Model-informed design of antibiotic therapy against antimicrobial resistance

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Synopsis

Antibiotics are one of the foundations of modern medicine. They are used not only to treat bacterial infections, but also to protect vulnerable patients during surgery, cancer treatment, organ transplantation, and other medical procedures. However, antibiotics are becoming less effective because bacteria can evolve ways to survive them. This process is known as antibiotic resistance, and it is now a major global health problem. At the same time, the development of new antibiotics has slowed down. This means that, instead of relying only on discovering new drugs, we also need to make better use of the antibiotics we already have.

This thesis focuses on how to design smarter antibiotic treatments that remain effective for longer and reduce the chance that resistance will emerge during therapy. The work brings together laboratory experiments, clinical data, and mathematical models. A central idea throughout the thesis is that successful antibiotic treatment depends on three factors working together: the patient, the drug, and the pathogen. In other words, it is not enough to know whether an antibiotic can kill bacteria in principle. We also need to understand how the drug moves through the body, how much of it reaches the site of infection, how bacteria respond over time, and how resistance may develop during treatment.

To study these questions, this thesis uses pharmacometrics: a mathematical and statistical modeling approach to describe how drugs are affected by the human body, and how they affect the body and disease. In the context of antibiotics, these models help combine many different types of information, such as bacterial growth experiments, drug concentration measurements, and patient data. This makes it possible to move from isolated observations to practical predictions about which treatments are most likely to work. Rather than replacing experiments or clinical studies, these models help connect them and turn their results into treatment strategies.

The first part of the thesis focuses on how antibiotics affect bacteria and how resistance develops. One study examined the antibiotic teicoplanin in several important bacterial species. By using a laboratory system that can mimic changing drug concentrations in patients over time, the study showed that the amount of drug needed for effective killing differs substantially between pathogens. This suggests that a "one-size-fits-all" exposure target may not always be appropriate. The same work also showed the value of dynamic laboratory systems, which can capture not only bacterial killing but also temporary loss of sensitivity during treatment. Another study used a more mechanistic model to investigate resistance to the antibiotic combination piperacillin-tazobactam in *Klebsiella pneumoniae*. That work suggested that changes in membrane entry and drug efflux may be important resistance mechanisms. A further study showed that antibiotic response can also depend on the presence of other bacteria in the same environment, meaning that treatment may be influenced by microbial communities rather than by

a single pathogen alone. Together, these studies show that resistance is not a simple on/off phenomenon and that antibiotic effects are shaped by biological context.

The second part of the thesis addresses how antibiotics move through the body and how this can be used to improve dosing. Even when an antibiotic is active against a bacterium, treatment can fail if the drug does not reach the infection site at the right concentration for long enough. One chapter therefore studied teicoplanin in patients with kidney failure receiving hemodialysis. Because kidney function strongly affects how this drug is cleared from the body, these patients showed large differences in drug exposure. The work found that standard dosing may not always achieve adequate levels and proposed improved dosing approaches, including the use of loading doses and individualized dose adjustment. This is clinically important because it highlights that vulnerable patient groups may need tailored dosing rather than standard schedules.

Another chapter explored how antibiotics distribute into the lungs, which is highly relevant for treating pneumonia and other pulmonary infections. Since direct measurement of antibiotic levels at infection sites is often difficult, the thesis used physiologically based pharmacokinetic models to predict concentrations in lung compartments. These models showed how drug properties can influence whether enough antibiotic reaches the lungs, and they demonstrated that this can sometimes be estimated even when only limited distribution data are available. This is valuable for both clinical use and early drug development, because it helps identify which compounds are more likely to work well in specific tissues.

The thesis also developed a framework for optimizing antibiotic dosing regimens. In real life, treatment design must balance several goals at once: clearing the infection, minimizing toxicity, and preventing resistance. These goals can conflict with each other, especially because patients differ in how they process drugs. The proposed framework combines drug behavior in patient populations with bacterial response models and uses optimization methods to search for dosing strategies that best satisfy multiple treatment objectives at the population level. Importantly, this work also recognizes that treatment decisions are not purely mathematical. Clinical judgment remains essential, so the framework was designed to allow expert priorities to be incorporated into the decision-making process.

The final part of the thesis investigates a particularly innovative concept called collateral sensitivity. This occurs when bacteria that become resistant to one antibiotic also become more sensitive to another. In theory, this creates an opportunity: if antibiotics are selected and scheduled carefully, treatment might steer bacterial evolution into a weaker state instead of allowing resistance to spread unchecked. However, this idea is only clinically useful if collateral sensitivity patterns are reliable and if treatment regimens can be designed to take advantage of them.

To address this, one study analyzed large clinical surveillance datasets to see whether collateral sensitivity can be observed in real-world bacterial isolates. This showed that some patterns appear reproducible across species, suggesting that collateral sensitivity is not only a laboratory curiosity. Other chapters examined this question more closely in the pathogens *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*. These studies showed that resistance evolution can be variable and unpredictable, but also that some collateral sensitivity relationships are consistent enough to be therapeutically useful. Using experimental data together with pharmacometric models, the thesis evaluated different treatment schedules and showed that collateral sensitivity-based combinations could outperform monotherapy in suppressing resistance and clearing infection. Most notably, the work proposed and tested an optimized combination regimen for *P. aerug-*

inosa in a laboratory infection model, showing that model-informed dosing could delay or suppress the rise of resistant bacteria. According to the thesis, this is the first demonstration of a specific collateral sensitivity-based dosing schedule that was both designed quantitatively and evaluated experimentally in this way.

Overall, this thesis shows that combating antibiotic resistance requires more than finding new drugs. It requires understanding how bacteria adapt, how drugs behave in different patients, and how treatment can be designed to achieve several goals at once. By integrating laboratory findings, clinical data, and mathematical models, this work provides tools to design antibiotic therapies that are more effective, safer, and better able to slow the emergence of resistance. In particular, it highlights the promise of model-informed combination therapies and collateral sensitivity as new ways to preserve the usefulness of existing antibiotics. These findings contribute to the long-term goal of making antibiotic treatment not only successful for today's patient, but also more sustainable for the patients of the future.