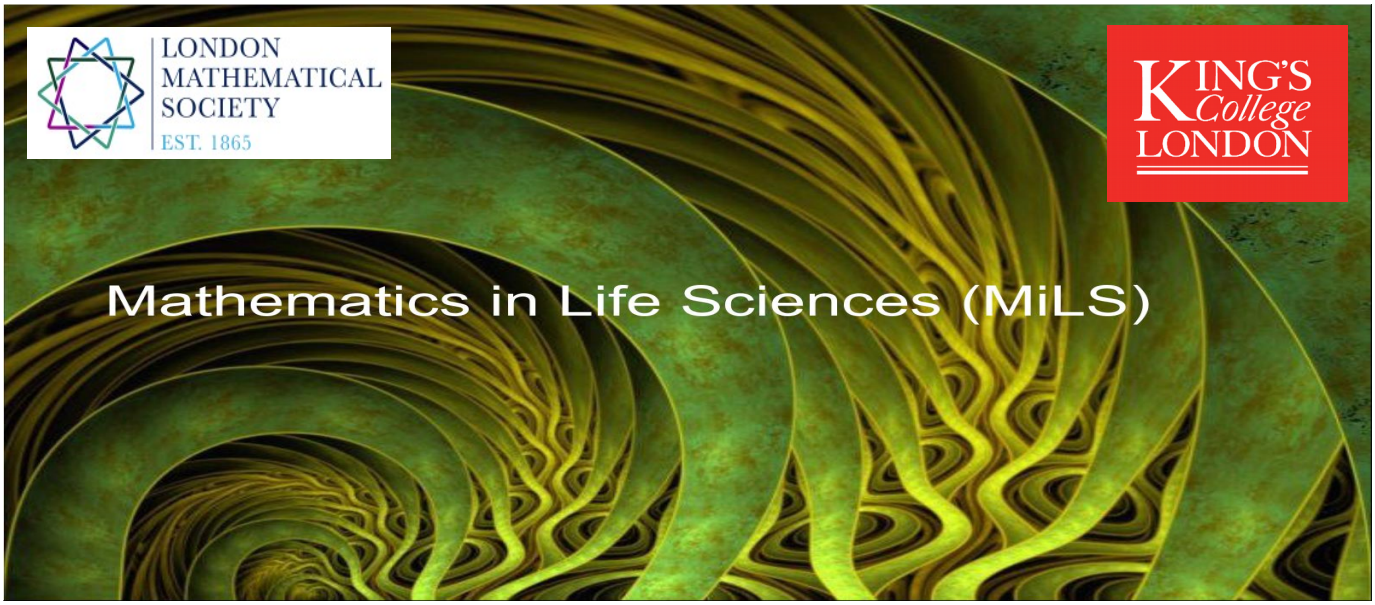


Modelling Challenges in Cancer and Immunology

One-day meeting of the LMS MiLS

KCL 28th June 2019

Schedule

Strand Building, Room S0.12 **--** *Talks and morning coffee*

King's Building, Council Room (K2.29) **--** *Lunch and afternoon coffee*

10:30-10:50 Arrival and coffee

10:50-11:50 Prof. Tim Elliott (Southampton) - *Keynote Talk 1*

11:50-12:50 Prof. Helen Byrne (Oxford) - *Keynote Talk 2*

12:50-14:20 Lunch & Posters Session

14:20-15:00 Prof. Benny Chain (UCL) – *Research Talk 1*

15:00-15:40 Dr. Sophia Karagiannis (KCL) – *Research Talk 2*

15:40-16:10 Joseph Egan (Southampton) – *Research Talk 3*

16:10-16:30 Close and coffee

Abstracts

TALKS

Tim Elliott (Southampton) – *Keynote Talk 1*

Title: Peptide selection in the MHC I antigen processing pathway and its relevance to cancer

Abstract: Antigen processing and presentation is the key pathway underpinning the natural or artificial induction of anti-tumour cytotoxic T lymphocytes (CTL) because it generates the ligands that activate them. These are short tumour-derived peptides presented by polymorphic MHC class I molecules. They are selected by a process of peptide editing involving several intracellular cofactors, some of which are themselves polymorphic. We have captured these features in computational models which can be used as tools to investigate how peptide editing influences the repertoire of tumour derived peptides that are displayed by MHC I and how they dictate the specificity of CD8+ T cell responses to tumours.

Helen Byrne (Oxford) – *Keynote Talk 2*

Title: Approaches to modelling tumour-immune interactions

Abstract: While the presence of immune cells within solid tumours was initially viewed positively, as the host fighting to rid itself of a foreign body, we now know that the tumour can manipulate immune cells so that they promote, rather than inhibit, tumour growth. Immunotherapy aims to correct for this by boosting and/or restoring the normal function of the immune system. Immunotherapy has delivered some extremely promising results. However the complexity of the tumour-immune interactions means that it can be difficult to understand why one patient responds well to immunotherapy while another does not. In this talk, we will show how mathematical modelling can contribute to resolving this issue and present recent results which illustrate the complementary insight that different modelling approaches can deliver.

Benny Chain (UCL**) –** *Research Talk 1*

Title**:** Neoantigen evolution shapes the cell receptor repertoire landscape in lung cancer

Abstract**:** Somatic mutations together with immunoediting drive extensive heterogeneity within primary lung tumors. We examine tumor heterogeneity through the lens of the T cell receptor repertoire, a key determinant of the tumor/host interaction. We evaluate TCR expansion and diversity across multi-region non-small cell lung cancer samples, non-tumor adjacent lung tissue and peripheral blood, identifying a set of TCR sequences selectively expanded in tumor tissue. The number of expanded TCRs varies both within and between tumors, and correlates with the number of non-synonymous mutations within each tumor region. The expanded TCRs can be sub-divided into ubiquitous TCRs, found in every tumor region and regional TCRs, found in some regions but not others. The number of ubiquitous and regional TCRs correlates with the number of ubiquitous and regional non-synonymous mutations respectively. Expanded TCRs form part of clusters of TCRs of similar sequence, and with similar spatial distributions, suggestive of a spatially

constrained antigen driven process. Expanded ubiquitous TCRs are a major fraction of PD1+CD57-CD8+ T cells bearing a classical tissue-resident and dysfunctional phenotype. Longitudinal analysis demonstrated that these ubiquitous TCRs are preferentially detected in the blood at the time of tumor resection, but not at subsequent follow-up. These findings highlight a non-invasive method to identify and track relevant tumor reactive TCRs for use in adoptive T cell immunotherapy.

Sophia Karagiannis (KCL) – *Research Talk 2*

Title: B cells and antibody responses in solid tumours: immune escape mechanisms and opportunities for translating novel antibody isotypes for cancer therapy

Abstract: The nature of immune responses in patients with solid tumours including the nature and roles of B cells and their expressed antibodies are largely unexplored. Evidence generated in our group and colleagues at King's through functional, cell-based and genomic approaches points to the presence of an active B cell immune surveillance and a mature memory B cell compartment with distinct immunoglobulin isotype-biased profiles in cutaneous melanoma and breast cancer. Inflammatory Th2-biased conditions featuring production of mediators such as IL-10, IL-4 and VEGF can promote B cell class switching to immunologically-inert antibody isotypes represents a mechanism by which tumours may divert antibody class/subclass expression and reduce the potency of immune responses. Dissecting the humoral response and alternatively-activated immunoglobulin profiles we are working to uncover new insights into immunosuppressive forces in the tumour microenvironment and to identify prognostic markers for patient stratification. Opportunities also arise for the design of novel therapeutic interventions, including monoclonal antibodies with enhanced effector functions and less prone to tumour-induced immune blockade.

Joseph Egan (Southampton) - *Research Talk 3*

Title: The Incoherent Feed-forward Loop: a mechanism by which T cells achieve biochemical memory?

Abstract: T cells of the immune system have surface receptors (TCRs) that can bind to antigens (hereafter referred to as p-MHC ligands) on the surface of antigen-presenting cells (APCs) potentially leading to activation of the T cell. A recently published mathematical model has identified that T cell activation is best explained by p-MHC-TCR bound complexes ultimately triggering a downstream signalling pathway which takes the form of an incoherent feed-forward loop (IFL). Briefly, the IFL consists of a direct inhibiting arm and an indirect activating arm which combine to provide an overall level of T cell activation. In the present study, we are investigating why a T cell might have evolved such biological circuitry. To this aim, we have extended the previously published analysis of the equilibrium (or steady state) of the model by considering the time-varying solution of a simplified version of the model. Our analysis indicates that when a T cell separates from an APC the IFL can allow the level of activation to pulse and then decay very slowly, particularly in the context of higher numbers of p-MHC-TCR bound complexes. Therefore, T cells may have evolved an IFL signalling pathway to act as a form of "memory" during periods in which the T cell and APC separate. For example, the IFL provides a mechanism by which T cells can integrate signals from short-lived "kinapses" during the priming stage of T cell activation. Gaining a better understanding of the mechanisms underpinning T cell activation is key to the development of improved immunotherapies.

POSTERS

1. Agent-based Modelling of Collective Algorithms Implementable by T Cells

Authors: Yamuna Krishnamurthy, Chris Watkins (Royal Holloway UoL)

Abstract: We are developing a large-scale agent-based modelling system in order to study possible collective computations in the adaptive immune system. This modeller is fast (implemented in Julia) and capable of feasibly modelling millions of cells with continuous-valued multivariate internal state and arbitrary programmable interactions between them. We have implemented an agent-based version of the model of peripheral tolerance introduced in "Immune tolerance maintained by cooperative interactions between T cells and antigen presenting cells shapes a diverse TCR repertoire" by Best K, Chain B, and Watkins C in Frontiers in Immunology, 07 August 2015. In this theory of peripheral tolerance, a collective algorithm autocalibrates the abundances of T cell clones to auto-calibrate the level of autoimmune response in the periphery. The collective algorithm used is a multiplicative update method of convex optimisation studied in computer science, which could be implemented in multiple biologically possible ways by the immune system, in order to co-adjust different T cell clone sizes to ensure a uniform level of response to self in the periphery. The effects of adjusting T cell clone sizes using this algorithm are shown in simulation. We also present a discussion of what classes of distributed algorithms could be implemented by the immune system, given the known constraints on communication between T cells, and that T cells cannot identify each other's receptor specificity, which is a strong constraint on what algorithms could be used.

2. Chronotherapy for Cancer: Using Mathematical Modelling to Get the Timing Right

Authors: Yansong Zhao, Helen Byrne (Oxford)

Abstract: Many species exhibit rhythmic variations, arguably the most common of which is the circadian rhythm. Clinical Oncologists have developed cancer chronotherapy, which captures the idea of appropriately coordinating the delivery of chemotherapy with a patient's circadian rhythm. We have developed a simple 2-compartment ODE model for the cell cycle of healthy cells and cancer cells, and use it to model the effects of circadian entrainment, competition for space and nutrients, and chemotherapy. The numerical simulations are then generated in order to predict the optimal time for drug delivery under different assumptions on the circadian entrainment and competition. We conclude the research with a remark that the 2-compartment ODE model is a reasonable simplification of the traditional 4-compartment model for the purpose of this research.

3. Profiling the normal colonic mucosa in synchronous colorectal cancer by Imaging Mass Cytometry

Authors: Michele Bortolomeazzi, Lucia Montorsi, Jo Spencer, Francesca Ciccarelli (KCL and The Francis Crick Institute)

Abstract: Synchronous colorectal cancers (syCRC) are defined as multiple independent primary tumours diagnosed less than six months apart. We have previously shown that both familial and sporadic syCRC patients have an increased frequency of germline alterations in immune-related pathways compared to solitary colorectal cancer (soCRC) patients. Interestingly, syCRC patients have also more T cells in the normal colonic mucosa, suggesting that they could be affected by a tumorigenic pro-inflammatory microenvironment. To enable investigation of the immune landscape in normal colonic mucosa from 10 syCRC and 6 soCRC patients we performed high-dimensional phenotyping by Imaging Mass Cytometry (IMC). First, we developed a panel of 26 antibodies allowing the quantification and characterisation of the main immune cell populations and tissue structures of the colonic mucosa, as well as its vascularisation and cell proliferation. From each sample we analysed an area of tissue including all the structures forming the colonic mucosa and we divided it into two regions of interest: epithelium and lamina propria. We then performed cell-segmentation of the lamina propria using DNA staining to identify nuclei and membrane

markers to define cell borders. Finally, we grouped cells into different populations, according to the intensity of immune markers in each cell, with unsupervised clustering. This cell-level high-dimensional analysis allowed the identification of 7 different immune cell populations: macrophages, dendritic cells, CD4, CD8 and regulatory T cells, B cells and plasma cells. CD16 intensity divided macrophages into two subpopulations, while IgA plasma cells formed two distinct groups according to CD45RA levels. Additionally, we identified two groups of non-immune cells characterised respectively by high and low PDL1 levels. Finally, we complemented this cell-level high-dimensional approach with a pixel-level single-marker analysis to examine different tissue properties of the mucosa. We examined cell proliferation in epithelial crypts, vascularisation of the lamina propria, and secreted IgA and IgM in the tissue. We will further leverage the spatial information provided by IMC by performing a neighbourhood analysis to characterise cell-types preferentially interacting with each other. Thus, IMC allowed us to combine the high-dimensional phenotyping of multiple cell populations with spatial and structural information. This consequently enabled a comprehensive characterisation of both the immune-cell populations and tissue-level properties of the colonic mucosa.

4. The immune response to cancer: a dynamical model of the interplay between CD4, CD8 and MHCI

Authors: Christian Hurry (KCL)

Abstract: The CD4/CD8 ratio has been shown to correlate with prognosis in cancer. This ratio is approximately equal to the ratio of helper and cytotoxic T cells which are known agents in the immune response to cancer. At the same time, the population of cancer cells is dynamic and can mutate to evade the immune response. Loss of MHC-I is a major contributor to this evasion. We construct a dynamical system which shows the helper/cytotoxic ratio and the expression of MHC-I to be the dominant factors in a working immune response against cancer. T-cells are treated as a chain of spins interacting with the immune environment, and non-equilibrium statistical mechanics approaches are used to construct a closed system of ODEs.

5. Statistical mechanics of clonal expansion in lymphocyte networks

Authors: Alexander Mozeika, Anthony CC Coolen (KCL)

Abstract: TBC We use statistical mechanical techniques to model the adaptive immune system, represented by lymphocyte networks in which B cells interact with T cells and antigen. We assume that B- and T-clones evolve in different thermal noise environments and on different timescales, and derive stationary distributions and study expansion of B clones for the case where these timescales are adiabatically separated. We compute characteristics of B-clone sizes, such as average concentrations, in parameter regimes where T-clone sizes are modelled as binary variables. This analysis is independent of the network topology, and its results are qualitatively consistent with experimental observations. References: A. Mozeika, A.C.C. Coolen. Journal of Physics A: Mathematical and Theoretical, 50 (3): 035602, 2016

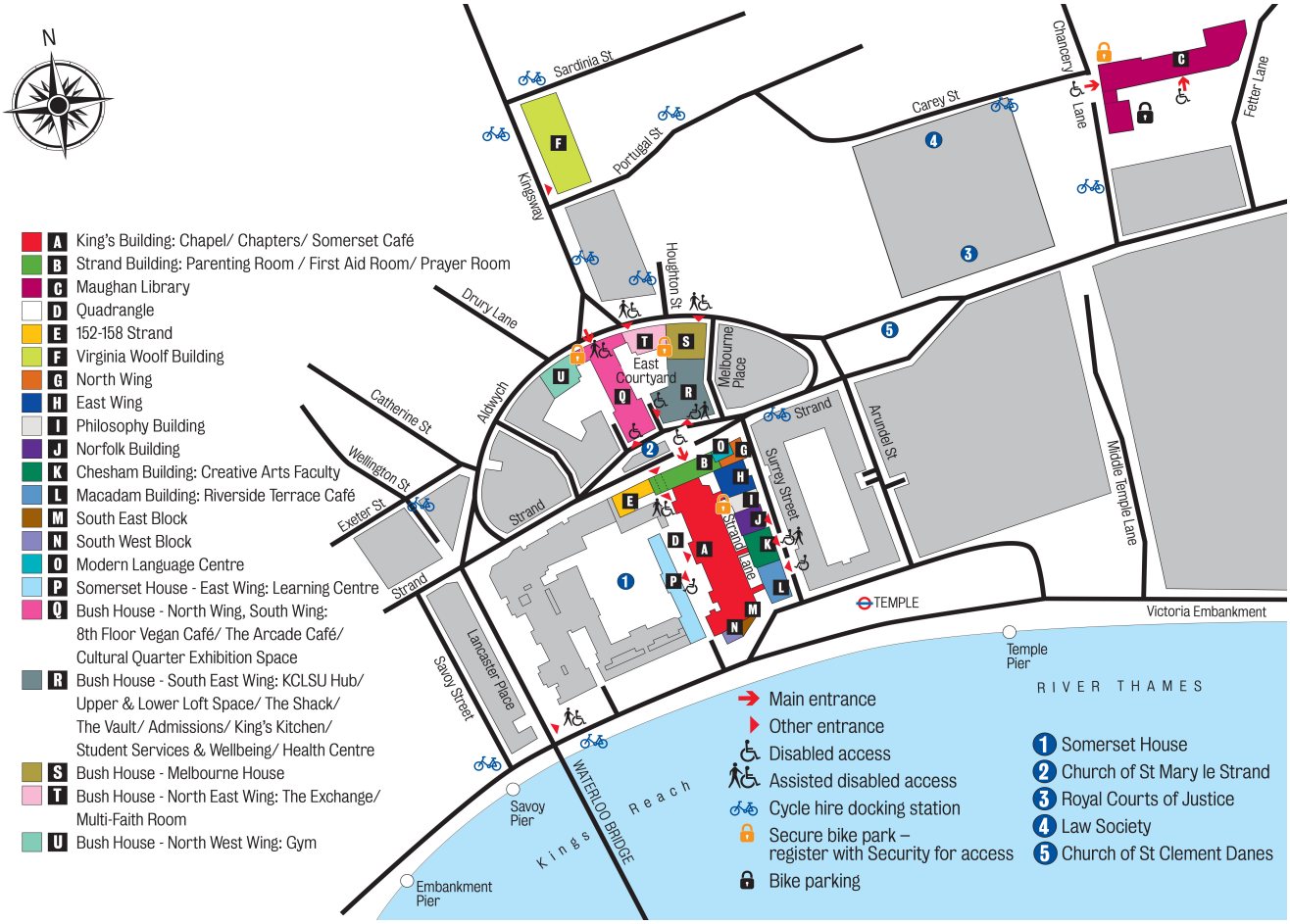
6. Circulating tumour cells detected prior to tumour resection predict relapse and seed future metastasis

Author: Simon Pearce

Abstract: In this study we show that the number of circulating tumour cells (CTCs) detected prior to surgery is predictive of patient outcome in non-small cell lung cancer. We undertook genomic profiling of single collected cells, finding that these CTCs show inter- and intra-patient heterogeneity. In a case study, we find that CTCs collected at surgery reveal mutations that were not detected in the primary tumour, but were shared with the metastasis that arose 10 months later, suggesting that these CTCs represented a minor subclone disseminating early that was responsible for disease relapse.

Room S0.12 is located on the Ground floor of Strand Building. This is accessed from the Strand, London WC2R 2LS (block B on the map).

A light refreshment and the afternoon coffee will be served in the Council Room K2.29, located on the Second floor of King's Building (block A, on the map). A cafeteria and a canteen can be found down the same corridor.



Organizers: Alessia Annibale (King's College London), Daniele Avitabile (University of Nottingham) and Sarah Waters (University of Oxford).

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