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Population Pharmacokinetics/PD Modelling: a Systematic Review

Mary Hexy,
Research Scholar
Department of Biomedical Engineering, Karunya Institute of Technology and Sciences, Coimbatore, India

Subha Hency Jose
Associate Professor
Department of Biomedical Engineering, Karunya Institute of Technology and Sciences, Coimbatore, India

***Abstract* – It is critical to administer the correct dose of medications during the treatment regimen. Dosing inappropriately might worsen the illness or possibly result in death. The first and only important approach in clinical drug development is to determine an individual's precise dose. Pharmacokinetic variability is characterized by interindividual changes in anatomical and physiological variables. Population modeling requires a strong foundation of processes to ensure accurate data, appropriate computational platforms, sufficient resources, and good communication are all required. This paper examines the various methods for developing pharmacokinetic and pharmacodynamic models. There are a variety of ways that can be used to build population modelling: Nonlinear Mixed-effects Modeling, Bayesian population pharmacokinetic (PBPK) models, Physiological covariate modeling, Visual predictive check are some of the modeling strategies that have been discussed here. The evolution of modeling software is explored in this article. The greatest way for determining the optimal treatment for a patient with a certain ailment is to optimize drugs through optimum control. Different control techniques are also explored in this article.**

Keywords— Precision dosing, Population pharmacokinetic models, mixed-effects modeling, Grey-box modeling, optimal therapy

I. Introduction

It's crucial to understand how a medicine impacts the body; To comprehend how a drug flows humans and animals'

flowing intravenous, oral dosing, transdermal delivery, etc. in humans and animals' the usage of mathematical models is employed. The modelling and simulation technique is quite useful in terms of drug discovery and development, but it fails at the point of treatment in the clinic The fundamental focal point of the survey paper is to abridge the latest mathematical modeling methods adopted in pharmacokinetic/ pharmacodynamic modeling and various approaches used in the population pharmacokinetic while considering many varieties of data for analysis.

Precision dosing[1] is another significant aspect unseen in pharmacokinetic/ pharmacodynamic modeling. For precision dosing, vital entities required are the system data, drug data, and trial design. If the different combinations of these three data companies, the result will be the right dose for the right patient at right time. This will be the solution for the improved use of modeling and simulation in health care.

Pharmacokinetic (PK)[2]describes the motion of drugs within the body, how the body deals with the drug. It was used to describe how medicines moved into, though, and out of the body. The key steps of pharmacokinetics are absorption, distribution, metabolism, and excretion [ADME], and this process is complicated. Many factors influence pharmacokinetics, including drug molecular characteristics, blood flow to and volume of various tissues, permeability of various membranes, tissue composition, and tissue affinity for the administered substance [3]. Pharmacokinetic models are the simplified description of true biological processes and this can be used for data reduction and interpolation.[4] These models comprehend mathematical quantity; the major value is derived from their ability to extrapolate relationships beyond the existing data.

Pharmacodynamics (PD) is a term that explains the strength of a drug in relation to its concentration in a bodily fluid, such as blood. 'What the drug does to the body. Pharmacodynamic modelling is required for the calculation of the parameters that describe the pharmacological effect, and it is associated to the profile of the drug concentration. The precision of the PK counterpart is crucial to the correctness of the PD model. The body's biological response in terms of biochemical and molecular interaction is investigated in pharmacodynamic (PD). It gives prominence to the dose-response relationship The link between drug concentration and effect, in other words. Sub-molecular, molecular, cellular, tissue/organ, and whole-body studies of PD have also been conducted [5]. For the development and approval of each drug, the exposure-

response relationship of PK/PD plays a prime role. PK/PD data contribute to quite a bit of what is on a medication bundle embed.

In preclinical research, PK/PD, as well as physiological modelling and allometric scaling, are used to evaluate toxicokinetic data. It's also utilised to extrapolate the effects of animals on people [5]. The PK/PD analysis is used for characterizing drug exposure, dosage requirement prediction, assessing the changes in dosage requirement, estimating the rate of elimination and rate of absorption, assessing the relative bioavailability/ bioequivalence, and establishing safety margins and efficacy characteristics.

This paper reviews the different modeling techniques used for the development of pharmacokinetic and pharmacodynamic models, different approaches for the development of population pharmacokinetic modeling, and drug optimization. The following is a description of the paper's structure. The importance of pharmacokinetics and pharmacodynamics is discussed in Section 1. In section 2, various methods for developing pharmacokinetic and pharmacodynamic models have been discussed. Section 3 gives a general description of the population pharmacokinetic models (Popp K) and the different software used for its analysis. Section 4 gives a review of the procedure for optimal control along with the different configurations of optimal control for drug optimization. Finally, section 5 provides conclusions for the paper.

II. PHARMACOKINETIC AND PHARMACODYNAMIC MODELING TECHNIQUES

The technique of PK/PD modelling integrates the two traditional pharmacological sciences. It is a series of mathematical expressions that combines a pharmacokinetic and pharmacodynamic model factor to represent the time course of effect strength in response to the delivery of a pharmaceutical dose. PK/PD relationships can be defined by simple equations beneath steady-state conditions which include constant impact model, linear model, Emax version, sigmoid Emax version, and log-linear model [2],[4]. Different methods adopted for the modeling of pharmacokinetic and pharmacodynamic modeling are discussed below.

A. Compartmental Models

Compartmental models feature several peripheral compartments that are connected to at least one important compartment, but no anatomical space or physiological volume. Based on the system norms the mathematical expression that determines the drug concentration inside every compartment, the method can be one or multiple compartmental. The role of linear, time-invariant, and nonlinear compartment models is discussed in [6]. Because all organs and tissues are consolidated into a single huge bucket, referred to as the central compartment, drug recirculation is not possible in the single-compartment model. From outside, the substance enters the middle compartment, then exits the central compartment. There will be a peripheral compartment as well as a center compartment in the two-compartment variant. Here the plasma concentration of the drug decays by multiple exponential phases[7]. The usefulness of the two compartmental models is in [8]. The three compartmental models will include the central compartment (which represents plasma), the highly perfused compartment (which depicts organs and tissues that are heavily perfused by blood), and the hardly perfused compartment (represents the organs and tissues scarcely perfused by blood)[9], [10]. Multicompartment models can be used to study the relationship between drug concentration in the plasma (or serum) and the intensity of a pharmacologic activity.

These models are used to forecast the concentration of a drug in any body fluid or tissue at any given moment. Flexible approaches in the compartmental model are postulated in [5]. The illustration of drugs distribution using mathematical compartment modeling has numerous limitations[11].

B. Noncompartmental Analysis (NCA)

Noncompartmental analysis (NCA) strategies are model-independent, they are not subject to assumptions about body compartments i.e., any specific compartmental model either for drug or metabolite not required. It depends upon the algebraic equations to estimate PK parameters. The linear trapezoidal rule and the Log-linear trapezoidal rule are used to calculate the area under a plasma-concentration curve. In zero-order kinetics, when plasma concentrations drop linearly with time, the linear trapezoidal technique will work. In the log-linear trapezoidal rule, large sample intervals are permissible. This method is more optimal within the first order[12]. NCA proves faster and more cost-efficient to conduct, especially when compared to more complex compartmental analyses. Thus Non-compartmental analysis is used to evaluate the exposure time of a drug and it is a simple and quick method [13].

C. Physiological Models

Physiologically based pharmacokinetic (PBPK) models use blood flow rates and drug binding qualities to numerous tissues and circulating proteins to reflect the distribution of drugs between the central compartment and specific organs and tissues. PKPB models feature several compartments that correspond to different organs or tissues in the body and are parameterized based on known physiology [14]. These compartments are connected by flow rates that are similar to those of the circulating blood system. Common PK properties such as clearance, distribution volume, and effective half-life are estimated using these models, as well as more empirical models. On the other hand, these more physiologically relevant models provide a quantitative mechanistic framework within which scaled drug-specific parameters (using IVIVE techniques) can be used to predict the plasma and, more importantly, tissue concentration-time profiles of new drugs after i.v. or oral administration. If the target group's physiological characteristics are known, they can be used to extrapolate a dose in healthy volunteers to a dose in a sick population. [15] The physiological parameters, whose values

are specified a priori and independent of kinetic data, are used to describe the distribution. A few parameters, usually the one representing metabolism, are tweaked until the data fits comfortably. The body is separated into five or more divisions in most PBPK versions. [16]

D. Grey-box Pharmacokinetic/Pharmacodynamic Systems Modeling

Modeling in a grey box aims to estimate model parameters by combining physiological knowledge with data. Grey-box modeling entails the use of stochastic differential equations (SDEs). In differential equations, disturbances, unmeasured/unknown system inputs, and unmodeled system dynamics all represent a stochastic term [17].

In a Gray-Box model, the state-space technique is utilized to represent the relationship between input and output signals in a dynamical system. In a continuous-time state-space model, internal parametric representation of input and output offers a precise physiological meaning for the parameters. The PK and PD parameters are effectively evaluated simultaneously, defining the uptake, delivery, and effect of the two different types of insulin. Grey-box modelling is used to investigate the influence of insulin on glucose disappearance, and the PK and PD parameters are effectively evaluated simultaneously, defining the uptake, delivery, and effect of the two different types of insulin in [18]. [19] describes glucoregulatory grey-box models based on SDE. The final model provides a comprehensive and well-supported explanation of the data, as well as far more precise and reasonable forecasts.

III. POPULATION PHARMACOKINETICS MODELLING

Drug development necessitates modelling. Population modelling is a complicated process that necessitates a solid set of rules to assure reliable data, proper computational platforms, sufficient resources, and good communication. Pharmacokinetic variability is caused by interindividual changes in anatomical and physiological features.

The only clear goal in clinical drug development is to determine an individual's precise dose. Population pharmacokinetic models (Popp K) are used to demonstrate the temporal history of drug exposure in patients and to identify wellsprings of variability in the quiet introduction. This can be used to test different dosing regimens. When building a population pharmacokinetic model, five major factors must be considered: I data, (ii) structural models, (iii) statistical model, (iv) covariate models, and (v) modelling software. [19], [20], [21]. The normal concentration-time course within a population is described by structural models. Statistical models account for "unprecedented" (random) variation in population concentration. Variability anticipated by subject characteristics is explained by covariate models (covariates).

To analyze data, specialized data analysis techniques and software are needed in the phase-III clinical trials, for drug development using Pharmacokinetic-pharmacodynamic modeling. History for the advancement of population modeling software is given in Table 3.1 [22], [23],[24], [25]

Sl. No	Year	Activity Name	Remark
1	1972	Conceptualization	The concept and the FO method were announced
2	1977	The first case study	Application to digoxin data
3	1980	Announcement of NONMEN	An IBM specific software intended for population kinetics
4	1984	NONMEM 77	A portable version of the software
5	1989	NONMEM III	An improved user interfaces with the NMTRAN front end. NONMEM Users Guide published
6	1989	BUGS software group forms Different	Different method: Markov chain Monte Carlo method
7	1991	USC*PACK	Different method: nonparametric population pharmacokinetic modeling (NPEM)
8	1992	NONMEM IV	New methodological developments, i.e., FOCE. NONMEM Users Guide updated
9	1992	Publication with NPEM	First publication using NPEM method
10	1994	NONMEM Users guide	New updated versions of NONMEM Users Guide including Alison Boeckmann as co-author
11	1998	NONMEM V	Advanced features including mixtures, improved installation, HELP guide
12	2001	Change in license holder NONMEM	NONMEM V licensed by Globomax
13	2001	Winbugs publication	First publication using Winbugs
14	2001	PFIM	Appeared in R and Matlab
15	2002	Publication with PKBUGs	Winbugs application designed for pharmacokinetic models
16	2003	PkStaMp, PopDes, PopED, and POPT	Software tools based on Matlab
17	2003	Monolix Group Forms	Different method: stochastic approximation expectation maximization (SAEM) 2003
18	2004	WinNonMix publication	Population modeling software with graphical user

			interface
19	2004	NONMEM VI	Informal discussions at PAGE 2004 of the advanced stage of beta-testing of NONMEM VI
20	2006	Monolix publications	First publications using Monolix
21	2009	Phoenix NLME	User-friendly GUI
22	2010	NONMEM 7	New methods: Bayes, SAEM, and others, parallel processing enabled
23	2012	Monolix 4.1	Full-script version (MLXTRAN, XML) and/or user-friendly GUI
24	2017	PK-Sim	Open-source platform for PBPK modelling[26]
25	2018	gPKPDSim	MATLAB based GUI (open source) application [27]
26	2019	Stan and GNU MCSim	Bayesian software inference tool [28]

Table 3.1

Detailed examples of PBPK model code conversions from acslX is compatible with the other three software programmes, including Berkeley Madonna, MATLAB, and the R language [29]. The fundamental aspect of population pharmacokinetic and its important deliberations while planning a population pharmacokinetic analysis are given in [25]. There is a need and try to standardize and develop the right practices by using modeling in various fields such as business, regulatory, academics, and clinical research as a whole.

The result of the modeling and the numerous software programs are linked to various mathematical and computational resources similar to the several methods used in population modeling. An effort to provide insight into these methods is given below.

1). Nonlinear Mixed-effects Modeling

Nonlinear mixed-effects models have become the major research framework for population-based pharmacometrics modelling, and NONMEM has become the gold standard software kit for implementing these approaches. The nonlinear relationship between the dependent variable (e.g., concentration) and the model parameters and independent variable is referred to as "nonlinear". "Mixed-effects" relates to parameterization: "Fixed effects" refers to variables that are constant across individuals., while "random effects" refers to parameters that do vary across individuals. [30]Describes the basic principles and assumptions of the nonlinear mixed-effects model (NLME) and compares it to the linear mixed-effects model (LME).

An ordinary differential equation (ODEs) based mixed-effects modeling package (nlmeODE) for population PK/PD research will provide an accurate parameter estimate.

Nonlinear mixed-effects models for repeated measures are a hierarchical model that combines both fixed and random effects to account for unexplained inter- and intra-individual variability.

The intra-individual (residual) variability reflecting the difference between the individual projected values and the observations is modelled as in the first-stage model.

$$y_{ij} = f(\varphi_i, x_{ij}) + \epsilon_{ij} \qquad i = 1,2,\dots\dots N \qquad j = 1,\dots\dots n_i \qquad (1)$$

Where y_{ij} is the jth for the ith individual, f (·) a non-linear function of a parameter vector that is unique to each person φ_i specific to that individual, and predictor vector x_{ij}, N reflects the number of individuals, the number of measurements for each individual i and the residual error terms ϵ_{ij} are assumed independently and identically with a mean of zero and variance of σ^2, distributed normal random variables are created.

The model connects the various parameter of persons in the second stage of the hierarchy, i.e.

$$\varphi_i = A_{ij}\beta + B_{ij}b_i \qquad (2)$$

Where A_{ij} and B_{ij} are the fixed-effects vector's β and random-effects vector's b_i, design matrices, respectively. The random-effects vector b_i, which consists of k zero-mean variables with variance-covariance matrix that are thought to be independent and identically distributed Ψ, is used to model inter-individual variability. i and j are independent of the residual error terms ϵ_{ij} and bi.

On the basis of the marginal density of y, the parameters in mixed-effects models are estimated using maximum likelihood (ML) or restricted maximum likelihood (REML). [31]. Individualization and Prediction of NLME using three different methods like Within-subjects and Between- Subjects variance, Maximum-Likelihood Estimation and Mixed -Effects Modelling and Bayesian Estimation for Predictive Modelling are discussed in[32]. The two population analyses used to determine the structural model are NONMEM (nonlinear mixed-effect modelling) and NPML (nonlinear principal component analysis). (nonparametric maximum-likelihood), Estimate population mean metrics like clearance and interindividual variability, then search for demographic factors that influence them. [33]. Nonlinear Mixed-Effects Model is Based on Stochastic Differential Equation,[34] The likelihood function is calculated and approximated by combining the extended Kalman filter with Bayesian judgments.

2). Bayesian population pharmacokinetic (PBPK) models

Using a mixed Bayesian population PBPK technique, physiologically relevant interindividual variability is characterized and identified. The method is based on a hierarchical model that represents experimental data at the individual level while also identifying physiological parameter variability at the population level. Large amounts of prior information about the population's physiology can be added when employing a Bayesian method for a model approach. The Bayesian population PBPK technique calibrates such knowledge to experimental results, resulting in a posterior distribution that contains all information about all parameters

in the population and their variance.[35].

The posterior distribution is expressed as follows in Bayes theorem,

$$p(\omega/_Y) = \frac{p(Y/_w).p(\omega)}{p(Y)} \qquad (3)$$

Where, $p(\omega)$ prior probability, $p(Y/_w)$ is the probability of the experimental results, The arbitrary experimental data is denoted by Y, and ω, arbitrary parameters. In the Individual Bayesian pharmacokinetic modeling approach, the model validation is carried out giving the estimate of the pharmacokinetic parameters in cases of gentamicin injection, this method has 100% accuracy. So that the drug dosage was carried out individually, giving the right dose for the right person[36]. Features of different models evaluated using Bayesian population pharmacokinetic (PBPK) models are listed in Table 2

Ref	Model evaluated	Features
[37]	Multiroute chloroform exposure	This helps in the optimization of certain PKPB parameters in the population. It can be used to calibrate models.
[38]	Marine mammals	The posterior distribution was computed using the previous results, and the PBPK model has been updated. It assists in the estimate of the population and vulnerability of protected marine mammal species.
[39]	Florfenicol residues in the tilapia tissues	It helps to improve the characterization of ambiguity and generate scenario-specific values
[40],[41]	Interindividual variability	Can contribute to improved drug development safety and effectiveness, as well as increased trust in personalized medicine efforts.
[42]	Perfluorooctane sulfonate in multiple species	The instability of model parameters was well described across organisms.
[43]	Trichloroethylene and its metabolites	By quantifying the volatility of dose-response interactions in noncancer and cancer risk assessment, this study enhances the extrapolation of dangerous Trichloroethylene (TCE) dosages from laboratory animals to people.

Table 3.2

Stan and GNU MCSim are two Bayesian software inference tools that estimate physiologically based pharmacokinetic (PBPK) model parameters using various Markov chain Monte Carlo (MCMC) methods. when they were compared *GNU MCSim* mixed much quicker and had a higher average computing efficiency than *Stan*.[28]

In Bayesian PKPD link models, implement a method for preventing unwanted feedback by Combining MCMC with 'sequential' PKPD modeling [44].

3). Physiological covariate modeling

Many physiological characteristics in the PBPK model are influenced by an organism's anthropometry, such as age, gender, or body height. To integrate such relationships, covariates and scaling functions are used. This minimises total variability as well as the dimensionality of the parameter space. The following are the components of the covariate model [35].

$$a_i = (A_i, G_i, H_i)$$
$$\beta = (M, S)$$
$$d = M_{AiGi} + S_{AiGi} b_i, \qquad b_i \sim N(0, I)$$
$$d^V = M_{AiGi}\left(\frac{H_i}{H_{AiGi}}\right)^{\propto} + S_{AiGi}\left(\frac{H_i}{H_{AiGi}}\right)^{\propto} . b_i \qquad (4)$$

where Ai, Gi, and Hi are the covariates for age, gender, and body height, respectively. The letters M and S represent for the population mean values and standard deviations, respectively, for fixed effects. [35]. A mean value M and standard deviation S for each grid point are used to describe age and gender-related distributions on a grid based on the configuration of the applicable physiological database. M_{AiGi} is the age-scaled vector of population standard deviations for individual I particular to gender, and S_{AiGi} is a gender-specific age-scaled vector of population mean values for individual I where age scaling was achieved using linear interpolation between grid points.

As a result of this formulation, the population model function d becomes linear. [35] The random effects b_i are believed to be independent of an individual's anthropometry, meaning that regardless of the variables, the unexplained variance in the parameters should be the same. is thought to be unrelated to A priori.

A defined function, d^V is formulated for organ volumes. The scaling coefficient is the ratio of an individual's body height H_i to the mean height of the constitutional covariates H_{AiGi} defined group. The vector α represents the allometric scaling factors for each organ[35].

In [45], the impact of body weight on paracetamol pharmacokinetics in newborns in the presence of missing time-dependent variables is investigated using population pharmacokinetic modelling.. Missing body weights have a minimal effect on population estimates of pharmacokinetic parameters, but they have a big impact on covariate relationship parameters, particularly the one that defines clearance reliance on body weight. When it comes to missing covariates, the simulation methodology helps you to borrow data from several experiments if they all address the same demographic.

Covariate modelling is an important stage in the analysis of clinical data for determining the dosage requirements for a specific group [46]. The identification of the true covariate is sometimes complicated because of the strong correlation among covariates. Three ways for balancing

data and prior knowledge when picking covariates: (1) full fixed effect modelling (FFEM), which incorporates covariate selection prior to data analysis, (2) simplified stepwise covariate modelling (sSCM), which is totally data-driven, and (3) Prior-Adjusted Covariate Selection (PACS), which incorporates both. [47]. Covariate pharmacokinetic considerations in pediatrics are discussed in [48]. Covariate studies in children are advancing our understanding of drug disposition and effects in children as they develop, ultimately leading to more effective medication use. [49].

4). Visual predictive check

A visual predictive check (VPC) is a useful approach for evaluating the auxiliary and stochastic applicability of population pharmacometrics models. Within user-specified intervals, or bins, of the independent variable, VPCs frequently entail computing quantiles of the reliant variable, such as the tenth, 50th, and 90th percentiles. These quantiles are used to compare populations and interpret observable data and information from a pharmacometrics model. Externally, the estimated quantiles for observed and simulated data are assessed. This natural analytic methodology can reveal model detail flaws and provide procedures for model improvement.[50]

In addition to bin selection, VPCs can be conducted utilizing suppression techniques such as additive quantile regression (AQR)[51],[52],[53], and local regression (LOESS). The independent variable's bins do not need to be stated because the AQR and LOESS are regression methods. VPCs and prediction corrected VPCs can both be performed using regression techniques (pcVPCs)[54] models of population pharmacometrics.

VPCs are carried out using regression methods. The following is the algorithm for calculating prediction corrected VPCs using LOESS and AQR:

1. Regress the observed population predictions (PREDs) of the population pharmacometrics model against the independent variable using LOESS. This will give you the estimated PRED for each independent variable measurement j. This phase should be optimized for (span parameter) before visual inspection to ensure that the LOESS fitted values match the observed data.[50].
2. Calculate the dependent variable's prediction adjusted values for an individual i at measurement j. pc_{ij}

$$pc_{ij} = y_{ij}\frac{E(PRED_j)}{PRED_{ij}} \quad (5)$$

where y_{ij} stands during measurement j, for the observed dependent variable for individual i, $E(PRED_j)$ stands for the population prediction for individual i at measurement j, and PREDij stands for population prediction for measurement j. If both sides of the data are modelled with a log transform, Eq. 5 can be changed to [50]:

$$\ln(pc_{ij}) = \ln(y_{ij}) + \left(E\left(ln(PRED_j)\right) - ln(PRED_{ij})\right) \quad (6)$$

where $E\left(ln(PRED_j)\right)$ is achieved by using the LOESS function on $ln(PRED_{ij})$ in comparison to the independent variable.

3. Use pc_{ij} (or $\ln(pc_{ij})$) as the dependent variable in the VPC procedure. [50]

When the population under study includes multimodal parameter distributions, nonlinear mixed-effects models do not hold up well. By capturing these multimodalities, mixture models enable the finding of parameters specific to a subpopulation. For mixture models with multimodal parameter distributions, visual predictive checks (VPC) have been established. [55]

IV. OPTIMAL CONTROL FOR DRUG OPTIMIZATION

What should you do if you only have a limited amount of time and resources? We figure out what the optimal therapy option is for a patient with a specific disease. The goal of optimal control is to find the controls (which may change over time) that get the system as close as possible to the desired output. An objective function, that is maximized or minimized is used to quantify the desired outcome. Figure 1 shows the Procedure for achieving the optimum control.[56]

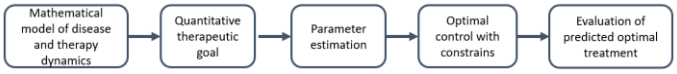

Fig. 1 Procedure for achieving the optimum control [56]

The first stage is to build a model of the disease's dynamics and how the treatment affects them. The model must be sufficiently detailed to account for the impacts of targeted therapy. After then, the treatment's objective must be quantified. In most cases, we want to maximize the benefits of a treatment while limiting its negative effects. We get a mathematical statement to optimise when we combine phrases indicating these affects with appropriate signs and weights. We'll go on to the following phase after we've determined the system's parameter values. We can come up with the ideal control system. The technique should next be evaluated by comparing the results of a predicted ideal treatment to the results of standard treatments. Mathematical modelling, simulation, and optimization of the therapy process may help doctors make better decisions, which could lead to fewer severe side effects and longer remissions. [57]. Our goal is to determine the optimum drug dosage schedule as well as anticipate absorption and concentration rates. The pharmacokinetic model was changed by adding a control vector, and the redesigned model was analyzed using optimal control theory [58].

V. CONCLUSION

This paper examines the various methods for developing pharmacokinetic and pharmacodynamic models. There are a variety of ways that can be used to build population modelling. This article examines the evolution of modelling software. The greatest way for determining the optimal treatment for a

patient with a certain ailment is to optimize medications through optimum management. This article also looks at various control approaches. As a result, optimal control is a well-established modelling technique that we can now use more widely to increase drug development success and provide patients more time with their families.

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