

# RIPS Problem Statement: Modelling and Measuring Unstable Behavior in Hematopoiesis

Mark Durst, David Balaban, Mikhail Toupikov, Gilles Gnacadja  
Amgen

## Problem Area

Amgen is a leading human therapeutics company in the biotechnology industry, with the mission of discovering, developing and delivering innovative medicines to treat grievous illnesses. Some of our supportive care medicines support aspects of *hematopoiesis* (the self-regulated production of all types of blood cells). Erythropoietin Stimulating Agents (ESAs, which stimulate the production of red blood cells) and Granulocyte Colony Stimulating Factors (GCSFs, which stimulate the production of white blood cells) are two classes of such medicines.

In a variety of papers (e.g., Bélair et. al. 1995), the blood production cycle is modelled in a PDE, usually under simplifying assumptions which permit expression as a delay differential equation. Such models are offered in explanation of conditions like chronic myelogenous leukemia (CML), which has a periodic form exhibiting oscillations of the white blood cell count. Hopf bifurcations are one of the mathematical techniques invoked in this effort.

## Problem Statement

Our group at Amgen has worked with an adapted PDE transport model to describe the part of the blood production cycle that involves red blood cells. This model permits another range of biology than the work described above, and in particular allows us to explore the role of red blood cells of different "vintages" — positions within the cell aging process — in influencing, for example, hemoglobin levels in the blood. The RIPS team could do simulations to explore different parts of the parameter space of this equation, and classify the ranges of feedback and oscillatory behavior that occur in simulation. Techniques could include stability profiles with respect to the parameters of the model and maps of instability regions.

Realistic data presents additional challenges that the RIPS team should also consider. While simulations can compute exact levels of cells at different ages, real data is limited to bulk measurements such as overall hemoglobin levels. In addition, sampling is only possible at limited intervals that are typically quite sparse; and noise, both random and systematic, is always significant in biological systems. For all the phenomena mentioned above, it would be helpful to know whether real data could actually identify a given behavior, and to what extent parameter values are effectively identifiable.

Finally, ESAs are used as a means of establishing control over hemoglobin levels. The team could explore through mathematical simulation the extent to which such control damps or excites undesirable unstable behaviors.

## Objectives and Deliverables

While we have existing simulation software written in MATLAB and in the functional programming language Haskell, the team will hopefully produce additional software with documentation. The suite of simulations performed should form the basis for a technical paper, and also for some kind of intelligent exposition of the space explored (both mathematical and biological) with appropriate visualizations.

## References

Bélair, J., M.C. Mackey and J.M. Mahaffy (1995), "[Age-Structured and Two-Delay Models for Erythropoiesis](#)", *Mathematical Biosciences* **128**: 317-346.

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