Optimal antimicrobial response to a changing microbial background at a mucus interface

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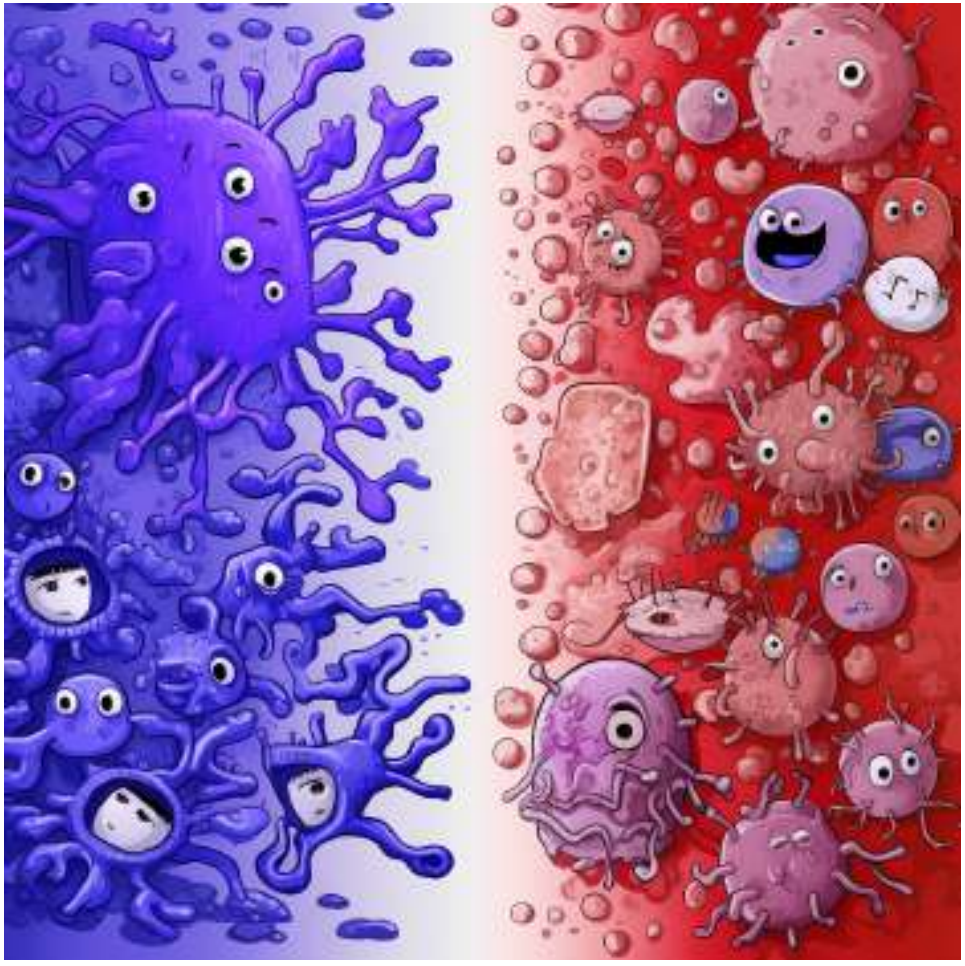
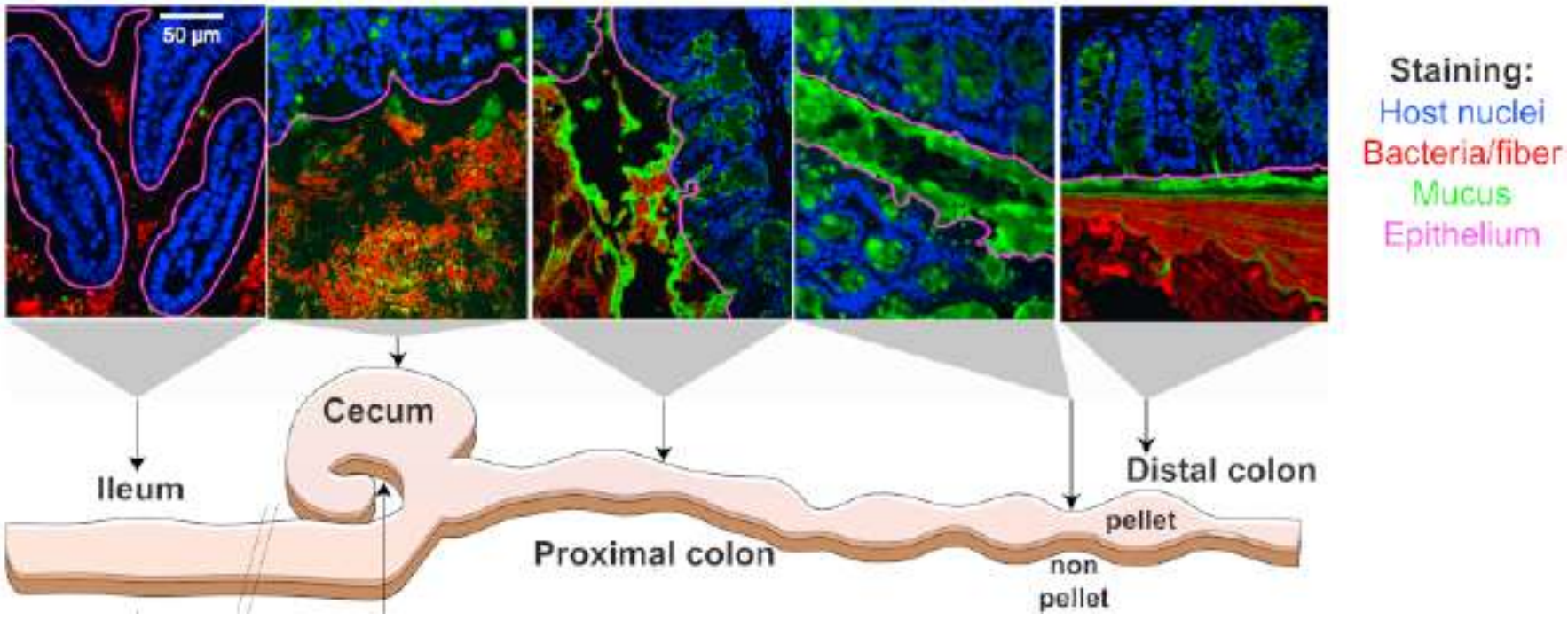
The mucus is where two worlds collide



- Living cells that respond strongly to the environment
- Barrier needs to be permeable but not too much
- Huge surface area and varying needs

The different GI mucus barriers have different properties



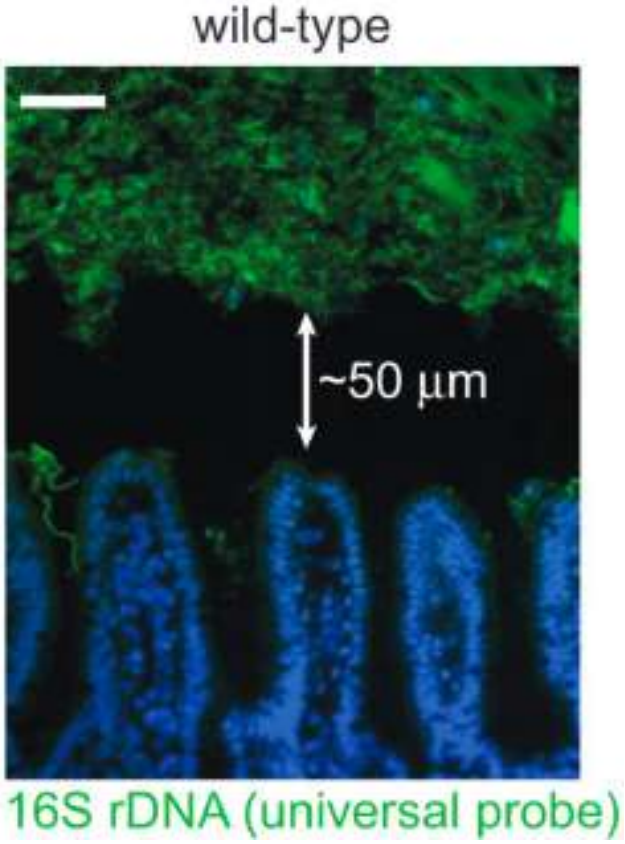
Tropini, Earl, Huang, Sonnenberg (2017)

- Obvious mucus wall in the distal colon.
- People can survive well without a colon.
- No obvious barrier in the ileum.

Ileum mucus defense: absorb nutrients but not bacteria

The ileum needs to be permeable to food but not bugs.

This is achieved by secreting antimicrobial peptides (AMP).



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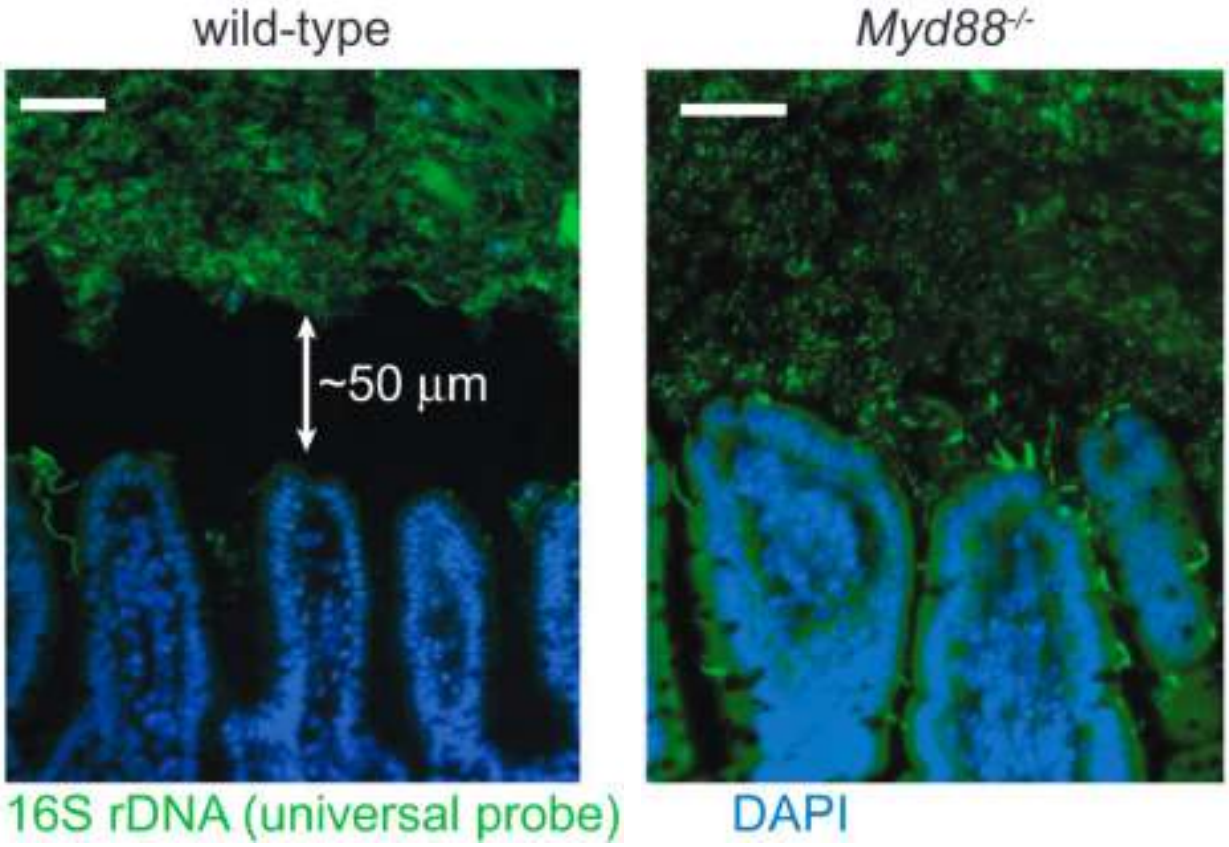
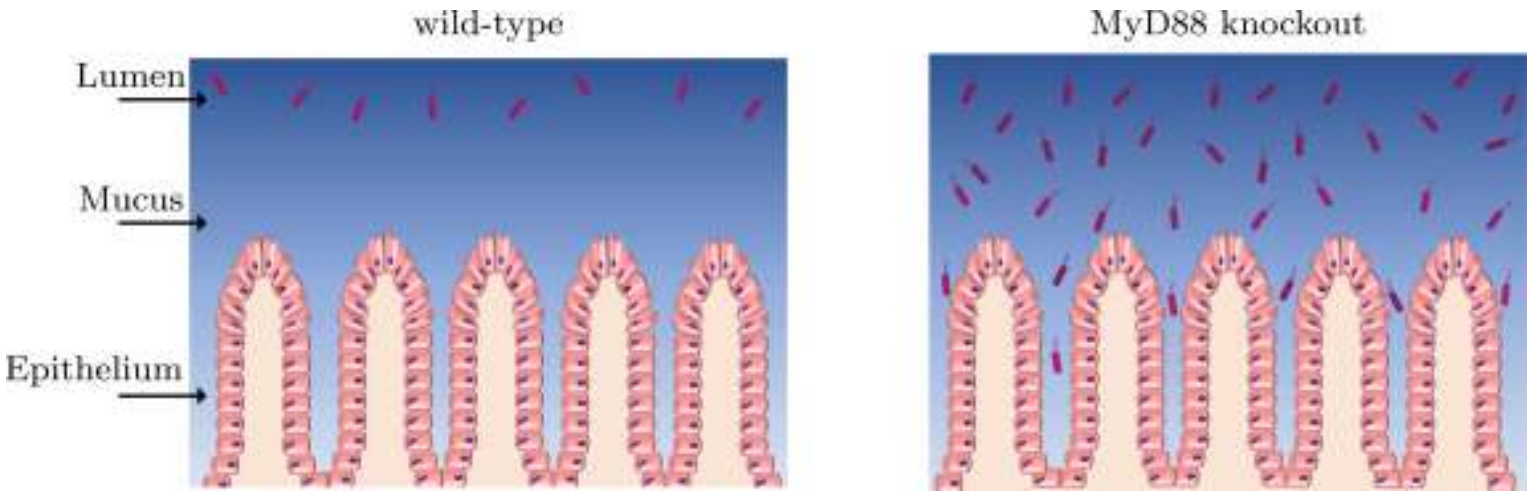


Vaishnava, ..., Hooper (2011)

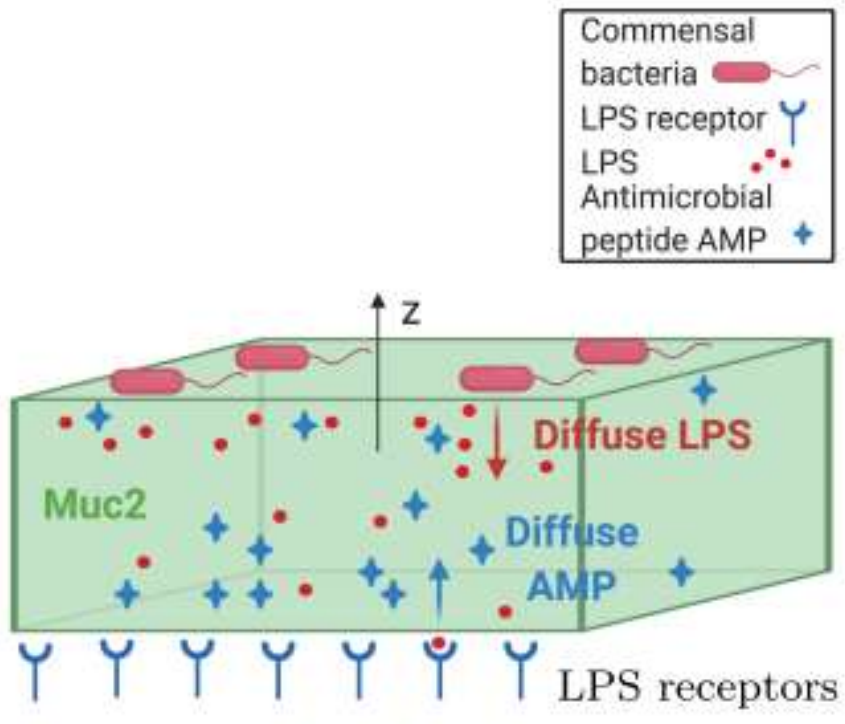
Problem: No existing framework to integrate observations



- What guiding principles keep the microbes in check, preventing them from invading the host?
- How does the host provide sufficient defense yet avoids excess inflammation?
- Why would the host rely on signals from foreign agents—adherent bacteria—to regulate vital defense decisions?
- How to intervene when things go wrong (e.g., ulcerative colitis)?

The conjugate-diffusion model

Microbial biproducts diffuse to the host epithelium.
The host senses microbial proximity and secretes AMP accordingly.



Here we use 'LPS' as an umbrella term for toll-like-receptor (TLR) activating molecules (also flagellin, etc.)

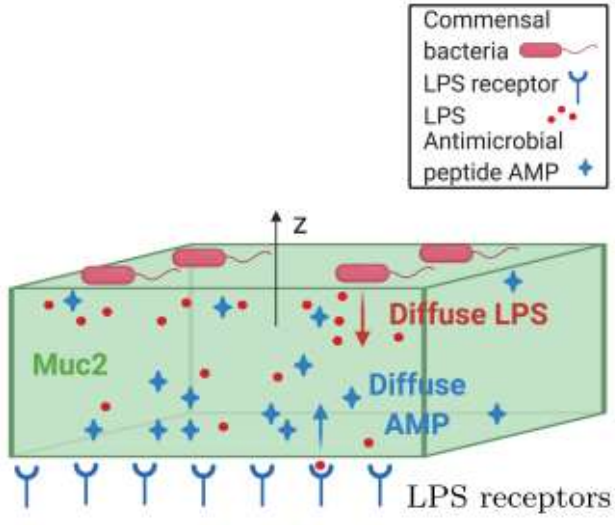
The conjugate-diffusion model equations

Dynamics:

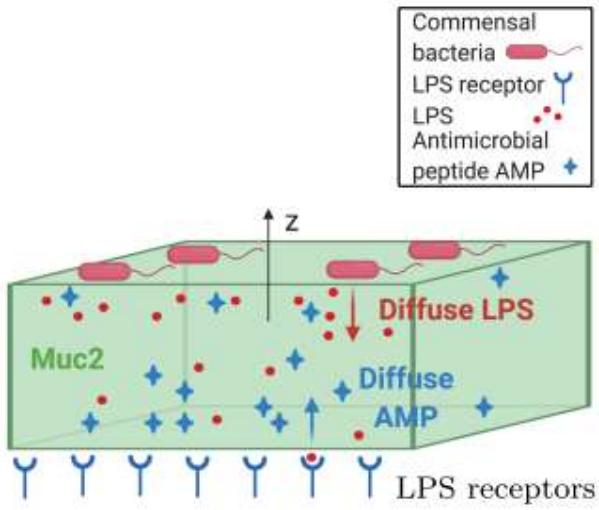
$$\begin{aligned}
\text{AMP:} \quad \frac{\partial a}{\partial t} &= D_A \frac{\partial^2 a}{\partial^2 z}, \\
\text{Bac:} \quad \frac{\partial b_i}{\partial t} &= \mathsf{v}_i \frac{\partial b_i}{\partial z} - a\mu_i b_i \,, \\
\text{LPS:} \quad \frac{\partial c}{\partial t} &= D \frac{\partial^2 c}{\partial z^2} + \sum_i b_i \,.
\end{aligned}$$

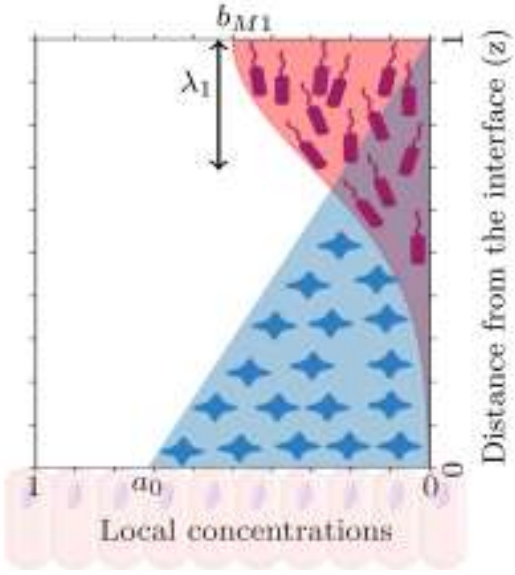
Boundary conditions:

$$\begin{aligned}
b(z=1) &= b_M \\
c(z=1) &= c_M \\
\left.\frac{dc}{dz}\right|_{z=1} &= 0 \\
a(z=0) &= \beta\, c(z=0)
\end{aligned}$$



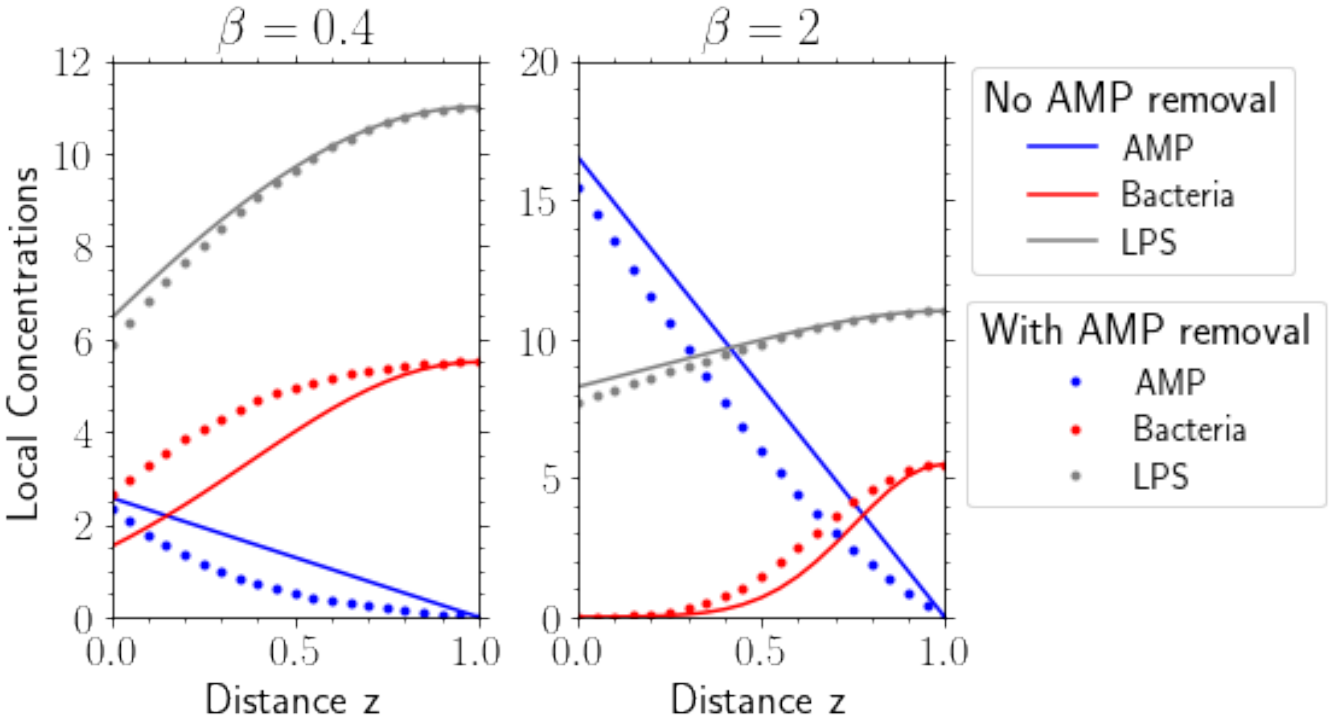
Exactly solvable at steady state neglecting AMP degradation





$$
\begin{aligned}
a(z) &= a_0\,(1-z), \quad \lambda_i = \sqrt{\frac{\mathsf{v}_i}{a_0\mu_i}}\,, \\
b_i(z) &= b_{Mi}\, e^{-\frac{(z-1)^2}{2\lambda_i^2}}\,, \\
c(z) &= c_M + \sum_i b_{Mi}\left[\lambda_i^2\left(1-e^{-\frac{(z-1)^2}{2\lambda_i^2}}\right) - \sqrt{\frac{\pi}{2}}\lambda_i(z-1)\,\mathsf{Erf}\sqrt{\frac{(z-1)^2}{2\lambda_i^2}}\right].
\end{aligned}
$$

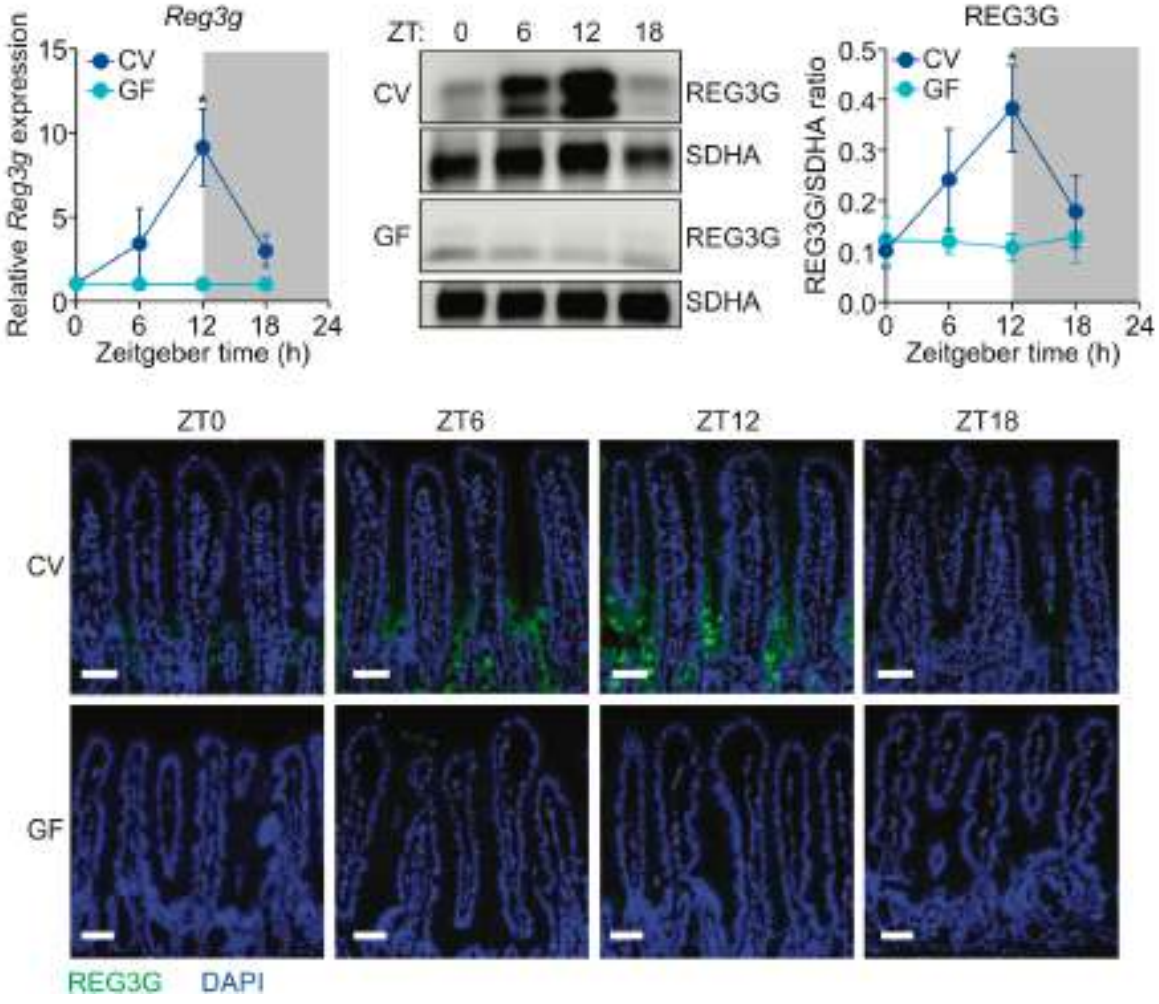
AMP degradation does not change the spatial profiles much



This is a static view, but...

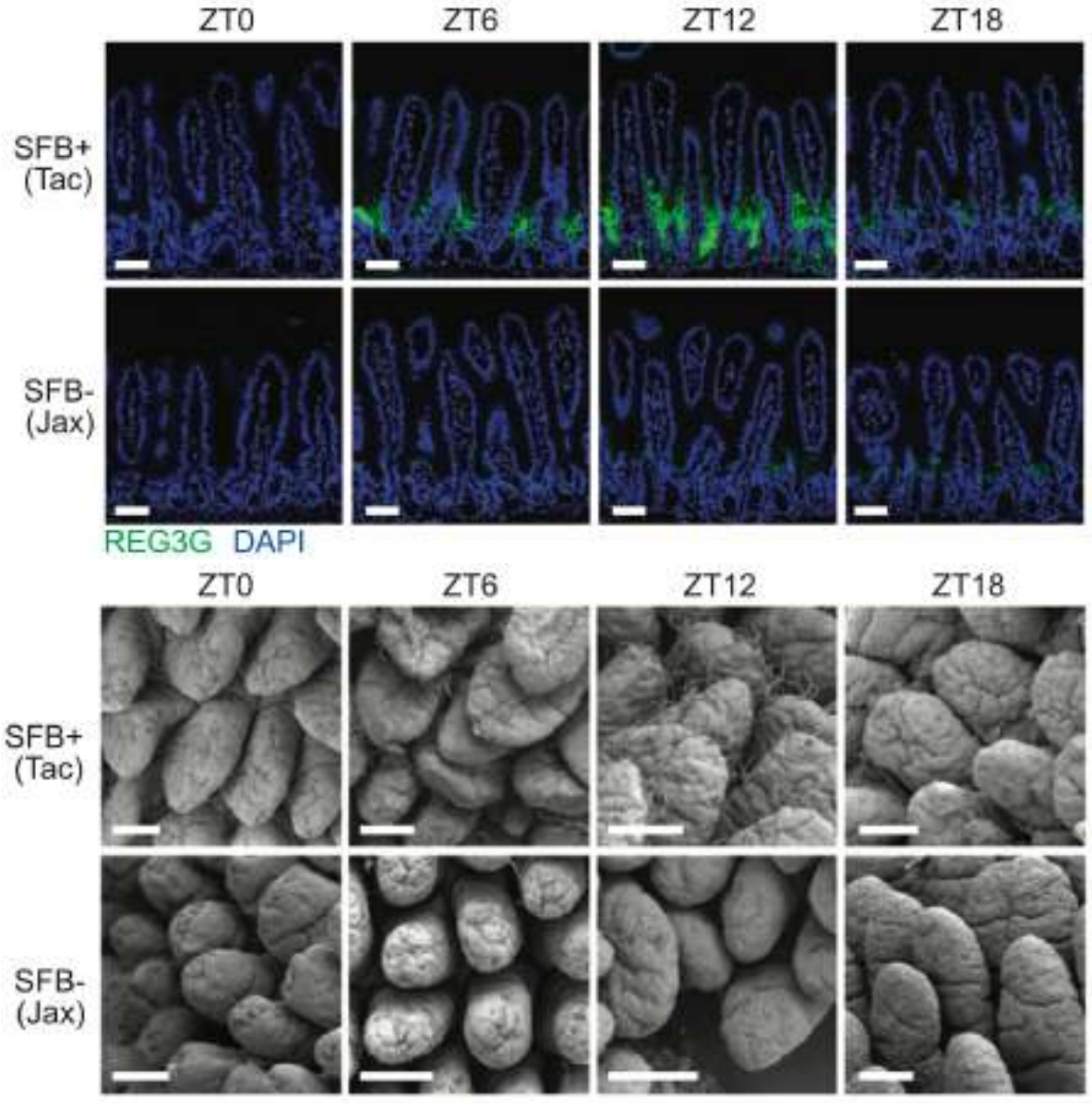
Life is cyclic

Diurnal rhythms in AMP production depend on the microbiota

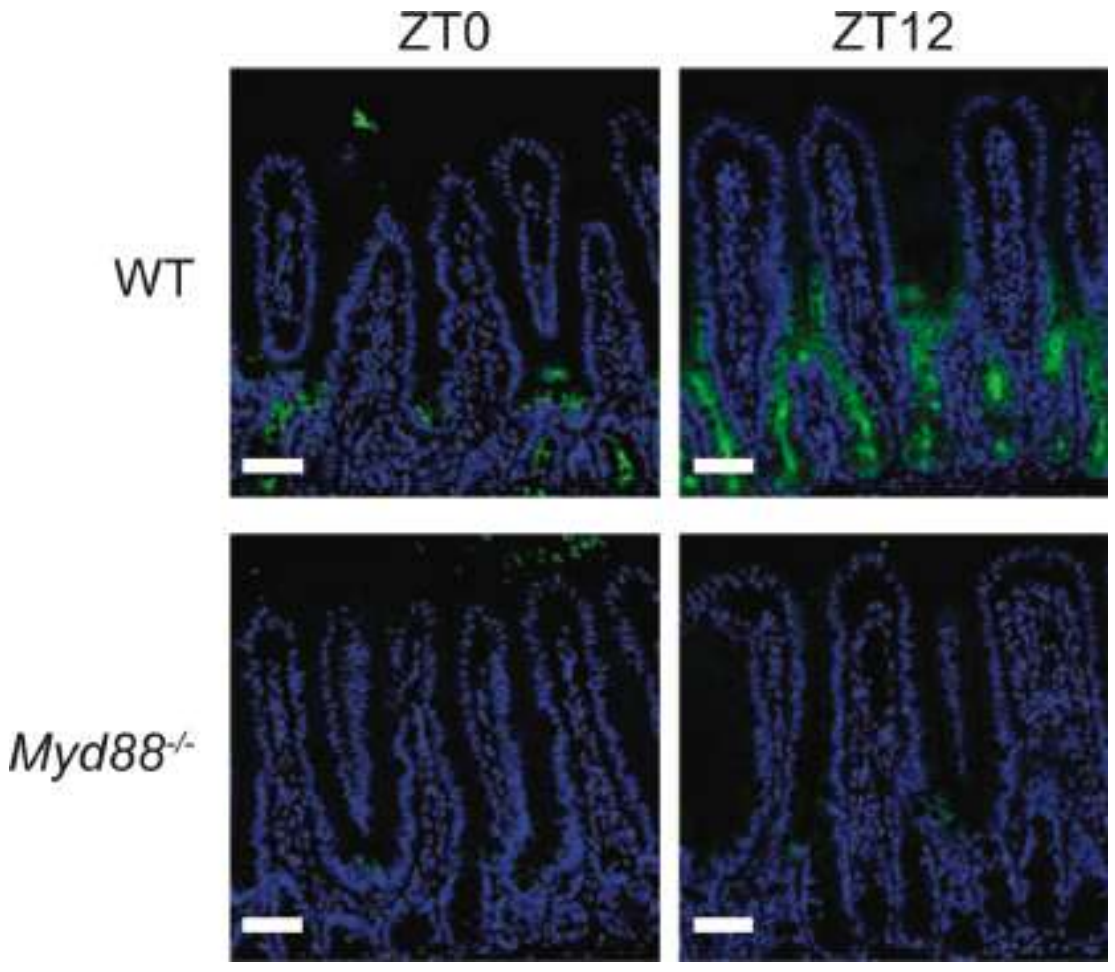


Brooks, ..., Hooper (2021) Scale bar: 50μm

Sensing of segmented filamentous bacteria (SFB) primes the host to changes in the bacterial background



The MyD88 signaling relay still drives diurnal rhythms in REG3G expression



Still sensing TLR receptor activation, but there's another player in the game: the SFB.

Experimental observations: connecting the dots

- Without microbiota, the antimicrobial peptide Reg3g isn't produced
- Sensing the microbial products through MyD88 signaling is required to produce AMP
- Segmented Filamentous Bacteria (SFB) rhythmically translocate to the epithelium and stimulate Reg3g defense
- The SFB appear to be harmless and are interpreted as a signal, rather than as antagonists that necessitate a defensive response
- There are two signals: the lumen microbiota, and the SFB

Why does the host outsource an essential defense mechanism to foreign agents that pursue their own agenda?

Would you employ alien mercenaries to patrol your border?

The mouse gut does. But why? This is where modeling can help!

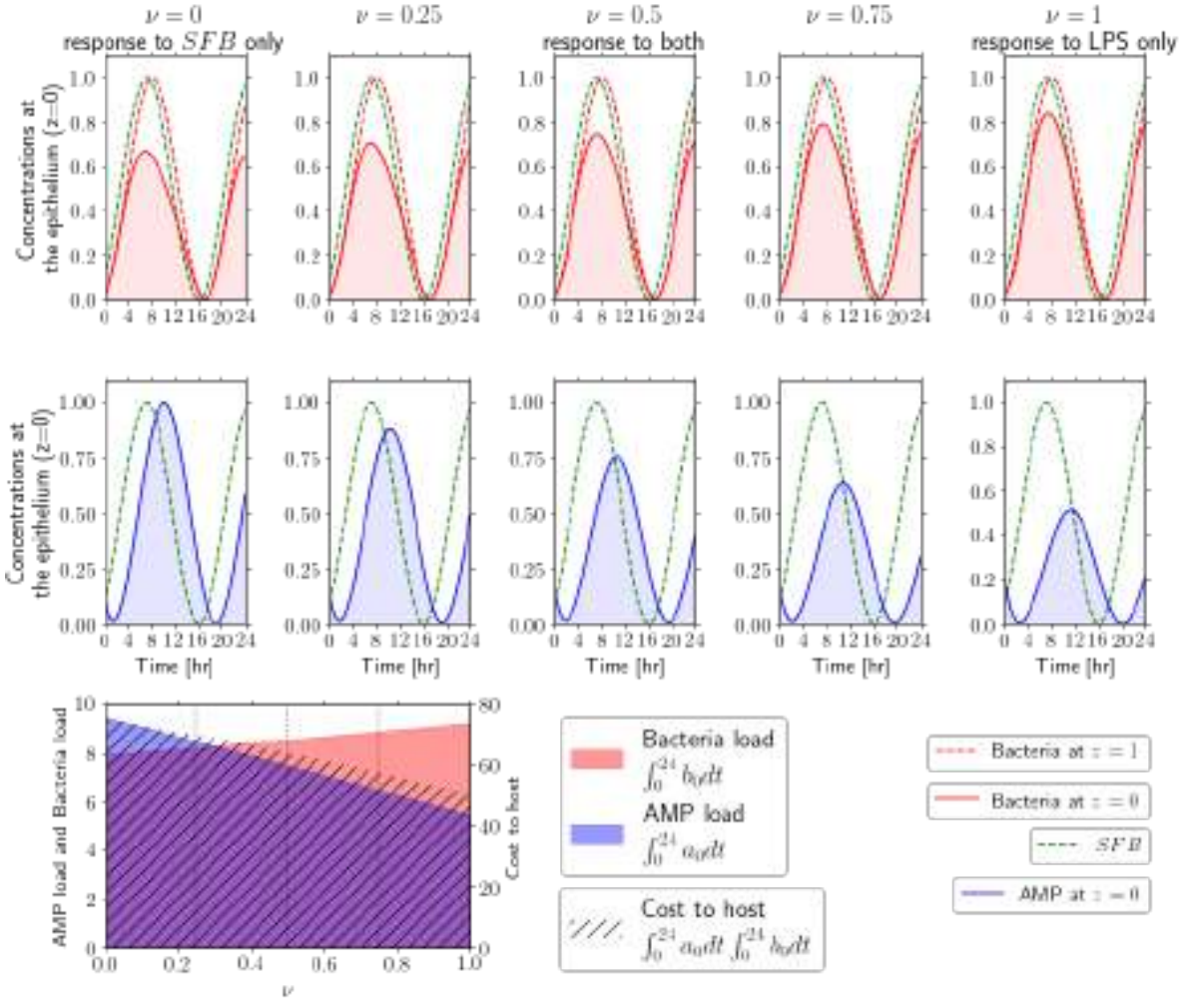
The host senses two signals (SFB, LPS) to determine AMP production

Counting the time with respect to the SFB translocation, we introduce two time delays:

ϕ_b	Delay in the rise of microbiota abundance (LPS)
ϕ_a	Delay in the secretion of Reg3g following stimulus
ν	Relative weight of sensing LPS vs. SFB

$$
\begin{aligned}
b_i(z=1,t) &= b_{Mi}\cos^2(\omega[t-\phi_b]/2)\,, \\
a(z=0,t) &= \beta(1-\nu)C_{SFB}(t-\phi_a) + \beta\nu\, c(0,t-\phi_a)\,.
\end{aligned}
$$

Host defense depends on division of attention between the SFB and LPS signals



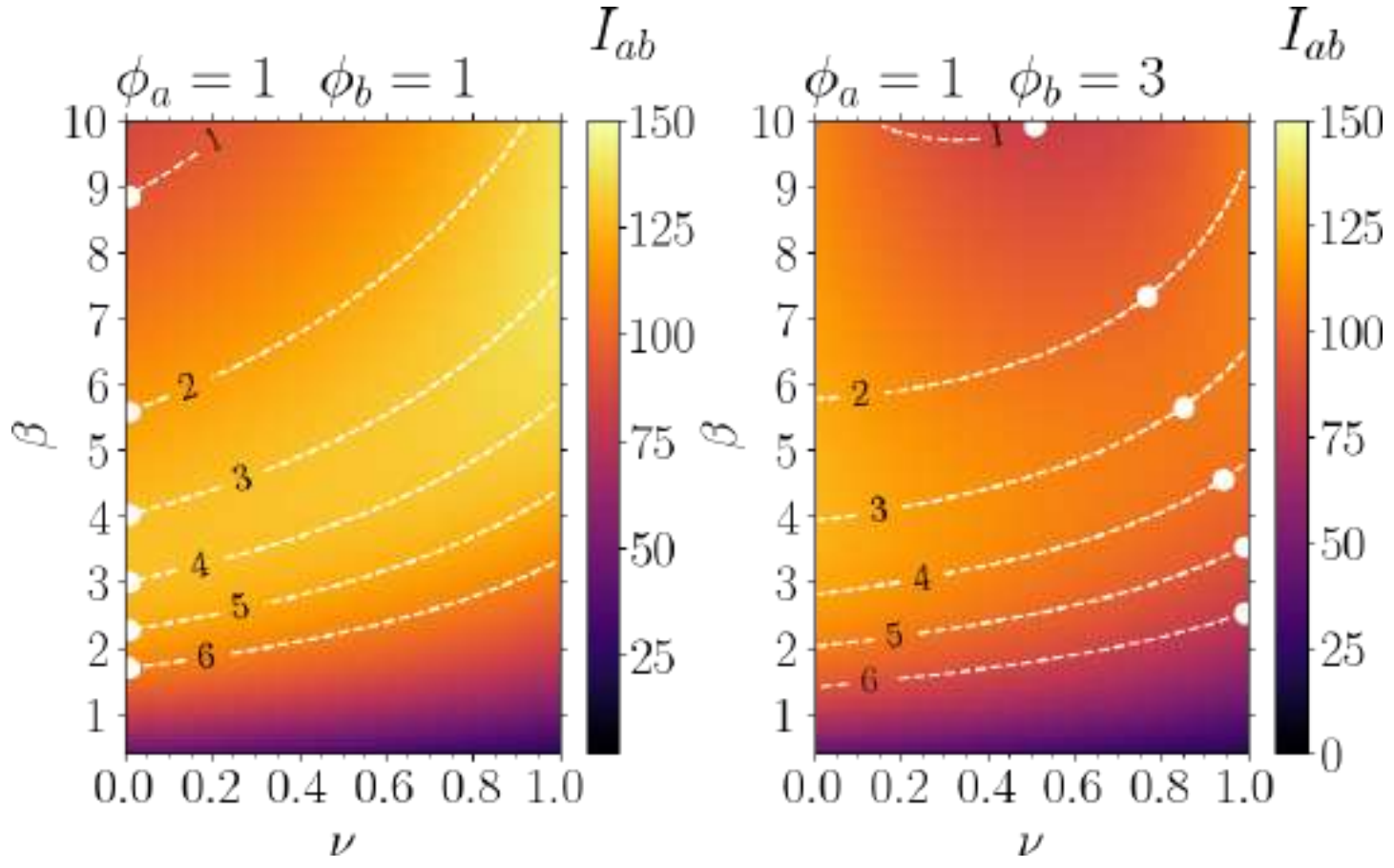
Here, $\phi_a = 3$, $\phi_b = 1$.

The optimal defense hypothesis

The host produces just enough AMP to protect against a maximal bacterial load,
but not too much to avoid excess inflammation from pathogen-associated molecular patterns (PAMPs).

If you produce too little AMP, you have inflammation; if you produce too much AMP, you also have inflammation.

Optimal host response depends on the time delays ϕ_a, ϕ_b



Dashed: $I_b = \int_0^{24} b_0 \, dt$ — Host microbial exposure in 24 hours

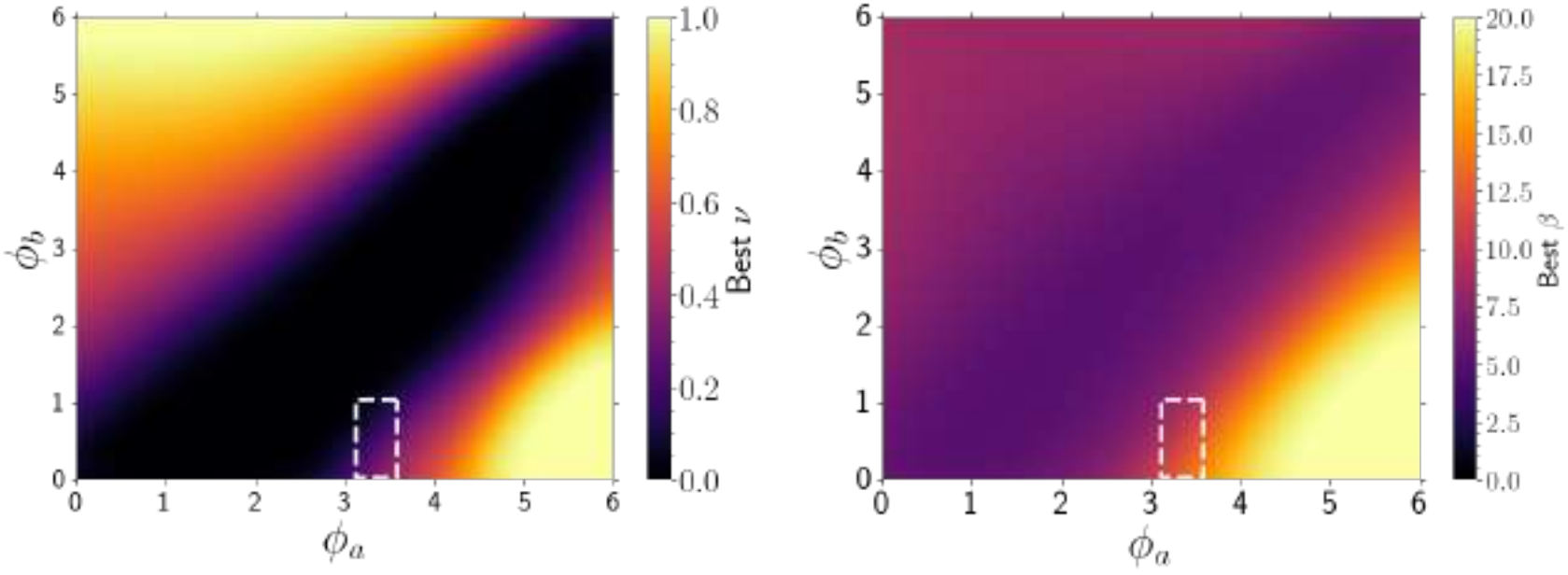
Heatmap: $I_{ab} = \left(\int_0^{24} b_0 \, dt\right) \left(\int_0^{24} a_0 \, dt\right)$ — Cost to host

White dots: minimal cost per contour

There exist intermediate ν that optimize response!

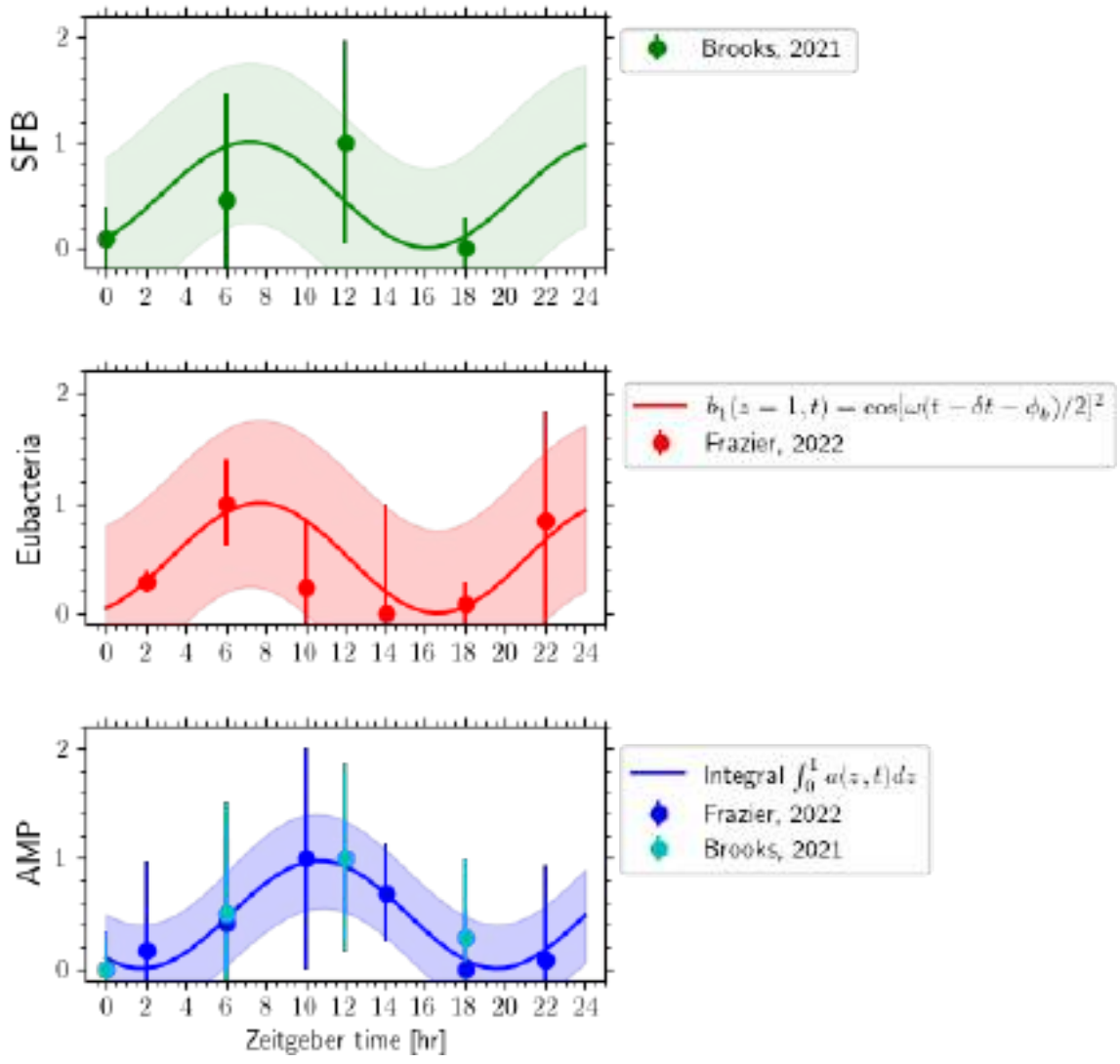
Generalize the optimal defense hypothesis to arbitrary ϕ_a, ϕ_b

The optimal ν and β values correspond to the coordinates of the minimum points (i.e., the white dots in the previous figure) along the contour $I_b = \int_0^{24} b_0 \, dt = 12$

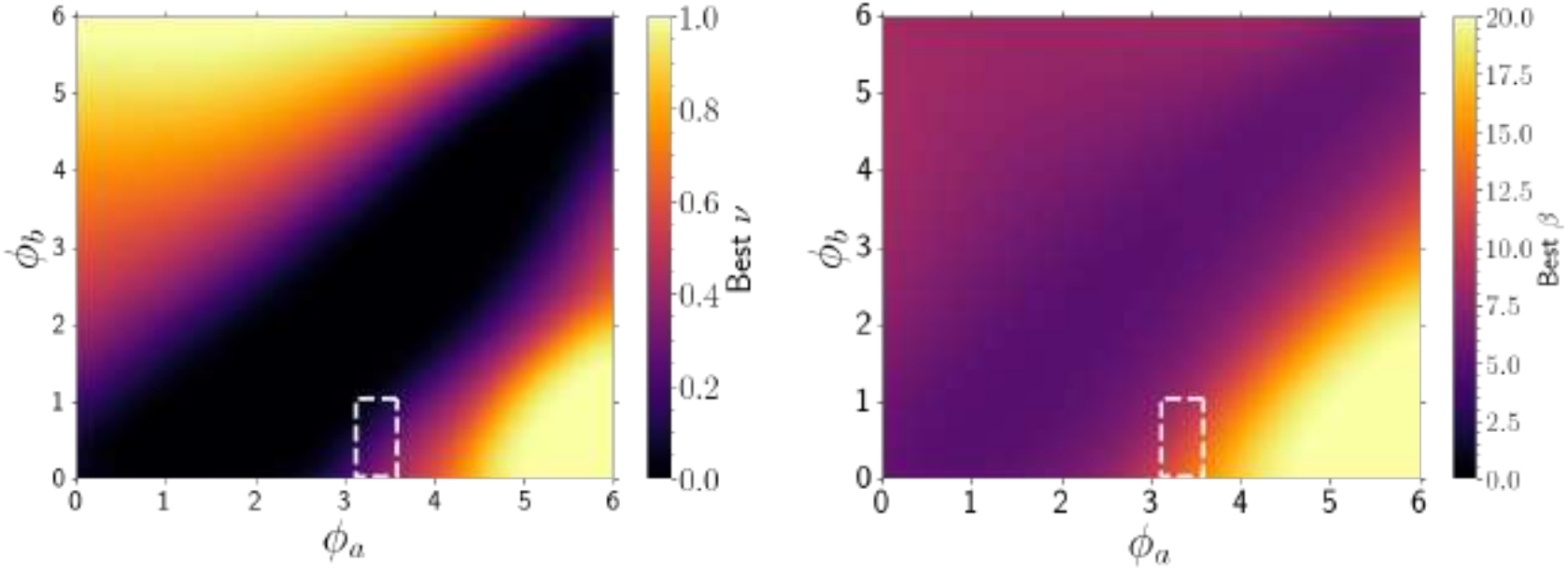


Proof-of-concept application on experimental data

Comparison between model predictions (solid curves) and experimental data previously reported (Brooks 2021, Frazier 2022).



Fit parameters consistent with the optimal defense hypothesis



Bossa, ...,Erez (2024)

Optimal ν is consistent with the fit $\nu \approx 0.3$ (purple color).
It appears ϕ_a sits at the boundary between the region where the optimal ν is the single-channel $\nu = 0$ and where listening to both channels is worthwhile.

Conclusions

- We presented an inaugural model for the ileum AMP defense.
- The model integrates experimental observations into a single framework.
- The model solution depends on a bacterial penetration length, λ. Extracting this length from imaging data is feasible, e.g., using 16S fluorescent in situ hybridization.
- The abundance of the intestinal microbiota oscillates during the diurnal cycle, in tune with feeding behavior.
- Hence, optimal defense of the mucus barrier requires synchronization of AMP secretion with the diurnal microbial cycles. But production of AMP takes time. Thus, listening to anticipatory signals is useful.
- There is a cost associated with the host response to microbial invasion. We elucidated how the host may minimize defense costs while sustaining the necessary protection: the 'optimal defense hypothesis'. Consistent with current observations.

Some thoughts

- The phenomenological $\cos^2(\omega t)$ should be improved. We hope that this study will inspire researchers to collect more densely-sampled time-series.
- We assumed that the lumen microbiota are equally susceptible to AMP, precluding pathogens known to be resistant to certain AMP.
- rRNA probes could enable quantification of such pathogens. Also: mutant bacteria lacking certain swimming capabilities ; drugs that stimulate or block AMP production.
- Why did the host evolve reliance on SFB to optimize AMP production? Relying on external factors for a critical defense mechanism is risky. Why not use neural signals from the mouth?
- Perhaps the ability to sense microbial background developed earlier in evolution?
- Maybe the SFB mechanism for immune regulation was already operational (mucosal Th17 cells) when the AMP system evolved.
- Are there analogous SFB-like mechanisms in other species, and in mucus barriers other than in the ileum?