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Minimal models of growth and decline of microbial populations

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Abstract

Dynamics of growth and decline of microbial populations were analyzed and respective models were developed in this investigation. Analysis of the dynamics was based on general considerations concerning the main properties of microorganisms and their interactions with the environment which was supposed to be affected by the activity of the population. Those considerations were expressed mathematically by differential equations or systems of the equations containing minimal sets of parameters characterizing those properties. It has been found that: 1) the factors leading to the decline of the population have to be considered separately, namely, accumulation of metabolites (toxins) in the medium and the exhaustion of resources; the latter have to be separated again into renewable ('building materials') and non-renewable (sources of energy); 2) decline of the population is caused by the exhaustion of sources of energy but no decline is predicted by the model because of the exhaustion of renewable resources; 3) the model determined by the accumulation of metabolites (toxins) in the medium does not suggest the existence of a separate 'stationary phase'; 4) in the model determined by the exhaustion of energy resources the 'stationary' and 'decline' phases are quite discernible; 5) there is no symmetry in microbial population dynamics, the decline being slower than the rise. Mathematical models are expected to be useful in getting insight into the process of control of the dynamics of microbial populations. The models are in agreement with experimental data.

Keywords: Population dynamics; Stationary phase; *Campylobacter jejuni*; *Escherichia coli*; *Kluyveromyces marxianus*

1. Introduction

When a population of microorganisms grows for long enough, it is likely to pass over all the phases of growth: when the rate of cell division prevails over that of their death, when both the rate of cell division and their death are equal, and the rate of death prevails over that of their division. The growth may follow a lag, if the environmental conditions before the beginning of the growth are unfavourable. Under favourable conditions the growth for some time may be considered to be unlimited (hence exponential), then the limits have to be taken into account, leading to decrease in the growth rate resulting in decline of the population size upon reaching a maximum.

Microbiologists usually consider four phases of growth: the lag, log, stationary, and death phases (Tortora et al., 2004). The growth is supposed to be limited by one of three factors: 1. exhaustion of available nutrients; 2. accumulation of inhibitory metabolites or end products; 3. exhaustion of space, in this case called a lack of "biological space". (Todar, 2005, <http://www.textbookofbacteriology.net/>). The "carbon sources" (see, e.g., (Narang, 2006)) sometimes are indicated specifically as the nutrients assumed to be used for energy generation by oxidation to CO₂.

It is clear that the rate of growth depends on the conditions of the environment which may change as a result of the activity of the population itself. The microorganisms along with the consumption of the nutrients (which are being exhausted) produce various substances including toxins, quorum sensing molecules (QSM, see, e.g. (Maddula et al., 2006; Jayaraman and Wood, 2008; Kruppa, 2009) and pheromones (which accumulate in the environment). Changes in the environment may cause a variety of physiological adaptation processes by which energy-converting subsystems of the cell are reconstructed and the whole metabolism

is affected. Models of the dynamics of growth and decline, therefore, have to take into account these dependencies.

The known models of the dynamics of microbial populations are mostly specialized. Those concerning the diauxie are reviewed by Narang (2006). The declining phase of the dynamics is not considered in these models. Both growth and decline phases are covered by quasi-chemical model in which the death of cells is supposed to be accelerated by quorum sensing molecules (see e.g., Doona et al., 2005). The model cannot be expressed analytically, and for the solution of respective ODE MATLAB software was used. Other factors (beyond quorum sensing) causing the decline in population dynamics are not considered in this paper.

The models concerning the therapy deal mostly with the reactions of microbial or viral populations to various drugs, antibiotics or mutagens (Lipsitch and Levin, 1997; Beaumont, 2003; Bull and Wilke, 2005; Handel et al., 2009) applied externally to the populations and changing their environment. These models, as a consequence, are not applicable for investigation of population dynamics in environment depending only on the activity of the population itself.

Mathematical modelling of the behaviour of the whole system is expected to be useful in getting insight into the process of control of the dynamics of microbial populations. The objective of this study, therefore, is to model the dynamics in environment affected by the activity of the population. The parameters introduced correspond to the factors affecting the dynamics and have biological meaning.

2. General considerations and supposed relationships

As long as growth of the population is not affected by changes in the environment, the rate of growth is supposed to be proportional to the population size, x , i. e.

$$\frac{dx}{dt} = \alpha x \quad (1)$$

where α is coefficient of proportionality or relative growth rate which is supposed to be comprised of rate of ‘birth’ of the cells and that of their ‘death’. The death rate may be supposed to be proportional to concentration of metabolites (toxins), y , in the medium making the relative growth rate

$$\alpha - \kappa y \quad (2)$$

where κ is coefficient of proportionality. The metabolites accumulate as a result of biological activity of the population,

$$y = \lambda \int_0^t x \, du \quad (3)$$

where λ is coefficient of proportionality of the accumulation. Growth rate depends also on the resources available. The renewable resources (‘building materials’) may be supposed to be consumed proportionally to the population size, and the remaining resources to be (see, e. g., (Juška et al., 2006))

$$\left(1 - \frac{x}{B}\right) \quad (4)$$

$1/B$ being coefficient of proportionality of the consumption. To account for the effect of exhaustion of the non-renewable (energy) resources on the growth rate, a variable z ($z \leq 1$) can be introduced, assuming

$$z = 1 - \mu \int_0^t x \, du \quad (5)$$

where μ is coefficient of proportionality. It should be noted that the variable z does not mean concentration of a substance (along with being positive, it can be negative as well; see below): it is just a function of the resources which are used to produce the energy.

Taking into account possible lag of the population growth determined by the ‘awakening’ of the ‘dormant’ cels upon inoculation, one more multiplier $(1 - \exp(-\beta t))$

has to be introduced, β being relative rate of the awakening (Juška et al., 2006) (in the simplest case the awakening can be considered to consist of a single step).

3. Modelling and model fitting

The models developed here are intended to simulate the dynamics of growth and decline of microbial populations rather than to provide a basis for fitting to experimental data. The data are used to illustrate the models. Most available data suggesting the decline are rather scarce and poor, not allowing discrimination or identifying the factors causing the decline.

The following system of equations takes into account the above assumptions and equations:

$$\begin{cases} \frac{dx}{dt} = \left[\alpha \left(1 - \frac{x}{B} \right) (1 - \exp(-\beta t)) z - \kappa y \right] x, \\ y = \lambda \int_0^t x \, du, \\ z = 1 - \mu \int_0^t x \, du. \end{cases} \quad (7)$$

The entire system, however, cannot be solved symbolically. Still, while comparing a model with experimental data, only specific conditions of the experiments have to be taken into account, and the system can be simplified. As long as effects of metabolite accumulation and depletion of energy resources can be ignored (or assumed that $\kappa = 0$ and $\mu = 0$), the system can be reduced to the equation of limited growth with a lag,

$$\frac{dx}{dt} = \alpha \left(1 - \frac{x}{B}\right) (1 - \exp(-\beta t)) x. \quad (8)$$

This equation can be solved symbolically. Its solution is presented in (Juška et al., 2006); the model is also depicted in Figs. 1B and 1C for reference. This model does not take into account the decline in the population size, but for a short time interval is quite acceptable (see the figure).

When the decline in population size is caused by metabolite accumulation (the lag and depletion of energy resources being ignored, i. e. $\beta \rightarrow \infty$, $\mu = 0$), System (7) results in

$$\begin{cases} \frac{dx}{dt} = \left[\alpha \left(1 - \frac{x}{B}\right) - \kappa y \right] x, \\ \frac{dy}{dt} = \lambda x. \end{cases} \quad (9)$$

Numerical solutions of System (9) under initial conditions $x(0) = X$ (initial size of the population or inoculation size) and $y(0) = 0$ (absence of metabolites initially) are depicted in Fig. 1. This model was fitted to experimental data of Wright et al. (2009) (Fig. 2). The data were taken from the PDF file by digitizing Figs. 1 and 7. The data suggest the absence of ‘stationary phase’, the dynamics being asymmetric (the decline being much slower than the rise); the illustration, therefore, seems to be justified. Parameter estimates obtained as a result of model fitting are presented in Table 1.

When the decline in the population size is caused by depletion of energy resources ($\kappa = 0$ and $\beta \rightarrow \infty$), System (7) is reduced to

$$\begin{cases} \frac{dx}{dt} = \alpha \left(1 - \frac{x}{B}\right) xz, \\ \frac{dz}{dt} = -\mu x. \end{cases} \quad (10)$$

Numerical solution of System (10) with respect to x under initial conditions $x(0) = X$ and $z(0) = 1$ are presented in Fig. 3. A ‘stationary’ (not being quite constant) phase followed by the ‘death phase’ are quite clear in this case. This model was fitted to experimental data taken from (Yu et al., 2006) (Fig.4). Parameter estimates obtained as a result of model fitting are presented in Table 2.

4. Discussion, model modifications and further fitting

The agreement of the model (System (9)) with experimental data (Fig. 2) suggests both the initial assumptions to be quite acceptable and there being no ‘stationary phase’ different from the ‘death phase’: population size declines immediately upon reaching a maximum. Those assumptions, as mentioned above, are very simple: proportionality of metabolite accumulation to the integral of population size and that of cell death on metabolite concentration. The latter proportionality holds true if the concentration is far below the equilibrium dissociation constant of the metabolite molecule and the target macromolecule of the cell. The non-proportionality, if any, would slow down rather than accelerate the decline of the population size, suggesting no further ‘phase’ of the decline. Experimental data, however, are rather scarce for more definite conclusions. Of course the decline in the size because of metabolite accumulation involves quite a few different metabolites, their targets being numerous as well, and the effects of the metabolites ranging from a slight inhibition of activity to complete block of vital elements (macromolecules) of the cell. Still the process seems to be determined by inhibition of the activity of the vital macromolecules by the metabolites. The model contains four independent parameters, the shape of the growth curve being determined by three parameters, the fourth one determining the shift of the curve (see Table 1).

The the model determined by the exhaustion of energy resources (System (10)) contains four independent parameters as well, their role being similar as above. Comparison of the

model with experimental data (Fig. 4, dotted curve) means the initial assumptions to be acceptable, though insufficient. This model is essentially different from that determined by the accumulation of metabolites (cf. Fig. 3 and Fig. 1). While in System (9) the initial quantity of metabolites was supposed to be 0, in System (10) the energy function was supposed $z(0) = 1$. Still whereas the model suggests a symmetry, the data point out to its absence. To facilitate the analysis, it seems reasonable to simplify the system. Under assumption that $B \rightarrow \infty$ (limits of growth caused by limits of renewable resources being ignored) System (10) is reduced to

$$\begin{cases} \frac{dx}{dt} = \alpha xz, \\ \frac{dz}{dt} = -\mu x \end{cases} \quad (11)$$

whose solutions under initial conditions $x(0) = X$ and $z(0) = 1$ are

$$x = \left\{ 1 - \tanh^2 \left[\left(t - \frac{\operatorname{arctanh} \left(\frac{\alpha}{\sqrt{\alpha(\alpha + 2X\mu)}} \right)}{\sqrt{\alpha(\alpha + 2X\mu)}} \right) \frac{\sqrt{\alpha(\alpha + 2X\mu)}}{2} \right] \right\} \frac{\alpha + 2X\mu}{2\mu} \quad (12)$$

and

$$z = \tanh \left[\operatorname{arctanh} \left(\frac{\alpha}{\sqrt{\alpha(\alpha + 2X\mu)}} \right) - \frac{t\sqrt{\alpha(\alpha + 2X\mu)}}{2} \right] \frac{\sqrt{\alpha(\alpha + 2X\mu)}}{\alpha} \quad (13)$$

It is clear that equations (12) and (13) depend only on three parameters. It can be seen as well that function (12) is even (mirror-symmetric), and (13) is odd (rotationally symmetric) with respect to the point T at which $z = 0$ or x is maximal (see Appendix A). Indeed, since $\tanh(-a) = -\tanh(a)$, $x(-\tau) = x(\tau)$ and $z(-\tau) = -z(\tau)$ for $\tau = t + T$. The symmetry holds true for the solutions of Systems (9) and (10) (Figs. 1 and 3).

Models (12) and (13) are depicted in Fig. 5. The symmetry means the decline of the curves being similar to the rise. It follows that the ratio μ/α being constant, the extent of the curves along the time axis is determined by parameter α (see Fig. 5A), and the height, by parameter μ for $\alpha = \text{const}$ (see Fig. 5B). Accordingly, $B \rightarrow \infty$ means $B \gg \mu/\alpha$. The shift of the curves along the time axis is determined by the initial size of the population, X , but depends also on the relative rate of growth, α (cf. Figs. 5A and 5C). That is related to the accuracy of model fitting to the data. Model (12) was fitted to experimental data of Tovar-Castro et al. (2008) (Fig. 6, dotted line). The model is acceptable in an interval of time, but its descending limb deviates considerably from the data suggesting a slower decline of the population. The decline is determined, presumably, by (remaining? alternative?) energy resources which in the experimental population seem to be exhausted not so fast as in the model. The cells are known to use for their activity not only the “carbon sources” but other compounds as well when needed.

As seen from Eq. (13) and Fig. 5C, function z , along with positive, acquires also negative values (since z is symmetric, its negative branch needs not to be shown in Fig. 5C), and its interpretation remains rather vague, though it is clear, that z reflects the consumption of ‘carbon sources’. The exponential function of z , $\exp(z - 1)$, however, is positive; there is good reason, therefore, to believe that it could reflect the energetic state of the cell taking into account all the available resources. The 1st equation of System (11) was modified, therefore, by a new function containing one more parameter resulting in

$$\frac{dx}{dt} = \alpha x z \exp(\zeta(z - 1)) \quad (14)$$

where parameter ζ takes into account the use of non-saccharide energy resources. It should be noted that the multiplier with αx in the above equation has to retain the possibility to acquire both positive and negative values (to make possible the decline) and for this reason z in

Eq. (14) is retained. Besides, while biological meaning of the variable z remains rather vague, the meaning of parameter ζ , as pointed out above, is clear. The fitting was acceptable in the case of decline in *E. coli* population (Fig. 4) and considerably improved by the modification in the case of *K. marxianus* (not shown) but further improvement was necessary. Further modification led to

$$\begin{cases} \frac{dx}{dt} = \alpha xz \exp(\zeta(z^3 - 1)), \\ \frac{dz}{dt} = -\mu x \end{cases} \quad (15)$$

Numerical solutions of System (15) under initial conditions $x(0) = X$ and $z(0) = 1$ are depicted in Figs. 5D–5F. The model is in agreement with the data presented in Fig. 6. Parameter estimates obtained as a result of model fitting are presented in Table 3. It should be kept in mind, however, that death rate (μ) and scale factor (A) are correlated and, therefore, cannot be estimated reliably. Still that is quite acceptable. Carbon dioxide production, e.g., can be easily calculated, using the above model. Indeed, the quantity of the dioxide produced, c , should be proportional to the integral of the quantity of microorganisms, x , or

$$c = A \int_0^t x \, du \quad (16)$$

or (see Eq. (5))

$$c = (1 - z) \frac{A}{\mu}. \quad (17)$$

It is clear that in realistic situation when not only the ‘carbon sources’ are used for energy generation, $c < 2A/\mu$ since $-1 < z < 1$ (see Eq. (5) and take into account the symmetry). The

modifications above are justified *mathematically* and the model using them is supported by experimental data (improving the fitting); they should, however, be considered empirical. Indeed, the metabolism of proteins and amino acids for energy generation is not expected to be a simple process. It does not seem possible to suggest any reasonable mechanism of control of this process keeping in mind the scarcity of available experimental data.

No additional assumption beyond those considered in section 2 were used in Models (9) – (13). Besides, in simplified models, retaining only the parameter corresponding to the factor responsible for the decline, allows to avoid factor interference, or, in mathematical terms, parameter correlation. The models, therefore, are minimal. A model can be considered minimal if no essential change of the dynamics results from addition of an extra parameter. Removal of a parameter, in contrast, results in essential change of the dynamics or destruction of the model. All the parameters of the models presented have biological meaning.

Exhaustion of space (see (Todar, 2005)) is related to high population density. The density is considered to be controlled by quorum sensing mechanism (Lazazzera, 2000; Swift et al., 2001; Jayaraman, A. and Wood, 2008). Asymptotic size of the population which is related to the asymptotic density can be controlled by the resources available (see Juška et al., 2006). Control of population density involving quorum sensing (Lazazzera, 2000; Swift et al., 2001; Ward et al., 2001; Maddula et al., 2006) is not expected to be simple.

Appendix A

The moment corresponding to the maximum of function x (Eq. (12)) or to $z = 0$ (Eq. (13)) is

$$T = \arctanh\left(\frac{\alpha}{\sqrt{\alpha(\alpha + 2X\mu)}}\right) \frac{2}{\sqrt{\alpha(\alpha + 2X\mu)}} \quad (\text{A1})$$

Accordingly,

$$x = \left[1 - \tanh^2 \left(\frac{\tau \sqrt{\alpha(\alpha + 2X\mu)}}{2} \right) \right] \frac{\alpha + 2X\mu}{2\mu} \quad (\text{A2})$$

and

$$z = -\tanh \left(\frac{\tau \sqrt{\alpha(\alpha + 2X\mu)}}{2} \right) \frac{\sqrt{\alpha(\alpha + 2X\mu)}}{\alpha} \quad (\text{A3})$$

where $\tau = t + T$.

Appendix B. Supporting Information

Supplementary illustration associated with this article can be found in the online version at doi Please make sure to Enable Macros when opening the Supplement.xls file.

Conclusions

Analysis of the decline in microbial populations was based on general considerations concerning the main properties of microorganisms and their interactions with the environment. Those considerations were expressed mathematically by differential equations or systems of the equations containing minimal sets of parameters. The models developed here produce essentially different patterns of the dynamics (see Figs. 1, 3 and 5). If a researcher is trying to fit a model to the data, the choice of the model will be determined by the data set suggesting the most likely factor causing the decline. If the data set does not suggest any decline, then Verhulst (logistic) or Gompertz models should be taken.

1. The factors leading to the decline of the population have to be considered separately: accumulation of metabolites (toxins) in the medium and the exhaustion of resources which have to be separated again into renewable ('building materials') and non-renewable (sources of energy).

2. Exhaustion of the renewable resources does not cause decline in the size of the population while that of the non-renewable ones does.

3. The model determined by the accumulation of metabolites (toxins) in the medium does not suggest the existence of a separate 'stationary phase': the population declines immediately upon reaching a maximum.

4. In the model determined by the exhaustion of energy resources the 'stationary' and 'decline' phases are quite discernible.

5. There is no symmetry in microbial population dynamics, the decline being slower than the rise.

Accepted manuscript

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Figure legends

Fig. 1. Dynamics (numerical solutions of System (9) under initial conditions $x(0) = X$ and $y(0) = 0$) of growth and decline of bacterial population, the decline being caused by accumulation of metabolites; dynamics of limited growth ($\kappa = 0$) are also presented for reference. (A) Models of the population size for various values of the ‘asymptotic size’ of the model of limited growth. (B) Models for various values of the death rate caused by metabolite accumulation. (C) Models of the growth and decline and metabolite accumulation for two values of the death rate.

Fig. 2. Dynamics of growth and decline of four strains of *Campylobacter jejuni* populations cultured at 42 °C under microaerobic conditions. Experimental data points are taken from Figs. 1 and 7 from Wright et al. (2009). The lines correspond to Model (9) whose parameter estimates are presented in Table 1.

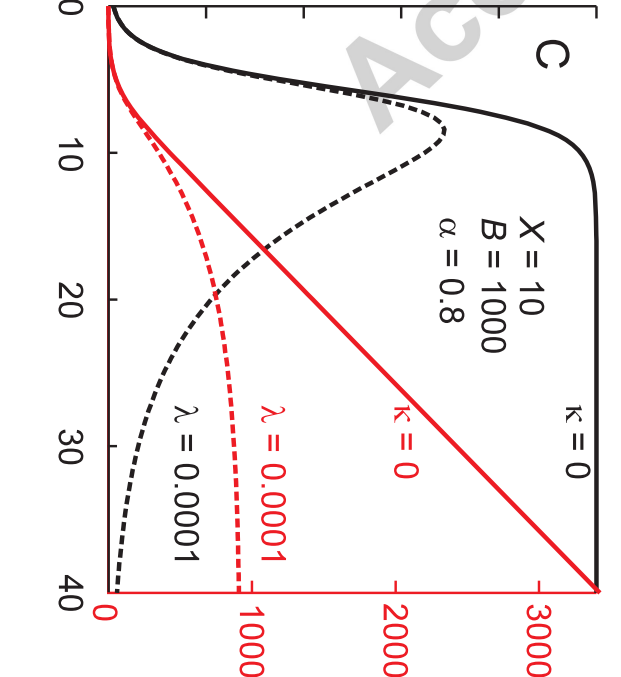
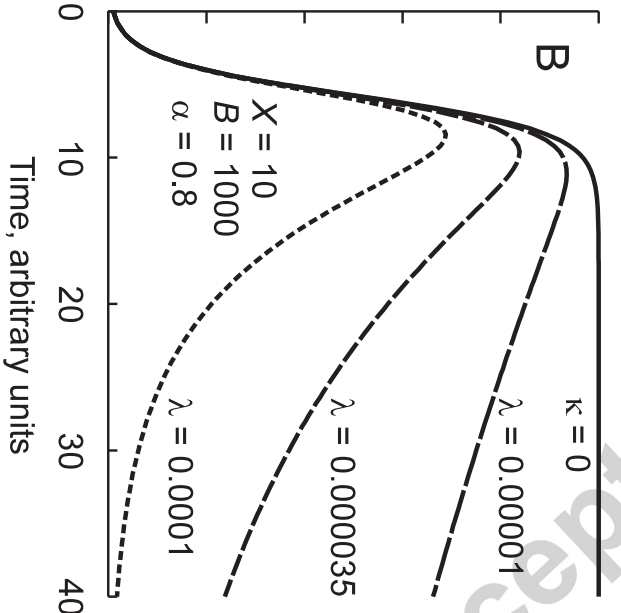
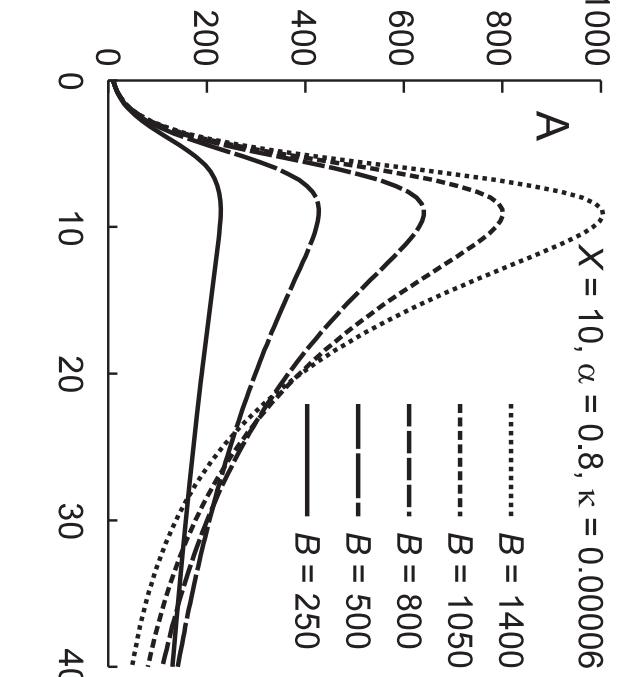
Fig. 3. Dynamics (numerical solutions of System (10) with respect to x under initial conditions $x(0) = X$ and $y(0) = 1$) of growth and decline of bacterial population, the decline being caused by exhaustion of energy resources; dynamics of growth and decline under assumptions that $B \rightarrow \infty$ and $x(0) = X$ and $z(0) = 1$ (Eq. (12)) are also presented for reference. (A) Models for various values of the death rate caused by exhaustion of energy resources. (B) Models for various values of the ‘asymptotic size’ of the model of limited growth. (C) Models of the growth and decline of the population for two values of the initial size, X , the ‘asymptotic size’ being infinite or finite.

Fig. 4. Dynamics of growth and decline of *Escherichia coli* population incubated in a shaker at 37 °C and 140 rev min⁻¹. Experimental data points are taken from Fig. 2 from Yu et al. (2006). The solid line corresponds to Model (10) modified by Eq. (14) whose parameter estimates are presented in Table 2. The dotted line corresponds to the unmodified model.

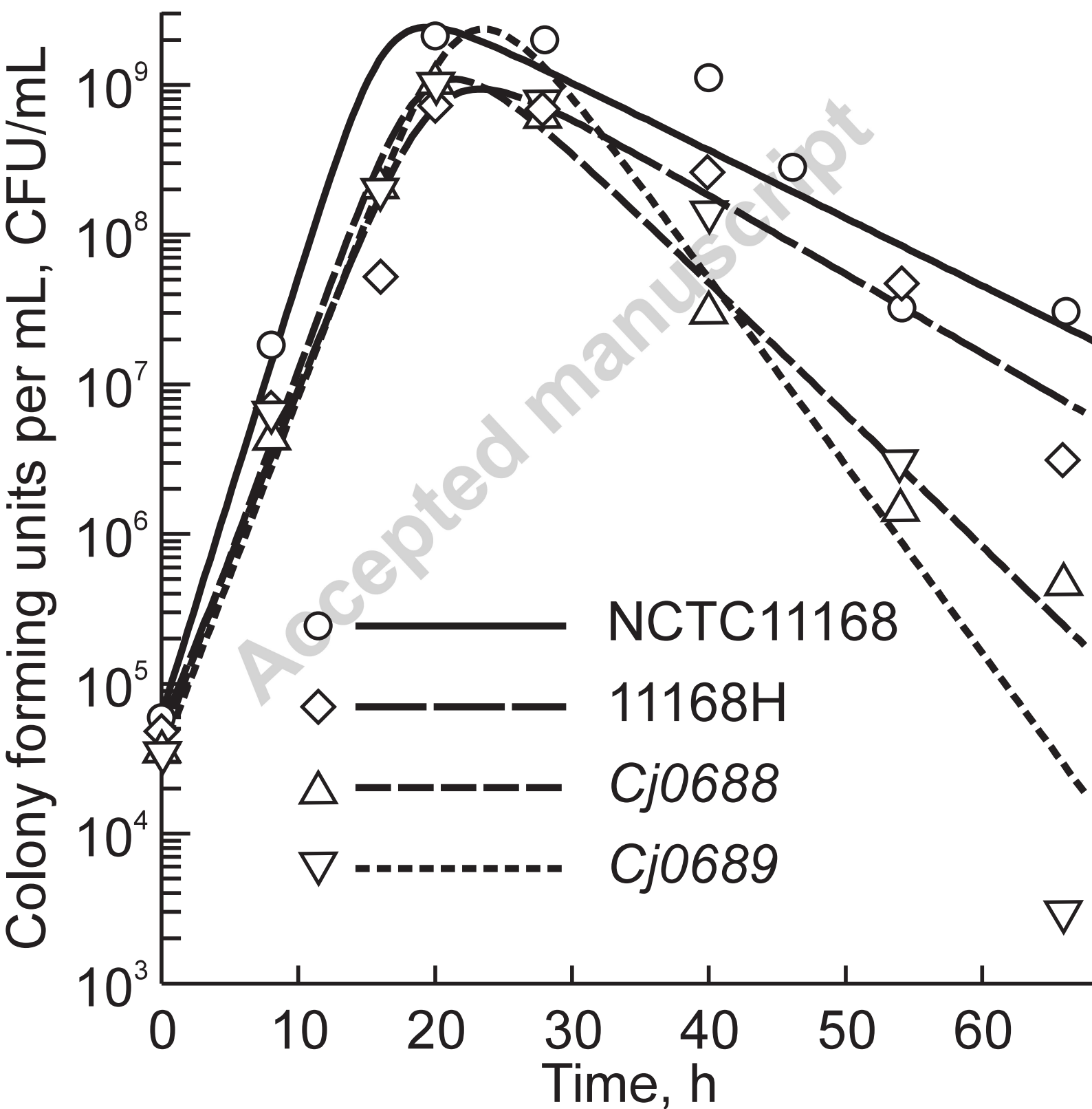
Fig. 5. Dynamics (Eqs. (12) and (13) (upper row) and solutions of System (15) (lower row) under initial conditions $x(0) = X$ and $y(0) = 1$ of growth and decline of microbial population, the decline being caused by exhaustion of energy resources. (A) Models for various initial sizes (X) of the population. (B) Models for various values of the death rate caused by exhaustion of energy resources. (C) Models of the size and two energy functions (see text for details). (D) Models for various values of the death rate caused by exhaustion of energy resources. (E) Models for various values of parameter ζ characterizing the use of non-saccharides as energy resources. (F) Models of the growth and decline and two energy functions (see text for details).

Fig. 6. Dynamics growth and decline of *Kluyveromyces marxianus* populations cultivated in solid-state medium, lactose being the only carbon source, at 30 °C. Experimental data points are taken from Fig. 2 from Tovar-Castro et al. (2008). The solid lines correspond to Model (15) whose parameter estimates are presented in Table 3. The dotted line corresponds to Eq. (12).

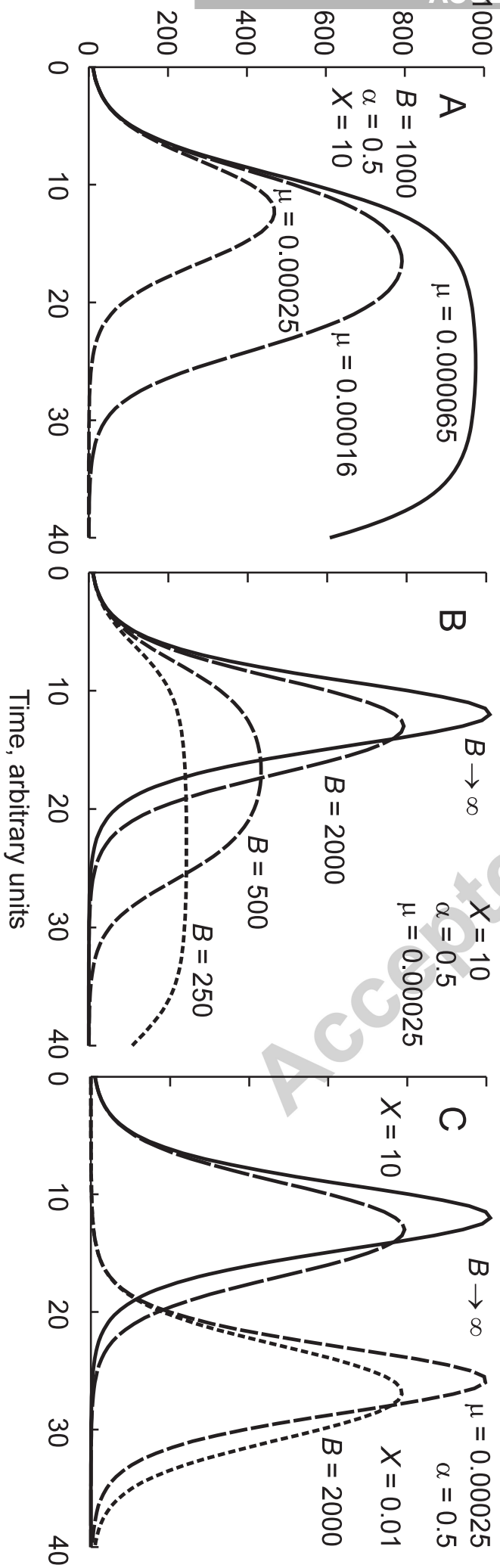
Abbreviations: gidm, initial dry matter; gwm, gramme of wet matter.

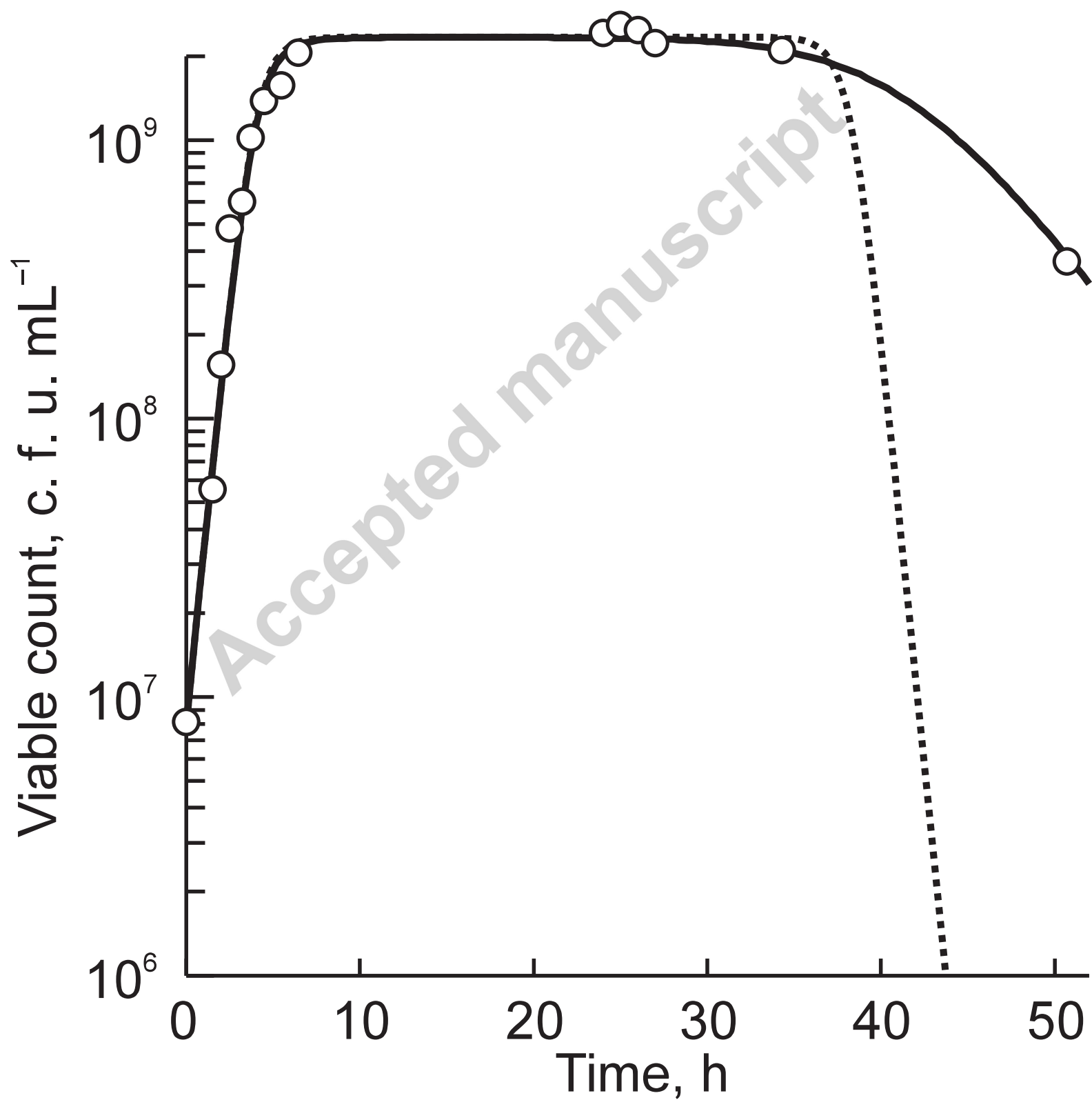


Metabolite concentration, arbitrary units

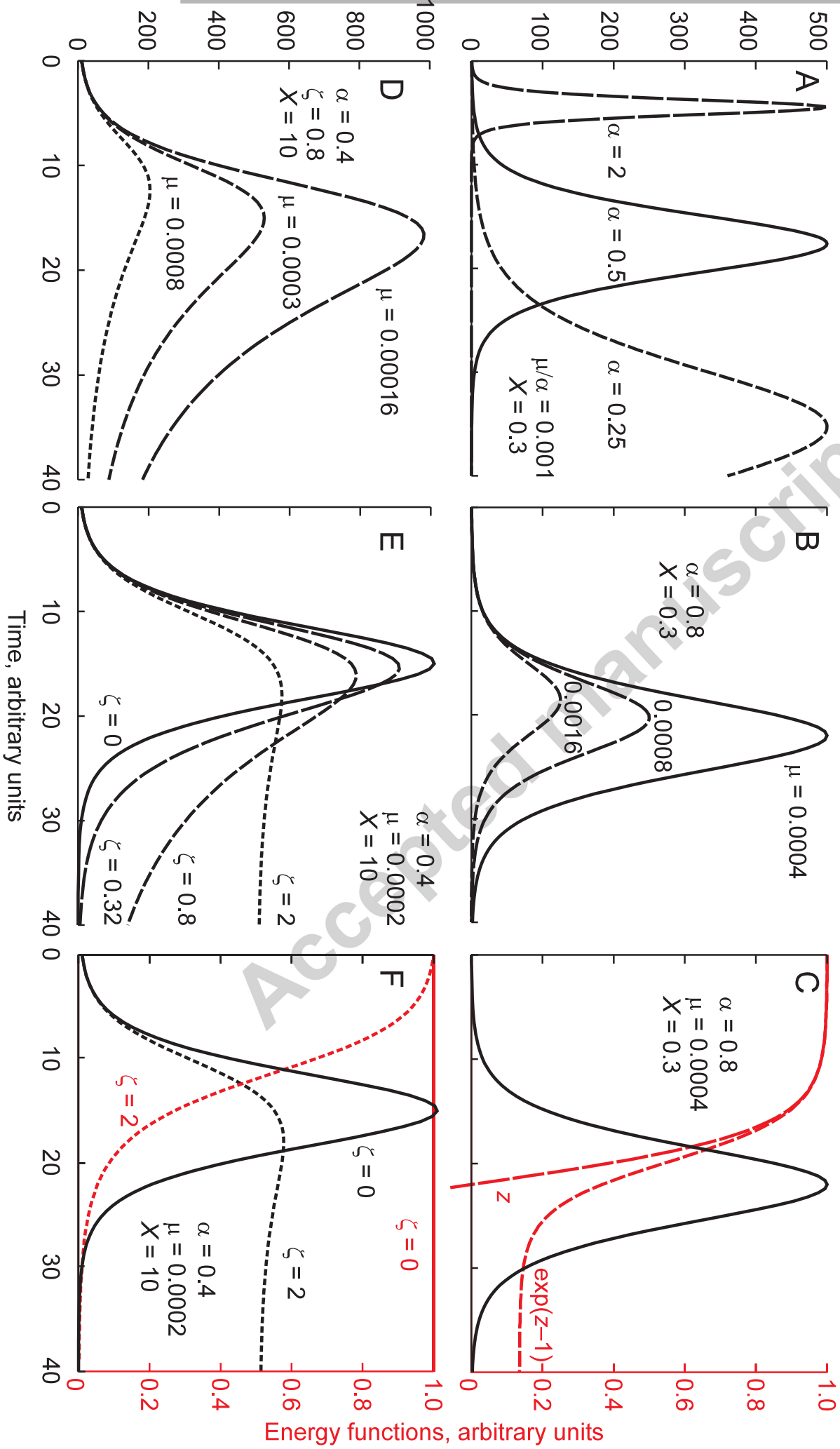


4. Figure Population size, arbitrary units





4. Figure



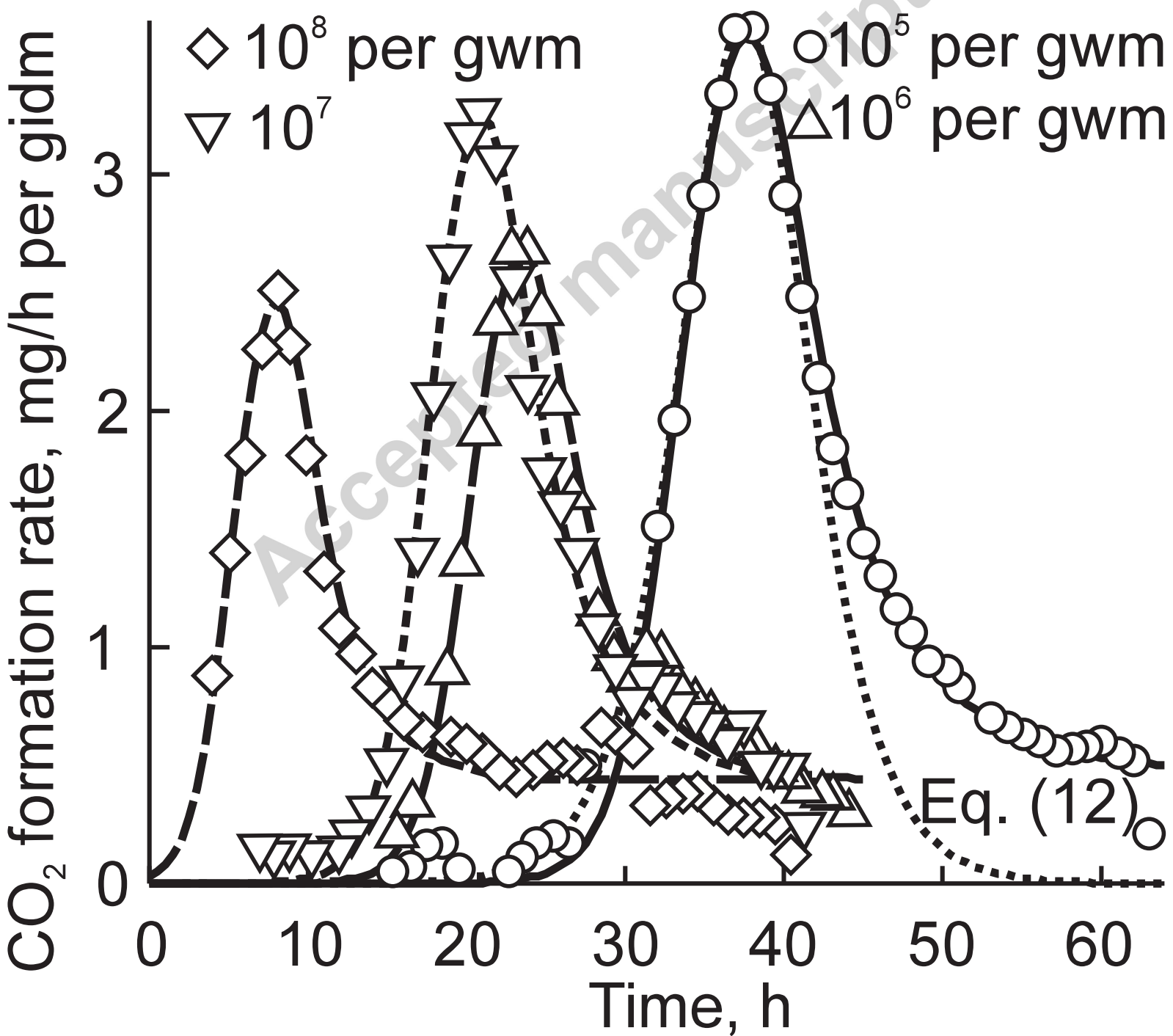


Table 1. Model parameters estimated* as a result of fitting the model (numerical solution of System (9)) to the experimental data concerning growth of 4 strains of *Campylobacter jejuni*, taken from Wright et al. (2009), Figs. 1 and 7

Parameter	Notation	Estimates			
Inoculation size (initial population size), 10^3 mL^{-1}	X	59.6	48.4	38.2	32.2
Relative growth rate, h^{-1}	α	0.67	0.52	0.57	0.55
Relative death rate, 10^{-12} h^{-1}	λ	20.4	43.0	61.4	36.5
Asymptotic size of the population, the death being ignored, 10^9 mL^{-1}	B	3.46	1.52	2.15	6.4

*Under assumption that $\kappa = 1$

Table 2. Model parameters estimated as a result of fitting the model (numerical solution of System (10) taking into account Eq. (14)) to the experimental data concerning growth of *Escherichia coli* population taken from Yu et al. (2006), Fig. 2

Parameter	Notation	Estimates
Inoculation size (initial population size), 10^6 mL^{-1}	X	7.92
Relative growth rate, h^{-1}	α	1.42
Relative death rate, 10^{-12} h^{-1}	μ	37.5
Consumption of non-saccharide resources	ζ	0.825
Asymptotic size of the population, the death being ignored, 10^9 mL^{-1}	B	2.34

Table 3. Model parameters estimated (except for the first row, Nominal inoculation size) as a result of fitting the model (numerical solution of System (15)) to the experimental data concerning growth of *Kluyveromyces marxianus* population taken from Tovar-Castro et al. (2008), Fig. 1; the last row is calculated from the results of the fitting

Parameter	Notation	Estimates
Nominal inoculation size, 1/gwm*	x_n	10^5 10^6 10^7 10^8
Model inoculation size (initial population size)†, 10^6	X	0.00034 0.2 1.7 5000
Relative growth rate, h^{-1}	α	0.62 0.77 0.75 0.88
Relative death rate, $10^{-9} h^{-1}$	μ	0.8 0.8 0.8 0.8
Consumption of non-saccharide resources	ζ	0.68 0.75 0.71 0.71
Scale factor, $10^{-9} mg h^{-1}$	A	14 9.0 11 6.6
CO ₂ produced per gidm, mg/gidm during (t) h	c	49.1 (63) 31.3 (44) 37.0 (41.5) 30.8 (41)

*Abbreviations: gwm, gram of wet matter; gidm, initial dry matter

†Lag being ignored (supposed to be negligible)