ATTI ACCADEMIA NAZIONALE DEI LINCEI

CLASSE SCIENZE FISICHE MATEMATICHE NATURALI

RENDICONTI

FILIPPA A. M. ALBERGHINA

Cell dynamics: analysis of a model

Atti della Accademia Nazionale dei Lincei. Classe di Scienze Fisiche, Matematiche e Naturali. Rendiconti, Serie 8, Vol. **56** (1974), n.6, p. 971–975.

Accademia Nazionale dei Lincei

<http://www.bdim.eu/item?id=RLINA_1974_8_56_6_971_0>

Atti della Accademia Nazionale dei Lincei. Classe di Scienze Fisiche, Matematiche e Naturali. Rendiconti, Accademia Nazionale dei Lincei, 1974.

SEZIONE III

(Botanica, zoologia, fisiologia e patologia)

Biofisica. — *Cell dynamics: analysis of a model.* Nota di Filippa A. M. Alberghina (*), presentata (**) dal Corrisp. E. Marrè.

Riassunto. — Viene analizzato un modello delle crescita cellulare in cui entrano le informazioni sui « goals » del sistema: ρ_1 (livello richiesto di ribosomi) e ρ_2 (livello richiesto di proteine) e sulla efficienza dei ribosomi nella sintesi proteica. Si dimostra che il modello è capace di predire con accuratezza la dinamica della crescita esponenziale e si presenta un esempio di simulazione di crescita. Infine si dimostra che una semplice relazione matematica lega i seguenti parametri del sistema: livello di proteine, di ribosoni, attività dei ribosomi e velocità di crescita.

ABBREVIATIONS USED

P, R and D are respectively the level of proteins (expressed as number of amino acids polymerized), the level of ribosomes (expressed as number of ribosomes) and the level of DNA (expressed as genome units) in cells in balanced exponential growth. P^x and R^x are the proteins and ribosome levels referred to 1 genome unit in the same conditions. K_2 is the integration constant for protein synthesis (amino acids polymerized, min^{-1}, per ribosome). T is the time constant (min) of the exponential growth. ρ_1 is the required ribosome level, ρ_2 is the required protein level.

INTRODUCTION

A growing cell is a system able to use the energy, derived from the conversion of the physical or chemical energy supplied by the environement, to carry on a number of reactions: take simple inorganic and organic compounds from the environment, convert them into cellular constituents, utilize some of these constituents to synthetize specific macromolecules and eventually divide into two daughter cells.

Few processes are now studied with more interest than cellular growth, but with results not too satisfactory. A large collection of data on several aspects of growth is now available, but it lacks a structure capable to interpret and interrelate the findings.

The approach followed in the studies on cellular growth has been the classic reductionistic approach of experimental biology. One could start wondering whether the unsatisfactory state of the studies on growth may be a consequence of the approach used. When studying cellular growth we are

---

(*) Istituto di Scienze Botaniche. Centro del CNR di Biologia Cellulare e Molecolare delle piante. Università di Milano. 20123 Milano.

(*) Nella seduta del 29 giugno 1974.

dealing with a very complex system and we try to understand the relevant relationship between the elements of the system. It seems therefore appropriate to approach these studies using the methods developed by cybernetics [1, 2]. Recently Alberghina and Golhke [3] have proposed a cybernetic model of cellular growth. In this model cells of a population in exponential growth behave like a system seeking two goals: a required ribosomal level and a required protein level, using a protein synthetizing machinery of a given efficiency. It was shown that the kinetics of exponential growth of microbial cells are simulated with great fidelity if the appropriate informations on the goals of the system and on the efficiency in protein synthesis are given [3].

In the present paper the model is further analyzed and it is put into evidence the relationship between the ribosome and protein levels, the efficiency of the protein synthetizing machinery and the rate of exponential growth which is implicit in the model. Experimental values of the above mentioned parameters determined for a *Neurospora* system are shown to verify the evidenced relationship. Thus this analysis gives further support to the validity of the model for representing the dynamics of cellular growth.

RESULTS AND DISCUSSION

The model.

Fig. 1 presents the model as a block diagram. A negative feed-back loop maintains the ribosome level at the goal value ρ_1 (required ribosome level per genome) a second feed-back loop controls DNA synthesis in such a way that a required protein level per genome (ρ_2) is maintained. The force driving growth is the rate of protein synthesis which in turn depends upon the level of ribosomes and the efficiency of the translation machinery (K_2, amino acids polymerized, min^{-1}, per ribosome). In fact when the content of protein increases to be more than that indicated by ρ_2, more DNA is made and this in turn causes an increase in ribosomes due to the interlocked feed-back loops indicated in fig. 1.

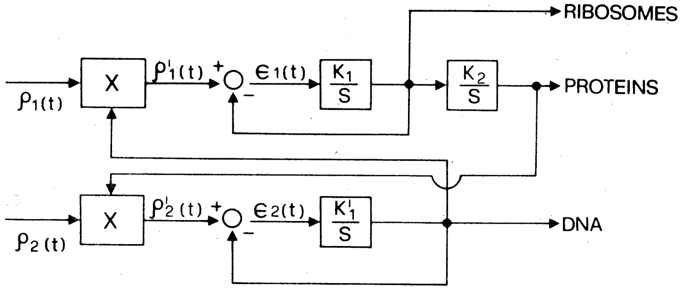

Fig. 1. – Dynamic model of cellular growth. For description see the text.

When a system in steady-state is considered the values of the goals ρ_1 and ρ_2 can be estimated by knowing the actual levels of ribosomes and of proteins per genome by making the same kind of assumptions that allows to deduce the setting of the temperature in a thermostat by monitoring the temperature of the connected system. Therefore the dynamics of a real system can be computed using as input values those of the levels determined experimentally.

Neurospora crassa cells (wild type strain 74 A) in exponential growth at 30° C in glucose plus casamino acids have $4.35 \cdot 10^5$ ribosomes per genome, a protein level of $2.75 \cdot 10^{10}$ amino acids per genome and an efficiency in protein synthesis of 479 amino acids, min^{-1} per ribosome [4]. These values were fed as ρ_1, ρ_2 and K_2 respectively and the dynamics of growth was simulated. In fig. 2 the simulation is reported and it indicates the relevant features of the simulated growth: the levels of DNA, ribosomes and proteins are exponential function of time; the growth is balanced because the constant of the exponential rate of growth is the same for each macromolecular component; the computed constant for the simulated growth is the same as that experimentally determined, 0.45 (hr^{-1}) [4].

Testing the model.

The dynamics of macromolecular synthesis generated by the model follow, as show in fig. 2, exponential functions having the same time constant (T). That is the following equations are verified:

$$D(t) = D(o)\, e^{t/T} \tag{1}$$

$$R(t) = R(o)\, e^{t/T} \tag{2}$$

$$P(t) = P(o)\, e^{t/T}. \tag{3}$$

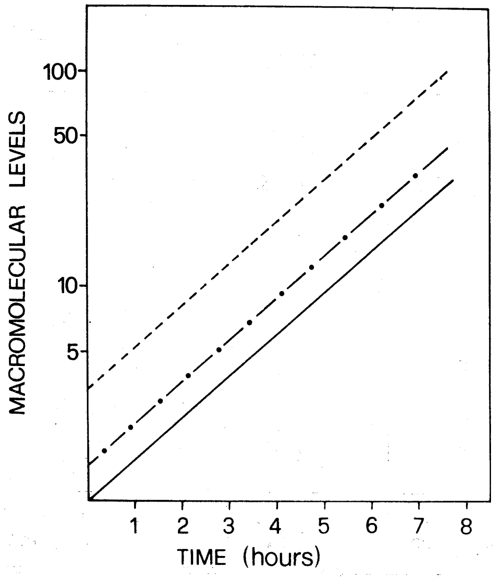

Fig. 2. – Simulated levels of DNA, ribosomes and proteins as a function of time. The levels of DNA (—), protein (– – –) and ribosomes (–·–) were calculated by the equations derived from the model of fig. 1 [3] using the inputs values of ρ_1, ρ_2 and K_2 indicated in the text.

On the other hand as indicated by fig. 1 the level of proteins $P(t)$ is given by:

$$P(t) = \int_0^t K_2 R(o) e^{t/T} dt = K_2 TR(o) e^{t/T}. \tag{4}$$

From equations (3) and (4) it follows:

$$P(o) = K_2 TR(o)$$

or considering the ribosome and protein levels per genome (R^x and P^x respectively):

$$P^x = K_2 TR^x. \tag{5}$$

Equation (5) gives the relationship between the levels of the system in exponential growth, the efficiency of the protein synthesis and the rate of growth.

The validity of equation (5) was then tested by applying it to the *Neurospora* system for which the values of R^x, P^x, K_2 and T have been experimentally determined in a previous study [4] in several different conditions of balanced exponential growth.

In Table I these values are reported and the experimental K_2 is compared with the K_2 value calculated from equation (5). The complete agreement between the computed and the experimental values of K_2 indicates the validity of the equation for the cell systems whose balanced exponential growth is adequately described by the model of fig. 1.

TABLE I

Testing the model for the Neurospora *system.*

T (min)	R^x (number of ribosomes) $\times 10^{-5}$	P^x (number of acids) $\times 10^{-10}$	K_2 (aa, min^{-1}, rib^{-1})	
			Experimental	Computed from Eq (5)
95.5	6.26	2.85	481	480
133	4.35	2.75	479	475
150	4.00	2.72	458	455
171	3.37	2.70	470	470
182	3.13	2.68	475	470
214	2.54	2.66	492	490
334	1.43	2.60	550	545
668	1.20	2.55	320	316

The values of T, R^x, K_2 and P^x experimentally determined in *Neurospora* cells in different conditions of balanced exponential growth are taken from a previous paper [4].

It is interesting to point out that equation (5) explains the proportionality observed in simulation studies [3] between K_2 and the constant of the exponential rate of growth (1/T) under conditions in which R^x and P^x were kept constant.

The relationship evidenced in this paper may be useful to calculate any of the four indicated parameters when three of them are known allowing for instance to evaluate K_2 in systems in which the experimental determination of K_2 is not too simple. Finally the results presented in this paper confirm the previous indications [3] that the exponential rate of growth of cells is determined when the ribosome and protein levels and the efficiency of the protein synthetizing machinery are set.

REFERENCES

[1] W. R. ASHBY (1961) – *Introduction to cybernetics*, Chapman and Hall, London.
[2] J. H. MILSUM (1961) – *Biological control systems analysis*, McGraw-Hill Inc., New York.
[3] F. A. M. ALBERGHINA and J. R GOHLKE – Submitted for publication.
[4] F. A. M. ALBERGHINA, E. STURANI and J. R. GOHLKE – Submitted for publication.