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Influence of Temperature on the Rate of Cell Growth: A Quantitative Approach Based on Non Equilibrium Thermodynamics

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Biologia. — *Influence of Temperature on the Rate of Cell Growth: A Quantitative Approach Based on Non Equilibrium Thermodynamics.* Nota di ALFONSO M. LIQUORI e ARNALDO FLORIO, presentata (*) dal Socio CLAUDIO BARIGOZZI.

RIASSUNTO. — L'equazione della crescita cellulare derivata da A.M. Liquori e A. Tripiciano in base a concetti della termodinamica dei Sistemi in Non Equilibrio viene estesa allo studio dell'influenza della temperatura sulle curve di crescita cellulare e sulla velocità di crescita.

1. INTRODUCTION

From a purely phenomenological viewpoint cell growth takes place in time according to a sigmoidal curve. The number of cells first increases slowly with increasing time, than increases exponentially until the homeostatic state is finally reached where no appreciable growth is observed [1]. This behaviour is common among unicellular organisms (prokaryotic and eukaryotic) and may also be observed in developing embryos or larvae.

Several « logistic » equations have been proposed to describe sigmoidal curves, the best known equations being those of Velhurst [2] and Gompertz [3]. These equations are however affected by a number of limitations inherent to their empirical or semiempirical bases.

Sometime ago Liquori and Tripiciano [4] introduced a novel growth equation which was derived with the following assumptions:

a) growth is an autocatalytic global cooperative chemical process;

b) it may be described by two concomitant global rate processes, a slow one (1) and a fast one (2);

c) both the slow and the fast growth processes fulfill detailed stationary conditions which allow the description of their corresponding rates according to linear differential equations;

d) a continuous irreversible interconversion from the slow to the fast process takes place during growth through a coupling between the slow and the fast process which may be described by an autocatalytic master equation.

(*) Nella seduta del 15 giugno 1984.

The rate equation of the slow (1) and the fast (2) processes are:

(1a) $$\frac{d\xi_1(t)}{dt} = -\frac{1}{\tau_1}(\xi_1(t) - \bar{\xi})_1$$

(1b) $$\frac{d\xi_2(t)}{dt} = -\frac{1}{\tau_2}(\xi_2(t) - \bar{\xi}_2)$$

where $\xi_1(t)$ is the extent of process 1 at time t, $\xi_2(t)$ is the extent of process 2 at time t, $\bar{\xi}_1$ and $\bar{\xi}_2$ are the extents of the two processes at the homeostatic state ($t \to \infty$). The solutions of (1) and (2) are

(2a) $$\xi_1(t) = \bar{\xi}_1(1 - \exp - t/\tau_1)$$

(2b) $$\xi_2(t) = \bar{\xi}_2(1 - \exp - t/\tau_2)$$

which may be reduced to

(3a) $$y_1(t) = \frac{\xi_1(t)}{\bar{\xi}_1} = (1 - \exp - t/\tau_1)$$

(3b) $$y_2(t) = \frac{\xi_2(t)}{\bar{\xi}_2} = (1 - \exp - t/\tau_2)$$

$y_1(t)$ and $y_2(t)$ may be given the meanings of probabilities of a cell dividing at time t according to process 1 and 2 respectively.

The autocatalytic master equation is

(4) $$y(t) = y_1(t)(1 - y(t)) + y_2(t)\, y(t)$$

where $y(t)$ is the average at time t of growth according to process 1 ($y_1(t)$) and 2 ($y_2(t)$). Solving equation (4) and replacing $y_1(t)$ and $y_2(t)$ according to (3a) and (3b) yields the normalized growth equation:

(5) $$y(t) = \frac{1 - \exp - t/\tau_1}{1 - \exp - t/\tau_1 + \exp - t/\tau_2}$$

The function $y(t)$ displays a sigmoidal shape and contains only two parameters, the relaxation times τ_1 and τ_2 having the dimension of time. The growth rate may be obtained as the time derivative of (5), namely

(6) $$\dot{y}(t) = \frac{1/\tau_2 \exp - t/\tau_2 + (1/\tau_1 - 1/\tau_2)\exp - (t/\tau_1 + t/\tau_2)}{(1 - \exp - t/\tau_1 + \exp - t/\tau_2)^2}$$

which is a non-linear differential equation.

In fig. 1 plots of $y(t)$, $y_1(t)$, $y_2(t)$ and $\dot{y}(t)$ are shown for arbitrary values of τ_1 and τ_2. The plots illustrate graphically how the sigmoidal curve $y(t)$ is the result of an autocatalytic transition from a slow to a fast growth process defined by (2a) and (2b) and how the maximum growth rate occurs at the inflection point of (5).

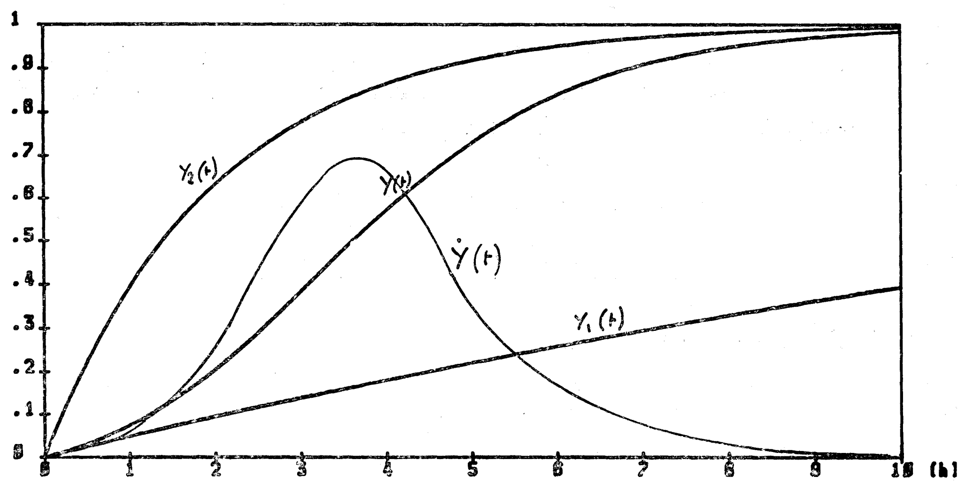

Fig. 1. – Reduced extent of growth $y(t)$ and growth rate $\dot{y}(t)$ calculated according to equation 5 and 6. The extents slow and fast growth $y_1(t)$ and $y_2(t)$ involved in the derivation of the autocatalytic growth rate equation 5 are also plotted. The values of the parameters τ_1 and τ_2 are arbitrary.

Equation (5) has been found to fit most satisfactorily growth curves of simple and complex biological organisms [4]. Furthemore it appears applicable to a number of autocatalytic processes ranging from the kinetics of crystal growth [5], to the kinetics of catastrophic conformational transitions, like protein denaturation, and of non-catastrophic transitions like allosteric transiti ns [6, 7]. Results of these studies will be reported shortly [8].

2. Activation-free energies of growth

The relaxation time τ_1 and τ_2 appearing in equation (1) and (5) have the physico-chemical meaning of the inverse of the rate constants of the global growth process 1 and 2. Their temperature dependence may therefore be expressed by

$$\tau_1 = \tau_1^0 \exp + \Delta G_1^*/RT \tag{7a}$$

$$\tau_2 = \tau_2^0 \exp + \Delta G_2^*/RT \tag{7b}$$

where τ_1^0 and τ_2^0 are the values of the relaxation times at a reference temperature

$T = T_0$ and ΔG_1^* and ΔG_2^* are the activation-free energies of the two processes [9].

3. Growth curves and growth rates as a function of temperature

(7a) and (7b) may be introduced into the growth equation (5) and into the growth rate equation (6) in order to study the influence of temperature.

Simple and complex biological organisms usually display a characteristic trend of the extent of growth and of the maximum growth rate as a function of temperature [9]. However, this behaviour may only be observed within a limited temperature range. Outside this optimal temperature range the ability of the organism to divide suddenly drops [9]. This catastrophic decay of the growth rate outside the optimal may be explained equilibrium denaturation of cellular proteins, as will be shown in a separate paper, through the application of a thermodynamic equation of state [10].

Within the optimal growth range equation (5) and the maximum of equation (6), corresponding to the inflexion point of equation (5) have been expressed as a function of temperature according to (7a) and (7b) and the resulting equations have been fitted with the available experimental data for a number of biological systems both simple and complex. The results are shown in fig. 2, fig. 3 and fig. 4, where the growth curves of mesophyllic [11] and thermophyllic [12] bac-

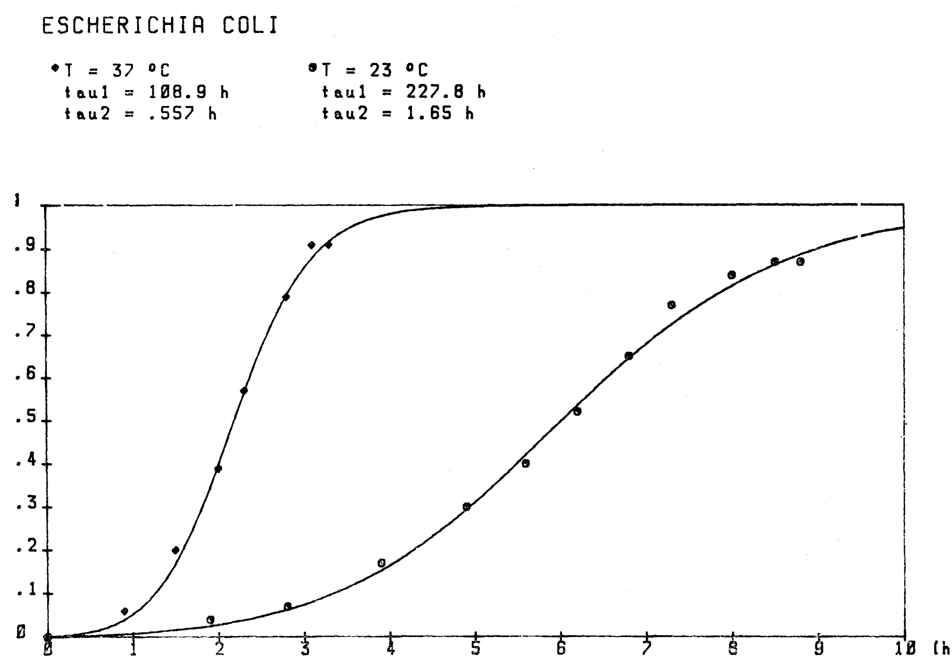

Fig. 2. – Reduced extent of growth of E. Coli at $t = 23$ °C and $t = 37$ °C. The experimental values are indicated by squares whereas the continuous curves have been calculated according to equations 5, 7a, 7b.

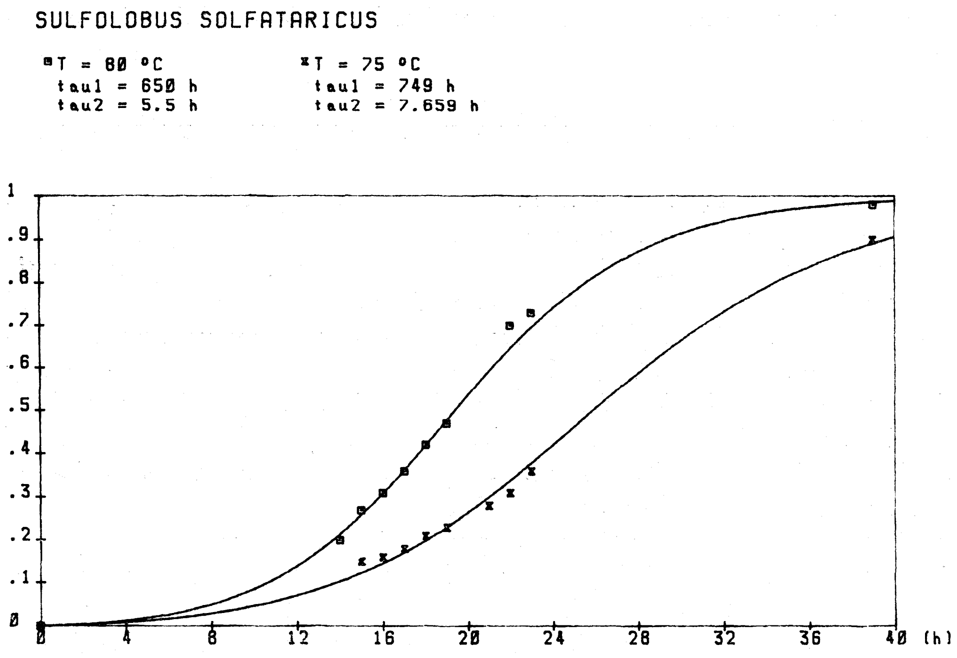

Fig. 3. – Reduced extent of growth of Sulfolobus Sulfataricus at $t = 75$ °C and $t = 80$ °C. The experimental values[12] are indicated by triangles and squares whereas the continuous curves have been calculated according to equations 5, 7a, 7b.

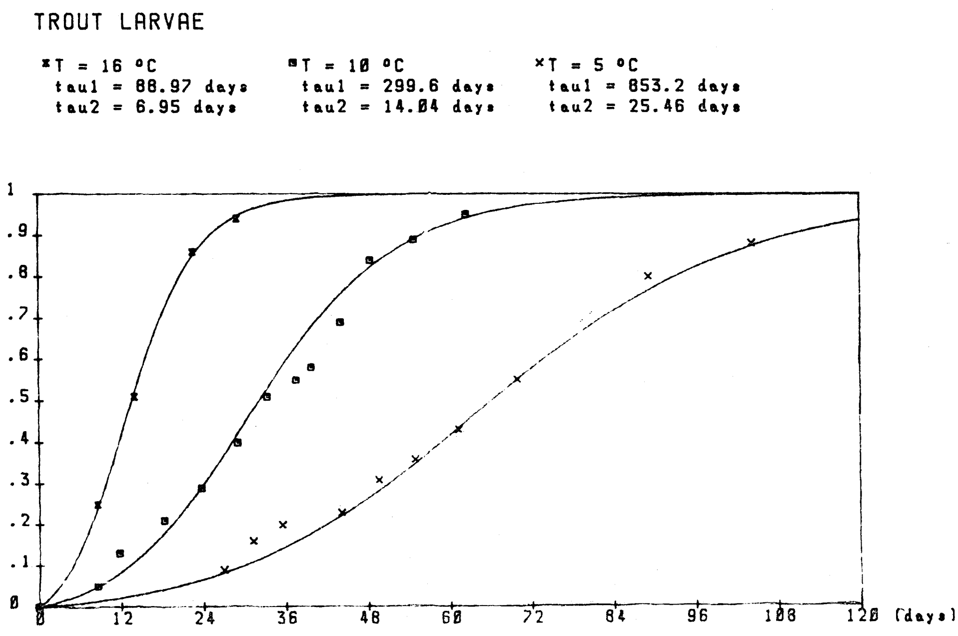

Fig. 4. – Reduced extent of growth of Trout Lowae at $t = 5$ °C, $t = 10$ °C and $t = 16$ °C. The experimental values[9] are indicated by squares and crosses whereas the continuous curves have been calculated according to equations 5, 7a, 7b.

teria genetically adapted at medium and high temperatures and of trout larvae [9] are shown at various temperatures. The agreement between the theoretical curves and the experimental data appears to be very satisfactory.

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