THE PROTECTIVENESS OF HLA ALLELES AGAINST INFECTION IN THE PRESENCE OF MULTIPLE PATHOGEN STRAINS

CONNOR WHITE

C.White.3@warwick.ac.uk

ESPRC & MRC Centre for Doctoral Training in Mathematics for Real-World Systems, University of Warwick

Joint work with Bridget Penman (Supervisor) and Lorenzo Pellis (Supervisor).

Keywords: Infectious Disease, Frequency Dependence, Multi-Strain.

Human Leukocyte Antigen (HLA) genes determine an individual’s response to infection. The odds ratios for infection in the presence/absence of particular HLA genes are commonly used to measure whether these genes are protective. Here we present an epidemiological model which incorporates the existence of a variety of host HLA genotypes, as well as the presence of multiple pathogen strains, to which individuals with different HLA genotypes will respond differently. We explore the circumstances under which individuals carrying particular HLA alleles/genotypes are associated with lower odds of being infected than the rest of the population. We show that the success of a pathogen strain is dependent on the genotypic structure of the host population and that the strain structure of the pathogen population determines how well an allele protects a host from infection. We also show that, counter-intuitively, increasing the rate at which an HLA allele causes a host to mount a memory immune response against a particular pathogen strain, restricts the set of circumstances where that allele is protective against infection in general.
EXPLORING THE DYNAMICS OF AN ENTERPATHOGENIC ESCHERICHIA COLI INFECTION VIA A COMPUTATIONAL MODEL

JAMES PRESTON

james.preston@nottingham.ac.uk

University of Nottingham

Joint work with Reuben O’Dea and Bindi Brook (Mathematical Sciences, University of Nottingham) and Robin Delahay (Centre for Biomolecular Sciences, University of Nottingham).

Keywords: Hybrid model, Bacteria, EPEC, Immune response, Antibiotic.

Enteropathogenic Escherichia Coli (EPEC) is a virulent species of bacteria that causes severe diarrhoea, and can be fatal in countries with inadequate healthcare. EPEC’s virulence comes from its ability to bind firmly to host intestinal cells and inject effector proteins into them via a type 3 secretion system (T3SS). These proteins inhibit the host’s immune response by shutting down the host’s pro-inflammatory signalling pathways, by regulating host cell survival and by inhibiting host leukocytes’ ability to phagocytose bacteria. The fact that EPEC shares its secretion mechanisms with many other species of bacteria (eg Salmonella) makes it key to study, with the aim of finding novel antibiotic treatments that eradicate bacterial infections that behave in this way.

In this research, we develop a computational model to explore the dynamics between EPEC and the host’s immune system both spatially and temporally. The resulting hybrid model couples a volume-excluding agent-based representation of bacterial and leukocyte behaviour, with a continuum description of the inflammatory response. In particular, we account for: i) stochastic subcellular Gene Regulatory Networks that govern bacterial replication and effector protein production and action of a generic aminoglycoside (antibiotic); ii) production of inflammatory mediators in response to infection (via a reaction-diffusion PDE); ii) recruitment of leukocytes to the infection site in response to inflammatory status via a chemotactically-biased random walk.

The infection dynamics are explored in detail via in silico experiments, to determine the key EPEC virulence mechanisms, and to explore antibiotic strategies. Our results indicate that EPEC’s ability to shut down pro-inflammatory signalling is its most effective virulence mechanism, followed by its ability to inhibit phagocytosis. Integration of collaborators’ transcriptomic data (from experimental work undertaken in the Centre for Biomolecular Sciences, University of Nottingham) within this model will provide new insight into infection dynamics, and to new treatment approaches.
MODEL-DRIVEN EXPERIMENTS INDUCE ELIMINATION OF STAPHYLOCOCCUS AUREUS CHRONIC INFECTION

LITO A. PAPAXENOPOLOU
lito.papaxenopoulou@helmholtz-hzi.de

Department of Systems Immunology and Braunschweig Integrated Centre of Systems Biology, Helmholtz Centre for Infection Research, Rebenring 56, 38106 Braunschweig, Germany

Joint work with Gang Zhao (Department of Systems Immunology and Braunschweig Integrated Centre of Systems Biology, Helmholtz Centre for Infection Research, Braunschweig, Germany), Sahamoddin Khailaie (Department of Systems Immunology and Braunschweig Integrated Centre of Systems Biology, Helmholtz Centre for Infection Research, Braunschweig, Germany), Eva Medina (Department of Infection Immunology, Helmholtz Centre for Infection Research, Braunschweig, Germany), Haralampos Hatzikirou (Department of Systems Immunology and Braunschweig Integrated Centre of Systems Biology, Helmholtz Centre for Infection Research, Braunschweig, Germany) and Michael Meyer-Hermann (Department of Systems Immunology and Braunschweig Integrated Centre of Systems Biology, Helmholtz Centre for Infection Research, Braunschweig, Germany and Institute for Biochemistry, Biotechnology and Bioinformatics, Technische Universität Braunschweig, Braunschweig, Germany).

Keywords: Staphylococcus aureus, Chronic infection, Myeloid Derived Suppressor Cells (MDSC), Clearance, Mathematical model.

Staphylococcus aureus is a hazardous bacterium, which is responsible for nosocomial- and community-acquired infections globally. It is notorious for its multidrug resistance, which leads to recurrent or chronic infections, and even life-threatening diseases. In chronic infections, the presence of a population of cells that suppress the function of T cells helps the persistence of the bacterium. These cells are known as Myeloid Derived Suppressor Cells (MDSC) and they consist of heterogeneous groups of immature myeloid cells. In this study, our mathematical model sheds light onto whether the expansion of the MDSC during chronic S. aureus infection takes place in the site of infection or systemically. We conclude that the origin of the proliferation is predominantly systemic, and our conclusion is validated by experimental data. Further analysis of the model suggests perturbation approaches to destabilize such chronic infection equilibria in the system, which could induce clearance. Experiments following up these mathematical predictions were conducted and experimental results confirmed the model-driven suggestions revealing MDSC reduction, recover of T cell function and complete clearance from S. aureus.

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INVESTIGATING VIREMIA REBOUNDS USING A PRSS DATA-SUPPORTED MODEL OF IMMUNE RESPONSE

Suzanne Touzeau
suzanne.touzeau@inra.fr
ISA, INRA, CNRS, Université Côte d’Azur, France & BIOCORE, Inria, INRA, CNRS, UPMC Univ Paris 06, Université Côte d’Azur, France
Joint work with Natacha Go (Ifremer, France), Catherine Belloc (Oniris, France) and Andrea Doeschl-Wilson (The Roslin Institute, UK).

Keywords: Within-host dynamics, Optimisation, Viremia rebound, Immune competence, Porcine Respiratory and Reproductive Syndrome (PRRS).

Viremia rebound is a common but undesirable phenomenon for various diseases, especially for the Porcine Respiratory and Reproductive Syndrome (PRRS), a major concern for the swine industry. What causes some individuals to experience viremia rebound while others manage to steadily clear the virus has however been subject to much speculation. Hypotheses are the emergence of viral escape mutants, re-infection and differences in immune competence.

To test this last hypothesis, we developed a mathematical model describing the within-host immune response to PRRS infection. We included the major mechanisms found to influence PRRS infection, as well as their regulations at the between-cell scale. We developed a rigorous ABC-like optimisation method to fit our model to an extensive set of experimental data, consisting of non-rebounder and rebounder viremia profiles. We then compared, between both profiles, the estimated parameter values, the resulting immune dynamics and the efficacy of the underlying immune mechanisms.

Confronted to experimental data, our model successfully captured the between-host variations observed in viremia data, including rebounds. Moreover, we found that rebound was promoted by high apoptosis, high cell infection and low cytolysis by cytotoxic lymphocytes, while increasing neutralisation was very efficient to prevent rebounds. These results show that viremia rebound can occur as a result of differences in the immune competence alone and offers, for the first time, insights into potential causative immune mechanisms generating rebound.

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CONCENTRATION OF T CELLS AND ANTIGENIC STIMULATION

BRUNO M. P. M. OLIVEIRA
bmpmo@fcna.up.pt
FCNA - UPorto and LIAAD - INESC TEC, Portugal

Joint work with Yusuf A. A. (FC - UPorto and LIAAD - INESC TEC, Portugal), Nigel J. Burroughs (Warwick Systems Biology, UK) and Alberto A. Pinto (FC - UPorto and LIAAD - INESC TEC, Portugal).

Keywords: T cells, Tregs, Antigenic stimulation, Dynamical Systems, Immunity.

We study an ODE system proposed by Burroughs et al. [1] that models immune responses by CD4⁺ T cells, with the presence of Regulatory T cells (Tregs). Following the model by Pinto et al. [2] and by Burroughs et al. [3], we assume that the secreting T cells have a lower death rate than the non secreting T cells and that the active Tregs also have a lower death rate than the inactive Tregs. Improving the results in Oliveira et al. [4], we present explicit formulas that give the relation at equilibria between the concentration of T cells, the concentration of Tregs and the antigenic stimulation of T cells. For some parameter values, we found a hysteresis, characterized by a region of bistability, with two stable equilibria and one unstable equilibrium, bounded by two thresholds of antigenic stimulation of T cells. At some parameter values, we observe an unfold of the hysteresis. Moreover, we consider a model with a linear tuning between the antigenic stimulation of T cells and the antigenic stimulation of Tregs. For this model, we also present explicit formulas for the relation at equilibria between the concentration of T cells, the concentration of Tregs and the antigenic stimulation of T cells. In this model, the hysteresis is also present. Furthermore, for some parameter values, we observe the appearance of an isolated region with equilibria, an isola, and for other values of the parameters, we observe a transcric bifurcation. Acknowledgements: Project Dynamics, optimization and modelling PTDC/ MAT-NAN/ 6890/ 2014. and project POCI-01-0145-FEDER-006961, by FCT - Fundação para a Ciência e a Tecnologia, and by the ERDF - European Regional Development Fund through the COMPETE 2020 Programme.

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