A MATHEMATICAL MODEL OF PATHOGEN-MACROPHAGE DYNAMICS

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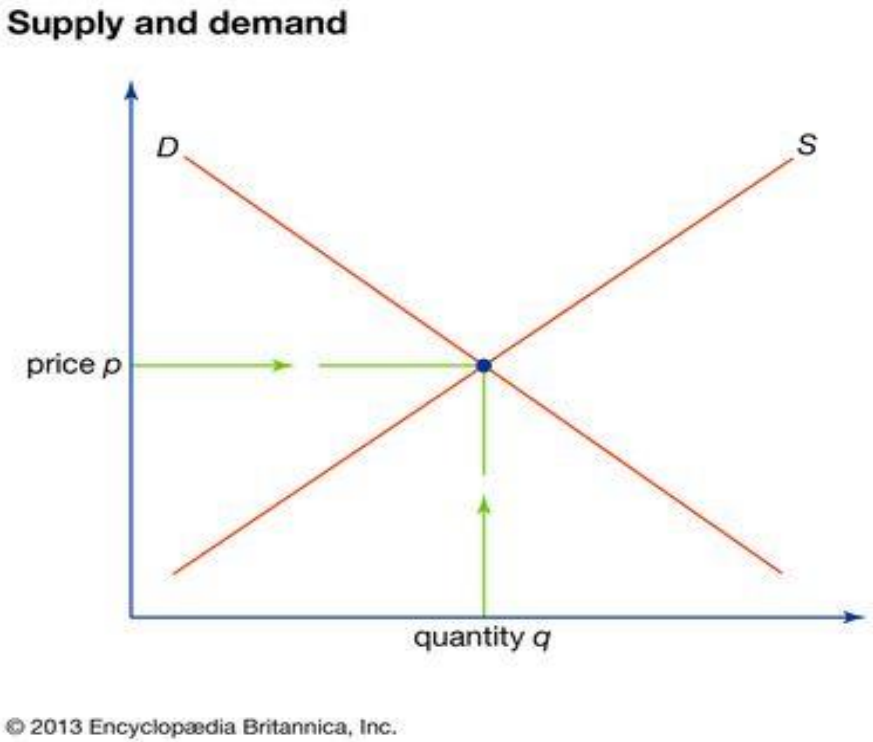
WHY BUILD A MATHEMATICAL MODEL?



- **Simplifies the Complexity** – Real Systems are usually too complex to obtain an exact mathematical representation
- **Tangible Results** – Simplified models still tell us important qualitative or quantitative information
- An example of this is the classic model of supply and demand

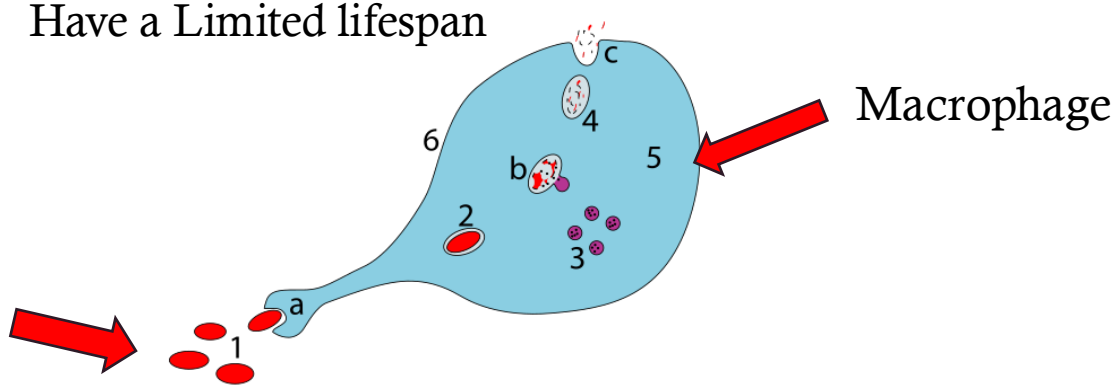
BIOLOGICAL BACKGROUND

Pathogens

- A pathogen is any microbe that invades and then multiplies within a host body, causing illness
- Most pathogens also work to bypass a host body's defenses
- Pathogens multiply by using the resources found in the host body

Generalist Macrophages

- One of the body's primary responses to an infectious disease
- Destroy pathogens by engulfing them which destroys the pathogens
- Continuously originate from hematopoietic stem cells in the bone marrow
- Have a Limited lifespan



FORMING A FIRST MODEL

Building a mathematical model for modeling how pathogens and macrophages interact

FORMING A FIRST MODEL

OUTLINING THE MODEL

- Mechanistic models are based on physical laws that prescribe the rate of change of the state variable in terms of the value of the variable. This differs from empirical models, which try to fit equations to data.
- For this model, we will use a system of autonomous differential equations in which our initial system will contain two equations:
  - $\frac{dP}{dT} = f_1(P, G)$ This equation will represent the rate of change of the pathogen population with respect to time
  - $\frac{dG}{dT} = f_2(P, G)$This equation will represent the rate of change of the macrophage population with respect to time

FORMING A FIRST MODEL:
ASSUMPTIONS

- **Pathogen Growth is Logistic:** Pathogens have a maximum carrying capacity, and as the pathogen population approaches its carrying capacity, the growth of the pathogen population slows down.
- **Macrophages Growth is Constant:** The rate at which macrophages grow is constant
- **One-to-One Killing:** Every time a macrophage hunts and destroys a pathogen, the macrophage itself also gets destroyed

FORMING A MODEL: BUILDING EQUATIONS

$$\frac{dP}{dT} = \alpha P\left(1 - \frac{P}{\beta}\right) - \mu GP$$

- α - the growth rate of pathogens
- β- the carrying capacity of the pathogens
- μ – represents the rate in which macrophages hunt and destroy pathogens

$$\frac{dG}{dT} = \delta - \sigma G - \mu GP$$

- δ – delta represents the constant growth of the macrophage population
- σ- sigma represents the natural death rate of the macrophages
- μ – represents the rate at which macrophages hunt and destroy pathogens

SCALING A MODEL

Reducing the complexity

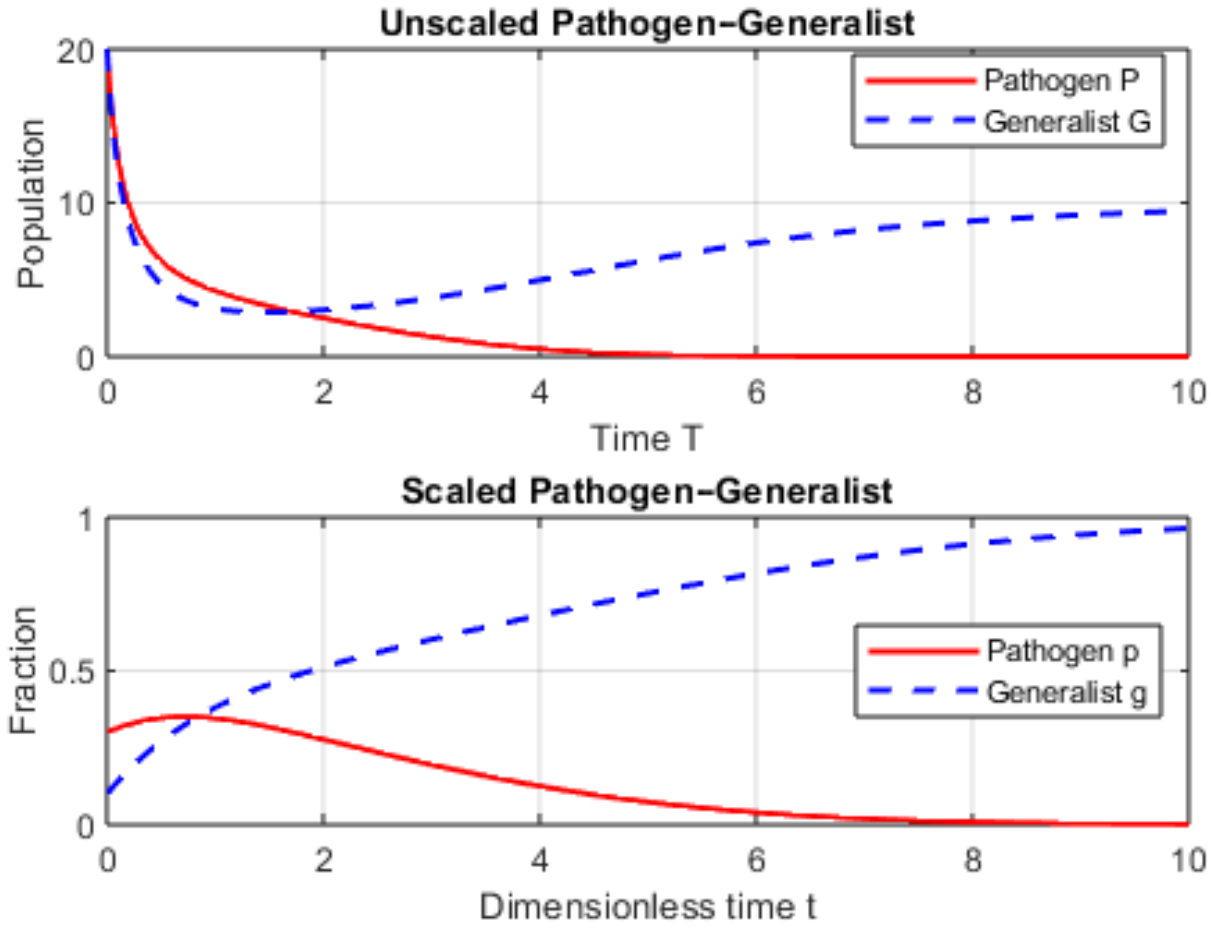
FORMING A MODEL:

ONE MORE STEP

Using the exact number of macrophages and pathogens when trying to model a system has its downfalls

- **Intuitive Meaning** – 7,000 pathogens means nothing until you know the max; 70 % of capacity is more understandable.
- **Parameters** – Our scaled model has dimensionless parameters that can be interpreted as ratios of process strengths rather than scale-dependent constants
- **Units** – The Model explains the process regardless of the unit choice

We can fix this scaling in our model through the use of clever variable substitutions



SCALING A MODEL:

SETTING UP THE EQUATIONS

$$\frac{dP}{dT} = \alpha P(1 - \frac{P}{\beta}) - \mu PG$$

$$\frac{dG}{dT} = \delta - \sigma G - \mu PG$$

We can scale a model by three useful substitutions

- $g = \frac{G}{\frac{\delta}{\sigma}}$
- $p = \frac{P}{\beta}$
- $t = \alpha T$

$$\frac{dp}{dt} = p(1 - p - \frac{\mu\delta}{\alpha\sigma})$$

$$\frac{dg}{dt} = \frac{\sigma}{\alpha}\left(1 - g - \frac{\mu\beta}{\sigma}\right)$$

The new system has parameters as combinations of the old system parameters

$$\boxed{\frac{dp}{dt} = p\,(1 - p - r\,g)}$$

$$\boxed{\frac{dg}{dt} = b(1 - g - m\,g\,p).}$$

Defining the new Parameters:

- $b = \frac{\sigma}{\alpha}$
- $m = \frac{\mu\,\delta}{\sigma}$,
- $r = \frac{\mu\delta}{\alpha\sigma}$

SCALING A MODEL

SCALED PARAMETERS MEANING

- $b = \frac{\sigma}{\alpha}$, relative strength of macrophage death vs. pathogen growth
- $m = \frac{\mu\,\delta}{\sigma}$, macrophage killing strength normalized by its death rate.
- $r = \frac{\mu\delta}{\alpha\sigma}$, macrophage killing rate scaled to pathogen production.

$$\frac{dp}{dt} = p\,(1 - p - r\,g)$$

$$\frac{dg}{dt} = b(1 - g - m\,g\,p).$$

ANALYSIS

With the model scaled now it is time to analysis the model

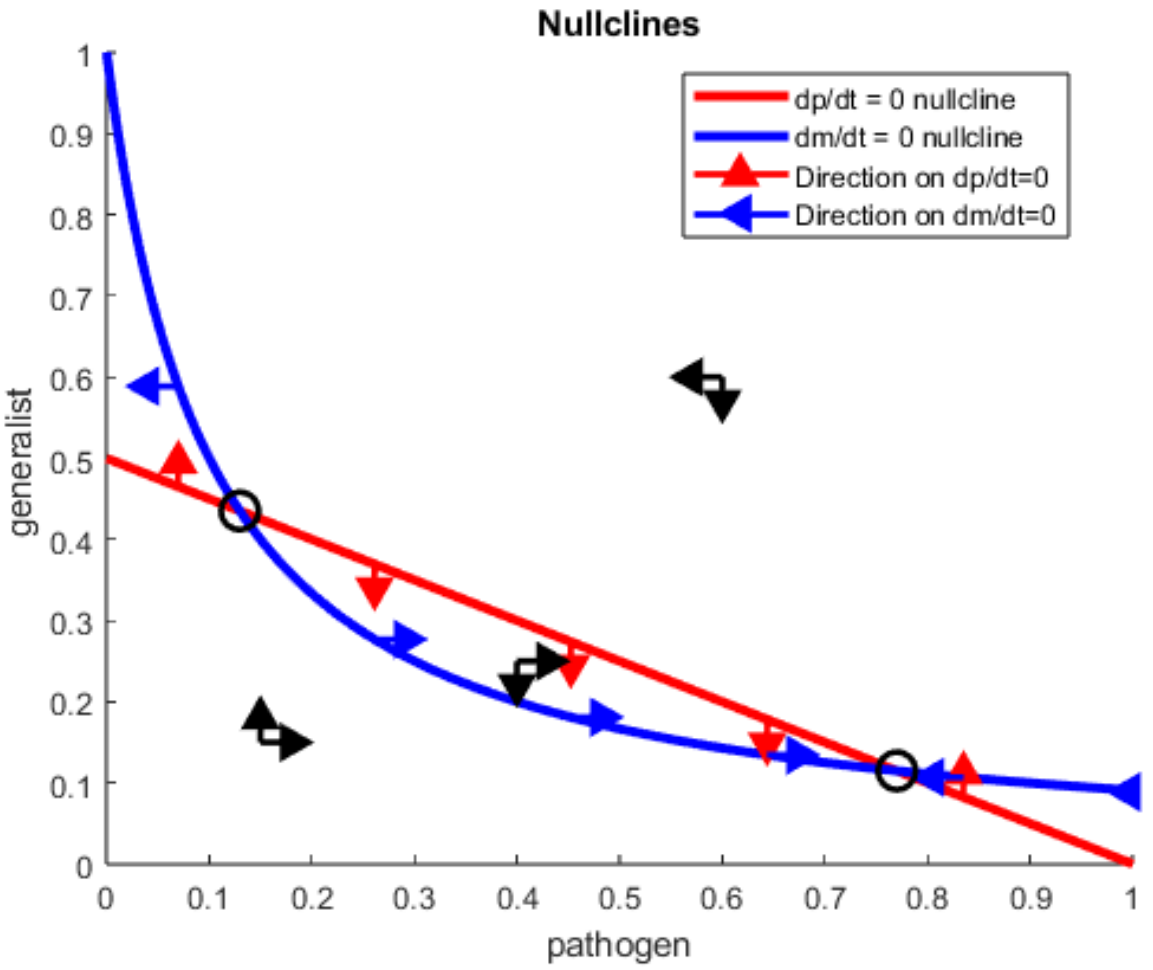
ANALYSIS:

NULLCLINES ANALYSIS

Since explicitly solving the system of differential equations isn't possible, we can try to draw a phase plane of the Pathogen-Macrophage Plane by:

1. Graphing the lines of where each equation equals zero
2. Figuring out whether each derivative is positive or negative in each section made by the nullclines

By doing this, we can see the equilibrium and how points move around the system



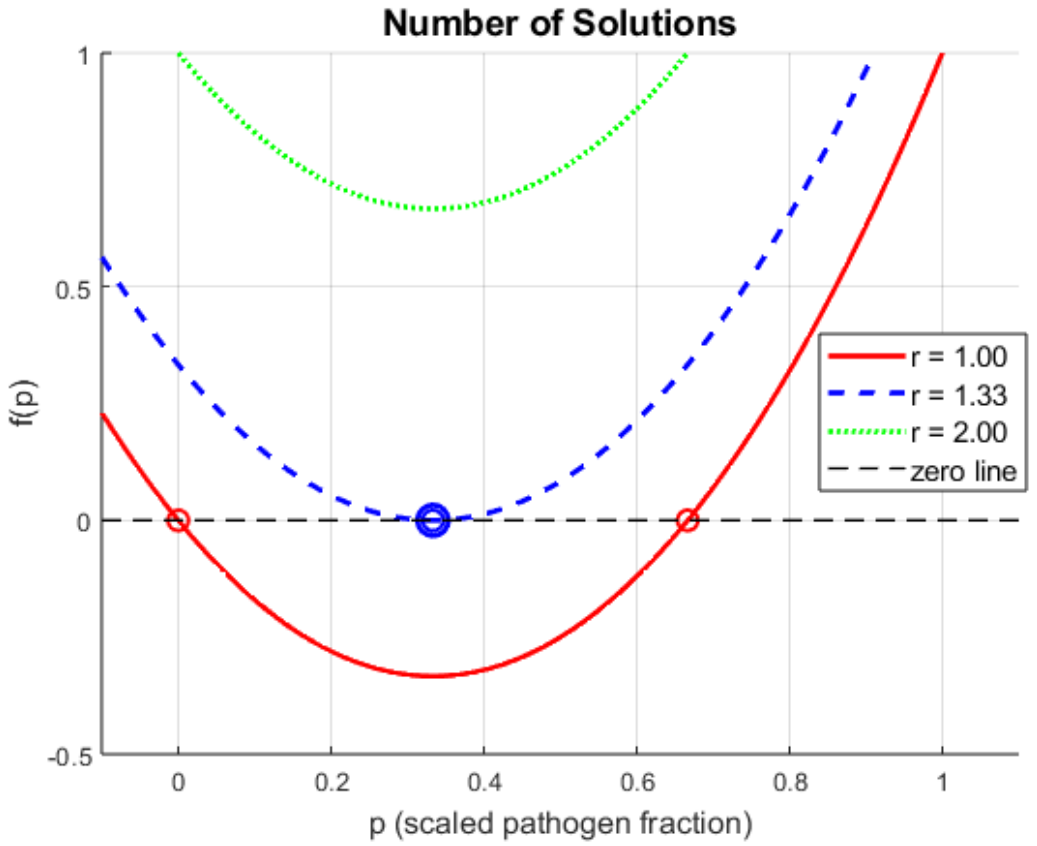
ANALYSIS:

FINDING EQUILIBRIA

To analytically find how many equilibrium points there are, we can use the following method:

- Set the two nullclines equal each other
- Build a quadratic equation and then solve the quadratic for its roots
- Check when the vertex is negative, and when the two endpoints f(0) and f(1) are both greater than or equal to zero

$$mp^2 - (m-1)\,p + (r-1) = 0,$$

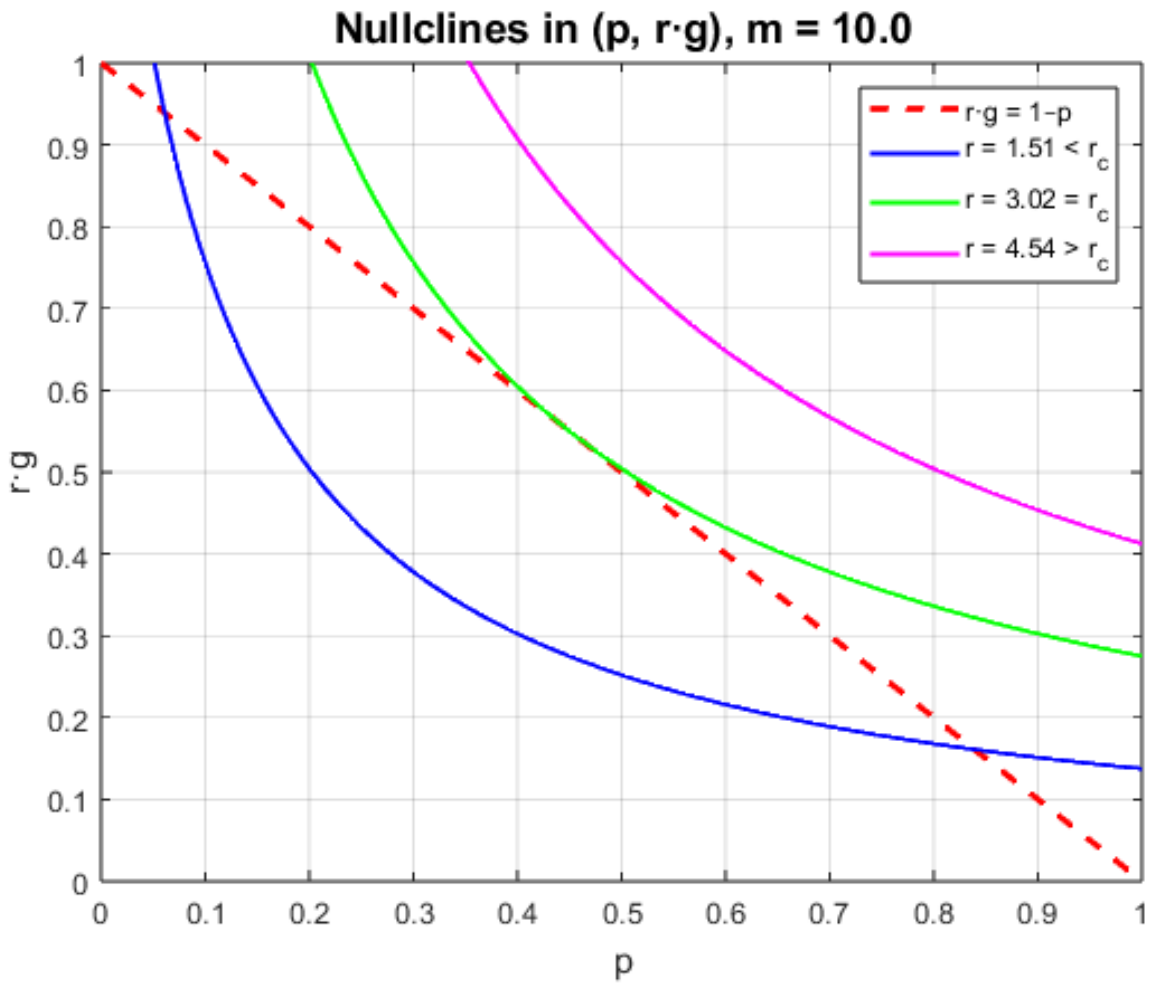


$$\#\{\text{equilibria}\} = \begin{cases} 2, & r > 1 \text{ and } r < \dfrac{(m+1)^2}{4m}, \\ 1, & r = 1 \text{ or } r = \dfrac{(m+1)^2}{4m}, \\ 0, & r < 1 \text{ or } r > \dfrac{(m+1)^2}{4m}. \end{cases}$$

ANALYSIS VERIFICATION

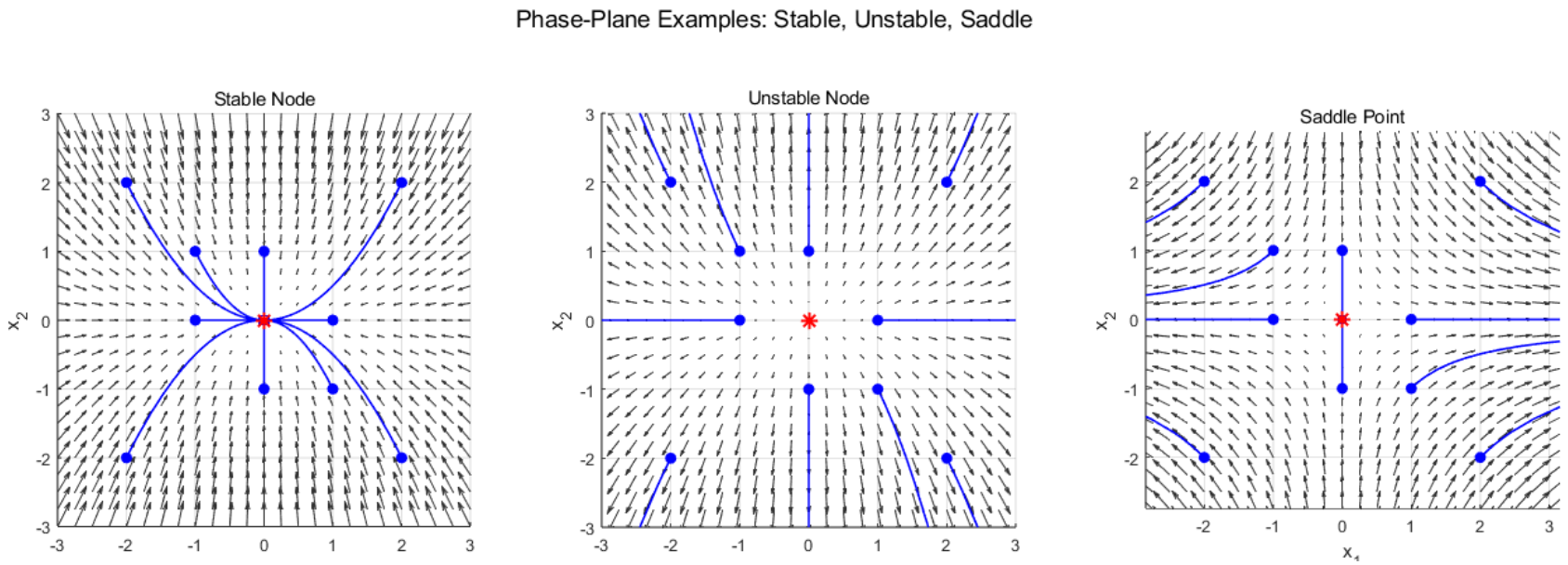
Plotting different m values for a set of values we can see the three different cases:

- Two Solutions: For a given m, if r is too small, there will be two solutions
- One Solution: Not likely in the real world, as there would have to be an exact parameter match
- Zero Solutions: If r is big enough, there will be no epidemic solutions



ANALYSIS

STABILITY



Knowing if the equilibria exist and how many exist is important, but a question that is just as important is the stability at those points.

- Stable – trajectories tend towards and stay at the equilibrium point
- Unstable- trajectories move away from the equilibrium point
- Saddle Point – some trajectories approach along one direction, others diverge along another.

ANALYSIS

JACOBIAN ANALYSIS

- The Jacobian is the matrix of first-order partial derivatives, giving the local linearization of our system
- Evaluating the Jacobian at each equilibrium and examining its eigenvalues allows us to classify the stability of the points
- We can also use other methods alongside the Jacobian to find the stability

$$\frac{dp}{dt} = p\,(1 - p - r\,g),$$

$$\frac{dg}{dt} = b\,(1 - g - m\,p\,g).$$

$$J(p,g) = \begin{pmatrix} \frac{\partial}{\partial p}\Big(p(1-p-rg)\Big) & \frac{\partial}{\partial g}\Big(p(1-p-rg)\Big) \\ \frac{\partial}{\partial p}\Big(b(1-g-mpg)\Big) & \frac{\partial}{\partial g}\Big(b(1-g-mpg)\Big) \end{pmatrix}$$

$$J(p,g) = \begin{pmatrix} (1-p-r\,g) - p & -r\,p \\ -b\,m\,g & -b\,(1+m\,p) \end{pmatrix}.$$

ANALYSIS

DISEASE FREE EQUILIBRIUM

- **Disease Free Point (0,1)** – The line p = 0 is where there are no pathogens and thus is disease-free.
- **Stability** – This point is stable if r > 1
- **Meaning** – this means that for any small infection with pathogen-macrophage values near this point, the infection gets cleared

$$J(0,1) = \begin{pmatrix} 1-r & 0 \\ -bm & -b \end{pmatrix}$$

$$\lambda_1 = 1 - r, \quad \lambda_2 = -b.$$

$$\text{if } r > 1$$

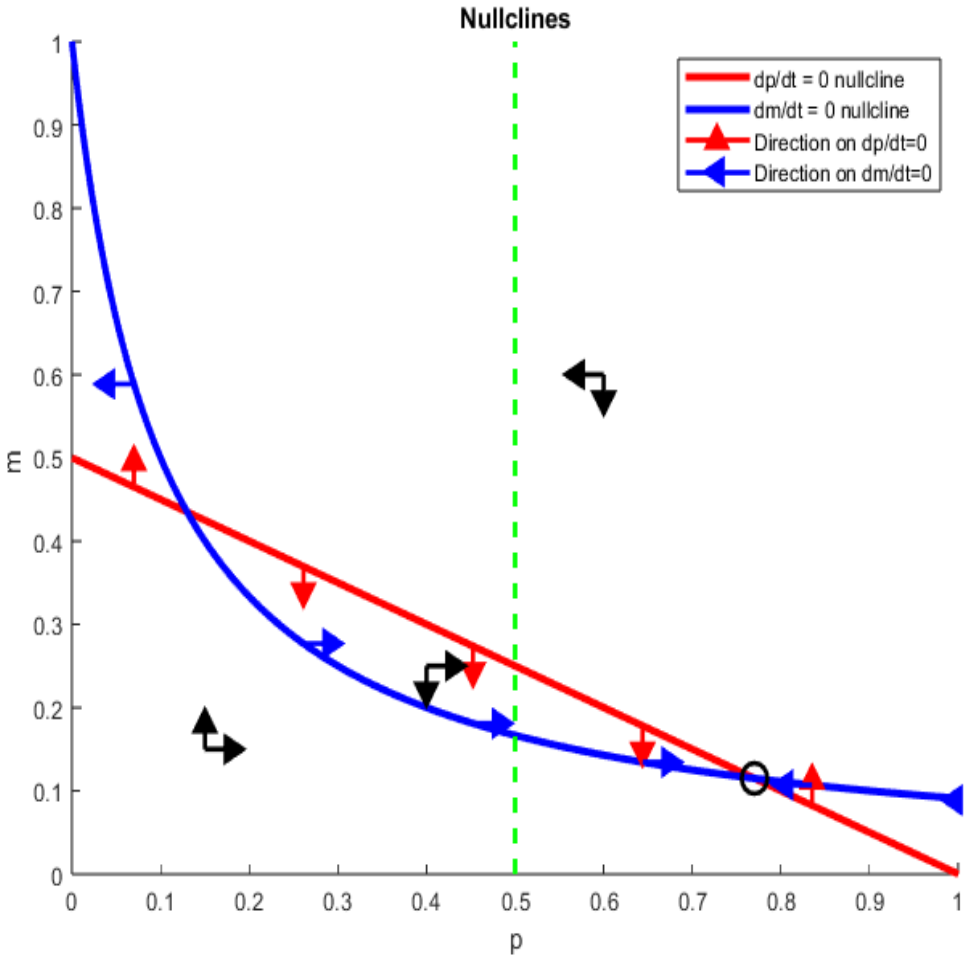
$$\lambda_1, \lambda_2 < 0$$

ANALYSIS

ROUTH–HURWITZ CRITERION: ENDEMIC SOLUTION

- Our equilibria occur when the nullclines cross which is where both $\frac{dp}{dt}$ and $\frac{dg}{dt}$ are equal to zero
- We can use our Jacobian to analyze the stability of these points
- For our system, the points are only stable if the p value for the equilibrium point meets the following criteria

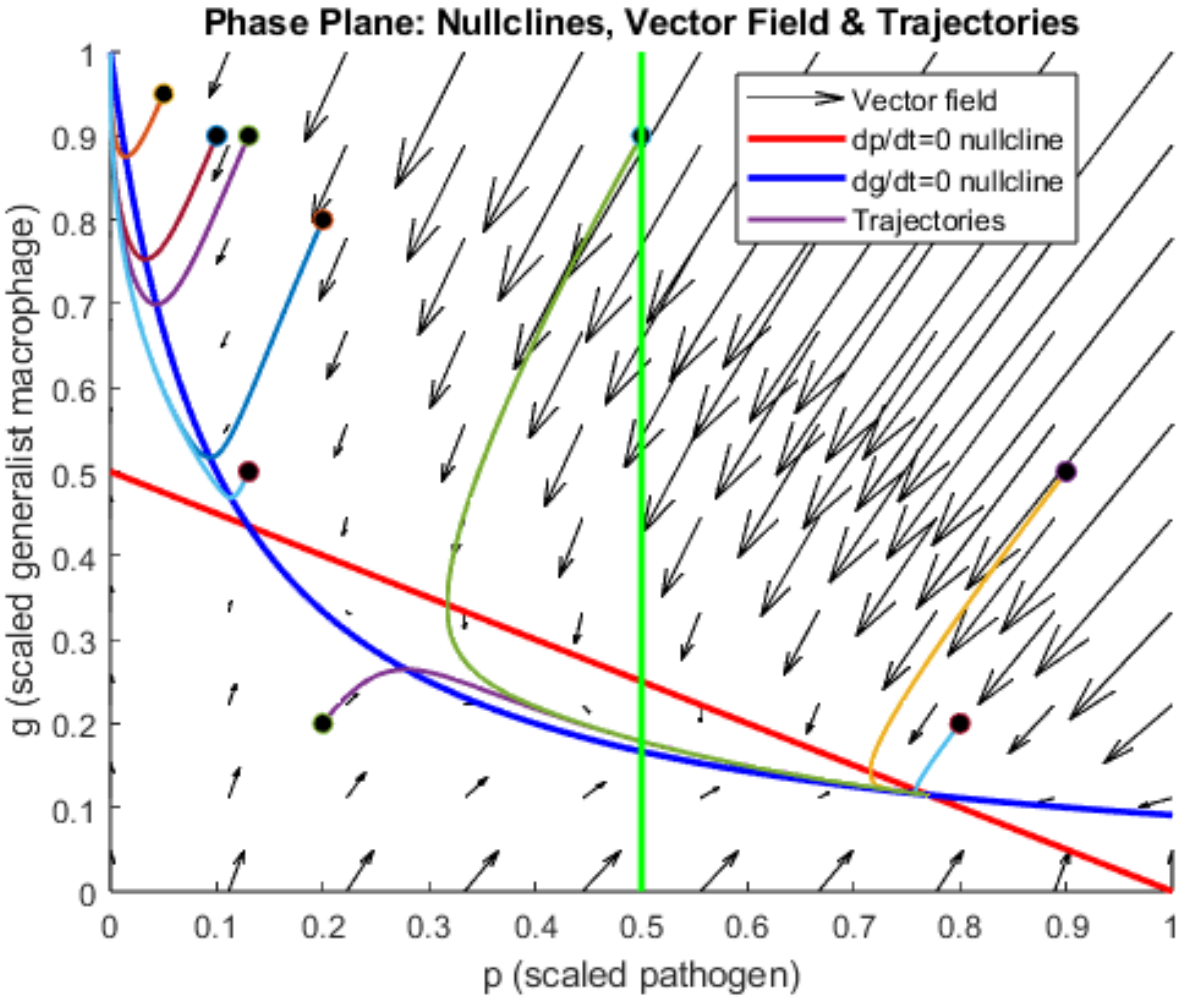
$$p^* > \frac{m-1}{2m}$$



ANALYSIS

VERIFYING MODEL

- Since r is small enough, we have two endemic solutions
- The larger equilibrium point is the stable point
- The smaller one is unstable
- Depending on your starting point, you end up in different places



A BETTER MODEL

A BETTER MODEL

FLAWS OF OUR FIRST MODEL

- **Infections almost always persist -** Our model requires an unrealistically high clearance threshold for r , so pathogens rarely die out. This is not reflective of the real world where people's immune systems usually clear a virus
- **New Assumptions** – We can fix this by making new assumptions or adding new components that better reflect our actual immune systems
- **New Results** – With a new model built with new assumptions, we can analyze it in the same way to hopefully uncover new insights about the immune system

A BETTER MODEL

NEW ASSUMPTIONS

Now that we have decided to make a new model, we must decide what assumptions we want to keep, add, or disregard

List of New Assumptions:

1. **Different Forms of Growth** - Generalists grow at a constant rate, specialists grow in response to the number of pathogens
2. **Limited One-to-one killing -** Every time a generalist hunts and destroys a pathogen, the generalist macrophage itself also gets destroyed, but not for the specialist macrophage
3. **Zero Inter-Macrophage Interaction** – The two different macrophages don't directly interact with each other

A BETTER MODEL

BUILDING THE MODEL

- With our assumptions made, we can now build a new model
- Our first two equations stay the same except for an interaction term between the specialist macrophages and the pathogens
- Our specialist with one term that is the growth rate in response to the number of pathogens, and another with its death rate

Specialist Equation

$$\frac{dS}{dT} = \frac{\phi P}{\eta + P} - \psi S$$

Generalist Equation (unchanged)

$$\frac{dG}{dT} = \delta - \sigma G - \mu G P$$

Pathogen Equation

$$\frac{dP}{dT} = \alpha P\left(1 - \frac{P}{\beta}\right) - \mu G P - \kappa S P$$

ϕ Growth rate of specialist macrophages

η Half-max pathogen level for specialist recruitment

ψ Death rate of specialist macrophages

κ Killing rate of pathogens by specialists

A BETTER MODEL

SCALING

- **Scale the model** – since we have built the new model, we can now scale it
- **Results** – this scaled model is very similar to the original except for two terms
- **Important Parameter** – The more important scaled parameter in this new model is k, which represents how many pathogens a newly recruited group of specialists clears over its lifetime.

Let

$$a = \frac{\psi}{\alpha}, \quad h = \frac{\eta}{\beta}, \quad b = \frac{\sigma}{\alpha}, \quad m = \frac{\mu\beta}{\alpha}, \quad r = \frac{\mu\delta}{\alpha\sigma}, \quad k = \frac{\kappa\phi}{\alpha\psi}$$

Then

$$\boxed{\frac{ds}{dt} = a\left(\frac{p}{h+p} - s\right)}$$

$$\boxed{\frac{dg}{dt} = b\,(1 - g - m\,p\,g)}$$

$$\boxed{\frac{dp}{dt} = p\,(1-p) - r\,p\,g \; - \; k\,p\,s}$$

ANALYSIS: NEW MODEL

A BETTER MODEL

NULLCLINES

- The first step to analyzing this model is to find the nullclines of this system of equations.
- An equilibria point occurs in this system when all three nullclines are equal to zero
- We can use the fact that nullclines are all equal to 0 to manipulate these equations

$$\frac{dg}{dt} = b(1 - g - mgp)$$

$$\frac{ds}{dt} = a\left(\frac{p}{h+p} - s\right)$$

$$\frac{dp}{dt} = p(1-p) \; - \; r\,g\,p \; - \; k\,s\,p$$

$$\boxed{1 - g - mgp = 0 \implies g = \frac{1}{1+mp}}$$

$$\boxed{s = \frac{p}{h+p}}$$

$$\boxed{1 - p - rg - ks = 0}$$

ANALYSIS: NEW MODEL

WORKING WITH THREE EQUATIONS

- We can use the first two equations to eliminate *s* and *g* from the third equation
- This gives us a cubic equation in terms of the pathogen population
- Where this cubic equation's zeros lie are the p values where there are equilibria
- However, explicitly finding understandable and meaningful formulas for a cubic equation is difficult

Starting from the equilibrium substitutions

$$s^* = \frac{p^*}{h + p^*}, \qquad g^* = \frac{1}{1 + m\,p^*},$$

$$p^*(1 - p^*) - r\,p^* \frac{1}{1 + m\,p^*} - k\,p^* \frac{p^*}{h + p^*} = 0.$$

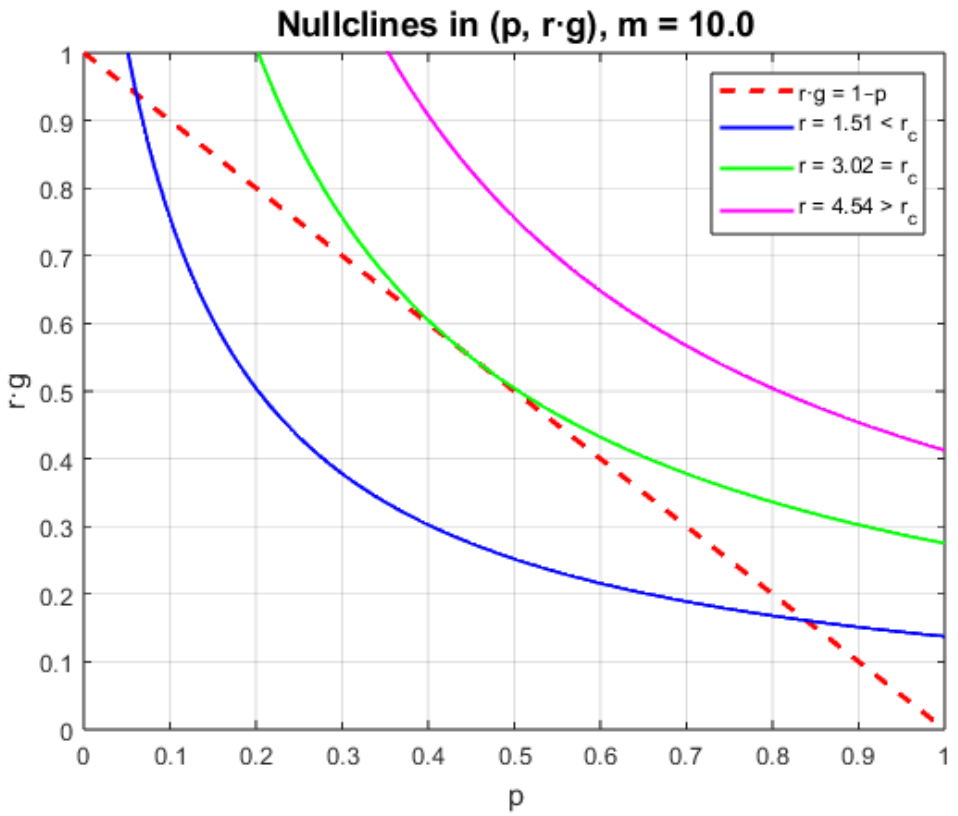
Multiply through by $(1 + m\,p^*)(h + p^*)$:

$$\boxed{-m\,p^3 + (m - 1 - hm - km)\,p^2 + (1 - h + hm - r - k)\,p + h(1 - r) = 0.}$$

ANALYSIS:

NEW MODEL WORKING WITH THREE EQUATIONS

- Even though directly solving the cubic for p is impractical, we exploit the system's nullcline structure to simplify the analysis.
- Using each nullcline, we derive two equivalent expressions for the expression rg
- When there is exactly one equilibrium, those nullclines intersect at a point tangential to each other
- This means that their derivatives are equal



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ANALYSIS: NEW MODEL

THE RESULTS

Since we have added a third equation, we can't solve for r(m) so that there is one equilibrium point

But when setting the generalist and pathogen nullclines equal, and enforcing a double root, we can find r(m,p) and m(p) such that there is one solution

$$m(p) = \frac{1 + \frac{k\,h}{(h+p)^2}}{1 - 2p - \frac{k\,p}{h+p} - \frac{k\,h\,p}{(h+p)^2}}$$

$$r(m,p) = (1 - p - \frac{kp}{h+p})(1 + mp)$$

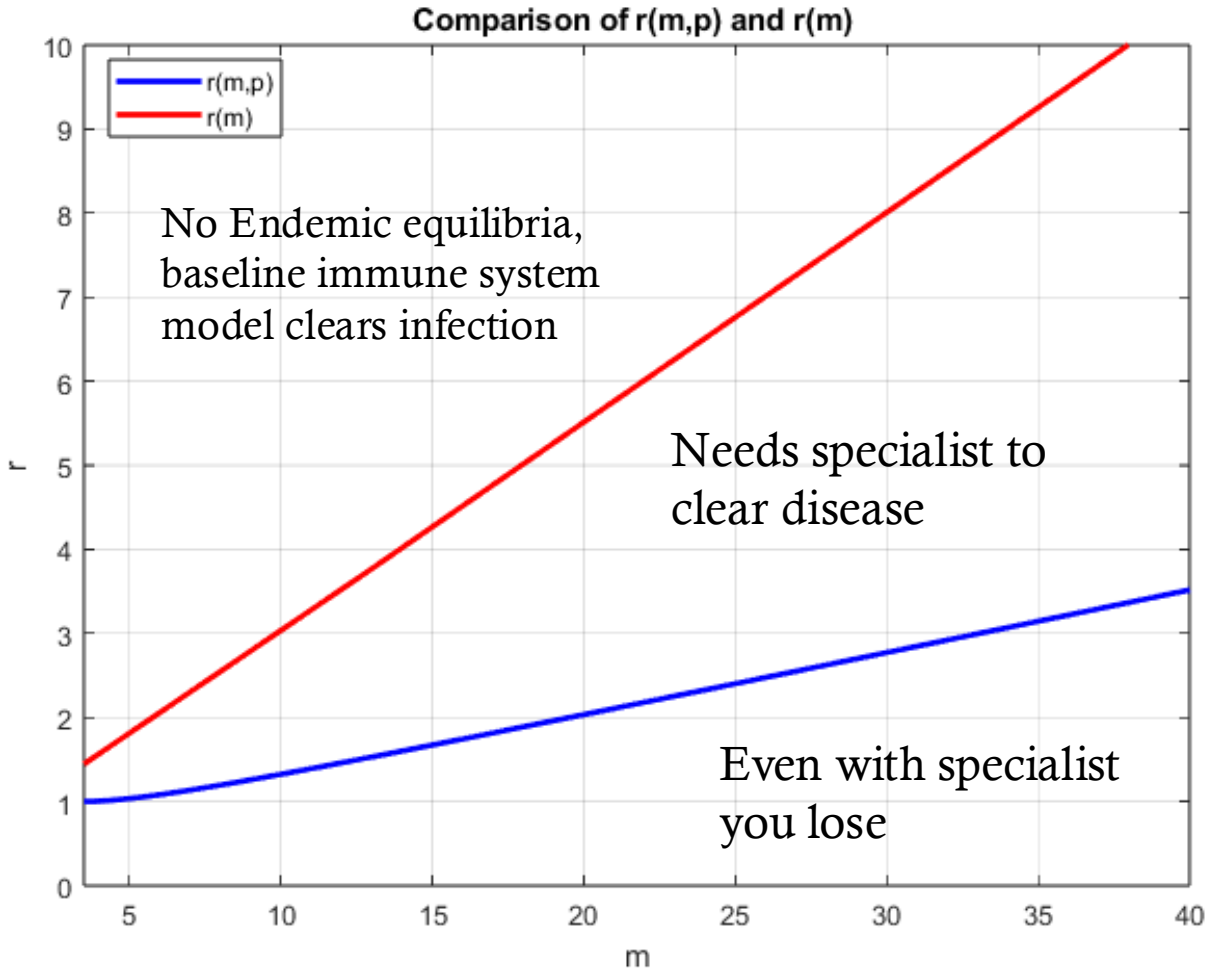
ANALYSIS: NEW MODEL

RESULTS

From this plot, we can see that when introducing a specialist, the needed value of r is greatly decreased.

This graph shows us the three distinct regions:

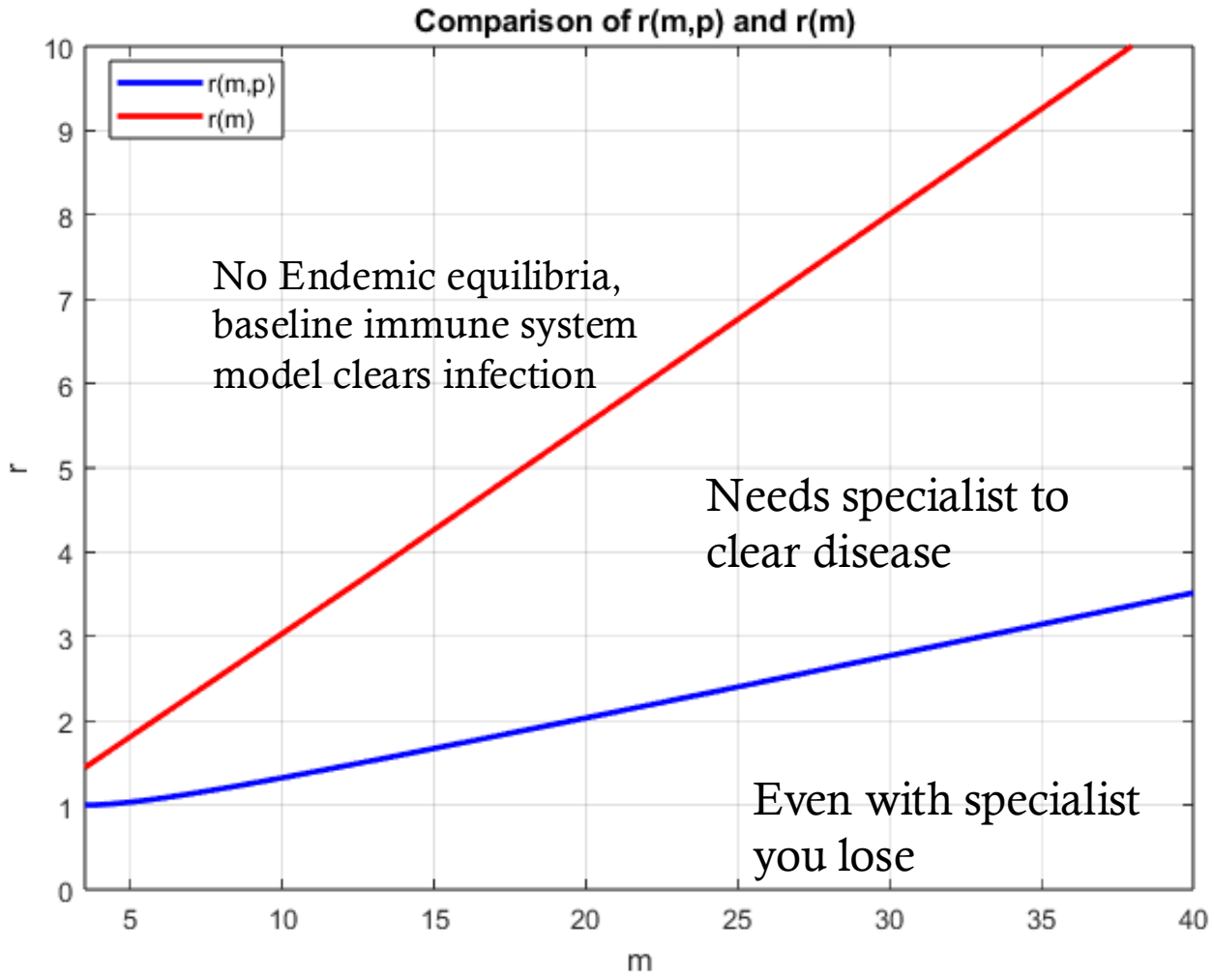
1. Both models clear disease
2. Need the specialist to clear the disease
3. Do not need the specialist



CONCLUSIONS

INTERPRETING THE RESULTS

- **Response Lowers the Bar for Clearance** – The response mechanism of the specialist lowers the need for an initial string generalist macrophage
- **Adaptive response** – This adaptive response mirrors the real-world immune system as it gets better at fighting pathogens as it destroys more of them
- **Take Away** – Our immune system is able to clear so many diseases not because of an initially strong macrophage attack, but because of a strong immune system response



CREDITS

Thank you to

- Glenn Ledder
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- Sophia Thompson

THE END

Questions?