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Genetica. — *A phenomenological approach to non equilibrium self-cooperative relaxation processes: Liquori-Tripiciano versus Verhulst cell growth equation.* Nota (*) di

ALFONSO M. LIQUORI (**), BERNARD LAVENDA (***) e ARNALDO FLORIO (****), presentata dal Socio G. MONTALENTI.

ABSTRACT. — An analytic function shown by Liquori and Tripiciano to be suitable to explain sigmoidal growth curves is compared with the classical logistic equation of Verhulst. It is shown that Liquori-Tripiciano function displays a higher flexibility and offers operational advantages with respect to Verhulst logistic equation. Furthermore at variance with the latter equation it allows to study the effect of temperature on growth curves.

For highly cooperative growth processes, the two sigmoidal curves calculated according to Liquori-Tripiciano equation and Verhulst equation virtually coincide.

KEY WORDS: Growth curves; Non equilibrium self cooperative relaxation processes; Growth equation.

RIASSUNTO. — *Un approccio fenomenologico allo studio di processi di rilassamento cooperativi di non equilibrio.* Una funzione analitica dimostrata da Liquori e Tricipiano adatta a spiegare le curve sigmoidali di crescita viene confrontata con la classica equazione logistica di Verhulst. Viene mostrato che la funzione di Liquori-Tripiciano presenta una maggiore flessibilità e presenta vantaggi operativi rispetto all'equazione logistica. Inoltre a differenza dell'equazione di Verhulst si presta ad uno studio dell'effetto della temperatura sulle curve di crescita. Per processi di crescita altamente cooperativi le due curve sigmoidali calcolate secondo le equazioni di Verhulst e di Liquori-Tripiciano virtualmente coincidono.

INTRODUCTION.

A novel phenomenological function was proposed sometime ago by one of us (A.M.L.) to deal with cooperative relaxation processes. It was shown to fit very accurately sigmoidal growth curves [1]. It also appears to be able to describe the kinetics of crystallization, of conformational transitions (to be published) and of autocatalytic chemical reactions [1]. The above function may be simply represented as:

$$\xi(t) = \zeta \frac{1 - \exp - t/\tau_1}{1 - \exp - t/\tau_1 + \exp - t/\tau_2} \tag{1a}$$

where $\xi(t)$ is the value at time t of a progress variable, $\bar{\zeta}$ is the corresponding equilibrium or steady state value and τ_1, τ_2 are relaxation times, *i.e.* constants having the dimension of time.

The sigmoidal shape of (1*a*) requires that $\tau_1 > \tau_2$.

Equation (1*a*) may also be represented as:

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

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Where $y(t) = \xi(t)/\bar{\zeta}$ is a dimensionless function which may also be given the meaning of a time varying probability.

It will also prove convenient to put (1*b*) into the form:

$$\frac{1 - \exp - k_1 t}{1 - \exp - k_1 t + \exp - k_2 t} \tag{1c}$$

where $k_1 = 1/\tau_1$ and $k_2 = 1/\tau_2$ are kinetic constants.

The function (1*c*) was found useful in the study of the temperature dependence of cell growth [2] through the generalized Arrhenius equations:

$$k_1 = k_1^0 \exp - \Delta G_1^{\#}/kT, \qquad k_2 = k_2^0 \exp - \Delta G_2^{\#}/kT \tag{2a}$$

where $\Delta G_1^{\#}$ and $\Delta G_2^{\#}$ are activation free energies.

The function (1*b*) was derived by assuming that a cooperative relaxation kinetics results from two concomitant processes: a slow one (1) and a fast one (2).

If each of these two processes takes place in a large number of small steps and there is no accumulation in any of the intermediate steps (*i.e.* stationary conditions) [3], the following linear differential equations describe their rates:

$$\dot{y}_1(1) = 1/\tau_1[1 - y_1(1)] \tag{3a}$$

$$\dot{y}_2(t) = 1/\tau_2[1 - y_2(t)] \tag{3b}$$

The solutions of (3*a*) and (3*b*) are:

$$y_1(t) = 1 - \exp - t/\tau_1 \tag{4a}$$

$$y_2(t) = 1 - \exp - t/\tau_2 \tag{4b}$$

Finally a non-linear coupling of $y_1(t)$ and $y_2(t)$ was assumed through the «master equation» [1]:

$$y(t) = y_1(t)[1 - y(t) + y_2(t)\,y(t)] \tag{5}$$

It is easily verified that by inserting (4*a*) and (4*b*) into the above equation, the function (1*b*) is easily obtained. The master eq. (5) expresses the self cooperativity of the global process. The fraction $y(t)$ may in be considered as a time dependent weighted average at time t of the slow (1) and the fast (2) process where $y(t)$ and $1 - y(t)$ are time dependent «weighting factors».

Function (1*b*) was also found to fit accurately diauxic growth curves as defined by J. Monod [4]. In fact it was used to analyse the kinetics of the early development of the sea urchin embryo which displays a bifasic curve [5].

The following equation was used

$$y(t) = y_\alpha x_\alpha + y_\beta x_\beta \tag{6}$$

where

$$y_\alpha = \frac{(1 - \exp - t/\tau_1^\alpha)}{(1 - \exp - t/\tau_1^\alpha + \exp - t/\tau_2^\alpha)} \tag{7a}$$

$$y_\alpha = \frac{(1 - \exp - t/\tau_1^\alpha)}{(1 - \exp - t/\tau_1^\beta + \exp - t/\tau_2^\beta)} \tag{7b}$$

and x_α and x_β are weighting factors such that $x_\alpha + x_\beta = 1$

A typical diauxic curve is drawn in fig. 1.

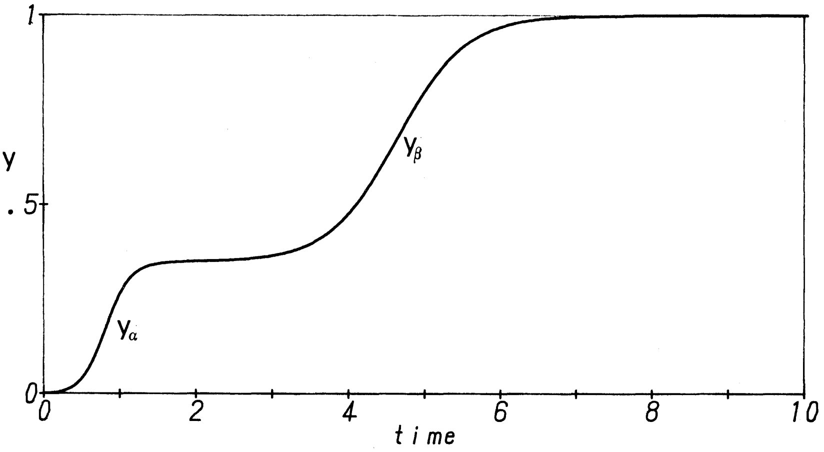

Fig. 1. – Plot of $y(t)$ according to equation (6) calculated for $\tau_1^\alpha = 50$, $\tau_2^\alpha = 0.2$, $\tau_1^\beta = 5 \cdot 10^4$, $\tau_2^\beta = 0.5$, $x_\alpha = 0.35$, $x_\beta = 0.65$.

FIRST ORDER DIFFERENTIAL EQUATIONS.

Differentiating (1*c*) with respect to time and using the fact that:

$$1 - y(t) = \frac{\exp - k_2 t}{1 - \exp - k_1 t + \exp - k_2 t} \tag{8}$$

we get:

$$\dot{y}(t) = [k_1(1 - y(t)) \exp - (k_1 - k_2)\, t + k_2\, y(t)]\, (1 - y(t)) \tag{9}$$

It should be noticed that for $k_1 = k_2 = k$, the differential equation (9) reduces to the simple differential equation:

$$\dot{y}(t) = k(1 - y(t)) \tag{10}$$

The solution of the equation (10) is:

$$y(t) = 1 - \exp - kt \tag{11}$$

which corresponds to a hyperbolic curve describing non-cooperative relaxation kinetics.

On the other hand for $k_1 \ll k_2$, the differential equation (9) reduces to a second order expansion of $y(t)$, namely:

$$\dot{y} = k_2\, y(t)\, (1 - y(t)) \tag{12}$$

The solution of the above differential equation corresponds to the well known Verhulst «logistic equation» [6]:

$$y(t) = \frac{1}{1 - a \exp - k_2 t} \tag{13}$$

where a is an integration constant of (12).

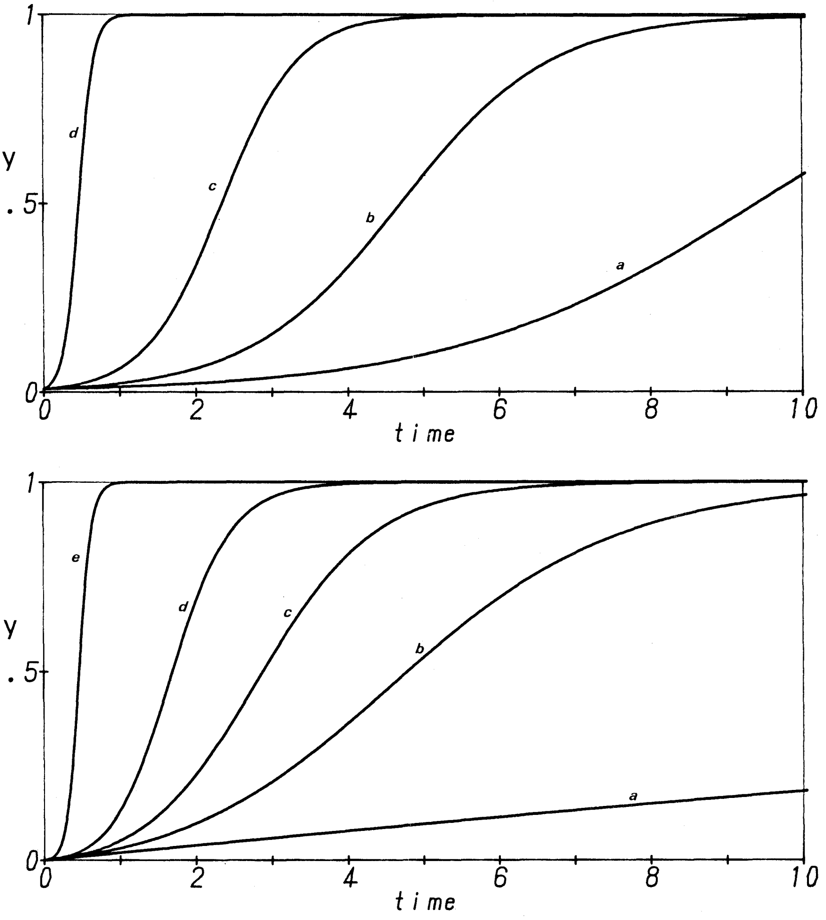

Fig. 2. – Plots of $y(t)$ according to eq. (1*c*) for $K_1 = \text{const} = 2 \cdot 10^{-2}$ and different values of K_2 (*a*: $K_2 = 2 \cdot 10^{-2}$, *b*: $K_2 = 0.5$, *c*: $K_3 = 1$, *d*: $K_4 = 2$, *e*: $K_2 = 10$. (fig. 2*a*). Plots of the Verhulst equation (13) calculated for $a = 110$ and different values of K2 (*a*: $K_2 = 2$, *b*: K_2 1, *c*: $K_2 = 0.5$, *d*: $K = 0.2$) (fig. 2*b*). Notice the similarities between the curves *e*) in fig. 2*a* and *d*) in fig. 2*b*.

This shows that, in contrast to the Verhulst equation, our relaxation kinetics offer a greater flexibility in so far as they can bridge the gap from non cooperative to highly cooperative phenomena, as shown in fig. 2*a, b,* simply by a continual variation of parameters.

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NOTE ADDED IN PROOF

Liquori-Tripiciano equation has been more recently employed with considerable success in studies on the kinetic expression of «Heat shock proteins» [1] and on the temporal evolution of AIDS manifestation in a HIV infected individuals [2].

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