

MONOD'S BACTERIAL GROWTH MODEL REVISITED

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An attempt to justify Monod's bacterial growth model is presented. The justification is based on a mechanistic approach to growth which leads to a differential equation with delay and then to Monod's model. An unexpected increase of parameter K_s with μ_m is predicted by the theory. A survey of literature shows that this effect is present in a large majority of published data.

Introduction. Monod's growth model (1941, 1949, 1950) was proposed as an empirical model to describe microbial growth. It differs from classical growth models, such as those proposed by Gompertz (1825), Verhulst (1845, 1847) or Richards (1959), because it introduces the concept of a *limiting nutrient*. A nutrient is said to be limiting when there is a causal relationship between its exhaustion and the end of growth. This deterministic aspect of Monod's model may be one of the reasons for its success.

The model defines the relation between the growth rate and the concentration of the limiting nutrient:

$$\frac{dx}{dt} = x \mu_m \frac{s}{K_s + s} \quad (1)$$

where x is the microbial concentration (shortly the biomass) at time t , s is the limiting nutrient (or substrate) concentration at time t , μ_m is the maximum specific growth rate, and K_s is the substrate concentration which supports half-maximum specific growth rate. Units for biomass and substrate are of various kinds, depending on the way growth is measured (Harris and Kell, 1985). The important features of the model are that the growth rate is zero when there is no substrate and tends to an upper limit when the substrate is in great excess, the link between these two extreme conditions being described by a rectangular hyperbola.

This work is an attempt to justify Monod's model from a mechanistic point of view. First this attempt is presented and the unexpected prediction made that an increase of parameter K_s with μ_m should be observed. Secondly we

present arguments supporting the theory with a reconsideration of published data, and then a discussion of the biological significance of parameters.

Theory. Consider that microbial cells and substrate are subject to Brownian motion so that they are randomly moving in the medium and from time to time came into collision. In idealized conditions it follows that the rate of growth is proportional to the product of biomass and substrate concentration:

$$\frac{dx}{dt} = kxs \quad (2)$$

where k is analogous to the rate constant of a chemical reaction. Note, however, that we are not dealing with a chemical reaction because biomass is not a chemically defined compound. This is the reason for requiring idealized conditions which are: that biomass composition is constant; that the contribution of substrate to biomass formation is constant; and that the ratio, surface/volume, for microbial cells is constant at a population level.

The differential equation (2) corresponds to the well-known logistic equation (Verhulst, 1845, 1848). The logistic model has been used extensively for description of the growth of various biological materials. Although it was created by Verhulst for human population growth modelling, and even rediscovered by Pearl and Reed (1920) for the same purpose, some applications to microbial growth have also been published (Richards, 1928; Mitsuhashi and Takeuchi, 1951; Jason, 1983; Corman *et al.*, 1986; Gibson *et al.*, 1987; Morrison *et al.*, 1987; Comby *et al.*, 1988; Rochet and Flandrois, 1989; Gould *et al.*, 1989; Zwietering *et al.*, 1990). The essence of the logistic law is that the growth rate is assumed to be proportional to the concentration of something that is being used up as the population grows. When the limiting substrate concentration is low, the logistic growth is a perfectly acceptable approximation.

The problem with equation (2) is that the growth rate can be increased indefinitely by increasing the substrate concentration. This is quite an undesirable property since it is well established that the growth rate cannot exceed a certain limit. We must then modify equation (2) to take into account this upper limit.

The main object of this paper is the consideration that the substrate-to-biomass conversion is not instantaneous. What happens after the substrate has penetrated into a microbial cell is very complex: thousands of different specific catalysed reactions and thousands of intermediary compounds are involved (Neidhart *et al.*, 1987). It seems then quite rational, from a biological point of view, to take into account this notion of a delay for biomass production. Therefore, a delay in biomass x is introduced, so that we obtain a differential equation with a discrete lag time:

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$$\frac{dx}{dt} = kx(t-\tau)s \quad (3)$$

where τ is the lag time for biomass production. Note that we have introduced a lag time in one variable only because there is a delay for biomass production and not for substrate consumption.

Differential equations with delay are an interesting tool because lags are omnipresent in biology (MacDonald, 1978). The problem is that these equations are not convenient to handle, and only few general results are available. This is the reason why we are going to transform equation (3) in the form of an ordinary differential equation. For this we use an approximation which consists of a Taylor expansion to express $x(t-\tau)$ as function of $x(t)$:

$$x(t-\tau) \approx x(t) - \tau \frac{dx}{dt} \quad (4)$$

With a simple combination of equations (3) and (4) we obtain:

$$\frac{dx}{dt} \approx \frac{1}{\tau} x \frac{s}{\frac{1}{k\tau} + s} \quad (5)$$

which is in fact Monod's model as defined by equation (1) provided that we have:

$$\begin{cases} \mu_m = \frac{1}{\tau} \\ K_s = \frac{1}{k\tau} = \frac{\mu_m}{k} \end{cases} \quad (6)$$

From examination of equation (6) an apparent linear increase of parameter K_s is expected to occur with parameter μ_m .

Summary and conclusions. As Monod's model is very popular we have been able to find published data where the parameter K_s has been estimated for different μ_m values. An apparent increase of K_s with μ_m is present in data published by Knowles *et al.* (1965), Caperon (1967), Jones and Hough (1970), Shelef *et al.* (1970), Muck and Grady (1974), Endo and Mochizuki (1979), Senft *et al.* (1981), Mechling and Kilham (1982), Tilman *et al.* (1982), Billen (1984), Itoh and Takahashi (1984), Simkins *et al.* (1986) and Billen and Servais (1989). An isolated decrease of K_s with μ_m is observed by Topiwala and Sinclair (1971).

A point that must be underlined is that parameter estimates are almost

always reported without an indication of their confidence regions. As a consequence, it is not possible to say whether the differences between parameter values are significant or not. We have then to be very cautious in interpreting the apparent increase of K_s with μ_m . It is not possible to consider that the expected relationship is experimentally assessed.

In conclusion, we can summarize the biological significance of parameters as follows. The growth of a microbial population, for a given culture condition set, is characterized by parameters μ_m and K_s . The interpretation of μ_m is straightforward. From equation (6) μ_m is inversely related to the lag time which is required to transform substrate into biomass. When this lag is short, the growth is fast in the presence of an excess of substrate. The biological significance of parameter K_s is less obvious. By analogy with Briggs and Haldane's (1925) justification of Michaelis-Menten's (1913) model for enzyme kinetics, the ratio $1/K_s$ is sometimes interpreted as a reflection of an intrinsic affinity of bacteria for the substrate. This seems dubious since K_s values may vary with μ_m . Healey's proposal (1980) to take the ratio μ_m/K_s as an indicator of advantage in nutrient competition at low nutrient concentration is more consistent with our results. From equation (6) the ratio μ_m/K_s is in fact the rate constant k , and then represents the competitiveness of a microbial population at low substrate concentration: the greater k is, the better the population grows at low concentrations of limiting nutrient. Thus, Healey's ratio is especially relevant to characterize microbial populations because in natural ecosystems limiting nutrient concentrations are very low.

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