



Quantifying the Impact of Cellular Heterogeneity on cGAS Pathway Regulation using Multiscale Agent-Based Modeling

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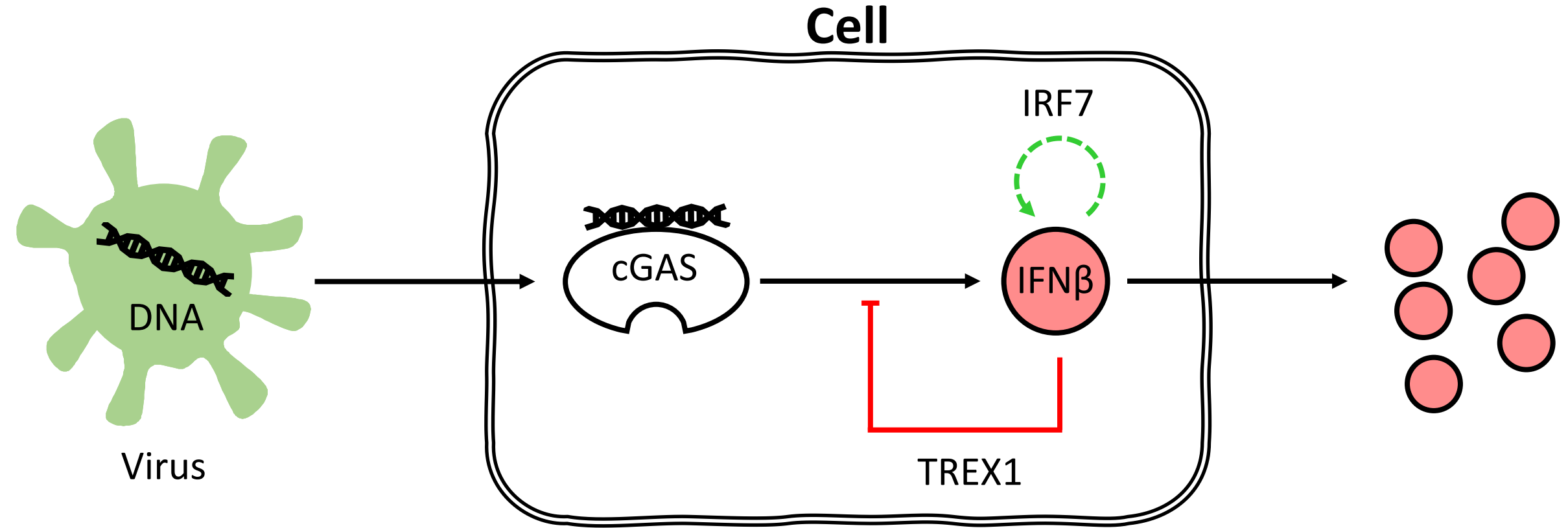
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Cells Produce Interferon in Response to DNA



Why is cGAS Important?



Viral Infection

- Herpes
- HIV

Bacterial Infection

- Tuberculosis
- Listeria

Cancer

- Prostate
- Brain
- Colon
- Ovarian

Autoimmunity

- Aicardi–Goutières syndrome
- Lupus

Aging

- Senescence
- DNA Damage

- To better understand this immune response, we **need to develop models** that can **capture cellular behavior**



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Mathematical modeling of the cGAS pathway reveals robustness of DNA sensing to TREX1 feedback



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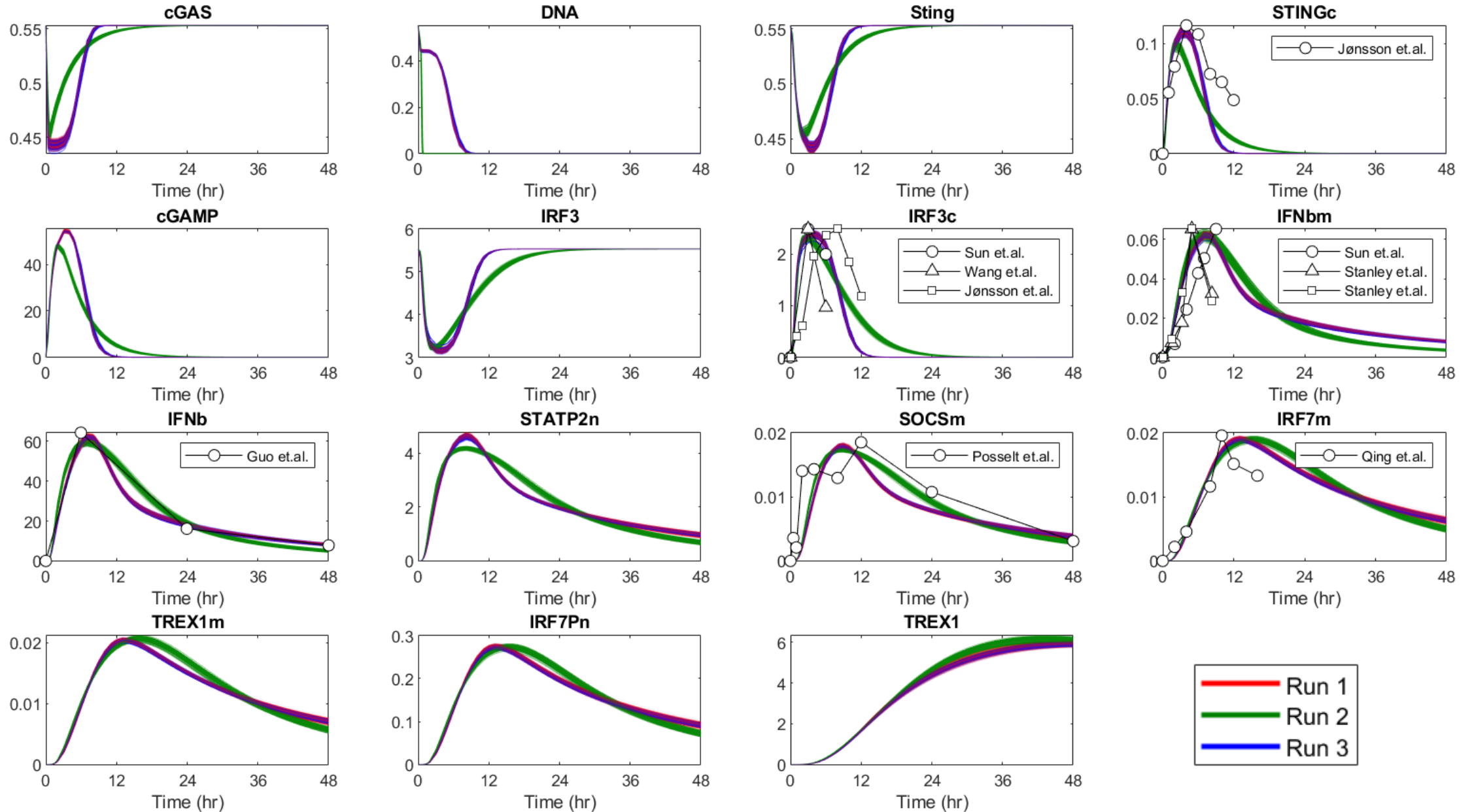
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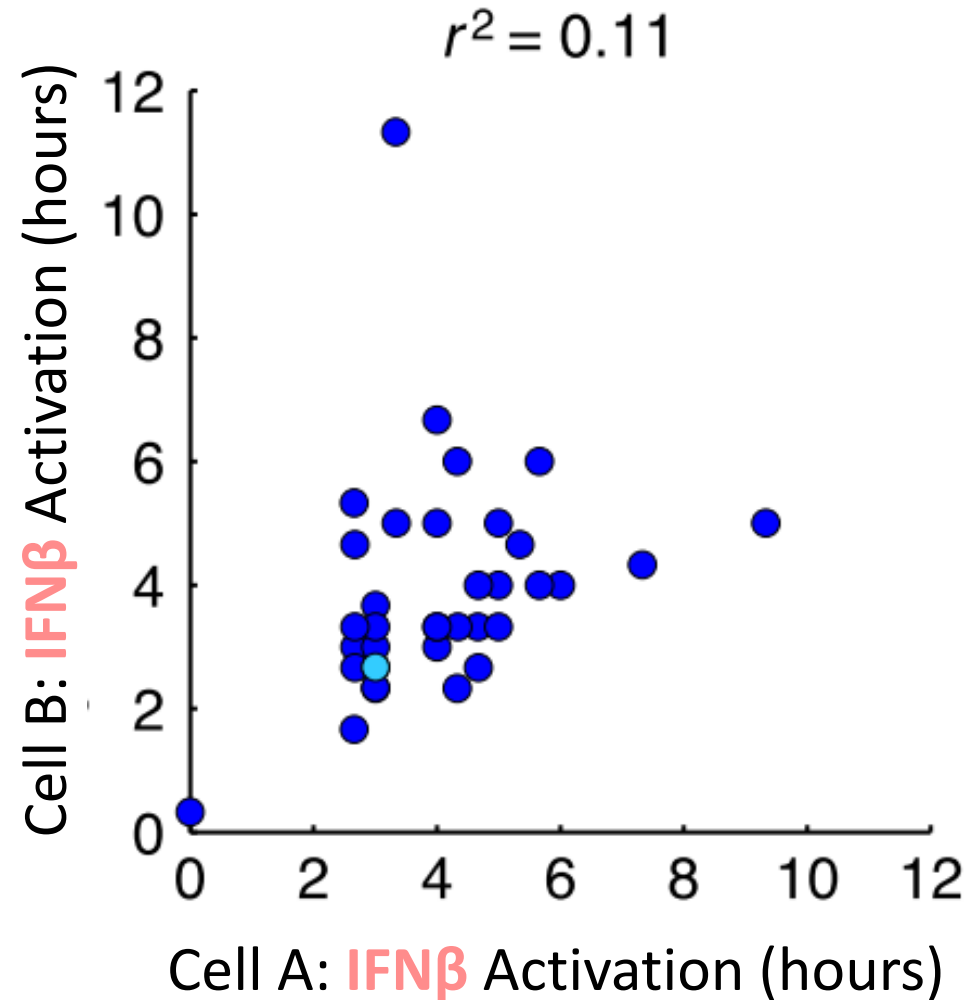
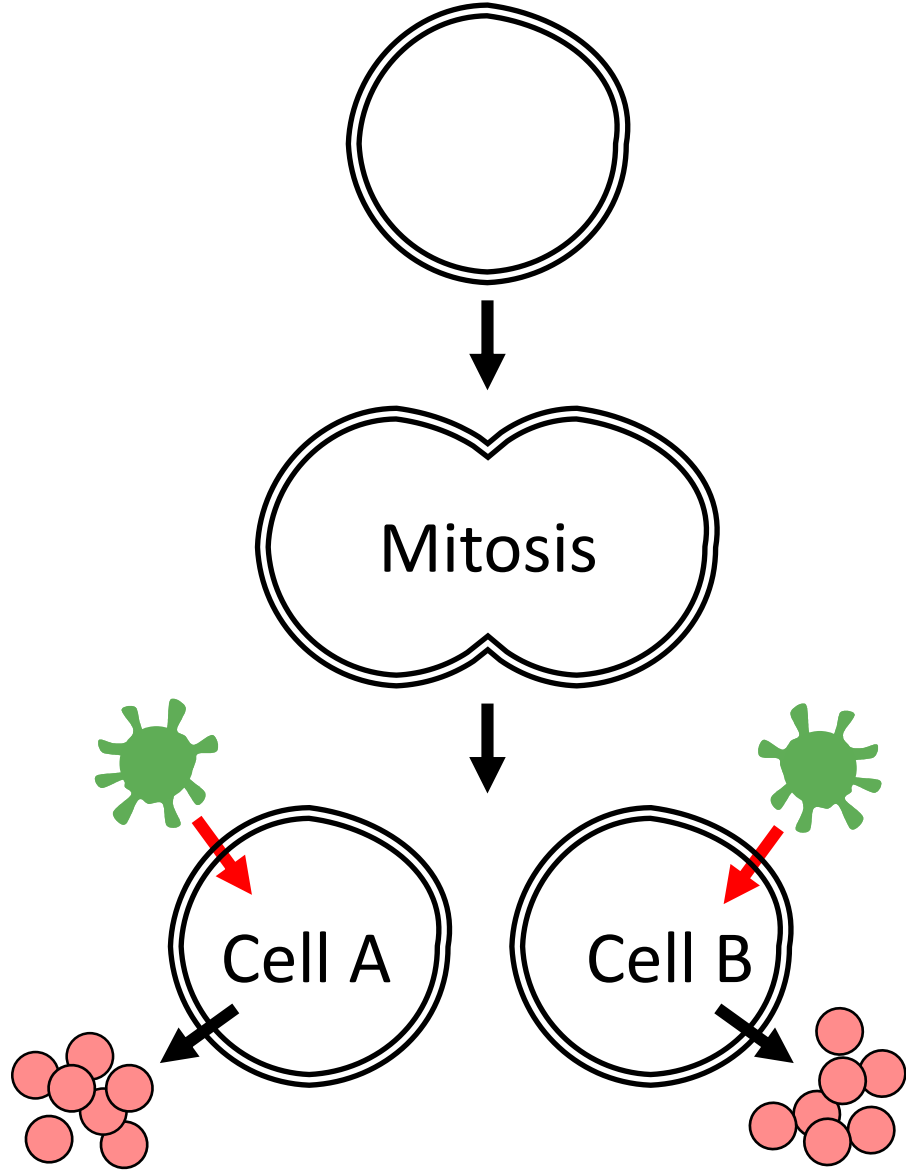
^c McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA, United States

^d Department of Computational and Systems Biology, University of Pittsburgh, Pittsburgh, PA, United States

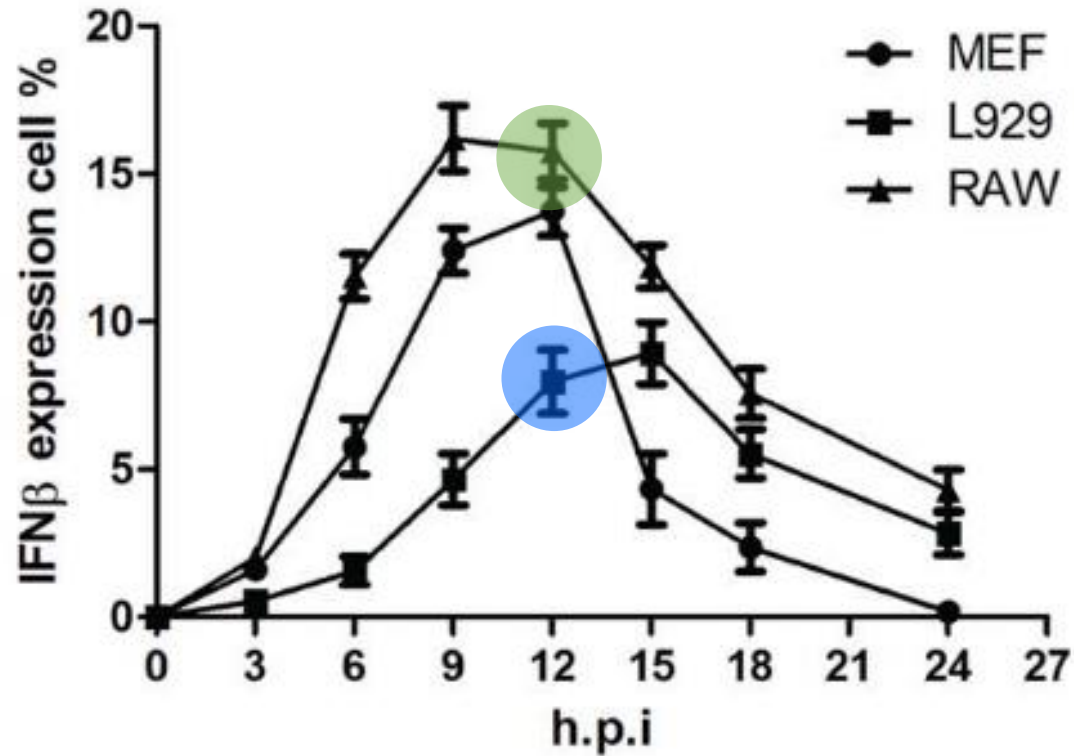
Using an ODE Model Approach



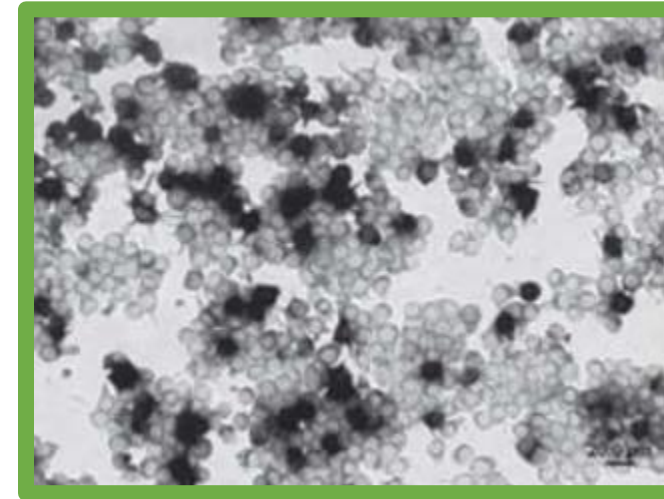
Interferon Producing Cells are Heterogeneous



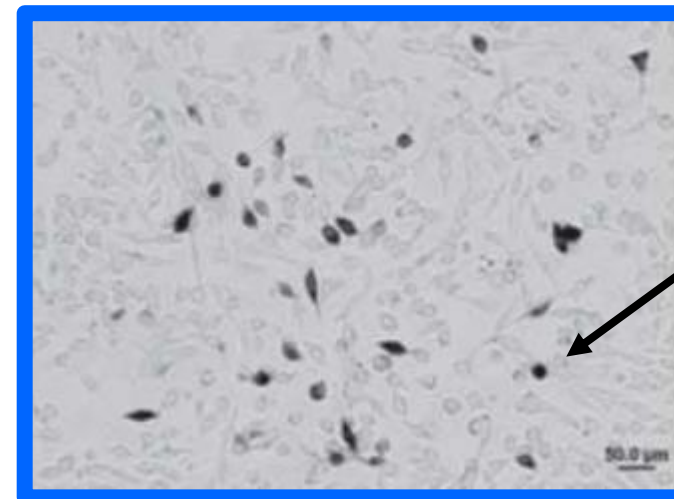
Interferon Signaling is Stochastic



RAW Cells



L929 Cells



Dark spots indicate IFN β mRNA

Sources of Heterogeneity and Stochasticity



Why are we doing this?



- We know IFN β signaling is heterogenous and stochastic
- We want to know what benefit this brings to a cell population
 - Conserve resources?
 - Prevent pathogens from circumventing immune signaling?

We hypothesize there exists an **optimal level of cell to cell variability** that **balances** pathogenic clearance and chronic IFN β signaling

Choosing a Modeling Scheme



Build on
previous work
(ODEs)

Model large
systems
($>10,000$ cells)

Be able to model
spatiotemporal
events

Incorporate
stochastic and
heterogeneous
behavior

ODE Modeling

PDE Modeling

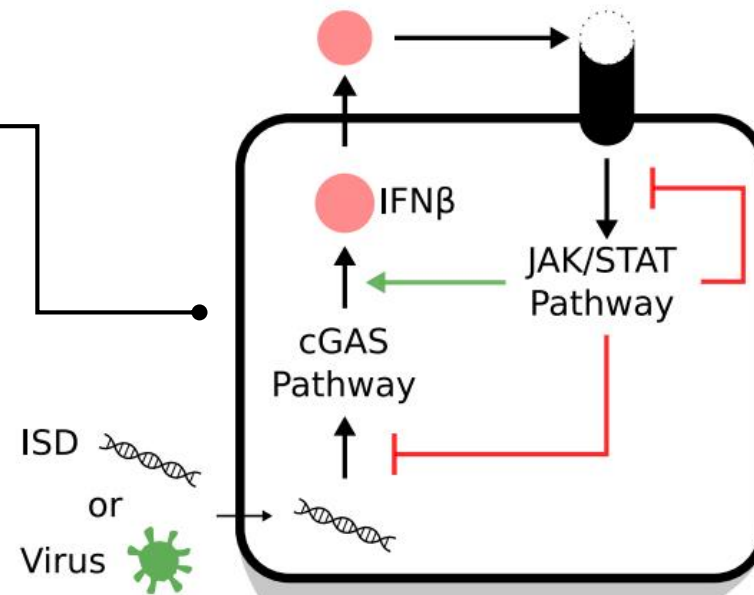
ABM Modeling

Hybrid PDE/ABM Modeling with ODE Rule Sets

Defining the Model

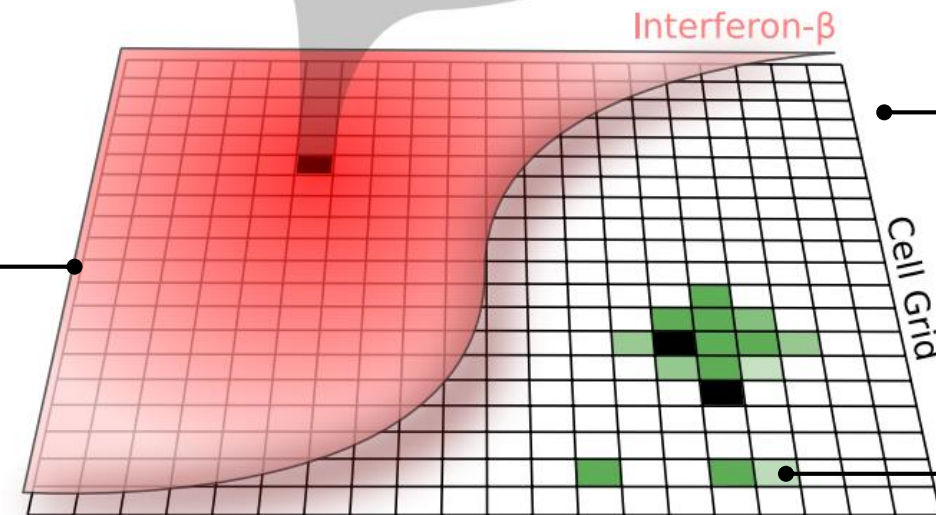


Each cell has its own ODE system



Grid of 40,000 cells

IFN β can diffuse across the cell population

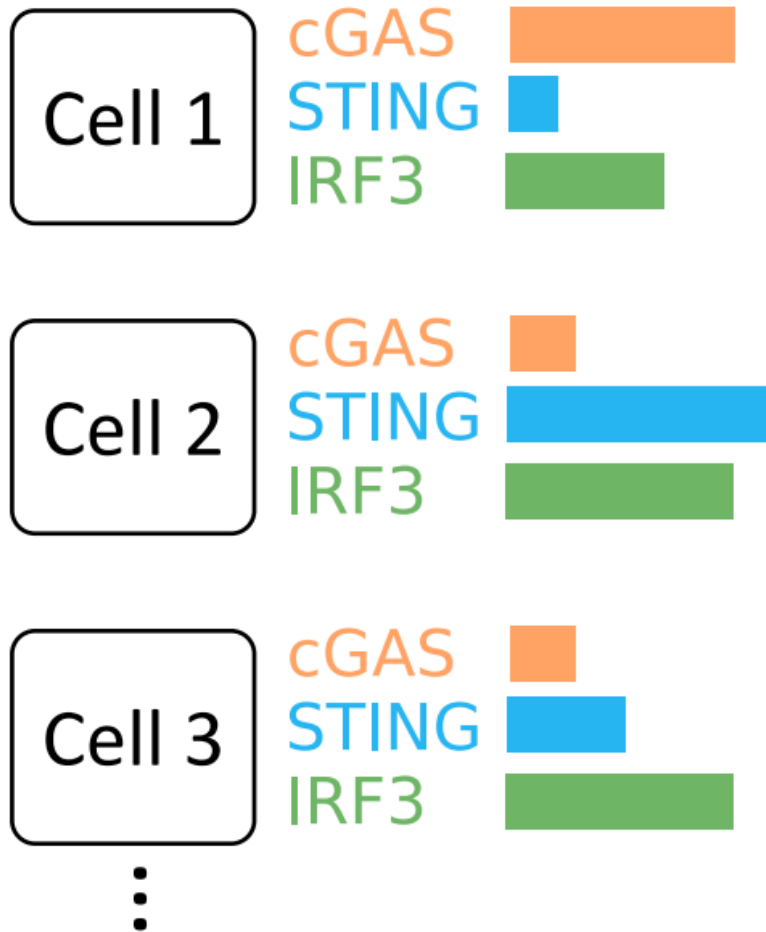


Cells states:
Healthy **Infected** **Dead**

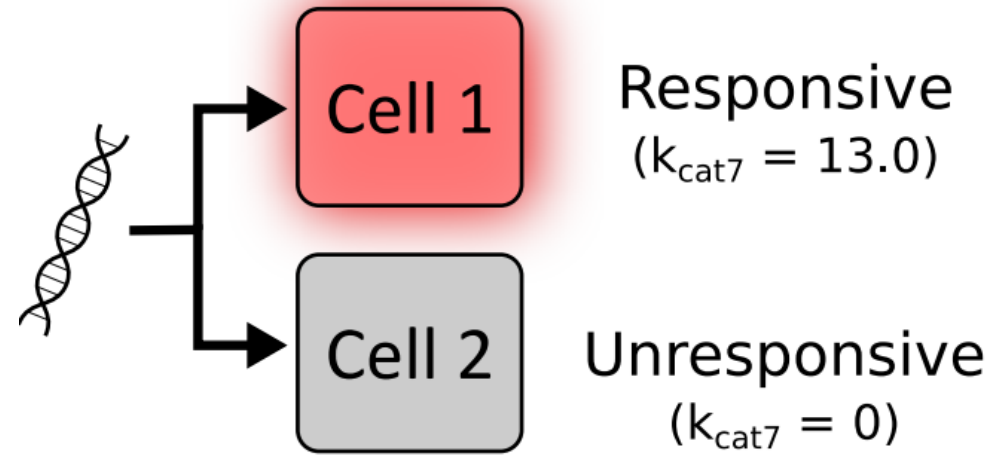
Incorporating Heterogeneity and Stochasticity



Heterogeneous Initial Conditions



Stochastic IFN β Activation



Vary Percentage of IFN β Responding Cells

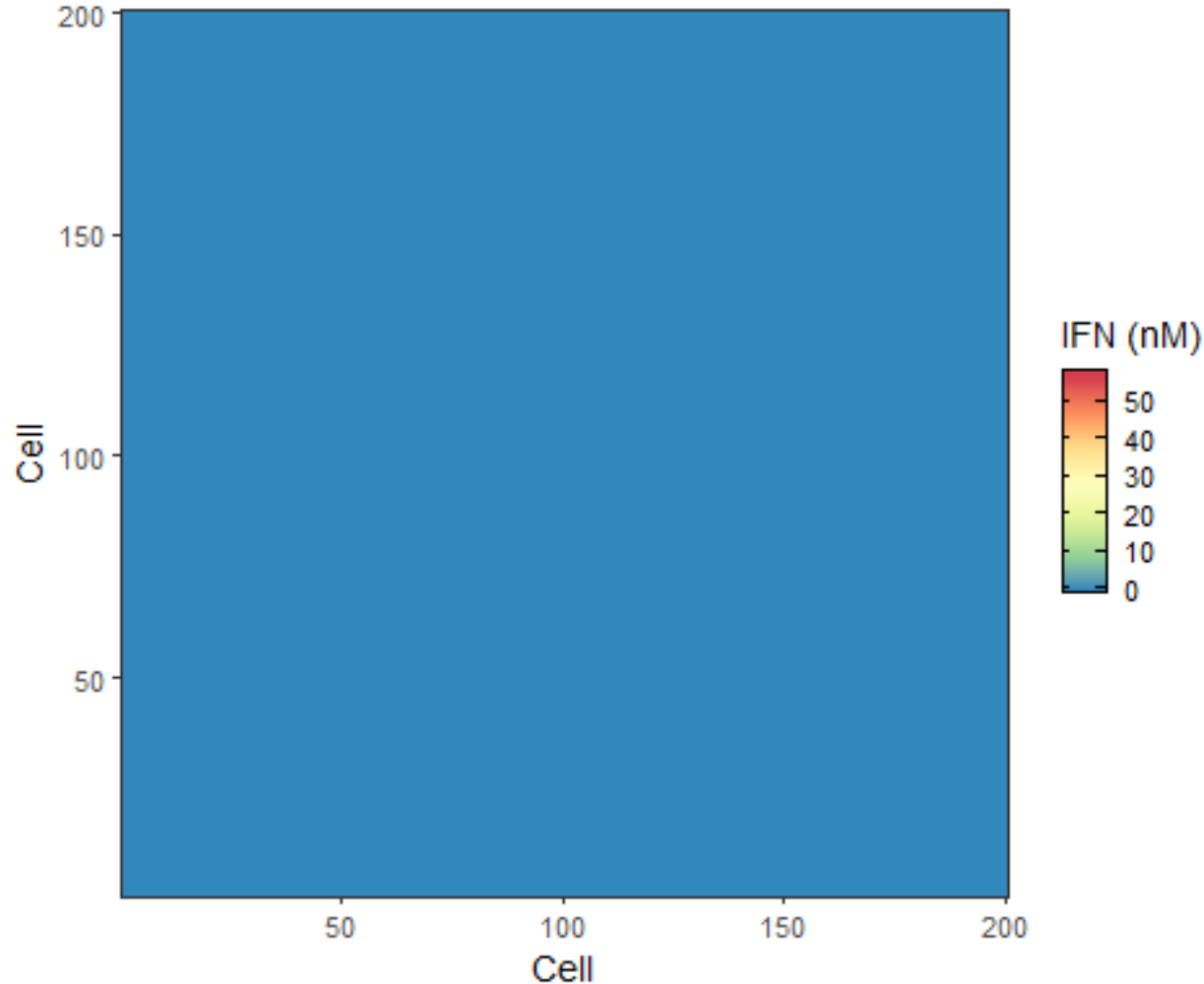


Simulating IFN β Transport



ISD Infection

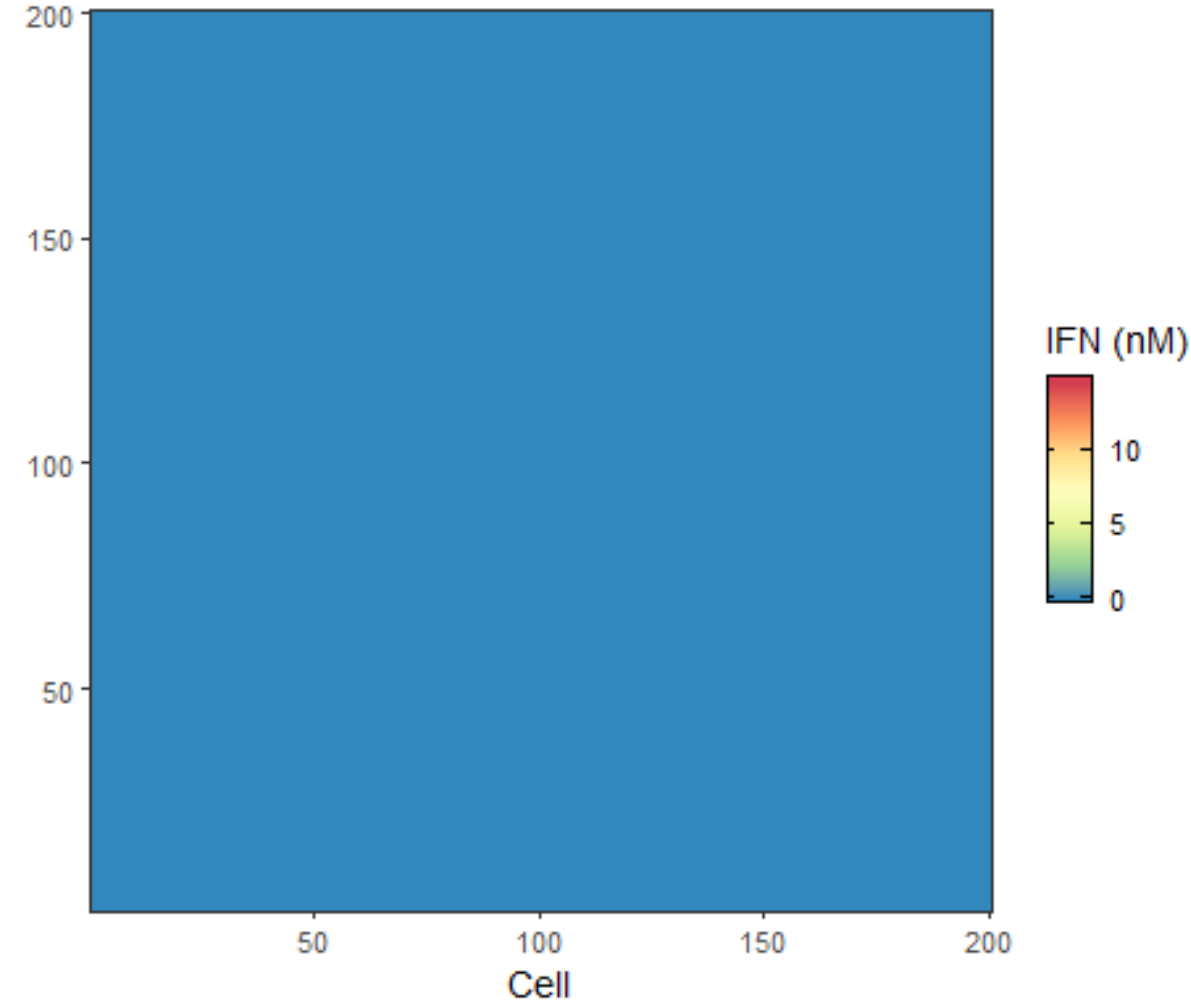
Time: 0.00 hours



“Drop” initial condition

Viral Infection

Time: 0.00 hours

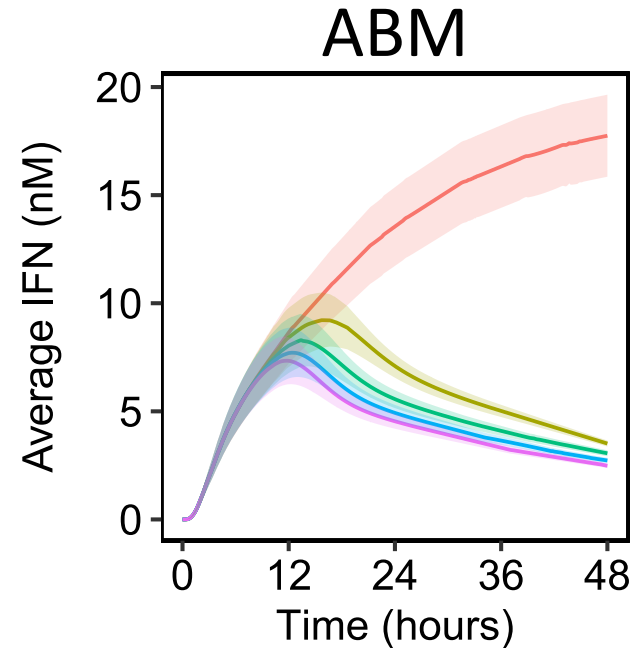
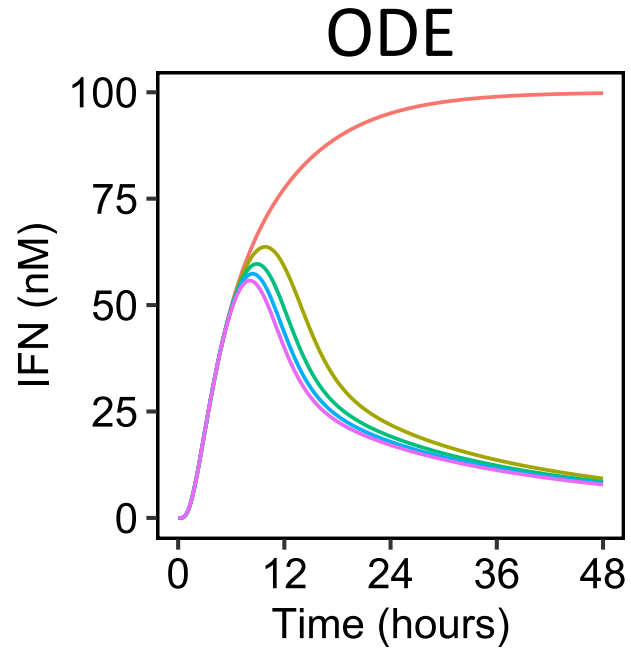


“Wash” initial condition

Heterogeneity does not Impact Bulk Cell Measurements



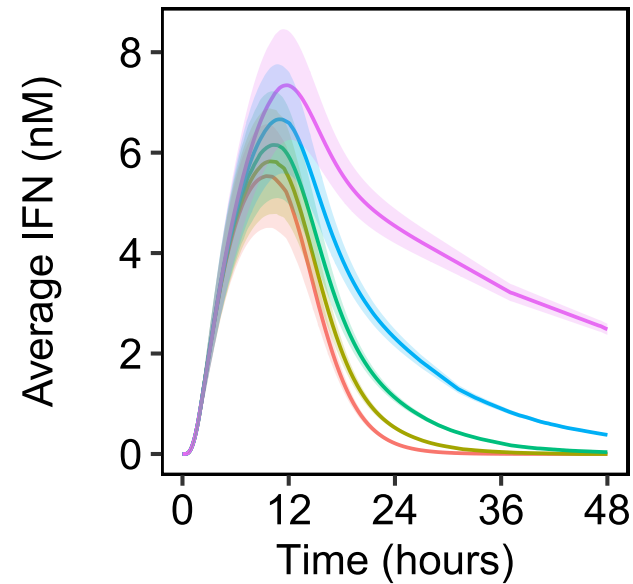
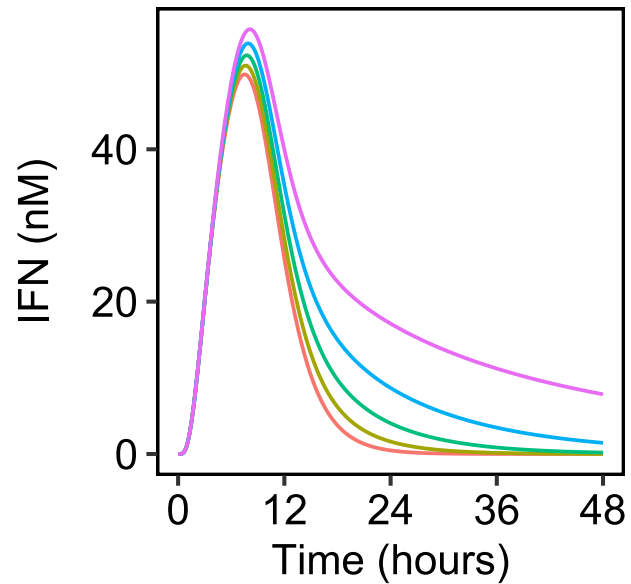
TREX1
Knock-Down
(negative feedback)



Percent
Knock-Down

- 100%
- 75%
- 50%
- 25%
- 0%

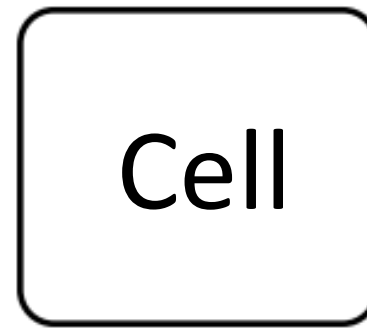
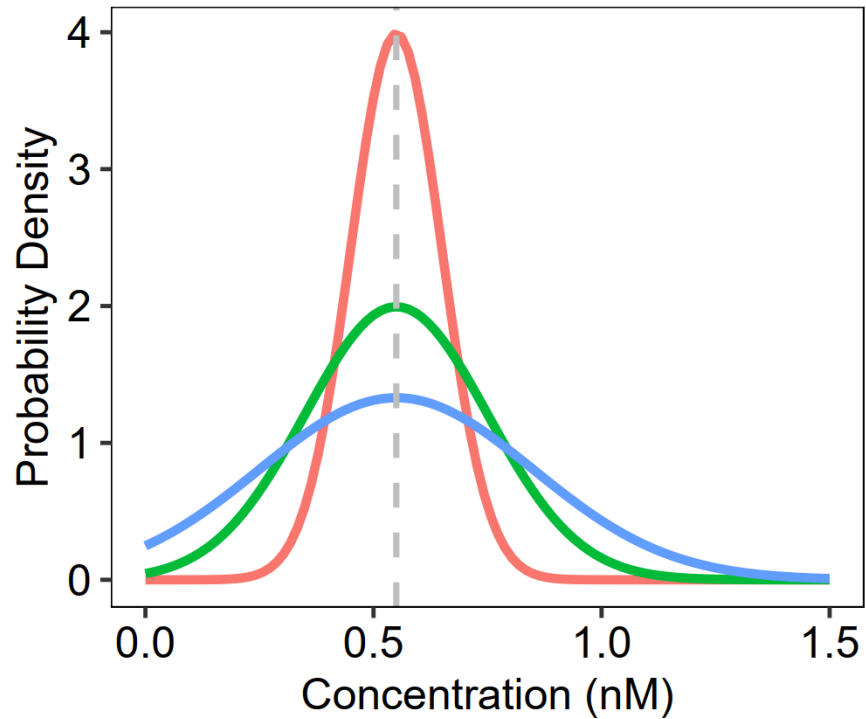
IRF7
Knock-Down
(positive feedback)



Heterogeneity in Cell Composition Increases IFN β Production



Adding Gaussian noise to initial conditions



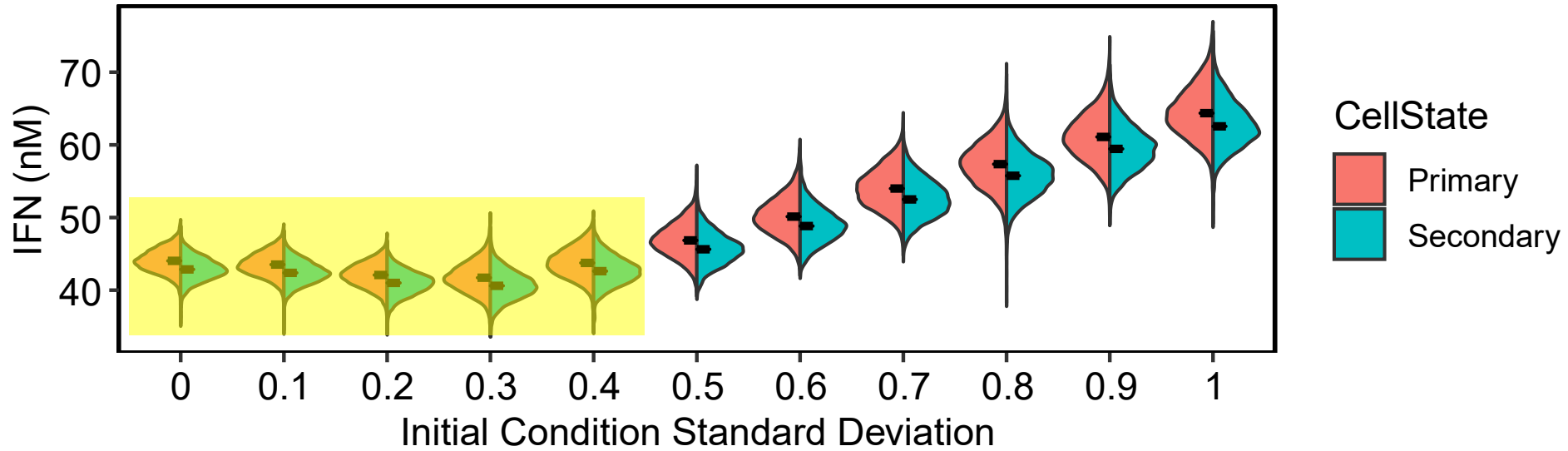
cGAS
STING
IRF3



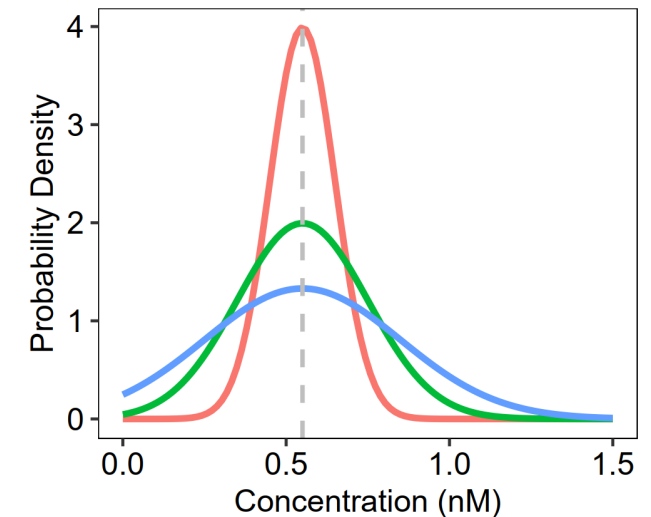
Heterogeneity in Cell Composition Increases IFN β Production



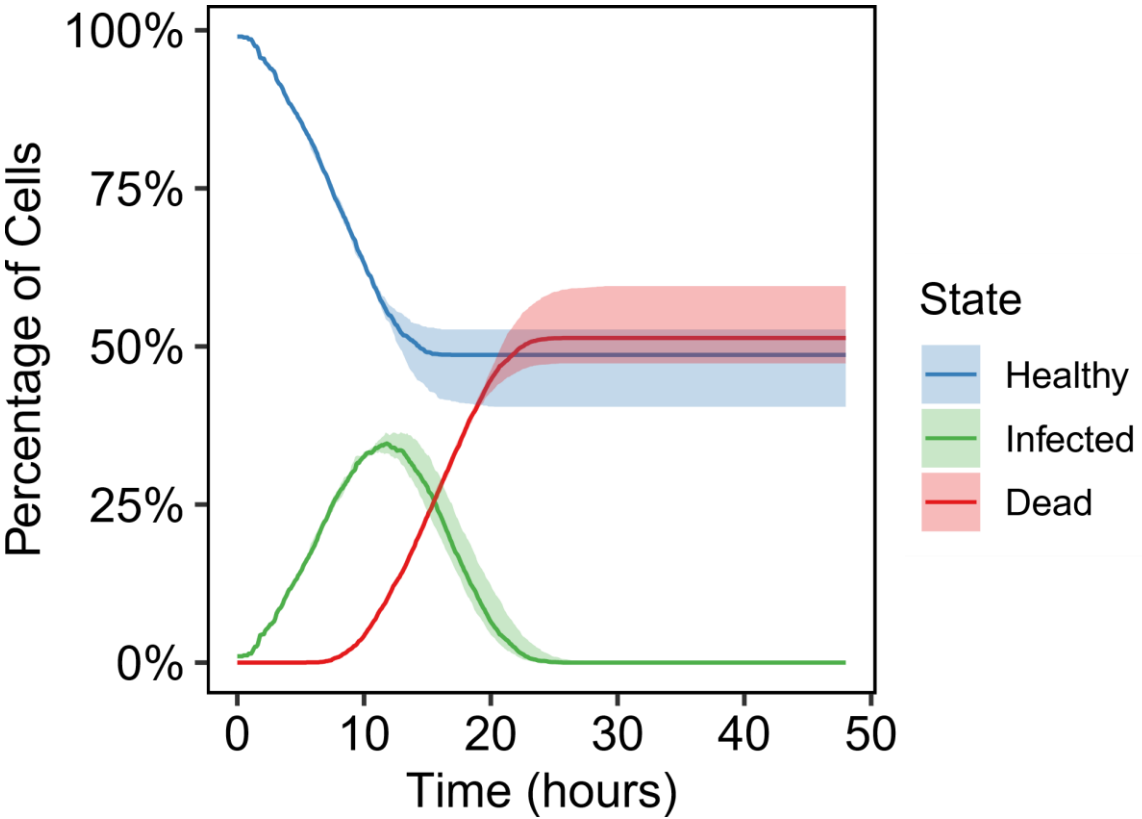
63% of Cells Initially Transfected



Cells can be **heterogeneous** and **sustain IFN β Response**



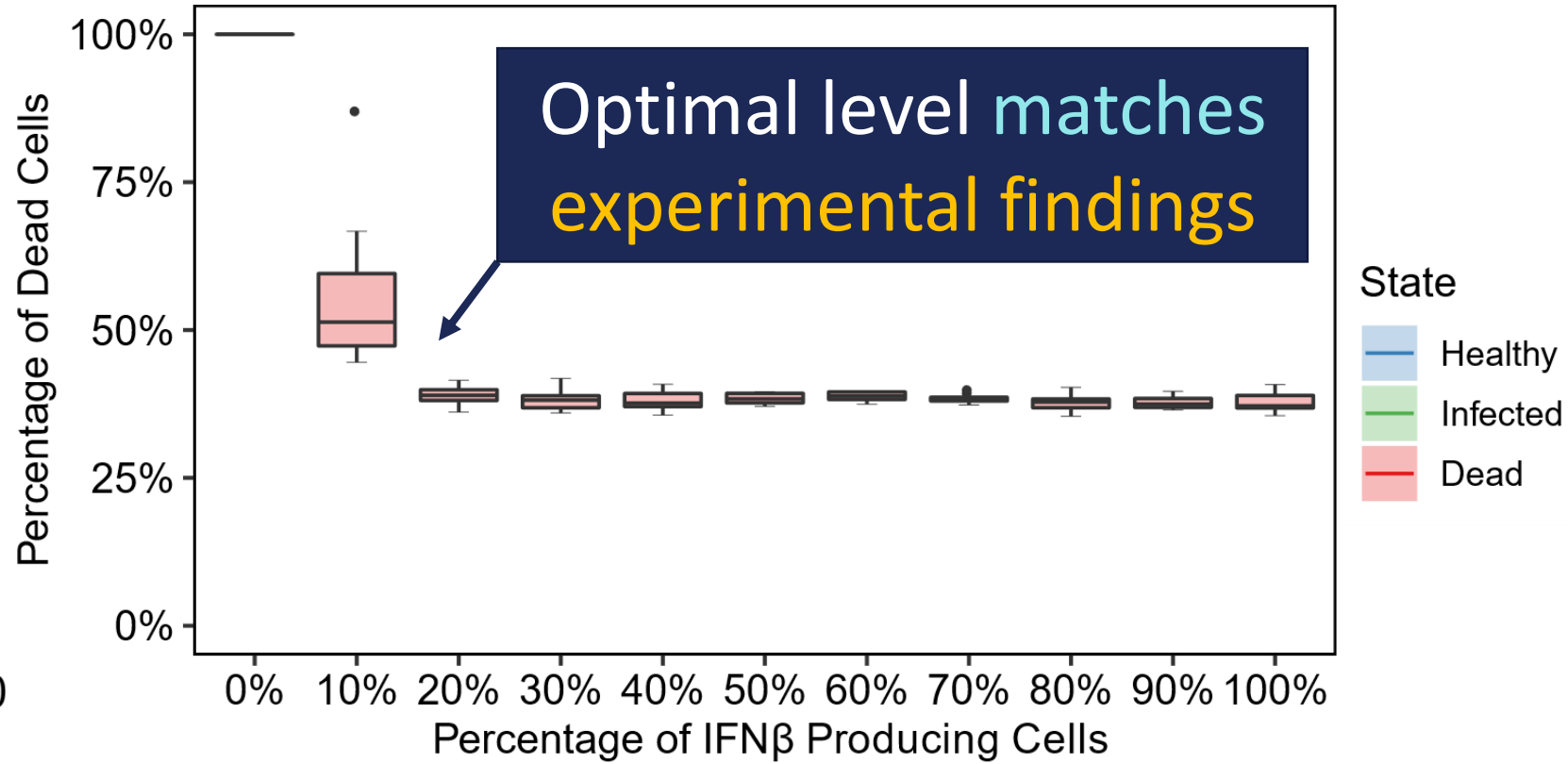
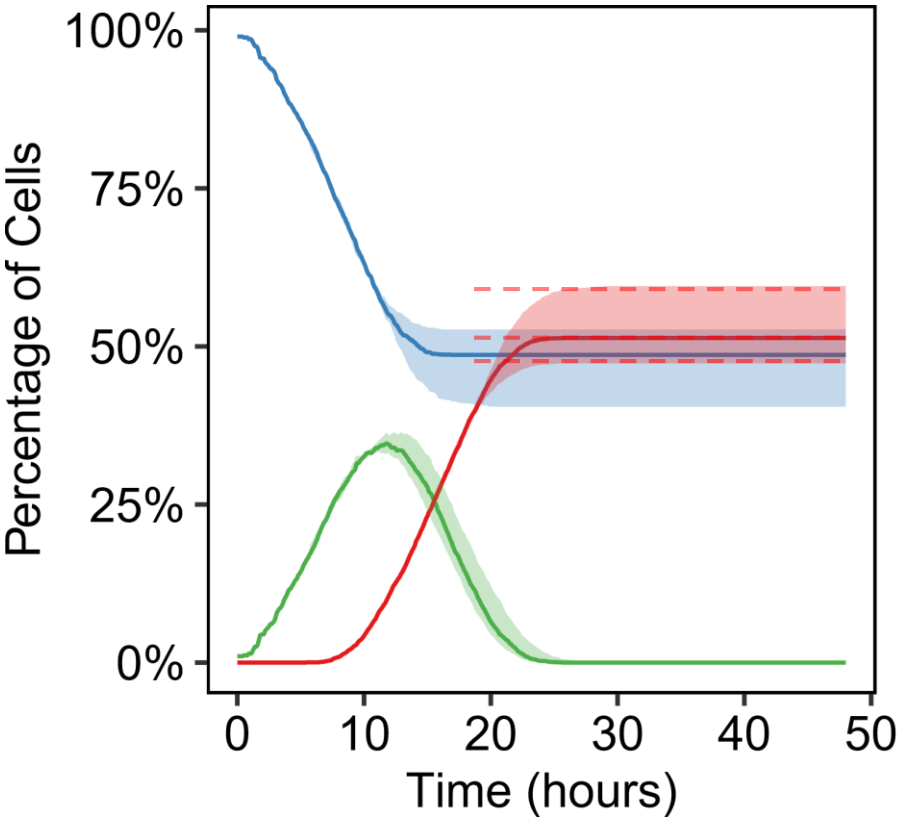
There is an Optimal Level of IFN β Producing Cells



There is an Optimal Level of IFN β Producing Cells



10% IFN β Producing Cells





Modern compiled languages like **Julia** allow for **large simulations**



Adding **heterogeneity** into the model had **no impact on bulk measurements**



Heterogeneity allows cells to maintain low molecular concentrations without sacrificing interferon production



Stochasticity allows cells to produce minimum interferon while maintaining cell survival

Acknowledgements

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