MINISYMPOSIUM

QUANTIFYING GENETIC AND NON-GENETIC HETEROGENEITY IN CANCER EVOLUTION

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Minisymposium Keywords: Mathematical Oncology, Phenotypic Plasticity, Clonal Evolution, Tumour Heterogeneity

Genetic and epigenetic, as well as non-genetic, or phenotypic heterogeneity, within cell populations are hallmarks of tumour evolution. These hallmarks co-determine tumour aggressiveness, and drive clinical outcomes. Quantifying the mechanisms that lead to, and maintain, tumour heterogeneity are important in order to understand selection for therapy resistance, cancer metastasis, and tumour relapse. Recent advances, e.g. in single-cell sequencing and gene-expression experiments, have elucidated the roles of (a) genetic heterogeneity, i.e. clonal evolution, and of (b) phenotypic plasticity and Darwinian selection on these phenotypes. We can now better understand how genetically identical cells can alter their phenotypes in response to external signals. Recent attempts by mathematical and computational biologists have demonstrated how multiple modeling techniques can be used to better understand dynamic heterogeneity. This understanding then can identify better treatment regimens, and help define new therapeutic dosing strategies. These modeling techniques range from population-based dynamical models of co-evolutionary dynamics in cancer cell population to mechanism-based models for signaling networks.

Different modeling attempts can benefit a lot by their integration with one another and with different data formats. For example, population-level models focus on interconversions between the tumour-initiating subpopulation of Cancer Stem Cells (CSCs) and non-CSCs, and have been used to describe patients' treatment outcomes. On the other hand, spatial multiscale models of tumour growth have demonstrated how different therapies–such as inhibiting blood vessel growth–can induce and select for more aggressive cancer cells, thus driving multi-therapy resistance. Future modeling efforts should identify new multi-scale spatiotemporal models that can quantifying tumour heterogeneity and evolution. With this mini-symposium we seek to point out fruitful avenues for such future developments.

In resonance with the spirit of ECMTB 2018 as a flagship event for the Year of Mathematical Biology, this minisymposium focuses on bringing together leading experts, to discuss recent work and emerging trends in cancer heterogeneity evolution. We aim to strengthen the community of quantitative oncologists, synergistically drive a better understanding of genetic and non-genetic intra-tumour heterogeneity, and help to understand how interdisciplinary approaches can guide finding novel anti-cancer treatment strategies.

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MEASURING SINGLE CELL DIVISIONS IN HUMAN CANCERS FROM MULTI-REGION SEQUENCING DATA

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Keywords: Multi-Region Tumour Sequencing, Tumour Evolution.

Cancer is driven by complex evolutionary dynamics involving billions of cells. Increasing effort has been dedicated to sequence single tumour cells, but obtaining robust measurements remains challenging. Here we show that multi-region sequencing of bulk tumour samples contains quantitative information on single-cell divisions that is accessible via mathematical modelling. Using high-throughput data from 13 human cancers and evolutionary theory, we measured the *in vivo* per-cell mutation rate and per-cell survival rate in individual patient tumours from colon, lung and renal cancers. Mutation rates varied 30-fold between individuals, and survival rates varied between nearly-homeostatic (1/3–almost as much death as proliferation), to almost perfect doubling per generations (1.0), equating to tumour ages between 1 and 30 years. Our analysis measures *in vivo* the most fundamental properties of human cancer evolution at single-cell resolution.

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UNDERSTANDING THE ROBUSTNESS AND PLASTICITY OF GENE REGULATORY CIRCUITS

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Keywords: Gene Regulatory Circuits, Stochasticity in Gene Expression.

Stochasticity in gene expression influences the functions and dynamics of gene regulatory circuits. Intrinsic noises, such as those caused by transcriptional bursting and low copy number of molecules, are typically studied by stochastic analysis using Gillespie algorithm and Langevin simulation. Yet, the role of other extrinsic factors, such as the heterogeneity in microenvironment and cell-to-cell variability, is still elusive. To identify the effects of both intrinsic and extrinsic noise, we integrate stochastic analysis with our newly developed algorithm, named random circuit perturbation (RACIPE). Unlike conventional methods, RACIPE generates and analyzes an ensemble of random models with distinct kinetic parameters. We showed that the expression profiles of stable steady states from random models form robust clusters. We further proposed using a constant-noise-based method to capture the basins of attraction and an annealing-based method to identify the most stable states. From the tests on several synthetic and biological gene regulatory circuits, we found that high intrinsic noises, but not high parameter variations, merge states together. Our study sheds light on a novel mechanism of noise-induced hybrid states and provides new analytic tools to measure the robustness and plasticity of gene regulatory circuits.

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DYNAMICS OF NON-HODGKIN LYMPHOMA CAR-T CELL THERAPY

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Joint work with Gregory Kimmel (Moffitt) and Frederick L. Locke (Moffitt)

Keywords: Cancer Immunotherapy, Dynamical Systems.

Non-Hodgkin Lymphoma (NHL) is the most common hematologic malignancy in the United States with an estimated 72,000 new cases (4.3% of all cancer cases) and 20,000 deaths (3.4% of all cancer deaths) in 2017; the median 5-year survival rate is 71%. Despite the possibility of cure with front-line chemotherapy, patients that do not response or relapse and develop refractory disease and have a median overall survival of less than seven months. Chimeric antigen receptor (CAR) T-cell therapy for refractory NHL relies on expansion of engineered T- cells that specifically target tumor cells expressing CD19. Here we combine mathematical modeling with statistical data-analysis based on recent results of clinical studies of CAR T-cell dynamics in individual patients, to elucidate the key mechanisms that drive evolutionary dynamics of anti-CD19 CAR T-cell therapy. The success of therapy depends on inflammatory cytokines in the tumor microenvironment, as well as on specific properties of the heterogeneous CAR T-cell population. Relative abundance of CD 4 and CD 8 cells, as well as the dynamic proportion of effector cells, are key factors driving the duration to treatment response and the immediate tumor killing rate of this specific novel immunotherapy. This modeling framework does not only elucidate disease and treatment specific dynamical properties, but can also inform genetically engineered T-cell properties related to toxicity and T-cell homeostasis after perturbation.

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MATHEMATICAL MODELING OF CELL DYNAMICS AND OPTIMIZATION PROBLEMS IN CHRONIC MYELOID LEUKEMIA THERAPY

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Keywords: Mathematical model, Chronic myeloid leukemia, Dynamic system, Optimization problem.

In this talk we consider a mathematical model which describes the evolution of the normal and abnormal cell populations in myeloid leukemia, a cancer of the blood. This mathematical model shows us the transition process from the normal hematopoiesis to the chronic and accelerated-acute stages in myeloid leukemia [4]. A particular case is considered in the papers of Dingli, Michor [2], Cucuianu, Precup [1] and Parajdi [3]. Based on this mathematical model we introduce some optimization problems for the treatment of chronic myeloid leukemia (CML) [5]. The mathematical condition which correspond to the chronic phase is given by the relation $d < D < d/s$, where d and D represents the homeostatic amounts of normal and abnormal cell populations and s is the relative sensibility rate. The therapeutic scenarios are related to the main objective of diminishing the proportion y/x between abnormal and normal cells under a prescribed threshold, and are planned to minimize the total dose. Our theoretical results could serve as a basis for further pharmaceutical research and personalized treatment protocols.

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