Thesis for the Degree of Licentiate of Philosophy

Data-driven modeling of combination therapy in oncology

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Cancerbehandling handlar om att hämma tumörtillväxt. Helst vill man inte bara att tumörerna ska växa långsammare, utan att de slutar växa och börjar krympa istället. Behandling med kombinationsterapi innebär att man ger två eller flera läkemedel samtidigt. Varför görs då detta? En viktig anledning är att läkemedel kan påverka varandra. Till exempel kan det ena läkemedlet kraftigt öka effekten av det andra och resultera i kraftig tumörhämning. Ett sådant samband mellan läkemedel kallas synergi. Men hur avgör vi utifrån data om det är synergi mellan två läkemedel eller inte? Kanske ännu viktigare, hur avgör vi om en kombinationsterapi är bättre än en annan? Då behövs ett bra sätt att rangordna kombinationer mot varandra. I ett annat scenario kanske vi har en kombination som vi tror på. Frågan blir då hur vi bäst administrerar läkemedlen. Ska den ena substansen ges först? Ska vi ge båda samtidigt? Skall vi ge en lägre dos dagligen eller en högre dos varannan dag?

Ett sätt att försöka svara på den här typen av frågor är med hjälp av matematisk modellering. Bygger vi en modell för att beskriva mätdata för hur tumörers storlek utvecklas över tiden för olika doseringsscheman kan vi sedan kvantifiera olika effekter. Vi kan även simulera modellen för andra doseringsscheman än vi hade data för. På så sätt får vi en prediktion som kan peka oss i rätt riktning för att hitta optimal dosering. Helst vill vi att modellen, eventuellt efter små ändringar, kan återanvändas för andra kombinationer. Då kan vi enkelt jämföra de olika kombinationerna och hitta den bästa.

I den här uppsatsen bygger vi modeller för två olika kombinationsterapier utifrån experiment gjorda på möss. Vi analyserar modellerna med vad vi kallar koncentration för statisk tumör eng. *tumor static concentration* (TSC). Om man bara administerar ett läkemedel är TSC den lägsta drogkoncentration för musen som gör att tumören börjar krympa. I figur 1 visar den blå kurvan hur drogkoncentrationen av läkemedlet cisplatin varierar hos en mus för ett särskilt doseringsschema. Vi ser hur kurvan över tiden varierar mellan att ligga över och under TSC-nivån (den gröna linjen). Under den tid som drogkoncentrationen ligger över kurvan kommer tumören att krympa, medan det är tvärtom den tid drogkoncentrationen ligger under kurvan - då växer tumören. Då skulle man till exempel vilja hitta ett doseringsschema som gör att man ligger över den gröna linjen så länge som möjligt.

Om man ger två läkemedel samtidigt blir motsvarigheten den så kallade TSC-kurvan (se figur 2). TSC-kurvan är ett sätt att visualisera vilka kombinationer av drogkoncentrationer som medför att tumören krymper. I figur 2 motsvarar det gröna området alla koncentrationer som gör att tumören krymper, medan det röda området motsvarar alla koncentrationer för vilka tumören fortfarande växer. Ett enkelt sätt att se på det är att man vill att det gröna området ska vara så stort som möjligt och det röda området så litet som möjligt. Då finns det fler koncentrationer som få tumören att krympa. Hur stor den gröna ytan blir, eller mer precist hur mycket kurvan som delar de två områdena kröker sig, är kopplat till synergin mellan läkemedlen. För den första

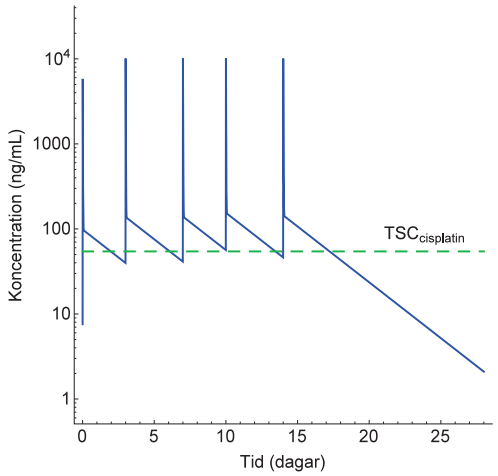

Figure 1: *Den blå kurvan visar koncentrationsprofilen över tid för cisplatin när man doserar dag 0,3,7,10 och 14. Den gröna kurvan visar TSC-värdet för cisplatin.*

kombinationsterapin vi testar får vi bara en liten krökning, medan vi för den andra kombinationen ser en betydligt kraftigare krökning och därmed synergi. Genom att titta på TSC och krökning kan vi även avgöra vilken utav flera kombinationer som är mest effektiv.

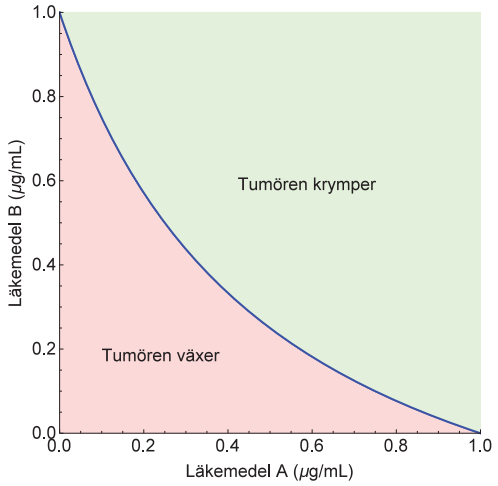

Figure 2: *I blått: TSC-kurva för kombinationsterapi med två olika läkemedel. Det gröna området ovanför TSC-kurvan innebär att tumören krymper. Det röda området under kurvan innebär att tumören växer.*

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Abstract

This thesis contains two manuscripts: *Tumor Static Concentration Curves in Combination Therapy* and *Extending the Tumor Static Concentration Curve to Exposure - A Combination Therapy Example with Radiation Therapy*. There is also an introductory chapter presenting some basic facts necessary to understand the appended manuscripts. The manuscripts share the common goal of developing model-based data-driven tools and techniques to quantitatively assess the effectiveness of anticancer combinations. The first paper presents a dynamical systems model for combination therapy with the anticancer drugs cetuximab and cisplatin. Using a mixed-effects approach the model is shown to adequately describe a preclinical dataset. The model is then analyzed by introducing the Tumor Static Concentration (TSC) curve, a curve of cetuximab-cisplatin concentration pairs all of which, if maintained, result in tumor stasis. The TSC analysis reveals a modest gain from combining the compounds. The variability of the TSC curve across the population is also explored. In the second paper we develop a dynamical systems model for combination therapy with ionizing radiation and a test compound. For this combination we introduce an extension of the TSC curve called the (average) *Tumor Static Exposure* (TSE) curve based on average, as opposed to pointwise, tumor stasis. The TSE analysis for combinations of radiation and the test compound demonstrates a large synergistic effect.

Keywords: Combination Therapy, Mathematical Modeling, Model-Based Drug Development, Nonlinear Mixed-Effects Models, Oncology, Pharmacokinetics/Pharmacodynamics

List of Appended Papers

The following papers are included in this thesis:

I Tim Cardilin, Joachim Almquist, Mats Jirstrand, Alexandre Sostelly, Christiane Amendt, Samer El Bawab, and Johan Gabrielsson, "*Tumor Static Concentration curves in Combination Therapy*," Accepted for publication in the AAPS Journal

II Tim Cardilin, Joachim Almquist, Mats Jirstrand, Astrid Zimmermann, Samer El Bawab, and Johan Gabrielsson "*Extending the Tumor Static Concentration Curve to Exposure - A Combination Therapy Example with Radiation Therapy*," preprint

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Tim Cardilin
Göteborg, September 2016

Contents

1 Introduction

The purpose of this introduction is to make it easier for the reader, who is assumed to have some knowledge of mathematics and statistics, to understand the appended manuscripts. It does not attempt to give a comprehensive view of the topics presented. For this, references are given to the appropriate works.

1.1 Combination Therapy in Oncology

By combination therapy in oncology we mean the simultaneous administration of two or more anticancer agents. These include substances given orally, intravenously, and intraperitoneally (injected into the stomach cavity) and also treatment with ionizing radiation. There are several reasons why combination therapy could be preferred over single-agent treatments. These include reduced toxicity through lower doses, decreased risk of developing resistances by targeting multiple sites, and the potential for synergistic effects (1, 7). A synergistic effect is a positive interaction between compounds leading to a greater effect, *e.g.*, a lower tumor growth rate, compared to the case with no interaction. Similarly, a negative interaction is called antagonism (9).

In recent years the importance of combination therapies has increased and is believed to be necessary to handle many diseases, particularly in light of the growing problem of drug resistances (8). However, there is currently a lack of understanding of how to select the best combinations for testing and how to get the best result out of a given combination. This is an area where mathematical modeling, together with knowledge of the underlying biology, can be a great asset. Mathematical tools and techniques that can be reused for different combinations can make it possible to rank combinations against one another. We can also use it to make predictions of the effects of new combinations as well as optimize the administration schedule of a given combination.

1.2 Pharmacokinetics and Pharmacodynamics

In simple terms pharmacokinetics is what the body does to the drug, and conversely, pharmacodynamics is what the drug does to the body. These are obviously connected and both need to be studied to properly ascertain the effects of a drug.

1.2.1 Pharmacokinetics

Building a pharmacokinetic model is often the first step. A drug is administered, *e.g.*, orally or intravenously, and we want to describe the exposure of drug in the body, usually by finding the drug plasma concentration as a function of both time and dose. It is most common to use so-called compartmental models are used although non-compartmental alternatives also exist. The simplest example of a compartmental model consist of a single compartment representing drug plasma concentration in the

subject, with a zero-order input, the drug dose, and a first-order output, corresponding to drug elimination or *clearance*. This one-compartment model may be written as an ordinary differential equation

$$\frac{dC}{dt} = -k_e C,\ C(0) = \frac{D}{V} \tag{1}$$

where C denotes the plasma concentration of the compound, D the administered dose, k_e the elimination rate and V the distribution volume. More complicated compartmental models consist of an absorption step, as well as other compartments corresponding to drug exposure to tissue or other organs. Higher-order input and output terms may occur, resulting in nonlinear systems of ordinary differential equations.

1.2.2 Pharmacodynamics

In oncology, the pharmacodynamic model usually describes the time evolution of tumor volume. The most basic model assumes that the tumor grows exponentially without drug intervention

$$\frac{dV}{dt} = k_g V,\ V(0) = V_0 \tag{2}$$

where V denotes tumor volume, k_g the net growth rate and V_0 the initial tumor volume. We then include drug action as a linear function of plasma concentration $C(t)$

$$\frac{dV}{dt} = k_g V - k_k C,\ V(0) = V_0 \tag{3}$$

where k_k is the kill-rate associated with the drug. In this case, we have viewed the drug as inducing death of tumor cells. The drug is then classified as *cytotoxic*. There is another important class of drugs called *cytostatic* comprised of drugs that inhibit the tumor cells' ability to proliferate. Note that the pharmacodynamic model is dependent on the pharmacokinetic model, since drug plasma concentration is used as input to drive the system.

For a more complete picture of pharmacokinetics and pharmacodynamics, we refer the reader to the book by Gabrielsson and Wiener (6).

1.3 Nonlinear Mixed-Effects Modeling

Pharmacokinetic and pharmacodynamic models contain unknown parameters that need to be somehow estimated. To do this we need measurement data, usually drug concentrations in plasma for pharmacokinetic studies and tumor volumes for pharmacodynamic studies. These data consist of time series from many different individuals in a population. To make a proper assessment of combination therapy with two compounds, it is further necessary to have data from four different treatment arms: vehicle (control), each compound given as a single-agent, as well as the combination.

The vehicle arm is needed as a reference to determine if the drugs have any effect at all. The single-agent arms are necessary to determine whether or not there is an interaction.

Once we have data and a model structure, we need a framework to estimate the parameters. The most appropriate and sophisticated one for population data, which we have used in the appended manuscripts, is called the Mixed-Effects framework. Mixed-Effects refers to effects composed of both fixed and random components. A fixed effect is something that is common to all individuals in the population, whereas a random effect is specific to a particular individual. Formally, we describe a population as a system of ordinary differential equations

$$\frac{dx_i}{dt} = f(x_i, Z_i, \theta, \eta_i),\ x_i(0) = g(Z_i, \theta, \eta_i) \tag{4}$$

where x_i, Z_i, and η_i are vectors of states, covariates, and random effects for the i:th individual. The vector θ denotes the fixed effects and is the same for the entire population. We assume that the random effects are multivariate normal distributed random variables with zero mean and covariance matrix Ω. The entries of Ω are usually fixed effects and are therefore included in the vector θ. Model observations at discrete time points t_j are then described by

$$y_{ij} = h(x_i(t_j), Z_i(t_j), \theta, \eta_i, t_j) + e_{ij} \tag{5}$$

where y_{ij} denotes the observation, or measurement, for individual i at time t_j, and e_{ij} is a multivariate normal distributed residual error.

In the context of tumor modeling the states are usually compartments of cancer cells representing different stages of degradation, and the observed tumor volume is thus the sum of all the states. Covariates are either drug doses D_i or functions describing drug plasma concentration $C_i(t)$.

Parameter estimation is done by maximizing the population likelihood, which in its exact form is

$$L(\theta) = \Pi_i \int p(d_i|\theta, \eta_i) p(\eta_i|\theta) d\eta_i \tag{6}$$

where d_i is the vector of observations for individual i and p denotes a conditional probability densitiy. The software used for the estimations in the appended manuscripts uses a version of the first-order conditional estimation method (commonly abbreviated as FOCE) to approximate the likelihood function. Details on the estimation method can be found in the paper by Almquist *et al.* (2). A thorough description of Mixed-Effects modeling framework can be found in the book by Davidian and Giltinan, which laid the theoretical foundations in the field (5).

2 Summary of Papers

These manuscripts are based on posters presented at the PAGE meeting in 2015 and 2016, respectively (3, 4).

2.1 Summary of Paper I

A model is constructed to describe combination therapy with the anticancer agents cetuximab and cisplatin based on preclinical data. Cetuximab inhibits cell proliferation, whereas cisplatin stimulates cell death via a chain of damage compartments. The model, which assumes no direct interaction between the compounds, is shown to adequately explain the data. From a steady-state analysis, we derive the *Tumor Static Concentrations* (TSC) for each compound, *i.e.*, the the plasma concentration of a drug such that if it were maintained indefinitely would result in tumor stasis. We further extend the TSC concept to the combination of two compounds. With an additional degree of freedom, the TSC value instead becomes the TSC *curve* of concentration pairs all of which result in tumor stasis if maintained. The curvature of the TSC curve is analyzed, with convexity associated with synergy and concavity associated with antagonism. In the particular case of the studied cetuximab-cisplatin combinations, the TSC curve exhibits a modest curvature. We finally explore how the TSC curve may vary between different individuals in a population and derive a TSC curve such that if the concentration pair is above the curve, 95% of the population is expected to show tumor regression.

2.2 Summary of Paper II

In the second paper we contruct a model for combination therapy with ionizing radiation together with a test compound. Preclinical data suggest that there is a strong synergistic effect. Ionizing radiation is modeled as an instant mass transfer between a proliferating compartment and a chain of damage compartments. The test compound stimulates both the natural and the radiation-induced cell deaths, the latter being an interaction effect only present when the treatments are combined. For this model, we derive a new TSC-like curve by requiring tumor stasis not at each time point, but on average over a given time period. This new curve, called the (averaged) *Tumor Static Exposure* (TSE) curve consists of pairs of test compound concentrations and radiation doses that yield (average) tumor stasis. For the combination of test compound and ionizing radiation the TSE curve is heavily curved, indicating a large synergistic effect.

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