Journal of Mathematical Biology 1, 311—315 (1975)

On the Existence of Oscillatory Solutions in Negative Feedback Cellular Control Processes

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Received October 8, 1974; revised November 5, 1974

Summary

It is shown that the differential equation

$$\frac{d^3 Z}{d t^3}+(\alpha+\beta+\gamma)\frac{d^2 Z}{d t^2}+(\alpha\beta+\beta\gamma+\gamma\alpha)\frac{dZ}{dt}+\alpha\beta\gamma Z=(1+Z^m)^{-1}$$

has at least one periodic solution past the instability of the stationary state solution, $Z=Z_0$, the unique real positive root of $\alpha\beta\gamma Z=(1+Z^m)^{-1}$.

Much has been written about the differential equations (Griffith, 1968)

$$\begin{aligned}\frac{dX}{dt}&=\frac{1}{1+Z^m}-\alpha X\\ \frac{dY}{dt}&=X-\beta Y\\ \frac{dZ}{dt}&=Y-\gamma Z\end{aligned}\tag{1}$$

because they describe in a simple fashion the dynamics of end-product inhibition of gene activity: $mRNA\,(X)$ codes for enzyme (Y), one of whose metabolic products (Z) inhibits further synthesis of $mRNA$ from its genetic locus. Representing such cellular control processes in terms of differential equations was first pursued in detail by Goodwin (1963).

The steady state solution of Eq. (1), namely

$$X_0=\beta Y_0=\beta\gamma Z_0 \tag{2}$$

where Z_0 is the unique real positive root of

$$\alpha\beta\gamma Z^{m+1}+\alpha\beta\gamma Z-1=0, \tag{3}$$

is not always stable. Goodwin (1965) presented analog computer simulations of sustained oscillations (limit cycles) for Eq. (1) with $m=1$. Griffith (1968) challenged

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this result by showing that the steady state is stable for $m \leq 8$, so that stable limit cycle oscillations are highly improbable for $m=1$. (There seem to have been errors in Goodwin's analog simulation.) In a large number of simulations on a digital computer, Griffith found limit cycles if and only if the steady state was unstable.

Morales and McKay (1967) considered a generalization of Eq. (1), with more than one intermediate between X and Z ($X \rightarrow Y_2 \rightarrow Y_3 \rightarrow \ldots \rightarrow Y_{N-1} \rightarrow Z$). They reported an analog simulation of a limit cycle for $N=4$, $m=4$; but Walter (1969) showed by linear stability analysis and digital simulation that the steady state was really stable under these conditions. For $N=5$, $m=4$ the steady state can be unstable and Walter presented a digitally computed limit cycle. As N increases, the co-operativity of the inhibition (m) necessary to destabilize the steady state decreases.

It is the purpose of this communication to prove analytically the existence of at least one periodic solution of Eq. (1) whenever the steady state (2) is unstable. Not only is the proof interesting from a mathematical point of view, but it also helps clear up some of the confusion mentioned above concerning negative feedback systems.

Proof:

To prove the existence of a periodic solution of Eq. (1):

(i) we must construct a toroidal integral manifold containing no singular points of Eq. (1); that is, a doughnut in the positive octant ($X \geq 0$, $Y \geq 0$, $Z \geq 0$) which does not contain the steady state (2) and on whose surface the vector field, defined by the kinetic equations, always points inward. Any trajectory entering the torus cannot leave, thus it cannot approach the steady state but must approach some more complicated limit path. That at least one trajectory within the torus is a simple closed orbit is implied by Brouwer's fixed point theorem, provided ...

(ii) we show that the differential equations define a continuous map of some cross section of the torus (a closed disc) into itself. Since there are no singular points within the torus, at least one trajectory must circulate once around the torus and come back on itself. Notice that we are not proving that this closed orbit is a global attractor for the torus. Though we might expect this from the computer simulations, it would be much more difficult to prove than simple existence.

Griffith (1968) has already shown that solutions of Eq. (1) are bounded, because "all motion is inward across the faces of a rectangular box which has its sides parallel to the axes of co-ordinates and two opposite vertices at $(0,0,0)$ and $(\beta\,\gamma\,A, \gamma\,A, A)$, where $\alpha\,\beta\,\gamma\,A > 1$". Every trajectory in the positive octant must eventually enter the smallest of these boxes, the one for which $A = (\alpha\,\beta\,\gamma)^{-1}$. This box, B, which still contains the steady state, can be converted into a doughnut by cutting a hole through it. We must be sure that the steady state is cut out of B by this hole.

Rauch (1950) has described a general method for cutting such holes, which works if one variable changes very fast with respect to the other two. Hastings and Murray (1974) have described an easier but more specific method, which works in this case. Following them, we divide B into eight smaller rectangular boxes by the planes $X=X_0$, $Y=Y_0$, $Z=Z_0$. These eight boxes (see Fig. 1) all meet at the singular point, and are numbered as follows:

$X<X_0$, $Y<Y_0$, $Z<Z_0$	Box 1
$X>X_0$, $Y<Y_0$, $Z<Z_0$	Box 2
$X>X_0$ $Y>Y_0$, $Z<Z_0$	Box 3
$X>X_0$, $Y>Y_0$, $Z>Z_0$	Box 4
$X<X_0$ $Y>Y_0$, $Z>Z_0$	Box 5
$X<X_0$, $Y<Y_0$, $Z>Z_0$	Box 6
$X>X_0$, $Y<Y_0$, $Z>Z_0$	Box 7
$X<X_0$, $Y>Y_0$, $Z<Z_0$	Box 8

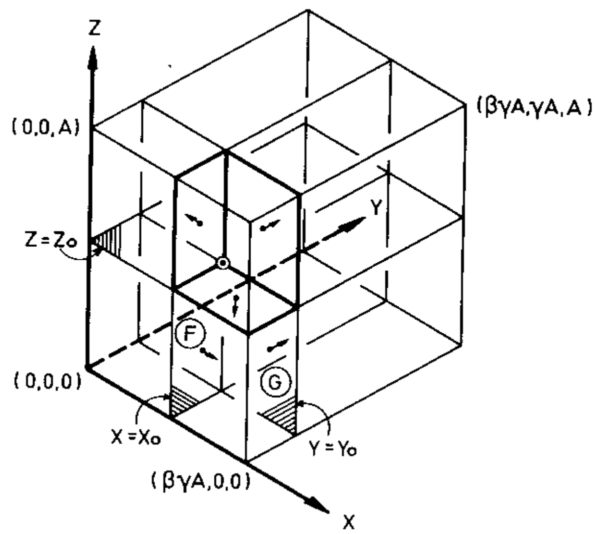

Fig. 1

The three internal faces of box 7 are heavily outlined in Fig. 1. On the face $X=X_0$ we must have $\dot{X}\leq 0$ because $Z\geq Z_0$. The direction of flow on the three internal faces, indicated by the arrows, is always out of box 7 into boxes 2, 4, 6. Similarly the flow on the internal faces of box 8 is into boxes 1, 3, 5.

The union of boxes 1—6 still contains the steady state. From local stability analysis (Appendix) we know that the steady state is unstable in two characteristic directions and stable in the third. In the Appendix, I show that close to the steady state the two singular paths approach the steady state along a line lying in boxes 7 and 8. Thus to cut out the steady state we need only surround it by a small cylinder whose long axis lies along the characteristic direction associated with the negative eigenvalue. (See Rauch (1950) for more details.) As the radius of the cylinder vanishes, we can be sure that the vector field points away from the steady state into boxes 1—6. This completes the construction of the toroidal integral manifold.

As for the continuous mapping, examine the flow on the face labelled F in Fig. 1, which separates boxes 1 and 2. Since $X = X_0$ and $Z < Z_0$, we have $\dot{X} > 0$ on F, i.e. the vector field points from box 1 to box 2. A trajectory started on F must leave F and enter box 2. In box 2, $X > X_0$ and $Y < Y_0$, so $\dot{Y} > 0$. Thus any trajectory in box 2 must approach either the steady state or one of the three internal faces of box 2. In the appendix we rule out the former possibility and from Fig. 1 we see that trajectories must approach face G. Since $\dot{Y} > 0$ on face G, minus the steady state, trajectories must pass through G from box 2 into box 3. Repeating these arguments, we find that trajectories must pass from box to box in the order $1 \to 2 \to 3 \to 4 \to 5 \to 6 \to 1$ from face F back to face F again in a finite time T. Thus the differential equations define a continuous mapping $M(T): F \to F$ of F into itself. Since F is closed, bounded, simply connected and contains no singularities of the vector field, Brouwer's fixed point theorem implies the existence of at least one periodic solution of period T.

This completes the proof for $N = 3$. A generalization of these arguments to higher dimensions is currently under consideration.

Appendix

Let $x = X - X_0$, $y = Y - Y_0$, $z = Z - Z_0$, then close to the steady state (2) the differential equations (1) appear

$$\frac{d}{dt}\begin{pmatrix} x \\ y \\ z \end{pmatrix} = \begin{pmatrix} -\alpha & 0 & -f \\ 1 & -\beta & 0 \\ 0 & 1 & -\gamma \end{pmatrix} \begin{pmatrix} x \\ y \\ z \end{pmatrix}$$

where $f = m\,\alpha\,\beta\,\gamma\,(1 - \alpha\,\beta\,\gamma\,Z_0) > 0$. The variational equation is

$$L(\lambda) = \lambda^3 + (\alpha + \beta + \gamma)\,\lambda^2 + (\alpha\,\beta + \beta\,\gamma + \gamma\,\alpha)\,\lambda + \alpha\,\beta\,\gamma + f = 0, \qquad (*)$$

which has three roots: $\lambda_1, \lambda_2, \lambda_3$. The steady state is stable if and only if the real parts of all three roots are less than zero.

Since α, β, γ, f are all positive, there can be no real positive roots of $L(\lambda)$. For the steady state to be unstable we must have a pair of complex conjugate roots with positive real part, $\lambda_2, \lambda_3 = \mu \pm i\,\sigma\,(\mu > 0,\ \sigma > 0)$, and a real negative root, $\lambda_1 = -\nu < 0$.

Let $(\hat{x}, \hat{y}, \hat{z})$ be the eigenvector associated with $\lambda_1 = -\nu$. Then

$$-\nu\,\hat{x} = -\alpha\,\hat{x} - f\,\hat{z}$$

$$-\nu\,\hat{y} = \hat{x} - \beta\,\hat{y}$$

$$-\nu\,\hat{z} = \hat{y} - \gamma\,\hat{z}.$$

So

$$\hat{y} = \frac{\hat{x}}{\beta - z}, \quad \hat{z} = \hat{x}\,\frac{\alpha - \nu}{-f}.$$

Normalize the eigenvector so that $\hat{x}=1$. Then the characteristic direction of the two singular paths which approach the steady state has direction cosines

$$\bar{X}=\frac{1}{D}, \quad \bar{Y}=\frac{1}{D}\,\frac{1}{\beta-v}, \quad \bar{Z}=\frac{1}{D}\,\frac{\alpha-v}{-f}$$

where

$$D=\sqrt{1+\left(\frac{1}{\beta-v}\right)^2+\left(\frac{\alpha-v}{-f}\right)^2}$$

From (*) we have $L(-\alpha)=L(-\beta)=L(-\gamma)=f>0$, so the negative eigenvalue λ_1 must have magnitude $v>\max(\alpha, \beta, \gamma)$. Thus the direction cosines satisfy $\bar{X}>0$, $\bar{Y}<0$, $\bar{Z}>0$; that is, the singular paths approach the steady state in boxes 7 and 8.

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