Chemical Oscillations by Substrate Inhibition

A Parametrically Universal Oscillator Type in Homogeneous Catalysis by Metal Complex Formation

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The general reaction $X+Y \rightarrow P+Q$, catalyzed by a metal M via $M+X \rightleftharpoons MX$ and $MX+Y \rightarrow M+P+Q$ (or, in another subcase, $MX+Y \rightleftharpoons MXY \rightarrow M+P+Q$) renders a chemical oscillator, if in an open system X and Y are supplied from appropriate sources by influxes j_1 and j_2, respectively, if X shows substrate inhibition by subtracting active catalyst by forming an inert complex MX_2, and if at least X is limited by an additional first order side reaction. Introduction of dimensionless variables and parameters and assumption of a partial steady state for the catalyst compounds, the sum of which is constant, leads to 5 (or 6) parameters, 3 of which can be easily adjusted in a wide range. It is shown that for any given values of the 2 (or 3) fixed parameters the adjustable ones can in principle be chosen in such a way that the conditions for oscillation are met. This type of oscillator is thus a parametrically universal one. By appropriate choice of the adjustable parameters the yield of products can be conducted in bursts instead of a continuous flow. Another possibility is an excitable system that fires only on triggering. Proposals toward chemical realization are discussed especially with respect to transition metal complexes.

Introduction

Chemical oscillations enjoy an ever increasing interest from chemists, biologists, biophysicists, and chemical engineers. However, oscillations are only one aspect of such non-classical phenomena (as they shall be called in the following text) like dissipative structures, chemical waves, multistability, hysteresis, excitability, etc. that can only arise in *open, nonlinear systems far from equilibrium*[1] and which are closely related to each other. Since the conditions just mentioned are evidently met in living organisms and as there is a need for an explanation of such complex biological events like the physiological clock, cell differentiation, morphogenesis, metabolic control and — on the interorganismic level — ecological interactions and evolution, the first demand for experimental chemical results and theoretical interpretation came from the biological sciences.

Meanwhile pure chemists have recognized these — from the standpoint of classical thermodynamics seemingly forbidden — phenomena as interesting in its own right. Nevertheless, the number of known real chemical oscillators is small[2], its most prominent representative being the well-known Belousov-Zhabotinskii-oscillator[3], whose complicated kinetic structure has recently been revealed by Field, Körös, and Noyes[4].

Whereas the role of these phenomena, that are evoked by some permanent or transient dynamical instability, is a highly productive one in biology, giving rise to development and successful adaptation to the environment, these instabilities, that can occur in open technical plants, too[5], are strongly disturbing there and thus unwanted.

On the other side, these non-classical phenomena represent states of lower entropy, or, which is the same, of a higher degree of information and it can be expected that by a sophisticated usage of this feature one can get at least partially rid of the disturbing side effects of classical kinetics in closed systems like the contamination of wanted products by inevitable side products that must be removed by complicated and costly techniques of separation and purification.

In this sense there arises some need for a more systematic theoretical treatment of the prerequisites of the non-classical phenomena and some simple and widely adjustable models that can lead to a successful design of new oscillators and which should therefore not contain such strange assumptions, like

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autocatalysis of higher order as in the well understood "brusselator" by Prigogine[6].

In the following paper, we strive at a thorough theoretical treatment of a special type already known, rather than at the discovery of new types or a general theory of chemical oscillation. We stick to the effect of substrate inhibition which is encountered with at least 30 enzymes[7] and which is already known to lead to hysteresis[8] and oscillatory states[9], e. g., in peroxidase as investigated by Degn[10]. An especially thorough theoretical treatment of the possibility of steady state multiplicity and oscillations of enzyme systems with two substrates, one of which inhibits the enzyme, has been given by Bruns, Bailey, and Luss[11], although they start from a rate law not derived in detail and differing from ours in substantial parts. But the main difference lies in the fact that these authors assume a first order side reaction or overflow (in the open system) of both substrates, which case is more general than the case treated in this paper, but adds so severe complications that those authors did not succeed in a complete discussion of the whole parameter space. On the other side they found the curious possibility of a stable limit cycle enclosing a stable critical point and separated from it by an unstable limit cycle.

In the following we want to expose the model, prove that under certain mild conditions there exists only one critical point (i. e. steady state) which cannot be a saddle point, formulate the criterion for its instability and show that there exists a certain bounded area in the 2-dimensional state space. In this sense it is proved with full rigour according to the Poincaré-Bendixson-theorem[12] that and under which conditions oscillations must occur. After this main part we shall leave the mathematical treatment and switch over to more chemical arguments where it is tried to give hints to experimentalists to achieve a chemical realization of the theoretical model. Phenomena connected to the conditions of oscillation will be discussed only qualitatively leading over to further technical applications.

Case I: Direct Reaction $MX + Y \rightarrow M + P + Q$

The complete reaction scheme of this somewhat simpler case is given in Figure 1. The constant influxes j_1 and j_2 to the substrates X and Y can be achieved by very different arrangements: by direct pouring of the corresponding solutions into the reacting mixture neglecting dilution by the solvent or by preceding first order reactions from predecessors whose concentrations are kept constant in appropriate pools. The efflux of X represented by the first order rate constant k_0 cannot be a mere overflow because in that case the same constant should be applied to the overflow of Y. In the simplest case, k_0 is characteristic of the back reaction to the pool substance without loss of substrate, e. g. when X is an enol and the pool of the predecessor is the corresponding ketone as the preferred tautomer. Another interpretation can be that X is supplied from another phase (e. g. a hydrophobic one) where its concentration is high and buffered.

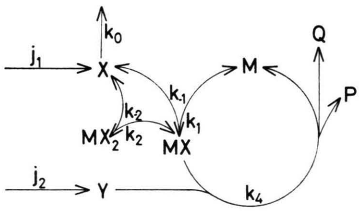

Fig. 1. Reaction scheme of Case I (fast reactions are formulated as reversible, slow ones as irreversible).

Application of the law of mass action yields

$$\mathrm{d}[\mathrm{X}]/\mathrm{d}t = j_1 - k_0[\mathrm{X}] - k_1[\mathrm{X}][\mathrm{M}] + k_{-1}[\mathrm{MX}] - k_2[\mathrm{X}][\mathrm{MX}] + k_{-2}[\mathrm{MX}_2]\,, \tag{1}$$

$$\mathrm{d}[\mathrm{Y}]/\mathrm{d}t = j_2 - k_4[\mathrm{X}][\mathrm{MX}]\,, \tag{2}$$

$$\mathrm{d}[\mathrm{M}]/\mathrm{d}t = -k_1[\mathrm{X}][\mathrm{M}] + k_{-1}[\mathrm{MX}] + k_4[\mathrm{Y}][\mathrm{MX}]\,, \tag{3}$$

$$\mathrm{d}[\mathrm{MX}_2]/\mathrm{d}t = k_2[\mathrm{X}][\mathrm{MX}] - k_{-2}[\mathrm{MX}_2]\,, \tag{4}$$

$$[\mathrm{M}]_{\mathrm{total}} = [\mathrm{M}] + [\mathrm{MX}] + [\mathrm{MX}_2]\,. \tag{5}$$

Equation (5) instead of an analogous differential equation for [MX] takes into account that the sum of the various forms of the catalyst M is constant and is represented by the adjustable parameter $[\mathrm{M}]_{\mathrm{total}}$. We assume a partial steady state for the concentrations of M, MX, and MX_2, because their concentrations are normally small compared to [X] and [Y] so that they can follow virtually inertless the movements of [X] and [Y]. This assumption is equivalent to setting $\mathrm{d}[\mathrm{M}]/\mathrm{d}t$ and $\mathrm{d}[\mathrm{MX}_2]/\mathrm{d}t$ equal to zero. Using incorrectly "$=$" instead of "$\approx$" for this approximation in the further treatment, we get

$$\mathrm{d}[\mathrm{X}]/\mathrm{d}t = j_1 - k_0[\mathrm{X}] - r\,, \tag{6}$$

$$\mathrm{d}[\mathrm{Y}]/\mathrm{d}t = j_2 - r\,, \tag{7}$$

$$r = k_4[\mathrm{Y}][\mathrm{MX}] \tag{8}$$

(r is the production rate of products P and Q).

By virtue of

$$[MX_2] = [MX]\,k_2[X]/k_{-2}\,, \tag{9}$$

$$[M] = [MX]\,(k_{-1} + k_4[Y])/(k_1[X])\,, \tag{10}$$

we get with (5)

$$r = k_{-1}[M]_{\text{total}} \frac{\dfrac{k_1[X]}{k_{-1}} \cdot \dfrac{k_4[Y]}{k_{-1}}}{1 + \dfrac{k_1[X]}{k_{-1}} + \dfrac{k_1 k_2 [X]^2}{k_{-1} k_{-2}} + \dfrac{k_4[Y]}{k_{-1}}}\,. \tag{11}$$

Here [X] and [Y] appear in dimensionless terms. Formulating the whole system in dimensionless variables and parameters renders it in a completely exact, but not unique way in the form

$$d\xi/d\tau = \varphi + \chi - \xi - \varrho\,, \tag{12}$$

$$d\eta/d\tau = a(\varphi - \varrho)\,, \tag{13}$$

$$\varrho = \gamma\varphi \frac{\xi\eta}{1 + \xi + \varkappa\xi^2 - \eta} \tag{14}$$

with the variables

$$\tau = k_0 t\,, \tag{15}$$

$$\xi = \frac{k_1}{k_{-1}}[X]\,, \tag{16}$$

$$\eta = \frac{k_4}{k_{-1}}[Y]\,, \tag{17}$$

and the linearly independent parameters

$$\varphi = \frac{k_1}{k_0 k_{-1}} j_2\,, \tag{18}$$

$$\chi = \frac{k_1}{k_0 k_{-1}} (j_1 - j_2)\,, \tag{19}$$

$$\gamma = \frac{k_{-1}[M]_{\text{total}}}{j_2}\,, \tag{20}$$

which are in a wide range adjustable by virtue of the fluxes j_1 and j_2 and the sum concentration of catalyst, $[M]_{\text{total}}$.

The only fixed parameters are

$$\varkappa = (k_{-1} k_2)/(k_1 k_{-2}) \tag{21}$$

and

$$a = k_4/k_1 \tag{22}$$

which represent essentially the equilibrium constant of $MX + X \rightleftharpoons MX_2$ and the ratio of the rates with which Y and X react with some form of the catalyst, respectively. All new parameters save χ are immediately seen to be positive real (abbreviated in the following "$\in \mathbb{R}_+$"), because all multiplicative constituents $\in \mathbb{R}_+$. Especially the definitions of χ and γ look here a little strange, but they yield particularly convenient expressions later on.

We consider now possible (total) steady states by setting $d\xi/d\tau$ and $d\eta/d\tau = 0$. We get (designating steady state values by the index "ss")

$$\xi_{ss} = \chi\,, \tag{23}$$

$$\eta_{ss} = (1 + \chi + \varkappa\chi^2)/(\gamma\chi - 1)\,. \tag{24}$$

So far no restrictions other than $\in \mathbb{R}_+$ were imposed on the original dimensioned parameters. From (23) and (24) we see that chemically relevant steady states (i. e. ξ_{ss} and $\eta_{ss} \in \mathbb{R}_+$, too) exist only if

$$\chi > 0\,, \tag{25}$$

$$\gamma\chi > 1; \tag{26}$$

so the dimensionless parameters span a 5-dimensional space $\subset \mathbb{R}_+^5$. Inequality (25) can be easily understood from the fact that Y has only an efflux via the catalyzed reaction, whilst X has the same efflux plus an extra drainage $k_0[X]$, so a steady state can only be achieved, if $j_1 > j_2$ or $j_1 - j_2 > 0$.

Provided Eqs. (25) and (26) are obeyed, which is assumed in the further treatment, there exists just one critical point $(\xi_{ss}, \eta_{ss}) \in \mathbb{R}_+^2$; no multiple steady states are possible. If Eqs. (25) and (26) are not fulfilled simultaneously, the system is characterized by [X] and [Y] growing over all limits (which case is not considered here further).

The stability of the single critical point is investigated in the usual way by evaluating the eigenvalues of the Jacobian matrix $\mathbf{J}$ at the critical point:

$$\mathbf{J}_{ss} = \begin{pmatrix} \left(\dfrac{\partial}{\partial\xi}\dfrac{d\xi}{d\tau}\right)_{ss} & \left(\dfrac{\partial}{\partial\eta}\dfrac{\partial\xi}{d\tau}\right)_{ss} \\ \left(\dfrac{\partial}{d\xi}\dfrac{d\eta}{d\tau}\right)_{ss} & \left(\dfrac{\partial}{\partial\eta}\dfrac{d\eta}{d\tau}\right)_{ss} \end{pmatrix} = \begin{pmatrix} -1 - \left(\dfrac{\partial\varrho}{\partial\xi}\right)_{ss} & -\left(\dfrac{\partial\varrho}{\partial\eta}\right)_{ss} \\ -a\left(\dfrac{\partial\varrho}{\partial\xi}\right)_{ss} & -a\left(\dfrac{\partial\varrho}{\partial\eta}\right)_{ss} \end{pmatrix} \tag{27}$$

with [by differentiation of Eq. (14) and insertion of Eqs. (23) and (24)]

$$\left(\frac{\partial\varrho}{\partial\xi}\right)_{ss} = \gamma\varphi \frac{\eta_{ss}(1 + \eta_{ss} - \varkappa\xi_{ss}^2)}{(1 + \xi_{ss} + \varkappa\xi_{ss}^2 + \eta_{ss})^2} = \varphi \frac{1 + 2\varkappa\chi + \gamma(1 - \varkappa\chi^2)}{(1 + \chi + \varkappa\chi^2)\gamma\chi}\,, \tag{28}$$

$$\left(\frac{\partial \varrho}{\partial \eta}\right)_{\mathrm{ss}} = \gamma \varphi \frac{\xi_{\mathrm{ss}}(1+\xi_{\mathrm{ss}}+\varkappa \xi_{\mathrm{ss}}^2)}{(1+\xi_{\mathrm{ss}}+\varkappa \xi_{\mathrm{ss}}^2+\eta_{\mathrm{ss}})^2} = \varphi \frac{(\gamma \chi-1)^2}{(1+\chi+\varkappa \chi^2)\gamma \chi}\,. \tag{29}$$

From

$$\det(\mathbf{J}_{\mathrm{ss}} - \lambda \mathbf{I}) = 0 \tag{30}$$

we get the eigenvalues λ as roots of the polynomial

$$\lambda^2 + \lambda\left(1 + \left(\frac{\partial \varrho}{\partial \xi}\right)_{\mathrm{ss}} + \alpha\left(\frac{\partial \varrho}{\partial \eta}\right)_{\mathrm{ss}}\right) + \alpha\left(\frac{\partial \varrho}{\partial \eta}\right)_{\mathrm{ss}} = 0\,. \tag{31}$$

Since the λ-free term is always positive, as follows from Eq. (29), the critical point cannot be a saddle point ($\lambda_1 \in \mathbb{R}_+$, $\lambda_2 \in \mathbb{R}_-$). So the stability depends only on the sign of the λ-term, with instability in the case of negativity; it is irrelevant in this context whether the critical point is a focus or a node, i. e. whether the eigenvalues λ_1, λ_2 form a pair of conjugate complex numbers or are real with equal signs.

The factor of λ yields the criterion for instability in the form

$$(1+\chi+\varkappa\chi^2)\gamma\chi + \varphi(1+2\varkappa\chi) + \varphi\gamma + \alpha\varphi(\gamma\chi-1)^2 - \varphi\gamma\varkappa\chi^2 < 0\,. \tag{32}$$

Instability can be evoked only by the last term, which is the single negative contribution. The hypersurface in $\mathbb{R}_+^5$

$$\Phi = \frac{(1+\chi+\varkappa\chi^2)\gamma\chi}{\gamma\varkappa\chi^2 - \gamma - 1 - 2\varkappa\chi - \alpha(\gamma\chi-1)^2} \tag{33}$$

is the border between stable and unstable regions, instability existing for $\varphi > \Phi$. $\Phi^{-1}(\gamma, \chi)$ is depicted in Figure 2.

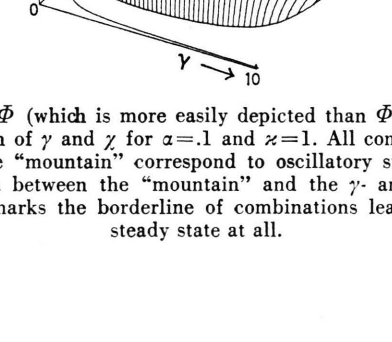

Fig. 2. $1/\Phi$ (which is more easily depicted than Φ itself) as a function of γ and χ for $\alpha = .1$ and $\varkappa = 1$. All combinations inside the "mountain" correspond to oscillatory states. The hyperbola between the "mountain" and the γ- and χ-axes, $\chi = 1/\gamma$, marks the borderline of combinations leading to a steady state at all.

Φ is singular at a hypersurface in $\mathbb{R}_+^4$ where the denominator of Eq. (33) approaches $+0$. This yields another condition

$$\chi > \frac{1}{\gamma} + \sqrt{\frac{1}{\gamma^2} + \frac{1+\gamma+\alpha}{\gamma(\varkappa - \alpha\gamma)}} \tag{34}$$

or

$$\chi > \left[1 + \sqrt{\frac{\varkappa + \gamma(\gamma+1)}{\varkappa - \alpha\gamma}}\right] \Big/ \gamma\,. \tag{35}$$

Since only real values are possible, we get finally a third limitation

$$\gamma < \varkappa/\alpha\,. \tag{36}$$

If this is fulfilled, Eq. (26) holds automatically, because

$$\gamma\chi > 1 + \sqrt{\frac{\varkappa + \gamma(\gamma+1)}{\varkappa - \alpha\gamma}} > 1\,. \tag{37}$$

This is the point to reflect the mathematical results a little bit. We remember that of the 5 parameters only 2, $\varkappa$ and α, are given in a fixed way by nature, the rest, φ, χ and γ, can be adjusted in a wide range; for them there are no principal limits, but in an experimental arrangement there are technical ones, of course. It is known that in a 2-dimensional system with only one steady state limit cycle oscillations occur inevitably if this steady state is unstable (but not a saddle point) and if the trajectories are bounded. Provided the boundedness (which will be proved a little bit later) is established, we get the following recursive recipe for oscillations for given fixed parameters ($\varkappa$, α):

1) Choose any positive $\gamma < \varkappa/\alpha$.

2) Let $\chi > \left[1 + \sqrt{\frac{\varkappa + \gamma(\gamma+1)}{\varkappa - \alpha\gamma}}\right] \Big/ \gamma$.

3) If finally

$$\varphi > \frac{(1+\chi+\varkappa\chi^2)\gamma\chi}{\gamma(\varkappa\chi^2 - 1) - 1 - 2\varkappa\chi - \alpha(\gamma\chi-1)^2}$$

the system will oscillate in a limit cycle.

Since with this algorithm suitable sets of γ, χ, φ can be constructed for any given set of $\varkappa$ and α, this type of oscillator is universal in principle. There are no forbidden regions with respect to the fixed parameters, nor small hidden corners with respect to the adjustable ones which can be found only with difficulty.

We have now to prove that the state space is bounded in the sense that either all trajectories stay within a bounded area or – if the starting point lies outside – they strive inward. For this aim we investigate the nullclines $\bar{\eta} = f(\xi)$, defined by $\mathrm{d}\xi/\mathrm{d}\tau = 0$ and $\bar{\bar{\eta}} = g(\xi)$, defined by $\mathrm{d}\eta/\mathrm{d}\tau = 0$.

We get

$$\bar{\eta} = \frac{(1+\xi+\varkappa\,\xi^2)\,(\varphi+\chi-\xi)}{\gamma\,\varphi\,\xi-(\varphi+\chi-\xi)} \tag{38}$$

and

$$\bar{\bar{\eta}} = (1+\xi+\varkappa\,\xi^2)/(\gamma\,\xi-1)\,. \tag{39}$$

Both curves are depicted for given parameters in Figure 3. $\bar{\eta}$ is characterized by a zero at $\bar{\xi}_0 = \varphi+\chi$ and a pole at $\bar{\xi}_{\mathrm{p}} = (\varphi+\chi)/(\gamma\,\varphi+1)$; in case of oscillations it has furthermore a minimum, a point of inflection, and a maximum, which, however, are not needed in the following discussion. $\bar{\bar{\eta}}$ is characterized by a pole at $\bar{\bar{\xi}}_{\mathrm{p}} = 1/\gamma < (\varphi+\chi)/(\gamma\,\varphi+1)$ for $\gamma\,\chi > 1$ (which is assumed throughout) and a minimum at

$$\bar{\bar{\xi}}_{\mathrm{m}} = (1+\sqrt{[\varkappa+\gamma+1)]/\varkappa})/\gamma\,,$$

$$\bar{\bar{\eta}}_{\mathrm{m}} = [2\,\varkappa+\gamma+2\,\sqrt{\varkappa^2+\varkappa\,\gamma\,(\gamma+1)}\,]/\gamma^2\,.$$

We now choose a rectangle

$$\xi_1 = (\varphi+\chi)/(\gamma\,\varphi+1) = \bar{\xi}_{\mathrm{p}}\,,\quad \xi_2 = \varphi+\chi = \bar{\xi}_0\,,$$

$$\eta_1 = (2\,\varkappa+\gamma+2\,\sqrt{\varkappa^2+\varkappa\,\gamma\,(\gamma+1)})/\gamma^2 = \bar{\bar{\eta}}_{\mathrm{m}}\,,$$

$$\eta_2 = (1+\varphi+\chi+\varkappa(\varphi+\chi)^2)/(\gamma\,(\varphi+\chi)-1) = g(\bar{\xi}_0)\,.$$

As can be seen from Fig. 3, and follows from the fact that $\mathrm{d}\xi/\mathrm{d}\tau > 0$ for $\eta < \bar{\eta}$ and $\mathrm{d}\eta/\mathrm{d}\tau > 0$ for $\eta < \bar{\bar{\eta}}$, the sign pattern of the trajectories at the borderline of that rectangle is always such that the component of the velocity vector normal to the appropriate side shows inward. A simulation of the oscillation for $\varkappa = 1$, $\alpha = .1$, $\gamma = 1.25$, $\chi = 20$, $\varphi = 80$ is given in Figure 4.

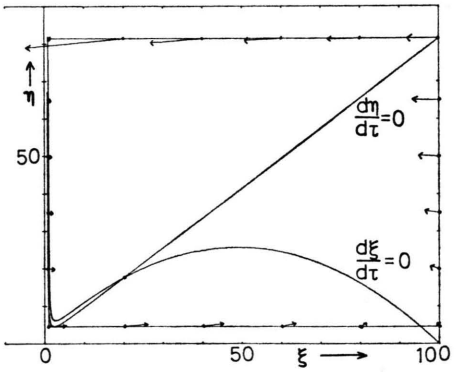

Fig. 3. Demonstration of the boundedness of the rectangle in the ξ,η-plane: the arrows represent velocity vectors. Parameters: $\alpha=.1$, $\varkappa=1$, $\gamma=1.25$, $\chi=20$, $\varphi=80$.

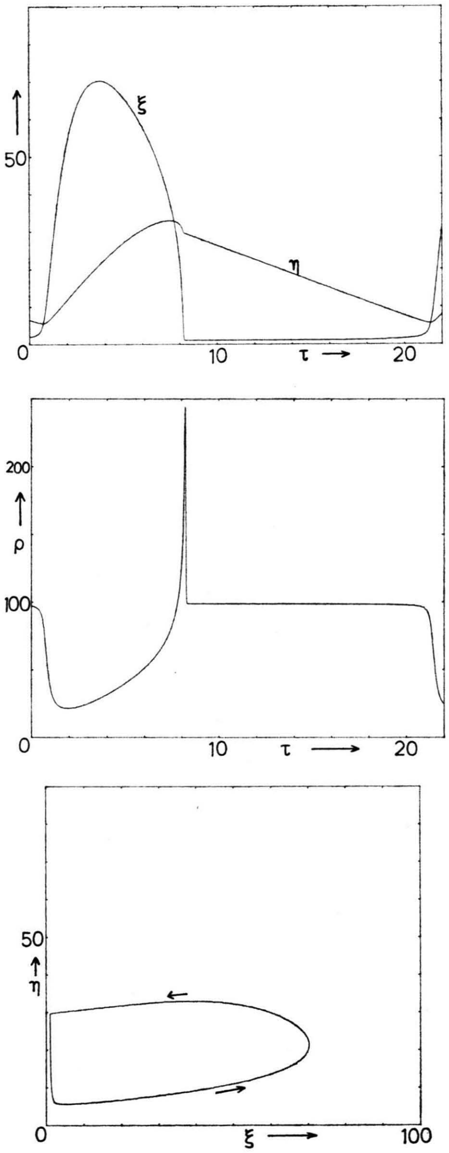

Fig. 4. Simulation results for the oscillation with the parameters of Fig. 3: a) ξ and η vs τ, b) production rate ϱ vs τ, c) limit cycle in the ξ,η-plane.

Case II: Formation of a Ternary Intermediate

$$MX + Y \rightleftharpoons MXY \rightarrow M + P + Q$$

Since the arguments for this case are very similar to those of the former case, we can proceed quickly. The reaction scheme is depicted in Figure 5. We use

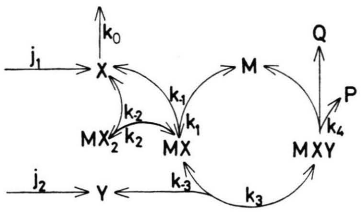

Fig. 5. Reaction scheme of Case II.

the same symbols as in the former model for the same quantities and drop any index which differentiates between the two models. The original differential equations are

$$d[X]/dt = j_1 - k_0[X] - k_1[X][M] + k_{-1}[MX] - k_2[X][MX] + k_{-2}[MX_2] , \tag{40}$$

$$d[Y]/dt = j_2 - k_3[Y][MX] + k_{-3}[MXY] , \tag{41}$$

$$d[M]/dt = -k_1[X][M] + k_{-1}[MX] + k_4[MXY] , \tag{42}$$

$$d[MX_2]/dt = k_2[X][MX] - k_{-2}[MX_2] , \tag{43}$$

$$d[MXY]/dt = k_3[Y][MX] - k_{-3}[MXY] - k_4[MXY] , \tag{44}$$

$$[M]_{\text{total}} = [M] + [MX] + [MX_2] + [MXY] . \tag{45}$$

Assuming a partial steady state for M, MX_2, MXY with respect to the slowly varying [X] and [Y], we get

$$d[X]/dt = j_1 - k_0[X] - r , \tag{46}$$

$$d[Y]/dt = j_2 - r , \tag{47}$$

$$r = k_4[MXY] , \tag{48}$$

and

$$[MX_2] = [MX]\, k_2[X]/k_{-2} , \tag{49}$$

$$[MXY] = [MX] \frac{k_3[Y]}{k_{-3}+k_4} , \tag{50}$$

$$[M] = [MX] \frac{k_{-1}}{k_1[X]} + [MXY] \frac{k_4}{k_1[X]} = [MX] \left(\frac{k_{-1}}{k_1[X]} + \frac{k_3 k_4 [Y]}{(k_{-3}+k_4) k_1[X]} \right) . \tag{51}$$

It follows that

$$r = k_4[M]_{\text{total}} \cdot \frac{\dfrac{k_1[X]}{k_{-1}} \cdot \dfrac{k_3[Y]}{k_{-3}+k_4}}{1 + \dfrac{k_1[X]}{k_{-1}} \left(1 + \dfrac{k_2[X]}{k_{-2}}\right) + \dfrac{k_3[Y]}{k_{-3}+k_4} \left(\dfrac{k_4}{k_{-1}} + \dfrac{k_1[X]}{k_{-1}}\right)} . \tag{52}$$

This suggests the following choice of dimensionless variables and parameters

$$\tau = k_0 t , \tag{53}$$

$$\xi = \frac{k_1}{k_{-1}} [X] , \tag{54}$$

$$\eta = \frac{k_3}{k_{-3}+k_4} [Y] , \tag{55}$$

$$\varphi = \frac{k_1}{k_0 k_{-1}} j_2 , \tag{56}$$

$$\chi = \frac{k_1}{k_0 k_{-1}} (j_1 - j_2) , \tag{57}$$

$$\gamma = \frac{k_4 [M]_{\text{total}}}{j_2} \tag{58}$$

$$\varkappa = (k_{-1} k_2)/k_1 k_{-2} , \tag{59}$$

$$\nu = k_4/k_{-1} , \tag{60}$$

$$\alpha = k_{-1} k_3/k_1 (k_{-3}+k_4) , \tag{61}$$

which renders the system in the form

$$d\xi/d\tau = \varphi + \chi - \xi - \varrho , \tag{62}$$

$$d\eta/d\tau = \alpha(\varphi - \varrho) , \tag{63}$$

$$\varrho = \gamma \varphi \frac{\xi \eta}{1 + \xi + \varkappa \xi^2 + \eta(\nu + \xi)} . \tag{64}$$

Save some slightly different transformations from the original variables and parameters to the dimensionless ones, the single difference to the former model is that now in the denominator of ϱ η is multiplied with $\nu + \xi$ which makes up a total of 6 instead of 5 parameters.

The steady state is

$$\xi_{\text{ss}} = \chi , \tag{65}$$

$$\eta_{\text{ss}} = \frac{1 + \chi + \varkappa \chi^2}{(\gamma - 1)\chi - \nu} \tag{66}$$

for $\chi > 0$ and $(\gamma - 1)\chi - \nu > 0$ which needs the stronger conditions compared to case I

$$\chi > \nu/(\gamma - 1) \tag{67}$$

and

$$\gamma > 1 \tag{68}$$

($\gamma < 1$, equivalent to $j_2 > k_4[M]_{\text{total}}$, would reflect a situation where more Y is forced into the system than can be maximally removed by the catalyst!).

The Jacobi matrix is the same as in Eq. (27), but now

$$\left(\frac{\partial \varrho}{\partial \xi}\right)_{\mathrm{ss}} = \varphi \frac{\nu(1+2\varkappa\chi) + (\gamma-1)(1-\varkappa\chi^2)}{(1+\chi+\varkappa\chi^2)\gamma\chi}, \qquad (69)$$

$$\left(\frac{\partial \varrho}{\partial \eta}\right)_{\mathrm{ss}} = \varphi \frac{((\gamma-1)\chi-\nu)^2}{(1+\chi+\varkappa\chi^2)\gamma\chi}. \qquad (70)$$

With the same arguments and procedures as in the preceding section, the criterion for instability is

$$(1+\chi+\varkappa\chi^2)\gamma\chi + \varphi\nu(1+2\varkappa\chi) + (\gamma-1)\varphi + a\varphi((\gamma-1)\chi-\nu)^2 - (\gamma-1)\varphi\varkappa\chi^2 < 0 \qquad (71)$$

or $\varphi > \Phi$ with

$$\Phi = \frac{(1+\chi+\varkappa\chi^2)\gamma\chi}{(\gamma-1)(\varkappa\chi^2-1) - \nu(1+2\varkappa\chi) - a((\gamma-1)\chi-\nu)^2} \qquad (72)$$

which describes a hypersurface in $\mathbb{R}_+^6$ with a pole, yielding

$$\chi > \frac{\nu + \sqrt{\dfrac{\varkappa\nu^2 + \nu(\gamma-1) + (\gamma-1)^2}{\varkappa - a(\gamma-1)}}}{\gamma-1} > \frac{\nu}{\gamma-1} \qquad (73)$$

[cf. Eq. (67)]; the expression in the root contains another pole, demanding

$$\gamma < 1 + \varkappa/a. \qquad (74)$$

Thus we have the situation that there are no limitations of instability with respect to the 3 fixed parameters $\varkappa$, a, ν. To get instability of the single critical point and thus limit cycle oscillations (provided it can be shown that the state space is bounded) we have the following recursive procedure:

1) Choose any γ with $1 < \gamma < 1 + \varkappa/a$;

2) Let $\chi > \dfrac{\nu + \sqrt{\dfrac{\varkappa\nu^2 + \nu(\gamma-1) + (\gamma-1)^2}{\varkappa - a(\gamma-1)}}}{\gamma-1}$.

3) If finally

$$\varphi > \frac{(1+\chi+\varkappa\chi^2)\gamma\chi}{(\gamma-1)(\varkappa\chi^2-1) - \nu(1+2\varkappa\chi) - a((\gamma-1)\chi-\nu)^2}$$

the system will oscillate in a limit cycle. The differences between this and the former model vanish if $\nu = 1$ and if $\gamma - 1$ is put here for γ in the former model.

The arguments for the boundedness are analogous to those in the former model and shall therefore not be repeated here.

Toward Chemical Realization

Although the reaction schemes underlying the given oscillator models are quite general and "M" may also represent an enzyme or any other catalyst, it is supposed that the widest field of application is entered, if M is interpreted as being a metal, especially a transition metal which is able to form strong complexes with great changes in the properties of the ligand, which can switch between different oxidation stages and which can convey effector influences of other ligands not directly involved in the reaction. Busch[13] was apparently one of the first to recognize the various possibilities of control of catalytic reactions via metal complexes. Decker[14] pointed out that complex formation could be a good and realistic interpretation of the otherwise unreasonable premise of the second order autocatalysis, $X + 2Y \rightarrow 3Y$, of the mentioned brusselator.

Whereas the formation of (transition) metal complexes in homogeneous catalysis is so widely accepted nowadays and experimental evidence is so abundant, some words have to be said about the phenomenon of substrate inhibition. Although in the models described here, total substrate inhibition was assumed for the sake of simplicity, the results do not change qualitatively – save the possibility of the emergence of an additional unstable limit cycle – if substrate inhibition is supposed to be only partial, i. e., that the complex MX_2 is not completely inert to further reaction with Y. It suffices that MX_2 reacts only much slower than MX. One well-known example with a slightly different reaction scheme is the intramolecular redox reaction of Mn(III)-oxalates: as reported by Taube[15], the mono-oxalato-complex reacts about 260 times faster than the bis-oxalato- and 560 times faster than the tris oxalato-complex. Another example of considerable complexity is the hydroformylation reaction where the reaction $HCo(CO)_3 + CO \rightleftharpoons HCo(CO)_4$ is responsible for the inhibition of the more active catalyst $HCo(CO)_3$ by one of the substrates, CO. It was shown by the author[16] that this might be the clue to observed instabilities leading to oscillations and hysteresis effects.

Substrate inhibition can be viewed as a quite trivial result of competition in the case $MX + Y \rightleftharpoons MXY \rightarrow M + P + Q$, if X and Y are bidentate and M has the coordination number 4 or if it has 6, but two sites are already occupied by one or two especially strong ligands. In this case MX_2 would mean that there is no further space for Y which is supposed to be a weaker ligand than X so that MY and MY_2 may not be considered.

Side Effects and Fields of Technical Application

In the introduction the hope was expressed that chemical oscillations could leave the range of merely academic interest and could lead to some technological usage. Preliminary results show that at least one marginal effect of oscillation yields some promise in that direction. It is known from other models and is the fundamental principle of nerve excitation and the propagation of nerve pulses that by slight variations of the (adjustable) parameters every oscillator can stop sustained oscillations and return to a steady state that is itself stable, but makes the system excitable in as far as a supercritical trigger pulse can make the system depart far from the steady state and return in a comparatively huge "hook" to the initial state. In this case the formerly astable multivibrator has become a monoflop. Combining the principle of an excitable monoflop whose "silent" phase represents a state of high substrate inhibition and consequently low production rate with the principle of convection as utilized in chromatography, it was possible to design the yet theoretical model of an "avalanche reactor", comparable in its mode of operation to the well-known laser. In this case, M has to be immobilized by binding to a polymeric ligand, the triggering wave can be in its simplest form a short interruption of the injection of the inhibiting substrate X at the entrance of the tube reactor. In "firing", each volume element then adds a sudden burst of product to the flowing avalanche on its way down the tube till the exit, where a strong pulse instead of a continuous low level production appears. In the recovery period the column is again loaded with substrates X and Y and ultimately ready for the next pulse released arbitrarily at will. This principle, which is in preparation for publication, could be interesting in the case of highly reactive reagents that normally evolve in tiny concentrations and undergo immediately further reactions, like carbenes and radicals. Another pleasant side effect of the pulselike rather than continuous production could be that unavoidable side products would probably emerge with phase shifts and would thus automatically be separated.

Computations and plots were performed on the Calculator HP 9820 with peripherals.

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[1] P. Glansdorff and I. Prigogine, Thermodynamic Theory of Structure, Stability and Fluctuations, John-Wiley Intersc., New York 1971.

[2] G. Nicolis and J. Portnow, Chem. Rev. **73**, 365 [1973].

[3] B. P. Belousov, Collection of Abstracts on Radiation Medicine, p. 145, Medgiz, Moscow 1959 (in Russian); A. M. Zhabotinskii, Biofizika **9**, 306 [1964].

[4] R. J. Field, E. Körös, and R. M. Noyes, J. Amer. Chem. Soc. **94**, 8649 [1972].

[5] R. A. Schmitz, Adv. Chem. Ser. **148**, 156 [1975].

[6] I. Prigogine and R. Lefever, J. Chem. Phys. **48**, 1695 [1968].

[7] T. E. Barman, Enzyme Handbook, Springer-Verlag, Berlin 1969.

[8] F. F. Seelig and B. Denzel, FEBS Letters **24**, 283 [1972].

[9] I. Yamazaki, K. Yokota, and R. Nakajima, Biochem. Biophys. Res. Commun. **21**, 582 [1965].

[10] H. Degn, Nature London **217**, 1047 [1968]; H. Degn, Biochim. Biophys. Acta **180**, 271 [1969].

[11] D. D. Bruns, J. E. Bailey, and D. Luss, Biotechnol. Bioeng. **15**, 1131 [1973].

[12] ref. R. Rosen, Dynamical System Theory in Biology, Vol. I, p. 146, John-Wiley Intersc., New York 1970.

[13] D. H. Busch, Science **171**, 241 [1971].

[14] P. Decker, J. Mol. Evol. **4**, 49 [1974]; Origins of Life **6**, 211 [1975].

[15] H. Taube, J. Amer. Chem. Soc. **70**, 1218 [1948].

[16] F. F. Seelig, Z. Naturforsch. **31 b**, 336 [1976]; **31 b**, in press.