In-host Modelling of COVID-19
Modélisation chez l'hôte du COVID-19
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MORGAN CRAIG, Sainte-Justine University Hospital Research Centre/Université de Montréal
Quantitative approaches to understanding immunological heterogeneity in COVID-19

In COVID-19, dysregulated inflammatory responses accompanied by lymphopenia are characteristic of severe disease. Nearly two years into the pandemic, much remains unknown about the mechanisms of immunopathology in patients with COVID-19, including what controls the diversity of responses to SARS-CoV-2 infection. In combination with clinical and experimental efforts, we have deployed a variety of mathematical and computational immunology approaches to help untangle complicated longitudinal immunological data, and to generate new hypotheses about factors influencing disease severity and dynamics.

To begin to answer fundamental questions about immunopathology and heterogeneity in COVID-19, we developed a mechanistic mathematical model of the immunological response to SARS-CoV-2 infection that includes several innate and adaptive immune cell populations and signalling pathways. By expanding a virtual patient cohort, we identified divergent monocyte-to-macrophage differentiation rates between virtual patients with either mild or severe COVID-19. Further, our results suggest that maximum IL-6 concentrations may act as a biomarker for CD8+ T cell depletion. In the same virtual patient cohort, we also studied how viral variants influence immunopathology by merging within-host SARS-CoV-2 evolutionary data and our cohort of realistic virtual patients. We predicted the combined effects of spike protein and interferon-evading mutations on COVID-19 severity, and our results suggest that an individual's immune response and their potential propensity for severe COVID-19 are the key factors distinguishing COVID-19 disease courses and outcomes. Our approaches provide a quantitative basis for exploring the drivers of immunopathology in COVID-19, and a framework for the continued study of heterogeneity during SARS-CoV-2 and other viral infections.

ASHISH GOYAL,

THOMAS HILLEN, University of Alberta
Personalized virus-load curves for acute viral infections

We introduce an explicit function that describes virus-load curves on a patient-specific level. This function is based on simple and intuitive model parameters. We validate our model on data from mice influenza A, human rhinovirus data, human influenza A data, and monkey and human SARS-CoV-2 data. We find wide distributions for the model parameters, reflecting large variability in the disease outcomes between individuals. Further, we compare the virus load function to the commonly used ODE model of Baccam, Smith and others. Our explicit formula gives an alternative way to estimate exponential growth and decay rates. The virus-load function offers a new way to analyse patient specific virus load data. (joint work with C. Contreras and J. Newby)

CHAPIN KOROSEC, York University
Long-term durability of immune responses to the BNT162b2 and mRNA-1273 vaccines based on dosage, age and sex

The current publicly deployed lipid nanoparticle (LNP) base-modified mRNA vaccines, mRNA-1273 (Moderna) and BNT162b2 (Pfizer), are our current front-line therapeutic defence against variants of concern (VOC). Emerging data has shown that third booster dose within one year of second dose are necessary to mount an effective protection against VOC; however, the optimal timeline is not clear. In this talk I will introduce our novel within-host mathematical model for the LNP-formulated mRNA vaccines. We fit our model to 22 clinical humoral and cytokine BNT162b2 and mRNA-1273 data sets and find robust estimates

for long-term within-host IgG humoral loss and inflammatory cytokine response [1]. We find that two doses of either Moderna or Pfizer leads a 99% loss of humoral immunity relative to peak immunity by eight months following the second dose. We then correlate humoral percent loss with time-dependent efficacy studies. The model-predicted inflammatory cytokine, CD8+ T-, CD4+ T-, and plasma B- cell responses levels also show significant drops from peak value over the same timeframe. Notably, eight months following the second dose was the original timeline by the U.S. Centers for Disease Control and Prevention for the third booster shot, which was later altered to 6 months post second dose; our model results agree with this proposed third-dose timeline.
(Ref [1]: C.S. Korosec et al. medRxiv 2021.10.13.21264957; doi: https://doi.org/10.1101/2021.10.13.21264957)

JAMES OOI, National Research Council Canada
Mathematical modelling of COVID-19 vaccine-induced immune response

At the onset of the COVID-19 pandemic, several vaccine candidates were approved for emergency use guided by clinical trial data performed within a limited study time frame. The vaccine candidates include adenovirus vector, mRNA and protein subunit vaccine are being administered to mitigate the effects of the pandemic. Due to the limited study time frame of the clinical trials, there exist gaps in understanding various aspects of these vaccines, including but not limited to immunogenicity beyond the study time frame, varying doses, age, sex and effects of adjuvants. By applying published clinical trial data, we developed within-host mathematical models for various vaccine types that are currently in use or in final stages of clinical trials in Canada and analyse its associated humoral and cellular adaptive immune response. The vaccine-induced immune response investigated includes the antibodies, T helper cells, cytokines and cytotoxic T lymphocytes. The models' prediction allows for a better understanding of relationship between immune cells and cytokines while parameter sensitivity analysis establish the factors that contributes to peak immune response of different vaccine types. The long-term antibody prediction shows a discernible degradation. This finding supports the current third dose booster guidelines. Our within-host models guide the vaccination strategy by health authorities to optimize the vaccine rollout and serve as an in-silico tool for future vaccine re-formulation.