# Project Notes:

**Project Title: Modeling the Effects of Bacteriophages on the Spread of Antibiotic Resistance**
**Name: Yan, Richy**

**Note Well:** There are NO SHORT-cuts to reading journal articles and taking notes from them. Comprehension is paramount. You will most likely need to read it several times, so set aside enough time in your schedule.

**Contents:**

# Knowledge Gaps:

This list provides a brief overview of the major knowledge gaps for this project, how they were resolved and where to find the information.

| Knowledge Gap | Resolved By | Information is located | Date resolved |
|---|---|---|---|
| How do antibiotics (specifically macrolides) work | Reading journal article | CellPress | 8/20 |
| Reproductive rate in relation to antibiotic resistance | Reading journal article | Nature | 9/23 |
| Bacteriophages and their effect on antibiotic resistance | Reading journal article | *Trends in Microbiology* | 10/6 |
| Mathematical modeling | Reading journal article | *Applied Mathematical Modeling* | 10/7 |
| Stochastic models | Reading journal article | *SpringerNature* | 10/21 |
| Antibiotics in mice | Reading journal article | *BMC* (part of *SpringerNature*) | 11/12 |
| How to implement bacteriophages into a math model | Reading journal article | *ScienceDirect* | 11/26 |
| Antibiotic/bacteria dynamics in aquatic environments | Reading journal article | *ScienceDirect, Wiley Online Library* | 12/19 |
| Antibiotic and bacteria dynamics at a human population scale | Reading journal article | *SpringerNature* | 12/19 |

# Literature Search Parameters:

These searches were performed between (8/13/2025) and XX/XX/2026.
List of keywords and databases used during this project.

| Database/search engine | Keywords | Summary of search |
|---|---|---|
| WPI Library | Antibiotics and bacteriophages | Found article on the relationship between phages and antibiotic resistance genes |
| WPI Library | Antibiotics | Found article on how resistance affects fitness cost |
| Nature Review Microbiology | Antibiotics | Found article on how macrolide antibiotics work |
| WPI Library | Antibiotics and math modeling | Found articles on U-Net CNN use in resistant bacteria detection and modeling how genetic mutations and plasmid transmission affects the spread of resistance |
| WPI Library | Antibiotics and mice | Found article on how various types of antibiotics affect the gut microbiome of a mouse |

# Tags:

| Tag Name | |
|---|---|
| #mathmodeling | #antimicrobialresistance |
| #bacteriophages | #computersimulations |
| | |

# Article #1 Notes: Title

Article notes should be on separate sheets

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| | |
|---|---|
| **Source Title** | |
| **Source citation (APA Format)** | |
| **Original URL** | |
| **Source type** | |
| **Keywords** | |
| **#Tags** | |
| **Summary of key points + notes (include methodology)** | |
| **Research Question/Problem/ Need** | |
| **Important Figures** | |
| **VOCAB: (w/definition)** | |
| **Cited references to follow up on** | |
| **Follow up Questions** | |

# Article #1 Notes: How Macrolide Antibiotics Work

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|---|---|
| **Source Title** | How Macrolide Antibiotics Work |
| **Source citation (APA Format)** | Vázquez-Laslop, N., & Mankin, A. S. (2018). How Macrolide Antibiotics Work. *Trends in biochemical sciences*, *43*(9), 668–684. https://doi.org/10.1016/j.tibs.2018.06.011 |
| **Original URL** | https://pmc.ncbi.nlm.nih.gov/articles/PMC6108949/ |
| **Source type** | Article |
| **Keywords** | ribosome, macrolide, ketolide, antibiotic, translation, resistance |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Before, macrolide antibiotics were thought to plug the NPET of a bacteria ribosome, inhibiting further protein synthesis. New evidence shows that rather than inhibiting protein synthesis in general, they selectively inhibit protein production depending on the NPET's peptide sequence and the antibiotic's structure. Ribosome profiling experiments were used to show that while all macrolides bind to the same site on the NPET, their chemical structure altered the sites of translation arrests and the spectra of affected proteins. |
| **Research Question** | Central question: How do macrolide antibiotics work? |
| **Important Figures** | Macrolides bond at the NPET, which restricts it but still allows certain proteins to exit https://cdn.ncbi.nlm.nih.gov/pmc/blobs/fcc6/6108949/98767618cd47/nihms980174f1.jpg |
| **VOCAB: (w/definition)** | Macrolide-Arrest Motifs- Amino acid sequences that a macrolide-bound ribosome can't effectively make. Nascent peptide exit tunnel – tunnel where polymerize proteins are threaded to then exit the ribosome. Ribo-seq – technique that shows the distribution of translating ribosomes along mRNAs in a cell. PTC – location of formation of peptide bonds between the C-terminal amino acid of the nascent peptide and incoming amino acid |
| **Cited references to follow up on** | Ribosome-targeting antibiotics and mechanisms of bacterial resistance<br>Ribosome-Targeting Antibiotics: Modes of Ation, Mechanisms of Resistance<br>Structural basis for the interaction of antibiotics |
| **Follodaw up Questions** | Are bacteria able to gain resistance against macrolide antibiotics as well?<br>How does the structure of a macrolide antibiotic determine their ability to block certain nascent peptides?<br>Can macrolides be designed in a way to also target the DNA chain (can they be designed to slow down resistance spread)? |

# Article #2 Notes: Antibiotic resistance and its cost: is it possible to reverse resistance?

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|---|---|
| **Source Title** | Antibiotic resistance and its cost: is it possible to reverse resistance? |
| **Source citation (APA Format)** | Andersson, D., Hughes, D. Antibiotic resistance and its cost: is it possible to reverse resistance?. *Nature Review Microbiology* **8**, 260–271 (2010). https://doi.org/10.1038/nrmicro2319 |
| **Original URL** | Antibiotic resistance and its cost: is it possible to reverse resistance? \| Nature Reviews Microbiology |
| **Source type** | Review article |
| **Keywords** | Antibiotic resistance, fitness cost, HGT, mutation rate, co-selection |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Summary: Fitness cost and antibiotic resistance are usually inversely proportional (if a bacterium is resistant to an antibiotic, they will have a slower reproductive rate). However, sometimes bacteria reproduction rates increase along with a mutation that resists antibiotics.<br>Antibiotic resistant bacteria growth is equal to mutation rate and horizontal gene transfer rate added up.<br>A mutated bacteria might have a high fitness cost in vitro, but not in vivo, and vice versa.<br>Reduced antibiotic use should allow susceptible strains to outcompete resistant strains, but that's not always the case due to compensatory evolution and co-selection.<br>Methodology: The authors first read and synthesized articles that contained data from in vitro and in vivo experiments. They then compared growth rates between resistant and susceptible strains and tracked the ratio of susceptible bacteria to resistant bacteria in vitro. The authors then created a mathematical model taking into consideration the rate of resistance emergence, the fitness cost (0.7% in this study),and the rate of reversal (faster reversal means higher fitness cost). |
| **Research Question/Problem/ Need** | How does antibiotic resistance affect a bacteria population's fitness cost (ability to reproduce)? |
| **Important Figures** | Antibiotic resistance and its cost: is it possible to reverse resistance? \| Nature Reviews Microbiology. The figures here show the growth rate of resistant and susceptible bacteria. In competition, the ratio of susceptible to resistant bacteria exponentially increases. |

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| **VOCAB: (w/definition)** | Fitness cost: a reduction in bacterial growth rate due to the presence of resistance genes, Compensatory evolution: the process by which bacteria acquire additional mutations to offset the fitness cost without losing resistance, Reversibility – the process by which frequency of resistant bacteria decreases due to decreased use of antibiotics, Selection coefficient: numerical measure of the relative fitness difference between two bacteria populations |
| **Cited references to follow up on** | Interplay in the Selection of Fluoroquinolone Resistance and Bacterial Fitness \| PLOS Pathogens<br>Population Genetics of Antibiotic Resistance \| Clinical Infectious Diseases \| Oxford Academic |
| **Follow up Questions** | How do different types of antibiotics, such as beta-lactams and fluoroquinolones, affect the fitness cost they impose on resistant bacteria?<br>What is the accuracy of this model?<br>Which resistance mechanisms will most likely persist |

# Article #3 Notes: Is Mathematics Mostly Chaos or Mostly Order? (Summer reading)

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|---|---|
| **Source Title** | Is Mathematic Mostly Chaos or Mostly Order? |
| **Source citation (APA Format)** | Barber, G., Sloman, L., & Howlett, J. (2025, June 20). Is mathematics mostly chaos or mostly order?. *Quanta Magazine*. https://www.quantamagazine.org/is-mathematics-mostly-chaos-or-mostly-order-20250620/ |
| **Original URL** | https://www.quantamagazine.org/is-mathematics-mostly-chaos-or-mostly-order-20250620/ |
| **Source type** | Journal Article |
| **Keywords** | N/A |
| **#Tags** | #foundations of mathematics #infinity #logic #mathematics #Quanta Podcast #set theory |
| **Summary of key points + notes (include methodology)** | In the 1870s, Georg Cantor proved that infinities can be different sizes when he discovered the size of the set of real numbers (which is infinite) is larger than the size of the set of all integers (which is also infinite). These two sets, as a result of their differing size, have different cardinalities (sizes of infinite sets). Set theorists continued to introduce more cardinalities, and discovered that these cardinalities form a neat hierarchy, which can be used to probe the boundaries of what is mathematically possible. So far, all new cardinalities have fit nicely in this hierarchy, suggesting that math is organized and ordered. However, Juan Aguilera recently discovered two cardinalities that didn't fit nicely in this hierarchy while following the ZFC (“Zermelo-Fraenkel set theory with the axiom of choice.”), the building blocks/rules of mathematics. As a result, the long standing belief that math is ordered has come crashing, and now it is believed that math is chaotic and unstable. |
| **Research Question/Problem/ Need** | Is mathematics more about *order* (neat structure, predictability, hierarchy) or *chaos* (wildness, unpredictability, undecidability)? |

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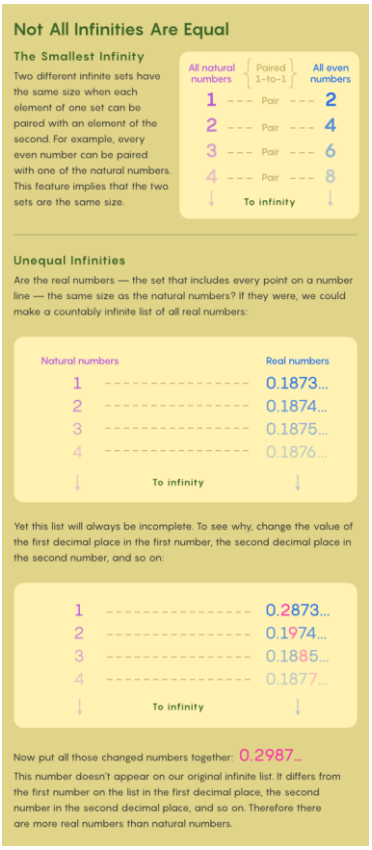
| **Important Figures** |  <br>The above visual shows how some infinities are “equal”, while others are “larger” infinities. |
| **VOCAB: (w/definition)** | Cardinal: the “size” of an infinite set, ZFC (Zermelo-Fraenkel set theory + Choice): A standard axiomatic foundation for much of mathematics, Axiom: Basic assumptions from that are the building blocks of more complex theorems. HOD (hereditarily ordinal definable): Class of sets that are definable in a rigid way, used as a basis for the idea that there is “order”/”predictability” in the universe of sets, Godel’s Theorem: In an axiomatic system, there are statements that are true but unprovable, V: the mathematical universe of all sets |
| **Cited references to follow up on** | No references, but some related articles<br>https://www.quantamagazine.org/to-settle-infinity-question-a-new-law-of-mathematics-20131126/<br>https://www.quantamagazine.org/how-many-numbers-exist-infinity-proof-moves-math-closer-to-an-answer-20210715/ |
| **Follow up Questions** | What would it mean for the mathematical universe V to diverge from the HOD (What happens if math isn’t predictable or ordered like we think it is)? Are there any real-life implications if V diverges from HOD? (Why should I or anyone else care?) |

# Article #4 Notes: **Bioinformatics in translational drug discovery (Summer reading)**

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|---|---|
| **Source Title** | **Bioinformatics in translational drug discovery** |
| **Source citation (APA Format)** | Wooller, S. K., Benstead-Hume, G., Chen, X., Ali, Y., & Pearl, F. M. G. (2017). Bioinformatics in translational drug discovery. *Bioscience reports*, 37(4), BSR20160180. https://doi.org/10.1042/BSR20160180 |
| **Original URL** | https://doi.org/10.1042/BSR20160180 |
| **Source type** | Review Article |
| **Keywords** | Computational biochemistry, drug discovery and design, genomics |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Currently, it takes over a decade and billions of dollars to bring a new drug into the market. Bioinformatics, a field that combines biology, computer science, and math, drastically cuts down the amount of time and money to release a drug by quickly analyzing large datasets of biological data and finding better treatment options. It identifies disease causing genes, and finds new uses for existing drugs. Bioinformatics also supports personalized medicine by grouping patients based on their genetic profiles, and helps create more customized treatment plans. After a new drug is released, it tracks its side effects and safety using patient data. Tools/databases like ChEMBL help organize and analyze patient information. |
| **Research Question/ Problem/ Need** | Since this is a review article, there isn't a clear research question. The closest possible thing to one is, "How can bioinformatic tools be used to improve and accelerate the translational drug discovery process" |

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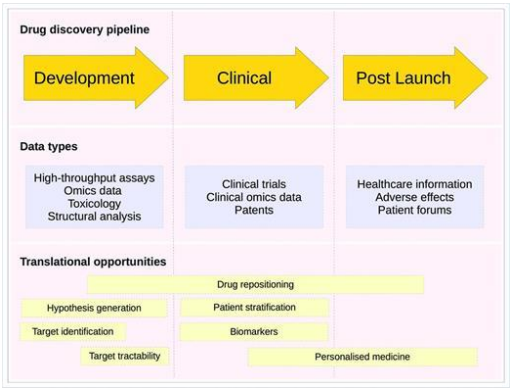
| **Important Figures** |  <br>A diagram showing the drug development process |
| **VOCAB: (w/definition)** | Translational drug discovery: converting scientific research into something useful to humans (usually drugs), bioinformatics: using computational methods to analyze biological data, target identification: finding biological molecules (genes, proteins) that can be acted upon by drugs, biomarkers: biological indicators that can be used to track disease progression. |
| **Cited references to follow up on** | https://www.nature.com/articles/nrd2265<br><br>https://www.sciencedirect.com/science/article/pii/S1359644611000742?casa_token=ANcYN6k5K3oAAAAA:tUNeI7tMk5KNUHV0zP1pjdDhJFGu7rgYqwvLxLAVOP5rep30tk4-29_JN6yw5oHDxS8aNw59yg<br><br>https://academic.oup.com/database/article/doi/10.1093/database/bar026/465210 |
| **Follow up Questions** | How do scientists decide which bioinformatics database to use?<br>How can AI improve the translational drug discovery process?<br>How does the translational drug discovery process differ when dealing with more complex diseases? |

# Article #5 Notes: **Antibiotic resistance in the environment (Summer reading)**

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|---|---|
| **Source Title** | **Antibiotic resistance in the environment** |
| **Source citation (APA Format)** | Larsson, D. G. J., & Flach, C. F. (2022). Antibiotic resistance in the environment. *Nature reviews. Microbiology*, 20(5), 257–269. https://doi.org/10.1038/s41579-021-00649-x |
| **Original URL** | https://doi.org/10.1038/s41579-021-00649-x |
| **Source type** | Review article |
| **Keywords** | Antibiotic resistance, environment, resistome, pollution, wastewater, agriculture, co-selection |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Antibiotic resistance is a major health concern, involving the transfer of resistant bacteria and genes between humans, animals, and the environment. They arise from genetic mutations or from the uptake of foreign DNA. Mutations that are effective against a certain antibiotic will rapidly spread, and eventually will be found in the majority of a bacteria population (Natural selection). Bacteria can also exchange small pieces of DNA which might hold the mutation for resistance. Additionally, the environment acts as a mirror of local resistance levels and an incubator for new resistance genes. In other words, resistant bacteria in an environment reflect the state of antibiotic resistance in local human and animal populations. Some mitigation strategies are to improve wastewater management, enforce stricter pharmaceutical manufacturing policies, and coordinate human, animal, and environmental interventions. |
| **Research Question /Problem / Need** | How does the environment contribute to the emergence and spread of antibiotic resistance? |

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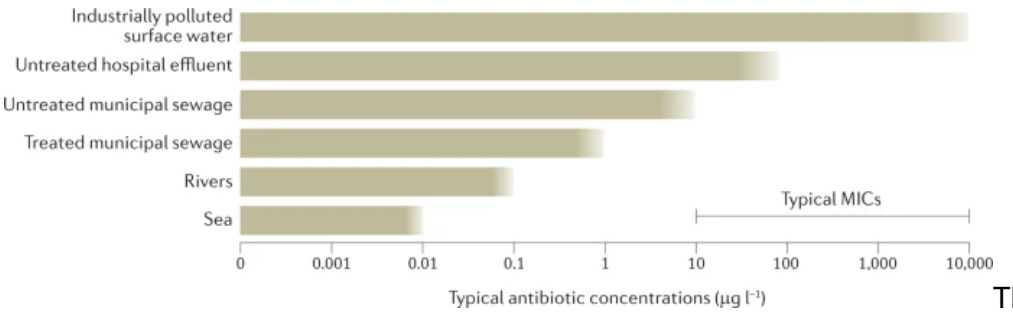
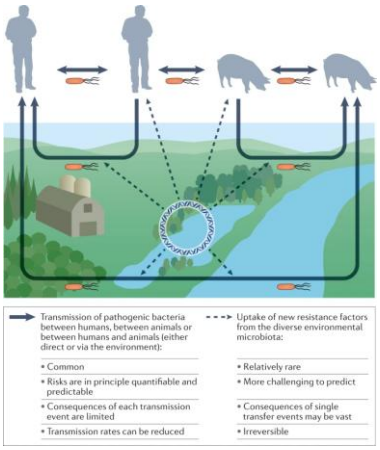
| **Important Figures** |  This graph shows antibiotic concentrations in various environments.<br>  <br>This diagram shows how bacteria can spread between animal and human populations. |
| **VOCAB: (w/definition)** | Antibiotic resistance: bacteria gaining the ability to resist antibiotics, Selective pressure: Environmental factors that favor resistant bacteria, HGT: movement of genetic material between microbes, Resistome: collection of all genes coding for resistance in a population, Hotspot: environment with a really high rate of resistance development, Co-selection: resistance selected by other pollutants with antibiotics, One Health: an integrated view that links humans, animals, and environmental health to tackle resistance |
| **Cited references to follow up on** | https://academic.oup.com/nar/article/48/D1/D517/5608993?login=false<br>https://academic.oup.com/femsre/article/42/1/fux053/4563583?login=false<br><br>https://www.science.org/doi/full/10.1126/science.1220761?casa_token=9vo32rq8N48AAAAA%3AySSRaWCllFjDExc5Kt1YcOEMKk1x13tZItdeQnXd8CvxfN3KFxAAoF_H4wopkodOTwbr4OhXBd6ALug |
| **Follow up Questions** | What policies can reduce antibiotic pollution from pharmaceutical production?<br>How can wastewater treatment plants be designed to minimize resistance spread?<br>How can we measure resistance mobility in real ecosystems? |

# Article #6 Notes: Bacteriophages as Environmental Reservoirs of Antibiotic Resistance

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|---|---|
| **Source Title** | Bacteriophages as Environmental Reservoirs of Antibiotic Resistance |
| **Source citation (APA Format)** | Calero-Cáceres, W., Ye, M., & Balcázar, J. L. (2019). Bacteriophages as Environmental Reservoirs of Antibiotic Resistance. *Trends in Microbiology*, *27*(7), 570–577. https://doi.org/10.1016/j.tim.2019.02.008 |
| **Original URL** | https://doi.org/10.1016/j.tim.2019.02.008 |
| **Source type** | Review article |
| **Keywords** | environmental settings, bacteria, antibiotic resistance, antibiotic resistance genes, mobile genetic elements, bacteriophages |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Bacteriophages are viruses that infect bacteria. They have 2 phases of life: the lytic cycle where they use bacteria to rapidly produce new phages which are released from the cell, or the lysogenic phase where the phage integrates its genome into the host's chromosome.<br>Many antibiotic-resistant genes (ARGs) have been found in reservoirs, and these ARGs are related to bacteria found in humans and animals.<br>Additionally, pollution sources such as sewage are filled with ARGs, which can then be spread to natural waterbodies (rivers, oceans, etc)<br>Phages containing ARGs are typically found closer to areas with human activity.<br>Wastewater treatment plants are the main hotspot for ARGs. Various methods (such as UV exposure) had variable results on resistant bacteria and ARGs. Phages with ARGs were shown to be incredibly resilient to these treatment methods.<br>Phages harboring ARGs highlight the importance of monitoring the evolution and spread of antibiotic resistance in a population. |
| **Research Question/Problem/ Need** | How do bacteriophages act as reservoirs for ARGs, and what role does human activity play in influencing their persistence and spread? |

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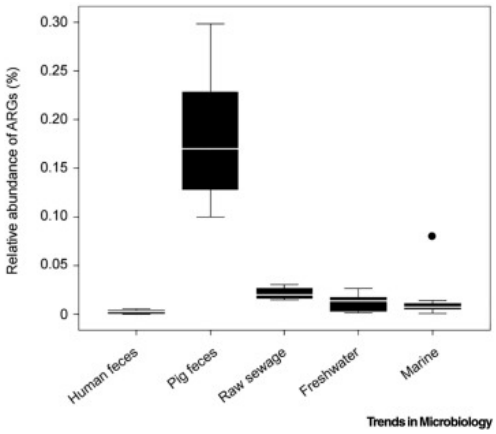
| **Important Figures** |  <br>This diagram shows the abundance of ARGs in various environments. Pig feces have by far the largest amount of ARGs compared to the other environments in the study. |
| **VOCAB: (w/definition)** | Bacteriophage: virus that infects bacteria, ARG: gene that gives bacteria the ability to resist antibiotics, Transduction: Phage-mediated transfer of bacterial DNA, Prophage: a phage genome integrated into a bacterial chromosome, Metagenomics: sequencing/analysis of DNA from a population rather than an individual, Virome: collection of viruses in a particular environment |
| **Cited references to follow up on** | A century of phage research: Bacteriophages and the shaping of modern biology - PMC<br>Frontiers \| The multifaceted roles of antibiotics and antibiotic resistance in nature |
| **Follow up Questions** | What factors facilitate the transfer of ARGs via transduction?<br>What ARGs are most commonly found in phages?<br>What are the limitations of metagenomics in accurately quantifying phage-borne ARGs? |

# Article #7 Notes: **Predictive Modeling of Antibiotic Susceptibility in E. Coli Strains Using the U-Net Network and One-Class Classification**

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|---|---|
| **Source Title** | **Predictive Modeling of Antibiotic Susceptibility in E. Coli Strains Using the U-Net Network and One-Class Classification** |
| **Source citation (APA Format)** | Ali, N., Kirchhoff, J., Onoja, P. I., Tannert, A., Neugebauer, U., Popp, J., & Bocklitz, T. (2020). Predictive Modeling of Antibiotic Susceptibility in *E. Coli* Strains Using the U-Net Network and One-Class Classification. *IEEE Access*, *8*, 167711-167720. https://doi.org/10.1109/ACCESS.2020.3022829 |
| **Original URL** | https://doi.org/10.1109/ACCESS.2020.3022829 |
| **Source type** | Research article |
| **Keywords** | Antibiotic resistance, E. coli, U-Net convolutional neural network, one-class SVM |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Background: E. coli, while often beneficial in the digestive track, can be harmful in the urinary or in the intestinal track. Because of their prevalence, antibiotics have been used to try and stop them, but overuse has led to many strains gaining resistance.<br>Summary: The authors developed an image-based approach to detect whether various E. coli strains were susceptible or resistant to three types of antibiotics: ciprofloxacin, cefotaxime, and piperacillin. They then took images of treated and un-treated E. coli cultures. They used a U-Net convolutional neural network to isolate bacterial regions in the taken images. After that, they repurpose the U-Net CNN model so that it takes in the morphological and structural information of a bacteria cluster.<br>Bacteria that looked like the control (untreated) population were considered resistant, while bacteria that have a different morphology than the control are considered susceptible, or anomalous. To do this, they used a one-class support vector machine (OCSVM) trained only on images of the control.<br>Using a U-Net CNN model leads to an 0.83 area under the Receiver Operating Characteristic curve, which indicates that the model is very accurate.<br>Cefotaxime had a 91.7% sensitivity rate, piperacillin had an 86.6% sensitivity |

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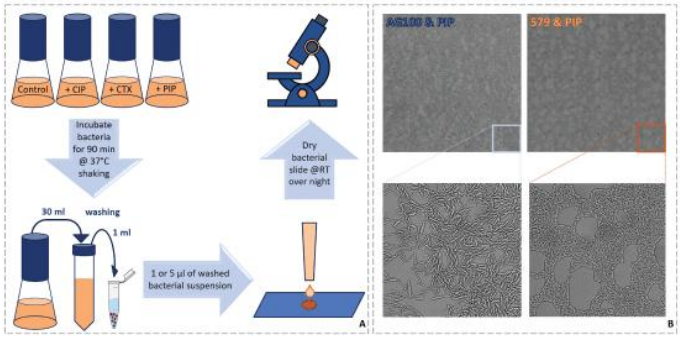
| | rate, and ciprofloxacin had a 59.7% sensitivity rate (the sensitivity rate is the rate at which the model successfully detects whether a bacterium is sensitive or not).<br>Methodology: 12 E. coli strains (AG100 and 11 other clinical isolates) were each treated with 0.5mg/L of ciprofloxacin, 2mg/L of cefotaxime, and 16mg/L of piperacillin. Then 5 microliters of each treatment are put onto slides, and the slides are imaged. The images are split into 128 * 128 patches, and then are put through the U-Net CNN, where bacterial regions that cover over 90% of the patch are selected for further study. The U-Net CNN is then modified to search for the morphology of each bacteria population. An OCSVM is then trained on control bacteria populations to detect which bacteria are susceptible or resistant. Sensitivity rates were then found for each antibiotic type based on the data from the OCSVM model. |
| **Research Question/Problem/ Need** | Can machine learning models be used to analyze images and accurately determine whether an E. coli is susceptible to antibiotics or not? |
| **Important Figures** |  <br>Bacteria are treated with various antibiotics. They then are washed, and a microliter of the bacteria-antibiotic solution is put on a slider. Zoomed-in images are then taken of the bacteria populations. |
| **VOCAB: (w/definition)** | U-Net: a deep learning convolutional neural network used for image segmentation, One-Class Support Vector Machine (OCSVM): an ML method used to classify data as “normal” and “not normal”, Threshold: a cutoff value for deciding whether a bacteria is resistant or sensitive, Receiver Operating Characteristic: a graph of true positive rate vs false positive rate |
| **Cited references to follow up on** | The Antibiotic Resistance Crisis: Part 1: Causes and Threats - PMC<br>Using Machine Learning To Predict Antimicrobial MICs and Associated Genomic Features for Nontyphoidal Salmonella \| Journal of Clinical Microbiology |
| **Follow up Questions** | Why does ciprofloxacin yield the weakest predictions out of all the antibiotics?<br>Could using a time-lapse instead of snapshot imaging improve resistance detection?<br>How would the performance of other models (random forest) compare with OCSVM? |

# Article #8 Notes: Stability and periodic solutions for a model of bacterial resistance to antibiotics caused by mutations and plasmids

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| **Source Title** | Stability and periodic solutions for a model of bacterial resistance to antibiotics caused by mutations and plasmids |
| **Source citation (APA Format)** | Ibargüen-Mondragón, E., Romero-Leiton, J. P., Esteva, L., Cerón Gómez, M., & Hidalgo-Bonilla, S. P. (2019). Stability and periodic solutions for a model of bacterial resistance to antibiotics caused by mutations and plasmids. *Applied Mathematical Modelling*, *76*, 238–251. https://doi.org/10.1016/j.apm.2019.06.017 |
| **Original URL** | Stability and periodic solutions for a model of bacterial resistance to antibiotics caused by mutations and plasmids - ScienceDirect |
| **Source type** | Research article |
| **Keywords** | Bacteria, drug resistance, plasmids, ordinary differential equations, stability |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | The authors created a mathematical model analyzing how bacterial populations develop resistance through genetic mutations and plasmid transfer. The researchers set S(t) as the population of susceptible bacteria, R(t) as the population of resistant bacteria, P(t) as the number of plasmids, and C(t) as antibiotic concentration. They also set two parameters, R_s as the basic reproductive number for susceptible bacteria, and R_r as the basic reproductive number for resistant bacteria. The model predicts three biological equilibrium points. In bacteria-free equilibrium (P_0), R_s and R_r are both less than one, and both bacteria populations are eliminated. In resistant-only equilibrium (P_1), R_r > 1 and R_s is below a certain threshold, and only susceptible bacteria are killed off. In coexistence equilibrium (P_2), R_s > 1 and R_r is below a certain threshold, meaning both susceptible and resistant populations survive. The authors then used real values from Staphylococcus aureus, and ran simulations which found the conditions for the three equilibrium cases above.<br>Methodology: The authors constructed a deterministic system of four ordinary differential equations describing the time evolution of S(t), R(t), P(t), and C(t). Each equation captures essential biological processes such as bacterial growth/carrying capacity, mutation rate, plasmid transmission rate, |

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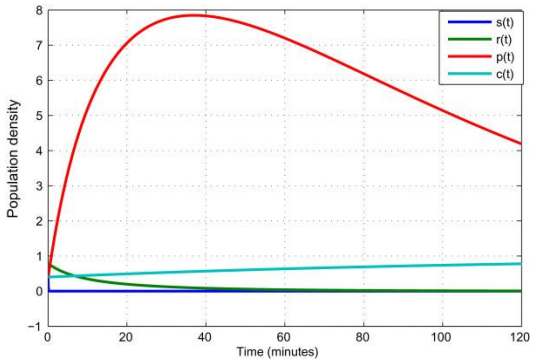
| | immune elimination rate, and antibiotic concentration changes. The model is then simplified so that it becomes easier to analyze while retaining important necessary info/equations. All of the ODEs are then set to 0 to find the states of equilibrium, which are bacteria-free equilibrium, resistance-only equilibrium, and coexistence equilibrium. The Jacobian matrix for the system is computed at each equilibrium point to gauge the stability of the system. The eigenvalues of the Jacobian matrices are analyzed. If they all have negative real parts, the system is stable. If they have at least one positive real part, the system is unstable. Through this, the researchers found at what basic reproduction numbers the system was stable at. Finally, the researchers performed numerical experiments to validate the model. |
| **Research Question/Problem/ Need** | How does genetic mutation and plasmid transmission affect susceptible and resistant bacteria populations when exposed to antibiotics? |
| **Important Figures** |  <br>This graph shows concentrations of antibiotics, resistant bacteria, susceptible bacteria, and plasmids in an example simulation. There are no susceptible bacteria in the system. As antibiotic concentration slowly rises, resistant bacteria concentration falls. Plasmid concentration rises first, but after it peaks at around 35 minutes, it starts to fall as well. |
| **VOCAB: (w/definition)** | Plasmid: small DNA molecule that can store genes (including ARGs) and be transferred between bacteria, Ordinary differential equation (ODE): mathematical equations used to describe how variables change over time, Equilibrium: a condition in which variables don't change over time, Jacobian matrix: mathematical matrix used to describe how small changes affect stability of a system near equilibrium, Eigenvalues: values that determine if a system is stable or not, Hopf bifurcation: phenomenon where a steady state becomes unstable and oscillating behavior begins, Basic reproduction number: threshold value that determines whether a population will survive or die out, Deterministic model: a model that assumes there is no randomness |
| **Cited references to follow up on** | Mathematical modeling on bacterial resistance to multiple antibiotics caused by spontaneous mutations - ScienceDirect<br>Mathematical modelling of bacterial resistance to multiple antibiotics and immune system response \| SpringerPlus |

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| | Comparison of stochastic and random models for bacterial resistance \| Advances in Continuous and Discrete Models \| Full Text |
| **Follow up Questions** | What additional factors could be added to make the model more realistic?<br>What parameters will be affected if another bacteria species is used?<br>How might the model's predictions differ if randomness is added into the model? |

Article #9 Notes: **Abundances of Tetracycline, Sulphonamide and Beta-Lactam Antibiotic Resistance Genes in Conventional Wastewater Treatment Plants (WWTPs) with Different Waste Load**

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|---|---|
| **Source Title** | **Abundances of Tetracycline, Sulphonamide and Beta-Lactam Antibiotic Resistance Genes in Conventional Wastewater Treatment Plants (WWTPs) with Different Waste Load** |
| **Source citation (APA Format)** | Laht, M., Karkman, A., Voolaid, V., Ritz, C., Tenson, T., Virta, M., & Kisand, V. (2014). Abundances of Tetracycline, Sulphonamide and Beta-Lactam Antibiotic Resistance Genes in Conventional Wastewater Treatment Plants (WWTPs) with Different Waste Load. *PLoS ONE*, *9*(8), e103705. https://doi.org/10.1371/journal.pone.0103705 |
| **Original URL** | https://doi.org/10.1371/journal.pone.0103705 |
| **Source type** | Research article |
| **Keywords** | Antibiotic resistance, ribosomal RNA, effluent, water pollution, tetracyclines, water quality, PCR |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Wastewater treatment plants are hotspots for bacteria to grow and mutate, and as a result have very high ARG concentrations. Researchers went to three plants of different sizes; one in Helsinki, one in Tallinn, and one in Tartu. They quantified 7 ARGs using qPCR. ARG levels were normalized against the 16S rRNA gene to account for differences in microbial abundance. The most commonly found ARGs across all wastewater samples were sul1, sul2, and tetM. After treatment, the proportion of each ARG to total bacterial load usually remained about the same. Sometimes, the number of specific types of ARG can experience a drastic decrease, and in each plant, it was a different ARG that experienced this decrease. |
| **Research Question/Problem/ Need** | What effect do wastewater treatment plants have on the prevalence of ARGs during the treatment process? |

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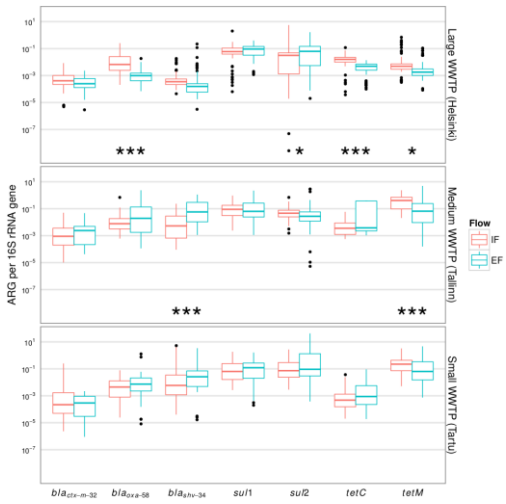
| **Important Figures** |  This diagram shows the relative abundance of each ARG in the three wastewater treatment plants. |
| **VOCAB: (w/definition)** | QPCR: amplifies and measures specific DNA sequences in real time, 16S rDNA gene: bacterial gene used as a marker for bacterial abundance, Normalization: adjusting raw data relative to a standard, Influent: untreated wastewater, Effluent: treated wastewater |
| **Cited references to follow up on** | Distribution and Quantification of Antibiotic Resistant Genes and Bacteria across Agricultural and Non-Agricultural Metagenomes \| PLOS One<br>Detection of antibiotic-resistant bacteria and their resistance genes in wastewater, surface water, and drinking water biofilms \| FEMS Microbiology Ecology \| Oxford Academic |
| **Follow up Questions** | Why was sulfonamide resistance gene (sul1, sul2) abundance stable across all the plants?<br>Does the size of wastewater treatment plant affect ARG behavior, or do the differences have to do more with the plant than size?<br>Would using metagenomics sequencing instead qPCR change the amount of ARGs tested? |

# Article #10 Notes: Evolution of Antibiotic Resistance without Antibiotic Exposure

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|---|---|
| **Source Title** | Evolution of Antibiotic Resistance without Antibiotic Exposure |
| **Source citation (APA Format)** | Knöppel, A., Näsvall, J., & Andersson, D. I. (2017). Evolution of Antibiotic Resistance without Antibiotic Exposure. *Antimicrobial Agents and Chemotherapy*, *61*(11), e01495-17. https://doi.org/10.1128/AAC.01495-17 |
| **Original URL** | https://doi.org/10.1128/AAC.0 95-17 |
| **Source type** | Research article |
| **Keywords** | Antibiotic resistance, decreased susceptibility, pleiotropy, coselection, selective pressure |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | It is well known that bacteria gain resistance when faced with antibiotics, but what about if there are no antibiotics? Researchers grew 500-1000 generations of E. coli and salmonella in four different growth media that contained no antibiotics. Many of these bacteria developed decreased susceptibility to multiple types of antibiotics, such as rifampin and streptomycin. Whole-genome sequencing revealed that mutations linked with resistance had occurred. These mutations were likely pleiotropic (they increased fitness and decreased susceptibility). It was found that 3.5% of the bacteria showed decreased susceptibility, while only 0.6% showed increased susceptibility. |
| **Research Question/Problem/ Need** | Can bacteria gain increased resistance to antibiotics without being exposed to them? |

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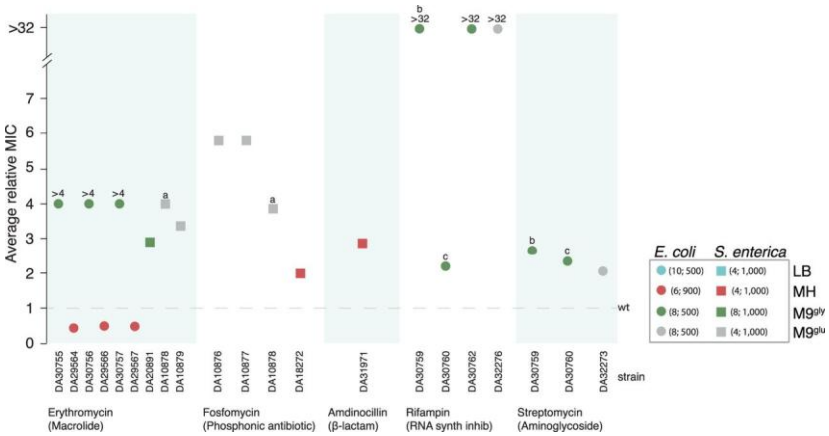
| **Important Figures** |  <br>The y axis of this diagram represents the average MIC, while the x axis represents different strains of E. coli and salmonella. Most strains experienced reduced susceptibility, but a couple of E. coli strains became more susceptible to erythromycin. |
| **VOCAB: (w/definition)** | Selective pressure: environmental factor that influences which organisms reproduce, Pleiotropy: when a single mutation affects multiple traits, MIC: lowest concentration of an antibiotic that prevents visible bacterial growth, Parallel evolution: when separate populations independently develop similar mutations under similar conditions |
| **Cited references to follow up on** | Evolution of Escherichia coli rifampicin resistance in an antibiotic-free environment during thermal stress \| BMC Ecology and Evolution<br>Molecular Microbiology \| Microbiology Journal \| Wiley Online Library |
| **Follow up Questions** | Why was decreased susceptibility more common than increased susceptibility? What role can climate play in affecting resistance to antibiotics? |

# Article #11 Notes: Comparison of stochastic and random models for bacterial resistance

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|---|---|
| **Source Title** | Comparison of stochastic and random models for bacterial resistance |
| **Source citation (APA Format)** | Merdan, M., Bekiryazici, Z., Kesemen, T., & Khaniyev, T. (2017). Comparison of stochastic and random models for bacterial resistance. *Advances in Differential Equations*, *2017*(1), 133. https://doi.org/10.1186/s13662-017- |
| **Original URL** | Comparison of stochastic and random models for bacterial resistance \| Advances in Continuous and Discrete Models \| Full Text |
| **Source type** | Research paper |
| **Keywords** | Antibiotic resistance, deterministic model, random differential equations, stochastic differential equations, immune system response, antibiotic therapy, Gaussian noise |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Summary: Traditional models of bacteria resistance, while effective, don't capture the variability found in real bacteria populations due to a lack of randomness within the model. The authors of this article decided to compare three modeling approaches (deterministic, stochastic, random) to address these limitations.<br>The model tracks 4 variables (susceptible bacteria population, resistant bacteria population, immune cell count, and antibiotic concentration) using differential equations. To add uncertainty into the model, the authors turned the regular differential equations into random differential equations, where each parameter is turned into a normally distributed random variable to represent biological variability between each individual, and into stochastic differential equations, where Brownian motion is added to introduce continuous fluctuations (represents environmental/temporal randomness). 100,000 simulations were then run using MATLAB to calculate expected values, variances, and the confidence interval, allowing the authors to observe how random variations affected model outcomes. When comparing the different types of models, the authors found they all displayed similar trends, such as a declination of susceptible bacteria, stabilization of resistant bacteria, an increase in immune cell count, and a decrease in antibiotic concentration. However, the random and stochastic models showed far greater variability, and deviations for resistant bacteria and immune cell count reached up to 22.9%.<br>Methodology: s(t), r(t), b(t), and a(t) are functions defined as the number of susceptible bacteria, resistant bacteria, immune cells, and antibiotics at time |

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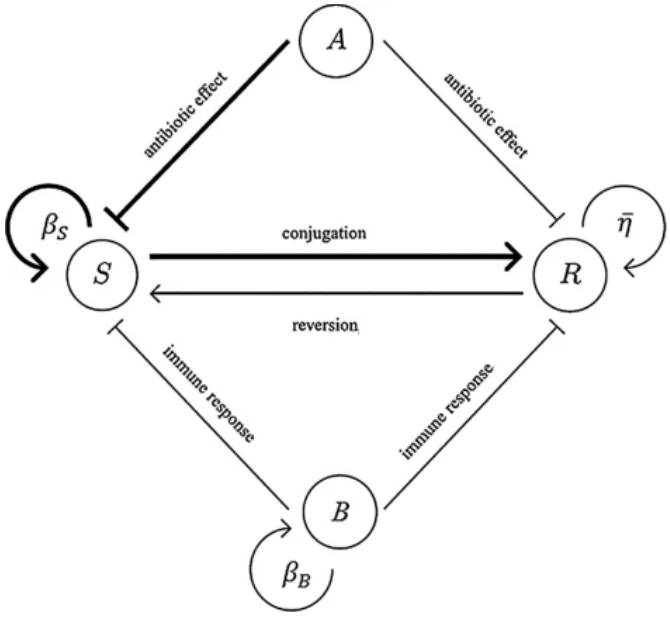
| | t. These functions are deterministic, and don't display any randomness. Numerical simulations for these equations were run using MATLAB. The parameters were then turned into normally distributed random variables with a standard deviation of 5%. This produced a system of random differential equations. 100,000 simulations were run on MATLAB, and expected values, variances, and confidence intervals were calculated based on these simulations. Stochastic noise was then added to the deterministic equations to produce stochastic equations. The time evolutions, extreme values, expected values/variances, and confidence intervals of each model were compared, and the random and stochastic models both had some uncertainty that deterministic models didn't reflect. |
| **Research Question/Problem/ Need** | How does incorporating random/stochastic effects into a deterministic model influence the predicted dynamics between resistant bacteria, susceptible bacteria, immune cells, and antibiotic concentration? |
| **Important Figures** |  <br>This diagram is a flowchart showing how each variable or function interacts with each other in the model. The arrows from S to R and vice-versa show susceptible bacteria and resistant bacteria turning into each other. The lines between A/B and S/R show how immune cells and antibiotics interact with the bacteria. The looping arrows represent bacteria/immune cell reproduction. |
| **VOCAB: (w/definition)** | Random model: a model where parameters are random variables drawn from a probability distribution, stochastic model: a model where randomness is introduced continuously through stochastic noise, Brownian motion: a continuous random process used to model unpredictable variation, confidence interval: a statistical interval indicating where the value of a variable is likely to fall, normally distributed random variables: a variable whose value is determined off a normal distribution |

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| **Cited references to follow up on** | Modeling antibiotic resistance in hospitals: The impact of minimizing treatment duration - ScienceDirect<br>Studies of antibiotic resistance within the patient, hospitals and the community using simple mathematical models \| Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences<br>Full article: A comparison of a deterministic and stochastic model for Hepatitis C with an isolation stage |
| **Follow up Questions** | How can one validate a stochastic resistance model using lab data?<br>How do random and stochastic models differ in how they convey uncertainty?<br>What biological processes correspond to the random fluctuations and noise found in a stochastic model? |

# Article #12 Notes: The effect of antibiotics on the gut microbiome: a metagenomics analysis of microbial shift and gut antibiotic resistance in antibiotic treated mice

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| **Source Title** | The effect of antibiotics on the gut microbiome: a metagenomics analysis of microbial shift and gut antibiotic resistance in antibiotic treated mice. |
| **Source citation (APA Format)** | Xu, L., Surathu, A., Raplee, I., Chockalingam, A., Stewart, S., Walker, L., Sacks, L., Patel, V., Li, Z., & Rouse, R. (2020). The effect of antibiotics on the gut microbiome: A metagenomics analysis of microbial shift and gut antibiotic resistance in antibiotic treated mice. *BMC Genomics*, *21*(1), 263. https://doi.org/10.1186/s12864-020-6665-2 |
| **Original URL** | The effect of antibiotics on the gut microbiome: a metagenomics analysis of microbial shift and gut antibiotic resistance in antibiotic treated mice \| BMC Genomics |
| **Source type** | Research paper |
| **Keywords** | Antibiotics, antimicrobial resistance, metagenomics, microbiome, microbiota, antibacterial drug resistance |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Summary: This study investigates how various oral antibiotics (ampicillin, ciprofloxacin, and fosfomycin) affect the gut microbiome composition and resistome in mice being treated for urinary tract infection. The researchers gave the mice the antibiotics mentioned above, and measured how the gut microbiome and ARG abundance changed before and after the antibiotics. Results revealed that all 3 antibiotics significantly disturbed the gut microbiome, though in different ways. Ampicillin drastically reduced the microbial diversity in the gut, killed off many beneficial bacteria, and led to the rise of many resistant bacteria (E. Coli). Additionally, the ampicillin's effect on the gut was long term, meaning even after treatment stopped, the mouse's gut microbiome never recovered. Ciprofloxacin also reduced diversity in the gut microbiome, although the effect was less pronounced than the ampicillin (it only targeted gram-negative bacteria), and partial recovery in the gut microbiome was observed. Fosfomycin was the least disruptive of all the antibiotics. While beneficial bacteria populations did dip, they rebounded very quickly. For all of the antibiotics, the gut resistome expanded and the gut microbiome was harmed, highlighting how they must be used in moderation.<br>Methodology: A mice population was divided into 4 groups. One was given ampicillin, another was given ciprofloxacin, the third one was given fosfomycin, |

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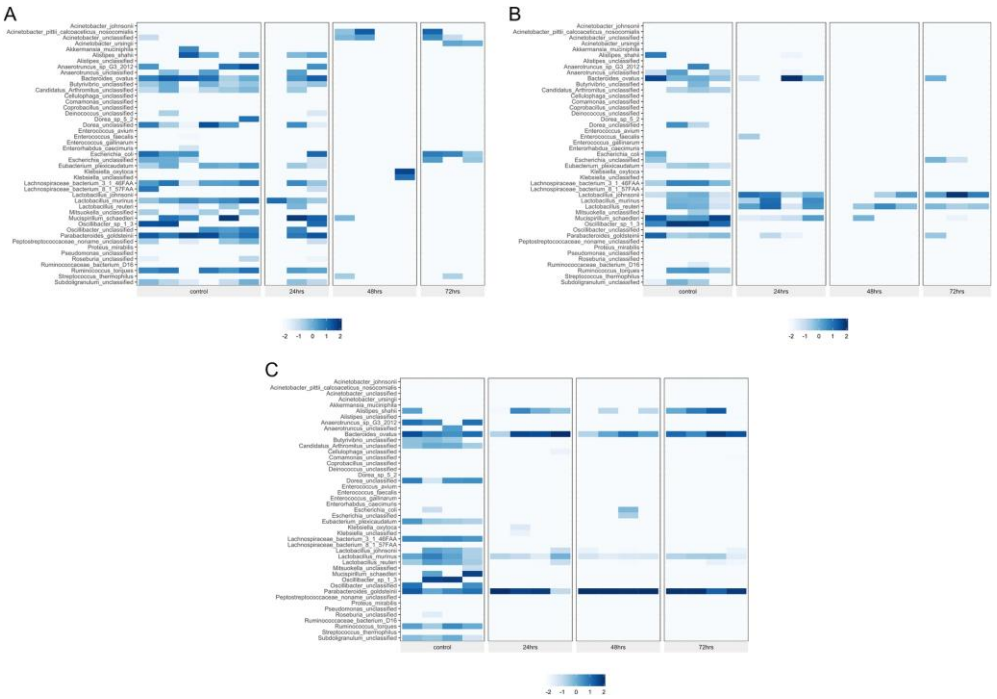
| | and the final group was given no antibiotics (served as control group). Fecal samples were collected multiple times before, during, and after antibiotic treatment. DNA was extracted from the samples and analyzed using metagenomic sequencing to detect beneficial bacteria and ARG concentrations. The data from the metagenomic sequencing was then processed through bioinformatics pipelines to filter out low-quality reads and align the found DNA sequences to sequences found in microbe and ARG databases. The Shannon diversity index for gut bacteria and ARG diversity were both found. Temporal trends were analyzed to determine how rapidly the gut microbiome and resistome responded to the antibiotics. |
| **Research Question/Problem/ Need** | How do antibiotic treatments for urinary tract infection affect the composition of gut bacteria in mice and the abundance/diversity of ARGs over time? |
| **Important Figures** |  <br>These figures show how various gut bacteria populations are affected by the presence of Ampicillin (A), Ciprofloxacin (B), and Fosfomycin (C). The rows are bacteria species, the columns are time periods, and the colors represent how the population has changed. Darker colors mean little to no decrease, while lighter colors represent a significant population decrease. |
| **VOCAB: (w/definition)** | Gut microbiome: collective genetic material of all microbes in the gut, commensal bacteria: beneficial bacteria that inhabit the gut and contribute to digestion, Ampicillin: an antibiotic that inhibits cell wall synthesis, Ciprofloxacin: an antibiotic that interferes with DNA replication, Fosfomycin: antibiotic that inhibits cell wall formation |
| **Cited references to follow up on** | Long-term ecological impacts of antibiotic administration on the human intestinal microbiota \| The ISME Journal \| Oxford Academic |

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| | Antibiotic-Induced Changes in the Intestinal Microbiota and Disease - ScienceDirect<br>Functional genomic and metagenomic approaches to understanding gut microbiota–animal mutualism - ScienceDirect |
| **Follow up Questions** | Would the results of this study remain the same if the host organism were different?<br>How might other factors such as age or diet have influenced the outcome?<br>Could gut microbiome changes caused by antibiotic use cause later complications such as diabetes? |

# Article #13 Notes: Modeling the interaction between bacteriophages and their bacterial hosts

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|---|---|
| **Source Title** | Modeling the interaction between bacteriophages and their bacterial hosts |
| **Source citation (APA Format)** | Beke, G., Stano, M., & Klucar, L. (2016). Modelling the interaction between bacteriophages and their bacterial hosts. *Mathematical Biosciences*, *279*, 27–32. https://doi.org/10.1016/j.mbs.2016.06.009 |
| **Original URL** | Modelling the interaction between bacteriophages and their bacterial hosts - ScienceDirect |
| **Source type** | Journal Article |
| **Keywords** | Bacteriophage, bacteria, phage therapy, model |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Summary: Existing models that describe phage-bacteria dynamics typically use delayed differential equations, but fail to account for environmental factors, most notably temperature and pH. To address this, the authors combine a model from literature (Shrag & Mittler, 1996) which describes phage-bacteria dynamics in a chemostat, and another model from literature (Rosso et al., 1995) which describe how bacteria populations are affected by the environment's temperature and pH, and is used to replace the maximum bacterial growth parameter (**μ-max**). By replacing the parameter with a function, the model now accounts for how deviations from optimal temperature and pH affect bacterial reproduction rate. Using R, the authors calculated expected populations based off the equations and plotted them on a graph.<br>Methodology: The authors first implemented the Schrag & Mittler (1996) delayed differential equation model, which models resource dynamics (inflow and outflow of nutrients into the system), uninfected bacteria population, infected bacteria population, and number of phage particles. The authors replaced the **μ-max** parameter with a microbial growth function (Rosso et al., 1995), which calculates the maximum growth rate for a bacteria based on the temperature and pH of an environment. The rest of the parameters for the models are derived from previous literature on E. coli. The authors then used R to solve and plot all of the differential equations. |
| **Research Question/Problem/ Need** | How do temperature and pH affect the population dynamics between bacteriophages and their bacterial hosts? |

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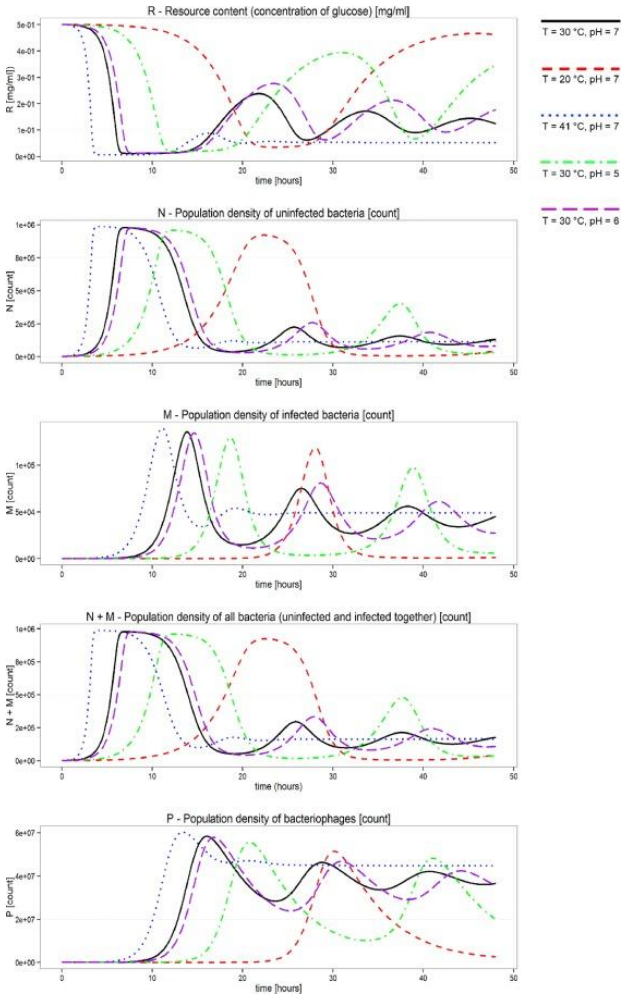
| **Important Figures** |  <br>These figures show how each population (resource content, uninfected bacteria, infected bacteria, bacteriophage) is affected by temperature and pH over time. Each of the graphs represents a population, and each of the lines in each graph represents the population at a specific temperature and pH. |
| **VOCAB: (w/definition)** | Chemostat: a system with constant nutrient inflow and outflow (used to mode continuous microbial growth), Delayed differential equation: a differential equation that incorporates time delays |
| **Cited references to follow up on** | Host-Parasite Coexistence: The Role of Spatial Refuges in Stabilizing Bacteria-Phage Interactions \| The American Naturalist: Vol 148, No 2<br>Convenient Model To Describe the Combined Effects of Temperature and pH on Microbial Growth \| Applied and Environmental Microbiology<br>The next generation of bacteriophage therapy - ScienceDirect |
| **Follow up Questions** | How might additional environmental factors such as O2 levels alter the predicted bacteria populations?<br>How sensitive is this model to small changes?<br>How can this model be adapted to phage therapy in humans, where temperatures and pH fluctuate constantly? |

# Article #14 Notes: Modeling Non-inherited Antibiotic Resistance

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| **Source Title** | Modeling Non-inherited Antibiotic Resistance |
| **Source citation (APA Format)** | Bootsma, M. C. J., Van Der Horst, M. A., Guryeva, T., Ter Kuile, B. H., & Diekmann, O. (2012). Modeling Non-inherited Antibiotic Resistance. *Bulletin of Mathematical Biology*, *74*(8), 1691–1705. https://doi.org/10.1007/s11538-012-9731-3 |
| **Original URL** | Modeling Non-inherited Antibiotic Resistance \| Bulletin of Mathematical Biology |
| **Source type** | Journal Article |
| **Keywords** | Antibiotics, antimicrobial resistance, biological models, genetic models, model prokaryotes, antibacterial drug resistance |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Summary: This article develops a mathematical model describing non-inherited resistance in E. coli. Unlike resistance caused by mutations or horizontal gene transfer, this form of resistance arises through reversible cell adaptations, such as increased production of efflux pumps. The authors collected laboratory time-series data on E. coli exposed to varying concentrations of tetracycline, amoxicillin, and enrofloxacin. They measured resistance using the MIC at multiple time points. Their observations showed that the MIC in the tetracycline and amoxicillin slowly increased, while the MIC in the enrofloxacin has a massive spike (evidence of genetic mutation). Therefore, the model was only applied to tetracycline and amoxicillin experiments. The model uses ODEs to measure external antibiotic concentration, internal antibiotic concentration, efflux pump concentration, and MIC. The equations are then combined into a single ODE that measures MIC value based on efflux regulation. Using a Monte Carlo Markov Chain, the authors show that the model can accurately predict the development of non-inherited resistance.<br>Methodology: The authors grew E. coli MG1655 under constant and stepwise increasing tetracycline/amoxicillin/enrofloxacin concentrations over 15-21 days. At multiple time points, bacteria samples were transferred into 96-well plates containing 2-fold dilution series of antibiotics. MIC values were recorded and used to create time-series MIC curves. Due to the sharp increase in MIC values for enrofloxacin, they were not considered when creating the model. When creating the model, the authors built a system of ODE equations describing external antibiotic concentration (A0), internal |

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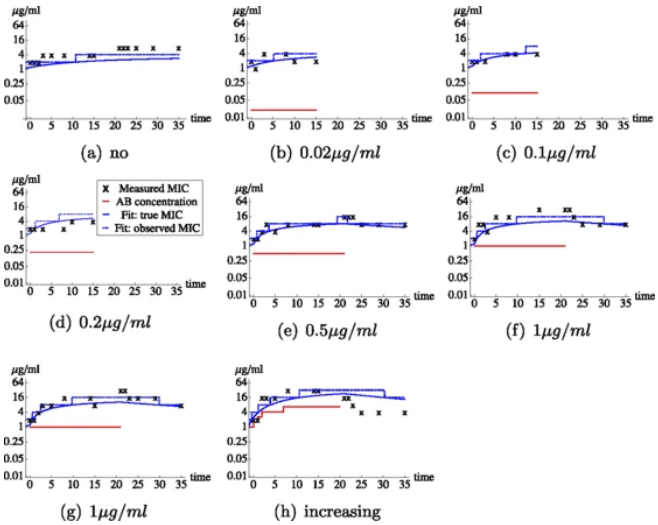
| | antibiotic concentration (A), and efflux pump concentration (E). The equations were then crunched into a singular ODE describing MIC value. The parameters of the equation were estimated using MCMC. The model was then fit to the tetracycline and amoxicillin experiments. |
| **Research Question/Problem/ Need** | How can we mathematically predict the development of non-inherited (physiological, reversible) antibiotic resistance in bacteria? |
| **Important Figures** |  <br>These figures show observed MIC values of bacteria over time when treated with tetracycline. In (a), the bacteria were grown without antibiotics. In (b)-(d), the bacteria were given tetracycline over a 15-day period. In (e)-(g), the bacteria were treated over a 21-day period and continued growing for another 14 days after treatment was over. In (h), the antibiotic concentration was stepwise increased. |
| **VOCAB: (w/definition)** | Non-inherited resistance: reversible increase in tolerance to antibiotics, efflux pumps: proteins that transport antibiotic molecules out of the cell, MIC: lowest antibiotic concentration that prevents visible growth after 24 hours, OD600: measure of bacterial growth based on light absorbance at 600 nm, Monte Carlo Markov Chain (MCMC): computational method used to estimate parameter distributions |
| **Cited references to follow up on** | De Novo Acquisition of Resistance to Three Antibiotics by Escherichia coli - Michael A. van der Horst, Jasper M. Schuurmans, Marja C. Smid, Belinda B. Koenders, Benno H. ter Kuile, 2011<br>Variations in MIC value caused by differences in experimental protocol - ScienceDirect<br>Gram-negative antibiotic resistance: there is a price to pay \| Critical Care |
| **Follow up Questions** | Why does tetracycline lead to predominantly physiological adaptations, while enrofloxacin leads to genetic mutations?<br>How sensitive are MIC measurements to growth conditions such as O2 levels?<br>Can this model be extended to include genetic mutation as well? |

# Article #15 Notes: Computer-assisted modeling of Quorum sensing in bacterial populations exposed to antibiotics

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| **Source Title** | Computer-assisted modeling of Quorum sensing in bacterial populations exposed to antibiotics |
| **Source citation (APA Format)** | Kuttler, C., & Maslovskaya, A. (2022). Computer-assisted modeling of Quorum sensing in bacterial population exposed to antibiotics. *Frontiers in Applied Mathematics and Statistics*, *8*, 951783. https://doi.org/10.3389/fams.2022.951783 |
| **Original URL** | Frontiers \| Computer-assisted modeling of Quorum sensing in bacterial population exposed to antibiotics |
| **Source type** | Journal article |
| **Keywords** | Antibiotic resistance, math modeling, Quorum sensing, partial differential equations, reaction-diffusion model, computer-assisted simulation |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Summary: This article presents a hybrid mathematical and computational study of quorum sensing in bacterial populations exposed to antibiotics. Using Pseudomonas putida IsoF as a representative gram-negative bacterium, the authors developed an in-silico model that captures the dynamics of bacterial growth, antibiotic-induced degradation, and quorum sensing signaling. The model specifically tracks the concentration of AHL, the primary quorum sensing signal molecule, and Lactonase, an enzyme that degrades AHL. Quorum sensing is modeled through a system of partial differential equations, while bacterial population growth is modeled through Monte-Carlo simulations. Antibiotic action is incorporated as a time-dependent process that reduces bacterial colony size. Computer simulations compared single and multi-antibiotic treatment strategies and examined their effects on population dynamics and signaling activity. It was found that even if population size was heavily reduced, they are still able to “communicate” once antibiotic pressure is removed. Methodology: The quorum sensing process is modeled using a system of semi linear reaction-diffusion partial differential equations that describe the concentrations of AHL and lactonase. The PDEs are then solved using the Peaceman-Rachford alternating direction scheme. Bacterial colony growth and antibiotic decay are simulated stochastically using Monte-Carlo simulations. Antibiotic action is defined as a time-dependent concentration that reduces colony size according to an empirical function. |

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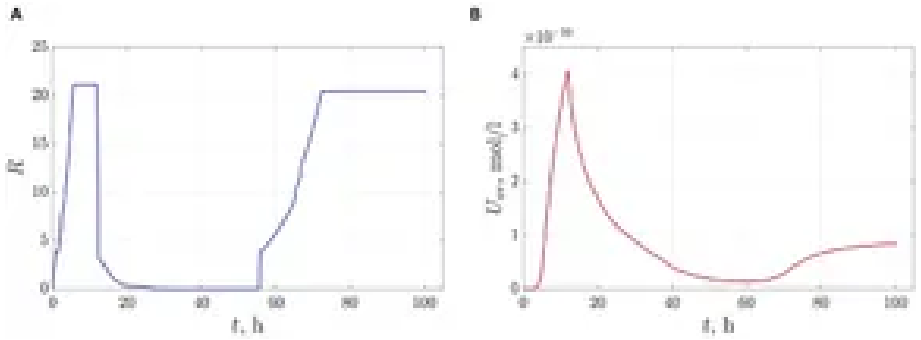
| **Research Question/Problem/ Need** | How does antibiotic treatment influence quorum sensing dynamics in a bacterial population? |
| **Important Figures** |  <br>The first graph shows the total linear size of bacterial colonies over time, and the second graph shows AHL concentration over time |
| **VOCAB: (w/definition)** | Quorum sensing: cell-to-cell communication mechanism that allows bacteria to coordinate behavior, AHL: primary quorum sensing signal molecule in Gram-negative bacteria, Lactonase: enzyme that degrades AHL, Partial differential equation: equations involving multivariable functions and their partial derivatives |
| **Cited references to follow up on** | Hybrid stochastic fractional-based approach to modeling bacterial quorum sensing - ScienceDirect<br>Numerical simulation of time-fractional diffusion-wave processes applied to communication in bacterial populations \| IEEE Conference Publication \| IEEE Xplore<br>Full article: Real-time monitoring of Pseudomonas aeruginosa biofilm growth dynamics and persister cells' eradication |
| **Follow up Questions** | To what extent does quorum sensing suppression, rather than population reduction, determine treatment success?<br>How would biofilm formation alter the quorum sensing dynamics observed in this model?<br>How might host immune responses interact with quorum sensing and antibiotic effects in vivo? |

# Article #16 Notes: Within-host mathematical modeling of antibiotic-phage treatments on lysogenic and non-lysogenic bacteria dynamics

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| **Source Title** | Within-host mathematical modeling of antibiotic-phage treatments on lysogenic and non-lysogenic bacteria dynamics |
| **Source citation (APA Format)** | Teytsa, H. M. N., Seydi, O., Tsanou, B., & Djidjou-Demasse, R. (2024). Within-host mathematical modeling of antibiotic-phage treatments on lysogenic and non-lysogenic bacteria dynamics. *Mathematical Methods in the Applied Sciences*. ttps://doi.org/10.22541/au.172114263.30963529/v1 |
| **Original URL** | Within-Host Mathematical Modeling of Antibiotic-phage Treatments on Lysogenic and Nonlysogenic Bacteria Dynamics - Ndongmo Teytsa - 2025 - Mathematical Methods in the Applied Sciences - Wiley Online Library |
| **Source type** | Journal article |
| **Keywords** | Phage therapy, antimicrobial resistance, mathematical modeling, lysogeny, within-host modeling, age-structured model |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Summary: This study develops a within-host model to analyze the dynamics of antibiotic-phage combination therapy with a focus on the impact of lysogeny. The model reveals that the system's behavior is governed by key threshold parameters, such as reproductive rates for susceptible bacteria, lysogens, and phages. The study identifies through sensitivity analysis that prophage induction probability, initial bacteria growth capacity, phage absorption probability, and antibiotic efficacy are the most influential parameters for achieving bacterial clearance.<br>Methodology: The authors developed a deterministic, age-structured model that tracks bacterial and phage populations over time. The model divides bacteria into 3 classes: susceptible, lysogen, and infected bacteria. The dynamics are described using a system of ordinary differential equations involving logistical bacteria growth, phage absorption, prophage induction, lysis delays, and antibiotic effects. Stability and bifurcation analyses are performed to find equilibrium states and threshold conditions for bacteria persistence or extinction. A Hopf bifurcation analysis shows how time delays in lysis can lead to periodic oscillations in bacterial populations, and sensitivity analysis found the most important parameters when it comes to bacterial clearance. |

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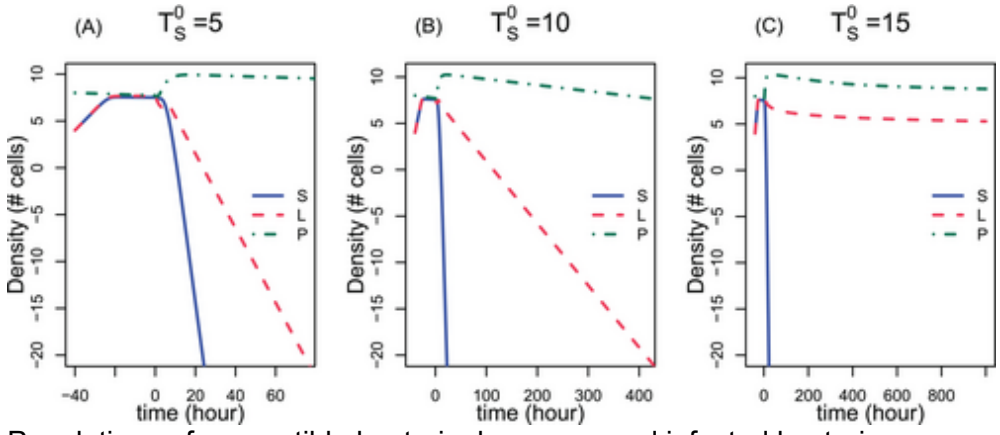
| **Research Question/Problem/ Need** | What is the impact of lysogeny on the effectiveness of antibiotic-phage combination therapy? |
| **Important Figures** |  <br>Populations of susceptible bacteria, lysogens, and infected bacteria over time. |
| **VOCAB: (w/definition)** | Lysogeny: a state in which a phage integrates its DNA into the bacterial chromosome as a prophage, lysogenic conversion: process by which bacterium gain new traits through the integration of a prophage, latent period: time delay between phage absorption and bacterial lysis, combination therapy: treatment strategies that involve both antibiotics and bacteriophages |
| **Cited references to follow up on** | Frontiers \| Fighting Pathogenic Bacteria on Two Fronts: Phages and Antibiotics as Combined Strategy<br>Coupling the modeling of phage-bacteria interaction and cholera epidemiological model with and without optimal control - ScienceDirect<br>Quantitative Models of Phage-Antibiotic Combination Therapy |
| **Follow up Questions** | How would immune response dynamics alter the predicted optimal treatment strategies?<br>How might stochasticity affect the deterministic outcomes presented in this paper?<br>Could phage cocktails (use of multiple types of phages) mitigate the effects of lysogeny and resistance evolution? |

# Patent #1 Notes: Co-incubating confined microbial communities

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| **Source Title** | Co-incubating confined microbial communities |
| **Source citation (APA Format)** | Boedicker, J., Ismagilov, R., & Kim, H. J. (2019, July 18). Co-incubating confined microbial communities. |
| **Original URL** | US11661577B2 - Co-incubating confined microbial communities - Google Patents |
| **Source type** | Patent |
| **Keywords** | Co-incubation, microbial community, bacteria, fungi, MIC, antibiotic susceptibility screening |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Summary: This device solves a major issue in microbiology: the inability to culture and study independent microbial communities in a laboratory. In nature, microbes survive through syntrophy. Traditional well-mixed culturing collapses these communities due to unchecked competition or diluted cooperation. This invention recreates this crucial spatial structure in a laboratory. It enables the compartmentalized co-incubation of different microorganisms, where they are kept physically separate to prevent excessive competition but are connected via controlled chemical diffusion, which enables cooperation. The technology manifests in 2 primary forms: a layered microfluidic device which allows molecular exchange between compartments, and structured gel microdroplets, which separates the microbe species from each other.<br>Methodology: The device was fabricated using a lower layer for cultures, an upper layer containing microfluidic channels, and a barrier membrane in between. Different microbial strains are first loaded into separate wells in the lower layer. The device is then connected to a nutrient medium reservoir, and the upper channel is given a slow flow to deliver nutrients and remove waste. Finally, molecules produced by the colony are sent into the communication channel and diffused into a partner colony. A mathematical model is then created to analyze how the concentration of shared nutrients changes with the distance between the two colonies. |
| **Research Question/Problem/ Need** | Microbes, in nature, exist in complex communities where stability and function rely on chemical cooperation and physical competition, mediated by spatial structure. However, traditional laboratory culturing methods fail to replicate spatial structures found in the real world. |

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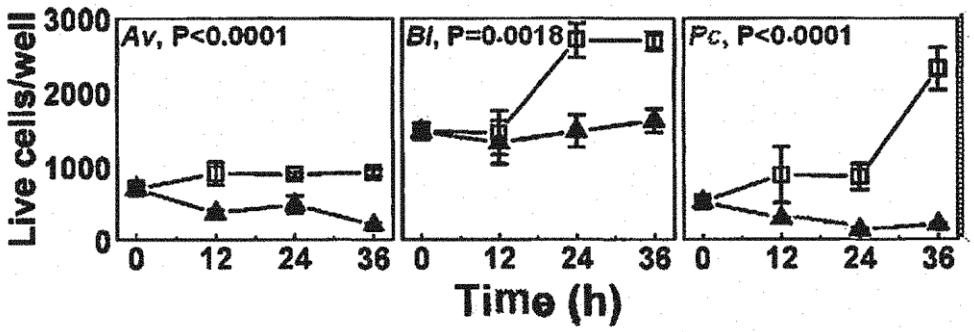
| **Important Figures** | FIG. 4A FIG. 4B FIG. 4C<br>  <br><br>Population of 3 different bacteria populations when isolated from other populations (triangles) and when connected with other populations (square) |
| **VOCAB: (w/definition)** | Spatial structure: the physical arrangement and separation of different microbial populations in an environment, Co-incubation: joint cultivation of 2 or more different types of microorganisms, Antibiogram: a profile of an organism's susceptibility to a panel of antibiotics, Bacillus anthracis: anthrax causing bacteria, Syntrophy: different species of microbes exchanging essential nutrients and signals within a spatial environment |
| **Cited references to follow up on** | US7968287B2 - In vitro evolution in microfluidic systems - Google Patents<br>WO1996019585A1 - Typing of microorganisms - Google Patents<br>US7011957B2 - Isolation and cultivation of microorganisms from natural environments and drug discovery based thereon - Google Patents |
| **Follow up Questions** | What are the practical upper and lower limits for the key parameters of this device?<br>Can this device be extended to co-culture more complex organisms such as fungi, micro-algae, or other protists?<br>How is the chemical concentration in the communication channel actively monitored/controlled? |

# Article #17 Notes: Large time behavior of nonautonomous differential systems modeling antibiotic-resistant bacteria in rivers

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| **Source Title** | Large time behavior of nonautonomous differential systems modeling antibiotic-resistant bacteria in rivers |
| **Source citation (APA Format)** | Mostefaoui IM, Moussaoui A, Jabbari S. Large time behavior of nonautonomous differential systems modeling antibiotic-resistant bacteria in rivers. *Mathematical Methods in the Applied Sciences*. 2023; 46(5): 5585-5603. 10.1002/mma.8854 |
| **Original URL** | Citation for: Large time behavior of nonautonomous differential systems modeling antibiotic-resistant bacteria in rivers |
| **Source type** | Journal article |
| **Keywords** | Antibiotic resistance, coincidence degree, nonautonomous differential systems, plasmid transfer |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | This paper presents a mathematical model for the dynamics of antibiotic-resistant bacteria in rivers, extending a previous model to incorporate more realistic assumptions. The model is a system of four ordinary differential equations, distinguishing between river and land bacteria, each subdivided into susceptible and resistant strains. The previous model is modified in the following ways:<br>- The transmission rate of resistance is modeled by nonlinear incidence instead of mass action<br>- The loss rate of resistance genes is represented by decreasing function g(L), where L is the total land bacteria<br>- Inflow of land bacteria is treated as periodic and continuous, reflecting regular pollution inputs<br>An autonomous system was first set up to figure out whether resistance persists once outside pollution stops. Three equilibrium states were identified: complete extinction, no resistance, and resistance coexistence. It was found that resistance only persists if the transmission rate exceeded the baseline loss rate g(0). A nonautonomous system was then set up to model continuous pollution, and periodic solutions were found to exist. |
| **Research Question/Problem/ Need** | How do antibiotic-resistant and susceptible bacteria in rivers behave over the long term, and under what conditions does resistance persist, die out, or oscillate? |

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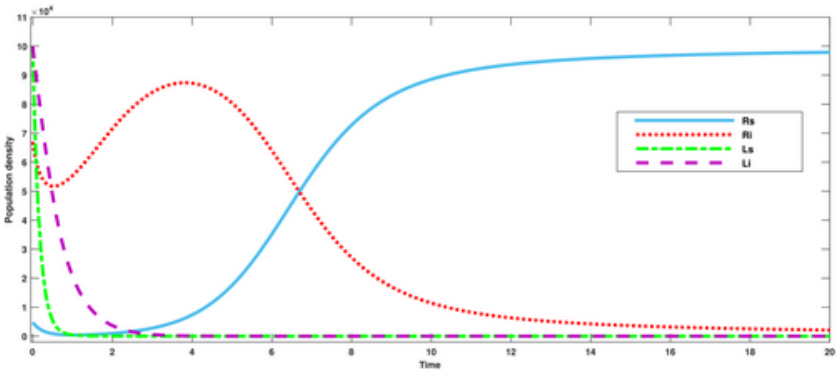
| **Important Figures** |  <br>This figure depicts a simulation of the model where the transmission rate is set to 3, the growth rate is set to 2, the death rate of land bacteria is 1, and the carrying capacity is 100,000. The blue line is river susceptible bacteria, the red line is river resistant, the green line is land susceptible, and the purple line is land resistant. In this simulation, the resistant bacteria population approaches the carrying capacity limit while the other populations approach to 0. |
| **VOCAB: (w/definition)** | Land bacteria: bacteria entering rivers from external sources, nonautonomous system: a system whose equations depend only on time, saturation incidence: nonlinear interactions that limits transmission when populations are large, coincidence degree theory: topological tool used to prove existence of solutions |
| **Cited references to follow up on** | Mathematical analysis of a model describing the number of antibiotic resistant bacteria in a polluted river - Mostefaoui - 2014 - Mathematical Methods in the Applied Sciences - Wiley Online Library<br>Antibiotic Resistance Among Coliform and Fecal Coliform Bacteria Isolated from Sewage, Seawater, and Marine Shellfish<br>Antibiotic resistance in drinking water systems: Occurrence, removal, and human health risks - ScienceDirect |
| **Follow up Questions** | How does introducing spatial structure change the persistence or extinction of antibiotic resistance?<br>How does adding predation (phages, protists) alter long-term resistance?<br>How does fitness cost affect equilibrium outcomes? |

# Article #18 Notes: Mathematical modeling of bacteria-virus interactions in Lake Michigan incorporating phosphorous content

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| **Source Title** | Mathematical modeling of bacteria-virus interactions in Lake Michigan incorporating phosphorous content |
| **Source citation (APA Format)** | Béchette, A., Stojsavljevic, T., Tessmer, M., Berges, J. A., Pinter, G. A., & Young, E. B. (2013). Mathematical modeling of bacteria–virus interactions in Lake Michigan incorporating phosphorus content. *Journal of Great Lakes Research*, *39*(4), 646–654. https://doi.org/10.1016/j.jglr.2013.09.003 |
| **Original URL** | Mathematical modeling of bacteria–virus interactions in Lake Michigan incorporating phosphorus content - ScienceDirect |
| **Source type** | Journal article |
| **Keywords** | virus, phytoplankton, bacteria, mathematical model, phosphorus limitation, cell quota |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Summary: This study integrates mathematical modeling with experimental limnology to investigate how phosphorous (P) availability influences virus-bacteria interactions in Lake Michigan. The authors modified an existing virus-host model that includes nutrient quotas by adding a phytoplankton component to account for algal phosphorous uptake. They then tested the model using data from a 14 day experiment with Lake Michigan water, comparing enriched and unenriched phosphorous conditions. The model fit the data well under enriched phosphorous conditions, producing realistic estimates for viral burst size, latent period, and decay rate. The model fit was much poorer for unenriched phosphorous conditions, suggesting that limited nutrients alter virus-host dynamics in ways not fully captured by the model. Methodology: The researchers first collected Lake Michigan water from a depth of 7.5 meters, filtered to remove any particles greater than 135 micrometers in length, and placed into four 20L carboys. Two of the carboys were then treated with 8 µM phosphate, while the other two served as controls. The carboys were kept at 16 degrees Celsius under a 16:8 light:dark cycle for 14 days. Bacteria and virus populations were recorded using SYBR Green staining and epifluorescence microscopy. For the mathematical model, they measured 6 populations/concentrations via ordinary differential equations:<br>- S: susceptible bacteria |

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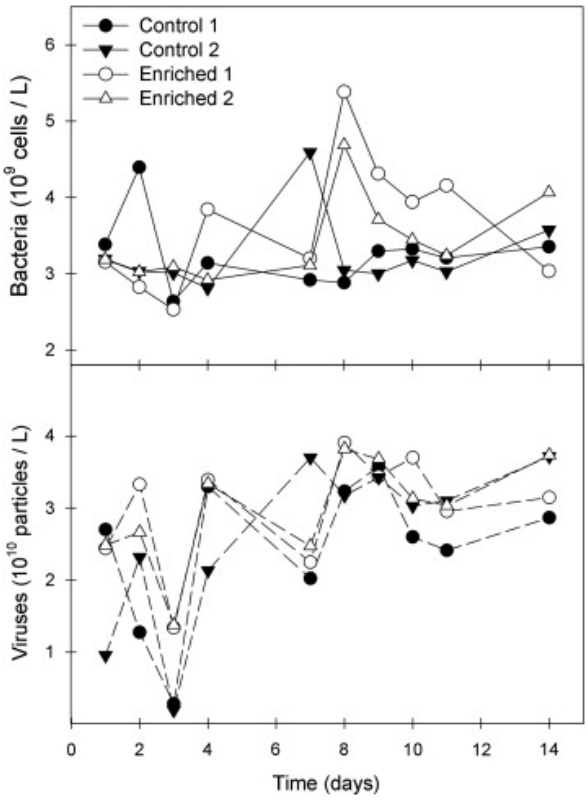
| | - I: infected bacteria<br>- V: viruses<br>- N: phosphorous<br>- Q, Qa: Cell quota of bacteria and algae<br>- A: algae biomass<br>Certain parameters, such as carrying capacity, were taken from literature, while other parameters, such as burst size, latent period, and virus decay, were fitted by the researchers. To fit the parameters, the differential equations were solved numerically using MATLAB, and then the parameters were optimized using the Nelder-Mead algorithm. Finally, the found parameters were compared with parameter values from other articles. |
| **Research Question/Problem/ Need** | How does phosphorous enrichment influence virus-host dynamics compared to unenriched conditions? |
| **Important Figures** |  <br>Graph showing bacterial and viral populations over time. Dark dots represent populations of 2 separate control groups, while light dots represent populations of 2 separate phosphorous enriched groups. |
| **VOCAB: (w/definition)** | Cell quota: internal amount of a type of nutrient in a single cell, oligotrophic: low nutrient & high oxygen aquatic systems, mesotrophic/eutrophic: moderate/high nutrient systems, trophic transfer: movement of energy through food webs |
| **Cited references to follow up on** | Modeling and analysis of a marine bacteriophage infection - ScienceDirect<br>Dynamic modelling of viral impact on cyanobacterial populations in shallow |

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| | lakes: implications of burst size \| Journal of the Marine Biological Association of the United Kingdom \| Cambridge Core<br>m089p103.pdf |
| **Follow up Questions** | How would seasonal changes affect the model's applicability and parameter estimates?<br>How would this model perform in marine systems where nitrogen or iron is limited instead of phosphorous?<br>How might climate change alter the outcomes of lake/river/ocean models like this one? |

# Article #19 Notes: A Theoretical Framework to Quantify the Tradeoff Between Individual and Population Benefits of Expanded Antibiotic Use

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| **Source Title** | A Theoretical Framework to Quantify the Tradeoff Between Individual and Population Benefits of Expanded Antibiotic Use |
| **Source citation (APA Format)** | LaPrete, C. R., Ahmed, S. M., Toth, D. J. A., Reimer, J. R., Vaughn, V. M., Adler, F. R., & Keegan, L. T. (2024). A theoretical framework to quantify the tradeoff between individual and population benefits of expanded antibiotic use. *Bulletin of Mathematical Biology*. https://doi.org/10.1101/2024.08.28.24312731 |
| **Original URL** | A Theoretical Framework to Quantify the Tradeoff Between Individual and Population Benefits of Expanded Antibiotic Use \| Bulletin of Mathematical Biology |
| **Source type** | Journal article |
| **Keywords** | N/A |
| **#Tags** | Antibiotics, antimicrobial resistance, health economics, health policy, pharmacoeconomics, antibacterial drug resistance |
| **Summary of key points + notes (include methodology)** | Summary: This paper challenges the common belief that more antibiotic use leads to a higher risk of resistance development. It proposes a counterintuitive strategy: expanding antibiotic treatment to moderately sick individuals during an outbreak can actually reduce total antibiotic use. Using cholera as a case study, the authors developed a mathematical model to identify when this strategy works. They defined two key thresholds:<br>- Outbreak prevention threshold (OPT): if the outbreak's initial transmissibility (R(q=0)) is <= 1.42, treating all moderate cases can stop an outbreak entirely<br>- Dose utilization threshold (DUT): if R(q=0) <= 1.53, treating a sufficient number of moderate cases leads to fewer total antibiotic doses.<br>Methodology: The authors built a compartmental model extending a classic SEIR (susceptible, exposed, infected, removed) framework. The model divides people into states based on:<br>- Disease status: susceptible (S), exposed (E), infected (I), removed (R)<br>- Infection severity: asymptomatic, moderate, severe<br>- Clinical state: symptomatic, post-symptomatic, treated with antibiotics<br>The authors then developed an equation for the force of infection, which modeled the rate at which new infections occurred. The OPT and DUT were then found by setting R(q) = 1 and equating the point at which the number of people treated |

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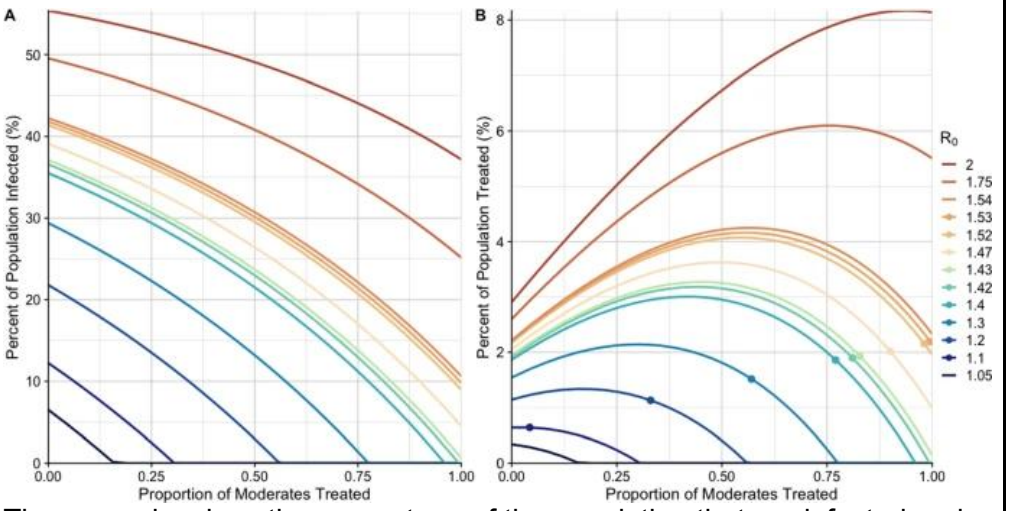
| | with the expanded policy equaled the number of people treated under the current policy. Finally, simulations were run to produce graphs. |
| **Research Question/Problem/ Need** | Under what conditions can expanding antibiotic treatment to include moderately symptomatic individuals during a disease outbreak provide a net population-level benefit? |
| **Important Figures** |  <br>These graphs show the percentage of the population that are infected and treated in relation to the proportion of moderate infections treated with antibiotics. Each curve represents a different initial reproductive number. |
| **VOCAB: (w/definition)** | Compartmental model: models that divide a population into multiple classes, shedding duration: the period during which an infected person excretes the pathogen, outbreak prevention threshold: condition where antibiotic treatment reduces the reproductive number under 1, preventing an outbreak |
| **Cited references to follow up on** | Modeling and analyzing cholera transmission dynamics with vaccination age - ScienceDirect<br>The construction of next-generation matrices for compartmental epidemic models \| Journal of The Royal Society Interface \| The Royal Society<br>Cholera transmission dynamic models for public health practitioners \| Discover Public Health |
| **Follow up Questions** | Can antibiotic delivery strategies (mass drug administration vs clinic-based treatment) be optimized using this framework?<br>How would combination therapy alter the reproductive number?<br>Could a model that includes heterogeneous mixing change the policy conclusions about whom to prioritize for expanded treatment? |

# Article #20 Notes: Stochastic Modeling of In Vitro Bactericidal Potency

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| **Source Title** | Stochastic Modeling of In Vitro Bactericidal |
| **Source citation (APA Format)** | Bogdanov, A., Kevei, P., Szalai, M., & Virok, D. (2022). Stochastic Modeling of In Vitro Bactericidal Potency. *Bulletin of Mathematical Biology*, *84*(1), 6. https://doi.org/10.1007/s11538-021-00967-4 |
| **Original URL** | Stochastic Modeling of In Vitro Bactericidal Potency \| Bulletin of Mathematical Biology |
| **Source type** | Journal article |
| **Keywords** | Stochastic calculus, MIC, bactericidal potency, chlamydia, in vitro, antibiotics |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Summary: This paper develops a stochastic model to quantify the effect of antibiotics on bacterial growth in vitro. Using a Galton-Walton branching process, the authors model a bacterial population where each cell either dies or reproduces with probabilities that depend on the antibiotic concentration. The model is applied to real data from Chlamydia trachomatis treated with azithromycin and ciprofloxacin, using qPCR to measure bacterial DNA.<br>Methodology: The authors created a two-type Galton-Watson branching (Xn, Yn), where:<br>- Xn = the number of live bacteria at generation n<br>- Yn = the number of dead bacteria<br>- Zn = total bacteria = Xn + Yn<br>Equations were then created for Ct value and MIC value, and simulations were run using these two equations. It was found the model fit the experimental data very well, as seen in graphs 3 and 4 where the curve for Ct value vs antibiotic concentration is nearly identical for experimental and simulation data. |
| **Research Question/Problem/ Need** | How can stochastic models be used to quantitatively describe bacterial population growth under varying antibiotic concentrations? |

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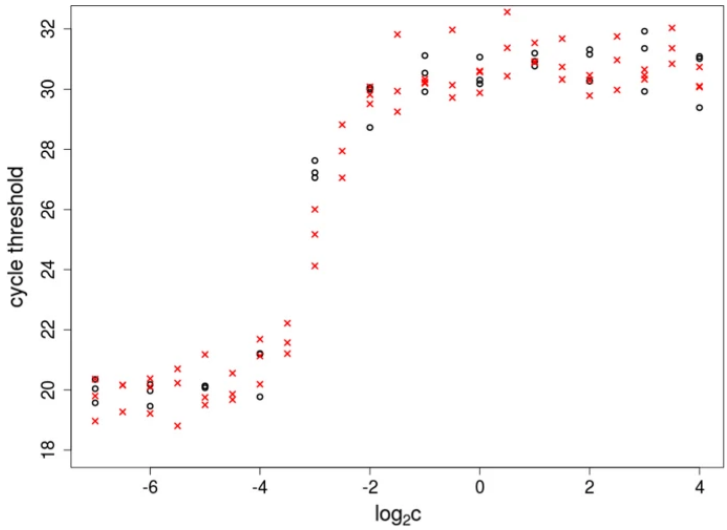
| **Important Figures** |  <br>This figure represents the cycle threshold in relation to the ciprofloxacin concentration. A lower Ct value indicates higher bacterial DNA concentration. Each circle represents actual experimental measurements of Ct values, while each x represents simulated Ct values. |
| **VOCAB: (w/definition)** | Bacteriostatic: an antibiotic that inhibits bacterial growth, aberrant body: a non-replicating bacterium, qPCR: molecular technique used to quantify the amount of bacterial DNA in a sample, Cycle threshold (Ct) value: the qPCR value at which fluorescence crosses a threshold, Galton-Watson branching process – a stochastic model where each individual independently produces a random number of offspring. |
| **Cited references to follow up on** | Stochastic Chlamydia Dynamics and Optimal Spread \| Bulletin of Mathematical Biology<br>Novel Concentration-Killing Curve Method for Estimation of Bactericidal Potency of Antibiotics in an In Vitro Dynamic Model \| Antimicrobial Agents and Chemotherapy<br>Limit theorems for decomposable multi-dimensional Galton-Watson processes - ScienceDirect |
| **Follow up Questions** | How would the model need to be modified to account for mutation/resistance emergence?<br>Does qPCR detecting DNA from dead bacteria overestimate the living population?<br>Could this framework be used to compare the potency curves of different antibiotics quantitatively? |

# Patent #2 Notes: Early diagnosis of infections

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| **Source Title** | Early diagnosis of infections |
| **Source citation (APA Format)** | Eden, E., Oved, K., Cohen-Dotan, A., Navon, R., Boico, O., & Paz, M. (2024, August 6). Early diagnosis of infections. |
| **Original URL** | US12055545B2 - Early diagnosis of infections - Google Patents |
| **Source type** | Patent |
| **Keywords** | Antibiotic resistance, group A streptococcus, TRAIL, algorithmic classification, co-infection |
| **#Tags** | N/A |
| **Summary of key points + notes (include methodology)** | Summary: This patent uses TRAIL as a novel host-response biomarker capable of accurately distinguishing bacteria and viruses within the first 48 hours of infection. Unlike traditional markers like CRP or PCT, TRAIL exhibits a unique characteristic: its serum concentration decreases in bacterial infections while increasing in viral infections. The patents claims methods for using this to “rule in” a bacterial infection and guide targeted antibiotic therapy via a rapid test. Methodology: The researchers first enrolled over 1000 patients who had an acute sickness or were non-infectious. Samples from the patients were then analyzed using ELISA kits to quantify TRAIL protein levels. Statistical analysis of this cohort proved the hypothesis: TRAIL levels were much lower in bacterial infection patients than in viral infection patients. |
| **Research Question/Problem/ Need** | Physicians currently lack a rapid, accurate test to distinguish bacterial and viral infections, leading to widespread antibiotic misuse. |

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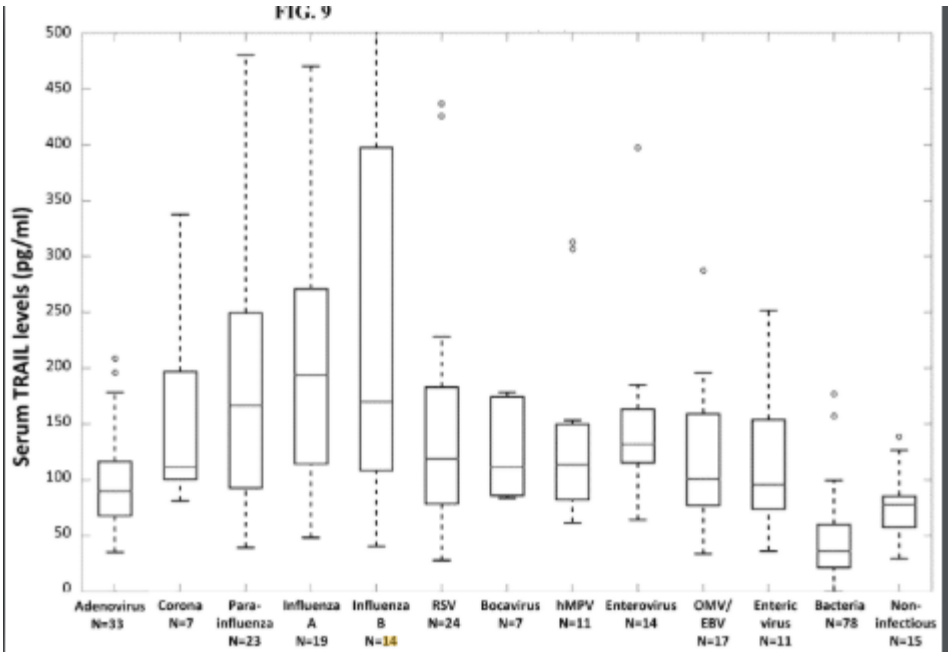
| **Important Figures** |  <br>This graph shows box and whisker plots of serum levels for each bacterium and virus. The viruses in general show higher serum levels than bacteria. |
| **VOCAB: (w/definition)** | TRAIL: a biomarker whose serum level decreases in bacterial infections and increases in viral infections, biomarker panel: combination of TRAIL and other biomarkers, co-infection: situation where a patient has both a bacterial and viral extension, immunoassay: method for detecting TRAIL |
| **Cited references to follow up on** | US20020001402A1 - System and method for generating a profile of particulate components of a body fluid sample - Google Patents<br>US20100297611A1 - Method and Device For Combined Detection Of Viral And Bacterial Infections - Google Patents<br>US8507210B2 - Detection of bacterial infections in subjects suffering from dyspnea - Google Patents |
| **Follow up Questions** | How does TRAIL compare in head-to-head studies with other biomarkers such as PCT or CRP, and in what ways is it better/worse?<br>How does the test perform in patients whose immune systems differ from an average immune system (autoimmune disease patients, infants)?<br>Has performance been validated on other sample types such as saliva or urine? |