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PROLIFERATION OF STEM CELLS IN A POPULATION MODEL

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ABSTRACT

In stem cell research, extending the stem cell phenotype which is undifferentiated, is among the most challenging aspects. The accuracy of the mathematical models often used to depict the stem cells growth is not as optimal as desired. The Deasy model is used to compare experimental results on polio stem cells with embryonic stem cells, with the aid of hyperbolastic growth model H3. Here, we offer multiple models that are applicable to the study of stem cell populations in general and are particularly useful for modeling cell proliferation in the real world. We talked about structured cell population models and contrasted various methodologies used in cell proliferation mathematical modeling. The findings of this study advance our scientific and mathematical knowledge of stem cell dynamics. The models are also expected to be useful in standardizing cell culture conditions and scalable systems, as well as in the development of clinical procedures for stem cell treatments. Moreover, it may be used to conduct a more accurate examination of preexisting data. Certain experiments' outcomes can be predicted. In this manuscript, all data analysis is shown in Figures 1-15.

Keyword: Embryonic stem cells, Polio cell, Hyperbolastic growth model and Deasy model.

1.Introduction:

Stem cells vary from other types of cells in that they may divide and self-renew to differentiate into multiple cell types (Arif, 2014; Pauklin & Vallier, 2013; Wang et al., 2020). Although the process is extremely dynamic, the stem cell population is continuous and close to constant.A list of fundamental claims is constructed based on experimental information regarding hemopoietic stem cells. This leads to the development of a simple mathematical model of the mechanisms controlling hemopoietic control (Catholic & Therapy, 2010; Loeffler & Wichmann, 1980; Michor, 2008).The use of stem cells in cell-based therapy and regenerative medicine has enormous potential. Key to progressing these initiatives include the creation of methods that grow cells to retaining the appropriate stem cell phenotype while obtaining therapeutically applicable numbers (Beerman et al., 2010; Words & Green, 2002).A simple mathematical model to depict the growth dynamics of stem cells is required in the field of stem cell research, which is currently of great interest. The goal of this study is to demonstrate the Tabatabai et al. (M. Tabatabai et al., 2005)hyperbolastic growth models as a precise and useful method of modeling the dynamics of stem cell proliferation. We talked about structured cell population models and contrasted various methodologies used in cell proliferation mathematical modeling. A time continuous daughter cell model that was investigated in (Arino, 1995; Arino & Kimmel, 1993)is presented in a somewhat expanded form.We illustrate the precision and potency of these models, which include the polio cell, adult stem cells, and embryonic stem cells, using experimental data (M. Tabatabai et al., 2005; M. A. Tabatabai et al., 2011).The cycle of interphase time and division time below enables us to observe the mitotic cell division of any steam cell.

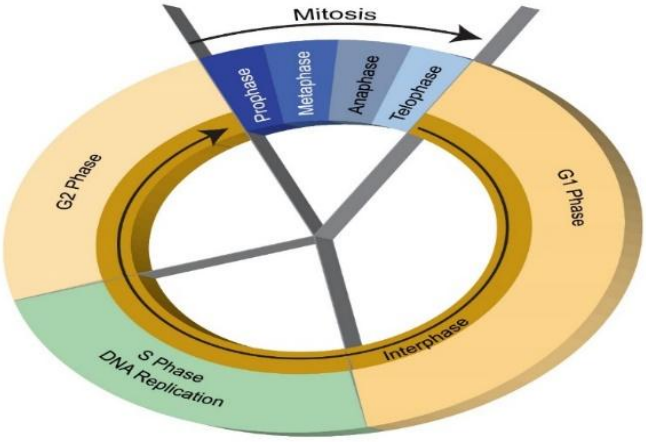


Fig:The presence of non-dividing cells in the population leads to nonlinear growth: Diagrammatic representation of the quiescence (G1), terminal differentiation, and apoptosis/senescence non-diverging cellular phases. Cells move through the cycle and divide to form daughter cells, which could start a fresh mitotic cycle. Alternately, the offspring cells could exit the cycle and go into senescence or apoptosis, or they could briefly enter the dormant G2 state.

The embryo is the body's first stem cell, also known as a cell population, and it has the ability to differentiate into every type of human body cell like polio, tumor, and cancer as well as the tissues that will support the development embryo(MacLean et al., 2013; Michor, 2008; Staddon, 2018).Self-renewal, differentiation, and proliferation are all crucial topics in the field of stem cell research. We join other academics who have previously investigated this topic and concentrate on providing an appropriate mathematical model for stem cell proliferation(Wadkin et al., 2019; Wilson & Trumpp, 2006).It is thought that adult stem cells maintain their steamness through intricate interactions with their surroundings and progeny. Here, we incorporate these findings into a population biology framework that enables us to draw from ecological principles and provide insight on the dynamics of the stem cell niche(MacLean et al., 2017).The efficacy of

many stem cell therapies will depend on the quantity of transplantable stem cells predicts (Aguila & Rowe, 2005; Hoang et al., 2022; Mousaei Ghasroldasht et al., 2022).

In our research, we address Thehyperbolastic growth model H3 is applied to experimental data involving polio stem cells and embryonic stem cells. The outcomes are compared to those of other well-known models, including the Deasy model and logistic, which are often employed in the polio and embryonic stem cell studies for stem cell proliferation.Finally, we show how to estimate the kinetic parameters more accurately. This research adds to our understanding of stem cell dynamics from both a biological and mathematical perspective. Additionally, it is anticipated that the models would be necessary for developing clinical procedures for stem cell treatments and will be helpful in standardizing cell culture conditions and scalable systems.

2.2 Cell Population dynamics models(methods)

2.2.1Deasy Model

The exponential equation is frequently used to compute population growth and estimates of parameters affecting proliferation: The equation $N = N_0 2^{\frac{t}{DT}}$ assumes that every cell is actively dividing to produce two daughter cells and that the number of cells *N*, at the time, t, entirely depends on the initial number of cells, and its division time, *DT*. The Sherley model **[hand-35]** incorporates a parameter that accounts for the existence of non-dividing cells to capture the dynamics. We created a mathematical technique to express the proliferation potential of cells as a single quantity α, which is referred to as the percentage of dividing daughter cells. Based on a sequence of photographs depicting the process of cell growth that included the concept of the production of both dividing and non-dividing daughter cells in a growing population (Klose et al., 2019; Sherley et al., 1995).

$$N(t) = N_0\left[0.5 + \frac{1-(2\alpha)^{\frac{1}{DT}+1}}{2(1-2\alpha)}\right] \quad (1)$$

Where α an is the mitotic fraction, N_0 is the starting number of cells, *DT* is the division time, and $N(t)$ is the population size at time *t*. As the percentage of cells whose cellular divisions are still occurring is represented by the parameter a, a must meet the conditions of $0 \leq \alpha \leq 1$. The Sherley model was used by Deasy et al. (Hayflick, n.d.)to explain the mechanisms of cytokine-induced muscle stem cell growth.One of the most widely used models for hPSCs comprises two populations of dividing and non-dividing cells, along with a term for accounting for cell loss due to death or differentiation (often referred to as the Deasy model, which is a development of the Sherley model to include cell loss) (Sherley et al., 1995; Words & Green, 2002).

In a set of discrete equations, where *M* is the total number of dead or lost cells at time *t* and *N* is the number of live cells at time *t*, we obtain

$$\mathrm{N}_i = (1-\alpha)(2\alpha)^0\mathrm{N}_0 + (1-\alpha)(2\alpha)^1(\mathrm{N}_0) + (1-\alpha)(2\alpha)^2(\mathrm{N}_0) + \cdots + (1-\alpha)(2\alpha)^{i-1}(\mathrm{N}_0) + (2\alpha)^i(\mathrm{N}_0) - \mathrm{M}_i$$

A geometric series is created by enlarging and rearranging the terms to

$$\mathrm{N}_i = \mathrm{N}_0\left[0.5 + 0.5\sum_{0}^{\mathrm{n}}(2\alpha)^{\mathrm{i}}\right] - \mathrm{M}_i$$

where N_i is the total number of live cells at time ***t***, M_i is the total number of dead cells at time ***t***, and N_0 is the initial number of cells, and ***i***is any positive value of ***t/DT***.

Following that, the model equation for growth with cell loss is given:

$$N(t) = N_0 \left[0.5 + \frac{1 - (2\alpha)^{\frac{1}{DT}+1}}{2(1-2\alpha)} \right] - M \qquad (2)$$

Under conditions of significant cell loss, the final factor, M, which is new to this equation, provides a more precise prediction. Without this phrase, the mitotic fraction is overstated since it gives the impression that fewer cells were generated overall than was the case.

The Deasy growth model is what we refer to as formula (2) in this article.

3.2.TheHyperbolastic Model H3

The hyperbolastic model H3 is used to analyze stem cell growth. The hyperbolastic growth models of(M. Tabatabai et al., 2005)were just recently developed to give growth models more accuracy as well as flexibility in the growth rate as the population reaches its carrying capacity.It has been shown that these models are very accurate, especially when it comes to simulating biological growth, as in (Ahmadi & Mottaghitalab, 2007; Eby et al., 2010; M. A. Tabatabai et al., 2011; Wadkin et al., 2020). For the sake of this paper, we will focus on H3, a type III hyperbolastic development model.

The nonlinear hyperbolastic differential equation of the following form, which takes into account a third growth curve

$$\frac{\mathbf{dp(t)}}{\mathbf{dt}} = (\mathbf{L} - \mathbf{P(t)} \left(\boldsymbol{\beta\gamma t^{\gamma-1}} + \frac{\boldsymbol{\theta}}{\sqrt{\mathbf{1+\theta^2 t^2}}} \right) (3)$$

Where$\boldsymbol{L}$ is the carrying capacity and β,γ and θ are parameters, with initial condition $P(t_0) = p_0$. Model (3) is the type III hyperbolastic ordinary differential equation.

This rate of increase is the result of two factors, one representing how far the existing population is from its limiting value and the other includingthe intrinsic rate β, an allometric constant γ, and an additional term θ allowing flexibility in growth rate over time.The solution to equation (3) is a four parameter model

$$\boldsymbol{P(t) = L - \alpha\, EXP[-\beta\, t^{\gamma} - \mathbf{arcsinh}(\theta t)]} \quad (4)$$

where

$$\boldsymbol{\alpha = (L - P_0)\, EXP[\beta\, t_0{}^{\gamma} + \mathbf{arcsinh}(\theta\, t_0)]}$$

The biological significance of the parameters L, β, γ, and θ is briefly discussed here. The carrying capacity or limiting value of the population size is represented by the parameter L, which has the same units as $P(t)$ and in this example, is the number of stem cells.The $arcsinh(x)$ function mustbe entered using its definition in terms of logarithms: $arcsinh(x) = \ln(x + \sqrt{1 + x^2})$. The parameter β is equivalent to the intrinsic biological growth rate; however, all of the parameters β, γ, and θ work together to determine the total rate of growth. $1/(time)^{\gamma}$or $1/(days)^{\gamma}$in the case of this article, is the unit of measurement for β. The Weibull model has a parameter akin to the allometric denoted as γ.In order to more accurately represent the biological significance of the parameter θ, which has units of 1/(time), in our instance 1/(days), we rewrite equation (4) as follows.

$$\boldsymbol{P(t) = \mathrm{L} - \frac{\alpha}{\theta t + \sqrt{1 + (\theta t)^2}}\, \mathrm{EXP}[-\beta\, t^{\gamma}]}$$

The term before the exponential simplifies to a for θ = 0, and the model then becomes the Weibull growth model. The expression $\alpha(t, \theta) = \frac{\alpha}{\theta t + \sqrt{1 + (\theta t)^2}}$permits this factor to change with time t when $\theta \neq 0$, based on this formula and the value of θ.

The hyperbolastic ordinary differential equation of typeIII can also be represented in the following form

$$\frac{\mathbf{dp(t)}}{\mathbf{dt}} = \mathbf{a(t)} - \mathbf{b(t)}$$

Where b(t) represents variables slowing or delaying population increase and a(t) represents forces causing population growth. Here

$$a(t) = L\left(\boldsymbol{\beta\gamma t^{\gamma-1}} + \frac{\boldsymbol{\theta}}{\sqrt{\mathbf{1} + \boldsymbol{\theta^2 t^2}}}\right)$$

and

$$b(t) = p(t)\left(\boldsymbol{\beta\gamma t^{\gamma-1}} + \frac{\boldsymbol{\theta}}{\sqrt{\mathbf{1} + \boldsymbol{\theta^2 t^2}}}\right)$$

We therefore refer to the function $P(t)$ of equation as the hyperbolastic growth model of type III or simply H3 (4). Any and all hyperbolastic growth models may, when necessary, include shift or delay effects.

3.3 Result and Disscussion

All areas of stem cell research are impacted by the variety of stem cell populations, including isolation, cell-cell signaling pathways, and mathematical modeling. Apparently, neither our models nor any other model can completely capture all biological phenomena that researchers come across in their work. The parameters of heterogeneous cell population expansion can be evaluated using the straightforward, approachable models described here. They could also act as a framework for more intricate models that include terminology to take interactions between subpopulations into account. When applied to the clinical setting, these models could be used as forecasting tools to determine how long it will take to expand from cell biopsy to cell

transplantation. In that study, it was demonstrated that H3 accurately represented the data in comparison to other sigmoidal models including Weibull, Gompertz, logistic, and Richards. The Mean Absolute Relative Error for the other models varied from roughly ten to over twenty times that of H3. The Deasy and Sherley models, which have been widely used to simulate the proliferation of stem cells, are a distinct kind of model, more akin to exponential growth than sigmoidal growth. We contrast the Deasy model with the others when analyzing the data related to embryonic stem cells because it is the more sophisticated and accurate of these models . We also analyze the data of polio cell. We contrast Deasy and H3 specifically in terms of how well they describe experimental data. we also compare the data with the logistic model. There are available NIH stem cell data **[hand 90-27]** online. Table 1 lists the calculated from the data predicted values for the Deasy model's parameters. Table 2 contains estimates for the H3 parameter.Note that the parameter values provided in (M. Tabatabai et al., 2005) for the H3 model were entered incorrectly; the values that should be used are those in Table 2. Table 3 lists the estimated stem cell counts for each of these models in relation to the actual data.

Parameter	Estimate
α	0.90
DT	2.031
M	81.670

Table 1

Parameter	Estimate
δ	3.237×10^{-6}
L	770.922

θ	0.058
γ	8.01

Table 2

Both the logistic and Deasy models fared poorly when their accuracy was evaluated, with a mean absolute relative error that was higher than that of H3. With more errors than the conventional sigmoidal models, which don't perform as well as H3, it becomes the least accurate model in the comparison research.

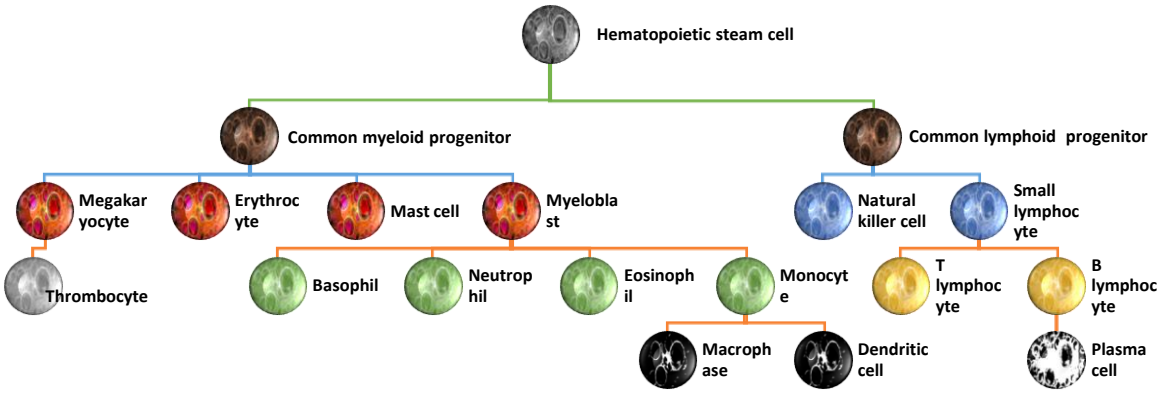


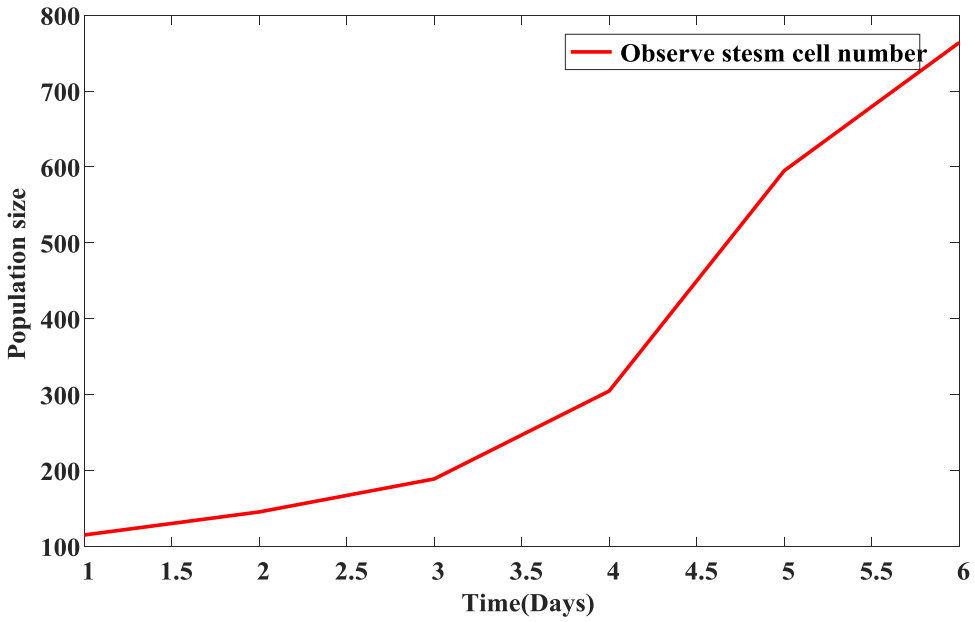
Fig:Steam cell prolification

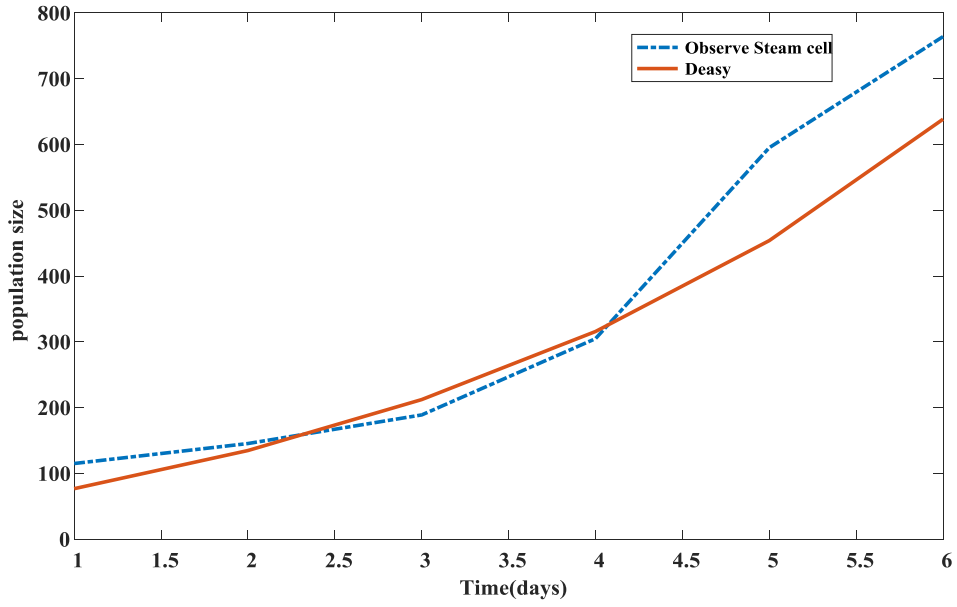
Currently, we calculate the projected steam cells over time using several population models, as well as the absolute relative error from the observed steam cell value.

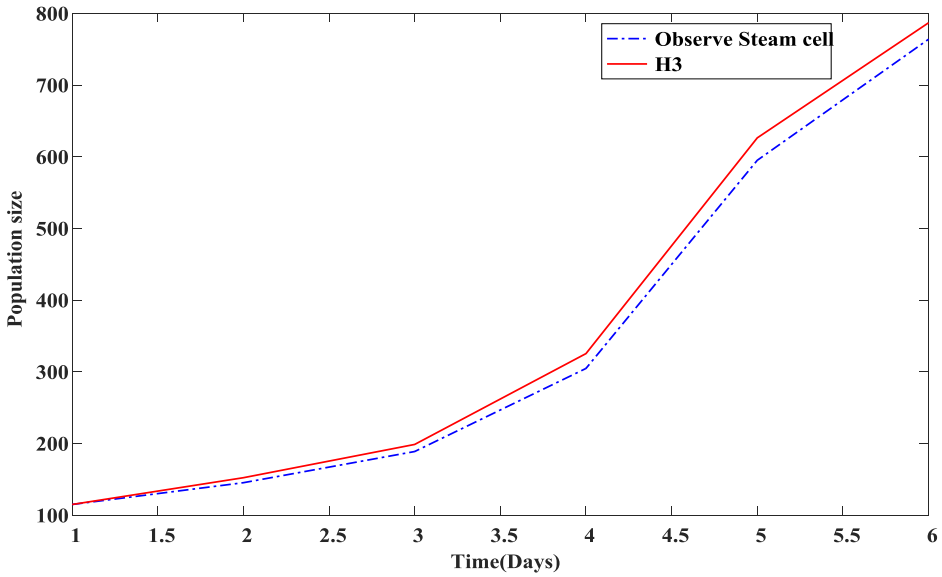
Days	Observe number of steam cell	Calculated number of steam cells		
		Deasy	H3	Logistic
1	115.000	76.752	115	154.85
2	145.375	134.749	152.335	207.78
3	188.872	212.213	198.76	277.55
4	304.78	315.657	325.49	368.48

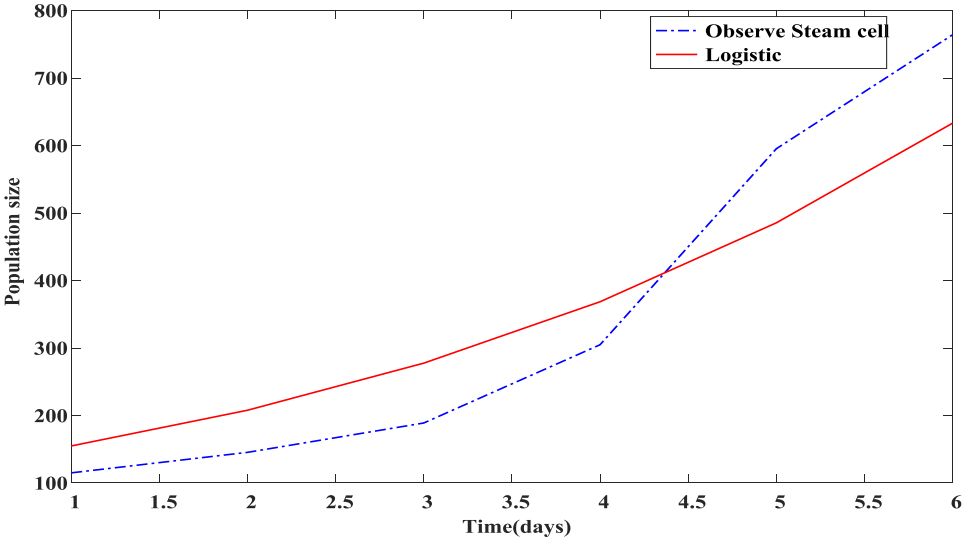
5	595.132	453.864	626.422	485.391
6	764.000	638.43	786.972	633.02

Table 3







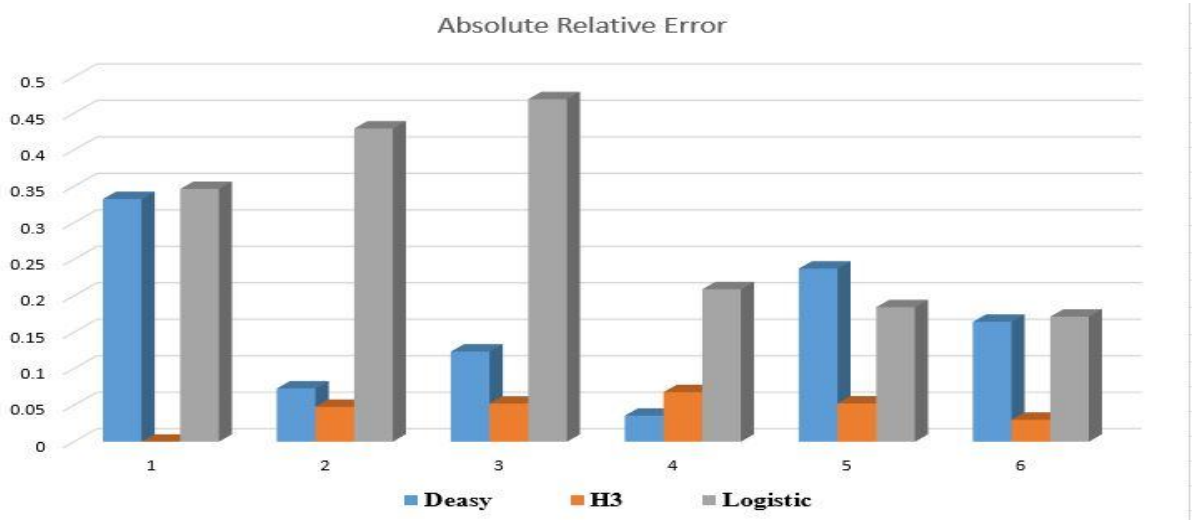


Absolute relative error

Deasy	H3	Logistic
0.332591	0	0.346522
0.073094	0.047876	0.429269
0.123581	104.2353	0.469514
0.035688	0.067951	0.209003

0.237373	0.052577	0.184398
0.164359	0.030068	0.17144

Table 4



We calculate the various errors of the three estimated models, such as Mean square error and R squared error, in order to compare models with varying numbers of parameters on an equal basis and to analyze the correctness of these models.The MSE error for the three model is MSE(Deasy)=6.3×10^3, MSE(H3)=3.4×10^2 and MSE(Logistic)=7.7×10^3.We also determine the vale of R^2.Now the value of R^2 for the three model are R^2_{Deasy}=0.962, R^2_{H3}=0.991 and $R^2_{Logistic}$=0.941. It is also possible to calculate other model errors like Weibull, Gompertz, Rechards H1 and H2, etc.

Evidently, neither our models nor any other model can completely capture all biological phenomena that researchers come across in their work. Many different sigmoid growth models have been created, and more are constantly being proposed [16-90]. Around the inflection point, the logistic function exhibits symmetric behavior. Additionally, the hyperbolic, decelerating growth model is remarkably correct. When these models are fitted to one set of data, the parameter values may be very different. The Richards model generalizes the logistic model by adding a third parameter (γ) to the equation to account for asymmetrical growth, whereas the

logistic model employed here is a two parameter symmetric model.When estimating the polio cell data using the observed value over time (month), we may detect an increase in growth rate and the spread of the disease throughout the body.The computed from the data projected values for the Deasy model's parameters are listed in Table 5 below. Estimates for the H3 parameter are shown in Table 6. The values in Table 6 should be used instead of the parameter values given in [90, 91] for the H3 model. According to the actual data, Table shows the estimated polio numbers for each of Deasy models.

Parameter	Estimate
α	1.00
DT	1.375
M	312.62

Table 5

Parameter	Estimate
δ	4.11×10^{-6}
L	41359.6
θ	0.001
γ	6.18

Table 6

Utilizing the various parameter values described above and the observed value, we calculate the polio cell data as the months pass. Because we can roughly estimate the quantity of polio cells without a checkup. It is really beneficial for the patient with polio as well as the doctor.

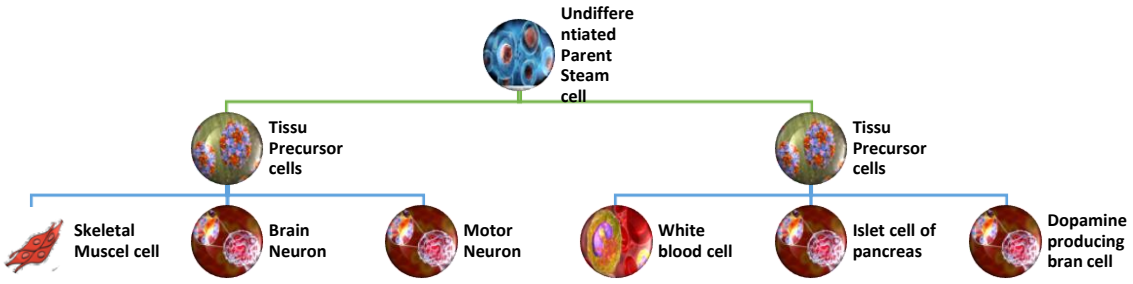
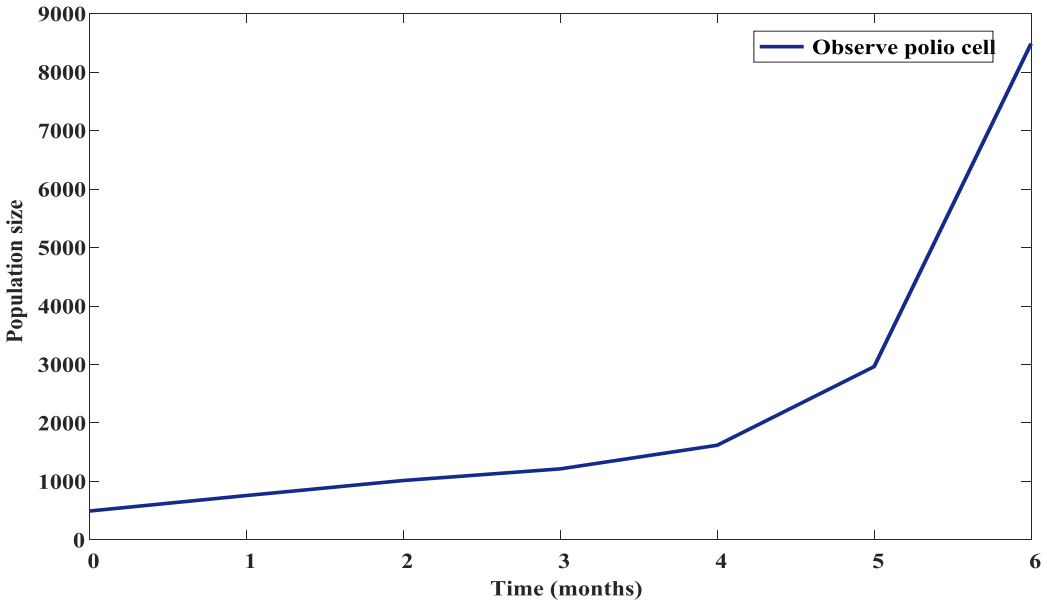


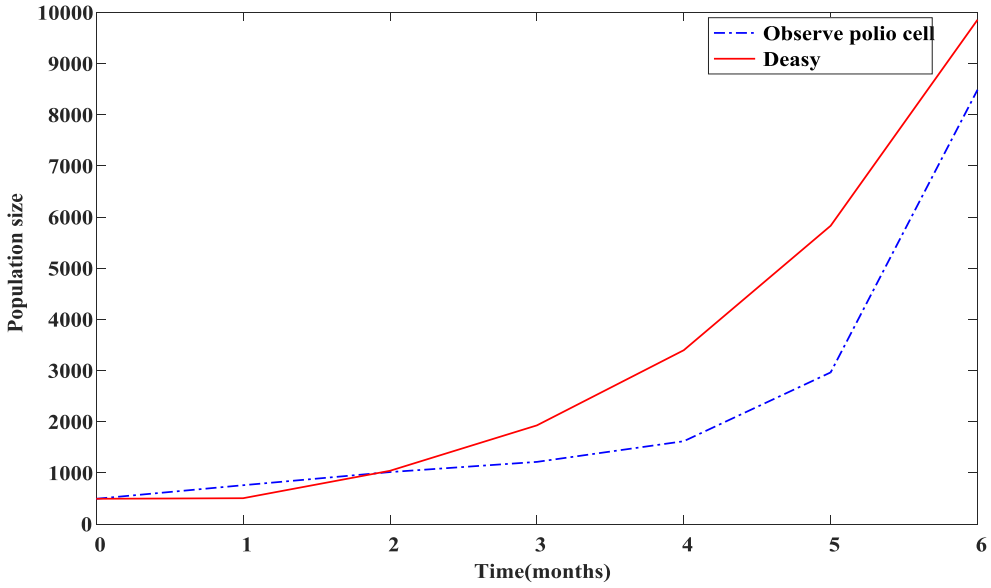
Fig:Syndrome of the pluripotent polio steam cell

We also use a variety of population growth models, including the logistic, hyperbolistic (H3), and deasy models for population growth, to calculate the absolute relative error from the estimated value.

Months	Observe number of Polio cell	Calculated number of Polio cell		
		Deasy	H3	Logistic
0	494	494	494	494
1	759	504.99	412.34	902.14
2	1016	1041.28	383.26	1638.63
3	1215	1928.78	479.58	2934.21
4	1619	3398.03	1166.84	5232.43
5	2964	5830.41	3628.12	8701.87
6	8489	9857.16	9778.64	13993.65

Table 7


Observe polio cell
Population size
Time (months)
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
0
1
2
3
4
5
6


Observe polio cell
Deasy
Population size
Time(months)
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
0
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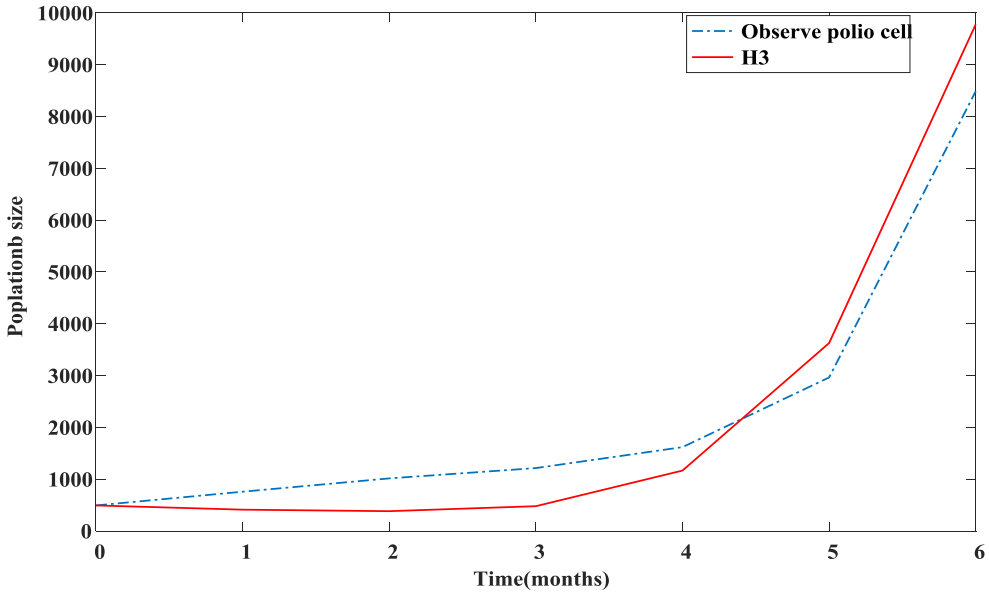
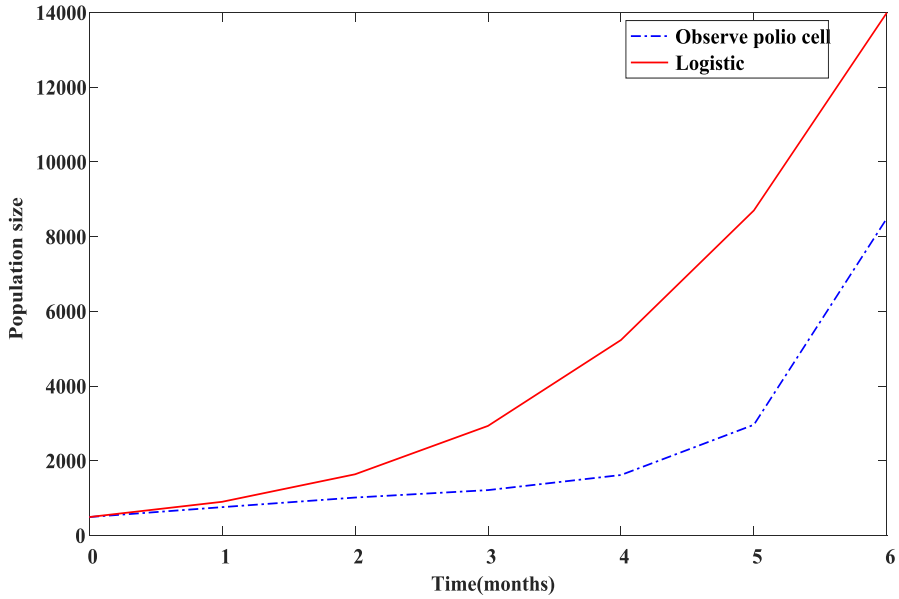
2
3
4
5
6

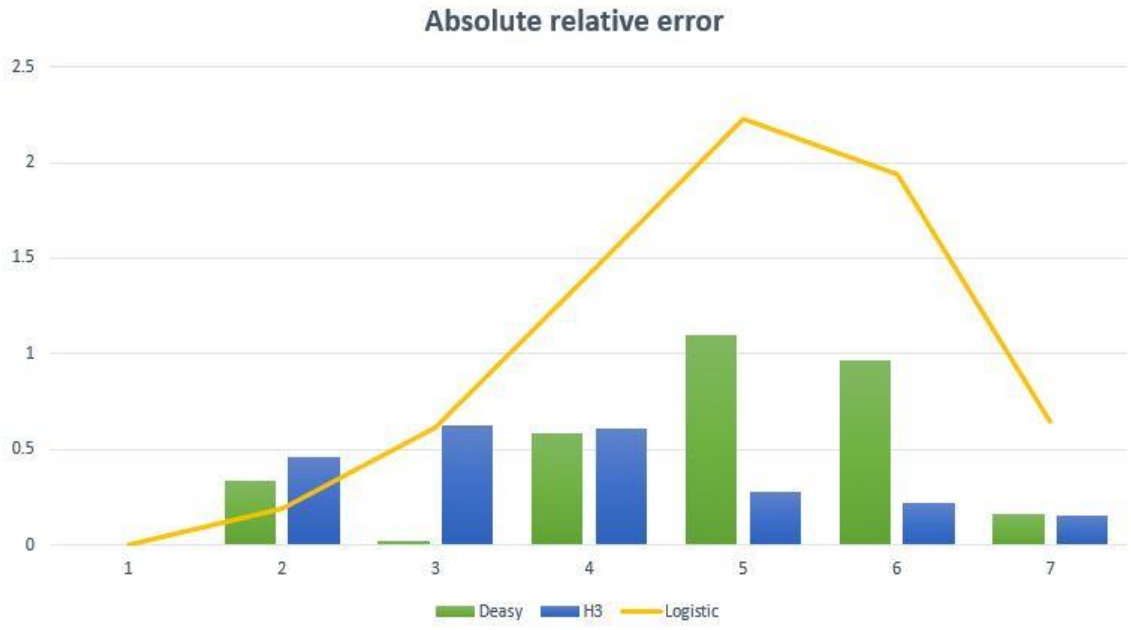




Absolute relative error		
Deasy	H3	Logistic
0	0	0
0.334664	0.456733	0.18859
0.024882	0.622776	0.612825
0.587473	0.605284	1.414988
1.098845	0.279284	2.23189

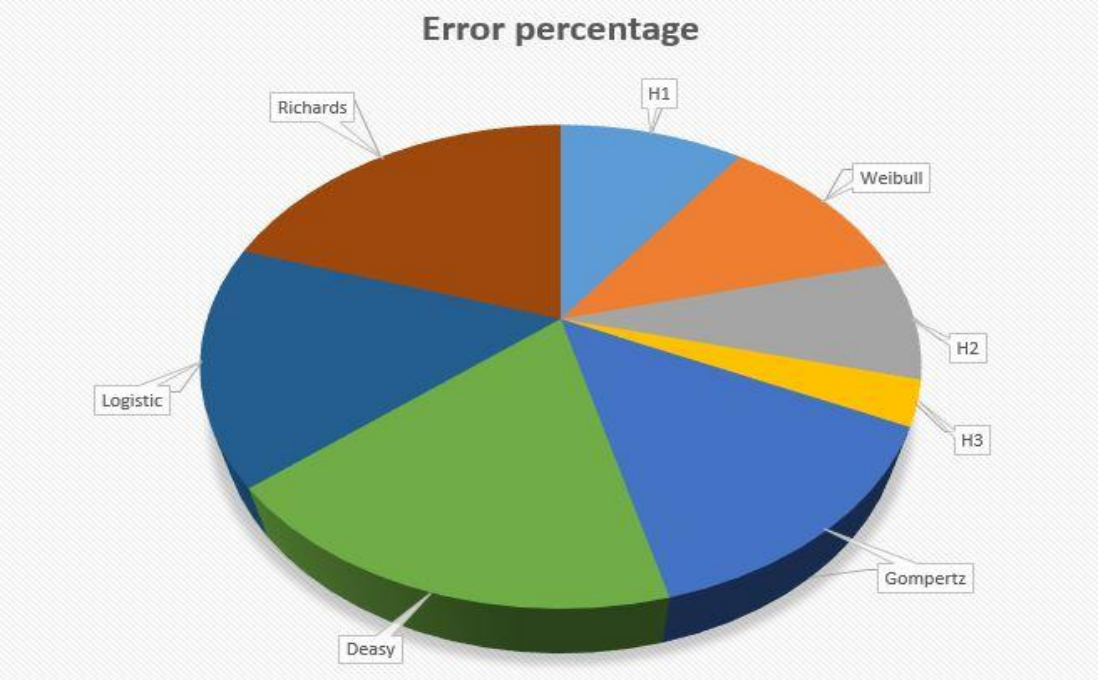
0.967075	0.224062	1.935854
0.161169	0.151919	0.648445

Table 8



To compare models with differing numbers of parameters on an equal footing and to assess the accuracy of these models, we compute the various errors of the three estimated models, such as Mean square error and R squared error. The MSE error for the three model is MSE(Deasy)=1.9×10^{6}, MSE(H3)=5.6×10^{5} and MSE(Logistic)=1.3×10^{7}.We also determine the vale of R^2.Now the value of R^2 for the three model are R^2_{Deasy}=0.862, R^2_{H3}=0.920 and $R^2_{Logistic}$=0.725. It is also possible to calculate other model errors like Weibull, Gompertz, Rechards H1 and H2, etc.

The hyperbolastic growth model H3 is the most effective at predicting the dynamic behavior of stem cells out of the three. The growth dynamics of cell populations, such as cell proliferation and quiescence rates, can be understood using this model.



Fig

Finally, the results from our hyperbolastic models are highly encouraging. In both of the aforementioned data sets, they provided a better fit to the data than the logistic, Richards, and Gompertz models, which were both the worst suited models in terms of MSE, mean RE, and prediction accuracy.

Our models generalize the logistic and weibull models, and two of them are accurate and straightforward.

In fact, stem cell research places a lot of emphasis on and struggles with managing cell differentiation. Although the potential of stem cell therapy depends on these cells' capacity for multilineage differentiation, practical treatments will call for in vitro augmentation of the undifferentiated phenotype. Both the differentiated phenotype and the self-renewing phenotype are represented in our model by words. Therefore, the models are may be used to analyze the growth kinetics brought on by mixed subpopulations and the heterogeneity of a cell

population.These models make use of a mathematical method to evaluate the proliferation of stem cells while paying close attention to the varied phenotypes produced by different stem cell fates. There are actually a number of intermediate phenotypes that may emerge at various speeds, despite the fact that we have reduced the model to only include the self-renewing and terminally differentiated stages. Although the estimate of the mitotic fraction is specifically enhanced for the instance of myogenic differentiation, the model might be used in subsequent studies to construct functions utilizing proliferation and differentiation rates based on the non-exponential model.

The models discussed in this study should make it easier to comprehend the dynamics and heterogeneity of stem cells from both a biological and mathematical perspective. With the help of these methods, we are able to statistically evaluate stem cell population growth parameters that are influenced by both intrinsic and extrinsic control. The creation of bioreactor systems intended for the mass production of phenotypically defined stem cells for use in cellular therapy strategies will be possible with an improved understanding of the intercellular and microenvironmental determinants of stem cell fate combined with suitable growth models.

Conclusion:

Stem cells are vital to human life and have great therapeutic promise, our understanding of their role is still imperfect at times. Because of both theoretical and experimental developments, the field of stem cell biology has significantly expanded recently.We may make sensible assumptions about medical information using a variety of mathematical methodologies, which will be very helpful for forecasting the growth of many sorts of cells over time, including leukemia, polio, and tumor cells. The mathematical models are therefore very helpful for

prescribing therapy and for further treatment, making the work and research for doctors and researchers easier.

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