Overview of Tumor Dynamics Module *

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Introduction: The Module on Tumor Dynamics is actually a **super-Module** containing **three distinct Modules** that make use of a shared motivating application. The application is the interaction of a growing tumor with an active immune response. The three Modules are

- **Module 1:** Numerical Solution of IVPs
- **Module 2:** Parameter Estimation
- **Module 3:** Bifurcation Analysis of ODE systems

This super-Module is best introduced at the beginning of a course on modeling or on scientific computing, since it is self-contained and presented from an introductory perspective.

Super-Module Goal: The main goal of this super-Module is to give the students an understanding of the steps involved in creating a continuous time deterministic model, from understanding the underlying biology of the system to developing the mathematical model itself to evaluating the model both analytically and numerically. We make heavy use of the research paper by Kuznetsov [KMTP94] as a guide for the students. If all three Modules are used, then by the end of the super-Module, the students should be able to understand, and in most cases even recreate, the processes and results described in Kuznetsov's article.

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We recommend that you provide copies of [KMTP94] to the all the students.

Super-Module Objectives: The objectives of this super-Module are to get the students to be able to carry out each of the steps needed for the development and analysis of the Kuznetsov model. In particular, after having been through all components of the super-Module, the students should be able to

- Understand the fundamental biology needed and choose which components to include in a model
- Develop the mathematical equations representing the biological dynamics
- Qualitatively analyze the resulting system of mathematical equations
- Understand how to numerically solve the system of equations for particular solutions
- Estimate the parameters used in the system
- Nondimensionalize the equations
- Carry out a bifurcation analysis to understand the impact of the parameters on the system
- Discuss and assess the model and its variants

Intended Audience: This course is aimed at sophomore, junior and senior level students with an interest in mathematics, in mathematical biology, or in mathematical models of interacting populations in general.

Combining Modules: The instructor can customize the Module by combining the submodules provided here in a way that addresses the particular needs of the students. The submodules we provide are titled:

1. Introduction:Tumor-Immune Interactions (This section includes Problem Statement and Biological Background)
2. Tumor-Immune Equation Development
3. Qualitative Analysis
4. Numerical Solution of ODE IVPs
5. Parameter Estimation
6. Non-dimensionalization
7. Bifurcation Analysis
8. Model Assessment and Conclusions

The three main Modules mentioned above can be structured as follows:

- **Module 1, Numerical Solution of IVPs:**
  Include submodule 1 → submodule 2 → submodule 3 → submodule 4
- **Module 2, Parameter Estimation:**
  Include submodule 1 → submodule 2 → submodule 3 → submodule 5
- **Module 3, Bifurcation Analysis:**
  Include submodule 1 → submodule 2 → submodule 3 → submodule 7

Note that submodule 6 can be added to any of these Modules, and submodule 8 can be modified for use with any of these, or used as provided if all three Modules are presented. Naturally, all submodules from 1 through 8 can be presented in sequence, or the instructor many choose to omit one or more of submodules 3 through 7. For example, if the students are already experienced with numerical simulation, submodule 4 is easily omitted without loss of continuity in presentation.

Background Needed: Before beginning with the Module components, the students should have had an introductory semester-long course in *linear algebra* and an introductory semester-long course in *ordinary differential equations*. However, since in our experience the students find it helpful, we do provide frequent review of ODEs material. A background in biology is helpful but not necessary, since we provide the background material needed to understand the basic biology needed for model development.

Format and Pedagogy: We created these Modules to be presented in a lecture format. To maximize efficiency and minimize preparation time for the instructor, we have written up our Modules as overhead slides, with additional notes and comments to the instructor. The overhead slides are designed precisely to be used as overheads, and also to be given as handouts to the students. Nearly every slide has one or more blank areas for the students to fill in. The notes to the instructors contain the answers that go in the blanks. The pedagogical purpose for the blanks is to engage the students in the lecture. It is sometimes the case that the student will be able to guess the answer in the blank, but many times there are either multiple possible answers, or the answer is not immediately apparent. This is intentional. The point of this format is to encourage active participation of the students, so we recommend that the instructor ask the class as often as seems appropriate what the class's guess at the answer in the blank should be, and acknowledge with positive feedback all suggestions from the class. We also suggest that the instructor explain this fill-in-the-blanks process to the class at the beginning of the Module. In the notes to the instructor we also provide suggestions for in-class demonstrations, reading asssignments, and student exercises, as well as additional explanation of the slides.

Exercises and Projects: The exercises we provide for each Module are intended to give the students practice in the developing the particular analysis skills related to that module. Some of the exercises help lay the groundwork for carrying out the larger projects. When appropriate, we have indicated which exercises inform particular projects. The projects we provide are more global, and are intended to suggest models on which the students can practice going through many of the development and analysis steps they have learned in the Modules. The model variants we provide are primarily based on research literature.

The goal of these projects is to provide open-ended, exploratory activities, so that the students can become more deeply involved with the modeling process. They could be done in groups or individually. We recommend that adequate time be given to these projects (minimum one week), and that the results be presented both orally and in written form. It is important to be able to critically evaluate the outcome of the modeling process, and to communicate any results to a rather wide audience. Some references have been provided, but the students should be encouraged to search the literature for other related articles. It is assumed that the students are familiar with most, if not all, of the material presented in the module before embarking on the projects. It might be expedient to have the students select a project early on, and to begin some background reading on their particular subject. For example, some background reading on cancer vaccines could be done before modifying the mathematical model to incorporate this type of therapy.

References

[KMTP94] Vladmir A. Kuznetsov, Iliya A. Makalkin, Mark A. Taylor, and Alan S. Perelson. Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. *Bulletin of Mathematical Biology*, 56(2), 1994.