

Nonlinear Hyperbolastic Growth Models and Applications in Cranofacial and Stem Cell Growth

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Abstract

Mathematical models describing growth kinetics are very important for predicting many biological phenomena such as tumor volume, number of stem cells and/or cranofacial growth. Growth models such as logistic, Gompertz, Richards, and Weibull have been extensively studied and applied in a wide range of medical and biological studies. We introduce a class of three and four parameter models called “hyperbolastic models” for accurately predicting and analyzing self-limited growth behavior. To illustrate the application and utility of these models, we apply them to two previously published sets of data. In both applications, based on several accuracy measures, at least one of newly proposed models provides a better fit to the data than the four classic models. Newly proposed H3 model performs the best in both instances. We strongly believe that the family of hyperbolastic models can be a valuable predictive tool in many areas of biomedical and epidemiologic research. Practitioners should test and compare the fit and prediction of these models to the standard ones before making a decision on the most appropriate one.

Keywords: Hyperbolastic models, Nonlinear models, Growth models.

1. Introduction

The analysis of growth is an important component of many clinical or biological studies. The evolution of the mathematical models such as Gompertz, Logistic, Richards, Weibull and Von Bertalanffy used to describe population growth, are great examples of how this field has evolved over the years. These models have proved useful in modeling a wide range of problems. The logistic model imposes the constraint that the growth path be symmetric about the point of maximum growth rate. On the other hand, the Gompertz model does not incorporate the symmetry restriction. Both Logistic and Gompertz have points of inflection

which are always at a fixed proportion of their limiting population values. A number of recent publications have utilized some of these models. Our purpose is to introduce three new growth models [1] which have flexible inflection points and can fit sigmoidal data with different shapes (Figure 5) and demonstrate their performance on two additional previously published data sources. We apply our proposed models to NIH BG01 embryonic stem cell growth data [2] and U1-SN angular data from the Ochoa et al. craniofacial growth study [3] and compare their fit with four classical models that include Logistic [4], Richards [5], Gompertz [6], and Weibull [7].

2. The Hyperbolastic Model H1

First we start by considering the following growth curve which produces flexible asymmetric curves, through nonlinear ordinary differential equation of the form

$$\frac{dP(t)}{dt} = \frac{1}{M} P(t)(M - P(t)) \left(M\beta + \frac{\theta}{\sqrt{1+t^2}} \right) \quad (1)$$

or

$$\frac{dP}{dt} = \left(\beta M + \frac{\theta}{\sqrt{1+t^2}} \right) P - \left(\frac{\theta}{M\sqrt{1+t^2}} + \beta \right) P^2$$

with initial condition

$$P(t_0) = P_0$$

where $P(t)$ represents the population size at time t , β is the parameter representing the intrinsic growth rate, θ is a parameter, and M represents the maximum sustainable population (carrying capacity), which is assumed to be constant, though in general the carrying capacity may change over time. For growth curves, β has to be positive, leading to an eventually increasing curve with an asymptote at M ; β can be negative only for eventual inhibition curves or decay profiles. We refer to growth rate model (1) as the hyperbolastic differential equation of type

I. If $\theta = 0$, then the model (1) reduces to a logistic differential equation, and equation (2) reduces to a general logistic model [4]. Solving the equation (1) for the population P gives

$$P(t) = \frac{M}{1 + \alpha \text{EXP}[-M\beta t - \theta \text{arcsinh}(t)]} \quad (2)$$

where

$$\alpha = \frac{M - P_0}{P_0} \text{EXP}[M\beta t_0 + \theta \text{arcsinh}(t_0)]$$

and $\text{arcsinh}(t)$ is the inverse hyperbolic sine function of t . We call the function $P(t)$ in equation (2) the hyperbolastic growth model of type I or simply H1. To reduce the number of parameters, observed values of P_0 and t_0 are used to obtain an approximate value of α . From equation (1) we can calculate the second derivative and if we set $\theta = 0$, the second derivative

$$\frac{d^2 P(t)}{dt} = 0$$

when

$$P = \frac{M}{2} .$$

In other words, when the population P reaches half the carrying capacity M , the growth is most rapid and then starts to diminish toward zero. If we assume $\theta \neq 0$, then the growth is most rapid at the time t^* , such that t^* satisfies the following equation

$$[M - 2P(t^*)] \left(M\beta + \frac{\theta}{\sqrt{1+t^{*2}}} \right)^2 - \frac{\theta M t^*}{(1+t^{*2})^{\frac{3}{2}}} = 0 .$$

3. The Hyperbolastic Model H2

Now we consider an alternative growth curve through nonlinear hyperbolastic differential equation of the form

$$\frac{dP(t)}{dt} = \alpha\beta\gamma P^2(t)t^{\gamma-1} \tanh \left[\frac{M - P(t)}{\alpha P(t)} \right] \quad (3)$$

with initial condition $P(t_0) = P_0$ and $\gamma > 0$, where \tanh stands for hyperbolic tangent function, M is the carrying capacity, and β and γ are parameters. As in the H1 model, parameter β has to be positive for increasing growth curves with an asymptote at M and is negative only for decay profiles. We refer to the growth rate model (3) as the hyperbolastic differential equation of type II. Solving equation (3) for population size P gives the three parameter model

$$P(t) = \frac{M}{1 + \alpha \text{arcsinh} \left[\text{EXP}(-M\beta t^\gamma) \right]} \quad (4)$$

where

$$\alpha = \frac{M - P_0}{P_0 \text{arcsinh} \left[\text{EXP}(-M\beta t_0^\gamma) \right]} .$$

We call the function $P(t)$ in equation (4) the hyperbolastic growth model of type II or simply H2. As in the H1 model, observed values of P_0 and t_0 are used to obtain an approximate value of α and to reduce the number of parameters. Notice from equation (4) that for positive values of β , $P(t)$ approaches M as t tends to infinity and for negative values of β , $P(t)$ approaches zero as t tends to infinity. Moreover, from equation (3), we calculate the second derivative for which the growth rate is most rapid at the time t^* , provided that $t = t^*$ satisfies the following equation

$$\beta\gamma t^{*\gamma} \left\{ \alpha P(t^*) - M \text{csch} \left[\frac{2(M - P(t^*))}{\alpha P(t^*)} \right] \right\} + (\gamma - 1) \coth \left[\frac{M - P(t^*)}{\alpha P(t^*)} \right] = 0$$

and if we set $\gamma = 1$, then the growth rate is most rapid at time $t = t^*$ if the following equality is true

$$P(t^*) = \frac{M}{\alpha} \text{csch} \left[\frac{2(M - P(t^*))}{\alpha P(t^*)} \right] .$$

4. The Hyperbolastic Model H3

Finally, we consider the third growth curve through the following nonlinear hyperbolastic differential equation of the form

$$\frac{dP(t)}{dt} = (M - P(t)) \left(\beta\gamma t^{\gamma-1} + \frac{\theta}{\sqrt{1+\theta^2 t^2}} \right) \quad (5)$$

with initial condition $P(t_0) = P_0$ where M is the carrying capacity and β , γ and θ are parameters. We refer to model (5) as the hyperbolastic ordinary differential equation of type III. The solution to equation (5) is a four parameter model

$$P(t) = M - \alpha \text{EXP}[-\beta t^\gamma - \text{arcsinh}(\theta t)] \quad (6)$$

where

$$\alpha = (M - P_0) \text{EXP}[\beta t_0^\gamma + \text{arcsinh}(\theta t_0)] .$$

We call the function $P(t)$ in equation (6) the hyperbolastic growth model of type III or simply H3. If $\theta=0$, then this model reduces to the Weibull function [7]. The growth rate is most rapid at time t^* such that

$$\left[\beta \gamma t^{*\gamma-1} + \frac{\theta}{\sqrt{1+\theta^2 t^{*2}}} \right]^2 = \left[\beta \gamma (\gamma-1) t^{*\gamma-2} - \frac{\theta^3 t^*}{(1+\theta^2 t^{*2})^{\frac{3}{2}}} \right]$$

5. Application of Hyperbolastic Models

5.1 Statistical Analysis

We perform analysis of two data sets by fitting general Logistic model of the form

$$P(t) = \frac{M}{[1 + \alpha \text{EXP}(-M \beta t)]} \quad [4], \text{ where}$$

$$\alpha = \frac{M - P_0}{P_0} \text{EXP}(M \beta t_0),$$

the Richards model of the form

$$P(t) = \frac{M}{[1 + \alpha \text{EXP}(-M \beta t)]^\gamma} \quad [5], \text{ where}$$

$$\alpha = \left[\left(\frac{M}{P_0} \right)^\frac{1}{\gamma} - 1 \right] \text{EXP}(M \beta t_0),$$

the Gompertz model of the form

$$P(t) = M \text{EXP}[-\alpha \text{EXP}(-M \beta t)] \quad [6], \text{ where}$$

$$\alpha = LN \left(\frac{M}{P_0} \right) \text{EXP}(M \beta t_0),$$

the Weibull model of the form

$$P(t) = M - \alpha \text{EXP}(-\beta t^\gamma) \quad [7], \text{ where}$$

$$\alpha = (M - P_0) \text{EXP}(\beta t_0^\gamma)$$

and the hyperbolastic models H1, H2, and H3 described above. Obviously some of these models are closely related. Nonetheless, the parameter values may be quite different when these models are fitted to a single set of data. The logistic model used here is a two parameter symmetric model, while the Richards model generalizes the logistic model by introducing an additional parameter (γ) to the equation to deal with asymmetrical growth. The Richards function reduces to the logistic equation if $\gamma=1$. The Gompertz equation, which is a two parameter asymmetric equation, attains its maximum growth rate at an earlier time than the logistic. In the Weibull equation, β and γ are constants defining the shape of the response. In all seven models M is a constant, the maximum value or the upper asymptote, which is estimated by non-linear regression. In each instance we express one model parameter (α) as the function of the other parameters and initial observed value P_0 at time t_0 , which allows us to reduce the number of parameters to be estimated and also anchors the first predicted value to the original value observed at the initial time point. Absolute value of the relative error (RE), which was defined as

$$\left| \frac{y_i - \hat{y}_i}{y_i} \right|,$$

was used to indicate the prediction accuracy or goodness of fit for all seven fitted models. The mean squared error and the R^2 value from the nonlinear regression were also examined but led to the identical conclusions so only RE are presented in this paper. All models were fitted using SAS v.9.1 PROC NLIN (SAS Institute Inc., Cary, NC) and SPSS v.12.0.1 (SPSS Inc., Chicago, IL). The best fitting functions and their derivatives can also be plotted in order to find the growth rates and accelerations which can be of interest to some researchers in specific fields.

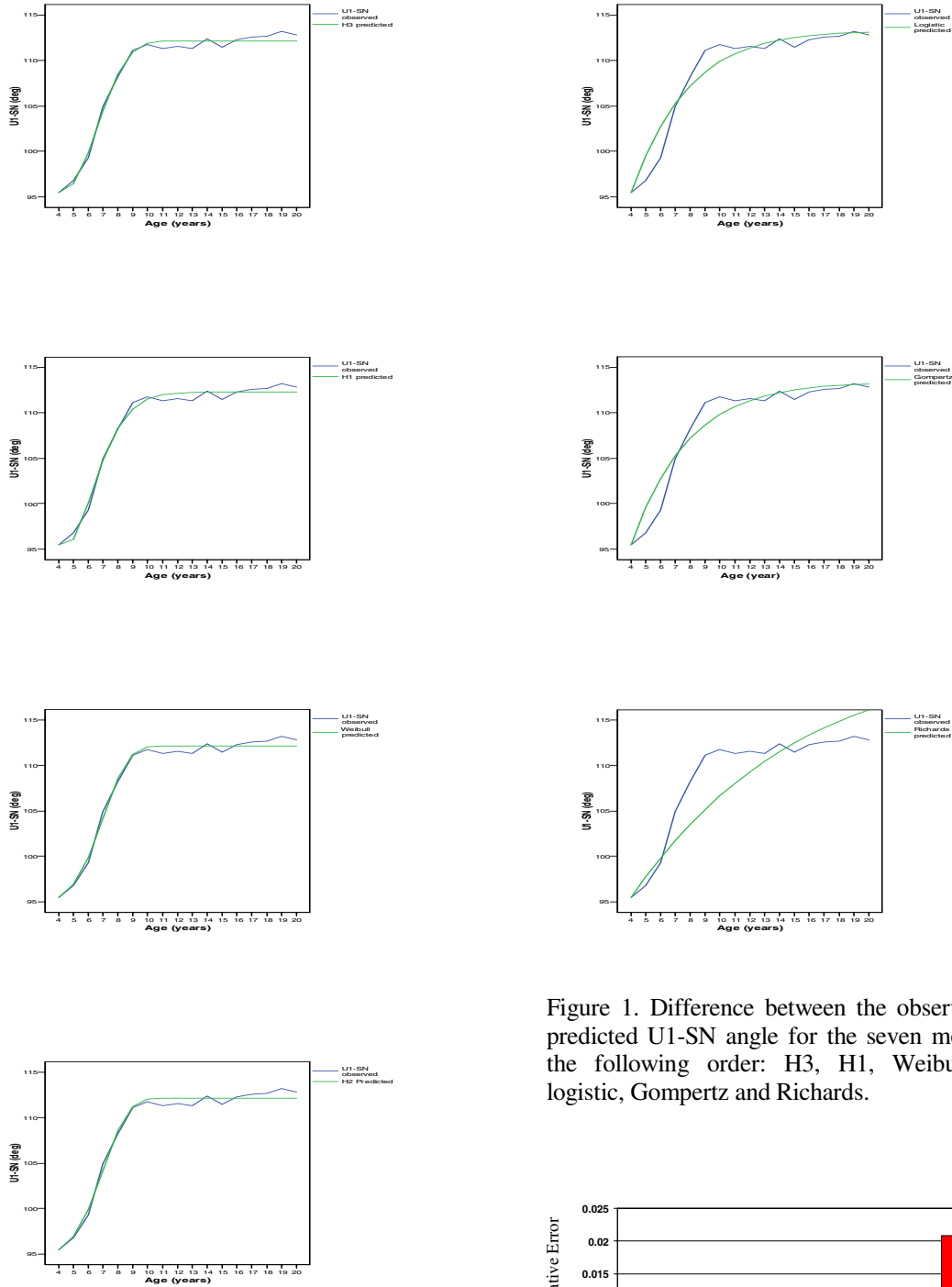


Figure 1. Difference between the observed and predicted U1-SN angle for the seven models in the following order: H3, H1, Weibull, H2, logistic, Gompertz and Richards.

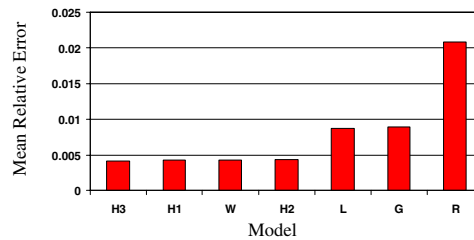


Figure 2. Bar graphs represent mean(s) of the relative error(s) for the U1-SN angle models.

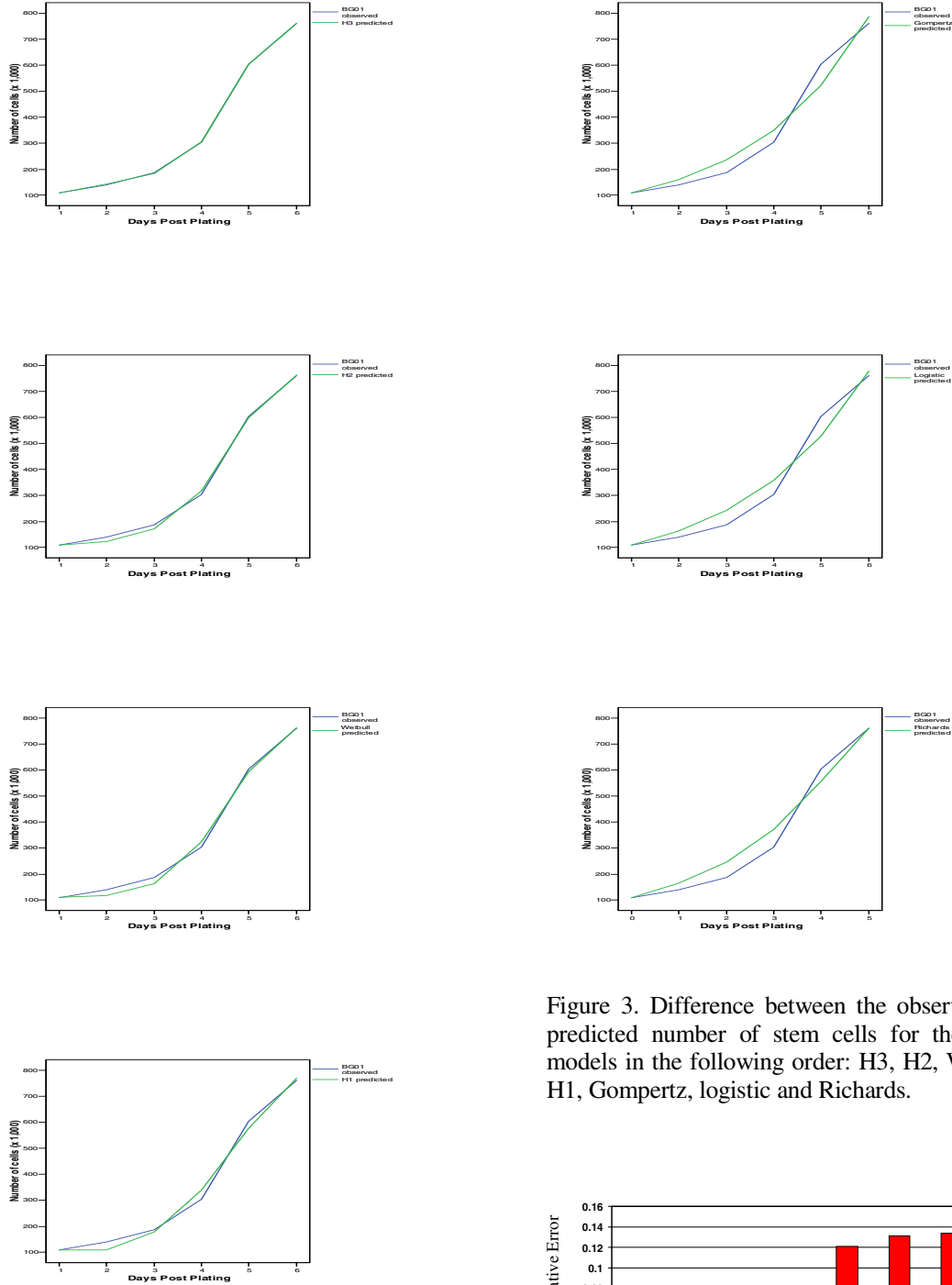


Figure 3. Difference between the observed and predicted number of stem cells for the seven models in the following order: H3, H2, Weibull, H1, Gompertz, logistic and Richards.

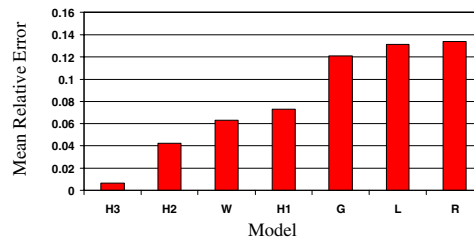


Figure 4. Bar graphs represent mean(s) of the relative error(s) for the stem cell models.

5.2 Analysis of the Cranofacial Growth Data

Ochoa et al. [3] studied cranofacial growth and development based on the large data base of more than 200 subjects that contains over 300 cranofacial measurements. U1-SN is an angular measurement that was selected because of its growth pattern in order to test the performance of our models. Seven models were fitted for ages ranging from 4 to 20 years of age. The results show that H3 ($RE=0.0042$) model provides the best fit to the data followed by the H1 ($RE=0.0043$), Weibull ($RE=0.0043$) and H2 ($RE=0.0044$) models. The logistic ($RE=0.0087$), Gompertz ($RE=0.009$) and Richards ($RE=0.021$) models are clearly inadequate in describing U1-SN growth pattern (Figures 1 and 2).

5.3 Analysis of the Stem Cell Growth Data

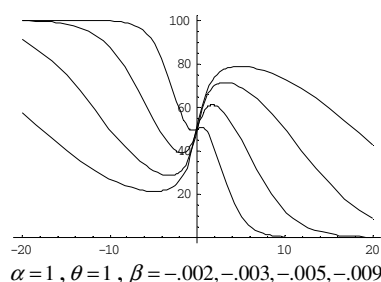
BG01 human embryonic stem cell growth data (in 1,000), posted on the NIH web site [2], were used as a second example for proposed models. Seven models were fitted to this data for 6 days post plating as a covariate for time. Results revealed that H3 ($RE=0.007$) model was by far the most superior model of seven. It was followed by H2 ($RE=0.043$), Weibull ($RE=0.063$), and H1 ($RE=0.073$) models respectively. Again, Gompertz ($RE=0.121$), logistic ($RE=0.131$) and Richards ($RE=0.134$) were the three models with highest mean RE (Figures 3 and 4). Even though the H2 model provides second best fit to the data note that H1 model has 6 times smaller RE (Figure 4).

6. Discussion

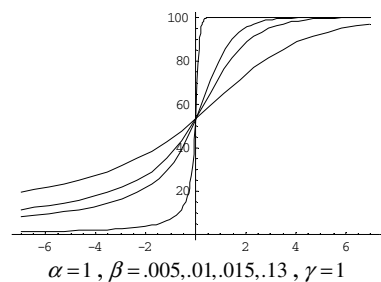
Obviously no model can accurately describe every biological phenomenon that researchers encounter in their practice; the same is true for our models. Many models have been developed to deal with sigmoid growth [8] and new ones are continuously being proposed. The logistic function is symmetric around the point of inflection. The Richards function is more flexible and can fit asymmetric growth patterns [9, 10]; however, it has more parameters than the logistic function. The Gompertz function has the same number of parameters as the logistic function and the Weibull function has the same number of parameters as the Richards function and both can fit asymmetric growth, but they are not very flexible [9].

The H1 function has one more parameter than the logistic and Gompertz functions, but it is more flexible and can fit asymmetric growth patterns as well as increasing and decreasing growth, as shown in the MTS volume example. The H2 function has the same number of parameters as H1 and can fit asymmetric curves, but it cannot fit decreasing growth patterns, so it is less flexible. The H3 function has the same flexibility as the H1 function at the expense of one more parameter, similar to the Weibull and Richards equations. Some of the flexibility of the H1, H2 and H3 functions is illustrated in Figure 5. More can be found in Tabatabai et al. paper [1].

H1



H2



H3

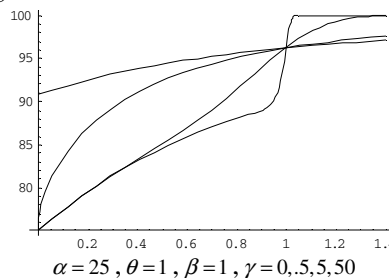


Figure 5. Functions illustrate the flexibility of the H1, H2 and H3 models. One parameter is varied while the others are held constant to demonstrate the capability of the models to fit different growth or decay patterns. In all examples parameter M is held constant at 100.

The logistic and Gompertz functions have two parameters that are easily interpretable. Like Yin [9], we encountered problems in trying to provide initial parameter values in the Weibull function. One can arrive at a satisfactory solution by trial and error, or using a grid search in SAS PROC NLIN by providing a range of starting values. These functions can be easily implemented in SPSS or SAS PROC NLIN or other readily available software packages. Free SAS code used to fit similar data can be found at <http://www.tbiomed.com/content/supplementary/1742-4682-2-14-S1.doc> or at <http://www.uams.edu/biostat/bursac/Hyperbolastic.htm>.

Non-linear function parameters that have biological meaning are more advantageous for statistical parameterization of such equations. The same can be said for some of the parameters in the three proposed models, which can be determined by summarizing the data or using the above suggestions. Table 1 provides estimates for the parameters of the H1, H2 and H3 models based on two applications presented in this paper. If necessary, an additional parameter called the shift parameter may be added to a model to improve the fit of the data to a model.

While the results presented are valid only for the data sets used in this study, these models can have much wider application than shown here. We successfully applied them to several other data sets including cancer volume [1,11] and polio outbreak [1,12] growth data and the results indicate supreme prediction accuracy for the hyperbolastic models. Based on the results presented in this and Tabatabai et al. paper [1], we can say that the H3 model performs the best with tumor volume, craniofacial and stem cell growth data. However, it is reasonable to compare models for fit before deciding on the selection of the “best” one. With appropriate parameter adjustments in H1 or H2, one can derive regression type models for dichotomous or polytomous response variables, or use variants of H3 model in survival data problems, reliability studies, business applications and many other situations.

Finally, our hyperbolastic models show very promising results. In both the above discussed data sets, they fitted the data with smaller mean RE and higher prediction accuracy than the logistic, Richards and Gompertz, which were the worst fit models in both cases.

Table 1. Parameter estimates (with standard errors in parentheses) for H1, H2 and H3 models applied in two examples.

Model	Parameter	U1-SN Estimates	Stem Cell Estimates
H1	M	112.3 (0.19)	896.4 (109.1)
	β	0.02 (0.002)	0.002 (0.001)
	θ	-7.34 (1.03)	-3.19 (1.13)
H2	M	112.1 (0.19)	784.5 (23.9)
	β	9.7×10^{-7} (1.1×10^{-6})	2.7×10^{-5} (1.1×10^{-5})
	γ	4.68 (0.55)	3.09 (0.29)
H3	M	112.2 (0.2)	764.1 (5.92)
	β	0.05 (0.05)	1.9×10^{-4} (0.9×10^{-4})
	γ	2.42 (0.61)	6.27 (0.33)
	θ	0.01 (0.09)	0.05 (0.01)

Our models are accurate and simple and two of them generalize the logistic and Weibull models. They can be easily implemented and tested in readily available software packages or routines. We strongly believe that choosing a flexible and highly accurate predictive model such as hyperbolastic can significantly improve the outcome of a study for it is the accuracy of a model that determines its utility. We strongly recommend usage of such models to the scientific community and practitioners and urge comparison of them with classical models before decisions on model selection are made.

References

Tabatabai M, Williams DK, Bursac Z. 2005. Hyperbolastic growth models: Theory and application. *Theor Biol Med Model*, 2(14):1-13. <http://stemcells.nih.gov/research/NIHresearch/scunit/growthCurves.asp>

Ochoa B and Nanda RS. 2004. Comparison of maxillary and mandibular growth. *Am J Orthod Dentofacial Orthop*, 125(2):148-59.

Verhulst PF. 1838. A note on population growth. *Correspondence Mathematiques et Physiques*, 10:113-121.

- Richards FJ. 1959. A flexible growth function for empirical use. *J of Exper Bot*, 10:290-300.
- Gompertz B. 1825. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Phil Trans of the Royal Soc*, 182:513-585.
- Weibull W. 1951. A statistical distribution function of wide applicability. *J of Appl Mech*, 18:293-297.
- Zeide B. 1993. Analysis of growth equations. *Forest Sci*, 39:594-616.
- Yin X, Goudriaan J, Latinga EA et al. 2003. A flexible sigmoid function of determinate growth. *Ann of Bot*, 91:361-371.
- Zhu Q, Cao X, Luo Y. 1988. Growth analysis on the process of grain filling in rice. *Acta Agronomica Sinica*, 14:182-193.
- Deisboeck TS, Berens ME, Kansal AR et al. 2001. Pattern of self-organization in tumour systems: complex growth dynamics in a novel brain tumour spheroid model. *Cell Prolif*, 34:115-134.
- Paul JR. 1971. History of Poliomyelitis. *New Heaven and London: Yale University Press*.