Investigating the impact of cell tropism on influenza infection spread in computer-simulated lung tissue

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Motivation

- Influenza A is an infectious disease that affects humans as well as other animal species.
- In its seasonal form, it mainly attacks the upper respiratory tract in humans and lasts for a few days.
- Pandemic strains of influenza can be very severe with sustained, high viral titer loads and an infection that can spread to the lower respiratory tract.
- Owing to the fact that it can infect multiple species, various strains of influenza are optimized for a specific host and/or cell type.
- One possible cause for the difference in disease course is cell tropism (preference of virus for certain cell types).

Objective

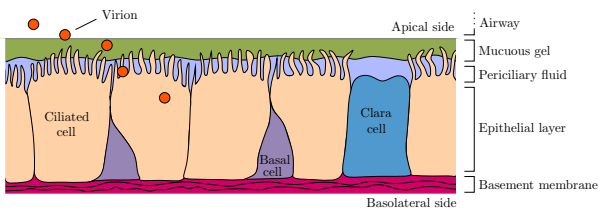
Explore the role of cell tropism in the severity of an influenza infection by using a spatially extended:

- partial differential equation (PDE) model; and
- agent-based model.

The two cell types

The cells of the human airway can be classified as:

- ciliated cells predominantly with α-2,3 surface receptors, mostly found in the lower respiratory tract; and
- non-ciliated cells predominantly with α-2,6 surface receptors, mostly found in the upper respiratory tract.



Cell tropism

Human-adapted influenza strains primarily infect non-ciliated cells whereas avian-adapted influenza strains primarily infect ciliated cells.

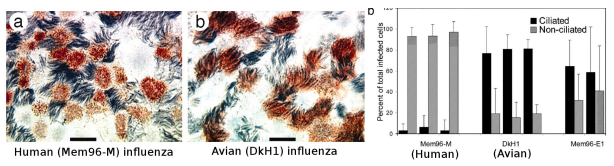
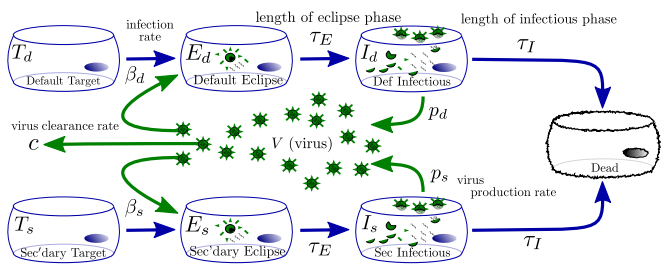


Image from: Matrosovich, et al. Human and avian influenza viruses target different cell types in cultures of human airway epithelium. *P. Natl. Acad. Sci. USA*, 101(13):4620–4624, 2004.

The two cell population model

The two cell types are assumed to differ only in:

- their susceptibility to infection, β; and/or
- their rate of viral production p.



The PDE model

Accounts for:

- the effect of diffusion in spreading (or restricting) a non-uniformly distributed amount of virus; and
- the depth-dependent distribution of the two cell types via a progressive depth-dependent change in infectivity, $\beta \to \beta(x)$, and viral production rates, $p \to p(x)$.

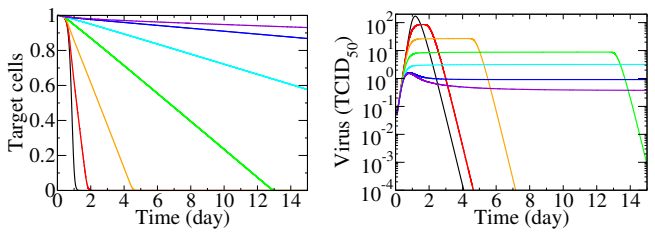
$$\frac{\partial T}{\partial t} = -\beta(x)T(x,t)V(x,t)$$
$$\frac{\partial E}{\partial t} = \beta(x)T(x,t)V(d,x) - \frac{E(x,t)}{\tau_E}$$
$$\frac{\partial I}{\partial t} = \frac{E(x,t)}{\tau_E} - \frac{I(x,t)}{\tau_I}$$
$$\frac{\partial V}{\partial t} = D\frac{\partial^2 V}{\partial x^2} + p(x)I(x,t) - cV(x,t)$$

In our model, the respiratory track is represented as a one-dimensional grid with the top of the respiratory tract at $x = 0$ and the bottom at $x = 30$ cm.

Initially all cells are in the target (T) state and infection is initiated by depositing a Gaussian-distributed virus concentration centred at $x = 1$ cm from the top of the respiratory tract with a standard deviation of 0.5 mm ($\sim 10\times$ the size of a large cough droplet [1]).

[1] Yang et al. The size and concentration of droplets generated by coughing in human subjects. *J. Aerosol Med.* 20(4):484–494, 2007.

PDE: Effect of diffusion

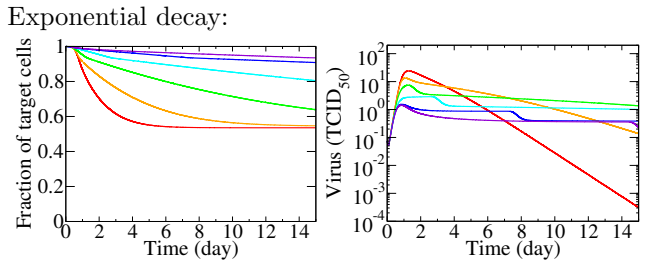


Colours as follows: ODE (infinite diffusion), or a diffusion of 10^{-8} m^2/s, 10^{-9} m^2/s, 10^{-10} m^2/s, 10^{-11} m^2/s, 10^{-12} m^2/s, 10^{-13} m^2/s.

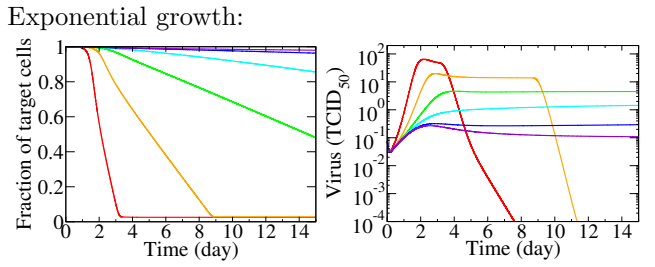
- The lower the diffusion, the slower the consumption of cells by virus leading to sustained viral loads.
- The viral titer decays once all cells are consumed.

PDE: Changing β with depth

Exponential decay:



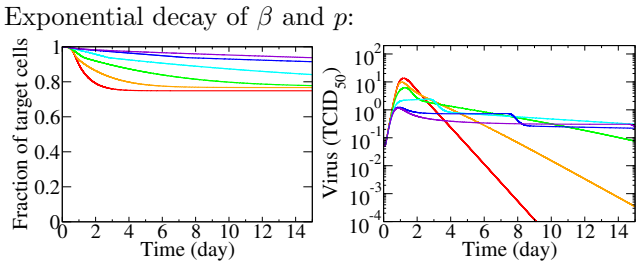
Exponential growth:



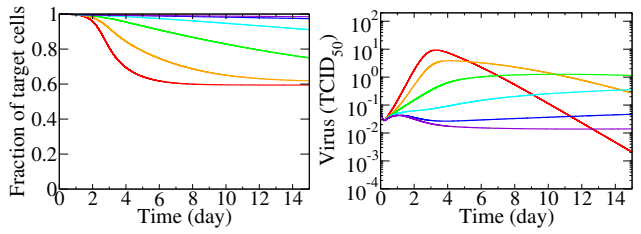
- We considered exponential growth/decay in β corresponding to $R_0 \in [0.12, 12]$ ($R_0 = 1$ at $x \approx 15$ cm).
- A depth-decreasing β leads to protection of the lower respiratory tract where $R_0 < 1$ and to sustained viral titers due to infection at a depth where $R_0 \sim 1$.
- A depth-increasing β leads to a delay in the infection as the virus diffuses to an infectible depth (where $R_0 \geq 1$) and greater protection is afforded to the respiratory tract at lower diffusion rates.
- The effect of changing p is similar to that of changing β and is therefore not shown.

PDE: Changing β and p

Exponential decay of β and p:



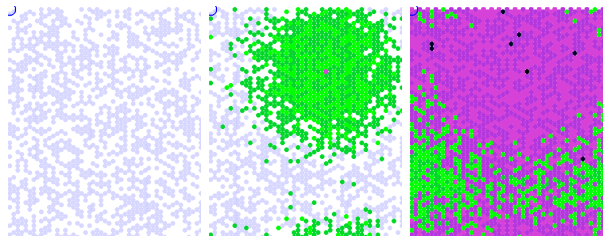
Exponential decay of β and growth of p:



- Depth-decreasing β and p lead to $R_0 \in [0.0012, 12]$ with $R_0 = 1$ at $x \approx 8$ cm resulting in increased protection of the lower respiratory tract.
- Increasing p while decreasing β gives profiles somewhat similar to those for decreasing β alone but the low p in regions where β is high and vice-versa led to slightly different viral dynamics.

The agent-based model

- ma_virions is a stochastic, agent-based model developed by our group.
- It treats every cell as an independent unit taking stochastic decisions based on its environment at rates equivalent to those defined by the PDE.
- It is readily comparable to the outcomes of experiments in vitro/in vivo.

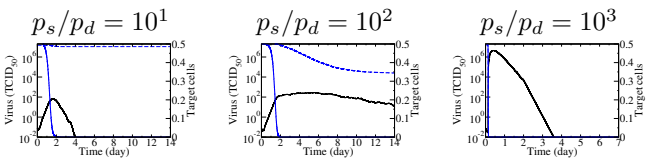


Colours as follows: **default target cells (white)**, **secondary target cells**, **eclipse cells**, **infectious cells**, **dead cells**, **virus**.

Agent-based model results

Considering one cell population which is $500\times$ harder to infect ($\beta_s/\beta_d = 1/500$) we explored the effect of varying p_s/p_d.

$p_s/p_d = 10^1$ $p_s/p_d = 10^2$ $p_s/p_d = 10^3$



Colours as follows: **target cells (solid: default, dashed: secondary)**, **virus.**

Conclusions

- Considering a realistic diffusion (10^{-12} m^2/s) led to sustained viral titers which suggests the immune response is required to control the infection.
- A depth-decreasing infection rate (β) was somewhat effective in controlling infection spread suggesting a role for cell tropism in restricting infection spread.

Future directions

A realistic model will require the addition of:

- A drift term to account for viral transport and clearance via the mucus escalator.
- An immune response to control the infection.