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ON A SIGMOIDAL GROWTH FUNCTION GENERATED BY REACTION NETWORKS. SOME EXTENSIONS AND APPLICATIONS

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ABSTRACT: In [2] S. Markov considered the possibility of approximating the input function $s(t)$ in the differential model $y'(t) = ky(t)s(t)$; $y(t_0) = y_0$ with the Bateman [3] type correction. In the present work we study a sigmoidal class of growth functions proposed by S. Markov. We prove upper and lower estimates for the one–sided Hausdorff approximation of the Heaviside step–function $h_{t^*}(t)$ by means of this new logistic family. The estimates can be used in practice as one possible additional criterion in "saturation" study. Some extensions of classes of sigmoidal functions generated by reaction networks in the general case $n \geq 2$ are given. The suggested models can be successfully used to approximating data from tumor growth, population dynamics and debugging theory.

Numerical examples, illustrating our results are given using *CAS Mathematica*.

AMS Subject Classification: 41A46

Key Words: nutrient supply $s(t)$, Bateman type correction, Heaviside step function, Hausdorff distance, upper and lower bounds, reaction networks, generalized growth–decay model

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1. INTRODUCTION

Dynamical models consisting of a systems of "reaction" differential equations are commonly used in chemistry, there the differential equations are called *reaction equations*.

In chemistry reaction differential equations are induced by chemical reactions networks via reaction kinetic principles, such as *mass action kinetics* [4]–[6].

In [1]–[2] the author focuses his attention on growth functions (models) formulated as solutions to differential equations or systems of differential equation.

New reaction networks realizations of some growth models are proposed.

The considered reaction networks involve an additional species interpreted as environmental resource.

Markov [2] proposed a class of growth–decay model formulated in terms that include various types of evolution of the resource species:

$$\begin{array}{rcl} S & \xrightarrow{k_1} P \xrightarrow{k_2} & Q, \\ P+X & \xrightarrow{k} & 2X+P. \end{array} \tag{1}$$

Reaction network (1) induces the following differential system

$$\left\{ \begin{array}{rcl} \dfrac{ds}{dt} & = & -k_1 s, \\ \dfrac{dp}{dt} & = & k_1 s - k_2 p, \\ \dfrac{dx}{dt} & = & kxp. \end{array} \right. \tag{2}$$

with $s(0) = s_0$; $p(0) = p_0$; $x(0) = x_0$.

With the Leibnitz's differential formulae we have

$$p(t) = \frac{k_1}{k_1 - k_2} s_0 \left(e^{-k_1 t} - e^{-k_2 t} \right) + p_0 e^{-k_2 t}.$$

Hence, the new model [2] can be written for the growth function in the form:

$$x'(t) = kxp = kx \left(\frac{k_1}{k_1 - k_2} s_0 \left(e^{-k_1 t} - e^{-k_2 t} \right) + p_0 e^{-k_2 t} \right). \tag{3}$$

In the present work we study a sigmoidal class of growth functions proposed by S. Markov.

We prove upper and lower estimates for the one–sided Hausdorff approximation of the Heaviside step–function $h_{t^*}(t)$ by means of a new logistic family.

The proposed model can be successfully used to approximating data from tumor growth, epidemics, population dynamics, debugging theory and computer viruses propagation theory.

2. PRELIMINARIES

Definition 1. The shifted Heaviside step function is defined by

$$h_{t^*}(t) = \begin{cases} 0, & \text{if} \quad t < t^*, \\ [0,1], & \text{if} \quad t = t^*, \\ 1, & \text{if} \quad t > t^*. \end{cases} \tag{4}$$

Definition 2. (see [7], [8]) The Hausdorff distance (the H–distance) $\rho(f,g)$ between two interval functions f, g on $\Omega \subseteq \mathbb{R}$, is the distance between their completed graphs $F(f)$ and $F(g)$ considered as closed subsets of $\Omega \times \mathbb{R}$. More precisely,

$$\rho(f,g) = \max\{ \sup_{A \in F(f)} \inf_{B \in F(g)} ||A - B||, \sup_{B \in F(g)} \inf_{A \in F(f)} ||A - B|| \}, \tag{5}$$

wherein $||.||$ is any norm in $\mathbb{R}^2$, e. g. the maximum norm $||(t,x)|| = \max\{|t|, |x|\}$; hence the distance between the points $A = (t_A, x_A)$, $B = (t_B, x_B)$ in $\mathbb{R}^2$ is $||A - B|| = \max(|t_A - t_B|, |x_A - x_B|)$.

Definition 3. We consider the following model with the Bateman [3] type correction [2]:

$$\begin{cases} \frac{dy(t)}{dt} = ky(t)\left(\dfrac{k_1}{k_1 - k_2} s_0 \left(e^{-k_1 t} - e^{-k_2 t}\right) + p_0 e^{-k_2 t}\right), \\ y(t_0) = y_0, \end{cases} \tag{6}$$

where k, k_1, k_2, s_0, p_0 are constants.

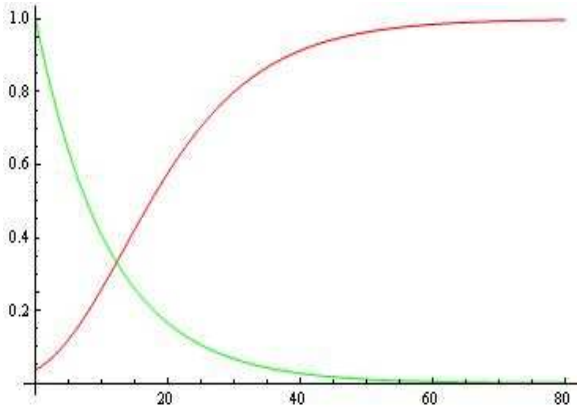

Figure 1: The functions $M(t)$–(red) and $p(t)$–(green) for $k = 0.3$; $k_1 = 0.1$; $k_2 = 0.09$; $s_0 = 0.001$; $p_0 = 1$.

3. MAIN RESULTS

The general solution of the differential equation (3) is of the following form:

$$\begin{aligned} y(t) &= y_0 e^{\frac{e^{-(k_1+k_2)t}k\left(-e^{k_2 t}s_0+\frac{e^{k_1 t}(p_0(k_2-k_1)+k_1 s_0)}{k_2}\right)}{k_1-k_2}} \\ &\times e^{-\frac{e^{-(k_1+k_2)t_0}k\left(-e^{k_2 t_0}s_0+\frac{e^{k_1 t_0}(p_0(k_2-k_1)+k_1 s_0)}{k_2}\right)}{k_1-k_2}}. \end{aligned} \tag{7}$$

It is important to study the characteristic - "super saturation" of the model to the horizontal asymptote.

Without loss of generality, we consider the following class of this family for:

$$t_0 = 0;\ y_0 = e^{\frac{k\left(-s_0+\frac{p_0(k_2-k_1)+k_1 s_0}{k_2}\right)}{k_1-k_2}} < 1$$

$$M(t) = e^{\frac{e^{-(k_1+k_2)t}k\left(-e^{k_2 t}s_0+\frac{e^{k_1 t}(p_0(k_2-k_1)+k_1 s_0)}{k_2}\right)}{k_1-k_2}}. \tag{8}$$

The function $M(t)$ and the "input function" $p(t)$ are visualized on Fig. 1.

Denoting by t^* the unique positive solution of the nonlinear equation $M(t^*) = \frac{1}{2}$.

The one–sided Hausdorff distance d between the function $h_{t^*}(t)$ and the

sigmoid - (5) satisfies the relation

$$M(t^* + d) = 1 - d. \tag{9}$$

The following theorem gives upper and lower bounds for d.

Theorem 1. *Let* $0 < y_0 < 1$ *and*

$$\begin{aligned} &p = -\tfrac{1}{2}, \\ &q = 1 + \tfrac{1}{2(k_1 - k_2)} \left(e^{-k_2 t^*} k p_0 (k_1 - k_2) + k k_1 s_0 \left(e^{-k_1 t^*} - e^{-k_2 t^*} \right) \right), \\ &\gamma = 2.1q. \end{aligned} \tag{10}$$

For the one–sided Hausdorff distance d between $h_{t^*}(t)$ *and the sigmoid (8) the following inequalities hold for the condition -* $\gamma > e^{1.05}$*:*

$$d_l = \frac{1}{\gamma} < d < \frac{\ln \gamma}{\gamma} = d_r. \tag{11}$$

Proof. Let us examine the function:

$$F(d) = M(t^* + d) - 1 + d. \tag{12}$$

From $F'(d) > 0$ we conclude that function F is increasing. Consider the function

$$G(d) = p + qd. \tag{13}$$

From Taylor expansion we obtain $G(d) - F(d) = O(d^2)$. Hence $G(d)$ approximates $F(d)$ with $d \to 0$ as $O(d^2)$. In addition $G'(d) > 0$. Further, for $\gamma > e^{1.05}$ we have

$$G(d_l) < 0; \quad G(d_r) > 0.$$

This completes the proof of the theorem.

Approximations of the $h_{t^*}(t)$ by model (8) for various k, α and β are visualized on Fig. 2–Fig. 3.

From the graphic it can be seen that the "saturation" is faster.

3.1. APPROXIMATING THE "REAL WEALTH DATA"

For example the appropriate lest–square fitting of the real wealth data by the model (8) yields for $k_1 = 17.9$, $k_2 = 30.8$, $s_0 = 0.001$, $p_0 = 1$, $k = 1.11687 \times 10^7$ (see, Fig. 4).

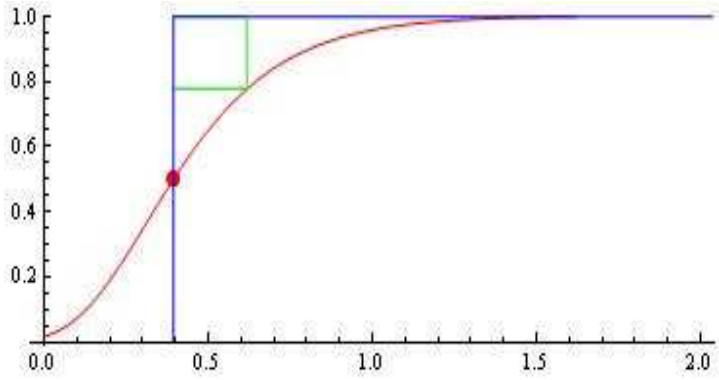

Figure 2: The model (8) for $k = 18.5$; $k_1 = 0.28$; $k_2 = 4.5$; $s_0 = 0.001$; $p_0 = 1$; $t^* = 0.394361$; Hausdorff distance $d = 0.222811$; $d_l = 0.185442$; $d_r = 0.312472$.

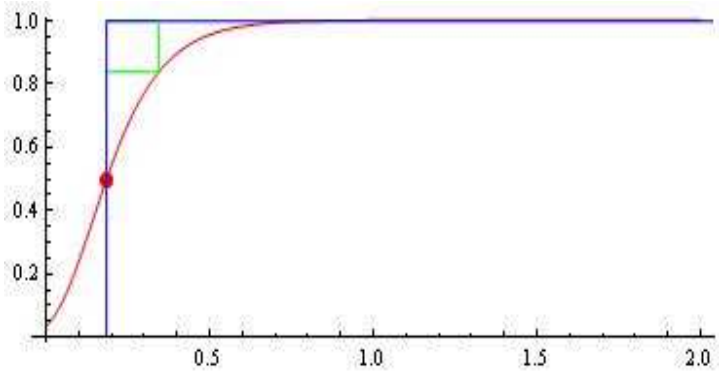

Figure 3: The model (8) for $k = 28.5$; $k_1 = 0.28$; $k_2 = 8.5$; $s_0 = 0.001$; $p_0 = 1$; $t^* = 0.1849$; Hausdorff distance $d = 0.160461$; $d_l = 0.120268$; $d_r = 0.254732$.

3.2. APPROXIMATING THE "GROWTH DATA (MEAN HEIGHT) OF SUNFLOWER PLANTS"

We analyze experimental growth data (mean height) of sunflower plants (DSP) (see, for example [9]):

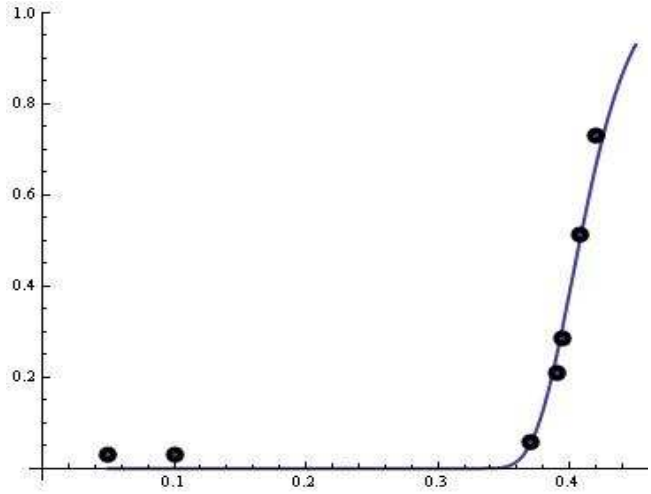

Figure 4: The fitted model (8).

$data\_DSP$
$:= \{\{14, 36.4\}, \{28, 98.1\}, \{49, 205.5\}, \{56, 228.3\}, \{70, 250.5\},$
$\{84, 254.5\}\}.$

For $k = 0.247702$, $k_1 = 8.9$, $k_2 = 0.055$, $s_0 = 0.00001$, $p_0 = 1$ and $\omega = 273.683$ we obtain the fitted model $M^*(t) = \omega M(t)$ (see, Fig. 5).

3.3. APPROXIMATING THE "UNINFECTED TUMOR GROWTH DATA"

One of the goals in study [10] is to predict tumor's response to oncolytic viral infection and using the model in [10] it is observed on Fig. 6 that the model fits (with the susceptible cell population taken as the baseline variable) the tumor growth data.

Here we will fit the data provided from [10] with new model, see Fig. 7.

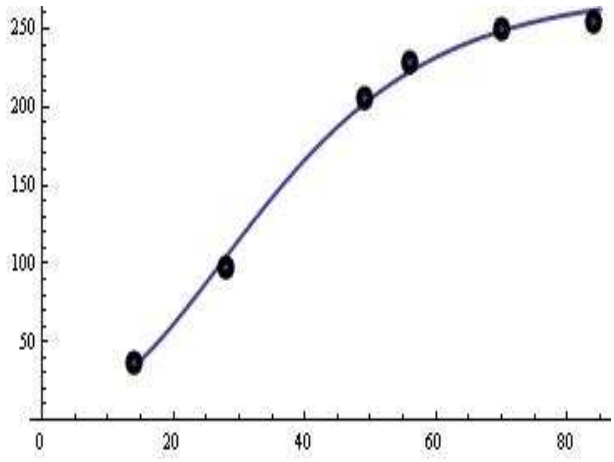

Figure 5: The fitted model $M^*(t)$.

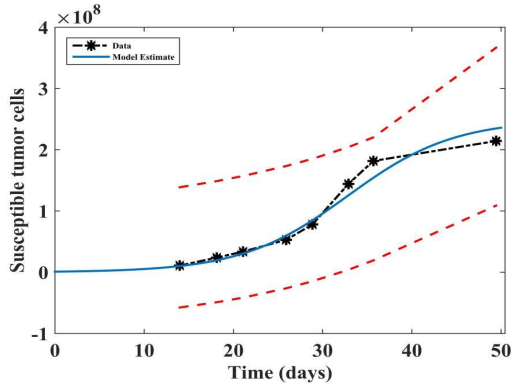

Figure 6: Model fit to uninfected tumor growth data from [10].

We analyze experimental growth data (see, for example [10]):

$$
\begin{aligned}
&uninfected\_tumor\_growth\_data\\
&:= \{\{0,0\},\{14,0.11290\},\{18,0.24194\},\{21,0.33871\},\\
&\{26,0.53226\},\{29,0.80645\},\{33,1.45161\},\{36,1.82258\},\\
&\{49,2.14516\}\}.
\end{aligned}
$$

For $k_1 = 1.3$, $k_2 = 0.108$, $s_0 = 0.00001$, $p_0 = 0.9$, $k = 2.57515$ and $\omega = 2.50047$ we obtain the fitted model $M^*(t) = \omega M(t)$ (see, Fig. 8).

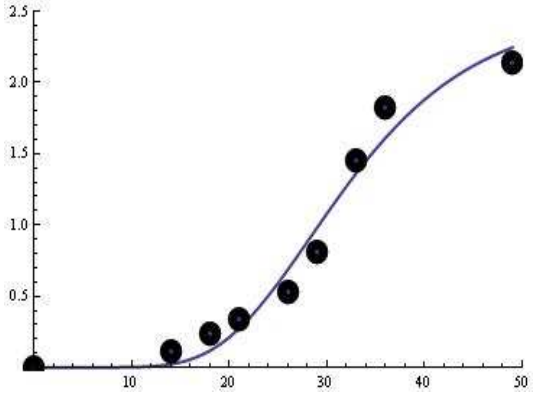

Figure 7: The fitted model $M^*(t)$.

4. SOME EXTENSIONS OF CLASSES OF SIGMOIDAL FUNCTIONS GENERATED BY REACTION NETWORKS.

We consider the following reaction network:

$$\begin{array}{rcl} S & \xrightarrow{k_1} P \xrightarrow{k_2} & Q \\ S & \xrightarrow{k_3} P1 \xrightarrow{k_4} & Q1 \\ P1 + X & \xrightarrow{k} & 3X + P1. \end{array} \tag{14}$$

Reaction network (14) induces the following differential system

$$\left\{ \begin{array}{rcl} \dfrac{ds}{dt} & = & -k_1 s - k_3 s = -(k_1 + k_3)s, \\ \dfrac{dp}{dt} & = & k_1 s - k_2 p, \\ \dfrac{dp1}{dt} & = & k_3 s - k_4 p1, \\ \dfrac{dx}{dt} & = & kxp1. \end{array} \right. \tag{15}$$

with $s(0) = s_0$; $p(0) = p_0$; $p1(0) = p1_0$; $x(0) = x_0$.

From the first equation of the dynamical system (15), we obtain:

$$s(t) = s_0 e^{-(k_1+k_3)t}.$$

Using Laplace transform we have

$$p(t) = \frac{k_1}{k_2 - (k_1 + k_3)} s_0 \left(e^{-(k_1+k_3)t} - e^{-k_2 t} \right) + p_0 e^{-k_2 t},$$

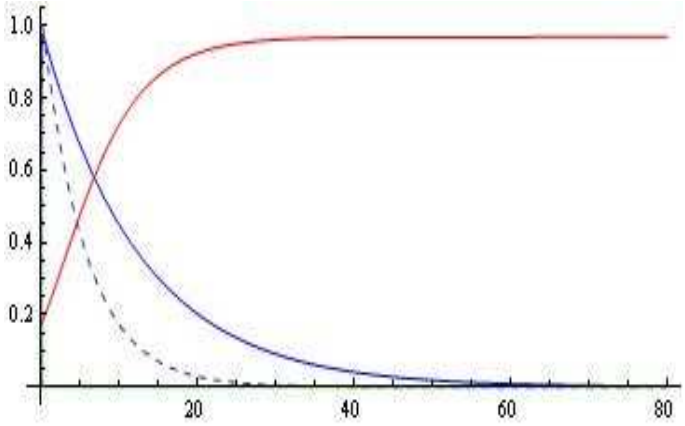

Figure 8: The solutions $x(t)$–(red); $p1(t)$–(dashed); $p(t)$–(blue) and $s(t)$–(green) for $k = 0.3$; $k_1 = 10.1$; $k_2 = 0.04$; $k_3 = 10.08$; $k_4 = 0.09$; $s_0 = 1$; $p_0 = 2$; $p1_0 = 2.1$; $x_0 = 0.17$.

$$p1(t) = \frac{k_3}{k_4 - (k_1 + k_3)} s_0 \left(e^{-(k_1+k_3)t} - e^{-k_4 t} \right) + p1_0 e^{-k_4 t}.$$

Hence, the new model can be written for the growth function in the form:

$$\begin{cases} x'(t) = kx \left(\frac{k_3 s_0}{k_4 - (k_1+k_3)} \left(e^{-(k_1+k_3)t} - e^{-k_4 t} \right) + p1_0 e^{-k_4 t} \right), \\ x(0) = x_0. \end{cases} \tag{16}$$

Evidently, the solution of the differential equation (16) is:

$$x(t) = x_0 e^{\frac{-kk_3 p1_0 s_0 \left(-\frac{1}{2k_4} + \frac{1}{k_1+k_3+k_4} \right)}{k_1+k_3-k_4} + \frac{e^{-(k_1+k_3+k_4)t} kk_3 p1_0 s_0 \left(-\frac{e^{(k_1+k_3-k_4)t}}{2k_4} + \frac{1}{k_1+k_3+k_4} \right)}{k_1+k_3-k_4}}$$

The solutions of the differential system (15) for various parameters are visualized on Fig. 8 – Fig. 9.

The estimates for the one–sided Hausdorff approximation of the Heaviside step–function $h_{t^*}(t)$ by means of the new sigmoidal class of growth functions can be studied in manner outlined in Theorem 1.

Issues related to research on "equilibrium" and "conservation relations" will be discussed in future developments.

As an example, a typical conservation relationship is visualized on Fig. 10.

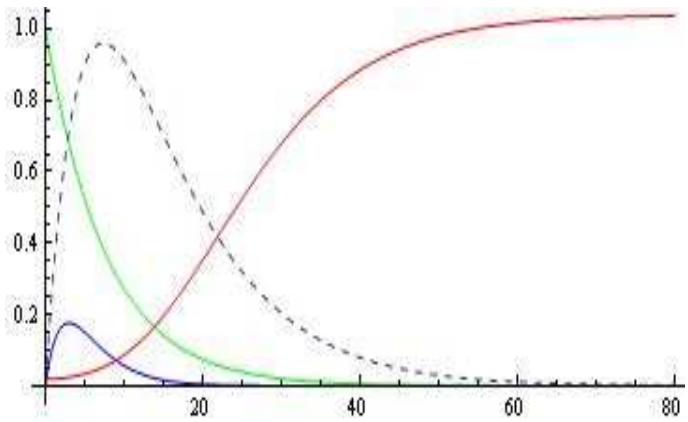

Figure 9: The solutions $x(t)$–(red); $p1(t)$–(dashed); $p(t)$–(blue) and $s(t)$–(green) for $k = 0.2$; $k_1 = 0.04$; $k_2 = 0.18$; $k_3 = 0.09$; $k_4 = 0.05$; $s_0 = 1$; $p_0 = 4.001$; $p1_0 = 4.002$; $x_0 = 0.019$.

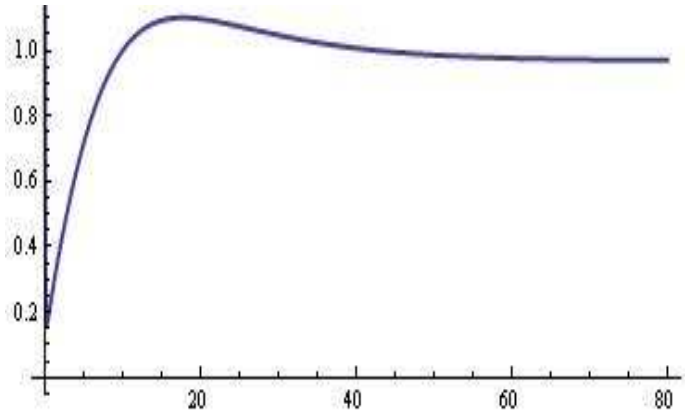

Figure 10: A typical conservation relationship.

5. CONCLUSION

In many cases, the nutrient supply $NS(t)$ in the differential equation

$$\frac{dy(t)}{dt} = ky(t)NS(t)$$

is considered as an input function.

This circumstance provokes us to consider the possibility of approximating the nutrient supply, with what we call "Bateman correction".

In the general case the reaction network (for $n \geq 2$) is of the form:

$$\begin{array}{rcl} S & \xrightarrow{k_1} P \xrightarrow{k_2} & Q \\ S & \xrightarrow{k_3} P_1 \xrightarrow{k_4} & Q_1 \\ & \cdots & \\ S & \xrightarrow{k_{2n-1}} P_{n-1} \xrightarrow{k_{2n}} & Q_{n-1} \\ P_{n-1} + X & \xrightarrow{k} & nX + P_{n-1}. \end{array} \tag{17}$$

The proposed reaction networks (17) involve additional species interpreted as environmental resource.

Hence, the general new model can be written for the growth function in the form:

$$\begin{cases} x'(t) = kxP_{n-1}(t) \\ x(0) = x_0. \end{cases} \tag{18}$$

where

$$P_{n-1}(t) = \frac{k_{2n-1}s_0}{k_{2n} - \sum_{i=1}^{n} k_{2i-1}} \left(e^{-\sum_{i=1}^{n} k_{2i-1}t} - e^{-k_{2n}t} \right) + p_{n-1,0}e^{-k_{2n}t}.$$

An important advantage of the new models is a prolonged lag time of the sigmoidal solutions of the growing species.

We propose a software module within the programming environment *CAS Mathematica* for the analysis of the considered family of functions.

We further plan to extend the Distributed Platform for e-Learning (DisPeL) [31]–[35] with specialized modules for simulation of chemical kinetics, solving nonlinear differential equations and verifying the mass action balance.

Of course, the model is very sensitive with respect to the reaction constants $k_1, \cdots, k_{2n}$, which is illustrated in Figures 9 and 10.

For other results, see [12]–[30].

Issues related to the study of the stability of the differential system solution are not discussed in this paper.

We recommend the reader the basic monograph [11] devoted to this issue.

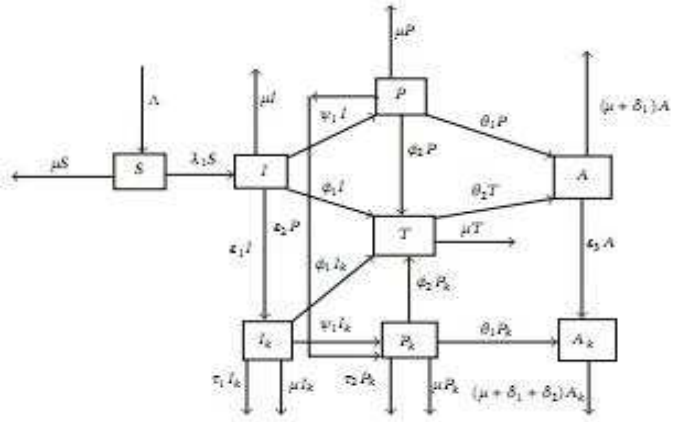

Figure 11: The flow diagram [36].

Remark. Let us consider the flow diagram for the simple mathematical model of the HIV/Kaposi's sarcoma coinfection dynamics (see, for example [36]; for other results, see [37]).

Let's focus only on the first two species of the reaction network (a susceptible to disease class - S and a class of individual infected - I) with all "incoming and outgoing" reaction constants.

Then

$$\begin{cases} \dfrac{dS}{dt} &= \Lambda - (\lambda_1 + \mu)S(t), \\ \dfrac{dI}{dt} &= \lambda_1 S(t) - (\epsilon_1 + \mu + \psi_1 + \varphi_1)I(t), \\ \dfrac{dX}{dt} &= kX(t)I(t). \end{cases}$$

The latter equation of the differential system expresses the dynamics of the growth function generated by said part of the reaction network.

Without be a specialists on this subject we will only note that the approximation by the models presented in this article for the similar data from this area gives us unexpected good results for which we have insufficient scientific reasoning at this stage.

The specialists working in the field of "reaction-kinetic mechanisms" have the word.

In any cases the reaction network (17) suggests hints for the intrinsic mechanism of the modeled growth process.

For the power law approximations for radioactive decay chains, see [38], [39].

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