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).

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, \( \beta \rightarrow \beta(x) \), and viral production rates, \( p \rightarrow p(x) \).

\[
\frac{\partial I}{\partial t} = -\beta(x)T(x,t)I(x,t)
\]
\[
\frac{\partial E}{\partial t} = \beta(x)T(x,t)V(x) - \frac{E(x,t)}{\tau_E}
\]
\[
\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} + \beta(x)I(x,t) - cV(x,t)
\]

In our model, the respiratory tract 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 (= 1/32 the size of a large conch droplet [1]).


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 \( \alpha = 2.3 \) surface receptors, mostly found in the lower respiratory tract; and
- non-ciliated cells predominantly with \( \alpha = 2.6 \) 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.

The two cell population model
The two cell types are assumed to differ only in:
- their susceptibility to infection, \( \beta \), and/or
- their rate of viral production, \( p \).

PDE: Effect of diffusion
Colours as follows: ODE (infinite diffusion), or a diffusion of \( 10^{-8} \text{m}^2/\text{s}, 10^{-7} \text{m}^2/\text{s}, 10^{-6} \text{m}^2/\text{s}, 10^{-5} \text{m}^2/\text{s}, 10^{-4} \text{m}^2/\text{s}, 10^{-3} \text{m}^2/\text{s} \).
- 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 \( \beta \) with depth
We considered exponential growth/decay in corresponding to \( \beta_0 \) in [0.12, 12] (\( \beta_0 = 1 \) at \( x = 15 \) cm).
- A depth-decreasing \( \beta \) leads to protection of the lower respiratory tract where \( R_0 < 1 \) and sustained viral titer due to infection at a depth where \( R_0 = 1 \).
- A depth-increasing \( \beta \) 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 \( \beta \) and is therefore not shown.

PDE: Changing \( \beta \) and \( p \)

Agent-based model results
Considering one cell population which is 500× harder to infect (\( \beta_0/p_0 \rightarrow 1/500 \)) we explored the effect of varying \( p_0/p_0 \).

Conclusions
- Considering a realistic diffusion (\( 10^{-12} \text{m}^2/\text{s} \)) led to sustained viral titers which suggests the immune response is required to control the infection.
- A depth-decreasing infection rate (\( \beta \)) 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.