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Gentamicin; PBPK modeling; Pharmacokinetics; Pharmacodynamics; Chronic kidney disease; Geriatric population.

Mechanistic PBPK–PD Modeling of Gentamicin: Impact of Renal Function and Age on Drug Exposure and Antibacterial Response

Shyam Nikethen Girivasan[1*]

[1]Assistant Professor, Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Tamil Nadu, India;
ORCID iD (0009-0000-6945-3647).

ABSTRACT:

Background: Gentamicin is a concentration-dependent aminoglycoside antibiotic with pharmacokinetics strongly influenced by renal function. Understanding its pharmacokinetic–pharmacodynamic (PK–PD) behavior across different physiological populations is essential for optimizing therapy.
Methods: A mechanistic PK–PD model was developed by integrating physiologically based pharmacokinetic (PBPK) modeling in PK-Sim with pharmacodynamic modeling in MoBi. A base model was established in a healthy adult population and extended to geriatric, chronic kidney disease (CKD), and combined CKD–geriatric populations by modifying physiological parameters. Plasma concentration–time profiles were linked to a bacterial growth–kill model to simulate pharmacodynamic response.
Results: The model reproduced the expected pharmacokinetic profile of gentamicin, characterized by rapid peak concentration followed by progressive decline. Differences in drug disposition were observed across populations, with slower decline in plasma concentrations in geriatric and CKD groups. These variations were reflected in pharmacodynamic outcomes, where bacterial suppression was prolonged and regrowth delayed in populations with reduced elimination. The most extended bacterial suppression was observed in the CKD–geriatric population.
Conclusion: The integrated PBPK–PD model demonstrates a clear relationship between gentamicin exposure and bacterial response across physiological conditions. The findings highlight the influence of renal function and age on drug behavior and provide a mechanistic framework for evaluating PK–PD relationships and supporting simulation-based dose optimization.

1. INTRODUCTION

Gentamicin is a widely used aminoglycoside antibiotic indicated for the treatment of severe Gram-negative infections, including sepsis, intra-abdominal infections, and complicated urinary tract infections [1]. Its clinical utility is largely attributed to its rapid bactericidal activity and concentration-dependent killing, where higher peak concentrations relative to the minimum inhibitory concentration (MIC) are associated with improved antibacterial efficacy [2,3].

The pharmacokinetics of gentamicin are characterized by high hydrophilicity, limited tissue penetration, and distribution predominantly within the extracellular fluid compartment [4]. Following intravenous administration, the drug exhibits a relatively small volume of distribution and is eliminated almost exclusively via renal excretion through glomerular filtration, with minimal metabolism [5]. In healthy individuals, this results in predictable pharmacokinetics, with an elimination half-life of approximately 2–3 hours [6].

Despite this predictable behavior in healthy populations, significant variability in gentamicin pharmacokinetics has been reported across specific patient groups. In particular, renal function plays a central role in determining drug clearance, and impairment can lead to prolonged elimination, increased systemic exposure, and a higher risk of toxicity [2,7]. Similarly, physiological changes associated with aging, including reduced renal function and altered body composition, may further influence drug disposition, necessitating careful dose adjustment in geriatric patients [8,9].

Given the narrow therapeutic index of gentamicin and its association with nephrotoxicity and ototoxicity, accurate prediction of drug exposure across different populations is essential for optimizing therapeutic outcomes while minimizing adverse effects [10]. Traditional pharmacokinetic approaches, however, may be limited in their ability to account for complex physiological variability.

Physiologically based pharmacokinetic (PBPK) modeling provides a mechanistic framework for integrating drug-specific properties with system-specific physiological parameters, enabling simulation of drug disposition under varying conditions [11]. Platforms such as PK-Sim allow the incorporation of population-specific physiological changes, including those associated with renal impairment and aging, to predict pharmacokinetic behavior. Furthermore, integration of PBPK models with pharmacodynamic (PD) models enables evaluation of drug effects, such as bacterial killing, in relation to drug exposure.

Despite the established clinical use of gentamicin, relatively few studies have developed integrated physiologically based pharmacokinetic–pharmacodynamic (PBPK–PD) frameworks capable of simultaneously evaluating drug exposure and antibacterial response across multiple physiologically altered populations. Previous PBPK investigations involving gentamicin have primarily focused on isolated populations such as neonates or dosing optimization strategies rather than integrated mechanistic exposure–response simulations across aging and renal impairment conditions [12]. Furthermore, recent reviews on PBPK modeling in older adults have highlighted the continuing limitations in incorporating age-associated physiological variability and dynamic pharmacodynamic behavior within unified mechanistic systems [13]. Therefore, the present study aimed to develop an integrated mechanistic PBPK–PD framework for gentamicin using PK-Sim and MoBi to evaluate pharmacokinetic variability and bacterial response across healthy adult, geriatric, CKD, and CKD–geriatric populations. Specifically, the objectives were to calibrate a baseline PBPK model using published intravenous pharmacokinetic data, extend the model to physiologically altered populations through renal and age-related parameter modification, integrate bacterial growth–kill dynamics, and evaluate the influence of altered renal clearance on systemic exposure, bacterial suppression, and delayed bacterial rebound kinetics.

2. MATERIALS AND METHODS

2.1 Overall modeling strategy

A mechanistic PK–PD modeling framework was developed by integrating PBPK modeling in PK-Sim® (Open Systems Pharmacology) with PD modeling in MoBi®. The modeling workflow involved development of a base PBPK model for gentamicin in a healthy adult population, followed by extension to geriatric, CKD, and combined CKD–geriatric populations. The population-specific PBPK models were subsequently exported to MoBi, where they were integrated with a pharmacodynamic bacterial growth–kill model to simulate antimicrobial response.

2.2 PBPK model development in PK-Sim

Gentamicin was implemented as a compound in PK-Sim using physicochemical and pharmacokinetic inputs derived from database sources and user-defined settings. Relevant compound-specific and physiological parameters applied in the model are summarized in **Table 1**. The compound was characterized as highly hydrophilic, consistent with limited membrane permeability and predominant distribution within the extracellular fluid compartment.

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Table 1. Model parameters used in PBPK–PD simulations

Category	Parameter	Value	Unit
Physicochemical	Lipophilicity (logP)	−3.1	–
	Fraction unbound (fu)	0.90	–
	Molecular weight	477.6	g/mol
	Solubility	50.00	mg/mL
	Reference pH	7.00	–
	Solubility gain per charge	1000.0	–
	pKa (base)	10.12	–
	pKa (acid)	12.55	–
Distribution	Partition model	Rodgers & Rowland	–
	Permeability model	Schmitt (charge-dependent)	–
	Liver permeability	32.00	cm/s
Elimination	Plasma clearance	70.00	mL/min/kg
	Specific clearance	0.80	L/min
Physiology	Hematocrit	0.47	–
	Kidney blood flow	1.33	L/min
Population (healthy)	Age	30	years
	Weight	70.00	kg
	Height	176.00	cm
Population (geriatric)	Age	70.00	years
	Weight	71.00	kg
	Height	167.37	cm
CKD parameters	eGFR	12.39	mL/min/1.73 m²
	GFR	13.53	mL/min
	GFR (specific)	5.00	mL/min/100 g organ
Pharmacodynamic	k	0.7	h^{-1}
	E_{max}	4	h^{-1}
	EC_{50}	3	mg/L
	IC_{50}	1.5	mg/dL
	k_1	0.5	h^{-1}
	k_2	0.15	h^{-1}

Category	Parameter	Value	Unit
	z	1	h^{-1}
	Initial bacterial load (N_0)	1×10^6	CFU

Tissue distribution was described using the Rodgers and Rowland method for tissue–plasma partition coefficient prediction, together with the charge-dependent Schmitt approach for cellular permeability. Default PK-Sim parameterization was applied without further modification.

A mechanistic PBPK model for gentamicin was developed and calibrated in PK-Sim using physicochemical and renal elimination parameters obtained from published literature, as shown in **Figure 1**. Drug disposition was modeled predominantly through glomerular filtration–mediated renal clearance, while hepatic metabolism was excluded due to the negligible metabolic contribution associated with gentamicin. A healthy adult virtual population was initially generated and administered a single intravenous bolus dose of 2 mg/kg, with simulations performed over 24 hours. Calibration of the model was achieved through iterative optimization of plasma clearance and distribution-related parameters to reproduce the observed concentration–time profile from published clinical data. The final calibrated model demonstrated a C_{max} of 0.774 μmol/L at 0.1 h, total plasma clearance of 2.26 mL/min/kg, apparent half-life of 0.99 h, and V_d of 193.9 mL/kg, producing a simulated elimination profile closely aligned with observed literature data. Model performance was assessed through visual predictive comparison of observed and simulated plasma concentrations, alongside evaluation of key pharmacokinetic parameters including AUC, clearance, half-life, and volume of distribution.

2.3 Model parameterization

Model parameters used in the PBPK–PD simulations were obtained from PK-Sim database inputs and user-defined settings. All physicochemical, physiological, and pharmacodynamic parameters applied in the model are summarized in **Table 1**.

The parameterization included compound-specific properties, distribution and elimination parameters, and population-specific physiological characteristics. Pharmacodynamic parameters governing bacterial growth and drug-induced killing were also incorporated as listed in **Table 1**.

2.4 Special population modeling

Following calibration in the healthy adult population, the model was extended to simulate physiological variability across special populations. A geriatric population was defined by increasing age to 70 years, allowing PK-Sim to incorporate age-related physiological changes such as reduced renal function, altered organ perfusion, and changes in body composition.

Renal impairment was implemented using a predefined chronic kidney disease (CKD) condition without dialysis, with an estimated glomerular filtration rate in the range of approximately 12–30 mL/min/1.73 m^2. This resulted in reduced renal clearance and prolonged drug elimination. A combined CKD–geriatric population was generated by applying both advanced age and renal impairment simultaneously.

2.5 Export to MoBi

The PBPK models developed in PK-Sim were exported to MoBi for pharmacodynamic modeling. The export preserved the full physiological structure, including organ compartments, parameter values, and simulated drug concentration–time profiles. These outputs were used as dynamic inputs for pharmacodynamic simulations.

2.6 Pharmacodynamic model

A bacterial growth–kill model was implemented in MoBi to describe the antimicrobial activity of gentamicin. The model incorporated first-order bacterial growth, concentration-dependent drug-induced killing, and additional modulation representing physiological variability.

The bacterial population (N) was described as:

$$\frac{dN}{dt} = k \cdot N - E(C) \cdot N$$

where the drug effect term E(C) was defined using an E_{max} model:

$$E(C) = \frac{E_{\max} \cdot C}{EC_{50} + C}$$

In addition to the primary drug effect, a modulation term was incorporated to account for system-level influences associated with renal function. This was represented using serum creatinine (Cr) as a scaling factor:

$$M(Cr) = \frac{k_1}{IC_{50} + Cr}$$

The overall system therefore integrates intrinsic bacterial growth, concentration-dependent killing, and physiological modulation related to renal function.

Model parameters used in the pharmacodynamic component are summarized in **Table 1**. Additional delay-related parameters were incorporated to represent temporal response dynamics.

3. RESULTS AND DISCUSSION

3.1 Pharmacokinetic–pharmacodynamic profile in healthy adults

The simulated pharmacokinetic–pharmacodynamic profile of gentamicin in the healthy adult population is presented in **Figure 2**. Following intravenous administration, plasma concentrations of gentamicin increased rapidly to a peak immediately after dosing and subsequently declined in a monophasic manner over time.

The pharmacodynamic response demonstrated a corresponding reduction in bacterial population following drug exposure. The decline in bacterial count was most pronounced during the early phase, coinciding with peak drug concentrations. As plasma concentrations decreased, the rate of bacterial killing diminished, and a gradual regrowth of the bacterial population was observed.

The temporal relationship between drug concentration and bacterial response highlights the concentration-dependent killing behavior of gentamicin, with higher initial concentrations associated with greater bacterial suppression. The simulated profiles demonstrate a clear coupling between pharmacokinetic exposure and pharmacodynamic effect in the healthy adult model.

3.2 Pharmacokinetic profiles across populations

The simulated plasma concentration–time profiles of gentamicin across different populations, along with literature data, are presented in **Figure 3**.

The simulated pharmacokinetic profiles of gentamicin demonstrated clear population-dependent differences in systemic exposure and elimination characteristics (**Table 2**). The healthy adult model showed the lowest drug exposure, with an AUC_{inf} of 17.49 μmol·min/L and a short half-life of 0.31 h, reflecting efficient renal clearance and rapid elimination. In contrast, the CKD adult population demonstrated a marked increase in exposure, with AUC_{inf} increasing to 64.46 μmol·min/L and half-life extending to 0.99 h, indicating impaired renal elimination. Similar findings have been reported in patients with renal dysfunction, where reduced creatinine clearance significantly prolonged gentamicin elimination and systemic retention [14]. The normal geriatric population exhibited intermediate pharmacokinetics, with increased AUC_{tEnd} (38.97 μmol·min/L) and reduced clearance compared to healthy adults, consistent with age-associated physiological decline [15]. The renal-failed geriatric population showed the most pronounced pharmacokinetic alteration, with the highest AUC_{inf} (125.36 μmol·min/L), prolonged mean residence time (2.67 h), and lowest total body clearance (1.16 mL/min/kg). Furthermore, this population demonstrated the highest C_{max} values, indicating substantial drug accumulation and delayed elimination. Collectively, these simulations confirm that renal impairment and aging synergistically increase gentamicin exposure and prolong systemic retention, emphasizing the importance of dose adjustment in vulnerable populations, as presented in **Table 2**.

Table 2. Pharmacokinetic parameters of the simulated models

Parameter	Healthy adult	Geriatric	CKD adult	CKD–geriatric
AUC_{inf} (μmol·min/L)	17.49	NC	64.46	125.36
$AUC_{inf,norm}$ (μg·min/L)	1.20×10^{11}	NC	4.43×10^{11}	8.61×10^{11}
AUC_{tEnd} (μmol·min/L)	17.49	38.98	64.46	125.34
$AUC_{tEnd,norm}$ (μg·min/L)	1.20×10^{11}	2.68×10^{11}	4.43×10^{11}	8.61×10^{11}
C_{max} (μmol/L)	0.585	0.733	0.775	0.823
$C_{max,norm}$ (mg/L)	4.02×10^{6}	5.04×10^{6}	5.32×10^{6}	5.65×10^{6}
C_{tEnd} (μmol/L)	6.91×10^{-14}	-1.04×10^{-10}	3.86×10^{-8}	9.48×10^{-5}
Total body clearance/F (mL/min/kg)	8.32	NC	2.26	1.16
AUC extrapolated, t_{last}–∞ (%)	1.06×10^{-13}	NC	5.14×10^{-8}	1.21×10^{-4}
MRT (h)	0.49	NC	1.43	2.67
t_{max} (h)	0.05	0.10	0.10	0.10
Half-life (h)	0.31	NC	0.99	1.84
V_d (plasma)/F (mL/kg)	224.21	NC	193.90	185.33
V_{ss} (plasma)/F (mL/kg)	245.33	NC	194.45	185.74

All simulations: single 2 mg/kg intravenous dose; values are for gentamicin in peripheral venous blood plasma. AUC, area under the concentration–time curve; C_{max}, maximum plasma concentration; C_{tEnd}, concentration at end of simulation; MRT, mean residence time; t_{max}, time to C_{max}; V_d, volume of distribution; V_{ss}, volume of distribution at steady state; NC, not calculated by the software for this simulation.

3.3 Pharmacodynamic profiles across populations

The pharmacodynamic profiles of gentamicin across the different populations are presented in **Figures 4–7**. The simulated bacterial population–time profiles demonstrated an initial reduction in bacterial count following drug administration in all populations.

In the healthy adult population (**Figure 4**), a rapid decline in bacterial population was observed during the early phase, followed by an earlier onset of regrowth as drug concentrations decreased.

In the geriatric population (**Figure 5**), bacterial suppression was maintained for a longer duration compared to the healthy adult model, with a delayed onset of regrowth.

In the CKD population (**Figure 6**), the reduction in bacterial population persisted over an extended period, and the regrowth phase occurred later in the time course relative to both the healthy adult and geriatric populations.

The CKD–geriatric population (**Figure 7**) demonstrated the most prolonged bacterial suppression among all groups, with the latest onset of regrowth and sustained reduction in bacterial population over time.

Overall, the pharmacodynamic profiles indicate a progressive delay in bacterial regrowth across populations, with the earliest regrowth observed in the healthy adult population and the most delayed response in the CKD–geriatric population.

3.4 Pharmacokinetic–pharmacodynamic integration

The relationship between gentamicin pharmacokinetics and pharmacodynamic response across different populations is summarized in **Figures 3–7**. Variations in plasma concentration–time profiles were reflected in corresponding differences in bacterial population dynamics.

In the healthy adult population, the rapid decline in plasma concentration (**Figure 3**) was associated with an earlier onset of bacterial regrowth (**Figure 4**). In contrast, the geriatric population demonstrated a slower decline in drug concentration (**Figure 3**), corresponding to a delayed regrowth phase in the bacterial population (**Figure 5**).

A more pronounced effect was observed in the CKD population, where sustained plasma concentrations over time (**Figure 3**) were associated with prolonged bacterial suppression and a later onset of regrowth (**Figure 6**). The CKD–geriatric population exhibited the most prolonged concentration profile (**Figure 3**), which corresponded to the most extended duration of bacterial suppression and the latest onset of regrowth (**Figure 7**).

Overall, populations with slower decline in plasma concentration demonstrated prolonged bacterial suppression, whereas populations with faster drug elimination showed earlier bacterial regrowth. These findings indicate a clear association between drug exposure and pharmacodynamic response across the simulated populations.

3.5 Discussion

The present study developed an integrated PBPK–PD model for gentamicin to evaluate how physiological variation influences drug exposure and bacterial response across healthy adult, geriatric, CKD, and CKD–geriatric populations. The overall behavior of the model is consistent with recent literature showing that gentamicin disposition remains strongly dependent on renal function across clinical populations and that this dependence is central to dose optimization. Hodiamont et al. (2022) [4] emphasized that gentamicin pharmacokinetics vary substantially across patient groups, with renal function being a major determinant of exposure and dosing requirements.

In the healthy adult model, the simulated concentration–time profile showed the expected rapid post-dose decline, while the linked PD profile showed an early reduction in bacterial burden followed by regrowth as exposure decreased. This general PK–PD pattern is in line with the recent pharmacodynamic work of Lee et al. (2023) [16], who modeled aminoglycoside concentration–response relationships against pathogenic *E. coli* and showed that gentamicin activity can be described using PD modeling linked to bacterial growth behavior and effective concentration metrics.

Extension of the model to geriatric and CKD populations produced progressively prolonged drug exposure, with the greatest persistence seen in renal impairment. This is consistent with recent clinical and methodological work. Hodiamont et al. (2022) [4] summarized that altered physiology across patient groups affects gentamicin exposure and dose selection, while Halouzková et al. (2022) [17] specifically highlighted that aminoglycosides have a markedly prolonged half-life in patients with kidney disease and that lower doses with extended dosing intervals are needed in severely reduced kidney function.

The present CKD-related findings are also supported by Pai et al. (2023) [18], who reported that the 2021 CKD-EPI eGFR equation without race and body-surface-area indexation provided better estimation of gentamicin and tobramycin clearance. That study reinforces the central interpretation of the current model: accurate representation of renal function is critical when predicting gentamicin exposure.

The PD simulations in the current study showed that delayed decline in plasma concentration was associated with delayed bacterial regrowth, particularly in CKD and CKD–geriatric populations. This exposure–response trend is directionally consistent with the modeling framework described by Lee et al. (2023) [16], in which antibiotic concentration was directly linked to bacterial growth dynamics through a pharmacodynamic model. In the present work, this relationship was extended across physiologically distinct populations, allowing comparison of bacterial suppression patterns under different elimination conditions.

These findings suggest that standard dosing strategies may require adjustment in CKD and geriatric populations to balance efficacy and toxicity. A strength of the present study is the integration of PBPK and PD components within a single mechanistic framework. At the same time, the model has limitations. It relies on literature-derived inputs and virtual population assumptions, and its evaluation was primarily based on visual agreement rather than formal quantitative validation. In addition, the PD

component represents a simplified bacterial system and does not incorporate organism-specific resistance mechanisms or host immune effects. Accordingly, the model should be interpreted as a mechanistic exploratory framework rather than a fully validated clinical dosing tool. Recent reviews also indicate that gentamicin dosing in special populations remains challenging and still depends heavily on careful exposure assessment and therapeutic monitoring.

Although the developed PBPK–PD framework successfully characterized gentamicin pharmacokinetics and bacterial response across multiple physiological populations, several limitations remain. The model was calibrated primarily using literature-derived plasma concentration data rather than individual patient-level datasets, which may limit its ability to fully capture interindividual variability. In addition, the pharmacodynamic component employed a simplified bacterial growth–kill system and did not explicitly incorporate adaptive resistance mechanisms, immune response interactions, or pathogen-specific minimum inhibitory concentration variability. The CKD and geriatric populations were simulated using generalized physiological modifications rather than clinically stratified renal stages or frailty indices. Furthermore, the study evaluated single-dose administration and did not investigate repeated dosing, accumulation toxicity, or therapeutic drug monitoring strategies commonly applied in clinical aminoglycoside therapy. Future work should therefore focus on integrating patient-specific clinical datasets, multiple dosing regimens, drug–drug interaction modeling, resistance development kinetics, and pediatric population simulations to enhance the translational applicability of the model for precision antimicrobial dose optimization and individualized therapy prediction.

4. CONCLUSION

An integrated PK–PD modeling framework for gentamicin was developed by combining PBPK modeling in PK-Sim with pharmacodynamic modeling in MoBi. The model captured the characteristic pharmacokinetic behavior of gentamicin and enabled evaluation of population-specific differences in drug exposure.

The results demonstrated that variations in renal function and age influence gentamicin concentration–time profiles and are reflected in corresponding differences in bacterial population dynamics. Prolonged drug exposure in geriatric and CKD populations was associated with delayed bacterial regrowth, indicating a consistent relationship between pharmacokinetic profiles and pharmacodynamic response.

Overall, the study provides a mechanistic framework for assessing gentamicin PK–PD relationships across different physiological conditions. This approach may support further simulation-based investigations and optimization of dosing strategies in populations with altered renal function.

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AUTHOR CONTRIBUTIONS

Shyam Nikethen Girivasan: Conceptualization, Methodology, Software, Formal Analysis, Visualization, Writing—Original Draft, Writing—Review & Editing.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ETHICS STATEMENT

Not applicable. This was an in silico modeling and simulation study using virtual populations and published literature data; no human participants or animals were involved, and ethical approval was not required.

DATA AVAILABILITY STATEMENT

The PK-Sim and MoBi model files and simulation outputs supporting the findings of this study are available from the corresponding author upon reasonable request.

DECLARATION OF GENERATIVE AI USE

During the preparation of this work, the author utilized ChatGPT (OpenAI) to assist with language editing, grammatical refinement, and structural polishing of the text. After using this tool, the author thoroughly reviewed and edited the content as necessary and takes full responsibility for the content, accuracy, and integrity of the published work.

ABBREVIATIONS

AUC, area under the curve; CFU, colony-forming units; CKD, chronic kidney disease; C_{max}, maximum plasma concentration; Cr, serum creatinine; EC_{50}, half-maximal effective concentration; eGFR, estimated glomerular filtration rate; E_{max}, maximum effect; fu, fraction unbound; GFR, glomerular filtration rate; IC_{50}, half-maximal inhibitory concentration; N, bacterial population; N_0, initial bacterial population; PBPK, physiologically based pharmacokinetic; PD, pharmacodynamics; PK, pharmacokinetics; PK–PD, pharmacokinetic–pharmacodynamic.

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FIGURES

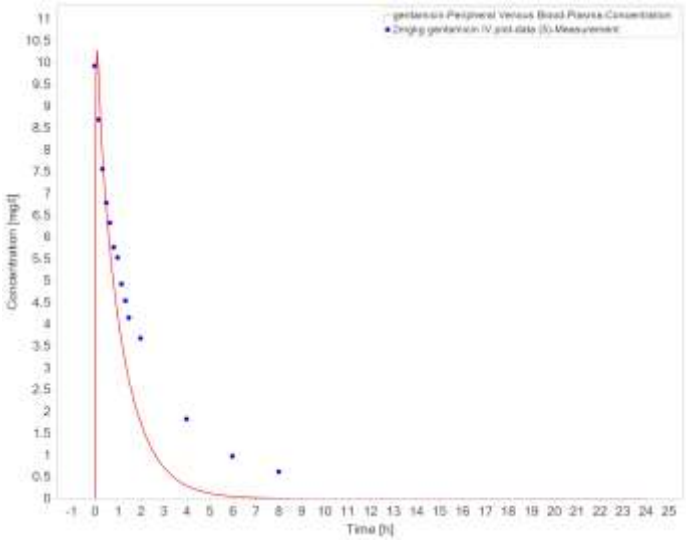


Figure 1. Comparison of simulated and literature-reported plasma concentration–time profiles of gentamicin in a healthy adult population following a 2 mg/kg intravenous bolus dose.

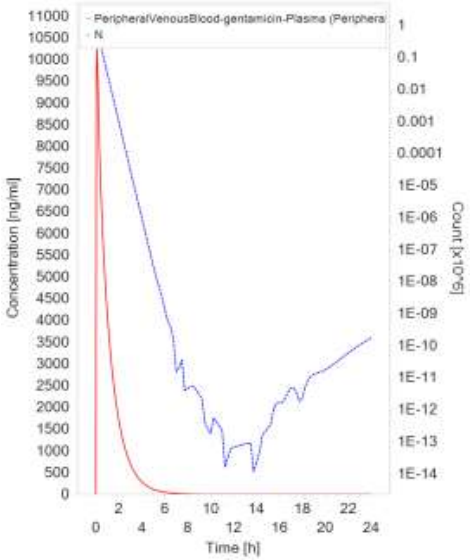


Figure 2. Simulated time–concentration profile of gentamicin (red solid line, primary y-axis) and corresponding bacterial population dynamics (blue dashed line, secondary y-axis) in the healthy adult population following a single 2 mg/kg intravenous bolus dose.

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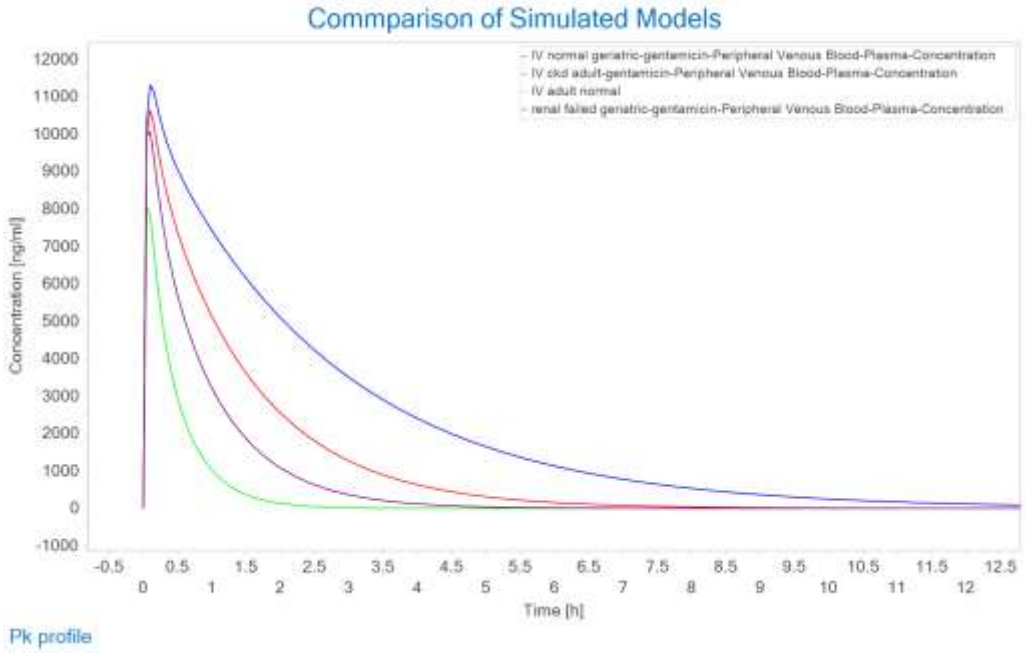


Figure 3. Simulated plasma concentration–time profiles of gentamicin in healthy adult (green line), geriatric (purple line), CKD adult (blue line), and CKD–geriatric (red line) populations, together with literature-reported data (green circles), following a 2 mg/kg intravenous dose.

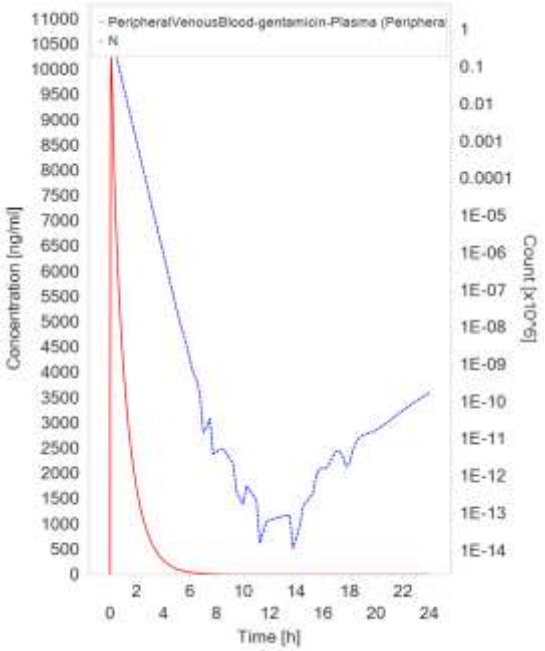


Figure 4. Simulated plasma concentration–time profile of gentamicin (red solid line, primary y-axis) and corresponding bacterial population (blue dashed line, secondary y-axis) in the healthy adult population following a 2 mg/kg intravenous dose.

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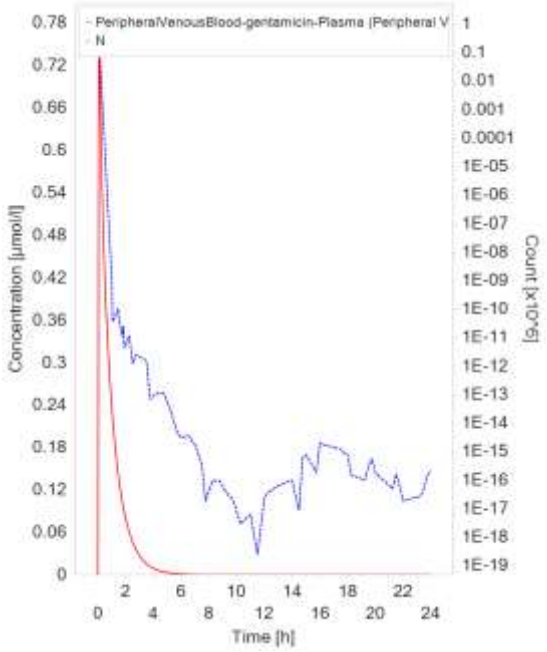


Figure 5. Simulated plasma concentration–time profile of gentamicin (red solid line, primary y-axis) and corresponding bacterial population (blue dashed line, secondary y-axis) in the geriatric population following a 2 mg/kg intravenous dose.

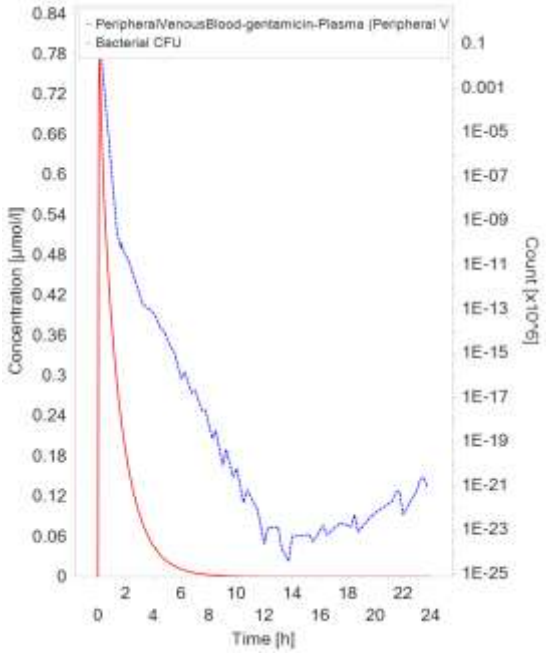


Figure 6. Simulated plasma concentration–time profile of gentamicin (red solid line, primary y-axis) and corresponding bacterial population (blue dashed line, secondary y-axis) in the CKD population following a 2 mg/kg intravenous dose.

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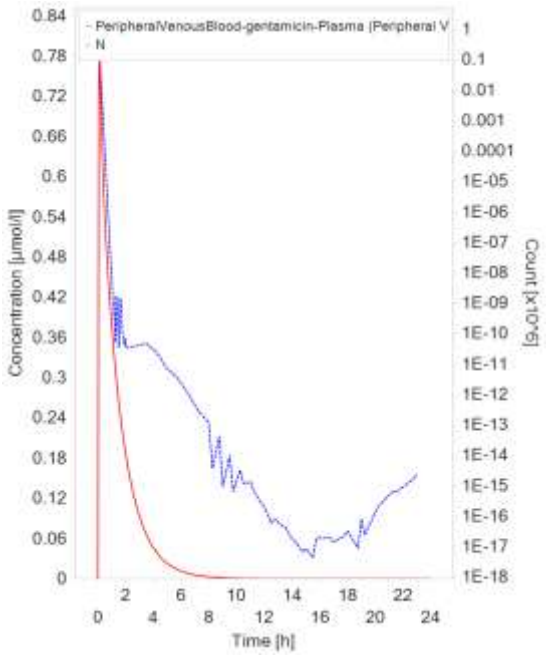


Figure 7. Simulated plasma concentration–time profile of gentamicin (red solid line, primary y-axis) and corresponding bacterial population (blue dashed line, secondary y-axis) in the CKD–geriatric population following a 2 mg/kg intravenous dose.