# Applying Neural ODEs to Derive a Mechanism-Based Model for Characterizing Maturation-Related Serum Creatinine Dynamics in Preterm Newborns

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## Abstract

Serum creatinine in neonates follows complex dynamics due to maturation processes, most pronounced in the first few weeks of life. The development of a mechanism-based model describing complex dynamics requires high expertise in pharmacometric (PMX) modeling and substantial model development time. A recently published machine learning (ML) approach of low-dimensional neural ordinary differential equations (NODEs) is capable of modeling such data from newborns automatically. However, this efficient data-driven approach in itself does not result in a clinically interpretable model. In this work, an approach to deriving an interpretable model with reasonable PMX-type functions is presented. This "translation" was applied to derive a PMX model for serum creatinine in neonates considering maturation processes and covariates. The developed model was compared to a previously published mechanism-based PMX model whereas both models had similar mechanistic structures. The developed model was then utilized to simulate serum creatinine concentrations in the first few weeks of life considering different covariate values for gestational age and birth weight. The reference serum creatinine values derived from these simulations are consistent with observed serum creatinine values and previously published reference values. Thus, the presented NODE-based ML approach to model complex serum creatinine dynamics in newborns and derive interpretable, mathematical-statistical components similar to those in a conventional PMX model demonstrates a novel, viable approach to facilitate the modeling of complex dynamics in clinical settings and pediatric drug development.

## Introduction

A steady state between creatinine synthesis and clearance is not reached during the first months of human life because of developmental changes in normal physiology as well as superimposed pathophysiological alterations. Until birth, the fetal renal clearance capacity remains very limited, with the placental circulation acting as a "physiological hemodialysis circuit," so that fetal serum creatinine values nearly equal maternal ones until (near-)term gestational age. From (near-)term gestational age onward, the fetal creatinine values are somewhat higher than the maternal ones, likely because of limitations of the placental clearance capacity and increasing fetal creatinine synthesis (muscle mass related).[1–3] Once disconnected from the placental circulation at birth, this placental dialysis circuit disappears and will be gradually substituted by an increasing, "endogenous" renal elimination capacity of the newborn. This phenomenon is mainly driven by a significant increase in renal blood flow from 3% to 25% of the fetal cardiac output, as the neonatal kidney is highly vasoreactive. Based on drug-specific observations in neonates and young infants, renal elimination hereby depends on prenatal (e.g., birth weight or gestational age) and postnatal maturation (e.g., current weight, or postnatal age).[4–6] In addition, there is some

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weight loss ($-6\%$ to $-8\%$ of the birth weight) in the first days of life, related to water losses, so that, for example, sodium and creatinine may increase due to volume constriction, while an increase in muscle mass will happen once the newborn is in anabolic condition.[7]

Since all these maturational physiological changes are most prominent in early infancy, this is reflected in extensive inter- and intraindividual variability in serum creatinine, resulting in widely dispersed data instead of information that can be interpreted and used at bedside by health care providers. This pattern results in what Boer et al[8] have described as the "broken stick" pattern in serum creatinine throughout infancy. Further reflecting on this, a "hockey" stick is perhaps a more accurate description to focus on the additional variability in the first 6–8 weeks of life. In the neonatal (intensive) care setting, these maturational changes are further modulated by pathophysiological changes like asphyxia, nephrotoxic drugs, or impaired hemodynamics, further increasing this intra- and interindividual variability in serum creatinine values.

Although the relevant covariates are reasonably well identified and quantified and there is knowledge on the mechanistic understanding of the postnatal creatinine patterns and its covariates, the conversions of these phenotypic clouds of serum creatinine in neonates into useful information to guide daily practices in the individual newborn or young infant necessitate more advanced data analytical approaches such as mechanism-based pharmacometric (PMX) modeling[9,10] or machine learning (ML)-based analyses.[11]

In this manuscript, a novel ML approach called neural ordinary differential equation (NODE)[11–13] is utilized to model serum creatinine dynamics in extreme-low birth weight (ELBW, <1 kg) neonates. NODEs approximate the dynamics, that is, the right-hand side (derivative) of a differential equation, with neural networks (NNs). Thus, NODEs are data-driven approaches that do not require prior knowledge about the dynamics. This is especially useful when complex dynamics need to be analyzed. ML models are usually considered to be black-box models, that is, the modeler does not get information about the explicit model structure and the underlying dynamics. However, that is essential information for their applicability in clinical pharmacology and PMX, particularly in pediatrics. Thus, a modeling approach was utilized to translate the dynamics learned by the ML approach back to an interpretable model, addressing the "black-box aspect". This scientific work aimed to utilize a purely data-driven model to investigate potential unidentified covariates and to test whether a NODE-based ML approach can confirm previously developed mechanism-based PMX models.

## Methods

Ethics approval was previously granted for the data collection and analysis (S63405). Informed consent was hereby waived because of the retrospective and observational nature of the dataset.

In this section, we describe the (i) neonatal dataset, (ii) serum creatinine and estimation of kidney function, (iii) NODE-based ML modeling, (iv) machine learning covariate modeling, (v) translation back to interpretable "mechanism-based" model, (vi) clinical model refinement and model evaluation, and (vii) model simulations to derive a simulation plot showing creatinine dynamics in preterm newborns.

### Neonatal Dataset

Data for this analysis were obtained from two cohorts of preterm ELBW newborns in the neonatal intensive care unit of the University Hospitals Leuven between June 2015 and March 2017, as described previously.[14] Serum creatinine concentrations of the first 6 weeks of life were considered. In addition, clinical data were collected including gestational age (GA), birth weight (BWT), current weight (CWT), sex, mode of delivery (MOD), maternal betamethasone treatment to induce fetal lung maturation, and treatment of the neonate with ibuprofen or inotropic antibiotics. For time points without CWT measurement, CWT was interpolated linearly. Patients with no information on GA or MOD were excluded from the analysis.

For evaluation, the dataset was randomly split into a training set, on which the models were developed, and an evaluation set, on which the developed models were evaluated. Neonates were randomly assigned to the training (80%) or evaluation set (20%).

### Serum Creatinine and Estimation of Kidney Function

To estimate kidney function or glomerular filtration rate (GFR), the most measured and readily accessible biomarker in human medicine is serum creatinine (Scr). Creatinine is a by-product of the nonenzymatic conversion of creatine to creatinine in the muscle. Creatinine is subsequently cleared from plasma almost exclusively by GFR with minimal active secretion by the renal tubules. Assuming a steady state, zero-order creatinine synthesis (Syn)[5] and clearance are in balance, so that Scr values can reliably be used to estimate the GFR.

$$Scr = \frac{Syn}{GFR} \tag{1}$$

### NODE-Based Machine Learning Modeling

A mixed-effects low-dimensional NODE[11] was utilized to model serum creatinine levels in the population of ELBW neonates. The structure of the NODE-based

ML model reads:

$$\frac{d}{dt} ScrC = f_{NN}^C \ (ScrC) + ScrC_0 \cdot f_{NN}^t \ (t)$$

$$ScrC \ (0) = ScrC_0 \tag{2}$$

where ScrC denotes the serum creatinine concentration, $ScrC_0$ serum creatinine concentration at birth, $f_{NN}^C$ a serum creatinine concentration-dependent neural network (NN), $f_{NN}^t$ a time dependent NN and t time after birth in days. Note that $f_{NN}^t$ represents the NN approximating the change in serum creatinine dynamics due to maturation processes in neonates, and $f_{NN}^C$ represents the NN approximating the overall serum creatinine dynamics. Details on the exact NN architecture are provided in the Supplemental Information. The data were modeled in Monolix (Monolix 2023R1, Lixoft SAS, a Simulations Plus company) where model parameters in $f_{NN}^C$ and $f_{NN}^t$, and $ScrC_0$ were estimated, and fitted NODEs were further analyzed in R.[15]

### Machine Learning Covariate Modeling

Model parameters in $f_{NN}^C$ and $f_{NN}^t$ were tested to correlate with time-independent covariates, that is, covariates that do not change over time. To this end, Pearson's correlation coefficient was calculated and tested in a Student's t-test with a significance level of $P < .05$ in Monolix. Covariates were included for a parameter in the NODE-based ML model in Equation (2) when a multivariate linear regression between the parameter and covariates resulted in a decreased Bayesian Information Criterion of the linear regression. As time-independent covariates, GA, BWT, MOD, and sex were considered. Time-dependent covariates, that is, covariates that change over time, were assessed by including them as regressors on the NN parameters in the model and testing for effects on modeled dynamics. Treatment with ibuprofen or inotropic antibiotics was investigated as time-dependent covariates, that is, covariates that may change on a daily basis, including possible delayed effects.

### Translation Back to Interpretable "Mechanism-Based" Model

While the NODE-based ML model in Equation (2) can fit clinical data, it is considered to be a "black box" because the structural model provides no insights into the equations that drive the dynamics. To translate the dynamics learned by the NODE-based ML model in Equation (2) back to an interpretable "mechanism-based" model, the dynamics learned by $f_{NN}^C$ and $f_{NN}^t$ were plotted in derivative versus state plots.[11] These plots allow us to assess the learned mechanism in the NNs of the NODE, that is, they allow us to open the "black-box." These plots were manually analyzed, and

interpretable functions were derived by visual comparison to commonly applied PMX functions. To obtain reasonable initial values, the derived functions were directly fitted to the derivative data. These functions were implemented in a mixed-effects model, refitted with Monolix, and the previously identified potential covariates according to Pearson's correlation test were tested to influence the model parameters. Note that the interpretable "mechanism-based" model is still a data-driven model, but it is based on mechanistic reasonable functions. However, it is not based on prior knowledge of physiological mechanisms and clinical considerations.

### Clinical Model Refinement and Model Evaluation

The NODE-based ML model developed here and the subsequent interpretable "mechanism-based" model developed from it are mainly data-driven and do not incorporate a priori clinical knowledge. For this model to be useful for clinicians at the bedside, it was further refined with clinical knowledge. Covariate analysis for the refined "mechanism-based" model was performed similarly to the machine learning covariate modeling.

To evaluate the NODE-based ML model in Equation (2), the interpretable "mechanism-based" model and the refined "mechanism-based" model for their capability of capturing general serum creatinine dynamics, population simulations on evaluation dataset with individual covariates but no interindividual variability was performed. Similar to the model evaluation in the original analysis of van Donge et al,[9] several measures of precision and bias[16] were calculated for the population simulations on the evaluation dataset. As a measure of precision, mean squared error (MSE) and relative mean squared error (RMSE) and as a measure of bias, relative mean prediction error (RMPE) were calculated according to:

$$MSE = \frac{1}{n} \sum_{i=1}^{n} (Pred_i - Obs_i)^2, \tag{3}$$

$$RMSE = \sqrt{\frac{1}{n} \sum_{i=1}^{n} \left( \frac{Pred_i - Obs_i}{Obs_i} \cdot 100 \right)^2}, \tag{4}$$

$$RMPE = \frac{1}{n} \sum_{i=1}^{n} \frac{Pred_i - Obs_i}{Obs_i} \cdot 100. \tag{5}$$

### Simulation Plot Showing Creatinine Dynamics in Preterm Newborns

Simulations with the refined "mechanism-based" model were performed for different GA to derive serum creatinine reference ranges. These reference ranges were

**Table 1.** Characteristics of Neonates in the Training and in the Evaluation Dataset

| Characteristic | Training, N = 174[I] | Evaluation, N = 43[I] |
|---|---|---|
| Obs. per patient | 19 [14, 24] | 17 [14, 26] |
| Gestational age (weeks) | 27.1 (2.0) | 26.5 (1.5) |
| Birth weight (gram) | 807.9 (135.1) | 799.6 (123.5) |
| Sex | | |
|   Female | 82 (47.1%) | 20 (46.5%) |
|   Male | 92 (52.9%) | 23 (53.5%) |
| Mode of delivery | | |
|   Vaginal | 54 (31.0%) | 16 (37.2%) |
|   Caesarean | 120 (69.0%) | 27 (62.8%) |
| Betamethasone treatment | | |
|   No | 25 (14.4%) | 5 (11.6%) |
|   Yes | 149 (85.6%) | 38 (88.4%) |
| Ibuprofen treatment | 99 (56.9%) | 32 (74.4%) |

[I] Median [min, max]; mean (SD); n (%).

compared to observed and previously published reference ranges.

## Results

In this section, we describe: (i) the statistics of the neonatal dataset, (ii) the results from NODE-based ML modeling, (iii) the machine learning covariate modeling, (iv) the translation back to an interpretable "mechanism-based" model, (v) the clinical model refinement and model evaluation, and (v) a simulation plot showing creatinine dynamics in preterm newborns.

### Neonatal Dataset
Data from 217 ELBW neonates were included in the overall dataset with a total of 4026 serum creatinine concentrations. Data from 174 neonates with a total of 3210 serum creatinine measures were included in the training dataset, and 43 neonates with a total of 816 serum creatinine measures were included in the evaluation dataset.

A summary of characteristics of the training and evaluation dataset is given in Table 1.

### Machine Learning Covariate Analysis
All time-independent covariates showed correlations to model parameters according to Pearson's correlation test with $P$-values $< .05$. However, based on multivariate linear regressions performed by Monolix, only GA and BWT were included in the NODE-based ML model in Equation (2), indicating GA and BWT to be the most important covariate effects.

As time-dependent covariates, only ibuprofen coadministration showed an effect on serum creatinine dynamics, reducing the creatinine elimination. Coadministration of inotropic antibiotics showed no effect on serum creatinine dynamics.

### Translation Back to an Interpretable "Mechanism-Based" Model
The learned dynamics of the serum creatinine concentration dependent NN, that is, $f_{NN}^C$, are plotted against serum creatinine in Figure 1A. The visualized serum creatinine–derivative relationship can be described approximately with a linear function according to:

$$f_{NN}^C (\text{ScrC}) \sim k_{in} - k_{out} \cdot \text{ScrC}. \tag{6}$$

For consistency with conventional modeling approaches, the y-axis intercept in such a linear function is called $k_{in}$ and represents the production rate of serum creatinine and the slope of the linear function is called $k_{out}$ and represents the elimination rate. The fitted linear function is visualized in Figure 1A.

The dynamics learned by the time-dependent NN, that is, $f_{NN}^t$, are plotted against time in Figure 1B. The visualized time–derivative relationship can be described approximately with a sigmoidal function, whereas the Emax function with a Hill-coefficient is the most common sigmoidal function in PMX. Thus, the following approximation is assumed:

$$f_{NN}^t (t) \sim E_{max,in} \cdot \left(1 - \frac{t^h}{t_{50}^h + t^h}\right), \tag{7}$$

where $E_{max,in}$ denotes the maximal increased input in immature neonates, h the Hill-coefficient describing the steepness of the curve, and $t_{50}$ the time point where half the effect is reached.

Thus, the resulting interpretable "mechanism-based" model can be written as:

$$\frac{d}{dt}\text{ScrC} = k_{in} - k_{out} \cdot \text{ScrC} + \text{ScrC}_0 \cdot E_{max,in}$$
$$\cdot \left(1 - \frac{t^h}{t_{50}^h + t^h}\right), \qquad \text{ScrC}(0) = \text{ScrC}_0 \tag{8}$$

### Clinical Model Refinement and Model Evaluation
In the interpretable "mechanism-based" model in Equation (8), serum creatinine concentrations are modeled directly as differential equations, and all estimated parameters are based on concentrations; that is, units of estimated parameters are in the form mg/dL. However, the volume of distribution for serum creatinine changes with increasing body weight. Thus, in the refinement of the interpretable "mechanism-based" model, the volume of distribution was introduced following the approach proposed by van Donge et al[9] to set the volume of distribution to 7 dL/kg and linearly interpolate the current weight CWT. The refined "mechanism-based" model describing serum creatinine changes in newborns then reads,
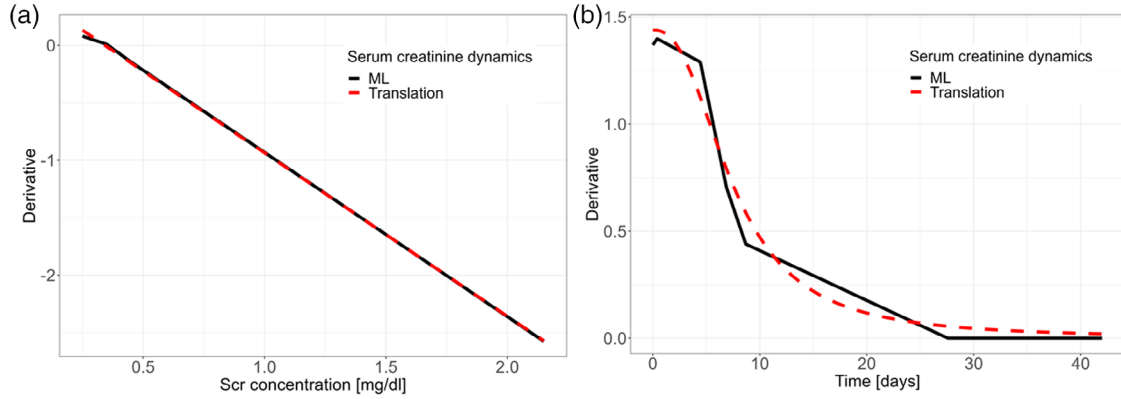
**Figure 1.** Learned dynamics of the NODE-based ML approach in Equation (2) (solid black) and the corresponding translation to a "mechanism-based" model (dashed red) for the serum creatinine concentration dependent $f_{NN}^C$ (A) and the time-dependent $f_{NN}^t$ (B).

**Table 2.** Model Parameter Estimates and Covariate Effects of the Refined "Mechanism-Based" Model in Equation (9) with Relative Standard Errors (RSE%) and Interindividual Variability (IIV)

Model Parameter Estimates

| Parameter (unit) | Estimates (RSE%) | IIV (RSE%) |
|---|---|---|
| $ScrA_0$ (mg) | 3.44 (1.74) | 0.23 (5.67) |
| $k_{in}^A$ (mg/day) | 0.33 (2.86) | 0.34 (5.92) |
| $k_{out}^A$ (1/day) | 0.94 (2.17) | 0.25 (6.01) |
| $E_{max,in}^A$ (1/day) | 1.08 (0.42) | - |
| h | 1.73 (5.70) | 0.73 (5.90) |
| $t_{50}^A$ (days) | 6.53 (5.89) | 0.71 (6.29) |

Covariate Effects

| Effect | Population Parameter (RSE%) | Equation |
|---|---|---|
| GA on $ScrA_0$ | 1.6 (15.7) | $ScrA_{0,i} = ScrA_{0,pop} \cdot \left(\frac{GA_i}{GA_m}\right)^{1.6} \cdot \left(\frac{BWT_i}{BWT_m}\right)^{0.45}$ |
| BWT on $ScrA_0$ | 0.45 (19.9) | |
| GA on $t_{50}^A$ | −6.45 (11.4) | $t_{50,i}^A = t_{50,pop}^A \cdot \left(\frac{GA_i}{GA_m}\right)^{-6.45}$ |
| Ibuprofen treatment on $k_{out}^A$ | −0.064 (4.31) | $k_{out,i}^A = k_{out,pop}^A \cdot (1 - 0.064 \cdot IBU_i)$ |
| V on $k_{in}^A$ | | $k_{in,i}^A = k_{in,pop}^A \cdot (7 \cdot CWT_i)$ |

$ScrA_0$, serum creatinine amount at birth; $k_{in}^A$, the zero-order production rate at amount level; $k_{out}^A$, the first-order elimination rate at amount level; $E_{max,in}^A$, the maximal increased input in immature neonates; h the Hill-coefficient; $t_{50}^A$, the time-point where half the effect is reached.

$$\frac{d}{dt}ScrA = k_{in}^A - k_{out}^A \cdot ScrA + ScrA_0 \cdot E_{max,in}^A$$

$$\cdot \left(1 - \frac{t^h}{t_{A,50}^h + t^h}\right),$$

$$ScrC = \frac{ScrA}{7 \cdot CWT}, \quad ScrA(0) = ScrA_0 \tag{9}$$

where ScrA is the serum creatinine amount in the blood, $ScrA_0$ the serum creatinine amount at birth, and parameters $k_{in}^A$, $k_{out}^A$, and $E_{max,in}^A$ the corresponding parameters on the amount level. Since $k_{in}$ in the interpretable "mechanism-based" model in Equation (8) was on concentration level, that is, the unit of $k_{in}$ is mg/dL/day, and $k_{in}^A$ in the refined "mechanism-based"

model in Equation (9) is on the amount level, that is, the unit of $k_{in}^A$ is mg/day, $k_{in}^A$ should be scaled with volume of distribution, as shown in Table 2.

Interindividual variability was not estimated on $E_{max,in}^A$ due to high shrinkage (> 50%). Parameter estimates and covariate effects are summarized in Table 2.

Serum creatinine concentration at birth $ScrC_0 = \frac{ScrA_0}{7 \cdot BWT}$ was estimated at 0.6 mg/dL with a median BWT of 0.83 kg. GA was identified as a covariate for $t_{50}$, and treatment with ibuprofen was identified to decrease the serum creatinine elimination. These covariate effects are visualized in Figure 2. Covariate analysis also showed increasing $ScrA_0$ with increasing GA and BWT. The combined effect of GA on maturation, that is, $t_{50}$, and of GA and BWT on initial serum creatinine $ScrA_0$ is visualized in the simulation plot in Figure 3.
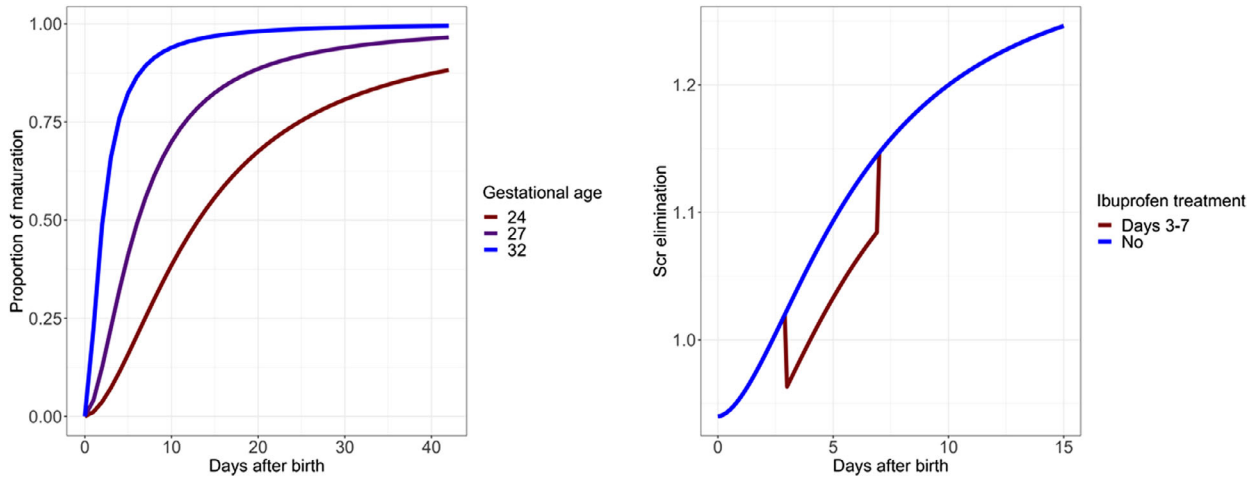
**Figure 2.** Simulations for the maturation process of serum creatinine elimination under different gestational ages (left), and simulation for influence of ibuprofen treatment (right) on days 3 to 7 (red line) compared to no ibuprofen treatment (blue line). Note that serum creatinine elimination is visualized for first 42 days after birth but maturation is not completed in all ELBW neonates.
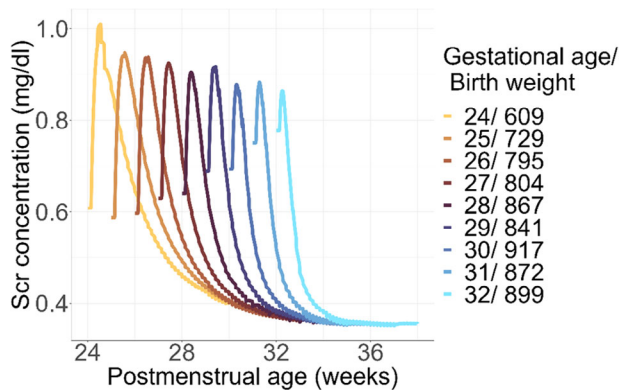


**Figure 3.** Simulations of serum creatinine concentrations for gestational ages from 24 to 32 weeks with the corresponding median birth weights over post-gestational age (weeks).

Measures of precision and bias for the NODE-based ML approach in Equation (2) were in similar ranges for the evaluation dataset compared to the training dataset, as presented in Table 3. This indicates that the NODE-based ML model did not overfit, and performs consistently between the data observed during development and new data. The interpretable "mechanism-based" model in Equation (8) had similar measures of precision compared to the NODE-based ML model. The refined "mechanism-based" model in Equation (9) including clinical knowledge shows slightly higher MSE and RMSE on the training data but a lower RMPE compared to the purely data-driven approaches. A similar pattern can be observed in the evaluation data; however, a lower RMSE and a higher RMPE are observed compared to the NODE-based ML model.

### Simulations Showing Creatinine Dynamics in Preterm Newborns

Simulations for newborns with different GA were performed with the refined "mechanism-based" model in Equation (9) and summarized in a simulation plot, as shown in Figure 3. The simulation plot illustrates the shorter time until maturation stabilizes serum creatinine dynamics, that is, the time of increasing serum creatinine concentration after birth and the increase of initial serum creatinine concentration with increasing GA, as already described by Wu et al.[17]

The median predictions and the 95% prediction intervals of Scr concentrations for neonates with GAs

**Table 3.** Measures of Precision and Bias for the NODE-Based ML Model Equation (2), the Therefrom Derived Interpretable "Mechanism-Based" Model Equation (8), and the Refined "Mechanism-Based" Model Equation (9) with Clinical Knowledge

| Model | Training Data | | | Evaluation Data | | |
|---|---|---|---|---|---|---|
| | MSE | RMSE | RMPE | MSE | RMSE | RMPE |
| ML | 0.024 | 23.61 | 2.448 | 0.023 | 23.02 | 1.471 |
| Interpretable | 0.024 | 22.93 | −1.621 | 0.022 | 21.84 | −1.888 |
| Refined | 0.027 | 24.93 | −0.426 | 0.025 | 22.36 | −2.170 |

Measures were calculated separately for training data and evaluation data.

MSE, mean squared error; RMSE, relative mean squared error; RMPE, relative mean prediction error.

**Table 4.** Median Predictions and 95% Prediction Intervals of Scr Concentrations (ScrC) for the First 6 Weeks of Life of Neonates with Gestational Ages of 24, 27, and 32 and the Average Observed Birth Weights in the Corresponding Group

| Postnatal Age (Days) | 24 Weeks GA 609 g BWT ScrC (mg/dL) | 27 Weeks GA 803 g BWT ScrC (mg/dL) | 32 Weeks GA 899 g BWT ScrC (mg/dL) |
|---|---|---|---|
| 1 | 0.63 [0.4–0.98] | 0.65 [0.42–0.99] | 0.79 [0.51–1.23] |
| 3 | 0.96 [0.67–1.33] | 0.88 [0.62–1.24] | 0.78 [0.51–1.2] |
| 7 | 0.84 [0.56–1.23] | 0.72 [0.46–1.15] | 0.53 [0.33–0.89] |
| 14 | 0.65 [0.42–1.02] | 0.53 [0.35–0.85] | 0.43 [0.28–0.67] |
| 21 | 0.55 [0.37–0.87] | 0.47 [0.31–0.71] | 0.39 [0.26–0.61] |
| 28 | 0.49 [0.33–0.75] | 0.43 [0.28–0.64] | 0.38 [0.25–0.6] |
| 35 | 0.46 [0.31–0.7] | 0.41 [0.27–0.61] | 0.37 [0.24–0.59] |
| 42 | 0.43 [0.29–0.65] | 0.39 [0.26–0.59] | 0.37 [0.24–0.6] |

Predictions were made with the refined "mechanism-based" model Equation (9).

**Table 5.** Median Observation and 95% Observation Intervals of Scr Concentrations (ScrC) for the First 6 Weeks of Life of Neonates with Gestational Ages of 24, 27, and 32 and the Average Observed Birth Weights in the Corresponding Group

| Postnatal Age (Days) | 24 Weeks GA 609 g BWT ScrC (mg/dL) | 27 Weeks GA 803 g BWT ScrC (mg/dL) | 32 Weeks GA 899 g BWT ScrC (mg/dL) |
|---|---|---|---|
| 1 | 0.62 [0.49–0.93] | 0.69 [0.51–0.98] | 0.66 [0.65–0.81] |
| 3 | 0.88 [0.77–0.98] | 0.99 [0.75–1.21] | 0.81 [0.55–0.9] |
| 7 | 1.04 [0.98–1.11] | 0.8 [0.52–1.07] | 0.52 [0.41–0.62] |
| 14 | 0.5 [0.43–0.56] | 0.54 [0.36–0.66] | 0.4 [0.3–0.5] |
| 21 | 0.54 [0.5–0.59] | 0.44 [0.32–0.58] | 0.37 [0.32–0.4] |
| 28 | 0.52 [0.5–0.53] | 0.42 [0.33–0.6] | 0.31 [0.28–0.35] |
| 35 | NA* [NA–NA] | 0.36 [0.29–0.47] | 0.31 [0.31–0.31] |
| 42 | 0.49 [0.49–0.49] | 0.33 [0.25–0.55] | 0.26 [0.26–0.26] |

*For GA of 24 weeks at a postnatal age of 35 days, no observations are available.

of 24, 27, and 32 weeks in Table 4 are generally in accordance with observed Scr concentrations, as presented in Table 5, and previously published reference values.[9]

### Comparison to Previously Published Mechanism-Based PMX Model

A previously published mechanism-based PMX model for serum creatinine by van Donge et al[9] proposes a model that is structurally similar to the refined "mechanism-based" model. The previously published model by van Donge can be written as:

$$\frac{d}{dt}ScrA = k_{in} - k_{out} \cdot ScrA - ScrA$$
$$\cdot E_{max,in} \cdot \frac{t^h}{t_{50}^h + t^h}, \quad ScrA(0) = ScrA_0, \quad (10)$$

whereas the refined "mechanism-based" model Equation (9) developed in this work can be written as:

$$\frac{d}{dt}ScrA = \left(k_{in}^A + ScrA_0 \cdot E_{max,in}^A\right)$$
$$- k_{out}^A \cdot ScrA - ScrA_0 \cdot E_{max,in}^A$$
$$\cdot \frac{t^h}{t_{A,50}^h + t^h}, \quad ScrA(0) = ScrA_0 \quad (11)$$

Thus, the main structural difference between both developed models is that the maturation in the previously published model from van Donge is scaled by the current serum creatinine amount in the blood while the maturation in the refined "mechanism-based" model is scaled by the serum creatinine amount at birth, which is due to the structure of the NODE-based ML model in Equation (2). In addition, no covariate effect of MOD was identified in the refined "mechanism-based" model. However, the effect of GA was estimated to be larger compared to the PMX model from van Donge et al.

## Discussion

Our data-driven NODE-based ML model in Equation (2) was capable of describing the complex dynamics of serum creatinine concentrations in ELBW neonates well. In addition, it was able to identify the three covariates, that is, GA, BWT, and ibuprofen as medication, which were also identified in the refined "mechanism-based" model including clinical knowledge in Equation (9). Further possible covariates were identified but not proposed to be included in the NODE-based ML model. An interpretable "mechanism-based" model in Equation (8) could be derived from the NODE-based ML model that had a reasonable structure for Scr concentration dynamics including a maturation process. Further, clinical

assumptions, such as the linearly assumed increase of volume of distribution with increasing CWT, could be leveraged to refine the interpretable "mechanism-based" model to improve clinical rationale. In this refined "mechanism-based" model in Equation (9), a maturation was proposed where the time to reach maturation was dependent on GA. GA and BWT might be representative of the overall maturity of the neonate at birth and thus influence the initial serum creatinine level and time until the maturation process in serum creatinine elimination has completed as the maturation process takes longer in neonates with lower GA. This could in part also be explained by the characteristics of the cohort, determined by ELBW, with consequent overrepresentation of growth-restricted preterm neonates. Similar behavior can be observed for serum creatinine concentration at birth, as less mature neonates with lower GA tend to have a more pronounced initial increase in serum creatinine concentration after birth. Consistent with previous reports, treatment with ibuprofen showed a decrease in serum creatinine elimination. In comparison to a previously published mechanism-based PMX model describing serum creatinine changes in newborns by van Donge et al[9] in Equation (10), the general model structure is identical with only differences in the scaling of the maturation process. In addition, except for MOD included in the previously published mechanism-based PMX model reported by van Donge et al, the same covariates were included in the refined "mechanism-based" model. This might be explained by the larger effect of GA, as GA correlates with MOD in the dataset. Further, a faster maturation is proposed, comparing $t_{50}$ values. This might be related to the limited observation period, that is, making it difficult to properly estimate a $t_{50}$ and Hill-coefficient for a process taking longer than the observation period. In addition, the structural difference where initial serum creatinine is utilized in our refined "mechanism-based" model in Equation (9), which is inherent to the ML approach utilized, compared to the current serum creatinine level in the previously published "mechanism-based" PMX model from van Donge et al might change the interpretation of the Emax function from maturation of clearance to maturation of ratio of Scr synthesis to elimination. A limitation of the presented refined "mechanism-based" model might be the assumption of linear scaling of the volume of distribution with CWT.

The measures of precision and bias calculated for the NODE-based ML model in Equation (2), the therefrom derived interpretable "mechanism-based" model in Equation (8), and the refined "mechanism-based" model in Equation (9) suggest a similar good description of training and new data that was not utilized for model development.

The presented approach of fitting data first with a data-driven NODE-based ML model has the advantage that the dynamics of data can efficiently and easily be visualized without prior assumptions about the biological processes. Combining the knowledge gained through the visualized dynamics with usually applied functions in PMX models allows us to translate such dynamics into an interpretable "mechanism-based" model and to develop a "mechanism-based" model for complex data within days. This is in contrast to mechanism-based or physiology-based PMX models as the development of such mathematical–statistical models can take weeks and months. While the sigmoidal curve in the derivative versus state plot makes it easy to derive the Emax function in the presented case, more complex derivative versus state plots may be more challenging to find one or a combination of reasonable PMX functions to describe the visualized dynamics. In such cases, however, the development of a PMX model directly from the data might be even more difficult. Further, the interpretable "mechanism-based" model allows us to propose hypotheses about the driving factors of the dynamics, such as the maturation term in the presented model. In addition, a NODE-based ML model allows identification of the most important covariates, thus facilitating covariate selection in PMX models. In conclusion, data-driven NODE-based ML models may provide a good starting point for the development of mechanism-based models, particularly if clinical and scientific knowledge is included for their refinement and application.

## Conclusion

The combination of efficient data-driven modeling and translation to an interpretable "mechanism-based" model with mathematical–statistical components similar to those in a conventional PMX model has the potential to revolutionize and facilitate the modeling of complex dynamics in clinical settings as well as in drug development, particularly in neonatology and pediatrics.

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## Conflicts of Interest

The authors declare no conflicts of interest.

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## Data Availability Statement

Karel Allegaert acts as the custodian of the dataset. Data sharing will be considered based on a reasonable request.

## References

1. Keles E, Wintermark P, Groenendaal F, et al. Serum creatinine patterns in neonates treated with therapeutic hypothermia for neonatal encephalopathy. *Neonatology*. 2022;119(6):686-694. doi:10.1159/000525574

2. Shimabukuro W, Nakada S, Shimada K, et al. Relationship between the serum creatinine concentrations of preterm neonates within 24 h of birth and their mothers before delivery. *Clin Exp Nephrol*. 2024;28(4):293-299. doi:10.1007/s10157-023-02435-w

3. Allegaert K, Smits A, Mekahli D, Van Den Anker JN. Creatinine at birth correlates with gestational age and birth weight: another factor of the imbroglio in early neonatal life. *Neonatology*. 2021;117:637-640. doi:10.1159/000510658

4. De Cock RFW, Allegaert K, Sherwin CMT, et al. A Neonatal amikacin covariate model can be used to predict ontogeny of other drugs eliminated through glomerular filtration in neonates. *Pharm Res*. 2014;31(3):754-767. doi:10.1007/s11095-013-1197-y

5. Krzyzanski W, Smits A, Van Den Anker J, Allegaert K. Population model of serum creatinine as time-dependent covariate in neonates. *AAPS J*. 2021;23(4):86. doi:10.1208/s12248-021-00612-x

6. van den Anker JN, Hop WCJ, de Groot R, et al. Effects of Prenatal Exposure to Betamethasone and Indomethacin on the glomerular filtration rate in the preterm infant. *Pediatr Res*. 1994;36(5):578-581. doi:10.1203/00006450-199411000-00006

7. Wilbaux M, Kasser S, Gromann J, et al. Personalized weight change prediction in the first week of life. *Clin Nutr*. 2019;38(2):689-696. doi:10.1016/j.clnu.2018.04.001

8. Boer DP, De Rijke YB, Hop WC, Cransberg K, Dorresteijn EM. Reference values for serum creatinine in children younger than 1 year of age. *Pediatr Nephrol*. 2010;25(10):2107-2113. doi:10.1007/s00467-010-1533-y

9. van Donge T, Allegaert K, Gotta V, et al. Characterizing dynamics of serum creatinine and creatinine clearance in extremely low birth weight neonates during the first 6 weeks of life. *Pediatr Nephrol*. 2021;36(3):649-659. doi:10.1007/s00467-020-04749-3

10. Koch G, Datta AN, Jost K, Schulzke SM, van den Anker J, Pfister M. Caffeine citrate dosing adjustments to assure stable caffeine concentrations in preterm neonates. *J Pediatr*. 2017;191:50-56.e1. doi:10.1016/j.jpeds.2017.08.064

11. Bräm DS, Nahum U, Schropp J, Pfister M, Koch G. Low-dimensional nerual ODEs and their application in pharmacokinetics. *J Pharmacokinet Pharmacodyn*. 2024;51(2):123-140. doi:10.1007/s10928-023-09886-4

12. Lu J, Deng K, Zhang X, Liu G, Guan Y. Neural-ODE for pharmacokinetics modeling and its advantage to alternative machine learning models in predicting new dosing regimens. *iScience*. 2021;24(7). doi:10.1016/j.isci.2021.102804

13. Janssen A, Bennis FC, Mathôt RAA. Adoption of machine learning in pharmacometrics: an overview of recent implementations and their considerations. *Pharmaceutics*. 2022;14(9). doi:10.3390/pharmaceutics14091814

14. Allegaert K. Creatinine assays in early infancy: how to aim for a moving target. In: Patel VB, Preedy VR, eds. *Biomarkers in Kidney Disease*. Springer Dordrecht; 2016. doi:10.1007/978-94-007-7699-9_1

15. R Core Team. *R: A Language And Environment For Statistical Computing*. R Foundation of Statistical Computing; 2022.

16. Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. *J Pharmacokinet Biopharm*. 1981;9(4):503-512. doi:10.1007/BF01060893

17. Wu Y, Allegaert K, Flint RB, et al. When will the glomerular filtration rate in former preterm neonates catch up with their term peers? *Pharm Res*. 2024;41(4):637-649. doi:10.1007/s11095-024-03677-3

## Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.