Rhythms and Chaos in Biological Systems

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Rhythmic phenomena are ubiquitous in biology and occur with periods ranging from a few milliseconds (nerve cells) to seconds (heart), minutes (oscillatory enzyme reactions), hours (periodic hormone secretion), days (circadian rhythms), and years (annual rhythms, and predator-prey oscillations in ecology). This list is by no means exhaustive; moreover, new rhythms are being uncovered at the cellular or supracellular levels. The reason why oscillations are so common in biological systems is primarily related to the fact that these systems are governed by nonlinear evolution equations, owing to the fact that they are regulated by a multiplicity of positive and negative feedback processes. The analysis of mathematical models for regulated biological systems confirms that oscillations are a conspicuous property of living systems, regardless of the level of biological organization at which these rhythms occur [1].

Mathematical models for biological rhythms are of two sorts: one class aims at providing a rough caricature whose very simplicity is well-suited to the analytical approach; such an approach allows us to obtain detailed information on the dynamics of the system. Models of the second kind are closely related to experimental data. The underlying equations for such models are often more complex, so that analytical tools have only limited use and one has to resort to numerical simulations.

Most oscillations in biological systems are of the limit cycle type. In recent years, however, the emphasis has shifted to more complex modes of oscillatory behavior [2]–[4]. Among these, particular interest has been devoted to complex periodic oscillations (bursting) and to aperiodic oscillations (chaos). Such complex phenomena have been studied in different biological contexts, particularly in neurobiology; bursting indeed characterizes the activity of many nerve cells [3]. Another field where simple and complex oscillatory phenomena have been studied by means of theoretical models is biochemistry [5]. The occurrence of rhythms and chaos in biological systems will be illustrated here by some examples taken from this field.

Limit Cycle Oscillations

Several experimental examples of sustained oscillations in biochemical systems are known, the prototype being that of glycolytic oscillations in yeast cells. These oscillations provided one of the first examples of a biological rhythm demonstrated in vitro; they occur when a sugar, injected constantly at an appropriate rate into a suspension of yeast cells or into yeast extracts, is transformed periodically into
ethanol and CO₂ (see [5] for further details and references). The oscillations, which have a period of some 5 minutes, originate from an enzymatic reaction transforming a substrate (S) into a product (P); the reaction is catalyzed by phosphofructokinase (PFK). As in many instances in other fields of chemistry or biology, periodic behavior originates from positive feedback, i.e., autocatalysis: the product of PFK indeed activates the enzyme and thereby enhances its own production.

A two-variable model for the autocatalytic enzyme reaction has been proposed [5]; it is governed by the system of ordinary differential equations (1):

\[
\begin{align*}
\frac{d\alpha}{dt} &= v - \sigma \phi \\
\frac{d\gamma}{dt} &= q \sigma - k_s \gamma
\end{align*}
\]

with

\[
\phi = \frac{\alpha(1 + \alpha)(1 + \gamma)^2}{L + (1 + \alpha)^2(1 + \gamma)^2}
\]

Function \(\phi\) denotes the nonlinear expression of the rate of the product-activated enzyme reaction; \(\alpha\) and \(\gamma\) denote, respectively, the dimensionless concentrations of substrate and product; \(v, s, q, k_s\) and \(L\) are parameters (see [5] for further details).

The main result of the analysis of equation (1) is that these equations admit a single steady-state solution which becomes unstable in a range of substrate injection rate \((v)\) bounded by two critical values of parameter \(v\) associated with Hopf bifurcations. In that range, the system evolves toward sustained oscillations corresponding to a limit cycle in the \((\alpha, \gamma)\) phase plane. Phase plane analysis proves particularly useful in establishing this result which accounts for the main experimental observation on glycolytic oscillations in yeast.

**Birhythmicity**

The question arises as to whether the stable limit cycle is always unique for a given set of parameter values — as is the case for equation (1) — or whether multiple stable limit cycles may sometimes coexist. A conjecture based on phase plane analysis leads to the following system of two differential equations, representing a direct extension of equation (1):

\[
\begin{align*}
\frac{d\alpha}{dt} &= v + \frac{\sigma_i \gamma^n}{K^n + \gamma^n} - \sigma \phi \\
\frac{d\gamma}{dt} &= q \sigma \phi - k_s \gamma - \frac{q \sigma_i \gamma^n}{K^n + \gamma^n}
\end{align*}
\]
where $\phi$ remains given by equation (2). In equation (3), the new term refers to a reaction of nonlinear recycling of product into substrate, characterized by the threshold constant $K$; the maximum rate of this process is denoted by $s_i$. The analysis of the model indicates that in a certain range of $s_i$ values, the system admits two stable limit cycles separated by an unstable cycle [5]; this phenomenon has been referred to as birhythmicity [6]. Birhythmicity has been demonstrated experimentally in several chemical reactions but has not yet been observed in biological systems.

**Bursting and Chaos**

More complex modes of oscillatory behavior require the interaction of at least three variables. To allow for the occurrence of more complex oscillatory phenomena, the model described by equation (1) was again extended to consider a sequence of two autocatalytic enzyme reactions coupled in series [5]–[7]: the first enzyme, $E_1$, transforms substrate $S$ into product $P_1$; the latter is transformed into product $P_2$ by the second enzyme, $E_2$. Both reactions are subjected to positive feedback as $E_1$ and $E_2$ are activated by $P_1$ and $P_2$, respectively. This system is governed by the three differential equations (4) (see [5]–[7] for further details):

\[
\begin{align*}
\frac{d\alpha}{dt} &= v - \sigma_1 \phi(\alpha, \beta) \\
\frac{d\beta}{dt} &= q_1 \sigma_1 \phi(\alpha, \beta) - \sigma_2 \eta(\beta, \gamma) \\
\frac{d\gamma}{dt} &= q_2 \sigma_2 \eta(\beta, \gamma) - k_3 \gamma
\end{align*}
\]

(4)

where the rate functions $f$ and $h$ of the enzymes $E_1$ and $E_2$ are given, respectively, by expressions (5) and (6):

\[
\phi(\alpha, \beta) = \frac{\alpha(1+\alpha)(1+\beta)^2}{L_1 + (1+\alpha)^2(1+\beta)^2}
\]

(5)

\[
\eta(\beta, \gamma) = \frac{\beta(1+\gamma)^2}{L_2 + (1+\gamma)^2}
\]

(6)

In these equations, $\alpha$, $\beta$ and $\gamma$ represent the normalized concentrations of $S$, $P_1$ and $P_2$, respectively. In addition to the modes of behavior exhibited by equations (1) and (3), depending on parameter values, the system governed by equations (4–6) displays the following dynamic properties:

(i) coexistence between a stable limit cycle and a stable steady state;

(ii) coexistence between two or even three stable limit cycles (bi- and trirhythmicity);
(iii) bursting oscillations, in which a constant number of spikes of \( b \) and \( g \) occur over a period;
(iv) aperiodic oscillations (chaos) corresponding to the evolution toward a strange attractor;
(v) coexistence between a stable limit cycle and a stable strange attractor.

The richness in behavioral modes originates in system (4) from the coupling of two instability-generating mechanisms. This result is analogous to obtaining bursting and chaos in oscillatory systems driven by some periodic input [2]–[4]; in contrast, chaos in system (4) is autonomous as it occurs in the absence of periodic forcing.

From periodic behavior to chaos in a cellular system:

\textbf{cAMP oscillations in Dictyostelium amoebae}

Another well-known example of biochemical oscillation occurs during the life cycle of \textit{Dictyostelium} amoebae. After starvation, these cells aggregate in a wavelike manner by a chemotactic response to pulses of cyclic AMP (cAMP) emitted periodically by aggregation centers; the period of cAMP pulses and of the associated waves is of the order of 5 minutes (see [5] for further references). A model for the signaling system has been proposed [8]; it is described by a system of four nonlinear differential equations. While reductions to three or even two variables account for the periodic synthesis of cAMP, the four-variable and three-variable versions also give rise to chaotic oscillations [5]. As in the system described by equations (4)–(6), chaos occurs as a result of the coupling of two endogenous oscillatory mechanisms. The domain of aperiodic oscillations in parameter space remains, however, much reduced as compared to the domain of simple or complex periodic oscillations.

Although originating from mathematical models based on biochemical kinetics, these results are of general significance and pertain to the occurrence of rhythms and chaos in other biological systems. The transitions between the various modes of dynamic behavior indeed remain largely independent of the detailed form of the underlying, nonlinear evolution equations.

\textbf{References}


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