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"MATHEMATICAL ONCOLOGY: NEW CHALLENGES FOR SYSTEMS BIOMEDICINE"

Book of Abstracts

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Mathematical Models Reveal a Mechanism of Fate Decision in Cancer Stem Cells and suggest Effective Oncotherapy Modalities

Coauthors: Kogan Y, Halevi K, Hochman G, Kirnasovsky O, Vasserman G. Harrison H, Lamb R, Clarke R.

Abstract

Theoretical and experimental analysis of a discrete mathematical model suggests that homeostasis in living organisms is maintained by a negative feedback on stem cell (SC) proliferation (Quorum Sensing; QS). To explore how QS in breast cancer SCs can be manipulated, we developed a differential equations model, integrating extracellular and intracellular signal transduction within the tumor. Experimentally verified analysis indicated that QS is mediated by Dickkopf1 protein, high levels of which drive cancer SCs into differentiation, and, hence, therapy. A more detailed model for events in the Wnt signal transduction pathway, enables precise calculation of the effect of inhibitors applied alone or in combination, and provides a flexible framework for identifying potential targets for intervention in the Wnt signaling pathway.

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Analysis of a Mathematical Model of Morphogenesis of Vascular Networks

Abstract

We prove existence of global weak solutions to the mophogeneis networks model proposed by D. Ambrosi, A. Gamba and G. Serini.
The method is based on the energy control by an entropy function, the solution is obtained by a vanishing artificial pressure.

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A Combined Experimental and Mathematical Approach for Molecular-based Personalization of Irinotecan Circadian Delivery

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Abstract

Irinotecan is an anticancer drug which is currently in use for chemotherapy against colorectal cancer. Its pharmacokinetics (PK- what the cells do to the drug, e.g. metabolization, transport), and pharmacodynamics (PD- what the drug does to the cells, e.g. DNA damage) are largely influenced by 24-hour-period rhythms of certain proteins including the drug target Topoisomerase I, the activation enzymes (Carboxylesterases), the deactivation enzymes (UGT1A1,UGT1A9) and the ABC transporters which are responsible for the efflux of the drug. Indeed circadian rhythms have been described for most of those proteins both in humans and in mice. A chronomodulated scheme of administration for Irinotecan is already used in clinic but recent findings highlight the need of personalized chronotherapeutics delivery pattern according to the patient gender and genetic background ([1]). Within the European project TEMPO, Irinotecan chronotoxicity has been studied in mice and three classes have been determined with regards to Irinotecan best circadian hour of administration (i.e. the hour which induces the minimal toxicity). Our modeling approach aims at identifying molecular biomarkers which could discriminate between the mouse classes and at designing optimal chronomodulated infusion scheme for each of them. A whole body physiologically-based PK-PD model has been built starting from a previous mathematical model designed thanks to a cell culture study ([2]) . Parameters are estimated for each mouse class by fitting available data on tissular PK after two different circadian hours of administration and on circadian rhythms of relevant proteins. Then the parameter set will be compared in order to find differences between the classes and optimization algorithms will be applied to the model to design theoretically optimal chronomodulated scheme of administration.

This study in mice may give a hint for determining molecular biomarkers, which should be measured in patients in order to tailored chronomodulated infusion schemes.

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The Calculus of Looping Sequences for Modelling Biological Systems

Abstract

We survey the formalism Calculus of Looping Sequences (CLS) and a number of its variants from the point of view of their use for describing Biological systems and compartments. The formalism CLS is based on term rewriting and allows describing biomolecular systems. A variant of CLS, called Stochastic CLS, extends the formalism with stochastic time. Another variant, called SCLS (Spatial CLS), allows the description of the position of biological elements, and of the space they take up in a 2D /3D space. The elements may move autonomously and may interact when constraints on their positions are satisfied. The space conflicts are resolved by an appropriate algorithm.

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PARAMETER SPACE EXPLORATION WITHIN DYNAMIC SIMULATIONS OF A SIGNALING-NETWORK DOWNSTREAM OF TGF-β, WNT AND EGF-FAMILY GROWTH FACTORS, WITH REFERENCE TO COLORECTAL CANCER*

Co-Authors : De Ambrosi Cristina, Tortolina Lorenzo, Castagnino Nicoletta, Pesenti Raffaele, Verri Alessandro, Ballestrero Alberto, Patrone Franco and Parodi Silvio.

Abstract

Motivation At the scale of biochemical interactions, when dealing with signaling-networks of the size of the MIM (Molecular Interaction Map) simulated for instance in a previous work [1], or the even larger MIM involved in this work, we are clearly over the breaking point of mental intuition of a field expert [2].The pathways reconstructed in our present MIM are downstream of TGF-?, Wnt and EGF-family growth factors, they include about 60 basic molecular species (proteins and other small molecules).Our signaling-network comprises about 390 modified species and complexes; it involves more than 800 reactions (reversibleand catalytic reactions). To our knowledge, this is probably one of the largest signaling-networks ever simulated at the biochemical-interaction scale level. Our signaling-network reconstructs important molecular controls related to the G0 -- G1 transition of cell cycle. Because of the crucial decisional role of this network region, mutations of dominant and recessive onco-proteins (genes) are often found in many cancers, including colorectal cancer. Effects of space compartmentalization (for instance cytoplasmic versus nuclear space) have been mostly ignored at this stage of MIM development. Aware of having introduced important simplifications, using Ordinary Differential Equations (Matlab, Simbiology, ODE23tb), we could simulate not only a physiological network, but also mutations /

alterations at the level of the molecular phenotype. Moreover, we could simulate the effects of selective inhibitors of onco-proteins affected by excess of function.Dynamic network simulations can be considered a crucial support for an *a posteriori* qualitative comprehension of the behavior of a network of this degree of complexity.Reconstruction of regulatory signaling networks at the biochemical level is of great relevance, however the information available for these reconstructions is often incomplete in many respects. It is therefore very interesting and important to analyze robustness/sensitivity of this type of networks to parameter and reaction-rate perturbations.

Methods In order to explore robustness / sensitivity to perturbations of the network, we perturbed one or a small number of species at a time, observing the effects induced on the remaining species.We introduced combinations of 10x and 10/ perturbations in multiple species (up to five), for about 60 total molecular concentrations. Perturbation of rates is not considered in this presentation. Perturbed species were obviously never coincident with perturbing species. When single species or pairs act as perturbator molecules, the expected wall-clock time required to evaluate the ODEs varies from few min to several hours (using a standard desktop PC - 3.00 GHz, CPU, 4.00GB RAM). For three perturbing species several days are required. Indeed, when considering more than three perturbing species, the problem becomes quickly intractable on a single standard desktop computer. One possible solution to overcome this computational issue is to follow a random sampling strategy. For instance, we randomly sorted out only 1,000 (perturbing x perturbed) combinations within the parameter space of all possible (perturbing x perturbed) combinations. It is evident that the ratio: random sampling size / overall parameter space, becomes very rapidly a vanishing number, for an increasing number of perturbator species. However, a consistent size of the random-sampling sample, can already be very informative about the general-trend properties of our network. To improve our strategy we devised a targeted quasi-random sampling procedure capable of a more efficient exploration of the parameter space. The underlying idea is to make explicit use of the available knowledge regarding the network structure. Note that a biochemical signaling-network region can be represented as a graph and an edge represents the interaction between two adjacent parameters (nodes). We have already observed that a perturbation is more intense at a close distance from perturbing parameters and rapidly attenuated for an increasing number of edges separating perturbing and perturbed parameters [1, 3, 4]. When we try to evaluate the distance of perturbed parameters (one at a time) from a multiplicity of perturbing parameters, things become definitely more complicated.

Results and conclusions We implemented perturbations of the concentrations concerning about 60 consumable basic molecular species following a random exploration of the parameter space. We obtained significant indications about sensitivity/robustness of the network

described in our MIM. We were able to note an interesting feature characterizing the network: the effect of a perturbing species becomes weaker and weaker for perturbed molecules that are positioned at increasing distances from the perturbing molecules. An efficient way of classifying a perturbed species in respect to a subset of perturbing species is the following: perturbing species at ? 1 edge distance are included (all included), only perturbing species at > 1 edge distance are considered, only perturbing species at > 2 edge distance are considered, only perturbing species at > 3 edge distance are considered, and so on. The perturbation strength of the subset of perturbing species decreases very rapidly for an increasing number of edges. For instance, for a subset of five perturbingspecies multiplied / divided 10 times in concentration, at an edge distance > 2, we didn't findany perturbed species perturbed more than three times, out of 1,000 random samplings. The entire population of perturbing combinations (parameter space) is of astronomical size. A simple size of 1,000 combinations already gives an idea ofproperties and tendencies of a parameter space. A simple size of 10,000 combinations is within reach of a grid computation distributed in parallel to (for instance) few dozen of personal computer, and we could know more details about very rare combinations of perturbations (very rare in terms of their effects). We explore parameter space because we know that in our MIMs some information could be inaccurate or even missing and therefore interpolated. To find that a possible "mistaken information" has very local effects is reassuring, in terms of general behavior of the network. It is of note that oncogenic mutations change the activity of a signaling-protein mostly in terms of all or none effects, and seem often to occupy hub-like locations, at least in terms of effects, in the network. Their effects should emerge even over a diffuse and significant noise background.We verified that, in every explored case, this is indeed what is happening. Finally, we also added selected references concerning mathematical modeling of signaling-networks, especially at the level of biochemical interactions, potentially of interest for the reader (5-12).

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Towards a Mathematical Theory of Complex Systems Reducing Complexity, Multiscale Aspects, and Applications

Abstract

This Lecture is devoted to the development of mathematical tools for the modeling, qualitative analysis and simulations of complex systems in life and human sciences. Namely of systems of many living individuals interacting in a non-linear manner. As known, it is very difficult to understand and model these systems based on the sole description of the dynamics and interactions of a few individual entities localized in space and time. Moreover, interactions are not additive and their modeling should take into account the ability of the interacting entities to develop specific strategies based on the states and localization of all interacting entities.
Focussing on living systems, definitely the most sophisticated class of complex systems, three main questions can be naturally posed:

- Do complex living systems exhibit common features?
- Which is the interplay between mathematical models and empirical data?
- Are the analytic and computational tools offered by mathematics able to capture, in the modeling approach, the above mentioned common features?

The first part of this lecture deals with suitable developments, based on the first question, of the, so called, kinetic theory for active particles [1], with interactions modeled by stochastic games methods. In particular, new mathematical tools are derived to model the dynamics of complex systems including learning dynamics and evolutive events [2].
The second part focuses on the other two questions, still remaining at a conceptual level. The third part presents some analytic problems posed by applications of models to real life phenomena. In particular, the qualitative analysis of initial and initial-boundary value problems for vehicular traffic crowd dynamics [3],[4] and the derivation of macroscopic equations from the underlying description at the microscopic scale [5].

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Mathematical modeling of the control of proliferation in cycling cell population

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Abstract:

Cell proliferation is controlled by circadian rhythms. Some clinical and biological data have shown that circadian rhythm disruptions can promote cancer growth, resulting in a poor prognosis for the patient [1,2]. Our purpose is to analyze, through mathematical modeling, interactions between circadian rhythms and cell division, in order to study the impact of such interactions on the proliferation process of healthy and cancer cells. Our work is based on an age-structured PDE-model of the cell division cycle within a cell population of a common tissue. It integrates a 24h-periodic time control of the transitions between the phases of the cell cycle. Cell proliferation tends to be exponential and so is characterized by its growth exponent, the first eigenvalue of the mathematical system we consider [3,4]. Moreover, this study relies on recent and innovative imaging data (fluorescence microscopy, [5]) to experimentally determine the parameters of the model and to validate numerical results. This model allows us to study the degree of simultaneity of phase transitions within a proliferating cell population and to analyze the role of the circadian clock in this process. This study will thus help elicit the impact of circadian rhythm disruptions in cancer growth, even identify new key mechanisms of tumor growth, and eventually design new cancer treatments.

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New approach to modeling of antiangiogenic treatment on the basis of Hahnfeldt et al. model

Coauthors Jan Poleszczuk and Urszula Forys

Abstract

We propose a new methodology in modeling of antiangiogenic treatment on the basis of well recognized model formulated by Hahnfeldt et al. in 1999. On the basis of the Hahnfeldt et al. model, with the usage of the optimal control theory, some protocols of antiangiogenic treatment were proposed. However, in our opinion the formulation of that model is valid only for the antivascular treatment, that is treatment that is focused on destroying endothelial cells. Therefore, we propose a modification of the original model which is valid in the case of the antiangiogenic treatment, that is treatment which is focused on blocking angiogenic signaling. We analyze basic mathematical properties of the proposed model and present some numerical simulations.

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Bio-physic-mathematical modeling of infected cell and neoplastic cell dynamics under therapy as tool for treatment tailoring.

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Abstract

Current antiviral therapy of chronic viral hepatitis (B and C) allows a complete cure of the disease from 15-95% of cases depending on both viral and host factors that characterize several patterns and prototypes of response to therapy. Major predictors of response to antiviral agents are:

- Viral and host genetic heterogeneity: i.e viral genotypes and antiviral resistant mutants and IL28B gene polymorphism;
- Early (1-4 weeks) viral load kinetics (virus markers serum levels);
- Early (1-4 weeks) viral dynamics (infected cell number simulated by bio-physic-mathematic modeling)

Algorithms considering the simultaneous analysis of the 3 categories of factors outlined above provide the best prediction of response to therapy and response guided rules for on-treatment modification of therapy which allowed a real personalized antiviral therapy with evidence based data of efficacy and cost-effectiveness. During the last decade with a multi-competent approach (team-work of key experts, biologists physicians, physics and mathematicians) we learned to use quantitative biomarkers of viral infection and disease to define algorithms and physic-mathematical models to study the infected cells dynamics in patients with chronic viral hepatitis udergoing antiviral therapy. Such a fruitful experience can be transferred to patients with hepatocellular carcinoma undergoing anticancer treatment. In fact, the quantitative measure of mutliple tumor biomarkers and the study of their early kinetics during therapy could allow the modelling the neoplastic cell dynamics during antineoplastic treatment providing the scientific basis for the identification of new patterns and prototypes of hepatocellular carcinoma which need different therapy strategies, and response guided rules to tailor anticancer therapy at the individual level ameliorating efficacy and reducing the costs of ineffective therapy.

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Mathematical modelling of cell-fate decision networks

Coauthors: Laurent TOURNIER, Simon FOURQUET, Denis THIEFFRY, Boris ZHIVOTOVSKY, Emmanuel BARILLOT, Andrei ZINOVYEV

Abstract

Engagement of death domain receptors such as TNFR1 or Fas can trigger cell death by apoptosis or necrosis, or lead to the activation of pro-survival signaling pathways such as NF-κB. Our study aims at identifying determinants of this cell fate decision process. Apoptosis represents a tightly controlled mechanism of cell death that is triggered by overwhelming stress conditions or external death signals, and results in vacuolization of cellular content followed by its phagocyte-mediated elimination. It is a physiological process that regulates cell homeostasis, development, and clearance of damaged, virus-infected or cancer cells. Necrosis results in plasma membrane disruption and release of intracellular content that can trigger inflammation in the neighboring tissues. Long seen as an accidental cell death, necrosis can also be a regulated process, possibly involved in the clearance of virus-infected or cancer cells that escaped apoptosis. Modeling of these pathways could help identify in which conditions and how the cell chooses between different types of cellular deaths or survival. Moreover, modeling could suggest ways to re-establish the apoptotic death when it is altered. The decision process appears to be very complex: it integrates many intertwined signaling pathways and the molecular interactions controlling this process are regulated by multiple positive and negative feedback loops. Mathematical modeling provides a good tool to understand and analyse the dynamical behaviours of such complex systems. For that purpose, based on the literature, we established a generic influence network that includes the main species that participate in cell fate decision in response to death signals (mediated by Fas and TNF). A first annotated version of this "master" model was built in a discrete framework. An initial study was performed on the steady states: eight different clusters of steady states that correspond to the expected cellular phenotypes were identified. This result constitutes a first validation of the proposed structure of the network. In order to propose a more refined dynamical analysis, we suggested a reduction of the model preserving the same dynamical properties. We went from 22 variables in the "master" model

to 11 variables in the reduced version. Thanks to this reduction, the realistic asynchronous updating strategy could be used and qualitative simulations were performed. In particular, the computation of all discrete trajectories starting from specific initial conditions allowed to identify the corresponding "reachable" phenotypes in the case of TNF and Fas-induced signals, for the wild-type and mutants models. The mutants mostly fit the expected behaviours and suggested some improvements in the "master" model.

This work is supported by the APO-SYS EU FP7 project and the authors of the work are members of the team "Systems Biology of Cancer," Equipe labellisée par la Ligue Nationale Contre le Cancer.

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Mathematical Modelling of Cancer Stem Cells. Population Behavior

Coauthors: E. Beretta N. Morozova

Abstract.

Stem cells are cells with two specific features - the ability to differentiate into all range of specialized cell types and the ability to renew themselves. There are several possible scenarios of cancer stem cells evolution, among which the asymmetric cell divisions providing self-renewing, is the main one. The main theory for today for either normal or cancer stem cells is that they differentiate when they receive some kind of "instructive" signal influencing the pattern and speed of cell divisions in the given conditions. All current experiments reporting the dynamics of cancer stem cell populations in culture allow to conclude that the main feature is the same - the eventual stability of the percentages of these cell populations in the whole population of cancer cells, independently of the starting conditions. In this paper we compare the qualitative behavior of mathematical models of stem cells evolution, without and with an underlying signal. In absence of an underlying field, we propose a mathematical model described by a system of ordinary differential equations, while in presence of an underlying field it is described by a system of delay differential equations, by admitting a delayed signal originated by the existing cells. In particular we show the stability of percentages for the ODE system, and the possibility of oscillations in the cell populations only in presence of an underlying field. The hope is that the results of this paper may stimulate further experiments to either validate or not the existence of the above mentioned "instructive" signals.

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COMPUTATIONAL MODELS: NOVEL TOOLS FOR CANCER VACCINES Parts I & II

Coauthor: Arianna Palladini

Abstract
(See A. Palladini's abstract)

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The Noise in the Biomarker Development Pathway

Abstract

Biomarkers have been claimed as a next frontier in cancer diagnosis and prognostic.

However, oncology pathways are the result of accumulating mutations that disrupt normal pathways and cause changes in metastases. Random fluctuations in biomarker are inevitable as chemical reactions are probabilistic. Moreover, there may be notable differences in specific biomarker among people. Such "noise" creates challenges in biomarker identification and validation.

I propose a statistical method to estimate the noise when subjects are measured more than one time point. Between-person variation is also taken into account.

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Invited Lecture: Dynamic networks of cooperators and defectors - implications to cancer?

Abstract.

Social, biological and economic networks evolve with recurrent fragmentation and re-formation, often explained in terms of external perturbations. We show that these phenomena can be a direct consequence of imitation and endogenous conflicts between 'cooperators' and 'defectors'. We employ a game-theoretic model of dynamic network formation, where prosperous individuals are more likely to be selected as role-models by newcomers who imitate their strategies and their connections. We find that cooperators promote well connected highly prosperous networks and defectors cause the network to fragment and lose its prosperity; defectors are unable to maintain the highly connected networks they invade. Once the network is fragmented, it can be reconstructed by a new invasion of cooperators. Prosperity is thus associated with instability and cooperation is most productive when it is unstable. We discuss how the presented model explains the dynamics of networks formed by financial institutions, social bacteria and how it can be used to model cell to cell interactions during tumorigenesis.

Contributed Talk: Feedback and feed-forward controls of cell cycle transitions

Abstract.

DNA replication, mitosis and mitotic exit are critical transitions of the cell cycle which should occur only once per cycle. The importance of various positive feedback and feed-forward loops in the irreversibility of these transitions has been investigated recently.
By computational modeling we investigate how these loops ensure proper timing and order of cell cycle events. We will show the dynamical features of such regulatory loops and discuss their role in the robustness of the transitions. We will present how various modeling approaches (differential equations, Petri-nets, Model-checking) can highlight different features of the regulatory network.

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Mathematical modelling in cancer: angiogenesis dynamics and antineoplastic chemotherapy

Abstract

Cancer is essentially characterized by the uncontrolled growth of cells that invade organs and tissues and it is now considered a serious public health problem worldwide. Despite the current and successful fight against the disease, there are some important questions concerning the efficient performance of its treatment modalities. For example, the anti-cancer chemotherapy requires further quantitative and analytical understanding. In this work we consider a mathematical model of ordinary differential equations to analyze chemotherapeutic schedules. We focus our studies on antiangiogenic schedule and, in order to get results closer to clinical practice, we use some experimental data for numerical simulations. At the implications for cancer therapy, our results indicate that administration of low doses and longer intervals between doses are related to therapeutic failure. Moreover, according to the model, metronomic chemotherapy, compared to the conventional treatment, gives the patient an increased survival. Thus, the antiangiogenic scheduling can be an alternative to cancer patients with no prospect of curing cancer.

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MODELLING Th1-Th2 CELL BALANCE DURING T CELL MEDIATED IMMUNE RESPONSE

Abstract.

Experimental observations show the relevance of Th1-Th2 cell balance in hypersensitive reactions. We propose a theoretical model of T cell mediated immune response focusing on Th1-Th2 cell balance, in the mathematical framework of the theory of reacting fluid mixtures with proliferative events.
In our model the proliferative events, i.e. events, which are not mass preserving, are the clonal expansions of Th1 and Th2 cells. Smooth approximate solutions of the resulting PDE's system are analyzed by using a double-scale approach enlightening some features regarding the multiscale complexity of the phenomenon under observation.

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Evolutionary strategies in immunoediting

Coauthors: M. Al-Taamemi, M.A.J. Chaplain, and A. Ciancio

Abstract

The competitive nonlinear interplay between a tumor and the host's immune system is not only spatio-temporally very complex but is also evolutionary.
A fundamental aspect of this issue is the ability of the tumor to slowly carry out processes that gradually allow it to become less harmed and less susceptible to recognition by the immune system effectors.
Here we propose two simple epigenetic escape mechanism that adaptively depends on the interactions per time unit between cells of the two systems.
From a biological point of view, our models are based on the concept that a tumor cell that has survived an encounter with a cytotoxic T-lymphocyte (CTL) has an information gain that makes it more fit than the naïve cells, which have never met a CTL. The consequence of this information increase is a decrease in both the probabilities of being killed and of being recognized by a CTL.
Numerical simulations of transitory phases complement the theoretical analysis.
Implications of the interplay between the above mechanisms and the delivery of immunotherapies are also illustrated.

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Towards quantitative modeling of tumor growth and regeneration on the histological scale

Abstract

In this talk we discuss different individual-cell-based models, so called "center-based" and "cellular automaton" models, to mimic aspects of tissue organization. We demonstrate how an iteratively applied process chain composed of experiments, image processing and analysis and mathematical modeling permits largely quantitative tissue modeling.
As a first example we demonstrate how a center-based model emerging from the aforementioned procedure was able to predict a subsequently validated fundamental order process during liver regeneration after toxic damage (Hoehme et. al., PNAS, 2010). Subsequently we show how this model can be combined with a metabolic compartment model to predict ammonia detoxication during the regeneration process.
As a second example we show how a cellular automaton model (Block et. al., Phys. Rev. Lett., 2007; Radszuweit et. al., Phys. Rev. E, 2009) of a growing multi-cellular spheroid could be parameterized from image material and which insight it permitted about spheroid growth. Finally we show how molecular core modules such as the beta-catenin core modulus can be embedded into a single-cell-based model to predict the change of the multi-cellular phenotype cancer invasion (Ramis-Conde et. al., Biophys. J. 2008).

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Cell-cell interactions in solid tumors - the role of cancer stem cells

Abstract

In recent years cancer stem cells have been identified as a minor subpopulation in numerous solid tumors that drives tumor initiation, development and metastasis. Although cancer stem cells have yet to be reliably isolated, populations enriched for tumor-initiating cells give an indication of the order of magnitude of the stem cells niche within primary tumors. Here we develop and discuss the predictions of a simple theoretical model of cancer stem cells and tumor growth dynamics. We evaluate the impact of cancer stem cell symmetric/asymmetric division and progeny cancer cell proliferation capacity on tumor progression and morphology. The model predicts that the frequency of symmetric cancer stem cell division determines the resulting stem cell pool size, and that the symmetric division frequency and the stem cell fraction are both typically small, consistent with the cancer stem cell hypothesis. At the same time, we show that intrinsic competition for space and environmental confinement can lead to an increasing stem cell fraction over time despite a fixed, low symmetric division probability. These findings offer a novel explanation for the apparent differences in reported stem cell numbers for different tumors as well as tumors of the same organ, and thus challenging the hypothesis of a fixed stem cell ratio for different tumors. The pivotal role of stem cell division strategies and stem cell ratio on spatio-temporal morphology evolution and self-organizing tumor patterning is discussed.

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On the role of ATP production in tumor spheroids.

Abstract.

An important phenomenon in the evolution of tumors is the switch of glucose metabolism from the aerobic to the anaerobic pathway. The aerobic pathway is characterized by a large consumption of oxygen and a large production of ATP (Adenosine-Three-Phosphate) , while the anaerobic mode requires no oxygen and leads to a much lower ATP production. The latter mode is associated to quiescence and gives the tumor cells two advantages: it hides them from chemotherapy and it raises the acidity of the environment to a level that can be toxic to the host tissue, while safe to the tumor. Thus the anaerobic pathway can also be a mean of progressive destruction of the host tissue, favoring invasion. The ability of cells to produce ATP can be taken as a measure of their viability. In the papers [1], [2] a model has been developed to illustrate the evolution of a multicellular spheroid supplied with oxygen and glucose, in which cell go to apoptosis when the ATP production rate falls below some threshold. The model was validated by fitting experimental data from EMT6/Ro spheroids.
On the wake of the seminal paper [3] some more considerations on the acid-mediated tumor invasion will be presented.

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Understanding TrkA and Myc dysregulation in neuroblastoma using dynamic modelling approaches

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Abstract

Neuroblastoma belongs to a group of childhood tumours and shows hallmark features of tumour biology including a high incidence of spontaneous regression and differentiation. However, aggressive forms are highly lethal. The clinical outcome is highly correlated with the expression patterns of the TrkA receptor and Myc oncogenes. For example, elevated TrkA and N-Myc expression is associated with a favourable outcome whereas low TrkA expression and N-Myc amplification relates to highly malignant behaviour. The diversity of outcomes is mirrored in cultured neuroblastoma cells, where TrkA signalling can lead to proliferation, differentiation and cell death depending on cell context and stimulation strength. The cells fate seems to be determined by a complex interplay of multiple pathways activated downstream of TrkA most likely involving transcription factors of the Myc family and several feedback loops. Such complex systems are notoriously difficult to comprehend intuitively, but can be understood using dynamic modelling. Here, we will present several methodologies whose theory is based on ordinary differential equations and that are aimed at deciphering the TrkA-Myc regulatory machinery in neuroblastoma.

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On the Mathematical Modelling and Treatment Strategies of Leukemia

Abstract

In the talk a mathematical model for leukemia therapy based on the Gompertzian law of cell growth will be presented. It is assumed that chemotherapeutic agents kill leukemic as well as normal cells. The effectiveness of the medicine is described in terms of a therapy function. Two types of therapy function, monotonic and non-monotonic are considered. In the former the effect of the chemotherapy increases if the quantity of the chemotherapeutic agent increases.In the latter the therapy function achieves its peak at a threshold value and then the effect of the therapy decreases.The amount of chemotherapeutic agents applied is constantly regulated by a control function with a bounded maximum. Additionally, the total quantity of chemotherapeutic agents which can be used during the treatment process is bounded. The problem is to find an optimal strategy of treatment to minimize the number of leukemic cells while at the same time retaining as many normal cells as possible. First, an optimization problem in Mayer form is examined. To determine the optimal treatment strategy, Pontryagin's maximum principle is used. In parallel, a /alternative/ control strategy is proposed. This strategy involves increasing the amount of medication up to a certain value in the shortest possible period of time, and holding this level until the end of the treatment. The comparison of the results from the numerical calculation using Pontryagin's Maximum Principle with the alternative control strategy shows that the difference between the values of cost function is negligibly small. Furthermore, we consider a multi-objective optimization problem. This consists of two conflicting objective functions: on the one hand minimizing the leukemia cells and on the other hand not allowing the number of healthy cells to fall below a minimum. We reduce this multi-objective problem using the epsilon-constraint method. With the aid of Pontryagin's Maximum Principle we calculate an analytical solution to this reduced problem and then take the constraints into account. The case of singular control was analyzed, where the optimal control was also determined.

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Cancer as a multifaceted disease

Abstract

Cancers are classified according to the tissue and cell type from which they arise. Carcinomas are cancers that arise from epithelial cells and they are the most common cancers and sarcomas are cancers that arise from muscle cells or connective tissue. Lymphomas and leukemias are derived from white blood cells. From a modeling point of view both carcinomas and sarcomas are referred to as 'solid tumors'. Solid tumors are typically modeled by a system of PDEs which depend on the cell type and on the microenvironment of the tumor. In this talk I will illustrate how mathematical models differ from one type of cancer to another, and how such differences lead to different approaches to cancer therapy. Examples will include breast cancer, glioblastoma, and prostate cancer.

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A new mathematical theory of the genetic code: a fresh look at the organization of genetic information

Coauthors: S. Giannerini and R. Rosa

Abstract

Recently (see Nature vol 474, 2 June 2011, 20, features) Anna Barker, Deputy Director of the US National Cancer Institute, asked for a help on a "war on cancer": "Forty years in the government's multibillion-dollar fight had barely budged cancer survival". The hope now is that physicists could bring some radical new ideas to the table. Furthermore, to date, the Genome Project somehow has failed to achieve the promised results (see S. S. Hall, Le Scienze n. 508, 2010). What is the reason behind this failure, or partially fulfilled enterprise? Perhaps some key aspects of the problem have been neglected; in order to achieve a major advance in our comprehension, we need an interdisciplinary cooperation between biologists, mathematicians, physicists, statisticians and computer scientists. Such cross-fertilization is crucial in order to get a new look on this old difficult problem. In this talk we review our work on a new mathematical approach to study genetic information. Such approach is motivated by the idea of error correction based on genetic redundancy and leads to a new mathematical model of the genetic code based on the theory of integer number representations, i.e., non-power positional integer number representations systems. The model is able to describe many features of the genetic code and to uncover a hierarchy of hidden symmetries (1-2). This mathematical organization can be relevant for the safe management of genetic information through different biological steps; interestingly, it is intimately related to some problems of dynamical system theory (3) and poses challenges both on group algebra and on time series analysis (4-8). Here, we present some of our results both on the theoretical side and on that of statistical analysis of coding DNA sequences.

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Immuno-oncology: what we have, what we need in the light of cancer complexity?

Abstract

Despite years of intensive investigation that has been made in understanding human cancer, it remains a major cause of death worldwide [1]. Human cancer emerges from multiple alterations that induce changes in expression patterns of genes and proteins that function in networks controlling critical cellular events [2, 3]. A primary task of the tumour research is the translation of molecular biomarkers candidates into clinical practice [4]. However, there is still not agreement with regard to the sequence and nature of steps that need to be taken to warrant efficient translation of prognostic and/or predictive biomarkers into clinical use and to the introduction of novel, effective and less toxic therapeutic strategies to diminish human suffering and cure life-threatening diseases [5].

Human cancer is a highly heterogeneous disease: more than 100 distinct types of cancers have been described, and various tumour subtypes can be found within specific organs. This genetic and phenotypical variability is what primarily determines the self-progression of neoplastic disease and its response to therapy [2, 3]. Individual cells from a clonal cell population respond differently to the same stimulus, some not responding at all [5, 6]. Variability in cell response can have important implications [7]. It is known that in a heterogeneous population, patients may display a multiplicity of genetic variations that respond differently to a given medical intervention [8, 9]. The same treatment could be of benefit to some patients yet harmful to others. Each cancer therapy can be therefore viewed as a filter that remove a subpopulation of cancer cells that are sensitive to this treatment while allowing other insensitive subpopulations to escape [10]. The above considerations, in conjunction with the complexity of tumour-host interactions within the tumour microenvironment caused by temporal changes in tumour phenotypes and an array of cells and immune mediators expressed in the tumour microenvironment [11-13] might partially explain the limited reliability

and applicability of current immunotherapeutic approaches. Carcinogenesis is a dynamical process that depends on a large number of variables and is regulated at multiple spatial and temporal scales and whose behaviour does not follow clearly predictable and repeatable pathways [2, 3]. This multiple scale causality not only recognizes multiple processes and controls acting at multiple scales but, unlike a strict reductionist approach, may also recognize the fact that relevant "first principles" may reside at scales other than the smallest micro-scales. In other words, the observed phenomenon at each scale has structural and behavioural properties that do not exist at lower or higher organizational levels. Although a number of tumours-associated antigens (TAA) have been recognized and it has been suggested that they could be useful in the immunological treatment of cancer, the expression of TAA in biological materials has mainly been studied at the level of gene expression and gene level measurement by RT-PCR analysis and the Quantitative (qrt) PCR technology [14]. However, the information provided by these approaches is limited by the fact that the phenomena observed at each level of anatomical organization (i.e. gene, cell, tissue, organ, system or apparatus and the organism as a Whole) have properties that do not exist at a lower or higher level[15]: RT-PCR and qrt-PCR may offer a satisfactory qualitative/quantitative description of small-scale structures, but this is likely to be irrelevant when it comes to large-scale features [14]. Cancer is a non-linear system [2, 3]. Non-linear systems are mainly characterized by three basic properties: (a) they do not react proportionally to the magnitude of their inputs; (b) they depend on their initial conditions. Small changes in the initial conditions may generate very different end-points; (c) their behaviour is not deterministic, *i.e.* periods of inactivity may be punctuated by sudden changes, apparent behavioural patterns may disappear and new patterns surprisingly emerge. Such behaviours emerge in complex systems, and are permanently sensitive to small perturbations. To understand human cancer as a complex system we need to determine the type of data that needs to be collected at each level of organization, the boundary conditions to use when describing the disease (i.e. a perturbed system), and the technologies and approaches best suited to reveal its underlying biological behaviour [2, 3]. Critical analysis of traditional clinical concepts is needed, as is reinterpretation of the clinical significance of failed therapies from the perspective of complexity. Two main concepts, *multiple scale causality* and *heterogeneity* need to be considered when generating new medical interventions. Since our understanding of human cancer, is still limited and pre-clinical models have shown a discouraging propensity to fail when applied to humans, a new way of thinking is strongly needed that unites physicians, biologists, mathematicians and

epidemiologists, in order to develop a better theoretical framework of tumour development, progression and tumour-host interactions [16-18]. The use of a holistic approach, which enables a more accurate selection of immunotherapeutic target antigens in the first phase of the experimental research, will reduce the notable fragmentation of the biological information in the post-genomic era, and will facilitate a more accurate transfer of the acquired knowledge to the bedside. This new way of thinking may help to clarify old concepts, categorize the actual knowledge, and suggest an alternative approach to discover biomarkers with potential clinical value.

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Introducing drug transport early in the design of hypoxia selective anticancer agents using a mathematical modelling approach

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Abstract

Extensive hypoxia is generally found only in tumours, and leads to radioresistance and tumour progression, making it a target for cytotoxic prodrugs which are activated selectively in hypoxic cells. However this activation is usually accompanied by extensive drug metabolism (by reductases in tumour cells) which can lead to limited drug penetration. We showed a major cause of sub-optimal efficacy of tirapazamine (TPZ), the most advanced hypoxia activated prodrug, is poor extravascular transport in the tumour tissue leading to reduced exposure in hypoxic cells which are generally most distant from the capillaries.

We investigated the transport of TPZ and analogues in multicellular layers (MCL), an in vitro technique where tumour cells are grown on a semipermeable support membrane to a thickness of 200-300 μm. In order to predict TPZ analogue distribution and cell killing in tumours we developed an in silico spatially resolved PKPD model based on a measured microvascular network from a rat window chamber preparation that already had an oxygen transport model based on a Green's function method. Using the transport (PK) parameters (diffusion in MCL, and metabolism as a function of oxygen concentration) and cytotoxicity parameters (potency as a function of drug metabolism) we showed that this in silico model predicted in vivo activity for a number of TPZ analogues.

In vitro drug transport and potency measurements and in vivo PK, combined with spatially resolved PKPD modelling were successfully used to screen drug candidates and select a second generation TPZ analogue with improved activity against hypoxic cells in tumour xenografts. The lead compound from this analogue program, SN 30000, is predicted to be highly active against hypoxic tumour cells by the in silico model, due to improved potency and extravascular transport. It has been shown to be substantially more active than TPZ across a range of tumour xenograft

types with both single dose and fractionated radiation, and is now entering clinical evaluation.

Potential applications of the techniques will be discussed. For example the in silico model will now be used to give an early indication of antitumour activity as human PK becomes available in clinical trials of SN 30000. We are also using the data on TPZ analogues to test the sensitivity of the predictions to tumour tissue structure (geometry) as new tumour networks become available. In addition we are extending this work to other classes of anticancer agents, for example those hypoxia selective prodrugs that selectively release molecularly targeted drugs and cytotoxins which can diffuse to and kill surrounding well oxygenated cancer cells.

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Modelling epilepsy dynamics and seizure prediction in human brain tumors

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Optimal control of cancer: challenges, limitations and open problems

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Modelling and mathematical analysis of various anti-angiogenic therapies

Abstract

In this talk we will introduce various models of anti-angiogenic therapies where the main feature is the flux of TAF and Endothelial cells on the boundary of the tumor. We will also present some theoretical results for those models.

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Modeling signaling transduction mediated by the tyrosine-kinase receptors

Abstract.

The tyrosine-kinase family of trans-membrane receptors plays a key role in relying signals mediating cell proliferation. In particular, over-expression of various HER receptors has been positively correlated to sustained cellular growth and therefore HER receptors are promising targets for the development of effective anticancer drugs. However, despite showing effective inhibition in vivo, tyrosine kinase inhibitors exhibit only limited activity against various types of tumors (e.g. on HER2-driven breast cancers, on HER1-driven lung cancer). The HER antagonists proposed therapies were initially based on some simplistic assumptions, as they ignored the complex set of self-regulation features of the HER receptors. For instance, while some breast-cancer treatments are attempting to switch off a signaling cascade by specifically targeting the HER2 receptors, the HER3 (and possibly other members of the same receptor family) are indeed actively modulating the signaling initiation, compensating for the effects of the drug with an increase in number and an amplification of their activity. This complex behavior is a good example of the intertwined relationships that exist at the molecular level in signaling networks. A reliable predictive tool has therefore to take into account the dynamical interactions among multiple components over time, whereas a reductionist view can hardly provide accurate answers to the evolution of cellular phenomena. The validity of the system level approach is exactly the core paradigm of Systems Biology, which aims at modeling the interactions among the various parts of a system, in a cycle composed of theory, analytic or computational modeling to propose specific testable hypotheses about a biological system, experimental validation, and then using the newly acquired quantitative description of biological processes to refine the computational model or theory. At COSBI, we are developing a modeling framework (COSBILAB) that deploys tools proper of Systems Biology to elucidate the molecular root of the outcomes of cancer treatments targeting the HER receptors, with the

objective of improving the ability to predict the efficacy of drugs on controlling the transduction of signals that induce cell proliferation. Detailed and comprehensive models of the molecular interaction networks of HER receptors can be defined with the COSBILAB BlenX modeling language to conduct accurate simulations of the dynamics of pharmacological treatments. Simplified, easy-to-define models can be developed with the tabular COSBILAB Model tool to grab the essential features and behaviors of the signaling networks.

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COMPUTATIONAL MODELS: NOVEL TOOLS FOR CANCER VACCINES Parts I & II

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Abstract

Prevention of tumor growth by immunological approaches is based on the concept that the immune system, if adequately stimulated before tumor onset, could be able to protect from specific cancers. In the last decade active immunization strategies effectively prevented some virus-related cancers in humans. Our research now has the goal to study cancer preventive vaccines against non-virus-related cancers. Among target tumor antigens for cancer immunopreventive strategies the HER-2 oncogene, overexpressed in 25-30% of human breast cancers, is widely studied. HER-2/*neu* transgenic mice are likely the most extensively studied models for the evaluation of immunopreventive approaches against mammary cancer.
We set up in HER-2/*neu* transgenic mice a cancer immunopreventive cell vaccine, referred to as Triplex, that administered with an intensive and life-long schedule, almost completely prevented HER-2/neu-driven mammary carcinogenesis. This vaccine, based on engineered murine mammary carcinoma cells, includes three stimuli: rat HER-2/*neu*, mIL-12 and allogeneic major histocompatibility complex (MHC). The main actors of cancer prevention were anti-HER-2/*neu* antibodies and IFN gamma.
To better understand the potential of Triplex vaccine the preventive efficacy of reduced schedules was investigated. We have used a computer model to study the effects of Triplex vaccine on murine mammary tumor. The model allows to test specific vaccination schedules in the quest for optimality. We evaluated the efficacy of the reduced schedules predicted by the computer model in HER-2/neu transgenic mice.
Testing in long-term *in vivo* experiments allowed us to identify specific aspects to improve both computational and biological models of cancer immunoprevention.

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Dynamic simulations of pathways downstream of TGF-beta, Wnt and EGF-family growth factors, in colorectal cancer, including mutations and treatments with onco-protein inhibitors.

Coauthors: L. Tortolina, N. Castagnino, C. De Ambrosi, A. Barla, F. Patrone, A. Ballestrero.

Abstract

Modern medicine and biomedical research is based on a detailed understanding of the development, function, maintenance and disease of our organs. While we have accumulated a vast amount of knowledge, we are still insufficiently capable of reconstructing, modeling and simulating how tissues and organs become diseased or how they would respond to potential therapies. A predictive simulation is the ultimate test of our basic understanding of a very complex set of phenomena.
At the level of networks of biochemical interactions we can simulate molecular changes for instance relevant in controlling different phases of the cell cycle. A typical example is the G0 – G1 transition, were cells decide to stay quiescent or to start the replication process.
At a higher multi-cellular scale level, it is potentially possible to simulate the physiological and pathological cell renewal of some tissues (colon crypts for instance).
Both at a biochemical and multi-cellular level we can try to test our real understanding of what is going on, introducing virtual mutations, alterations, aberrant behaviors, that progressively occur during the process of malignant transformation, with the goal of better understanding the biological rules governing health and disease. The activity of target-selective drugs and / or siRNAs capable of inhibition of mutated genes / proteins affected by excess of function, can also be simulated in our mathematical modeling; new altered functions introduced via gene transfection can be simulated equally well.
An important point is the distinction between wet lab information used during the training phase of a given software (introduction of multiple

constraints), usually a rather large and multifaceted set of information, and subsequent independent wet lab verification experiments. It seems appropriate that during the training phase we tend to consider satisfactory only behaviors in agreement with whatever known and sufficiently sound preclinical and clinical datum. The molecular oncologist "culture" concerning a specific cancer becomes important at this stage. An extensive and successful training phase, followed by dynamic simulations, will make expected some of the subsequent verification experiments. It is however of note that these expectations will take place only a posteriori of the mathematical modeling, because the size of our signaling-network is largely beyond the breaking point of a direct a priori intuitive capability of an expert human observer [1, 2].

We adopted the approach of reconstructing the molecular anatomy of a network relevant in colorectal cancer through a Molecular Interaction Map (MIM) [3], drawn according to the syntactic rules devised by Kurt W. Kohn [4]. We simulated the attainment of a stationary state in our biochemical network, immediately above the activation of transcription factors, through ordinary differential equations (ODEs).

The pathways reconstructed in our MIM are downstream of TGF-β, Wnt and EGF-family growth factors, they include about 60 basic molecular species (proteins and other small molecules).

In our signaling-network we have included about 390 modified species and complexes, more than 800 reactions (reversible and catalytic reactions) are involved. To our knowledge, this is probably one of the largest signaling-networks ever simulated at the biochemical-interaction scale level.

The pathways reconstructed in our MIM are not just parallel walks but, to some extent, they also intersect each other forming a veritable signaling-network structure.

We can summarize the involved pathways (in some cases converging pathways) as follows:

1) **pathway [ErbB-family receptors – PI3K – PTEN – Akt – GSK3β – APC – β-catenin – TCF/LEF – DNA binding site 1, agonist];**
2) **pathway [ErbB-family receptors – Grb2 – Shc – SOS– GAP– KRAS – BRAF – MEK – ERK- AP1– DNA binding site 2, agonist];**
3) **pathway [ErbB-family receptors-E-Cadherin (Cadherin/Catenin adhesive complex)];**
4) **pathway [ErbB-family receptors – PLCγ – PIP2 – PKC – BRAF – MEK – ERK- AP1– DNA binding site 2, agonist, converging with pathway 2];**
5) **pathway [WNT – Frz/LRP5/6 – Dvl – AXIN – APC – GSK3β - β-catenin];**
6) **pathway [TGFβ-receptors – SMAD2/3 – SMAD4 – DNA binding site 1, antagonist];**
7) **pathway [TGFβ-receptors – TAK-1 – TAB2 – NLK – TCF/LEF, converging with 8];**

8) **pathway [WNT – Frz/LRP5/6 – TAK-1 – TAB2 – NLK – TCF/LEF, converg. with 7].**

All the pathways described above, converge on two distinct DNA-binding sites, exerting cooperative and / or antagonistic transcriptional controls. We made reference to the final transcription of two important molecules (among others): cyclin D1 and c-Myc. These two molecules play key roles in the regulation of cell-cycle G0 – G1 transition, and their expression is carefully regulated.
Mutations belonging to a single pathway tended to be mutually exclusive, especially if they were relatively close within the pathway. Only inhibitors acting at, or downstream (not upstream), of a given mutation were active. This phenomenon was faithfully reproduced in our virtual simulations. A double alteration along two distinct pathways required the inhibition of both pathways, in order to restore an efficient control of a multi-altered network. We had previously observed a similar trend in a breast-cancer focused dynamic-simulation paper [5].
We started an analysis of sensitivity / robustness of our network, and we systematically introduced
several individual fluctuations of total concentrations (or reaction rates), concerning distinct independent molecular species. A perturbed species is affected by perturbing variations in protein concentration (or reaction rate), usually with decreasing intensity according to distance among perturbing and perturbed nodes (distance measured in terms of intervening edges). Practically no perturbations effects of a ten times change could be observed when a perturbing node was separated more than four edges from a perturbed node. This also confirms previous observations [5, 6, 7].
At a biochemical-interaction level, a dozen dynamic-simulation studies of limited signaling-network regions, have been published during the last ten years (six of them just in 2009-2010). These works tend to confirm the feasibility, the interest and the innovative potential of these studies. One of the most recent and advanced works of this kind is reported in [8].
In a complementary contributed presentation, we will discuss problems related to robustness / sensitivity of our network, subjected to perturbation of concentrations and / or rates. We will discuss possible strategies of random sampling and reasoned targeted sampling, in exploration of parameter space. We will also discuss the possibility of implementing forms of grid computing.

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Multiscale modeling of vascular tumor growth and therapy

Coauthors: Philip K. Maini, Tomás Alarcón, Markus R. Owen, Helen M. Byrne

Abstract

A 3D multiscale model for vascular tumour growth and angiogenesis is presented (Perfahl et al. [1]). The model combines blood flow, angiogenesis, vascular remodelling, interactions between normal and tumour cells and diffusive nutrient / VEGF transport as well as cell-cycle dynamics within each cell. We follow two different strategies to reproduce vascular structures in silico. The first one is purely virtual, where we start with a few straight initial vessels and then simulate angiogenesis that is induced by hypoxic normal or quiescent tumour cells. The resulting network ensures that the tissue domain under consideration is adequately nourished by oxygen. As a second approach we follow a hybrid strategy in which the initial vascular structure is based on a real network obtained from mouse window chamber models which then further evolves under the influence of the tumour. A simplified version of the multiscale model is then applied to describe the effects of TRAIL therapy on avascular in vitro tumour spheroids. We include a TRAIL apoptosis pathway model in each cell. The apoptosis model accounts for the observed heterogeneity of cellular responses to TRAIL therapy by sampling one parameter from a bimodal parameter distribution. The dynamics of the apoptosis pathway is influenced by the extracellular TRAIL concentration that is described by a reaction diffusion equation. TRAIL induced tumour cell death is initiated if the intracellular concentration of the active caspase 3 exceeds a death-threshold. In our simulations, we aim to answer the question of how the interplay of the cell heterogeneity together with the spatial heterogeneity influences the drug's efficacy.

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A multiphase and multiscale overview of cancer modelling

Abstract

The aim of the talk is to give an overview of some mathematical models developed in the last ten years to describe the growth of tumour masses and their interactions with the surrounding environment and in particular the extracellular matrix, in the different phases of growth: from the avascular phase to the vascular phase, the detachment of metastases and the intravasation process. Whenever possible a comparison between the different modelling framework will be attempted, e.g., between continuum mechanics-based models and individual cell-based models.

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Mathematical Models of Cancer Vaccines

Abstract

Therapeutic cancer vaccines are designed to heighten the immune system's effectiveness in fighting tumors. The first step in the specific immune response is triggering of immune cell production in the lymph organs. In this talk we present mathematical models of this immune response, and demonstrate how these models, once calibrated to laboratory or clinical data, can be helpful in designing treatment protocols. Two models will be presented, showing how mathematical formulations of immune responses can be developed, tested, and applied. The first model describes the cellular interactions in the spleen as the first stage of the immune response to a cancer vaccine. The goal of this model is to suggest dose and scheduling protocols that would maximize this cellular immune response. The second model describes a dendritic cell vaccine, and includes the trafficking of cells between compartments in the body. The goal of this second model is to not only test dosage schedules, but to also test different treatment sites.

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Systems based approach to understand and target networks in cancer

Abstract

Cellular responses are directed by environmental cues, which are processed through intracellular networks within the cells. Cancer cells contain several aberrations that alter network functions. In order to target these changes in the cancer cellular network we need to understand how network function are altered. We have used a systems approach of integrating functional proteomics and genomics coupled to siRNA screens, cellular responses to drugs and computational modeling in order to determine optimal targets for therapy.

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A tumor growth inhibition model for diffuse low-grade gliomas

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Homeostasis and oncogenesis: mathematical model

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Abstract

Background There is now abundant evidence pointing to the relation between the rate of tumor development and the state of the energy budget. Caloric excess and obesity favor the tumor growth and in contrast the caloric restriction slows it down [1,2,3].
Purpose and Methods: The purpose of the current work is to investigate the influence of homeostasis maintenance and the rate of tissue regeneration on carcinogenesis. We suggest the mathematical model describing the relationship between the fidelity of DNA replication and the rate of tissue regeneration. The system of differential equations depicts the processes of energy reserving and consumption on homeostasis and tissue regeneration. The fidelity of DNA replication is supposed to be determined by the rate of tissue regeneration. Improving the accuracy of DNA replication is accompanied by increasing in energy consumption on regeneration and maintenance of reserve cells. It leads to decrease in fitness.
Results: By means of the model the observations from [2,3] are quantitatively simulated. It is shown that there is such level of the accuracy of DNA replication that minimizes running cost of the organism.
Implications: By means of the simulation we demonstrate that the organism must balance the risk of low fidelity during DNA replication and the risk of excess expenditure on maintenance of reserve cells. In an obese subject processes of tissue regeneration and homeostasis maintenance do not compete for common energy resource. Both reserve cells and cells with damaged DNA could be supported.

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Stability of solutions for chemotaxis systems

Abstract

Chemotaxis is the phenomenon whereby living organisms respond to chemical substance by motion and rearrangement. After the publication of the first mathematical model of Chemotaxis (Keller-Segel, 1970) many different biological phenomena have been modelized with chemotactic terms, as Angiogenesis, where the endothelial cells move towards the tumor following a chemical gradient of Tumor Angiogenesis factors. One of the challenges of the modeling is to obtain the values of the parameters of the systems, which determine the behaviour of the phenomenon. We consider different types of mathematical models of chemotaxis, containing reaction terms in the systems. We study the long time behaviour of the solution for a range of the parameters and we study the stability of the steady states.

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Full rendering of the proliferation process at the cell population level during the response to anticancer treatments

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Abstract

Multicellular systems like cell populations are currently studied both in vitro and in vivo using different platforms, providing high throughput data of different types. Mathematical modeling is now called to interpret this reality and thus has to face more and more with quantitative data. This requires a connection between the basic theoretical model and the data structures, taking into account of the processes of measure.
Working on the response to anticancer treatment, we considered the data provided by flow cytometry (FC) and time-lapse live cell imaging (TL) in time-course experiments in vitro where exponentially growing cells were exposed to X-rays. A number of replicated samples were measured and different experiments were made varying the X-ray exposure. Following a first analysis of the row data, using established methodologies for analysis of FC and TL data, we obtained two parallel databases snapping the same phenomenon (i.e. the antiproliferative activity of X-rays) from the different points of view of the two platforms, FC focusing on distributions of cells in G1, S, G2M cell cycle phases, TL on lineage trees following cells in subsequent generations. The two platforms, considered singularly, convey a piece of the information, but are unable to render unequivocally the dynamics of the underlying cell cycle progression.
Exploiting our previous modeling experience [1-3] we used a cell cycle simulator including subsequent cell generations to achieve a full reconstruction in silico of the cell cycle progression. The model is based on an age- and phase-structure (G1, S, G2M phases) with drug effects superimposed. Cell cycle during unperturbed growth of the ovarian cancer cells under study was described taking into account of intercellular variability of G1 S, S and G2M transit times, of quiescent cells and of natural cell loss [4]. The effect of X-rays is modeled by "perturbative modules" associated to each checkpoint of the cell cycle, in the subsequent generations. Each module includes a submodel modifying the normal flux

of cells at the desired level of complexity, introducing delays, block, recycling from block and cell kill in each cell phase in each cell generation. Upon input of a hypothetical scenario of the parameters associated to unperturbed growth and perturbative modules, the program reproduces the time course of cell cycling through subsequent generation, giving as output data equivalent to both TL and FC experiments, that can be directly compared with the experimental databases. The inverse problem is also currently tackled, in the attempt to give the best fit scenario(s) for the databases, avoiding overparametrization by using simplifying, although biologically consistent, regularity assumptions on the time and dose dependence of the parameters.
We will show preliminary data and modeling disclosing the heterogeneity of the response of cancer cells to X ray exposure, demonstrating that some cells were intercepted by G1, S, G2M checkpoints before dividing (generation 0), others after one or even two mitoses (generation 1 and 2 respectively). Some cells experienced repeated delays in different phases and generations. The fate of the cells was also heterogeneous, even within the same lineage, some descendant remained definitively arrested (particularly in G1 in generation 1 and 2), some refused originating polyploid cells and others died. In conclusion we demonstrated that modeling can be successfully applied to integrate flow cytometry and time-lapse live cell imaging in studies of cell cycle dynamics, reaching a generation-wise picture of G1, S, G2M perturbations induced by anticancer treatment.

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Treatment Protocols for a Mathematical Model of the Enhancement of Tumor Vaccine Efficacy by Immunotherapy

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Abstract

TGF-beta is an immunoregulatory protein that contributes to inadequate anti-tumor immune responses in cancer patients. Recent experimental data suggests that TGF-beta inhibition alone, provides few clinical benefits, yet it can significantly amplify the anti-tumor immune response when combined with a vaccine designed to boost the number of tumor-specific T cells. We develop a mathematical model in order to gain insight into the cooperative interaction between anti-TGF-beta and vaccine treatments. The mathematical model follows the dynamics of the tumor size, TGF-beta concentration, activated cytotoxic effector cells, and regulatory T cells. In past work, we have shown that monotherapy is not sufficient to eradicate the tumor and that tumor eradication requires the combination of these therapeutic approaches. These mathematical results are consistent with biological data. Our current focus is on obtaining feasible protocols for combined vaccine and anti-TGF-beta treatment administration. The mathematical model together with the experimental data imply that there may be feasible, clinical approaches to tumor treatment with immunotherapy.

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Mathematical Modelling of Cancer Invasion: the importance of cell-cell adhesion and cell-matrix adhesion

Abstract

The process of invasion of tissue by cancer cells is crucial for Metastasis - the formation of secondary tumours - which is the main cause of mortality in patients with cancer. In the invasion process itself, adhesion, both cell-cell and cell-matrix, plays an extremely important role. In this paper, a mathematical model of cancer cell invasion of the extracellular matrix is developed by incorporating cell-cell adhesion as well as cell-matrix adhesion into the model.
Considering the interactions between cancer cells, extracellular matrix and matrix degrading enzymes, the model consists of a system of reaction-diffusion partial integro-differential equations, with nonlocal (integral) terms describing the adhesive interactions between cancer cells and the host tissue, i.e. cell-cell adhesion and cell-matrix adhesion. Having formulated the model, we prove the existence and uniqueness of global in time classical solutions, which are uniformly bounded. Then, using computational simulations, we investigate the effects of the relative importance of cell-cell adhesion and cell-matrix adhesion on the invasion process. In particular, we examine the roles of cell-cell adhesion and cell-matrix adhesion in generating heterogeneous spatio-temporal solutions. Finally, in the discussion section, concluding remarks are made and open problems are indicated.