

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/226070591>

# Monod's bacterial growth model revised

Article in Bulletin of Mathematical Biology · January 1992

DOI: 10.1007/BF02458623

CITATIONS

98

READS

6,442

4 authors, including:



Jean Lobry

Claude Bernard University Lyon 1

81 PUBLICATIONS 6,052 CITATIONS

[SEE PROFILE](#)



Alain Pave

Claude Bernard University Lyon 1

116 PUBLICATIONS 1,596 CITATIONS

[SEE PROFILE](#)

## MONOD'S BACTERIAL GROWTH MODEL REVISITED

■ J. R. LOBRY, J. P. FLANDROIS, G. CARRET and A. PAVE  
CNRS URA 243,  
Laboratoire de Biométrie,  
Université Claude Bernard,  
43 Boulevard du 11 Novembre,  
69622 Villeurbanne, France  
(E-mail: DYNBACT@FRCISM51-(EARN))

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  $\mu_m$  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  $t$ ,  $\mu_m$  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  $\mu_m$  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:



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

where  $\tau$  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  $\mu_m$ .

**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  $\mu_m$  values. An apparent increase of  $K_s$  with  $\mu_m$  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  $\mu_m$  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  $\mu_m$ . 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  $\mu_m$  and  $K_s$ . The interpretation of  $\mu_m$  is straightforward. From equation (6)  $\mu_m$  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  $\mu_m$ . Healey's proposal (1980) to take the ratio  $\mu_m/K_s$  as an indicator of advantage in nutrient competition at low nutrient concentration is more consistent with our results. From equation (6) the ratio  $\mu_m/K_s$  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.

This work was supported in part by a grant from API-SYSTEM, BioMérieux, to J. R. Lobry. Constructive suggestions were received from referees.

## LITERATURE

- Billen, G. 1984. Heterotrophic utilization and regeneration of nitrogen. In *Heterotrophic Activity in the Sea*, J. E. Hobbie and P. J. L. Williams (eds), pp. 313-355. New York: Plenum Press.
- Billen, G. and P. Servais, 1989. Modélisation des processus de dégradation bactérienne de la matière organique en milieu aquatique. In *Micro-organismes dans les Écosystèmes Océaniques*, M. Bianchi, D. Marty, P. Caumette, J. C. Bertrand and M. Gauthier (eds), pp. 219-245. Paris: Masson.
- Briggs, G. E. and J. B. S. Haldane. 1925. A note on the kinetics of enzyme action. *Biochem. J.* **19**, 338-339.
- Caperon, J. 1967. Population growth in micro-organisms limited by food supply. *Ecology* **48**, 715-722.
- Comby, S., J. P. Flandrois, G. Carret and C. Pichat. 1988. Mathematical modelling of bacterial growth at subinhibitory levels of aminoglycosides. *Annls Inst. Pasteur/Microbiol.* **139**, 613-629.
- Corman, A., G. Carret, A. Pavé, J. P. Flandrois and C. Couix. 1986. Bacterial growth measurement using an automated system: mathematical modelling and analysis of growth kinetics. *Annls Inst. Pasteur/Microbiol.* **137B**, 133-143.
- Endo, K. and T. Mochizuki. 1979. Relation between specific growth rate of rotifer, *Brachionus*





- plicatilis*, and concentration of food, marine species of *Chlorella*. *J. Ferment. Technol.* **57**, 372-374.
- Gibson, A. M., N. Bratchell and T. A. Roberts. 1987. The effect of sodium chloride and temperature on the rate and extent of growth of *Clostridium botulinum* type A in pasteurized pork slurry. *J. appl. Bacteriol.* **62**, 479-490.
- Gompertz, B. 1825. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Phil. Trans. R. Soc. Lond.* **115**, 513-585.
- Gould, I. M., A. C. Jason and K. Milne. 1989. Use of the Malthus microbial growth analyser to study the post antibiotic effect of antibiotics. *J. Antimicrob. Chemother.* **24**, 523-531.
- Harris, C. M. and D. B. Kell. 1985. The estimation of microbial biomass. *Biosensors* **1**, 17-84.
- Healey, F. P. 1980. Slope of the Monod equation as an indicator of advantage in nutrient competition. *Microb. Ecol.* **5**, 281-286.
- Itoh, S. and K. Takahashi. 1984. Calorimetric studies of microbial growth: kinetic analysis of growth thermograms observed for Bakery Yeast at various temperature. *Agric. Biol. Chem.* **48**, 271-275.
- Jason, A. C. 1983. A deterministic model for monophasic growth of batch cultures of bacteria. *Antonie van Leeuwenhoek* **49**, 513-536.
- Jones, R. C. and J. S. Hough. 1970. The effect of temperature on the metabolism of Baker's Yeast growing on continuous culture. *J. gen. Microbiol.* **60**, 107-116.
- Knowles, G., A. L. Downing and M. J. Barrett. 1965. Determination of kinetic constants for nitrifying bacteria in mixed culture, with the aid of an electronic computer. *J. gen. Microbiol.* **38**, 263-278.
- MacDonald, N. 1978. Time lags in biological models. *Lect. Notes Biomath.* **27**, 1-112.
- Mechling, J. A. and S. S. Kilham. 1982. Temperature effects on silicon limited growth of the lake Michigan diatom *Stephanodiscus minutus* (Bacillariophyceae). *J. Phycol.* **18**, 199-205.
- Michaelis, L. and M. L. Menten. 1913. Die Kinetik der Invertinwirkung. *Biochem. Z.* **49**, 334-369.
- Mitsuhashi, S. and S. Takeuchi. 1951. On the bacterial growth by shaking culture method. *Jap. J. exp. Med.* **21**, 1-5.
- Monod, J. 1941. *Recherches sur la croissance des cultures bactériennes*. Thèse de docteur ès sciences naturelles, Paris.
- Monod, J. 1949. The growth of bacterial cultures. *A. Rev. Microbiol.* **3**, 371-394.
- Monod, J. 1950. La technique de culture continue: théorie et applications. *Annls Inst. Pasteur* **79**, 390-410.
- Morrison, K. A., N. Thérien and B. Marcos. 1987. Comparison of six models for nutrient limitations on phytoplankton growth. *Can. J. Fish. aquat. Sci.* **44**, 1278-1288.
- Muck, R. E. and C. P. L. Grady. 1974. Temperature effects on microbial growth in CSTR's. *J. environ. Engng Div.* **100**, 1147-1163.
- Neidhardt, F. C., J. L. Ingraham, K. B. Low, B. Magasanik, M. Schaechter and H. E. Umbarger (eds). 1987. *Escherichia coli and Salmonella typhimurium, cellular and molecular biology*, Vol. 1, pp. 127-806. Washington: Library of Congress.
- Pearl, R. and L. J. Reed. 1920. On the rate of growth of the population of the United States since 1790 and its mathematical representation. *Proc. natn. Acad. Sci. U.S.A.* **6**, 275-288.
- Richards, O. W. 1928. The growth of the yeast *Saccharomyces cerevisiae* I. The growth curve, its mathematical analysis, and the effect of temperature on the yeast growth. *Annls Bot.* **42**, 271-283.
- Richards, F. J. 1959. A flexible growth function for empirical use. *J. exp. Bot.* **10**, 290-300.
- Rochet, M. J. and J. P. Flandrois. 1989. Bacterial strain characterization using mathematical modelling of growth. *Zbl. Bakt.* **271**, 2-10.
- Senft, W. H., R. A. Hunchberger and K. E. Roberts. 1981. Temperature dependance of growth and phosphorus uptake in two species of *Volvox* (Volvocales, Chlorophyta). *J. Phycol.* **17**, 323-329.
- Shelef, G., W. J. Oswald and C. C. Golueke. 1970. Assaying algal growth with respect to nitrate concentration by a continuous flow turbidostat. *Proc. Int. Conf. Water Pollut. Res.* **3**, 1-9.



- Simkins, S., R. Mukherjee and M. Alexander. 1986. Two approaches to modeling kinetics of biodegradation by growing cells and application of a two-compartment model for mineralization kinetics in sewage. *Appl. environ. Microbiol.* **51**, 1153–1160.
- Tilman, D., S. S. Kilham and P. Kilham. 1982. Phytoplankton community ecology: the role of limiting nutrients. *Ann. Rev. ecol. Syst.* **13**, 349–372.
- Topiwala, H. and C. G. Sinclair. 1971. Temperature relationship in continuous culture. *Biotech. Bioeng.* **13**, 795–813.
- Verhulst, P. F. 1845. Recherches mathématiques sur la loi d'accroissement de la population. *Mém. Acad. r. Sci. Lett. Belg.* **18**, 1–38.
- Verhulst, P. F. 1847. Deuxième mémoire sur la loi d'accroissement de la population. *Mém. Acad. r. Sci. Lett. Belg.* **20**, 1–32.
- Zwietering, M. H., I. Jongenburger, F. M. Rombouts and K. Van't Riet. 1990. Modeling of the bacterial growth curve. *Appl. environ. Microbiol.* **56**, 1875–1881.

Received 15 July 1990  
Revised 3 October 1990

