BIFURCATIONS IN A MODEL OF THE PLATELET REGULATORY SYSTEM

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ABSTRACT

Modelling of the control mechanism for the regulation of platelet production leads to a functional differential equation with two time delays, one accounting for the senescence time of platelets, and the other one due to the maturation time of megakaryocytes. Local stability analysis and numerical simulations are performed to evaluate the possible behaviours of the solutions as clinically relevant, physiologically realistic parameters are varied. In particular, possible mechanisms for the onset of cyclic thrombocytopenia and idiopathic thrombocytopenic purpura are discussed.

I  INTRODUCTION

Dynamical diseases have been defined [5] as the manifestation, in an intact physiological regulatory system, of the control parameters taking values outside their normal range, the latter being operationally defined as the range of values for which the system can be considered 'healthy'. This concept has led to the interpretation of various haematological and respiratory disorders in terms of bifurcations occurring in the corresponding mathematical systems.

In this short paper, we present preliminary analysis of a model for the regulation of platelet production: this model can be reduced to a differential equation containing two time delays. The main (unusual) feature of our model is the presence of a second time delay, in addition to the one usually incorporated in most population models. This significantly complicates the analysis, even the local stability of the stationary solutions being difficult to assess in all generality. The results of numerical integration of our equation are shown: the main parameter we vary is a factor of "random" destruction which we suppose small in normal conditions, and leads to singular, although periodic, oscillations.
Normal mammalian thrombopoiesis is accepted to be organised as follows [7]. A self-maintaining population of pluripotential stem cells gives rise to more mature stem cells committed to the eventual production of platelets. The signal responsible for triggering cells in the pluripotential stem cell population into the committed platelet series is unknown. From these committed cells derive the first morphologically recognisable platelet precursors, the megakaryocytes. The latter form intracellular cytoplasmic platelet units which are subsequently released into the circulation as platelets. Unlike the precursors of the erythrocytes and neutrophils, maturation of the megakaryocytes is not accompanied by cellular division. The total time elapsed between the appearance of a recognisable megakaryocyte and when it may start to produce platelets is about 9 days in the normal human [8]. Once released into the circulation, platelets normally disappear primarily through senescence, living for approximately 10 days [6]. There is, however, evidence for the random destruction of platelets at a low level in normal humans, and this may be exacerbated in certain disease states.

The regulation of platelet production is accomplished via the humoral stimulator thrombopoietin, analogous to the erythropoietin present in erythropoiesis. The control of thrombopoiesis is somewhat less well understood than that of erythropoiesis. What is clear, though, is that a fall in platelet number leads to an increase in thrombopoietin levels and a subsequent increase in platelet production [7], thought to be primarily accomplished by an increase in the flux of cells entering the megakaryocyte compartment from the committed stem cell population.

Let \( \mathcal{P}(t) \) denote the total number of circulating platelets of all ages, \( TM \) stand for the maturation time of a megakaryocyte (from the time it becomes recognisable to the time it may start to produce platelets), and \( TS \) represent the age of death, due to senescence, of a platelet. If, in addition, we let \( \gamma \) be an age-independent rate of random destruction of platelets, then we may derive [2] the equation

\[
\frac{d\mathcal{P}}{dt} = -\gamma \mathcal{P}(t) + \beta(\mathcal{P}(t-TM)) + \beta(\mathcal{P}(t-TM-TS))\exp(-\gamma TS)
\]  

(1)

where the function \( \beta \) reflects the feedback ruling the influx of cells into the recognisable megakaryocyte compartment. For definiteness purposes, we let \( \beta(u) = \beta_0 u^n/(\theta^u + u^n) \). The parameters \( \beta_0, \theta \) and \( n \) will be evaluated from clinical data.

Equation (1) possesses the stationary solution \( P_1 = 0 \) for all values of the parameters. Another steady state appears at \( P_2 = \theta[\beta_0(1-\exp(-\gamma TS))/\gamma - 1]^{1/n}, \) when \( \beta_0 > \gamma/(1-\exp(-\gamma TS)), \) and the trivial solution \( P_1 \) is locally asymptotically unstable for the parameter values satisfying this last relation. We have been able to locate geometrically a curve of Hopf bifurcations in the plane of the parameters \( \gamma \) and \( \beta_0 \) [1]: these occur when the characteristic equation of equation (1) linearised around \( P_2 \) possesses a pair of pure imaginary roots, and all other solutions are in the left half of the complex plane.

We now consider, by numerical integration, the influence of an increase in the level of random destruction of the platelets, corresponding to a variation in the values of the parameter \( \gamma \). To find appropriate estimates for the other parameters appearing in the feedback function, we have used published clinical data [3] to obtain \( \beta_0 = 37, \theta = 0.068 \) and

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