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Analysis of the hematopoiesis process in mammalian bone using homotopy perturbation method

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Abstract. In this study, the mathematical model that describes blood cell development in the bone marrow (i.e., hematopoiesis) has been studied via the Homotopy Perturbation Method (HPM). The results from the present work compared very well with the numerical solutions from published literature. This work has shown that the HPM is viable for solving delay differential equations born from hematopoiesis problem. The influence of the proliferating cells loss rate, time delay rate and the phase re-entry rate on the population densities of both the proliferating and resting cells were also determined through the underlined procedure.

Keywords: blood cells; bone marrow; hematopoiesis; homotopy perturbation method; delay differential equations

1. Introduction

The bone marrow is a thick, gelatinous tissue that fills the spinal cavities that is at the bone centres (Angelucci *et al*. 2014). There are two types of bone marrow, namely, the myeloid tissue branded as the red bone marrow and the fatty tissue, also known as the yellow bone marrow. The two-bone marrow has the capillaries and blood vessels. The bone marrow is produced by blood cells in the body, and two contains the hematopoietic and mesenchymal stem cells. Cell biologists divide the stem cells into cells that increase, and the rest (*Stem Cells: Sources, types and uses*). While resting cell is a quiescent stage in cellular development, the Proliferating cells are cells that undergo mitosis after entering the proliferating phase.

Since the 1960s, cellular population problems and models have been of interest by many researchers. Earlier researchers like Nooney (1967) studied age showed shown that the distribution of age appears to be restricted for each cell population which die or divide according to age-based schedules. The distribution limit tends to be independent of the original age distribution. His result shows that non-stationary periodic behaviour in time is impossible. Other earlier researchers in this lineage could be found in An der Heiden and Mackey (1982) and Bélair *et al*. (1995).

Recently, within a pluripotent stem cell dynastic statistical model, Adimy *et al.* (2005b) studied

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the stability and Hopf bifurcation. The model was a differential equation with a time delay. They obtained the stability conditions independent of the delay. It was also shown that distributed delay could destabilise the entire system and that Hopf bifurcation can occur. A couple of work (Banerjee *et al*. 2019, Cullen *et al*. 2014, Kumar *et al*. 2019, Laurenti and Göttgens 2018, Mikkola and Orkin 2006, Notta *et al*. 2016, Salem and Thiemermann 2010, Tomasetti and Vogelstein, 2015, Varn *et al*. 2015) have also centred on mathematical models for hematopoiesis and the stem cells.

Here, we consider the model for the hematopoiesis process. The focus of this work is to expand the application domain of the analytic HPM to solve for the Hematopoiesis process problem. The HPM, initiated by the Chinese mathematician Prof. Ji Huan (1999), has been the subject of detailed theoretical and computational studies to solve differential and integral equations, both linear and nonlinear. The method has a significant advantage of not requiring a small parameter in an equation. It offers a wide variety of linear and nonlinear applied science problems through a theoretical approach (Adamu and Ogenyi 2017, El-Dib 2017, He 2006, 2014, 2012a, b, Wu and He 2018).

This algorithm was used to solve Cveticanin's (Cveticanin 2006) purely nonlinear differential equations of the second order. Ganji and Sadighi (2006) employed the scheme to find the solution to nonlinear boundary value problems and extended it to solve nonlinear travelling wave equations (He 2005). The method was adopted by Wang (2008) to solve nonlinear fractional partial differential problems, and by Ganji and Rafei (2006) for solving the nonlinear Hirota-Satsuma coupled KdV partial differential equations. Ganji and Sadighi (2007) addressed the nonlinear model that comes from convective–radiative thermodynamic cooling problem via the process. Rafei *et al*. (2007) have solved the system of nonlinear ordinary differential equations that control the issue of non-fatal diseases spread in people with HPM. HPM appears in the solution sequence in most situations very quickly converging; Just a few variations typically lead to concrete solutions. Interested readers can see references (Dehghan and Shakeri 2007, 2008a, b, Rafei *et al*. 2007) for further submissions of the method in several problems of engineering, mathematical physics, together with bioengineering.

In this paper, an analytical solution for the population densities of proliferating and resting cells is sort. The homotopy perturbation method is employed to this end. The influence of changes in the values of the cell cycle time, resting cells loss rate and proliferating cells loss rate on the population densities of both cell types were obtained.

2. The hematopoiesis model

Let P(t) and M(t) represent the population densities of proliferating and resting cells, respectively, which have spent time $t \geq 0$ in their phase. Resting cells can either be lost randomly at a rate $\delta \geq 0$ (Adimy *et al*. 2005a), which takes into account the cellular maturity, or entry into the proliferating phase at a rate β. Proliferating cells can be lost by apoptosis at a rate $y \geq 0$ and at mitosis, where cells with age τ divide into two daughter cells which immediately enter the G_0-phase (Crauste 2014). The conservation equations governing the hematopoiesis process have been given by Mackey (1978) as

$$\frac{dP(t)}{dt} = -yP(t) + \beta(M)M - e^{-\gamma\tau}\beta(M_\tau)M_\tau \tag{1}$$

$$\frac{dM(t)}{dt} = -[\beta(M) + \delta]M + 2e^{-\gamma\tau}\beta(M_\tau)M_\tau \tag{2}$$

where $M_\tau = M(t-\tau)$ illustrates the time retardation/delay. The term $e^{-\gamma\tau}\beta(M_\tau)M_\tau$ in Eq. (1) represents the fraction of surviving cells about to leave the proliferating phase that entered a time τ earlier, the term $yP(t)$ represents the amount of proliferating cells lost by apoptosis, and the term $\beta(M)M$ represents the amount of resting cells that have just entered the proliferating phase from the resting phase. The term $2e^{-\gamma\tau}\beta(M_\tau)M_\tau$ in Eq. (2) represents the new daughter cells produced from the surviving mother cells, the term $[\beta(M)+\delta]M$ represents the amount of resting cells lost as a result of the entry of the cells into the proliferation phase and also the amount of resting cells lost due to cellular differentiation or maturity. Since during entry into the proliferation phase, the stem cells require a binding affinity to combine and increase in number or spread rapidly; therefore, the rate of entry into the proliferation phase β is taken to be a monotone decreasing Hill function (Pujo-Menjouet and Mackey 2004). Hill function coefficient provides a measure of the binding/ligand affinity between a biomolecule and its binding partner. Therefore, β is given as (Pujo-Menjouet and Mackey 2004)

$$\beta(M) = \beta_0\left[\frac{\theta^n}{\theta^n + M^n}\right] \tag{3}$$

where θ is the number of resting cells at which has its maximum rate of change with respect to the resting phase population, n describes the sensitivity of the reintroduction rate with changes in the population, and β_0 is the maximal rate of re-entry in the proliferating phase.

Substituting Eq. (3) into Eqs. (1) and (2), we have

$$\frac{dP(t)}{dt} = -\gamma P(t) + \beta_0\left[\frac{\theta^n}{\theta^n + M^n}\right]M - e^{-\gamma\tau}\beta_0\left[\frac{\theta^n}{\theta^n + M_\tau^n}\right]M_\tau \tag{4}$$

$$\frac{dM(t)}{dt} = -\beta_0\left[\frac{\theta^n}{\theta^n + M^n}\right]M - \delta M + 2e^{-\gamma\tau}\beta_0\left[\frac{\theta^n}{\theta^n + M_\tau^n}\right]M_\tau \tag{5}$$

Therefore, Eqs. (4) and (5) become

$$\frac{dP(t)}{dt} = -\gamma P(t) + \frac{\beta_0\theta^n M}{\theta^n + M^n} - e^{-\gamma\tau}\frac{\beta_0\theta^n M_\tau}{\theta^n + M_\tau^n} \tag{6}$$

$$\frac{dM(t)}{dt} = -\frac{\beta_0\theta^n M}{\theta^n + M^n} - \delta M + 2e^{-\gamma\tau}\frac{\beta_0\theta^n M_\tau}{\theta^n + M_\tau^n} \tag{7}$$

Mostafa *et al*. (2005a) identified the values of the parameters to be $\delta = 0.05\,day^{-1}$, $y = 0.2\,day^{-1}$, $\beta_0 = 1.77\,day^{-1}$, $n = 3$, $\theta = 1.62\times10^8$cells/kg, $\tau = 7\,days$. These values will also be used while investigating the influence of one or more parameters on the behaviour of the population densities of both the resting and proliferating cells. The resulting equations become

$$\frac{dP(t)}{dt} = -0.2P(t) + \left[\frac{1.77\times(1.62\times10^8)^3}{(1.62\times10^8)^3 + M^3}\right]M - e^{-0.2\tau}\left[\frac{1.77\times(1.62\times10^8)^3}{(1.62\times10^8)^3 + M^3}\right]M(t-7) \tag{8}$$

$$\frac{dM(t)}{dt} = -0.05M(t) + \left[\frac{1.77\times(1.62\times10^8)^3}{(1.62\times10^8)^3 + M^3}\right]M + 2e^{-0.2\tau}\left[\frac{1.77\times(1.62\times10^8)^3}{(1.62\times10^8)^3 + M^3}\right]M(t-7) \tag{9}$$

The initial population densities of both proliferating and resting cells are taken as $M(0) = b$ and $P(0) = a$.

3. Concept of the homotopy perturbation method

Consider a general nonlinear differential equation represented in the form of Eq. (10) as

$$L(u) + N(u) = f(r), \qquad r \in \Omega \tag{10}$$

with the boundary conditions

$$B\left(u, \frac{\partial u}{\partial n}\right) = 0, \qquad r \in \Gamma \tag{11}$$

where L, N, B denote linear, and nonlinear and boundary operators correspondingly, while Γ and $f(r)$ represent the boundary of the domain Ω and the analytic function. By adopting the homotopy perturbation technique, a homotopy will be constructed thus: $v(r,p): \Omega \times [0,1] \to R$ which satisfies

$$H(v,p) = (1-p)[L(v) - L(u_0)] + p[L(v) + N(v) - f(r)] = 0 \tag{12}$$

or

$$H(v,p) = [L(v) - L(u_0)] + pL(u_0) + p[N(v) - f(r)] = 0 \tag{13}$$

where $r \in \Omega, p \in [0,1]$ are impeding parameters and u_0 is an initial approximation which satisfies the boundary conditions.

4. The solution of the homotopic process through the HPM

Using Eqs. (12) and (13), we can construct the deformation equation thus

$$H(v,0) = L(v) - L(u_0) = 0 \tag{14}$$

$$H(v,1) = L(v) - N(v) - f(r) = 0 \tag{15}$$

The cycle of transition from zero to unity is just of $v(r,p)$ from $u_0(r)$ to $u(r)$. In topology, this is called deformation. $L(v) - L(u_0)$ and $L(v) + N(u_0) - f(r)$ are called homotopic functions. The premise behind this is that the result of Eqs. (12) and (13) could be represented as a set of power in p

$$v = v_0 + pv_1 + p^2v_2 + p^3v_3 + \cdots \tag{16}$$

The approximate solution of Eq. (10), thereafter can be accessed conveniently as

$$v = \lim_{p \to 1} v_0 + v_1 + v_2 + v_3 + \cdots \tag{17}$$

Using the series perturbed solution given as

$$P(t) = P_0(t) + pP_1(t) + p^2P_2(t) + \ldots + p^nP_n(t) \tag{18}$$

and

$$M(t) = M_0(t) + pM_1(t) + p^2M_2(t) + \ldots + p^nM_n(t) \tag{19}$$

The homotopy perturbation of Eqs. (1) and (2) could be written as

$$HPMEq1 = (1-p)\frac{d}{dt}P(t) + p\left(\frac{d}{dt}P(t) + yP(t) + \beta M(t) + \beta_n M(t)e^{-y\tau}\right) \tag{20}$$

and

$$HPMEq2 = (1-p)\frac{d}{dt}M(t) + p\left(\frac{d}{dt}M(t) + (\beta+\delta)M(t) - 2\beta_n M(t)e^{-y\tau}\right) \tag{21}$$

which in expanded forms become

$$\begin{aligned} HPMEq1 = {} & (1-p)\left(\frac{d}{dt}P_0(t) + p\frac{d}{dt}P_1(t) + p^2\frac{d}{dt}P_2(t) + p^3\frac{d}{dt}P_3(t) + p^4\frac{d}{dt}P_4(t)\right) \\ & + p\begin{pmatrix} \frac{d}{dt}P_0(t) + p\frac{d}{dt}P_1(t) + p^2\frac{d}{dt}P_2(t) + p^3\frac{d}{dt}P_3(t) + p^4\frac{d}{dt}P_4(t) \\ + y\big(P_0(t) + pP_1(t) + p^2P_2(t) + p^3P_3(t) + p^4P_4(t)\big) \\ + \beta\big(M_0(t) + pM_1(t) + p^2M_2(t) + p^3M_3(t) + p^4M_4(t)\big) \\ + \beta_n(M_0(t) + pM_1(t) + p^2M_2(t) + p^3M_3(t) + p^4M_4(t))e^{-y\tau} \end{pmatrix} \end{aligned} \tag{22}$$

$$\begin{aligned} HPMEq2 = {} & (1-p)\left(\frac{d}{dt}M_0(t) + p\frac{d}{dt}M_1(t) + p^2\frac{d}{dt}M_2(t) + p^3\frac{d}{dt}M_3(t) + p^4\frac{d}{dt}M_4(t)\right) \\ & + p\begin{pmatrix} \frac{d}{dt}M_0(t) + p\frac{d}{dt}M_1(t) + p^2\frac{d}{dt}M_2(t) + p^3\frac{d}{dt}M_3(t) + p^4\frac{d}{dt}M_4(t) \\ + (\beta+\delta)\big(M_0(t) + pM_1(t) + p^2M_2(t) + p^3M_3(t) + p^4M_4(t)\big) \\ - 2\beta_n\big(M_0(t) + pM_1(t) + p^2M_2(t) + p^3M_3(t) + p^4M_4(t)\big)e^{-y\tau} \end{pmatrix} \end{aligned} \tag{23}$$

Collecting like terms based on the power of p, and solving the decomposed equations with the corresponding initial conditions, the term by term solution becomes

$$P_0(t) = a \tag{24}$$

$$M_0(t) = b \tag{25}$$

$$P_1(t) = -e^{-y\tau}b\beta_n t - b\beta t - bty \tag{26}$$

$$M_1(t) = 2e^{-y\tau}b\beta_n t - b\beta t - b\delta t \tag{27}$$

$$P_2(t) = \begin{pmatrix} -1/2e^{-y\tau}b\beta\beta_n t^2 + 1/2e^{-y\tau}b\beta_n\delta t^2 - e^{-y\tau}b\beta_n t^2 y - e^{-2y\tau}b{\beta_n}^2 t^2 \\ +1/2b\beta^2 t^2 + 1/2b\beta\delta t^2 + 1/2b\beta t^2 y + 1/2b\delta t^2 y \end{pmatrix} \tag{28}$$

$$M_2(t) = \begin{pmatrix} -2e^{-y\tau}b\beta\beta_n t^2 - 2e^{-y\tau}b\beta_n\delta t^2 + 2e^{-2y\tau}b{\beta_n}^2 t^2 + 1/2b\beta^2 t^2 \\ +b\beta\delta t^2 + 1/2b\delta^2 t^2 \end{pmatrix} \tag{29}$$

$$P_3(t) = \begin{pmatrix} 1/2e^{-y\tau}b\beta^2\beta_n t^3 + 1/3e^{-y\tau}b\beta\beta_n\delta t^3 + 2/3e^{-y\tau}b\beta\beta_n t^3 y - 1/6e^{-y\tau}b\beta_n\delta^2 t^3 \\ +2/3e^{-y\tau}b\beta_n\delta t^3 y - 2/3e^{-3y\tau}b{\beta_n}^3 t^3 + 2/3e^{-2y\tau}b{\beta_n}^2\delta t^3 - 2/3e^{-2y\tau}b{\beta_n}^2 t^3 y \\ -1/6b\beta^3 t^3 - 1/3b\beta^2\delta t^3 - 1/6b\beta^2 t^3 y - 1/6b\beta\delta^2 t^3 - 1/3b\beta\delta t^3 y - 1/6b\delta^2 t^3 y \end{pmatrix} \tag{30}$$

$$M_3(t) = \begin{pmatrix} e^{-y\tau}b\beta^2\beta_n t^3 + 2e^{-y\tau}b\beta\beta_n\delta t^3 + e^{-y\tau}b\beta_n\delta^2 t^3 + 4/3e^{-3y\tau}b{\beta_n}^3 t^3 - 2e^{-2y\tau}b\beta{\beta_n}^2 t^3 \\ -2e^{-2y\tau}b{\beta_n}^2\delta t^3 - 1/6b\beta^3 t^3 - 1/2b\beta^2\delta t^3 - 1/2b\beta\delta^2 t^3 - 1/6b\delta^3 t^3 \end{pmatrix} \quad (31)$$

$$P_4(t) = \begin{pmatrix} -1/3e^{-y\tau}b\beta^3\beta_n t^4 - e^{-y\tau}b\beta^2\beta_n\delta t^4 - e^{-y\tau}b\beta\beta_n\delta^2 t^4 - 1/3e^{-y\tau}b\beta_n\delta^3 t^4 \\ +2/3e^{-4y\tau}b{\beta_n}^4 t^4 - 4/3e^{-3y\tau}b\beta{\beta_n}^3 t^4 - 4/3e^{-3y\tau}b{\beta_n}^3\delta t^4 + e^{-2y\tau}b\beta^2{\beta_n}^2 t^4 \\ +2e^{-2y\tau}b\beta{\beta_n}^2\delta t^4 + e^{-2y\tau}b{\beta_n}^2\delta^2 t^4 + 1/24b\beta^4 t^4 + 1/6b\beta^3\delta t^4 + 1/4b\beta^2\delta^2 t^4 \\ +1/6b\beta\delta^3 t^4 + 1/24b\delta^4 t^4 \end{pmatrix} \quad (32)$$

$$M_4(t) = \begin{pmatrix} -1/3e^{-y\tau}b\beta^3\beta_n t^4 - e^{-y\tau}b\beta^2\beta_n\delta t^4 - e^{-y\tau}b\beta\beta_n\delta^2 t^4 - 1/3e^{-y\tau}b\beta_n\delta^3 t^4 \\ +2/3e^{-4y\tau}b{\beta_n}^4 t^4 - 4/3e^{-3y\tau}b\beta{\beta_n}^3 t^4 - 4/3e^{-3y\tau}b{\beta_n}^3\delta t^4 + e^{-2y\tau}b\beta^2{\beta_n}^2 t^4 \\ +2e^{-2y\tau}b\beta{\beta_n}^2\delta t^4 + e^{-2y\tau}b{\beta_n}^2\delta^2 t^4 + 1/24b\beta^4 t^4 + 1/6b\beta^3\delta t^4 + 1/4b\beta^2\delta^2 t^4 \\ +1/6b\beta\delta^3 t^4 + 1/24b\delta^4 t^4 \end{pmatrix} \quad (33)$$

and the general solution for the process becomes as described below

$$P(t) = P_0(t) + pP_1(t) + p^2P_2(t) + \ldots + p^nP_n(t) \quad (34)$$

and

$$M(t) = M_0(t) + pM_1(t) + p^2M_2(t) + \ldots + p^nM_n(t) \quad (35)$$

Making necessary substitutions, we obtain

$$P(t) = \sum_{\xi=0}^{N} p^{\xi}P_{\xi} \qquad p = 1 \quad (36)$$

which in expanded form becomes

$$P(t) = \left\{ \begin{array}{c} a - e^{-y\tau}b\beta_n t - b\beta t - bty \\ + \left(\begin{array}{c} -\dfrac{1}{2e^{-y\tau}b\beta\beta_n t^2} + \dfrac{1}{2e^{-y\tau}b\beta_n\delta t^2} - e^{-y\tau}b\beta_n t^2 y - e^{-2y\tau}b{\beta_n}^2 t^2 \\ + \dfrac{1}{2b\beta^2 t^2} + \dfrac{1}{2b\beta\delta t^2} + \dfrac{1}{2b\beta t^2 y} + \dfrac{1}{2b\delta t^2 y} \end{array} \right) \\ \left(\begin{array}{c} 1/2e^{-y\tau}b\beta^2\beta_n t^3 + 1/3e^{-y\tau}b\beta\beta_n\delta t^3 + 2/3e^{-y\tau}b\beta\beta_n t^3 y \\ -\dfrac{1}{6e^{-y\tau}b\beta_n\delta^2 t^3} + \dfrac{2}{3e^{-y\tau}b\beta_n\delta t^3 y} - \dfrac{2}{3e^{-3y\tau}b{\beta_n}^3 t^3} \\ + \dfrac{2}{3e^{-2y\tau}b{\beta_n}^2\delta t^3} - \dfrac{2}{3e^{-2y\tau}b{\beta_n}^2 t^3 y} - \dfrac{1}{6b\beta^3 t^3} - \dfrac{1}{3b\beta^2\delta t^3} \\ -\dfrac{1}{6b\beta^2 t^3 y} - \dfrac{1}{6b\beta\delta^2 t^3} - \dfrac{1}{3b\beta\delta t^3 y} - \dfrac{1}{6b\delta^2 t^3 y} \end{array} \right) \\ + \left(-\dfrac{1}{3e^{-y\tau}b\beta^3\beta_n t^4} - e^{-y\tau}b\beta^2\beta_n\delta t^4 - e^{-y\tau}b\beta\beta_n\delta^2 t^4 \right) \end{array} \right\}$$

$$\left\{+\left(\begin{array}{c}-\frac{1}{3e^{-y\tau}b\beta_n\delta^3t^4}+\frac{2}{3e^{-4y\tau}b{\beta_n}^4t^4}-\frac{4}{3e^{-3y\tau}b\beta{\beta_n}^3t^4}-\\ 4/3e^{-3y\tau}b{\beta_n}^3\delta t^4+e^{-2y\tau}b\beta^2{\beta_n}^2t^4+2e^{-2y\tau}b\beta{\beta_n}^2\delta t^4+\\ e^{-2y\tau}b{\beta_n}^2\delta^2t^4+1/24b\beta^4t^4+1/6b\beta^3\delta t^4+1/4b\beta^2\delta^2t^4\\ +\frac{1}{6b\beta\delta^3t^4}+\frac{1}{24b\delta^4t^4}\end{array}\right)\right\}+\cdots \tag{37}$$

Similarly

$$M(t)=\sum_{\xi=0}^{N}p^{\xi}M_{\xi}\qquad\qquad p=1 \tag{38}$$

which in expanded form becomes

$$M(t)=\left(\begin{array}{l}b+2e^{-y\tau}b\beta_nt-b\beta t-b\delta t\\ +\left(\begin{array}{c}-2e^{-y\tau}b\beta\beta_nt^2-2e^{-y\tau}b\beta_n\delta t^2+2e^{-2y\tau}b{\beta_n}^2t^2+\frac{1}{2b\beta^2t^2}\\ +b\beta\delta t^2+\frac{1}{2b\delta^2t^2}\end{array}\right)\\ \left(\begin{array}{c}e^{-y\tau}b\beta^2\beta_nt^3+2e^{-y\tau}b\beta\beta_n\delta t^3+e^{-y\tau}b\beta_n\delta^2t^3+4/3e^{-3y\tau}b{\beta_n}^3t^3\\ -2e^{-2y\tau}b\beta{\beta_n}^2t^3-2e^{-2y\tau}b{\beta_n}^2\delta t^3-\frac{1}{6b\beta^3t^3}-\frac{1}{2b\beta^2\delta t^3}\\ -\frac{1}{2b\beta\delta^2t^3}-\frac{1}{6b\delta^3t^3}\end{array}\right)\\ +\left(\begin{array}{c}-\frac{1}{3e^{-y\tau}b\beta^3\beta_nt^4}-e^{-y\tau}b\beta^2\beta_n\delta t^4-e^{-y\tau}b\beta\beta_n\delta^2t^4\\ -\frac{1}{3e^{-y\tau}b\beta_n\delta^3t^4}+\frac{2}{3e^{-4y\tau}b{\beta_n}^4t^4}-\frac{4}{3e^{-3y\tau}b\beta{\beta_n}^3t^4}\\ -\frac{4}{3e^{-3y\tau}b{\beta_n}^3\delta t^4}+e^{-2y\tau}b\beta^2{\beta_n}^2t^4+2e^{-2y\tau}b\beta{\beta_n}^2\delta t^4\\ +e^{-2y\tau}b{\beta_n}^2\delta^2t^4+\frac{1}{24b\beta^4t^4}+\frac{1}{6b\beta^3\delta t^4}+\frac{1}{4b\beta^2\delta^2t^4}\\ +\frac{1}{6b\beta\delta^3t^4}+\frac{1}{24b\delta^4t^4}\end{array}\right)\end{array}\right)+\cdots \tag{39}$$

5. Results and discussion

Table 1 demonstrates the comparison between the results obtained from numerical simulations, previous study and analytic solutions from the homotopy perturbation method.

Table 1 Proliferating cells (10^8 cells/kg) for different number of days

t (days)	Proliferating cells (10^8 cells/kg)		
	Numerical result	Adimy *et al.* (2005a)	Present study
0	0	0	0
20	1.69	1.65	1.68
40	2.1	2.1	2.1
60	2.2	2.1	2.2
80	2.05	2.01	2.04
100	2.1	2.1	2.1
120	2.15	2.13	2.15
140	2.05	2.05	2.05
160	2.01	2.02	2.01
180	2.01	2.01	2.01
200	2.01	2.01	2.01

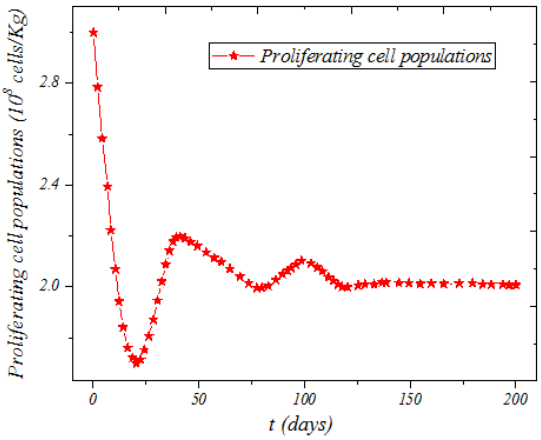

Fig. 1 Proliferating cells population density

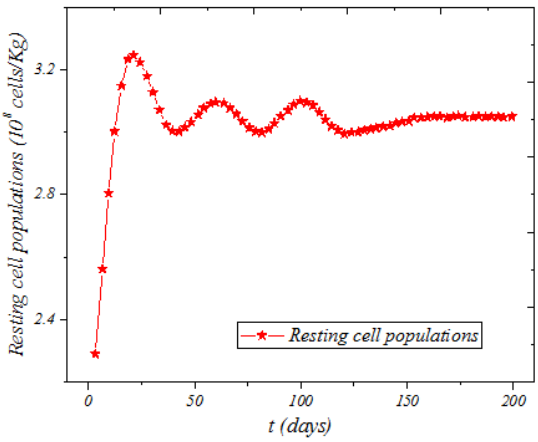

Fig. 2 Resting cells population density

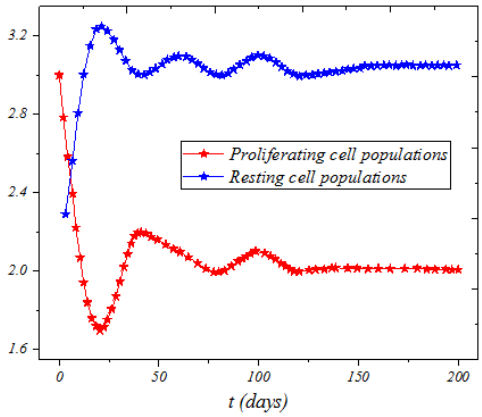

Fig. 3 Super-imposed plot of the proliferating and resting cells population

5.1 Time history of the proliferating and resting cells population density

Figs. 1 and 2 depict the visualisation of the time history of the proliferating and resting cells in terms of population. The proliferating function possesses a higher density function at the initial state but decreases through the history plot as the graph becomes asymptotic. However, the resting cells initially produce cells at moderate population density and increase its production after sometimes. This increment is maintained until similar asymptotic behaviour is also attained. One of the importance of these functions is that they are parameter sensitive. These parameters that directly affect them may be employed as monitoring devices for generating the required output.

5.2 Super-imposed plot of the proliferating and resting cells

Fig. 3 portrays the super-imposed scenario of the proliferating and resting cells population. The critical assessment shows that the quiescent cells increase throughout history while the proliferating cells diminish. These two cells population function can be used to augment each other to generate the desired output.

5.3 Super-imposed plot of the proliferating and resting cells

Illustrated in Fig. 4 is the influence of the resting cells loss rate δ on the proliferating cells population density. When δ varies from $1\,day^{-1}$ to $3\,day^{-1}$, we observe a general decrease in the population density of the proliferating cells as compared to the initial value of $\delta = 0.05\,day^{-1}$ used in Fig. 1. The higher the amount of δ, the lower the population density of the proliferating cells. It can also be observed that the variation in the value of δ results in differences in the time or period that the proliferating cells population density becomes asymptotic. The lower the value of δ, the longer the periods of oscillations and the more time it takes to be asymptotically stable. We also note that the higher the value of δ, the shorter the cell cycle of the proliferating cells.

5.4 Effect of proliferating cells loss rate γ on the history of the proliferating cells

Fig. 5 shows the influence of the proliferating cells loss rate γ on the proliferating cells

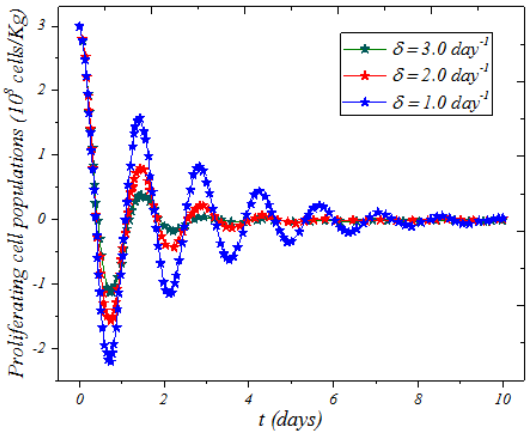

Fig. 4 Influence of the resting cells loss rate δ on the proliferating cells population

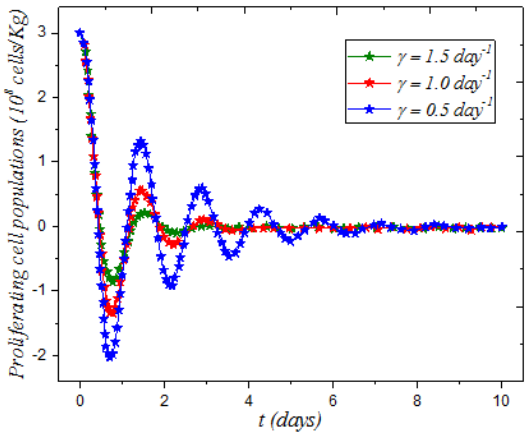

Fig. 5 Influence of the proliferating cells loss rate γ on the proliferating cells population

population density. When γ varies from $0.5\,day^{-1}$ to $1.5\,day^{-1}$, we also observe a general decrease in the population density of the proliferating cells as compared to the initial value of $\gamma = 0.2day^{-1}$ used in Fig. 1. The higher the value of γ, the lower the population density of the proliferating cells. It can also be observed that the variation in the value of γ results also in differences in the time or period that the proliferating cells population density becomes asymptotic. The lower the value of γ, the longer the periods of oscillations and the more time it takes to be asymptotically stable. It can also be established from Fig. 5 that the higher the value of γ, the shorter the cell cycle of the proliferating cells.

5.5 Effect of time delay rate τ on the history of the proliferating cell

The influence of the time delay rate τ on the proliferating cells population density is depicted in Fig. 6. The cell cycle time is short when τ is closest to 0 and the population density of the proliferating cells is rapidly extinguished. As the value of τ increases, the time taken for the cells to die out also increases. This also tends to increase the concentration of the proliferating cells at

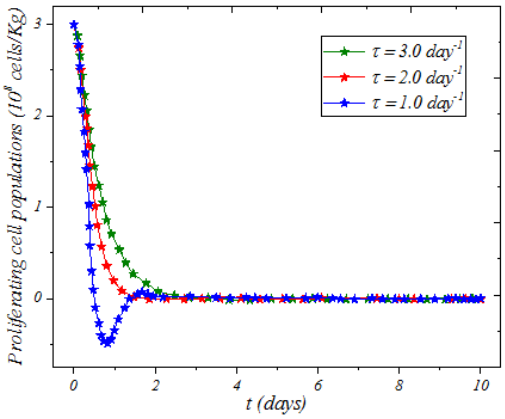

Fig. 6 Influence of the time delay rate τ on the proliferating cells population

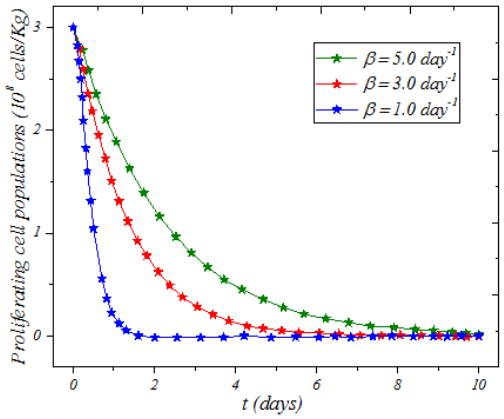

Fig. 7 Influence of the proliferating phase re-entry rate β on the proliferating cells population

the initial state. This effect is annulled as the time delay is eliminated.

5.6 Effect of the proliferating phase re-entry rate β on the history of the proliferating cell

It could be observed from Fig. 7, that as β decreases from $5\,day^{-1}$ to $1\,day^{-1}$, there is a steep decrease in the population density of the proliferating cells. This implies that the higher the value of β, the higher the population density of the proliferating cells. The absence of oscillations could also be observed in all values of β used. This shows that the proliferating phase re-entry rate does not contribute to the oscillation of the population density of the proliferating cells.

5. Conclusions

This study aimed to analyses the population density of embryonic pluripotent stem cells model using the homotopy perturbation method. The reports show that the homotopy perturbation method effectively provides comparable solutions to the hematopoiesis models considered. The parametric

investigation shows that:

• The values of δ, γ, τ and β, all have effects on the population densities of both resting and proliferating cells. Both the resting cells loss rate δ and the proliferating cells loss rate γ resulted in a decrease in the population densities of the pluripotent stem cells with increasing values. Also, the lower the value of δ, the longer the periods of oscillations and the more time it takes to be asymptotically stable.

• The higher the value of δ, the shorter the cell cycle of the cells. These features are essential in the prediction of certain haematological diseases.

• The cell cycle time is short when τ is closer to 0, and the population density of the proliferating cells is rapidly extinguished. This can also be used to predict certain diseases that display such characteristics.

The higher the value of β, the higher the population density of the proliferating cells. This shows that the proliferating phase re-entry rate does not contribute to the oscillation of the population density of the proliferating cells.

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