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AN EXTENDED MATHEMATICAL MODEL OF TRANSCRIPTION AND TRANSLATION DURING EMBRYOGENESIS

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INTRODUCTION

Oscillation in biological processes and chemical reactions has drawn an increasing interest both in the experimental and the mathematical fields of investigations. Experimental observations of biological oscillation have been reviewed by Mazia [13] , Chance et al. [3] , Brodsky [2] and a few others. Mano [12] has reported a rhythm of protein biosynthesis superimposed on a basal rate of increase in early cell cycles of sea urchin embryos. Cyclic RNA synthesis in slime mould cells has been observed by Cummins and Rusch [4] . A similar rhythm of RNA synthesis in early mitotic cycles of Limnaea has been observed by Brahmachary, Ghosal and Tapaswi [1] .

Mathematical investigations in this field have been carried out mostly on hypothetical systems. These have been principally based on the Jacob-Monod operon concept [10] utilising the process of feed-back inhibition by the end product. Goodwin's model [6] of mRNA and protein synthesis which may be claimed to be based on recognised biological theories has been subsequently investigated exhaustively by several workers. Goodwin's approach is a very simple one wherein he has considered only the three component mRNA, protein and the repressor molecules in constructing his model of transcription and translation. He did not consider the other important elements of this process such as heterogeneous nuclear RNA, Ribosomal RNA, transfer RNA, Polysomes, etc. the incorporation of which could make the model more realistic.

Goodwin's principle of feed-back inhibition has been extended to investigate the oscillatory nature of higher dimensional hypothetical biochemical reactions by several workers (Griffith [7] , Rapp [17, 18] , Walter [24] , Tyson [22] , Hastings and Murray [8] , Hastings et al. [9]

and others). Tapaswi and Roy [21] constructed a model of transcription and translation considering only the three variables DNA, mRNA and protein. This model gives a stable periodic synthesis of mRNA and protein.

In this paper an extended mathematical model of the real biological process of transcription and translation during embryogenesis has been developed. This has been more realistic and akin to nature as this considers the nearly entire genetic machinery of transcription and translation consisting of DNA, hRNA (heterogeneous nuclear RNA), rRNA (ribosomal RNA), aminoacyl transfer RNA, polysome, protein and the repressor molecules.

THE MATHEMATICAL MODEL

The model is based on the following recognized principles of transcription and translation :

1) hRNA synthesis is directly proportional to the activation of mRNA genes and inversely proportional to the synthesis of repressor molecules (end product negative feed-back);

2) rRNA synthesis is directly proportional to the activation of rRNA genes and inversely proportional to the concentration of tRNA molecules (negative feed-back) (Smith [20] , Davidson [5]);

3) tRNA synthesis is directly proportional to the tRNA genes and inversely proportional to the concentration of tRNA molecules itself (self feed-back inhibition);

4) mRNA synthesis is directly proportional to the amount of hRNA;

5) Aminoacylation of tRNA is directly proportional to available tRNA;

6) Formation of polysomes is directly proportional to the available amount of rRNA and mRNA;

7) Protein synthesis is directly proportional to the available amount of aminoacyl tRNA and polysomes;

8) The synthesis of the repressor molecules is directly proportional to the amount of protein;

9) Each of the components under investigation decays at a rate which is proportional to its own amount of accumulation.

A schematic representation of the above theories is given in Figure 1.

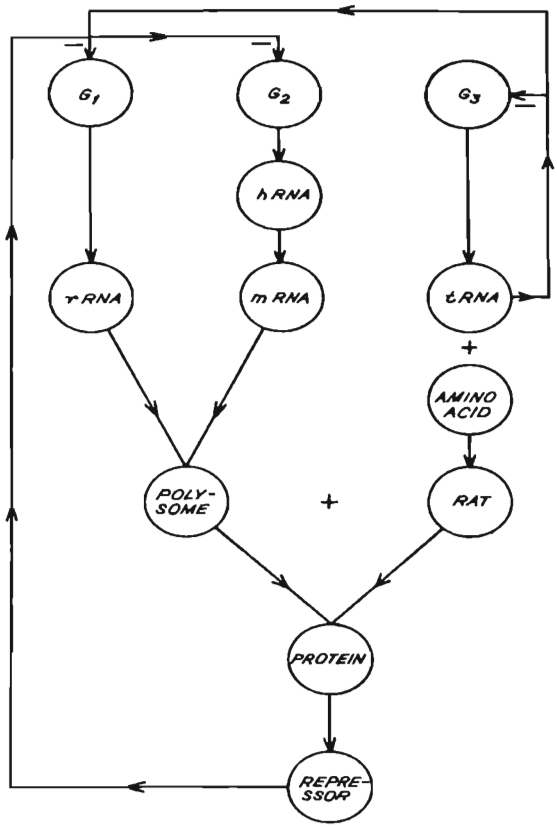

Fig. 1. - A schematic diagram of the epigenetic process of transcription and translation during embryogenesis. G_1, G_2 and G_3 are the respective genes from which rRNA, hRNA and tRNA are transcribed. The '——' sign denotes the negative feedback. Amino acid is available from the intracellular pool and RAT denotes the aminoacyl tRNA (i.e., tRNA charged with amino acid).

Let us denote the concentrations of rRNA, hRNA, mRNA, tRNA, aminoacyl tRNA, polysome, protein and repressor per cell by x_1, x_2, ... x_8 respectively. (Throughout the whole investigations these variables will represent the respective concentrations per cell of the embryo).

Then according to the principles (1-9) the rates of synthesis of the components x_1, x_2, ... x_8 will be determined by the following set of simultaneous ordinary differential equations.

$$\dot{x}_1 = \frac{\alpha_1}{1+h_1 x_4^{m_1}} - \beta_1 x_1$$

$$\dot{x}_2 = \frac{\alpha_2}{1+h_2 x_8^{m_2}} - \beta_2 x_2$$

$$\dot{x}_3 = \beta_2 x_2 - \beta_3 x_3$$

$$\dot{x}_4 = \frac{\alpha_4}{1+h_4 x_4^{m_3}} + \beta_5 x_5 - (\alpha_5 + \beta_4) x_4 \qquad (1)$$

$$\dot{x}_5 = \alpha_5 x_4 - \beta_5 x_5$$

$$\dot{x}_6 = \alpha_6 x_1 x_3 - \beta_6 x_6$$

$$\dot{x}_7 = \alpha_7 x_5 x_6 - \beta_7 x_7$$

$$\dot{x}_8 = \alpha_8 x_7 - \beta_8 x_8$$

$\alpha_i (i = 1, 2, \ldots, 8)$, h_i $(i = 1, 2, 4)$ and β_i $(i = 1, 2, \ldots, 8)$ are the rate constants of synthesis, inhibition and degradation respectively of the respective components whereas m_i $(i = 1, 2, 3)$ denotes the stochiometry (Hill's coefficient) of inhibition of the respective reactions. Note that the system (1) consists of five nonlinear diff. equations coupled with three linear ones and the nonlinear feed-back loops are associated with three members of this system.

Again it is noted that a subsystem consisting of the first, the fourth and the fifth equation can be picked up from the total system (1) the former system being independent of the latter but not the reverse.

The system (1) can be represented in a more elegant manner by the following dimensionless form.

$$\dot{z}_1 = \frac{1}{m_1} - \gamma_1 z_1$$
$$1+z_4$$

$$\dot{z}_2 = \frac{1}{m_2} - \gamma_2 z_2$$
$$1+z_8$$

$$\dot{z}_3 = z_2 - \gamma_3 z_3$$

$$\dot{z}_4 = \frac{1}{m_3} + \gamma_5 z_5 - \gamma_4 z_4 \qquad (2)$$
$$1+z_4$$

$$\dot{z}_5 = z_4 - \gamma_5 z_5$$

$$\dot{z}_6 = z_1 z_3 - \gamma_6 z_6$$

$$\dot{z}_7 = \rho_7 z_5 z_6 - \gamma_7 z_7$$

$$\dot{z}_8 = z_7 - \gamma_8 z_8$$

The steady states $(z_{10}, \ldots, z_{80})$ of the system can be obtained by making the left hand side of each of the equations in (2) equal to zero. Now linearizing the above system around this steady state after applying the transformation $y_i = z_i - z_{io}$ we have

$$\dot{y}_1 = - \gamma_1 y_1 - \frac{y_4}{k_4}$$

$$\dot{y}_2 = - \gamma_2 y_2 - \frac{y_8}{k_8}$$

$$\dot{y}_3 = y_2 - \gamma_3 y_3$$

$$\dot{y}_4 = -\left(\gamma_4 + \frac{1}{k_4}\right) y_4 + \gamma_5 y_5 \qquad (3)$$

$$\dot{y}_5 = y_4 - \gamma_5 y_5$$

$$\dot{y}_6 = k_3 y_1 + k_1 y_3 - \gamma_6 y_6$$

$$\dot{y}_7 = \varrho_7 k_6 y_5 + \varrho_7 k_5 y_6 - \gamma_7 y_7$$

$$\dot{y}_8 = y_7 - \gamma_8 y_8$$

where $k_1 = z_{10}$, $k_3 = z_{30}$, $k_4 = (1+z_{40}^{m_1})^2 / m_1 z_{40}^{m-1}$, $k_5 = z_{50}$
$k_6 = z_{60}$ and $k_8 = (1+z_{80}^{m_2})^2 / m_2 z_{80}^{m_2-1}$

The secular equation determining the solution for y_2, y_3, y_6, y_7 and y_8 is given by

$$\lambda^5 + p_4 \lambda^4 + p_3 \lambda^3 + p_2 \lambda^2 + p_1 \lambda + p_0 = 0 \qquad (4)$$

with the eigen values λ, where p_1, p_2, p_3 and p_4 stand for the summations of the constants γ_2, γ_3, γ_6, γ_7, and γ_8 taking four, three, two and one respectively at a time, i.e. $p_1 = \Sigma \gamma_2 \gamma_3 \gamma_6 \gamma_7$, $p_2 = \Sigma \gamma_2 \gamma_3 \gamma_6$, $p_3 = \Sigma \gamma_2 \gamma_3$, $p_4 = \Sigma \gamma_2$, and $p_0 = \gamma_2 \gamma_3 \gamma_6 \gamma_7 \gamma_8 + k_1 k_5 \varrho_7 / k_8$.

It is clear that if $k_1 k_5 \varrho_7 / k_8 = 0$ then all the roots of the linearised system (3) will be purely negative real numbers in which case the system (1) will be asymptotically stable without any oscillation. The oscillation is possible only when this term is not equal to zero since if we examine the secular equation (4) we can see that all the constants are positive so that by Descarte's rule of signs we have all the roots are either negative or at least one pair of roots are complex conjugate and there is no positive root.

Since we are interested in oscillation we are to find out the necessary condition which will confirm the existence of complex roots in (4). To do

so we are to take the help of the Routh-Hurwitz criterion (Uspensky [23]), which gives the condition for all the roots of the characteristic equation to have negative real parts.

Thus the violation of Routh-Hurwitz criterion in the present case will indicate that at least one root of (4) will not have negative real part and combining this with Descarte's rule of signs which shows that there is no purely positive root in (4) we can conclude that there is at least one pair of complex conjugate roots in (4) having positive (or zero) real part.

Thus for the existence of a periodic solution of (3) around an unstable equilibrium the criterion to be violated is :

$$p_1 p_2 - p_0 p_3 > 0$$

i.e.

$$(\Sigma \gamma_2 \gamma_3 \gamma_6 \gamma_7)(\Sigma \gamma_2 \gamma_3 \gamma_6) - (\gamma_2 \gamma_3 \gamma_6 \gamma_7 \gamma_8 + k_1 k_5 \varrho_7 / k_8)(\Sigma \gamma_2 \gamma_3) > 0 \qquad (5)$$

Following Cauchy's inequality we have

$$\Sigma \gamma_2 \gamma_3 > 10 (\gamma_2 \gamma_3 \gamma_6 \gamma_7 \gamma_8)^{4/10}$$

$$\Sigma \gamma_2 \gamma_3 \gamma_6 > 10 (\gamma_2 \gamma_3 \gamma_6 \gamma_7 \gamma_8)^{6/10}$$

and

$$\Sigma \gamma_2 \gamma_3 \gamma_6 \gamma_7 > 5 (\gamma_2 \gamma_3 \gamma_6 \gamma_7 \gamma_8)^{4/5}$$

Then (5) can be written as

$$50 (\gamma_2 \gamma_3 \gamma_6 \gamma_7 \gamma_8)^{1/5} (\gamma_2 \gamma_3 \gamma_6 \gamma_7 \gamma_8 + q)(\Sigma \gamma_2 \gamma_3) > 0 \text{ (where } q = k_1 k_5 \varrho_7 / k_8)$$

i.e., $50 (\gamma_2 \gamma_3 \gamma_6 \gamma_7 \gamma_8) - (\gamma_2 \gamma_3 \gamma_6 \gamma_7 \gamma_8 + q) 10 (\gamma_2 \gamma_3 \gamma_6 \gamma_7 \gamma_8)^{4/10} > 0$

i.e., $5 (\gamma_2 \gamma_3 \gamma_6 \gamma_7 \gamma_8) - (\gamma_2 \gamma_3 \gamma_6 \gamma_7 \gamma_8 + q) > 0$

The last inequality will be violated if

$$\Pi \gamma_2 + q > 5 \Pi \gamma_2 \text{ (writing } \Pi \gamma_2 \text{ for } \gamma_2 \gamma_3 \gamma_6 \gamma_7 \gamma_8)$$

i.e. $$q > 4\,\Pi\gamma_2 \tag{6}$$

Again from (2) we have

$$z_{80} = \frac{q\,k_8}{\Pi\gamma_2(1+z_{80}^{m_2})} = \frac{q(1+z_{80}^{m_2})}{m_2 z_{80}^{m_2-1}\,(\Pi\gamma_2)}$$

i.e. $$m_2 z_{80}^{m_2}\,(\Pi\gamma_2) = q(1+z_{80}^{m_2}) > 4\,(\Pi\gamma_2)(1+z_{80}^{m_2})$$

i.e. $$m_2 z_{80}^{m_2} - 4z_{80}^{m_2} > 4$$

i.e. $$z_{80}^{m_2}(m_2 - 4) > 4$$

which implies that $m_2 > 4$.

Thus the necessary conditions that the system (1) will have a periodic solution in the neighbourhood of equilibrium point are that

$$q > 4\,\Pi\gamma_2 \tag{7}$$

and $$m_2 > 4$$

Since all the periodic solutions of biological interest should be stable, we next investigate the stability of the periodic solution of the system (1). To prove the existence in the small the Hopf Friedrich theory of bifurcations can be used. MacDonald [11] has examined the application of this theory in the light of Poore's [15, 16] methods in the case of a hypothetical system of n equations coupled chainwisely of which only one has a nonlinearity But Poore's method will be very tedious and cumbersome to apply in the present system which has been developed on the theories based on real experimental evidences so that too much simplification of the model is not possible within the natural domain.

However, since at least one pair of the roots must be of the type $\mu \pm i\,\omega_0$ where μ and ω_0 are positive, the equilibrium point is unstable by growing oscillations. From Hopf bifurcation theorem we then have at least small amplitude limit cycle solutions in the neighbourhood of the bifurcation values of γ_1 and ϱ_7 which just make the point z_{10} unstable (i.e., the values for which $\mu = 0$) so that there are two purely imaginary values (Murray [14]).

Hence, substituting $\lambda = i\omega_0$ in the secular equation (4), we have $i(\omega_0^5 - p_3\omega_0^3 + \omega_0 p_1) + (p_4\omega_0^4 - p_2\omega_0^2 + p_0) = 0$, when equating real and imaginary parts separately to zero, we get,

$$p_4\omega_0^4 - p_2\omega_0^2 + p_0 = 0$$

and

$$\omega_0^4 - p_3\omega_0^2 + p_1 = 0$$

i.e.

$$\frac{\omega_0^4}{p_0p_3 - p_1p_2} = \frac{\omega_0^2}{p_0 - p_1p_4} = \frac{1}{p_2 - p_3p_4}$$

or

$$(p_0 - p_1p_4)^2 = (p_2 - p_3p_4)(p_0p_3 - p_1p_2) \ldots \qquad (8)$$

Since at $\lambda = \pm i\omega_0$, the routh-Hurwitz criterion (5) will be just violated we have $p_0p_3 - p_1p_2 = 0$.

Hence from (8) we get the relation

$$\frac{p_0}{p_1} = \frac{p_2}{p_3} = p_4 \text{ i.e., } p_0 = p_1p_4 \text{ and } p_2 = p_3p_4$$

Thus eliminating p_0 and p_2 from (4) we get,

$$(\lambda + p_4)(\lambda^4 + p_3\lambda^2 + p_1) = 0$$

Then the purely imaginary roots are given by

$$(\lambda^4 + p_3\lambda^2 + p_1) = 0$$

i.e.

$$\lambda = \pm i \left[\tfrac{1}{2} \left\{ p_3 \pm (p_3^2 - 4p_1)^{\frac{1}{2}} \right\} \right]^{\frac{1}{2}}$$

which are the critical values of λ attained when

$$\frac{p_0}{p_1} = \frac{p_2}{p_3} = p_4.$$

The period is given by

$$\frac{2\pi}{\omega_0} = 2\pi / \left[\tfrac{1}{2} \left\{ p_3 \pm (p_3^2 - 4p_1)^{\frac{1}{2}} \right\} \right]^{\frac{1}{2}}$$

Also, if $p_1 = p_3 - 1$, we will have $\omega_0 = 1$ and the period $= 2\pi = 360°$, i.e., one full cycle and thus if we consider the duration of each mitotic cycle equal to 360° the same pattern will be repeated in each mytotic cycle. The amplitude of each cycle will be different in the early stages and then it will come to a stable value in the later stages of the embryonic development.

As already mentioned the first, the fourth and the fifth equations of (1) form an independent subsystem of the total, the behaviour of the former subsystem can be analyzed separately.

The secular equation of the linearised form of these three equations are given by

$$(\gamma_1 + \lambda)\left[(\gamma_5 + \lambda)(\gamma_4 + \frac{1}{k_4} + \lambda) - \gamma_5\right] = 0 \qquad (9)$$

When the roots are $\lambda = -\gamma_1$ and $\lambda_{2,3} = \tfrac{1}{2}\left[-(\gamma_4 + \gamma_5 + \frac{1}{k_4}) \pm \right.$

$$\left. \left\{ (\gamma_4 - \gamma_5 + \frac{1}{k_4})^2 + 4\gamma_5 \right\}^{\frac{1}{2}} \right] \qquad (10)$$

From the fourth and fifth equation of (2) we see that at the steady state :

$$\frac{1}{1+z_{40}} + \gamma_5 z_{50} - \gamma_4 z_{40} = 0$$

and

$$z_{40} - \gamma_5 z_{50} = 0$$

Combining the above two equations we have

$\frac{1}{1 + z_{40}} + z_{40} - \gamma_4 z_{40} = 0$, i.e., $z_{40}^2 (1 - \gamma_4) + z_{40} (1 - \gamma_4) + 1 = 0$ which gives

$$z_{40} = \frac{1}{2(1-\gamma_4)} \left[-(1-\gamma_4) \pm \left\{ (1-\gamma_4)^2 - 4(1-\gamma_4) \right\}^{\frac{1}{2}} \right] \qquad (11)$$

Since z_{40} cannot be negative or imaginary we must have

$$\gamma_4 > 1 \qquad (12)$$

Now the part under square root of (10) is positive and so the roots

λ_2, λ_3 are real. Thus all the roots being real there cannot be any oscillation.

To find out the signs of the roots, we note that

$$(\gamma_4 + \gamma_5 + \frac{1}{k_4})^2 - \left\{(\gamma_4 - \gamma_5 + \frac{1}{k_4})^2 + 4\gamma_5\right\}$$

$$= 4\gamma_5(\gamma_4 + \frac{1}{k_4} - 1) > 0 \text{ (since } \gamma_4 > 1)$$

Hence $$\left|\gamma_4 + \gamma_5 + \frac{1}{k_4}\right| > \left|\left\{(\gamma_4 - \gamma_5 + \frac{1}{k_4}) + 4\gamma_5\right\}^{1/2}\right|$$

Thus all the roots of the secular equation are both negative and real. In other words the sub-system consisting of x_1, x_4 and x_5 i.e., rRNA, tRNA and aminoacyl tRNA is asymptotically stable indicating that the three components unlike the rest of the system (1) asymptotically approach their steady state values. The numerical and computer analysis is shown in Figures 2(b) and 3(b).

To investigate the existence of a globally stable periodic solution of (1) we have adopted the method of numerical analysis prescribing different values for the constants satisfying the condition (7). The computor simulation (Fig. 2(a) and 3(a))shows the existence of a stable limit cycle solution in the large around an unstable equilibrium which supports the analytical findings.

NUMERICAL ANALYSIS

The dimensionless form (2) of the system of simultaneous ordinary non-linear differential equations (1) have been solved numerically by the method of Runge-Kutta and by using an EC-1033 computer. Since it has long been evident that the early embryogenesis starts with some maternal store of ribosomal RNA, heterogeneous nuclear RNA, transfer RNA, etc. (Davidson [5]), two sets of initial values have been considered as follow :

i) At $t = 0 : z_1 = \ldots = z_8 = 0$

ii) At $t = 0 : z_1 = 66.2,\ z_2 = 5,\ z_4 = 10$ and $z_3 = z_5 = z_6 = z_7 = z_8 = 0$.

The values of the constants γ_i and ρ_7 have been chosen in such a way that the conditions (7) and (12) are satisfied. For example, we have chosen

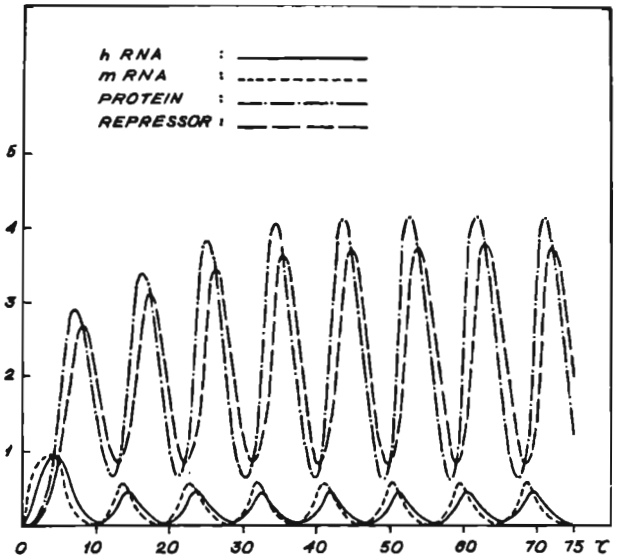

Fig. 2(a). - Periodic solutions, with growing oscillation approaching a stable limit cycle of z_2, z_3, z_6, z_7 and z_8 of the system (2) obtained by numerical analysis by Runge-Kutta method on EC-1033 computer. z_2, z_3, z_6, z_7 and z_8 are the dimensionless concentrations of hRNA, mRNA, polysomes, protein and the repressor enzyme respectively. The initial values are as in (i) and the coefficient values are as in (a) in the text.

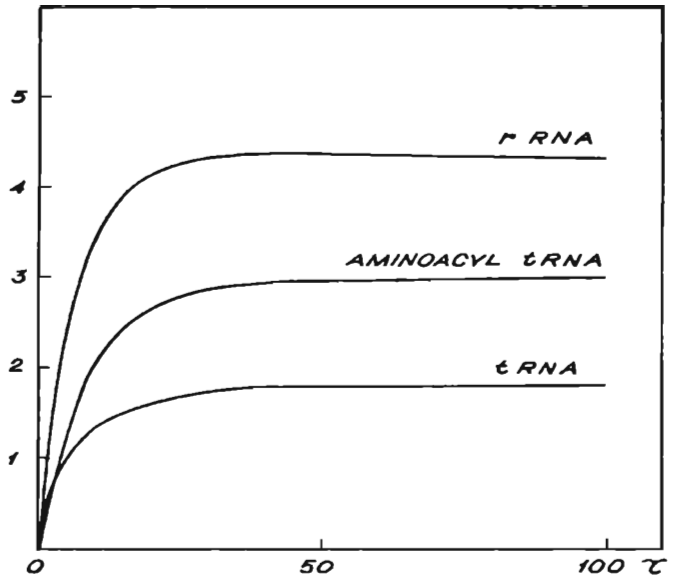

Fig. 2(b). – Solutions of the stable sub-system represented by the first, fourth and fifth equations of the system (2) obtained by the same numerical analysis as in fig. 2(a). z_1, z_4 and z_5 are the dimensionless concentration of the rRNA, tRNA and aminoacyl tRNA respectively. The initial values and the coefficient values are same as in fig. 2(a).

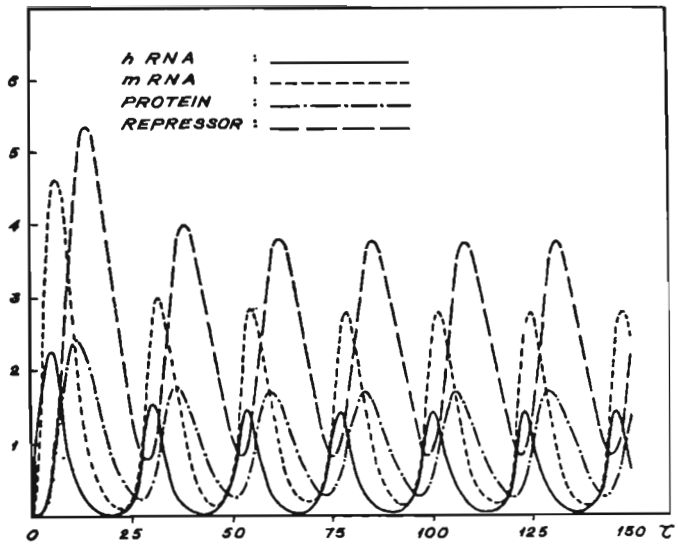

Fig. 3(a). – Periodic solutions, with decaying oscillation approaching (from outside) the same stable limit cycle, of the same components z_2, z_3, z_6, z_7 and z_8 with the same initial values as in fig. 2(a) but for different values of the constants (as in (b)).

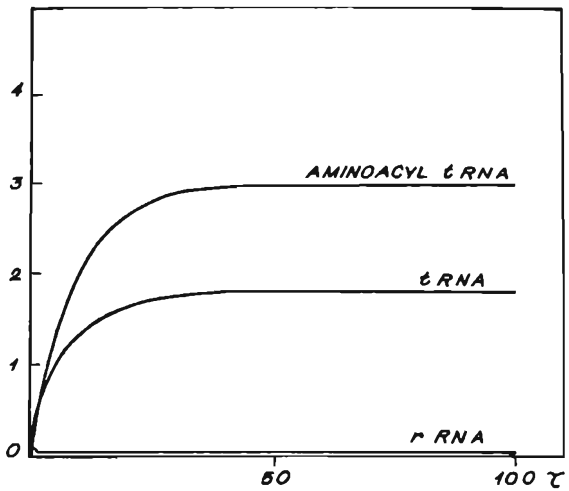

Fig. 3(b). - Stable solutions of z_1, z_4 and z_5 i.e., dimensionless concentrations of rRNA, tRNA and aminoacyl tRNA obtained in the same numerical analysis as in fig. 3(a).

after scrupulous considerations of and speculations from the available biological informations (Davidson [5]), two sets of values for these constants in dimensionless units such as

a) $\gamma_1 = 0.083$, $\gamma_4 = 1.2$, $\gamma_5 = 0.6$, $\gamma_2 = \gamma_3 = \gamma_6 = \gamma_7 = \gamma_8 = 1$ and $\varrho_7 = 1$.

b) $\gamma_1 = 8$, $\gamma_4 = 1.2$, $\gamma_5 = 0.6$, $\gamma_2 = \gamma_3 = \gamma_6 = \gamma_7 = \gamma_8 = 0.4$ and $\varrho_7 = 1$, with $m_1 = m_3 = 1$ and $m_2 = 5$ in both the cases.

From a) we have $k_1 = z_{10} = \frac{1}{0.08\,(1 + z_{40})}$. Again putting $\gamma_4 = 1.2$ in (11) we get $z_{40} = 1.79$. Then from the above expression we get, $k_1 = 4.3$ and $k_5 = z_{50} = \frac{z_{40}}{\gamma_5} = 2.98$. Again $z_{80} = \frac{\varrho_7 k_1 k_5}{\gamma_2 \gamma_3 \gamma_6 \gamma_7 \gamma_8 (1 + z_{80}^5)} = \frac{12.81}{1 + z_{80}^5}$ i.e., $z_{80}^6 + z_{80} - 12.81 = 0$ which gives $z_{80} = 1.5$. Hence $k_8 = (1 + z_{80}^5)^2/5\, z_{80}^4 = 2.92$. Thus $q = k_1 k_5 \varrho_7 / k_8 = 12.81/2.92 = 4.39 > 4 = \Pi \gamma_2$.

Similarly from b) we get, $k_1 = 04$, $k_5 = 3$ and $k_8 = 2.91$ so that $q = 0.046 > 4\, \Pi \gamma_2 = .041$.

Numerical solutions of the system (2) with the initial values (i) and the values of the coefficient as in (a) have been plotted in Figures 2 (a) and 2 (b). The solutions of the same initial values and with coefficients as in (b) are plotted in Figures 3 (a) and 3(b).

The results with the initial values (ii) are shown in Table 1 and Table 2 for coefficient values (a) and (b) respectively.

Both the Figures 2(a) and 3(a) show oscillatory pattern of synthesis of hRNA, mRNA, protein and the repressor molecules. In Figure 2(a), each of the protein and the repressor molecules exhibits a growing oscillation terminating into a stable periodic nature whereas each of the hRNA and mRNA shows all along an almost stable periodic solution except an outburst in the first cycle. On the other hand, Figure 3(a) shows a decaying oscillation for each of the components followed by a stable periodicity. These two figures strongly suggest that there exists a stable limit cycle in the large which is approached by all the trajectories lying in its neighbourhood.

Figures 2(b) and 3(b) show the pattern of synthesis of rRNA, tRNA and aminoacyl tRNA. Each of these three components increase in the first few cycles of division after which each tends to a stable steady state.

Tables 1 and 2 are the results of numerical analysis with some initial values as given in (ii) and coefficient values as in (a) and (b) respectively. From Table 1 it can be seen that hRNA and mRNA follow the similar pattern with growing oscillation as in Figure 2(a), although protein and the repressor enzyme have a decaying oscillation unlike Figure 2(a). But the existence of the same stable limit cycle as in Figure 2(a) can be traced here also. Regarding rRNA and tRNA, table 1 shows a continuously decreasing nature of accumulation of these molecules from their initial values which ultimately approach asymptotically the same stable steady state values for these molecules as in Figure 2(b).

Table 2 is to be compared with Figures 3(a) and 3(b). From this table it is apparent that all the oscillatory components follow the same pattern of decaying oscillation which ultimately approaches the same stable periodic solution as in Figure 3(a) proving the existence of the unique stable limit cycle. rRNA decreases sharply below the stable steady state value and then approaches it like Figure 3(b) whereas tRNA decreases to its stable steady state value.

From the analytical findings we have already seen that the system consisting of the five components represented by the second, third, sixth, seventh and eighth equations of system (1) has a stable periodic solution in the small around the unstable equilibrium. The numerical results confirm the existence of a stable periodic solution in the large.

CONCLUSIONS

Mathematical investigations on the complicated process of transcription and translation have been carried out in this paper. A compact dynamical model parametrised by time based on the known biological facts and comparising the main components of this fundamental process has been developed first. The model has then been analysed with particular emphasis to its stability and oscillatory properties.

The merit of this work may be claimed due to the fact that unlike most of the previous hypothetical ones this is on a perfectly real and complicated biological system with due considerations to most of the cardinal components playing equal roles in the process. Analytical investigations of the model reveal a stable periodic solution for five out of the eight components with asymptotically stable solution for the rest three. The conditions for a stable periodic solution has also been worked out and finally this analytical findings has been confirmed by numerical investigations.

t	z_1	Time for peaks (p) toughs (t)	z_2	Time for peaks (p) toughs (t)	z_3	z_4
0	66.20		5.0		0.0	10.0
1	61.064		2.0877		2.0077	4.2804
				1.05 (p)	2.0081	
10	30.6733		0.0003		.0025	2.3237
		11.5 (t)	.0001	12.6 (t)	.0003	
		15.4 (p)	.4187	16.0 (p)	.2777	
20	15.5688		.0053		.0261	1.9778
		22.12 (t)	.0009	23.1 (t)	.0027	
		25.8 (p)	.4515	26.45 (p)	.3227	
30	9.1338		.0098		.0437	1.8552
		31.85 (t)	.0023	32.8 (t)	.0060	
		35.85 (p)	.5094	36.25 (p)	.3797	
40	8.3857		.0102		.0458	1.8130
		41.37 (t)	.004	42.32 (t)	.0098	
		45.2 (p)	.5438	45.85 (p)	.4159	
50	5.2080		.0081		.0365	1.7986
...	...		...		...	...
		91.7 (p)	.5656	92.35 (p)	.4449	
100	4.33	97.05 (t)	.0083	95 (t)	.0178	1.7913

Table 1. - Results of the numerical analysis of the system (2) (in dimensionless units) for initial values (t = 0) : $z_1 = 66.20$, $z_2 = 5.0$, $z_4 = 10.0$, $z_3 = z_5 = z_6 = z_7 = z_8 = 0$ and $\gamma_1 = .083$, $\gamma_4 = 1.2$, $\gamma_5 = 0.6$, $\gamma_2 = \gamma_3 = \gamma_6 = \gamma_7 = \gamma_8 = 1$, $e_7 = 1$, $m_1 = m_3$ m 1 and $m_2 = 5$ by Runge - Kutta method on EC-1033 computer. Interpretation of the results are given in the text.

Time for peaks (p) troughs (t)	z_5	Time for peaks (p) troughs (t)	z_6	Time for peaks (p) troughs (t)	z_7	Time for peaks (p) troughs (t)	z_8
	0.0		0.0		0.0		0.0
	4.5880		61.7065		82.0726		18.099
2.15 (p)	5.1891	1.9 (p)	88.2057	2.95 (p)	368.7383	3.9 (p)	314.43
	4.0548		0.5079		8.4310		23.73
		13.5 (t)	.0304	14.2 (t)	.3582	14.85 (t)	0.85
		16.85 (p)	4.2844	17.75 (p)	12.4810	18.7 (p)	10.92
	3.3628		1.1354		6.9028		9.19
		22.9 (t)	.0839	24.8 (t)	.5258	25.3 (t)	0.87
		27.25 (p)	2.7493	28.15 (p)	7.3512	29.15 (p)	8.50
	3.1152		0.9798		4.9332		6.98
		33.6 (t)	.1029	34.35 (t)	0.55	35.05 (t)	0.83
		37.05 (p)	2.1816	38.0 (p)	5.6844	38.95 (p)	5.08
	3.0296		0.7211		3.6043		4.51
		43.1 (t)	.1140	43.85 (t)	.5630	44.6 (t)	0.82
		46.65 (p)	1.8911	47.55 (p)	4.8996	48.5 (p)	4.38
	3.0004		.4950		2.6268		3.54
	...		...		...		...
		93.2 (p)	1.5999	94.1 (p)	4.1549	91.05 (t)	0.81
	2.9855	98.8 (t)	.1327	99.5 (t)	.5969	95 (p)	3.73

Table 1. - (Continuation).

t	Time for peaks (p) troughs (t)	x_1	Time for peaks (p) troughs (t)	x_2	Time for peaks (p) troughs (t)	x_3
0		66.20		5.0		0.0
1		0.0458		3.8766		3.6867
	1.4 (t)	0.0270			2.5 (p)	5.2148
10		0.0375		0.1059		1.0541
			19.5 (t)	0.0032		
20		0.0418		0.0035		0.0397
			28.8 (p)	1.7503	21.5 (t)	0.0290
30		0.0438		1.5107		3.3642
					30.4 (p)	3.3955
40		0.0444		0.0232		0.3767
			43.1 (t)	0.0152	45.5 (t)	0.0907
50		0.0447		0.8540		0.6901
			52.7 (p)	1.1783	54.4 (p)	2.8944
60		0.0447		0.1403		1.0655
			66.3 (t)	0.0192	68.7 (t)	0.1054
70		0.0448		0.1019		0.1324
75		0.0448		1.3229		1.8434
...		...		...		..
					77.6 (p)	2.7987
			89.5 (t)	.0202		
			99.1 (p)	1.4131	99.9 (t)	0.1099
100		.0448				

Table 2. - Results of the numerical analysis of the system (2) (in dimensionless units) for the same initial values (t = 0), as in table 1 but with values of the coefficients : $\gamma_1 = 8$, $\gamma_4 = 1.2$, $\gamma_5 = .6$, $\gamma_2 = \gamma_3 = \gamma_6 = \gamma_7 = \gamma_8 = 0.4$, $\varrho_7 = 1$, $m_1 = m_3 = 1$ and $m_2 = 5$. The method used is the same as in table 1. Detailed interpretation is to be found in the text.

z_4	z_5	Time for peaks (p) tough (t)	z_6	Time for peaks (p) tough (t)	z_7	Time for peaks (p) tough (t)	z_8
10.0	0.0		0.0		0.0		0.0
		0.6 (p)	3.9674				
4.2804	4.3880		3.5765		9.2788		3.0750
	5.1889			3.2 (p)	21.4395	5.8 (p)	40.7817
3.3237	4.0546		0.2799		6.8380		27.7417
1.9778	3.3629		0.0168		0.4918		3.2958
		23.2 (t)	0.0076	25.1 (t)	0.1371	27.2 (t)	0.6403
1.8552	3.1153		0.2338		0.9680		1.2716
		32.5 (p)	0.3038	34.7 (p)	2.0166	37.1 (p)	4.4982
1.8130	3.0297		0.1001		1.2510		3.9541
		47.4 (t)	0.0148	49.3 (t)	0.2213		
1.7986	3.0004		0.0426		0.2333		0.5474
		56.5 (p)	0.2670	58.7 (p)	1.7339	61.2 (t)	0.7832
1.7938	2.9905		0.1946		1.6739		3.8123
						81.0 (p)	3.8890
1.7921	2.9872		0.0217		0.3358		1.4990
		70.7 (t)	0.0207	72.6 (t)	0.2350	74.4 (t)	0.8071
1.7918	2.9864		0.1002		0.3926		0.6245
...	...		...		...		...
		70.7 (p)	0.2583	82 (p)	1.6824	84.3 (p)	3.7784
		93.8 (t)	0.0211	95.7 (t)	0.2381	97.6 (t)	0.8126
1.7913	2.9855						

Table 2. - (Continuation).

Although from the Figures 2(a), 2(b) and 3(a), 3(b), the pattern of synthesis of different size classes of RNA can be easily visualized, tables 1 and 2 serve more practically the purpose of comparing the theoretical results with the experimental findings. This is because all the living organisms start the process of embryogenesis with some amount of maternal RNA prepared during oogenesis (Davidson [5]) and Tables 1 and 2 are the results after consideration of the initial values of RNA at t = 0. Enough experimental evidences are there that both the ribosomal and transfer RNA synthesis is very much repressed during the early part of embryogenesis and not cleary vivid in most cases before the blastula stage from which the rate of synthesis goes on increasing. A detailed discussion on this topic can be found in Davidson [5] and Weissbach and Pestka [25] . Both table 1 and table 2 show a similar oscillatory pattern of synthesis approaching a stable periodic nature for each of the five components represented by z_2, z_3, z_6, z_7 and z_8. The marked outburst of protein synthesis in the first cycle interestingly coincides with experimental evidences.

Regarding rRNA (z_1), tRNA (z_4) and aminoacyl tRNA (z_5), the final interpretation as obtained from the figures and tables is that the three variables z_1, z_4 and z_5 approach the stable steady state in a decreasing or an increasing manner according as the initial values are respectively above or below these steady state values.

The rhythmic pattern of hRNA, mRNA, proteins etc. has been experimentally observed in many organisms (Mazia [13] , Mano [12]). Both the figures (2a and 3a) and the tables (1 and 2) simulate these patterns qualitatively. In fact the most important property of biological interest of this model is that it exhibits a stable periodic solution with the Hill coefficient for the repressor molecules $m_2 > 4$. Griffith [7] working with Goodwin's type of model in the three variable case observed that for $m_2 > 8$ there will be always one limit cycle. But experimental investigations indicate that the value of the Hill coefficient i.e., the number of molecules required to cooperatively inactivate a gene cannot be of such a high order as obtained by Griffith. The present result is definitely more in the line of biological reality. A stable periodic solution for the components rRNA, tRNA and aminoacyl tRNA which have shown aperiodicity in this investigation, can be obtained by introducing a time lag in one of the equations representing the rate of synthesis of these molecules. The time lag analysis is based on the concept of threshold concentration of tRNA at which the process of feedback self inhibition is switched on.

Due to the meagre supply of reliable biological data such as the specific rate constants, initial values etc. true simulation of the biological process is impossible. The degree of simulation of the natural systems depends on the accuracy of these values for different species of organisms. Only a mathematically oriented experimental investigation i.e., a combined effort of the Mathematicians and the Biologists can pave the way to the desired goal of establishing the validity of the mathematical models.

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