Mathematical Modeling of *Pseudomonas aeruginosa* Quorum Sensing

Aleksandra Gavrilova[1], Winn Gillen[2], Brendan Shrader[3]

Denison University[1], University of Vermont[2], University of Central Florida[3]

Introduction

- Bacteria use **quorum sensing** to communicate with each other by sending signals in the form of molecules.
- The **signal concentration** is indicative of the **population density** of the bacteria.

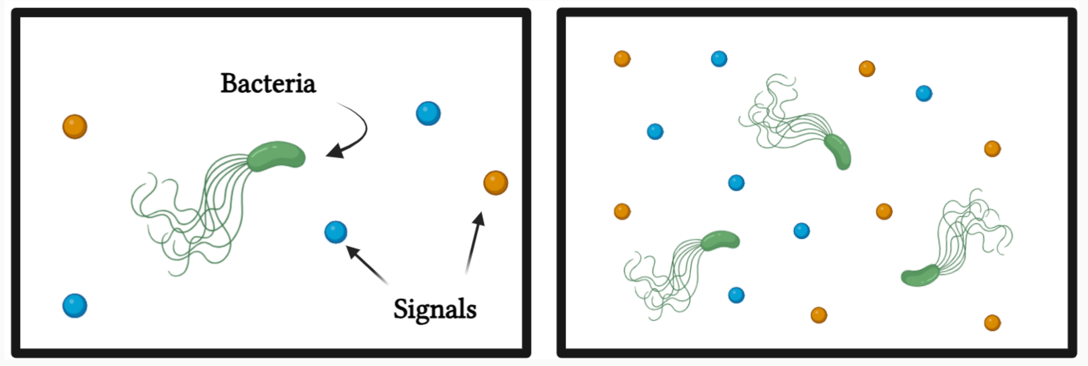


Figure 1. Single bacterium with low signal (left), bacteria community with high signal (right).

- Quorum sensing allows bacteria to act as a group rather than as individuals and regulate factors such as virulence and biofilm formation.
- Bacteria can have **multiple quorum sensing systems**. Each system consists of a synthase, signal, and receptor.

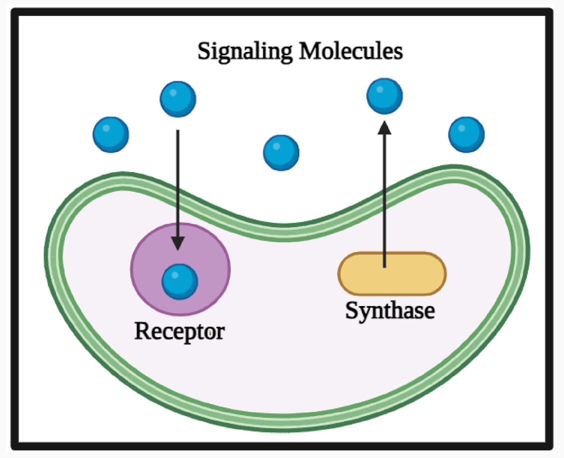


Figure 2. Bacterium with its synthase, signal, and receptor.

- *Pseudomonas aeruginosa* has many quorum sensing systems, including *las* and *rhl*.
- The systems have a beneficial **reciprocal** relationship in which the production of signal drastically increases when both signals are present.

System	Synthase	Signal	Receptor
las	*lasI*	3-oxo-C_{12}-HSL	*lasR*
rhl	*rhlI*	C_4-HSL	*rhlR*

Table 1. *Pseudomonas aeruginosa* quorum sensing systems.

- The reciprocal relationship is illustrated by the following model which was proposed by Thomas et al.

$$E_i(S_1,S_2) = \alpha_{i,0} + \sum_{j=1}^{2} \frac{\alpha_{i,j}\cdot S_j}{S_j + K_{i,j}} + K(S) \tag{1a}$$

$$K(S_1,S_2) = \frac{\alpha_{i,1,2}\cdot S_1 S_2}{(S_1+K_{Qi,1,2})\,(S_2+K_{Qi,2,1})} \tag{1b}$$

- Recent studies developed a system of differential equations to model signal concentration dynamics over time.

$$\frac{dS_i}{dt} = \frac{c_i}{\delta_2} N\cdot E_i(S_1,S_2) - \frac{\delta_i}{\delta_2} S_i - \frac{m}{\delta_2} S_i \tag{2}$$

- S_1 is the concentration of 3-oxo-C_{12}-HSL and S_2 is the concentration of C_4-HSL.

Motivation

- ☐ Model (1b) has complicated rational expressions; are there **simplifications** that can be made to the model while still maintaining **biological accuracy**?
- ☐ Additionally, model (2) treats population density, N, as a constant. What is the best way to incorporate **population dynamics** into the existing model?

Constant Approximation

Using a **constant approximation** $K(S_1,S_2) = \alpha_{i,1,2}$ instead of the original interaction term in equation (1b) simplifies the model significantly. The constants $\alpha_{1,1,2}$ and $\alpha_{2,1,2}$ are sufficient to account for the interaction of both signals in the reciprocal Double-Signal model (2) for $N > 0.1$.

Signal Concentration vs. Time

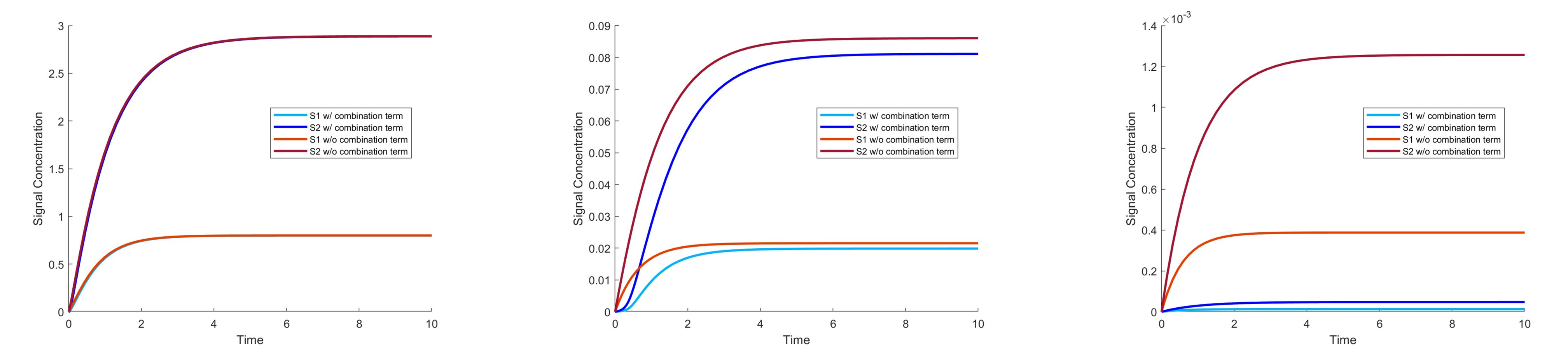


Figure 3. In the figure on the left where N is fairly large ($N = 1$), the models exhibit similar behavior. In the middle figure, $N = 0.05$, and the behavior of the models starts to diverge. In the figure on the right, when N is very small at a value of 0.001, the models no longer exhibit the same behavior.

Population Dynamics

In equation (2), N is a parameter. Population dynamics are incorporated into the model via a **logistic growth** equation. In order to account for how quorum sensing positively benefits the population's carrying capacity, a **cooperation** term is introduced into the model.

$$\frac{dN}{dt} = \frac{r}{\delta_2} N\cdot\left(1 - \frac{N}{L} + \frac{g\cdot S_1 S_2}{(S_1+M)(S_2+M)}\right) \tag{3}$$

Signal Concentration and Population Density vs. Time

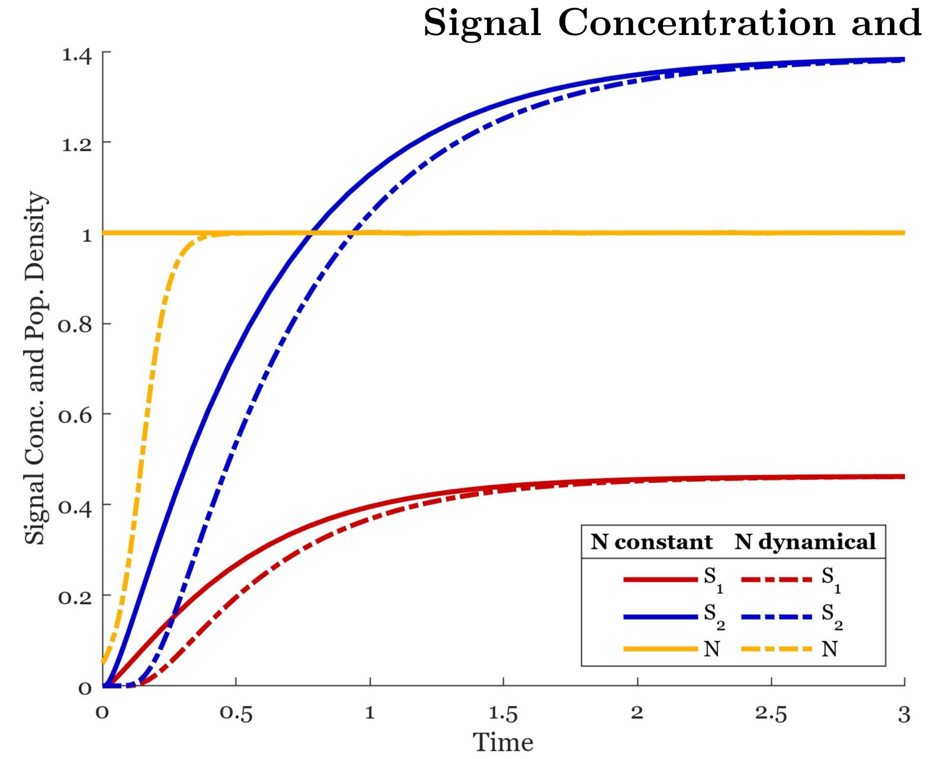


Figure 4. Time series for model (2) with $N = 1$ and model (3) with $L = 1$ and $g = 0$.

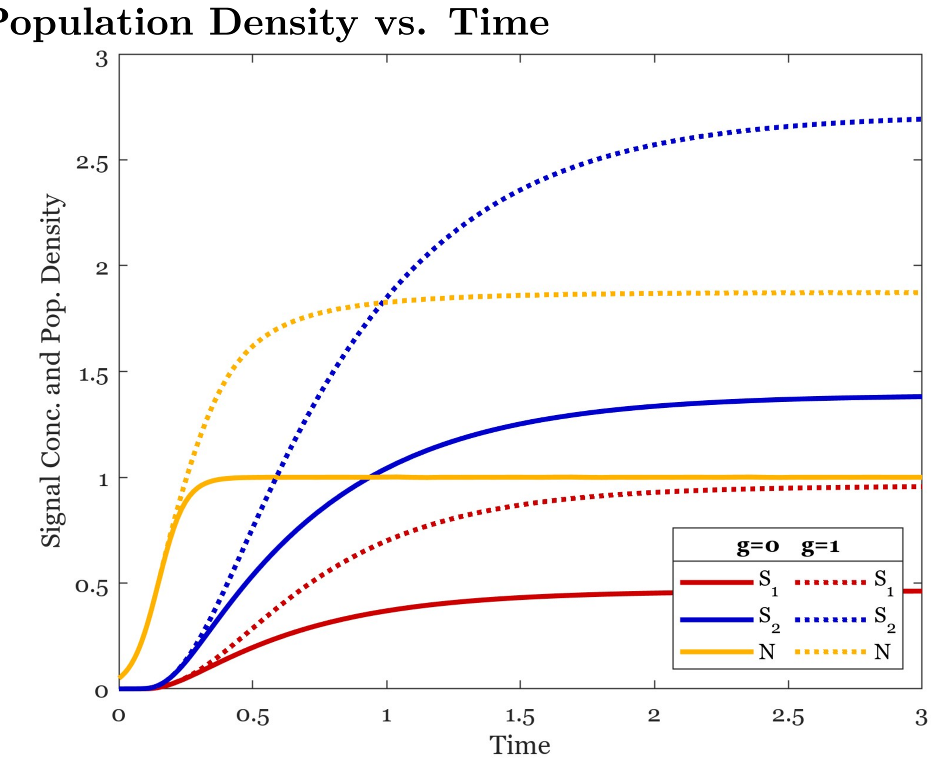
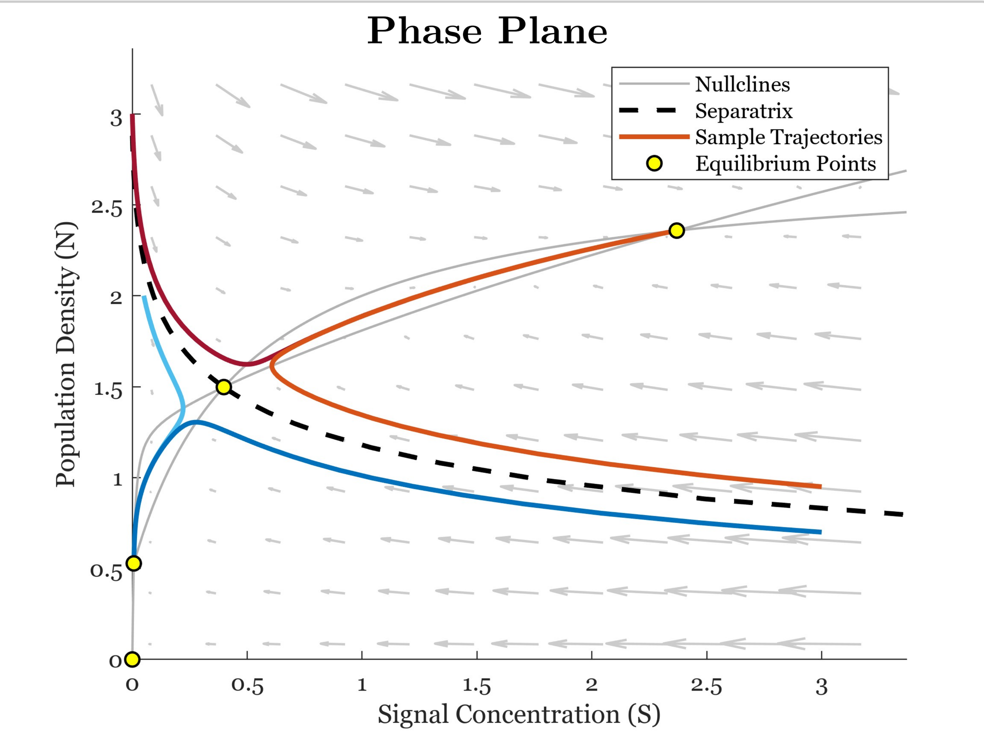


Figure 5. Time series for model (3) with $g = 0$ and $g = 1$, both with $L = 1$.

Multiple Equilibria with Single-Signal

Phase Plane



- In a model with only one signal and population dynamics, it is possible to have multiple equilibria for certain parameter regimes.
- Depending on initial conditions, the bacteria can receive a benefit which incentivizes them to signal more.
- Alternatively, bacteria may not receive the benefit in which case they stop signaling.

$$\frac{dS}{dt} = \left(\rho + \frac{\alpha S}{K+S}\frac{N}{L}\right) N - \delta S \tag{4a}$$

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{L} + \frac{gS}{S+M}\right) \tag{4b}$$

Parameters

Figure 6. QR Code for Parameters of Double-Signal Model

Conclusions

- The **constant approximation** term accounts for biological behavior of quorum sensing for large values of signal concentrations and population density. However, the approximation does not account for the biological behavior at small values of signal concentrations.
- The addition of the **cooperation term** into the population density equation increases the equilibrium population density and signal concentrations.
- The **constant population density** assumption is generally correct for large population growth rates.
- Under certain parameter regimes, it is possible to have **multiple equilibria** for a Single-Signal model with population dynamics. We have not yet found multiple equilibria for the double signal model.

Future Research

- In the presence of viruses, bacteria can use quorum sensing to express genes linked to immunity. Further modifications to the model could involve incorporating **viral and immune dynamics**.

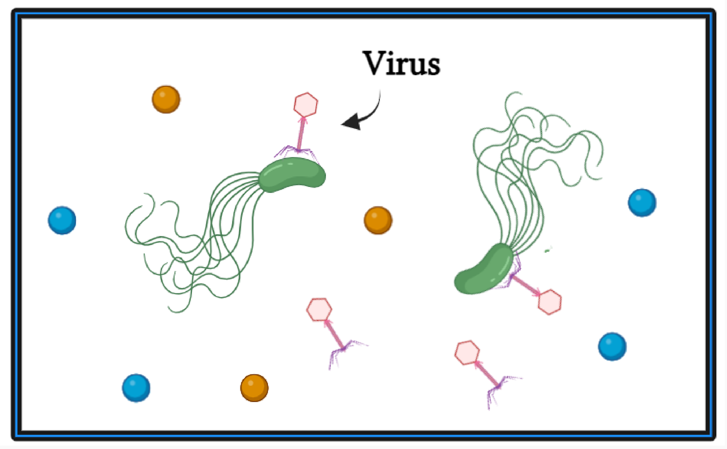


Figure 7. Bacteria signalling while under bacteriophage attack

- *Pseudomonas aeruginosa* has other quorum sensing systems, so another possible direction is to incorporate the dynamics of these other systems into the current model as well as population dynamics.

References

1. Steven Thomas. "Linking Molecular Mechanisms to Population-Level Behavior Using Pseudonomonas Aeruginosa Quorum Sensing". PhD thesis. Georgia Institute of Technology, 2023.
2. Stephen Thomas et al. "Quantifying multi-signal quorum sensing: The las and rhl systems in Pseudomonas aeruginosa form a biased reciprocal network that can tune responses to physical and social environments." *arXiv*, 2024.

Acknowledgements

- We would like to extend a special thanks to our **mentors Dr. Rachel Kuske, Dr. Sam Brown, and Dr. Maria Martignoni** for their invaluable feedback, suggestions, and support throughout this project.
- This work was sponsored by NSF Grant 2244427 and Georgia Institute of Technology College of Sciences.