Mammalian myelopoiesis (white cell production) is regulated in a negative feedback fashion by the cytokine G-CSF (granulocyte colony stimulating factor), which has multiple roles including:

- inhibiting preprogrammed cellular death (apoptosis),
- moderating the speed of neutrophil (a component of white blood cells) precursor maturation and release,
- moderating the differentiation rate of hematopoietic stem cells to neutrophil precursors.

Mathematical models of myelopoiesis involve highly nonlinear negative feedback systems with state dependent time delays. The physiological system has been modeled at different levels of sophistication with varying levels of success [1, 2, 3, 4, 5]. Most of the modeling to date has either neglected the G-CSF pharmacodynamics and pharmacokinetics or considered them as measurable outputs of the system. Unfortunately, this assumption is unrealistic when exogenous G-CSF is injected in to the system. The relationship between G-CSF and circulating neutrophil populations has not been adequately modeled. Recent work by Craig et al. [6] shows promise.

Imperfect regulation of myelopoiesis produces interesting dynamics in the human body, including neutropenia. Patients suffering from neutropenia (low white blood cell counts) are at severe risk of infection. Neutropenia is a well known side effect of chemotherapy; as the drugs that attack the cancer also effect the proliferating neutrophil precursors. It also occurs in a rare disease called cyclical neutropenia, which is characterized by high amplitude oscillations in neutrophil populations with a period of about 21 days [5, 7]. Neutropenic patients are often administered synthetic G-CSF to stimulate the production of white blood cells [8]. This injection of G-CSF invalidates the assumptions made in the majority of models, leading to a corresponding decrease in accuracy.

Data from patients suffering from cyclical neutropenia is available in the form of blood samples. However, the data is highly oscillatory and very sparse in time [5, 7]. The sparse nature of the data makes traditional parameter fitting nearly meaningless, as the traditional fit will be extremely sensitive to small perturbations in the parameters and result in phase shift errors over time. Each parameter in the model corresponds to a different physiological process in the regulation of myelopoiesis and improving the parameter fit of the model should accordingly increase understanding of the disease. Further, understanding which parameters are responsible for the introduction of oscillations in the mathematical model should indicate avenues of experimentation to fully study the origin of cyclical neutropenia in the body. Understanding the origin of the disease could in turn lead to improved treatment options that correspond to the cause, rather than the effect, of the disease.

In this project, we will derive a fitting technique that is independent of the sparsity of the data. Instead of fitting the solution of the mathematical model directly to the data points, we will fit the solution to the defining properties of the disease. This will involve using Lomb periodograms [9, 10] to analyze the periodicity of the data and applying statistical techniques to extract other pertinent information from the shape of the data. This information will be combined with sparse data techniques from other branches of mathematics [11] to produce an improved parameter fitting technique. The technique will fit numerical solutions of the mathematical model to the defining characteristics of the disease. Applying the fitting technique to the model presented in [6] will produce a better understanding of the disease.

As cyclical neutropenia is one of many different dynamical diseases caused by defects in hematopoiesis regulation, the fitting technique produced in this project will be directly applicable to many other problems of interest in mathematical physiology.

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