



Individualized Prediction of Gentamicin Concentration in Neonates: A Multimodal Approach of PBPK Modeling and Machine Learning

Sergio Sánchez-Herrero^{1,2}, Marina Cuquerella-Gilabert^{1,4}, Serna, Jenifer¹, Rueda-Ferreiro, Almudena¹, Hinojal Zazo^{3,4}, José M. Lanao^{3,4}.

¹Simulation Department, Empresarios Agrupados Internacional S.A., Madrid, Spain;

²Computer Science, Multimedia and Telecommunication Department, Universitat Oberta de Catalunya. Barcelona (Spain);

³Pharmaceutical Sciences Department, University of Salamanca, Salamanca, Spain

⁴Institute of Biomedical Research of Salamanca (IBSAL), Salamanca, Spain.



INTRODUCTION

The efficacy of drug therapy in neonates critically depends on selecting appropriate dosage regimens. Physiologically based pharmacokinetic (PBPK) modelling emerges as a valuable tool for assessing the clinical efficacy and safety of current adult treatments in paediatric populations [1]. However, challenges such as significant pharmacokinetic variability, a narrow therapeutic index, and limited sample sizes underscore the need for precise dosing strategies to ensure adequate drug exposure [2]. In addressing these complexities, machine learning (ML) methods offer promising support for clinical research due to their data-driven nature, robustness, and adaptability in managing intricate systems. Consequently, the integration of hybrid approaches emerges as a potential solution to enhance the accuracy of model-informed precision dosing (MIPD) strategies

OBJETIVES

The objective of this study was to assess the potential of various hybrid (PBPK-ML) continuous learning approaches in enhancing PBPK modelling, including semi-mechanistic or physiological models, and subsequent simulation outcomes. Our primary focus was on evaluating the effectiveness of Artificial Neural Networks (ANNs) algorithm in predicting gentamicin plasma concentrations over time.

METHODS

The Gentamicin PBPK models [1] were developed using the **PhysPK® v.2.4.1 platform** through Monte Carlo simulations. These simulations generated a range of potential outcomes by considering various variables and scenarios based on a priori probabilities. Virtual populations were used to train machine learning methods, enhancing the accuracy of predicting 2-hour and 24-hour dosage regimens of Gentamicin in neonates following Figure 1 workflow.

RESULTS

External validations corroborated the model's alignment with theoretical assumptions and its accurate prediction in 2 and 24 hours. Performance metrics model's efficacy for PBPK model and performance metrics with the algorithm ANNs for PBPK-ML model:

Term (38 weeks)*

	PBPK	PBPK-ANN
AFE 2 hours	0.96	1.18
AAFE 2 hours	1.25	1.23
PPE 2 hours	0.4	20.58
MVP 2 hours	12.3	14.6
AFE 24 hours	0.86	0.99
AAFE 24 hours	1.52	1.21
PPE 24 hours	0.99	1.76
MVP 24 hours	1.31	1.38

Pre-Term (38-33 weeks)*

	PBPK	PBPK-ANN
AFE 2 hours	0.95	1.21
AAFE 2 hours	1.22	1.23
PPE 2 hours	-0.51	27.72
MVP 2 hours	15.62	19
AFE 24 hours	0.91	0.97
AAFE 24 hours	1.33	1.23
PPE 24 hours	-2.72	0.04
MVP 24 hours	2.34	2.41

Pre-Term (32-24 weeks)*

	PBPK	PBPK-ANN
AFE 2 hours	0.88	0.9
AAFE 2 hours	1.32	1.3
PPE 2 hours	-5.8	-5.8
MVP 2 hours	8.49	9.73
AFE 24 hours	0.74	1.15
AAFE 24 hours	1.72	1.4
PPE 24 hours	0.44	51
MVP 24 hours	1.44	2.6

*Average-fold error (AFE), absolute average-fold error (AAFE), prediction error (PPE) and average population concentration (MVP)). MVP at 2 hours for real data 12.26, 17.3 and 9.49 Term (38 weeks), Pre-Term (38-33 weeks) and Pre-Term (32-24 weeks) respectively. MVP at 24 hours for real data 1.42, 2.7 and 2.09 Term (38 weeks), Pre-Term (38-33 weeks) and Pre-Term (32-24 weeks) respectively.

CONCLUSIONS

Despite not getting significant improvements, hybrid PBPK and ML models could be a way of research for provide better recommendations for an optimal dosing regimen in neonates. This approach could represent an innovative way to predict dosage regimens. Other algorithms, methods or ML approaches will be analyse in the future

REFERENCES

- [1] Zazo Gómez, Hinojal, et al. (2022). Physiologically-based pharmacokinetic modelling and dosing evaluation of gentamicin in neonates using PhysPK. *Frontiers in Pharmacology*, 13 (977372).
- [2] Wicha, Sebastian G., et al. "From therapeutic drug monitoring to model-informed precision dosing for antibiotics." *Clinical Pharmacology & Therapeutics* 109.4 (2021): 928-941.

ECO-FRIENDLY SECTION:



WEB



LINKEDIN



WEBINAR



PAPER ZERO



EMAIL



POSTER

Carry The PhysPK®
Poster/Information On With You.

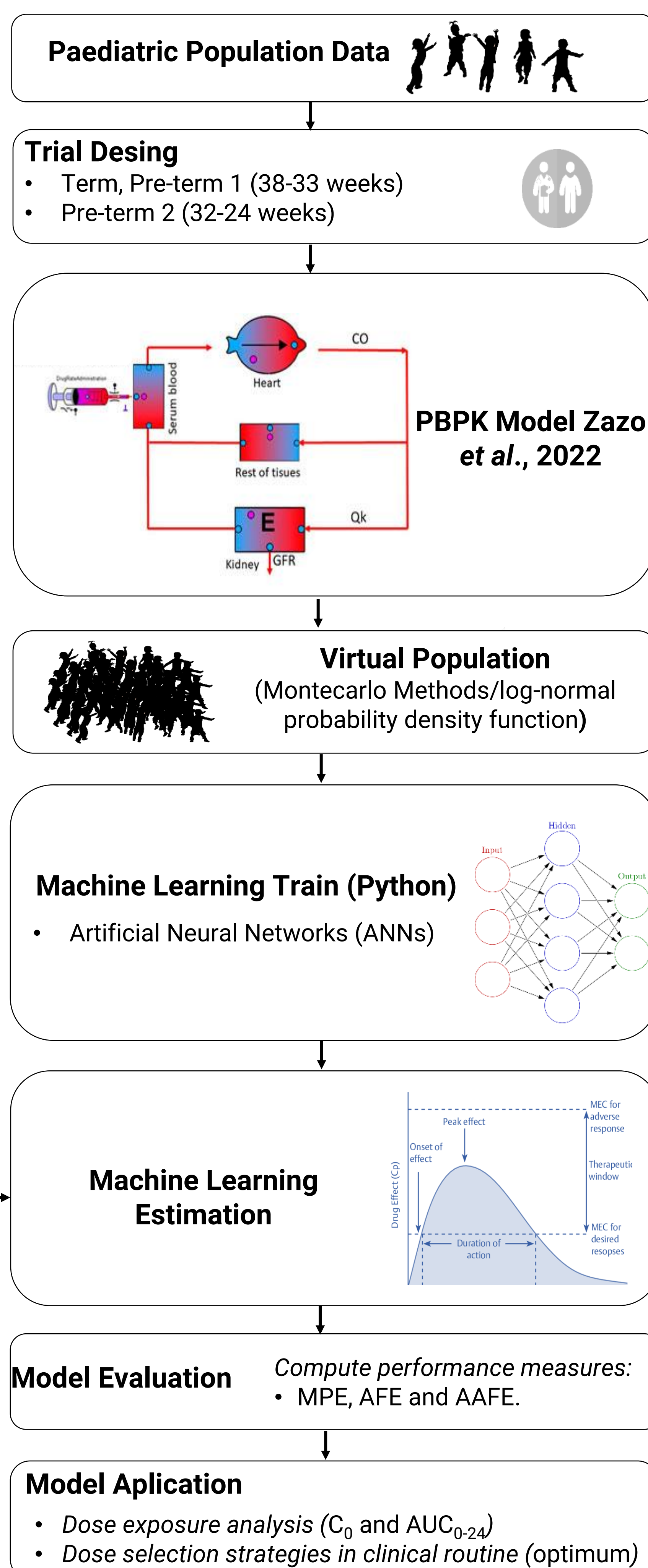


Figure 1. Workflow Dosage Regimens of Gentamicin in Neonates