On the Chemical Meaning of some Growth Models possessing Gompertzian-type property

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Dedicated to the memory of Prof. Rene Alt

Abstract

Growth models are often used when modelling various processes in life sciences, ecology, demography, social sciences etc. Dynamical growth models are usually formulated in terms of an ODE (system of ODS's) or by an explicit solution to an ODE, such are e.g. the logistic, Gompertz and Richardson growth models. In order to choose a suitable growth model it is useful to know the physics-chemical meaning of the model. In many situations this meaning is best expressed by means of a reaction network that possibly induces the dynamical growth model via mass action kinetics. Such reaction networks are well-known for a number of growth models, such as the saturation-decay and the logistic Verhulst models. However, no such reaction networks exist for the Gompertz growth model. In this work we propose some reaction networks using mass action kinetics that induce growth models that are (in certain sense) close to the Gompertz model. The discussion of these reaction networks aims to a better understanding of the chemical properties of the Gompertz model and "Gompertzian-type" growth models. Our method can be considered as an extension of the work of previous authors who "recasted" the Gompertz differential equation into a dynamical system of two differential equations that, apart of the basic species variable, involve an additional variable that can be interpreted as a "resource". Two new growth models based on mass action kinetics are introduced and studied in comparison with the Gompertz model. Numerical computations are presented using some specialized software tools.

93A30; 80A30; 92D25; 92B05

Sigmoidal growth functions, logistic growth model, Gompertzian growth model, mass action kinetics, nonlinear ODE's, fitting biological measurement data.

1 Introduction

When studying the time evolution of various growth processes from the fields of life sciences, ecology, demography, social sciences etc. , we often have a set of measurement data of the form (t_i, y_i), where y_i is an experimental measurement (or a vector of such measurements) value obtained at the time moment $t_i, i = 1, ..., n$. We then have to choose a model (vector) function $y = f(t)$ that fits the measurement data. In some cases the function f is chosen from a class of explicitly defined functions, e.g. the class of linear functions of the form $f = at+b$, in other situations the function f is determined as a solution to a class of dynamical systems. The dynamical system involves the rates of certain characteristics of the process, which allows for a better interpretation of the intrinsic properties of the process. It is still more useful to be able to find, if possible, a reaction network that induces (precisely) the dynamical model via reaction kinetics [22, 18].

In this way we obtain a physics-chemical interpretation of the dynamical model and its ingredients (rate constants, reacting variables, interaction relations, etc.). Such reaction networks are known for a number of basic dynamical growth models, such as the saturation-delay and the logistic Verhulst models. However, no reaction network exists that induces the Gompertzian growth model, which is often used in modeling various dynamical processes (in demography, cancer research, etc.). In this work we focus attention to Gompertzian type growth models, proposing several reaction networks that induces dynamical models that are close to the Gopmertzian one. Our method can be considered as an extension of the work of previous authors who "recast" the Gompertz differential equation into a dynamical system of two differential equations that, apart of the species variable, involve an additional variable that can be interpreted as "resource". Let us mention that vast literature has been devoted to such a "recasting" procedure [19], [20], [23], [24], [25], [26], [27], [28], [29]. Numerical computations are presented using specialized software tools.

Growth models and their interpretation. We shall be interested in growth models that can be formulated solutions of differential equations. For simplicity we shall consider growth functions defined in $[0, \infty)$ with values ranging in the interval [0, 1]. In many situations the dynamical system provides some insight of the behavior of the solutions. In this work we shall demonstrate two powerful methods that, if possible to apply, provide more information for the nature of the growth proves: i) the method of "recasting" the dynamical model into a system having additional species, and ii) the method of finding realization of the system in the form of a reaction network possibly satisfying mass action kinetics. For some references on related areas the order may consult [3–17, 30–32]. The next section is of preliminary character and may be ignored by expert readers.

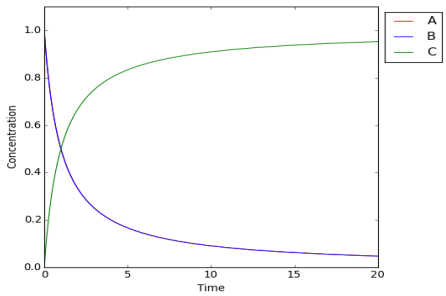

Figure 1: Solutions to reaction $A + B \xrightarrow{k} C$; $k = 1.0$, $A(0) = B(0) = 1$, $C(0) = 0$.

2 Preliminaries: mass action kinetics reaction networks, examples

Recall the mass action kinetic (MAK) on the simple reaction network:

$$A + B \xrightarrow{k} C \qquad (*)$$

Applying the MAK principle, reaction $(*)$ is "translated" into the dynamical system:

$$c' = kab,\ a' = b' = -kab \qquad (P)$$

where k is a rate constant. System (P) possesses the conservation relations:

$$c + a = C_1 = \text{const}, \quad c + b = C_2 = \text{const} \qquad (CL)$$

which allows to reduce (P) to a differential equation for a single variable, say $c' = k(C_1 - c)(C_2 - c)$.

We can then formulate a mathematical problem, e.g. an initial value (IV) ODE problem and find an algebraic or numerical solution to it. For example, an initial value (IV) problem related to (P): $c(0) = 0$, $a(0) = b(0) = 1$ yields solutions for $a = b$ and c as function of time t. The solutions can be expressed analytically or computed numerically and visualized as shown on Fig.1. Note that the solutions are symmetric relative to the line $y = (C_1 + C_2)/2$, as can be expected from relation (CL).

2.1 The saturation-decay model

The above approach will be demonstrated in the examples to follow in the sequel.

The saturation-decay model (SD-model) is induced by the following reaction network:

$$X \xrightarrow{k} Y \qquad (1)$$

Using MAK, we obtain the following dynamical system

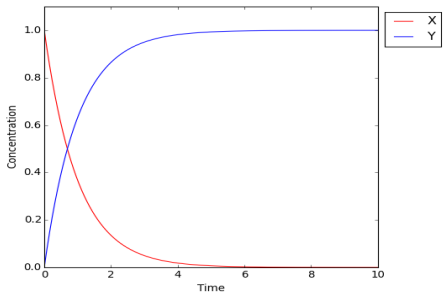

Figure 2: Solutions to SD-model $X \overset{k}{\to} Y$; $k = 1.0$, $X(0) = 1$, $Y(0) = 0$.

$$x' = -kx, \quad y' = kx \tag{2}$$

The reactant x decays whereas the reactant y grows. We have $x' + y' = 0$, leading thus to the conservation law

$$x + y = \text{const} = a, \qquad (SDCL)$$

hence y is a solution to the differential equation

$$y' = k(a - y), \tag{3}$$

known as saturation growth model. The solution of model (3) can be explicitly written as

$$y(t) = y(0)(a - e^{-t}). \tag{4}$$

The solutions to model (1-2) are visualized on Fig.2.

2.2 The iterated saturation-decay model

Reaction (3) can be iterated meaning that the product of each SD-reaction becomes the substrate of another SD-reaction:

$$S_1 \overset{k_1}{\to} S_2 \overset{k_2}{\to} S_3 \overset{k_3}{\to} \cdots \overset{k_{n-1}}{\to} S_n \quad \text{(ISD)}$$

As can be seen on Fig.3 the graph of concentration S_n is a sigmoidal function.

The iterated saturation-decay model is a special case of the general linear reaction network considered in [5].

2.3 Catalyzed growth models

We shall next focus on so-called catalytic reaction networks that are characterized by having a reactant simultaneously in both sides of the reaction.

The SD model (1) describing the transformation of a substrate S into a product P ($S \to P$) can be catalyzed via a catalyst X according to the reaction network

$$S + X \overset{k}{\to} P + X. \qquad \text{(CSD)}$$

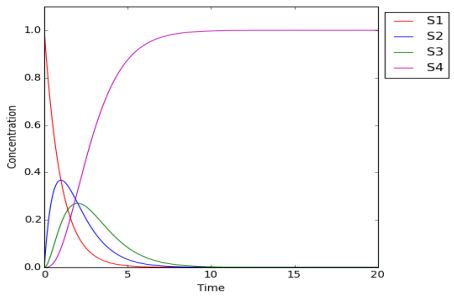

Figure 3: Solutions to ISD-model $S_1 \overset{k_1}{\to} S_2 \overset{k_2}{\to} S_3 \overset{k_3}{\to} \cdots \overset{k_{n-1}}{\to} S_n$; $n = 4,\ k_i = 1.0$, $S_1(0) = 1,\ S_2(0) = S_3(0) = S_4(0) = 0$.

If X does not participate in other reactions that change its concentration, than x is constant and plays the role of a coefficient that multiplies the rate constant in the induced dynamical system. Hence, if $x < 1$, then X acts as inhibitor of the reaction, and if $x > 1$, then X is an accelerator of the reaction.

Analogously to (ISD), the CSD-model can be repeatedly iterated in the sense that the product of any single CSD-model becomes the substrate for another CSD-model:

$$\begin{array}{rcl} S_0 + X & \overset{k_1}{\to} & S_1 + X \\ S_1 + X & \overset{k_2}{\to} & S_2 + X \\ & \cdots & \\ S_{n-1} + X & \overset{k_n}{\to} & S_n + X \end{array} \qquad \text{(ICSD)}$$

Remarks. The catalyst X in the above reaction network may be different species (having different rate constants). If the catalyst X in the reaction network varies in time, say by adding some reaction like $X \to P$, then the behavior of the reaction network may totally change.

3 Autocatalytic reaction networks and growth models

In autocatalytic reaction networks a catalyst is also a product. Such is the case with the logistic (Verhulst) reaction network. Vethust model is probably the most important catalytic reaction. Its solution is S-shaped (sigmoidal). This model is widely applicable in practice.

3.1 The logistic (Verhulst) growth model

The logistic (Verhulst) growth (V-model) is presented by the following differential equation [2]:

$$x' = kx(a - x) \qquad \text{(V)}$$

We shall be interested in solutions of (V) ranging in the interval [0, 1], hence we shall set $a = 1$ in (V) and consider initial conditions $x(0) = x_0$, such that $0 < x_0 < 1$. An explicit solution has the form

$$V(t) = \frac{1}{1 + e^{-kt}}. \qquad (VE)$$

Consider the dynamical system

$$s' = -ksx,\ x' = ksx \qquad \text{(DV)}$$

We have $s' + x' = 0$, hence the following conservation relation

$$s + x = \text{const} = a \qquad \text{(CR)}$$

holds true.

Proposition 1. i) Assume that x is a solution to model (V) with initial condition $x(0) = x_0$ and let $s(0) = a - x_0$. Then the functions $x, s = a - x$ satisfy the differential system (DV) with initial conditions $x(0) = x_0, s(0) = a - x_0$. ii) Conversely, assume that the functions $x, s = a - x$ satisfy the differential system (DV) with initial conditions $x(0) = x_0, s(0) = a - x_0$. Then x is a solution to model (V) with initial condition $x(0) = x_0$.

Proof. Substituting $s = a–x$ in (VD): $x' = ksx$ leads to (V).

Remark. The procedure of passing from the dynamical model (V) to model (DV) is called "recasting" in [24]. Such a procedure gains to a better understanding of the physical meaning of the model. Indeed, the introduction of the additional variable s suggests that the growth of species x happens for the expenses of another species s that can be interpreted as a (nutritional) resource for the species x. Based on this suggestion, we arrive to the following proposition that throws further light on the interaction between the species x and s.

Proposition 2. [33]. The V-model is induced by the autocatalytic reaction network

$$S + X \xrightarrow{k} X + X \qquad \text{(V*)}$$

Proof. Applying MAK to reaction network $(V*)$ yields the dynamical system (DV). According to proposition 1 system (DV) induces Verhulst model (V).

The V-model can be repeatedly iterated in the manner applied to the SD-model, that is, the product of a V-model becomes the substrate for another V-model.

3.2 A modified Verhulst growth model (VM-model)

The VM-model is presented by the following dynamical system

$$x' = kx(a - x)^n \qquad \text{(VM)}$$

Remark. The V-model is a special case of the VM-model for $n = 1$.

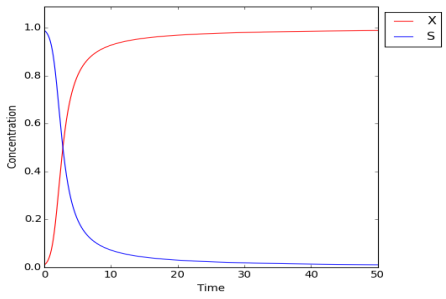

Figure 4: Solutions to $2S + X \xrightarrow{k} 3X$; $k = 1.0$; $S(0) = 0.99,\ X(0) = 0.01$.

Proposition 3. The VM-model is induced by the following autocatalytic reaction network:

$$nS + X \xrightarrow{k} X + nX \qquad \text{(VM*)}$$

The biochemical interpretation of the VM-model is as follows: the VM-model takes into account the interaction between various species (and resources), such as various types of foods and other environmental resources (water, air, light, etc.).

According to [18], it is unlikely in reality that more than three species react simultaneously. Therefore we shall focus our attention to the restriction $n = 2$.

The solutions for $n = 2$ are graphically presented on Fig. 4.

3.3 Another modified Verhulst growth model (VSM-model)

The VSM-model is presented by the following dynamical system

$$x' = kx(a - x)(b - x) \quad \text{(VSM*)}$$

Proposition 4. The VSM-model is induced via MAK from the following autocatalytic reaction network:

$$S_1 + S_2 + X \xrightarrow{k} X + X + X \quad \text{(VSM)}$$

The solutions to model (VSM) for $a = 1, b = 2$, are visualized on Fig. 6.

4 The Gompertz model

The Gompertz growth function is a solution $y = y(t)$ to the dynamical equation [1]

$$dy/dt = ky(c - \ln y) \qquad \text{(G)}$$

4.1 Some properties of the Gompertz model

The following propositions hold true.

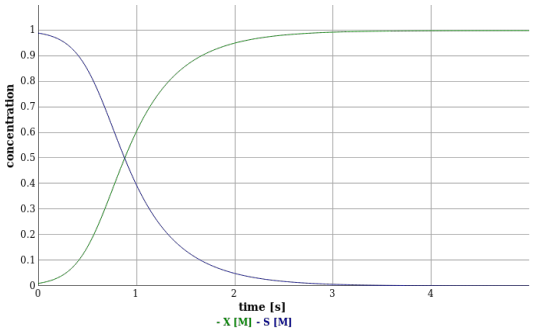

Figure 5: Solutions to $S_1 + S_2 + X \xrightarrow{k} X + X + X$; $k = 1.0$; $X(0) = 0.01,\ S(0) = 0.99,\ a = 2,\ b = 3$.

Proposition 5. The solution y to (G) is the exponent of the solution to the SD-model.

Proof. Let $z(t) = \ln y(t)$. Then $dz/dt = (dy/dt)/y$. Substituting in (G) written as

$$y'/y = k(c - \ln y) \qquad (G^*)$$

we obtain the ODE to the SD-model:

$$dz/dt = k(c - z). \qquad (G^{**})$$

Lemma 1. The solutions s, y to the dynamical system

$$ds/dt = -ks,\ dy/dt = ksy \qquad (SG)$$

satisfy the "conservation" relation

$$s + \ln y = c = \text{const} \qquad (gg)$$

Proof. From (SG) we have

$$ds/dt + dy/dt/y = 0$$

hence (gg).

Proposition 6. The functions y, s, such that y is a solution to (G) and $s = c - lny$, satisfy the dynamical system (SG). Conversely, if y, s are solutions to system (SG), then y is a solution to (G).

Proof. According to the Lemma from (SG) we have the relation (gg), thus $s = c - \ln y$. Substituting s in the equation: $dy/dt = ksy$ we obtain equation (G).

Remark. System (SG) is discussed in [20] and [23] as belonging to the class of "synergistic and saturable systems" considered in [24]. System (SG) is considered as "recasted" variant of equation (G) in the terminology of [24].

Remark. If $c = 0$ in (gg), then $\ln y \to 0$ with $t \to \infty$ (as $s \to 0$), resp. $y \to 1$. The G-model then has the form

$$dy/dt = ky(-\ln y) \quad \text{(G0)}$$

or

$$y'/y = -k \ln y = e^{-kt}$$

known as *Gompertz law of mortality.*

Remark. System (SG) shows that the Gompertz model cannot be realized as a MAK-network in the sense of [21]. Indeed, the first equation of system (SG) tells us that the species S does not interact with the other species X, whereas the second equation tells the opposite. Knowing this important fact, we shall look for MAK networks that possibly possess the G-property.

4.2 The G-property

Definition. it G-property (Gompertz property). A (sigmoidal) growth function $y = f(t)$ defined in $[0, \infty)$, such that $f(t) > 0$,$\lim_{t\to\infty} f(t) = 1$, has the G-property, if it grows slower than the logistic curve v, that is, for every logistic curve $v \in (0, 1)$,there exists f, such that $f(t) \leq v(t)$ for all $t \geq 0$.

Remark. As mentioned, the Gompertz model possesses no realization in the sense of [21], that is in terms of mass action reaction network. However, there are sigmoidal curves induced by MAK, that possess Gompertzian property. To this end we shall need the following Lemma.

Lemma 2. Let $x_0 \in (0, 1)$. For all $x \in [x_0, 1)$ the inequality

$$\frac{-\ln x}{-\ln x_0} \leq \frac{1-x}{1-x_0}$$

holds true.

Proof. Notice that for $0 < x \leq 1$, we have $1-x \leq -\ln x$. Since function $-\ln x$ is convex (has positive second derivative), $1 - x \leq l(x)$, where $l(x)$ is the line passing through the points $(x_0, -\ln x_0)$ and $(0, 1)$ lying on $-\ln x$. We have

$l(x) = (-\ln x_0)((1 - x)/(1 - x_0))$.

Let us divide the lime by the value $l(0) = (-\ln x_0)/(1-x_0)$, then the line $l/l(0)$ coincides with the line $1 - x$ (both lines pass through the points $(0, 1)$ and $(1, 0)$). Hence, $(-\ln x)/l(0) \leq 1 - x$, which proves the lemma.

Proposition 7. The Gompertz model (G) possesses the G-property.

Proof. We shall prove that for each logistic curve $v(t), t \in [0, \infty)$ there is a Gompertz curve $g(t), t \in [0, \infty)$ that lies below the logistic one in the interval $t \in [0, \infty)$. Consider model (V) with $a = 1$: $x' = kx(1 - x)$, and fix an arbitrary initial condition $x(0) = x_0$ and a rate constant $k > 0$. Consider the Gompertzian model (G) with $c = 0$. Choose initial condition $y(0) = x_0$, and determine the Gompertzian rate constant h so that $y'(0) = x'(0)$. Under these conditions the chosen Gompertzian curve satisfies the initial value ODE problem:

$$dy/dt = hy(-\ln y), y_0 = x_0, \qquad (\mathrm{G}_0)$$

wherein h is determined from the conditions $y_0 = x_0$, $y'(0) = x'(0)$, that is, $hy_0(-\ln y_0) = kx_0(a - x_0)$, hence $h(-\ln x_0) = k(1 - x_0)$, $h = k\frac{1-x_0}{-\ln x_0}$.

We shall show that for all points in the phase plane (t, u), $t \geq 0, 0 < u < 1$, the slope of the Gompertz curve at (t, u) is less than the slope of the logistic curve at the sane phase point (t, u), that is:

$$y'|_{(t,u)} \leq x'|_{(t,u)},$$

hence

$$hu(-\ln u) \leq ku(1 - u),$$

that is

$$k\frac{1 - x_0}{-\ln x_0}u(-\ln u) \leq ku(1 - u)$$

.

Dividing the above inequality by $ku > 0$, we obtain

$$\frac{1 - x_0}{-\ln x_0}(-\ln u) \leq (1 - u),$$

or

$$(-\ln u)/(-\ln x_0) \leq (1 - u)/(1 - x_0),$$

which is true according to Lemma 2.

We thus obtain the proof of the proposition.

Remarks. The solutions to the logistic and Gompertzian model as defined in the proposition are visualized on Fig. 6. Fig. 6 presents the logistic function $x = x(t)$ and the Gompertz function $y = y(t)$ in the interval $t \in [0, \infty)$, as solutions to the following two ODE initial value problems

$x' = kx(1 - x)$, $k = 1, x_0 = 0.01$;
$dy/dt = hy(-\ln y), y_0 = x_0$, $h = k\frac{(1-x_0)}{(-\ln x_0)}$.

Proposition 8. The modified Verhulst models (VM) and (VSM) possess the G-property.

Remark. The proof is similar to the proof of the G-property of the Gompertz model (Proposition 7). Proposition 8 is graphically visualized on Figures 7–9.

Solutions of the logistic and Gompertz models as well the two modified Verhulst models are graphically presented on Fig. 7. and Fig. 8.

Fig. 9. Solutions to the logistic model (blue), Gompertz model (purple) and the two modified Verhulst models.

5 Computational experiments

For numerical simulations we used SmoWeb – an open source web computational platform (developed in Python) that provides an infrastructure for rapid development of scientific applications with graphical user interface. The applications are

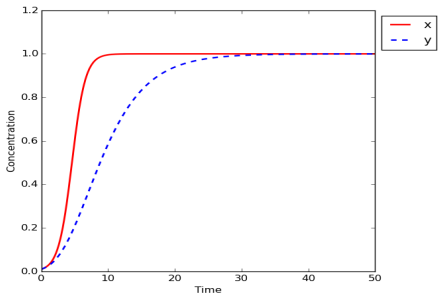

Figure 6: The logistic (red) and Gompertz (blue dashed) curves starting from same point with same slopes

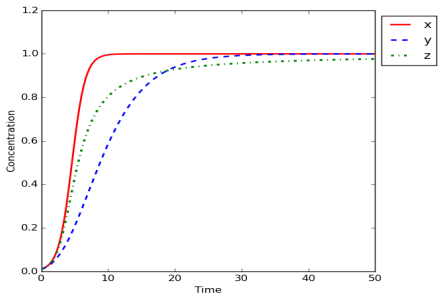

Figure 7: Same as Fig. 6 plus the solution of the VM-model (green dashed)

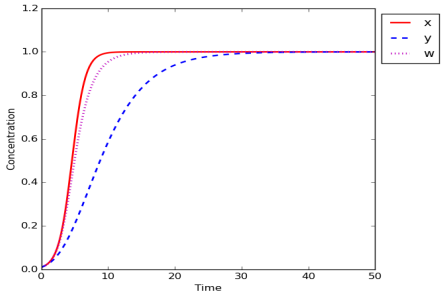

Figure 8: Same as Fig. 6 plus the solution of the VSM-model

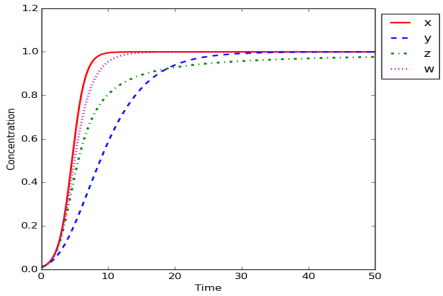

Figure 9: Figures 6–8 plotted together

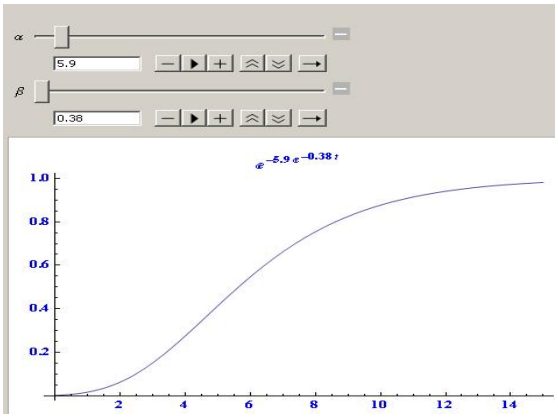

Figure 10: Software tools for animation and visualization in *CAS Mathematica*.

in the fields of thermodynamics, heat and fluid flow, and bioprocess modeling. All computations are performed in Web Cloud [34].

A software tool has been developed in CAS Mathematica for testing the closeness between growth functions, a screenshot is visualized on Fig. 10. Figures 11–12 present graphically computer experiments fir testing the closeness between the Gompertz model and the modified Verhulst models.

6 Conclusion remarks

A possible approach to achieve a G-property of a growth logistic-type model curve using MAK is to introduce additional resources and reactions in the logistic reaction network influencing the growth process. A general interpretation of this result is that a more involved reproduction mechanism leads to the Gompertzian property.

Biological growth functions are usually presented in the literature by means of their explicit form or as solutions of a dynamical system. In a situation when the growth model possesses a realization in terms of a chemical reaction network,

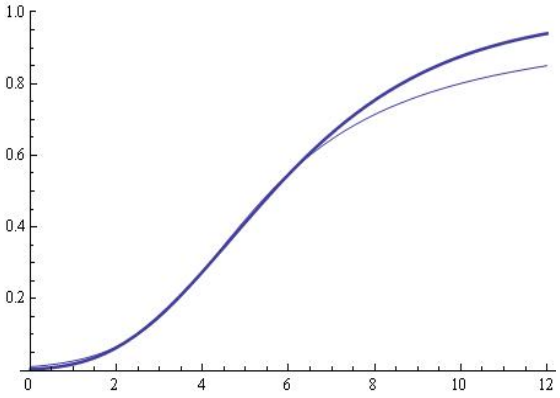

Figure 11: Comparison between $x(t)$ from (VM) for $n = 2$ (blue) and $G(t)$ (thick) for $\alpha = 5.9$ and $\beta = 0.38$

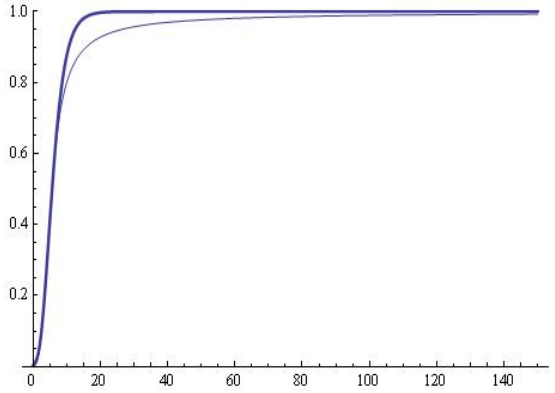

Figure 12: Comparison between $x(t)$ from (VM) for $n = 2$ (blue) and $G(t)$ (thick) for $\alpha = 5.9$ and $\beta = 0.38$ for large values of t.

the modeler has an additional possibility of a (bio-)chemical interpretation of the model. We have demonstrated this on the case of the Gompertz model, that cannot be realized in terms of a reaction network; however there are reaction networks that induce a model close to the Gompertzian one. In the process of constructing reaction network to a specific growth model the approach of introducing additional species (recasting) may be useful.

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