Mathematical Models in Cancer, August 2019

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Combination Therapies and Drug Resistance in Heterogeneous Tumoral Populations

Marcello Delitala
Politechnico di Torino

How combination therapies can reduce the emergence of cancer resistance? Can we exploit intra-tumoral competition to modify the effectiveness of anti-cancer treatments?

Bearing these questions in mind, we present a mathematical model of cancer-immune competition under therapies. The model consists of a system of differential equations for the dynamics of two cancer clones and T-cells. Comparisons with experimental data and clinical protocols have been performed.

In silico experiments confirm that the selection of proper infusion schedules plays a key role in the success of anti-cancer therapies. The outcomes of protocols of chemotherapy and immunotherapy (separately and in combination) differing in doses and timing of the treatments are analyzed.

In particular, we highlight how exploiting the competition between cancer populations seems to be an effective recipe to limit the insurgence of resistant populations. In some cases, combination of low doses therapies could yield a substantial control of the total tumor population without imposing a massive selective pressure that would suppress the sensitive clones leaving unchecked the clonal types resistant to therapies.

- E. Piretto, M. Delitala and M. Ferraro (2018). Combination therapies and intra-tumoral competition: insights from mathematical modelling, Journal of Theoretical Biology, 446, 149-159.
- E. Piretto, M. Delitala and M. Ferraro (2019). How combination therapies shape drug resistance in heterogeneous tumoral populations, Letters in Biomathematics, 1-18.

Predicting Healthy and Cancerous Tissue Samples by Applying Predictive Modeling Techniques on Epigenetic Markers

Alexander Tolios
Medical University of Vienna

Introduction. DNA methylation is known to have a major impact on the protein biosynthesis of tissues. Those epigenetic modifications could theoretically also be used for tissue classification. In this study we hypothesized that machine learning algorithms could be applied to distinguish between different tissue samples.

Methods. Methylation data was taken from NCIs 'The Cancer Genome Atlas' (TCGA) repository. Methylation proportion (beta-values) of 650 samples from 9 different tissues types were used for subsequent analysis. 2/3 of the data was randomly chosen to be used for algorithm training, the rest was reserved as an independent test set. Principal component analysis (PCA) was performed for dimensionality reduction. Classification was performed by applying linear discriminant analysis, penalized logistic regression, neural networks, random forests, support vector machines and k-nearest neighbors algorithms using different numbers of principal components. To enhance model performance, nested cross validation was applied in each run.

Results. When using up to 6 principal components, a steady increase in model performance could be detected throughout all algorithms, whereas more PCs did not result in a higher predictive accuracy. Although good results could be generated with most of the algorithms, the more complex machine learning algorithms generally performed better than the linear ones on the training data. The highest overall classification performance on the training set was generated using a random forest approach (accuracy > 95%, CI 92-98%). When being used on the separate test set, classification accuracy was similar (accuracy > 95%, Cohen's Kappa > 0.90).

Conclusion. The application of predictive modeling techniques allows to confidently differentiate between different tissue types. This might be useful in cases where histopathological sample examination is not possible.

Mathematical Model of CRC Lung Metastases Growth Patterns

Svetlana Bunimovich
Ariel University

Colorectal cancer (CRC) is one of the most common causes of cancer-related mortality worldwide. Most cases of deaths result from metastases, assumed to be shed, in many cases, before disease detection. Providing reliable predictions of the metastases' growth pattern may help planning treatment. Available mathematical tumor growth models rely mainly on primary tumor data, and rarely relate to metastases growth. The aim of this talk was to explore CRC lung metastases growth patterns.

We used data of a metastatic CRC patient, for whom ten lung metastases were measured while untreated by seven serial computed tomography (CT) scans, during almost three years. Three mathematical growth models – Exponential, logistic and Gompertzian – were fitted to the actual measurements. Goodness of fit of each of the models to actual growth was estimated using different scores. Factors affecting growth pattern were explored: size, location and primary tumor resection.

Exponential growth model demonstrated good fit to data of all metastases. Logistic and Gompertzian growth models, in most cases, were overfitted and hence unreliable. Metastases inception time, calculated by backwards extrapolation of the fitted growth models, was 8-19 years before primary tumor diagnosis date. Three out of ten metastases demonstrated enhanced growth rate shortly after primary tumor resection.

Our unique data provide evidence that exponential growth of CRC lung metastases is a legitimate approximation, and encourage focusing research on short-term effects of surgery on metastases growth rate.

Early Evaluation of Cancer Treatment Using Modeling and AI

Olivier Saut
CNRS, INRIA Monc Bordeaux

The main goal of this talk is to present examples of how mathematical modeling and AI may help clinicians following the evolution of cancer.

The first example uses machine learning to evaluate the efficacy of neoadjuvant chemotherapy of soft-tissue sarcoma. Standard of care for advanced stages (grade 3) is the following: neoadjuvant chemotherapy (6 cycles), curative surgery and then adjuvant radiotherapy. Unfortunately, for some patients, chemotherapy does not improve the situation. In clinical routine, two MR exams are performed on patients: one before the chemotherapy and one after two cycles. Using a retrospective study of more than 60 patients from Institut Bergonié, we investigate whether the differences between these two exams may be correlated with response to chemotherapy. For this matter a radiomics approach is used with novel handcrafted features specific to the disease. On the cohort, the results we obtain are better than state of the art.

In the second example, we try to evaluate the efficacy of tyrosine kinase inhibitors (TKI) for patients with EGFR mutated Non-Small Cell Lung Carcinoma. Patients almost always end up relapsing. Our goal is to analyze if an insight on this relapse may be obtained from the early response to treatment. We built a mathematical model — based on a set of PDE - of the response to TKI. This model is personalized for each patient of a retrospective cohort from Institut Bergonié. For the patient-specific model, we compute a novel marker that we show to be correlated with risk of relapse.

Finally, a new data assimilation technique will be presented that is able to recover patient-specific parameters of a PDE model of growth of brain metastases. It may be used to predict the evolution of these metastases.

Treasure Hunting in the NCI60 Anticancer Drug Screen Database

Gergely Szakacs
Medical University of Vienna

Molecular descriptor (2D) and three dimensional (3D) shape based similarity methods are widely used in ligand based virtual drug design. In the present study pairwise structure comparisons among a set of 4858 DTP compounds tested in the NCI60 tumor cell line anticancer drug screen were computed using chemical hashed fingerprints and 3D molecule shapes to calculate 2D and 3D similarities, respectively. Additionally, pairwise biological activity similarities were calculated by correlating the 60 element vectors of pGI50 values corresponding to the cytotoxicity of the compounds across the NCI60 panel. Subsequently, we compared the power of 2D and 3D structural similarity metrics to predict the toxicity pattern of compounds. We found that while the positive predictive value and sensitivity of 3D and molecular descriptor based approaches to predict biological activity are similar, a subset of molecule pairs yielded contradictory results. By simultaneously requiring similarity of biological activities and 3D shapes, and dissimilarity of molecular descriptor based comparisons, we identify pairs of scaffold hopping candidates displaying characteristic core structural changes such as heteroatom/heterocycle change and ring closure. Attempts to discover scaffold hopping candidates of mitoxantrone recovered known Topoisomerase II (Top2) inhibitors, and also predicted new, previously unknown chemotypes possessing in vitro Top2 inhibitory activity.

Benchmarking Differential ChIP-Seq Tools

Thomas Eder & Florian Grebien
University of Veterinary Medicine, Vienna

Chromatin immunoprecipitation followed by sequencing (ChIP-seq) is widely used in the global investigation of protein-DNA interactions. One of its main applications is the analysis of differential chromatin binding patterns of the proteins of interest in varying biological states. While various algorithms can be used to quantitatively compare ChIP-seq datasets, different computational tools apply different normalization strategies, which can strongly influence the results of the analyses.

Applying inappropriate normalization can lead to erroneous outcomes, and the performance of different tools can strongly depend on the nature of the investigated dataset. Therefore it is hard to choose the most appropriate differential ChIP-seq tool. To overcome this limitation, we systematically assessed available tools for differential ChIP-seq analysis to provide recommendations which tools to use for different biological scenarios and data types.

We created standardized reference datasets by in-silico simulation of ChIP-seq data to represent different biological scenarios, including global reduction of genomic regions in one sample versus the other, but also up- and down-regulation of equal proportions of genomic regions in both samples. We used these scenarios to evaluate the performance of 24 computational tools for differential ChIP-seq analysis.

We found enormous differences in precision and recall across differential ChIP-seq analysis tools. The performance was strongly dependent on the sizes and shapes of simulated peaks as well as on the regulation scenario. We are currently extending these findings to publicly available and unpublished experimental ChIP-seq datasets.

Our analysis provides unbiased recommendations which tools to use for particular biological scenarios. The application of appropriate analysis tools will greatly improve the outcomes of ChIP-seq studies, and will thus contribute to improved identification of molecular mechanisms.

Network Analysis for Hypothesis Generation, Target Definition, and (Multiomics) Data Integration

Dietmasr Pils
Medical University of Vienna

In high grade serous ovarian cancer patients with peritoneal involvement have an unfavorable outcome and would benefit from targeted therapies. In the last years we comprehensively described two types of peritoneal tumor spreading, miliary, with many millet sized tumor nodules in the peritoneal cavity, and non-miliary, with few larger and exophytically growing tumors. The former showed significant shorter survival, therefore we aimed to find a druggable target against miliary peritoneal metastasizing. We constructed a planar – scale free and small world – co-association gene expression network from RNA-sequencing data using mutual information as the association measure, defined sub-clusters with multiscale clustering, and searched for sub-clusters with hub genes up-regulated in miliary tumors. A sub-cluster of 38 genes and Nectin 4 as hub-gene was among the highest significant up-regulated sub-clusters. Using the genes of this sub-cluster for a gene signature we validated the impact on survival with six publicly available expression datasets. Protein expression and impact on survival of Nectin 4 was validated via immunohistochemistry and correlated to other omics and medium-dimensional data. Results were condensed to a network and used for biological interpretation of the impact of Nectin 4 on peritoneal ovarian cancer metastasizing. An anti-Nectin 4 antibody with a linked antineoplastic drug – already used in clinical trials for cancer treatment – could be a promising candidate for a targeted therapy in patients with miliary peritoneal involvement.

Friday, August 2, 2019

Dissecting the Evolutionary Dynamics of Cancer Cell Populations in Fluctuating Environments

Tommaso Lorenzi
University of St. Andrews

A number of studies have demonstrated that the disordered process of angiogenesis occurring in malignant tumours produces stochastic variations in blood flow leading to cycles of perfusion, cessation of flow, and then re-perfusion. This produces corresponding fluctuations in environmental conditions that include the concentration of nutrients, such as oxygen and glucose. In order to support a deeper understanding of the adaptive role of spontaneous phenotypic variations in cancer cell populations exposed to fluctuating environments, we consider a system of non-local partial differential equations modelling the evolutionary dynamics of two competing populations in the presence of periodically oscillating nutrient levels. Exploiting the analytical tractability of our model, we study the long-time behaviour of the solutions to obtain a detailed mathematical depiction of evolutionary dynamics. Our analytical results formalise the idea that when nutrient levels experience small and slow periodic oscillations, and thus environmental conditions are relatively stable, it is evolutionarily more efficient to rarely undergo spontaneous phenotypic variations. Conversely, under relatively large and fast periodic oscillations in the nutrient levels, which lead to alternating cycles of starvation and nutrient abundance, higher rates of spontaneous phenotypic variations can confer a competitive advantage, as they may allow for a quicker adaptation to changeable environmental conditions. In the latter case, our results indicate that higher levels of phenotypic heterogeneity are to be expected compared to those observed in slowly fluctuating environments. Finally, our results suggest that bet-hedging evolutionary strategies, whereby cancer cells switch between antithetical phenotypic states, can naturally emerge in the presence of relatively large and fast nutrient fluctuations leading to drastic environmental changes.

Contribution of Immune Mechanisms to the Anticancer Activity of Platinum Drugs

Walter Berger [1,2], Christian R. Kowol[2,3], Petra Heffeter[1,2], Bernhard K. Keppler[2,3]

[1]*Institute of Cancer Research and Comprehensive Cancer Center Vienna, Medical University Vienna, Borschkegasse 8a, 1090, Vienna, Austria.*

[2]*Research Cluster "Translational Cancer Therapy Research", University of Vienna and Medical University of Vienna, Austria*

[3]*Departement of Inorganic Chemistry, University of Vienna, Währinger Strasse 42, Vienna, Austria.*

Currently, immunotherapy with checkpoint inhibitor antibodies is revolutionizing clinical oncology even allowing cure of highly aggressive cancer types like melanoma and lung cancer. However, response to these immunotherapies is restricted to patient subgroups and currently conclusive predictive biomarkers are not available. Classically, anticancer metal drugs are considered to target predominantly nucleic acids, hence killing cancer cells by inducing genomic damage and apoptotic cell death. However, during the last years it became clear that metal drugs are not pure cytotoxic agents, but might also strongly interact with the fidelity of anticancer immune responses. Central underlying mechanisms include upregulation of cancer cell immunogenicity or depletion of regulatory immune cell compartments[1]. As one example, we have found that an intraperitoneal colon cancer model can be cured when combining oxaliplatin with bacterial ghosts as adjuvants[2]. Bacterial ghosts are empty envelopes of gram-negative bacteria with a distinct immune-stimulatory potential. In contrast, oxaliplatin alone only retarded tumor growth. Interestingly, animals cured by this immunochemotherapy approach were vaccinated against the original cancer cells making regrowth of the tumor graft impossible. As this vaccination effect was entirely depending on the presence of activated T cells, induction of an immunogenic cell death by oxaliplatin supported by innate immune activation via the adjuvant can be anticipated. This hypothesis was proven be induction of endoplasmic reticulum (ER) stress, calreticulin cell surface exposure, as well as HMGB1 and ATP release be the combination-treated cancer cells. A platinum(IV) prodrug of oxaliplatin targeted for tumor-specific activation based on albumin binding was able to cure CT26 murine colon cancer even without additional adjuvant in immunocompetent but not severe combined immunodeficient (SCID) mice[3]. The question arises whether mathematical modelling of at least parts of the complex interplay between DNA damage and immune activation by anticancer platinum drugs would be conceivable.

References

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Multiscale models to investigate IntraTumor Heterogeneity

Francesca Cordero
University of Torino

In cancer research most efforts are devoted on the decipher of the IntraTumoral Heterogeneity (ITH). In ITH the action of the evolutionary forces of mutation and selection are essential to determinant the tumor progression, diagnosis and treatment. ITH gives rise to cancer cell populations with distinct genotypic and metabolic characteristics contributing to the failure of cure, by initiating phenotypic diversity and enabling more aggressive and drug resistant clones.

I will present multi-scale models of cancer linking the tumor growth to the intracellullar signalling and metabolic events to genomic profiles. The models consider several heterogenous omics data (metabolomics, proteomics, transcriptomics, genomics) to investigate the ITH associated with different genomic and metabolic traits.

An Individual-Based Model for Inter-Kinetic Nuclear Movement

Sophie Hecht
Imperial College, London

Understanding how tissues develop and regulate their growth is crucial in biology. Both proliferation and regulation of cells growth are fundamental for the development of healthy tissue in animals and plants, as well as for the progression of tumours. In pseudostratified epithelia, the organisation of the nuclei and their movement inside the tissue influence the final architecture of the tissue and impact growth. In particular, nuclei move along the apical/basal axis during the inter-kinetic phases of the cell cycle. This movement is called the inter-kinetic nuclear movement. Because pseudostratified epithelia have a high density of nuclei, their movement is likely to be influenced by the crowing inside the tissue. We developed an Individual-based model for the interkinetic nuclear movement in pseudostratified epithelia based in a minimisation framework. The model focuses is placed on the nuclei and their deformation. We study the influence of crowding the specific case of the Imaginal Disc of Drosophila and tuned the model with biological data. We then show that the crowding increases the cell cycle duration, resulting in the slow down of growth.

Making Sense of Signaling Complexity

Michal Komorowski
Polish Academy of Sciences

An engineer designing a communication system would use few distinct signaling components while ensuring that the output of each component is highly accurate. However, natural evolution came up with a different solution: cells have many interconnected, cross- reactive components that individually produce noisy signals. Why?

In the talk, I will present the perspective of mathematical information-theory at the two intriguing properties of cellular signaling pathways: noisiness and cross-talk. Specifically, I will discuss their
(i) evolutionary origins;
(ii) implications for interpretation of single cell data; and
(iii) consequences for the design of therapeutic interventions in signaling.

Modelling Adhesion-Independent Cell Migration: How Cells Can Cross Biological Barriers

Diane Peurichard
INRIA, Paris

One of the most important cellular behaviors is cell crawling migration. It is observed in many cellular systems both in culture and in vivo, and involved in many essential physiological or pathological processes (wound healing, embryonic development, cancer metastasis etc). As in the last decade adhesion-independent migration has been observed in confining environement and has emerged as a possibly common migration mode, we propose a simplified 2D model for focal adhesion-free cell migration: A cell is modeled through its membrane represented as a set of connected springs which undergo internal pressure forces. The renewal of the actin network is modelled by creation/suppression of springs in the membrane, and we suppose that a cell generates internal counter-forces compensating mass displacement due to membrane renewal. Numerical simulations show that these simple rules can account for the behavior observed in experiments, suggesting a possible mechanical mechanism for cell motility in confined environment.

From Protein-Protein to Drug-Drug Interactions

Jörg Menche
CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna

From protein interactions to signal transduction, from metabolism to the nervous system: Virtually all processes in health and disease rely on the careful orchestration of a large number of diverse individual components ranging from molecules to cells and entire organs. Networks provide a powerful framework for describing and understanding these complex systems in a wholistic fashion. They offer a unique combination of a highly intuitive, qualitative description, and a plethora of analytical, quantitative tools. In my presentation, I will introduce three ongoing projects of my group, each highlighting a different aspect of how network science can help us understand the pathobiological processes of human disease: First, I will sketch out how protein-protein interaction networks can be understood as maps to investigate relationships between diseases. Second, I will discuss how drug-drug interaction networks can be used to identify basic principles of the cellular response to multiple perturbations. Lastly, I will present our vision of a virtual reality platform for the next generation of network-based data integration and exploration.

Interplay of Therapy and Tumor Microenvironment in Human Colorectal Cancer

Michael Bergmann
Medical University of Vienna

Advances in tumor immunology now calls for a novel understanding of the immunological consequence of standard cancer therapy. At the same time the expression of proteins mediating immunogenic cell death should have a positive predictive and prognostic impact. This molecular understanding of the disease will allow a more rational design of immunomodulating drugs and standard therapy.

Murine models clearly indicate that irradiation induced DNA damage can stimulates the innate and adaptive immune system. However, there is little evidence that irradiation leads to apiscopal effects in the clinic. We here show that neoadjuvant irradiation applied in rectal cancer patients induces the polarization of tumor associated M2-like macrophages to an M1-like phenotype in surgical resection specimen. Ex vivo primary cultures and organotypic assays were used to better dissect this re-polarization. Using ex-vivo cultures we further show that the shift of irradiation-induced macrophage polarization could be mediated by exosomes. Those data clearly indicate that radiotherapy induced DNA damage using 25 Gy actively stimulates the innate immune system. This pro-inflammatory effect of radiotherapy might now be complemented by immunomodulating drugs modulating the adaptive part of the immune system.

In contrast, when analyzing the prognostic and predictive impact of spontaneous DNA damage and associated pathways in colorectal liver metastases we demonstrate that DNA damage had a strong negative impact on response to neoadjuvant applied chemotherapy but also on disease free and overall survival. Spontaneous DNA damage was not associated with an induction of the innate immune response in this setting and inversely correlated with infiltrates of CD8+ or CD45RO+ cells. This calls for a more detailed understanding of spontaneous DNA damage induced pathways in colorectal liver metastases as their blockade might enhance prognoses.

- Stary *et al.,* submitted
- Laengle *et al.,* Theranostics 2018