Bottoms up! How pointy-headed mathematical biologists approach cell biology and what we could gain from computational biologists

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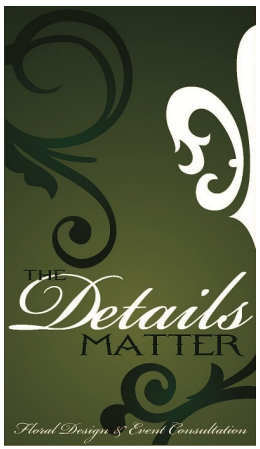
- Mathematical biologists use models to understand how nonlinear feedbacks create surprises
- In particular, we'll look out how the details of these feedbacks amplify, filter, and control responses to external challenges



Outline

I'll illustrate this approach with three projects:

- HPV and cancer
- The cellular stress response
- How viruses can trigger asthma

Acknowledgments

- HPV: Anna Miller, Karl Munger
- Integrated stress response: Laura Strube, Julie Hollien, Nels Elde
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- Modeling the Dynamics of Life fund
- James S. McDonnell Foundation
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- Soonchunhyang University Research Fund

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NSF

Soon Chun Hyang University sch.ac.kr

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HPV Overview

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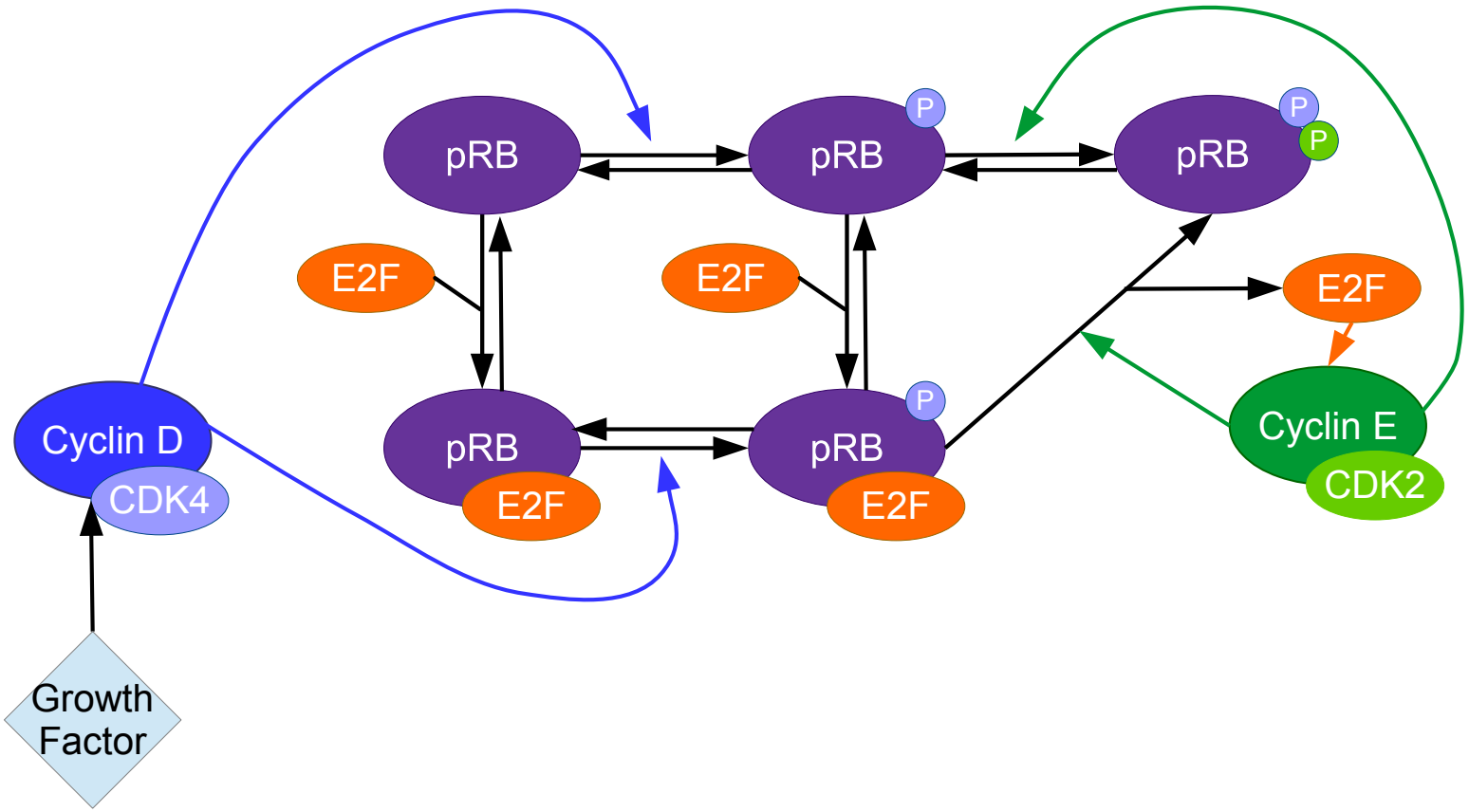
  - E7 leads to aberrant proliferation by interfering with the checkpoint controlled by the famous RB protein (pRB)
  - E6 leads to uncontrolled proliferation by interfering with apoptosis controlled by the even more famous p53 protein
- Low risk types lead to warts, high risk types to cancer

Questions for modeling

- Which aspects of the hijacking control cancer initiation?
- What are the key differences between high and low risk viruses?
- Why is the delay between infection and cancer so long?

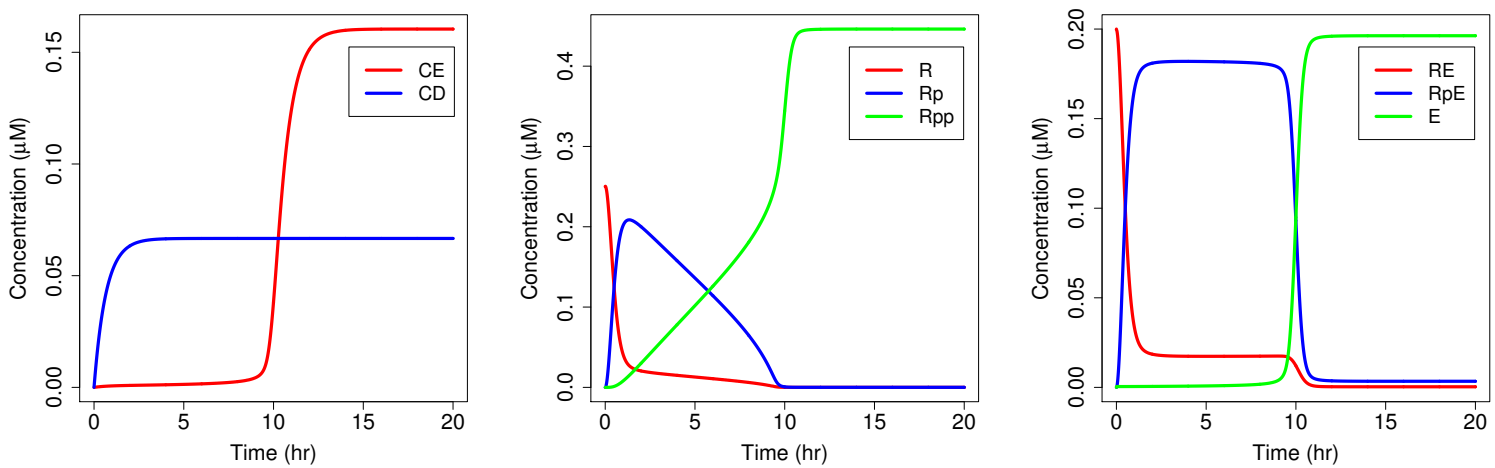
The normal cell cycle



- Cyclin D initiates the cell cycle
- E2F controls transcription
- pRB sequesters E2F
- Free E2F promotes cyclin E
- Cyclin E initiates positive feedback

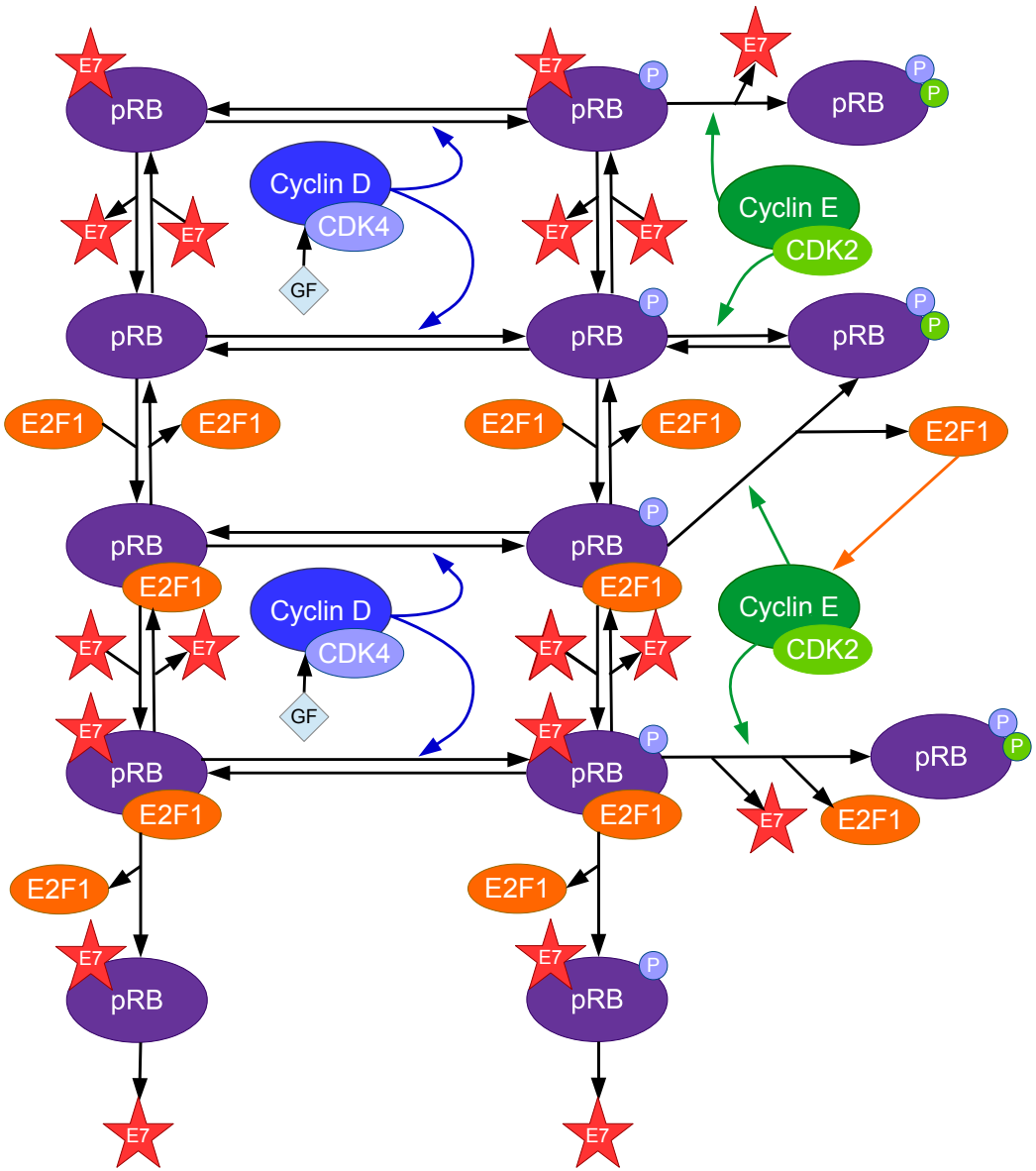
The behavior of the basic model

System of 8 differential equations.



The key output is whether and when the positive feedback kicks in.

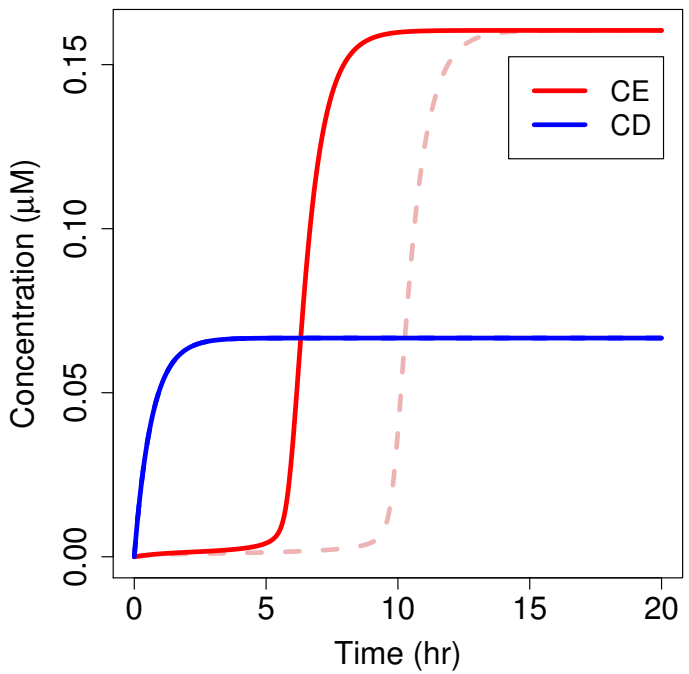
The model with the E7 protein from HPV

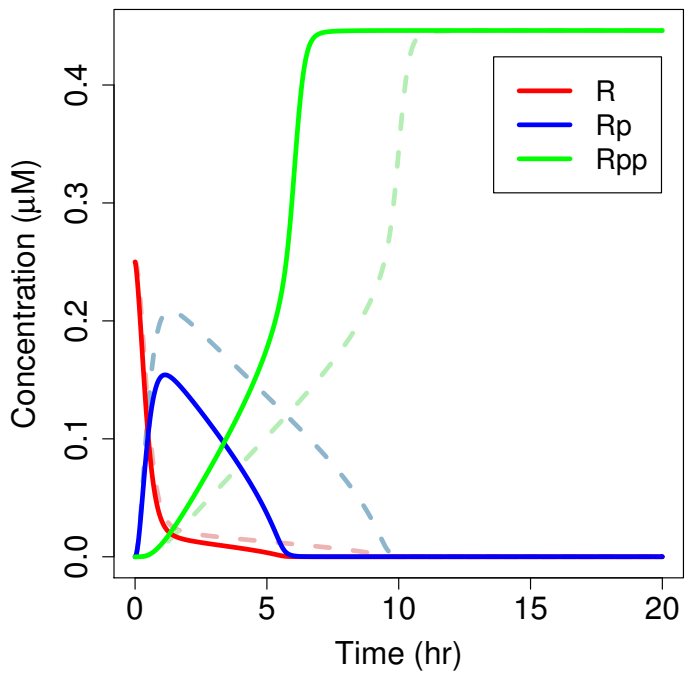


- E7 binds pRB and releases E2F
- High risk E7 also degrades pRB.

E7 accelerates cell division

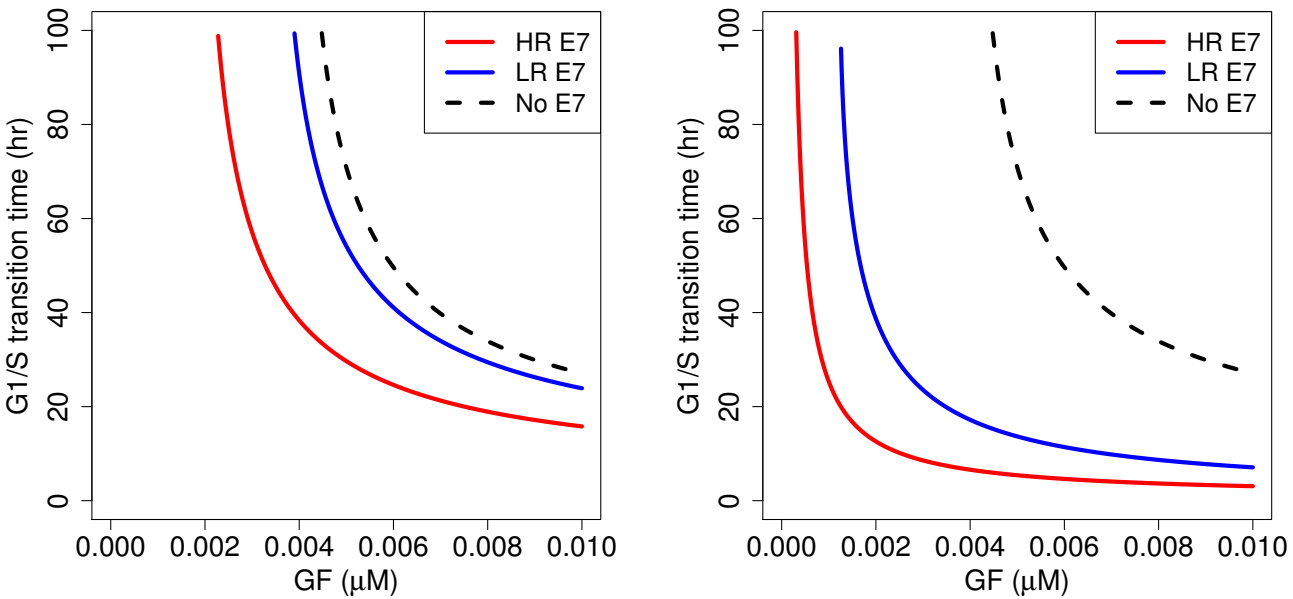
Solid lines are infected cells, dashed lines uninfected.





E7 reduces dependence on growth factor

Effects of a low (left) or high (right) concentration of high risk (HR) or low risk (LR) E7.



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- And for predicting the slow and relatively rare progression to cervical cancer

Outline

- Modeling HPV and cancer
- Modeling the cellular stress response
- Modeling asthma within the body

You got problems?

Cells got problems.

- Need oxygen

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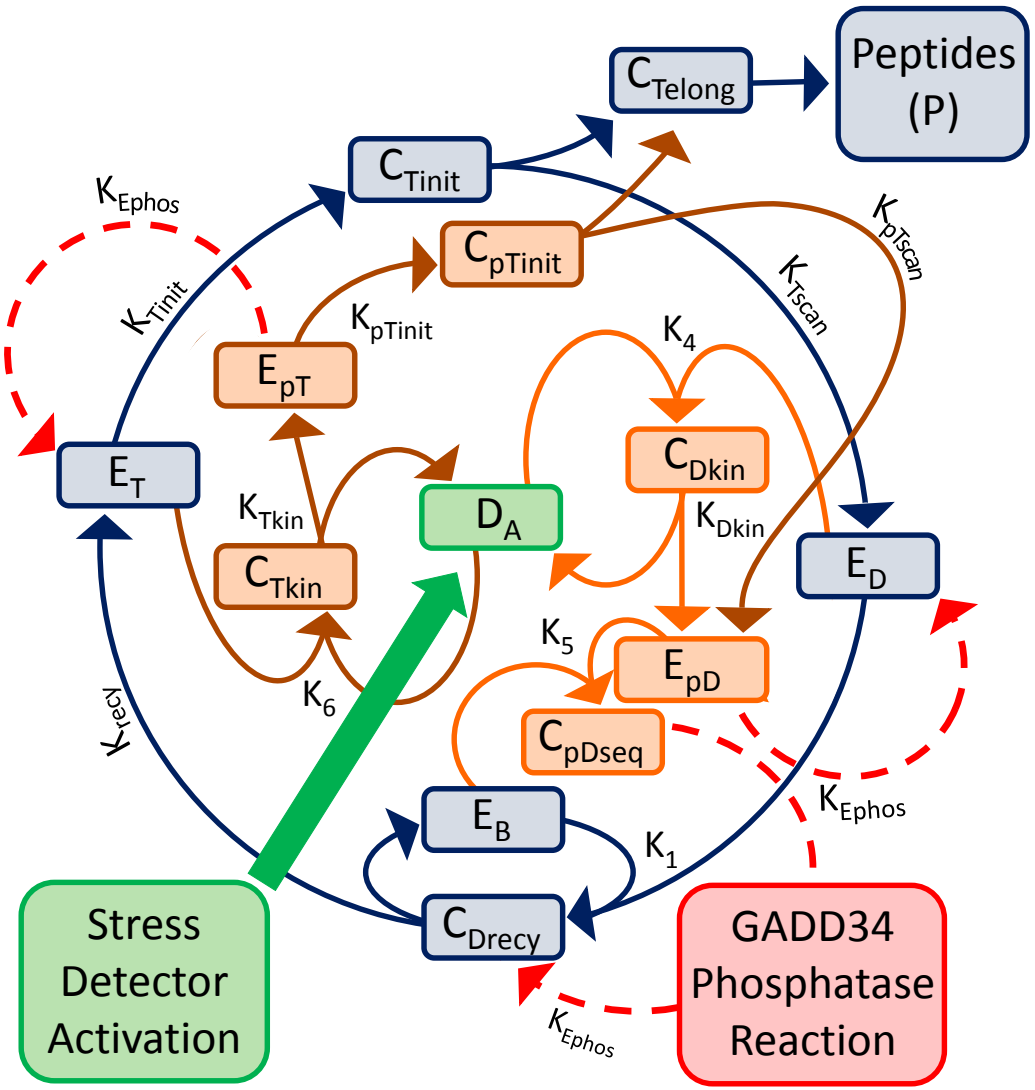
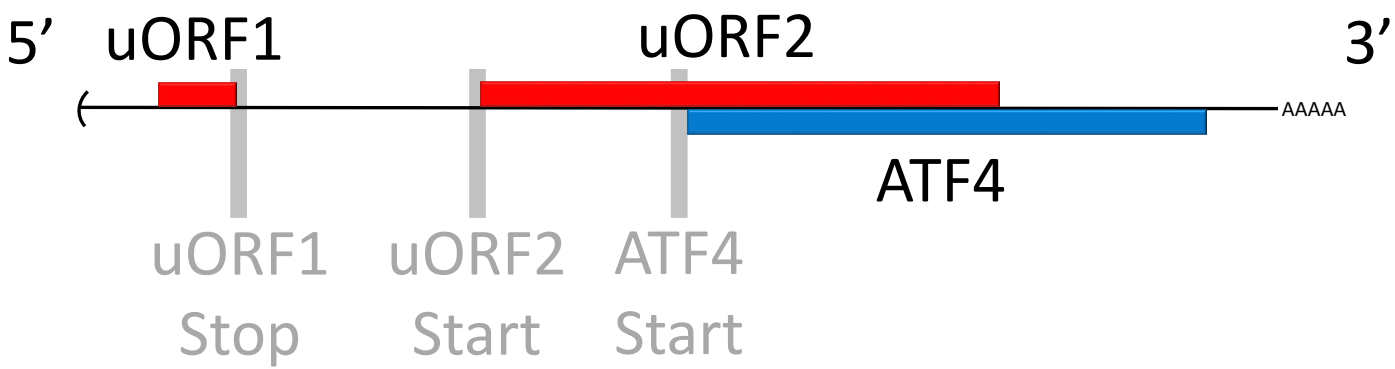
Cells have specialized detectors that initiate a pathway to reduce production of most proteins by sequestering the eukaryotic initiation factor eIF2α, but somehow upregulate specific stress response proteins that eventually reverse the process.

State diagram of the stress response



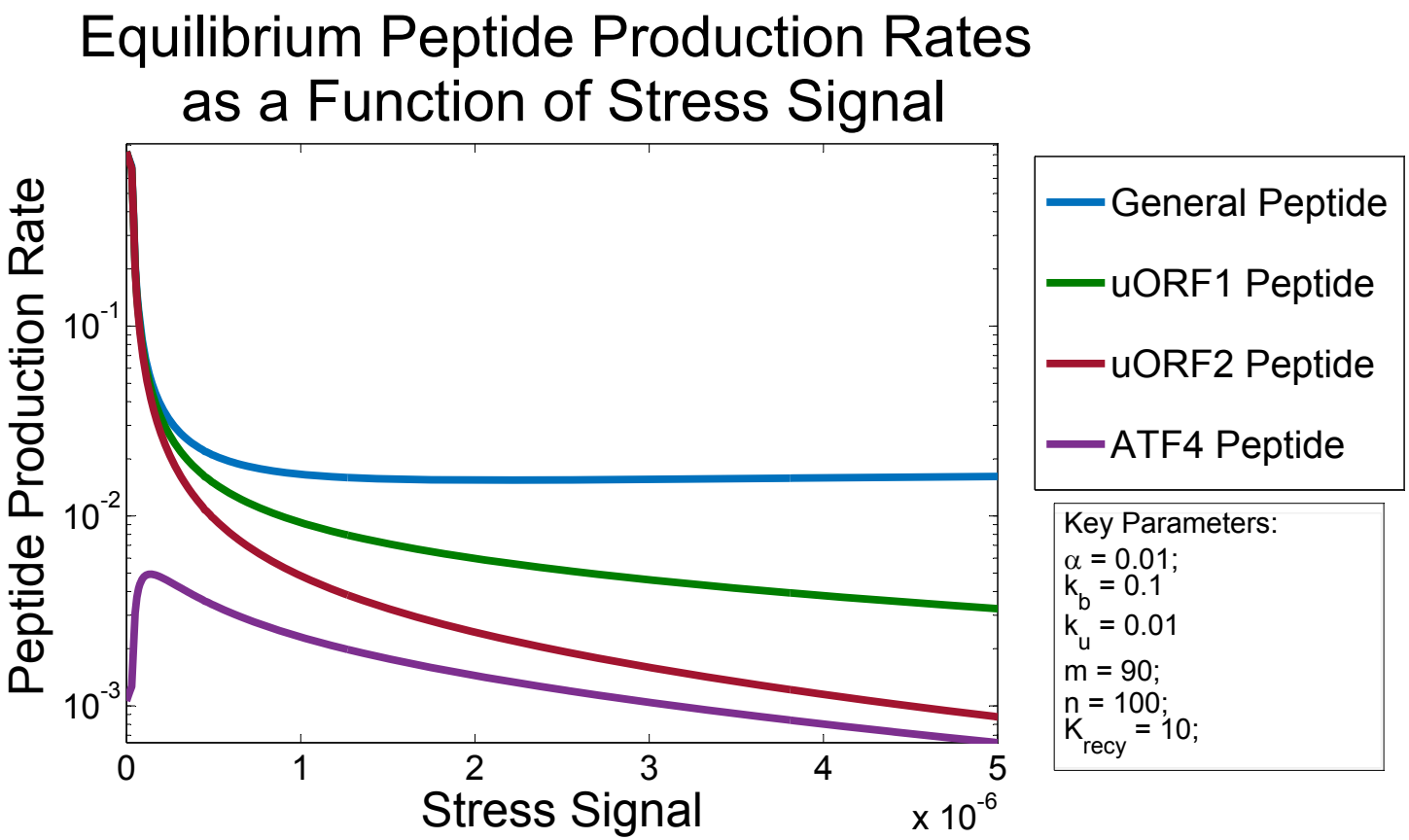
ATF4 dynamics

ATF4 is a transcription factor that should be upregulated when other proteins are downregulated.



Uses a nifty system that turns on when eIF2α is at an intermediate level.

Main result



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- Turning off always starts simultaneously with turning on
- The details are crucial for understanding whether a cell will recover or fail
- The details also indicate the points of weakness that viruses can and do exploit

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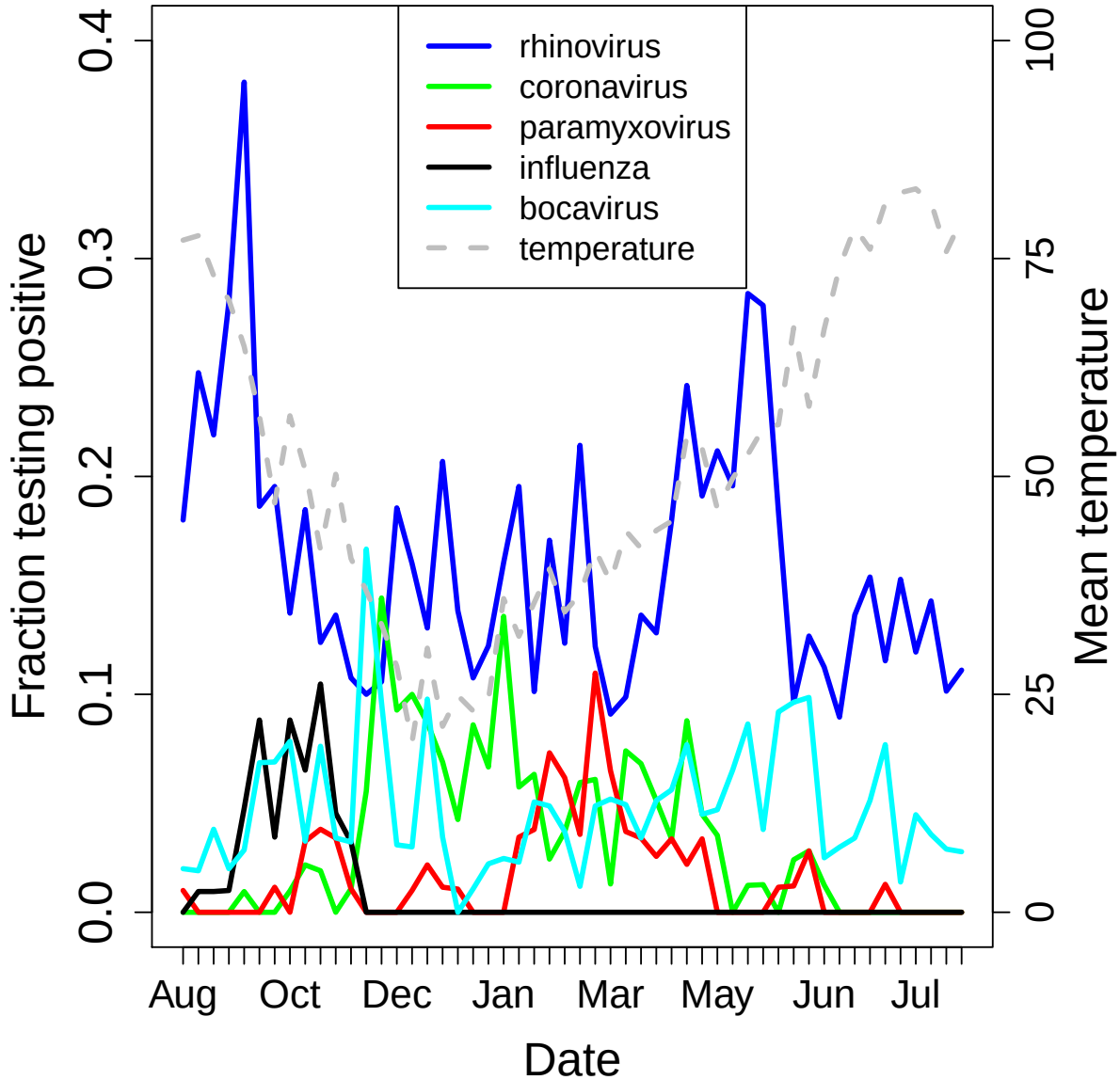
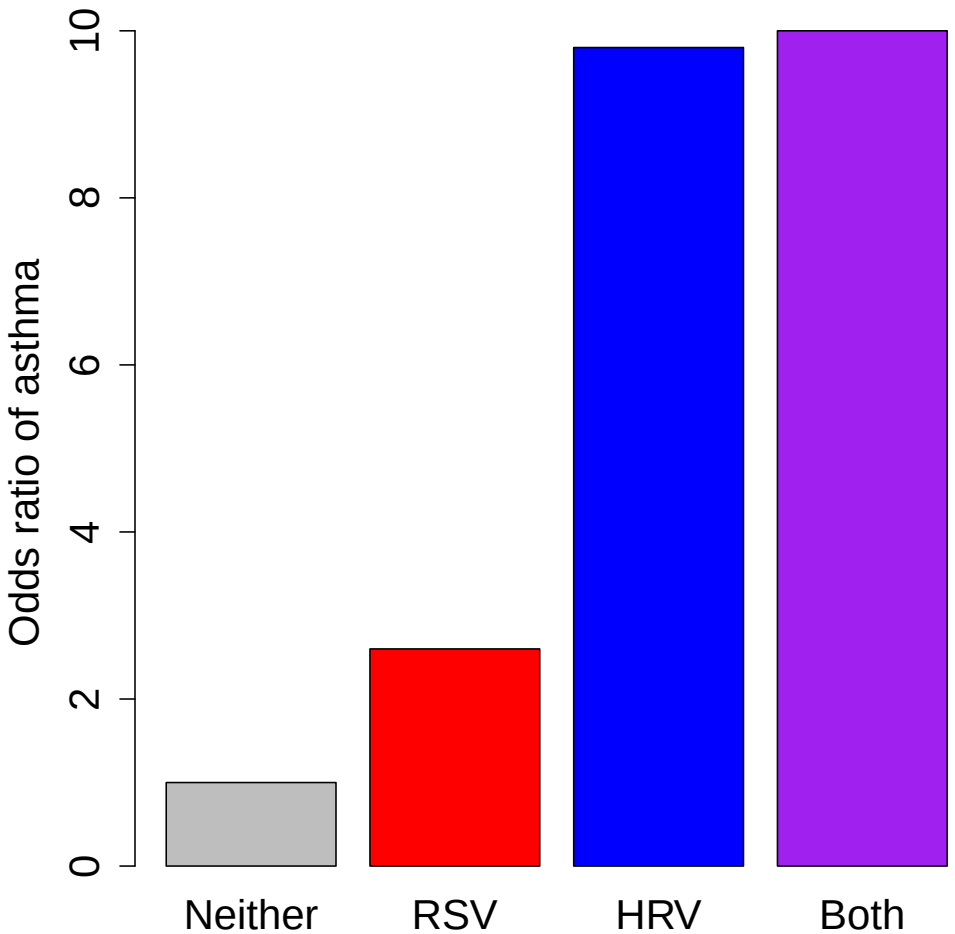
First, some background on viruses



Rhinovirus is more than a nuisance

- Severe early infections predispose children to develop asthma many years later
- Infections are a chief trigger of asthma exacerbations
- Infections severe in those with asthma

Early infections and later asthma



Most evidence indicates that severe viral infections cause later asthma rather than merely being markers of susceptibility

Jackson, 2008

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- Cells scream (chemically) with interferon
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- Alternative activated macrophages release IL-4 (a chemical signal associated with asthma)
- IL-4 promotes allergic response and airway remodeling

The state diagram

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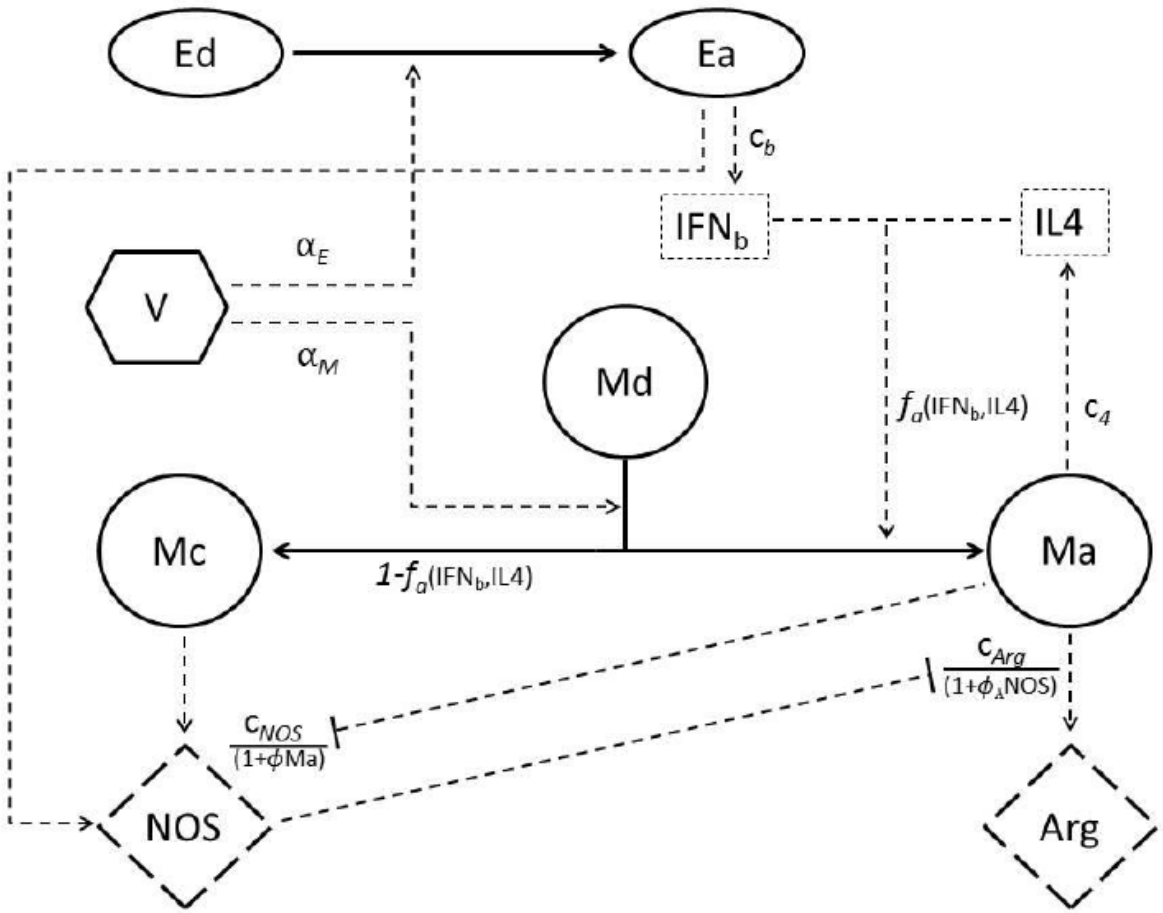
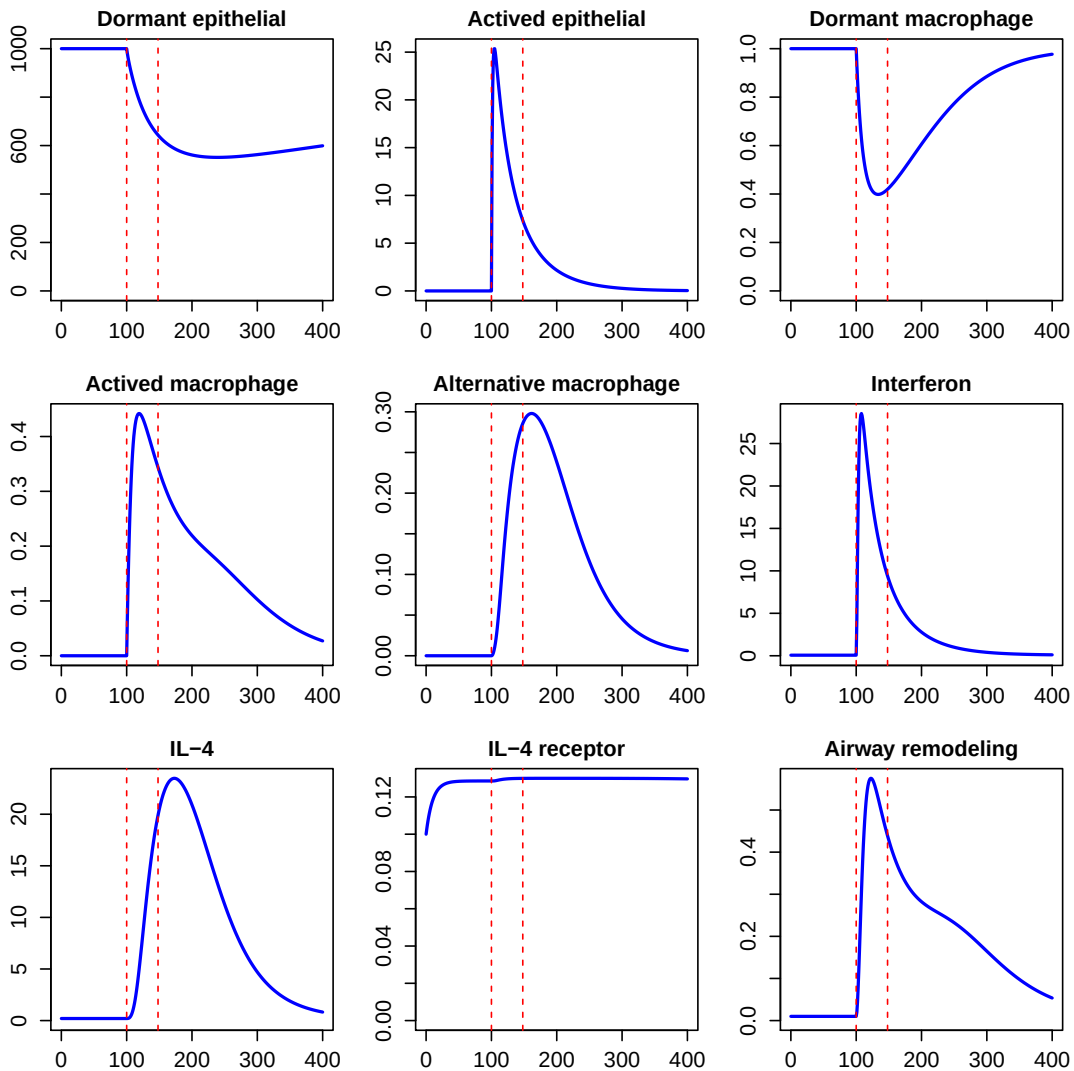


What the model looks like

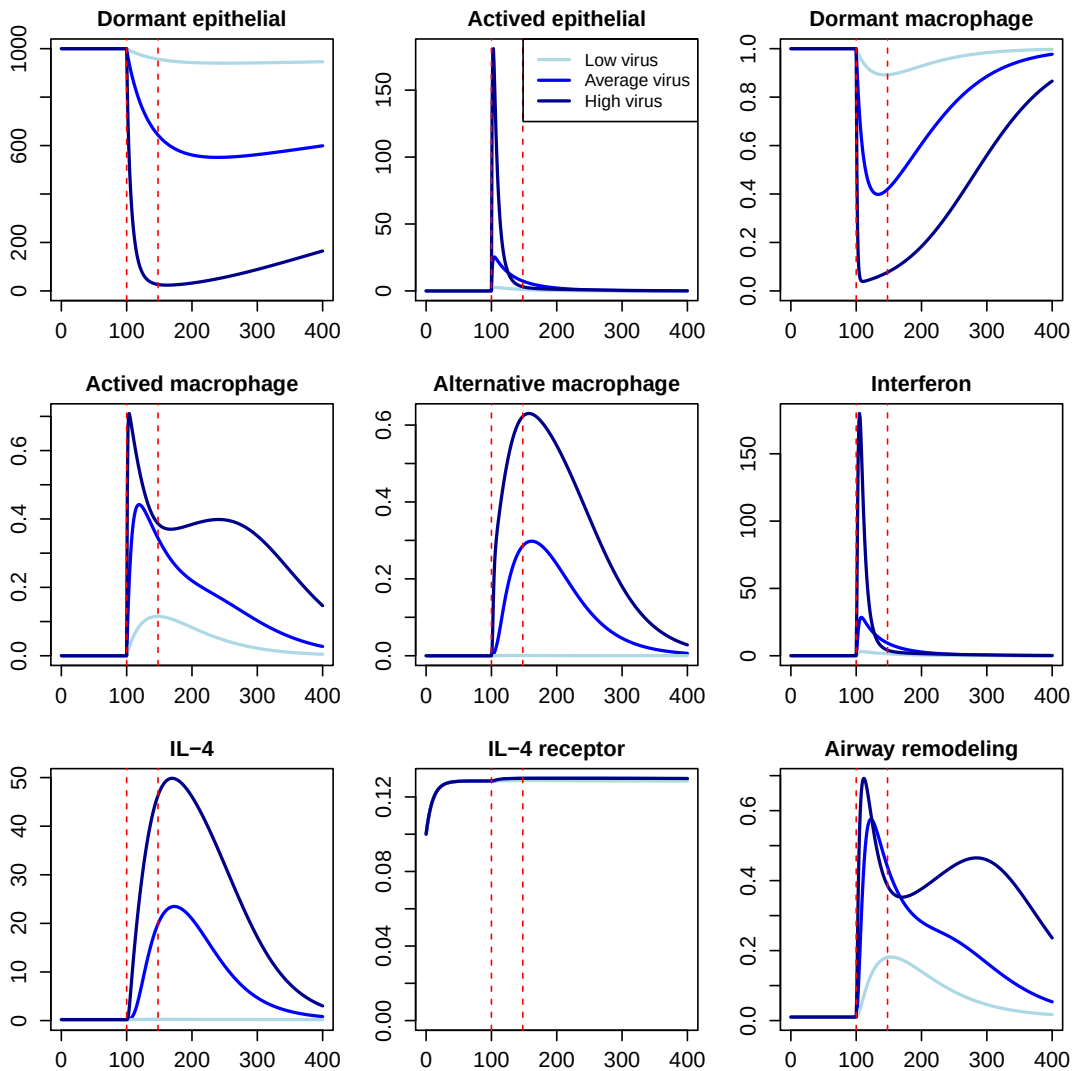
Differential equations for epithelial cells (E_d), interferon (F), dormant and alternatively activated macrophages (M_d and M_a), IL4, and some other stuff that didn't fit on the slide.

$$\begin{aligned}
\frac{dE_d}{dt} &= -\alpha_E V E_d + \gamma_E E_a - \delta_{Ed}(E_d - E_{d0}) \\
\frac{dF}{dt} &= c_b E_a - \delta_F (F - F_0) \\
\frac{dM_d}{dt} &= -\alpha_M V M_d - \delta_{Md}(M_d - M_{d0}) \\
\frac{dM_a}{dt} &= f_a \alpha_M V M_d - \delta_{Ma} M_a \\
\frac{d\mathrm{IL4}}{dt} &= c_4 M_a - \delta_{\mathrm{IL4}}(\mathrm{IL4} - \mathrm{IL4}_0)
\end{aligned}$$

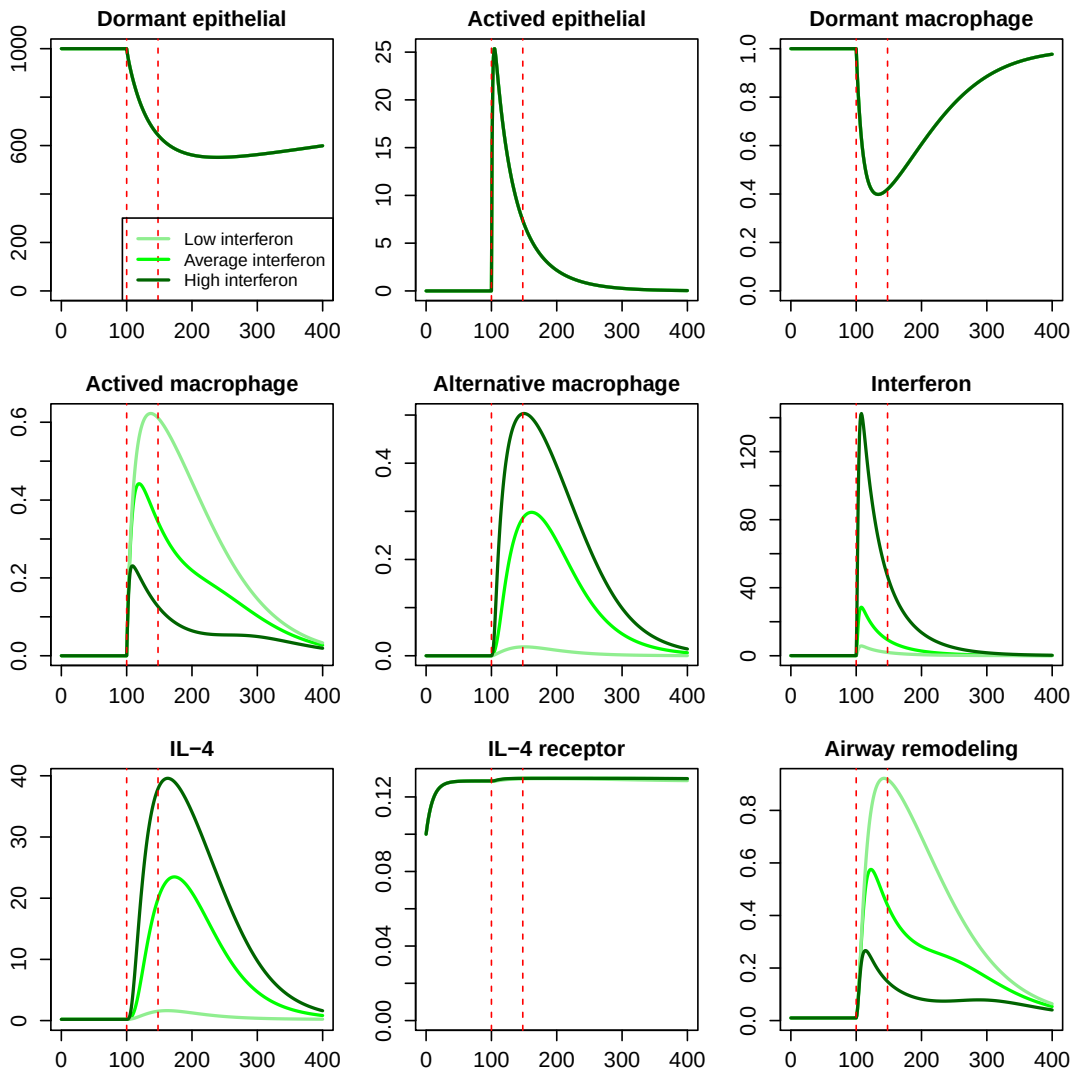
Behavior of model



Effects of infection severity



Effects of interferon production



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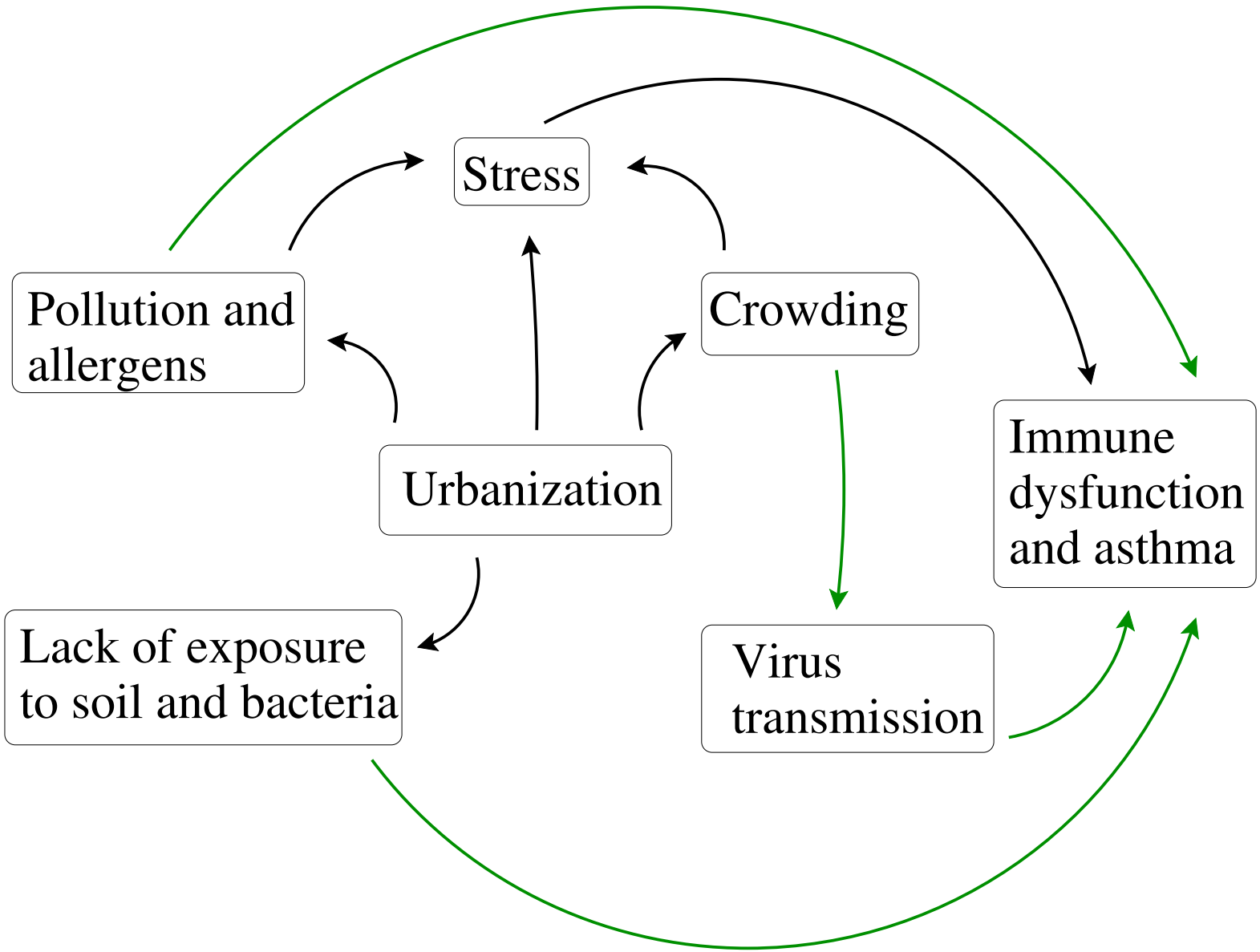
- Connect with the full complexity of how asthma is initiated

Pathways to asthma



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- **What we hope:** Big Data and Computational Biology will establish the interactions, feedbacks and parameters efficiently, and we can establish new collaborations to deeply understand the dynamics