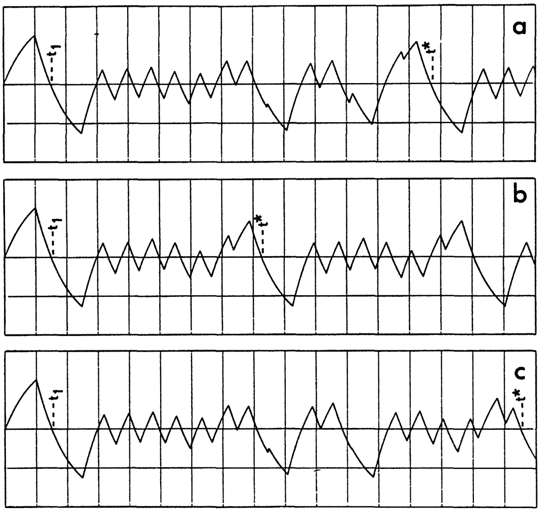

Fig. 4 As in Fig.3 with (a) a=1.0015 (b) a=1.0125 (c) a=1.001

Similar considerations hold for the pair a=1.001 (see Fig. 4c) and a=1.0015, where there is a reduction from a period of length 15 to a period of 12.2 (the example in Fig. 4c shows 16 minima within one period).

It should be noted that though this criterion is sufficient for the existence of a periodic solution, it is not necessary. Fig. 5a shows a periodic solution for a=2.75 which does not satisfy the criterion. However, a situation as in Fig. 5a is quite exceptional since it requires a very special composition and fitting of pieces of increasing and decreasing exponentials. Indeed Figs.5b (a=2.7) and 5c (a=2.775) again exhibit periodic solutions of the more general type (now with periods 72.4 and 20.2 respectively, count the number of minima!).

Figs.6a and 6b show two records of solutions where the period, if there is any at all, is longer than the time for which the solution has been computed. It is noteworthy that within time unit (i.e. the time delay) there occur many oscillations if a is large, and thus the time scale of the fine structure of the solutions for large a is much smaller than the time delay.

All of the periodic solutions satisfying the discussed criterion of periodicity are stable in the following sense: If $y(t)$, $-1 \leq t \leq 0$, is any other initial condition satisfying $b < y(t) < c/a$ (assuming $c/a > 1$) and not crossing the value 1 from above, then the corresponding solution $y(t)$, $t > 0$, converges to some time shift $x(t-t_0)$ of the periodic solution $x(t)$, $t > 0$ (as may be seen by following the solutions for two time units).

3.2 Existence of Stable Limit Cycles of Spiral Type

The previous sections give some intuition into how complexity may successively arise if some parameter is varied systematically. The

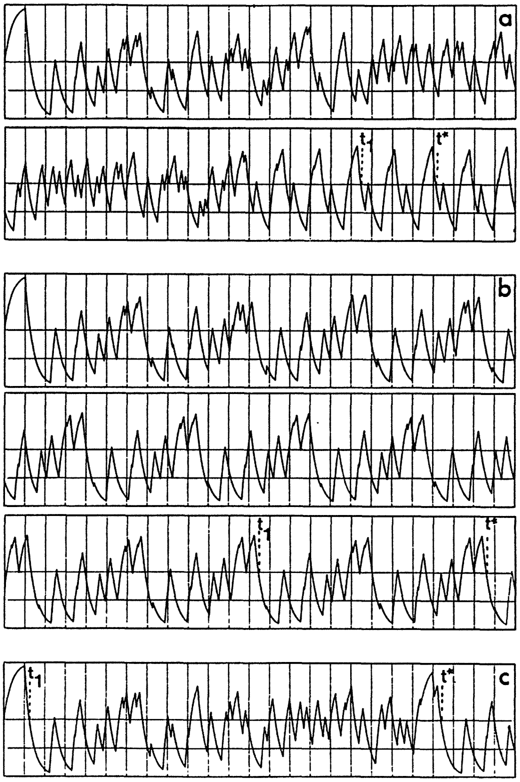

Fig. 5 As in Fig. 3 with 25 time units per panel.
(a) a=2.75, t=0 to 50,
(b) a=2.7, t=0 to 75,
(c) a=2.775, t=0 to 25

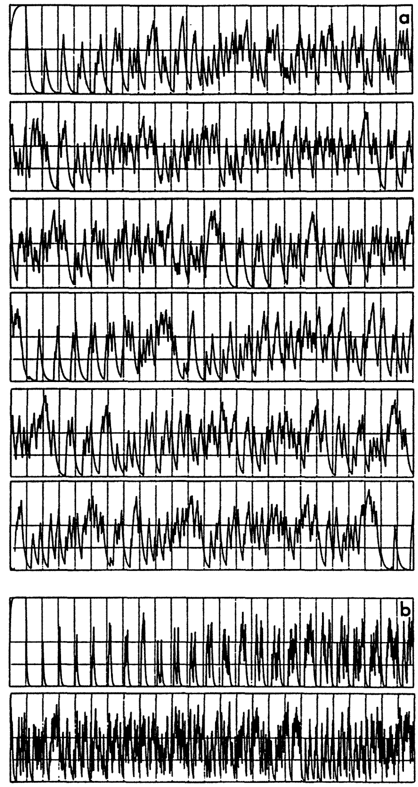

Fig. 6 As in Fig. 3 with 25 time units per panel. (a) a=6, t=0 to 150, (b) a=20, t=0 to 50

indicated techniques can be much more sharpened and extended such that it is possible to prove some far-reaching results. In the following sections we shall describe some of these results. For the proofs the reader is referred to the literature, essentially to the papers /30/, /31/, /32/.

A periodic solution is called of spiral type if one of its periods contains several maxima with increasing amplitude. In other words, during such a period the values of the solution at successive times of local maxima increase, and after this period the cycle repeats starting with a maximum with lowest value. It has been proved (see /31/) that there are values of the parameters a and c for which the following proposition holds:

There is a sequence of values (b_n), $n=1,2,\ldots$, $b_n < b_{n+1}$, such that for any b satisfying $b_n < b < b_{n+1}$ there exists an asymptotically orbitally stable periodic solution (limit cycle) of spiral type to Equations (3) & (4) having n maxima within one smallest period. As $n \to \infty$ the length of the period of the corresponding periodic solutions tends to ∞ .

3.3 Existence of Chaotic Solutions

There are many different definitions of chaos in the literature. For nonlinearities f of the form

$$f(x) = \begin{cases} 0 & \text{if } x < b \\ c & \text{if } b \leq x \leq 1 \\ d & \text{if } 1 < x \end{cases} \tag{10}$$

the following type of chaos can be proved to exist for at least some of the parameter values a, b, c, and d (for specification see /31/).

Let (n_i), $i=1,2,\ldots$, be an arbitrary sequence of natural numbers satisfying $n_{i+1} > n_i$. Then there exists a solution x(t) of Equations (3) & (10) with the following properties:

x(t) has infinitely many maxima occurring at times t_j, $j=1,2,3,\ldots$, $t_{j+1} > t_j$. At other times no maxima occur. The relations

$$x(t_j) > 1 \text{ if } j = n_i \text{ for some } i$$

and

$$x(t_j) < 1 \text{ if } j \neq n_i \text{ for all } i$$

are satisfied.

More loosely speaking, there are solutions with arbitrary mixtures of small oscillations (where values at the maxima do not exceed the value one) and large oscillations (where values at the maxima do exceed 1).

3.4 Statistical Behavior

There is at least one difficulty with this and similar types of chaos. Just as a limit cycle or a steady state may be stable or unstable, the chaotic domain in the state space may be stable or unstable (or equivalently attractive or repelling). If it is unstable and if, moreover, its measure in the state space is zero, then generally the chaotic orbits will not be observed in any physical realization of the system. Indeed, it can be shown that for certain regions of the parameters (a, b, c, d) the chaotic set exhibited in the previous section has the structure of a Cantor set, hence has measure zero, and is unstable. Therefore it is important to find other domains in the parameter space where the chaotic behavior is not exceptional. This problem is considered in the paper /32/. In fact, it could be proved that for certain parameter values (a,b,c,d) there exists an attractive set of solutions to (3) & (10) such that the values of these solutions at their (infinitely many) maxima are distributed according to a continuous probability distribution.

More precisely it could be proved /32/ that there is an interval I and a map G: I $\rightarrow$ I such that the following conditions are satisfied:

For each $s \in I$ there is a solution x_s of (3) & (10) with the following properties:

(i) There are infinitely many times (t_i), $i=1,2,\ldots$, $0 < t_i < t_{i+1}$, such that x_s has a maximum at t_i

(ii) $x_s(t_1) = s$ and $x_s(t_{i+1}) = G(x_s(t_i))$ for $i=1,2,\ldots$

(iii) There is a density $h: I \to \mathbb{R}_+$ such that G is invariant, ergodic, mixing, and exact with respect to h.

The notions of ergodicity, mixing, and exactness describe increasing degrees of random and chaotic types of behavior. For an extensive discussion of these notions the reader is referred to the book by LASOTA & MACKEY /33/. The notion of mixing is really adapted to and from the ordinary idea of turbulence: Take any (arbitrarily small) subinterval J of I. Applying iteratively G on the points of J these in the long run become distributed in a random fashion across the whole interval I (just like in a turbulent pool of water the molecules of any small volume become distributed randomly across the whole pool in the course of time). In particular the phenomenon of "critical dependence of time courses on initial conditions" is realized.

3.5 The Influence of Discontinuities on the Solutions

When viewing the solutions presented in the previous sections as a is varied, one naturally wonders if the results are in some sense artifactual and due to the discontinuities in the slope and value of the function f as given in Eqs.(4) and (10). That this is definitely not the case can be shown analytically by techniques which have been successfully applied for a class of nonlinearities and the same delay-differential equation in /30/. All of the described qualitative phenomena are also obtained with smooth feedback functions f, at least if these are in a certain sense close to the described discontinuous nonlinearities.

Of course there are even large quantitative differences between solutions to equation (3) with different functions f. In order to give an impression about the variability in the appearance of solutions in Fig.7 numerical solutions are shown with other types of functions f, some aspects of which are, however, related to the previously discussed f. All of these types are encompassed by

$$f(x) = \begin{cases} 0 & \text{if } 0 \leqq x < \delta \\ c(x-\delta)/(\varepsilon-\delta) & \text{if } \delta \leqq x < \varepsilon \\ c & \text{if } \varepsilon \leqq x \leqq \psi \\ c(x-1)/(\psi-1) & \text{if } \psi < x \leqq 1 \\ 0 & \text{if } 1 < x \end{cases} \tag{11}$$

In Eq.(11) the parameters satisfy $0 \leqq \delta \leqq \varepsilon \leqq \psi \leqq 1$ and $c > 0$. Eq.(11) reduces to Eq.(4) if $\delta = \varepsilon = b$ and $\psi = 1$. As in the previous sections time is scaled, so d=1. In all calculations we used a=1.7 and c=3.4 (thereby preserving the previous relationship $\gamma = c/a = 2$), and an in-

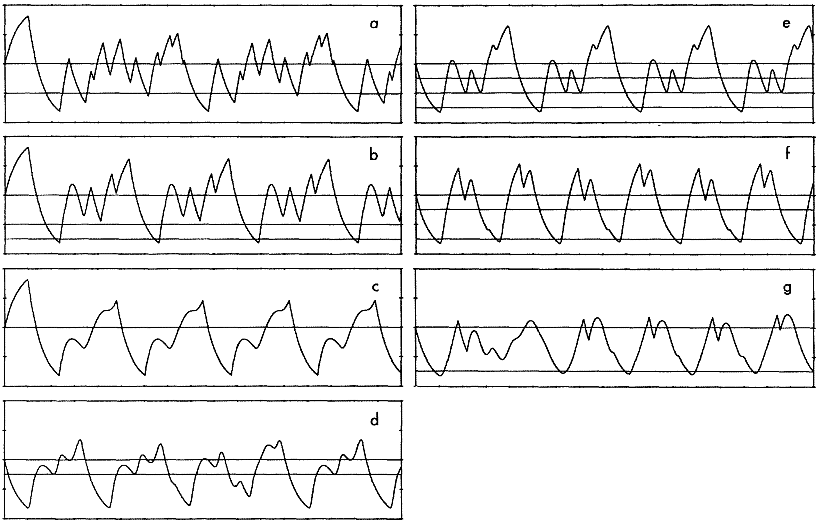

Fig. 7 Numerical solutions /x(t) vs. t/ to Eq.(3) in conjunction with Eq.(11) with various combinations of the parameters δ, ε, and ψ. In each panel t=0 to 17 and x=0 to 2. A predictor-corrector integration scheme with a step size of 5×10^{-3} was used, and a=1.7, c/a=2, d=1, and x(t)=1.0 for $-1 \leqq t \leqq 0$ throughout. In each case the values $x=\delta$, $x=\varepsilon$, $x=\psi$ are indicated by horizontal lines.
$(\delta, \varepsilon, \psi)$ =: (a) (1/2,1/2,1); (b) (1/4,1/2,1); (c) (0,1,1);
(d) (0,3/4,3/4); (e) (1/4,1/2,3/4); (f) (1/4,1/4,3/4);
(g) (1/4,1/4,1/4)

itial condition of x(t)=1 for $-1 \leqq t \leqq 0$. The other parameters (ε, δ, ψ) are different for each of the numerical solutions in Fig. 7a-g and are given in the legend. The interested reader may graphically realize which types of nonlinearities we captured by these choices of parameters. By help of the horizontal lines in Fig. 7, corresponding to the levels $x=\delta$, $x=\varepsilon$, $x=\psi$, the discussion of the first part of this section may be continued to obtain some understanding why the solutions behave as they do.

The essential points to note here are that: (1) the same techniques developed in the previous sections may be applied to understand the evolution of complex patterns; and (2) the removal of discontinuities in the values of f at x=1/2 and (or) at x=1 has smoothed the solutions. Further, the numerically generated solutions obey the general criteria for the determination of periodicity set forth previously (e.g. on this basis the period in Fig. 7b is approximately 4.3). Note, however, that some of the numerical solutions (Figs. 7d, g) are not periodic over the time displayed here.

4. Discussion

We have shown that simple mathematical tools (essentially knowing some qualitative properties of the exponential function) are sufficient to obtain insight into how complex, and at first sight somewhat unpredictable, temporal patterns may arise from simple deterministic mechanisms. As we pointed out, with somewhat more difficult mathematical techniques it has been proved that for a class of smooth nonlinearities f, Eq.(3) has infinitely many periodic solutions with differing periods (depending on initial conditions) and, moreover, infinitely many (so-called) aperiodic solutions. Aperiodicity may be defined in a way which incorporates properties essential for random processes /33/. Therefore deterministic and stochastic behavior are not mutually exclusive categories. For an observer not knowing the underlying deterministic structure (as given, e.g., by Eq.(3)) the process appears to be lacking in order despite the fact that all its details can be reproduced, and are determined by, a single equation.

It is important to note that in an experimental context the question of periodicity in a process is unanswerable if the period is longer than the period of observation. Moreover, as observed above, small changes in the parameters may lead to entirely different periodic patterns. Since in practice parameters are seldom absolutely constant, this is yet another potential source of complexity and irregularity.

Here, we have only discussed situations in which system dynamics are sensitive to the properties of the system some fixed time d in the past. However, there are two much more general situations which occur in a variety of applied sciences and which have received little attention.

1. State-dependent delays. In the first of these, the characteristic time delay d of the system is no longer constant but now depends on the state of the system at the current time, i. e., d=d(x). Though this may seem to be a quite peculiar situation, a simple example will suffice to illustrate how it may occur.

In mammals, platelets are produced from cells in the bone marrow known as megakaryocytes. The production of immature megakaryocytes is controled by the number of circulating platelets, probably mediated by a poorly characterized hormone known as thrombopoietin. As megakaryocytes age, they undergo repeated rounds of DNA synthesis and nuclear division but without cytokinesis, so they may exist at ploidy values of 2 N, 4 N, 8 N, 16 N, or 32 N. Thus ploidy value is a convenient index of megakaryocytic age. In the normal situation, the vast majority of platelets are produced by megakaryocytes of 8 N ploidy, and the age of the megakaryocyte at this ploidy value is equivalent to a time delay in the platelet production system because of the platelet regulation of megakaryocyte production.

However, a variety of animal experiments as well as clinical observations in humans have shown that the ploidy value at which megakaryocytes produce platelets is proportional to circulating platelet numbers. Thus,the consequence of this is that the essential time delay in the platelet production system is a monotone increasing function of platelet number.

Numerical simulations of the platelet control system (BELAIR & MACKEY /34/) reveal that time delay differential equations with a state-dependent delay of this type may display an astonishing array of dynamical behavior. Many other biological and physical examples also exist in which state-dependent delays certainly exist and which may play a crucial role in determining dynamical behavior. Other than existence and uniqueness theorems of DRIVER /35/ there seems to be no analytic treatment of these problems in the literature. FELDSTEIN & NEVES /36/ have developed techniques for the numerical investigation of state-dependent delay differential equations.

2. Future effects. A second example of complicating behavior may arise in systems where the current dynamics depend, in some fashion, not only on the behavior in the present and in the past but also on future dynamics. Though we are totally unaccustomed to thinking about the possibility of the future affecting the present because of our perceptions of macroscopic causality, there are serious reasons for considering such possibilities. Two examples will suffice for illustration.

In the first instance, a wide variety of learned neural programs, e. g. catching a ball, walking on a treadmill, must integrate not only past and present system states but must also attempt to estimate future system states in order to operate smoothly. As a second example we might consider economic commodity markets in which the current market dynamics are a reflection of what has transpired in the past, what the current situation is, and what the anticipated future market position will be. All of these factors play a role in the operating of futures markets but have not, to our knowledge, ever been considered from a formal mathematical point of view.

Other examples from the physical sciences exist, and we mention only that arising in electromagnetic field theory in which, mathematically equally valid, advanced and retarded solutions to Maxwell's equations exist. Customarily, only the retarded solutions (with the time delay dependent on particle position, thus state dependent) are taken, though there is no a priori reason to reject the equally valid advanced solutions that are dependent on the future dynamics. Again, this is a poorly explored area in the mathematical literature.

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