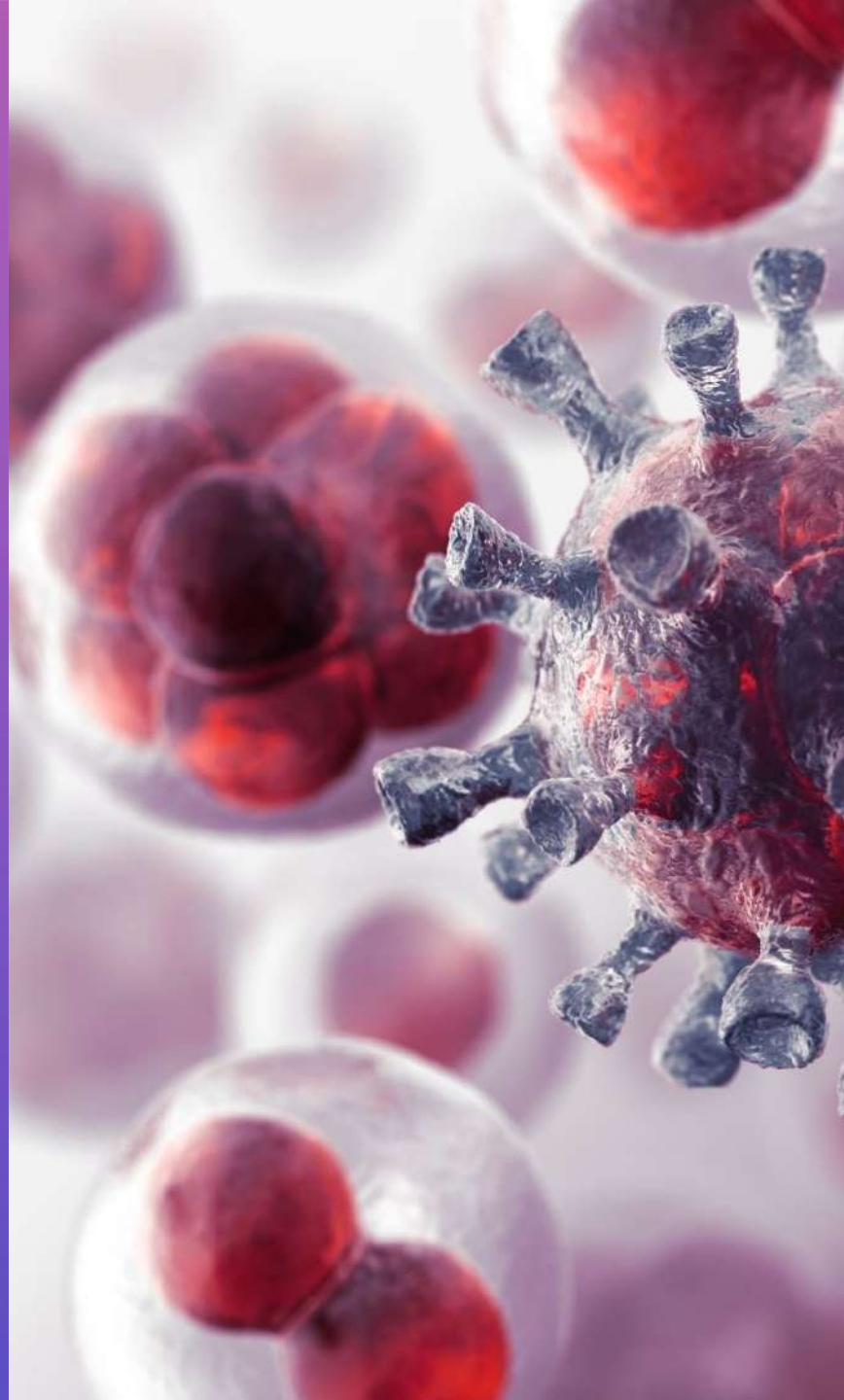
SINGLE SCALE AND MULTI-SCALE MODELS OF VIRAL INFECTIONS AND ANTI-VIRAL IMMUNE RESPONSES: APPLICATIONS TO INFECTIOUS AND NON-INFECTIOUS DISEASES

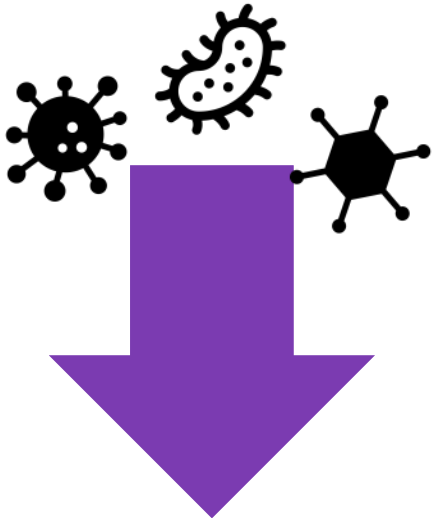
RALUCA EFTIMIE

(RALUCA.EFTIMIE@UNIV-FCOMTE.FR)

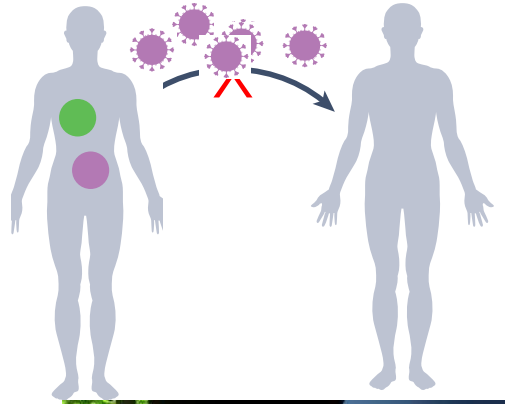
Workshop: "NEW TRENDS IN BIOMATHEMATICS: Applications in Oncology and Immunology"

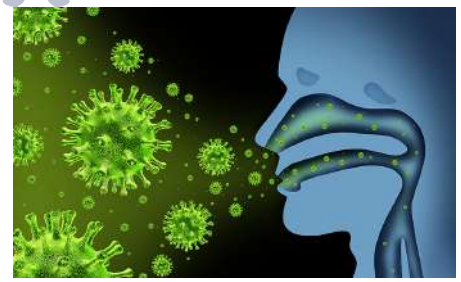


Non-infectious diseases: oncogenic viruses: we want to control & eliminate them…



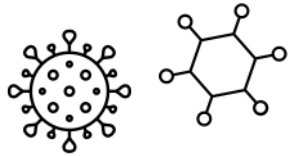
Infectious diseases: we want to control the infections & eliminate viruses causing them…



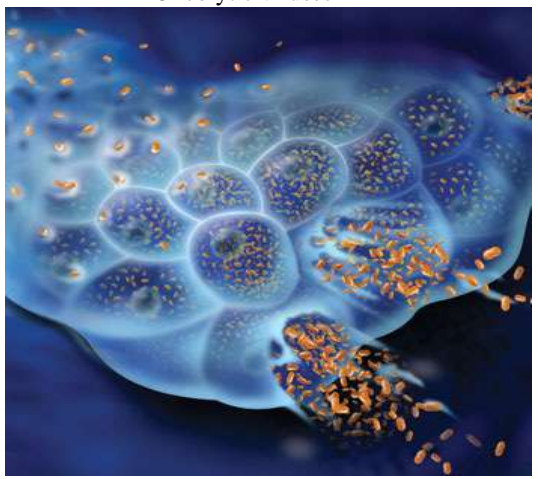


Non-infectious diseases: viruses can be used as treatments for these diseases (control & increase replication)

(e.g., oncolytic viruses in cancer treatment)



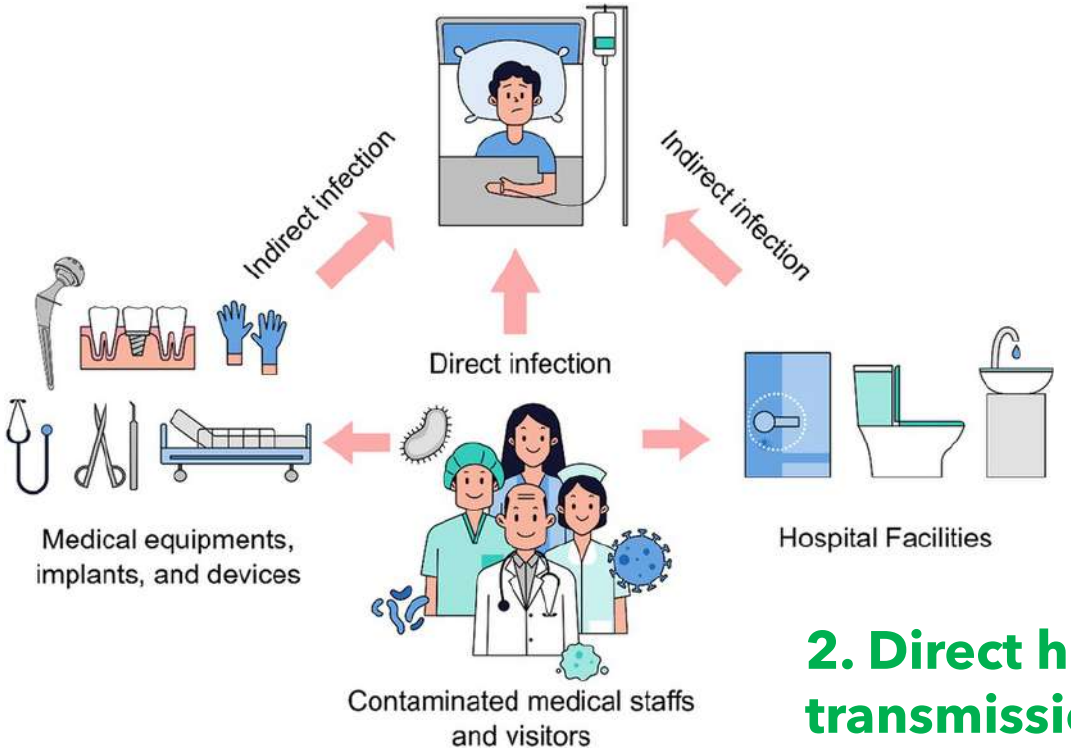
Oncolytic viruses



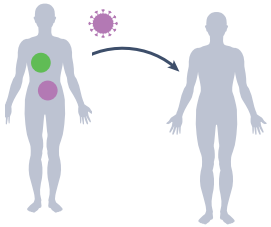
http://oncolyticvirus.files.wordpress.com/2010/12/oncolytic–virus–in–action.

VIRUS SPREAD ACROSS MULTIPLE SPATIAL & TEMPORAL SCALES:

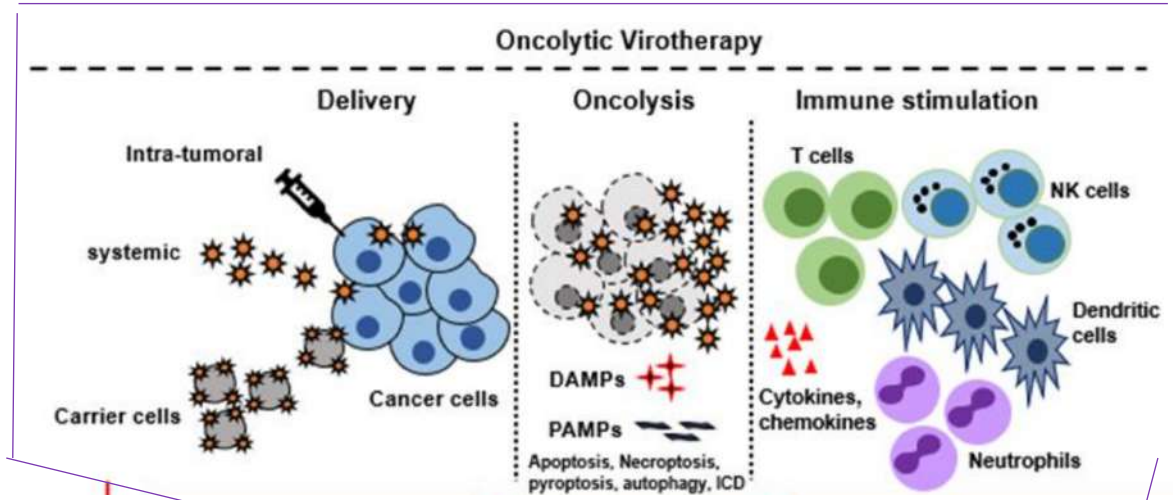
1. Environmental transmission of viruses: nosocomial infections: hospital wards/ bays/operating rooms/facilities/… => infected patient



2. Direct human-to-human transmission: infected – susceptible interactions



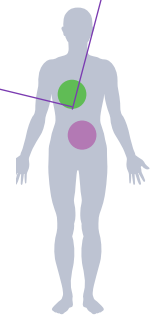
3. Cell-to-cell transmission: anti-viral immune responses that control the infection…



Review

Oncolytic Viruses: Newest Frontier for Cancer Immunotherapy

Masmudur M. Rahman * and Grant McFadden



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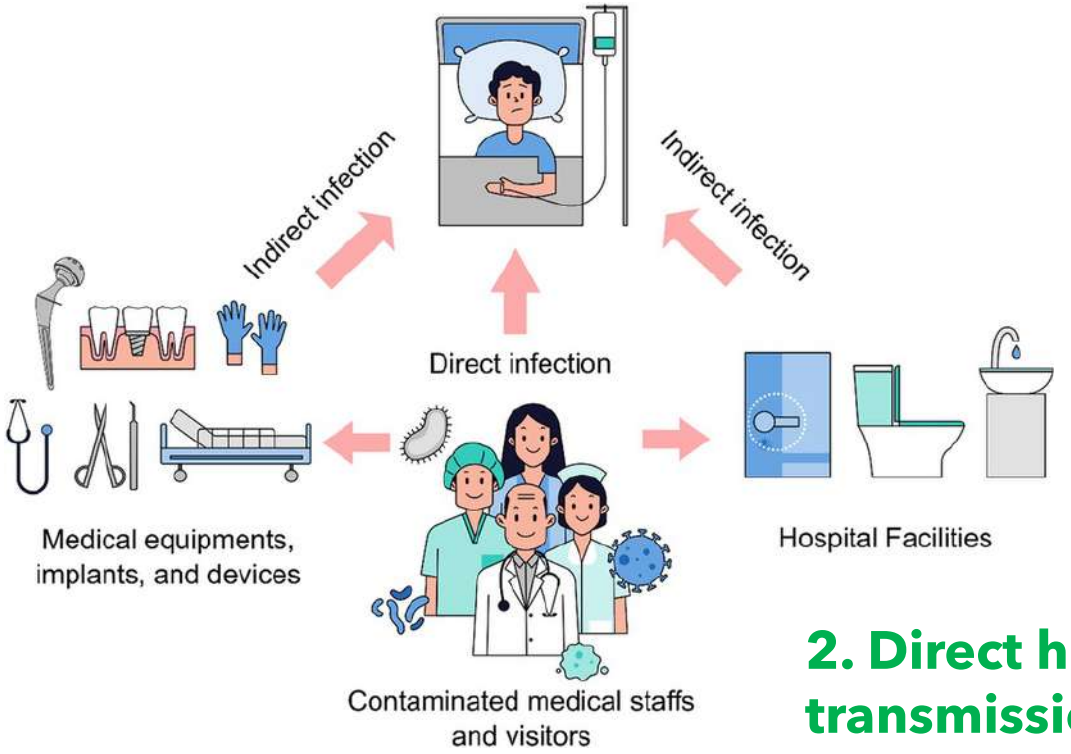

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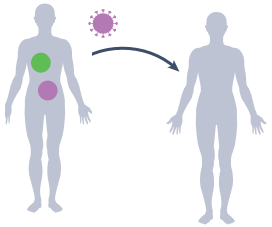

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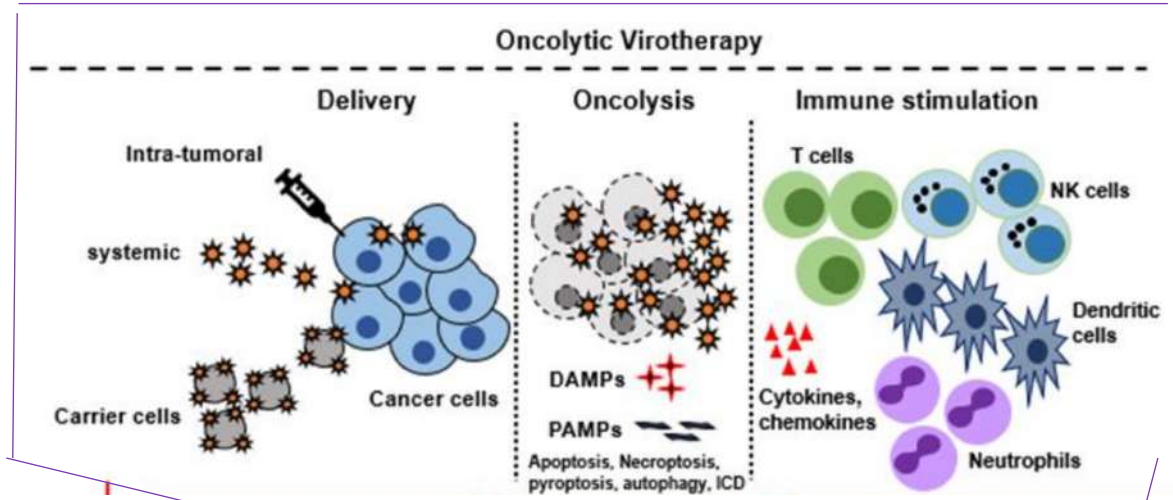

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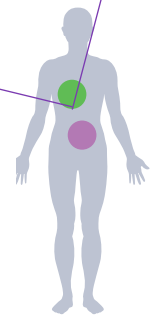
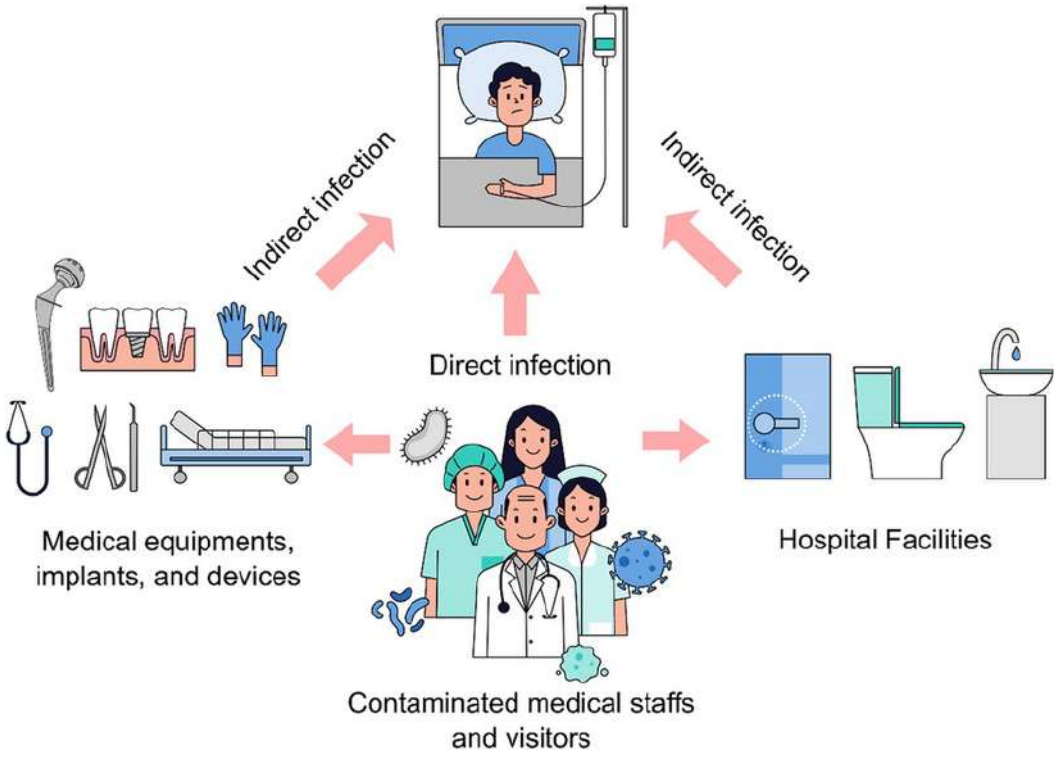


Here: focus on infectious diseases

Here: focus on non-infectious diseases (cancer)

Environmental & human-to-human transmission of viruses: nosocomial infections

- Nosocomial infections in the context of COVID-19 (collaboration with Dr. B. Parcell, Ninewells Hospital, UK)



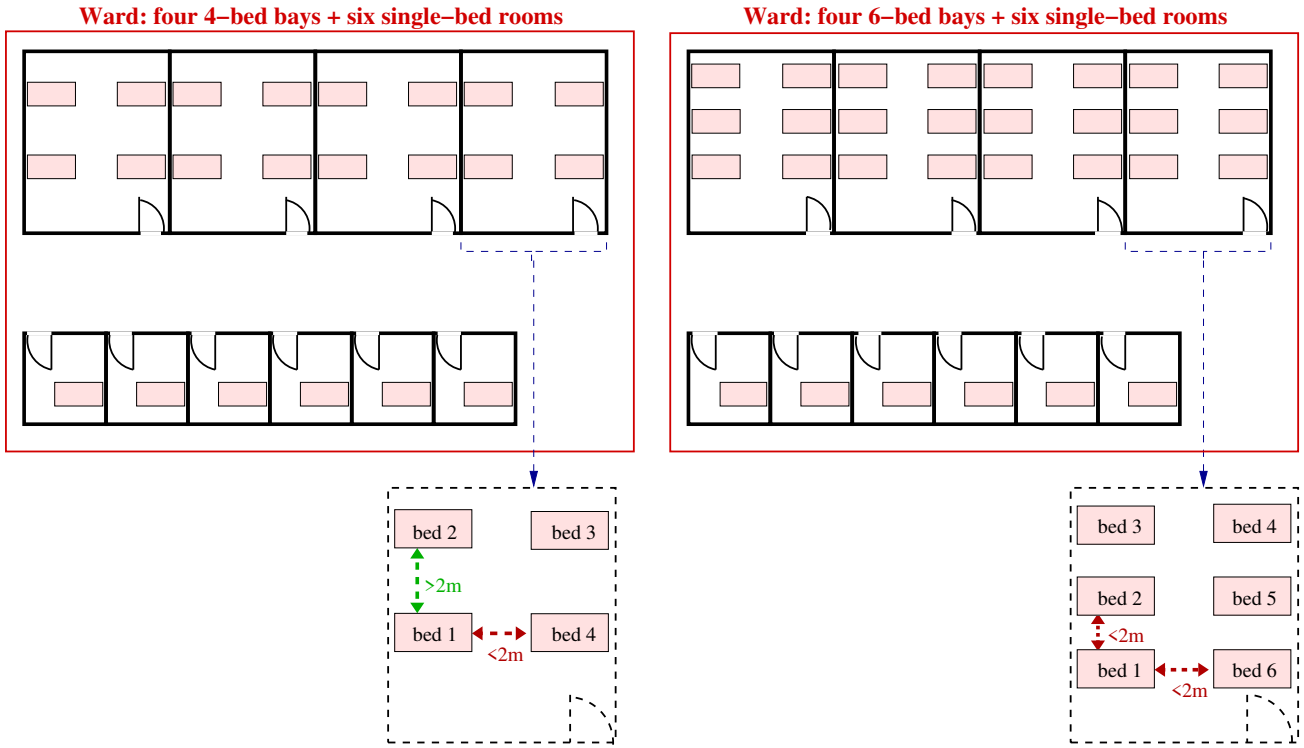
https://link.springer.com/article/10.1007/s00449-022-02733-9

Environmental & human-to-human transmission of viruses: nosocomial infections

- Nosocomial infections in the context of COVID-19 (collaboration with Dr. B. Parcell, Ninewells Hospital, UK)

Question (asked in summer 2020) :
How to distribute the hospitalized patients in wards with
- 4-bed bays + single-bed rooms vs.
- 6-bed bays + single-bed rooms

to reduce SARS-CoV-2 spread across the hospital?



- ➢ Infected patients moved to single rooms (if available)
- ➢ Infected rooms were closed for cleaning… no new patients admitted to hospital

D. Moreno Martos, B. Parcell, RE (2020). Modelling the transmission of infectious diseases inside hospital bays: implications for Covid-19 . Math. Biosci. Eng., 17(6) , 8084-8104

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Environmental & human-to-human transmission of viruses: nosocomial infections

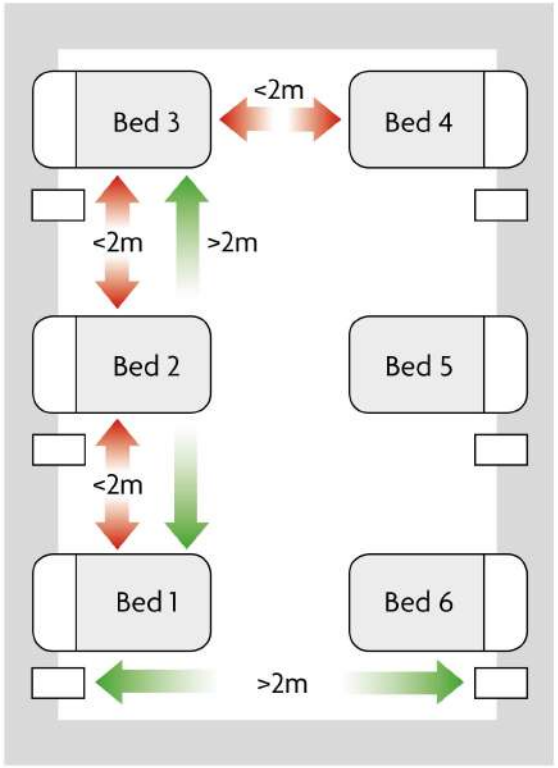

B. Parcell

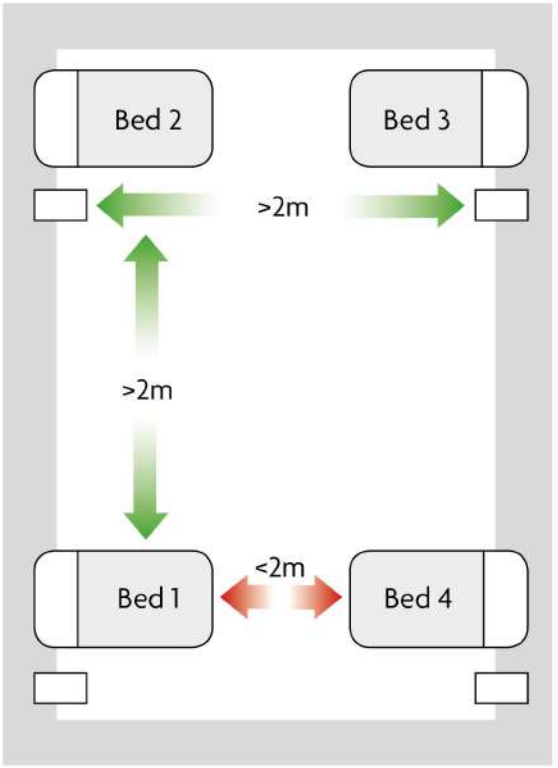
- Nosocomial infections in the context of COVID-19 (collaboration with Dr. B. Parcell, Ninewells Hospital, UK)

Agent-based network model: each node is a patient (in a bed) with specific characteristics:

$$I_{n,t} = [C_{n,1,t}, C_{n,2,t}, ..., C_{n,m,t}]$$

1. Epidemiological status (susceptible, exposed, infected, recovered)
2. Bed # in which the patient is placed …
3. Start of the incubation period
4. Duration of incubation period
5. Time since individual has become infectious
   -> viral transmission possible
1. Recovery time





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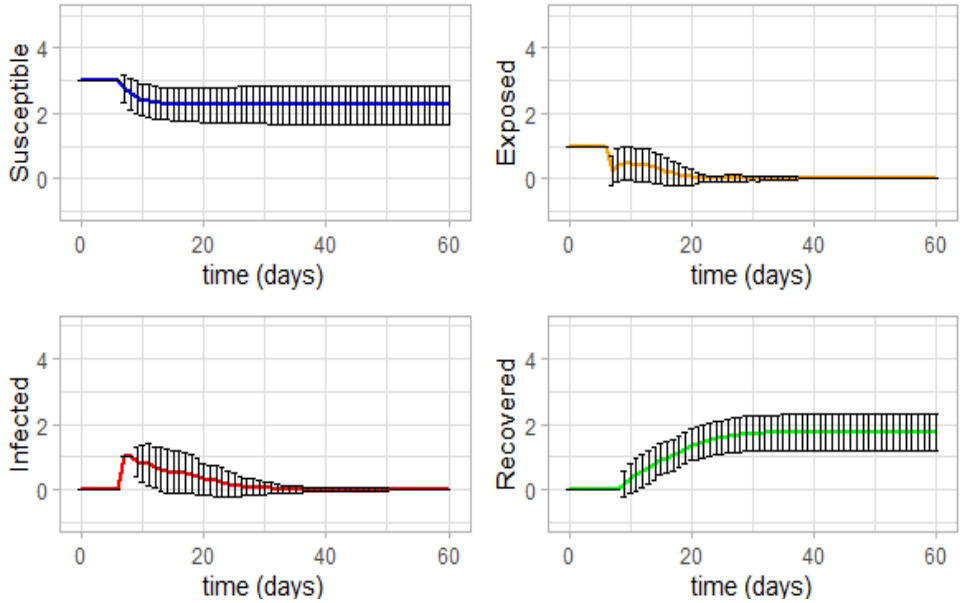
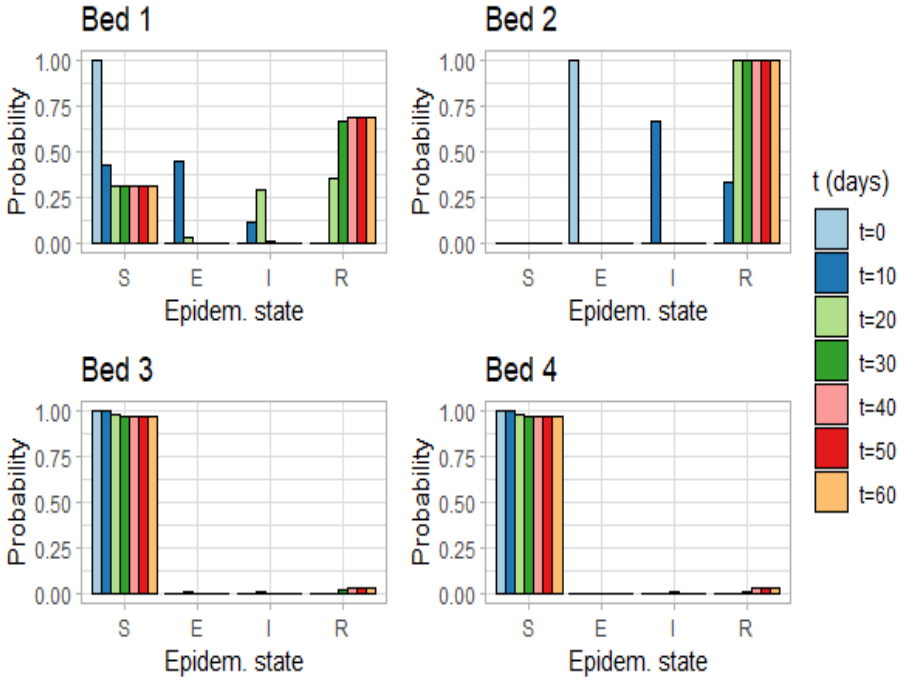
Model can account for stochastic fluctuations between interconnected individuals inside the bay

(a) 4–bed bays:

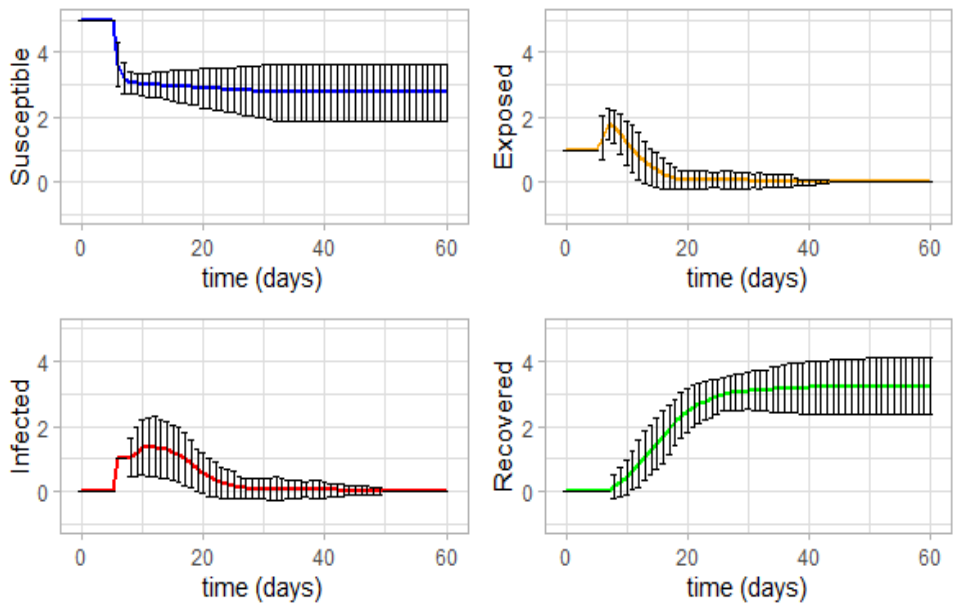
Average number of individuals per time

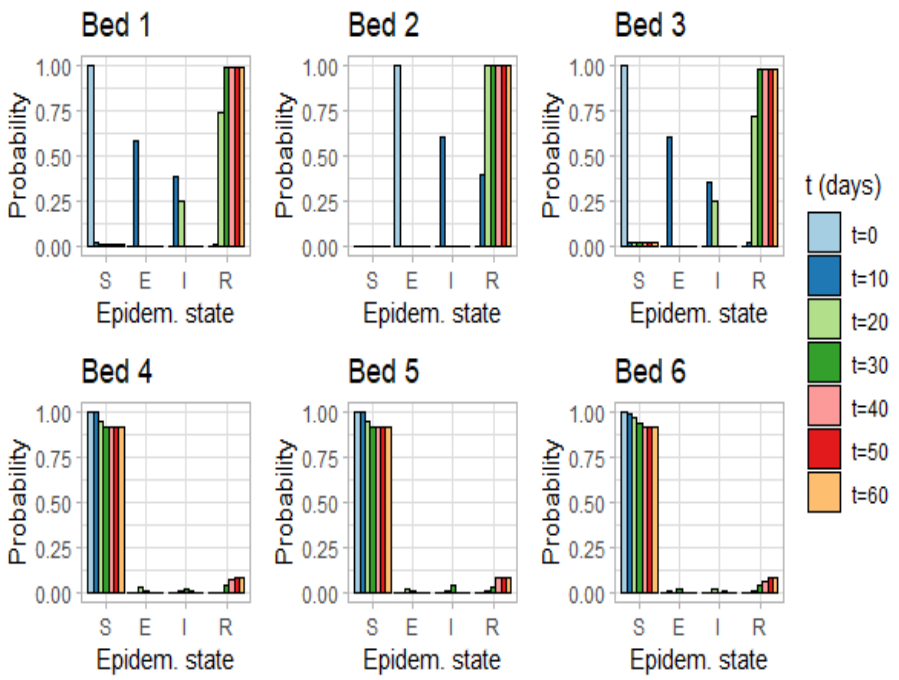




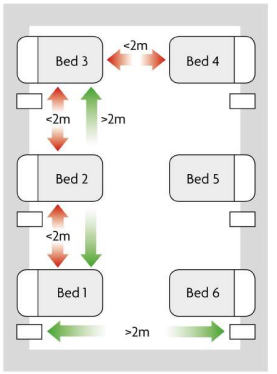
(c) 6–bed bays:

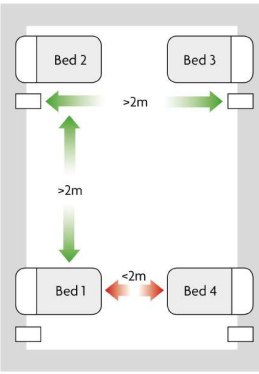
Average number of individuals per time





B. Parcell



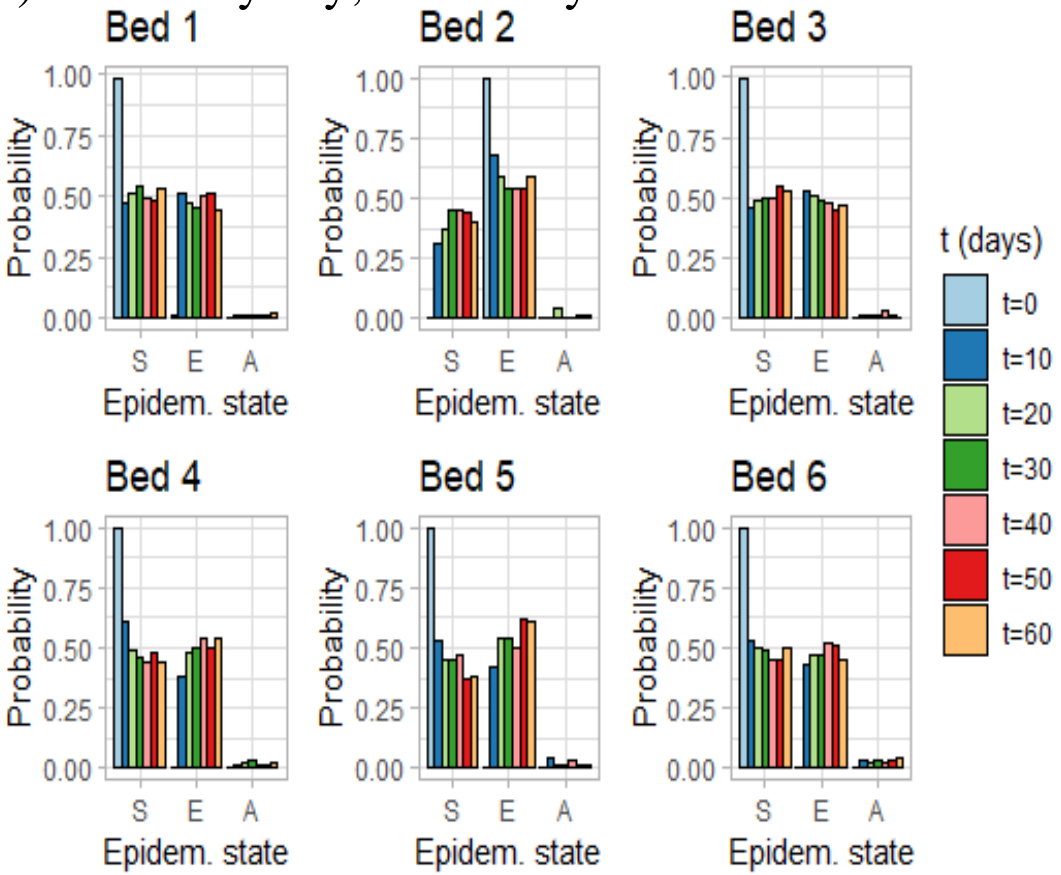


Hypotheses tested & confirmed *in silico*:

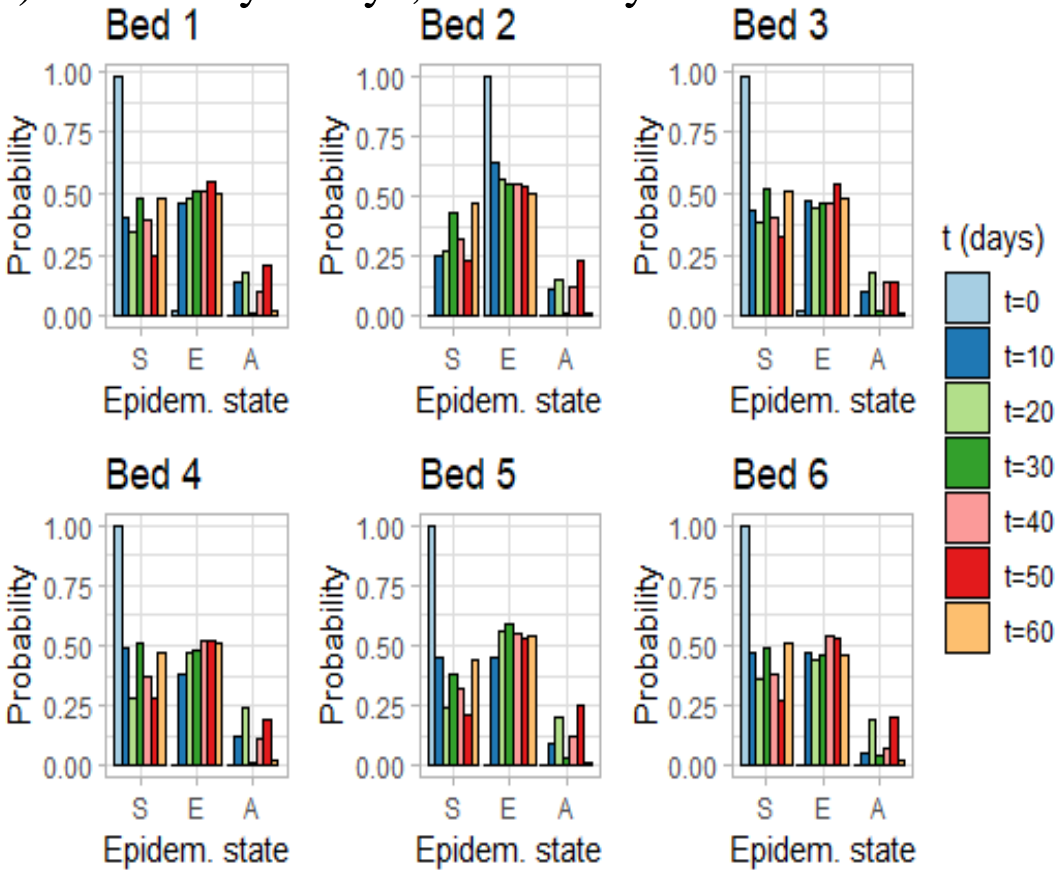
Having only 4-bed bays is better to reduce the spread of the infection

D. Moreno Maros, B. Parcell, RE (2020). Modelling the transmission of infectious diseases inside hospital bays: implications for Covid-19 . Math. Biosci. Eng., 17(6) , 8084-8104

(d) tests every day; 6–bed bays



(d) tests every 3 days; 6–bed bays



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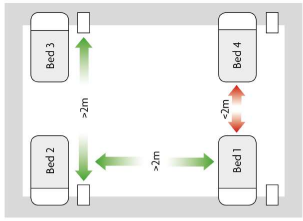

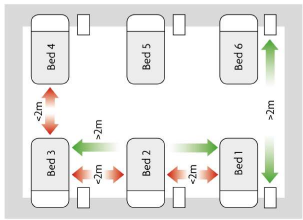

Hypotheses tested *in silico*: the role of asymptomatic individuals

- More often RT-PCR tests (every day vs. every 3 days) are better at detecting exposed/infected patients (in particular for 6-bed bays)
- Impact of mask wearing by medical staff… and infected staff infecting patients …

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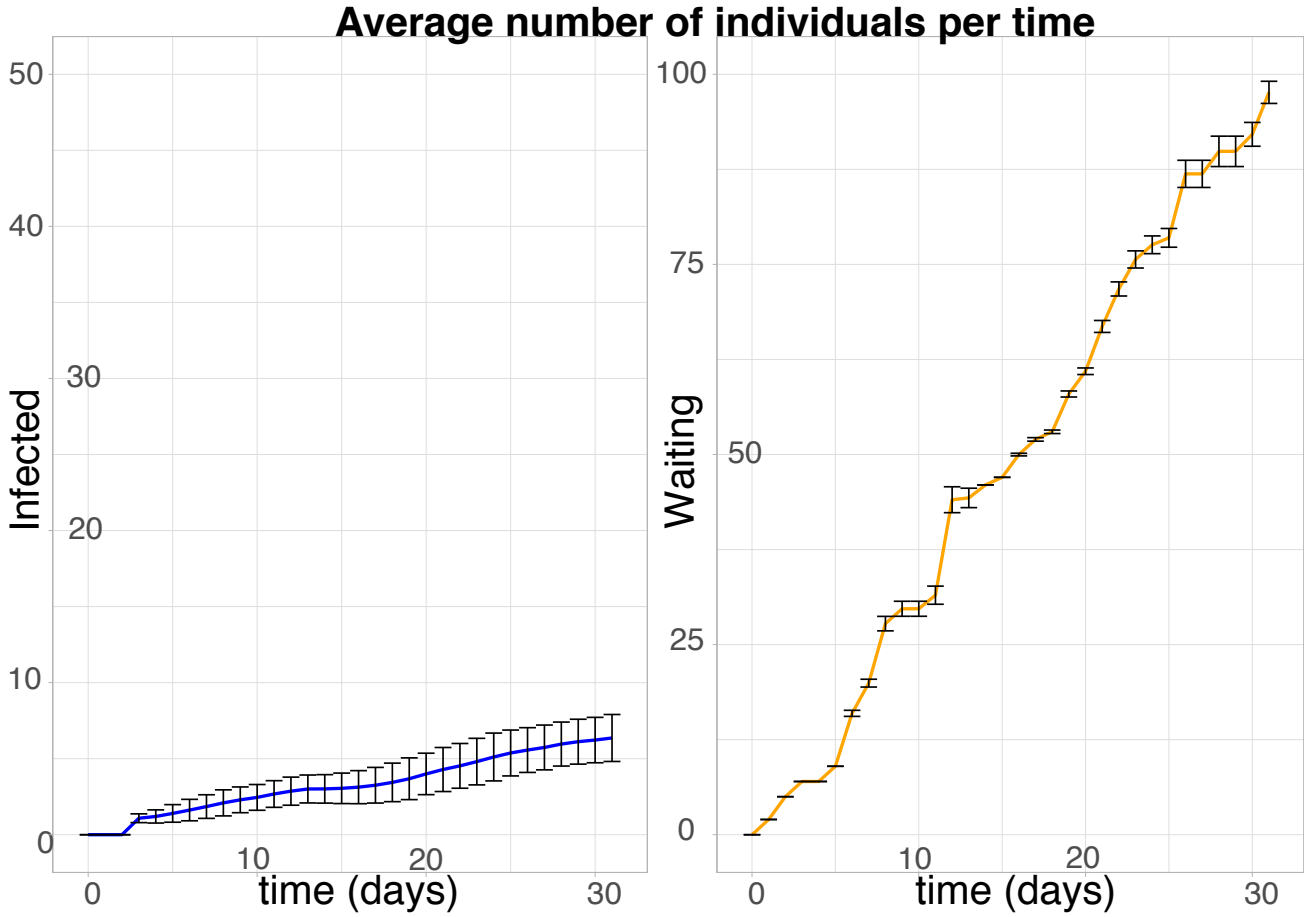
D. Moreno Maros, B. Parcell, RE (2020). Modelling the transmission of infectious diseases inside hospital bays: implications for Covid-19 . Math. Biosci. Eng., 17(6) , 8084-8104

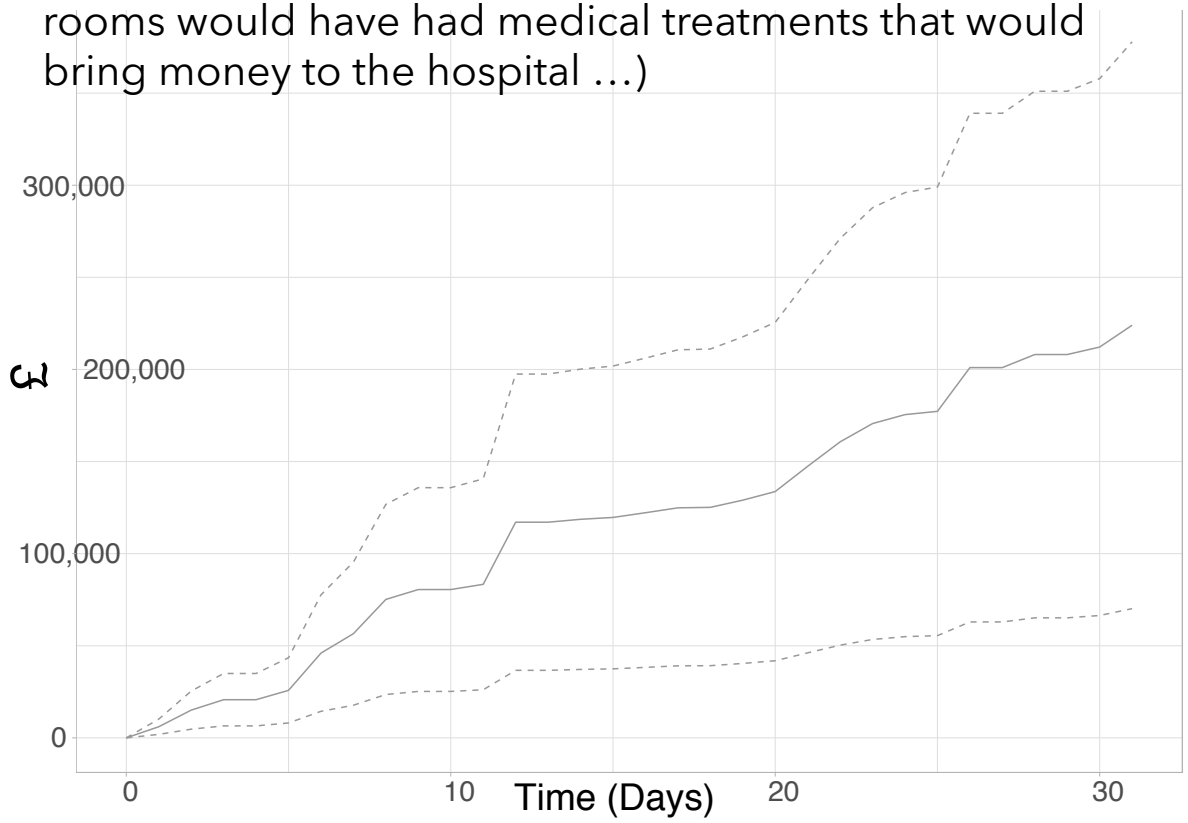
Models, even if not perfectly calibrated (scarce data), can be used to make administrative (& public policy) decisions… especially in exceptional times…

- Open the hospital for elective surgery procedures..



(a) 1 Bay with 4 Beds; $\beta(d_{ij}) = e^{-\frac{3}{2}d_{ij}}$

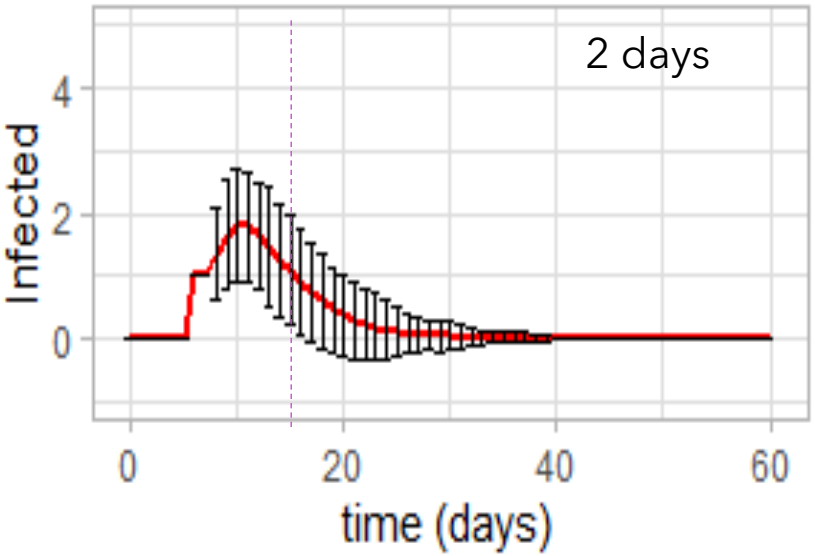
Costs related to patients on the waiting list for admission (which, if they were admitted to 4-bed bays + 6 single rooms would have had medical treatments that would bring money to the hospital …)

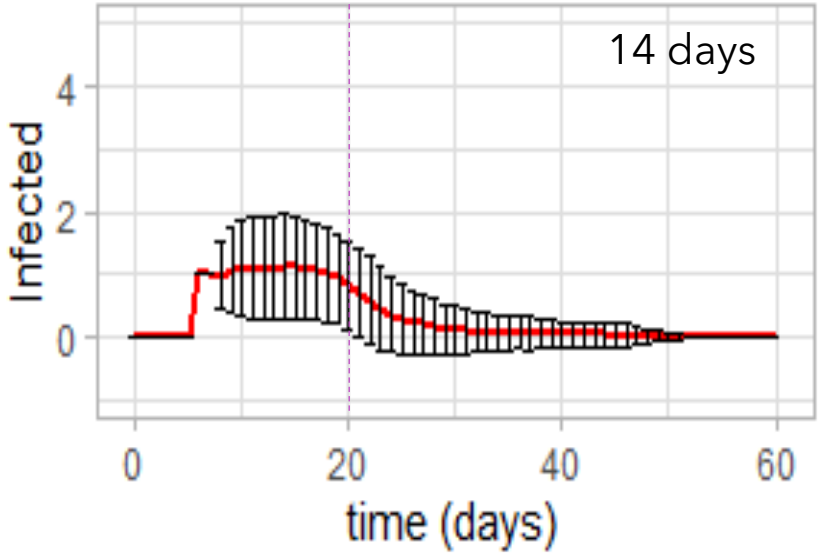


(a) 4 Beds

D. Moreno Maros, S. Folley, B. Parcell, D. Trucu, RE (**2022**). A computational investigation of COVID-19 transmission inside hospital wards and associated costs. Math. Biosci. Eng., 17(6) , 8084-8104

Changes in the incubation period for human-to-human transmission…





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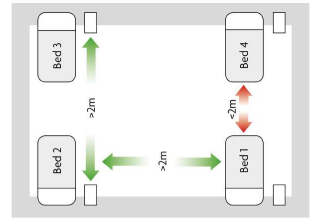

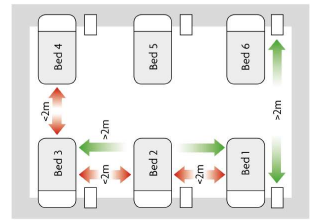

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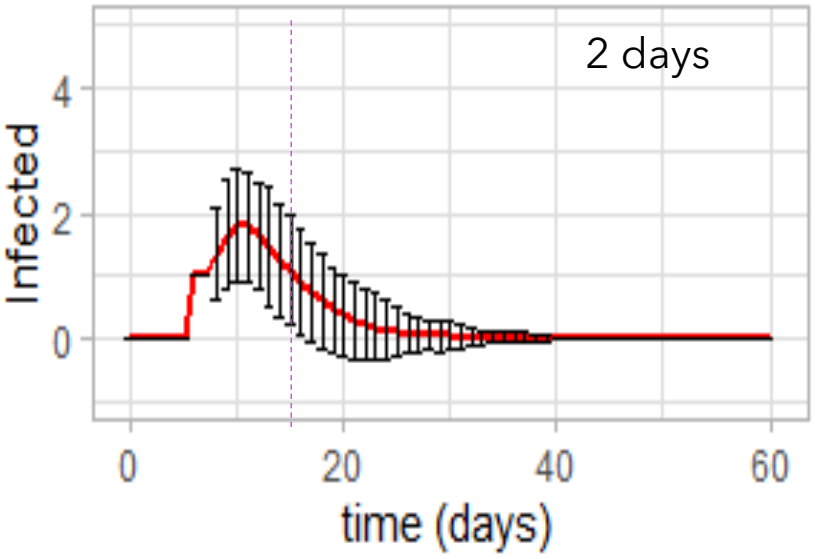

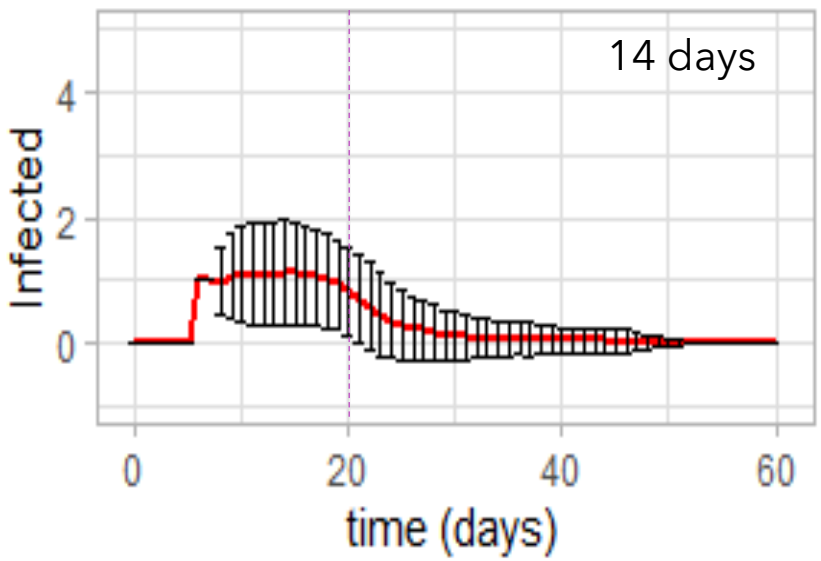

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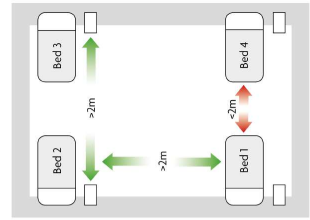
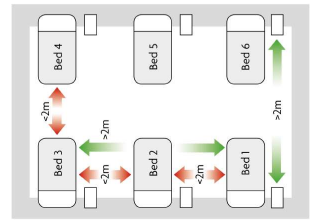
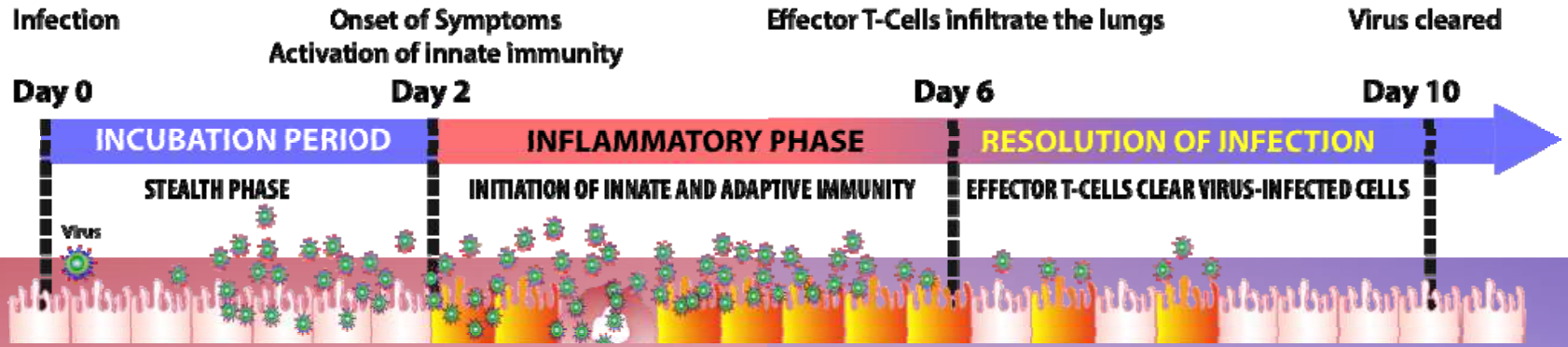




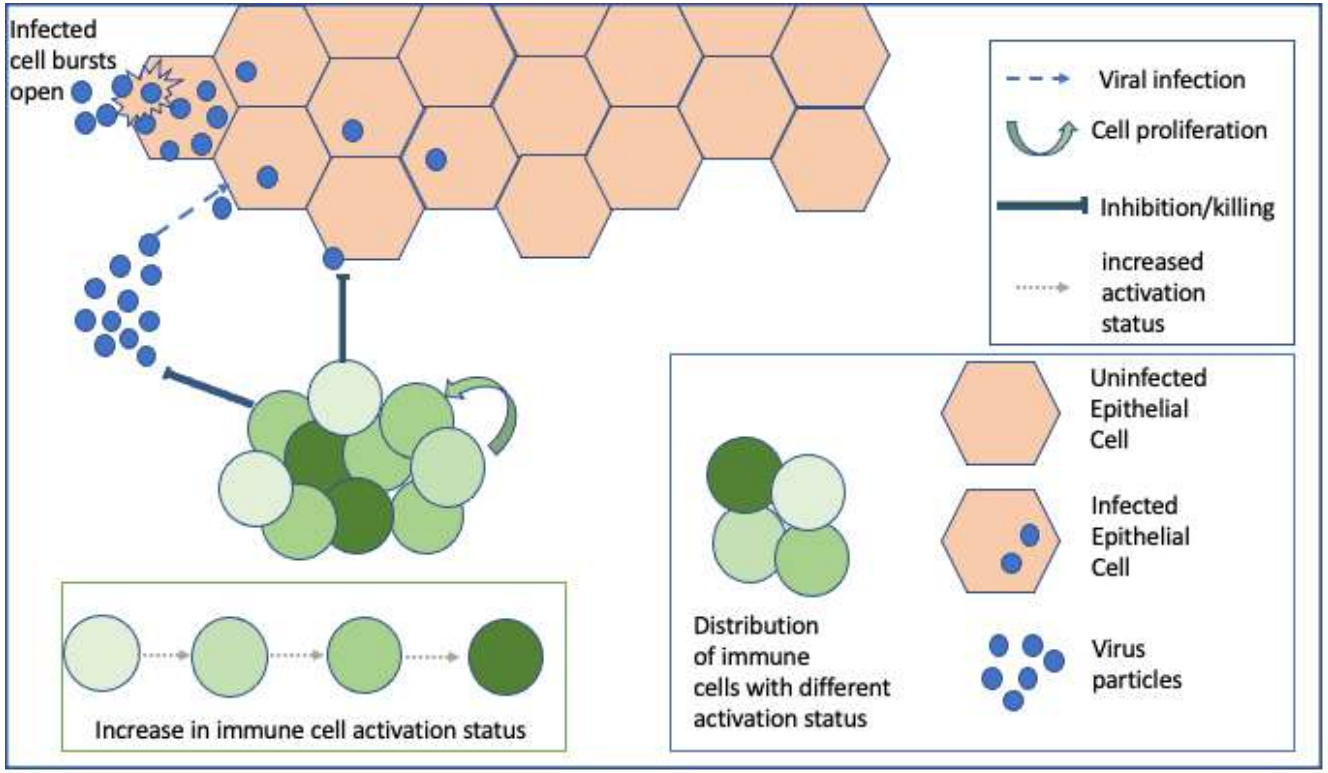
Buying Time—The Immune System Determinants of the Incubation Period to Respiratory Viruses

Tamar Hermesh [1,†], Bruno Moltedo [1,†], Carolina B. López [1,2] and Thomas M. Moran [1,*]



Also viral transmission probably depends on the immune system (& anti-viral immune response) of the infected individuals …

Cell-to-cell transmission



What is the in-host dynamics of SARS-CoV-2 virus?
A challenge within a multiscale vision of living systems

N. Bellomo * R. Eftimie † G. Forni ‡

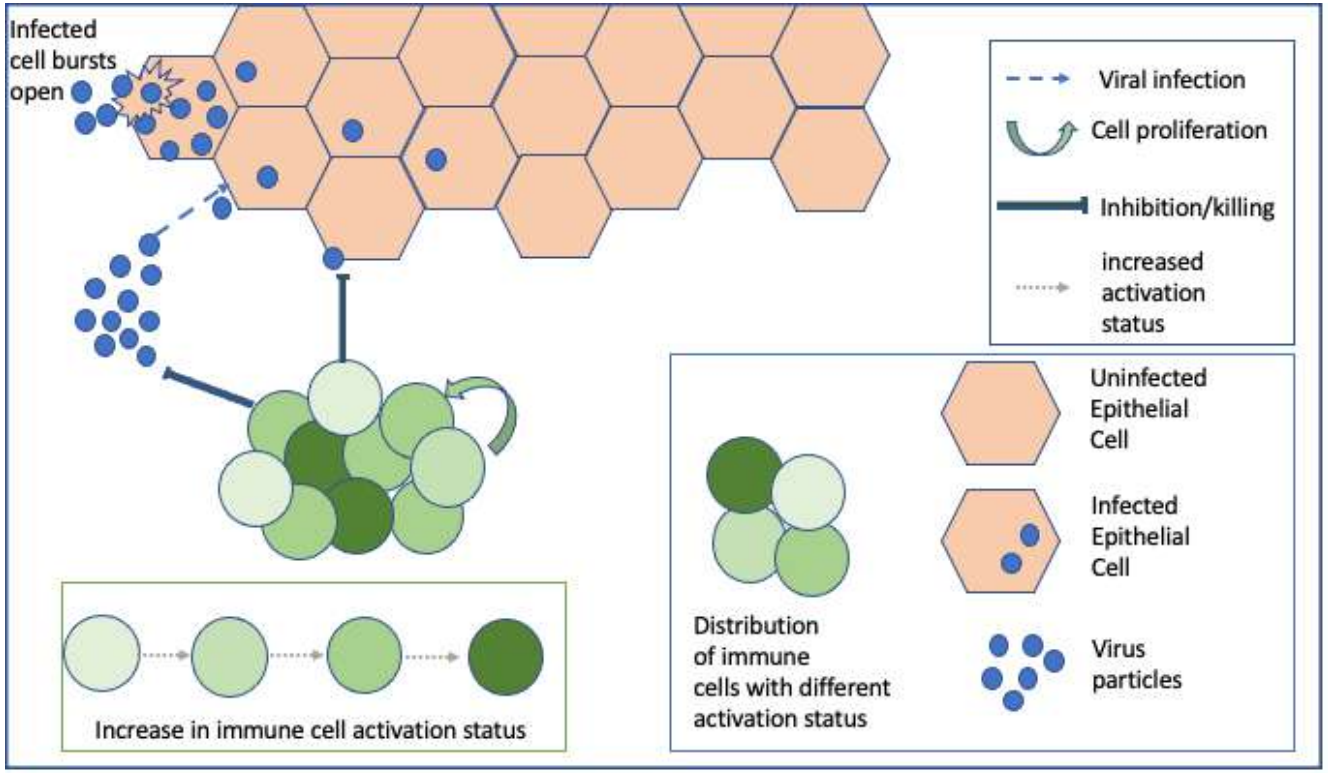
Free viruses

Infected epithelial cells

Immune cells

$$\begin{cases} \dfrac{d}{dt}n_1(t) = \gamma N_c n_2(t) - \mu n_1(t)\displaystyle\int_0^1 K(u) f_3(t,u)du, \\ \dfrac{d}{dt}n_2(t) = \alpha n_1(t)\,(N_H - n_2(t)) - \gamma n_2(t) \\ \qquad\qquad -\mu n_2(t)\displaystyle\int_0^1 K(u) f_3(t,u)du, \\ \dfrac{\partial}{\partial t}f_3(t,u) = \kappa(u)\, f_3(t,u) n_1(t) - \lambda f_3(t,u) \\ \qquad\qquad +\beta n_1(t)\displaystyle\int_0^1 \mathcal{A}(u_* \to u) f_3(t,u_*)du_* \end{cases}$$

Cell-to-cell transmission



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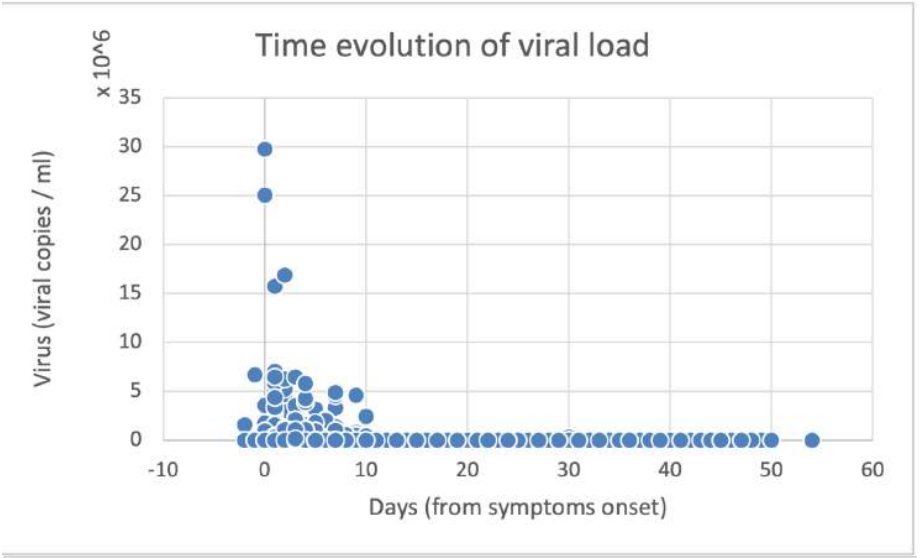
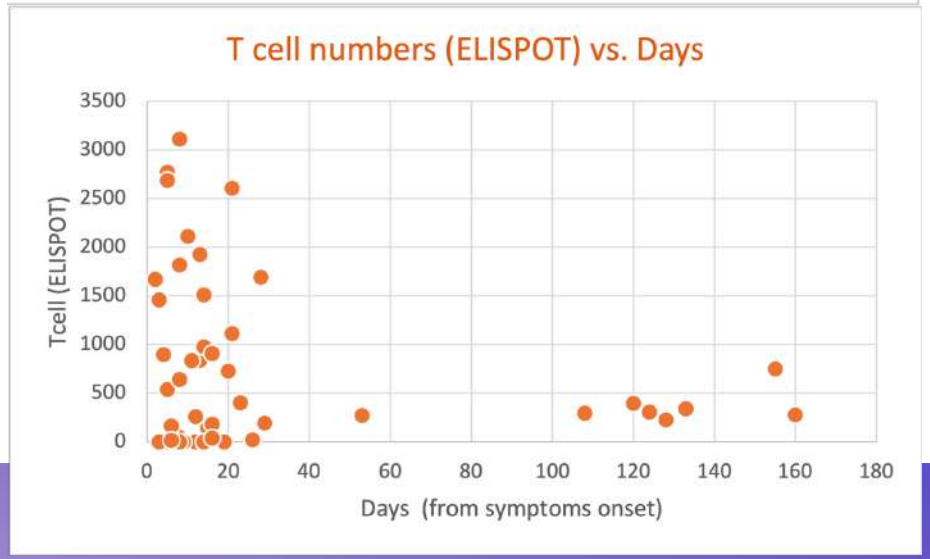
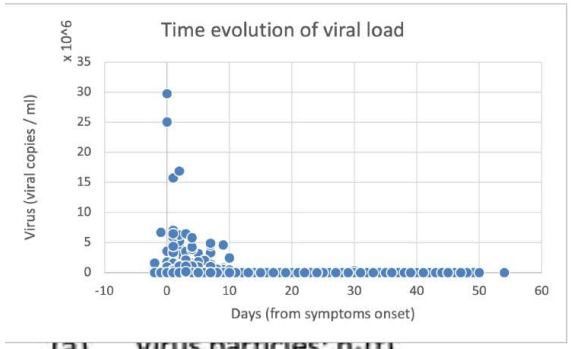
What is the in-host dynamics of SARS-CoV-2 virus?
A challenge within a multiscale vision of living systems

N. Bellomo * R. Eftimie † G. Forni ‡





Cell-to-cell transmission



Qualitative investigation (& exploration) of model dynamics

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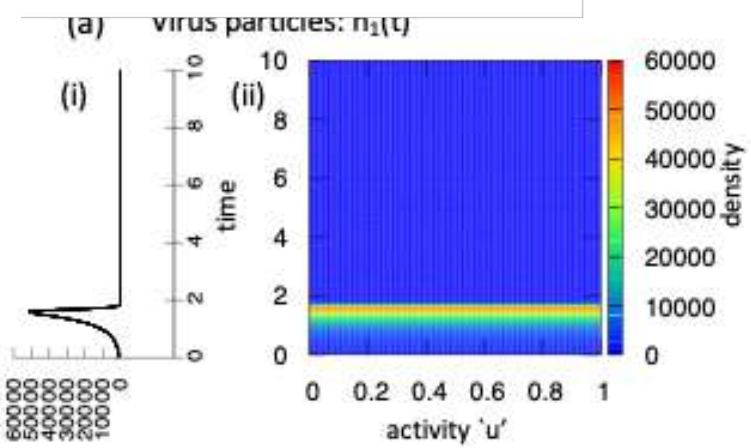
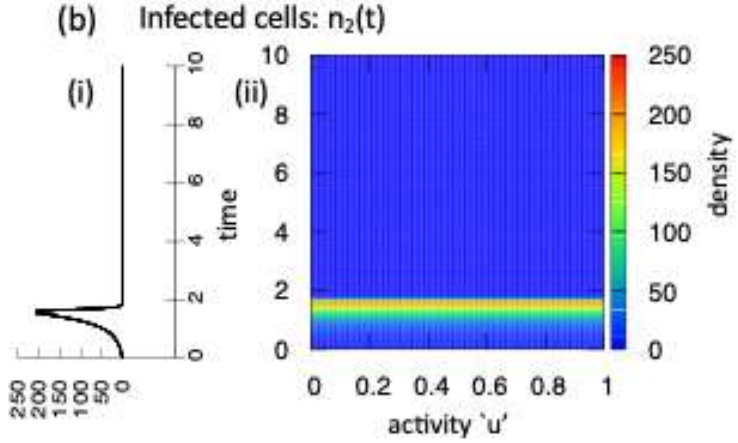
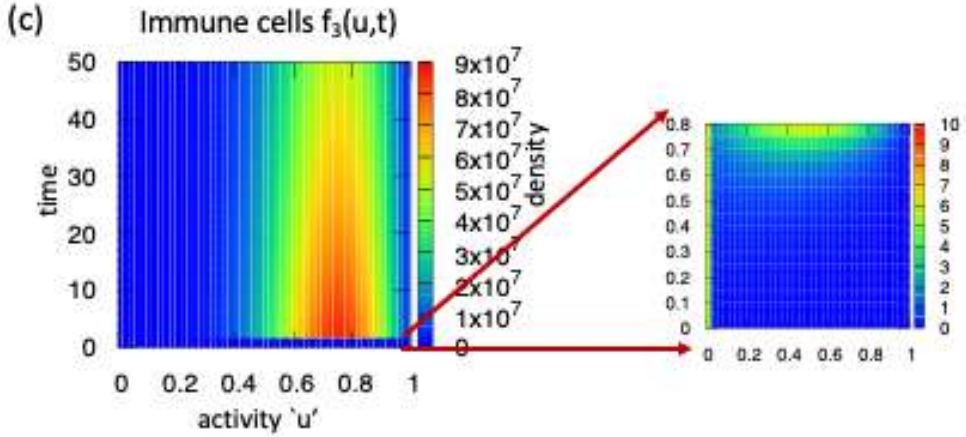
A challenge within a multiscale vision of living systems

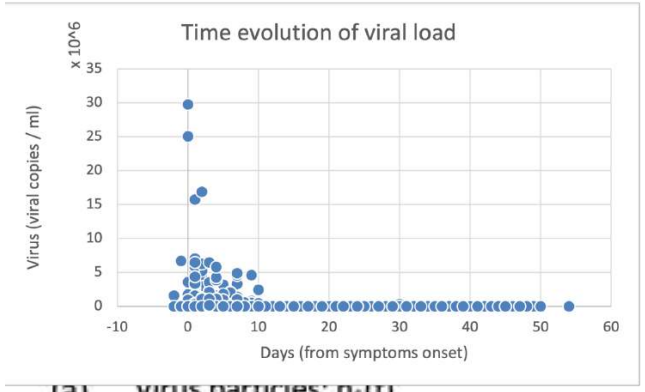
N. Bellomo * R. Eftimie † G. Forni ‡







Cell-to-cell transmission



Qualitative investigation of model dynamics

What is the in-host dynamics of SARS-CoV-2 virus?
A challenge within a multiscale vision of living systems

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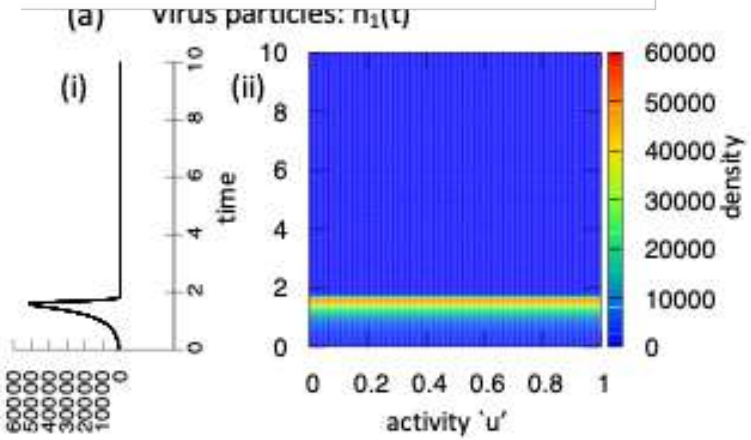
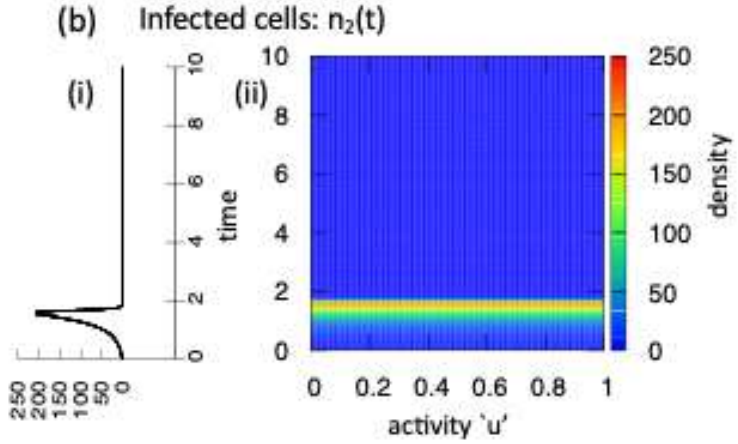
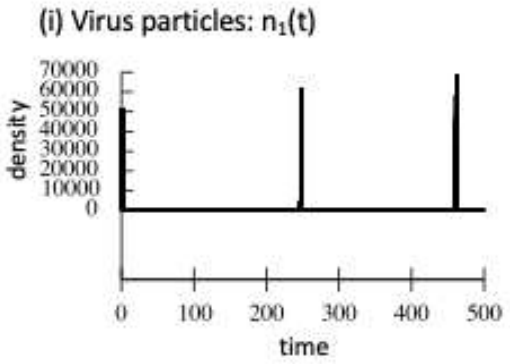
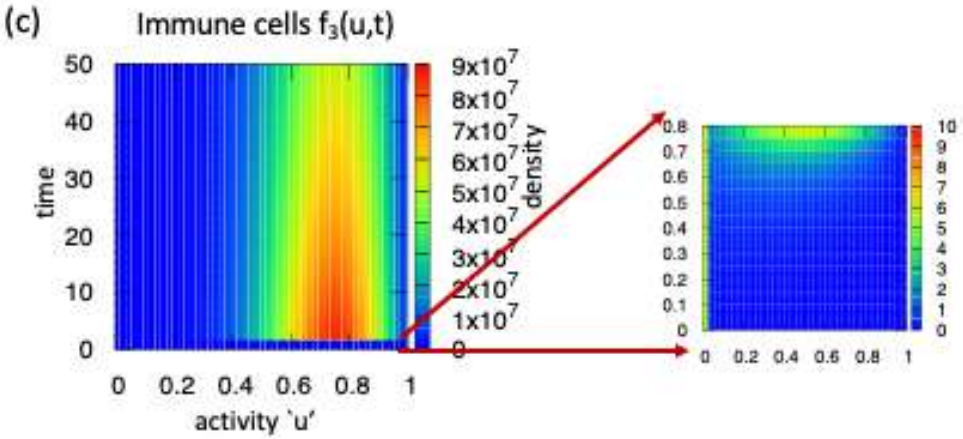
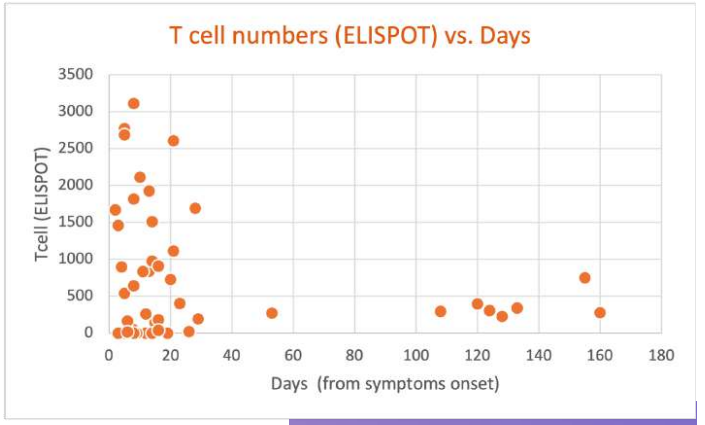


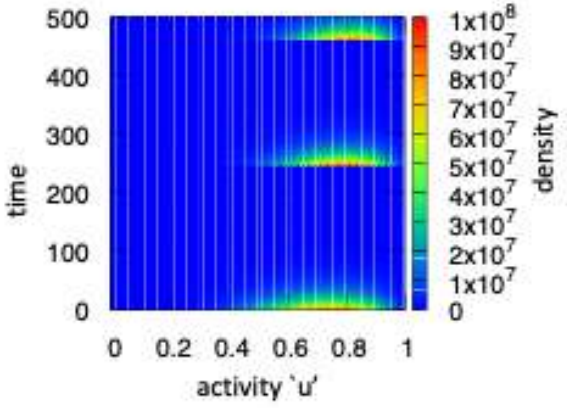


Re-infections are possible...







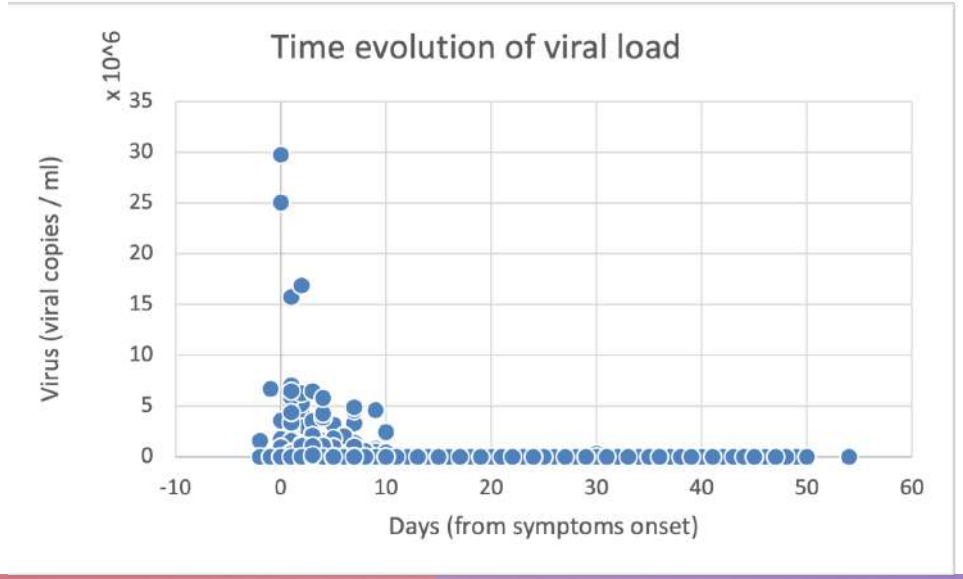


Timeline of mathematical models

Virus enters the body & infection starts

Timeline of (many) clinical datasets

Day from symptoms onset

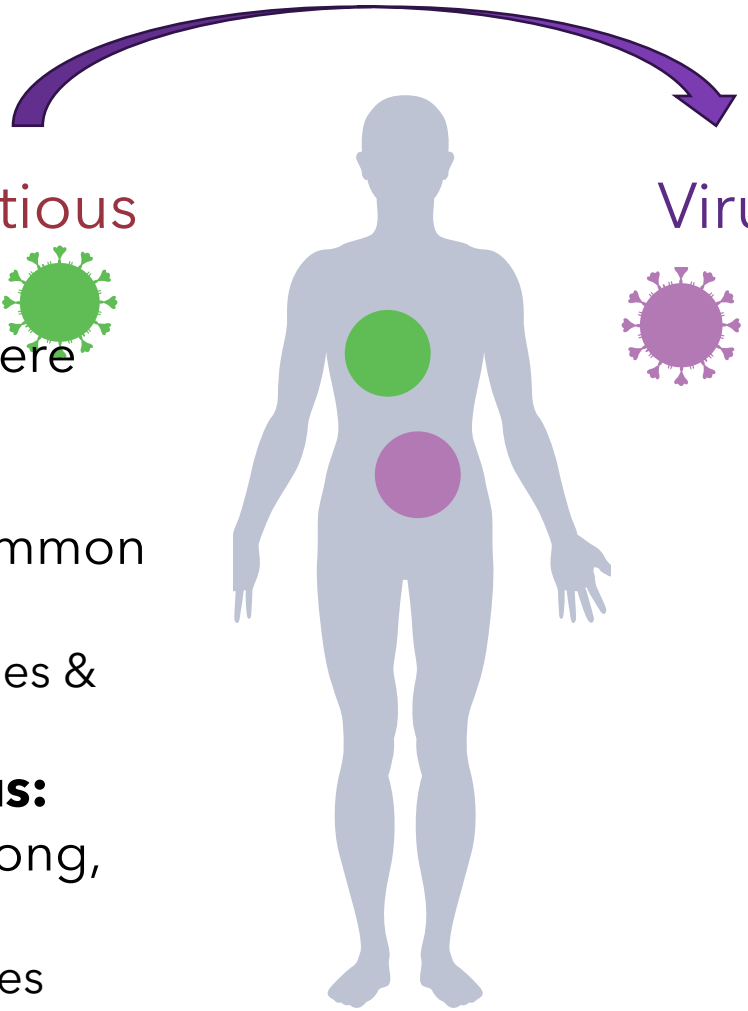


There are datasets to validate the models, but maybe not in the form modellers want them

=> adapt the models

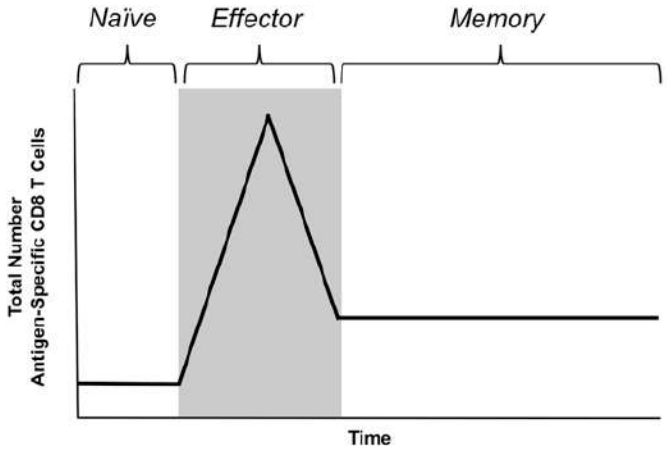
Viruses that cause infectious diseases…

- **SARS-CoV-2:** mild to severe infections
- **Adenoviruses:** mild respiratory infections (common cold)
  - ✓ infect mammalian species & birds
- **Vesicular stomatitis virus:** vesicles develop on the tong, excess salivation,…
  - ✓ Infects cattle, pigs, horses
- *…many other viruses…*



Viruses used to treat cancers:

- **Vaccine viruses:** trigger tumour-specific immunity that eradicate tumours & maintain immunological memory



- **Oncolytic viruses:** genetically modified to selectively infect, replicate in and kill tumour cells

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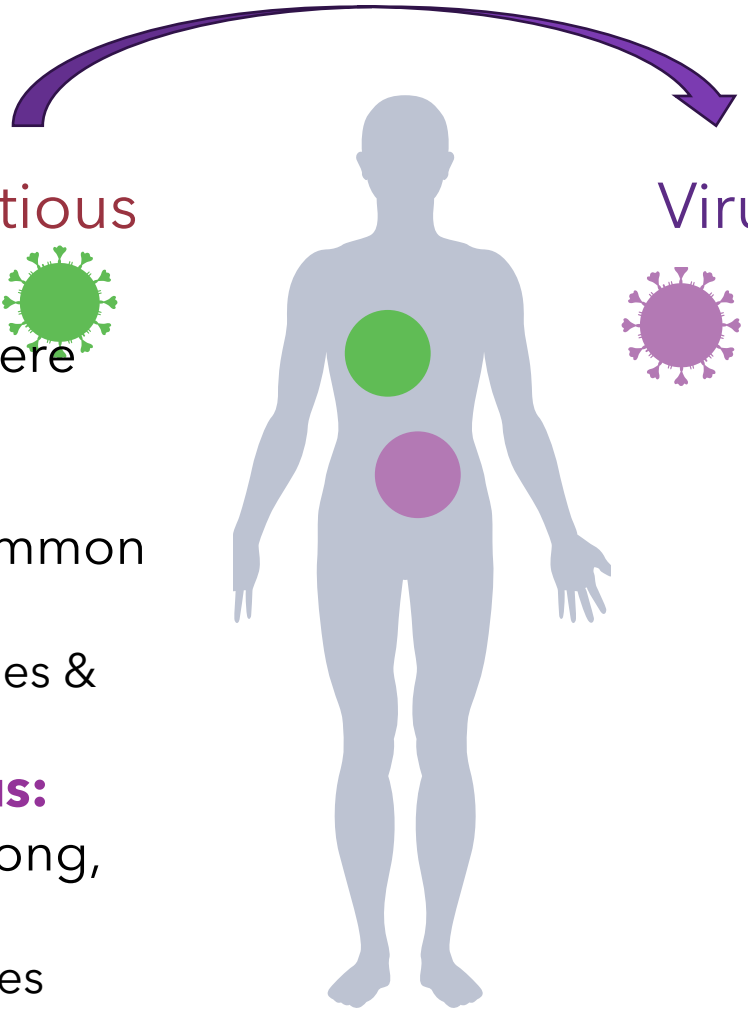

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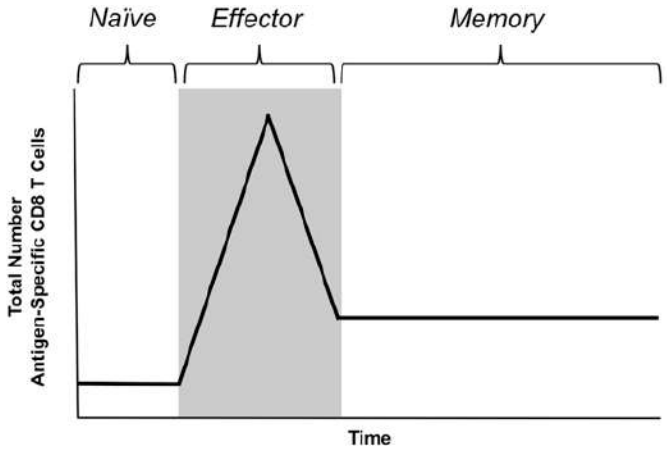

- **Oncolytic viruses:** genetically modified to selectively infect, replicate in and kill tumour cells

SARS-CoV-2 replicates and displays oncolytic properties in clear cell and papillary renal cell carcinoma

Oi Kuan Choong[1,2], Rasmus Jakobsson[1,3], Anna Grenabo Bergdahl[4,5], Sofia Brunet[2,6], Ambjörn Kärmander[2,6], Jesper Waldenström[2,6], Yvonne Arvidsson[1,7], Gülay Altiparmak[1,7], Jonas A. Nilsson[2,8,9], Joakim Karlsson[2,8,9], Kristina Nyström[2,6]*, Martin E. Johansson[1,2,7]*

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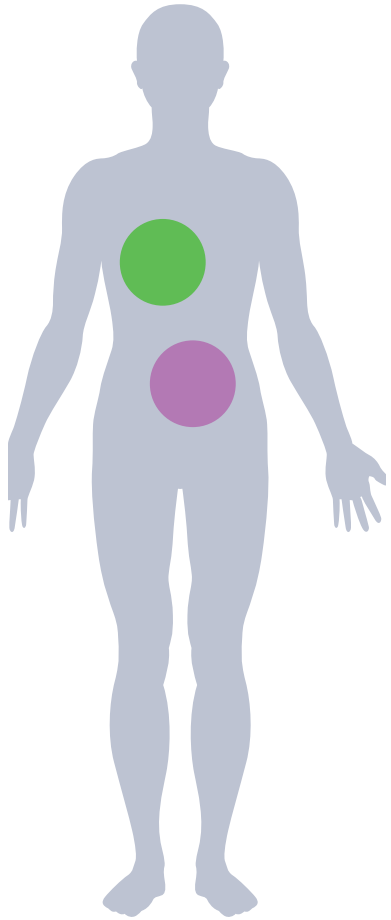

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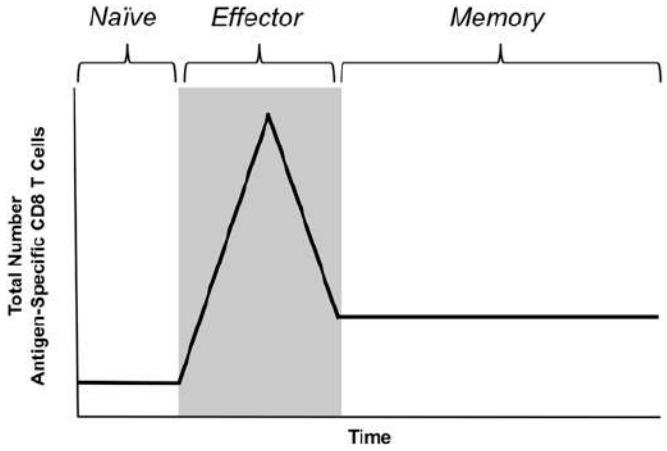


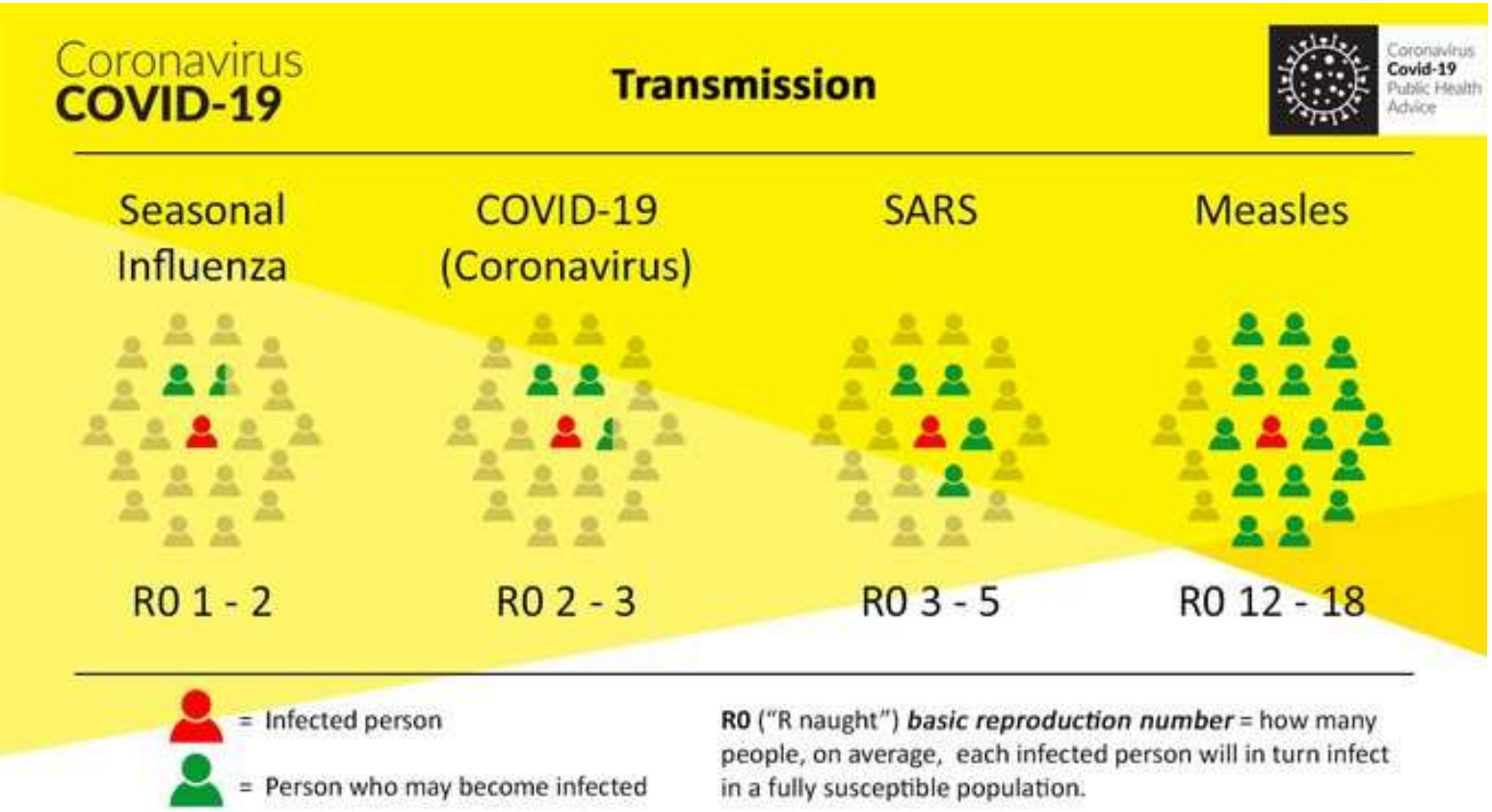
- **Oncolytic viruses:** genetically modified to selectively infect, replicate in and kill tumour cells

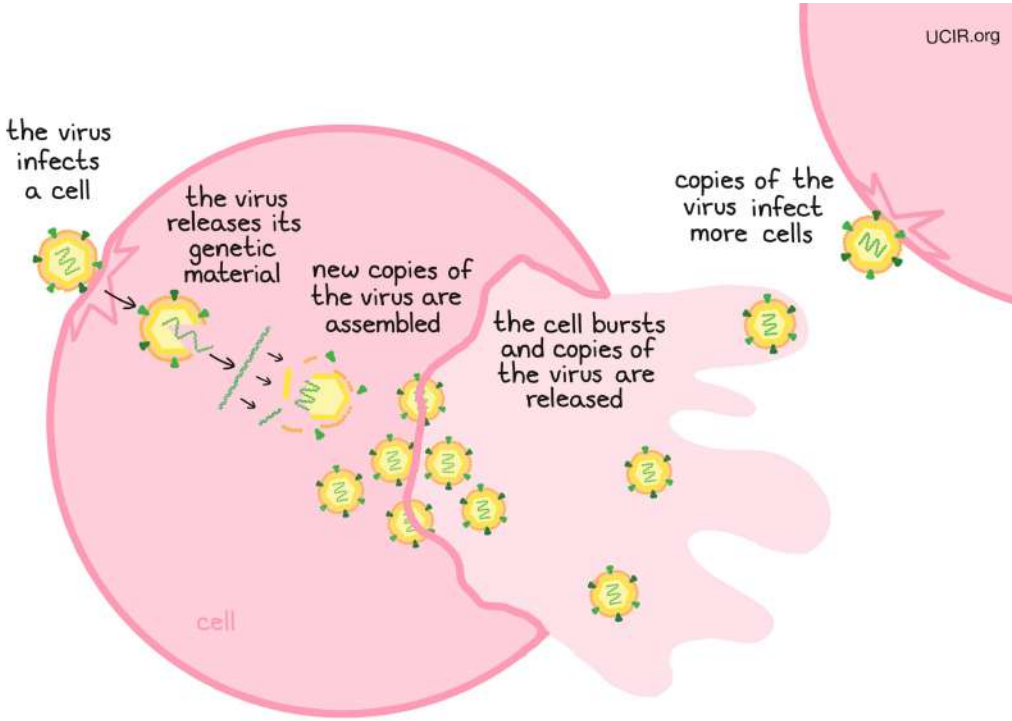
Repurposing the oncolytic virus VSVΔ51M as a COVID-19 vaccine

Almohanad A. Alkayyal[1,2]*, Manar Darwish[2], Reham Ajina[2,3], [illegible] Y. Alabbas[2], Mohammed A. Alotaibi[2], Abeer Alsofyani[4,5], Maha [illegible]khamseen[2], Maumonah Hakami[2], Omar A. Albaradie[2,6], Abdulaziz M. [illegible]aglan[2,6], Sharif Hala[5,7], Abdullah Faisal Alsahafi[5,7], Samer Zakri[5,7], Adnan Almuzaini[8], Khamis Alsharari[8], Feras Kaboha[8], Mustafa Y. Taher[9], Haggag S. Zein[illegible], Fayhan Alroqi[2,11,12] and Ahmad Bakur Mahmoud[9,13,14]*

Basic reproductive number (epidemiological & in-host levels)

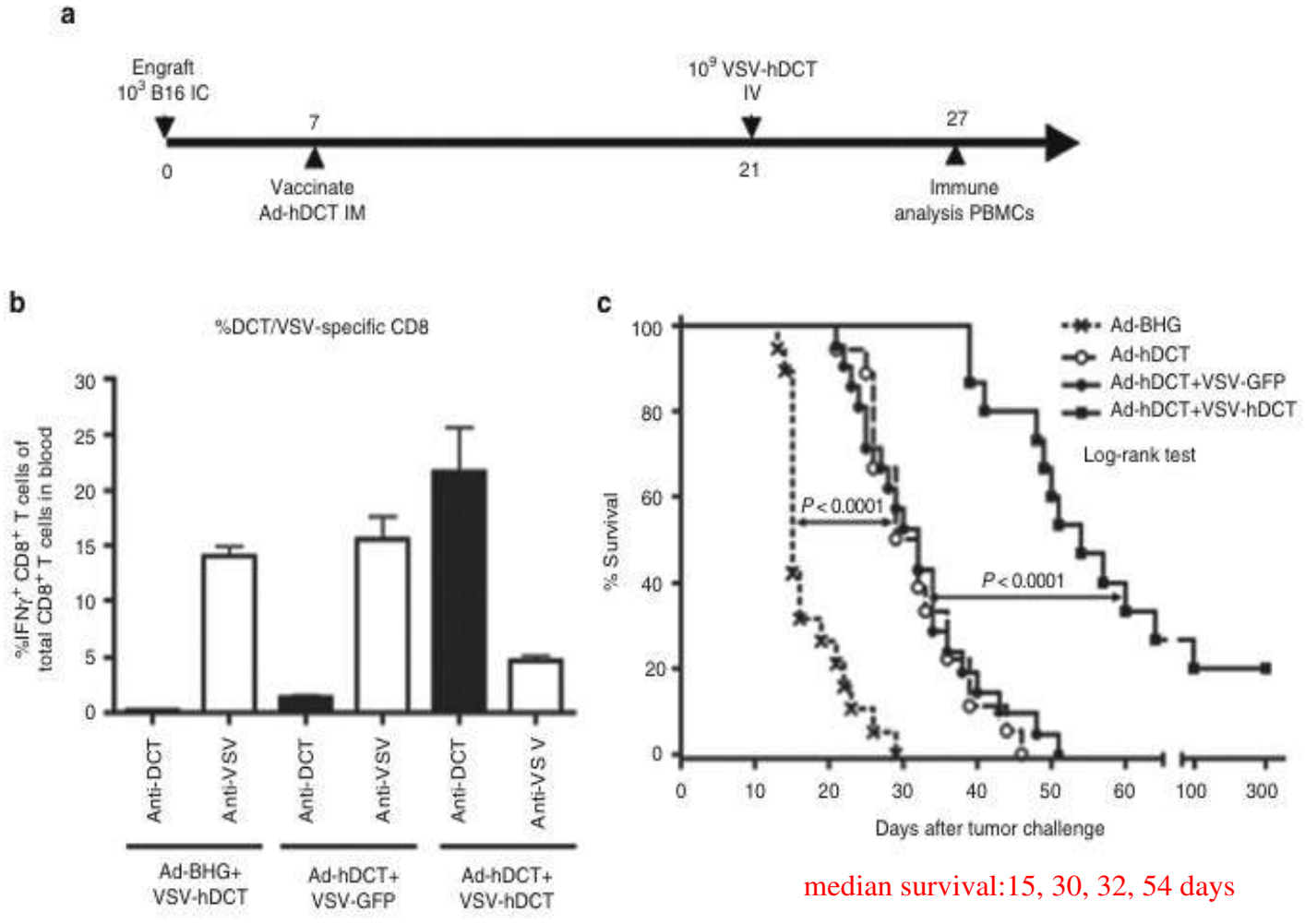
- As small as possible for controlling the spread of an infectious disease (spread of a virus) through a population (of humans, of cells, …)
- As large as possible to ensure the spread of an oncolytic virus through a cell population
  - Not only how many viral particles are released from 1 infected cell, but also how many of these particles infect other cells due to various physical and immune barriers





ONCOLYTIC VIRAL THERAPIES: THE FINE BALANCE BETWEEN THE ANTI-VIRAL IMMUNE RESPONSES AND ANTI-TUMOUR IMMUNE RESPONSES

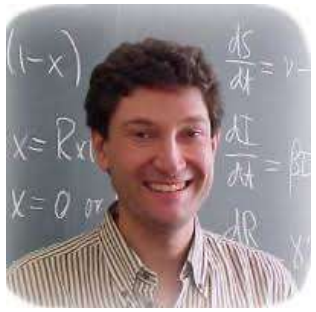
B.W. Bridle et al., Molecular Therapy, 2010, 1430–1439.



median survival:15, 30, 32, 54 days

J. Bramson

B. Brydle



D.J.D. Earn

Double immunization (prime-boost) experimental protocol for murine melanoma (at McMaster University, Canada)

1) Vaccine Adenovirus (Ad) expressing a human tumour antigen, to prime the anti-tumour immune response;
2) Injection of oncolytic Vesicular Stomatitis Virus (VSV) carrying the same tumour antigen => virus replication & tumour elimination

But tumour relapses (median survival 54 days)

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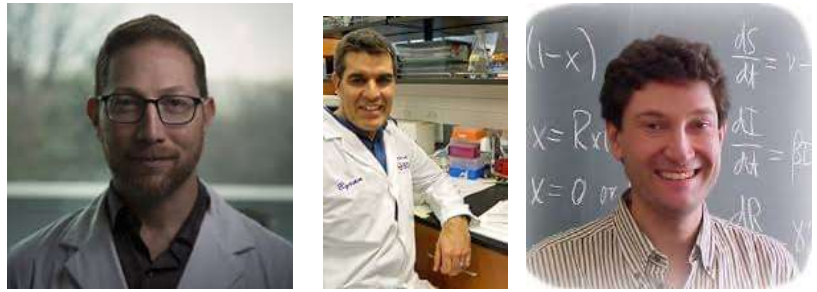
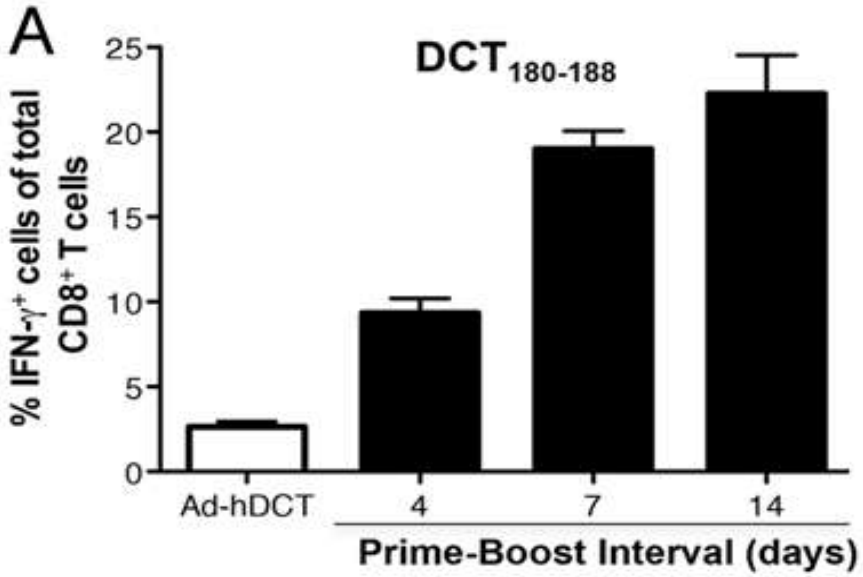
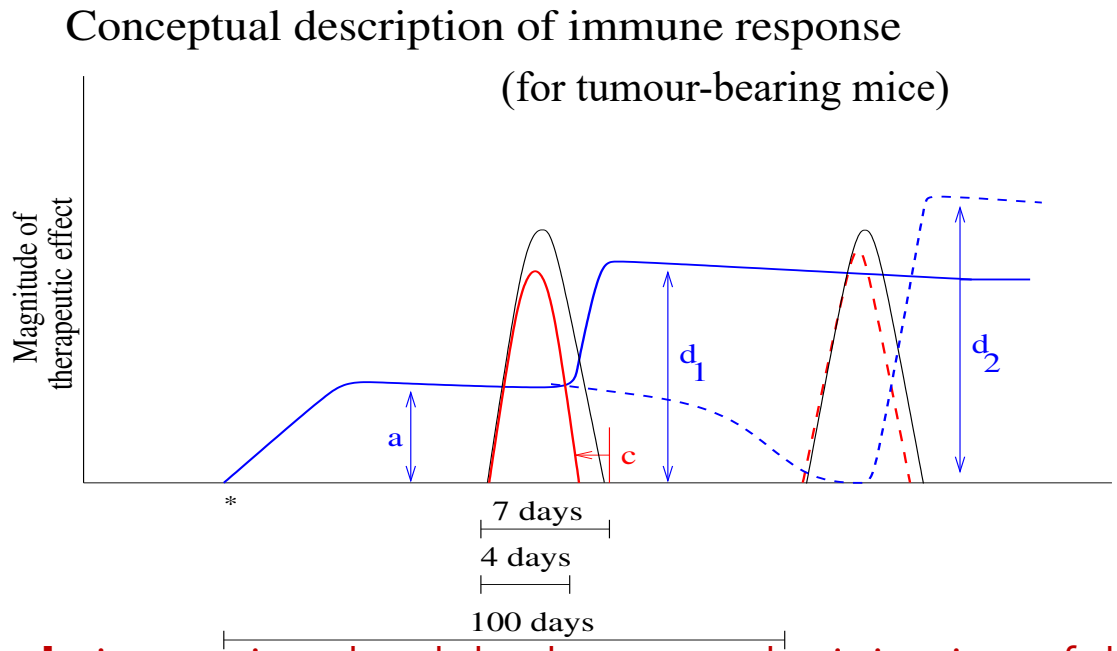




Delaying the 2nd injection with VSV(in tumour-free mice) leads to an increased nbr. of IFN-producing CD8 T cells



Oncolytic vesicular stomatitis virus quantitatively and qualitatively improves primary CD8+ T-cell responses to anticancer vaccines

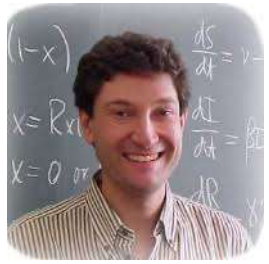
Byram W Bridle[1], Derek Clouthier[2], Liang Zhang[2], Jonathan Pol[2], Lan Chen[2], Brian D Lichty[2], Jonathan L Bramson[2], and Yonghong Wan[2,*]

Hypothesis proposed: increasing the delay between the injection of the two viruses should allow for a higher secondary immune response (with better anti-tumour effects) => cannot test it on mice for ethical reasons…

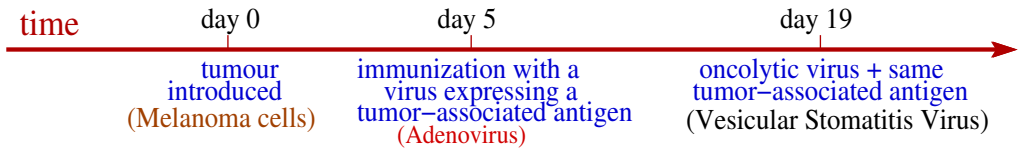
& experiments (to increase the delay by 1 day at a time) are expensive…

ONCOLYTIC VIRAL THERAPIES: THE FINE BALANCE BETWEEN THE ANTI-VIRAL IMMUNE RESPONSES AND ANTI-TUMOUR IMMUNE RESPONSES

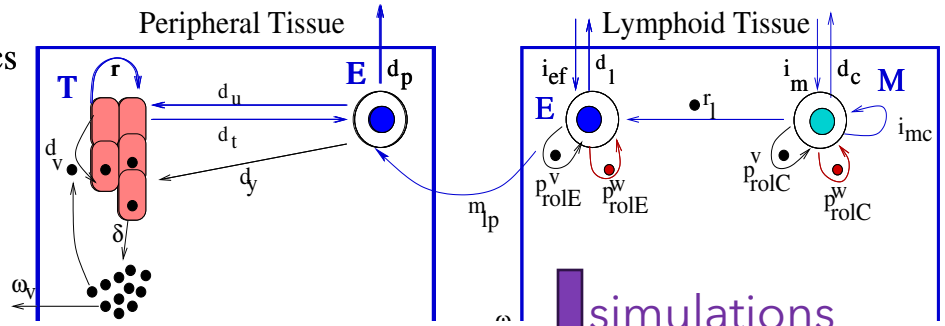




Protocol: (mice)

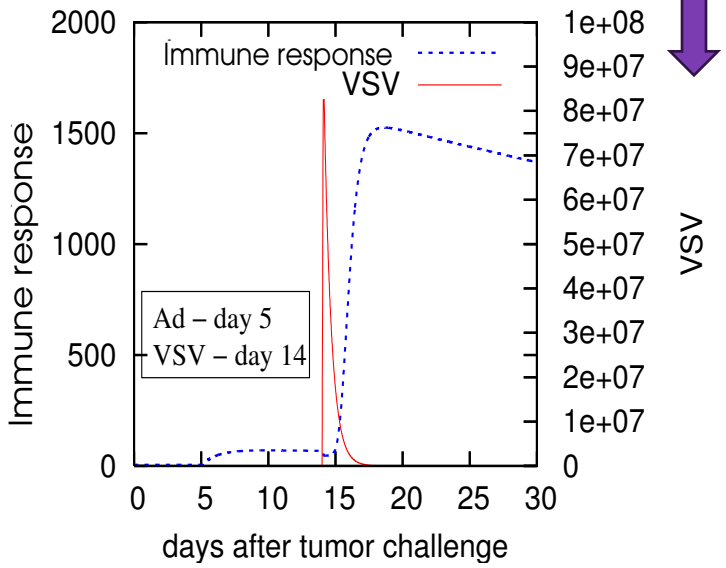


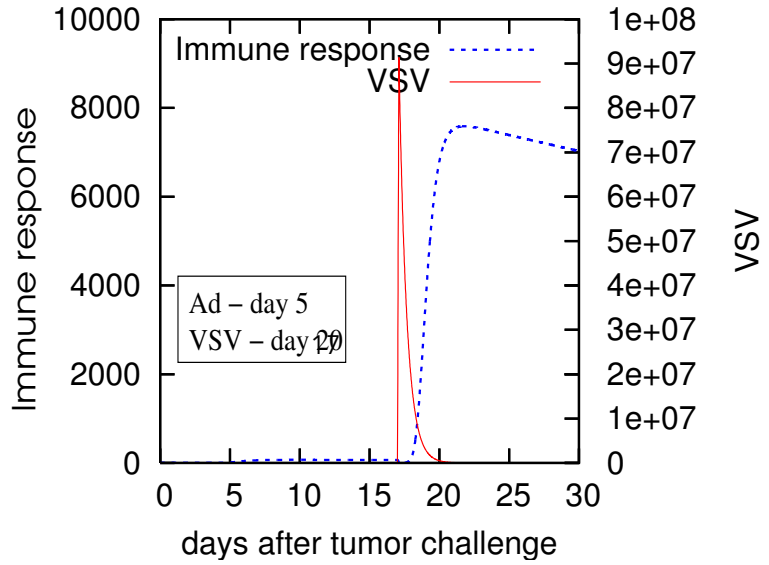
Dynamics of cells: (model)



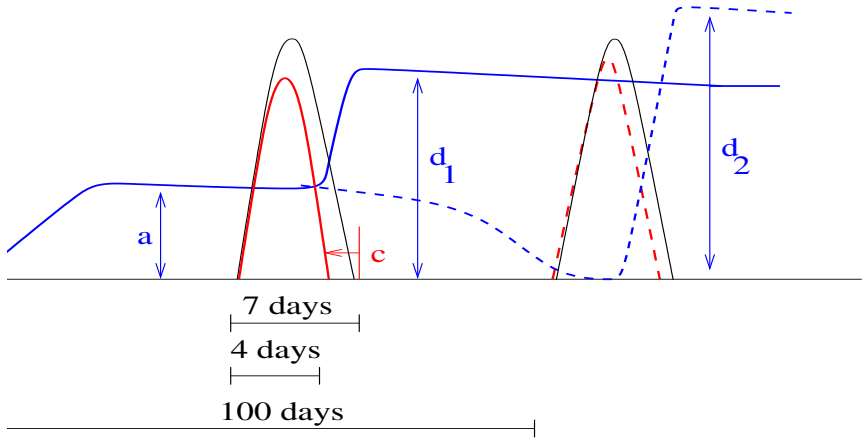
Mathematical model

simulations





Conceptual description of immune response (for tumour-bearing mice)

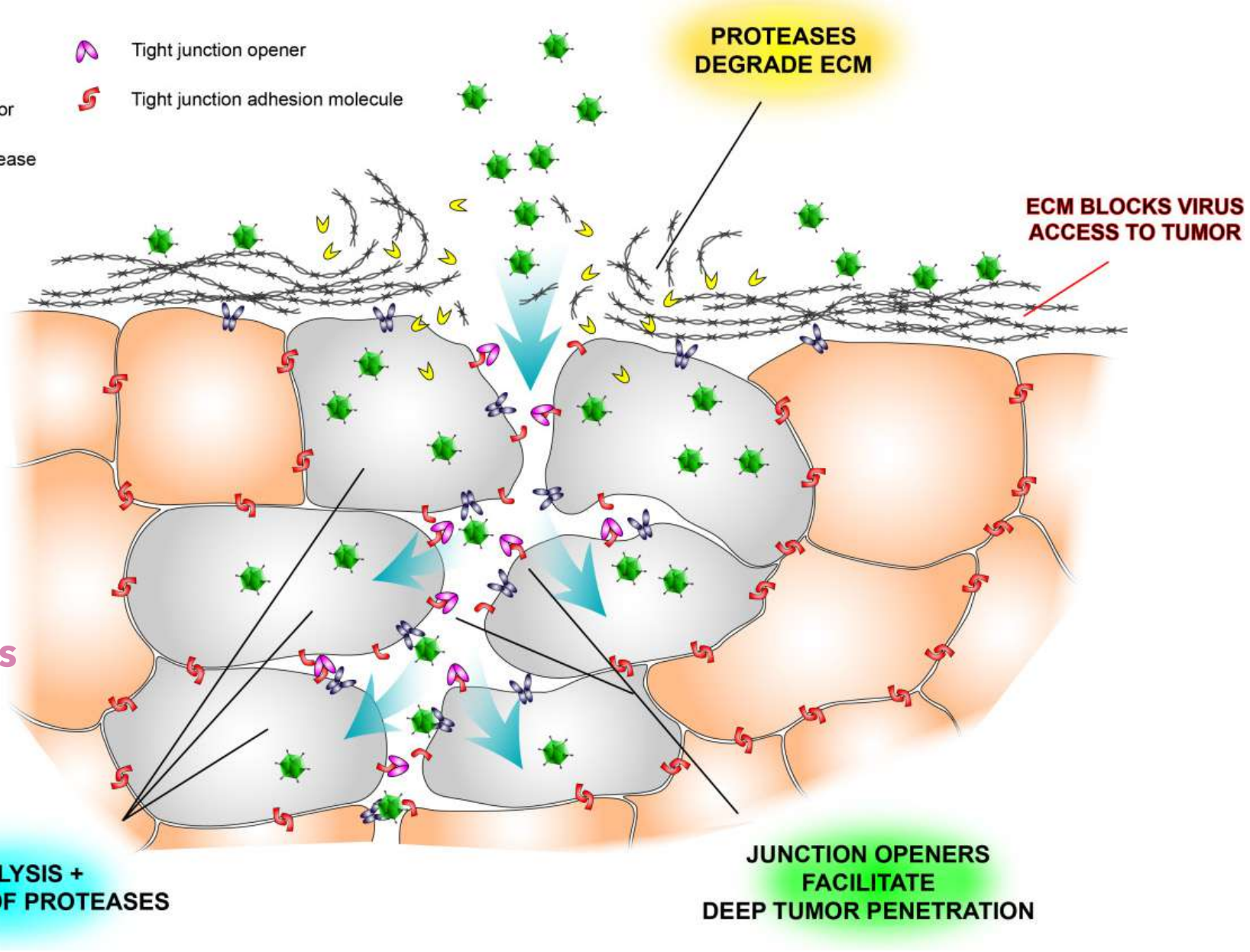


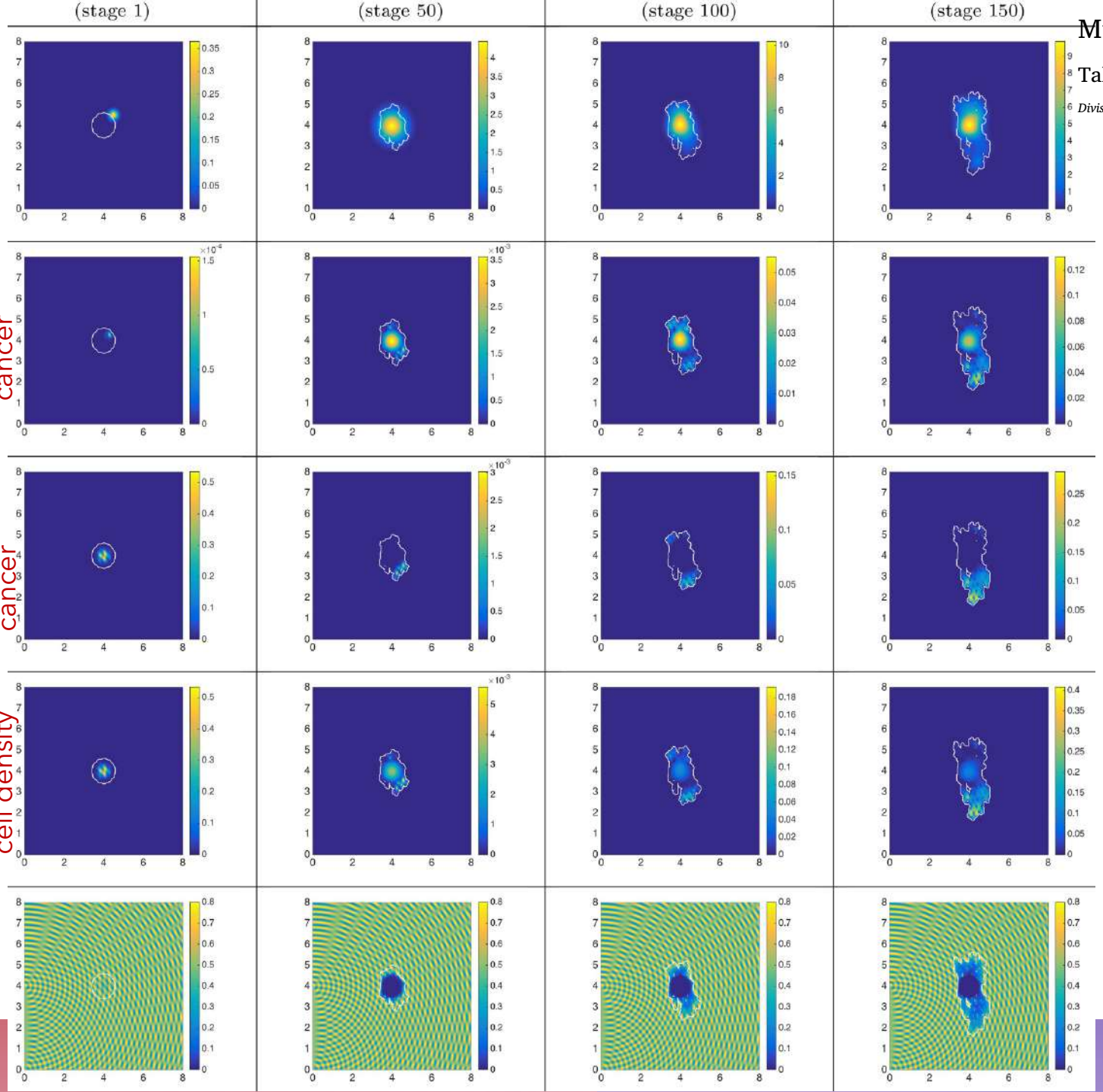
sing the delay between the injection of the igher secondary immune response (with

Physical barriers to oncolytic viruses spread:

- Extracellular Matrix (ECM) prevents viruses from reaching tumour cells
- Tight junctions hide virus receptors and limit virus diffusion into tumour

Immune barriers to oncolytic virus spread: IFN, innate immune cells, …





Multiscale modelling of cancer response to oncolytic viral therapy

Talal Alzahrani, Raluca Eftimie, Dumitru Trucu*

Division of Mathematics, University of Dundee, Dundee DD1 4HN United Kingdom

D. Trucu

Viral spread into a 2D domain...with ECM degradation by tumour cells

=> qualitative exploration of outcomes

Macroscale dynamics (cells, ECM):

$$\begin{cases} \dfrac{\partial c}{\partial t} &= D_c \Delta c - \eta_c \nabla\cdot(c\nabla u) + \mu_1 c(1-c) - \rho c v, \\ \dfrac{\partial i}{\partial t} &= D_i \Delta i + \rho c v - \delta_i i, \\ \dfrac{\partial u}{\partial t} &= -u(\alpha_c c + \alpha_i i) + \mu_2 u(1-u-c-i), \\ \dfrac{\partial v}{\partial t} &= D_v \Delta v + b i - \rho c v - \delta_v v. \end{cases}$$

A 2nd layer of complexity: Microscale dynamics

$$\frac{\partial a}{\partial \tau} = \underbrace{D_a \Delta h_1}_{\text{diffusion}} - \underbrace{\psi_{11} a p}_{\text{uPA/PAI-1}} + \left(\underbrace{\psi_{12}}_{\text{production}} - \underbrace{\psi_{13} u}_{\text{uPA/uPAR}} \right) f^{\epsilon Y}_{uPA}(y,\tau)$$

$$\frac{\partial p}{\partial \tau} = \underbrace{D_p \Delta p}_{\text{diffusion}} - \underbrace{\psi_{21} a p}_{\text{uPA/PAI-1}} - \underbrace{\psi_{22} p f^{\epsilon Y}_{PAI-1}(y,\tau)}_{\text{PAI-1/ECM}} + \underbrace{\psi_{23} m}_{\text{production}}.$$

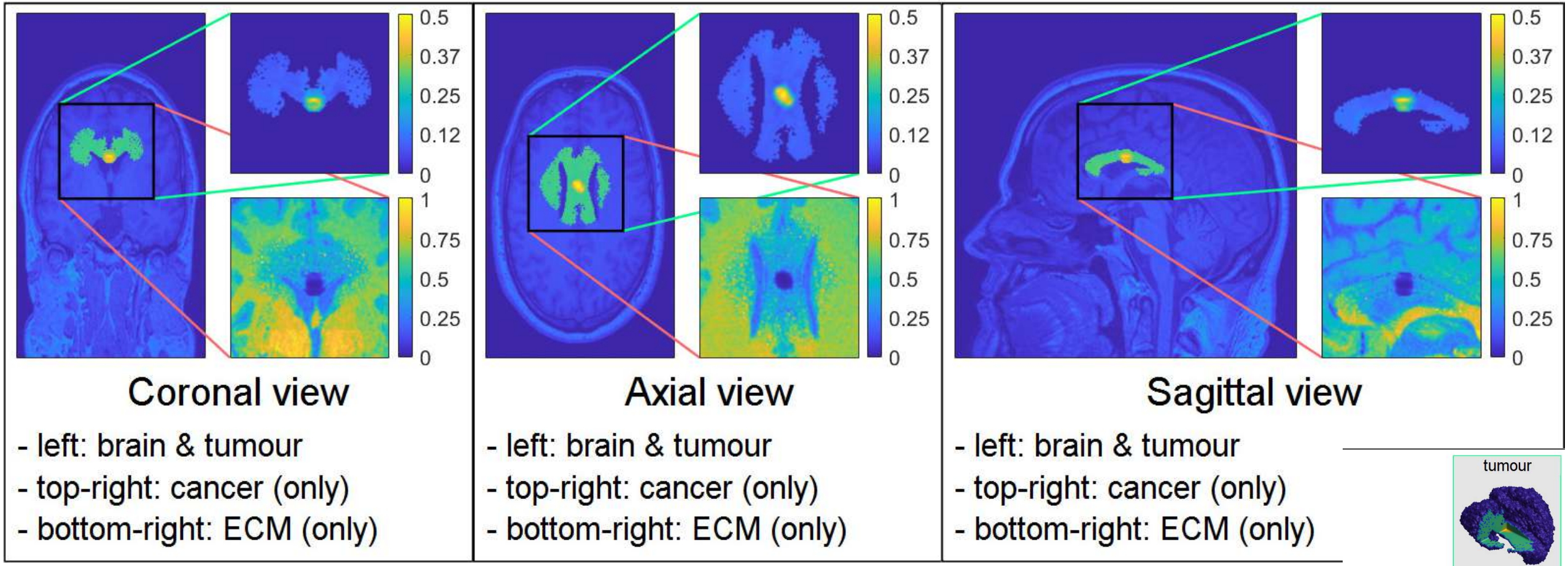
$$\frac{\partial m}{\partial \tau} = \underbrace{D_m \Delta m}_{\text{diffusion}} + \underbrace{\psi_{31} a f^{\epsilon Y}_{uPA}(y,\tau)}_{\text{uPA/uPAR}} + \underbrace{\psi_{32} p f^{\epsilon Y}_{PAI-1}(y,\tau)}_{\text{PAI-1/ECM}} - \underbrace{\psi_{33} m}_{\text{decay}}.$$

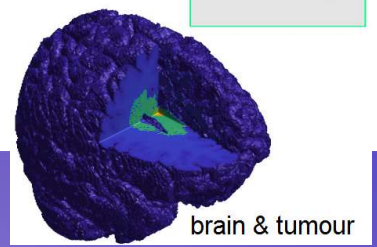
Viral spread into a 3D domain…with ECM degradation by tumour cells

… but NO virus yet…

Mathematical Modelling of Glioblastomas Invasion within the Brain: A 3D Multi-Scale Moving-Boundary Approach

Szabolcs Suveges [1], Kismet Hossain-Ibrahim [2,3], J. Douglas Steele [4], Raluca Eftimie [5] and Dumitru Trucu

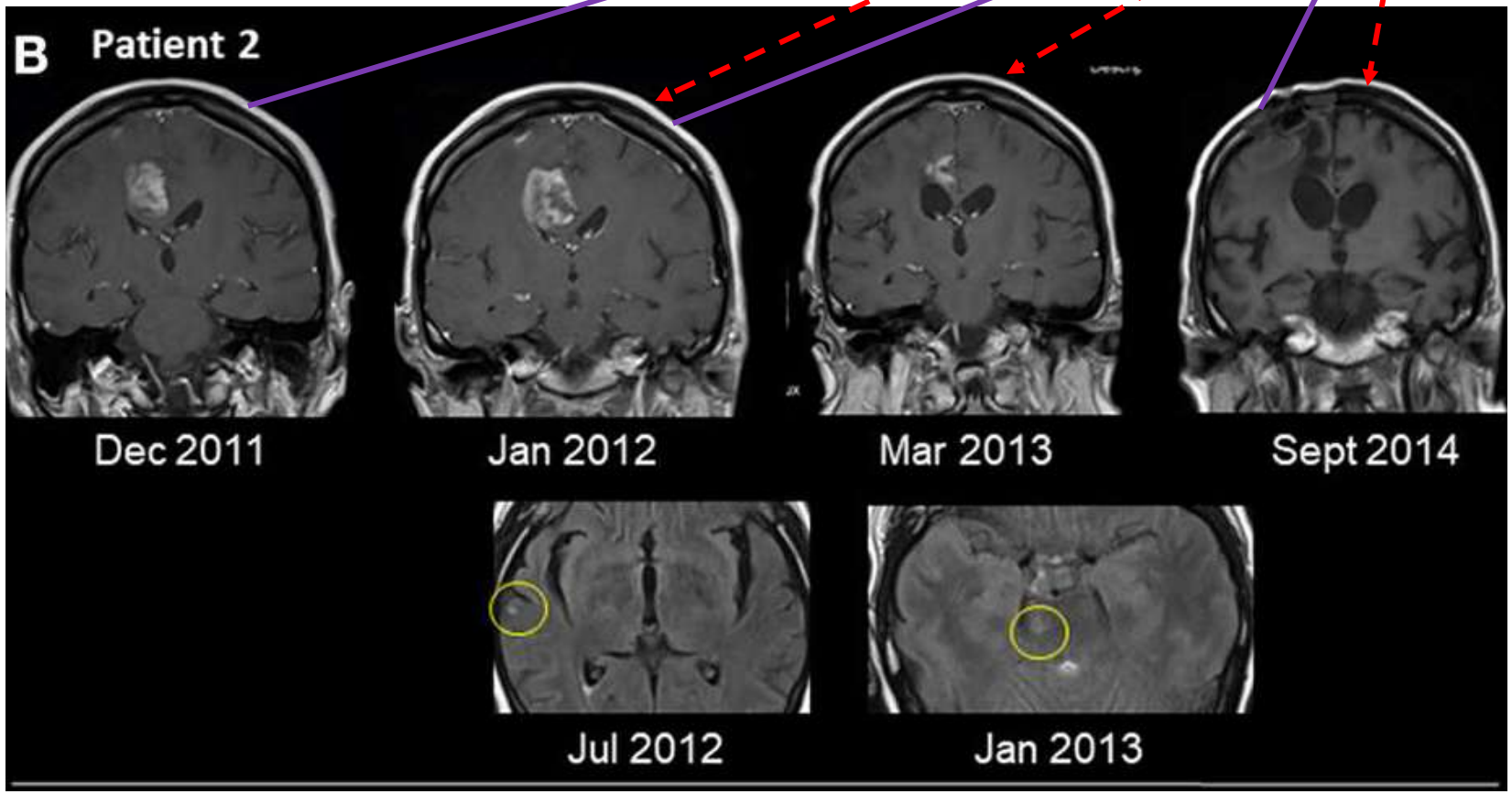


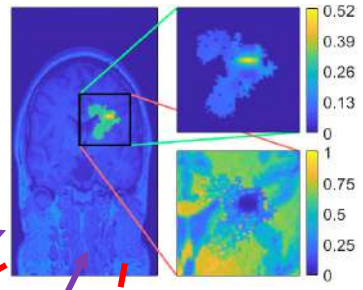


…where Diffusion Tensor Imaging (DTI) scans were used to estimate the anisotropic cell diffusion term ; T1 weighted images => image segmentation => white/gray matter densities

Effective Treatment of Glioblastoma Multiforme With Oncolytic Virotherapy: A Case-Series

Benjamin Gesundheit[1], Eliel Ben-David[2], Yehudit Posen[1], Ronald Ellis[1], Guido Wollmann[3,4], E. Marion Schneider[5], Karl Aigner[6], Lars Brauns[7], Thomas Nesselhut[8], Ingrid Ackva[9], Christine Weissleir[9] and Arno Thaller[9]*





For the future...

- **Macroscale-level** spatial and spatio-temporal data is available
- For model validation & quantitative predictions we need also **microscale-level** data

Summary:

- Viral dynamics involves different multi-scale aspects that can be incorporated into mathematical/computational models
  - But multiscale (spatial & spatio-temporal) data not always available… (or if available: very few data points => no ML)
  - Technical aspects associated with parameter identification in these multi-scale models…
  - Open problems associated with the modelling of multi-scale within-host/between-host dynamics …
- Many (complex) mathematical models are used only for qualitative exploration of possible model dynamics
  - Quantitative predictions require more data (& new computational approaches) to estimate parameters/functions