Generation and Application of Avatars (Digital Twins) in Pharmacometric Modelling

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Objectives

The concept of Avatars or Digital Twins is well established in health, engineering, and systems biology. It is the creation of a digital representation of a physical or a biological system in order to explore and control its behaviour [1,2]. In this work we aim to explore aspects of **generating and utilizing avatars** for pharmacometric population models, accounting for clinical interests. We use a neutropenia model as example.

Material

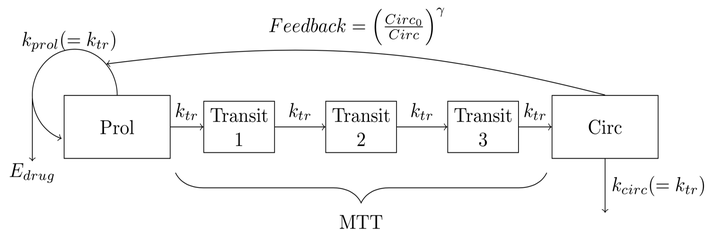

*Figure 1: **Pharmacodynamic model** describing the **neutrophils** count[3].*

- Data (fig. 2): 3553 observation for 601 individuals (ID).
- NONMEM v7.3.0 and R v3.3.0 were used for the simulations (n=10000 unless stated otherwise) and the selection process.

Methods: Steps in avatar generation and use

1. Clinical relevance

Select clinically relevant criteria where the simulated individuals (avatars) should match the real patient. For example:

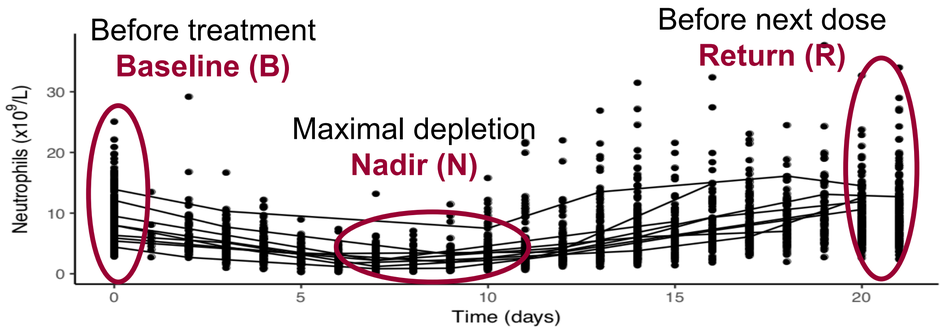

*Figure 2: **Clinically relevant markers** of neutrophil count.*

2. Closeness vs observed data

The error margin between observed and simulated data will define the **accuracy of agreement**. Stringent criteria will produce more accurate avatars but be more difficult to satisfy.

Table 1: Impact of the accuracy of agreement on the percentage of ID with at least 1 avatar according to different combinations of relevant criteria.

	Error margin			
Criteria	**10%**	**20%**	**30%**	**50%**
NADIR (N)	98.6	100	100	100
Baseline and NADIR (BN)	97.1	99.1	99.7	99.8
Baseline and NADIR and Return (BNR)	64.0	90.5	96.7	98.5

3. Number of avatars per ID

For a given error margin, the number of simulations will impact the number of ID without any avatars.

Figure 3: Impact of the number of simulations on the number of subjects without any avatars for BNR. Numbers are percentages of ID.

Results and Discussion

Avatars for population models are a **subset of simulated individuals** based on their **closeness to the clinically relevant criteria.**

What this type of avatar may be used for:

1. Additional assurance that **clinically relevant profiles** are generated in the simulations (fig. 4)

2. **Refined clinical trial simulations** agreeing with the model but also with observed clinical endpoints (fig. 4)

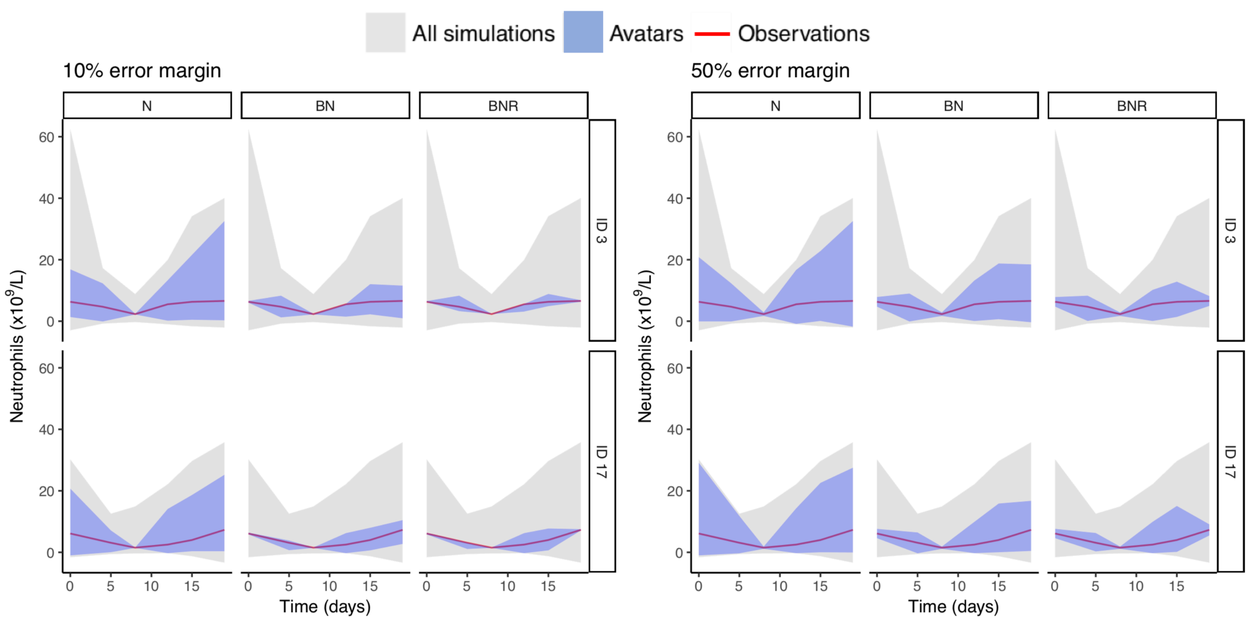

Figure 4: Individual avatars versus all the individual simulations.

3. The frequency of avatars is a measure of **subject uniqueness** for a given model - difficulty to generate avatars could indicate that the subject is “unusual” according **diagnostic** to the model and be a warning for model-based dose adjustment in therapeutic individualization

4. **Model :** comparing parameter distributions (fig. 5)

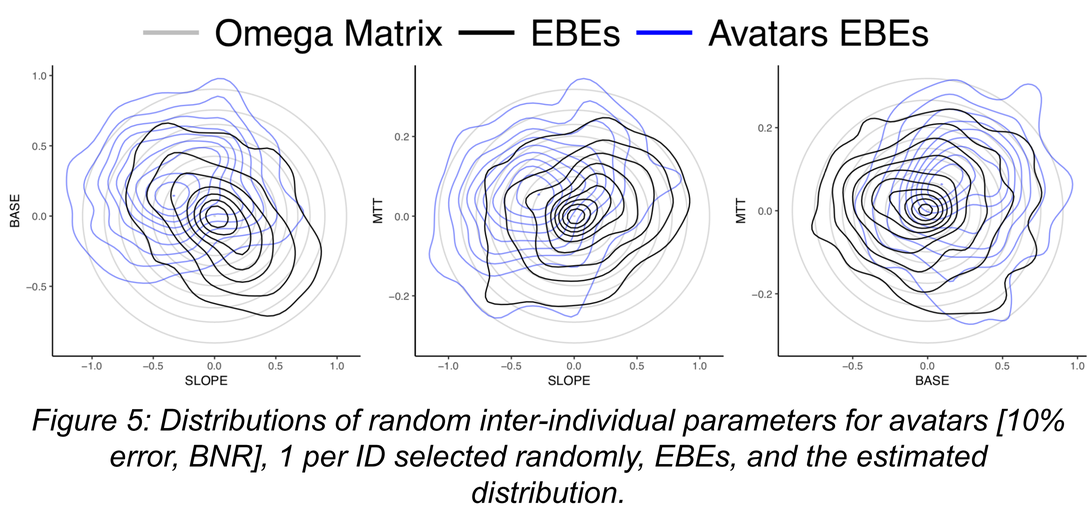

Figure 5: Distributions of random inter-individual parameters for avatars [10% error, BNR], 1 per ID selected randomly, EBEs, and the estimated distribution.

5. Multi-variable simulations that assure **agreement** with data not only variable by variable but also **across variables**

Conclusions

- **Many potential uses** for pharmacometric model avatars
- We developed a **method to generate clinically relevant avatars** for population PK/PD models
- A **dynamic simulation method**, that stop simulating an ID when the desired number of avatars has been reached, would be more efficient and is being tested

[1]Parrott, A. & Lane, W. Industry 4.0 and the digital twin. Deloitte University Press (2017). 11‘Grand.’ Webster’s Third New International Dictionary, Unabridged. 2018. Web. 18 Feb. 2018.
[2]Spanakis, M., Spanakis, E., G., Kafetzopoulos, D., Sakkalis, V., Tsiknakis, M., Marias, K., Dong, F. (2015). MyHealth Avatar with the generated virtual profiles from clinical trials. Poster presented at the PAGE (Population Approach Group of Europe) conference of 2015.
[3]Friberg, L. E., Henningsson, A., Maas, H., Nguyen, L., & Karlsson, M. O. (2002). Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. *Journal of clinical oncology*, *20*(24), 4713-4721.