Parallel Session

Cancer III

NEOADJUVANT TRADE-OFFS IN ER+ BREAST CANCER: A GAME THEORETIC APPROACH

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Keywords: Cancer, Evolutionary game theory, Combination therapy, Metastasis, Immunotherapy.

The preoperative endocrine prognostic index (PEPI score) is a prognostic indicator for relapse-free survival for estrogen-receptor-positive breast cancer patients. An upcoming clinical trial at the Moffitt Cancer Center for women with stage 2/3 ER+ tumors will combine an aromatase inhibitor (primarily anastrozole) with a checkpoint inhibitor against PD-L1 (durvalumab) with an endpoint of lowering the PEPI score.

However, the PEPI score is a fundamentally a static index, measured at the end of neoadjuvant therapy before surgery. We have developed a mathematical model to mimic the essential indicators of the PEPI score (status of lymph metastases, tumor size, proliferation rates, and hormone receptor status) in order to 1) identify successful combination therapies that minimize both tumor burden and metastatic potential; and 2) track the time-dependent trade-offs associated with the PEPI score using combinations of aromatase inhibitors and checkpoint inhibitors.

To accomplish this, two axes of (measurable) expression were identified: CCR7 and PD-L1, modelled as players in an evolutionary game, each with known correlations to metastatic potential and response to drug therapy. Evolutionary game theory is used to generate hypotheses, test the model platform, and aid with clinical intuition. The coupling of tumor ecology (competition of CCR7 and PD-L1 phenotypes) with a model of tumor population growth dynamics is able to highlight the inherent *time-dependent* trade-off between metastatic risk (and non-responsiveness of therapy due to phenotypic evolution) and tumor progression.

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Parallel Session

Cancer III

CANCER AS A DEFAULT OF EVOLUTIONARY COHERENCE BETWEEN TISSUES IN METAZOA

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Keywords: Cancer, Multicellularity, Evolution, Differentiation, Coherence.

My talk will be organised as questions with possible tracks to answer them.

•Cancer may be defined as a spatially *localised loss of coherence* between tissues in the same multicellular organism, 'spatially localised' meaning initially starting from a given organ in the body, but also possibly due to flaws in an individual's epigenetic landscape such as imperfect epigenetic control of differentiation genes. Do we agree on this?

•What does such coherence consist of? Some known biological pathways provide hints to answer this question; in particular the interferon way is likely to be involved.

•"The genes of cellular cooperation that evolved with multicellularity about a billion years ago are the same genes that malfunction in cancer." (*Davies and Lineweaver, 2011*): How can these genes be systematically investigated, looking for zones of fragility - that may depend on individuals - in the tinkering (*F. Jacob, 1977*) evolution is made of, tracking local defaults of coherence?

•What is the part of *lack of communication* (e.g., by gap junctions) occurring between cells of a given differentiated tissue in this lack of coherence, what intercellular signalling may be involved, and how is it dependent on local / general energetic / metabolic conditions?

•Some specific genes related to stress response have been identified as cold genes (*A. Wu et al., PNAS 2015*), i.e., with no variability, highly conserved throughout evolution to make a cell population able to resist destruction coming massive external insult (such as cytotoxic drugs at high doses) by launching distributed-phenotype stress response, and these cold genes seem to be overexpressed in cancer, leading to drug-induced drug resistance. *Bet hedging* of the drug resistance mechanisms launched by cold genes, related to *within-tissue heterogeneity*, seems to be specific of cancer. Is there not only lack of coherence between cell types, but also within the population of a same cell type (heterogeneity), in cancer?

•Whereas the Evolution of species contains in itself evolutionary branching, leading to isolated species, little communicating between them and allowing for nonconflicting coexistence, the evolutionary branching yielding about 200 different cell types in a spatially constrained human organism inevitably leads to communications between these cell types, that can be of competitive or mutualistic type, but all these cell types derive from the same initial cell. How do normally differentiated cells recognise other cells as of the same kin *and*

normally differentiated, i.e., what sort of self is involved in this friend-or-foe recognition and how does it call immunogenic response when such recognition returns negative?

•Related to this question of self, what parallelism can be established between the *development of multicellularity* in different species proceeding from the same origin and the *development of the immune system* in these different species?

•Finally, what mathematical models, aiming at providing rules for prediction and prevention of cancer, and relying on what biological - both genetic and epigenetic - substrate, should be developed to investigate coherence within and between cell populations in a multicellular organism?

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Parallel Session

Cancer III

HYPOXIA-ACTIVATED PRODRUGS AND RADIATION: AN *IN SILICO* INVESTIGATION TO STUDY THE SYNERGETIC EFFECTS OF BYSTANDER RESPONSES IN TUMOUR SPHEROIDS

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Keywords: Cancer, Multiscale Model, Hypoxia-Activated Prodrug, Radiation, Cellular Automaton.

Hypoxic cancer cells in solid tumours express reduced sensitivity to anticancer treatments such as radiotherapy and some chemotherapeutic drugs. Thus hypoxia has an adverse effect on treatment delivery and significantly impacts clinical outcome. Consequently, multiple strategies to combat hypoxia have been explored. Hypoxia-Activated Prodrugs (HAPs) present a means to not only combat, but also exploit, hypoxia. HAPs are bioreductive prodrugs that reduce, and thus convert, to active cytotoxins upon reaching hypoxic regions. These drugs act as trojan horses, being harmless until they are converted in target areas.

Despite being conceptually promising, clinical trials of HAPs have produced mixed results. In order to closely study the appropriate conditions and optimal delivery of multimodality treatment regimes that involve HAPs, we have developed a three-dimensional *in silico* framework. Our framework is based on a multiscale mathematical model, specifically a cellular automaton incorporating intracellular, extracellular and intercellular dynamics. Our results indicate that the successfulness of HAP-Radiation combination treatments depend on multiple factors including tumour oxygenation status and synergistic bystander responses in cells induced by both HAPs and radiotherapy.

MATHEMATICAL MODEL DESCRIBING LOW GRADE GLIOMAS AND ITS REACTION TO CHEMOTHERAPY

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Keywords: Tumour, Low grade glioma, Ordinary differential equation, Mathematical model.

We consider a model of low grade gliomas and its response to the chemotherapy treatment. The presented model is a modification of the model proposed in [1]. The model presented in [1] fits well to medical data. In that model tumours growth is governed by a logistic term. However, there are biological evidence, that shows that tumour proliferation does not stop but rather the proliferation process is balanced by death. This is important in this modelling approach as it is assumed that damaged tumour cells die when they try to divide. Moreover, one of parameters of the model presented in [1], that reflects the number of division tries of damaged tumour cell before its death, was estimated to be smaller than one. We propose a model that overcame both issues. We prove mathematical properties of the model, global stability of tumour-free equilibrium (under suitable conditions). We also discuss the stability of the positive equilibrium (if it exists).

In the second part of our work we show that the model fits well to the medical data, we investigate the stability of the fitting procedure. Finally, we perform sensitivity analysis of the model identifying parameters that have the largest influence on the model outputs.

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Parallel Session

Cancer III

A MULTISCALE MODEL FOR PREDICTING THE RESPONSE OF 3D SPHEROIDS TO COMBINATIONS OF RADIATION AND HYPERTHERMIA

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Keywords: Multiscale, Hybrid cellular automaton, Radiation, Hyperthermia, Tumour spheroid.

Thermo-radiosensitisation offers great potential for the successful treatment of radio-resistant tumours such as those having hypoxic subregions. However, the influence of tumour response heterogeneity, due to intrinsic, or micro-environmental factors, on treatment outcome should also be considered for treatment optimization. 3D tumour spheroids offer the possibility of studying these effects in a physiologically relevant environment *in vitro*. We present an experimentally calibrated high performance systems oncology simulation framework to study their response to radiation (RT), hyperthermia (HT), and combinations of these.

Our simulation framework developed a hybrid cellular automaton model for RT and HT treatments[1] which has been extended to simulate 3D tumour spheroids. This included modelling of 3D geometries, oxygen diffusion, treatment specific cell death mechanisms and cell clearance. The framework was calibrated by modelling selected (un-) treated spheroids while accounting for the influence of hypoxia induced necrosis at their core. This was achieved by iteratively solving the oxygen reaction diffusion equation (finite differences) followed by a probability driven cellular response cascade. The calibrated framework was then validated against experimental data for additional treatments.

For experimental comparison, human colorectal carcinoma (HCT116) 3D cultures were exposed to RT (0-20Gy), HT (0-240CEM), and combinations thereof, in 3D cultures. Spheroid growth was monitored for different sized spheroids (diameter on treatment day 250 μm or 500 μm) for 25 days using a cytometer. Immunohistochemical staining of spheroid sections was performed to analyse viable (KI67), hypoxic (pimonidazole), and necrotic (haematoxylin and eosin) subregions.

A high performance implementation of the model allowed simulation of large (10^5–10^7 cells) cell populations within minutes. The results of the computational simulations were matched with selected experimental growth curves, and distributions of simulated hypoxic cells were

comparable to pimonidazol staining in histological spheroid sections. Within the uncertainty range of the parameters used, simulated oxygen distributions also were able to reproduce results of an experimentally validated analytical oxygenation model [2]. It was found to be essential to consider the influence of key underlying cellular response mechanism such as necrosis, delayed mitotic catastrophe, and cellular senescence because modelling only immediate cell death greatly overestimated spheroid shrinkage. The introduction of a clearance rate for dead cells (delaying their detachment) also better captured the dynamic growth response.

The proposed framework provides an important step towards *in silico* modelling of combination treatments of radiation and hyperthermia *in vivo*. This was achieved by modelling treatment response under physiological conditions and accounting for effects of differences in oxygenation.

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Parallel Session

Cancer III

AN INTEGRO-DIFFERENTIAL EQUATIONS MODEL TO STUDY THE DEVELOPMENT OF MULTIDRUG RESISTANCE IN CANCER

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Keywords: Cancer, Multidrug Resistance, Partial Differential Equations.

Resistance to chemotherapeutic agents is one of the major obstancles during cancer treatment. One of the most important mechanisms in cancer resistance is the over expression of membrane efflux transporters, such as the P-glycoprotein (P-gp). These transporters are capable of releasing a broad panel of chemotherapeutic agents thus contributing to multidrug resistance. Malignant transformation and the presence of cytotoxic agents are two mechanisms that can drive the overexpression of these proteins. Are these the only two processes that can confer a resistant phenotype in cancer cells?

In this talk the extragenetic transmission of P-gp, mediated by microvesicles, from cells overexpressing this protein to non-expressing cells is studied and compared to the other two processes. For that purpose, a system of hyperbolic integro-differential equations is presented. The **selection** of the more resistant phenotypes, the **induction** of resistance due to the presence of cytotoxic agents, and the **transfer** of efflux transporters are the three processes included in the model.

By considering two populations, sensitive and resistant cells, the model captures the changes in their P-gp distribution functions in different scenarios. The model is validated with a large number of *in vitro* experiments using a lung carcinoma cell line and the relevance of each of the processes is analyzed and quantified.

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