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Numerical Verification of Tucuxi, a Promising Bayesian Adaptation Tool for Model-Informed Precision Dosing

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ABSTRACT

Tucuxi, a Swiss-developed Model-Informed Precision Dosing (MIPD) software, aims to support clinical dosage decision-making to achieve therapeutic concentration targets. This study assessed its predictive accuracy compared to NONMEM, a gold-standard tool for Bayesian PK predictions. A panel of models was created to mimic various pharmacokinetic scenarios following oral, bolus, or intravenous administration. For each scenario, a virtual population of 4000 patients receiving doses ranging from 10 to 120 mg every 24 h was created. Sparse and rich profiles were simulated, with either one or four samples taken per patient. Tucuxi and NONMEM predicted concentrations at sampling times, trough (C_{min}) and peak (C_{max}) concentrations, and area under the curve ($AUC_{0\text{-}24h}$) were compared by calculating their relative differences, mean prediction error (MPE) and relative root mean square error (RMSE). The bioequivalence criterion was additionally applied to compare $AUC_{0\text{-}24h}$, C_{min}, and C_{max}. All the outcomes predicted by Tucuxi closely matched those predicted by NONMEM. A median of 99.8% of predicted concentrations at sampling times presented relative errors smaller than 0.1%. For all outcomes predicted, MPE and relative RMSE were 0% (−0.09, 0.07) and 0.82% (0%, 18.79%) respectively. The bioequivalence criterion, calculated for $AUC_{0\text{-}24h}$, C_{min}, and C_{max}, was verified for all models, with median values of 100%. This project highlights Tucuxi's excellent predictive accuracy compared to NONMEM, demonstrating its reliability and potential for adoption in clinical practice.

1 | Introduction

Over the last few years, a strong movement in favor of precision medicine has emerged regarding therapeutic decisions, emphasizing personalized dosing adapted to patients' needs, and moving away from the traditional approach based on standard dosages [1–3]. One of the main reasons for this change is that preclinical and clinical studies, which often focus on a narrow subset of the population meeting specific restricted criteria, may not sufficiently capture the variability of drug disposition within the broader population [4, 5]. As a result, dosage recommendations derived from these studies may be inadequate to ensure appropriate concentration exposure in specific subsets of patients, potentially resulting in either therapeutic failure

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Summary

- What is the current knowledge on the topic?
  - Tucuxi is a versatile model-informed precision dosing software developed in Switzerland, designed to assist clinicians in individual dosage decisions based on TDM to optimize the achievement of in-target concentration exposure using popPK models.
- What question did this study address?
  - This study aimed to perform a numerical verification of Tucuxi by comparing its predictive performance versus NONMEM.
- What does this study add to our knowledge?
  - Tucuxi's predictive accuracy was found comparable to NONMEM's, with over 98% excellent predictions. The predictions of pharmacokinetic indicators used as therapeutic targets were excellent as well and largely outperformed the bioequivalence criterion.
- How might this change drug discovery, development, and/or therapeutics?
  - Thanks to its excellent predictive accuracy, together with its user-friendliness, robustness, and versatility, Tucuxi might become a promising MIPD tool for routine clinical use.

or increased toxicity. To overcome this problem, therapeutic drug monitoring (TDM) is one of the most widely recognized strategies. Introduced mainly in the 1960s, TDM involves measuring drug concentrations and adjusting doses accordingly to achieve the therapeutic target, thereby optimizing treatment while minimizing adverse effects [6, 7]. TDM is performed using various empirical methods, such as simple arithmetic rules or nomograms, as well as Bayesian approaches [6, 7]. Bayesian TDM adjusts patients' dosage by estimating the individual pharmacokinetic (PK) parameters based on a population pharmacokinetic (popPK) model, specific patient information, and collected plasma drug concentrations [7, 8]. This approach became progressively adopted following the introduction of the first nonlinear mixed effect modeling software NONMEM in 1982 [9, 10]. Population approaches as allowed by NONMEM and its more recent competitors enable the development of models that describe drug absorption and disposition within a population while quantifying the impact of clinical, demographic, and environmental factors that explain variations observed among patients [11, 12]. These models allow the estimation of maximum likelihood individual PK parameters and simulations to test different dosage regimens [11]. Unlike traditional non-compartmental analysis (NCA), population approaches provide a deeper understanding of population-level characteristics that may influence PK profiles and parameters. They are now widely adopted in drug development and considered a gold standard and a requirement for regulatory submissions of drugs to the Food and Drug Administration (FDA) [13]. Furthermore, population approaches require fewer samples compared to NCA, making them particularly advantageous, as NCA relies on rich PK datasets that are challenging to obtain in clinical practice. By contrast, the model-based nature of population approaches is well-suited to the sparse clinical data, typically available in TDM. Consequently, popPK analysis methods can be utilized in TDM for their ability to estimate maximum likelihood individual PK parameters, thus enabling precise dosage adjustments and providing a layer of refinement to clinical decision-making. However, the use of popPK software such as NONMEM for TDM in clinical practice presents several challenges: it requires specialized training, familiarity with its programming language (Fortran), and the ability to manage its complex workflow and technical constraints. Furthermore, although it allows for simulations, NONMEM does not directly provide dosage recommendations, which complicates its application in routine clinical settings. To enhance TDM, the integration of dedicated, user-friendly Model-Informed Precision Dosing (MIPD) software tools allows an easier democratization of population approaches in the hands of clinicians [14]. These tools use popPK models, developed with software such as NONMEM, coupled with patients' information to suggest dosage adjustments aimed at achieving therapeutic targets more accurately [15]. Compared to empirical TDM methods, MIPD offers several significant advantages, including greater flexibility in accommodating blood sampling schedules and a faster determination of appropriate dosage adjustments. Empirical methods usually require waiting for the treatment to reach a steady state before verifying target achievement, as therapeutic targets are typically established for steady state. On the other hand, MIPD allows direct prediction of SS concentration, enabling earlier and more timely dosage adjustments. Additionally, therapeutic targets are generally based on standard PK indicators such as minimal (C_{min}) or maximal (C_{max}) concentrations, or area under the curve (AUC). Empirical TDM therefore requires precise blood sampling at specific times after the last dose intake. With MIPD, however, these PK indicators can easily be extrapolated from random sampling time results [7, 16].

According to a recent review, several MIPD tools have been developed since 1979, including DoseMe, BestDose, InsightRX, NextDose, and Tucuxi [14]. Despite the progress made, their adoption in clinical practice remains uneven and limited to few drugs, with potential for further expansion [4, 14, 17–19]. This limitation may be due in part to the complexities of the software, often not user-friendly for non-specialists, the high cost of access, and a lack of robust evidence supporting their clinical utility. Furthermore, the implementation of an MIPD tool in a clinical setting requires a twofold validation process. First, numerical verification is essential to ensure the accuracy and robustness of the software's predictions. Secondly, clinical validation is required to confirm whether the software can propose dosages comparable to those of a clinical pharmacologist. Although the specifications of certain software mention some elements of validation, the methodology used is rarely detailed in the literature [20]. Only a few MIPD applications have provided comprehensive descriptions of their numerical verification processes, highlighting a gap that needs to be addressed to enhance their credibility and usability in clinical practice [21–25].

This study focused on the MIPD software Tucuxi, developed by the School of Engineering and Management of the Canton of Vaud (HEIG-VD) and the University Hospital of Lausanne (CHUV) in Switzerland [26]. Tucuxi is still under development and tested in some Swiss, French, and Australian hospitals [27–29]. The current version is available as open source on https://github.com/sotalya and compiled versions can be found on https://www.tucuxi.ch. Tucuxi is available in various

implementations: as a desktop application (Tucuxi), as an application run from the command line (Tucucli) or through a Python package (Sotalya). Several popPK models have already been implemented, enabling Bayesian TDM to be performed on different categories of drugs (e.g., antibiotics, anticancer agents, anticoagulants). The Tucuxi software is versatile and can handle any type of popPK model, whether developed for neonates, pediatric, adult, or elderly populations, as long as the selected models have been properly validated for the target population. The core of the Bayesian engine is implemented in C++, but various models can be defined in external files (i.e., "drug files"), following a structure somewhat similar to that of a NONMEM run file. These "drug files" completed by the user also specify the possible doses and dosing intervals, routes of administration, infusion durations, and the desired therapeutic target (i.e., type of PK indicators and aimed values). A drug file editor is available at https://drugeditor.tucuxi.ch.

Tucuxi uses closed-form expressions for 1- and 2-compartment popPK models with linear absorption and elimination, while other implemented models are specified using differential equations and solved with the Runge–Kutta 4th-order method. Tucuxi's predictions, when blood concentration results are available, rely on the Bayesian maximum a posteriori probability (MAP) method, using the Polak-Ribière variant of the conjugate gradient descent algorithm. The algorithm is initialized with typical population parameters (possibly depending on patient covariates) and reaches the most likely parameter values (i.e., MAP individual departure from population values) minimizing the gradient. Various requests can be made to Tucuxi. A priori predictions, using only the popPK model and patient covariates, or a posteriori predictions, which also incorporate measured plasma concentration data, can be computed. Tucuxi can also calculate a priori and a posteriori concentration percentiles that depict probability distributions of circulating exposure. Finally, Tucuxi provides dosage adjustment hints making use of the "drug file", which supports the user in his/her elaboration of a dosage readjustment based on TDM observations.

While Tucuxi is regarded as easy to use and accessible to everyone due to its open-source status, it still lacks formal validation for clinical use [14, 19]. Clinical validation must be conducted for each drug to ensure that Tucuxi's dosing recommendations align with real-world clinical practice. Recent examples of this validation have been published for cefepime, busulfan, and piperacillin in adults, where dose adjustments suggested by Tucuxi were compared with those made by clinicians to assess the software's clinical relevance [27, 30, 31]. Since Tucuxi is not certified as a medical device, its implementation heavily depends on the user. Drug specification files are pre-filled based on international guidelines but must be reviewed and adapted by clinicians to reflect their hospital's specific practices. Our study focused on an internal verification of the software, specifically ensuring its mathematical correctness independently of any clinical context or user influence. To achieve this, we aimed to generalize the verification process by mathematically verifying Tucuxi predictions against NONMEM, which, despite not being originally designed for TDM, is a reference for PK modeling in order to demonstrate that the software's numerical performances are robust across a broad range of popPK models.

2 | Methods

We used the verification method, inspired by Le Louedec et al. [25] described in Figure 1. NONMEM (version 7.4.2) was used to simulate virtual populations with virtual "observed" concentrations at pre-established time points. For this purpose, we built popPK models with different inter- and intra-individual variabilities and pre-established study designs, as detailed below. We then used NONMEM and Tucuxi to predict concentrations and estimate individual PK characteristics through the same models and study designs employed for virtual data generation. We relied on Python (version 3.6.9) and R Studio (version 4.3.2) to automate the numerical verification process and to analyze the results. All the NONMEM and Tucuxi files used to make this project are available on GitHub: https://github.com/sotalya/tucuxi-numericalvalidation.

2.1 | Virtual PopPK Models

A series of 36 models were created to investigate various pharmacokinetic scenarios following oral, intravenous (IV), or bolus administration. We considered different structural models (ranging from 1 to 3 compartments), absorption models (linear, lag time, Erlang), elimination models (linear, Michaelis–Menten, or both), as well as error models (proportional, additive, mixed). Inter-individual variabilities (IIV) ranging from 45% to 141% on all the pharmacokinetic parameters, with or without a correlation between clearance and volume of distribution, were examined. We also investigated constant and time-varying covariate models including an allometric effect of body weight and creatinine clearance, as well as a proportional effect of sex on clearance. Table 1 presents the characteristics of the virtual popPK models tested. Two clinically used models already implemented in Tucuxi were also verified, and are presented in detail in Supporting Information—S1 [32, 33].

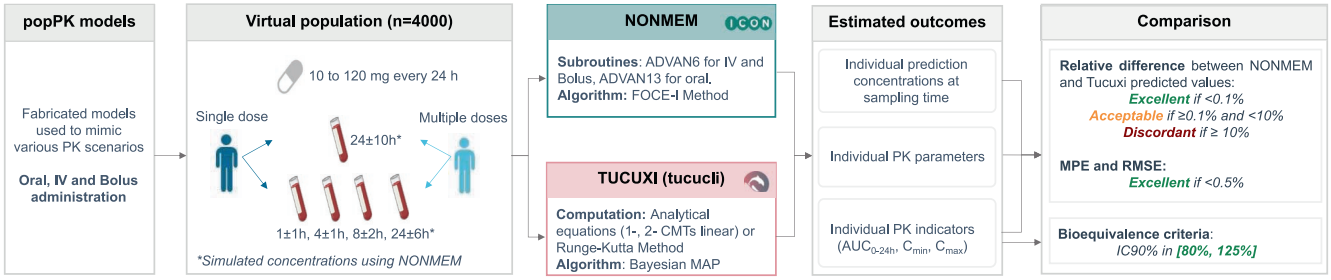

FIGURE 1 | Diagram of the methodology for comparing Tucuxi and NONMEM performance.

TABLE 1 | Characteristics of the virtual popPK models studied.

PopPK model characteristic	Model *n*°	PopPK model characteristic	Model *n*°
Structural model[a]		Inter-individual variability	
1- CMT model	10,000	IIV of 63% on all PK parameters	
2- CMT model	20,000	1-CMT model	10,001
3- CMT model	30,000	2-CMT model	20,001
Absorption model[a]		3-CMT model	30,001
Absorption with a lag time	11,000	IIV of 77% on all PK parameters	
Bioavailability (logit function)	12,000	1-CMT model	10,002
Erlang absorption with a 2- CMT model		2-CMT model	20002
1 Erlang CMT	23,000	3-CMT model	30,002
2 Erlang CMT	24,000	IIV of 89% on all PK parameters	
3 Erlang CMT	25,000	1-CMT model	10,003
4 Erlang CMT	26,000	2-CMT model	20,003
5 Erlang CMT	27,000	3-CMT model	30,003
6 Erlang CMT	28,000	IIV of 100% on all PK parameters	
Elimination model[a]		1-CMT model	10,004
Michaelis Menten elimination		2-CMT model	20,004
1- CMT model	10,100	3-CMT model	30,004
2- CMT model	20,100	IIV of 141% on all PK parameters	
Linear and Michaelis Menten elimination		1-CMT model	10,007
1-CMT model	10,300	2-CMT model	20,007
2- CMT model	20,300	3-CMT model	30,007
Residual Error Model[a]		Covariates (i.e., body weight, creatinine clearance and sex) on CL[a]	
Additive	10,010	1-CMT model	10,009–1
Mixed	10,020	2-CMT model	20,009–1
Correlation of 20% between CL and V[a]	10,008	3-CMT model	30,009–1

Abbreviations: CL, clearance; CMT, compartment; IIV, inter-individual variability; V, volume of distribution.
[a]IIV of 45% on Ka, CL, Vc, V_{MAX}, and K_M.

2.2 | Virtual Study Design

For each popPK model, we created a virtual population of 4000 random patients receiving doses ranging from 10 to 120 mg every 24 h, and we divided them into two groups ($n = 2000$): one under a single-dose regimen and the other under a multiple-dose regimen. We set up sparse and rich sampling schemes, with respectively one sample taken at 24 ± 10 h and four samples taken at 1 ± 1, 4 ± 1, 8 ± 2 h, and 24 ± 6 h after the last dose administration. Simulations based on the study virtual models with variabilities were performed in NONMEM, using ADVAN6 and ADVAN13 subroutines for the IV/Bolus and oral models, respectively, to obtain "true" individual PK parameters and "observed" plasma concentrations for each patient in this *in silico* exercise. Individual PK parameter values were generated from a log-normal distribution according to the pre-established IIV set in the model. Additive, proportional, or mixed residual errors, depending on the model studied, following a normal distribution centered at 0 with a standard deviation of 1, were added to the concentration values. We fixed concentration values generated below 0.1 μg/L at this floor value. We also imposed a constraint on the half-life, which had to be between 1/5 and 5 times the typical population half-life to simulate clinically realistic PK profiles.

For models requiring covariates (i.e., model 10,009, 20,009, and 30,009 detailed in Table 1), we assigned to each patient body weight values drawn from a uniform distribution ranging from 20 to 100 kg, and a creatinine clearance randomly drawn from a uniform distribution between 20 and 250 mL/min. To evaluate the impact of time-varying covariates (i.e., model 100,091, 200,091, and 300,091 detailed in Table 1), body weight was allowed to vary randomly by up to 5% at each dosing event.

Similarly, creatinine clearance could fluctuate by up to 30% with each new dose administration. The population was also divided between 2000 males and females.

2.3 | NONMEM Predictions

We obtained predictions of individual PK parameters, individual a posteriori concentrations at the sampling time, and individual PK indicators (i.e., $AUC_{0\text{-}24h}$, C_{min}, and C_{max}) for all the virtual patients using NONMEM with the FOCEI method [34]. The estimation was performed with the following settings: *$EST method = 1 inter maxeval = 0 noabort sig = 3 print = 1 posthoc*, ensuring that only individual post hoc estimates were computed without re-estimating population parameters while accounting for ETA variability in the optimization process [34]. The ADVAN6 and ADVAN13 subroutines of NONMEM were used for the IV/Bolus and oral models, respectively, to code the differential equations solved with LSODA, requisite to retrieve $AUC_{0\text{-}24h}$.

The default handling of time-varying covariates differs between NONMEM and Tucuxi. Tucuxi can either use the "last value carried forward" method or apply linear interpolation between covariate measurements, whereas NONMEM applies the "next value carried forward" approach. In this study, we chose to validate the "last value carried forward" method, as it is more intuitive for clinical applications than the "next value carried forward" approach. To ensure consistency between the two software, the NONMEM code had to be adapted. Specifically, additional rows were inserted into the dataset just before a covariate change, using the previous covariate value and setting EVID = 2. This adjustment forces NONMEM to retain the previous covariate value until a new one is explicitly provided.

2.4 | Tucuxi Predictions

We implemented each model in Tucuxi with the drug file editor, providing information on the number of compartments, the type of absorption and elimination, and the population average values of the PK parameters along with corresponding variabilities. For each virtual patient, a data sheet was automatically generated, containing the patient's individual characteristics (i.e., body weight, sex), the time and amount of the doses received, and the observed concentrations [26]. We then ran the software from the command line using Tucucli via a Python script. As with NONMEM, individual a posteriori predictions were obtained to predict the outcomes studied: concentrations predicted at the sampling time, estimated individual PK parameters, and characteristic indicators of the PK profile (i.e., $AUC_{0\text{-}24h}$, C_{min}, and C_{max}). More details on the calculation method used in Tucuxi and the objective function are available in the article by Y. Thoma et al. [35].

2.5 | Software Comparison

We compared all the predicted outcomes (i.e., individual PK parameters, concentrations predicted at the sampling time, $AUC_{0\text{-}24h}$, C_{min}, C_{max}) of Tucuxi and NONMEM by calculating in each virtual patient the relative difference between both estimated values, using the following formula:

$$\Delta\text{Outcome}_i = \frac{\text{Outcome}_i^{\text{Tucuxi}} - \text{Outcome}_i^{\text{NONMEM}}}{\text{Outcome}_i^{\text{NONMEM}}} \quad (1)$$

with $\text{Outcome}_i^{\text{Tucuxi}}$ and $\text{Outcome}_i^{\text{NONMEM}}$ being the predicted outcome obtained for individual i with Tucuxi or NONMEM, respectively.

Tucuxi predictions were considered *excellent* if the relative difference was less than 0.1%, *acceptable* if it ranged between 0.1% and 10%, and *discordant* if it exceeded 10% [25].

To globally assess the agreement of all outcomes produced by Tucuxi with those produced by NONMEM, taken as reference, we evaluated their bias and accuracy. We quantified the bias by calculating the mean prediction error (MPE, equation 2) on log-transformed outcomes and its 90% confidence interval. It was considered non-significant if the interval included the value 0. Log-transformation of the outcomes was necessary to ensure normality, reduce the influence of outliers, and thus enhance the robustness of the analysis. We quantified the accuracy by computing the relative root mean square error (RMSE, equation 3). The smaller the relative RMSE, the more accurate the predictions.

$$\text{MPE}_{\text{outcome}}(\%) = \left(\exp\left(\frac{1}{n}\sum\left(\ln\left(\text{Outcome}_i^{\text{Tucuxi}}\right) - \ln\left(\text{Outcome}_i^{\text{NONMEM}}\right)\right)\right) - 1\right) \times 100 \quad (2)$$

$$\text{RMSE}_{\text{outcome}}(\%) = \left(\exp\left(\sqrt{\frac{1}{n}\sum\left(\ln\left(\text{Outcome}_i^{\text{Tucuxi}}\right) - \ln\left(\text{Outcome}_i^{\text{NONMEM}}\right)\right)^2}\right) - 1\right) \times 100 \quad (3)$$

With $\text{Outcome}_i^{\text{Tucuxi}}$ and $\text{Outcome}_i^{\text{NONMEM}}$ as previously defined, n being the number of virtual patients. Predictions of concentrations at sampling time were also verified by calculating the MPE and relative RMSE using observed concentrations as a reference.

The bioequivalence criterion, widely used to establish the equivalence between two pharmaceutical products, was additionally applied to compare the individual PK indicators (i.e., $AUC_{0\text{-}24h}$, C_{min}, C_{max}) obtained with both software packages. These specific outcomes were submitted to bioequivalence testing because they are used to define therapeutic targets, which directly influence clinical decisions. Concretely, the 90% confidence interval of the ratios of log-transformed $AUC_{0\text{-}24h}$, C_{min}, and C_{max} predicted by Tucuxi over the reference value (i.e., predicted by NONMEM) should lie between 80% and 125%. The individual bioequivalence ratios were calculated as follows:

$$\text{Bioequivalence}_{\text{PKindicator},i}(\%) = \frac{\ln\left(\text{PKindicator}_i^{\text{Tucuxi}}\right)}{\ln\left(\text{PKindicator}_i^{\text{NONMEM}}\right)} \times 100 \quad (4)$$

with $\text{PKindicator}_i^{\text{Tucuxi}}$ and $\text{PKindicator}_i^{\text{NONMEM}}$ being the predicted characteristic of the individual PK profile *j* (i.e., $AUC_{0\text{-}24h}$, C_{min},

C_{max}) obtained for individual i with Tucuxi or NONMEM, respectively. The means and corresponding confidence intervals were calculated with R.

3 | Results

All the outcomes predicted by Tucuxi closely matched those predicted by NONMEM. As illustrated in Figure 2, a median of 99.8% of Tucuxi-predicted concentrations at sampling time for oral and IV/bolus were considered excellent (i.e., showing relative errors of less than 0.1%). Only 0.2% and 0.1% of predictions were respectively classified as acceptable and discordant. These discrepancies were mainly observed in models with significant inter-individual variabilities and depended on the study design, particularly evident in the multi-sample group (see Figure 3). However, these differences involved only a small subset of patients, ranging from 4 to 253 depending on the model, with the highest number of patients corresponding to the model with the greatest variability. For these specific patients, as shown in Figure 4, Tucuxi provided a posteriori concentration predictions at sampling times that were closer to the observed values than those of NONMEM.

Similar results were obtained for the individual PK parameters as well as for the PK profile characteristics and are detailed in (Figures S1–S4).

Across all MPE and relative RMSE values calculated for the different outcomes (predicted concentrations, AUC, C_{min}, C_{max}, PK parameters), the median (min, max) values were 0% (−0.09, 0.07) and 0.82% (0%, 18.79%), respectively, reflecting the strong predictive performance of Tucuxi. The detailed MPE and relative RMSE values for each outcome are provided in Table S1. The concentrations predicted by the software closely align with reality, as evidenced by a median MPE of −4% and a relative RMSE of 8% for both Tucuxi and NONMEM, respectively, demonstrating the software's strong predictive performance (Table S2).

Furthermore, the bioequivalence criterion, calculated for $AUC_{0\text{-}24h}$, C_{min}, and C_{max}, was verified for all models, with a median value of 100%. Detailed results for each model are provided in Table S3.

The results obtained with the two clinical models were comparable and are provided in the (Figure S5 and Tables S1–S3).

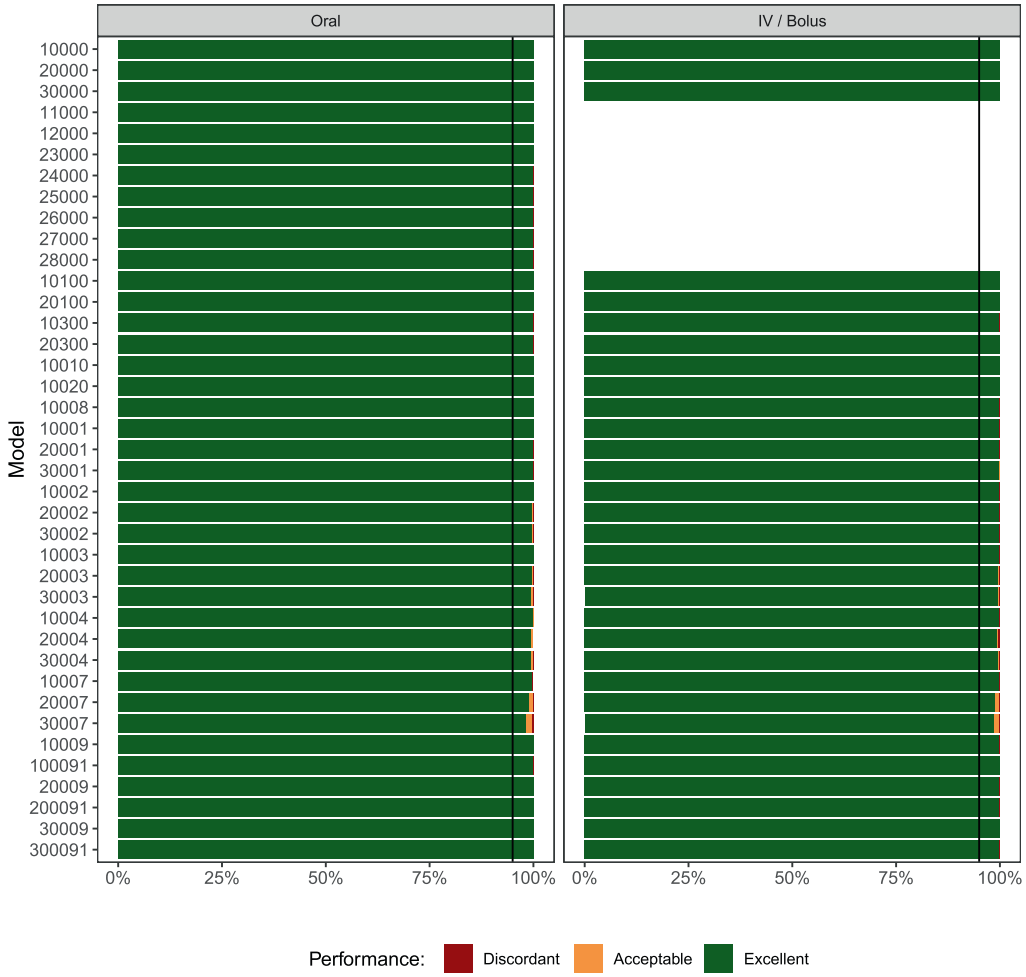

FIGURE 2 | Barplot describing the predictive performance of Tucuxi versus NONMEM based on the relative difference criteria for concentrations predicted at sampling times across all models. Models 11,000, 12,000, 23,000, 24,000, 25,000, 26,000, 27,000, and 28,000 test different types of absorption and do not apply to IV and bolus administrations. The black vertical line indicates the 95% percentile.

FIGURE 3 | Barplot describing the predictive performance of Tucuxi versus NONMEM based on the relative difference criteria for concentrations predicted at sampling times according to study design for IIV variabilities popPK models, all administrations combined. The black vertical line indicates the 95% percentile.

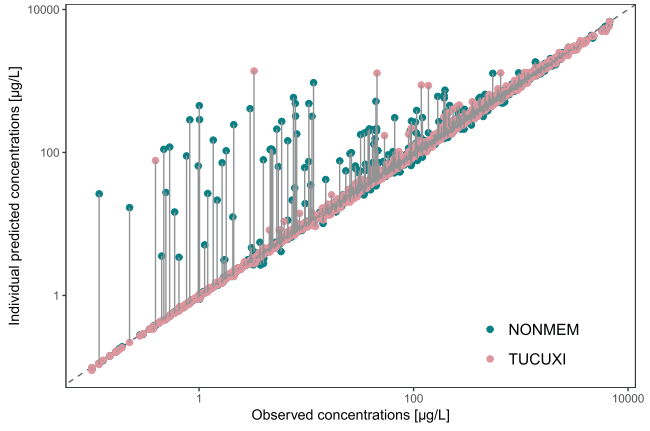

FIGURE 4 | Comparison of individual concentrations predicted by Tucuxi and NONMEM with a relative difference criteria greater than 0.1% with observed concentrations.

4 | Discussion

This project compared the numerical predictions obtained by Tucuxi with those of NONMEM, one of the gold standards in popPK, which can be accommodated to compute maximum a posteriori estimates of individual PK parameters and indicators in the framework of TDM. The analysis numerically verified Tucuxi as a reliable tool in this area, as the predictions of both tools were very similar, with a remarkably low relative error. This verification is particularly robust as it was conducted on a large scale, including a wide range of pharmacokinetic profiles that could be observed in marketed drugs.

Still, slight differences were observed between the predictions generated by NONMEM and those provided by Tucuxi for models with high IIVs for all PK parameters, which can be explained by differences in the algorithms used by each software to find maximum likelihood estimations [34]. Our analyses showed particularly pronounced discrepancies in studies with rich data profiles. An increase in the number of data points contributes to the complexity of the likelihood function, which increases the risk of the minimization process getting trapped in local minima during parameter estimation. However, models with such high variability in all PK parameters are not representative of the models typically applied to clinical TDM. Therefore, the differences observed between NONMEM and Tucuxi in high variability contexts may not be as significant when working with typical clinical data, where conditions are generally less extreme.

An important aspect to highlight is the similarity of the PK indicators estimated by Tucuxi and NONMEM, where the bioequivalence criterion was rigorously verified for each model. These results are particularly promising for the clinical use of Tucuxi. $AUC_{0\text{-}24h}$, C_{min}, and C_{max} are key parameters often used in clinical settings to evaluate the therapeutic efficacy and toxicity of drugs during TDM [6]. Verification of these comparisons using the bioequivalence criterion, a widely recognized standard required by regulatory authorities, was therefore considered essential. All bioequivalence estimates indicated an average value of 100%, with confidence intervals narrower than ±0.003%. This excellent precision was essentially reached thanks to the simulation of 4000 virtual patients, a number rarely reached in clinical bioequivalence trials. Nevertheless, this strengthens the credibility of Tucuxi as a robust MIPD that can be used to support clinical decision-making in TDM practice.

This large-scale verification enabled us to further improve Tucuxi, specifically for complex popPK model structures. This helped us to better equip the software for providing accurate PK outcomes, even with complex models and high inter-individual variability. The virtual models used for this verification were more complex than those typically seen in clinical TDM practice, which sometimes led to the generation of unrealistic data or even data inconsistent with typical clinical scenarios. These anomalies were corrected by introducing half-life constraints to prevent the simulation of biologically unlikely scenarios. We also chose to impute concentrations below the LOQ by assigning them the LOQ value itself, a commonly used and pragmatic approach in routine TDM. Tucuxi does not include specific methods for handling LOQ data, and imputation with the LOQ value provides sufficient information to support individual PK parameter estimations. However, this limitation is not problematic given the tool's intended clinical use. Ultimately, it is the clinician's role to interpret the results in context, assessing whether a low concentration is clinically plausible or potentially indicative of external factors such as poor adherence. The decision to follow the method developed by Le Louedec et al. is part of an effort to harmonize numerical verification approaches for MIPD software. Using a methodology already adopted for two other MIPD computer applications should promote the standardization of verification processes, which facilitates comparisons between different tools [24, 25]. We complemented this approach with the comparison of MPE and relative RMSE values, which casts further light on the respective merits of the compared MIPD tools. Adopting an established methodology ensures that Tucuxi performance is evaluated according to recognized criteria, thereby increasing the credibility of the results obtained.

Tucuxi is currently being tested in several hospitals. Comparative studies of different MIPD software have shown that Tucuxi is a robust MIPD tool [14, 19]. It distinguishes itself from other MIPD tools through several unique features. Its intuitive interface facilitates a rapid learning process without needing programming skills. The software also provides clear visual support for therapeutic decision-making. Unlike most existing MIPD software, Tucuxi displays both individualized predictions and population/a priori percentiles, providing additional insights for clinical interpretation. In addition, as an open-source tool, Tucuxi is not only freely available but also highly customizable, allowing users to adapt the software to their specific needs, for example by incorporating their own popPK models. This flexibility enhances its usefulness in a variety of therapeutic contexts. Finally, this project has demonstrated the excellent predictive performances of Tucuxi compared to NONMEM, one of the gold standards in PK modeling known for its robust and reliable equation resolution capabilities. This comparison with NONMEM shows that Tucuxi can provide highly accurate results, which is essential for its adoption in clinical settings. In the future, the scripts developed within this project might be used as a verification tool for new models. When new pharmacokinetic scenarios are introduced into Tucuxi, these models can be easily verified by creating a corresponding NONMEM control file and re-running the scripts. This process ensures that future model updates in Tucuxi can be quickly and efficiently verified for numeric consistency, contributing to a (semi-)automated verification workflow that aligns with best practices for software reliability and potential regulatory applications. Clinical validation projects are currently underway to assess the accuracy of dosage adjustment recommendations assisted by Tucuxi, intending to secure confidence in its clinical use.

Author Contributions

A.R. wrote the manuscript. M.G., Y.T., C.C., and T.B. designed the research. A.R., A.E.C., Y.T., and M.G. performed the research. A.R., A.E.C., M.G., and Y.T. analyzed the data. Open access publishing facilitated by Haute Ecole Specialisee de la Suisse Occidentale, as part of the Wiley - Haute Ecole Specialisee de la Suisse Occidentale agreement via the Consortium Of Swiss Academic Libraries.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.