Analyzing the Dynamics of an Inflammatory Response to a Bacterial Infection in Rats

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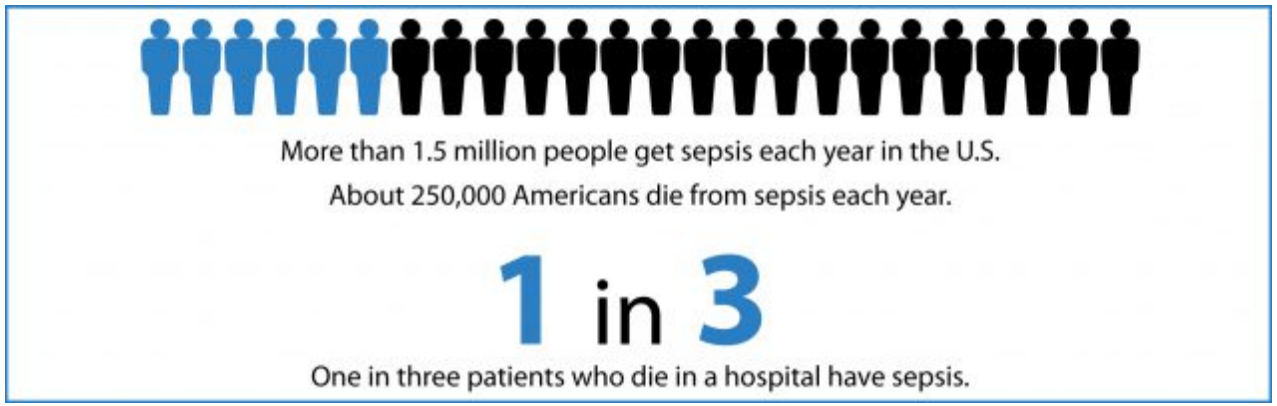
Sepsis



- Sepsis is a life threatening condition that results from an overwhelming inflammatory response to a bacterial infection

Inflammation

- Inflammation is the body's response to an infection
- Too much inflammation can cause damage to healthy tissue
- Bacterial infections that often cause sepsis:
  - *Staphylococcus aureus* (*staph*)
  - *Escherichia coli* (E. coli)
  - some types of *Streptococcus*

Virulence

- The strength of the pathogen
  - Low virulent strains - large quantity in blood does not cause significant damage
  - High virulent strains - small quantity will cause significant damage
- We interpret virulence as a pathogen's ability to cause more inflammation
- Bacteria are constantly mutating, so the virulence may vary over time

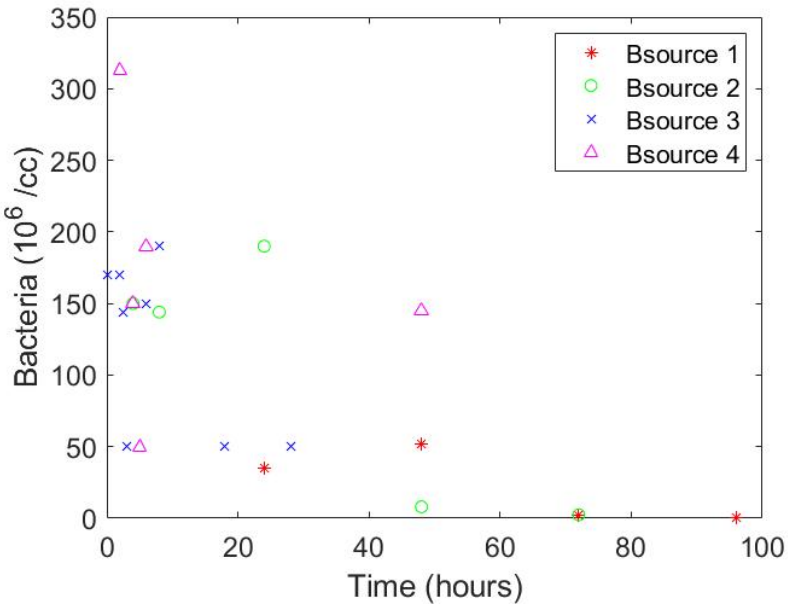
Experimental Observations

- Rats were injected with a fibrin clot containing four different levels of bacteria (E. coli)
  - For very high levels of bacteria, the clot was saturated and the bacteria was released immediately
- The bacteria levels in the blood were measured over time
- Once the bacteria levels in the blood reached a certain level, the rats were unable to recover
- Used the data to parameterize sepsis model and predict health or disease outcome

Data Set: Time Dynamics

Dose administered to rats:

Bsource	Amount ($x10^6$/cc)
1	128
2	248
3	505
4	1940



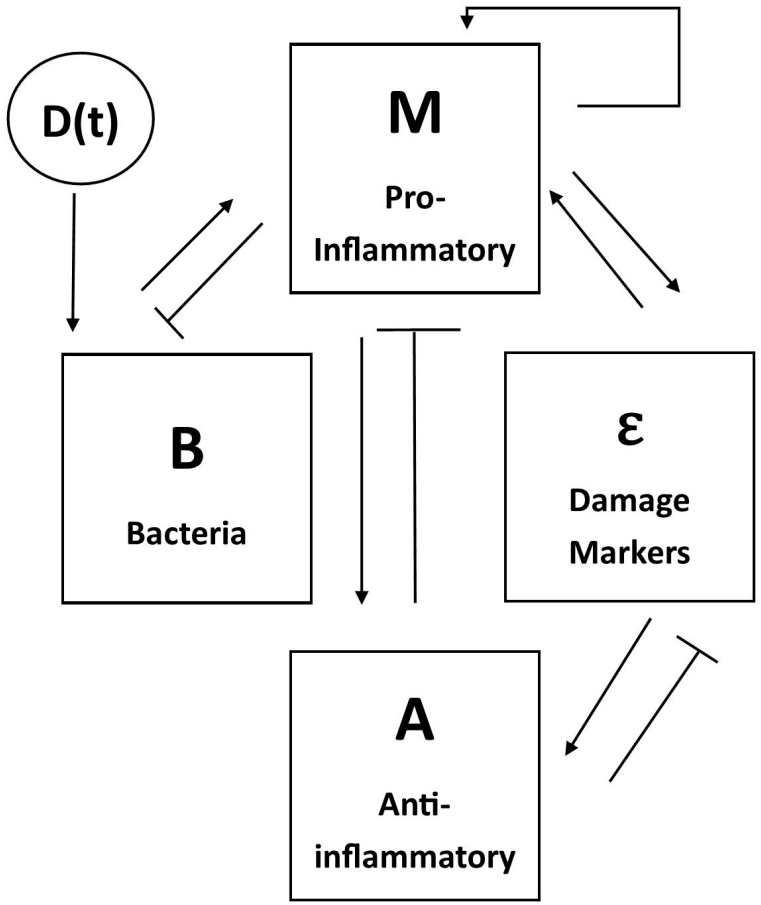
Expected Outcomes

- **Septic death:** bacteria remains in the blood
- **Aseptic death:** bacteria is eliminated but damage remains elevated
- **Health:** both bacteria and damage are eliminated

Objective

Our goal is to use a mathematical model to predict the survivability range in rats for an infection while varying the initial dose, growth rate, or virulence of the bacteria

Model Schematic



Model

Bacteria:

$$\frac{dB}{dt} = D(t) + k_1 B(1 \quad \frac{B}{B_1}) \quad \frac{k_2 s_I B}{_I + k_3 B} \quad \frac{k_5 BM}{1 + k_A A} \tag{1}$$

Pro-inflammatory Response:

$$\frac{dM}{dt} = \frac{_1(k_M M + k_B c_1 B + k \ )}{(\ _2 + k_M M + k_B c_1 B + k \ )(1 + k_A A)} \quad _M M \tag{2}$$

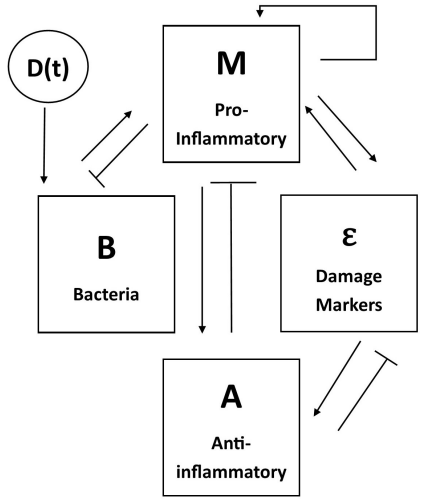
Anti-inflammatory Response:

$$\frac{dA}{dt} = s_A + \frac{a_1(M + k_4 \ )}{(1 + M + k_4 \ )(1 + k_A A)} \quad _A A \tag{3}$$

Damage Markers:

$$\frac{d}{dt} = — + \frac{[f M \quad T]_+}{1 + k_A A} \tag{4}$$

Model: Bacteria

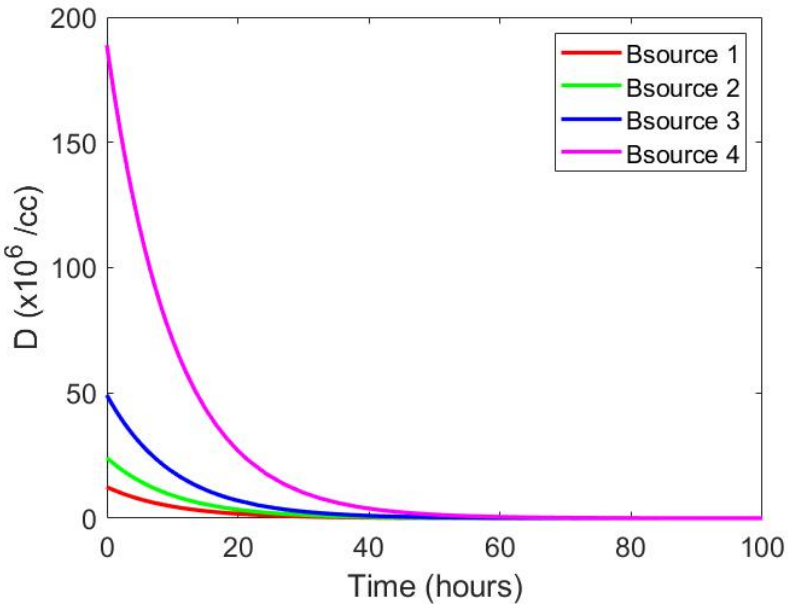


$$\frac{dB}{dt} = \underbrace{D(t)}_{\text{Dosing function}} + \underbrace{k_1 B\left(1 - \frac{B}{B_1}\right)}_{\text{growth}} - \underbrace{\frac{k_2 s_l B}{l + k_3 B}}_{\text{local immunity}} - \underbrace{\frac{k_5 BM}{1 + k_A A}}_{\text{immune response}}$$

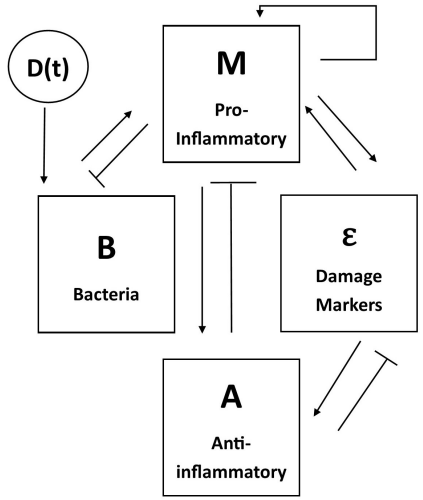
Dosing Function

$$D(t) = k_D B_{source} e^{k_D t}$$

- The dosing function simulates how bacteria is released from the fibrin clot
- No initial bacteria in the blood, $B(0) = 0$
- Constant rate of decay, k_D

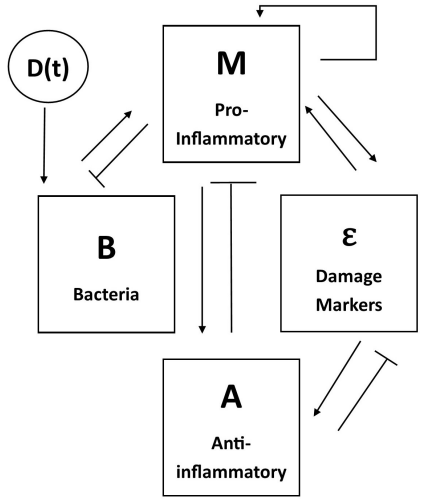


Model: Bacteria



$$\frac{dB}{dt} = \underbrace{D(t)}_{\text{Dosing function}} + \underbrace{k_1 B\left(1 - \frac{B}{B_1}\right)}_{\text{growth}} - \underbrace{\frac{k_2 s_l B}{l + k_3 B}}_{\text{local immunity}} - \underbrace{\frac{k_5 B M}{1 + k_A A}}_{\text{immune response}}$$

Model: Pro-inflammatory Response

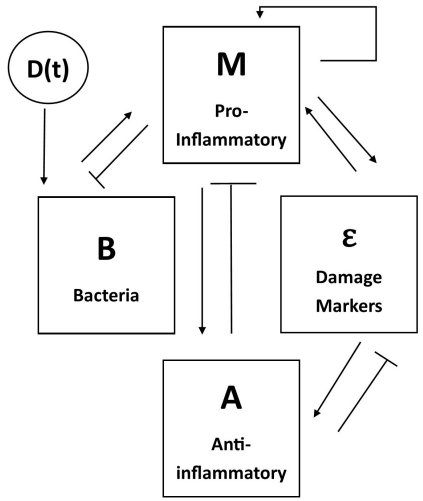


$$\frac{dM}{dt} = \frac{{}_1(k_M M + k_B c_1 B + k \quad)}{\{ \quad {}_2 + k_M M + k_B c_1 B + k \quad)(1 + k_A A)\}} \quad |\{M M\}$$

inflammation activation

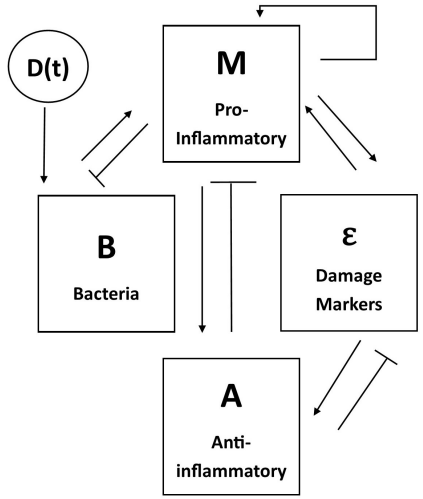
natural decay

Model: Anti-inflammatory Response



$$\frac{dA}{dt} = \underbrace{s_A}_{\text{source term}} + \underbrace{\frac{a_1(M + k_4)}{(1 + M + k_4)(1 + k_A A)}}_{\text{anti-inflammation activation}} \quad \underbrace{-k_A A}_{\text{natural decay}}$$

Model: Damage



$$\frac{d}{dt} = \underbrace{\quad}_{\text{repair}} + \underbrace{\frac{[f\,M \quad T]_+}{1 + k_A A}}_{\text{damage from pro-inflammatory response}}$$

Model Parameters

	Description	Value/ unit	Reference
k_1	pathogen growth rate		varied
B_∞	maximum carrying capacity	$145x10^6$=*cc*	optimized
k_2	rate at which the non-specific local response eliminates pathogen	.6/l-units/h	Reynolds (2006)
s_I	source of non-specific local response	.005/l-units/h	Reynolds (2006)
$_I$	decay of non-specific local response	.002/h	Reynolds (2006)
k_3	rate at which the non-specific local response is exhausted by pathogen	.01 B-units	Reynolds (2006)
k_5	rate at which activated inflammatory response consumes pathogen	1.6/ M-units /h	optimized
k_A	inhibition rate of the anti-inflammatory response	2.6/ A-units	optimized
$_1$	source of pro-inflammatory response	.08 M-units/h	Reynolds (2006)
$_2$	decay of pro-inflammatory response	.12/h	Reynolds(2006)
k_M	activation of resting inflammatory response by activated inflammatory response	.01/M-units/h	Reynolds (2006)

Model Parameters Cont.

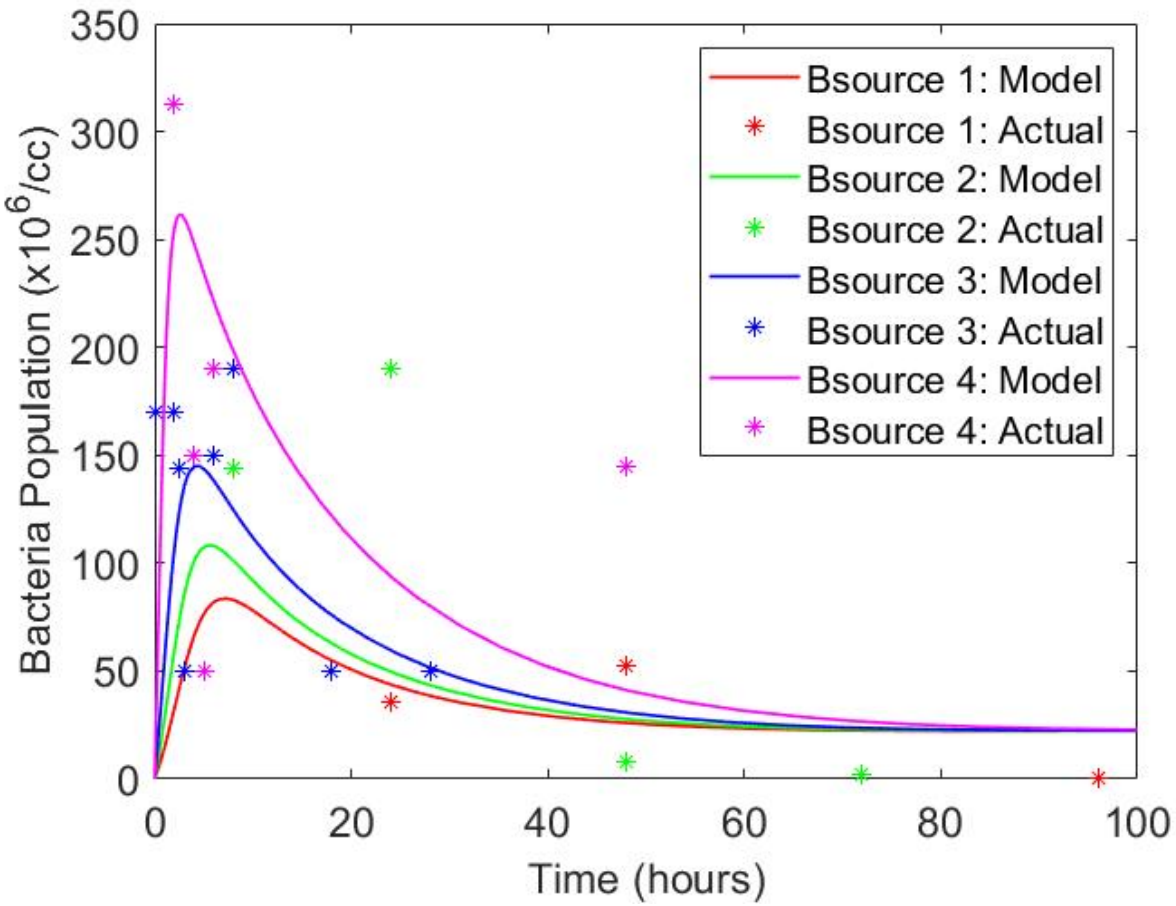
	Description	Value/unit	Reference
k_B	activation of resting inflammatory response by pathogen	.1 /B-units/h	Reynolds (2006)
c_1	virulence of pathogen		varied
k_ϵ	activation of resting inflammatory response by damage	.02/ -units h	Reynolds (2006)
M	decay of pro-inflammatory response	.12/h	Reynolds (2006)
s_A	source of anti-inflammatory response	.0125 A-units/h	Reynolds (2006)
a_1	maximum production rate of anti-inflammatory response	.04 A-units/h	Reynolds (2006)
k_4	relative effectiveness of pro-inflammatory response and damage inducing the production of the anti-inflammatory response	48 M-units/ -units	Reynolds (2006)
A	decay of the anti-inflammatory response	.1/h	Reynolds (2006)
	rate of recovery from damage		estimated
f	maximum rate of damage produced by the pro-inflammatory response	15 /M-units h	optimized
T	threshold for damage		estimated

Parameter Estimation

- Using least squares optimization, the following parameters are fit to the data set
  - k_A
  - k_5
  - f
  - B_∞
  - k_D

$$min[\frac{\sum_{B_{source};1}^{B_{source};4}(B_{actual} - B_{model})^2}{\sum_{B_{source};1}^{B_{source};4} B_{actual}^2}]$$

Fitting the Model to the Data



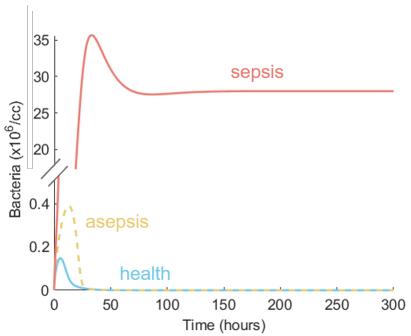
Steady States

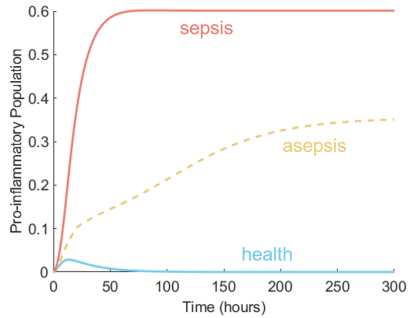
$$(B\ ,M\ ,A\ ,\ \ )$$

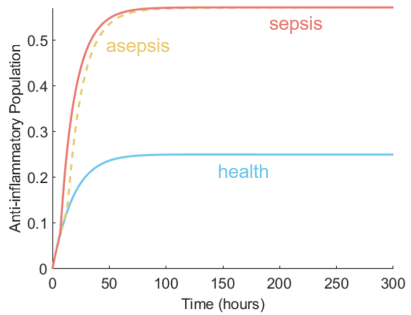
- Health: $(0,0,A_1,0)$
- Aseptic Death: $(0,M_2,A_2,\ _2)$
- Septic Death: $(B_3,M_3,A_3,\ _3)$

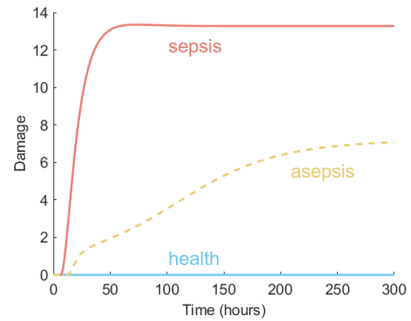
Time Dynamics

- Sepsis: $B_{source} = 2$
- Asepsis: $B_{source} = 1{:}3$
- Health: $B_{source} = 1$
- $k_1 = :5$

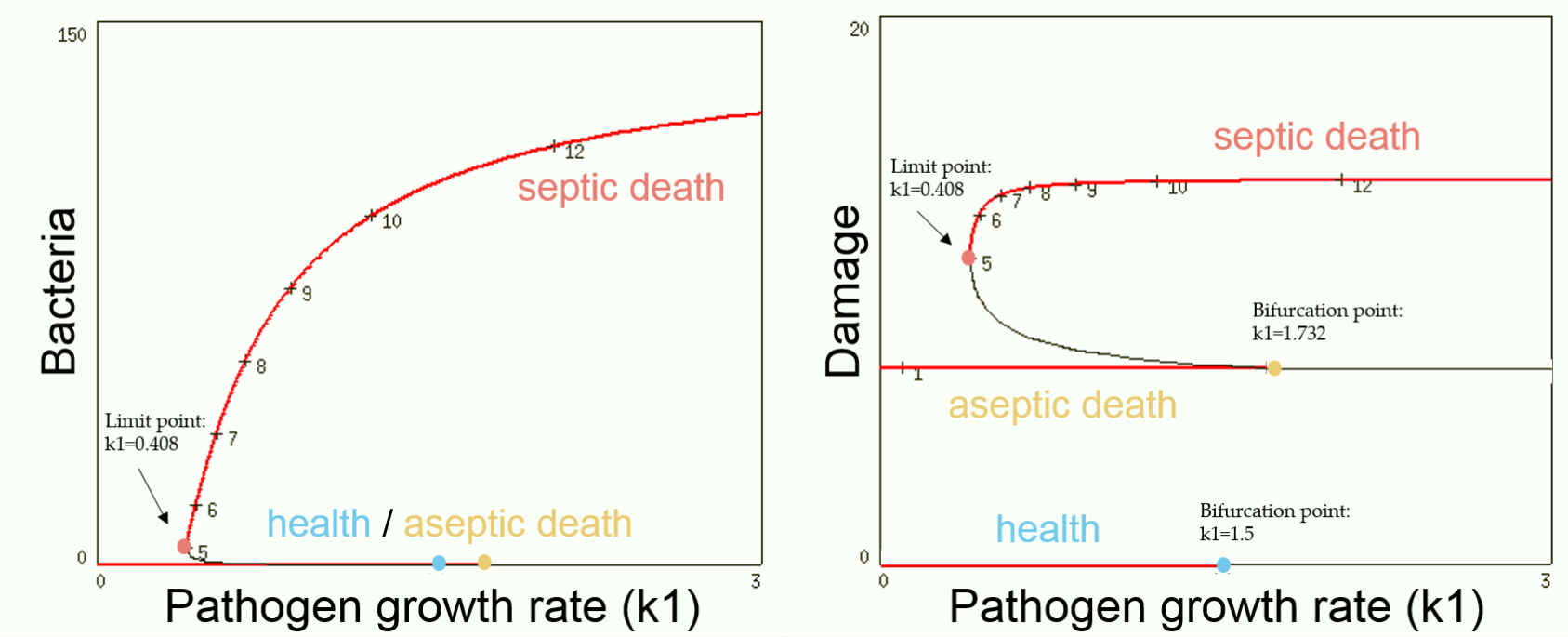




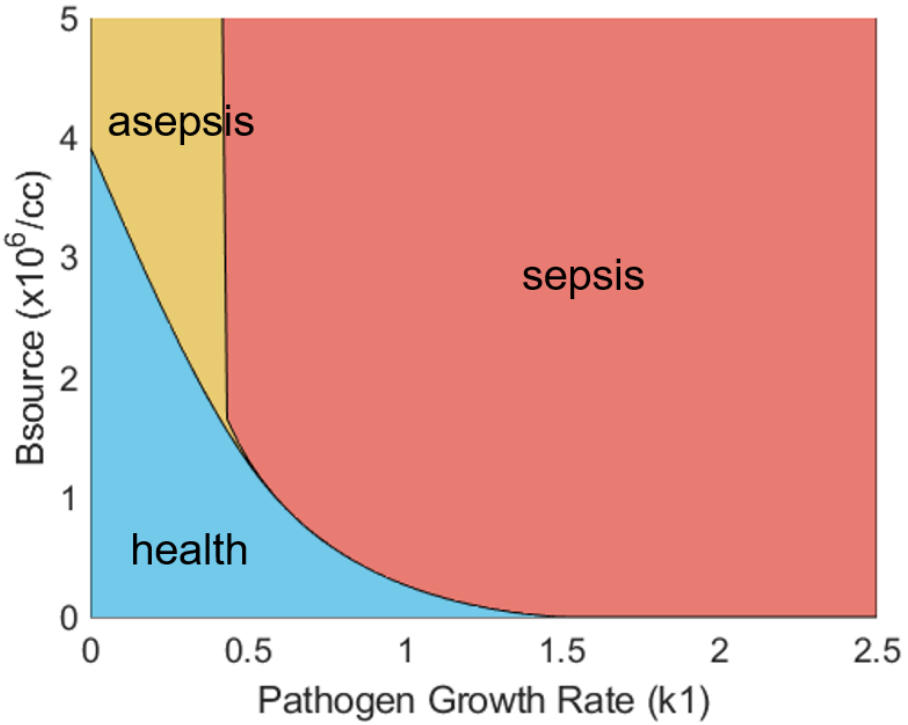




Bifurcations

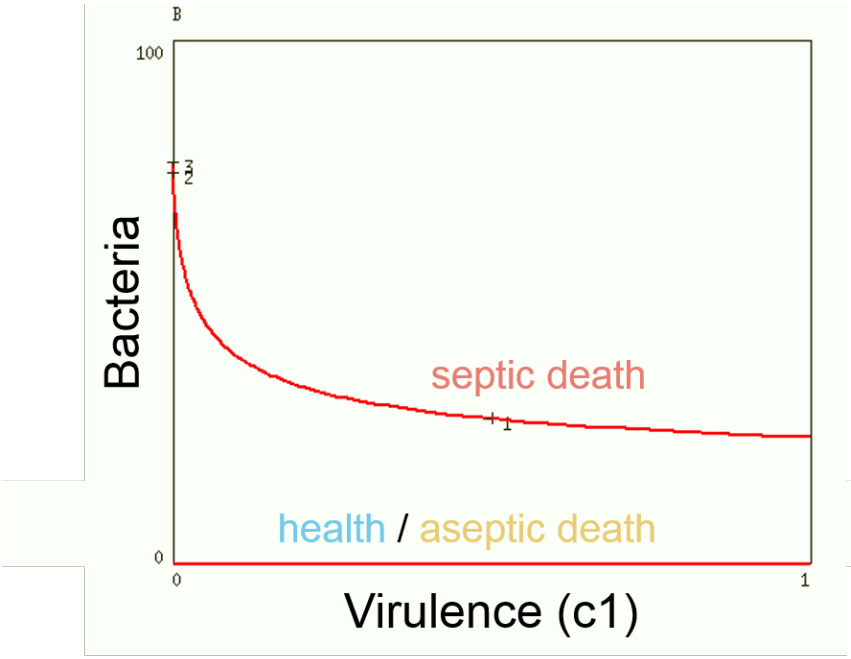


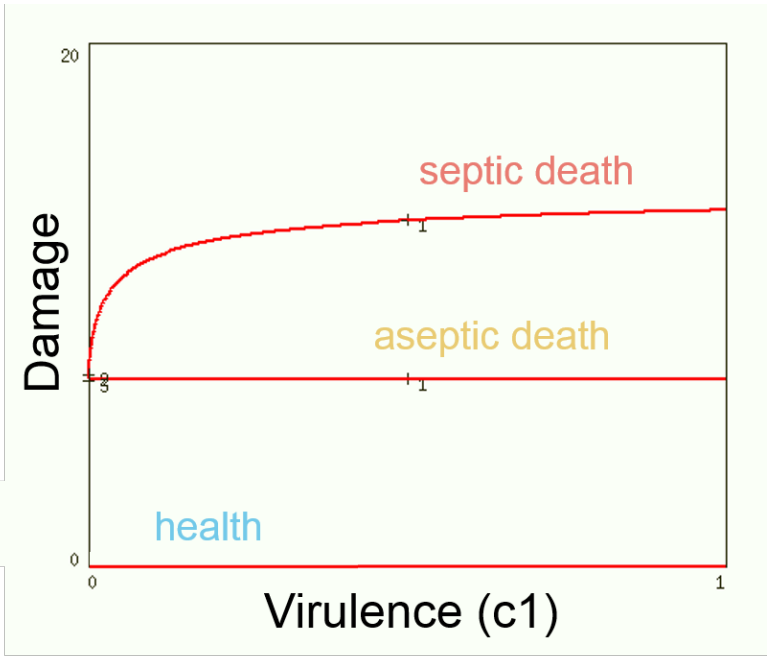
B_{source} vs. Pathogen Growth Rate



Bifurcations - Virulence

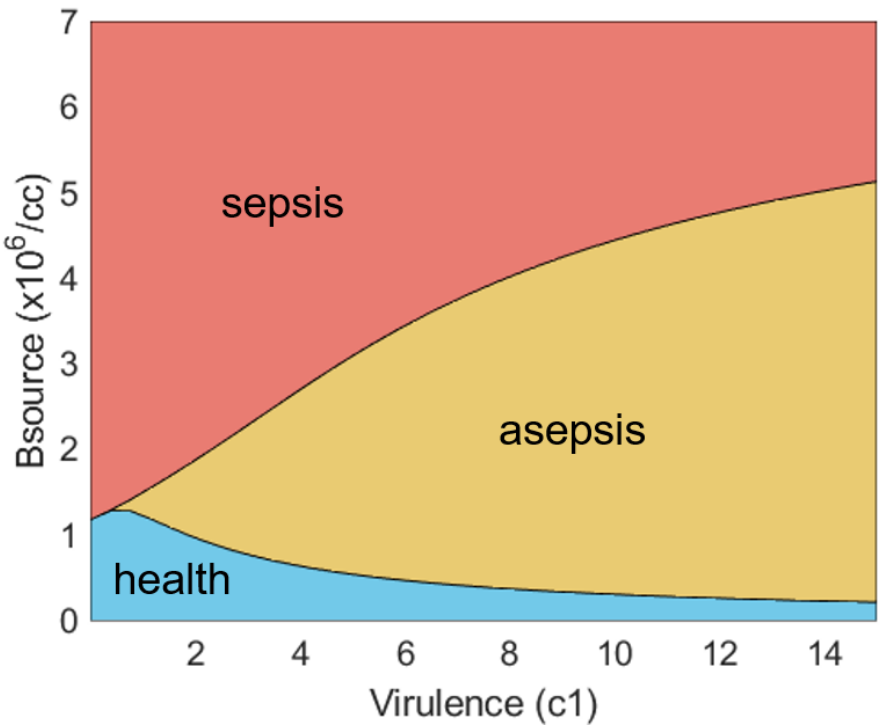
$(k_1 = 0.5)$





Bsource vs. Virulence

$(k_1 = 0{:}5)$



Conclusions

- This model highlights the balance between the pro-inflammatory response and the damage caused to the healthy tissue
- Parameters ranges are predicted that yield outcomes: health, aseptic death, and septic death
- May be useful for determining optimal treatment strategies (e.g. timing and amount of antibiotics or anti-inflammatory medication)

Future Work

- Collect more data to be able to improve parameter estimation
- Compare model to patients with peritoneal sepsis

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References

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Questions?