PROPOSAL NARRATIVE

(Maximum of 5 double-spaced pages including figures/tables, 1" margins, 12-point font)

I. Abstract

Chronic myelogenous leukemia (CML) is a cancer that begins in the bone marrow and spreads to the bloodstream and other organs if left uncontrolled. Although most patients undergo some sort of remission with the standard drug imatinib, patients will inevitably relapse [1]. Many CML researchers utilize mathematical models to understand leukemia and immune-response interaction and to create novel methods of treatment. We adopt a time-delay differential equation model, used by Michor et. al [2], which incorporates biologically significant parameters and leukemia –T-cell interactions. Inconveniently, the model is a system of nine nonlinear differential equations encompassing over two dozen parameters. This project intends to mitigate the complexities of the model by analyzing each parameter over an acceptable range of values by numerical simulations in MATLAB and visualizing the effects these variations have on the system. Our ultimate goal is to give immunologists additional insight into which biological mechanisms have the greatest effect on the efficacy of imatinib treatment. Communication of these results would be fostered through presentations at conferences and publishing papers in peer-reviewed journals.

II. Introduction

5,980 new cases of CML and 810 deaths in 2014 alone [7]. Although phase II clinical

trials have shown new drugs [3] the cure is still unknown. To understand CML holistically, mathematical biologists employ compartmental models to track the evolution of CML within a patient. One such model is the hierarchal Michor model [4]. This model assumes leukemia can be partitioned into four stages: stem cells, progenitor cells, differentiated cells, and terminally differentiated cells. Under this assumption, this model noted that " … imatinib is a potent inhibitor of the production of differentiated leukaemic cells, but does not deplete leukaemic stem cells." In 2008, researchers at Stanford University extended this model to incorporate the immune-response [5]. Furthermore, they found that properly timed vaccines autologous leukemic cells combined with imatinib treatment may potentially eradicate all leukemic cells. Dr. Paquin, our faculty advisor, took a different approach. She used the model to simulate strategic treatment interruptions (STIs) [6]. In her work she found that in some cases STIs lead to complete elimination of leukemic cells from the body. Needless to say, this time-delay differential equation model allows CML researchers to make key insights. However, the parameters are not understood which prevents widespread use of this model. Our research will analyze each parameter individually to demystify the complexities of this model.

III. Objective(s)

(1) Analyze each parameter in the model individually via numerical simulations. Understand and explain how exactly each parameter affects leukemia and the immune response.

(2) Communicate the findings through attendance of conferences and publication of papers to provide immunologists with additional insight into which biological

mechanisms seem to have the greatest effect on the efficacy of imatinib treatment.

IV. Methodology

We will meet at least once per week (or totaling no less than four hours a week) to discuss the literature, run simulations, present findings, and so on. We are enrolled and will continue to enroll in MATH 400: an advanced topics course taught by Dr. Paquin upon which we will read about current research on imatinib resistance, multiple drug treatment strategies, clinical trial results, and other pertinent topics. This research will also act as John's and possibly the other student participants' senior projects, which will begin Winter quarter and finish in by Spring quarter.

V. Timeline

November: Become acquainted with the time delay differential equation model. Continue reading current literature.

December - January: Develop an aggregated list of how each parameter affects the interplay between leukemia and the immune-response. Use figures and tables to illustrate findings.

January - March: Begin paper composition.

March - June: Submit paper to journals. Present research at conferences.

VI. Final Products and Dissemination

We will participate in the annual College of Science & Mathematics student research conference by either presenting a poster or delivering an oral presentation on this research. Additionally, a paper will be prepared throughout the research to be published through peer-reviewed journals such as

Bulletin of Mathematical Biology, Mathematical Biosciences and Engineering, PLOS Computational Biology, and/or Journal of Applied Mathematics. With the aid of funding it will also be possible to present the research at nationwide or regional conferences such as Society for Industrial and Applied Mathematics, the Society of Mathematical Biology, and/or Mathematical Association of America.

VII. Budget Justification

The proposed budget would cover travel and lodging expenses for each of the participating students to attend one of the major conferences (listed above). Presenting at nationwide scientific conferences would allow us to disseminate our findings to a broad audience, including other CML researchers.

[1]
Cortes J, Talpaz M, O'Brien S, Jones D, Luthra R, et al. (2005) Molecular responses in patients with chronic myelogenous leukemia in chronic phase treated with imatinib mesylate. Clin Cancer Res 11: 3425–3432.

[2]
F. Michor, T. Hughes, Y. Iwasa, S. Branford, N. Shah, C. Sawyers, and M. Nowak, (2005), Dynamics of chronic myeloid leukemia, Nature, 435, 1267–1270.

[3]
Olshen A, Tang M, Cortes J, Gonen M, Hughes T, Branford S, Quintás-Cardama A, and Michor F. Dynamics of chronic myeloid leukemia response to dasatinib, nilotinib, and high-dose imatinib. Haematologica. 2014; 99:xxxdoi:10.3324/haematol.2013.085977

[4]
F. Michor, T. Hughes, Y. Iwasa, S. Branford, N. Shah, C. Sawyers, and M. Nowak, (2005), Dynamics of chronic myeloid leukemia, Nature, 435, 1267–1270.

[5]
P. Kim, P. Lee, and D. Levy, (2008), Dynamics and potential l impact of the immune response to chronic myelogenous leukemia, PLoS Comput. Biol. 4(6).

[6]
D. Paquin, P. Kim, P. Lee, D. Levy, (2009). Strategic Treatment Interruptions During Imatinib Treatment of Chronic Myelogenous Leukemia

[7]
http://www.cancer.gov/cancertopics/pdq/treatment/CML/HealthProfessional/page1

Warren J. Baker Endowment for Excellence in Project-Based Learning
Robert D. Koob Endowment for Student Success

PROPOSAL BUDGET

Student Applicant(s):	
Faculty Advisor:	
Project Title:	**Requested Baker Endowment Funding**
Travel *subtotal*	**$**
Travel: In-state	**$ 300**
Travel: Out-of-state	**$ 2500**
Travel: International	**$**
Operating Expenses *subtotal*	**$**
Non-computer Supplies & Materials	**$**
Computer Supplies & Materials	**$**
Software/Software Licenses	**$**
Printing/Duplication	**$**
Postage/Shipping	**$**
Registration	**$**
Membership Dues & Subscriptions	**$**
Multimedia Services	**$**
Advertising	**$**
Journal Publication Costs	**$**
Contractual Services *subtotal*	**$**
Contracted Services	**$**
Equipment Rental/Lease Agreements	**$**
Service/Maintenance Agreements	**$**
TOTAL	**$**

Warren J. Baker Endowment

Excellence in Project-Based Learning

CAL POLY

Letter of Support from Faculty Advisor

Dr. Dana Paquin
Assistant Professor of Mathematics
California Polytechnic State University
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Dear Baker Endowment Coordinator,

This letter is to express my support for the project proposal titled "Analysis of a Delay Differential Equations Mathematical Model for Imatinib Treatment of Chronic Myelogenous Leukemia" submitted by Cal Poly undergraduate students David Kato and John Shamshoian. I have worked closely with both of these students, both in mathematics courses and on research projects outside of class, and both David and John have the mathematical and computational expertise necessary to be successful in the proposed project. They have completed coursework in and have experience with differential equations, mathematical modeling, and numerical analysis and simulation, and they both have hands-on experience with Matlab (the computer programming and numerical simulation package that will be used for this research project). Additionally, both students have spent significant time learning the background of the delay-differential equations model that I have used in previous research to mathematically describe the interaction of leukemia cells with the immune system, and they have learned the necessary biology and immunology to understand the dynamics of the model. I am confident that they have the abilities and motivation necessary to meet the objectives described in their proposal narrative.

The proposed project has significant intellectual merit, both for the students involved and for the larger research community. Mathematical modeling of chronic myelogenous leukemia (CML) and simulations of alternative treatment programs have the potential to significantly increase the success of treatment strategies for CML. Working with me and with collaborators from the Stanford University Medical Center, the students will carefully analyze the role played by each of the numerical (universal and patient-specific) parameters in the delay differential equations model for imatinib treatment of CML. The students will numerically simulate the mathematical model in Matlab and analyze and interpret their results in terms of the biological and immunological consequences.

As faculty advisor, I will support the students by assisting with the model development and verification and by coordinating collaboration efforts with the Stanford University Medical Center (where I have existing collaborators) and other immunology researchers. I will also assist the students with using Matlab and in developing, implementing, analyzing, and refining the numerical simulations for this project.

In conclusion, I strongly support the project proposal titled "Analysis of a Delay Differential Equations Mathematical Model for Imatinib Treatment of Chronic Myelogenous Leukemia" submitted by Cal Poly undergraduate students David Kato and John Shamshoian. If I can be of any assistance as you evaluate their proposal, please do not hesitate to contact me.

Best regards,
Dana Paquin, Ph.D.