Analyzing a Mathematical Model for Virus Propagation in the Trachea

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Introduction

Inside the respiratory tract, there are two layers of fluid coating the surface: a periciliary layer and a mucus layer. Virus will get caught in the fluid, then ciliated epithelial cells lining the tract push the fluid up and out of the trachea in a process called mucociliary clearance (MCC). This fluid transfer is an example of physical motion called advection. Researchers have established that MCC affects viral dynamics in the respiratory tact, however they have yet to quantify specifically how spatial distribution of virus in the respiratory tract is altered in the presence of advection and how that spatial distribution reduces severity of symptoms. We used a system of partial differential equations to simulate spatial and time-dependent behaviors of viral transfer in the respiratory tract with advection. We intend to show that advection manages viral infection by preventing virus from entering the lower respiratory tract.

The Model

The model describes dynamics between various stages of a viral infection. Cells start as uninfected, but vulnerable target cells (T). Target cells turn into inactive infected cells during an eclipse phase (E). After the eclipse phase, cells turn into infectious, virus producing cells (I). During this entire process, the concentration of virus is changing (V).

$$\partial_t T = -\beta T V$$

$$\partial_t E = \beta T V - \frac{E}{\tau_E}$$

$$\partial_t I = \frac{E}{\tau_E} - \frac{I}{\tau_I}$$

$$\partial_t V = pI - cV + D\partial_x^2 V + \nu \partial_x V$$

Parameters:

- τ_E: duration of eclipse phase
- τ_I: productively infected cell lifespan
- c: virus clearance rate
- β: infection rate of cells by virus
- p: virus production rate
- D: diffusion coefficient
- ν: advection speed

Viral Dynamics for Human Respiratory Tract (HRT):

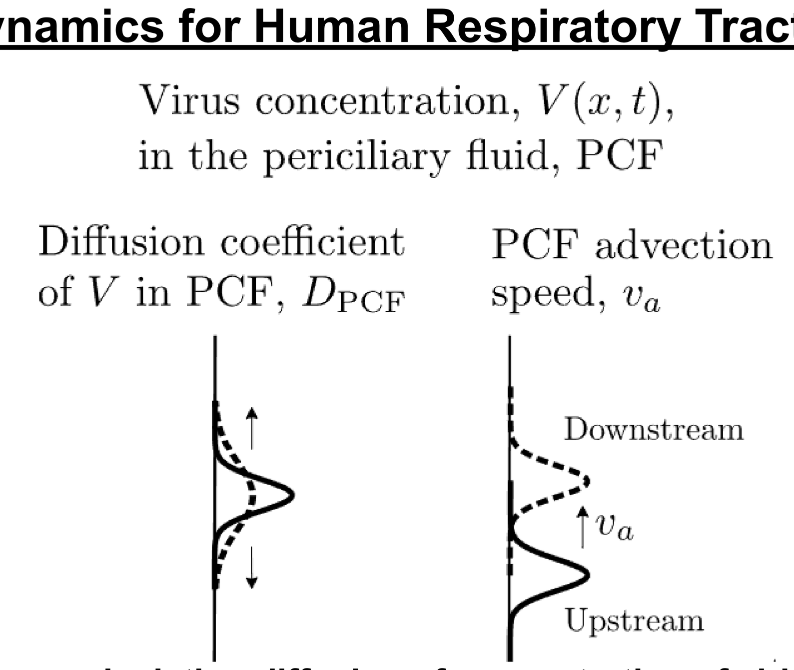

Figure 1: Diagram depicting diffusion of concentration of virions (left) and special effects of advection (right). *(From Quirouette et.al Quantitative Biology, 2019)*

Mathematical Analysis

Fourier Series Expansion: To solve this system, each function is expanded as a spatial Fourier Series with functions of time as our constants. This converts partial differential equations into ordinary differential equations. For initial conditions, we used a gaussian deposit of virus at 15 cm and uniform distribution of target cells with concentration 1 everywhere in the respiratory tract.

$$T = \sum_{n_T} c_{T,n}(t)e^{-in_T x} \qquad E = \sum_{n_E} c_{E,n}(t)e^{-in_E x}$$

$$I = \sum_{n_I} c_{I,n}(t)e^{-in_I x} \qquad V = \sum_{n_V} c_{V,n}(t)e^{-in_V x}$$

Analyzing each derivative the virus equation:

$$\partial_x^2 V = \sum_{n_V} -n_V^2 c_{V,n}(t)e^{-in_V x} \qquad \partial_x V = \sum_{n_V} -in_V c_{V,n}(t)e^{-in_V x}$$

Substituting our derivatives into our virus equation:

$$\frac{\partial}{\partial t} C_{V,n}(t) = pC_{I,n}(t) - c * C_{V,n}(t) - n_V^2 DC_{V,n}(t) - in_V \nu C_{V,n}(t)$$

Conclusion

Our models show that advection plays a significant role in controlling spread of virus within the respiratory tract. To our knowledge, our models are among the first attempts to quantify how different advection speeds for mucociliary clearance affects spatial distribution of virus over time. We have shown that varying the advection speed by an order of magnitude can result in changes of behavior for how virus spreads in the respiratory tract over the course of an infection. Notably there are discernable differences for viral spread for low and high advection speeds.

For low advection speeds (speeds ranging from $0.4-0.8$ μm/s), target cells located at the initial deposition of virus quickly become exposed to virus, transitioning from eclipse cells to infectious cells. As they die, they release virus to neighboring cells, exposing them to virus. This process is repeated, resulting in a traveling wave of virus in both directions of the respiratory tract. The lower the advection speed, the deeper the traveling wave of virus penetrates the respiratory tract.

For higher advection speeds (4 μm/s), mucociliary clearance can completely stunt the traveling wave propagating down the respiratory tract. This results in one wave traveling up the respiratory tract. This demonstrates that higher advection rates can completely prevent virus from entering the lower respiratory tract, which would prevent the associated symptoms. In addition, high advection speeds lowered the maximum viral titer reached, demonstrating that advection also clears virus from the respiratory tract.

Results:

Varying the advection rate can significantly alter the spatial-temporal distribution of cell stages and virus. Lower advection rates allow virus to penetrate deeper into the respiratory tract. Higher advection rates can stunt the traveling wave front, preventing virus from entering the lower respiratory tract.

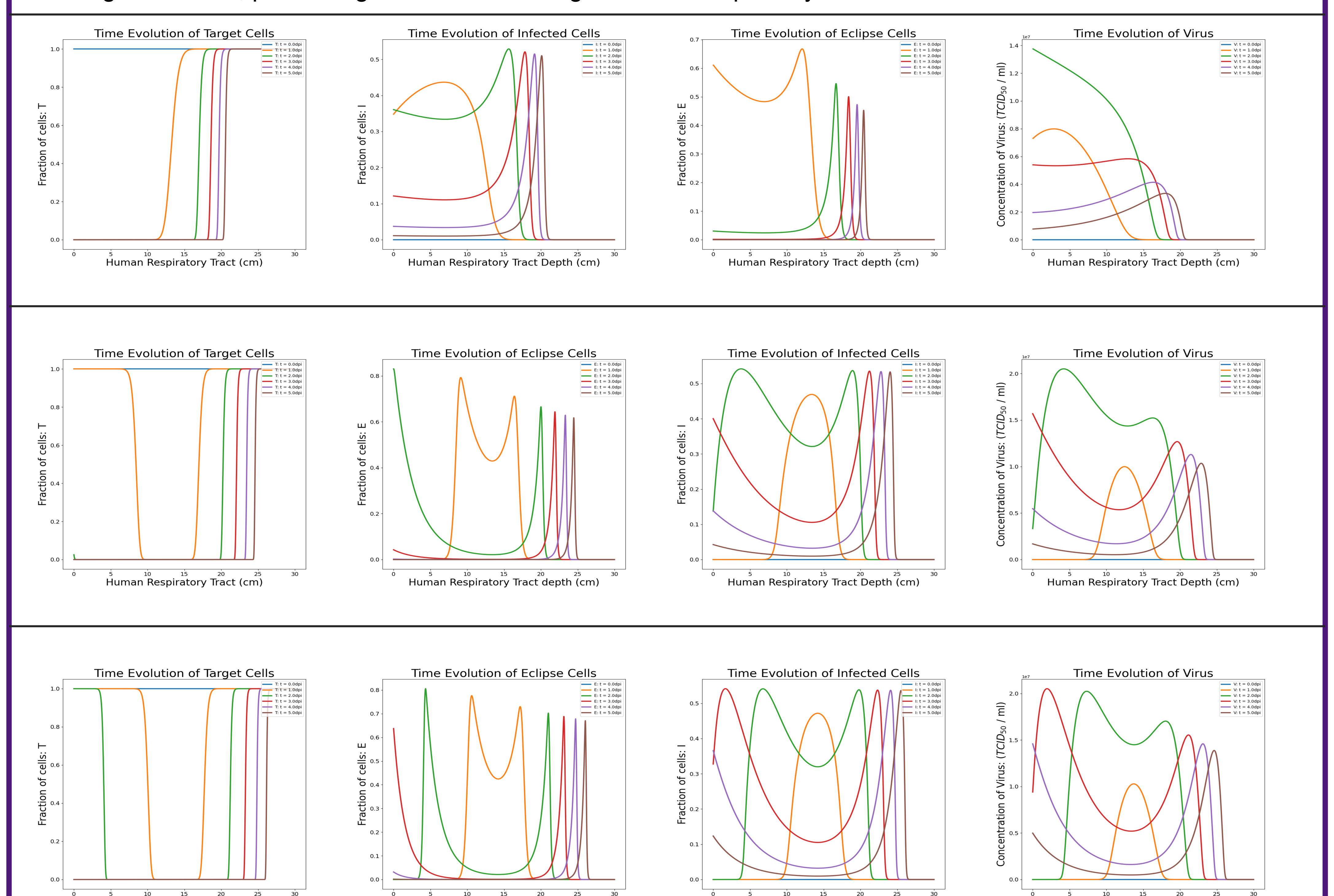

Figure 2: Spatial distribution of fraction target cells, fraction of eclipse cells, fraction of infectious cells, and viral titer for various advection rates. Advection values are 4.0 μm/s (top), 0.8 μm/s (center), and 0.4 μm/s (bottom)

Future Work

- Find a critical advection speed that prevents virus from entering the lower respiratory tract
- Modify the model to include other biological behaviors present in the respiratory tract: cell heterogeneity, regeneration, immune response
- Model damage to mucociliary clearance and examine how this affects viral kinematics
- Examine sensitivity of viral spread to advection speeds

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During a viral infection, the concentration of virus and their location are constantly changing over time, making the infection very difficult to understand. However, mathematics has tools to describe these changes. We use these tools to simulate how viruses spread down the human throat. We believe our simulations will reveal important information on when and why a viral infection becomes dangerous.

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