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# Learning from machine learning - how to deduce a mechanism-based pharmacometrics model for serum creatinine in preterm neonates from neural ordinary differential equations

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Oral: Methodology - New Modelling Approaches

**Objectives:** Machine learning (ML) is an emerging field in pharmacometrics (PMX) [1], providing methods for a variety of PMX tasks, including data preparation [2], data analysis, and data modeling. One ML approach gaining special attention in PMX are neural ordinary differential equations (NODEs) [3, 4, 5, 6]. Although an NODE is basically an ordinary differential equation (ODE), the difference is that the right-hand side of the ODE is not described with mechanism-based functions, as it is typically done in PMX, but it consists of neural networks (NNs). Consequently, these NNs learn the dynamics observed in the training data. However, there are some major criticisms regarding NODEs, including that (i) they are “black box” models, (ii) they have poor extrapolation capabilities, e.g., for unseen dose ranges, due to their structure, and (iii) they do not include prior clinical knowledge. In this work, a reverse modeling approach is presented that leverages the learned knowledge by a NODE, to deduce a mechanism-based model allowing to additionally include clinical knowledge. This enables to overcome the criticism of NODEs mentioned above, and to make them a more viable approach in the field of PMX.

**Methods:** As endurance test, a dataset consisting of serum creatinine concentration measurements (n = 4026) from extremely low birth weight neonates (n = 217) with marked renal maturation processes was applied [7]. The low-dimensional NODE approach was utilized [6] where the right-hand side of the NODE consists of two types of NNs specifically tailored to PMX. The first NN takes the state as input, reflecting the autonomous behavior of the dynamics. The second NN takes explicit time as input, reflecting behavior of the dynamics that change over time, e.g., maturation processes. First, the serum creatinine measurements were fitted with the low-dimensional NODE in the non-linear mixed-effects context in Monolix and a covariate analysis was performed. Second, the learned dynamics of the NNs were visualized in derivative versus state or time plots [6]. Based on visual inspection of these plots, PMX functions were selected that described the shape of the trajectories in these plots. Third, these PMX functions were combined to deduce a mechanism-based model that is capable to characterize the dynamics of serum creatinine concentrations. Fourth, this deduced mechanism-based model was further refined with clinical knowledge about the influence of body weight on the volume of distribution. As last step, this deduced final mechanism-based model was fitted to the data, a covariate analysis was conducted with the previously gained information from the NODE-covariate analysis, and simulations were performed.

**Results:** The developed low-dimensional NODE was capable of learning complex dynamics of serum creatinine in preterm neonates with good measures of precision and bias (mean squared error MSE = 0.023 and relative mean prediction error RMPE = 1.471). In comparison to the previously published model [7], the NODE model provided similar data fitting and simulated similar gestational age dependent reference values. Further it was able to identify the most important covariates found in the previously published model. Based on the visualized trajectories in the derivative versus state or time plots, a linear function for the NN characterizing the state, and an Emax function for the NN describing time were chosen. Remarkably, the deduced mechanism-based model had a similar structure as the previously published serum creatinine model [7]. In addition, clinical knowledge was included, i.e., volume of distribution for serum creatinine was assumed to be 7 dL/kg, resulting in the final mechanism-based model with similar measures of precision and bias as the NODE model (MSE = 0.025, RMPE = -2.17). It should be noted that NODE-based ML approach dramatically reduced time effort associated with the development of a mechanism-based model describing serum creatinine dynamics in neonates.

**Conclusions:** A mechanism-based model was successfully deduced from the dynamics learned by the NODE. Structure of the deduced mechanism-based model was in accordance with a previously published, conventionally developed model for serum creatinine concentration in preterm neonates. Hence, we demonstrated the potential that initially learning the dynamics by an NODE is expected to accelerate development of mechanism-based models, particularly in pediatrics.