Banff International Research Station
for Mathematical Innovation and Discovery

Partial Differential Equations in Cancer Modelling
Feb 1-6, 2015

MEALS

*Breakfast (Buffet): 7:00 – 9:30 am, Sally Borden Building, Monday – Friday
*Lunch (Buffet): 11:30 am – 1:30 pm, Sally Borden Building, Monday – Friday
*Dinner (Buffet): 5:30 – 7:30 pm, Sally Borden Building, Sunday – Thursday
Coffee Breaks: As per daily schedule, in the foyer of the TransCanada Pipeline Pavilion (TCPL)
***Please remember to scan your meal card at the host/hostess station in the dining room for each meal.**

MEETING ROOMS

All lectures will be held in the lecture theater in the TransCanada Pipelines Pavilion (TCPL). An LCD projector, a laptop, a document camera, and blackboards are available for presentations.

SCHEDULE

Sunday

16:00 Check-in begins (Front Desk – Professional Development Centre - open 24 hours)
17:30-19:30 Buffet Dinner
20:00 Informal gathering in 2nd floor lounge, Corbett Hall (if desired)
Beverages and small assortment of snacks are available on a cash honor system.

Monday

7:00 - 8:45	Breakfast	
8:45 - 9:00	Introduction	Welcome by BIRS Station Manager, TCPL
9:00 - 9:40	Siv Sivaloganathan	High Intensity Focussed Ultrasound as a Therapeutic Modality
9:40 - 10:20	Jean Clairambault	Drug resistance in cancer cell populations: Mathematical and biological assessment
10:20 – 10:40	Coffee Break	TCPL
10:40 - 11:20	Joel Brown	
11:20 - 11:50	Rebecca Everett	Dynamics of a Data-Validated Ovarian Tumor Growth Model
12:00 - 13:30	Lunch	
13:00 - 14:00	Guided Tour	Guided tour of the Banff Centre meet in the 2nd floor lounge, Corbett Hall
15:00 – 15:30	Coffee Break	
16:15	Group Photo	meet in foyer of TCPL (photograph will be taken outdoors so a jacket might be required).
16:30 - 17:30	Discussion	Collection of open problems, selection of working groups
17:30 - 19:30	Dinner	

Tuesday

7:00 – 8:45	Breakfast	
9:00 – 9:40	Jacques Demongeot	
9:40 – 10:20	Yangjin Kim	Oncolytic virus spread and CSPG-driven tumor cell infiltration in glioblastoma
10:20 – 10:40	Coffee Break	
10:40 – 11:20	Robert Strehl	Showcase of Applications of a Versatile Stabilized Finite Element Framework for Chemotaxis
11:20 – 11:50	Hildur Knutsdottir	Emergence of leader cells in collective cell migration
12:00 - 13:30	Lunch	
	Working groups	
15:00 –15:30	Coffee Break	
16:30-17:00	Jake Taylor-King	Generalised velocity jump processes
17:00-17:30	Andreas Buttenschoen	Macrophage-Cancer Cell Interactions drive Tumor Invasion Types
17:30-19:30	Dinner	
20:00	Poster Session	TCPL

Wednesday

7:00 – 8:45	Breakfast	
9:00 – 9:40	Philip Maini	Modelling Aspects of Cancer Development
9:40 - 10:20	Lisette de Pillis	Cancer-Immune System Modeling
10:20 – 10:40	Coffee Break	
10:40 – 11:20	J. Hector Morales Barcenas	Mathematical modeling of drug delivery in solid tumors
11:20 – 11:50	Amanda Swan	An anisotropic diffusion model for glioma spread
12:00 - 13:30	Lunch	
	Working groups	
17:30 - 19:30	Dinner	

Thursday

7:00 – 8:45	Breakfast	
9:00 – 9:40	Peter Kim	A maturity-structured PDE model for leukemia stem cell differentiation
9:40 – 10:20	Adrian Lam	On the Stability of Steady States in a Free-Boundary Problem in a Model of Granuloma
10:20 - 10:40	Coffee Break	

10:40 – 11:20	Min Tang	Tumor Hele-Shaw type model at the stiff pressure limit
11:20 – 11:50	Oluwole Olobatuyi	The Dynamics of Radiation-Induced Bystander Signals
12:00 - 13:30	Lunch	
	Working groups	
15:00 – 15:30	Coffee Break	
16:30 - 17:00	Tracy Stepien	Data-Validated Modeling of Glioblastoma Tumor Growth
17:00 - 17:30	Tommaso Lorenzi	Effects of space structure and combination therapies on phenotypic heterogeneity and chemotherapeutic resistance in solid tumors
17:30 - 19:30	Dinner	

Friday

7:00 – 8:45	Breakfast	
9:00 – 9:40	Jack Tuszynski	Modeling the energetic cost of cancer as a result of altered energy metabolism: implications for cachexia
9:40 - 10:20	Dominik Wodarz	Mathematical models of ibrutinib therapy of chronic lymphocytic leukemia
10:20 – 10:40	Coffee Break	TCPL – available from 10:00 am onwards, but must finish by 11:00 am
10:40 – 12:00	Working groups	Results and ideas from the working groups
12:00 - 13:00	Lunch	

Checkout by 12 noon.

** 5-day workshop participants are welcome to use BIRS facilities (BIRS Coffee Lounge, TCPL and Reading Room) until 3 pm on Friday, although participants are still required to checkout of the guest rooms by 12 noon. **

Abstracts to follow (if desired) in alphabetical order by last name of speaker.

ABSTRACTS

(in alphabetic order by speaker surname)

Andreas Buttenschoen
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Macrophage-Cancer Cell Interactions drive Tumor Invasion Types

The interactions between cancer cells and immune cells is one of the hallmarks of cancer. In this talk we present an individual based model, including the interactions between macrophages and cancer cells at the tumor invasion front. The model is based on the Glazier-Graner-Hogeweg modeling approach (Cellular Potts Model). In this model the macrophages and cancer cells interact via adhesion modeled using the Differential Adhesion Hypothesis and a paracrine loop (Epidermal Growth Factor (EGF) and Colony Stimulating Factor (CSF)). We show that the paracrine loop drives invasion depth, whereas cellular adhesion drives invasion types (ie. individual, collective invasion). This research has been supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) and Alberta Innovates.

Jean Clairambault
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Drug resistance in cancer cell populations: Mathematical and biological assessment

Rebecca Chisholm, Jean Clairambault, Alexandre Escargueil, Tommaso Lorenzi, Alexander Lorz, Benoit Perthame, Emmanuel Trelal

Considering cancer as an evolutionary disease, we aim at understanding the means by which cancer cell populations develop resistance mechanisms to drug therapies, in order to circumvent them by using optimised therapeutic combinations. Rather than focusing on molecular mechanisms such as overexpression of intracellular drug processing enzymes or ABC transporters that are responsible for resistance at the individual cell level, we propose to introduce abstract phenotypes of resistance structuring cancer cell populations. The models we propose rely on continuous adaptive dynamics of cell populations, and are amenable to predict asymptotic evolution of these populations with respect to the phenotypic traits of interest.

Drug-induced drug resistance, the question we are tackling from a theoretical and experimental point of view, may be due to biological mechanisms of different natures, mere local regulation, epigenetic modifications (reversible, nevertheless heritable) or genetic mutations (irreversible), according to the extent to which the genome of the cells in the population is affected. In this respect, the models we develop are more likely to be biologically corresponding to epigenetic modifications, although eventual induction of emergent resistant cell

clones due to mutations under drug pressure is not to be completely excluded. From the biologist's point of view, we study phenotypically heterogeneous, but genetically homogeneous, cancer cell populations under stress by drugs.

According to the cell populations at stake and to the exerted drug pressure, is drug resistance in cancer a permanently acquired phenotypic trait or is it reversible? Can it be avoided or overcome by rationally (model-guided) designed combinations of drugs (to be optimised)? These are some of the questions we will try to answer in a collaboration between a team of mathematicians and another one of biologists, both dealing with cancer and Darwinian evolution of cell populations.

Lisette de Pillis
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Cancer-Immune System Modeling

We will present a sample of mathematical models of cancer-immune interactions that have resulted from interdisciplinary collaborations with practicing oncologists and experimentalists. We will discuss modeling treatment approaches that account for immune system behavior.

Rebecca Everett
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Dynamics of a Data-Validated Ovarian Tumor Growth Model

It is well-known that cancer is a world-wide major public health problem and that there is a need for new approaches in order to better understand cancer and improve treatment. One recent interdisciplinary approach is to apply a combination of mathematics and ecology to cancer biology since tumor cells live in an ecological setting; they interact with and compete against normal and other cancerous cells for space and nutrients. The phycologist Droop determined that specific growth rate depended on the concentration of a limiting nutrient within the cell, also known as the cell quota, and developed a mathematical expression that links growth rate to intracellular nutrient concentration. We apply this idea of a limiting nutrient to cancer modeling using the Droop equation, specifically considering angiogenesis in ovarian cancer. Our simple model fits both the on-treatment and off-treatment data and generates testable hypotheses.

Peter Kim
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A maturity-structured PDE model for leukemia stem cell differentiation

We present a model of leukemia stem cell differentiation as a as a system of maturity-structured partial differential equations. The model is formulated from the theory that cancer originates from cancer stem cells that reside in a microenvironment called the stem cell niche. Depending on a stem cell's relation to the niche, the cell may remain quiescent or begin proliferating. This theory states that leukemia and other cancers are potentially caused by misregulation within the stem cell niche. This model is based on the agent-based formulation of Roeder et al. (2006).

We then simplify the PDE model and then conduct a stability analysis of the simplified system, which reveals three modes of behavior: stability at 0 (cancer dies out), stability at a nonzero equilibrium (a scenario akin to chronic myelogenous leukemia), and periodic oscillations (a scenario akin to accelerated myelogenous leukemia). As a future direction, the PDE formulation provides a framework for extending the model to include other aspects, such as the spatial distribution of stem cells within the niche.

Yangjin Kim
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Oncolytic virus spread and CSPG-driven tumor cell infiltration in glioblastoma

Oncolytic viruses are genetically engineered viruses that are designed to kill cancer cells while doing minimal damage to normal healthy tissue. After being injected into a tumor, they infect cancer cells, multiply inside them, and when a cancer cell is killed they move on to spread and infect other cancer cells. Glioblastoma is the most aggressive type of brain cancer with the median survival time of one year. The primary treatment option is surgery but invasive cells in brain tissue eventually regrow back even with chemo- and radio-therapy, generating poor clinical outcomes. Chondroitinase ABC (Chase-ABC) is a bacterial enzyme that can remove a major glioma ECM component, chondroitin sulfate glycosoamino glycans (CSGG) from proteoglycans without any deleterious effects in vivo. It has been shown that Chase-ABC treatment is able to promote the spread of the viruses, increasing the efficacy of the viral treatment. In this paper we develop a mathematical model to investigate the effect of the Chase-ABC on the treatment of glioma by oncolytic viruses (OV). We show that the model's predictions agree with experimental results for a spherical glioma. We then use the model to test various treatment options in the heterogeneous microenvironment of the brain. The model predicts that separate injections of OV, one into the center of the tumor and another outside the tumor will result in better outcome than if the total injection is outside the tumor. In particular, the injection of the ECM-degrading enzyme (Chase-ABC) on the periphery of the main tumor core need to be administered in an optimal strategy in order to infect and eradicate the infiltrating glioma cells outside the tumor core in addition to proliferative cells in the bulk of tumor core. Our mathematical model also tests several strategies and show the non-linear effect of virus treatments on infecting both primary and secondary tumors as well as invasive cells.

In this talk, we will also present a mathematical model of CSPG-driven glioma infiltration. It is important to distinguish invasive glioma phenotypes from non-invasive cells. Experiments by Silver et al illustrated that concentrations of CSPG, one of major extracellular matrix component within a tumor, determine invasive and non-invasive phenotypes. We developed a mathematical model of CSPG-driven dynamics of a growing glioma, using a free boundary framework.We take into account the rich dynamics of astrocytes and microglia in brain tissue as illustrated in Silver et al. The simulation results are in good agreement with experimental data in Silver et al. We also show how oncolytic virus therapy can be used to eradicate tumor cells. There is a critical threshold value of CSPG levels for optimal killing of both invasive and noninvasive tumor cells.

Hildur Knutsdottir
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Emergence of leader cells in collective cell migration

Metastasis requires migration of cancer cells away from the primary tumor. When sheets or clusters of cancer cells move collectively they have three distinct properties, (1) cells remain connected, (2) multicellular polarity

is maintained and (3) the cell cluster structurally modifies the tissue and migration path. In experiments with 2D sheets of certain cancer cell lines, the invasion front has been shown to have a finger-like morphology. At the leading edge of a migrating sheet or cluster of cells there are a few leader cells that have distinct properties from the rest of the cells. The leader cells align collagen fibres which form a path of least mechanical resistance for the following cells. The emergence of leader cells remains unclear and that is the focus of my collaboration with Calvin Roskelly's laboratory at UBC. To understand the role of cell-cell and cell-ECM adhesions in leader cell emergence and in the finger like morphology of a leading edge, I use a discrete model. Recently, I started looking into a PDE version of this system to mathematically study the adhesion parameter space that can result in leader cell emergence.

Adrian Lam

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On the Stability of Steady States in a Free-Boundary Problem in a Model of Granuloma

We develop a simple free-boundary type model of granuloma involving just macrophages and bacteria, and was introduced earlier, in the radially symmetric case, in [Friedman-Kao-Leander, submitted]. We first establish the existence of radially symmetric steady state granulomas with any radius R; $0 < R < R^*$, where R^* is given explicitly by the model's parameters. Then we consider mathematically the linearized stability/instability of small radially symmetric steady states. We will interpret the connection of our analytical results the clinically observed phenomenon that smaller granulomas tend to be stable and yet larger, caseous ones tend to spread. This is joint work with Avner Friedman (Ohio State).

Tommaso Lorenzi

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Effects of space structure and combination therapies on phenotypic heterogeneity and chemotherapeutic resistance in solid tumors

We present a model that describes cell dynamics inside a tumor microspheroid under the effects of cytotoxic and cytostatic drugs. Cancer cells are assumed to be structured as a population by two real variables standing for space position and the expression level of a phenotype of resistance to cytotoxic drugs. The model takes explicitly into account the dynamics of resources and anti-cancer drugs as well as their interactions with the cell population under treatment. We analyze the effects of space structure and combination therapies on phenotypic heterogeneity and chemotherapeutic resistance. Furthermore, we study the efficacy of combined therapy protocols based on constant infusion and/or bang-bang delivery of cytotoxic and cytostatic drugs.

Philip Maini

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Modelling Aspects of Cancer Development

We present a number of case studies in which mathematical modelling has been used to address certain aspects of tumour growth and development. This will include a model for the metabolic aspects of tumour growth, a multiscale model for intestinal crypt dynamics, and a model for angiogenesis.

J. Hector Morales Barcenas
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Mathematical modeling of drug delivery in solid tumors

We are working on the mathematical modeling of drug delivery in solid tumors. We build models for diffusion and dispersion of coloidal suspensions (liposomes) through solid tumors. Liposomes are artifically-designed small vesicles made of phospholipids to carry radionuclides or drugs. Once the liposomes get into developed tumors in animal models, there are barries that obstruct their spatial distribution diminishing the treatment efficiency. The main goal of modeling is to gain inside of physics and geometry of biomechanical properties of tumors, in order to improve anticancer therapies. We incorporate geometry and physics of the solid tumor's intricate inner structure by means of barrier potentials in the Fokker-Planck equation's drift and diffusivitycoefficients. Our departure point is the Langevin's formulation for Brownian particles (colloidal suspension) to proceed to average the movement of such particles in a medium where low Reynolds numbers dominates over inertial terms. With these models we will able to implement inverse problems in order to estimate tumor's parameters to suggest improvements on the design of anticancer carriers of pharmaceuticals and radiopharmaceuticals.

Oluwole Olobatuyi
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The Dynamics of Radiation-Induced Bystander Signals

It has been observed that unirradiated cells located in the neighborhood of a region irradiated at low irradiation dosage undergo the same order of effects as those cells that are directly irradiated. These effects are called radiation-induced bystander effects (RIBE). These RIBE are due to some diffusive proteins which are capable of reacting with the DNA of nearby cells, and thereby triggering these so-called bystander effects. These diffusive proteins are generally referred to as bystander signals. RIBE have implications for radiation therapy and unfortunately, the dynamics/kinetics of the signals responsible for these RIBEs are still largely unknown. In particular, we are interested in the signal's lifespan and factors that can affect its longevity. In this talk, I will present a partial differential equation models that investigates the lifespan of this signal and factors that may affect its longevity. I also use this model to study its dynamics under fractionated radiation treatments and examine its impact at subsequent fractions of irradiation. Lastly, I will examine the contribution of this signal to the region of hypersensitivity observed at low irradition dose in the traditional survival curve.

Siv Sivaloganathan
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High Intensity Focussed Ultrasound as a Therapeutic Modality

Although chemotherapy, radiotherapy and surgery represent the primary therapeutic interventions used to treat cancer patients. High Intensity Focussed Ultrasound (HIFU) has emerged, over the past decade, as a potentially powerful alternative treatment for various cancers. Apart from avoiding the side effects associated with chemo

and radiotherapies, it also presents an alternative to surgery which is non-invasive but yet has the potential to completely ablate solid tumours. In this talk, I will describe the possible clinical set-up to administer HIFU, and then discuss the mathematical modeling of HIFU in the context of bone sarcomas. However, the treatment modality has several possible alternative applications ranging from clot lysis to a potential method for overcoming the obstacle to the delivery of chemotherapeutic agents (the Blood Brain Barrier) in the context of brain tumours, and these lead to interesting questions that should be amenable to mathematical modeling.

Tracey Stepien

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Data-Validated Modeling of Glioblastoma Tumor Growth

Glioblastoma multiforme is an aggressive brain cancer that is extremely fatal. Gliomas are characterized by highly diffusive growth patterns, which makes them impossible to remove with surgery alone. To give insight on the mechanisms most responsible for tumor growth and the difficult task of forecasting future tumor behavior, numerical and analytical results from various reaction-diffusion models, including ones with density-dependent diffusion, are compared to experimental data.

Robert Strehl

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Showcase of Applications of a Versatile Stabilized Finite Element Framework for Chemotaxis

From the first formulation of chemotaxis-driven partial differential equations (PDEs) by Keller and Segel in the 1970's up to the present, much effort has been invested in modeling complex chemotaxis related processes (such as angiogenesis). It is already the sheer complexity of resulting PDEs that crucially limits the postulation of analytical results. In this context, the support by numerical tools are of utmost interest which renders the implementation of a numerically well elaborated solver an undoubtedly important task. This talk presents applications of a stabilized Finite Element based framework on chemotaxis-driven PDEs. It also promotes extensions to surface PDEs which results in a highly versatile framework for models that combine bulk and surface PDEs for chemotaxis-related processes.

Amanda Swan

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An anisotropic diffusion model for glioma spread

In this talk, I will present a model for glioma, or brain tumour spread. These tumours pose an interesting modelling problem, as the cells prefer to spread along the white matter tracts of the brain. This behaviour leads to irregular shapes that cannot be captured using traditional isotropic diffusion. To remedy this, an anisotropic diffusion model is derived from a transport equation describing the individual cell movement. I will present some simulations for this anisotropic diffusion model using real patient data, and compare the results to the real tumour boundaries.

Min Tang
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Tumor Hele-Shaw type model at the stiff pressure limit

Several mathematical models of tumor growth are now commonly used to explain medical observations and predict cancer evolution based on images. These models incorporate mechanical laws for tissue compression combined with rules for nutrients availability, which can differ depending on the situation under consideration, in vivo or in vitro.

We formulate Hele-Shaw type free boundary problems for a tumor growing under the combined effects of pressure forces, cell multiplication and active motion, coupled to a diffusion equation for a nutrient. The free boundary model is derived from a description at the cell level using the asymptotic of a stiff pressure limit.

Numerical solutions exhibit, as expected from medical observations, a proliferative rim and a necrotic core. Remarkable is the pressure distribution, which vanishes at the boundary of the proliferative rim with a vanishing derivative at the transition point to the necrotic core.

Jake Taylor-King
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Generalized velocity jump processes

There are various cases of animal movement where behaviour broadly switches between two modes of operation, corresponding to a long distance movement state and a resting or local movement state. Here a mathematical description of this process is formulated, adapted from Friedrich et. al. (2006). The approach allows the specification any running or waiting time distribution along with any angular and speed distributions. The resulting system of partial integro-differential equations are tumultuous and therefore it is necessary to both simplify and derive summary statistics. An expression for the mean squared displacement is derived which shows good agreement with experimental data from the bacterium Escherichia coli and the gull Larus fuscus. Finally a large time diffusive approximation is considered via a Cattaneo approximation (Hillen, 2004). This leads to the novel result that the effective diffusion constant is dependent on the mean and variance of the running time distribution but only on the mean of the waiting time distribution.

Jack Tuszynski
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Modeling the energetic cost of cancer as a result of altered energy metabolism: implications for cachexia

Cachexia affects most patients with late stage cancer and is associated with reduced survival. We hypothesize that the energetic burden of late stage cancer is a substantial contributor to cachexia and that a tumor's level of anaerobic energy metabolism plays a critical role in describing the energetic cost of cancer. To derive an

estimate of the specific energetic cost per unit of tumor mass, we model the energetic cost of cancer as a function of the percentage of energy the cancer produces anaerobically. We find that a 100% anaerobic tumor will cost three times as much energy as a 100% aerobic tumor on the body. Based on quantitative data from a range of cancer patients, if 25% of energy is generated by the tumor anaerobically, 50% more energy is lost to the body compared to if the tumor generated energy predominantly aerobically, as do most organs. In this case, the energetic cost on the body from the tumor is estimated at 338 kcal/day per kg of tumor. In the fasting state, cancer patients may lose to the tumor 10-25% of the energy they should be receiving from glucose. The tumor's high level of glucose and glutamine consumption is predicted to cause muscle breakdown to fuel the tumor, especially in the fasting state. A shift of energy metabolism of a tumor to becoming more anaerobic will increase the cost of the tumor on the body, and potentially lead to increased muscle wasting due to increases in glucose and glutamine usage. Monitoring glucose and glutamine consumption of tumors, along with patient resting energy expenditure and Cori cycling, would potentially predict the onset of cachexia.
Authors: Douglas E. Friesen, Vickie E. Baracos, Jack A. Tuszynski

Dominik Wodarz
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Mathematical models of ibrutinib therapy of chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is a malignancy of B cells and is the most common leukemia in adults. Patients have typically been treated with a combination of chemo and immuno-therapies. These have resulted in relatively good responses except in high risk patients in which p53 has been inactivated. Recently, new, targeted treatment approaches have been developed which have so far shown great promise in the clinic. One such drug is the Bruton tyrosine kinase (BTK) inhibitor ibrutinib. Upon treatment initiation, a lymphocytosis phase is observed during which the number of CLL cells can show a pronounced rise in the blood. The number of cells eventually reaches a peak and declines during therapy. It is thought that the lymphocytosis phase represents the redistribution of cells from tissue where the majority of the disease burden lies (lymph nodes, spleen, bone marrow) into the blood. One question is whether upon treatment the majority of the tissue CLL cells redistributes to blood, or whether only a small fraction of the tumor cells redistributes while a large fraction of tissue cells dies. We used mathematical models, applied to clinical data, in order to kinetically characterize the treatment responses to ibrutinib, and to investigate this question. In addition, the measurements of all crucial CLL parameters allowed us to build evolutionary mathematical models in order to study the emergence of ibrutinib-resistant cells. An important aim of this work is the development of a predictive computational framework that can give personalized predictions for patients about the long-term outcome of ibrutinib therapy.