Over the past years, my research has focused on mathematical problems in biology and medical sciences. The various projects have been conducted in close collaboration with experimentalists and medical doctors. Most of the activities were motivated by clinical & biological questions. These lead to the derivation of new mathematical models. A considerable amount of work was then put into the analysis and simulations of these models, with the hope that the conclusions and conjectures of the mathematical analysis will be of interest to the practitioners. The mathematical tools we have been using include discrete models, probabilistic and stochastic methods, ordinary differential equations, delayed differential equations, and partial differential equations. Following is a summary of some of the main results I published with my students and collaborators over the past several years. The research results are reported under three main categories: (1) cancer dynamics; (2) Immunology; and (3) cell motility.

1. Cancer Dynamics

Our main activities in cancer studies have been focused on Chronic Myelogenous Leukemia and on drug resistance. We also mention our recent results on immune suppression and on the control of small tumors by their microenvironment.

1.1 Chronic Myelogenous Leukemia

Chronic Myelogenous Leukemia (CML) is a blood cancer with a common acquired genetic defect resulting in the overproduction of malformed white blood cells. It constitutes nearly 20% of all leukemias. The cause of CML is an acquired genetic abnormality in hematopoietic stem cells due to a reciprocal translocation between chromosomes 9 and 22. This translocation, creating the Philadelphia chromosome, has associated oncogenic properties. The BCR-ABL fusion gene, drives an increased and aberrant tyrosine kinase activity due to the chromosomal rearrangement. It is this abnormal activity that leads to dysfunctional regulation of cell growth and survival, and consequently to cancer. The standard first-line therapy against CML is imatinib (also known as Gleevec), a molecular-targeted drug that inhibits the abl tyrosine kinase. Under imatinib, nearly all patients attain hematologic remission and 75% achieve cytogenetic remission (no Ph+ cells). However, imatinib does not completely eliminate residual leukemia cells and patients inevitably relapse after stopping treatment.

The goal of our research program on CML is to develop new mathematical models and integrate them with clinical and experimental data in order to improve the clinical methodologies for treating CML patients. This research has been conducted
in close collaboration with my former Ph.D. student, Peter Kim, and with Prof. Peter Lee, an Associate Professor at the Division of hematology, Stanford Medical School. Our joint research has been supported by the NIH R01 grant: “Interplay between cancer and immune cells on targeted therapy”.

1.1.1 Dynamics and Potential Impact of the Immune Response to CML
(with my Ph.D. student Peter Kim and Dr. Peter Lee from the Division of Hematology at Stanford Medical School)

Various mathematical models have been developed to study the dynamics of CML under imatinib treatment. Recent experimental data that was published by the group of my collaborator, Dr. Peter Lee, show that imatinib treatment may promote the development of anti-leukemia immune responses as patients enter remission. Since existing mathematical models did not incorporate the anti-leukemia immune response, and given the experimental data, we developed a mathematical model that takes into account the immune response. Our goal was to gain insights into the dynamics and potential impact of the resulting anti-leukemia immune response on CML. The mathematical model we developed is based on the model of Michor et al. to which we added interactions with T cells. Accordingly, we follow the dynamics of stem cells, progenitor cells, differentiated cells and terminally differentiated cells. Each cell-type exists in two states: with or without resistance mutations to imatinib. T cells interacting with leukemia cells may be stimulated to proliferate or to become anergic and die. The mathematical model is formulated as a system of delay differential equations, in which the delay term accounts for the duration of cell division.

Analysis and simulations of the mathematical model suggest that anti-leukemia T cell responses may play a critical role in maintaining CML patients in remission under imatinib therapy. Furthermore, it proposes a novel concept of an ‘optimal load zone’ for leukemic cells in which the anti-leukemia immune response is most effective. Imatinib therapy may drive leukemic cell populations to enter and fall below this optimal load zone too rapidly to sustain the anti-leukemia T cell response. This is a surprising result as the role of the immune response in the dynamics of CML is largely unknown.

As an example, we use clinical data on the anti-leukemia immune response of a patient to compare the solutions of our model and of Michor’s model. The result is shown in the following figure. Time is measured in months. Time zero corresponds to the time in which the disease was diagnosed and the drug therapy started. The dashed line represents the level of a cytogenetic remission. The “no immune response” curve corresponds the model of Michor et al. The Michor model does not provide a good fit as it always predicts a quick relapse of the disease, which does not usually happen. The dots show the magnitude of the anti-leukemia immune response as measured in the clinic at different times. The solid “T cells” line is the fit that we used in our model in order to evaluate the patient’s specific model parameters. The “Leukemia” curve is the time-dynamics of the cancer cells as predicted by our mathematical model. Unlike Michor’s model, our model suggests that the patient enters a sustained remission since the leukemic cells remains under...
the level of the cytogenetic remission for a long time. This is consistent with clinical observations.

The experimental results of Lee’s group further suggest that autologous leukemia cells may be collected from a patient, inactivated, and strategically reintroduced to enhance the anti-leukemia T cell response. Ideally, these cancer vaccines stimulate the immune system enough to derive the residual leukemia population to zero. To study the feasibility of this approach we introduce inactivated leukemia cells into our model. We then use optimization techniques to study potential vaccine plans, in which the vaccines are combined with imatinib therapy in order to potentially eradicate residual leukemic cells for a durable cure of CML. To demonstrate this approach, we show in the following figure a simulation of the time evolution of cancer and T cells populations for a patient that is undergoing drug therapy, and is receiving cancer vaccines. In this case, five vaccines are delivered starting from day 233 in intervals of 10 days apart. On the RHS we show the time evolution of the four types of leukemia cells throughout the combined therapy: stem cells, progenitor cells, differentiated cells, and terminally differentiated cells. Time is measured in months and cell-concentrations are shown on a logarithmic scale.
Indeed, this simulation suggests that repeated stimulation of the T cells by the vaccines may completely eliminate leukemia. The timing and pacing of the vaccine strategies are critical to the success of the outcome. For example, if they are initiated too early (or too late), the immune response is too weak to be amplified. The timing and pacing of the vaccinations must be adaptively adjusted to the patient’s immune response in order to be effective.

Among all mathematical models of CML, our approach is unique in the sense that the experimentally observed anti-leukemia immune response is incorporated into the mathematical model. A group of hematologists at Stanford Medical School is preparing a clinical trial to test the results of this work. This work has been our most visible work on CML. It was featured in a variety of articles in press and on the internet, including Reuters, Forbes, Science Daily, Scientific American, Future Oncology, and the NSF Discoveries. Is was also the topic of my keynote address in the American Mathematical Society briefing to the US Congress in September 2008.

1.1.2 Modeling imatinib-treated CML: reducing the complexity of agent-based models  
(with my Ph.D. student Peter Kim and Dr. Peter Lee from the Division of Hematology at Stanford Medical School)

We develop a model for describing the dynamics of imatinib-treated CML that is based on the recent agent-based model of Roeder et al., which we will refer to as “the Roeder Model”. The Roeder Model for Leukemia assumes that hematopoietic stem cells exist in two growth compartments: noncycling and proliferating. At each time step (of 1 hour), there is a positive probability that a stem cell will change its compartment. Each cell has an affinity \( a(t) \in [a_{\text{min}}, a_{\text{max}}] \). A cell with a high affinity has a high chance of remaining in or transferring to the non-proliferating compartment. Likewise, a cell with a low affinity is more likely to remain in or transfer to the proliferating compartment. Proliferating cells progress through various stages of the cell cycle. Only cells in the \( G_1 \) phase (the longest phase of growth during which the cell generates new organelles) can transfer to the non-proliferating compartment. When the affinity of the cell drops below \( a_{\text{min}} \) it differentiates into a precursor cell. Precursor cells proliferate for 20 days, dividing once per day. At the end of 20 days, precursor cells differentiate into mature cells and live for 8 additional days without dividing. The Roeder Model is summarized in the following state diagram:
The original Roder Model has been written as an agent-based model. As such, it is very computationally demanding. In fact, to make the computations feasible, Roeder et al. down-scaled the absolute cell numbers to 1/10 of the realistic values. Our goal was to replace the Roeder model by a model that is more computationally appealing. To that effect, we replaced the agent-based model by a system of deterministic difference equations. These difference equations describe the time-evolution of clusters of individual agents that are grouped by discretizing the state space. Hence, unlike standard agent-base models, the complexity of our model is independent of the number of agents, which allows to conduct simulation studies with a realistic number of cells. An additional substantial gain can be obtained by converting the stochastic agent-based model into a deterministic model. This is done by replacing all binomial random variables $\text{Bin}(N,p)$ with the constant expected value $Np$ and allowing the population sizes to be continuous. This modification eliminates all random number generations, leading to an immense increase in the computational speed. Due to the reduced computational complexity of our approach, it is also possible to easily conduct sensitivity studies. In our case, the deterministic model runs about 80 times faster than the original Roeder Model (with $10^5$ stem cells).

As an example we show in the following figure the calculated steady state profiles for the Ph− stem cell population. Cells are grouped into wells based on their affinity values. The upper graph corresponds to the proliferating cells, and the bottom graph corresponds to the non-proliferating cells. The rugged line is the result of a typical agent-based-model simulation (the original model). The solid line is the result of our deterministic model.

In another related work, we reformulated the Roeder Model as a system of PDEs. These PDEs describe various stages of differentiation and maturation of normal hematopoietic cells and of leukemic cells. A PDE model has several advantages over the stochastic agent-based model: in addition to being able to solve it much faster, it provides a direct access to macroscopic quantities. Various quantities can depend on densities and constants can be treated from a macroscopic point of view instead of keeping track over individual parameters that correspond to individual cells.

The derivation of the system of PDEs is far from being straightforward. The main difficulty is the concentration of cells with an internal affinity counter that

\[ \frac{dN_i}{dt} = r_i N_l \]
reaches its maximum value $a_{\text{max}}$. To address this difficulty, we introduce a new cell population that corresponds to the point mass at $a = 1$. The system of equations that we obtain is a hyperbolic system of maturity-structured PDEs. Since in this model stem cells can switch between increasing and decreasing their maturity arbitrarily many times, cells do not necessarily mature in finite time. Furthermore, the “left-moving” and “right-moving” populations continually interact and exchange members so that information does not only travel in one direction. These are some of the issues that should be addressed in the derivation of the model equations. The following figure is a state-space diagram for the PDE CML model. The variable $A(x, t)$ represents cells in the non-proliferating compartment that have log affinity $x$ at time $t$. The variable $A^*(t)$ represents cells in the non-proliferating compartment that have attained the minimum log affinity. The variable $\Omega(x, c, t)$ represents cells in the proliferating compartment that have log affinity $x$ and time counter $c$ at time $t$. The variable $\Omega^*(x, t)$ corresponds to the population of $\Omega$ cells supplied by $A^*$. These cells travel along the characteristic curve originating at point source $P$.

The numerical simulations for the PDE model shows similar features to the difference-equations model, as can be seen in the following steady state profile diagram for the case when no leukemia stem cells are present.
1.1.3 Post-transplantation Dynamics of the Immune Response to CML
(with an undergraduate student Rob DeConde, my Ph.D. student Peter Kim and Dr. Peter Lee from the Division of Hematology at Stanford Medical School)

We model the dynamics between T cells and cancer cells in CML patients after a bone marrow (or a stem cell) transplant. Allogeneic bone-marrow or stem-cell transplantation is the only known curative treatment for CML. Our work is the first mathematical model to study the dynamics of the cancer-immune interaction after an allogeneic transplant. We do not assume any drug therapy, rather we focus on the mechanisms that lead to a successful transplant. We use a system of six delay differential equations to track the following cell-populations: from the donor we consider anti-cancer T cells, anti-host T cells, and all other donor cells. From the host, we consider cancer cells, anti-donor T cells, and general host blood cells. The anti-cancer T cells represent the cells that respond to a cancer-specific antigen and mediate the graft-versus-leukemia effect, while the anti-host T cells represent those that respond to a general blood antigen and mediate blood-restricted graft-versus-host disease. Our approach incorporates time delays and accounts for the progression of cells through different modes of behavior. To demonstrate the complexity of the mathematical model, we show in the following figure a state diagram for the anti-donor T cells, which is one of the six cell populations we model. The anti-donor T cells (coming from the host and denoted by $T_D$) can interact with the donor cells ($D$), with the anti-host cells ($T_H$), and with the anti-cancer T cells ($T_C$). The circles represent the time delays. Interactions occur with different probabilities as shown in the diagram.

![State diagram of immune response to CML](image)

We use the model to explore possible mechanisms behind a successful cure, whether mediated by a blood-restricted immune response or a cancer-specific graft-versus-leukemia effect. Characteristic features of this model include sustained proliferation of T cells after initial stimulation, saturated T cell proliferation rate, and the possible elimination of cancer cells, independent of fixed-point stability.
We use numerical simulations to examine the effects of varying initial cell concentrations on the likelihood of a successful transplant. Among the observed trends, we note that higher initial concentrations of donor-derived, anti-host T cells slightly favor the chance of success, while higher initial concentrations of general host blood cells more significantly favor the chance of success. These observations lead to the hypothesis that anti-host T cells benefit from stimulation by general host blood cells, which induce them to proliferate to sufficient levels to eliminate cancer.

In a follow-up work, we focus on a mathematical study of mini-transplants. In mini (or non-myeloablative) transplants, patients receive milder doses of chemotherapy that do not ablate the myeloid stem cells. As a result, the treatment depends more heavily on the donor immune cells to expand and destroy remaining leukemia cells. Our initial study suggested that the expansion of donor T cells depends more on general host blood cells than on leukemia cells alone. This is because a successful transplant relies on a blood-restricted graft-versus-host disease, in which donor T cells react to antigen that is present on general host blood cells. This less discriminate reactivity results in greater proliferation of immune cells and often proves necessary because leukemia cells usually do not provide sufficient stimulus.

In this work we our goal is to study the dynamics of mini-transplants and to determine conditions that increase the chance of a successful cure. We seek to understand the tradeoff between eliminating leukemia and host immune cells and maintaining the stimulus to donor immune cells. To address this question, we derive an extended mathematical model in which all target cells are divided into two states: alive and dying. This modification accounts for the delay between the time that a T cells engages a target cell and the time that the target cell actually die. During this time period, target cells may continue to stimulate other circulating T cells. Our model is written as a system of nine delay differential equations that incorporate multiple time delays and account for the progression of cells through different stages.

We conduct a sensitivity analysis of the model parameters with respect to the minimum cancer concentration attained during the first remission and the time until the first relapse. In addition, we examine the effects of varying the initial host cell concentration and the cancer cell concentration on the likelihood of a successful transplant. We observe that higher initial concentrations of general host blood cells increase the chance of success. Such higher initial concentrations can be obtained, e.g., by reducing the amount of chemotherapy that is administered prior to the transplant, a procedure known as a mini-transplant. Our results suggest that mini-transplants may be advantageous over full transplants. We use statistical tools to identify the regions of the parameters for which mini-transplants are advantageous.

This is the only quantitative, non-clinical, study of mini-transplants in the literature.

1.1.4 Stability Crossing Boundaries of Delay Systems Modeling Immune Dynamics in Leukemia Control model
(with K. Gu, P. Kim, P. Lee, and Silviu Niculescu)
Some of our mathematical models for CML are written as systems of delayed differential equations. The presence of time delays may induce complex behaviors (such as instability, oscillations, and chaotic behaviors). The difficulty in analyzing time-delayed systems is mainly related to the fact that such systems are infinite dimensional.

In this work we consider a simplification of our mathematical model of the post-transplantation dynamics of the immune response to CML. The system we study is:

\[
\begin{align*}
\frac{dT(t)}{dt} &= -d_T T(t) - kC(t)T(t) + p_T kC(t - \sigma)T(t - \sigma) \\
&\quad + 2^N p_1 q_1 kC(t - \rho - N\tau)T(t - \rho - N\tau) + p_2 q_2 kC(t - \rho - \nu)T(t - \rho - \nu) \\
\frac{dC_A(t)}{dt} &= r C_A(t)(1 - C_A(t)/K) - \bar{p}_1 kC_A(t)T(t) \\
\frac{dC_D(t)}{dt} &= \bar{p}_1 kC_A T(t) - \bar{p}_1 kC_D(t - \rho)T(t - \rho) \\
C &= C_A + C_D
\end{align*}
\]

Here, \(T\) are the T cells, \(C_A\) are the active cancer cells, and \(C_D\) are the dying cancer cells. \(N\) is the number of times a T cell may divide after an interaction with a cancer cell. Each cycle of division takes \(\tau\) units of time to complete. If the T cells ignore the stimulus, they return to their base state after a delay \(\sigma\). If the T cells react with the cancer cells, they have a chance of destroying them through a cytotoxic response with delay \(\rho\). Recovering their cytotoxic capabilities happens after a delay of \(\nu\). All together the system has four distinct delays, \(\sigma, \rho + N\tau, \rho + \nu,\) and \(\rho\), ranging from minutes to days. Due to this scale difference, we can define wlog \(\rho\) and \(\sigma\) as small the delays and the other two as large.

Stability analysis is appropriate for this model, because a stable solution may imply full remission of cancer or at least a state in which the cancer cells remain controlled. On the other hand, an unstable solution implies the eventual relapse of the cancer population, corresponding to an unsuccessful transplant. For our particular application we are interested in analyzing the effects induced by the presence of delays on the asymptotic stability of the corresponding linearized model, and to derive the stability/instability mechanisms in the delay-parameter space. At the same time, we are interested in understanding how small delays interact with large delays in defining stability/instability properties.

To study such a system with multiple delays, we defined two types of T cells and cancer cells interactions: weak and strong. Heuristically, weak interactions correspond to a case where the large delays have a very low impact on stability, while strong interactions describe the situation where the stability of the model is sensitive also of the large delays. We define the weak and strong interactions in a way that is computationally tractable, and prove that indeed the large delay values have a low influence on the stability properties in the weak cell interaction case. We
analyze the strong cell interaction case in terms of stability crossing curves, and give a classification of such crossing curves. Under certain assumptions, these curves are shown to be either closed curves, open ended curves with both ends approaching infinity or spiral-like curves. Numerical simulations that are based on the analytical study are conducted and the stability crossing curves are plotted in certain cases of interest. An example is shown in the following Figure in which we show the stability crossing curves with respect to \( \tau \) and \( \nu \). The values of \( \rho \) and \( \sigma \) are held fixed. Crossing the curve increases or decreases the number of roots of the characteristic polynomial that have a positive real part by two. Stable regions are those that correspond to zero such roots. We see in the right figure a relatively large region of stability that is isolated from the origin. Without the theory it is difficult to predict the existence of such a region, or to find its location.

![Stability Crossing Curves](image)

Surprisingly, our results indicate that the stability of the controlled state benefits from high values of \( \nu \). This corresponds to \( T \) cells that have long turn around times after killing cancer cells. These results imply that highly reactive \( T \) cells with low turn around times may, in fact, be disadvantageous to the stability of the system. Hence, in this formulation of the problem, more gradual reduction of the cancer population is favored over rapid elimination. In addition to the specific CML-related conclusions, our work initiated a program to study the stability in the delays-space of similar systems that incorporate multiple delays with different time-scales.

### 1.2 Drug Resistance and Cancer Stem Cells

#### 1.2.1 An Elementary Approach to Modeling Drug Resistance in Cancer
(with my Ph.D. student Cristian Tomasetti)

Resistance to drugs has been an ongoing obstacle to a successful treatment of many diseases. In this work we consider the problem of drug resistance in cancer, focusing on random genetic point mutations. Most previous works on mathematical models of such drug resistance have been based on stochastic methods. In contrast, our approach is based on an elementary, compartmental system of ordinary differential equations. We use our very simple approach to derive results on drug
resistance that are comparable to those that were previously obtained using more complex mathematical techniques. The simplicity of our model allows us to obtain analytic results for resistance to any number of drugs. Assuming that \( n \geq 1 \) denotes the number of drugs, the amount of resistance that is present when the therapy starts is given by

\[
R(t^*) \approx M \left[ \frac{u \ln(M / N_0)}{L(1 - D / L)} \right]^n.
\]

Here, \( M \) denoted the total number of cancer cells when the therapy begins, \( L \) and \( D \) are the birth and death rates, respectively, \( u \) is the mutation rate, and \( N_0 \) is the number of pretreatment wild-type cancer cells. Hence, what we show is that the amount of resistance generated before the start of the treatment, and present at some given time afterward, always depends on the turnover rate \((D / L)\), no matter how many drugs are simultaneously used in the treatment. Our result contradicts the results of Komarova that showed that in the single drug case, the amount of resistance that is present when the therapy starts does not depend on the turnover rate. The study of Komarova is an asymptotic study that provides a result that is valid only at \( t = \infty \), but is not valid for any finite time. Indeed, it is more desirable in the problem of drug resistance to study the dynamics for a finite time. To further study the difference between the approaches we used techniques of branching processes to calculate the probability to have resistant mutants generated before the beginning of the treatment and present, including their progeny, at some given time afterward. When time is measured from the beginning of the treatment, this probability is given by

\[
P_R(t) = 1 - \exp \left( -uM \frac{L}{De^{-(L-D)t}} \right) \ln \left( \frac{1}{1 - \frac{De^{-(L-D)t}}{L}} \right).
\]

Clearly, this quantity depends on the turnover rate, which further validates our results.

The main strength of our approach in studying this problem is in its simplicity. Obtaining these initial results allowed us to study more complicated problems using similar techniques, this time providing substantial improvements over known results, as will be explained below.

1.2.2 The Role of Symmetric and Asymmetric Division of Stem Cells in Developing Drug Resistance
(with my Ph.D. student Cristian Tomasetti)

One of the main ingredients that has been recently introduced into the rapidly growing pool of mathematical cancer models is stem cells. Surprisingly, this all-so-
important subset of cells, has not been fully incorporated into existing mathematical models of drug resistance. For example, there are no rigorous estimates of the probability of developing drug resistance within the context of a cancer stem cell model. From the point of view of drug resistance, the heterogeneity in the tumor cell population implies that it is only the stem-like long-lived cells, those cells that have the ability of self-renewal, that propagate the drug resistance. Cancer cells that do not have self-renewal capabilities cannot propagate resistance in the long run and should be disregarded.

In this work we incorporate the various possible ways in which a stem cell may divide into the study of drug resistance. We assume that a stem cell may divide in the following three ways:

1. Asymmetric division: a stem cell divides into one progenitor cell and one stem cell (with probability $a$).
2. Symmetric differentiation: a stem cell divides into two progenitor cells (with probability $b$).
3. Symmetric renewal: a stem cell divides into two stem cells (with probability $1-a-b$).

We denote the birth rate by $L$, the death rate by $D$, the mutation rate by $u$, and the total number of cancer stem cells by $M$. We prove that the probability of developing drug resistance by the time a tumor is detected is given by

$$P_R = 1 - \exp\left(-uM \left(\frac{1 - a - b}{1 - a - b} \frac{1}{C} \ln\left(\frac{1}{1-C}\right)\right)\right),$$

with $C = \frac{D + Lb}{L(1-a-b)}$. The expected number of resistance cancer stem cells at the time of tumor detection (conditioned on the development of resistance) is then given by

$$E(T | \text{resistance}) = \frac{M}{P_R} \frac{u \left(1 - \frac{a - b}{2}\right)}{1 - a - 2b - \frac{D}{L} \ln(M)}.$$

Our mathematical model for drug resistance is derived using ODEs for the wild-type cancer stem cells and branching processes for the mutant cells. It is common in the literature to use Markov chains for the wild-type cells. Our approach amounts to using a partially deterministic model in which the averaged behavior of the wildtype population is considered. Intriguingly, our approach provides identical results to those found in Iwasa et al. if we also assume a homogeneous cell population (as was done by Iwasa et al.). Nothing is being lost by using a partially deterministic approach. On the contrary, our simplified approach enables us to extend the result to the case of a heterogeneous cell population.

Our model is thus suitable as a framework for mathematically studying stem cells and their role in developing drug resistance. This is an important result: it is the
first work in the mathematical literature of drug resistance that incorporates the
dynamics of stem cells.

1.2.3 From Asymmetric Division to Symmetric Renewal in CML
(with my Ph.D. student Cristian Tomasetti)

One of the fundamental characteristics possessed by stem cells is their ability to
divide both symmetrically and asymmetrically. It has been experimentally observed
that stem cells may be able to switch between symmetric and asymmetric cell
divisions. For example, both neural and epidermal stem cells change from primarily
symmetric divisions that expand stem-cell pools during embryonic development to
primarily asymmetric divisions that expand differentiated cell numbers. Asymmetric cell division seems to be a natural setting for a population in
equilibrium; for example this has been observed for healthy hematopoietic stem
cells in homeostasis. In contrast, symmetric stem-cell divisions have been observed
and appears to be a common way to divide during development, wound healing and
regeneration. Due to the contemporary interest in the role that stem cells may play
in the origination and progression of various types of cancer, it is intriguing to study
the pattern of division of cancer stem cells. Do they follow the original division plan
of their healthy counterparts or do they change their mode of division? It would
seem natural to assume that cancer stem cells increase their numbers by means of a
symmetric self-renewal. While this is an intuitive hypothesis, at present there is
sparse experimental data that supports it. For example, it has been observed that
when the mechanism regulating asymmetric divisions is disrupted, Drosophila
neuroblasts begin dividing symmetrically and form tumors. Also, it is known that
some gene products can both induce symmetric cell divisions and function as
oncogenes in mammalian cells. Morrison et al. recently stated that “the idea that
symmetric divisions are required for neoplastic proliferation remains hypothetical, but
raises the possibility that studies of the asymmetric division machinery could identify
important new tumour suppressor mechanisms” (Morrison and Kimble, 2006).

In this work we study the dynamics of cancer stem cells by combining mathematical
analysis, experimental, and clinical data. We focus on Chronic Myeloid Leukemia
(CML) for which a recent study has been published on a six-year follow up of
patients that receive imatinib as the first line of treatment (Hochhaus et al., 2009).
This clinical study provides us with concrete estimates on the total number of
patients that shift from the chronic phase to the acute phase (or enter into a blast
crisis) of the disease. We note that the number of relapses of the disease due to the
development of drug resistance must be a subset of the total number of relapses
reported by Hochhaus. Since only the stem-like cells are able to self-renew and
propagate the drug-resistance, we trace back the origin of the resistance to the
cancer stem cells. This observation then allows us to incorporate the clinical data
into our mathematical model of drug resistance, which is the only mathematical
model that takes into account cancer stem cells. The result predicts a large shift
from asymmetric division to symmetric renewals in the case of CML. What the
application of the formula indicates is that the leukemic stem cells should have a much
lower than normal tendency to divide asymmetrically, shifting toward an increased
symmetric renewal. This is a conclusion of the mathematical analysis that incorporates the clinical and experimental data. It provides a fundamental contribution to the understanding of cancer stem cells.

1.3 Cancer Research – Other

1.3.1 B7-H1 and a Mathematical Model for Cytotoxic T Cell and Tumor Cell Interaction
(with my Ph.D. student Amanda Galante and Dr. Koji Tamada from the Department of Otorhinolaryngology-Head and Neck Surgery, University of Maryland School of Medicine)

The surface protein B7-H1 is found on carcinomas of the lung, ovary, colon and melanomas but not on most normal tissues. B7-H1 has been experimentally determined to be an anti-apoptotic receptor on cancer cells, where B7-H1-positive cancer cells have been shown to be immune resistant, and in vitro experiments and mouse models have shown that B7-H1-negative tumor cells are significantly more susceptible to being repressed by the immune system. Phase I clinical trials with an antibody which blocks B7-H1/PD-1 interactions yielded complete remission in one patient with non-Hodgkin’s lymphoma. A better understanding of the mechanisms and dynamics may allow medical researchers to develop a cancer treatment schedule specifically targeting this molecular shield, allowing the immune system to more effectively repress a tumor.

We derive a new mathematical model written as a system of nonlinear ODEs for studying the interaction between cytotoxic T cells and tumor cells as affected by B7-H1. We consider apoptosis by two different mechanisms: Fas/FasL binding and perforin. We show how the model can be used to fit percent lysis data for in vitro interactions between CTLs and cancer cells, transfected with either B7-H1 or a mock protein. To demonstrate our results we show in the following figure the percent lysis experimental data fit by the model at 4 and 12 hours for both B7-H1+ and B7-H1- for various effector to target cell ratios.

![Graph showing percent lysis for 4 and 12 hours for B7-H1+ and B7-H1-](image)

This model can now be extended to in vivo data, including the upregulation of B7-H1 on tumor cells and interaction with an antibody.
1.3.2 A Mathematical Model for Microenvironmental Control of Tumor Growth  
(with my Ph.D. students Amanda Galante & Cristian Tomasetti)

It is known that the majority of tumors are monoclonal, i.e., cancer generally develops starting from a single cell that has undergone a mutation. It is calculated that 3 mutations occur on average every time the cell’s DNA base pairs are duplicated, an event that occurs $10^{16}$ times in the life of a person. Furthermore, there are a lot of genetic and epigenetic changes that can promote cancer. This raises one of the most challenging questions in cancer studies: why do approximately two out of three people never develop cancer? Furthermore, why does it appear that at least for some types of tumors, the disease progresses for some patients while remaining latent in other patients. It is a striking fact, supported by a large amount of evidence, that the majority of disseminated tumor cells present in the human body never develop into clinical tumors. Some examples are the cancerous cells found in the prostate, the mammary gland, and the epithelium. It has been proposed that this variability in cancer resistance may be due to differences in the efficiency of certain protective mechanisms, which are known to inhibit the growth of neoplastic cells.

In this work we focus on the mechanism known as microenvironmental control (also known as an intercellular mechanism), in which healthy neighboring cells inhibit neoplastic growth. A number of mathematical models have focused on the immunological mechanism of resistance to cancer, but environmental control has never been the focus of mathematical studies. We take the simplest point of view, in which we consider only direct physical contact. In our mathematical model, which is written as a system of nonlinear ODEs, normal cells are allowed to interact with cancer cells that are located on the surface of the tumor. Upon interaction of a normal cell with a cancer cell, we allow for the formation of a two-cell complex which can either dissociate or result in the death of the cancer cell. We study the model and show that it can capture the three tumor growth modes: controlled, suppressed, and uncontrolled. The following figure demonstrates a simulation of tumor stability (left) and a simulation of tumor suppression (right). Here, $T$ and $X$ represent the total number of cancer cells and complexes, respectively.

![Simulation of tumor stability](image1)  
![Simulation of tumor suppression](image2)

Interestingly, it is not necessary to assume that the complexes are capable of killing cancer cells. This assumption can be relaxed to a situation when cancer cells in
complexes are put into a quiescent state. Our conclusion is that the model supports the feasibility of contact-based microenvironment control. Our study is relevant for small tumors, in which it is possible to make certain simplifying assumptions. More sophisticated models in which other mechanisms are incorporated, are currently studied.

2. Immunology

2.1 Modeling Regulation Mechanisms in the Immune System
(with my Ph.D. student Peter Kim and Dr. Peter Lee from the Division of Hematology at Stanford Medical School)

We develop a mathematical framework for modeling regulatory mechanisms in the immune system. In the model we begin with an immune repertoire that has already been shaped by thymic selection and formulate a system of DDEs for the dynamics of key agents of the adaptive immune system within the lymph node and tissue. The delays in the equations account for the durations of T cell divisions and capture the time lag between T cells receiving stimulatory signals and completing proliferation. We incorporate the following populations into the model: APCs, CD4+ (non-regulatory) T cells, CD8+ T cells, regulatory (CD4+CD25+) T cells, positive and negative cytokine signals, virus-infected and normal self cells, and virus and self antigen. APCs exist in either mature or immature states, and T cells can be naïve, primed, or suppressed. This is the most comprehensive study that was done on the topic in the mathematical literature. In fact, one of the comments that we received from a reviewer was that the paper should be published even all that it had in it, is the table of parameters. Indeed, the resulting model is very complex. This can be demonstrated, e.g., with the following diagram that is only a fraction of the overall model. This figure summarized the APCs interactions. The inner cube corresponds to the lymph node. The outer cube corresponds to the tissue. Every cell may also perish at a natural death rate, which is not shown in the figure.

Appendix B. Derivation of the discounting factor
Suppose we have a one-variable system in which a substance flows in at rate \( r(t) \) and flows out after \( t \) units of time. Suppose we also have a continuous depletion rate of \( d(t) X(t) \), where \( X(t) \) represents the amount of substance in the system at time \( t \).

Since there is depletion throughout the time period \( t/C_0 \) to \( t \), the outflow rate at time \( t \) should be less than \( r(t/C_0) \).
By conducting numerical simulations we demonstrate several key features of our mathematical model. In particular we show that it can eliminate virus-infected cells, which are characterized by a tendency to increase without control (in absence of an immune response), while tolerating normal cells, which are characterized by a tendency to approach a stable equilibrium population. This issue is clearly related to one of the most important open questions in immunology: the self-non-self discrimination problem, i.e., how can self-tolerance be understood from an individual agent and from the system’s perspective. We experiment with different combinations of T cell reactivities that lead to effective systems and conclude that slightly self-reactive T cells can exist within the immune system and are controlled by regulatory cells. We observe that CD8+ T cell dynamics has two phases. In the first phase, CD8+ cells remain sequestered within the lymph node during a period of proliferation. In the second phase, the CD8+ population emigrates to the tissue and destroys its target population. We also conclude that a self-tolerant system must have a mechanism of central tolerance to ensure that self-reactive T cells are not too self-reactive. Furthermore, the effectiveness of a system depends on a balance between the reactivities of the effector and regulatory T cell populations, where the effectors are slightly more reactive than the regulatory cells.

2.2 Group Dynamics of Adaptive Regulatory Cells: How a Robust Primary T Cell Response is Produced
(with my Ph.D. students Peter Kim, Shelby Wilson, Cristian Tomasetti, and Dr. Peter Lee from the Division of Hematology at Stanford Medical School)

This is the first work on regulatory mechanisms in the immune system that uses a mathematical model to study the robustness of the immune response to the levels of precursor frequencies. The currently accepted paradigm for the primary T cell response is that effector T cells commit to autonomous developmental programs. This concept is based on several experiments that have demonstrated that the dynamics of a T cell response is largely determined shortly after antigen exposure and that T cell dynamics do not depend on the level and duration of antigen stimulation. Another experimental study has also shown that T cell responses are robust to variations in antigen-specific precursor frequency. Various mathematical models have corroborated the first result that programmed T cell responses are insensitive to the level of antigen stimulation. We claim that programmed responses do not entirely explain the robustness of T cell dynamics to variations in precursor frequency. To address this point, we formulate two mathematical models based on T cell developmental programs. In one model, effector cells undergo a fixed number of divisions before dying. This model is formulated as a system of delayed differential equations. In the second model, written as a system of hyperbolic PDEs, effector cells live for a fixed time during which they may divide. The study of these models suggests that developmental programs are not sufficiently robust as they produce an immune response that directly scales with precursor frequencies. Consequently, we hypothesize that the dynamics of a T cell response may also be governed by a feedback loop involving adaptive regulatory
cells rather than by intrinsic developmental programs. Accordingly, we derive a model that is based on the principle that adaptive regulatory T cells develop in the course of an immune response and suppress effector cells. Our simulations show that this feedback mechanism responds robustly over a range of at least four orders of magnitude of precursor frequencies. An example is shown in the following figure in which we show the phase portraits of iTregs versus effector dynamics over 20 days. Shown are phase portraits for five initial concentrations of naïve cells, demonstrating the relation between the concentration of the regulatory cells and the total number of T cells.

![Phase portraits of iTreg versus effector dynamics](image)

We conclude that the proliferation program paradigms do not entirely capture the observed robustness of T cell responses to variations in precursor frequency. Our main result is the proposed alternative mechanism by which the primary T cell response is governed by an emergent group dynamic and not by individual T cell programs.

In a series of follow-up works, we extended our immune regulation model in various ways. Instead of considering only the dynamics for the lymph node, we extend the model to include the infected tissue. Furthermore, we assume that adaptive regulatory T cells induce CTLs to a temporary (reversible) non-proliferative state rather than assuming that regulatory T cells suppress CTLs upon interaction. Notwithstanding the fact that such assumption is weaker, we still obtain the desired robustness of the immune response. Finally, we studied the interplay between the regulation of helper T cells and the regulation of effector T cells. Regulation of either effector or helper T cells is shown to be sufficient for guaranteeing a robust response.

### 2.3 A Theory of Immunodominance and Adaptive Regulation
(with my Ph.D. student Peter Kim and Dr. Peter Lee from the Division of Hematology at Stanford Medical School)
Immunodominance refers to the phenomenon in which simultaneous T cell responses against multiple target epitopes organize themselves into distinct and reproducible hierarchies. In many cases, eliminating the response to the most dominant epitope allows responses to subdominant epitopes to expand more fully. The mechanism that drives immunodominance is still not well understood, although various hypotheses have been proposed. One of the more prevalent views is that immunodominance is driven by passive T cell competition for space on antigen presenting cells (APCs) or for access to specific MHC:epitope complexes on the surface of APCs. However, several experimental studies suggest that passive competition alone may not fully explain the robustness of immunodominance under physiological conditions or varying proportions of antigen-specific precursor T cells and APCs. These studies propose that a mechanism of active suppression among T cells gives rise to immunodominance.

In this work, we present the novel hypothesis that mutual suppression of simultaneous T cell responses results from the appearance of adaptive regulatory T cells (iTregs) during the course of the overall T cell expansion. Hence, we assume that iTregs not only contribute to the timely contraction of the T cell response to a pathogen, but also contribute to a focused response that directs the memory repertoire toward the most reactive clones. In other words, immunodominance provides a means of peripheral positive selection that may be optimal in most cases since it generates highly adapted responses against specifically targeted antigen. To study this hypothesis, we extend our mathematical model of T cell expansion to consider multiple, concurrent T cell responses. The model is formulated as a system of independent feedback loops, in which antigen-specific T cell population produces a nonspecific feedback response. A simplified version of our immunodominance model can be written as the following system of delayed differential equations:

\[
\begin{align*}
\dot{A}_0(t) &= s_A - d_0A_0(t) - a(t)A_0(t) \\
\dot{A}_1(t) &= a(t)A_0(t) - d_1A_1(t) \\
N(t) &= s_N - \delta_0N(t) - kA_1(t)N(t) \\
\dot{E}(t) &= 2^n kA_1(t-\sigma)N(t-\sigma) - kA_1(t)E(t) + 2kA_1(t-\rho)E(t-\rho) \\
&\quad - (\delta_1 + r)E(t) + kR(t)E(t) \\
\dot{R}(t) &= rE(t) - \delta_1R(t).
\end{align*}
\]

Here, \(A_0\) is the concentration of APCs at the site of infection, \(A_1\) is the concentration of APCs that have matured, started to present target antigen and migrated to the lymph node, \(N\) is the concentration of naïve T cells in the lymph node, \(E\) is the concentration of effector cells, and \(N\) is the concentration of iTregs. Our simulations show that the fastest response to expand gives rise to a de novo generated population of iTregs that induces a premature contraction in slower or weaker T cell responses, leading to a hierarchical expansion as observed in immunodominance. Furthermore, removing the dominant T cell response allows previously subdominant responses to develop more fully.
The results of our study may have implications for improving therapy via T cell vaccinations: according to our model, temporarily suppressing the generation of iTregs following a T cell vaccination may result in a broader T cell response than normal against multiple target epitopes, which will then make it more likely for the immune system to eliminate rapidly evolving targets that would otherwise escape immune detection.

2. Cell Motility: Phototaxis

Microorganisms live in environments that are often severely limited in resources or in which vital inputs such as light and nutrients fluctuate unpredictably. Thus, their ability to sense and respond quickly to environmental cues is finely regulated and well-evolved. In this project we are interested in the studying the ability of photosynthetic microorganisms (like cyanobacteria) to sense and respond to both light intensity and quality; a process called phototaxis. A typical pattern the emerges from the motion is shown in the following figure. In this case, there is a light source that is located at the upper-right corner of the domain. Figure (a) shows the edge of the colony with single cells showing as dark dots. Figure (b) shows the fingers that are created from the areas of initial higher density.

![Figure 1. Fingering. The light source is at the upper-right corner of the domain. Figure (a) shows the edge of the colony with single cells showing as dark dots. Figure (b) shows the fingers that are created from the areas of initial higher density.](image)

This research has been conducted in close collaboration with Dr. Devaki Bhaya, from the Plant Biology Department at the Carnegie Institute of Washington located in Stanford University. Our research has been supported by the NSF-NIGMS grant: “Social dynamics, signaling, and surface motility in Cyanobacteria”.

While the motion of bacteria towards a chemical attractant, known as chemotaxis, has been extensively studied in the mathematical literature, the motion towards a light source has been mostly ignored in the mathematical world. There are some fundamental differences between phototaxis and chemotaxis: while in chemotaxis the chemical attractant is usually located in the vicinity of the bacteria (and hence the resulting aggregation patterns), with phototaxis the attractant is located at infinity (and aggregation patterns are not observed). In spite of an ongoing stimulus, the motion towards light starts only after a substantial time delay (and even then, not all bacteria move, or move in the direction of the lights). Such a delay
in the initiation of the motion is not typically observed with chemotaxis. The bacteria that we study “walk” towards the light source (using web-like motion organelles) as opposed to the swimming mechanisms that are associated with most chemotactic motion patterns. These differences required us to conduct a mathematical study that was focused on deriving the first mathematical models for phototaxis. The highlights of our work are described below.

2.1 Modeling Group Dynamics of Phototaxis: from Particle Systems to PDEs (with my Ph.D. student Tiago Requiejo)

This is the first mathematical work that studies the dynamics of phototactic bacteria. Based on experimental observations, we conjecture that the pattern of motion of the colony towards light is the result of group dynamics. We assume that this group dynamics is encoded as an individual property of each bacterium, which we refer to as ‘excitation’. The excitation of each individual bacterium changes based on the excitation of the neighboring bacteria. Under these assumptions, we derive a hierarchy of mathematical models for describing the motion of phototactic bacteria. Our first model is a stochastic model that describes the evolution in time of the location of bacterium $i$, $X_i(t) \in \mathbb{R}^2$, its excitation, $S_i(t) \in \mathbb{R}$, and a surface memory effect, $L(t;x,y)$. The stochastic model is of the form:

$$L(t;x,y) = \max_{i=1,...,N} \delta_{(x,y)}(X_i(s))$$

$$\frac{dS_i(t)}{S_i(t)} = (\mu_i(t) - S_i(t))dt + \sigma dW_i(t)$$

$$dX_i(t) = v, q\left((S_i(t) - K)^+, L(t;x,y), \nabla L_N(t;x,y)\right)\xi t dt + v, d\tilde{W}_i(t).$$

Here, $dW_i$ and $d\tilde{W}_i$ are one- and two-dimensional Brownian motions, respectively, $\xi t$ is the (possibly time-dependent) direction of the light source, $K$ is a threshold that the excitation must exceed in order for the bacteria to move towards the light-source, and $\mu_i$ is the averaged excitation in a neighborhood of bacterium $i$.

A typical simulation of this model is shown in the following figure. In this case, a simulated light source is located on the left side. The initial distribution (a) has one area with high density (where a finger forms), and one area with low density. Over time, a left-moving finger forms in the high-density area (b-d).
The second model we derive is an interactive stochastic many-particle system that is obtained from a discretization of the stochastic model. This model is given as a system of rules for the motion of the particles as well as their birth & death. For example, and increase in the excitation of a bacterium results in the birth of new excitation particles that are located where the bacterium is, and move with it. The advection terms for the bacteria, excitation, and surface particles, respectively, are:

\[
\begin{align*}
  dP_N^k(t) &= g^k_N(t, P_N^k(t)) dt + \sqrt{2\mu} dW^k(t) \\
  dP_N^v(t) &= dP_N^v(t) \\
  dP_N^l(t) &= \sqrt{2\eta} dW^k(t).
\end{align*}
\]

These rules are augmented with birth & death processes for the three particle populations. Finally, our third model is a system of PDEs that is obtained as the continuum limit of the stochastic particle system. Denoting the density of bacteria by \( u \), the density of the excitation by \( v \), and the density of the surface particles by \( l \), the resulting system of PDEs is takes the form of the following reaction-diffusion system with a nonlinear advection term:

\[
\begin{align*}
  \frac{\partial u}{\partial t} &= \mu \Delta u - \nabla \cdot (g(u, v, l, \nabla l)u) \\
  \frac{\partial v}{\partial t} &= \mu \Delta u - \nabla \cdot (g(u, v, l, \nabla l)v) + \beta(u, v)u - \gamma(u, v)v \\
  \frac{\partial l}{\partial t} &= \eta \Delta l + \lambda(u, l)u.
\end{align*}
\]
Here, \( u, v, l \) are the density of bacteria, excitation, and surface marking, respectively. Our main analytic result establishes the validity of the new system of PDEs as the limit dynamics of the multi-particle system. It is given as the following theorem on the convergence in probability of the multi-particle system to the system of PDEs:

**Theorem** [Levy-Requeijo]: Assume that the initial distribution of particles is controlled in the limit

\[
\lim_{N \to \infty} \sup_{n \in \mathbb{N}} P\{\langle S_{N,u}(0), \psi^2 \rangle + \langle S_{N,v}(0), \psi^2 \rangle + \langle S_{N,l}(0), \psi^2 \rangle \geq n\} = 0
\]

where \( \psi(x) = \log(2 + x^2) \). Then for \( \delta > 0 \),

\[
\lim_{N \to \infty} P\left[ \sup_{t \leq T} d(S_{N,u}(t), u(t, \cdot)) + \sup_{t \leq T} d(S_{N,v}(t), v(t, \cdot)) + \sup_{t \leq T} d(S_{N,l}(t), l(t, \cdot)) \geq \delta \right] = 0.
\]

The analysis follows the methods of Oelschlager and Stevens. The excitation, which is a property of the individual bacterium, adds another layer of difficulty to the analysis. Over all, this work is the first to study the dynamics of phototaxis. It combines experiments, modeling, analysis, and simulations. Furthermore, it provides the biologists with new insights on internal communication mechanisms between the bacteria.

### 2.2 Particle, Kinetic, and Fluid Models for Phototaxis
(with S.-Y. Ha)

In this work we derive another hierarchy of new mathematical models for describing the motion of phototactic bacteria. These models are based on the experiments conducted by our collaborators that suggest that the motion of such bacteria depends on the individual bacteria, on group dynamics, and on the interaction between bacteria and their environment. Our first model is a collisionless interacting particle system in which we follow the location of the bacteria, their velocity, and their internal excitation. In this model, the light source acts as an external force. The resulting particle system is of the form:

\[
\begin{align*}
\frac{dx_i}{dt} &= v_i \\
\frac{dv_i}{dt} &= \frac{\lambda_1}{N} \sum_{j=1}^{N} k_1(x_j, x_i)(v_j - v_i) + I_0(u_\infty \cdot \hat{e}_s - v_i)(1 - \varphi(\zeta_i; \zeta_{cr})) \\
\frac{d\zeta_i}{dt} &= \frac{\lambda_2}{N} \sum_{j=1}^{N} k_2(x_j, x_i)(\zeta_j - \zeta_i) + I_0 \varphi(\zeta_i; \zeta_{cr}).
\end{align*}
\]

Here, \((x_i, v_i, \zeta_i)\) denote the location, velocity, and excitation of particle \(i\), \(I_0\) is the intensity of a light source that points in the direction of a unit vector \(\hat{e}_s\), \(u_\infty\) is a predetermined terminal velocity, \(k(x_j, x_i)\) is a communication function, and \(\varphi\) is an admissible cutoff function. This system can be viewed as an extension of the Cucker-Smale flocking model with an external forcing term. For this system, our
main result is a proof that when all particles are fully excited, their asymptotic velocity tends to an identical (pre-determined) terminal velocity. Numerical simulations support the theory and provide insights on the dynamics in regions where the theory is no longer valid. The second model we derive is a kinetic model for the one-particle distribution function that includes an internal variable representing the excitation level. The kinetic model is a Vlasov-type equation that is derived from the particle system using the BBGKY hierarchy and a molecular chaos assumption. Since bacteria tend to move in areas that were previously traveled by other bacteria, a surface memory effect is added to the kinetic model as a turning operator that accounts for the collisions between bacteria and the environment. The resulting collisional kinetic model (which is obtained under the standard molecular chaos assumption) for the one-particle distribution function \( f(x,v,t;\zeta) \) and for the surface memory effect function \( l(x,t) \) is:

\[
\begin{align*}
\partial_t f &+ \text{div}_x (vf) + \text{div}_v \left((u_*^e \hat{e}_z - v)(1 - \varphi(\zeta;\zeta))f + \lambda_1 K_1[f]f\right) \\
+ \partial_z \left(I_0 \varphi(\zeta;\zeta_c) \rho + \lambda_2 K_2[f]f\right) &= T[l]f \\
\partial_t l &= \eta \Delta l + \lambda(l,\rho) \rho.
\end{align*}
\]

Our third model is derived as a formal macroscopic limit of the kinetic model. It is shown to be the Vlasov-McKean equation coupled with a reaction-diffusion equation:

\[
\begin{align*}
\partial_t \rho &+ \text{div}_x \left(D(l) \nabla \rho + C_1(l) \rho L[\rho] + C_2(l) \rho\right) \\
\partial_t l &= \eta(l,\rho) \Delta l + \lambda(l,\rho) \rho.
\end{align*}
\]

While the derivation of the Vlasov-McKean equation is formal, it is the only case we are aware of in which this equation is derived starting with a particle system, and not as an ad-hoc model of a physical phenomenon that requires non-local interactions. 

**In addition to the novelty of the models (and the corresponding analysis and numerics), we view this work as laying the groundwork in developing tools that will further enable us to address the intriguing biological questions on phototaxis.**

### 2.3 Time-Asymptotic Flocking in a Stochastic Cucker-Smale System
(with S.-Y. Ha & K. Lee)

Motivated by the phototaxis problem we decided to study flocking in a stochastic Cucker-Smale flocking system in which particles interact with the environment through white noises. As it turns out, this is the first study of a Cucker-Smale system with a random forcing term. The system we introduced and studied is the following Ornstein-Uhlenbeck process:
\[ dx_i = v_i dt \]
\[ dv_i = \frac{\lambda}{N} \sum_{j=1}^{N} \psi(x_j, x_i)(v_j - v_i) dt + \sqrt{D} dW_i \]

Here, \((x_i, v_i) \in \mathbb{R}^{2d}\) are the location and velocity of particle \(i\), \(\psi(x_j, x_i)\) is the communication function, and the noise term \(dW_i\) is an i.i.d. \(d\)-dimensional white noise characterized by mean zero and the following covariance relations: for \(1 \leq \alpha, \beta \leq d\), \(1 \leq i, j \leq N\):
\[
\langle dW_i^\alpha(t) \rangle = 0, \quad \langle dW_i^\alpha(t) dW_j^\beta(t_*) \rangle = \delta_{\alpha\beta} \delta_{ij} \delta(t - t_*) .
\]

We define flocking in the stochastic system. We then prove that when the communication rate, \(\psi\), is constant, the system exhibits a flocking behavior independent of the initial configurations. For the case of a radially symmetric communication rate with a positive lower bound, we prove that the relative fluctuations of the particle velocity around the mean velocity have a uniformly bounded variance in time. In addition to the analytical study we conduct numerical simulations that allow us to further investigate the dynamics of the system. An example of the results of a simulation is shown in the following figure. In this case the communication rate \(\psi\) is constant. On the left each curve shows the variance of one out of 100 particles in the \(x\) component of the velocity over 250 realizations. On the right we show the average over all the realizations plotted on top of the curve given by our theorem.

This is an exciting beginning of studying such stochastically driven systems. The numerical simulations provide many clues as to what can be potentially proved on the dynamics of the system. We expect to include similar stochastic terms in our future studies of interacting many particle systems.