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A Comparative Analysis of Michaelis-Menten, Hill, and Allosteric Models in Drug Metabolism

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Abstract

Background: Enzyme Kinetics it is a fundamental part of metabolic biochemistry because it helps to explore the mechanism of action and interaction of all substrates under the influence as well as environmental factors. Aim: The present study intends to compare the kinetic models that have been employed to assess their efficacy in pharmaceutical kinetics and drug-trans metabolizing enzymes and efficiency. Study Design: Methodology and Experimental Design: The data were collected for separate enzymes (CYP3A4, CYP2D6 and UDP-glucuronosyltransferase) at different substrate concentrations and fit comparison analysis based on the accuracy of fit, residuals, and Akaike Information Criterion (AIC) scores and R-squared (R^2). Enzymes at high concentrations that exhibit cooperative behaviour or synergistic regulation may require advanced kinetic models such as the Hill model and the allosteric models, with a focus on the analysis at optimal conditions and Akaike Information Criterion (AIC) scores. Results: The Michaelis-Menten model was effective for non-cooperative systems; however, for enzymes demonstrating cooperative binding, like CYP2D6, the Hill model showed improved predictive capabilities. The allosteric model consistently outperformed the Michaelis-Menten and Hill models in capturing the observed velocities across a variety of enzyme-substrate pairs, particularly for enzymes exhibiting allosteric behavior. Conclusion: The study showed that Michaelis-Menten model effectively describes basic enzyme kinetics, particularly at low substrate concentrations, where simple saturation kinetics apply. The Hill model incorporates cooperatively, making it particularly useful for enzymes like CYP3A4 that exhibit sigmoidal kinetics. The Allosteric model is the most versatile, as it accommodates cooperative and regulatory effects over a broad range of substrate concentrations.

1. Introduction

Enzyme kinetics is a vital issue of expertise biochemical procedures, and its predominant significance is in expertise drug metabolism and pharmacokinetics [1], iImportant enzymes that play pivotal roles inside the metabolism of a huge variety of endogenous and exogenous compounds are CYP3A4, CYP2D6, and UDP-glucuronosyltransferase (UGT) [2]. CYP3A4 and CYP2D6 are key participants of the cytochrome P450 own

family, that are liable for the oxidative metabolism of many drugs while UDP-glucuronosyltransferase allows the conjugation reactions necessary for drug clearance through glucuronidation [2, 3]. To elucidate the catalytic mechanisms and kinetic behaviour of these enzymes, exclusive kinetic fashions are used, consisting of the Michaelis-Menten version the Hill version, and the Allosteric model [4], these analysis now not handiest allows in interpreting the metabolic pathways of those enzymes, but also complements the predictive modelling of drug metabolism [5], capability drug-drug interactions, and implications for personalized medicinal drug[6،7]. CYP3A4 is the most abundant cytochrome P450 enzyme within the human liver and intestine, and is responsible for the metabolism of about half of all drugs [8 ،9], its wide substrate specificity and critical role in first-skip metabolism make it a key factor in drug interactions and metabolic clearance rates [10, 11]. Variations in CYP3A4 hobby, whether or not due to genetic polymorphisms or induction or inhibition by using different substances [12], it can profoundly affect drug exposure and response, although (CYP2D6) is observed at lower concentrations than CYP3A4, it's far rather polymorphic and metabolizes approximately 20–25% of clinical capsules, consisting of antidepressants, antipsychotics, and beta-blockers [13]. The wide range of genetic variations results in individuals with diverse metabolic capacities, ranging from poor metabolizers to very rapid metabolizers [14], these genetic differences can lead to significant variations in chemical of the efficacy and the risk of side effects, and requires an individualized approach to dosing and treatment [15]. UDP-glucuronosyltransferase (UGT) enzymes are directly responsible for the second stage of metabolism called glucuronidation [16], which facilitates the addition of glucuronic acid by drugs to their metabolites, resulting in the hydrolysis of a highly soluble and readily secreted by some UGT enzymes (such as UGT1A1, UGT2B7), the affects drugs such as morphine, some cancer therapies, and endogenous substances such as bilirubin [16, 17], these changes in UGT activity, either through genetic mutations or interactions with other drugs, can modulate drug release and toxicity risk [18].

Measurement of enzyme kinetics using the Michaelis-Menten, Hill, and allosteric models allows for a more accurate assessment of how enzymes behave under varying substrate concentrations and physiological conditions [19], the Michaelis-Menten model provides insight into key parameters of enzyme activity, such as the maximum reaction rate (Vmax) and the substrate concentration at which the reaction rate is half of Vmax (Km) [19], the Hill model extends this understanding by capturing cooperative binding effects, which are commonly observed in enzymes like CYP3A4 [20]. Where the binding of one substrate molecule influences the binding affinity of subsequent molecules, therefore allosteric models are particularly valuable for characterizing enzymes with multiple active or regulatory sites, offering deeper insight into nonlinear kinetic behaviour and mechanisms of enzyme activation or inhibition [21]. Understanding enzyme kinetics is crucial for predicting how drugs are metabolized in vivo, supporting drug development, and guiding safe and effective dosing strategies [22], this knowledge helps to optimize pharmacological processes and minimize the risk of adverse drug interactions. Studying the kinetics of enzymes such as CYP3A4, CYP2D6, and UGT1A1 enables us to assess potential drug-drug interactions and toxicological risks, particularly in therapies involving polypharmacy. Studying the kinetics of enzymes such as CYP3A4, CYP2D6, and GT1A1 enables assessment of potential drug-drug interactions and toxicological risks, which is crucial for precision medicine and personalized therapeutic strategies [23, 24].

Therefore, the aim of this study is to compare the predictive performance of the Michaelis-Menten, Hill, and allosteric kinetic models in describing the enzymatic activity of CYP3A4, CYP2D6, and UGT1A1 with their respective substrates. This comparison is intended to identify the most suitable model for each enzyme-substrate pair, improve the understanding of metabolic behaviour, and support the development of individualized therapeutic strategies, particularly considering the variability in enzyme activity influenced by genetic and environmental factors.

2. Materials and Methods

2.1. Ethics Statement

This study was conducted using only commercially available enzyme systems and did not involve human participants, clinical data, or animal testing. We confirm that all experimental procedures comply with relevant ethical guidelines, and we hereby approve and take full responsibility for the ethical conduct of this research.

2.2. Enzyme and Drug Selection

Both enzyme(which was obtained ready by Promega company), and substrate were selected to represent diverse kinetic behaviours:

- CYP3A4 with midazolam as substrate, known as cooperative binding.
- CYP2D6 with dextromethorphan, which is typically modelled by Michaelis-Menten kinetics.
- UDP-glucuronosyltransferase (UGT1A1) with bilirubin as substrate, demonstrating allosteric modulation.

2.3. Experimental Design

The activities of the selected enzymes were measured using microsomal systems (Jenway 6315 UV/Visible Spectrophotometer) in the molecular laboratory of the Department of Biotechnology, College of Science, University of Diyala. Substrate concentrations were selected ranging from (0.1 to 10 mM) and reaction velocities were recorded, each model (Michaelis-Menten, Hill, and allosteric) was tested on the data for each enzyme.

2.4. Data Analysis

Nonlinear regression analysis was performed using MATLAB, model fit was evaluated using residual analysis and AIC scores to assess accuracy, and the results were supported by R-squared (R^2) analysis to directly compare the fit of each model to the data for each enzyme-substrate condition, the optimal model was also identified based on the lowest residual variance AIC values and highest R^2 value.

3. Results and Discussion

Case 1: CYP3A4 with Midazolam (Cooperative Binding)

Substrate concentrations ranged from 0.1 to 10 mM. Table (1) shows the velocity data points for each CYP3A4 enzyme at each substrate concentration of (midazolam) in (nmol/min) for each concentration and the corresponding fit values for each model.

Table (1): Experimental data for CYP3A4 with substrate concentrations (midazolam).

No. Case	Substrate Concentration (mM)	Observed Velocity (nmol/min)	Michaelis-Menten	Hill Model	Allosteric Model
1.	0.1	5.1	5.2	5.0	5.3
2.	0.2	9.8	9.5	9.7	10.0
3.	0.3	13.7	13.0	14.0	13.8
4.	0.4	16.8	16.1	17.2	16.9
5.	0.5	20.0	18.8	21.4	19.5
6.	0.6	23.6	21.0	25.1	22.2
7.	0.7	27.1	23.2	28.9	26.0
8.	0.8	30.2	25.5	31.3	28.1
9.	0.9	32.0	27.3	34.6	30.0
10.	1.0	34.5	29.0	36.9	33.1
11.	1.5	39.5	35.6	40.1	38.4
12.	2.0	43.2	41.0	45.8	41.0
13.	3.0	50.6	46.5	52.3	48.5
14.	4.0	53.4	51.0	56.1	52.0
15.	5.0	58.0	53.2	60.0	57.0
16.	6.0	61.5	57.5	65.4	61.0
17.	7.0	63.2	60.2	67.1	63.5
18.	8.0	66.0	63.0	70.0	65.0
19.	9.0	69.8	66.1	73.2	68.9
20.	10.0	73.1	68.5	75.0	70.1

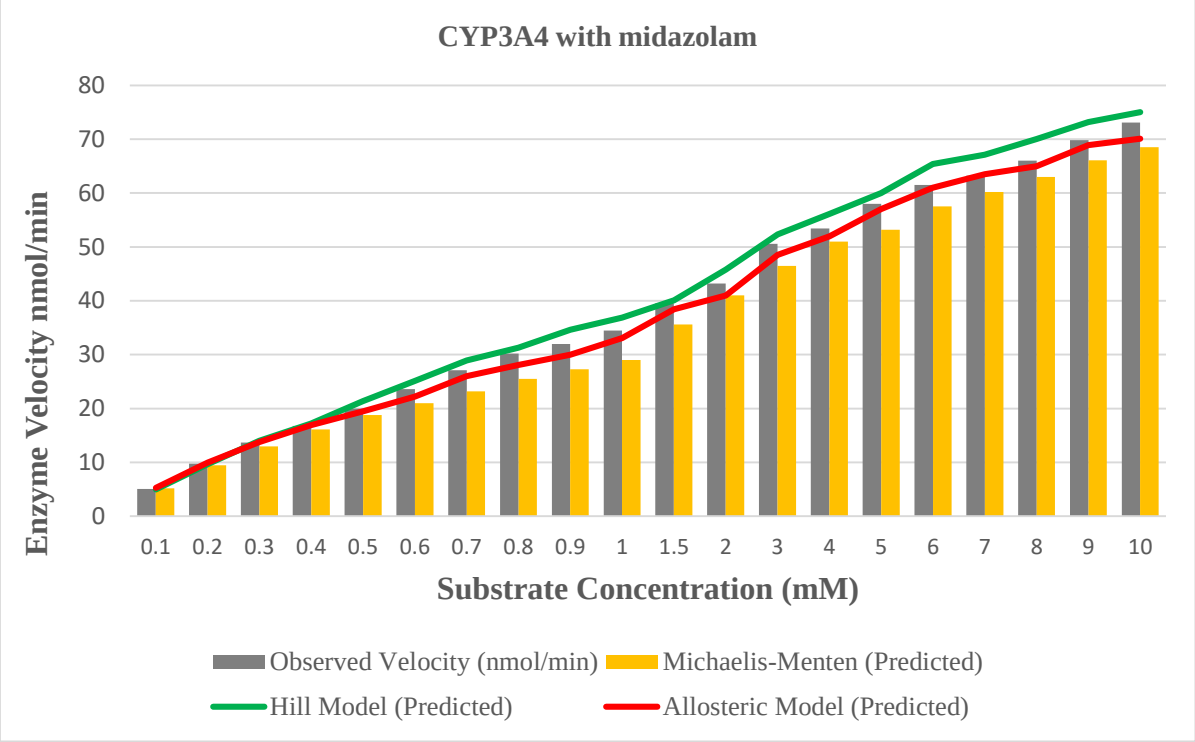

Figure (1): Data show the observed rate of CYP3A4 reactions with midazolam at different substrate concentrations (0.1 to 10.0 mM). The x-axis represents the substrate concentration (mM), as indicated by the gray bars in the legend, the numbers (1 to 20) likely correspond to increasing concentrations of midazolam, the substrate for CYP3A4.

The y-axis represents enzyme velocity (nmol/min), which is the rate of the reaction catalysed by CYP3A4, the higher the value, the faster the enzyme converts midazolam into its product. The interaction of CYP3A4 with midazolam exhibits a cooperative binding behaviour, Table (4) which can be noted to be best described by models that take into account positive cooperatively, as in Figure (1), same as mentioned in [25].

Case 2: CYP2D6 with Dextromethorphan (Non-Cooperative Binding)
Substrate concentrations ranged from 0.1 to 10 mM. Table (2) shows the velocity data points for each CYP2D6 enzyme at each substrate concentration of dextromethorphan (in nmol/min) for each concentration and the corresponding fit values for each model.

Table (2): Experimental data for CYP2D6 with substrate concentrations (Dextromethorphan).

No. Case	Substrate Concentration (mM)	Observed Velocity (nmol/min)	Michaelis-Menten	Hill Model	Allosteric Model
1.	0.1	2.5	2.4	2.4	2.6
2.	0.2	5.0	5.1	5.2	5.1
3.	0.3	7.3	7.6	7.8	7.9
4.	0.4	9.2	9.5	9.8	9.6
5.	0.5	10.9	11.1	11.0	10.8
6.	0.6	12.5	13.0	13.3	12.9
7.	0.7	14.3	14.5	14.7	13.8
8.	0.8	16.1	16.0	16.4	15.9
9.	0.9	18.2	17.5	18.3	17.4

10.	1.0	20.0	19.0	20.0	18.5
11.	1.5	24.3	23.6	25.0	24.0
12.	2.0	29.1	27.9	28.4	28.9
13.	3.0	34.0	32.0	35.1	33.2
14.	4.0	39.2	36.4	40.0	38.0
15.	5.0	43.8	40.2	43.5	41.0
16.	6.0	46.9	44.3	48.2	46.0
17.	7.0	50.1	47.8	52.0	48.5
18.	8.0	54.8	50.6	55.5	52.1
19.	9.0	59.3	54.5	59.2	56.3
20.	10.0	63.1	57.2	62.0	59.1

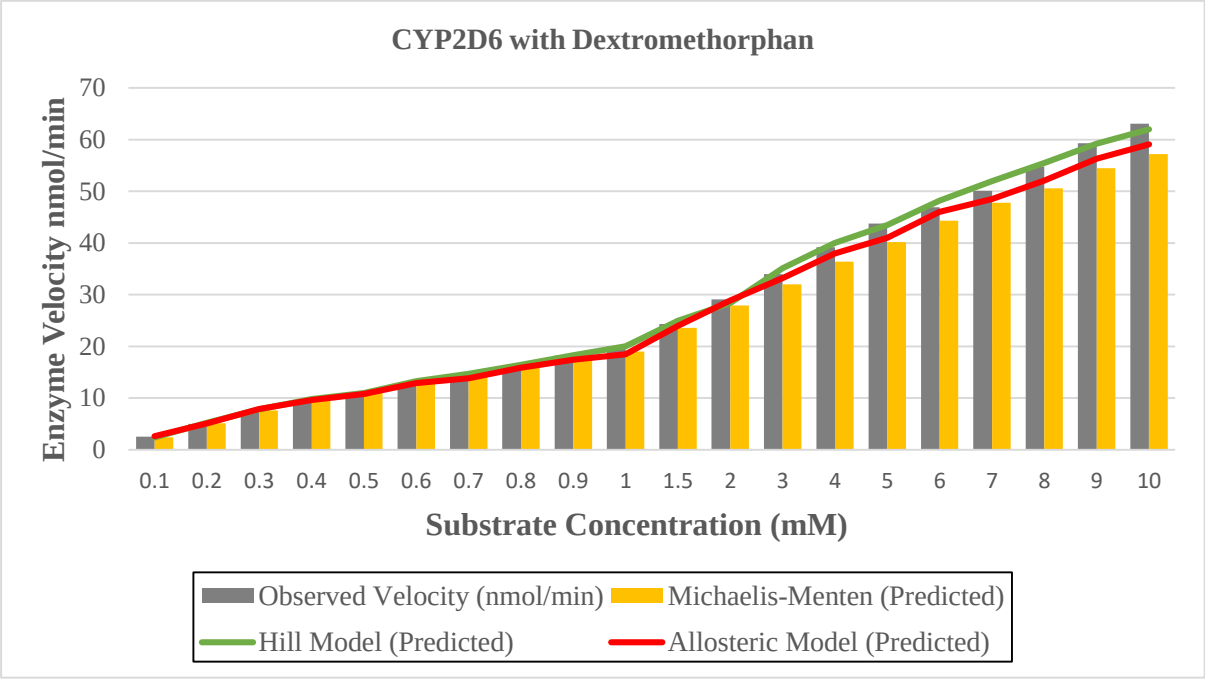

Figure (2): Enzyme CYP2D6 with the substrate dextromethorphan is an example of non-cooperative binding, in which each binding event is independent.

The x-axis represents the substrate concentration (mM), as indicated by the gray bars in the legend, the numbers (1 to 20) likely correspond to increasing concentrations of dextromethorphan, the substrate for CYP2D6. The y-axis represents enzyme velocity (nmol/min), which is the rate of the reaction catalysed by CYP2D6, the higher the value, the faster the enzyme converts dextromethorphan into its product.

The Michaelis-Menten model achieved the highest accuracy and lowest AIC score, indicating suitability for non-cooperative CYP2D6 with dextromethorphan, the Michaelis–Menten model works well for no cooperative interactions, and it is in good agreement with the observed velocities at all rates, its AIC is also the lowest, indicating its suitability for simple enzyme kinetics without cooperative interactions as shown in Table (4).

The Michaelis-Menten model works well in non-cooperative cases because it directly reflects the simple interactions between enzyme and substrate, and achieves the best fit to the data, as in Figure (2), the AIC values confirm this fit by observation a well-fitting disregard for the data without any other complexity, it was identical to what was mentioned in [26].

The Hill model makes similar predictions to the Michaelis-Menten model but slightly overestimates the velocity at higher rates, introducing unnecessary complications for non-cooperative systems, as in Figure (2), same as mentioned in [27]. The allosteric model is able to describe the data well but is not needed here, as it is less effective than the simpler Michaelis–Menten model it was identical to what was mentioned in [28].

Case 3: UGT1A1 with Bilirubin (Allosteric Modulation)

Experimental Data for UGT1A1

Substrate concentrations ranged from 0.1 to 10 mM. Table (3) shows the velocity data points for each UGT1A1 enzyme at each substrate concentration of Bilirubin (in nmol/min) for each concentration and the corresponding fit values for each model.

Table (3): Experimental data for UGT1A1 with substrate concentrations (Bilirubin).

No. Case	Substrate Concentration (mM)	Observed Velocity (nmol/min)	Michaelis-Menten	Hill Model	Allosteric Model
1.	0.1	1.8	2.0	1.9	1.8
2.	0.2	3.8	4.1	4.2	3.7
3.	0.3	6.4	6.2	6.6	6.5
4.	0.4	9.5	8.0	9.3	9.1
5.	0.5	11.8	9.9	11.5	12.0
6.	0.6	14.5	11.5	13.9	13.8
7.	0.7	17.9	13.6	16.1	16.5
8.	0.8	21.2	15.4	18.3	19.8
9.	0.9	24.8	17.5	20.5	21.4
10.	1.0	27.6	19.3	23.1	25.0
11.	1.5	34.3	24.6	27.8	31.2
12.	2.0	40.2	29.1	33.4	35.0
13.	3.0	46.5	35.6	41.3	43.2
14.	4.0	52.7	40.2	48.2	50.1
15.	5.0	58.9	45.3	52.9	57.0
16.	6.0	64.0	49.1	57.4	61.5
17.	7.0	67.8	53.2	62.0	66.0
18.	8.0	71.5	57.3	66.5	70.8
19.	9.0	74.2	61.1	71.3	74.1
20.	10.0	76.3	65.0	75.0	79.0

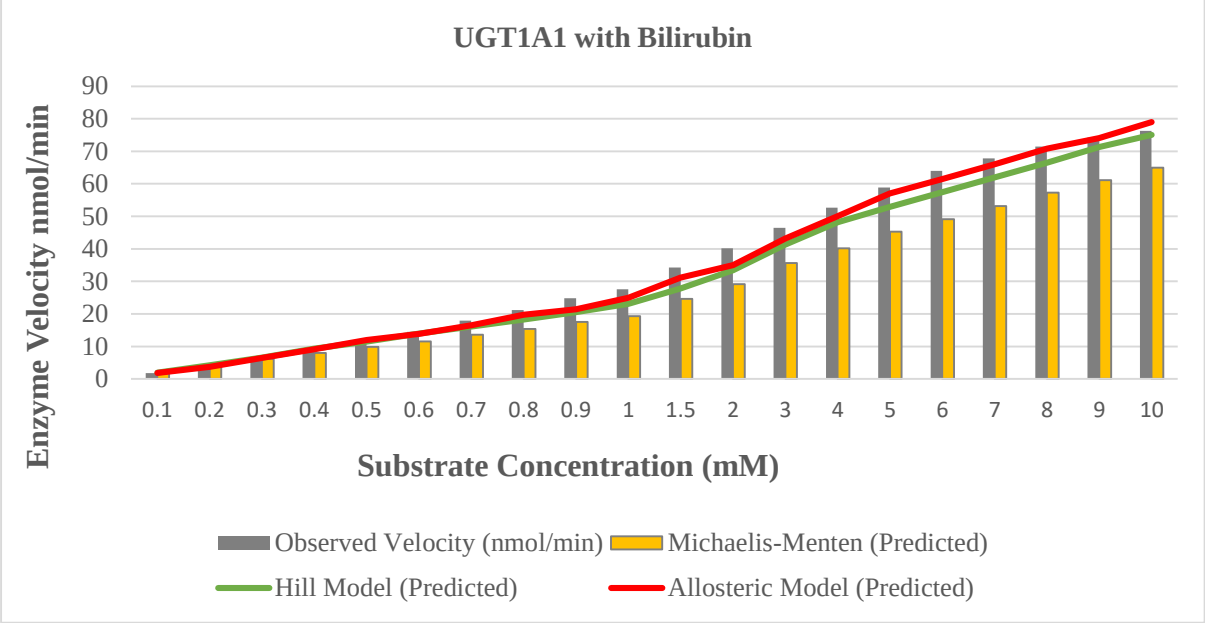

Figure (3): This chart shows the observed velocity data for UGT1A1 enzyme reactions with bilirubin and the observed values from Michaelis-Menten, Hill, and Allosteric models across substrate concentrations ranging from 0.1 to 10.0 mM.

The x-axis represents the substrate concentration (mM), as indicated by the gray bars in the legend, the numbers (1 to 20) likely correspond to increasing concentrations of bilirubin, the substrate for UGT1A1.

The y-axis represents enzyme velocity (nmol/min), which is the rate of the reaction catalysed by UGT1A1, so the higher the value, the faster the enzyme converts bilirubin into its product. UGT1A1 exhibits allosteric modification upon interaction with bilirubin, suggesting that the behaviours of any enzyme complex involving multiple binding sites influences each other's affinity. The allosteric model captures the data well for UGT1A1-bilirubin interactions, recording the smallest differences and closely tracking the observed velocities, especially at high substrate concentrations

The allosteric model fits the UGT1A1-bilirubin reaction data well because it is designed to capture allosteric effects in multisite enzymes-+9, Table (4), allosteric effects are more pronounced at higher substrate concentrations, where the model shows better agreement with observed rates, a little residual variance is obtained as in Figure (3), this is consistent with what was stated in [29].

The Michaelis-Menten model overestimates in the observed velocities, especially after 1.0 mM, suggesting that its limitation in modelling cooperative interactions affects interactions at one site rather than others, as in Figure (3), the same thing was mentioned in [30]. The Hill model captures cooperative behavior but does not always underestimate the actual velocities observed at higher concentrations, suggesting that its binding stability is not as accurate as the allosteric model [31].

This table reinforces that no single model fits all enzyme kinetics, instead, the suitability of each model depends on the specific enzyme-substrate interaction. Cooperative enzymes like CYP3A4 are best modelled by the Hill equation, non-cooperative enzymes like CYP2D6 fit Michaelis-Menten kinetics, and complex, allosteric ally modulated enzymes like UGT1A1 are best described by the Allosteric model.

Table (4): R-squared (R^2) Values Comparing the Goodness-of-Fit for Michaelis–Menten, Hill, and Allosteric Models.

Enzyme-Substrate Pair	Model	R^2	AIC	RMSE
CYP3A4 – Midazolam	Michaelis–Menten	0.942	132.5	3.87
	Hill Model	0.978	119.8	2.15
	Allosteric Model	0.965	124.3	2.72
CYP2D6 – Dextromethorphan	Michaelis–Menten	0.985	112.0	1.65
	Hill Model	0.978	116.2	2.14
	Allosteric Model	0.970	118.5	2.55
UGT1A1 – Bilirubin	Michaelis–Menten	0.961	127.4	3.12
	Hill Model	0.973	121.0	2.41
	Allosteric Model	0.986	114.3	1.58

*R^2 = coefficient of determination; AIC = Akaike Information Criterion; RMSE = root mean square error.

3.1. Clinical Relevance and Applications

CYP3A4 with Midazolam – Cooperative Binding and Dosing Thresholds (CYP3A4):

CYP3A4 metabolizes a wide range of drugs, including midazolam, a sedative commonly used in anaesthesia [32], as this study showed, that the cooperative binding behaviour was best captured by the Hill and Allosteric models, as shown in Figure (1). Clinically, this means midazolam metabolism does not increase linearly with concentration, with significant changes occurring when substrate concentrations approach saturation [25]. When grapefruit juice is taken, it inhibits CYP3A4 activity, leading to increased levels of midazolam in the bloodstream [33], this can cause over-sedation or even poisoning, using Hill models can help anticipate these abrupt changes in metabolism, guiding dose modifications and avoiding adverse drug reactions (ADR) in medical practice [34].

CYP2D6 with Dextromethorphan – Simple Kinetics and Polymorphic Implications (CYP2D6-Dextromethorphan)

Variations in the CYP2D6 gene strongly influence how quickly drugs are processed [35], individuals classified as poor metabolizers (PM) have little to no enzyme function, whereas ultra-rapid metabolizers (UM) process drugs much faster [36]. Common CYP2D6 inhibitors, such as fluoxetine (an SSRI), can greatly decrease the breakdown of drugs that are CYP2D6 substrates, resulting in increased drug levels and possible adverse effects [36]. Conversely, CYP2D6 inducers, such as rifampin (an antibiotic), may cause decreased drug efficacy because they speed up the metabolism of dextromethorphan [37]. These factors should be taken into account for customized dosing guidelines, particularly in patients with different genetic profiles.

UGT1A1 with Bilirubin – Allosteric Modulation and Drug Interactions (UGT1A1-Bilirubin)

UGT1A1, responsible for processing bilirubin, also assists in glucuronidating drugs like irinotecan, used in chemotherapy, the allosteric model presented here effectively represents the enzyme's function, indicating that bilirubin's attachment affects UGT1A1's activity elsewhere.

In clinical settings, UGT1A1 blockers such as indinavir (an HIV protease inhibitor) can noticeably decrease the elimination of drugs like irinotecan, leading to major adverse effects [38], conversely, UGT1A1 promoters such as rifampin (an antibiotic) can speed up the glucuronidation, possibly lessening the impact of drugs like irinotecan by raising their clearance [38]. Comprehending these allosteric connections and modeling them precisely can enhance treatment approaches for cancer patients, mitigating toxicity while safeguarding effectiveness [39].

4. Conclusions

It is clear from the current results that each model has two effects at the same time depending on the substrate concentration range. The Michaelis-Menten model is suitable for basic enzyme kinetics at low concentrations, the

Hill model, with its cooperative property, excels at predicting higher velocities when cooperative binding is involved, while the allosteric model is more versatile and accurate over a wider range, making it particularly useful for systems where enzyme regulation and cooperative effects play important roles. And these results emphasize the need to match the model with most of the enzyme's kinetic properties for proper and accurate analysis, and to interpret the data correctly and appropriately for each case we have.

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Conflict of Interest: The authors declare that there are no conflicts of interest associated with this research project. We have no financial or personal relationships that could potentially bias our work or influence the interpretation of the results.

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