A Mathematical Analysis of Red Blood Cell and Bone Marrow Stem Cell Control Mechanisms: Summary

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In this paper, authors developed a dynamic systems with 4 ODE to describe the red blood cell systems and bone marrow stem cell system. The models included 4 important variables which were R-red blood cell population, E-erythropoietin, S-stem cell population and C-chalone. There are two loops in the system. The first loop is mitotic loop which reveals the interaction between stem cell population and mitotic inhibitor, chalone. The second loop is red cell loop which contains the interaction of red cell, stem cells and erythropoietin. The models were defined as following:

$$\frac{dE}{dt} = \frac{\alpha}{1+\beta R^z} - \epsilon E \text{ (1)}$$

$$\frac{dS}{dt} = S_1 A_1 \mathscr{M}_1 - SA(\omega + \mathscr{E}) \text{ (2)}$$

$$\frac{dC}{dt} = \gamma S - \mu C \text{ (3)}$$

$$\frac{dR}{dt} = k\mathscr{E}_x A_x S_x - F(R) \text{ (4)}$$

In (1), E is negatively correlated with R and is catabolized by a proportion of its population. In (2), the period of generation of stem cells by mitosis is 1 day, so there are always some stem cells in mitosis process and they can do nothing else. Thus authors denoted A as the fraction of stem cells which are not in mitosis. Stem cells daily replenishment rate is $\mathscr{M}$ and they are replenished by the population of available stem cells 1 day ago, namely, S_1A_1. Stem cells are drain due to their differentiation into red blood cells and other channels with fractions $\mathscr{E}, \omega$ respectively. In (4), reticulocytes derived from stem cells need x days to mature and become red blood cells and one stem cell can derive k reticulocytes which is a constant. Thus the increasing term is $k\mathscr{E}_x A_x S_x$. The decreasing term is denoted as a function of R namely $F(R)$ which contains information about the age distribution of the red blood cells and the rate they die at each age.

It is found that the reactions in authors' models basically follow mass action law. The authors took 1 day as an integration step because they found important biological events took much longer than 1 day. Such a time step would not introduce artefacts into the system. Authors also assumed that channels of stem cells differentiation other than blood cell channel only acted as a drain to stem cells.

Authors used experimental data to obtain the value of parameters. $\mathscr{M}$ is the stem cells daily replenishment rate controlled by chalone. The experimental data showed a relationship between the concentration of chalone and mitotic fractional inhibition. The data can be roughly fitted by a function mitotic fractional inhibition= mC^n. Therefore $\mathscr{M} = 1 - mC^n$. Values of m,n can be various in different cases. The values of parameters are $m = 0.45$, $n = 0.162$ in the fit of experimental data but were adjusted to $m = 0.5$, $n = 0.7$ to fit the situation. (Fig.1)

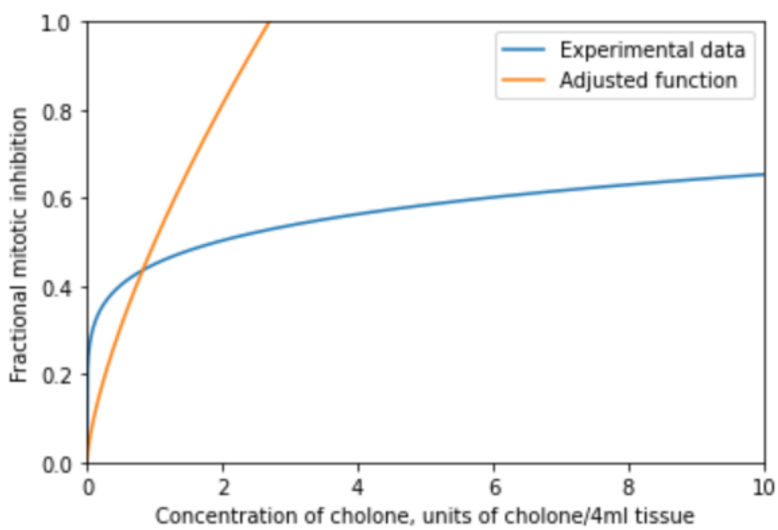

Figure 1: Relation between chalone concentration and mitotic inhibition

Another data revealed the relationship between the concentration of erythropoietin and the increase of red blood cells (Fig.2). The function is increase in red blood cells=bE^q. $\mathscr{E}$ is therefore specified as $\mathscr{E} = pbE^q$ where p is a parameter dependent on red cell mean life and the red cell and stem cell population sizes. The constants here were b=0.39, q=0.34 to fit the data and were adjusted into b=23.13 and q is still 0.34 in this case.

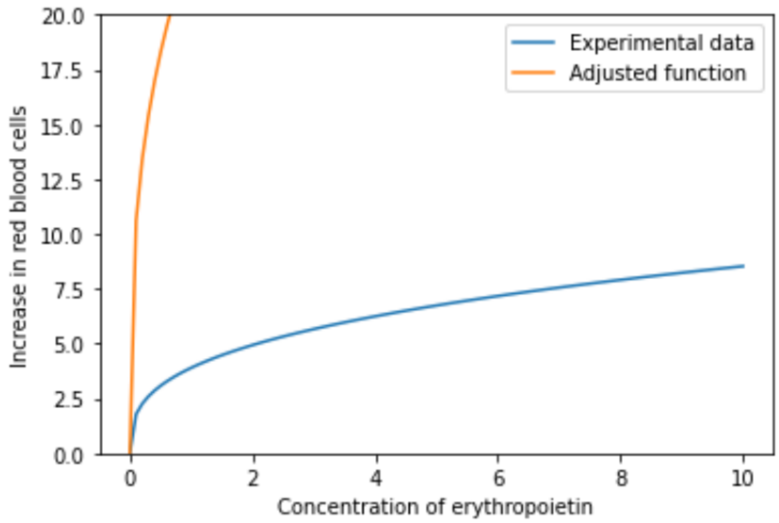

Figure 2: Relation between concentration of erythropoietin and the increase of red blood cells

Besides $\mathscr{E}$ and $\mathscr{M}$ which are dependent on variables, for other parameters, z took values to be at least 8, k was taken to be 20. Other parameters were not clearly specified or were specified in the next section in this paper.

To examine the practical meaning of the models, authors considered three particular situations with experimental data compared with estimated values by the models. The first situation author considered a mice which was hypertransfused which means the red cell differentiation channel of the mice is cut off. By this point of view, we only need to consider equation (2) and (3). Figure 3 is the experimental data from Alexanian et 61. (1963) and figure 4 is the numerical simulation of our formulation. We can see that there were not a lot of data points in figure 3 but the shape and trend of it is similar to those in figure 4. We also generated a long term behavior of total stem cells and chalone which is showed in figure 5. We can see that without the red cell loop in the system, the population of them tend to be stable. Chalone has inhibition to stem cell population but is delayed by 1 day.

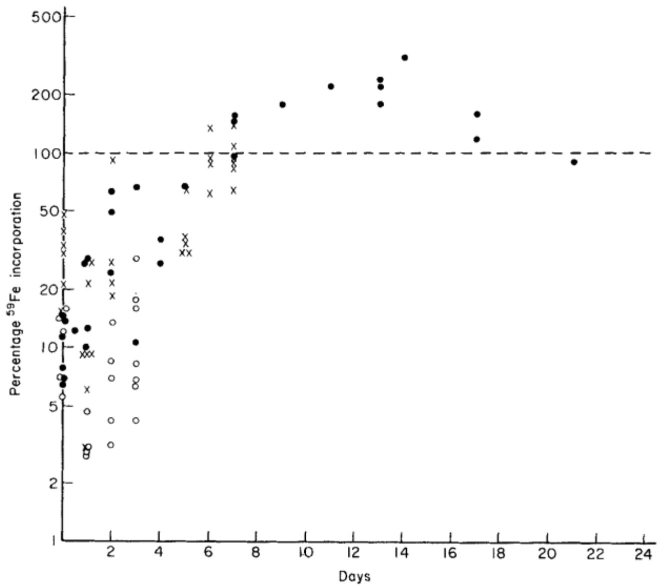

Figure 3: Stem cell recovery in polycythaemic mice. (From Alexanian et al., 1963.)

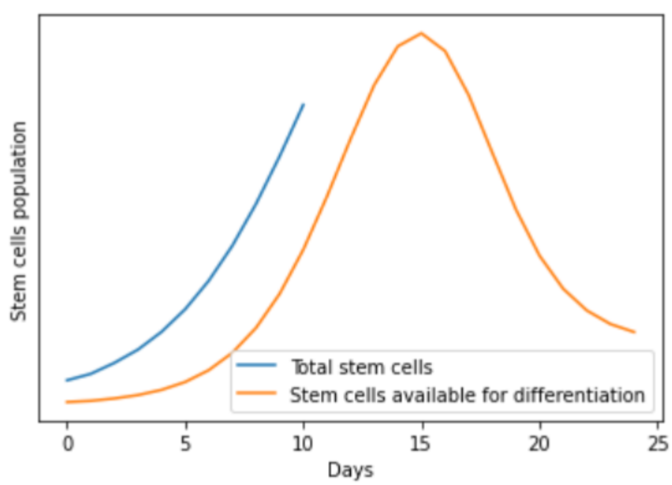

Figure 4: Stem cell simulation.

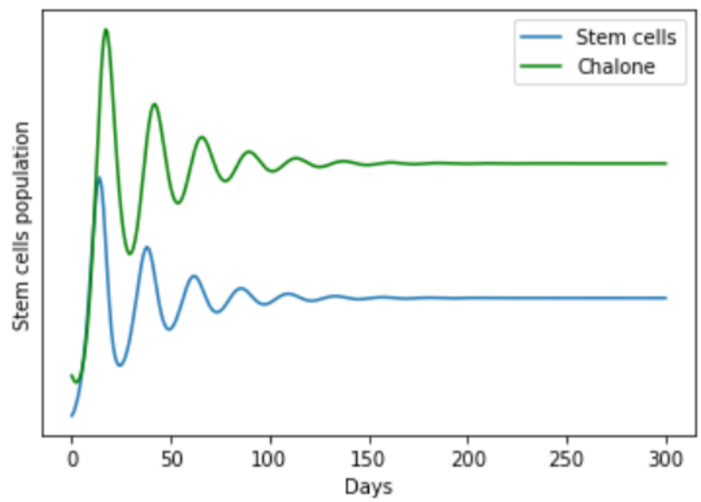

Figure 5: Long term behavior of S,C.

The second experiment data authors used was a group of rabbits which were given a course of iso-antibody. This would lead to a reduce of red cell life time. In this case, under certain parameters, the mathematical formulation revealed that population of stem cells and red cells keep oscillating with with different phase and they never cancel out. Without values of those parameters, it is time-consuming to find such a set of parameters so we directly introduce the figure in the paper (figure 6.).

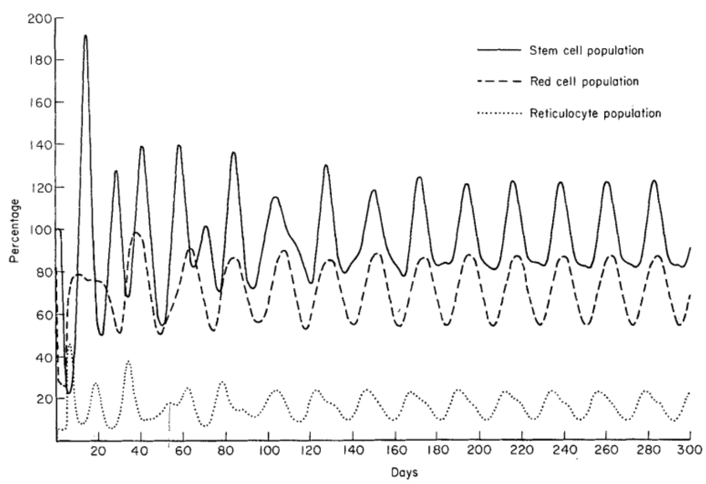

Figure 6: Behaviour of the mathematical formulation of the system under conditions of sustained reduction in red cell life.

The last expmple was rats which were given various doses of radiation. This irradiation naturally damages the stem cells, thus in this case, the effect of the was the stem cell level reduced to 0.1 percent. The experimental data and mathematical simulation are showed below(figure 7 and 8). The lack of experimental data failed to show the details of the reticulocyte behavior but we can see that the amplitude of the oscillation reduces and becomes stable as time goes by.

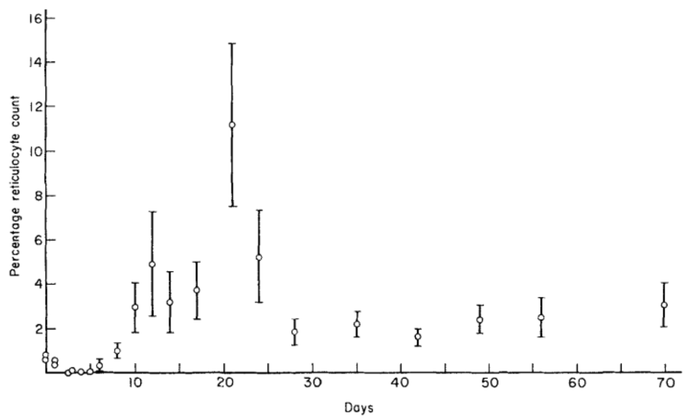

Figure 7: Reticulocyte response to irradiation of 400 rads. (From Hulse, 1967.)

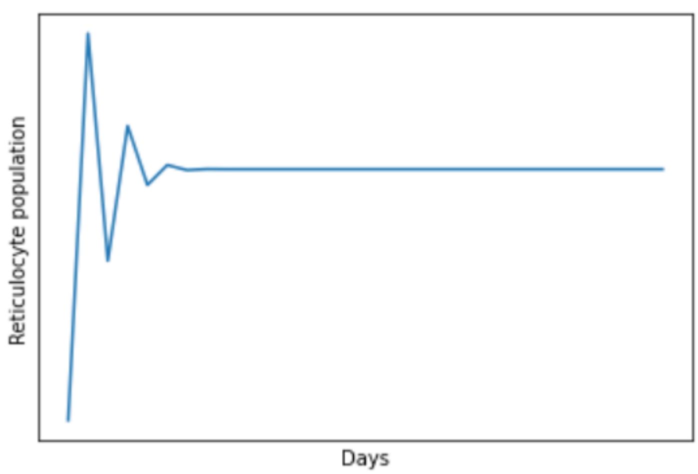

Figure 8: Reticulocyte population of the mathematical simulation

From these three examples, authors concluded that the oscillation cannot happen when there is only loop like the first example. The oscillation also needs to be under some certain conditions where the the frequencies of two loops are approximately the same but the phases are different like the second example. There are also some limitations in this paper. The biggest obstacle was that the experimental data was scarce in 1960s so many parameters were hard to be accurately specified, which leaded to a difficulty and inaccuracy in mathematical simulation. Another limitation was that only 4 components were considered in the system, the real situation might be much more complex than that.