Dynamic Systems and Applications, **28**, No. 3 (2019), 587-606 ISSN: 1056-2176

ON A SPECIAL CHOICE OF NUTRIENT SUPPLY FOR CELL GROWTH IN A CONTINUOUS BIOREACTOR. SOME MODELING AND APPROXIMATION ASPECTS

NIKOLAY KYURKCHIEV[1], ANTON ILIEV[2] AND ASEN RAHNEV[3]

[1,2,3]Faculty of Mathematics and Informatics
University of Plovdiv Paisii Hilendarski
24 Tzar Asen Str., 4000 Plovdiv, BULGARIA

ABSTRACT: In this article we will consider the possibility of approximating the input function $s(t)$ (the nutrient supply for cell growth in a continuous bioreactor) with the Lindley type correction.

We prove upper and lower estimates for the one–sided Hausdorff approximation of the shifted Heaviside function $h_{t^*}(t)$ by means of the general solution of the differential equation $y'(t) = ky(t)s(t)$ with $y(t_0) = y_0$.

We will illustrate the advances of the solution $y(t)$ for approximating and modelling of: "data on the development of the *Drosophila melanogaster* population", published by biologist Raymond Pearl in 1920 (see, also Alpatov, Pearl [32]), "cancer data" (see, [33]–[34]), "data on the development of Saccharomyces culture in nutrient medium", published by biologist T. Carlson in 1913 (see, also [67], [69]), "growth data (mean height) of sunflower plants" [69] and "data on the growth of population of *Rhizapertha* in wheat" by Crombie in 1945 [68].

We also define a new parametric activation function based on "amendments" of "Lindley - type".

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

AMS Subject Classification: 41A46

Key Words: nutrient supply, prototype of model used in bioreactor modelling, "supersaturation" of the model, Heaviside function, Hausdorff distance, upper and lower bounds

Received: February 11, 2019; **Revised:** April 23, 2019;
Published (online): May 22, 2019 **doi:** 10.12732/dsa.v28i3.5
Dynamic Publishers, Inc., Acad. Publishers, Ltd. https://acadsol.eu/dsa

1. INTRODUCTION

Sigmoidal functions find multiple applications to population dynamics, biostatistics, analysis of nutrient supply for cell growth in bioreactors, controllability of tumor growth, population survival functions, classical predator–prey models, neural networks, debugging and test theory and others [37]–[66].

The Verhulst model can be considered as a prototype of models used in bioreactor modelling.

In batch growth, the rate of biomass production is given by $\frac{dx}{dt} = \kappa x$, where: $x =$ biomass concentration; $\kappa =$ specific growth rate; $t =$ time. The rate κ is a function of nutrient supply and therefore can be a function of time (i.e., if nutrient supply is changing with time.)

In general, $\kappa = F(S, P, I, X, T, osmotic\, pressure)$; $S =$ substrate concentration; $P =$ product concentration; $I =$ inhibitor concentration.

There, especially in the case of continuous bioreactor, the nutrient supply is considered as an input function $s(t)$ as follows:

$$\frac{dy(t)}{dt} = ky(t)s(t) \tag{1}$$

where s is additional specified.

To the role and choice of nutrient supply for cell growth in bioreactors are devoted to a number of studies [1]–[12].

Some concepts of multiple–nutrient–limited growth of microorganisms and its application in biotechnological processes can be found in [3].

In [13], the author consider the following hyper–logistic equation:

$$\begin{aligned} &\tfrac{dy(t)}{dt} = ky(t)\frac{2e^{-pt}}{1+e^{-pt}} \\ &y(t_0) = y_0, \end{aligned} \tag{2}$$

where $k > 0$ and $p > 0$ with general solution:

$$y(t) = y_0 e^{2k(t-t_0) + \frac{2k}{p}\ln(1+e^{pt_0}) - \frac{2k}{p}\ln(1+e^{pt})}.$$

For other results, see [14].

In this paper we will consider the possibility of approximating the input function $s(t)$ in the equation (1) with the Lindley type correction.

Some results for Lindley [15]–[16], power Lindley distribution, discrete Poisson–Lindley distribution, modified discrete Lindley distribution, generalized Lindley distribution, exponential modified discrete Lindley distribution, quasi Lindley distribution, Kumaras–wamy–Lindley distribution and transmuted Kumaraswamy quasi Lindley distribution are given in [17]–[31].

Following the ideas given in [13] we consider the following new logistic equation:

$$\begin{aligned} &\tfrac{dy(t)}{dt} = ky(t)\frac{1+\theta+\theta t}{1+\theta}e^{-\theta t} \\ &y(t_0) = y_0 \end{aligned} \tag{3}$$

where $\theta > 0$.

We prove upper and lower estimates for the one–sided Hausdorff approximation of the shifted Heaviside function $h_{t^*}(t)$ by means of the general solution of this differential equation.

We will illustrate the advances of the solution $y(t)$ for approximating and modelling of:

- "data on the development of the *Drosophila melanogaster* population", published by biologist Raymond Pearl in 1920 (see, also Alpatov, Pearl [32]);

- "cancer data" (see, [33]–[34]);

- "data on the development of Saccharomyces culture in nutrient medium", published by biologist T. Carlson in 1913 (see, also [67], [69]);

- "growth data (mean height) of sunflower plants" [69];

- "data on the growth of population of *Rhizapertha* in wheat" by Crombie in 1945 [68].

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. [35], [36] 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 $||A - B|| = \max(|t_A - t_B|, |x_A - x_B|)$.

3. MAIN RESULTS

3.1. A NEW MODEL

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

$$y(t) = y_0 e^{-\frac{k(2+\theta+\theta t)}{\theta(1+\theta)} e^{-\theta t} + \frac{k(2+\theta+\theta t_0)}{\theta(1+\theta)} e^{-\theta t_0}}. \tag{6}$$

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

In this Section we prove upper and lower estimates for the one–sided Hausdorff approximation of the Heaviside step–function $h_{t^*}(t)$ by means of families (6).

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

$$t_0 = 0;\ y_0 = e^{-\frac{k(2+\theta)}{\theta(1+\theta)}}$$

$$M(t) = e^{-\frac{k(2+\theta+\theta t)}{\theta(1+\theta)} e^{-\theta t}}. \tag{7}$$

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

Denoting by t^* the unique positive solution of the nonlinear equation:

$$(2+\theta+\theta t^*)e^{-\theta t^*} - \frac{\theta(1+\theta)\ln 2}{k} = 0. \tag{8}$$

Evidently, $M(t^*) = \frac{1}{2}$.

The one–sided Hausdorff distance d between the function $h_{t^*}(t)$ and the sigmoid - (7) satisfies the relation

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

The following theorem gives upper and lower bounds for d

Theorem 1. Let

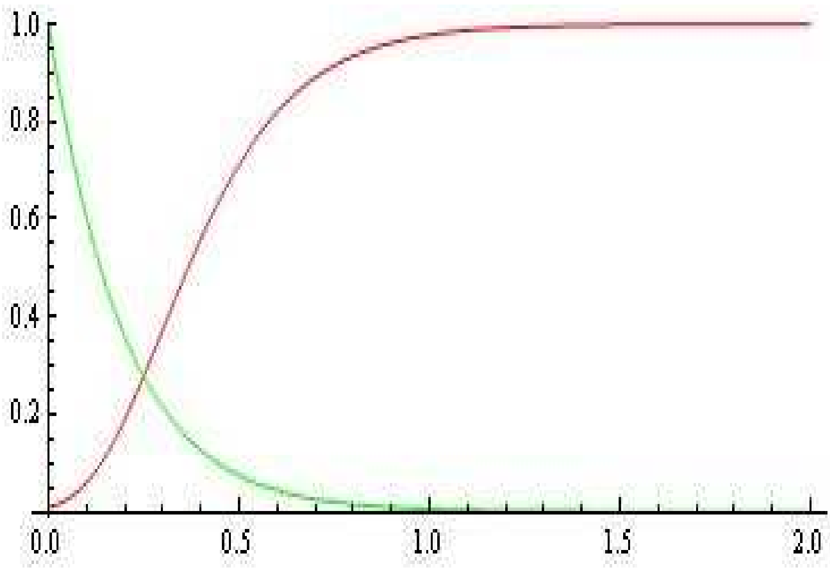

Figure 1: The functions $M(t)$–(red) and $s(t)$–(green) for $k = 24.3$; $\theta = 5.9$.

$$\alpha = -\tfrac{1}{2},$$
$$\beta = 1 + \tfrac{k(1+\theta+\theta t^*)}{2(1+\theta)} e^{-\theta t^*} \tag{10}$$
$$\gamma = 2.1\beta.$$

For the one–sided Hausdorff distance d between $h_{t^*}(t)$ and the sigmoid (7) 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

$$G(d) = \alpha + \beta d. \tag{13}$$

From Taylor expansion we obtain $G(d) - F(d) = O(d^2)$.

Hence $G(d)$ approximates $F(d)$ with $d \to 0$ as $O(d^2)$ (see Fig. 2).

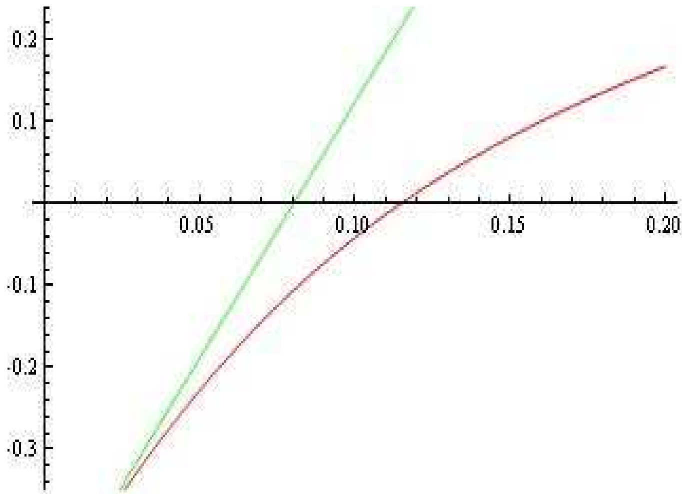

Figure 2: The functions $F(d)$ and $G(d)$ for $k = 68.3$; $\theta = 15.9$.

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 (6) for various k and θ are visualized on Fig. 3–Fig. 4.

4. SOME APPLICATIONS

The proposed model can be successfully used to approximating data from Population Dynamics.

4.1. APPROXIMATING THE "DATA ON THE DEVELOPMENT OF THE *DROSOPHILA MELANOGASTER* POPULATION"

We will illustrate the advances of the solution $y(t)$ for approximating and modelling of "data on the development of the *Drosophila melanogaster* population", published by biologist Raymond Pearl in 1920 (see, also [32]).

We consider the following data:

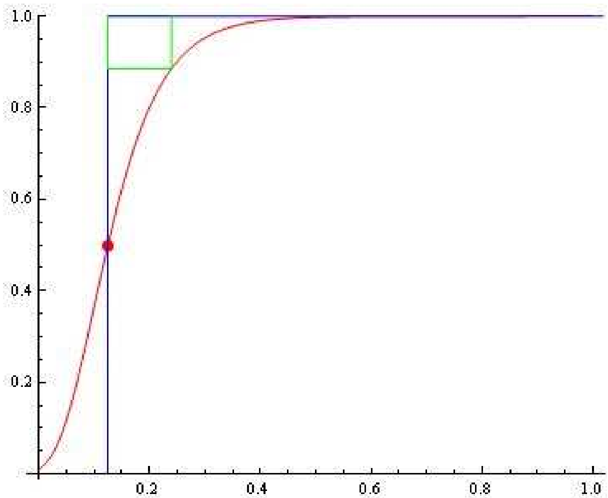

Figure 3: The model (7) for $k = 68.3$; $\theta = 15.9$; $t^* = 0.124959$; Hausdorff distance $d = 0.114808$; $d_l = 0.076393$; $d_r = 0.196472$.

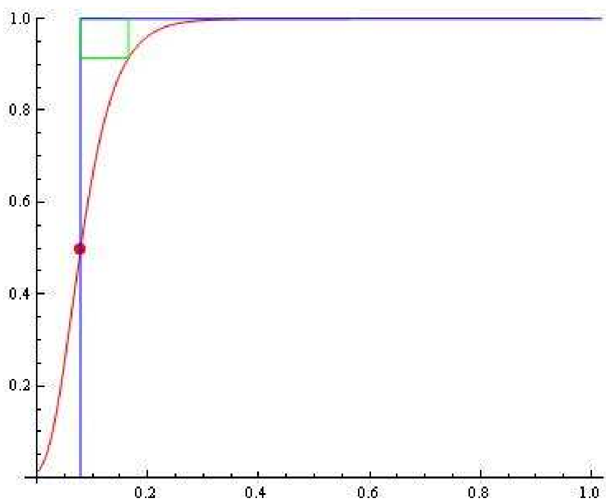

Figure 4: The model (7) for $k = 105.1$; $\theta = 24.5$; $t^* = 0.0788398$; Hausdorff distance $d = 0.0861885$; $d_l = 0.0518027$; $d_r = 0.153352$.

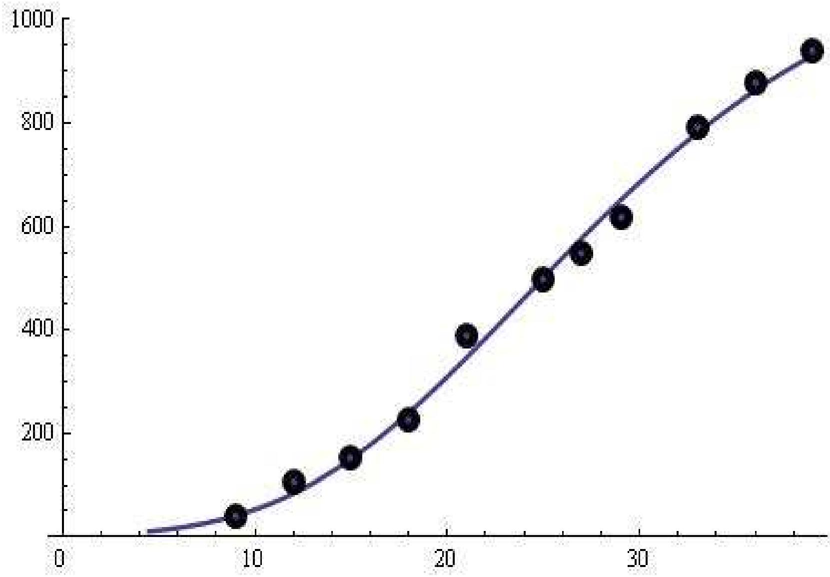

Figure 5: The fitted model $M^*(t)$.

$data\_Pearl$

$:= \{\{9, 39\}, \{12, 105\}, \{15, 152\}, \{18, 225\}, \{21, 390\}, \{25, 547\},$

$\{29, 618\}, \{33, 791\}, \{36, 877\}, \{39, 938\}\}.$

After that using the model

$$M^*(t) = \omega e^{-\frac{k(2+\theta+\theta t)}{\theta(1+\theta)} e^{-\theta t}}$$

for $\omega = 1162.27$, $k = 0.383217$ and $\theta = 0.115$ we obtain the fitted model (see, Fig. 5).

4.1.1. SOME COMPARISONS BETWEEN THE NEW LOGISTIC MODEL AND THE CLASSICAL LOGISTIC MODEL OF VERHULST–PEARL.

The classic model of Verhulst -Pearl for the $data\_Pearl$ looks like this (see, for example, [69]):

$$M^*_{VP}(t) = \frac{1035}{1 + e^{4.27 - 0.17t}}$$

and is illustrated in Fig. 6

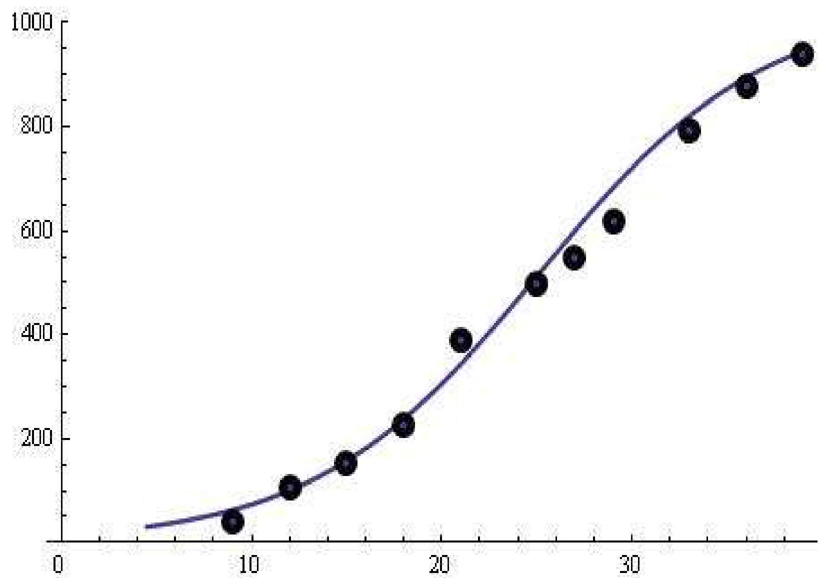

Figure 6: The fitted model $M^*_{VP}(t)$.

Of the accompanying illustrations see Fig. 5 and Fig. 6, it can be concluded that the proposed model $M^*(t)$ (7) is reliable.

4.2. APPLICATION OF THE NEW CUMULATIVE SIGMOID FOR ANALYSIS OF THE "CANCER DATA"

.

We will illustrate the advances of the solution $y(t)$ for approximation and modelling of "cancer data" (for some details see, [33]–[34]).

days	4	7	10	12	14	17	19	21
$R(t)$	0.415	0.794	1.001	1.102	1.192	1.22	1.241	1.3

Table 1: The "cancer data" [33]–[34]

Consider the model $M^*(t) = \omega e^{-\frac{k(2+\theta+\theta t)}{\theta(1+\theta)}e^{-\theta t}}$.

The model $M^*(t)$ based on the data from Table 1 for the estimated parameters:

$$\omega = 1.32845;\ \theta = 0.268;\ k = 0.306626$$

is plotted on Fig. 7.

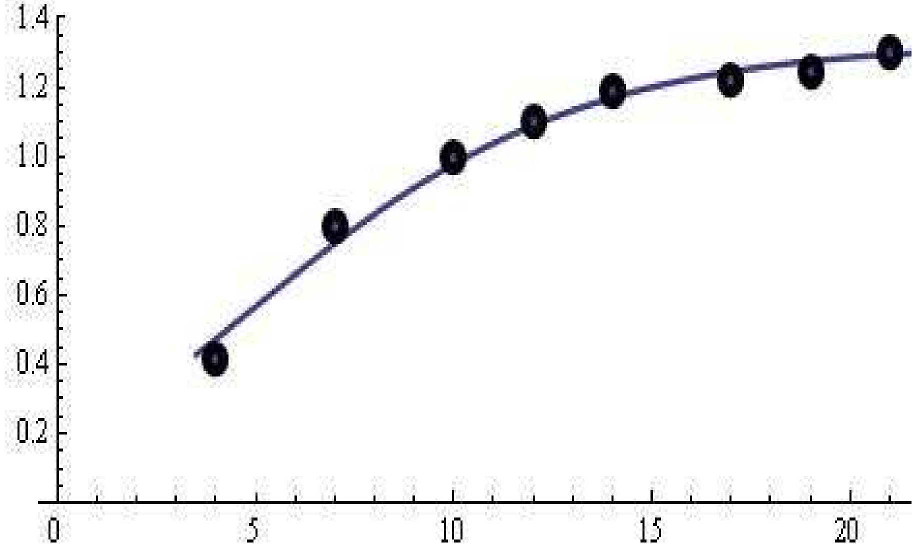

Figure 7: The model $M^*(t)$ based on the "cancer data".

4.3. APPROXIMATING THE "DATA ON THE DEVELOPMENT OF SACCHAROMYCES CULTURE IN NUTRIENT MEDIUM"

We will now analyze a sample of experimental data obtained by the biologist T. Carlson in 1913 about the development of Saccharomyces culture in nutrient medium (see, for example [67], [69]:

$$data\_Carlson$$
$$:= \{\{5, 19.1\}, \{6, 174.6\}, \{7, 257.3\}, \{8, 350.7\}, \{9, 441\},$$
$$\{10, 513.3\}, \{11, 559.7\}, \{12, 594.8\}, \{13, 629.4\}, \{14, 640.8\},$$
$$\{15, 651.1\}, \{16, 655.9\}, \{17, 659.6\}\}.$$

After that using the model $M^*(t)$ for $\theta = 0.47$, $k = 2.9600117$ and $\omega = 673.513$ we obtain the fitted model (see, Fig. 8).

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

We analyze experimental growth data (mean height) of sunflower plants (DSP) (see, for example [69]):

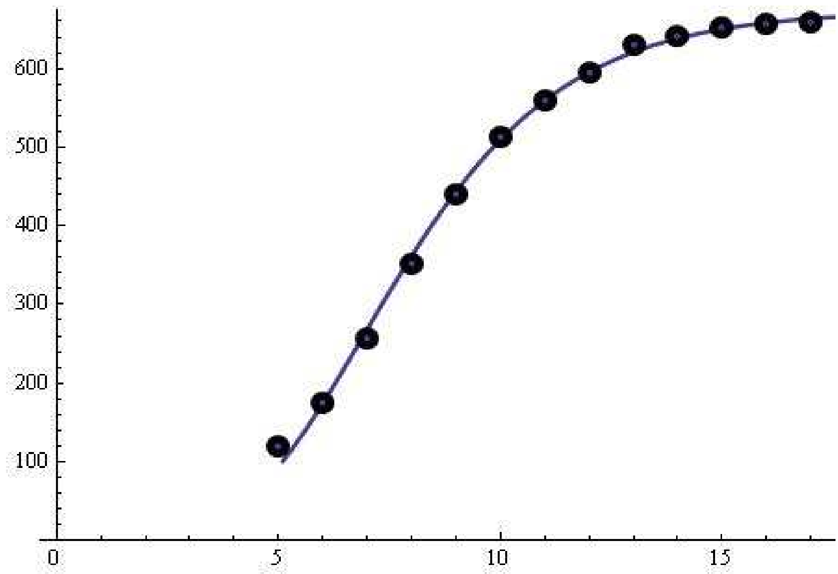

Figure 8: The fitted model $M^*(t)$.

$data\_DSP$

$:= \{\{14, 36.4\}, \{28, 98.1\}, \{49, 205.5\}, \{56, 228.3\}, \{70, 250.5\},$

$\{84, 254.5\}\}.$

For $\theta = 0.08$, $k = 0.176917$ and $\omega = 262.988$ we obtain the fitted model (see, Fig. 9).

4.5. APPROXIMATING THE DATA: "THE GROWTH OF POPULATION OF *RHIZAPERTHA* IN WHEAT"

We analyze a experimental data obtained by the Crombie in 1945 [68]:

$data\_Crombie$

$:= \{\{0, 2\}, \{14, 2\}, \{28, 2\}, \{35, 3\}, \{42, 17\}, \{49, 65\}, \{63, 119\},$

$\{77, 130\}, \{91, 175\}, \{105, 205\}, \{119, 261\}, \{133, 302\},$

$\{147, 330.6\}, \{161, 315\}, \{175, 333\}, \{189, 350\}, \{203, 332\},$

$\{231, 333\}, \{245, 335\}, \{259, 330\}\}.$

After that using the model $M^*(t)$ for $\theta = 0.036$, $k = 0.113865$ and $\omega = 343.284$

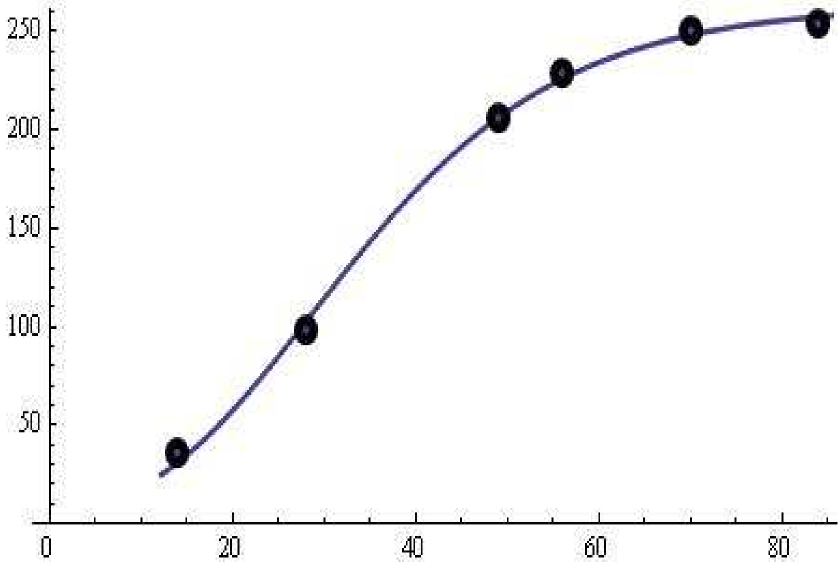

Figure 9: The fitted model $M^*(t)$.

we obtain the fitted model (see, Fig. 11).

As should expected, the experiments conducted (see, Sections 4.1 - 4.5) show a very good approximation of data from the field of population dynamics, with suggested in this article, modified logistic model.

4.6. THE NEW ACTIVATION FUNCTION BASED ON "AMENDMENTS" OF "LINDLEY - TYPE"

Definition 3. The sign function of a real number t is defined as follows:

$$sgn(t) = \begin{cases} -1, & \text{if} \quad t < 0, \\ 0, & \text{if} \quad t = 0, \\ 1, & \text{if} \quad t > 0. \end{cases} \tag{14}$$

Definition 4. The new parametric activation function based on "amendments" of "Lindley - type" is defined as follows

$$A(t) = \frac{e^{-\frac{k(2+\theta+\theta t)}{\theta(1+\theta)}e^{-\theta t}} - e^{-\frac{k(2+\theta+\theta t)}{\theta(1+\theta)}e^{\theta t}}}{e^{-\frac{k(2+\theta+\theta t)}{\theta(1+\theta)}e^{-\theta t}} + e^{-\frac{k(2+\theta+\theta t)}{\theta(1+\theta)}e^{\theta t}}}. \tag{15}$$

Approximation of the $sgn(t)$ by function A(t) for $k = 10.1$ and $\theta = 2.5$ is visualized on Fig. 12.

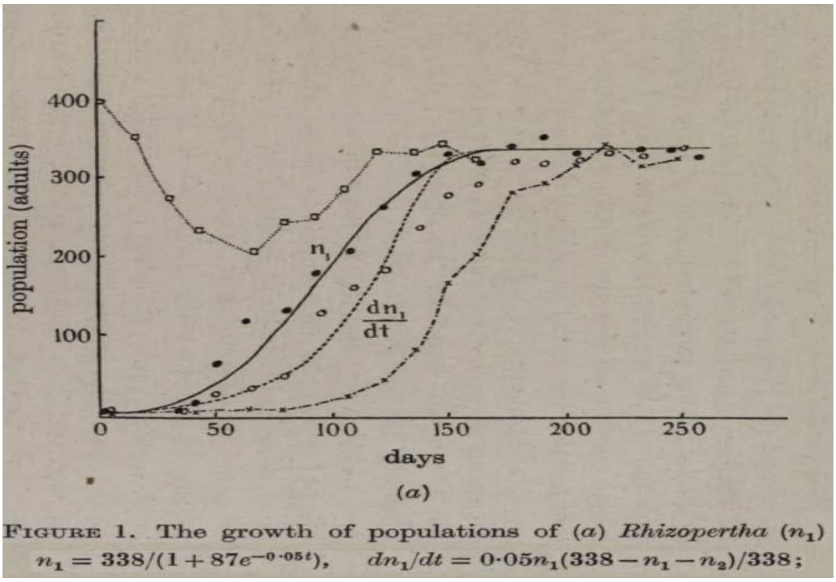

Figure 10: The fitted model by Crombie [68].

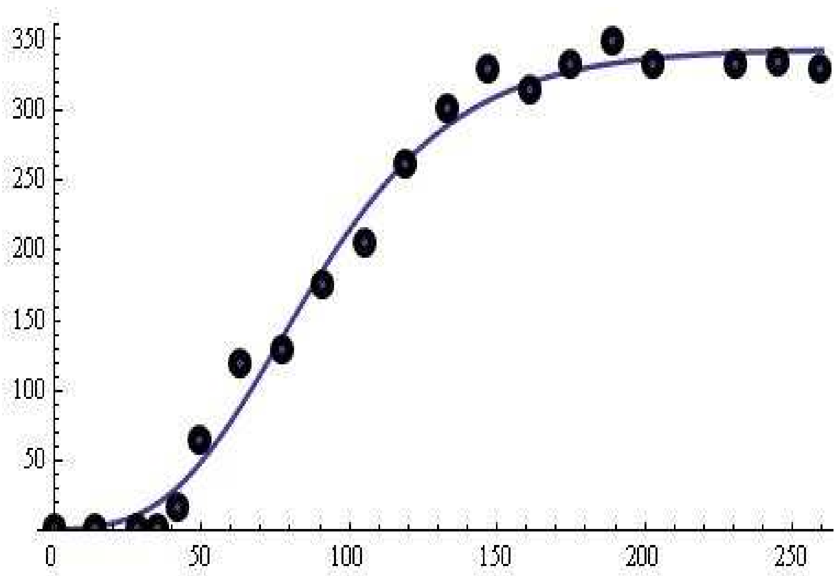

Figure 11: The fitted model $M^*(t)$.

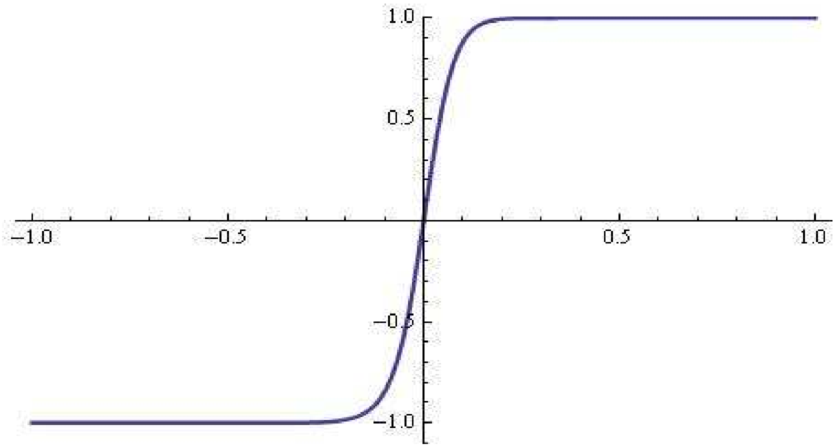

Figure 12: Approximation of the $sgn(t)$ by $A(t)$ for $k = 10.1$ and $\theta = 2.5$.

We will note that the study of the Hausdorff's approximation of the sign function by means of this new family can be done in a way given in [60] and we will omit it.

Similarly to the article cited above, recursively generable families of higher order activation functions can also be constructed.

5. CONCLUSION

A special choice of nutrient supply for cell growth in a continuous bioreactor with the Lindley type correction is introduced.

We prove upper and lower estimates for the one–sided Hausdorff approximation of the shifted Heaviside function $h_{t^*}(t)$ by means of the general solution of the differential equation $y'(t) = ky(t)s(t)$ with $y(t_0) = y_0$, where $s(t)$ is the correction of Lindley type.

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

The module offers the following possibilities:

- calculation of the H-distance between the h_{t^*} and the model $M(t)$ (7);
- generation of the functions under user defined values of the parameters k and θ;
- numerical solution of the differential model (3) and opportunities for comparison with other logistics models;
- software tools for animation and visualization.

We will explicitly note that similar approximation and modeling results associated with the use of "input function" $S(t)$ in the differential model (1) with Sen, Maiti and Chandra–type [70]:

$$S(t) = \frac{1 + \theta + \theta t + 0.5\theta^2 t^2}{1 + \theta} e^{-\theta t}$$

and also with Yousof, Korkmaz and Sen–type [71]:

$$S(t) = \frac{1 + \theta + \theta t^b + 0.5\theta^2 t^{2b}}{1 + \theta} e^{-\theta t^b}$$

can be obtained with the mathematical apparatus outlined in this article and here we will miss them.

ACKNOWLEDGMENT

This paper is supported by the National Scientific Program "Information and Communication Technologies for a Single Digital Market in Science, Education and Security (ICTinSES)", financed by the Ministry of Education and Science.

REFERENCES

[1] P. Pathi, T. Ma, R. Locke, Role of nutrient supply on cell growth in bioreactor design for tissue engineering of hematopoietic cells, *Biotechnology and Bioengineering*, **89**, No. 7 (2005).

[2] N. Li, H. Y. Sun, Q. L. Zhang, The dynamics and bifurcation control of a singular biological economic model, *Int. J. of Automat. and Comp.*, **9**, No. 1 (2012), 1–7.

[3] T. Egli, M. Zinn, The concept of multiple–nutrient–limited growth of microorganisms and its application in biotechnological processes, *Biotechnol. Adv.*, **22**, 2003, 5–43.

[4] D. F. Gerson, M. M. Kole, B. Ozum, M. N. Oguztoreli, Substrate concentration control in bioreactors, *Biotechnology and Genetic Engineering Reviews,* **6** (1), 1988, 67–150.

[5] Y. Zhang, Q. L. Zhang, L. C. Zhao, Analysis and feedback control for a class of bioeconomic systems, *J. Control Eng. of China*, **14**, No. 6 (2007), 599–603.

[6] Y. Zhang, Q. L. Zhang, L. C. Zhao, Bifurcations and control in singular biological economic model with stage structure, *J. of Syst. Eng.*, **22**, No. 3 (2007), 233–238.

[7] S. Luan, B. Liu, L. X. Zhang, Dynamics on a single-species model in a polluted environment, *J. of Biomath.*, **26**, No. 4 (2011), 689–694.

[8] V. Noris, E. Maurice, D. Maurice, Modelling Biological Systems with Competitive Coherence, *J. of Appl. Math.*, (2012), 1–20.

[9] M. Borisov, N. Dimitrova, V. Beshkov, Stability analysis of a bioreactor model for biodegradation of xenobiotics, *Comp. and Math. with Appl.,* **64**, (2012).

[10] N. Dimitrova, Local bifurcations in a nonlinear model of a bioreactor, *Serdica J. Computing*, **3** (2009), 107–132.

[11] T. Ivanov, N. Dimitrova, Analysis of a Bioreactor Model with Microbial Growth Phases and Spatial Dispersal, *Biomath Communications*, **2**, No. 2 (2016).

[12] N. Kyurkchiev, S. Markov, G. Velikova, The dynamics and control on a singular bio-economic model with stage structure, *Biomath Communications*, **2**, No. 2 (2015).

[13] N. Kyurkchiev, Investigations on a hyper-logistic model. Some applications, *Dynamic Systems and Applications*, **28**, No. 2 (2019), 351–369.

[14] E. Angelova, A. Golev, T. Terzieva, O. Rahneva, A study on a hyper–power–logistic model. Some applications, *Neural, Parallel and Scientific Computations*, **27** No. 1 (2019), 45–57.

[15] D. Lindley, Fiducial distributions and Bayes' theorem, *Journal of the Royal Statistical Society, Series B*, **20**, 1958, 102–107.

[16] D. Lindley, *Introduction to Probability and Statistics from Bayesian Viewpoint*, Part II: Inference, Cambridge University Press, New York (1965).

[17] C. Kilber, S. Kotz, *Statistical Size Distributions in Economics and Actuarial Science*, Willey, New York (2003).

[18] E. Gomez–Deniz, E. Calderin–Ojeda, The discrete Lindley distribution: properties and applications, *Journal of Statistical Computation and Simulation*, **81**, No. 11 (2011), 1405–1416.

[19] E. Calderin–Ojeda, E. Gomez–Deniz, An Extension of the Discrete Lindley Distribution with Applications, *Journal of the Korean Statistical Society*, **42**, No. 3 (2013), 371–373.

[20] M. Ghitany, B. Atieh, S. Nadarajan, Lindley distribution and its application, *Mathematics and Computers in Simulation*, **78** (2008), 493–506.

[21] M. Ghitany, D. Mutairi, N. Balakrishnan, E. Enezi, Power Lindley distribution and associated inference, *Computational Statistics and Data Analysis*, **64** (2013), 20–33.

[22] S. Nadarajah, M. Bakouch, R. Tahmasbi, A generalized Lindley distribution, *The Indian J. of Statistics, Series B*, **73**, No. 2 (2011), 331–359.

[23] M. Yilmaz, M. Hamaldarbandi, S. Kemaloglu, Exponential–modified discrete Lindley distribution, *SpringerPlus*, (2016), 5:1660.

[24] F. Merovci, I. Elbatal, Transmuted Lindley–Geometric Distribution and its Applications, —it J. of Statistics Applications and Probability, **3**, No. 1 (2014), 77–91.

[25] D. Granzotto, J. Mazucheli, F. Louzada, Statistical study of monthly rainfall trends by using the transmuted power Lindley distribution, *Int. J. of Statistics and Probability*, **6**, No. 1 (2017), 111–125.

[26] R. Shanker, A. Mishra, A quasi Lindley distribution, *African J. of Math. and Comp. Sci. Res.*, **6**, No. 4 (2013), 64–71.

[27] P. Kumaraswamy, A generalized probability density function for double-bounded random processes, *Journal of Hydrology*, **46**, No. 1–2, (1980), 79–88.

[28] S. Cakmakyapan, G. Ozel, A new customer lifetime duration distribution: the Kumaraswamy Lindley distribution, *Int. J. Trade Econ. Finance*, **5**, No. 5 (2014), 441–444.

[29] M. Elgarhy, I. Elbatal, M. Ahsan ul Haq, M. Hassan, Transmuted Kumuraswamy quasi Lindley distribution with applications, *Ann. Data. Sci.*, (2018).

[30] A. Malinova, V. Kyurkchiev, A. Iliev, N. Kyurkchiev, Some new approaches to Kumaraswamy-Lindley cumulative distribution function, *Int. J. of Innovative Sci. and Techn.*, **5**, No. 3 (2018).

[31] A. Malinova, V. Kyurkchiev, A. Iliev, N. Kyurkchiev, A note on the transmuted Kumaraswamy Quasi Lindley cumulative distribution function, *Int. J. for Sci., Res. and Developments*, **60**, No. 2 (2018), 561–564.

[32] W. Alpatov, R. Pearl, Experimental studies on the duration of life. XII. Influence of temperature during the larval period and adult life on the duration of the life of the imago of Drosophila melanogaster, *Am. Nat.*, **69**, No. 63 (1929), 37–67.

[33] M. Vinci, S. Gowan, F. Boxall, L. Patterson, M. Zimmermann, W. Court, C. Lomas, M. Mendila, D. Hardisson, S. Eccles, Advances in establishment and analysis of three-dimensional tumor spheroid-based functional assays for target validation and drug evaluation, *BMC Biology*, **10** (2012).

[34] A. Antonov, S. Nenov, T. Tsvetkov, Impulsive controllability of tumor growth, *Dynamic Systems and Appl.*, **28**, No. 1 (2019), 93–109.

[35] F. Hausdorff, *Set Theory*, 2nd ed., Chelsea Publ., New York (1962).

[36] B. Sendov, *Hausdorff Approximations*, Kluwer, Boston (1990).

[37] N. Kyurkchiev, S. Markov, On the Hausdorff distance between the Heaviside step function and Verhulst logistic function, *J. Math. Chem.*, **54**, No. 1 (2016), 109–119.

[38] N. Kyurkchiev, S. Markov, *Sigmoid functions: Some Approximation and Modelling Aspects*, LAP LAMBERT Academic Publishing, Saarbrucken (2015), ISBN 978-3-659-76045-7.

[39] N. Kyurkchiev, A. Iliev, S. Markov, *Some techniques for recurrence generating of activation functions*, LAP LAMBERT Academic Publishing (2017), ISBN: 978-3-330-33143-3.

[40] R. Anguelov, N. Kyurkchiev, S. Markov, Some properties of the Blumberg's hyper-log-logistic curve, *Biomath*, **7** No. 1 (2018), 8 pp.

[41] A. Iliev, N. Kyurkchiev, S. Markov, On the Approximation of the step function by some sigmoid functions, *Mathematics and Computers in Simulation*, **133** (2017), 223–234.

[42] A. Iliev, N. Kyurkchiev, S. Markov, Approximation of the cut function by Stannard and Richards sigmoid functions, *IJPAM*, **109** No. 1 (2016), 119–128.

[43] S. Markov, A. Iliev, A. Rahnev, N. Kyurkchiev, A note on the Log-logistic and transmuted Log-logistic models. Some applications, *Dynamic Systems and Applications*, **27** No. 3 (2018), 593–607.

[44] S. Markov, N. Kyurkchiev, A. Iliev, A. Rahnev, On the approximation of the cut functions by hyper-log-logistic function, *Neural, Parallel and Scientific Computations*, **26** No. 2 (2018), 169–182.

[45] N. Kyurkchiev, A Note on the Volmer's Activation (VA) Function, *C. R. Acad. Bulg. Sci.*, **70**, No. 6 (2017), 769–776.

[46] N. Kyurkchiev, A note on the new geometric representation for the parameters in the fibril elongation process. *C. R. Acad. Bulg. Sci.*, **69**, No. 8 (2016), 963–972.

[47] N. Kyurkchiev, On the numerical solution of the general "ligand-gated neuroreceptors model" via CAS Mathematica, *Pliska Stud. Math. Bulgar.*, **26** (2016), 133–142.

[48] N. Kyurkchiev, S. Markov, On the numerical solution of the general kinetic "K-angle" reaction system, *Journal of Mathematical Chemistry*, **54**, No. 3 (2016), 792–805.

[49] N. Guliyev, V. Ismailov, A single hidden layer feedforward network with only one neuron in the hidden layer san approximate any univariate function, *Neural Computation*, **28** (2016), 1289–1304.

[50] D. Costarelli, R. Spigler, Approximation results for neural network operators activated by sigmoidal functions, *Neural Networks*, **44** (2013), 101–106.

[51] D. Costarelli, R. Spigler, Constructive Approximation by Superposition of Sigmoidal Functions, *Anal. Theory Appl.*, **29** (2013), 169–196.

[52] B. I. Yun, A Neural Network Approximation Based on a Parametric Sigmoidal Function, *Mathematics*, **7** (2019), 262.

[53] N. Kyurkchiev, A. Iliev, *Extension of Gompertz-type Equation in Modern Science: 240 Anniversary of the birth of B. Gompertz*, LAP LAMBERT Academic Publishing (2018), ISBN: 978-613-9-90569-0.

[54] S. Markov, N. Kyurkchiev, A. Iliev, A. Rahnev, On the approximation of the generalized cut functions of degree $p + 1$ by smooth hyper-log-logistic function, *Dynamic Systems and Applications*, **27** No. 4 (2018), 715–728.

[55] A. Malinova, O. Rahneva, A. Golev, V. Kyurkchiev, Investigations on the Odd-Burr-III-Weibull cumulative sigmoid. Some applications, *Neural, Parallel, and Scientific Computations*, **27**, No. 1 (2019), 35–44.

[56] O. Rahneva, H. Kiskinov, I. Dimitrov, V. Matanski, Application of a Weibull Cumulative Distribution Function Based on m Existing Ones to Population Dynamics, *International Electronic Journal of Pure and Applied Mathematics*, **12**, No. 1 (2018), 111–121.

[57] N. Kyurkchiev, A. Iliev, A. Rahnev, T. Terzieva, A new analysis of Code Red and Witty worms behavior, *Communications in Applied Analysis*, **23**, No. 2 (2019), 267–285.

[58] N. Kyurkchiev, A. Iliev, A. Rahnev, T. Terzieva, Some New Approaches for Modelling Large–Scale Worm Spreading on the Internet. II, *Neural, Parallel, and Scientific Computations*, **27**, No 1 (2019), 23–34.

[59] N. Kyurkchiev, A. Iliev, A. Rahnev, T. Terzieva, A New Analysis of Cryptolocker Ransomware and Welchia Worm Propagation Behavior. Some Applications. III, *Communications in Applied Analysis*, **23**, No. 2 (2019), 359–382.

[60] N. Kyurkchiev, A. Iliev, A. Rahnev, A new class of activation functions based on the correcting amendments of Gompertz-Makeham type, *Dynamic Systems and Applications*, **28**, No. 2 (2019), 243–257.

[61] R. Anguelov, M. Borisov, A. Iliev, N. Kyurkchiev, S. Markov, On the chemical meaning of some growth models possessing Gompertzian-type property, *Math. Meth. Appl. Sci.*, (2017), 12 pp.

[62] N. Pavlov, A. Iliev, A. Rahnev, N. Kyurkchiev, *Some software reliability models: Approximation and modeling aspects*, LAP LAMBERT Academic Publishing, (2018), ISBN: 978-613-9-82805-0.

[63] N. Pavlov, A. Iliev, A. Rahnev, N. Kyurkchiev, *Nontrivial Models in Debugging Theory (Part 2)*, LAP LAMBERT Academic Publishing, (2018), ISBN: 978-613-9-87794-2.

[64] N. Kyurkchiev, A. Iliev, A. Rahnev, *Some Families of Sigmoid Functions: Applications to Growth Theory*, LAP LAMBERT Academic Publishing, (2019), ISBN: 978-613-9-45608-6.

[65] A. Iliev, N. Kyurkchiev, A. Rahnev, T. Terzieva, *Some models in the theory of computer viruses propagation*, LAP LAMBERT Academic Publishing, (2019). (to appear)

[66] V. Calsavara, A. Rodrigues, R. Rocha, F. Louzada, V. Tomazella, A. Souza, R. Costa, R. Francisco, Zero–adjusted defective regression models for modeling lifetime data, *J. of Appl. Stat.*, (2019).

[67] E. Bohl, *Mathematik in der Biologie*, 4., vollständig überarbeitete und erweiterte Auflage, Springer, Berlin (2006).

[68] A. C. Crombie, On competition between different species of graminivorous insects, *Proceedings of the Royal Society B*, **132** (1945), 362–395.

[69] Bl. Sendov, R. Maleev, S. Markov, S. Tashev, *Mathematics for Biologists*, University Publishing House, "St. Kliment Ohridski", (1991).

[70] S. Sen, S. Maiti, N. Chandra, The xgamma distribution: statistical properties and applications, *J. Mod. Appl. Stat. Methods*, **15**, No. 1 (2016), 774–788.

[71] H. Yousof, M. Korkmaz, S. Sen, A new two-parameter lifetime model, *Annals of Data Sciences*, (2019).