Conference Booklet

Workshop

The 7th Workshop on Virus Dynamics in Bordeaux (France) will continue the meeting series previously started in Frankfurt (2013), Toronto (2015), Heidelberg (2017), Paris (2019), Seattle-Online (2021) and Nagoya (2023).

This workshop brings together virologists and immunologists with mathematical modelers and system biologists to discuss current approaches and challenges in modeling and analyzing different aspects of virus dynamics. A specific focus will be made this year on vaccine development and immunology.

Université de Bordeaux, Bordeaux population Health - SISTM, Inserm U1219, Inria

BORDEAUX POPULATION HEALTH | Research Center - U1219

SISTM / Statistiques pour la médecine translationnelle

The workshop is co-organized by the "Statistics in System Biology and Translational Medicine" team in Bordeaux. This group is devoted to the development of statistical methods for the integrative analysis of data in medicine and biology, with a particular focus in immunology and vaccinology.

It belongs to Inserm and the French research institute for digital sciences (Inria). It belongs to the Bordeaux population Health center (Inserm). The BPH Bordeaux Population Health Research Centre is dedicated to research on key public health priorities across a diverse range of disciplines.

Université de Paris, IAME, Inserm U1137

iame RESEARCH CENTER ON INFECTIOUS DISEASES

IAME is an alliance from basic to clinical and population-based research towards medical progress in the fight against infectious diseases. Located at the University of Paris / Bichat Medical School campus in the north of Paris and connected to several University Hospitals in close proximity, it provides a unique opportunity to mix basic scientists and clinicians involved in infectious disease research.

General Information

Organizers of the Workshop

Jérémie Guedj
jeremie.guedj@inserm.fr
+33(0)6.95.23.74.16

Mélanie Prague
melanie.prague@inria.fr
+33(0)6.81.65.50.49

Administrative and logistics
Claire Augagneur
(UB Event)
ub.event@u-bordeaux.fr

Final support
Christine Lopes Monteiro
christine.lopes-monteiro@u-bordeaux.fr

https://virusdynamics25.sciencesconf.org
virusdynamics25@sciencesconf.org

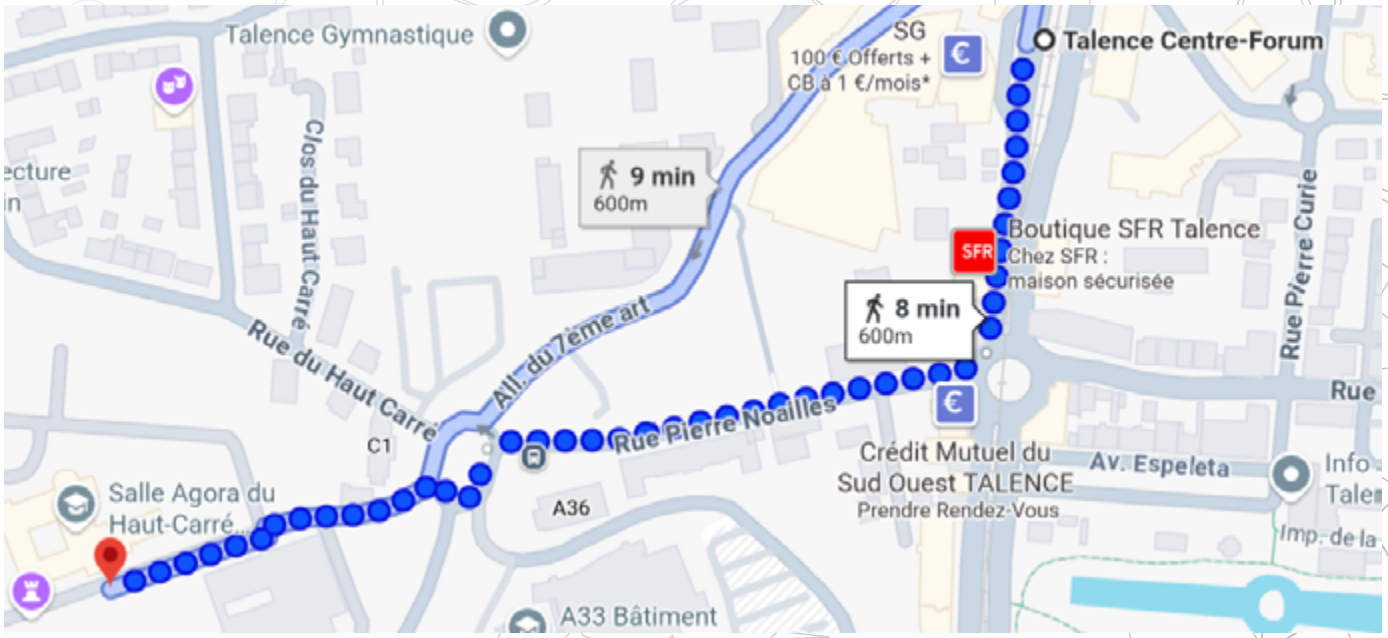
Conference Venue

Practical Information

University of Bordeaux
Domaine du Haut-Carré
43, rue Pierre Noailles
33400 TALENCE

Conference room: Auditorium Agora
Lunch and Coffee breaks: room Badiane
Access by tramway: Line B, stop Forum + 8 min walk (600m)

The site is 25 minutes by taxi from the airport and 15 minutes by taxi from the SNCF St Jean train station (outside peak hours)



Internet access

Internet access is available for all participants through the eduroam network (academic institution in US & Europe).

If you don't have eduroam, you can use the guest network with the code:

LOGIN : VIRUS

PASSWORD : Xnh8@D+4

Important note: No security measures (i.e. encryption, firewalling, etc.) have been enabled. We highly recommend that you do not share personal or system files and use a personal firewall.

Gala Dinner

The gala dinner is open to everyone who signed up when registering at the conference.

Wednesday, October 15, 2025, 19h30

Restaurant Le café français

5 Pl. Pey Berland

33000 Bordeaux

Access by tramway : 20-25 min

Line B, stop Hotel de ville + 1 min walk (170m)

Meet the Scientific Committee

The scientific committee is in charge of the conference program. A votation system was set up to decide invited speakers, as well as selecting oral and poster presentations. Thanks for bringing up this exciting program !

Lead organizer

Mélanie Prague, Inserm Bordeaux Population Health, Inria, Université de Bordeaux, France.

Dr. Mélanie Prague is researcher in Biostatistics at the University of Bordeaux, at the Bordeaux Population Health Research Center (Inserm U1219) and at Inria Bordeaux. After obtaining her doctoral degree in 2013 in Biostatistics at University of Bordeaux, she did a post-doc at Harvard School of Public Health.

Her research focuses on the development and application of statistical and mathematical models for infectious disease dynamics, vaccine evaluation, and public health decision-making. She specialize in the treatment and control of HIV, HBV, Nipah virus, SARS-CoV-2 and Ebola. She combines mechanistic modeling, Bayesian inference, and machine learning to improve the interpretation of complex biomedical data (possibly in high dimension), particularly from vaccine and clinical trials.

Within Bordeaux Population Health, she is leading a group named SISTM (Statistics in immunology and translational medicine) devoted to accelerate vaccine development, gathering about 50 scientists, medical doctors and young researchers.

Lead co-organizer

Jérémie Guedj, Infection Antimicrobials Modelling Evolution, INSERM, Université Paris Cité, France.

Jérémie Guedj is a research scientist in biostatistics/pharmacometrics at the French Institute of Health & Medical Research (Inserm), specialized in infectious diseases and antiviral treatment. His researches have theoretical objectives, such as developing mathematical models to understand quantitative aspects of host/pathogen interaction. They also aim to impact clinical research by optimizing drug combination, dosing regimen and identify characteristics associated with a differential response to antiviral treatment.

His researches have initially focused on chronic viral infections (HIV, HBV, HCV) and have progressively shifted to acute emerging viral infections (SARS-CoV-2, viral hemorrhagic fever). He also applyies the models and the statistical methods developed in virus dynamics to other fields of research, in particular bacterial dynamics (microbiota, phage therapy) and cancer. He works in the INSERM IAME laboratory devoted to infectious diseases, and located on the premises of Hospital Bichat campus, in the north of Paris. Within IAME, he is leading a group named MOCLID devoted to modeling and clinical investigation in infectious diseases, gathering about 50 scientists, medical doctors and young researchers.

Meet the Scientific Committee

Catherine Beauchemin, iTHEMS @ RIKEN

Catherine Beauchemin is a computational biophysicist and her research primarily aims to mathematically and computationally describe the processes driving diseases in vitro and in vivo, spanning virology, oncology, and neurodegenerative diseases, with the aim to predict and control their trajectory and outcome. She is a Deputy Director of the RIKEN Centre for Interdisciplinary Theoretical and Mathematical Sciences (iTHEMS) in Japan, and a Full Professor in the Department of Physics at Toronto Metropolitan University (TMU) in Canada. She obtained her Ph.D. in Physics at the University of Alberta, working on spatiotemporal modelling of virus infections. She was a postdoctoral fellow jointly at the Los Alamos National Laboratory's Theoretical Biology and Biophysics Division with Dr. Alan S. Perelson, and at the Adaptive Computation Laboratory in the Computer Science Department of the University of New Mexico with Dr. Stephanie Forrest.

Frederik Graw, FAU Erlangen-Nürnberg/ University Hospital Erlangen, Germany

Frederik Graw works on mathematical and computational methods to analyse the immune system and its complex dynamics in the context of infection, inflammation and malignant diseases. His research especially focuses on deciphering the spatio-temporal dynamics of immune and disease processes within tissues, and the development and maintenance of cellular immune responses, with the aim to improve vaccination and immunotherapy design. Frederik Graw studied mathematics and obtained his PhD in Theoretical Immunology at the ETH Zurich. After a postdoctoral stay at the Los Alamos National Laboratory with Alan S. Perelson, he became a group leader at the BioQuant-Center for Quantitative Biology and the Interdisciplinary Center for Scientific Computing (IWR) at Heidelberg University in Germany. Since 2023, he is a Professor for Modelling of Immune Processes at the Friedrich-Alexander-University Erlangen-Nürnberg and the University Hospital Erlangen.

Nathanaël Hoze, Inserm Paris

Nathanaël Hozé is a researcher in infectious disease modeling with the Statistical Modelling and Clinical Investigation in Infectious Diseases team at Inserm IAME in Paris, France, where he has worked since 2024. His research focuses on mathematical and computational approaches to infectious disease dynamics, with particular emphasis on multiscale modeling of infections. He is also a specialist in Bayesian statistics, parameter inference, and related methodologies for analyzing epidemiological data.

Meet the Scientific Committee

Shingo Iwami, Nagoya University

In 2021, I was appointed as a full professor in the Division of Natural Science, Graduate School of Science at Nagoya University, with a mission to pioneer the history of interdisciplinary research. I established the interdisciplinary Biology Laboratory (iBLab) to pursue this goal. Currently, I collaborate with medical institutions both in Japan and abroad to collect prospective and retrospective clinical and cohort data on various diseases. My research integrates mathematical modeling with data analysis and artificial intelligence, creating new approaches to understanding complex biological phenomena. Furthermore, I am developing frameworks for interdisciplinary research to implement mathematical models in clinical settings where mathematical sciences have rarely been applied, aiming to fundamentally transform healthcare through the power of mathematics.

Udo Reichl, Max Planck Institute, Germany

Udo Reichl received his biology diploma in 1987 from Saarland University in Saarbrücken, Germany, and his Ph.D. in chemical engineering from the Institute for Systems Dynamics and Control at the University of Stuttgart, also in Germany. After conducting postdoctoral research at the Biotechnology Laboratory at the University of British Columbia in Vancouver, Canada, and at the Biotechnology Group of the Institute for Systems Dynamics and Control at the University of Stuttgart, he began his industry career as a project leader for microcarriers at Pitman-Moore GmbH in Burgwedel, Germany. He was soon promoted to head of virus production and, in 1996, acting head of production at Pittman-Moore/Mallinckrodt Vet/Essex Animal Health GmbH (Burgwedel, Germany). Since 1999/2000, Udo Reichl has led two closely related bioprocess engineering groups at the MPI and the Otto von Guericke University in Magdeburg, Germany. These groups have extensive expertise in developing and optimizing cell culture–based virus and viral vector production for vaccines, defective interfering particles (antivirals), gene therapy, and oncolytic therapy. The group evaluates different cell lines for their suitability for virus propagation and develops process strategies and conditions to achieve high viral yields. The group established sophisticated analytical tools to monitor cellular metabolism and viral titers as well as infection dynamics and apoptosis induction in host cells in bioreactors. Additionally, they employ molecular biological methods to gain insight into virus-host cell interactions, such as virus-induced alterations in host cell protein expression and the impact of cellular pathogen defense on viral yields. They use the enormous amount of data derived from these analytical tools to develop and validate mathematical models that provide a quantitative understanding of metabolic pathways, the complex interactions between viruses and their host cells, and defective interfering particle formation. These models are essential for analyzing and optimizing viral replication at the single-cell and cell-population levels, which supports the design and optimization of virus-based production processes.

Meet the Scientific Committee

Joshua Schiffer, Fred Hutchinson Cancer Center, USA

Josh is an infectious diseases physician and researcher based at the Fred Hutchinson Cancer Center and the University of Washington. His research group focuses on modeling HSV-2, HIV, SARS-CoV-2, and other viruses. He is particularly interested in accurate clinical trial simulation.

Elissa Schwartz, Washington State University, USA

Elissa J. Schwartz is a Professor at Washington State University (USA) with a joint appointment in the School of Biological Sciences and the Department of Mathematics & Statistics. She received her training from University of California, Los Angeles (postdoc, Biostatistics and Biomathematics), Mount Sinai – New York University (PhD, Biomedical Sciences) and University of California, Berkeley (BA, Mathematics). Her current research uses data-driven mathematical and computational modeling to understand the immune response to lentiviral infection (particularly HIV and Equine Infectious Anemia Virus (EIAV)). She also investigates epidemiological and within-host dynamics of influenza, SARS-CoV-2, and other infections. She teaches courses in both mathematics and biological sciences as well as interdisciplinary workshops in the United States, Canada, India, Nepal, and South Africa. She previously served on the Board of Directors for the Society for Mathematical Biology (SMB) and she currently co-chairs the SMB Mentoring Program.

In order to encourage young scientists to attend the meeting, we have created this year the «student prize», that awards outstanding PhD achievement. Eligible candidates were current PhD students or postdocs having defended their thesis after March, 15, 2016.

Congratulations Nils Gubela !

Nils Gubela

nils.gubela@fu-berlin.de

Nils Gubela studied mathematics and bioinformatics at the University of Cologne and the University of Vienna. He is currently a PhD student in Max von Kleist's «Mathematics of Data Sciences» group at FU Berlin and a member of the Berlin Mathematical School as well as the International Max Planck Research School for Biology and Computation.

His research focuses on the applications of complex systems and network science to understand outbreak and evolutionary dynamics on a population scale.

SARS-CoV-2 evolution on a dynamic immune landscape

N. Alexia Raharinirina[1], Nils Gubela[*1], Daniela Börnigen, Maureen Rebecca Smith, Oh Djin-Ye[2], Matthias Budt[2], Claudia Schillings[1], Stephan Fuchs[2], Ralf Dürrwald[2], Thorsten Wolff[2], Martin Hölzer[2], Sofia Paraskevopoulou[2], and Max Von Kleist[2,1]

1 Freie Universit¨at Berlin – Germany

2 Robert Koch Institute [Berlin] – Germany

Since the onset of the COVID-19 pandemic, numerous variants of SARS-CoV-2 have emerged, each displaying significant evolutionary changes, particularly in the virus' spike protein. This protein serves as the primary target for neutralizing antibodies, which are crucial in the immune response. A plausible hypothesis suggests that the virus is undergoing evolutionary changes to escape antibody-mediated neutralization, whether those antibodies are induced by vaccination or by prior infection. Such evolution would allow the virus to enhance its infectivity in populations where individuals have pre-existing immunological exposure.

The process of viral infection naturally stimulates the production of neutralizing antibodies. Consequently, the evolution of the virus is likely navigating a dynamic immune landscape that has been shaped by the local history of infections. Although inter-country differences in viral evolution existed early in the pandemic, the geographical variation of emerging Omicron sublineages reflects an increasing complexity of the global immunological landscape, in which the course of infection waves with new (sub)variants in a particular region could

be substantially influenced by the infection history of that region (that is, which variants dominated the preceding waves and at what time). In response to this complex scenario, we have developed a comprehensive mechanistic model designed to predict the variant-specific relative susceptibility of individuals over time across different regions.

Our model takes into account the waning of antibodies post-infection and assesses the immune escape potential of new variants based on their spike protein mutation profiles. To achieve this, we integrate deep mutational scanning data, waning pharmacokinetics of antibodies, and regional genomic surveillance data, thereby creating a robust framework for analysis.

To evaluate the risk of spreading for each variant, we deploy a fitness metric that compares the number of susceptible individuals per variant to the mean susceptibility across circulating variants. This metric proved exceptionally effective, aligning closely with historical patterns of variant spread, forecasting future variant trends, and explaing global variations in variant dynamics.

Our findings underscore the notion that the ongoing pandemic continues to create variantspecific population immunity, which in turn determines a variant's transmission potential, thus defining its fitness. Moreover, our model is adaptable to any geographical region through the use of local genomic surveillance data. This adaptability enables precise risk assessments for emerging variants and provides vital information that can inform vaccine design and public health strategies.

Keywords: Mathematical model, immune landscape, immune escape, pharmacokinetics

Topical collection

We proposed a Topical collection in Bulletin of Mathematical Biology. The editors will be these druing the meeting, so don't hesitate to contact them and discuss possible publication of your work !

Submission opening date: 17 October 2025

Submission deadline: 30 June 2026

Submission type: General submission with strong invitation to people attending the workshop on virus dynamics in Bordeaux France in October 2025.

Title :

Use of Mathematical Modeling of Virus–Immune Dynamics from Cell to Host to accelerate advances in infectious diseases control and treatment.

Editors :

- Mélanie PRAGUE (Université de Bordeaux, Inserm, Inria, France)
- Nathanael HOZE (Université de Paris, Inserm, France)
- Shingo Iwami (iBLab, Graduate School of Science, Nagoya University, Japan)
- Jane Heffernan (York University, Canada)

Description :

This topical collection is related with the 7th Workshop on Virus dynamics held in October 2025 in Bordeaux France. This workshop brings together virologists and immunologists with mathematical modelers and system biologists to discuss current approaches and challenges in modeling and analyzing different aspects of virus dynamics. A specific focus is made this year on vaccine development and immunology. In this special topical collection, we expect to highlight recent advances in mathematical modeling of virus–immune dynamics across cellular, tissue, and host scales. Emphasis is placed on approaches that integrate mechanistic modeling, quantitative data, and computational methods to elucidate fundamental processes of infection, immune response, and disease progression. Contributions may address both theoretical and applied questions. The aim is to foster progress in mathematical biosciences by promoting innovative methodologies that support interdisciplinary collaboration across mathematics, immunology, virology, and computational science.

Tuesday, October 14 2025, Morning

Session 1: Chronic viral infections (chair Rodolphe Thiébaut, Université de Bordeaux, Inserm, Inria France)	
09:00-09:20	Welcome and opening Mélanie Prague, organizing comittee, Université de Bordeaux, Inserm BPH, Inria Jérémie Guedj, organizing comittee, Université de Paris, Inserm IAME Rodolphe Thiébaut, Head of Bordeaux Population Health, Inserm
09:20-10:00	**Alan Perelson (Los Alamos Laboratory, USA)** Multiscale Modeling of Hepatitis B and C Infection and Treatment
10:00-10:20	**Rob de Boer (Utrecht University, Netherland)** Immune Responses May Make HIV-1 Therapeutic Interfering Particles Less Effective
10:20-10:40	**Amar Kumar Garg (Helmholtz-Zentrum, Braunschweig,Germany)** Induction of multiple broadly neutralizing antibody lineages is modulated by precursor B cell composition and antibody epitope masking
10:40-11:00	**Bharadwaj Vemparala (IISC, Bangalore, India)** Early treatment initiation preserves memory CD8 T cells and improves the likelihood of post-treatment control of HIV infection
11:00-11:20	**Lucero Rodriguez Rodriguez (Fred Hutch, Seattle, USA)** Differential longevity and potency of four broadly neutralizing antibodies elicited distinct viral load kinetics and resistance patterns in people with chronic HIV
11:20-11:50	Coffee break
Session 2: Viral dynamics in respiratory infections (1/2) (chair:Jérémie Guedj, Université de Paris, Inserm, France)	
11:50-12:10	**Keisuke Ejima (Nanyang Technological University, Singapore)** Patient Characteristics Modify the Antiviral Efficacy of SARS-CoV-2 Therapies: Insights from Meta-Analysis and Real-World Viral Load Data
12:10-12:30	**Shadi Esmaeili-Wellman (Fred Hutch, Seattle, USA)** Clinical trial simulation suggests PCR underestimates molnupiravir's true potency against SARS-CoV-2
12:30-12:50	**Katherine Owens (Fred Hutch, Seattle, USA)** SARS-CoV-2 viral load kinetic profiles correspond with observed intra-host viral diversity and mutation rates during infections in immunocompetent individuals
12:50-14:00	Lunch break

Tuesday, October 14 2025, Afternoon

Session 3: Methodology & Statistics (chair: Jane Heffernan, York University, Canada)	
14:00-14:40	**France Mentré (INSERM, Paris, France)** From Exploration to Decision: Modeling for Optimal Study Design
14:40-15:00	**Boris Hejblum (Inserm Bordeaux Population health, France)** RISE: Two-Stage Rank-Based Identification of High-Dimensional Surrogate Markers Applied to Vaccinology
15:00-15:20	**Mélanie Prague (Inserm Bordeaux Population health, France)** Regularization estimation in high-dimensional mechanistic models
15:20-15:40	**Avidan Neumann (University of Augsburg, Germany)** Skin microbiome dynamics as biomarker for severe radiodermatitis in breast cancer patients and for treatment response in atopic dermatitis
15:40-16:10	Coffee break
Session 4: Immune and viral response to vaccination (1/2) (chair: Rob de Boer, University of Utrecht, Netherland)	
16:10-16:30	**Jose Borghans (University of Utrecht, Netherland)** Dynamic maintenance of tissue-resident memory T cells
16:30-16:50	**Adrien Mitard (Inserm, Paris, France)** Exposure history shapes SARS-CoV-2 viral dynamics in Non-Human Primates and provides insights into correlates of protection against infection and transmission
16:50-17:10	**Marie Alexandre (John Hopkins, USA, Inserm Bordeaux Population Health, France)** Joint mechanistic modeling of viral and antibody responses to vaccines in Non-Human Primates to quantify SARS-CoV-2 mechanistic correlate of protection
17:10-17:30	**Jane Heffernan (York University, Canada)** COVID-19 vaccination and waning immunity
17:30-17:50	**Beatrix Haddock (Fred Hutch, Seattle USA)** Modeling broadly neutralizing antibody neutralization curves for biomarker discovery
18:00-20:30	Poster Session with Wine & Cheese

Wednesday, October 15, 2025

Session 5: Viral dynamics in respiratory infections (2/2) (chair: Joshua Schiffer, Fred Hutch, USA)	
09:00-09:40	**Olivier Schwartz (Institut Pasteur, Paris, France)** Entry and kinetics of replication of human seasonal coronavirus HKU1: mechanisms and impact of temperature
09:40-10:00	**Jérémie Guedj (Inserm, Paris, France)** Viral dynamics of the Respiratory Syncytial Virus during experimental human challenge infections : insights for transmission and treatment
10:00-10:20	**Laura Liao (MSD, USA)** Viral Dynamics Modeling: Helping Translate Human Challenge Study Results to Late-Stage in RSV
10:20-10:40	**Ke Li (Yale School of Public Health, USA)** Relating In Vivo Respiratory Syncytial Virus Infection Kinetics to Host Infectiousness in Different Age Groups
10:40-11:10	Coffee break
Session 6: Vaccine development (chair: Mélanie Prague, Université de Bordeaux, France)	
11:10-11:50	**Jeff Sachs (MSD, USA)** Vaccines Versus Viruses (and Bacteria) - Modeling Helps Humans Win the Battle
11:50-12:10	**Hirst Cora (Emory University Atlanta, USA)** Quantitative constraints limit the generation of a universal influenza vaccine
12:10-12:30	**Riley Drake (Emory University Atlanta, USA)** Modelling Antibody Dependent Enhancement: Implications for Vaccine Design
12:30-14:00	Lunch break
Session 7: Immune and viral response to vaccination (2/2) (chair: Rustom Antia, Emory university, USA)	
14:00-14:40	**Véronique Godot and Yves Lévy (Vaccine Research Institute, Paris, France)** Broad and durable antibody responses against SARS-CoV2 through an antibody-mediated vaccine (AMV) targeting the CD40 receptor
14:40-15:00	**Jair Andrade (University of Cambridge, UK)** Assessing the impact of vaccination against dengue viruses using long-term antibody measurements
15:00-15:20	**Rituparna Banerjee (University of British Columbia, Vancouver, Canada)** How Vaccines Shape B Cell Evolution: A Modeling Approach
15:20-15:40	**Andreas Handel (University of Georgia, USA)** Modeling the impact of high-dose versus standard-dose influenza vaccines on antibody breadth and vaccine efficacy
15:40-16:10	Coffee break
Session 8: Viral dynamics and evolution (Chair: Frederik Graw, FAU Erlangen-Nunberg Universitat, Germany)	
16:10-16:50	**Best paper Student Award – Nils Gubela (Freie Universitet Berlin, Germany)** SARS-CoV-2 evolution on a dynamic immune landscape
16:50-17:10	**Samuel Alizon (College de France, CNRS Paris, France)** Inferring virus dynamics from sequence genomic data
17:10-17:30	**Rolland Regoes (ETH Zurich, Switzerland)** Experimental epidemiology with viruses: toward assessing phylodynamics
19:30	Gala diner

Thursday, October 16, 2025, Morning

Session 9: Viral dynamics in cell systems (Chair: Catherine Beauchemin, iTHEMS@ RIKEN & Toronto Metropolitan University, Canada)	
09:00-09:40	**Udo Reichl (Max Planck Institute, Magdeburg, Germany)** Cell Culture-based Influenza Virus Production: Challenges, Analytics and Mathematical Modeling
09:40-10:00	**Cailan Jeynes-Smith (The University of Tennessee, USA)** Exploring IFN-Œ≥'s Role in Alveolar Macrophage Depletion During Influenza A Virus Infection
10:00-10:20	**Yusuke Asai (Laboratory of Mathematical Epidemiology, Japan)** Traveling Waves in a Cell-to-Cell Transmission Model
10:20-10:40	**Melanie Moses (The University of New Mexico, Albuquerque, USA)** Modeling Spatial Spread of SARS-CoV-2 infection in Lung
10:40-11:00	**Pascal Lukas (Friedrich-Alexander-Universitet Erlangen, Germany)** Determining viral spread and innate immune dynamics in human respiratory epithelium
11:00-11:30	Coffee break
Sessions 10 : Modeling viral load and transmission (chair: Elissa Schwartz, Washington State University, USA)	
11:30-11:50	**Nathanaël Hoze (Inserm, Paris, France)** A multi-scale modelling framework to assess the relationship between SARS-CoV-2 viral load and transmission in household studies
11:50-12:10	**Somsen Elizabeth (Emory University Atlanta, USA)** Quantifying viral transmissibility and pandemic potential from experimental transmission studies
12:10-12:30	**Daniel Coombs (University of British Columbia, Canada)** Time and Space in Models of Nascent Viral Infection
12:30-12:50	**Assefa Woldegerima Woldegebriel (York University, Canada)** Impact of infection routes on within-host MPXV dynamics: insights from a modeling study
12:50-14:00	Lunch break
Sessions 11 : Epi models (Chair: Nathanael Hoze, université de Paris, Inserm, France)	
14:00-14:40	**Christophe Frazer (Oxford University, Pandemic Sciences Institute, UK)** Virus dynamics and epidemic control: the evolving science of contact tracing
14:40-15:00	**Narendra Dixit (Indian Institute of Science, Bangalore, India)** Prevalence of asymptomatic infections: a window to the basal immunity to SARS-CoV-2
15:00-15:20	**Max Von Kleist (Freie Universitet Berlin, Germany)** Modelling the dynamic Interplay between SARS-CoV-2 Infection, Immunity and Evolution
15:20-16:00	Closing remarks – Vote for 2027 End of the conference Coffee Available
16:30-18:00	Young researchers mentoring session Q&A – Elissa Schwartz

Tuesday, October, 14th to Thursday, Octobre 16th
Exposition space

1 - Tissue Correlates of Humoral Breadth After COVID-19 Vaccination - Juliane Schroeter

2 - Model-based prediction of the therapeutic and prophylactic treatment window of the influenza defective interfering particle OP7 - Daniel Rüdiger

3 - Atopic Dermatitis severity correlation with Staphylococcus aureus and skin pH as function of demographic and environmental factors - Anna Reiter

4 - On the use of Tecovirimat for MPXV infections: why do we not see shortened times to viral clearance in treated patients? - Thomas Beneteau

5 - Within-Household SARS-CoV-2 Transmission Reveals Limitations of Lineage-Based Classification - Rafael Schulman

6 - A mechanistic model describing SARS-CoV-2 viral loads and antibody response - Shengyuan Zhang

7 - Is Simpler Better? Effects of Phylodynamic Model Misspecification on Epidemiological Estimates - Anna Zhukova

8 - Development of a Predictive Diagnostic Model for Mpox Using Clinical Features in Japan - Raiki Yoshimura

9 - Zika virus induces monocyte recruitment in the immunocompetent adult brain driving chronic inflammation - Josefina Garcia Diaz

10 - A Stochastic Evolutionary Model of the Vaccine-Elicited B-Cell Repertoire - Ollivier Hyrien

11 - Efficacy of Dolutegravir-Based Antiretroviral Therapy and Preventive Needs in Advanced HIV Patients in Gabon - Berthe Amélie Iroungou

12 - Use of viral clearance as a surrogate marker of epidemiological efficacy for anti-SARS-CoV-2 therapies - Shoya Iwanami

13 - Optimizing sequential immunization regimens via dynamic models - Sarafa A. Iyaniwura

14 - Quantitative classification of primary versus secondary dengue infections using IgG and IgM antibody dynamics - Ines Jimenez

15 - Probability of early infection extinction depends linearly on the virus clearance rate - Nóra Juhász

16 - Within- and between-host dynamics influence the evolution of oncogenic viruses - Yoshiki Koizumi

17 - Modeling the COVID-19 pandemic: Variants and vaccines - Kubik Alicja B.

18 - An epidemiological-like model for defective-helper betacoronavirus infection in cell cultures - Tomás Lázaro

19 - A novel mechanistic viral dynamics modeling (MVDM) framework to characterize the effect of combination therapies in chronic hepatitis B and evaluate the influence of individual characteristics in the Piranga phase 2 platform study - Annabelle Lemenuel-Diot

20 - Global bifurcation in a virus, defective genomes, satellite RNAs tripartite system: breakdown of a coexistence quasi-neutral curve - Llopis-Almela Oriol

21 - Models of budding and bursting - Grant Lythe

22 - Modeling HIV rebound after stopping ART using a virtual cohort trained on primary infection data - Bryan Mayer

23 - Maximum likelihood framework for inference of disease burden in unsampled locations. - Sarah Ooi

24 - Epidemiological analysis of HIV in France using metagenomic sequence data - Paul Petit

25 - Understanding the evolution of a 'stealth' phenotype of the SARS-CoV-2 Omicron variant - Lucía Ramírez Torres

26 - Modelling the viral dynamics of SARS-CoV-2 in the general community in a context of emerging variants - Maxime Beaulieu

27 - Do random cell-virus interactions during in vitro infections affect TCID50 measurements and parameter estimation by math models? - Catherine Beauchemin

28 - Multiscale Modeling of Vector-Borne Diseases: The Role of Dose-Dependent Transmission - Fernando Saldana

29 - Quantitative evaluation of the impact of random ecDNA segregation on cell populations. - Marwa Akao

30 - Type I IFN receptor blockade modulates HCV-associated immune responses and alleviates liver fibrosis through macrophage-derived STAT3 signaling - Tina Comlekoglu

31 - Quantifying the recruitment, expansion and contraction of influenza-specific CD4 and CD8 T-cell clones - Arpit C Swain

32 - Mathematical modeling sheds light on the role of the CXCR4-receptor on memory T cell maintenance - Szilard Varga

33 - Visualizing depressive states during the COVID-19 pandemic as topographical maps - Daiki Tatematsu

34 - The kinetics of Influenza A and B viruses infection based on a human challenge study - Angela Tower

35 - Clinical impact of antiviral medications for influenza in preventing hospitalization, ICU admission and mortality among non-hospitalized patients using a multi-center global database - Tsuzuki Shinya

36 - Acute and rebound timeseries from SHIV-infected macaques can be jointly explained by a model containing a non-cytolytic CD8 T cell response - Christiaan Van Dorp

37 - Integrated population PKPD modelling of viral dynamics and host immune response in hiv patients undergoing antiretroviral monotherapy - Alberto Vegas Rodriguez

38 - Predicting clinical efficacy of HIV combination therapies from monotherapy data using QSP viral dynamics modelling - Dominic Whittaker

39 - A variational deep-learning approach to modeling memory T cell dynamics - Andrew Yates

40 - Apparent cooperativity between human CMV virions introduces errors in conventional methods of calculating multiplicity of infection - Vitaly Ganusov

41 - Memory B Cell and Neutralising Antibody Kinetics Following Dengue Virus Infection - Bethan Cracknell Daniels

42 - Applications of mechanistic model-based in silico clinical trials for optimal vaccine development - Rajat Desikan

Alan Perelson

Alan Perelson is a Senior Fellow in the Theoretical Biology and Biophysics Group at Los Alamos National Laboratory. His research focuses on mathematical and theoretical biology, particularly in immunology, virology, and cell and molecular biology. He has developed viral kinetic models describing infection dynamics and responses to antiviral therapy.

Multiscale Modeling of Hepatitis B and C Infection and Treatment

Alan Perelson
Los Alamos National Laboratory – United States

Standard viral dynamic models have been expanded to include intracellular events in the viral lifecycle. I will discuss why these models were needed in the case of HCV and discuss various implementations of the the model including a new version that includes hepatocyte proliferation and partitioning of intracellular HCV RNA between daughter cells. I will then discuss the use of a multiscale model of HBV that includes the intracellular dynamics of encapsidated pre-genomic RNA (pgRNA) that is reverse transcribed into relaxed circuar DNA which is then assembled and secreted as viral particles. Interestingly, encapsidated pgRNA is also secreted in virus-like particles. I will show that the intracellular model can be used to simultaneously fit longitudinal data on the concentrations of serum HBV DNA and HBV RNA in HBV-infected individuals treated with a first or second generation capsid assembly modulator (CAM), and thus obtain estimates of the in vivo effectiveness of these compounds. Finally, I will show how the relative decline in log10 HBV RNA from baseline but not HBV DNA measured at a single timepoint can be used to estimate the in vivo effectiveness of a CAM, thus hopefully facilitating clinical trials of new CAMs and encouraging the measurement of serum HBV RNA in such clinical trials.

Keywords: HBV, HCV, multiscale model, capsid assembly modulator, viral dynamics

Udo Reichl

Udo Reichl is the Director of the Bioprocess Engineering Group at the Max Planck Institute for Dynamics of Complex Technical Systems in Magdeburg, Germany. His research focuses on optimizing viral-based production processes, developing chromatographic methods for viral antigen purification, and mathematical modeling of bioprocesses and cellular systems.

Cell Culture-based Influenza Virus Production: Challenges, Analytics and Mathematical Modeling

U. Reichl[1,2], J. Küchler[1], D. Benndorf[1,3], Y. Genzel[1], S. Y. Kupke[1], D. Rüdiger[1]

1 Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany
2 Otto-von-Guericke University Magdeburg, Chair of Bioprocess Engineering, Magdeburg, Germany
3 Applied Biosciences and Process Engineering, Anhalt University of Applied Sciences, Köthen, Germany

In recent decades, significant research and development efforts have focused on designing and optimizing cell culture-based influenza virus production processes. In case of pandemics, the flexibility and scalability of cell cultures can reduce the time to production significantly and overcome the limitations of traditional technologies, such as egg-based vaccine manufacturing platforms. In addition to technical measures aimed at process optimization and intensification, mathematical modeling can contribute to improving the characterization of process options, guiding the selection of cultivation conditions, and exploring details of virus-host cell interactions relevant to increase cell-specific yields and virus productivity. This applies to both conventional batch processes and continuous cultivation systems.

Most mathematical models of viral replication in animal cell cultures rely on ordinary differential equations (ODEs), appropriate kinetics, and parameter estimation based on quantitative experimental data. Unlike approaches focusing on within-host modeling of viral infections — such as models of the human immunodeficiency virus that are limited by the small number of assays developed to study acute infections and drug therapy responses — detailed studies of the intracellular aspects of virus-host cell interactions and comprehensive analyses of the supernatant of homogeneously mixed bioreactors are feasible. This significantly increases the amount of quantitative experimental data that can be used for model validation and challenges parameter estimation and model selection.

In accordance with the studies conducted by our group in recent years, the presentation will offer an overview of the dynamics of influenza A virus replication in batch processes with low and high cell concentrations, as well as in continuous production systems. With regard to the

latter, the challenges resulting from the accumulation of defective interfering particles will be addressed. Furthermore, the presentation will show options for in-depth analyses of virus-host cell interactions. This includes the metabolism of infected cells, the intracellular dynamics of viral RNAs, and the quantification of viral proteins. Finally, the integration of the resulting comprehensive sets of quantitative data into mathematical models, as well as the challenges associated with model validation and selection will be discussed.

Selected References

Frensing, T. Heldt, F.S., Pflugmacher, A., Behrendt, I., Jordan, I., Flockerzi, D., Genzel, Y. & Reichl, U. (2013). Continuous Influenza Virus Production in Cell Culture Shows a Periodic Accumulation of Defective Interfering Particles. PLOS ONE, 8(9): e72288.

Frensing, T., Kupke, S. Y., Bachmann, M., Fritzsche, S., Gallo-Ramirez, L. E. & Reichl, U. (2016). Influenza virus intracellular replication dynamics, release kinetics, and particle morphology during propagation in MDCK cells. Applied Microbiology and Biotechnology, 100(16):7181-7192.

Laske, T., Heldt, S., Hoffmann, H., Frensing, T. & Reichl, U. (2016). Reprint of "Modeling the intracellular replication of influenza A virus in the presence of defective interfering RNAs. Virus Research, 213, 86-95.

Rüdiger, D., Kupke, S. Y., Laske, T., Zmora, P. & Reichl, U. (2019). Multiscale modeling of influenza A virus replication in cell cultures predicts infection dynamics for highly different infection conditions. PLoS Computational Biology, 15(2): e1006819

Rüdiger, D., Pelz, L., Hein, M.D., Kupke, S.Y. & Reichl, U. (2021). Multiscale model of defective interfering particle replication for influenza A virus infection in animal cell culture. PLoS Computational Biology, 17(9), e1009357.

Rodrigues Correia Ramos, J., Bissinger, T., Genzel, Y. & Reichl, U. (2022). Impact of Influenza A Virus Infection on Growth and Metabolism of Suspension MDCK Cells Using a Dynamic Model. Metabolites, 12(3), 239.

Rüdiger, D., Piasecka, J., Küchler, J., Pontes, C., Laske, T., Kupke, S.Y. & Reichl, U. (2024). Mathematical model calibrated to in vitro data predicts mechanisms of antiviral action of the influenza defective interfering particle "OP7". Iscience, 27(4), 109421.

Küchler, J., Opitz, P., Jordan, I., Genzel, Y., Benndorf, D., Reichl, U. (2025). Quantification of intracellular influenza A virus protein dynamics in different host cells after seed virus adaptation. Applied Microbiology and Biotechnology, 109(74).

Words: (613/1000 incl. references)

Keywords: Mathematical modeling, influenza A virus, defective interfering particles, virus-host cell interaction, virus production

Jeff Sachs

Jeff (Jeffrey R.) Sachs is a Distinguished Scientist and Executive Director in the Quantitative Pharmacology and Pharmacometrics Department in MSD's Research Laboratories. His primary responsibility is for the modeling and simulation supporting vaccine program decisions from early discovery through late-stage clinical development and post-approval.

Vaccines Versus Viruses (and Bacteria) - Modeling Helps Humans Win the Battle

Jeff Sachs MSD

Although expected and with near-ubiquitous impact on drug development and regulatory deci-sions for small molecules and other biologics, model-based analyses, or "model informed drug development" (MIDD), is only more recently being impactful for vaccines. Applications and impact of modeling and simulation will be presented, focusing on how they can help enable innovation in the design, execution, and interpretation of data for earlier decision-making while mitigating risk. Examples of past and ongoing impact include:

> supporting vaccine R&D decisions like dose-level and regimen through compartmental (sem-mechanistic) models;

> model-based meta-analysis (MBMA) methods and their applications for decision support for RSV and COVID vaccines;

> how MBMA models (1) enabled prediction of efficacy (RSV prophylaxis for infants) of maternal RSV vaccination and of a monoclonal antibody; and (2) improved interpretation of the immuno-genicity of pneumococcal conjugate vaccines ("PCVs"), enabling better prediction of the potential public health impact of novel PCVs on breakthrough invasive pneumococcal disease;

> methods using subject-level data to estimate risk curves as a function of immunological mea-sures of response to vaccination (e.g., serum neutralizing titer) and to estimate efficacy, and ef-fects of demographic subgroups (e.g., age group, past infection); and

> an approach to mitigate the surprisingly large potential impact (on efficacy estimation and clini-cal trial duration) of false positive and false negative sample-testing errors.

Before providing examples, we will summarize the impact and development of vaccines. The pre-sentation will also touch on how the field could evolve and on opportunities for future research. Attendees are also welcome to watch the related, non-technical 6-minute introductory video linked to here.

https://www.linkedin.com/pulse/vaccines-math-stem-education-jeff-sachs/

Véronique Godot

Véronique Godot is a full professor of immunology at the University of Paris-Est Créteil since 2012. She is affiliated with the Institut Mondor de Recherche Biomédicale (IMRB). Her research focuses on immunology of infectious diseases, inflammation, and immune regulation. She is also involved with the Vaccine Research Institute, contributing to preclinical models.

Broad and durable antibody responses against SARS-CoV2 through an antibody-mediated vaccine (AMV) targeting the CD40 receptor

Pr Yves Lévy & Pr Véronique Godot

For over a decade, INSERM-U955/VRI has dedicated its research efforts to developing innovative vaccines aimed at antigen-presenting cells (APCs) for HIV and emerging infectious diseases. We utilize monoclonal antibodies (mAbs) that target endocytic receptors on APCs. By linking infectious antigens to the constant regions of these monoclonal antibodies, we can deliver antigens directly into antigen-presenting cells, thereby enhancing the immune response, including its durability. Our primary technology focuses on the human CD40 receptor, utilizing a monoclonal anti-CD40 antibody (clone 12E12) as the foundation for all vaccines developed from the CD40 platform. In HIV-1 research, we have shown the safety and long-term immunogenicity of our CD40.HIVRI.Env vaccine in a first-in-human trial. The CD40.HIVRI.Env is currently entering a new phase of evaluation in the HVTN318 clinical trial (NCT06665646), which is sponsored by the NIAID and is part of the HVTN network. Preclinical studies demonstrated that our antibody-mediated vaccines (AMV), CD40.CoV2 and CD40. Niv, protect against lethal infections from SARS-CoV-2 and the Nipah virus, respectively, by clearing the virus from the upper airways and inducing long-lasting T and B cell immunity.

Our current research investigates the immunological mechanisms that contribute to the enhanced and long-lasting antibody responses generated by our AMV against SARS-CoV-2 variants. Through immunological analyses, we have identified significant biological differences between our AMV and the Pfizer mRNA vaccines. These findings have raised important questions about the longevity of the antibody responses, which our experimental methods alone could not fully address. This biological complexity has prompted us to explore mathematical modeling approaches to better understand how antibody responses are maintained over time.

France Mentré

France Mentré is a Professor of Biostatistics at Université Paris Cité. Her research focuses on biostatistical modeling and pharmacometrics, particularly in infectious diseases. She develops methods to support dose optimization and individualized therapy.

From Exploration to Decision: Modelling for Optimal Study Design

France Mentré

Université Paris Cité, INSERM, IAME, 75018, Paris, France

Viral dynamic modelling increasingly uses non-linear mixed effect models (NLMEM) to cope with inter-individual variability in sets of longitudinal observations. NLMEM is a tool widely used in pharmacometrics and in model-informed drug development, for analysis of pharmacokinetic and/or pharmacodynamic data.

To make pivotal inference using NLMEM, for instance for test of treatment effect, pre-specification of the analysis and of the model(s) is needed. Regulatory agencies might require simulation studies to show the control of the type I error, are often those tests are based on asymptotic (LRT or Wald). Model-averaging is also suggested when model is not a priori known as model misspecification would affect the test.

An important step before performing a trial is its design. Indeed, it has been extensively shown that the number of patients, number of observations per patient and their allocation in time, influences the estimation error and the power of tests. Designs can be explored by clinical trial simulations but also using specific software tools as PFIM (www.biostat.pfim.fr), developed in our team.

A specific example of a bi-exponential viral load decay with treatment and age effects on first slope will be shown. We will illustrate notably the influence of the design and of the size of the effect on the uncertainty and the power. Number of subjects needed for an 80% power of showing treatment effect can be computed.

Those design tools assume a model and given values of the parameters and sensitivity analysis should be performed, or extensions using robust approaches across models and/or parameters (not shown here).

In conclusion, viral dynamic modelling with NLMEM can be used to make pivotal inferences given that analyses are pre-specified and that designs are evaluated and show adequate power.

Olivier Schwartz

Olivier Schwartz is a professor at the Institut Pasteur, where he has led the Virus and Immunity Unit since 2007. His research focuses on the cellular and molecular mechanisms of HIV-1 and SARS-CoV-2 replication, as well as the interactions between these viruses and the host immune system.

Entry and kinetics of replication of human seasonal coronavirus HKU1: mechanisms and impact of temperature

Olivier Schwartz, Virus & Immunity Unit, Institut Pasteur

Four endemic seasonal human coronaviruses causing common colds, HKU1, 229E, NL63 and OC43 circulate worldwide. After binding to cellular receptors, coronavirus spike proteins are primed for fusion by transmembrane-serine protease 2 (TMPRSS2) or endosomal cathepsins. HKU1 has been shown to bind 9-O-acelytated sialic acid but its protein receptor remained elusive. We recently identified TMPRSS2 as the high-affinity functional receptor for HKU1. We also elucidated the crystal structure of the HKU1 spike RBD in complex with TMPRSS2, showing that it recognizes residues lining the catalytic groove of the enzyme. HKU1 has not yet been amplified in large amounts in cell culture systems. We designed novel cell lines sensitive to HKU1. We are characterizing HKU1 entry, fusion, tropism, sensitivity to innate and humoral responses, in comparison with other coronaviruses. HKU1, like some other respiratory viruses, replicate more efficiently at 33°C, the temperature of the nasal cavity, through mechanisms that we are studying.

Christophe Fraser

Christophe Fraser is a Senior Group Leader in Pathogen Dynamics at the Big Data Institute and a professor in the Nuffield Department of Medicine. He is interested in studying the population dynamics and epidemiology of pathogens and translating this knowledge into public health applications. His research group primarily uses mathematical modeling and pathogen genomics as key tools.

Virus dynamics and epidemic control: the evolving science of contact tracing

Christophe Fraser, Pandemic Sciences Institute, University of Oxford, UK

From an operational public health perspective, contact tracing is simple: find contacts of cases, inform them of risk, and give advice and instructions. Delivery is complex, and it's a behavioural intervention, but the basic idea is straightforward. It is therefore surprising that the theoretical basis of contact tracing is so difficult to model.

The two aims of contact tracing are, first, to control an epidemic while minimising harm, and second, to learn about transmission risks in ways that improve the response.

For the first aim, I will outline how models link the effectiveness of contact tracing to both within-host virus and immune dynamics and to population-level epidemic and network processes. For the second, I will give examples from SARS-1, MERS-CoV and mpox, before focusing on SARS-CoV-2.

Our work began with modelling early public contact tracing data from Singapore in January 2020. That led to the co-development of the exposure notification system, a privacy-preserving form of digital contact tracing designed to address pre-symptomatic transmission, and later to a privacy-preserving analytics platform applied to seven million high-risk exposure events in the UK to provide real-time insights. The NHS COVID-19 app is estimated to have prevented more than 10,000 deaths in its first year.

This response gave a hint of what a future adaptive privacy-preserving decentralised digital epidemic response could look like. I will end by describing current efforts to make such systems ready for day one deployment in future epidemics.

List of participants

A.
Akao Marwa
Alexandre Marie
Alizon Samuel
Andrade Jair
Antia Rustom
Asai Yusuke

B.
B Franceschi Vinicius
Banerjee Rituparna
Beauchemin Catherine
Beaulieu Maxime
Bénéteau Thomas
Boespflug Nicolas
Borghans Jose
Bracis Chloe

C.
Cardozo Fabian
Cecilia Hélène
Ciavarella Constanze
Ciupe Stanca
Clairon Quentin
Comlekoglu Tina
Coombs Daniel
Cracknell Daniels Bethan
Crépin Lisa

D.
De Boer Rob
de Waard Gerbert
Débarre Florence
Desikan Rajat
Dixit Narendra
Drake Riley
Duke Elizabeth

E.
Ejima Keisuke
Elena Santiago
Esmaeili-Wellman Shadi

F.
Fraser Christophe
Furuse Yuki

G.
Ganusov Vitaly
Garcia Diaz Josefina
Garcia-Orueta Gaston
Garg Amar
Godot Veronique
Gouna Ange-Marie
Graw Frederik
Gubela Nils
Guedj Jeremie

H.
Haddock Beatrix
Hahn Young
Handel Andreas
Heffernan Jane
Hejblum Boris
Hirst Cora
Hozé Nathanaél
Huang Angkana
Hyrien Ollivier

I.
Iroungou Berthe Amélie
Iwanami Shoya
Iyaniwura Sarafa

J.
Jeynes-Smith Cailan
Jimenez Ines
Juhász Nóra

K.
Katherine Owens
Kitagawa Kosaku
Koelle Katia
Koizumi Yoshiki
Kubik Alicja B.

L.
Laval Quentin
Lazaro J. Tomas
Lemenuel-Diot Annabelle
Levy Yves
Li Ke
LI Zhe
Liao Laura
Lukas Pascal
Lunel Perrine
Lythe Grant

M.
Marc Aurélien
Mayer Bryan
McCaw James
Mentré France
Mitard de Girardier Adrien
Morita Yoshihisa
Moses Melanie
Mulas Laura

N.
Neumann Avidan

List of participants

O.

Olivier Schwartz
Olson Natalie
Ooi Sarah
Oriol Llopis-Almela
Ottavi Anton

P.

Perelson Alan
Petit Paul
Planas Delphine
Prague Mélanie
Puisieux Nathan

R.

Ramírez Torres Lucía
Reeves Daniel
Regoes Roland
Reichl Udo
Reigadas Sandrine
Reiter Anna
Richert Laura
Rodriguez Rodriguez Lucero
Rost Gergely
Rüdiger Daniel
Ruiz Anne-Andrée

S.

Sachs Jeff
Saldana Fernando
Savel Hélène
Schiffer Joshua
Schroeter Juliane
Schulman Rafael
Schwartz Elissa
Seddon Benedict
Shinya Tsuzuki
Smith Amber
Somsen Elizabeth
Suresh Madheshvaran
Swain Arpit

T.

Tatematsu Daiki
Thiébaut Rodolphe
Tower Angela
Tran Nam-Anh

V.

van Dorp Christiaan
van Tilburg Sander
Varga Szilard
Vegas Rodriguez Alberto
Vemparala Bharadwaj
von Kleist Max

W.

Whittaker Dominic
Winkler Benjamin
Wittkop Linda
Woldegerima
Woldegebriel Assefa

Y.

Yates Andrew
Yoshimura Raiki

Z.

Zarnitsyna Veronika
Zhang Shengyuan
Zhukova Anna

Thanks to our sponsors !

ISOP
The mission of the International Society of Pharmacometrics (ISoP) is the promotion and advancement of the discipline of pharmacometrics, through Integration, Innovation, and Impact.

Gilead
This conference has received support from Gilead.

ANRS
ANRS (Emerging infectious diseases) is an autonomous agency of Inserm that facilitates, evaluates, coordinates and funds research into HIV/AIDS, viral hepatitis, secually transmitted infections, tuberculosis and emerging or re-emerging infectious diseases. This conference has received support from ANRS MIE.

Université de Bordeaux and France 2030
This project has received financial support from the French government within the framework of the France 2030 programme IdEx université de Bordeaux.

Vaccine Research Institute
The Vaccine Research Institute (VRI), Laboratory of excellence, was established by the French National Agency for Research on AIDS and viral hepatitis (ANRS - France REcherche Nord&sud Sida-HIV Hépatites) and the University of Paris-Est Créteil (UPEC) to conduct research to accelerate the development of effective vaccines against HIV/AIDS, HCV and emerging infectious diseases.

Math Bio Santé
This conference has received support from Réseaux thématique Math Bio Santé at CNRS.

Merck
This conference has received support from MSD.

PEPR MATH VIVES
This conference has received support from France 2030 Program - Mathématiques en interactions.

Inserm
This conference has received support Departement of Public Health at University of Bordeaux; Inserm Bordeaux Population Health and Inserm Paris IAME.

Table of contents

Oral Presentation (by alphabetical order of speaker)

Table of contents

Joint mechanistic modeling of viral and antibody responses to vaccines in Non-Human Primates to quantify SARS-CoV-2 mechanistic correlate of protection

Marie Alexandre*[1,2], Romain Marlin[3], Roger Le Grand[3], Rodolphe Thiébaut[1], Yves Lévy[4,5], and Mélanie Prague[1]

[1]University of Bordeaux, Inria Bordeaux Sud-Ouest, Inserm, Bordeaux Population Health Center, SISTM Team, UMR1219, Bordeaux – University of Bordeaux, Inria Bordeaux Sud-Ouest, Inserm, Bordeaux Population Health Center, SISTM Team, UMR1219, Bordeaux – France

[2]Institute for Computational Medicine, Johns Hopkins University, Baltimore, MD – United States

[3]CEA-Université Paris Sud, INSERM U1184, Immunology of Viral Infections and Autoimmune Diseases, IDMIT departement, IBFJ, Fontenay-aux-Roses, France – CEA-Université Paris Sud-Inserm U1184, IMVA/IDMIT Department/DRF/IBFJ – France

[4]Vaccine Research Institute – VRI – Henri Mondor Hospital, 94010 Créteil, France

[5]Institut Mondor de Recherche Biomédicale – INSERM U955, équipe 16 physiopathologie et immunothérapies dans l'infection VIH – Institut National de la Santé et de la Recherche Médicale - INSERM – 94010, Créteil, France

Abstract

Introduction The identification of correlates of protection (CoPs) against a pathogen could accelerate the development of vaccines. In a context of constant and rapid viral evolution leading to a large landscape of hybrid immunity as in SARS-CoV-2, it appears essential to identify and quantify CoPs in a global context of viral evolution. In a previous mechanistic modeling work, we identified the marker quantifying the inhibition of ACE2/RBD binding as a consistent mechanistic CoP against SARS-CoV-2 (Alexandre Elife 2022).

Methods We propose here to extend our previous study using mathematical modelling of preclinical data from SARS-CoV-2 vaccines. Our within-host mechanistic model was set up to quantify the protective threshold of this CoP against the spread of viral infection. To this end, we proposed a new within-host mechanistic model based on ordinary differential equations jointly describing viral and antibody dynamics following infection, and their mutual interactions. In particular, we focused on the generation of antibody-secreting cells induced by the presence of virions and their production of antibodies, as well as on the ability of antibodies to block new infections. From the estimated model parameters, we derived a protective threshold using the basic reproduction number (R0), indicative of the secondary infections one infected cell can cause. We then performed counterfactual simulations to better understand the immune mechanisms driving viral control depending on the immunological background of the NHPs. We used data from non-human primate studies evaluating three SARS-CoV-2 vaccines (two next-generation protein-based vaccines targeting the RBD

*Speaker

of Spike protein to CD40-expressing cells , and the original BNT162b2 mRNA vaccine) in n=34 animals (11 naïve and 23 Wuhan SARS-CoV-2 convalescent NHPs, of which 6 and 17 were vaccinated, respectively). Following vaccination, all animals were challenged with B.1.617.2 Delta SARS-CoV-2 variant and were intensively monitored with viral genomic and subgenomic RNA, and IgG binding to Delta RBD and inhibition of binding to human ACE2 measured for 30 days post-infection.

Results We validated the reduction of the rate at which cells are infected as the primary mechanism of protection against infection and its capture by the ACE2/RBD binding inhibition marker. An additional effect of natural immunity beyond antibodies and enhancing the elimination of infected cells was identified. An inhibitory antibody concentration against Delta variant of 20 AU/mL was deemed protective against viral replication following SARS-CoV-2 Delta infection in naïve animals. Additionally, we pointed out, qualitatively and quantitatively, the impact of the immunological background (naïve or convalescent vaccinated or not) on the inhibitory functionality of antibodies. In particular, we showed the stronger efficacy of antibodies to neutralize viruses in case of hybrid immunity. Finally, counterfactual scenarios highlighted first the role of the memory B-cell immune responses to elicit fast and efficient antibody response in immunized animals. Second, it emphasized the major role of target-cell depletion and humoral immune responses in viral control in naïve immune systems and immunized animals, respectively.
Discussion This original modeling study identified a threshold of protection relying on binding inhibitory antibodies generated either after infection or vaccination. These results were consistent regardless of the vaccines. This modeling work can be applied to other preclinical platforms and infectious diseases. The inclusion of a broader description of B-cell immune responses and the role of T-cell responses in viral control might enhance our understanding of natural and vaccine-induced protection, especially with the emergence of Omicron variants and their ability to escape neutralizing antibodies. Extending this work to human infection is now required to enhance knowledge on CoP and accelerate vaccine development.

Keywords: Mechanistic modeling, Viral dynamics, Neutralizing antibodies, Correlate of protection, Vaccines, SARS, CoV, 2, Non, human primates

Inferring virus dynamics from sequence genomic data

Samuel Alizon*[1], Louis Colliot[2], Vincent Garot[3,4], Laurent Jacob[3], Laurence Meyer[5,6], and Anna Zhukova[7,8]

[1]Centre interdisciplinaire de recherche en biologie – Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique, Collège de France, Paris, France, Université PSL – France

[2]Centre interdisciplinaire de recherche en biologie – Collège de France, Paris, France, Centre National de la Recherche Scientifique - CNRS, Institut National de la Santé et de la Recherche Médicale - INSERM, Université PSL – France

[3]Biologie Computationnelle et Quantitative = Laboratory of Computational and Quantitative Biology – Sorbonne Universite, Centre National de la Recherche Scientifique, Institut de Biologie Paris Seine – France

[4]Centre interdisciplinaire de recherche en biologie – Collège de France, Paris, France, Centre National de la Recherche Scientifique - CNRS, Institut National de la Santé et de la Recherche Médicale - INSERM, Université PSL – France

[5]Centre d'Epidémiologie et de Santé des Populations – Université Paris-Saclay, UVSQ, Inserm, CESP, Villejuif – France

[6]Département d'Epidémiologie et de Santé Publique – APHP, Université Paris-Saclay, Le Kremlin-Bicêtre – France

[7]Institut Pasteur, BB Hub – Bioinformatics and Biostatistics Hub, Institut Pasteur, Université de Paris – France

[8]Institut Pasteur, EDID – Evolutionary Dynamics of Infectious Diseases, Department of Computational Biology, Institut Pasteur, Université de Paris – France

Abstract

The way a virus spreads leaves footprints in its genome. The field of phylodynamics leverages this genetic information to estimate population dynamics parameters. This estimation is typically done in a likelihood-based framework.

Using data from the ANRS HIV PRIMO cohort in France, I will present results obtained using the state-of-the-art software package Beast2, which allows us to perform Bayesian inference on a time-scaled phylogenetic tree inferred from virus sequences. I will show how these can shed light on the epidemic trends in France and complement classical monitoring.

I will then introduce Teddy, our likelihood-free inference method which uses machine learning (neural network and transformers architecture) to obtain a function linking a multiple sequence alignment (MSA) to the median and quantiles of the posterior distribution of the value of population dynamics parameter interest. Under the common and tractable birth-death model on simulated data, HCV, and early COVID data, the inference obtained by

*Speaker

Teddy matches Beast2. An important difference is that the inference is done in a matter of milliseconds, which opens the possibility for website implementations.

These results show how phylodynamics can contribute to the surveillance of human virus infections and how new developments can further help the routine implementation of these methods.

Keywords: evolution, epidemiology, genomics, phylodynamics, Bayesian inference, machinea learning

Assessing the impact of vaccination against dengue viruses using long-term antibody measurements

Jair Andrade*[1], Adrien Mitard-De Girardier[2], Angkana Huang[1], Maria-Teresa Alera[3], Mary Noreen Chua[4], Taweewun Hunsawong[3], Derek Cummings[5], Heather Friberg[6], Jeffrey Currier[6], Adam Waickman[7], Aaron Farmer , Kathryn Anderson , In-Kyu Yoon , Alan Rothman[8], and Henrik Salje[1]

[1]University of Cambridge [UK] – United Kingdom
[2]Université Paris Cité and Université Sorbonne Paris Nord, Inserm, IAME, F-75018 Paris, France – Université Paris Cité – France
[3]Armed Forces Research Institute of Medical Sciences [Bangkok] – Thailand
[4]Chong Hua Hospital [Cebu City, Philippines] – Philippines
[5]Johns Hopkins Bloomberg School of Public Health [Baltimore] – United States
[6]Walter Reed Army Institute of Research – United States
[7]SUNY Upstate Medical University – United States
[8]University of Rhode Island – United States

Abstract

Dengue is a mosquito-borne infection caused by any of the four dengue virus serotypes (DENV1-4). This disease represents a significant global public health burden, with millions of infections occurring each year, resulting in several thousand deaths. Vaccination has long been recognised as a cornerstone of a multifaceted approach to mitigating the impact of the disease. However, for more than 75 years, developing a safe and effective dengue vaccine has been challenging, with only live-attenuated virus vaccines achieving licensure or reaching advanced clinical development. Progress in this area has been hampered by an incomplete understanding of immune responses following vaccination. To further complicate matters, reports of reinfections with the same serotype have challenged the paradigm that infections induce lifelong homotypic immunity. Here, we present the results of an analysis integrating data from a cohort study with a probabilistic framework that enables the evaluation of hypotheses regarding the level of protection against dengue virus infection conferred by vaccination. The cohort study data come from a long-term follow-up of individuals (N = 611) in a phase III vaccine study, which included annual blood draws and active disease surveillance in Cebu, Philippines, where DENV1-4 co-circulate. All participants, most of whom were dengue-experienced, received three doses of either Dengvaxia or a placebo. In this study, the degree of protection was defined as the number of serotypes against which the vaccine prevents infection, accounting for the individual's infection history and the possibility that the vaccine elicits immune responses to specific serotypes. The results suggest that the vaccine's protection is skewed towards a single dominant serotype, and this protection is of shorter duration compared to natural infection.

Keywords: Dengue, Vaccine, Antibodies, Vaccine Efficacy, Temporal Immunity

*Speaker

Traveling Waves in a Cell-to-Cell Transmission Model

Yusuke Asai*[1], Shingo Iwami[2], and Yoshihisa Morita[3]

[1]Laboratory of Mathematical Epidemiology, Department of Data Science, Center for Clinical Sciences, Japan Institute for Health Security – Japan

[2]Interdisciplinary Biology Laboratory (iBLab), Division of Natural Science, Graduate School of Science, Nagoya University – Japan

[3]Department of Applied Mathematics and Informatics, Ryukoku University – Japan

Abstract

Introduction:
Viral infections progress through a process in which an invading virus infects a host target cell, which then produces progeny viruses that go on to infect new target cells. While cell-free infection -in which viral particles released by infected cells infect other target cells-has been the conventional model, cell-to-cell infection, in which infected cells directly transfer significant quantities of viral particles to target cells, is also increasingly recognized.

Iwami et al. revealed that cell-to-cell infection accounts for 60% of HIV-1 infections (1) and that this transmission route plays an important role in transmission dynamics. Cell-to-cell infection involves the spread of a virus from infected cells to neighboring target cells and can be regarded as a nonlinear diffusion process. In this study we describe the cell-to-cell infection using a system of differential equations and demonstrate the emergence of traveling waves representing the spreading process.

Methods:

Using Kim et al.'s experimental system as a reference, we considered a discrete spatio-temporal model consisting of four compartments (target cells, eclipse phase cells, infectious phase cells, and dead cells) (2), in which target cells are infected by the neighboring infected cells (3). We performed numerical simulations to explore the spread of the infection and, using a moving coordinate frame, derived a lattice dynamical system describing the profile of traveling waves. By applying a Taylor expansion to the infection-related terms, we approximated this system to obtain a system of four-dimensional ordinary differential equations with the traveling wave speed as an unknown parameter.

Results:

We verified through numerical simulations that the solutions to the model system, consisting of target cells, eclipse phase cells and infectious phase cells, indeed generated traveling waves at the spreading fronts. To justify the existence of these traveling waves, we analyzed an approximate system derived from the model. By reducing the original four-dimensional system to a two-dimensional one with the wave speed as a parameter, we applied phase plane analysis and identified heteroclinic orbits corresponding to traveling waves in a specific

*Speaker

parameter regime. We also compared the rigorous solutions of the approximate system with the profiles obtained from the numerical simulations, and they showed good agreement.

Discussion:

While it is difficult to rigorously demonstrate the existence of travelling wave solutions in the original spatially discrete model, the approximate system yields a well-structured dynamical system exhibiting heteroclinic orbits corresponding to traveling waves. Our numerical computations show that the solutions of the approximate system provide a good approximation to those of the original model. We emphasize that, unlike conventional diffusion models, the cells themselves do not move but the infectious state spreads. Furthermore, the spreading process is described by nonlinear coupling between infectious phase cells and target cells, which leads to an ill-posed diffusion system when directly approximated in continuous form. Therefore, the approximation is only allowed in the lattice dynamical system formulated with a moving coordinate.

Although the present study focused on qualitative evaluation, we believe that the proposed model has potential for quantitative analysis, which we leave for future work. We hope that our approach will be applicable to other viral dynamics, including plaque assays and fitting to real experimental data.

Reference:

1. Iwami S, Takeuchi JS, Nakaoka S, Mammano F, Clavel F, Inaba H, Kobayashi T, Misawa N, Aihara K, Koyanagi Y, Sato K. Cell-to-cell infection by HIV contributes over half of rivus infection. Elife. 2015 Oct 6:4:e08150. doi: 10.7554/eLife.08150.

2. Kim KS, Kondoh T, Asai Y, Takada A, Iwami S. Modeling the efficiency of filovirus entry into cells in vitro: Effects of SNP mutations in the receptor molecule. PLoS Comput Biol. 2020 Sep 28;16(9):e1007612. doi: 10.1371/journal.pcbi.1007612.
3. Kendall DG. Mathematical models of the spread of infection, Mathematics and Computer Science in Biology and Medicine, Medical Research Council, 213-225, 1965.

Keywords: viral infection, cell to cell transmission, traveling wave, differential equations

Dynamic maintenance of tissue-resident memory T cells

Jose Borghans*[1], Elena De Dios Panal[1], Lyanne Derksen[1], Carina Bruckmaier[1], Erdem Sanal[2], Rob De Boer[2], and Kiki Tesselaar[1]

[1]UMC Utrecht – Netherlands
[2]Utrecht University – Netherlands

Abstract

Introduction: Tissue-resident memory T (TRM) cells are essential for long-term immunological protection. They vastly outnumber memory T cells in the blood, provide rapid, local protection, and play a major pathogenic role in localized autoimmune diseases. Various studies have demonstrated the remarkable persistence of TRM cell populations across different tissues in both humans and mice. These observations have fueled the idea that TRM cells are long-lived cells. In fact, the long-term persistence of a TRM cell population does not imply that the individual TRM cells are long-lived. TRM cell populations may equally well maintain themselves through continuous cell division, similar to circulating T cells, and their maintenance mechanisms may even depend on the tissue in which they reside.
Methods: Here, we investigated the maintenance mechanisms of TRM cells in different tissues in mice and humans using *in vivo* stable isotope labelling. We gave deuterated water (2H2O) to humans and mice and followed the uptake and loss of deuterium from the DNA of different TRM cell populations. Because standard lab mice have hardly any memory T cells in tissues, we made use of wildling mice, i.e. C57Bl/6 mice born to wild mice, which carry the natural microbiome of their wild mothers, leading to more natural frequencies of memory T cells, especially in tissues. TRM cells from humans were obtained from patients undergoing an elective hip operation or abdominoplastic surgery, who drank 2H2O in the weeks prior to their operation. We isolated memory T cells from various mouse (bone marrow (BM), spleen, lung, and liver) and human tissues (blood, BM, adipose tissue, dermis, and epidermis), and followed their deuterium incorporation over time using gas chromatography/mass-spectrometry. The resulting labelling data were interpreted using mathematical models.

Results: In mice, we found that the lifespans of TRM cells depended on the tissue they were isolated from. Nevertheless, all TRM cells had shorter lifespans than naive T cells. CD69- memory T cells had the same kinetic behavior across tissues, consistent with a model of constant exchange of CD69- memory T cells between tissues and blood. CD69+ CD4+ (but not CD8+) memory T cells from BM and spleen had approximately two-fold longer lifespans than their CD69- counterparts. We found no evidence for a substantial subpopulation of long-lived TRM cells in any of the tissues in mice. In humans, the expected lifespans of CD69+ and CD69- TRM cells were not significantly different, whether in skin, adipose tissue or BM. Most TRMcells had expected lifespans that were very similar to those of memory T cells circulating through the blood. Only BM-derived TRM cells had significantly (approximately two-fold) longer lifespans. Similar to our observations in mice, we found that all

*Speaker

memory T cells, whether in circulation or in the tissues, had shorter expected lifespans than naive T cells.
Conclusion and discussion: Taken together, our data suggest that both in mice and humans, the expected lifespan of TRM cells depends on their tissue of residence. The vast majority of TRM cells in wildling mice and humans are as short-lived as circulating memory T cells, while the BM might offer a niche for longer-lived memory T cells. The observation that all memory T cells, whether in circulation or in tissues, were shorter-lived than naive T cells suggests that longevity is not an intrinsic characteristic of memory T cells. Instead, immunological memory is due to memory T cells, including TRM cells, that are maintained dynamically.

Keywords: T cells, Trm cells, tissue, resident T cells, lifespan, deuterium, dynamics

Time and Space in Models of Nascent Viral Infection

Daniel Coombs*[1], Catherine Byrne[1,2], and Soren Gantt[3]

[1]University of British Columbia – Canada
[2]Eupraxia Pharmaceuticals – Canada
[3]Centre de recherche du CHU Sainte-Justine, Montréal – Canada

Abstract

Introduction: The first few hours and days following exposure to a virus are critical to the success or failure of a potential infection, or from another point of view, failure or success of the early immune response. Given low numbers of viral particles present at this point, stochastic mathematical models are useful tools for building understanding and suggesting important topics for experimental investigation. A second important feature of many infections is virus dissemination from the immediate environment of the site of infection to other tissues. Spatial effects of this type can be modelled using coupled systems of equations for the different compartments. In this talk, I will describe the simplest possible models for nascent viral infection (originally developed in the context of HIV) and then move on to more complex scenarios, especially including a multi-site model developed for murine CMV (MCMV).
Methods: I will describe multi-type branching process models, which are analogues of more familiar differential equation models, and show how they can be fit to data in a Bayesian fitting framework. To study the relationship between the immune response and viral replication in MCMV infection of mice, and viral dissemination from the site of infection to other tissues, we characterized the viral and immunological dynamics at the site of infection, in blood and lymphoid tissue, and identified organ-specific immune correlates of protection. Experiments were performed to directly visualize the spread of labelled MCMV within mice, and we used flow cytometry to assess the activation of immune cell responses to infection.
Results and Discussion: Simplistic branching process descriptions of viral infection can yield interesting general insights into infection processes. However, many questions remain concerning the details of the processes, and these details are likely to be critical determinants of the efficacy of pharmaceutical or immune-based prevention of infection. In the context of MCMV, we provide detailed data on the spatial and temporal spread of infection throughout the body and identify key immune correlates of the control of viral replication. By translating our experimental findings into mechanistic mathematical models, we are able to estimate the importance of organ-specific immune responses, and particularly the ability of cytokines TNF-α and IFN-γ to control infection within the salivary glands. Our work underlines the importance of cellular immune responses in different organs and points to a threshold of infection at the original site of infection which is necessary for the establishment and spread of infection throughout the animal. Looking forward, additional work in other virus host systems will tell us whether our results can be more broadly generalized. Overall, we hope that mathematical models of this type will give guidance for developing targeted vaccines and therapeutics to prevent infection and disease.

*Speaker

Keywords: viral infection, dissemination, mathematical modelling, stochastic models, murine cytomegalovirus

REGULARIZED ESTIMATION IN HIGH-DIMENSIONAL MECHANISTIC MODELS

Lisa Crépin*[1], Sarafa Iyaniwura[2], Joshua Schiffer[3], Morgan Craig[4], Cécile Proust-Lima[5], and Mélanie Prague[6]

[1]Université de Bordeaux, Inria, Inserm, Bordeaux Population Health Research Center, Vaccine Research Institute, Créteil, France – Univ. Bordeaux; Inserm U1219 BPH ; Inria SISTM team; VRI; – France
[2]Fred Hutchinson Cancer Center, Seattle, USA – United States
[3]University of Washington, Vaccine and Infectious Disease and Clinical Research Divisions at the Fred Hutchinson Cancer Center – United States
[4]Université de Montréal, Centre de recherche Azrieli du CHU Sainte-Justine, Montréal, Canada – Canada
[5]Université de Bordeaux, Inserm, Bordeaux Population Health Research Center – Bordeaux Population Health Center, INSERM U1219, Bordeaux, Biostatistic team, University of Bordeaux – France
[6]Université de Bordeaux, Inria, Inserm, Bordeaux Population Health Research Center, Vaccine Research Institute, Créteil, France – Univ. Bordeaux; Inserm U1219 BPH ; Inria SISTM team; VRI; – France

Abstract

Mechanistic models are widely used to describe and explain biological processes over time. However, they typically rely on a limited number of observable compartments and sparse longitudinal data. As a result, these models are often either too simple to capture complex biological phenomena, such as immune response dynamics following vaccination, or they face identifiability issues, particularly when considering interindividual variability in the form of nonlinear mixed-effects models based on systems of differential equations. In parallel, with ongoing technological advances, longitudinal high-throughput data (e.g., -omics, including transcriptomics and proteomics data) are increasingly available in various contexts and could bring valuable information into mechanistic models to better capture underlying biological processes. However, when considering complex models with multiple unobserved compartments, integrating such high-dimensional data to inform the dynamics of unobserved biological compartments remains a major challenge, both mathematically and for broader public health applications. We hypothesize that observed -omics biomarkers can be used to infer and explain the dynamics of unobserved immune compartments. Our goal is therefore to find biomarkers that can accurately translate the dynamics of these compartments.

Here, we propose an estimation and regularization method for mechanistic models that involve multiple unobserved compartments, measured by high-dimensional longitudinal biomarker data. We aim to identify relevant biomarkers by regularizing the parameters linking them to the latent unobserved compartments while simultaneously estimating the population parameters from the structural mechanistic model. To do so, we are developing an iterative algorithm able to estimate and regularize all the parameters of the model. The algorithm iterates between a regularization step and a mechanistic inference step. The first step updates

*Speaker

coefficients linking latent compartments to biomarkers by computing penalized log-likelihood derivatives, approximated via second-order Taylor development. The mechanistic inference step focuses on estimating the mechanistic parameters using the Stochastic Approximation Expectation-Maximization (SAEM) algorithm, implemented through the Monolix software, considering the updated regularized coefficients from the first step. This approach allows us to find which biomarker's dynamics can accurately describe the dynamics of the unobserved compartments of our model.

To demonstrate our methodology, we investigated the robustness of the proposed approach in simulation and use it in an application of virus dynamics. Killingley et al. (*Nature Medecine*, 2022) examined early immune responses in infection-naïve individuals and measured cytokines levels of 36 individuals for 17 days after challenge with SARS-CoV-2. We also use the measures of viral load across time to inform on the observed compartment of viruses. To find which cytokine accurately translates the dynamics of unobserved compartments of our model of SARS-CoV-2 viral dynamics, in particular target cells (cells that can become infected when in contact with infectious virions) or infectious cells (cells that are infected and produce virions), we therefore apply our developed method implemented in the REMixed R package. Here, we will discuss this particular application and show how REMixed performs when integrating cytokine dynamics into a mechanistic model of viral dynamics after viral infection.

Keywords: Statistical learning, Regularization, High dimension, Model selection

Immune Responses May Make HIV-1 Therapeutic Interfering Particles Less Effective

Rob De Boer*[1] and Griffin Kutler Dodd[1]

[1]Utrecht University – Netherlands

Abstract

The current standard treatment for HIV-1 infection is antiretroviral therapy, which effectively suppresses viral replication but requires a lifelong drug regimen. An alternative treatment approach is a single injection of a modified version of the HIV-1 virus, termed a therapeutic interfering particle (TIP), that lacks replication machinery and suppresses the wild-type virus by competing for viral proteins. Here, we derive a novel model of TIP dynamics. We confirm results from previous models that TIPs can reduce viral load when doubly infected cells produce at least as many virus particles as singly infected cells. By deriving the basic reproduction number R0 of a TIP, we predict that concurrent antiretroviral therapy should make it more difficult for a TIP to persist in a host. Adding an immune response to our model reveals that even a moderate immune response against virally infected cells drastically decreases the range of parameter values for which therapy is effective. Together, these results show that the success of TIPs depend on the properties of the wild-type virus and even more strongly on the immune response, which makes it hard to predict therapeutic success.

Keywords: therapeutic interfering particles, HIV, modeling, immune response

*Speaker

Prevalence of asymptomatic infections: a window to the basal immunity to SARS-CoV-2

Akshay Tiwari[1], Shreya Chowdhury[1], Ananthu James[1], Budhaditya Chatterjee[1], and Narendra Dixit*[1]

[1]Indian Institute of Science [Bangalore] – India

Abstract

Introduction: The burden of the COVID-19 pandemic varied widely across nations. Was this variation due to the differences in the availability and/or access to healthcare or were there, additionally, intrinsic differences in the ability of the populations in the different nations to fight the pathogen? Commonly reported metrics of disease burden such as the hospitalization rate and the infection fatality ratio are dependent on health infrastructure, precluding an accurate assessment of the basal immunity to the pathogen. Yet, the pandemic offered a unique opportunity to assess the variation in basal immunity because it exposed the entire world's population to the same, new pathogen within a short time span. We reasoned that unlike severe infections, which most current metrics use, the prevalence of asymptomatic infections (psi), could serve as a measure of basal immunity unconfounded by health infrastructure. The higher the psi, the stronger would be the basal immunity of the population. Estimates of psi would thus help assess the role of basal immunity in the variation in disease burden across nations. Reliable estimates of psi, however, are lacking. Current methods to estimate psi suffer from an important methodological limitation. They rely on serosurveys, where individuals are tested for SARS-CoV-2 infections and simultaneously inquired about the occurrence of symptoms over a pre-defined recall period. Individuals who test positive but declare no symptoms are deemed asymptomatically infected. This method is compromised because the symptoms elicited by SARS-CoV-2 can also be elicited by other infections like common cold and influenza. Thus, individuals who may be asymptomatic for SARS-CoV-2 but may have acquired these latter infections during the recall period and experienced their symptoms may be misclassified as symptomatic for SARS-CoV-2. This misclassification is compounded by suboptimal test specificity and sensitivity. No methods exist to correct for this misclassification.

Methods: We developed a rigorous formalism that accounts for symptom overlap with other conditions as well as test specificity and sensitivity and enables accurate estimation of psi. The method exploits information of the occurrence of symptoms in individuals who test negative for the infection as a route to estimate the extent of symptom overlap. Next, we performed a comprehensive literature search to identify serosurveys that reported the information needed to apply our formalism. For comparison between nations, we considered surveys conducted on large samples representative of the general populations of nations and restricted to the early days of the pandemic, before mass vaccination programs began. We applied our formalism to data from each of the serosurveys and obtained estimates of psi. Finally, we collated national level metrics of demographic and socio-economic status of nations and evaluated factors that could explain the variation in psi across nations.

*Speaker

Results: Our formalism yielded a facile, analytical formula to estimate psi accounting for symptom overlap and test specificity and sensitivity. We applied it to data from 50 published serosurveys, collectively sampling _˜0.8 million individuals. We found that our corrected estimates of psi were significantly higher than previously reported estimates (psi_c) (median _˜60% versus _˜40%; P=4×10). In some instances, psi exceeded psi_c by over 100%. Symptom overlap explained _˜85% of the deviation between psi and psi_c, highlighting the importance of our correction. Further, in countries with multiple serosurveys, the variance in psi was significantly lower than in psi_c (P=0.015, one-tailed paired Student's t-test), implying that at least part of the variation in psi_c may have been due to the confounding from symptom overlap, which our formalism corrected. The correction, however, did not reduce the variation across nations, pointing to causes beyond methodological limitations.

To establish the latter variation further, we considered 26 serosurveys selected from our literature search that employed large, nationally representative samples. The nations spanned wide geographic locations, covering 4 continents, and the entire spectrum of socio-economic status. We observed an enormous variation in psi across the nations (range: 18%–99%; I^2 = 99.7%), highlighting the variation in the basal immunity across the respective populations.

To explain this variation, we performed meta-regression using national-level metrics of demographic and socio-economic status of nations. The human development index (HDI) emerged as the most powerful predictor of psi, with a significant negative correlation (P=5.6×10^1; R^2=58.5%). Demographic median age and the prevalence of cardiovascular disease, the latter a surrogate for comorbidities, were also negatively correlated with psi but explained much lesser of the variation in psi than HDI (R^2=43.8% and 25.1%, respectively). The correlation between psi and HDI was robust to confounding factors, including variability in the symptoms assessed and skewness in age distributions. The negative correlation implied that less developed nations tended to suffer fewer symptomatic infections.
Discussion: The higher prevalence of asymptomatic infections than previously estimated has significant implications. First, it will enable more accurate prediction of pandemic spread, which is driven substantially by asymptomatic infections. Second, it may help better assess vaccine efficacies, which are measured by estimating the fraction of potentially symptomatic infections they render asymptomatic. Third, it will inform ongoing efforts to ascertain the genetic and immunological origins of asymptomatic infections. The variation in the basal immunity of populations will help reassess the origins of the wide variation in disease burden across nations. That less developed nations were less vulnerable to symptomatic infections, and hence possibly also to severe infections, may have contributed to their ability to combat the pandemic despite limited healthcare access. Conversely, because asymptomatic infections go undetected, it may also have contributed to the greater spread of the pandemic in these nations. Future studies will ascertain the resultant of these opposing effects. We speculate that in addition to younger populations, the higher prevalence of other circulating pathogens in less developed countries may have offered greater protection from severe infection via trained immunity. Overall, these findings have implications for our understanding of immunity to novel pathogens as well as for future pandemic preparedness.

Keywords: asymptomatic infections, prevalence, serosurveys, immunity, HDI

Modelling Antibody Dependent Enhancement: Implications for Vaccine Design

Drake Riley*[1], Hasan Ahmed[1], and Rustom Antia[1]

[1]Emory University [Atlanta, GA] – United States

Abstract

Introduction

Dengue fever is a disease of global importance, causing approximately 400 million infections and 24 million deaths annually (1). The human immune system responds to dengue virus infection through a combination of innate (non-specific) and adaptive (specific) immune processes, including humoral and T-cell-based immunity. Specific antibodies against most viruses typically attenuate viral replication. In contrast, a characteristic of dengue virus is antibody-dependent enhancement (ADE), a phenomenon in which the presence of low antibody titers against the virus can enhance, rather than attenuate, viral replication (2, 3). High antibody titers prevent viral replication.

The phenomenon of ADE has been investigated both in vitro and in vivo, as well as in the context of epidemiological studies. In vitro studies have demonstrated that viral replication is enhanced at specific low antibody titers and curtailed at high antibody titers (4, 5). Similar results were observed in non-human primate studies conducted by Goncalves et al. (4). Goncalves et al. demonstrated in rhesus macaques that the passive transfer of low amounts of anti-dengue antibody prior to experimental dengue infection led to enhanced viral replication over the course of infection (compared to animals that did not receive antibody). In humans, prospective pediatric cohort studies have led to the epidemiological observation that individuals with low antibody titers within a specific range, so-called "enhancing titers," have a higher risk of severe infection than either naïve individuals or those with high antibody titers (6, 7). Surprisingly, then, a recent epidemiological study found that prior dengue infection (classified by IgM:IgG ratio) had little effect on the severity of subsequent dengue infections (8).

If immunization produces ADE, this could complicate the development of a dengue vaccine. This was an issue with Sanofi's Dengvaxia dengue vaccine, which in some cohorts enhanced disease severity.

The puzzle that emerges from these data is that while the in vitro and NHP studies show a pronounced effect of ADE - specifically, that infection severity is consistently and dramatically enhanced when enhancing concentrations of antibodies are present - the effect is muted or absent in some epidemiological studies (8). What other factors might play a role in the development of ADE-mediated severe disease?

Methods

*Speaker

To address these questions, we developed a mathematical (ODE) within-host model of dengue infection dynamics. The model builds on our previous modeling framework, which incorporates the following populations: target cells, virus, innate immunity, and adaptive immunity (9). We extend the earlier model by explicitly incorporating adaptive cellular immune responses, specifically the killing action of CD8+ (killer) T-cells, as well as a more detailed model for antibody production that includes plasma cells.

We use the model to explore the dynamics of dengue infections in the different scenarios mentioned above. We test the predictions of the model.

Results

We used the model to simulate how variable combinations of B and T-cell immunity, as they might exist prior to primary infection, secondary infection, after passive antibody transfer, and after vaccination, impacted the timing of viral clearance and the total amount of viral replication throughout the infection (AUC). We systematically varied initial conditions to explore the parameter space that determines ADE severity and to identify factors that differentiate individuals who develop severe disease (defined as higher AUC) from those who remain protected despite similar antibody profiles. We found the following:

1. Absence of immunity – in vitro infections: Our results recapitulate the dynamics of viral replication in cell culture conditions, and in the presence of low concentrations of antibody, in-vitro, demonstrate ADE. This finding is similar to our earlier results (9).

2. In vivo infections following transfer of antibody: Our simulation of the dynamics of infection in vivo in the presence of transferred antibodies recapitulates the results of the NHP studies mentioned earlier. Transfer of low concentrations of antibodies prior to infection resulted in enhanced viral titers during infections, whereas transfer of high levels of antibodies prevented infection.

3. Secondary infections: Since natural infection typically results in the development of both B- and T-cell immune memory, we investigated how altering the relative levels of these two types of immune responses impacted the dynamics of recall (secondary) responses. We found that while a regime existed in which prior humoral immunity could enhance virus replication through antibody-dependent enhancement (ADE), the presence of dengue-specific CD8+ T cells significantly limited viral replication and prevented severe disease enhancement, even in individuals with the enhancing antibody titers typically associated with an increased risk of ADE. The protective effect was dose-dependent, with higher levels of T-cell memory providing greater protection against enhancement.

Discussion

Our results suggest that considering CD8+ T-cell immunity could explain the apparent discrepancy between the pronounced effect of ADE observed in vitro and NHP studies and the muted effect observed in some epidemiological studies. The results of our simulations may also help explain the findings of the first Phase 3 Dengue vaccine trial, Dengvaxia, which was halted because, during the third year of the trial, dengue vaccination increased-rather than decreased-the risk of hospitalization resulting from subsequent dengue infection in participants under nine years old (10, 11). We hypothesize that this enhancement occurred because the vaccine primarily stimulated humoral responses without robust T-cell activation. Our results suggest that vaccines that elicit CD8+ T cell responses could generate protective immunity against severe dengue infections.

References

1. World Health Organization, Dengue and severe dengue (Fact sheet) (2024).

2. R. A. Hawkes, K. J. Lafferty, Virology 33, 250 (1967)

3. S. B. Halstead, Microbiol. Spectr. 2, 1 (2014)

4. A. P. Goncalvez et al., Proc. Natl. Acad. Sci. 104, 9422 (2007).

5. T. C. Pierson et al., Cell Host Microbe 1, 135 (2007)

6. H. Salje et al., Nature 557, 719 (2018).

7. L. C. Katzelnick et al., Science 358, 929 (2017).

8. C. Aggarwal et al., Nat. Med. 30, 670 (2024).

9. J. B. Nikas, H. C. Low, Z. Feng, PLoS One 17, e0266832 (2022).

10. S. R. S. Hadinegoro et al., N. Engl. J. Med. 373, 1195 (2015).
11. A. Wilder-Smith, E. Massad, PLoS Negl. Trop. Dis. 10, e0004566 (2016).

Keywords: antibody, dependent enhancement, ADE, within, host models, dengue, vaccine design

Patient Characteristics Modify the Antiviral Efficacy of SARS-CoV-2 Therapies: Insights from Meta-Analysis and Real-World Viral Load Data

Keisuke Ejima*[1]

[1]Nanyang Technological University [Singapour] – Singapore

Abstract

Introduction:
Antiviral treatments such as remdesivir, molnupiravir, and Paxlovid have been widely used against SARS-CoV-2, yet their clinical trial results show substantial heterogeneity. These inconsistencies may stem from differences in host characteristics that influence antiviral effectiveness, such as age and vaccination status. While prior studies have speculated on these modifying effects, quantitative insights remain limited. In this study, we employed a dual approach-meta-analysis of clinical trials and mathematical modeling using real-world viral load data-to systematically assess how host factors shape antiviral efficacy, focusing on drugs targeting viral replication (i.e., RdRp and Mpro inhibitors).

Methods:

We first conducted a systematic review and meta-analysis of registered clinical trials assessing the virological impact of remdesivir, molnupiravir, and Paxlovid. Trials were included if they compared viral load outcomes between treatment and control groups. Using logistic regression, we examined whether trial success (i.e., statistically significant viral load reduction) was associated with patient characteristics such as age, vaccination status, treatment timing, and hospitalization status.

In parallel, we analyzed high-resolution viral load data from 3,475 patients admitted to designated hospitals in Shanghai during the Omicron BA.2 outbreak. After propensity score matching, we applied a viral dynamics model incorporating pharmacokinetics/pharmacodynamics (PK/PD) of Paxlovid. The model estimated individual-level parameters, including infected cell clearance and treatment efficacy. We then explored associations between these parameters and patient attributes (e.g., age, sex, comorbidities, vaccination status) via multivariable regression.

Results:

Meta-analysis identified 22 eligible trials. Trial success was significantly associated with

*Speaker

younger participant age (OR 0.90 per year increase, p=0.04), higher vaccination coverage (OR 1.06 per 1% increase, p=0.05), early treatment initiation (OR 0.38 per day delay, p=0.03), and outpatient status (OR 44.0 vs hospitalized, p=0.004). Trials on remdesivir were significantly less likely to demonstrate efficacy compared to molnupiravir (p=0.02). The real-world analysis revealed notable heterogeneity in Paxlovid efficacy. Older adults (≥65 years) exhibited reduced infected cell clearance and lower average treatment efficacy (–0.08, 95% CI: –0.14 to –0.01), whereas booster-vaccinated individuals had significantly enhanced treatment efficacy (+0.13, 95% CI: 0.06 to 0.20). Simulations indicated that early treatment-especially before peak viral load-resulted in transient viral suppression with frequent rebound after treatment cessation. These findings paralleled those observed in recent clinical trials.

Discussion:
This study integrates evidence from clinical trials and real-world modeling to demonstrate that antiviral efficacy is not uniform but strongly shaped by host factors. Age-related changes in immunity and pharmacodynamics likely diminish antiviral performance in older individuals, while vaccination-especially booster doses-enhances both innate and drug-mediated viral clearance. These findings underscore the importance of stratified analyses and individualized treatment approaches in antiviral trial design and clinical guidelines. Mechanistic modeling of viral dynamics complements empirical research by elucidating biological underpinnings and supporting more precise scenario-based planning for antiviral use. Future work should extend these analyses to other antiviral agents and viruses, and incorporate additional host variables such as immunocompromised status and genetic polymorphisms to further refine precision therapeutics in infectious diseases.

Keywords: antivirals, heterogeneous treatment efficacy, COVID

Clinical trial simulation suggests PCR underestimates molnupiravir's true potency against SARS-CoV-2

Shadi Esmaeili-Wellman*[1], Katherine Owens[1], Joshua Schiffer[2,1], Stephen Polyak[2], and Jessica Wagoner[2]

[1]Fred Hutchinson Cancer Research Center [Seattle] – United States
[2]University of Washington [Seattle] – United States

Abstract

Introduction

Molnupiravir is a mutagenic antiviral that introduces replication errors into the SARS-CoV-2 genome, rendering most viral particles nonviable. In the MOVe-OUT trial involving high-risk individuals, molnupiravir reduced hospitalizations by 50%, though it only lowered viral load by 0.3 log10 compared to controls. In the PLATCOV and PANORAMIC trials, the drug reduced viral load by _˜1 log10 relative to usual care. These inconsistent virologic and clinical outcomes across trials, conducted in different populations and against various variants, suggest causes beyond the drug's intrinsic efficacy. Furthermore, the SARS-CoV-2 polymerase chain reaction (PCR) detects replication-competent and replication-incompetent, drug-mutated viruses, potentially overestimating viral load, a factor not accounted for in trial analyses. We previously developed a pipeline combining a viral immune dynamics model (VID), validated against 1500 infections with different SARS-CoV-2 variants of concern, with pharmacokinetics (PK) and pharmacodynamics (PD) of nirmatrelvir/ritonavir to reproduce the results of two major trials. We expanded our pipeline to model molnupiravir's mechanism of action and fit the model to the virologic outcomes of MOVe-OUT, PLATCOV, and PANORAMIC trials.

Methods

We developed and validated our clinical trial simulation platform in multiple steps. 1)We established a SARS-CoV-2 VID model by fitting competing models to viral load trajectories from participants in a large natural history study of untreated individuals. 2)We established and validated a PK model for molnupiravir by fitting competing models to plasma drug concentrations from a phase one clinical trial. 3)We estimated dose-response model parameters by fitting a PD model to in vitro dose escalation data. 4)We merged the VID, PK and PD models into a single mathematical model to allow fits to viral load data from clinical trials. 5)We fit the combined model to longitudinal mean viral load reductions in the treatment versus control arms of the MOVe-OUT, PLATCOV and PANORAMIC trials. 6)We fit the combined models to individual viral load trajectories from treated and untreated participants in the PLATCOV and PANORAMIC trials. 7)We estimated the individual and population values of the potency adjustment factor (paf) for molnupiravir in each trial. The paf is the

*Speaker

ratio of molnupiravir's in vitro EC50 to its in vivo EC50 (=paf*EC50in vitro) defined as the plasma drug concentration associated with 50% reduction in viral replication. 8)We used the validated model to perform a detailed analysis of each trial's outcomes and to assess various virologic endpoints that account for the mutagenic mechanism of action of molnupiravir.

Results

We estimated the paf using two approaches. First, we used population-level fitting using combined VID+PKPD model to the average viral load drop from the baseline of the three trials. We randomly selected 400 individuals from the large natural history cohort with the closest matching viral variant and symptom status. We simulated the viral load kinetics of the virtual cohort without treatment, and then compared the control arm of each trial to validate how closely the virtual cohort represents the trial participants. We then simulated the viral load drop of the virtual participants under treatment and estimated a population value of paf. Second, we fit the combined model to the individual viral load data from the PLATCOV and PANORAMIC trials and estimated paf values for each individual. Overall, our results suggest that the in vivo potency of molnupiravir is 6-7 fold higher than the value estimated from the in vitro data in PLATCOV and PANORAMIC and _˜2.5 fold lower in MOVe-OUT.

We then used our validated model to project and compare the trajectory of non-mutated viral RNA during treatment relative to the total viral RNA detected by PCR. Our results show that in PLATCOV and PANORAMIC trials, the non-mutated viral RNA dropped _˜0.4 log more than total viral RNA by day 5 after treatment. In all three trials, the area under the curve for non-mutated viral RNA during the treatment was significantly lower than total viral RNA in treated individuals. A high percentage of detected SARS-CoV-2 viral RNA after a day of therapy was drug-mutated.

Our results also showed that the trial design, including the baseline viral load and the limit of detection of the assay used to assess viral load, can impact the drug's observed efficacy.

As with nirmatrelvir/ritonavir, our model suggests that five-day treatment initiated early during infection increases the chance of viral rebound.

Discussion

Our combined VID+PKPD model recapitulated virologic endpoints and individual viral load trajectories in three molnupiravir trials. Our results suggest that the limited observed viral load reduction in the MOVe-OUT is due to the drug's lower in vivo efficacy against pre-omicron variants of concern. In contrast, our model estimated a lower paf value for PLATCOV and PANORAMIC trials, suggesting enhanced in vivo potency against the omicron variant. Our results confirm previous work showing that in vitro assays are unreliable proxies for assessing the true potency of an antiviral. The in vitro EC50 is sensitive to assay conditions, including cell types, multiplicity of infection, and viral variants.

A key outcome of our study is that the PCR assay, which detects replication-incompetent drug-mutated viruses, likely underestimates the true potency of the drug and suggests that the trial endpoint should be tailored to the drug's mechanism of action. Similar to the HIV reservoir, an assay that only detects genetically intact virus would more reliably assess therapeutic efficacy.

Our results highlight challenges in trial design associated with the timing of enrollment, the selection of PCR assays, and the corresponding limits of detection. Different baseline viral loads and PCR assays' limit of detection impact the degree of viral load decrease that can be observed in a trial.

Our model had a few limitations. We assumed all mutated viruses are noninfectious; however, while rare, clustered infections with the molnupiravir mutation signature have been

detected in regions where the drug was widely used. Another limitation is that due to the lack of individual drug plasma concentration for the individuals in the trials, the same PK parameters were estimated using data from healthy individuals.
In summary, our model provides a more accurate assessment of molnupiravir potency and selection of trial design and virologic endpoints in future trials.

Keywords: Clincial Trial Simulation, SARS, COV, 2, Trial desing, Molnupiravir

Induction of multiple broadly neutralizing antibody lineages is modulated by precursor B cell composition and antibody epitope masking

Amar Kumar Garg*[1]

[1]Helmholtz-Zentrum für Infektionsforschung GmbH – Germany

Abstract

Induction of multiple broadly neutralizing antibody lineages is modulated by precursor B cell composition and antibody-epitope-masking
Amar K. Garg1, Michael Meyer-Hermann1,2

1Department of Systems Immunology and Braunschweig Integrated Centre of

Systems Biology, Helmholtz Centre for Infection Research, Braunschweig, Germany

2Institute for Biochemistry, Biotechnology and Bioinformatics, Technische Universität Braunschweig, Braunschweig, Germany

Introduction

An efficacious vaccine against HIV will likely need to generate broadly neutralizing antibodies (bnAbs) against distinct epitopes on the pathogen's envelope protein. However, elicitation of even individual bnAbs via vaccination has not been possible, partly because naive B cell precursors of mature bnAbs are physiologically rare and have poor affinity for native envelope proteins. To circumvent this, germline-targeting immunogens that can prime bnAb lineages by strongly binding and activating their precursors have been developed. Advanced versions of these immunogens can even bind to precursors of multiple bnAb lineages. However, it is not known if simultaneous targeting of numerous lineages with a single immunogen can diminish individual lineage output when compared to isolated targeting of lineages with distinct immunogens. A comprehensive understanding of the underlying competitive process is lacking and is an important knowledge gap. Illuminating this will be useful in assessing the utility of immunogens that parallelly target multiple bnAb lineages.

*Speaker

Methods

To address the above, we constructed an *in silico* model of naive B cell activation and affinity maturation in germinal centers (GCs). Here, activation of naive B cells was dictated by their affinity and abundance. The GC reaction model was based on a sophisticated agent-based simulation framework that extensively accounted for the spatio-temporal dynamics of its various constituents. In this scheme, bnAb lineage priming in primary GCs was modulated by the combined impact of precursor features such as affinity and frequency and antibody-epitope-masking.

Results

The model recapitulated prior observations made in experiments with humanized mouse models, thus producing a comprehensive picture of B cell interlineage competition. We then used this validated model to predict how variations in the binding-competent B cell precursor pool of germline-targeting immunogens impact priming of individual and multiple bnAb lineages. Our simulations revealed that simultaneous targeting of multiple bnAb lineages did not diminish individual lineage output at physiologically relevant precursor frequencies.

Discussion
Overall, our work suggests that simultaneous maturation of early bnAb lineages in GCs is viable under physiological conditions. As multiple bnAbs are likely needed for protection against HIV transmission, these results provide important evidence in support of immunogens targeting multiple bnAb lineages, thus guiding rational vaccine development.

Keywords: bnAbs, T and B cells, HIV cure and prevention, germinal centres

Viral dynamics of the Respiratory Syncytial Virus during experimental human challenge infections : insights for transmission and treatment

Jeremie Guedj*[1]

[1]INSERM U738 – Inserm : U738 – CHU Bichat 75018 Paris, France

Abstract

Introduction: Respiratory syncytial virus (RSV) is a major public health concern, particularly in infants and elderly (1). Despite its epidemiological burden, the severity of RSV infection is largely underestimated, and the scarcity of data available has limited the development of mathematical models to characterize host-pathogen interaction in RSV infection. Consequently fundamental aspects of virus pathogenesis remain poorly understood, such as its viral dynamics, the duration of infectiousness, the onset of adaptive immunity or the optimal treatment window for potential antiviral treatment strategies (2)(3)(4). In that perspective, experimental challenge studies provide unique insights to characterize in detail within-host infection kinetics, as shown during Covid-19 Pandemic (5).
Objective:

Here we aimed to couple a mathematical modelling approach with high-resolution experimental challenge study data to uncover fundamental aspects of RSV infection:

- Characterize RSV viral dynamics and its variability in the population
- Estimate basic within-host and epidemiological metrics
- Anticipate the antiviral efficacy of direct antiviral agents and monoclonal antibodies

Methods: We analyzed data from 252 RSV infected individuals aged between 18 and 45 years who participated in experimental challenge studies with frequent sampling of both RNA viral load (V) and infectious virus (VI).
For the construction of the model, we started with a target cell limited (TCL) model and sequentially incorporated innate and adaptive immune responses. We also defined the relationship between VI and V. Model selection was done by using the corrected Bayesian Information Criterion (BICc.)
We computed key metrics, including area under viral curve (AUC), time to viral peak, time to viral clearance and the generation time which is the mean interval between infection of a primary case and his secondary case.
Finally, we evaluated the efficacy of different antiviral treatment strategies, depending on the timing of administration (prior or after exposure), the mechanism of action (neutralizing virus or blocking viral production), the drug EC50 and the duration of protection.

Results: Our analysis reveals that infectious titers increase sub-linearly relative to viral

*Speaker

RNA levels. Adaptive immunity was estimated to start around day 7 post-infection, with humoral immunity driving a decrease in infectivity and cell-mediated immunity significantly reducing cell lifespan (infected cell half-life) decreasing from 1.38 to 0.12 days.

Infectious virus was cleared by day 8 (95% prediction interval: 5-10 days), while viral RNA persisted until day 12 (95% prediction interval: 8-15 days.) The probability of detectable infectious virus was close to 0 after day 8, regardless of viral load level.

Using the model to simulate post-exposure prophylaxis of a putative drug, we found that a 7-day treatment with average drug concentrations greater than the drug EC90 was required to reduce AUC of viral load and infectiousness by more than 80%, but the impact on the time to viral clearance was more modest. Pre-exposure prophylaxis with monoclonal antibodies could achieve more than 80% on both AUC and time to clearance.

Conclusion: The combination of a rich dataset and a mathematical model enables the first detailed characterization of RSV within-host dynamics, capturing both population-level trends and individual variability. Our findings suggest that an 8-day isolation period post-infection could limit RSV transmission. Additionally, our treatment simulations highlight the challenges in achieving optimal virological efficacy. These results offer valuable guidance for the optimization of RSV treatment strategies in clinical trials.

References:

1. Y. Li, *et al.*, Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. *Lancet Glob Health* **7**, e1031–e1045 (2019).

2. N. Viguria, *et al.*, Effectiveness of palivizumab in preventing respiratory syncytial virus infection in high-risk children. *Hum Vaccin Immunother* **17**, 1867–1872.

3. D. Arbetter, *et al.*, Lower respiratory tract infections following respiratory syncytial virus monoclonal antibody nirsevimab immunization versus placebo: Analysis from a Phase 3 randomized clinical trial (MELODY). *Clin Infect Dis* ciae596 (2024). https://doi.org/10.1093/cid/ciae596.

4. D. Duong, What RSV interventions are in the research pipeline? *CMAJ* **195**, E19–E20 (2023).

5. B. Killingley, *et al.*, Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge in young adults. *Nat Med* **28**, 1031–1041 (2022).
6. S. A. Iyaniwura, *et al.*, The kinetics of SARS-CoV-2 infection based on a human challenge study. *Proceedings of the National Academy of Sciences* **121**, e2406303121 (2024).

Keywords: RSV, experimental challenge, mathematical model, transmission

Modeling broadly neutralizing antibody neutralization curves for biomarker discovery

Beatrix Haddock*[1], Bryan Mayer[1], and Daniel Reeves[1]

[1]Fred Hutchinson Cancer Center – United States

Abstract

Introduction: The HIV Vaccine Trials Network (HVTN) has tested passive administration and vaccine induction of broadly neutralizing antibodies (bnAbs) for HIV prevention and therapy. Typically, the quality of bnAb response is quantified by its IC50 or IC80, or concentration at which 50 or 80% of viral infection is blocked during in vitro TZM-bl assays. We previously showed that in vivo neutralization by the bnAb VRC01 could be indirectly connected to IC50, though in vivo activity was _˜600x weaker than predicted by in vitro estimates. Therefore, we sought to develop models that could fully interrogate "neutralization curves": the complete relationship between the concentration of a bnAb (or bnAb combination) and percent neutralization against a certain HIV virus. In particular, our goals were to 1) rigorously model variability across all data using population nonlinear mixed effects (pNLME) modeling with covariates for each bnAb and virus combination, 2) confirm in vitro neutralization resembles ex vivo neutralization (where serum from people who received bnAb infusions is used as a product), 3) determine accurate combination models, and 4) identify extended metrics summarizing neutralization curves beyond IC50 and IC80.

Methods: We analyze data from 5 HVTN clinical trials and include 3 monoclonal bnAbs tested for neutralization against 32 HIV viruses. We also explore neutralization curves derived from 2 double and triple bnAb combinations against 21 viruses. We fit 4- and 5-parameter logistic (4PL/5PL) models using pNLME in Monolix to neutralization curves, iterating each model to reduce the number of random effects and covariates. For each bnAb or bnAb combination we chose a best model based on parameter stability and Monolix-calculated likelihoods. We tested two models for combination neutralization. First, we took the models fit to each bnAb (i) and combined them with a mean-parameter model, such that each parameter
theta is the mean of the individuals, e.g.,
*theta*_combo=⟨
*theta*_i⟩. Second, we used a Bliss Hill model such that the total neutralization () follows _combo=1-Π_i(1-_i). We also compared the R^2 of these models against those of a 5PL model fit directly to the combination bnAb data. We repeated the above exercise with ex vivo samples from two clinical trials: HVTN 127 and HVTN 130. We calculated interpretable summary metrics of the 4PL and 5PL model curves, examined their variance across samples, and their correlation with one another and to IC50 and IC80.

Results: We successfully fit large pNLME models to all bnAb and virus pairs both for in vitro and ex vivo data and for monoclonal and combination bnAbs. We examined VRC07-523LS for correlation between in vitro and ex vivo parameter estimates for the same virus,

*Speaker

and found good agreement for most but not all viruses. Both mean-parameter and Bliss Hill models performed well (R^2> 0.94 for all), with Bliss Hill performing slightly better on average. Additional metrics including neutralization AUC, inflection point (concentration and height), and Hill slope had low Spearman rank correlation with IC50 and IC80 (ρ< 0.16 for all), suggesting they are possible novel biomarkers that summarize different information from neutralization curves.

Discussion: We developed a pNLME modeling framework to comprehensively model bnAb neutralization data across bnAb (and bnAb combinations) / virus pairs for both in vivo and ex vivo data. We saw significant variability in neutralization curves across replicates and for different bnAb / virus pairs such that borrowing strength via pNLME across all data allows us to fit a more robust model. Our combination models fit well but data for combination bnAbs were relatively limited to near 1:1 concentrations, such that further investigation is required to determine the optimal combination models in more skewed concentrations. These models will be critical to predict future combination bnAb studies in which each bnAb has different pharmacokinetics such that ratios vary after infusion. In our preliminary investigation of different summary metrics of neutralization curves, we found several that do not correlate with IC50 or IC80, suggesting they encapsulate additional information and could be alternative biomarkers. In the future, we plan to extend our model to available data from 27 more trials and test our metrics for correlation with in vivo efficacy from existing treatment and prevention trials.

Keywords: broadly neutralizing antibodies (bnAbs), neutralization, IC50, IC80, biomarkers, population nonlinear mixed effects modeling, covariates

Modeling the impact of high-dose versus standard-dose influenza vaccines on antibody breadth and vaccine efficacy

Andreas Handel*[1]

[1]University of Georgia – United States

Abstract

Introduction:

Older adults are at increased risk of severe influenza outcomes due to immunosenescence, yet standard inactivated influenza vaccines often elicit suboptimal immune responses in this population. To address this limitation, a high-dose (HD) formulation of the Fluzone vaccine was developed and recommended for individuals aged 65 years and older. Previous studies have shown improved homologous antibody responses and reduced clinical severity with HD vaccines. However, the impact of HD vaccination on heterologous antibody responses-critical for protection against mismatched strains-and the degree to which HD vaccines improve overall vaccine efficacy (VE) compared to standard-dose (SD) vaccines remains less well characterized.

Methods:

We applied models to data from an ongoing prospective influenza vaccination cohort, spanning the 2013–2014 to 2021–2022 seasons across study sites in Florida, Pennsylvania, and Georgia. Participants aged ≥65 years could elect to receive either SD or HD Fluzone vaccines, while younger participants received SD vaccines. Hemagglutination inhibition assays measured antibody titers pre- and post-vaccination against vaccine strains and several historical influenza A strains. To quantify the causal effect of HD versus SD vaccination, we fitted Bayesian multilevel regression models to titer outcomes, accounting for confounders including age, prior immunity, study site, and influenza season. Models incorporated random intercepts and flexible smoothing splines to capture non-linear covariate effects. We computed average causal effects (ACEs) for titer increases and additional outcomes such as post-vaccination titers, seroprotection, and seroconversion. Separately, using a previously published logistic model that relates HAI titers to protection probability, we estimated VE for different groups by comparing risks derived from pre- and post-vaccination titers. Comparisons were made among younger adults receiving SD vaccines (YASD), older adults receiving SD vaccines (OASD), and older adults receiving HD vaccines (OAHD).

Results:

*Speaker

We found that HD vaccines generally led to improved heterologous antibody responses, but the magnitude and consistency of the benefit varied substantially by influenza strain and vaccine component. For H1N1 vaccine strains, HD vaccination produced higher titer increases across most historical strains. However, responses to older H1N1 strains were sometimes diminished or unchanged. For H3N2 vaccine components, HD vaccination induced slightly higher responses for some strains, but showed neutral or even negative effects for other strains. Overall, while the models indicated a positive trend favoring HD vaccines, the effects were modest and not consistent. When examining estimated vaccine efficacy, HD vaccination improved VE in older adults relative to SD vaccination in the same age group, but the magnitude of improvement was again modest. Younger adults receiving SD vaccines often achieved higher estimated VE than older adults receiving HD vaccines. Overall, the estimated impact of HD vaccine on modeled VE was positive but small.

Discussion:

Our findings suggest that while HD Fluzone vaccination provides a modest improvement in heterologous antibody responses and estimated vaccine efficacy in older adults compared to SD vaccination, the overall effect sizes are small and vary by influenza subtype, vaccine strain, and season. Importantly, HD vaccination often did not fully restore the level of protection observed in younger adults. Evaluation of further increased doses across all age groups might be warranted.

Keywords: influenza, vaccines, Bayesian modeling, correlate of protection, dosing

COVID-19 vaccination and waning immunity

Jane Heffernan*[1]

[1]York University – Canada

Abstract

We study the amplification and waning of COVID-19 vaccined-induced immunity using a mathematical model of immune system and vaccine dynamics in-host. The model is used to quantify outcomes in many COVID-19 studies using different vaccines, and different laboratory protocols and assays. It is also used to quanitfy outcomes by age and sex.

Keywords: COVID, 19, vaccination, waning, assay

*Speaker

RISE: Two-Stage Rank-Based Identification of High-Dimensional Surrogate Markers Applied to Vaccinology

Arthur Hughes[1,2,3], Layla Parast[4], Rodolphe Thiébaut[5], and Boris Hejblum[*6]

[1]Bordeaux population health – Université de Bordeaux, Institut de Santé Publique, d'Épidémiologie et de Développement (ISPED), Institut National de la Santé et de la Recherche Médicale, Institut National de la Santé et de la Recherche Médicale : U1219 – France

[2]Vaccine Research Institute [Créteil, France] – Université Paris-Est Créteil Val-de-Marne - Paris 12 – France

[3]Statistics In Systems biology and Translational Medicine – Inria Bordeaux - Sud-Ouest, Bordeaux population health – France

[4]University of Texas at Austin [Austin] – United States

[5]University of Bordeaux, Department of Public Health, Inserm Bordeaux Population Health Research Centre, Inria SISTM – Inserm Bordeaux Population Health Research Center UMR 1219, Inria centre of Bordeaux University, team SISTM, F-33000 Bordeaux, France – France

[6]Univ. Bordeaux, ISPED ; Inserm U1219 BPH ; Inria SISTM team – Institut de Santé Publique, d'Épidémiologie et de Développement (ISPED) – France

Abstract

In vaccine trials with long-term participant follow-up, it is of great importance to identify surrogate markers that accurately infer long-term immune responses. These markers offer practical advantages such as providing early, indirect evidence of vaccine efficacy, and can accelerate vaccine development while identifying potential biomarkers. High-throughput technologies like RNA-sequencing have emerged as promising tools for understanding complex biological systems and informing new treatment strategies. However, these data are high-dimensional, presenting unique statistical challenges for existing surrogate marker identification methods. We introduce Rank-based Identification of high-dimensional SurrogatE Markers (RISE), a novel approach designed for small sample, high-dimensional settings typical in modern vaccine experiments. RISE employs a non-parametric univariate test to screen variables for promising candidates, followed by surrogate evaluation on independent data. Our simulation studies demonstrate RISE's desirable properties, including type one error rate control and empirical power under various conditions. Applying RISE to a clinical trial for inactivated influenza vaccination, we sought to identify genes whose expression could serve as a surrogate for the induced immune response. This analysis revealed a signature of genes appearing to function as a reasonable surrogate for the neutralising antibody response. Pathways related to innate antiviral signalling and interferon stimulation were strongly represented in this derived surrogate, providing a clear immunological interpretation.

Keywords: Surrogate markers, Transcriptomics, High, dimension, Vaccine, Biostatistics

[*]Speaker

Quantitative constraints limit the generation of a universal influenza vaccine

Cora Hirst*[1], Rajat Desikan[2], and Rustom Antia[3]

[1]Emory University – United States
[2]GSK – United Kingdom
[3]Emory University – United States

Abstract

Introduction
Viruses such as influenza escape protective immunity by changes in the structure of surface proteins (antigens) such as hemagglutinin (HA) that are the targets of neutralizing antibodies. This results in individuals being infected with many new virus variants of influenza over their lifetime, and requires the frequent reformulation of vaccines to generate antibodies to these new virus variants. One approach to overcome this problem is to generate broadly neutralizing antibodies (BNAbs) that target conserved sites on HA such as that are shared by the different virus variants. We develop a quantitative framework for primary and recall responses to respiratory virus infections. We then use these models to explore why repeated natural infections and conventional vaccinations do not generate protective levels of BNAbs to conserved epitopes, focusing on the conserved receptor binding site (RBS) and stem of HA. Our analysis considers the generation, function, and waning of BNAbs in the context of humoral immunity to antigenically variable sites on HA.
Methods
We develop models to describe the generation of responses to multiple epitopes on the head and stem of the HA. These models extend earlier studies by incorporating the multiple mechanisms by which preexisting immunity affects boosting: clearance of antigen by antibody; interference via epitope masking which prevents two antibodies binding to the same epitope and via steric hindrance from antibodies binding to nearby epitopes; and enhancement of humoral immunity via the generation of immune-complexes (antigen-antibody complexes).

We then use the outcome of the models for the generation and boosting of antibody responses to explore the effect of pre-existing antibodies on the function of BNAbs and how this can enhance or inhibit the clearance of virus.

We consider how the effect of pre-existing antibodies on the generation and function of new responses changes as antibody titers wane over time, both in the respiratory tract and systemically. We use these models to explore how waning immunity affects the generation and selection of new antigenic variants both at the within host and population levels.

Results and Discussion

*Speaker

We show that there are three modes of interference between antibodies which bind to variable and conserved epitopes. We term these kinetic, stoichiometric and asymmetric interference. We find that kinetic and stoichiometric interference limits the generation and boosting of BNAbs to the receptor-binding site while stoichiometric and asymmetric interference limit the generation and boosting of responses to the stem of HA.

Our models explore how polyclonal responses to multiple epitopes on the virus affect virus replication and clearance, and how these depend both on the site to which the antibody is bound and its isotype. We show that analogous to models of drug action antibody mixtures can show synergistic or antagonistic effects, but antibodies to variant-specific epitopes generally show antagonistic interactions with the functioning of BNAbs.

We show that the rapid waning of antibodies in the respiratory tract introduces intermediate levels of immunity within a host. Our models suggest that the intermediate levels of immunity generate a regime where antigenic variants are selected during the course of infection. We also find that this regime of intermediate immunity provides a selective advantage for the transmission of immune escape variants at the epidemiological level.

We explore the consequences of these constraints for the design of vaccination strategies and the development of universal influenza vaccines.

Keywords: Universal Influenza vaccine, multi, epitope models, waning immunity, antibody responses

A multi-scale modelling framework to assess the relationship between SARS-CoV-2 viral load and transmission in household studies

Nathanaël Hozé*[1], Lulla Opatowski[2], and Jérémie Guedj[3]

[1]IAME: Infection, Anti-microbiens, Modélisation, Evolution – Institut National de la Santé et de la Recherche Médicale - INSERM – France

[2]Epidemiology and Modelling of Antibacterial Evasion Unit – Université Paris-Saclay, UVSQ, Inserm, CESP, Villejuif, Institut Pasteur de Paris – France

[3]Université de Paris, IAME, Inserm, Paris, France – Centre de Recherche Inserm – France

Abstract

Understanding the drivers of SARS-CoV-2 transmission is essential for designing effective interventions, particularly in close-contact settings such as households. While viral load is widely believed to be a key determinant of transmission, quantifying its role remains challenging due to individual variability, asymptomatic infections, and the unobservability of transmission events. Household studies offer a controlled context for investigating the link between viral load dynamics and transmission, especially when combined with high-frequency sampling. However, such designs are costly, and their added value relative to simpler approaches remains unclear.

We present a multi-scale modelling framework that integrates within-host viral dynamics and between-host transmission processes in household settings. We developed a stochastic agent-based model of within-host viral kinetics that incorporates inter-individual variability. We developed a Bayesian inference approach implemented in Rstan, in which we jointly estimate individual-level parameters, infection times, and the relation between viral load and transmissibility. We conducted simulations under diverse scenarios of transmission potential and pathogen natural history to assess whether high-resolution viral load monitoring improves the reconstruction of transmission chains and the estimation of key epidemiological parameters.

We compare this rich sampling design to two more commonly used alternatives: (i) a design based solely on dates of symptom onset, and (ii) one incorporating qualitative viral detection (i.e., positive/negative status without quantification). We show that incorporating quantitative viral load data improves the accuracy of transmission chain reconstruction and enhances the estimation of key epidemiological metrics, including the probability of infection, generation interval, and incubation period. These findings provide quantitative evidence for the value of detailed viral load monitoring in household transmission studies and offer guidance for the design of future studies aiming to elucidate the role of viral kinetics in infectious disease spread.

Keywords: SARS, CoV, 2, multiscale model, transmission chain

*Speaker

Exploring IFN-γ's Role in Alveolar Macrophage Depletion During Influenza A Virus Infection

Cailan Jeynes-Smith*[1], Amanda Smith[1], and Amber Smith[1]

[1]The University of Tennessee Health Science Center [Memphis] – United States

Abstract

Introduction:
Influenza A virus infection has been repeatedly shown to decrease survival and impair bacterial clearance when followed by, or coinfected with, *Streptococcus pneumoniae*. The primary cause is the depletion of alveolar macrophages (AMs); however, the mechanism responsible for AMs depletion during influenza infection remains undefined. Studies have demonstrated that IFN-γ-/- or IFNγR-/- mice models have improved survival outcomes and bacterial clearance but inconsistently reduced AM depletion.

Methods:

We developed a mechanistic model of IFN-γ production during influenza A virus infection. We utilized cell data specific to the IFN-γ-producing subsets, and integrated median fluorescence intensity (iMFI) measurements. This model was validated against IFN-γ production during CD8+ T cell depletion. We then utilized the model to test the hypothesis that IFN-γ directly depletes AMs, alongside several alternate mechanisms of depletion, including: a combination of IFN-γ and TNFα signaling, direct viral infection of AMs, contributions from IFN-γ+ cell subsets, or exhaustion of AMs due to clearing dead cells.

Results:

Our modelling framework quantified relative contributions and nonlinear regulations, in addition to demonstrating the necessity of using the iMFI to define the balance between production and uptake to explain observed IFN-γ levels in the supernatant. We identified a potential compensatory mechanism for CD4+ T cell production of IFN-γ in the absence of a robust CD8+ T cell response. Furthermore, several mechanisms were found to equivalently explain AM depletion during influenza A virus infection. Notably, during CD8+ T cell depletion, we observed elevated IFN-γ levels in the supernatant without corresponding changes in AM abundance. If IFN-γ directly depletes AMs, we identified that there must be an increased rate of AM replenishment post infection to account for this discrepancy.

Discussion:

Our findings indicate that IFN-γ may contribute to AM depletion during influenza A virus infection; however, this is likely dependent on other cell types and signals. We identify that during CD8+ T cell depletion, there must be other interactions with IFN-γ which regulate

*Speaker

the depletion – either through secondary signals such as TNFα, or increased AM replication via enhanced monocyte recruitment.

Depletion studies, particularly those targeting signaling cytokines, can drastically alter other cell populations and cytokine profiles outside of the study target, making it difficult to identify direct effects. Mathematical modelling offers a complimentary method which can directly test mechanisms.
This work also highlights the importance of incorporating both cell subset data and functional intensity (iMFI) into cytokine modeling, enabling more accurate inference of production mechanisms and improved model predictions.

Keywords: Interferon, gamma, Influenza A, Alveolar macrophages, T cells, NK cells, Applied mathematics

Relating In Vivo Respiratory Syncytial Virus Infection Kinetics to Host Infectiousness in Different Age Groups

Ke Li*[1]

[1]Yale School of Public Health – United States

Abstract

Background: Respiratory syncytial virus (RSV) is a significant public health threat, particularly affecting pediatric populations and older adults. While viral kinetics-the within-host dynamics of infection-are known to vary by age, the contribution of these differences to population-level transmission remains poorly understood.
Methods: We developed a mathematical model within a hierarchical Bayesian framework to analyze viral kinetics in 53 individuals across different age groups. The model estimated key infection parameters and linked viral load trajectories to transmission probability through a probabilistic formulation.

Results: Our analysis revealed that children exhibited higher peak viral loads and longer shedding durations compared to other age groups. These characteristics imply a greater likelihood of transmission during the infectious period. To validate our model, we compared the estimated secondary attack rates by age group with empirical data from household transmission studies, observing strong concordance.
Conclusion: These findings underscore the critical role of age-specific viral kinetics in RSV transmission and suggest that targeted strategies considering age-dependent infectiousness may enhance control efforts.

Keywords: bayesian inference, mathematical model, RSV transmission, RSV viral load kinetics

*Speaker

Viral Dynamics Modeling: Helping Translate Human Challenge Study Results to Late-Stage in RSV

Laura Liao*[1] and Brian Maas[1]

[1]Merck Co., Inc., Rahway, NJ, USA – United States

Abstract

Introduction: Human challenge studies (HCS) in healthy participants are commonly used in development of respiratory syncytial virus (RSV) antivirals to quickly establish clinical proof of concept; however, their utility is unclear due to lack of translation to late-stage trials (1). To aid in the interpretation of challenge study results, a viral dynamics model (VDM) was developed for RSV.
Methods: The RSV VDM we developed is based on a previous model of within-host RSV infection (2), which is an extension of the standard target cell-limited model of acute viral infection (3-5). Our RSV VDM additionally includes: (i) compartments describing total virus (as measured by reverse transcription polymerase chain reaction (RT-PCR)) and infectious virus (as measured by plaque assay), (ii) a term to account for the rise of IgA and inability to detect infectious virus, (iii) a time-dependent infected cell death rate as a simple representation of the immune response.

Our approach was to inform the RSV VDM viral replication parameters with viral load (VL) data from challenge infection studies in healthy adults, and subsequently extrapolate into other late-stage populations such as pediatric and immunocompromised using observational VL data from natural infection. Parameter estimation was performed with nonlinear mixed effects modelling (Monolix) using individual level VL from HCS placebo arms, both published (6, 7) and in-house (8, 9). With healthy adults in a challenge setting as a reference group, we assumed that other populations (pediatric and immunocompromised) mainly differed in their immune response and effective virus inoculum size. Individual and summary level VL from published observational studies of untreated natural infection (10, 11) informed parameter differences in these other populations.

Results: VDM was used to estimate the drug effect of competitor antivirals from the treatment arms of published RSV HCS mean VL curves (6, 12). Clinical trial simulations of competitor HCS recapitulated the reported percent reduction in area under the curve (AUC) of log10 VL between treated and placebo arms at various dose levels. Extrapolating the estimated antiviral effect from competitor HCS into a Phase 2b trial, we simulated treatment in an immunocompromised population and predicted VL curves consistent with published competitor results (11). Our simulation suggested minimal reduction in viral load in the competitor's Phase 2b trial was likely due to late intervention time rather than a lack of drug effect.

Discussion: We discuss the utility of the RSV VDM to support decision-making for development of antivirals. The RSV VDM is a platform to explore the effect of antivirals on

*Speaker

VL in other populations where treatment start times, doses, and treatment duration can be varied. VDM provides a way to translate the virological effect of antivirals in HCS to late-stage studies.

References:

1. Lowensteyn, Y.N. and L.J. Bont, *Clinical Development of Respiratory Syncytial Virus Antivirals-What We Can Learn From Oseltamivir.* Clin Infect Dis, 2020. **71**(11): p. 2796-2798.

2. Gonzalez-Parra, G. and H.M. Dobrovolny, *A quantitative assessment of dynamical differences of RSV infections in vitro and in vivo.* Virology, 2018. **523**: p. 129-139.

3. Holder, B.P., et al., *Design considerations in building in silico equivalents of common experimental influenza virus assays.* Autoimmunity, 2011. **44**(4): p. 282-93.

4. Baccam, P., et al., *Kinetics of influenza A virus infection in humans.* J Virol, 2006. **80**(15): p. 7590-9.

5. Simon, P.F., et al., *Avian influenza viruses that cause highly virulent infections in humans exhibit distinct replicative properties in contrast to human H1N1 viruses.* Scientific Reports, 2016. **6**(1): p. 24154.

6. DeVincenzo, J.P., et al., *Oral GS-5806 activity in a respiratory syncytial virus challenge study.* N Engl J Med, 2014. **371**(8): p. 711-22.

7. Kelly, G., et al., *Use of qualitative integrative cycler PCR (qicPCR) to identify optimal therapeutic dosing time-points in a Respiratory Syncytial Virus Human Viral Challenge Model (hVCM).* J Virol Methods, 2015. **224**: p. 83-90.

8. Maas, B.M., et al., *Forward and reverse translational approaches to predict efficacy of neutralizing respiratory syncytial virus (RSV) antibody prophylaxis.* EBioMedicine, 2021. **73**: p. 103651.

9. Cheng, M.H., et al., *A Phase 2a, Randomized, Placebo-Controlled Human Challenge Trial to Evaluate the Efficacy and Safety of Molnupiravir in Healthy Participants Inoculated with Respiratory Syncytial Virus.* Pulm Ther, 2025.

10. Brint, M.E., et al., *Prolonged viral replication and longitudinal viral dynamic differences among respiratory syncytial virus infected infants.* Pediatr Res, 2017. **82**(5): p. 872-880.

11. Chemaly, R.F., et al., *A Phase 2, Randomized, Double-blind, Placebo-Controlled Trial of Presatovir for the Treatment of Respiratory Syncytial Virus Upper Respiratory Tract Infection in Hematopoietic-Cell Transplant Recipients.* Clin Infect Dis, 2020. **71**(11): p. 2777-2786.

12. Ahmad, A., et al., *EDP-938, a Respiratory Syncytial Virus Inhibitor, in a Human Virus Challenge.* N Engl J Med, 2022. **386**(7): p. 655-666.

Keywords: RSV, Human challenge study, mathematical modelling, viral dynamics

Determining viral spread and innate immune dynamics in human respiratory epithelium

Pascal Lukas*[1], Aurélien Gibeaud[2], Clarisse Schumer[3,4], Jonas Arruda[5], Olivier Terrier[6], Jérémie Guedj[7], and Frederik Graw[8,9,10]

[1]Department of Internal Medicine 5, Haematology and Oncology, Friedrich-Alexander-Universität Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany – Germany
[2]CIRI, Centre International de Recherche en Infectiologie, Team VirPath, Université de Lyon, INSERM U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, ENS de Lyon, 69007 Lyon, France – CIRI, Inserm, U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, École Normale Supérieure de Lyon, Univ Lyon, F-69007, Lyon, France – France
[3]Infection, Anti-microbiens, Modélisation, Evolution – INSERM, IAME, UMR 1137 – Faculté de médecine Paris Diderot Paris 7 - site Bichat - 16 rue Henri Huchard 75890 Paris Cedex 18, France
[4]Université Paris Cité and Université Sorbonne Paris Nord, Inserm, IAME, F-75018 Paris, France – Université Paris Cité and Université Sorbonne Paris NordUniversité Paris Cité and Université Sorbonne Paris Nord, Inserm, IAME, F-75018 Paris, France – France
[5]Bonn Center for Mathematical Life Sciences Life and Medical Sciences Institute, University of Bonn, Bonn 53115, Germany – Germany
[6]CIRI, Centre International de Recherche en Infectiologie, Team VirPath, Université de Lyon, INSERM U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, ENS de Lyon, 69007 Lyon, France – Institut National de la Santé et de la Recherche Médicale - INSERM – France
[7]Université Paris Cité and Université Sorbonne Paris Nord, Inserm, IAME, F-75018 Paris, France – Centre de Recherche Inserm – France
[8]Department of Internal Medicine 5, Haematology and Oncology, Friedrich-Alexander-Universität Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany – Germany
[9]Deutsches Zentrum Immuntherapie (DZI), Erlangen, Germany – Germany
[10]Bavarian Cancer Research Centre (BZKF), Erlangen, Germany – Germany

Abstract

Introduction

Understanding the mechanisms that govern viral spread in human airway epithelium (HAE) remains a major challenge, particularly with regard to identifying and quantifying key factors such as cell-type-specific infectivity, viral transmission pathways, and innate immune dynamics. Although mathematical models and experimental advances have provided valuable insights into respiratory viral infections, revealing the complex spatio-temporal interactions of infection and immune processes on a tissue-level that determine disease progression and therapeutic success have remained elusive. Here, we present an innovative workflow that combines time-resolved bulk measurements and spatially-explicit image information to allow the inference of viral and immune kinetics within HAE for various respiratory viruses.

*Speaker

Methods

While standard inference methods typically require custom summary statistics and resourceful fitting procedures for each individual data set, our workflow relies on the combination of different simulation-based trained neural networks within BayesFlow, a framework for neural posterior estimation. This framework allows for amortized inference and the integrative analysis of various types of data. To this end, invertible neural networks (INNs) are trained based on simulated data that comprise time-resolved bulk measurements and spatially-explicit image information, thereby individually learning appropriate summary features that are associated with particular viral and immune kinetics. These trained networks are then inverted and applied to actual experimental data and measurements to infer viral and innate immune kinetics for various respiratory viruses.

Results

We validated our approach by simulating viral infection dynamics in HAE using systems of increasing complexity that account for tissue heterogeneity, cell-type specific infection and turnover kinetics, as well as interferon-mediated immune responses, with generated data mirroring experimental measurements accounting for disrupted sampling, i.e., not being able to follow the same culture over time. Thereby, we could show that integrating spatial information is essential to reliably infer viral transmission kinetics and innate immune interactions. By additionally inducing perturbations in the time-resolved resolution and frequency of replicates per time points within the potential dataset, we demonstrated how experimental design influences the identifiability of these dynamics. These findings suggested that INNs conditioned on a limited number of timepoints (n$<$ 3) achieve the same accuracy as INNs conditioned on the full available time-span (n=5), even considering similar variability in measurements as observed within experimental cultures.

Discussion

Our approach can be readily applied to data from HAE culture systems to infer viral and innate immune kinetics for different respiratory viruses, including IAV, SARS-CoV-2 and RSV, without the need for retraining or further simulations for each particular virus. In summary the presented workflow provides a computationally efficient general framework to assess viral and immune dynamics within tissues for a diverse range of viral infections by integrating longitudinal bulk and spatially-resolved measurements.

Keywords: Viral Spread, Innate Immunity, Tissue Dynamics, Bayesian Inference, Multimodal Data Integration

Exposure history shapes SARS-CoV-2 viral dynamics in Non-Human Primates and provides insights into correlates of protection against infection and transmission

Adrien Mitard*[1,2], Cécile Hérate[3], Romain Marlin[4], Flora Donati[5], Yannis Rahou[5], Laetitia Bossevot[4], Quentin Sconosciuti[4], Mariangela Cavarelli[4], Nathalie Dereuddre-Bosquet[4], Francis Relouzat[4], Sylvie Van Der Werf[5], Etienne Simon-Loriere[6], Roger Le Grand[4], Mélanie Prague[2,7], and Jérémie Guedj[1]

[1]Université Paris Cité and Université Sorbonne Paris Nord, Inserm, IAME, F-75018 Paris, France – Institut National de la Santé et de la Recherche Médicale, Université Paris Cité, Université Sorbonne Paris nord – France

[2]Bordeaux Population Health Research Center, SISTM Team, UMR1219, Bordeaux – University of Bordeaux, Inria Bordeaux Sud-Ouest, Inserm – France

[3]CEA, Center for Immunology of Viral, Auto-immune, Hematological and Bacterial diseases (IMVA-HB/IDMIT), – CEA/ DRT/LIST – Fontenay-aux-Roses Le Kremlin-Bicêtre, Paris, France, France

[4]CEA, Center for Immunology of Viral, Auto-immune, Hematological and Bacterial diseases (IMVA-HB/IDMIT), – CEA/ DRT/LIST – France

[5]CNR Virus Respiratoires – Institut Pasteur de Paris – France

[6]Institut Pasteur [Paris] – Institut Pasteur de Paris – 25-28, rue du docteur Roux, 75724 Paris cedex 15, France

[7]Vaccine Research Institute [Créteil, France] – Université Paris-Est Créteil Val-de-Marne - Paris 12 – France

Abstract

Introduction: COVID-19 vaccination has dramatically reduced the risk of severe disease and prevented around 60% of expected deaths in Europe (1). Although vaccines have been progressively adapted to the evolution of the virus and the emergence of Omicron strains (2,3), they do not prevent infection and transmission. Vulnerable population such as immune-compromised individuals remain at risk. Therefore, assessing the pertinence of binding and neutralisation as Correlates of Protection (CoP) against infection and not only severe disease is crucial (4). The question becomes even more complex due to the diversity of immune backgrounds, with most individuals having hybrid immunity conferred by both vaccination and infection with different variants (5).
Experimental challenges offer the ideal setting to address those questions thanks to a controlled environment, regular measurements of viral and immune markers and a known infection date. We used a non-human primate (NHP) study designed to look into viral replication

*Speaker

given different immunological backgrounds.

Many modelling studies have studied viral (6,7) or antibodies dynamics (8) but very few fitted both jointly, especially with rich longitudinal data.

Objectives:

- Develop a model bridging mechanistically viral and immune dynamics to explore the influence of exposure history
- Investigate neutralizing and binding antibodies levels as CoP against infection and transmission.

Methods:
NHP data:

Our study includes 22 NHP challenged with BQ.1.1 that are split in 4 groups:

- N: 6 naive NHP
- M/M (6 NHP): 2 doses of monovalent BNT162b2 vaccine
- M/B (6): 1 dose of monovalent and 1 dose of bivalent (Wuhan/BA.4-BA.5) vaccine
- C/B (4): Infected by a previous omicron strain (BA.2) and then received a dose of bivalent vaccine

Viral kinetics and immune response model:

We used a target cell limited model to characterize the viral load of infected animals (6,7). Regarding the immune response, Short (S) and long-lived B Cells (L) replicate proportionally to L, a proxy of the memory cells. Their recruitment is triggered either through vaccination or by the viral load. They produce binding antibodies that form immune complexes with free virions inducing a quicker clearance (9,10). A fraction γ of them is fully neutralized and cannot infect new cells. Those mechanisms allow our model to decouple the information given by binding and neutralisation assays.

Results: We developed a model fitting viral load and antibodies dynamics over multiple patterns of infections and vaccinations. We highlight a lower neutralisation ability against BQ1.1 of antibodies elicited by a monovalent vaccination comparing to those following an infection or a bivalent dose (ratio around 22%). However, the antibody response isn't enough to explain how exposure history does shape viral dynamics. Including covariates, we found that an infection increases the loss rate of infected cells by 24.5 (respectively by 1.2 and 1.9 after a monovalent or bivalent vaccination) protecting completely convalescents from infection. Using parameter estimates and the observed mean binding levels, we estimated the within-host reproductive number, R0, to 4.9, 3.3, 1.6 and 0.06 in N, M/M, M/B and C/B, respectively.

We simulated infections varying the neutralisation and binding levels at the time of the challenge to characterise viral kinetics in a more general setting. we predicted that infection could be averted at a binding level of 3*104 and 4*105 AU.mL-1 after M/B and M/M vaccination, respectively. Assuming that viral dynamics are similar in saliva and nasopharynx, antibody binding levels about 10-fold lower were sufficient to protect against transmission.

Conclusion: This study demonstrates that antibodies conferred by vaccination and/or infection reduce viral replication through both binding and neutralisation. However, the strong covariate effect on the loss rate following an infection hints towards a crucial role of the T response that needs to be further characterised. A strength of this model is that it could be used in more complex settings without needs for more parameters a priori. It could then be used to predict virus circulation in the general population and assess the impact of a vaccination campaign. More directly, it could select individuals in need of a booster depending on its binding and neutralizing antibody levels.

References:

(1) M. M. I. Meslé *et al.*, " Estimated number of lives directly saved by COVID-19 vaccination programmes in the WHO European Region from December, 2020, to March, 2023: a retrospective surveillance study ", *Lancet Respir. Med.*, vol. 12, no 9, p. 714-727, sept. 2024, doi: 10.1016/S2213-2600(24)00179-6.

(2) S. Chalkias *et al.*, " A Bivalent Omicron-Containing Booster Vaccine against Covid-19 ", *N. Engl. J. Med.*, vol. 387, no 14, p. 1279-1291, oct. 2022, doi: 10.1056/NEJMoa2208343.

(3) D. Cromer *et al.*, " Predicting COVID-19 booster immunogenicity against future SARS-CoV-2 variants and the benefits of vaccine updates ", *Nat. Commun.*, vol. 15, no 1, p. 8395, sept. 2024, doi: 10.1038/s41467-024-52194-9.

(4) P. B. Gilbert, R. O. Donis, R. A. Koup, Y. Fong, S. A. Plotkin, et D. Follmann, " A Covid-19 Milestone Attained - A Correlate of Protection for Vaccines ", *N. Engl. J. Med.*, vol. 387, no 24, p. 2203-2206, déc. 2022, doi: 10.1056/NEJMp2211314.

(5) S. Crotty, " Hybrid immunity ", *Science*, vol. 372, no 6549, p. 1392-1393, juin 2021, doi: 10.1126/science.abj2258.

(6) A. Marc *et al.*, " Impact of variants of concern on SARS-CoV-2 viral dynamics in non-human primates ", *PLOS Comput. Biol.*, vol. 19, no 8, p. e1010721, août 2023, doi: 10.1371/journal.pcbi.1010721.

(7) M. Alexandre *et al.*, " Modelling the response to vaccine in non-human primates to define SARS-CoV-2 mechanistic correlates of protection ", *eLife*, vol. 11, p. e75427, juill. 2022, doi: 10.7554/eLife.75427.

(8) Q. Clairon *et al.*, " Modeling the kinetics of the neutralizing antibody response against SARS-CoV-2 variants after several administrations of Bnt162b2 ", *PLoS Comput. Biol.*, vol. 19, no 8, p. e1011282, août 2023, doi: 10.1371/journal.pcbi.1011282.

(9) T. Igarashi *et al.*, " Human immunodeficiency virus type 1 neutralizing antibodies accelerate clearance of cell–free virions from blood plasma ", *Nat. Med.*, vol. 5, no 2, p. 211-216, févr. 1999, doi: 10.1038/5576.

(10) T. Phan *et al.*, " Modeling the emergence of viral resistance for SARS-CoV-2 during treatment with an anti-spike monoclonal antibody ", *PLOS Pathog.*, vol. 20, no 4, p. e1011680, avr. 2024, doi: 10.1371/journal.ppat.1011680.

Keywords: Correlates of Protection, SARS, CoV, 2, Vaccination, Hybrid immunity, Antibody dynamics

Modeling Spatial Spread of SARS-CoV-2 infection in Lung

Humayra Tasnim[1], Melanie Moses*[1], and Judy Cannon*[1]

[1]The University of New Mexico [Albuquerque] – United States

Abstract

Introduction:
Despite the significant amount of data and research surrounding SARS-CoV-2 viral dynamics and disease progression, there is still a gap in our understanding of how the virus infects the lung space and spreads within the specialized lung structures, which include alveolar sacs connecting to branching airways. The lung structure is difficult to assess in patients, but computed tomography (CT) scans have been a valuable tool for studying SARS-CoV-2 infection spread in the lung since the beginning of the COVID-19 pandemic. CT scans of patients with SARS-CoV-2 infection are characterized by multifocal distribution of lesions, particularly Ground Glass Opacities (GGOs) and consolidations, which are likely to indicate tissue damage caused by inflammatory cell infiltration. Existing models of infection dynamics cannot capture spatial features, limiting their ability to shed light on viral dynamics in the specialized lung space. We initially developed the Spatial Immune Model of Coronavirus, or SIMCoV, as an agent-based, computational model of SARS-CoV-2 infection in the lung that compares favorably to existing ODE models of SARS-CoV-2 infection. We have now extended SIMCoV to include the lung as a structured 3D lattice of alveolar sacs with biologically relevant cell types and spatial diffusion features, called SIMCoV-MS (Multisac). SIMCoV- MS demonstrates how the lung's spatial architecture influences viral spread to allow a more fine-tuned understanding of disease mechanisms at the cellular level. This study takes advantage of CT data from COVID-19 patients to evaluate how well SIMCoV-MS simulations compare with temporal and spatial growth of lung lesions in patients. Our novel spatially faithful lung model sheds new light on how initial conditions of viral dynamics might impact viral spread and lung damage.

Methods:

In SIMCoV-MS, alveolar sacs are modeled as cubic structures composed of voxels (each 15ˆ3μmˆ3) representing air, infectable and non-infectable epithelium cells, and lung tissue. Every sac is 100 voxels or 1500μm per dimension. The outer layers of the sac (cubic structure in simulation) have two types of epithelial cells: a) Type I Pneumocytes that form 95% of the alveolar surface and are non-infectable. b) Type II Pneumocytes contain 5% of the surface and are infectable. Inside the sac are multiple alveoli. Each alveolus is like a grape with air inside and alveolar epithelium outside (Type I and II). Instead of modeling each alveolus in fine detail, we used a uniform random distribution of air, infectable, and non-infectable epithelial cells, proportioned based on an estimated 125 alveoli per sac, each 200μm in diameter. The space around the alveolar sacs is modeled as lung tissue. Each cell

*Speaker

type has specific spatial and diffusion properties. This explicit modeling captures the acinus structure of alveoli and surrounding tissue, enabling biologically relevant simulation of viral diffusion, inflammation spread, and containment consistent with actual lung microanatomy. T cells are represented as agents, as in the default SIMCoV model, and virions and inflammatory signals are represented as concentrations. Simulations are initialized by infecting the volume of one alveolar sac. Virions diffuse across this space and infect susceptible epithelial cells, initiating an inflammatory response. T cells are recruited based on inflammatory signal diffusion and arrive at a parameter-defined day post-infection. The model introduces heterogeneity in virion diffusion rates across tissue types. Inflammatory signals in the model serve as proxies for lesion visibility in CTs. The study conducts a comparative analysis of inflammatory signal growth in SIMCoV-MS to lesion volume growth measured from CT scans of 20 COVID-19 patients over the course of infection. Lesions from CT scans of patients are segmented using radiologists' input with computer vision approaches, and the volume growth of lesions is tracked over days.

Results:

We performed SIMCoV-MS simulations under varying initial conditions, including seeding foci of infection (FOIs) at multiple spatial locations and infecting a single alveolar sac with different numbers of FOIs to represent varying initial infection levels. We compared SIMCoV-MS results with the default SIMCoV (3D). Both SIMCoV-MS and SIMCoV started with the same number of infected cells, ensuring identical initial conditions. All other parameters are validated defaults from SIMCoV. We found that SIMCoV had a higher infection lesion growth rate than SIMCoV-MS. This is likely because in the default SIMCoV model, all cells are uniformly infectable without the structure and varying diffusion rates. The initial growth rate in SIMCoV-MS closely follows the patient CT lesion analysis, suggesting SIMCoV-MS more accurately captures the early infection dynamics than SIMCoV. SIMCoV-MS successfully matched the average lesion growth trajectory across patients without parameter tuning, relying only on the previously validated defaults from SIMCoV. By varying parameters, namely initial conditions and diffusion rates, we show that SIMCoV-MS can generate patient-specific scenarios, simulating growth properties of lesions matching the CTs of patients. Additionally, the structured sac model in SIMCoV-MS produced patchy, localized spread patterns that visually closely resembled CT opacities, in contrast to the default SIMCoV simulation, which produces a more uniform and diffuse spread that cannot capture the irregularities of viral spread in the lung.

Discussion:

We have developed a novel extension of the SIMCoV model named SIMCoV-MS, which uses spatially faithful representation of alveolar structures. SIMCoV-MS replicates the average growth and spread of lung damage observed in CT scans of COVID-19 patients. SIMCoV-MS simulates the spatial volume and growth of these damages by incorporating the structural properties of the alveolar sac. SIMCoV-MS illustrates how lung structure affects inflammation by controlling the diffusion of virus and inflammatory signals, suggesting that the structured alveolar model in SIMCoV-MS restricts the spread of infection to specific cell types (type II pneumocytes), resulting in a more controlled and realistic simulation of lung infection progression. The model's ability to recapitulate lesion growth rates in patients using default parameters suggests its robustness and potential applicability for patient-specific forecasting. The analysis suggests that the inherent structure of lung tissue, particularly the distribution and density of alveolar sacs, plays an important role in controlling viral spread and growth of inflammation in COVID-19 patients. This work highlights the importance of incorporating essential features of lung structure in simulations to better model dynamics of viral infection.

Keywords: SARS, CoV, 2, CT scans, inflammation, viral dynamics, spatial spread, SIMCoV, Agent

Skin microbiome dynamics as biomarker for severe radiodermatitis in breast cancer patients and for treatment response in atopic dermatitis

Avidan Neumann*[1,2], Claudia Hülpüsch[1,3], Matthias Reiger[1,2], Nicole Engelbert[1,3], Laura Maintz[4], Kai Borm[5], and Claudia Traidl-Hoffmann[1,2,3]

[1]Institute of Environmental Medicine and Integrative Health, Faculty of Medicine, University of Augsburg – Germany
[2]Institute of Environmental Medicine, Helmholtz Munich, Augsburg – Germany
[3]Christine Kühne Center for Allergy Research (CK-CARE), Davos – Switzerland
[4]Department of Dermatology and Allergy, University Hospital Bonn – Germany
[5]Department of Radiation Oncology, Klinikum Rechts der Isar, School of Medicine, Technical University of Munich – Germany

Abstract

Background: Skin microbiome presents a diverse and dynamic biota that is sensitive to changes in patients' physiology and immune status.
Radiodermatitis is commonly observed during radiotherapy in post-surgery breast cancer patients. However, the factors associated with severe radiodermatitis, which poses important clinical complications, are not currently understood.

Atopic Dermatitis (AD) is a chronic inflammatory skin disease associated with microbial dysbiosis due to increased *Staphylococcus aureus* abundance in lesional skin. JAK-inhibitors were recently approved for the treatment of moderate to severe AD and show partial success. To date, there are no known accurate predictive markers for successful response to JAK inhibitor therapy.

Aims: We longitudinally studied the kinetics of skin microbiome composition and absolute numbers to elucidate its role in the development of radiodermatitis in breast cancer patients and in response to therapy in atopic dermatitis patients.

Materials and Methods: A longitudinal pilot study with 20 women, undergoing radiotherapy after breast cancer operation, was conducted with a total of 360 skin swabs taken before, during, and after radiotherapy, from both the treated and contralateral healthy sides.

30 AD patients in phase 1-2 clinical study of gusacitinib for 4 weeks and 34 AD patients in a real-world study of baricitinib were recruited and both lesionsl and non-lesional skin swabs were taken every 2-4 weeks over 12 weeks.

Skin microbiome composition was analyzed using 16S (V1-3) rRNA gene amplicon-based

*Speaker

next generation sequencing. Quantification of skin total bacterial load and *Staphylococcus aureus* absolute numbers was measured by standardized qPCR with *16S* and *nuc* genes, accordingly.

Results: Strikingly, in breast cancer patients undergoing radiotherapy, 16S sequencing revealed that low (< 5%) relative abundance of commensal skin bacteria (the sum of *Staphylococcus epidermidis, Staphylococcus hominis,* and *Cutibacterium acnes*) at baseline, in both the affected and unaffected breasts, was predictive of the development of severe radiodermatitis with 100% accuracy. Commensal bacteria relative abundance on the skin was significantly inversely correlated with the skin pH, breast volume and BMI, but the latter were not as good predictors of severity.

Interestingly, only in the same patients with severe radiodermatitis, qPCR bacterial quantification revealed a general non-species-specific overgrowth of skin total bacterial load, only in the affected breast, after initiation of radiotherapy but prior to the onset of severe radiodermatitis. Subsequently, again in same severe patients, the abundance of commensal bacteria was increased, coinciding with a decline in total bacterial load.

In atopic dermatitis patients treated with either of the 2 different JAK inhibitor therapies, *S. aureus* relative and absolute abundance declined in patients with a successful clinical response. Furthermore, low baseline *S. aureus* abundance in lesional skin was the most accurate predictor of a successful treatment response. In the baricitinib study, baseline combination of age, *S. aureus* and *S. epidermidis* relative abundances, was predictive of therapy response with up to 100% accuracy. In the gusacitinib study, low lesional skin *S. aureus* abundance at the end of treatment was accurately predictive of both sustained clinical response and sustained microbial response after treatment cessation.

Conclusions: These findings indicate the importance of skin microbiota and its dynamics in understanding disease pathogenesis and as a biomarker to predict severity and treatment response. First, skin microbiome dynamics may explain the mechanism for the pathogenesis of severe radiodermatitis, and can be used as a predictive biomarker for personalized treatment of radiodermatitis. Second, skin *S. aureus* quantification can be used as a biomarker for accurate prediction of AD treatment response and its personalization, as well as, importantly, allow to define safe stopping rules for biologics based therapy of atopic dermatitis.

* The preliminary results of the radiodermatitis study were published in:
Hülpüsch C*, Neumann AU*, Reiger M, et al. Association of Skin Microbiome Dynamics with Radiodermatitis in Patients with Breast Cancer. ***JAMA Oncol***. 2024 Apr 1;10(4):516-521.

Keywords: microbiome, Staphylococcus aureus. radiodermatitis, atopic dermatitis, biomarker, prediction, bacterial dynamics

SARS-CoV-2 viral load kinetic profiles correspond with observed intra-host viral diversity and mutation rates during infections in immunocompetent individuals

Katherine Owens*[1], Joshua T. Schiffer[2,1], and Daniel B. Reeves[2,1]

[1]Fred Hutchinson Cancer Center – United States
[2]University of Washington – United States

Abstract

Novel SARS-CoV-2 variants of concern (VOC) extended the COVID-19 pandemic, leading to millions of excess deaths and adverse health outcomes worldwide. Most new mutant strains differed from previously documented strains by only a single base pair change and contributed to a constant global nucleotide substitution rate of approximately 2 base pair changes per month since 2020. An exception has been "saltation variants" which are characterized by the immediate appearance of dozens of new mutations relative to contemporaneously circulating strains. A leading hypothesis is that these highly mutated VOC developed in immunocompromised individuals who were unable to eliminate the virus, leading to months of persistent rapidly evolving infection, followed by reintroduction into the general population and subsequent rapid sweeps across the globe. Yet, persistent infection is extremely rare, and most SARS-CoV-2 infections are acute and self-limited, clearing within 1-3 weeks of infection. The conditions within a transiently infected individual that allow transmission of a typical variant distinguished by a single base pair change remain unknown. The percentage of infected people who transmit a new mutant is also unspecified. Moreover, the bottlenecks resulting in the low observed global nucleotide substitution rate are undefined.

To establish baseline rates and mechanisms of intra-host evolution in individuals with self-limited infection, we developed a mechanistic evolutionary model of SARS-CoV-2 infection and validated it using virologic and genetic data from 18 individuals with acute SARS-CoV-2 infections (duration $<$ 40 days). Documented infections occurred between June 2020 and August 2021 with the earliest sample taken within a median of 4 (min = -3, max= 17) days of symptom onset. The average shedding duration was 22 days, with an average of 4 samples sequenced per infection. High-throughput, single-genome amplification sequencing was employed on each sample, an approach that demonstrates mutational linkage patterns across the 3.8-kilobase spike region that are not detectable by short-read whole-genome sequencing.

*Speaker

Our stochastic model combined viral and immune kinetics with a branching process describing nucleotide mutations that occur during viral RNA replication. We used the viral dynamic model structure and parameter values from our previous deterministic model which was trained on viral load data from over 1500 infections. We calibrated the stochastic model simultaneously to longitudinal paired viral load and spike sequencing data. We estimated the bulk mutation rate and the distribution of fitness changes that occured after non-synonymous mutations, achieving excellent model fit against 3 phylodynamic metrics (number of strains detected, average pairwise distance between the sequence of strains, and frequency of the founding strain) at sequential time points throughout infection, and 3 viral dynamic metrics (peak viral load, time of peak viral load, and duration of infection). We then used the calibrated parameter values to simulate thousands of acute infections and analyzed the relationship between viral dynamic quantities and ecological and genetic diversity. Finally, we implemented an existing model that relates viral RNA levels to transmission probability given an exposure via a saturating function previously calibrated using paired PCR and viral culture data. We used this model to estimate the proportion of infections in which transmission of a virus with at least a single base pair change was possible.

Our optimized model suggests that evolution during acute infection can mostly be explained by an inherent viral fitness distribution, without selective immune pressure. The optimal inherent viral fitness distribution is highly skewed-we estimated that of the 65% of mutations that are non-synonymous, 99.3% are deleterious, and only 0.7% are advantageous. We determined that peak viral load and area under the viral load curve are strong predictors of the number of variants generated during acute infection. However, we estimated that $> 99\%$ of minor variants remain undetected due to under sampling: most variants are deleterious and peak at frequencies that are too low for detection, even with high-resolution sequencing assays. The number of variants that reach detectable levels instead correlates with infection duration. Across 1500 simulations of acute infection, we found that evolution produced a median of 3 new detectable mutant strains (IQR = 1-14). A median of 1 mutation (IQR = 1,2) defined the most divergent novel strain detected in each infection. In the event of a selective sweep, the novel viral mutant surpassed 50% of the detectable viral population at a median of 13.8 days (IQR = 11-18) into infection, when viral load was already decreasing in most cases. We calculated the area under the transmission risk curve for each strain as a metric of transmission potential. By summing the area under the transmission risk curves across all modeled infections, we estimated that 6% of transmissions would be with a new intra-host variant. Among the 28% of infections in which a selective sweep of a new variant occurs, we estimated that a median of 8% of transmissions would be with this new variant (IQR = 6%, 13%).

We calibrated a stochastic model for the within-host evolution of SARS-CoV-2 to a unique data set to study the connection between viral dynamics and viral evolution. Our results imply that acute, self-limited infections in immunocompetent individuals generate many new variants but only rarely at high enough viral loads and for sufficient duration to allow their transmission. This suggests that infection duration exceeding two weeks may be a prerequisite not only for transmission of saltation variants, but also for new variants defined by a single base pair change. Overall, within host viral kinetics and mutation rates during acute infections present a substantial bottleneck limiting viral evolution in the general population.

Keywords: SARS, CoV, 2, intra, host evolution, transmission risk, stochastic model

Experimental epidemiology with viruses: toward assessing phylodynamics

Eva Bons , Hélène Chabas , Hannelore Macdonald , Alejandro Escalera Ledermann , Nicolas Ochsner , Daniel Angst , Sebastian Bonhoeffer , and Roland Regoes*[1]

[1]Institute of Integrative Biology, ETH Zurich – CH-8092 Zurich, Switzerland

Abstract

Introduction

Genetic sequences of organisms contain imprints of their population biology and migration history. To recover this history, phylodynamic inference has been developed that combines phylogenetics with population biological models. Although phylodynamic methods are being applied widely in epidemiology and macro-evolutionary studies, they have not yet been experimentally validated.

We set out to test phylodynamic methods by simulating epidemics in vitro, in which we control epidemiological parameters, and compare them to those estimated by phylodynamic inference methods.

Methods

To do this, we developed an automated viral passaging pipeline using an automated liquid handling platform. Specifically, we passage the phage phiX174 in its host E. coli C. We implemented various passaging schemes that mirror epidemiological scenarios. After passaging the phage, we sample at two time-point during the experiment, extract phage DNA, and perform long-read sequencing.

Because the genome of the phage is only 5386 nucleotides long, long-read sequencing yields whole-genome reads. Exploiting the circular consensus reads, and computationally correcting for sequencing and other procedural sources of error, we obtain not just the whole-genome sequence of many phage genotypes in each sample, but also their relative frequency in the sampled phage population.

In the first experiment, we evolved the phage phiX174 in four independent evolution lines for over 400 generations. We did not impose any direct selection pressure in these evolution experiments because phylodynamic inference works best in neutrally evolving systems.

On the resulting high-throughput sequence data, we performed a phylodynamic analysis using treetime, estimating migration rates between the evolution lines. (Since the evolution lines were independent the true migration rate between them was zero.)

Results

*Speaker

Using this approach allowed us to follow the genetic diversification of four independent phage populations in unprecedented detail. The ancestor population consists of 53 genotypes, that carry 37 mutations compared to the most common, consensus genotype. Throughout the experiment, we trace over 80'000 bacteriophage genomes and their frequencies over time, of which 884 are unique. During the experiment 147 new mutations evolved in the four evolution lines.

We found that evolution is largely neutral but document multiple instances of parallel evolution.
47 out of the 147 newly evolved mutations were found in multiple evolution lines. We also found many instances of combinations of mutations that had evolved in parallel, and even observed 26 genotypes that had evolved in multiple evolution lines being identical in every of the 5386 positions of their genomes.

As a result of this parallel evolution phylodynamic methods wrongly estimate significantly positive migration rates between the independent evolution lines.

Discussion
Despite not imposing selection in our in vitro epidemics, we observed parallel evolution, most likely driven by selective advantages to the passaging environment. This lead to biases in phylodynamic inference. We conclude that the effects of selection should be included into phylodynamic methods for more reliable estimation of migration rates.

Keywords: phylodynamics, bacteriophage phiX174, experimental evolution, long, read sequencing, parallel evolution

How Vaccines Shape B Cell Evolution: A Modeling Approach

Rituparna Banerjee*[1], Matt Pennell[2], and Daniel Coombs[3]

[1]Bioinformatics Graduate Program, University of British Columbia [Vancouver] – Canada
[2]College of Agriculture and Life Sciences, Cornell University [Ithaca] – United States
[3]Department of Mathematics, University of British Columbia [Vancouver] – Canada

Abstract

Introduction: Vaccinations enhance the body's preparedness for future infections, with their success influenced by factors like dose composition and timing. B cells play a key role in this immune response, maturing to produce antibodies via two main pathways: Extrafollicular (EF) and Germinal Center (GC). While these mechanisms are well understood individually, how they jointly shape B cell responses under homologous versus heterologous vaccination, and whether this leaves an evolutionary signature in B cell clonal families, remains unclear. In this study, we use simulations and phylogenetic tools to explore how EF and GC pathways influence repertoire diversity in these systems. This will offer insights into B cell evolution that could inform future vaccine strategies.
Methods: We built a simplified mechanistic model of B cell evolution (mutation and selection) during the immune response to vaccination, explicitly including the GC and EF pathways. The model simulates the production of EF B cells, GC B cells, Memory B cells (MBC) and Antibody Secreting cells (ASC) post administration of each dose in a two-dose vaccine regimen (homologous or heterologous vaccination). Phylogenetic trees of the simulated B cell clonal families were recorded at the end of simulation for each dose and tree metrics were calculated over time to discern differences in immune response. The tree metrics used in this study were the Colless index, Mean Pairwise Distance (MPD), Phylogenetic Diversity (PD) and mean number of lineages through time.

Results: Preliminary simulations began with a "naïve" repertoire of 50 B cell strains, each 20 bits long. In the homologous vaccination scenario, a stronger EF response was observed after the second dose. While the mean number of B cell strains was initially higher following the first dose, it was eventually surpassed by that of the second. Phylogenetic trees after the first dose exhibited higher values for the Colless index, PD, MPD, and the number of lineages over time. In contrast, heterologous vaccination triggered a strong GC response after both doses. The mean number of B cell strains was higher after the second dose, and all four tree metrics (Colless index, PD, MPD, and number of lineages) showed similar trends between doses, reflecting a robust response to the new strain. However, early in the simulation, the Colless index and number of lineages increased more steeply after the first dose. When comparing second doses across vaccination types, heterologous vaccination produced phylogenetic trees with consistently higher values across all four metrics for the second dose compared to that of the homologous case, indicating a more diverse B cell response. Additionally, varying the antigenic distance between strains in heterologous vaccination revealed

*Speaker

that while Colless index and MPD remained largely unchanged between doses, PD and number of lineages were higher after the first dose when antigenic distance was reduced.
Discussion: Simulations were conducted to model B cell repertoire evolution under homologous and heterologous vaccination, followed by phylogenetic tree reconstruction and metric-based comparisons of immune responses. In homologous vaccination, where both doses contain the same strain, EF responses increased after the second dose. MBCs and ASCs generated via the GC pathway after the first dose contributed to the EF response upon boosting. The second dose also induced some GC B cells that were not MBCs or ASCs, suggesting a broader, possibly less strain-specific response. Phylogenetic trees from the first dose were larger and more imbalanced than those from the second dose, indicated by higher mean B cell strain counts, greater PD, higher number of lineages, and elevated Colless index. These trends suggest stronger selection pressure and more viable mutant generation following the first dose. In heterologous vaccination, where two different strains were used, simulations revealed strong GC responses after both doses, producing MBCs and ASCs specific to each strain. Trees post-second dose had similar PD, MPD, Colless index and number of lineages to post-first dose. This indicates continued repertoire evolution in response to novel antigens. Upon comparing second-dose responses across vaccine types, heterologous vaccination produced larger, more imbalanced trees with slightly greater tip divergence, pointing to a more robust and diverse response. When antigenic distance between strains was varied, MPD and tree imbalance remained similar between doses. However, with decreased antigenic distance, first-dose trees were larger than second-dose trees, suggesting that greater diversification occurs when strains are more antigenically distinct. Ongoing analyses will explore how varying the inter-dose interval impacts immune dynamics. Future work includes comparing simulated trees with those from longitudinal datasets to validate these findings.

Keywords: B cells, phylogenetic trees, immune response, mathematical modelling

Differential longevity and potency of four broadly neutralizing antibodies elicited distinct viral load kinetics and resistance patterns in people with chronic HIV

Lucero Rodriguez Rodriguez*[1], Jonah Hall[2], Erwing Fabian Cardozo-Ojeda[3], Alan Perelson[4], Joshua Schiffer[1], and Daniel Reeves[1]

[1]Fred Hutch Cancer Center – United States
[2]University of British Columbia – Canada
[3]Regeneron – United States
[4]Los Alamos National Laboratory – United States

Abstract

Introduction: Broadly neutralizing antibodies (bnAbs) are potentially useful therapeutics and/or preventative agents for HIV. Phase 1 clinical trials were performed by the NIH Vaccine Research Center to assess the safety and effectiveness of the bnAbs VRC01 (n=8), VRC01LS (n=8) and VRC07-523LS (n=9) to reduce viremia in people living with HIV (PWH) with untreated chronic infection. Another study from Rockefeller University assessed the safety and effectiveness of the bnAb 3BNC117 (n=31). In 26 of 36 individuals who received a single bnAb infusion of (10 – 40 mg/kg), viremia was transiently reduced by more than 1 log. Viral decline was not observed in 2 individuals from the VRC01 study, 6 from VRC01LS, 1 from VRC07-523LS, and 1 from 3BNC117. In most participants with a therapeutic response, viral load returned to equilibrium as bnAb levels waned. 37 individuals' viruses were tested for sensitivity to the infused bnAb using in vitro IC50. In 14 individuals, rebounding viruses were more resistant (higher in vitro IC50) than those from the same individual pre-infusion (wild type). In other participants, rebounding viruses were similarly sensitive. Using mathematical models, we sought to both define the in vivo potency of each bnAb after accounting for pharmacokinetics and viral load kinetics and identify determinants of wild type versus resistant virus rebound.

Methods: We developed a "PKPDVD" model that integrated a biphasic pharmacokinetic model (PK) of bnAb kinetics, a pharmacodynamic model (PD) of antibody potency that estimates in vivo efficacy, and an HIV viral dynamic mathematical model (VD) that incorporates two categories of viruses, wild-type and resistant, each with their own sensitivity to the infused bnAb. We defined sensitivity according to the in vivo IC50, or plasma concentration required to neutralize 50% of viruses from entering susceptible cells. Assuming specific bnAb as a covariate, we used population nonlinear mixed effects modeling to fit the PK model to bnAb concentrations and to fit the full PKPDV model to viral load kinetics after bnAb infusion. We estimated 13 viral, PK and PD parameters, including the in vivo IC50 of the wild-type and resistant virus variants.

*Speaker

Results: We estimated median terminal half-lives of 10 days for VRC01, 38 days for VRC01LS, 34 days for VRC07-523-LS and 15 days for 3BNC117. The terminal half-life was significantly shorter in PWH than in HIV seronegative controls for 3BNC117 (median 13 vs 19 days, respectively). Across bnAbs, we estimated the median wild-type virus in vivo IC50 to be _˜0.18 (range 0.01-33) μg/mL whereas fully resistant rebound viruses had an in vivo IC50 $>$ 100 μg/mL. 3BNC117 was the most potent therapy in vivo with a median in vivo IC50=0.047 μg/mL. VRC01, VRC01LS, and VRC07-523LS had median wild type estimated in vivo IC50 of 5.54, 0.47 and 0.21 μg/mL, respectively. The model captured instances where viral rebound was due to either fully or partially resistant pre-existing variants, or due to sensitive virus – indicating subtherapeutic bnAb levels. Across PWH and bnAbs, we estimate viruses would rebound absent selection of resistant mutants within 8-75 days of infusion due to waning antibody levels.

Discussion: In conclusion, our model recapitulated observed bnAb and HIV dynamics within bnAb-treated PWH and differentiated the bnAbs by their half-lives and their in vivo efficacy against wild type viruses. Selective pressure for resistant emergence was observable, but sensitive (or partially resistant) HIV rebound also frequently occurred due to waning bnAb levels and insufficient in vivo efficacy.

Keywords: Chronic HIV, broadly neutralizing antibodies (bnAbs), PK modeling, rebound, remission, viral dynamics, nonlinear mixed effects modeling, sensitive and resistant, in vivo IC50

Quantifying viral transmissibility and pandemic potential from experimental transmission studies

Elizabeth Somsen*[1], Kayla Septer[2], Cassandra Field[2], Devanshi Patel[2], Kayla Brizuela[3], Anice Lowen[3], Seema Lakdawala[3], Troy Sutton[2], and Katia Koelle[4]

[1]Graduate Program in Population Biology, Ecology, and Evolution, Emory University – United States
[2]Department of Veterinary and Biomedical Sciences, The Pennsylvania State University – United States
[3]Department of Microbiology and Immunology, Emory University – United States
[4]Department of Biology, Emory University – United States

Abstract

Experimental transmission studies are commonly used to assess spillover risk of zoonotic viruses into humans. However, these experiments often only quantify transmission efficiency (the proportion of contact animals that became infected following exposure to a challenged donor animal). Not only are these estimates coarse, there is also no straightforward way to translate them into projections of viral dynamics at the population level. To address these gaps, we present an analytical framework that relies on longitudinal within-host viral titer data from donors and contacts of experimental transmission studies to provide finer estimates of viral transmissibility and to translate these estimates up to epidemiological parameters. We first apply this framework to transmission experiments using two different pandemic influenza viruses, A/California/07/2009 (H1N1pdm09) and A/Hong Kong/1/1968 (H3N2) and find a higher transmissibility for H1N1pdm09 than for H3N2. We next apply this framework to quantify the impact that pre-existing population-level immunity may have on viral transmissibility and higher-order epidemiological parameters of a pandemic influenza virus. Specifically, we use H1N1pdm09 transmission experiments where hosts were either naïve or had pre-existing immunity ("pre-immunity") to a seasonal H3N2 to quantify reductions in viral transmission that occur in the context of pre-immunity. We find that pre-immunity reduces susceptibility to infection by approximately 72%, whereas it does not appear to significantly impact viral dynamics or infectiousness of hosts experiencing breakthrough infections. We use these results to estimate the extent to which H1N1pdm09's reproduction rate is altered through population immunity, examining different scenarios for the proportion of the host population that has immunity to seasonal H3N2. In sum, our approach uses viral dynamics at the within and between host scales to provide finer resolution estimates of viral transmissibility and to project values of key epidemiological parameters that inform pandemic risk assessment.

Keywords: mathematical modeling, influenza, pandemics, risk assessment, transmission

*Speaker

Early treatment initiation preserves memory CD8 T cells and improves the likelihood of post-treatment control of HIV infection

Bharadwaj Vemparala*[1], Caroline Passaes[2,3], Delphine Desjardins[4], Anaïs Chapel[5,3], Valérie Monceaux[5,3], Julien Lemaitre[4], Adeline Mélard[6], Federico Perdomo-Celis[5], Cyril Planchais[7], Maël Gourvès[3], Nastasia Dimant[4], Annie David[5], Nathalie Dereuddre-Bosquet[4], Aurélie Barrail-Tran[4,8], Hélène Gouget[4], Céline Guillaume[4], Francis Relouzat[4], Olivier Lambotte[4,9], Michaela Müller-Trutwin[5], Hugo Mouquet[10], Christine Rouzioux[11], Véronique Avettand-Fenoel[6,12], Roger Le Grand[13], Asier Saez-Cirion[5,3], Narendra M Dixit[14,15], and Jérémie Guedj[16]

[1]Department of Chemical Engineering, Indian Institute of Science – India
[2]HIV Inflammation and Persistence Unit – Institut Pasteur – France
[3]Viral Reservoirs and Immune Control Unit – Institut Pasteur – France
[4]Centre de recherche en Immunologie des Infections virales et des maladies auto-immunes – Institut National de la Santé et de la Recherche Médicale, Hôpital Bicêtre [AP-HP, Le Kremlin-Bicêtre], Université Paris-Saclay – France
[5]HIV Inflammation and Persistence Unit – Institut Pasteur – France
[6]Université Paris Cité; INSERM, U1016; CNRS, UMR8104 – INSERM U1016, CNRS UMR8104, Institut Cochin, Université Paris Cité, Paris, France – France
[7]Immunologie humorale - Humoral Immunology – Institut National de la Santé et de la Recherche Médicale, Université Paris Cité – France
[8]Université Paris-Saclay, AP-HP, Hôpital Bicêtre, Service de Pharmacie, Le Kremlin Bicêtre – Hôpital Bicêtre – France
[9]Université Paris-Saclay, AP-HP. Hôpital Bicêtre, Clinical Immunology Department, Le Kremlin Bicêtre – Hôpital Bicêtre – France
[10]Immunologie humorale - Humoral Immunology – Institut Pasteur [Paris], Institut National de la Santé et de la Recherche Médicale, Université Paris Cité – France
[11]Hôpital Necker - Enfants Malades [AP-HP] – Assistance publique - Hôpitaux de Paris (AP-HP), Paris Cité – France
[12]APHP Hôpital Cochin, Service de Virologie – AP-HP, Hôpital Cochin, Service de Virologie – France
[13]CEA-Université Paris Sud, INSERM U1184, Immunology of Viral Infections and Autoimmune Diseases, IDMIT departement, IBFJ, Fontenay-aux-Roses, France – CEA-Université Paris Sud-Inserm U1184, IMVA/IDMIT Department/DRF/IBFJ – France
[14]Department of Chemical Engineering, Indian Institute of Science – India
[15]Department of Bioengineering, Indian Institute of Science – India
[16]Infection, Anti-microbiens, Modélisation, Evolution – Institut National de la Santé et de la Recherche Médicale, Université Paris Cité, Université Sorbonne Paris nord – France

*Speaker

Introduction

Antiretroviral therapy (ART) for HIV-1 infection is not curative. Treatment interruption typically results in viral rebound and progressive disease, necessitating lifelong ART (1). However, a small fraction of people living with HIV (PLWH) under ART, termed post-treatment controllers (PTCs), are able to achieve long-term virus control after treatment interruption (2). Studies on PTCs are driving efforts to develop novel therapeutics aimed at eliciting such long-term control in chronic progressors (CPs): PLWH who fail to achieve post-treatment control. Both human and primate studies have shown that early ART initiation is associated with a higher chance of post-treatment control, driven by superior CD8 T cell responses (3, 4). However, the underpinning mechanisms are unclear. While the extant models (5) recapitulate the differences in the likelihood of post-treatment control when the latent reservoir sizes are different, they fail to explain studies where PTCs and CPs have equally sized latent reservoirs (4). Moreover, initiating treatment very early seems to worsen the likelihood of achieving control (2, 6). Thus, there exists no mechanistic explanation for the CD8 T cell–dependent effect of ART initiation time on the likelihood of achieving post-treatment control.

Methods

We developed a within-host mathematical model for analyzing the influence of ART initiation time on virus and immune response dynamics, and the occurrence of post-treatment control. Our hypothesis is the following. Upon infection, virus-specific CD8 T cells accumulate 'antigenic experience' through continual exposure to the antigen. Antigenic experience governs the differentiation and survival rates of memory CD8 T cells, required for antiviral responses. Following experimental evidence, we let the survival of memory CD8 T cells be dependent on their antigenic experience (7, 8). Thus, early ART treatment is expected to preserve the memory CD8 T cell pool, enabling better response to rebounding virus post-ART. We constructed coupled ODEs to describe the time courses of viral load, latent reservoir, and CD8 T cell responses before, during, and after ART. We fit the model to longitudinal data from a recent SIV–cynomolgus macaque study containing early- and late-treated macaques (4), using a nonlinear mixed effects approach. We then performed *in silico* trials with 10,000 virtual individuals generated by sampling from the estimated parameter distributions to quantify the population-level variability in PTCs.

Results

The model exhibited bistability. One stable steady state had low viral load and high memory cell levels, and the other vice versa, recapitulating the post-treatment control and progressive disease states, respectively. Early treatment initiation made the control state more accessible. Our model provided good fits to the experimental data. Using the virtual population simulations, we predict that the macaques have the highest chance of establishing post-treatment control if ART is initiated about 20 days post-inoculation, in agreement with multiple experimental studies (6). The simulations recapitulated the non-monotonic dependence of the likelihood of achieving post-treatment control on ART initiation time: initiating ART very early does not allow enough memory cells to accumulate, while initiating ART very late irreversibly damages the CD8 T cell pool, compromising post-treatment control in both cases. We estimate the memory CD8 T cell pool size and its quality necessary to achieve post-treatment control in CPs, setting quantitative targets for interventions.

Discussion

The existence of the PTC phenotype, although rare, indicates the possibility of therapeutically eliciting long-term control in PLWH. Previous models predicted PTC as arising from restricting latent reservoir sizes and preventing CD8 T cell exhaustion (5). The SIV–macaque study we employed here found that latent reservoir sizes and exhaustion levels were not different between controllers and non-controllers (4), suggesting alternative mechanisms. Our model provides an alternative mechanistic explanation, based on the preservation of memory responses, consistent with experiments. Moreover, it explains the non-monotonic influence

of ART initiation time on the emergence of post-treatment control. The model thus supports the notion that an optimal window of opportunity for ART initiation that maximizes the likelihood of post-treatment control exists (2). Future studies may delineate conditions under which latent reservoir and exhaustion versus memory responses dominate in establishing post-treatment control. The framework would enable the development of quantifiable targets for therapies under development for eliciting long-term control.

References

1. J. D. Siliciano, R. F. Siliciano, HIV cure: The daunting scale of the problem. *Science* **383**, 703–705 (2024).

2. P. Goulder, S. G. Deeks, HIV control: Is getting there the same as staying there? *PLoS Pathog* **14**, e1007222 (2018).

3. A. Sáez-Cirión, *et al.*, Post-Treatment HIV-1 Controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. *PLoS Pathog* **9**, e1003211 (2013).

4. C. Passaes, *et al.*, Early antiretroviral therapy favors post-treatment SIV control associated with the expansion of enhanced memory CD8+ T-cells. *Nat Commun* **15**, 178 (2024).

5. J. M. Conway, A. S. Perelson, Post-treatment control of HIV infection. *Proc Natl Acad Sci USA* **112**, 5467–5472 (2015).

6. M. Pinkevych, *et al.*, Timing of initiation of anti-retroviral therapy predicts post-treatment control of SIV replication. *PLoS Pathog* **19**, e1011660 (2023).

7. C. C. Zebley, S. Gottschalk, B. Youngblood, Rewriting history: epigenetic peprogramming of CD8+ T cell differentiation to enhance immunotherapy. *Trends Immunol* **41**, 665–675 (2020).

8. J. M. Angelosanto, S. D. Blackburn, A. Crawford, E. J. Wherry, Progressive loss of memory T cell potential and commitment to exhaustion during chronic viral infection. *J Virol* **86**, 8161–8170 (2012).

Keywords: HIV, post, treatment control, CD8 T cell, memory responses, ART initiation

Impact of infection routes on within-host MPXV dynamics: insights from a modeling study

Woldegebriel Assefa Woldegerima*[1], Qi Deng , Jianhong Wu , Ali Asgary , and Nicola Bragazzi L.

[1]York University – Canada

Abstract

The unprecedented mpox outbreak in non-endemic regions during 2022-2023, which has seen a recent resurgence in late 2023-2024, poses a significant public health threat. Despite its global spread, the viral dynamics of mpox infection and the specific characteristics driving these outbreaks remain insufficiently explored. We develop mathematical models to examine the interactions between host immune responses and the virus across three distinct infection routes (intravenous, intradermal, and intrarectal). The models are calibrated using viral load data from macaques infected through each of these three infection routes. Subsequently, we calculate the infectiousness of each infected macaque, finding that the proportion of presymptomatic infectiousness is highest in those infected via sexual contact, followed by skin-to-skin contact. These observations demonstrate that close contact during sexual activity is a significant route of viral transmission, with presymptomatic spread playing a crucial role in the 2022-2023 multi-country outbreak and potentially also in the 2023-2024 multi-source outbreak. Leveraging model predictions and infectiousness data, we assess the impact of antiviral drugs on interventions against mpox infection. Model simulations suggest that early administration of antiviral drugs can reduce peak viral loads, even in individuals with compromised immunity, particularly in cases of infection through skin-to-skin and sexual contact. These results underscore the importance of initiating antiviral treatment as early as possible for mpox-infected patients with compromised immune systems, such as those who are HIV-positive. **Note: My talk will be based on a published article**: https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1013073

Keywords: mathematicla modelling, within, host mpox virus dynamics, immune response, mpox virus infection routes, antiviral drugs, model fitting

*Speaker

Modelling the dynamic Interplay between SARS-CoV-2 Infection, Immunity and Evolution

Max Von Kleist*[1], Martin Hölzer , Djin-Ye Oh , Sofia Paraskevopoulou , Nils Gubela , Alexia N. Raharinirina , and Benjamin Winkler

[1]Robert Koch Institute – Germany

Abstract

While SARS-CoV-2 infection has lead to an unprecedented public health crisis, it also lead to the generation of a wealth of data that may help us to understand mechanisms driving the evolution and spread of respiratory viruses. A plausible hypothesis is that SARS-CoV-2 continues to evolve to evade antibody-mediated neutralization to maximize its ability to infect an immunologically experienced population. Because viral infection induces neutralizing antibodies, viral evolution may thus navigate on a dynamic immune landscape that is shaped by local infection history. We reconstructed local infection incidence and developed a comprehensive mechanistic model, incorporating deep mutational scanning data, antibody pharmacokinetics and regional genomic surveillance data, to predict the variant-specific relative number of susceptible individuals over time. We show that the model-computed variant-specific relative number of susceptible individuals predicts historical variant dynamics, future variant dynamics and explains their global differences. This work strongly suggests that the ongoing pandemic continues to shape variant-specific humoral immunity in the population, which determines the relative transmission fitness of variants. While this model is useful in assessing the vulnerability of a population to infection with a new SARS-CoV-2 variant, we further develop the model to predict the expected size of infection waves with distinct variants from the expected number of susceptible individuals per lineage, as well as its variance. Moreover, we discover that the model may be used to predict expected levels of T-cell induced immunity at the population, which predicted case severity, as well as the expected number of severe infections with SARS-CoV-2 over the entire pandemic. Overall, our modelling highlights drivers of SARS-CoV-2 evolution and showcases how pathogen surveillance data may be used for supporting public health risk assessment and pandemic preparedness.

Keywords: SARS, CoV, 2, evolution, antibodies, deep mutational scanning, T, cell immunity, fitness, selection

*Speaker

Impact of infection routes on within-host MPXV dynamics: insights from a modeling study

Woldegebriel Assefa Woldegerima*[1], Qi Deng , Jianhong Wu , Ali Asgary , and Nicola Bragazzi L.

[1]York University – Canada

Abstract

The unprecedented mpox outbreak in non-endemic regions during 2022-2023, which has seen a recent resurgence in late 2023-2024, poses a significant public health threat. Despite its global spread, the viral dynamics of mpox infection and the specific characteristics driving these outbreaks remain insufficiently explored. We develop mathematical models to examine the interactions between host immune responses and the virus across three distinct infection routes (intravenous, intradermal, and intrarectal). The models are calibrated using viral load data from macaques infected through each of these three infection routes. Subsequently, we calculate the infectiousness of each infected macaque, finding that the proportion of presymptomatic infectiousness is highest in those infected via sexual contact, followed by skin-to-skin contact. These observations demonstrate that close contact during sexual activity is a significant route of viral transmission, with presymptomatic spread playing a crucial role in the 2022-2023 multi-country outbreak and potentially also in the 2023-2024 multi-source outbreak. Leveraging model predictions and infectiousness data, we assess the impact of antiviral drugs on interventions against mpox infection. Model simulations suggest that early administration of antiviral drugs can reduce peak viral loads, even in individuals with compromised immunity, particularly in cases of infection through skin-to-skin and sexual contact. These results underscore the importance of initiating antiviral treatment as early as possible for mpox-infected patients with compromised immune systems, such as those who are HIV-positive. **Note: My talk will be based on a published article**: https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1013073

Keywords: mathematicla modelling, within, host mpox virus dynamics, immune response, mpox virus infection routes, antiviral drugs, model fitting

*Speaker