Virtual patient populations for quantitative pharmacology with its application in antibiotic treatment optimization

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Chapter 1

General introduction and outline

1.1 Modelling and simulation in quantitative pharmacology

Modelling and simulation (M&S) approaches in quantitative pharmacology provide a powerful strategy to optimize dose schedules in the context of drug development and treatment optimization in patient care. These approaches use a combination of mathematical and statistical models to characterize and predict drug pharmacokinetics (PK) and pharmacodynamics (PD), which in turn drive drug efficacy or toxicity responses. PK concerns the time course of drug concentration profiles in the body, through the occurrence of drug absorption, distribution, metabolism and elimination, whereas PD concerns the relationship between drug concentrations and the time course of pharmacological effects. Through quantitative understanding of PK and PD, dosing regimens or clinical trial designs can be systematically evaluated and optimized, and forms the cornerstone of translational and clinical drug development and dosing optimization, and an essential approach to support regulatory assessment [1, 2].

PK and PK/PD models are typically defined as compartmental models based on ordinary differential equations (ODEs). Compartmental models provide a conceptually intuitive representation of underlying biological and pharmacological processes that govern drug disposition and effect [3]. Key processes, such as drug distribution, receptor binding, and turnover of e.g. proteins, can be naturally expressed using rate equations that quantify how quickly a substance enters or leaves a compartment or how it is produced or degraded over time. In this framework, ODEs describe how the drug amount or concentration, or a pharmacodynamic variable, changes over time. ODE-based models are straightforward to simulate numerically and can be readily integrated with parameter estimation methodologies that fit models to experimental or clinically observed data [4]. In addition, when drug concentrations or effects involve additional dimensions beyond time, such as spatial distribution of drugs in physiological compartments, partial differential equations (PDEs) can be used to capture such temporal and spatial dynamics [5].

Mathematical models employed in M&S generally fall into two broad categories, which determine how they are defined and developed. Data-driven models, also referred to as top-down approaches, describe observed PK or PD based on mathematical models where model parameters can be directly estimated from preclinical or clinical data. Because such data often concerns repeated measurements over time and potentially multiple sources of variability, e.g., between individuals, data-driven models are often fitted using a non-linear mixed effect modelling framework [6, 7]. Nonlinear mixed effect models, or population PK or PK/PD models, enable characterization of inter-individual variability (IIV) in PK or PD related parameters, as well as identification of influential patient characteristics, or covariates, that can (partially) explain such variability. This is of key relevance in clinical pharmacology, as many therapeutic agents exhibit substantial variability among patients. A dosing regimen effective in one patient group may not be as effective in another, necessitating treat-

ment strategies that account for these differences [8]. By identifying covariates that explain IIV in PK or PD, population PK(/PD) models can be used to perform simulations to derive dosing recommendation for the populations of interest.

In contrast, mechanistic pharmacological models take a bottom-up approach, and integrate relevant biological, physiological, or disease-related knowledge into a structured model framework. For mechanistic models, model parameters are typically informed by biological knowledge derived through various experimental studies rather than being fitted to a single clinical dataset with PK or PD data. Mechanistic models include both physiologically based PK model (PBPK) models and quantitative system pharmacology (QSP) models. PBPK models integrate knowledge of body physiology (e.g., organ volumes, blood flow and enzyme abundance) with drug-specific properties (e.g., molecular weight, lipophilicity, solubility) to predict the distribution of drugs in different organs and tissues [9]. QSP models incorporate the mechanism of the interaction between drug, biological system, and the disease state to predict the drug efficacy or safety [10]. Mechanistic models are particularly valuable in the translational setting as they allow scaling across species or (sensitive) patient populations such as paediatrics, where clinical data is often limited for data-driven modelling approaches [11, 12, 13]. In these situations, PBPK and QSP models can utilize the drug-specific data and account for relevant physiological and pathophysiological information to predict PK/PD behaviour and guide dosing recommendations.

Importantly, data-driven or mechanistic M&S approaches are not mutually exclusive. Middle-out approaches which combine top-down and bottom-up methods or model components are commonly applied [14, 15, 16, 17], i.e., in situations when mixed knowledge or data is available.

1.2 Virtual patient populations

Effective treatment optimization strategies using M&S require generation of plausible, realistic predictions across the patient population of interest, correctly reflecting variability between individuals [18]. To this end, patient characteristics, such as body weight and other clinical or demographic factors, are commonly included as covariates in population PK or PK/PD models to generate predictions for populations with defined attributes. In real-world settings, such patient covariates can vary extensively across individuals. Accurate reflection of this real-world patient variability in simulations, i.e., during the application of developed models, is essential for producing reliable population predictions.

Virtual populations serve as a digital counterpart to real-world populations, that capture patient variability. A virtual population can be defined as a realistic distribution of patient-specific values for different patient characteristics in a defined population. Incorporating virtual populations into PK/PD workflows based on either data-driven population models or mechanistic PBPK or QSP models, allows such patient-associated variability to be integrated into the prediction of drug exposure and treatment response [19, 20, 21].

Virtual patients are based on real-world patient characteristics and can be developed using different approaches. Sampling-based methods generate virtual populations via random sampling from the observed data, for example bootstrap- or conditional distribution sampling [22, 23]. These approaches perform well, but do require access to the associated individual-level patient data. A second approach involves distribution models, which describe patient characteristics using observed data, after which virtual population data can be generated via random sampling from the distribution.

Distribution-based approaches, when developed, do not require access to the underlying source data, allowing sharing of the distribution model rather than individual-level patient data. Distribution based approaches thereby support collaborative research while protecting sensitive information. Examples of this approach include modelling covariates/parameters using a series of marginal distributions or applying (log -transformed) multivariate normal distribution as a fundamental joint distribution model [19]. In this context, the use of copula models has been recently proposed [24]. Copula models can flexibly capture complex dependency structures between covariates of interest. This is important to generate realistic virtual patient populations. To illustrate, when generating virtual populations for covariates body weight, age and renal function in pediatrics, one expects a clear correlation between these covariates that must be accounted for. This thesis focuses on the further development and application of copula models for simulating virtual patient populations, and establishes streamlined workflows for virtual population generation, which are currently absent [25].

A key application for the generation of virtual populations is to support dosing optimization across different patient groups. By providing a representative sample of the target patient population covariates, previously published quantitative pharmacology models can be used to evaluate different treatment strategies and the expected treatment responses for specific patient groups. For example, when the PK and PD of a drug is well characterized in adults, a pediatric virtual population can be used to predict expected treatment outcomes in children, thereby informing dosing and study design [12, 26]. Similarly, translational predictions can extend findings from healthy volunteers to patient populations [27]. Moreover, this approach allows the investigation of therapeutic strategies in rare diseases or difficult-to-study subgroups or scenarios, where clinical data are often sparse.

1.3 Antibiotic therapy

Antibiotics have been regarded as one of the most instrumental and fundamental treatments in healthcare in controlling infectious diseases, which is the leading causes of human morbidity and mortality [28]. One major clinical challenge threatening the efficacy of antibiotic therapy is antimicrobial resistance, which renders antibiotics ineffective. Adding to this challenge is the limited development of new antimicrobial drugs [29]. These factors underscore the urgent need to optimize treatment strategies of

existing antibiotics. In this context, when optimizing antibiotic treatment strategies using PK and PD modelling, it is important to account for antimicrobial resistance, relevant exposure metrics, and patient variability.

Antimicrobial resistance

Antimicrobial resistance poses an escalating global health threat, causing roughly 1.27 million related deaths each year [30]. The choice of dose and treatment duration can affect the emergence of resistance, and a growing number of studies have used PK/PD models to quantitatively characterize the interactions between antimicrobials and pathogens in order to optimize dosing regimens [31, 32, 33].

Bacterial pathogens can acquire resistance through mechanisms such as enzymatic inactivation, drug target modification, efflux, and reduced permeability [34, 35]. In PK/PD models, these processes are often represented by distinct bacterial subpopulations, including susceptible and resistant cells, and sometimes persisters: dormant cells that are highly tolerant to antibiotics [36, 37]. Mathematical PD models for antibiotics can incorporate resistance-related features, for example by including mutation rates, changes in bacterial growth rate due resistance related fitness costs, and reductions in antibiotic potency of resistant cells. Integrating these resistance mechanisms into PK/PD or QSP modelling enables the prediction of resistance emergence and helps guide optimal dosing.

Antibiotic efficacy can also be impaired due to development of bacterial biofilms, which are structured communities embedded in an extracellular matrix [38]. Biofilms contain heterogeneous bacterial populations, including metabolically active, slow-growing and dormant cells. Because of the protection from the extracellular matrix, metabolic dormancy and altered antibiotic target production, biofilm bacteria are capable of surviving the harsh environments imposed by antimicrobials and the immune system [39]. Consequently, biofilm-forming bacteria tend to exhibit greater antimicrobial resistance than their planktonic counterparts, i.e., free-floating cells, and become the main cause of chronic infections. *Pseudomonas aeruginosa* is a bacterial species that forms biofilm and causes recurrent lung infections in patients with cystic fibrosis (CF), a genetic disorder characterized by highly viscous airway mucus [40]. Most current antimicrobial PK/PD studies and dosing strategies are derived from planktonic bacteria. Therefore, improving quantitative understanding of biofilm susceptibility and resistance is essential for refining antibiotic treatment for biofilm-associated infections.

Infection site exposure of antibiotics

Total antibiotic plasma concentrations, i.e., including the fraction bound and unbound to plasma proteins such as albumin, are often used to guide antimicrobial dosing, although ultimately it is only the unbound concentration at the site of infection which is the primary determinant of antimicrobial effect [41]. Inadequate antibiotic exposure at the site of infection can lead to treatment failure and selection for antibiotic-resistant bacteria. Therefore, a growing number of studies support assessing antibiotic concentrations at the tissue site of infection [42, 43]. For respiratory tract infections, ensuring the antibiotic concentration at therapeutic levels in the epithelial lining fluid

is essential to achieve treatment success. However, drug distribution in tissues and organs is often uneven, with physiological barriers sometimes limiting penetration. For instance, the airway mucus in patients with CF can hinder antibiotic diffusion. Additional factors, such as muco-ciliary clearance (i.e., the regular movement of cilia propelling the particles in the respiratory tract) can further reduce the effective concentration of drugs at target sites [44]. In tissues, drugs can also bind and interact with local macromolecules. For example, antibiotics may bind to mucin protein in the airway mucus of CF patients, influencing the concentration of active drug at the infection site [45]. This highlights the complexity of correctly accounting for local infection site antibiotic drug exposure and the need to develop predictive models.

Antimicrobial treatment variability

Many antibiotics exhibit high inter-individual variability in the drug exposure and clinical outcomes, for which variability in PK and PD can be one important driver. Quantifying and predicting this variability is therefore essential to improve treatment outcomes [41]. In terms of PK, drugs can be cleared from the body at different rates and distribute into tissues to different extents, often due to differences in liver and kidney function as well as body composition [46]. Differences in PK can influence treatment outcomes as too low or high exposure may lead to treatment failure, promote resistance or cause side effects [47]. In addition to antibiotic exposure, factors such as the initial bacterial load, the bacterial species and lifestyle, and even the spatial organization of bacteria at the infection site can influence PD and ultimately shape the therapeutic outcome [48, 49, 50, 51]. Quantitative pharmacological models can quantify these potential sources of variability and can be used to subsequently derive optimized antibiotic treatment strategies that maximize the probability of achieving desired outcomes across the population, rather than only for the average patient. This approach requires the key model parameters and covariates to reflect the real-world variability of target patient population, i.e. virtual populations. Using a top-down (i.e. population PK/PD) modelling approach, incorporating covariate distributions from a virtual population into simulations enables to generate personalized or stratified treatment recommendations. For instance, colistin exhibits high exposure variability in critically ill patients. Population PK analysis identified renal function as the primary covariate, therefore, simulations using a virtual population can determine the renal function-adjusted dose required for treating patients [52]. In contrast, for bottom-up approaches such as PBPK modelling, patient variability can be incorporated through capturing physiological parameter distributions that define a virtual population to assess the expected exposure and outcomes across patient populations.

1.4 Scope

The central topic to this thesis is to advance the development approaches for the generation of virtual patient populations for applications in quantitative pharmacological models, and the subsequent use of such quantitative pharmacological models in antibiotic therapy to understand variability in PK and PD. This thesis consists of

three sections, where section I is focused on describing development and applications of copulas for generating realistic virtual populations. In Section II, the focus is on capturing variability in PK and PD, its relationship with patient characteristics, and its impact on antibiotic treatment response. Section III contains a general summary and discussion of the research described in this thesis.

Section I: Virtual patient population generation

Section I explores methodologies for virtual population generation and establishes streamlined workflows, with a focus on copula models. First, in Chapter 2, we provide a comprehensive tutorial including the theory and application of copulas for covariate simulation, to enable researchers to understand and apply copulas in their research. In Chapter 3, we apply copula models to support the generation of virtual adult populations for population PK simulations and develop tools to share patient data. Since copula models are typically developed on large datasets, Chapter 4 extends this framework to PBPK modelling, focusing on scenarios with limited sample sizes. Using gene expression data of drug metabolizing enzymes and transporters as an example, we evaluate different joint distribution models for virtual patient generation in PBPK analysis and identify the cases where simple or flexible distribution models are appropriate.

Section II: Antibiotic treatment optimization

Section II includes two chapters on antibiotic PK and PK/PD models to account for variability that is not explained by known patient covariates. In Chapter 5, we describe semi-mechanistic PD models for biofilm-associated infections of *Pseudomonas aeruginosa* treated with colistin or imipenem, informed by *in vitro* time-kill studies. These PD models are integrated with human PK models to translate experimental insights into clinical dosing optimization with virtual populations. Next, in Chapter 6, we describe the application of a PBPK model framework to characterize spatial drug distribution in airway mucus, a potential barrier in pulmonary drug delivery, using virtual CF patients.

Section III: General discussion and summary

Chapter 7 summarizes the key findings of this thesis and discusses future perspectives on generating virtual populations to support quantitative pharmacology for antibiotic treatment optimization. Key lessons and themes for effective dose optimization are also addressed.

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