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Nonlinear Mixed Effects Modeling of Combination Therapies in Oncology

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Abstract

It has been shown that simultaneous administration of two or more anticancer agents can have a beneficial effect on cancer patients. This type of treatment is called combination therapy and is nowadays commonly used in the fight against cancer. New anticancer drugs are constantly being developed and what drugs to proceed with to the next development phase can be challenging. This thesis introduces the reader to how mathematical modeling can be used to inform such decisions by modeling the relationship between, *e.g.*, drug concentration and *in vivo* efficacy. Specifically, compartment models based on ordinary differential equations and the nonlinear mixed-effects (NLME) framework are examined.

The thesis contains three papers in manuscript form. The first paper, "Model-Based Assessment of Combination Therapies – Ranking of Radiosensitizing Agents in Oncology" explores preclinical radiation treatment data, inter-study variability, and ranking of test compounds.

The second paper is entitled "A Model-Based Approach for Translation in Oncology - From Xenografts to RECIST". Here the focus is on the translational potential of semi-mechanistic NLME models. Preclinical data is used to calibrate three models, which are then translated using commonly used techniques, and used to predict the result of clinical studies.

The third paper, "Probabilistic Analysis of Tumor Models to Support Early Clinical Trial Design", details how one can derive probabilistic expressions for the predicted proportion of patients in each RECIST category in a clinical study. These are used to develop a method for predicting the required sample size to show a certain significance level and test power, for newly developed drugs.

Keywords: Mathematical Modeling, Nonlinear Mixed Effects, Pharmacology, Oncology, Combination Therapy, Radiation Therapy

List of publications

This thesis is based on the work represented by the following papers:

I. **M. Baaz**, T. Cardilin, F. Lignet, A. Zimmermann, S. El Bawab, J. Gabrielsson, M. Jirstrand, Model-Based Assessment of Combination Therapies – Ranking of Radiosensitizing Agents in Oncology

II. **M. Baaz**, T. Cardilin, F. Lignet, M. Jirstrand, A Model-Based Approach for Translation in Oncology - From Xenografts to RECIST

III. **M. Baaz**, T. Cardilin, T. Lundh, M. Jirstrand, Probabilistic Analysis of Tumor Models to Support Early Clinical Trial Design

Authors contribution

I. Implemented an already existing model as well as the simulation-based TSE method in Mathematica. Performed all computations, further analyzed and refined the model, created all figures and tables, drafted and edited the manuscript.

II. Searched for preclinical and clinical data. Implemented two existing models in Mathematica as well as developed the code for the clinical predictions and procedure for finding optimized scaling exponents. Created all figures and tables, drafted and edited the manuscript.

III. Derived the probabilistic equations and their derivatives. Developed all code in Mathematica to validate the results. Created all figures and tables, drafted and edited the manuscript.

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Marcus Baaz,
Gothenburg, February 2022

Contents

1 Introduction

We first give the reader a brief introduction to combination therapies used in oncology. This is followed by a chapter detailing how drug concentration, tumor growth, and the effect of different treatment modalities can be modeled. Next, the nonlinear mixed effects framework is introduced and some details are given on how the parameter estimation is performed within this framework. Finally, we discuss how to translate preclinical models and use to them to predict clinical efficacy and support the design of clinical studies.

1.1 Combination Therapy in Oncology

Combination therapies imply that several treatment modalities are given simultaneously to a patient in need of medical care. In oncology, this can, *e.g.*, be radiation therapy combined with a class of anticancer drugs called radiosensitizers. As the name implies, this type of drug causes the tumor tissue to be more sensitive to radiation and thus, a lower radiation dose can be given while still achieving the desired treatment outcome [1, 2]. Another example of a combination therapy currently used is the concomitant treatment with the two anticancer drugs encorafenib and binimetinib, inhibitors of the BRAF and MEK gene, respectively, for patients with cutaneous melanoma [3]. The benefits of this type of treatment can, *e.g.*, be the potential for synergistic effects between the drugs and longer time for the patient to develop drug or radioresistance. [4, 5].

In the last decades, there has been a growing interest in this field and many anticancer drugs are nowadays used in combination [6]. However, there is still a lack of appropriate tools for identifying drug combinations with sufficient clinical efficacy early in the drug development process [7]. Before anticancer drugs are tested in clinical (human) trials, preclinical (animal) studies first have

to be conducted. The most commonly used animals for this are mice that have been implanted with human tumor tissue. These animals are called xenograft mice and studies conducted with them are frequently structured in such a way as to resemble a clinical trial as much as possible. Two of the objectives of these studies are to measure how tumor volume and drug concentration changes over time. These measurements result in time series that often display high variability and appropriate tools are required to analyze these for drug efficacy estimates.

A major problem in the drug development process is estimating clinical efficacy from preclinical studies [8, 9]. Commonly, drugs with sufficient preclinical efficacy fail to show similar efficacy in a clinical setting [10]. Although this is the case, studies have also found a correlation between preclinical and clinical efficacy [11]. This highlights the need for new and improved methods of analysis and concepts that can facilitate the translation of preclinical information for clinical use. Mathematical modeling is such a method of analysis that is especially suitable for combination therapies, as all possible combinations cannot be tested experimentally [12].

1.2 Pharmacokinetics and Pharmacodynamics

Two important branches of pharmacology are pharmacokinetics (PK) and pharmacodynamics (PD). PK describes what the body does to the drug and PD what the drug does to the body [13].

1.2.1 Pharmacokinetics

PK describes how drugs are absorbed, retained, and eliminated by the body. This is commonly done through compartment models [14]. The compartments in the models represent different parts of the body, *e.g.*, gut and blood plasma, and the movement of drug from one compartment to another is governed by a set of ordinary differential equations (ODEs). To exemplify this, we look at how one can model the absorption and elimination of an orally given drug. We consider C_A and C_B to be the drug concentration in the gut and blood plasma, respectively. The drug first has to be absorbed from the gut to the blood plasma before being eliminated from the body. These two processes can be modeled as first-order processes with rate parameters k_a and k_e, respectively. The system of ODEs that describes this is

$$\begin{aligned} \frac{\mathrm{d}C_A}{\mathrm{d}t} &= -k_a C_A, \quad C_A(0) = \frac{D}{V_d}, \\ \frac{\mathrm{d}C_B}{\mathrm{d}t} &= k_a C_A - k_e C_B, \quad C_B(0) = 0, \end{aligned} \tag{1.1}$$

where D denotes the drug dose and V_d the volume of distribution.

1.2.2 Pharmacodyamics

In oncology, PD typically describes how tumor volumes are affected by a given treatment. Compartment models are often also used here, but the compartments consist of different types of tumor cells, such as proliferating or damaged cells. One of the simplest ways of modeling tumor growth is by assuming exponential growth and that all cells are proliferating. Under these assumptions, the tumor dynamics are given by,

$$\frac{\mathrm{d}V}{\mathrm{d}t} = k_{ng} V, \quad V(0) = V_0, \tag{1.2}$$

where V is the tumor volume, V_0 the initial tumor volume, and k_{ng} the net tumor growth rate constant [11]. Two examples of slightly more complex models are the logistic and Gompertz growth models [15].

There can be a delay between when an anticancer treatment is given and when the effects of the treatment can be seen. To account for these delayed treatment effects, a chain of transit compartments can be introduced to the model [16]. Moreover, this also allows for a more biologically reasonable model that differentiates between proliferating and non-proliferating cells. The following set of equations gives the tumor dynamics,

$$
\begin{aligned}
\tfrac{dV_1}{dt} &= (k_g - k_k)\, V_1, \\
\tfrac{\mathrm{d}V_2}{\mathrm{d}t} &= k_k V_1 - k_k V_2, \\
\tfrac{\mathrm{d}V_3}{\mathrm{d}t} &= k_k V_2 - k_k V_3, \\
\tfrac{\mathrm{d}V_4}{\mathrm{d}t} &= k_k V_3 - k_k V_4. \\
V_i(0) &= V_0\, (\tfrac{k_k}{k_g})^{i-1} \quad i = 1, 2, 3, 4,
\end{aligned}
\tag{1.3}
$$

where V_1 is the volume of proliferating cells, V_2, V_3, and V_4 the volume of non-proliferating cells, k_g the growth rate, and k_k the natural kill rate. The total tumor volume, V_{tot} is given by,

$$V_{tot} = V_1 + V_2 + V_3 + V_4. \tag{1.4}$$

The initial conditions are chosen such that in the absence of treatment, the tumor cells have strictly exponential growth [17]. Note that to estimate both k_g and k_k the system must be perturbed, *e.g.,* by also modeling the effects of an anticancer drug. Otherwise, only the net growth rate constant introduced in equation Eq. 1.2 can be estimated.

1.2.3 Combination of Anticancer Drugs

The effect of an anticancer drug can be modeled by, *e.g.,* adding a linear drug specific term to Eq. 1.2,

$$\frac{\mathrm{d}V}{\mathrm{d}t} = (k_{ng} - aC)\, V, \quad V(0) = V_0, \tag{1.5}$$

where a and C denote the potency and exposure of the drug in question, respectively [18]. The exposure can, *e.g.,* be the maximum drug concentration or the simulated concentration profile. When several drugs are given simultaneously, there is also the potential for an interaction effect between the drugs [19]. This can be modeled by the following ODE,

$$\frac{\mathrm{d}V}{\mathrm{d}t} = (k_{ng} - a_1 C_1 - a_2 C_2 - \gamma C_1 C_2)\, V, \quad V(0) = V_0, \tag{1.6}$$

where a_i and C_i denote the potency and concentration of drug i, respectively, and γ is a quadratic interaction effect parameter.

1.2.4 Radiation and Radiosensitizer Treatment

The so-called linear-quadratic equation is typically used to quantify cell damage as a result of radiation [20, 21]. The proportion of cells that are damaged after one radiation application with radiation dose, D_R, is given by

$$F(D_R) = 1 - e^{-(\alpha D_R + \beta D_R^2)}, \tag{1.7}$$

where α and β are radiosensitivity parameters. Turnover of cells at each radiation application, t_i, can be described by

$$V(t_i^+) = V(t_i^-) - F(D_R)\, V(t_i), \tag{1.8}$$

where t_i^- and t_i^+ denote the time immediately before and after each radiation application, respectively. Between radiation sessions, the dynamics are again described by Eq. 1.2, if no other types of treatment effects are considered.

1.3 Nonlinear Mixed Effects Modeling

Both the PK and PD models presented above contain unknown parameters to be estimated using experimental data. As mentioned in the introduction, this kind of experimental data is often in the form of time series and obtained by performing experiments on a population of xenograft mice. Moreover, to perform the actual computations, a mathematical framework is necessary. The most suitable for this kind of population data with high variability is the nonlinear mixed effects (NLME) framework [22]. We first introduce this

framework generally and then tie it together with the previously explored models.

1.3.1 Between-Subject Variability and Measurement Model

In the NLME framework we consider models where the dynamical system can be represented by a set of ODEs or stochastic differential equations (SDEs). We assume that the model in question describes the dynamics of a population of N subjects, indicated by $i = 1, \ldots, N$. The set of ODEs specific for individual i can be written on the following form,

$$\mathrm{d}x_i = f(x_i, t, u_i, \theta, \eta_i)\mathrm{d}t \quad x_i(0) = g(\theta, \eta_i), \tag{1.9}$$

where t is time and the four vectors x_i, u_i, θ, and η_i denotes the state variables, system inputs, fixed effect parameters, and random effects parameters. The fixed effects are the same for the entire population, whereas the random effects are specific for each individual. Moreover, the random effects are assumed to be multivariate normal distributed with zero mean and covariance matrix Ω,

$$\eta_i \sim \mathcal{N}(0, \Omega). \tag{1.10}$$

Once estimated given the estimates of the population parameters, these η-values are also known as EBEs (Empirical Bayes Estimates). The between-subject variability (BSV) is described by the random effects and a chosen distribution. Typically, a log-normal distribution is assumed and the specific values for all parameters for individual i, ϕ_i, is denoted by

$$\phi_i = \theta e^{\eta_i}. \tag{1.11}$$

The observations, y_{ij}, for individual i at each discrete time point t_{ij}, is typically described by a deterministic output term and a residual error,

$$y_{ij} = h(x_i, u_i, t_{ij}, \theta, \eta_i) + e_{ij}. \tag{1.12}$$

Here a zero mean normally distributed additive residual error with observation error covariance matrix Σ is assumed, $e_{ij} \sim N(0, \Sigma(x_i, t_{ij}, u_i, \theta, \eta_i))$.

We return to the tumor growth model introduced in Eq. 1.2 and write it as an NLME model. As we typically use these types of models to describe data with BSV, we first have to chose what model parameter we let vary between individuals. In this case, we assume that k_{ng} is log-normally distributed. Moreover, as an analytical solution to the ODE can be found, each tumor volume observation for the *ith* individual is given by

$$y_{ij} = V_0 e^{(k_{ng} e^{\eta_i}) t_{ij}} + e_{ij}. \tag{1.13}$$

1.3.2 Inter-Study Variability

As studies are carried out by different researchers, at different times, or with different study designs, it is possible to get essential differences in data even for the same drug [23, 24]. This is known as inter-study variability (ISV) or inter-occasional variability and it can be essential to quantify it for the assumptions in the model to be valid.

Depending on the nature of the ISV, it can be handled in two ways in the NLME framework. If there are differences between studies for the median individual, ISV should be applied to one or several fixed effects. If there instead are significant differences in BSV across studies, ISV should be applied to the random effects. Of course, both of these differences can also occur simultaneously and then ISV can be applied to both the fixed and random effects.

We exemplify this by once again returning to the exponential tumor volume model (Eq. 1.2). Assume that we are analyzing the data from two xenograft mice studies. A comparison of the median growth rate showed that the mice grew significantly faster in one of the studies. Moreover, the specific growth rate of each mouse in that study was also more centered around the median growth rate, *i.e.*, less variability between the mice. We, therefore, apply ISV to both the fixed and random effect of k_{ng} and the specific value of this parameter for individual i is then given by,

$$k_{ng,i} = (Study_1 \cdot k_{ng}^1 + Study_2 \cdot k_{ng}^2)\, e^{(Study_1 \cdot \eta_i^1 + Study_2 \cdot \eta_i^2)}, \tag{1.14}$$

where the superscripts denote the estimated parameter values specific to study k and $Study_k$ is a function that is 1 if individual i is in study k and 0 otherwise.

1.3.3 Parameter Estimation

Now with the introduction of the NLME model complete, it remains to describe how the parameters in the model are estimated. The three sets of parameters to be estimated are the fixed effects, θ, the random effects covariance matrix Ω, and the observation error covariance matrix Σ. We simplify the notation in the derivation of the population likelihood by denoting all these parameters with θ. We again assume a population of N subjects, indicated by $i = 1, \ldots, N$, and denote the set of all observations for individual i by y_i. The likelihood for a single individual is the probability density of the observed data given the model parameters $p(y_i \mid \theta)$. The individual likelihood is obtained by marginalizing over the random effects, as they are not observed,

$$p(y_i \mid \theta) = \int p(y_i, \eta_i \mid \theta) d\eta_i. \tag{1.15}$$

Using the definition of the conditional probability, we have that,

$$\begin{aligned} \int p(y_i, \eta_i \mid \theta) \mathrm{d}\eta_i = \int \frac{p(y_i, \eta_i, \theta)}{p(\theta)} \mathrm{d}\eta_i = \\ \int p(y_i \mid \eta_i, \theta) \frac{p(\eta_i, \theta)}{p(\theta)} \mathrm{d}\eta_i = \int p(y_i \mid \eta_i, \theta) p(\eta_i \mid \theta) \mathrm{d}\eta_i. \end{aligned} \tag{1.16}$$

Assuming all individuals are independent of each other, the population likelihood is given by

$$L(\theta) = \Pi_i \int p(y_i \mid \eta_i, \theta) p(\eta_i \mid \theta) \mathrm{d}\eta_i. \tag{1.17}$$

This likelihood is maximized to find the model parameters that best fit the data, which is done through a software using the first-order conditional estimation method (FOCE). For more information regarding both the software and the estimation step in detail, we refer the reader to Leander *et al.* [25].

1.4 Translational Methods

Another type of variability, besides the types discussed in the previous chapter, that is very important when developing drugs, is inter-species variability. Differences in shape, anatomy, and physiology lead species to react differently to the same drug [26]. In oncology, this can, *e.g.,* be differences in drug exposure or tumor growth rate. Translating information from preclinical studies for clinical use is a tough challenge and it is thought that insufficient knowledge in this field is a major contributing factor to the high attrition rates seen for anticancer drugs [9]. Currently, translation from xenograft mice to humans is often based on replacing mouse exposure with human exposure and allometrically scaling of PD rate parameters, θ_r [27, 28, 29].

1.4.1 Allometric Scaling

Allometry describes the relationship between variables such as heart rate and body weight and can be applied to account, to some extent, for inter-species variability [30]. Allometric scaling, based on bodyweight, of an arbitrary parameter θ between humans and mice is given by,

$$\theta_{Human} = \theta_{Mouse} \left(\frac{BW_{Human}}{BW_{Mouse}} \right)^{a}, \tag{1.18}$$

where the parameter BW_i denotes the bodyweight of specie i and the value of the exponent a depends on the type of parameter θ. Nominal values often used for the bodyweight of a human and a mouse are 70 kg and 20 g, respectively.

It has been shown that the heart rate of an organism is approximately proportional to its bodyweight raised to the power of -0.25 . Moreover, the proportionality constant is similar for organisms in the same taxonomic or functional group [30]. This serves as a justification for scaling all PD parameters, with

units containing the inverse of time, θ_r, between mice and humans according to,

$$\theta_{r,Human} = \theta_{r,Mouse} \left(\frac{BW_{Human}}{BW_{Mouse}} \right)^{-0.25}. \tag{1.19}$$

To illustrate how allometric scaling is incorporated into the model equations, assume that we have fitted the exponential growth model with one anticancer drug, Eq. 1.5, to xenograft data and want to use it to make clinical predictions. The model contains two parameters, k_{ng} and a, with a rate aspect and we scale both of these allometrically using the standard exponent (-0.25). This results in the following ODE,

$$\frac{dV}{dt} = \left(\frac{70}{0.02} \right)^{-0.25} (k_{ng} - aC)\ V, \quad V(0) = V_0. \tag{1.20}$$

By assuming this allometric relationship and calculating the scaling factor, we see that tumors are assumed to grow or shrink approximately seven times slower in humans compared to mice.

However, the allometric scaling relationship applies to endogenous mouse and human tumors, and some consideration should be made to the fact that in xenograft mice, human tumors are growing in a mouse microenvironment. Moreover, if all rate parameters approximately follow this allometric relationship, or if it is primarily the tumor growth rate constant is not completely clear [31]. Thus, scaling exponents might exist that are different for various rate parameters and better capture the differences between xenograft mice and humans. Model predictions can be compared with clinical data to identify such exponents empirically.

1.5 Clinical Model Predictions

In this section we discuss how preclinical models can be used to support the design of clinical studies. First, we look at one type of clinical data and how to use a translated preclinical model to predict this data through model simulations. Next, we show how to estimate the required sample size for a clinical study to achieve a specific significance level and test power. Finally, we

detail a methodology for improving the translational capabilities of preclinical models

1.5.1 Clinical Data

In clinical oncology studies, patient response is categorized using the RECIST criteria. The sum of the longest diameters (SLD) for all target lesions is measured at the start of treatment (baseline) and at subsequent checkups. When the trial is over, each patient is categorized based on their best response using four response categories: Complete Response (CR), Partial Response (PR), Progressive Disease (PD), and Stable Disease (SD) [32]. CR and PR are in some studies combined and for a patient to be in this combined category, SLD has to be decreased by at least 30% compared to baseline. For a patient to be PD, SLD has to be increased by at least 20% and if neither a CR&PR nor PD has been achieved, the patient is categorized as SD. The proportion of patients in each of these categories are typically reported in clinical studies. We illustrate the categorization process in Fig 1.1 with $t = 0$ being the baseline and $t = 56$ (black vertical line) being the time of the first checkup.

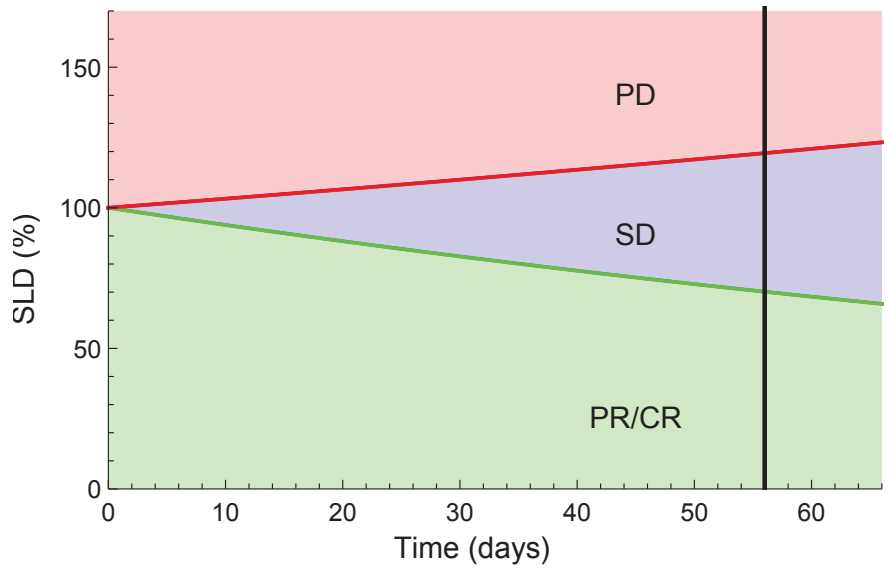

Figure 1.1: Percentage change in SLD plotted against time. Red, blue, and green areas represents patients being categorized as PD, SD, and PR/CR, respectively, at day 58 (black vertical line).

The percentage change in SLD between baseline and time T, denoted by ρ, is estimated as,

$$\rho = 100 \left(\frac{SLD(T) - SLD(0)}{SLD(0)} \right). \tag{1.21}$$

This equation is only valid for $\rho > -100$, as the tumor diameter cannot be reduced with more than 100%.

1.5.2 Simulation of a Clinical Study

The preclinical NLME models introduced in Chapters 1.2-1.3 can be used to generate artificial mice by drawing new η-values from the multivariate normal distribution in Eq. 1.10, after estimating the Ω-matrix. After applying translation methods, the models can instead generate artificial human patients. Each artificial patient can be categorized according to the RECIST criteria by simulating the time evolution of tumor volume and converting it to diameter, assuming, *e.g.*, spherical or ellipsoid tumors. Thus, by drawing and categorizing the same number of artificial patients as participated in each treatment arm of a clinical trial, the proportion of patients in each RECIST category in the clinical study can be predicted. Furthermore, by repeating this procedure many times, the uncertainty of the predictions, which come from the limited number of patients in the clinical trial, can be quantified. The uncertainty can, *e.g.*, be presented as a 95% confidence interval around the point estimate of each predicted proportion. The point estimates and confidence intervals can then be compared with clinical data to evaluate the translational capability of the translated model.

Moreover, the estimated proportion of patients in a each RECIST category is the same as the probability that a patient is placed in each of that categories. These probabilities can for some models be estimated analytically by considering the distribution of the random effects (see the third appended paper).

1.5.3 Sample Size of Clinical Studies

Recruiting a large enough sample size of patients for clinical trials is essential to statistically ensure the superiority of one treatment over another [33]. As placebo often is not given to cancer patients, new drugs are typically evaluated against the current standard of care (SOC) [34]. New efficacious combination therapies can be found by, *e.g.*, combining the SOC with a drug that is hypothesized to be beneficial to the patient based on preclinical studies [35]. The efficacy of the combination can then be evaluated by, *e.g.*, comparing the proportion of patients classified as CR&PR for both treatments.

We now derive an equation for the sample size required to show a significant difference between the proportion of CR&PR, p, of two studies. Denote the number of patients classified as CR&PR with x and the total number of patients in the study with n. The proportion of CR&PR is then estimated with the sample proportion, $\hat{p} = \frac{x}{n}$, where $x \sim Bin(n, p)$. When n is sufficiently large $x \sim \mathcal{N}(np, n(1-p)p)$, according to the law of large numbers, and thus $\hat{p} \sim \mathcal{N}\left(p, \frac{(1-p)p}{n}\right)$.

Denote the proportion of patients classified as CR&PR in two independent studies (same sample size) by p_1 and p_2. These proportions are estimated using the sample proportions, $\hat{p_1}$ and $\hat{p_2}$. Since both $\hat{p_1}$ and $\hat{p_2}$ are normally distributed we have, $\epsilon = \hat{p_1} - \hat{p_2} \sim \mathcal{N}\left(0, \frac{(1-p_1)p_1}{n} + \frac{(1-p_2)p_2}{n}\right)$.

The assumption of equality between the two treatments groups can then be tested using the two proportion Z-test, with the following two hypotheses [36],

$$H_0 : \epsilon = 0 \quad \text{and} \quad H_a : \epsilon \neq 0. \tag{1.22}$$

The null hypothesis is rejected with confidence level α if

$$\left| \frac{\sqrt{n}\epsilon}{\sqrt{\hat{p}_1\left(1-\hat{p}_1\right) + \hat{p}_2\left(1-\hat{p}_2\right)}} \right| > z_{\alpha/2}, \tag{1.23}$$

where z_i is the standard score. If the alternative hypothesis is accepted, the power of the test is approximated by

$$\Phi\left(\frac{\sqrt{n}|\epsilon|}{\sqrt{\hat{p}_1\left(1-\hat{p}_1\right) + \hat{p}_2\left(1-\hat{p}_2\right)}} - z_{\alpha/2} \right). \tag{1.24}$$

Thus, the sample size that is required to achieve $1-\beta$ power is found by solving,

$$\frac{\sqrt{n}|\epsilon|}{\sqrt{p_1\left(1-p_1\right) + p_2\left(1-p_2\right)}} - z_{\alpha/2} = z_{\beta}. \tag{1.25}$$

$$n = \frac{\left(z_{\alpha/2} + z_{\beta}\right)^2}{\epsilon^2}\left(p_1\left(1-p_1\right) + p_2\left(1-p_2\right)\right) \tag{1.26}$$

However, to perform these calculations, some prior knowledge of each treatment is required, *i.e.,* we require approximations of both p_1 and p_2. As these are the two values we want to estimate in the clinical trial, an adequate approximation of them might not be available. However, we can predict them, and thus also the required sample size, by either simulating the clinical study or deriving an analytical equation for the probability that a patient is classified as $CR\&PR$. Such an expression can for certain models be found by considering the model equations, random effects, and the classification thresholds.

1.5.4 Optimized Allometric Scaling

An optimization problem can be formulated and solved to investigate if a more appropriate allometric exponent can be found that better describes the differences between xenograft mice and humans. Instead of using the standard exponent, we introduce exponent λ_i for rate parameter i. The scaling of each type of rate parameter is then given by,

$$\theta^i_{r,Human} = \theta^i_{r,Mouse}\left(\frac{BW_{Human}}{BW_{Mouse}}\right)^{\lambda_i}. \tag{1.27}$$

The clinical predictions thus depend on what value each element of λ takes. We denote the predictions and clinical data for treatment arm j and RECIST category k by $\hat{y}(\lambda)_{jk}$ and y_{jk}, respectively. A least-squares problem can then be formulated as finding λ such that the difference between $\hat{y}(\lambda)_{jk}$ and y_{jk} is minimized. Mathematically, the objective function that describes this is given by

$$f(\lambda) = \sum_{j,k}((\hat{y}(\lambda)_{jk} - y_{jk})^2, \tag{1.28}$$

and the optimization problem can be formulated as,

$$\text{minimize} \quad f(\lambda). \tag{1.29}$$

A penalty term can be added to the objective function to take the uncertainty in the prediction into account. This can, *e.g.*, be done by heavily penalizing solutions where the 95% confidence interval does not cover the clinical data.

Potentially, a λ that allows for adequate clinical predictions for as many combinations as possible can be found after solving this optimization problem for several different drug combinations. These exponents would be used to better predict clinical efficacy from preclinical experiments, but could conceivably be specific to the cancer type and the drugs' mechanisms.

Having analytical expressions for the probability that a patient is placed in each of the RECIST category can also be used to support this analysis. A sensitivity analysis can be performed by differentiating the probabilistic equations with respect to different model parameters. Thus, a deeper insight into how the allometric scaling affects the model can be acquired.

2 Summary of Papers

In this thesis, semi-mechanistic nonlinear mixed effects models are analyzed both for their preclinical and clinical predictive capabilities. The topic of Paper I is modeling preclinical radiation treatment and ranking of test compounds. An NLME model describing the effects of radiation in combination with radiosensitizers is calibrated to xenograft data from three studies that tested the efficacy of three radiosensitizers. The radiosensitizers are ranked based on their anticancer efficacy and inter-study variability is incorporated into these predictions. The ranking is performed through a simulation-based method which also is proposed in the paper. Paper II instead focuses on evaluating how well these types of models can be used to predict results from clinical oncology studies. Volumetric xenograft data for three drug combinations and two cancer types are used to calibrate two tumor growth inhibition models. Commonly used translational methods are applied to the models. The translated models are used to make clinical predictions, which are compared with clinical data. We also developed a methodology for improving the translational capabilities of semi-mechanistic models. This paper was presented as a poster at the PAGE conference in 2021. Paper III continues the analysis of clinical model predictions. Analytical equations for the probability that a patient responds to a certain treatment are derived for the model in Paper II. This is used to support design of early clinical trials.

2.1 Paper I

In this paper, we refine and further validate the long-term radiation and radiosensitizer model first proposed by Cardilin *et al.* [37]. This semi-mechanistic model assumes that the total tumor volume is divided into different compartments: proliferating cells, dying cells, and radiation damaged cells. The application of radiation is modeled by a short and long-term effect. The short-

term effect is included to account for proliferating cells being lethally damaged due to double-stranded DNA breaks caused by the radiation treatment. Mathematically speaking, this is accomplished by an instant mass transfer of proliferating cells to radiation damaged cells at each radiation session. The number of cells that suffer this type of damage is determined through Eq. 1.7 [20]. The long-term effect instead describes a permanent reduction of the tumor growth rate based on the accumulated radiation dose that the patient has been subjected to. That this second effect is necessary can be observed in the data and biological explanations for this phenomenon may be, *e.g.*, changes in the tumor microenvironment [38]. The radiosensitizers stimulate both of these effects to different degrees by interfering with the body's natural DNA repair mechanisms. We use volumetric xenograft data from three studies provided by Merck to calibrate this model. The studies tested the efficacy of three radiosensitizers in xenograft mice and we ranked them based on anticancer efficacy. To do this, we quantify both inter-study variability and between-subject variability in the model. This allows for both more robust model predictions as well as predictions on a population level. Tumor Static Exposure (TSE) is defined as all combinations of exposure levels that if kept constant result in tumor stasis [39, 40]. When two treatment modalities are given in combination TSE can be represented as a curve in a diagram with each axis representing the exposure of one modality. We use this concept to develop a simulation-based method for ranking compounds. The method utilizes Monte-Carlo simulation and the calibrated model and is in this paper used to determine necessary exposure pairs of radiation dose and radiosensitizer concentration that lead to tumor stasis for different population percentiles, *e.g.*, 50% or 95%. Two strengths of the simulation-based method are that it is suitable for complex models and that it directly incorporates the treatment schedule in the predictions. Therefore, it can potentially be used to select which compounds to proceed with to subsequent drug development phase.

2.2 Paper II

In this paper, we focus on evaluating how well semi-mechanistic models can be used to predict clinical oncology results. In clinical oncology studies, patients are categorized based on how well they respond to a given treatment using the so-called RECIST criteria [32]. The proportion of patients in each RECIST category is what we predict. To accomplish this, volumetric xenograft tumor volume data was first searched for in the literature. We found preclinical data for three drug combinations, for which we were also able to find clinical phase II/III data.

To model the preclinical data, one tumor growth inhibition model is used for each cancer type. In these models, all tumor cells are assumed to be proliferating and the net tumor growth rate is reduced by each drug given. The reduction is modeled by linear functions of either the unbound maximum or daily average concentration. A quadratic interaction effect between the drugs is also included for those combinations where the analysis showed it was necessary. The preclinical models are translated by replacing mouse exposure with human exposure and allometric scaling of all PD rate parameters.

Clinical predictions are made by using the translated preclinical models to generate as many artificial individuals as participated in the clinical studies. Each individual is categorized using the RECIST criteria and the proportion of individuals in each RECIST category is thus estimated. Through a bootstrap procedure, a 95% confidence intervals of these predictions are also estimated. Furthermore, instead of using the standard allometric exponents, we estimate optimal scaling exponents given the observed clinical data. This is accomplished by solving an optimization problem. This aims to evaluate if it is possible to find a generally applicable exponent that better describes the differences between humans and xenograft mice models. These hypothesized exponents may be drug and cancer type specific and their purpose is to allow all preclinical data to be leveraged early in the drug development process.

2.3 Paper III

In the third paper, we continue working with clinical predictions by deriving analytical expressions for the probability that a patient is placed in each of the RECIST categories. Such expressions are possible to find for all tumor growth models where an analytical solution is available and when there only is one random effect in the tumor volume derivative.

We use these expressions to first find an equation that predicts the necessary sample size of a clinical study to achieve a certain significance level and power. This equation can be used after calibrating the model to preclinical data and can thus potentially be used to support design of early clinical studies.

Furthermore, by differentiating the probability functions with respect to the drug concentration, we also find an equation that describes what concentration maximizes the probability that a patient is classified as SD. This can potentially serve as a sort of target concentration for newly developed drugs entering the early stages of clinical trials.

3 Outlook

In this thesis, preclinical oncology data have been studied to improve and support the drug development process. Contributions have been made to better describe preclinical data, rank test compounds, and make predictions of clinical efficacy. Although advances have been made, there is always room for further refinements. In this final chapter, we touch upon some of the possible avenues of continued research.

The models that have been used in the appended papers are based on systems of ODEs. The analysis could be extended by incorporating SDEs into the models. This would allow for a more accurate description of the different types of variability present in the data and, thus, more informative predictions. A good starting point would be the radiation model used in paper I, as there is typically more variability in data from radiation treatment experiments compared with anticancer drug experiments. Moreover, SDEs could be used to further validate the deterministic model dynamics by evaluating how the stochastic part of the model changes with respect to time. In the case of a radiation model, this could be a method for investigating if the subjects develop radioresistance as the treatment progresses. Based on this analysis a decision can then be made on if the deterministic part of the model needs to describe this phenomenon as well.

If more data can be acquired the methodology presented in paper II can be further explored to try to find an optimal way of translating preclinical models. Moreover, performing sensitivity analyses using the derivatives of the RECIST probabilities from paper III could facilitate this analysis. Furthermore, with more detailed preclinical data, *e.g.*, data from studies where drugs were tested on more than one dose level, more advanced preclinical models can be used. This should minimize the error in the clinical predictions coming from, *e.g.*, the need to extrapolate drug potency functions, which in turn should give a better idea of how well the translational methods work.

To know how well an anticancer treatment will work in a population requires not only knowledge of the anticancer efficacy of the treatment, but also of the toxicological effects. With toxicological data, models that describe it can be investigated, evaluated, and refined. The combination of such a model with an anticancer efficacy model would give decision-makers a tool to use when deciding what drug to keep developing.

Another possibility is continuing the work on mathematical method development for population modeling from a hierarchical Bayesian perspective. In case this line of research persuade, it will be based on Particle Markov Chain Monte Carlo (MCMC) methodology.

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