Pharmacometrics

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Chapter 1

Introduction

Pharmacometrics is a novel field that works within the intersection of medicine, computer science, and math. The field analyzes the interactions between foreign objects—known as xenobiotics—and their relationship within biological systems. This is primarily used to model existing drug improvements and understand the implications of new therapeutic treatments.

Chapter 2

Background

Pharmacometrics was created as a field after the strengthening of various pharmaceutical companies within the 1960s. Specifically working towards modeling the various reactions the body would have against drugs, the field led to major advancements within the field of therapeutic pharmaceuticals. Much of the current literature seeks to model the body's reaction to a drug on five diffrent guidelines, including Liberation, Absorption, Distribution, Metabolism, Excretion. This paper will specifically analyze the current literature and detail the possible advancements within computation and *in silico* modeling within the pharmacometrics field.

Chapter 3

Pharmacometric Models: Overview

There are two models of pharmacometric analysis: noncompartmental and compartmental analysis. Noncompartmental analysis, which is the older of the two methods, combines both *in vivo* and *in vitro* results to estimate a concentration time graph, generating data that is then used to analyze a drug based on the LADME model. Noncomparmental models are quite simple, as they simply integrate the function and determine absorption from the resulting value.

Compartmental models take a more biological approach, seeking to analyze the absorption of a drug by dividing biological systems into "compartments" of bodily fluid, and then seek to measure the absorption and presence of drugs within the body over that period. They also use the LADME model.

Chapter 4

Pharmacometric Models: Noncompartmental Analysis

Noncompartmental analysis is the most primitive pharmacometric system. The system is created by running thousands of *in vivo* and *in vitro* experiments that are monitored over a 24-hour period. After absoprtion is completed, the data is synthesized, and placed into a spreadsheet. After this, a simple linear regression is run, which follows the well known formula:

$$y = \alpha + \beta x$$

One simply integrates the function from their desired points, and generates an absorption profile from that process. Since this process is incredibly simple, noncomparmental analysis is the preferred method for modeling novel substances at the early design phase. However, its lack of depth prevents any detailed analysis, meaning that it will likely be phased out in the future.

Chapter 5

Pharmacometric Models: Compartmental

Compartmental analysis is more advanced, yet it collects its data in the same manner of noncompartmental analysis: by running thousands of *in vivo* tests. This data is then measured against bodily 'compartments'—which are usually a few milliliters of blood—and inputted into a spreadsheet as well. Then, a Michaelis–Menten kinetic regression is ran. The regression follows the following formula:

$$v = \frac{d[P]}{dt} = V_{max}\frac{[S]}{K_M + S}$$

where v is the rate of reaction, [P] is the rate of product/treatment formation, and [S] is the formation of the substrate. This model, which was generated by analysis of empirical data, creates an absorption function, which is then integrated.

This method is also preferred when modeling the absorption of enzyme based substances, a mainstay of the biotechnology industry. Noncompartmental analysis can be modified to realize absorption within enzyme based therapies, which is shown within the below formula:

$$\mathrm{E} + \mathrm{S} \underset{\mathrm{k}_r}{\overset{\mathrm{k}_f}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{\mathrm{kq}} \mathrm{E} + \mathrm{P},$$

where k_f is the rate of the forward reaction, k_r is the rate of the reverse reaction, and k_q is the rate of the catalytic constant. This process is likely to be phased out in the future in lieu of compartmental analysis, which will eventually be superseded by *in silico* machine learning analysis.

Chapter 6

Machine Learning - Pharmacometrics

The rapid introduction of various new therapies—particularly to treat rather difficult 'orphan diseases,' has led to the introduction of various ML models that seek to model the absorption of a drug *in silico*, with little to no lab based requirements.

At the lowest level of complexity, a simple neural network is trained against drugs with well known absorption curves: generally benzodiazepines such as *clonopin* or antibiotics such as *penicillin*. Since the majority of these drugs contain complex chemical processes, compartmental analysis is generally used. Noise is generally introduced to remove inefficiencies.

Once the following have taken place, neural network is modified to respond to different bodily spaces and organs—generally by shifting absorption time and methodology. This is once again applied against the LADME method, which benchmarks the drug at certain periods of time.

The network is then trained against novel substances—generally ones that can be easily simulated and confirmed within a laboratory setting. Once high efficiency is reached, the net is pruned, and is finally tested against other well known substances. Confirmation of the absorption curve cements the network as a reliable method of analysis, and allows for experimentation and truly novel substances at the cutting edge of science.