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Simulation of virtual pharmacometric patient profiles using generative artificial intelligence

Verena Schöning and Felix Hammann

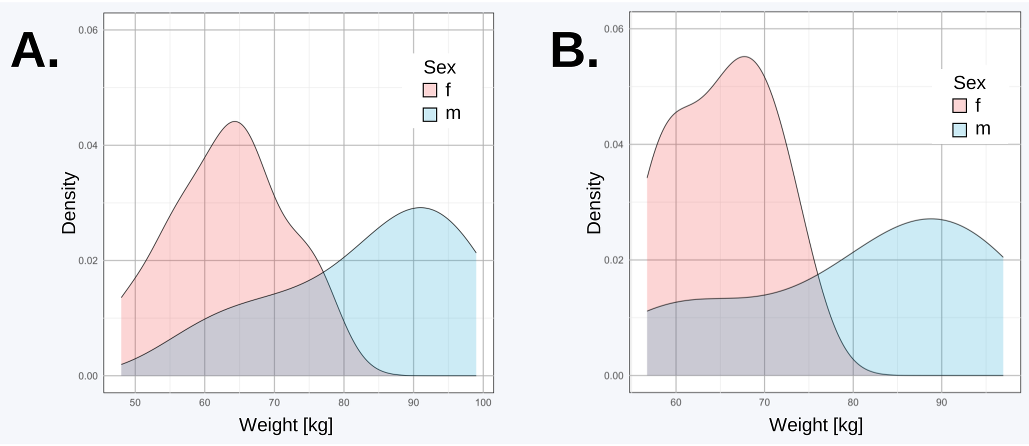
Division of Clinical Pharmacology and Toxicology, Department of General Internal Medicine, Inselspital, Bern University Hospital, Switzerland
Presenting author: verena.schoening@insel.ch, corresponding author: felix.hammann@insel.ch,

Introduction

Non-linear mixed effects (NLME) models simultaneously describe the pharmacokinetic (PK) and -dynamic (PD) data from all patients within a population in a system of ordinary differential equations (ODEs), while also accounting for inter-subject variability and residual error by estimating subject-specific fixed effects (covariates such as sex or weight).[1] The resulting population PK (PopPK) models are an estimated description of the fate of a drug within the body and its effects. Currently, artificial intelligence is not yet widely used in pharmacometrics. One study used **Wasserstein Generative Adversarial Networks (WGANs)**[3] to increase sample size within clinical studies by adding virtual patients.[2] WGANs are powerful machine learning algorithms that are able to learn the underlying probability distribution of a dataset and, based on that, create new artificial data samples.[4,5] A WGAN setup consists of two competing **deep neural network (DNN) sub-models**: a generator and a critic. The generator receives random noise and produces artificial data samples. These generated samples are passed to the critic along with real data samples. The critic evaluates these samples and computes the Wasserstein distance between the two data distributions. The critic's feedback is used to update the generator, which learns to produce data that minimizes the Wasserstein distance. Over time, the generator improves its output, eventually generating new data that is indistinguishable from real data, though not identical to any specific real data observation.

In this study, we aimed to **create virtual patients with covariates** and corresponding **blood concentration curves** based on a relatively small original patient population. While the distribution of the covariates can be compared directly, the accuracy of the concentration curves is compared by modelling of the parameter estimates.

Figure 1: Weight distribution curves (A) original patients (B) artificial patients



Conclusions

WGANs can learn temporal progression of the concentration of the drug in the blood, **covariate distributions**, as well as the **influence of covariates**. The estimated parameters of the original and virtual patient populations are comparable. Due to the small sample size, the estimated parameters deviate from the ground truth in both models. Therefore, generative artificial intelligence **can be used to generate patients with the same underlying statistical distribution** as the original patient population. Future applications could include augmenting data sets from underpowered clinical trials or sparse sampling strategies.

Results

The **distribution of the modeled covariates** (age, height, weight) are comparable between the "original" and virtual patients (Fig 1). Furthermore, the parameter estimates of absorption constant (ka), volume of distribution (Vd), and clearance (Cl), as well as the effect of weight on clearance, are also comparable between the two patient populations (Tab. 1, Fig. 2). However, the **ground truth for these parameters** is different from both populations.

Table 1: Ground truth and estimated PopPK parameters

Fixed Effects	Ground truth	Original	Artificial
ka_{pop}	0.5	0.3	0.3
Vd_{pop}	14	8.4	8.3
Body weight on Vd	0.75	0.4	0.3
Cl_{pop}	5.0	5.0	5.2
Standard Deviation of Random Effects			
ω_{ka}	0.2	0.3	0.4
ω_{Vd}	0.3	0.1	0.2
ω_{Cl}	0.2	0.2	0.2
Error Model Parameters			
Additive	0.2	0.2	0.3
Proportional	0.1	0.1	0.1

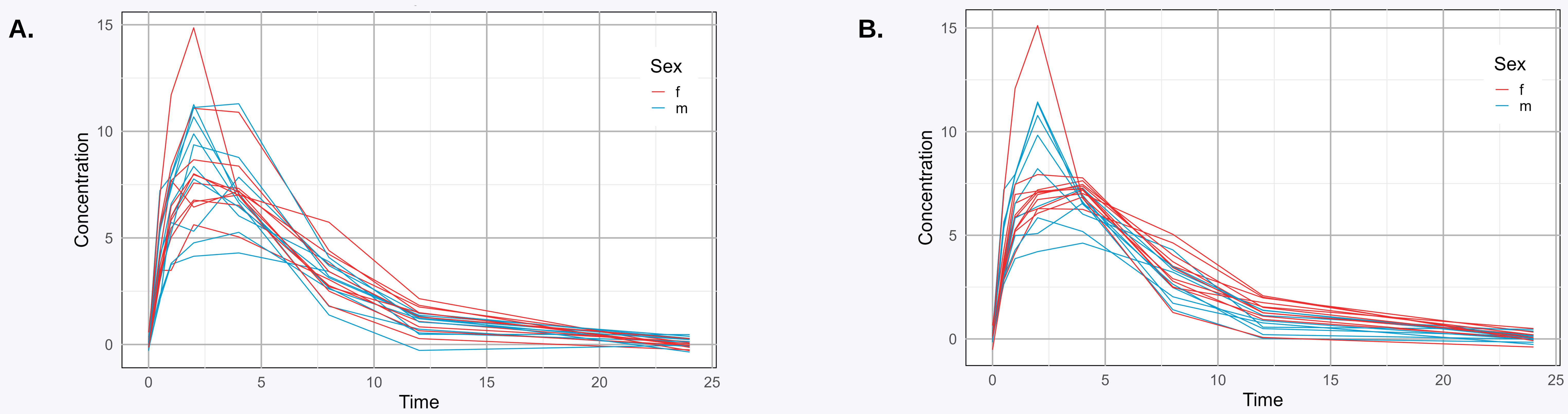


Figure 2: Concentration curves of (A) original patients, (B) artificial patients

Methods

We created a dataset of 20 "original" patients (10 males, 10 females) with a random age and sex-specific, normally distributed height and weight. We simulated blood concentrations after extravascular administration of a hypothetical drug with **first order absorption, one compartment distribution and linear elimination** (ground truth). Weight was set as a covariate for volume of distribution (Vd). Virtual patients were generated by **WGAN with gradient penalty** (GP)[6] (Fig. 3). We estimated and compared the ground truth with the parameter estimates for the "original" and virtual patient population using Monolix (2021R1, Lixoft, Anthony, France).

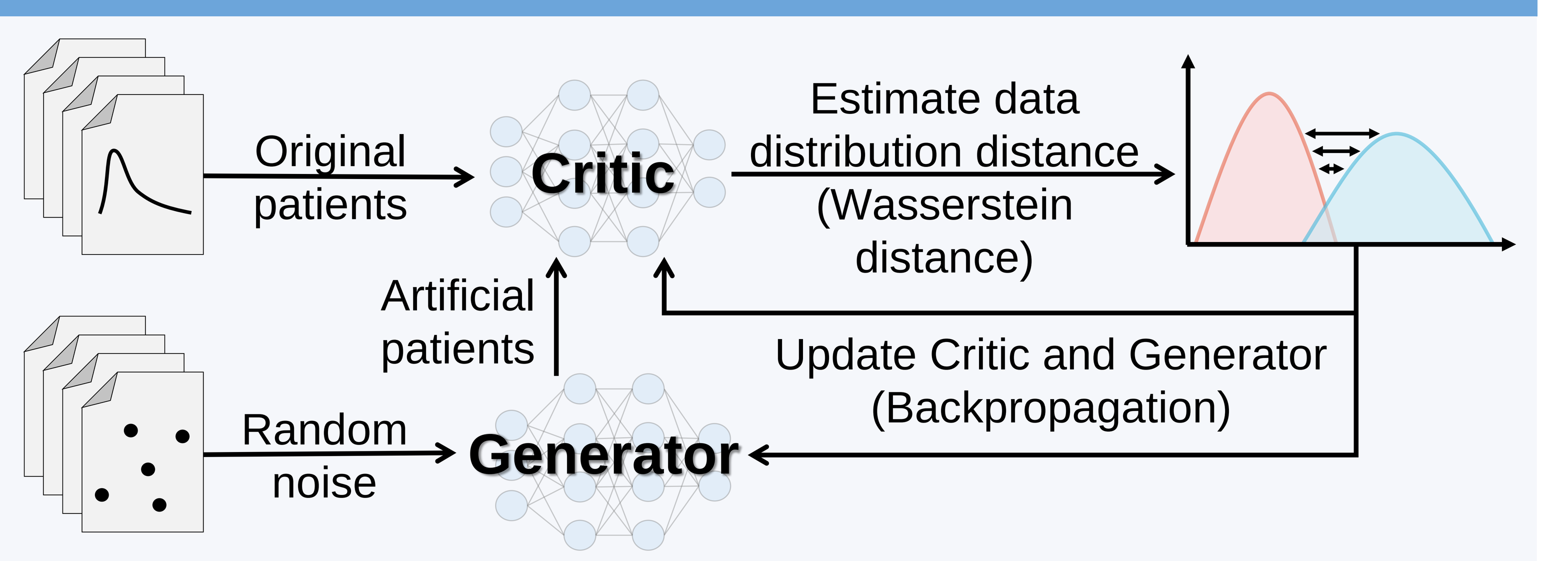


Figure 3: General WGAN-GP workflow

References: (1) Nguyen (2017) CPT: Pharmacometrics & Systems Pharmacology, 6(2): 87. (2) Nikolopoulos (2024) Applied Sciences, 14(11): 4570. (3) Arjovsky (2017) Proceedings of the 34th International Conference on Machine Learning, PMLR: Proceedings of Machine Learning Research: 214. (4) Goodfellow (2020) Commun. ACM, 63(11): 139. (5) Goodfellow (2014) Proceedings of the 27th International Conference on Neural Information Processing Systems - Volume 2, MIT Press: Montreal, Canada: 2672. (6) Gulrajani (2017) Advances in neural information processing systems: 30.