

Visual Predictive Check (VPC) in models with Forcing Functions

INTRODUCTION

BACKGROUND

Visual predictive check (VPC) [1] is a commonly used tool to evaluate the performance of PK and PKPD models. However this diagnostic tool presents some pitfalls in the simulation step when **models with forcing functions (FF)** are evaluated. In fact in this case there is a **mismatch between each set of simulated parameters and the associated individual FF** which can cause an incorrect profile simulation. Models with FF are commonly used in the metabolic field because the physiology that they explain is really complex and so are the models. In these cases it is preferable to use a FF rather than adding another level of complexity to the model by estimating it.

AIM

This study aims to overcome this VPC limitation by taking into account in the simulation step a **correlation term** that bounds the set of simulated parameters with the most appropriate FF. We assessed the technique on four nonlinear models that present one or two FFs: the IVGTT and the ORAL glucose and C-peptide minimal models (MM) [2-3-4-5]. Here the oral glucose MM results are shown since this model with respect to the others three presents two independent FFs with the highest variability.

METHODS

DATABASE

A mixed meal (10 kcal/kg, 45% carbohydrate, 15% protein and 40% fat) containing 1 0.02 g/kg glucose was administered to **120 nondiabetic subjects** (71 males and 49 females age 62 17.5 and bodyweight 79.2 13.5 kg). Plasma samples were collected at -120, -30, -20, -10, 0, 5 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, 240, 260, 280, 300, 360, 420 min and plasma glucose, insulin and c-peptide samples were measured. A **simulated dataset A** of 120 individuals was generated adding measurement noise equal to the 2% of the simulated concentrations to the profiles obtained using NONMEM individual estimates considered as true.

ORAL GLUCOSE MINIMAL MODEL

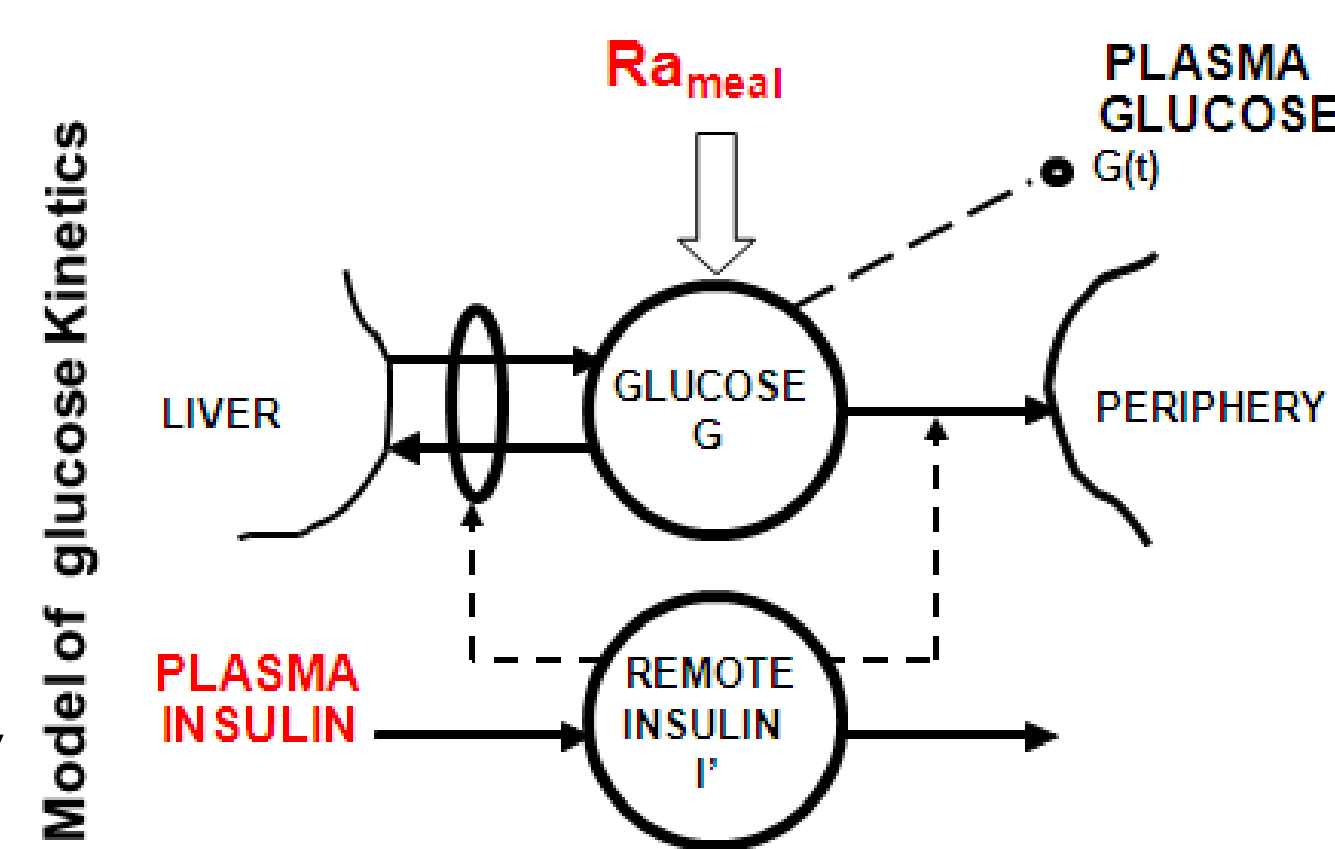
The **oral glucose minimal model (OMM)** has two independent FFs: the **insulin** and the **rate of appearance** (Eq. 1). The general formulation of the OMM model is the following:

$$\begin{cases} \dot{Q}(t) = -(S_G + X(t)) \cdot Q(t) + S_G \cdot Q_b + \mathbf{Ra}(t) & Q(0) = G_b \cdot V \\ \dot{X}(t) = -p_2 \cdot X(t) + p_2 \cdot S_I \cdot (\mathbf{I}(t) - I_b) & X(0) = 0 \end{cases} \quad (\text{Eq. 1})$$

$$\mathbf{p} = [S_G, S_I, V, p_2]$$

$$\mathbf{FFs} = [\mathbf{Ra}, \mathbf{I}]$$

where Q is the glucose mass in plasma and Q_b its basal value, G_b is the basal glucose concentration in plasma, I is insulin plasma concentration and I_b its basal value, X is insulin action, Ra is the glucose rate of appearance in plasma, V is the volume of distribution, S_G is the glucose effectiveness, S_I is the insulin sensitivity and p_2 is the insulin action parameter.



THE VPC IN PRESENCE OF FF IN THE MODEL

To introduce the correlation term in the simulation step of the VPC, we calculated for each set of simulated parameters (SIM) both the **normalized euclidean distance (NED)** and the **Mahalanobis distance (MD)** between the SIM and the previously estimated parameters (EST). This helped us to find the vector of EST parameters that was closer to SIM and consequently to match the EST corresponding FF to the SIM parameters in the simulation step. The estimation step was carried out using **NONMEM VII** whereas the simulation step was done with **Matlab**.

RESULTS

The FFs used in the four metabolic models that are assessed in this study exhibit a **large inter-individual variability**. In Figure 1 are presented the median and the 5% and the 95% percentiles of the two FFs of the glucose oral MM: insulin and the glucose rate of appearance.

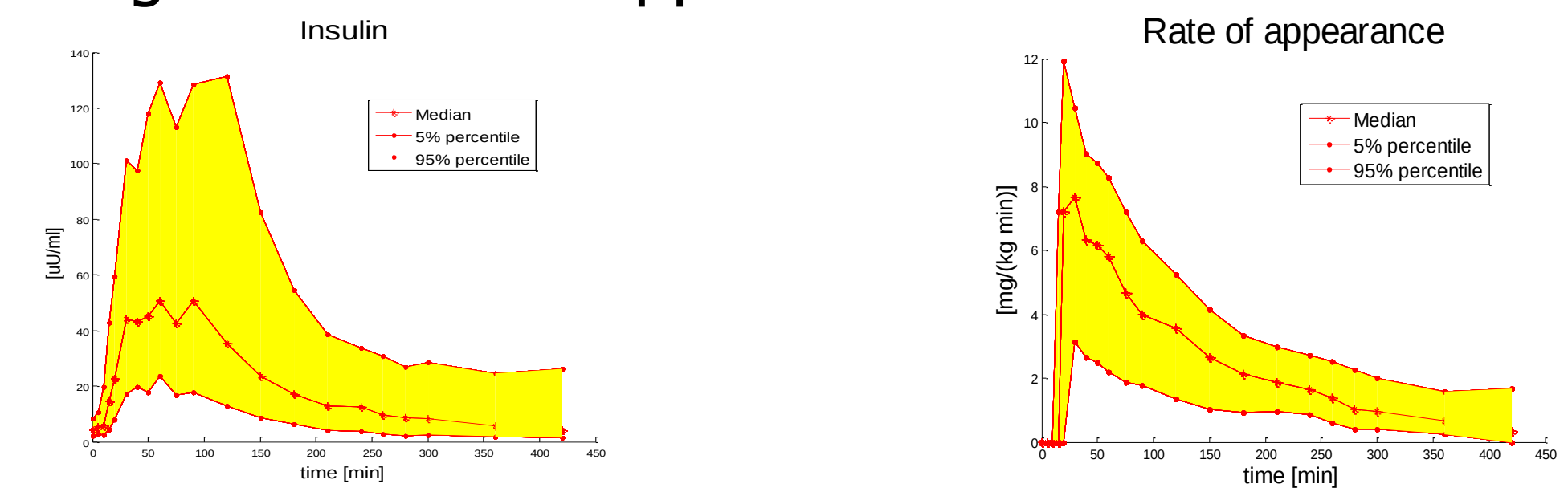


Figure 1. Median and 5% and 95% percentiles of Insulin and Rate of appearance of glucose.

If the VPC is applied, the FFs large inter-individual variability can cause a **significant mismatch** between each set of simulated parameters and the associated individual FF that leads to a wrong simulation and so to wrong conclusions about the model capability of explaining the variability in the data. In figure 2 is presented the VPC of the oral glucose MM.

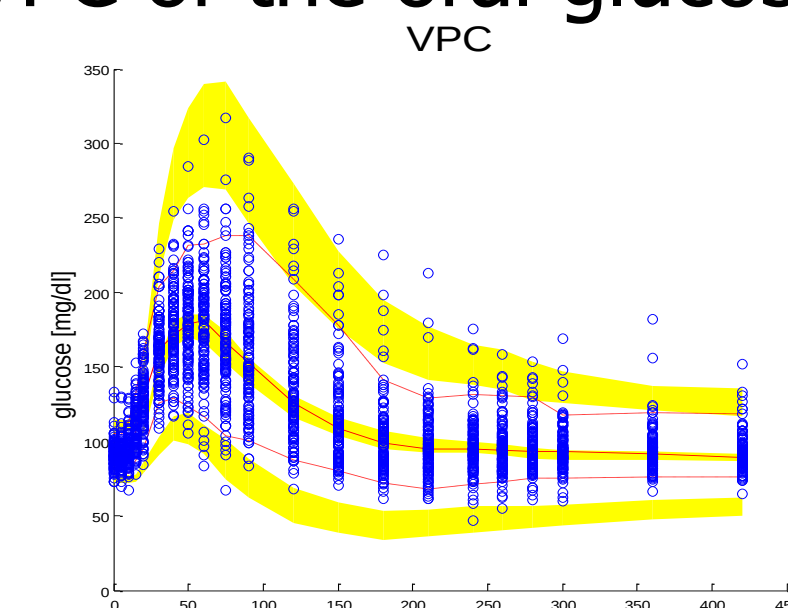


Figure 2. The "classical" VPC

By taking into account a **correlation term** the VPC improves significantly. In particular we used both the **NED** and the **MD**. Taking into account the covariance terms, as it is done in the MD, does not improve the results significantly (Figure 3).

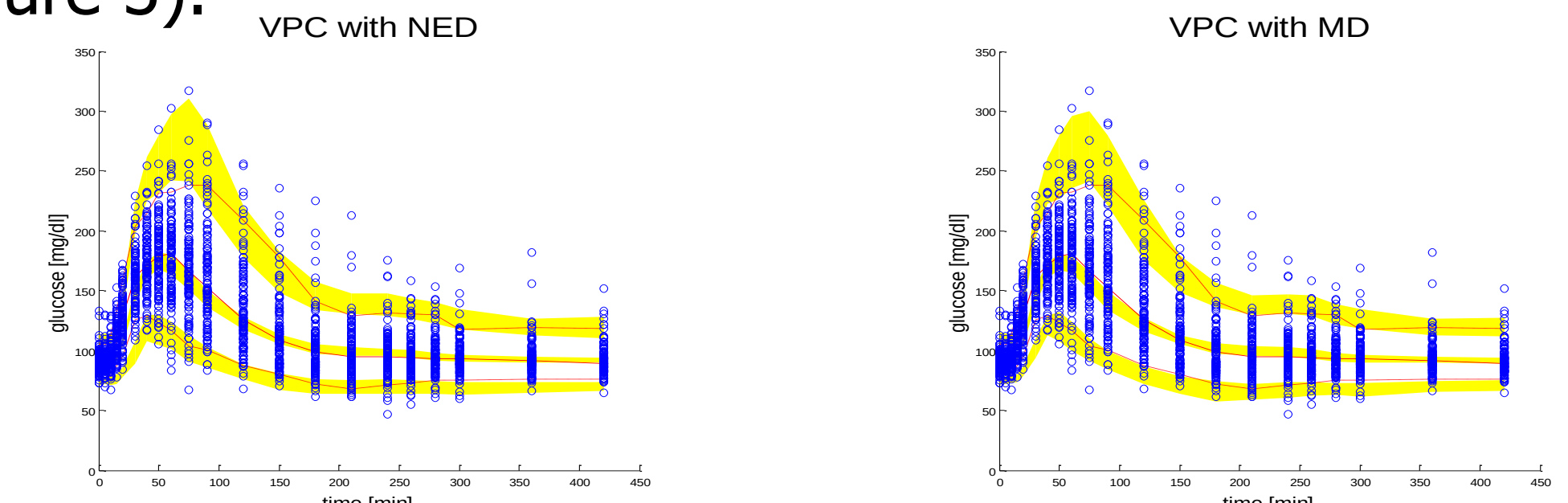


Figure 3. The VPC with the NED and MD.

The analysis was repeated on an **individually simulated dataset A** in order to be sure about the correctness of the estimates and evaluate then just the method performance (Figure 4).

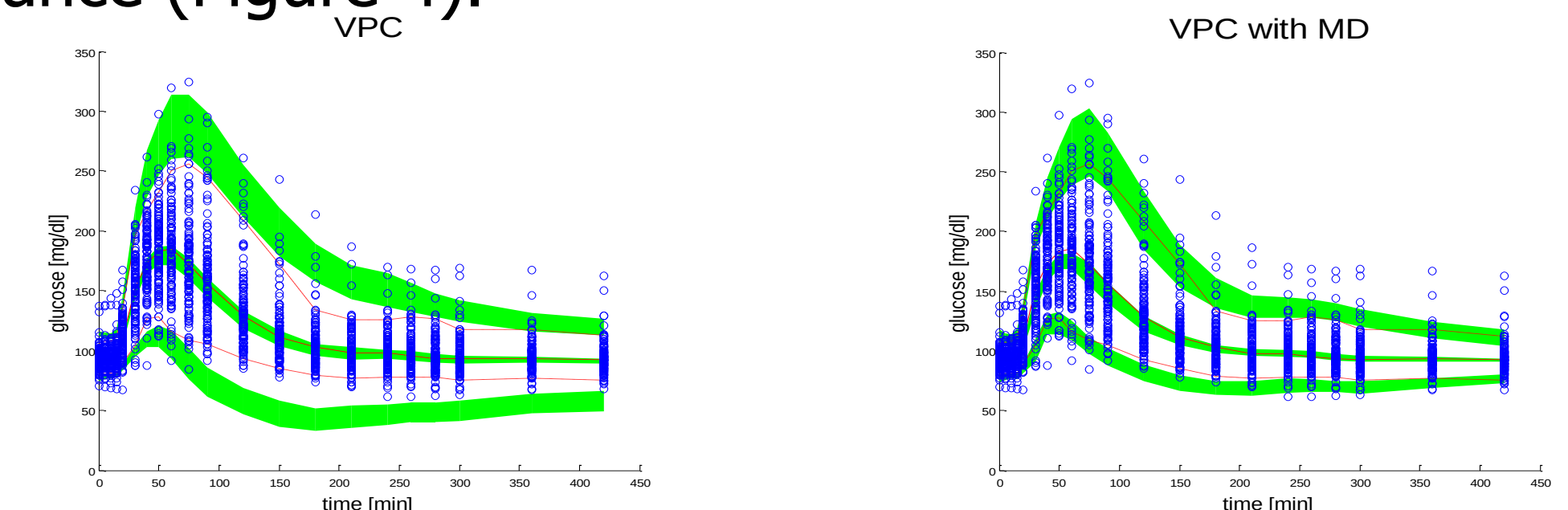


Figure 4. The "classical" VPC vs the VPC with MD in the simulated dataset A.

Finally we suppose to be in case of a **low FF variability** that is a common situation in PK/PD experiments. Before applying the MD we applied a clustering analysis to detect the most important FF kinetics that are used to simulate a new dataset whose parameters are estimated, then the MD is applied. The **VPC improves further** since there is no error in the association of FF with the set of SIM (Figure 5).

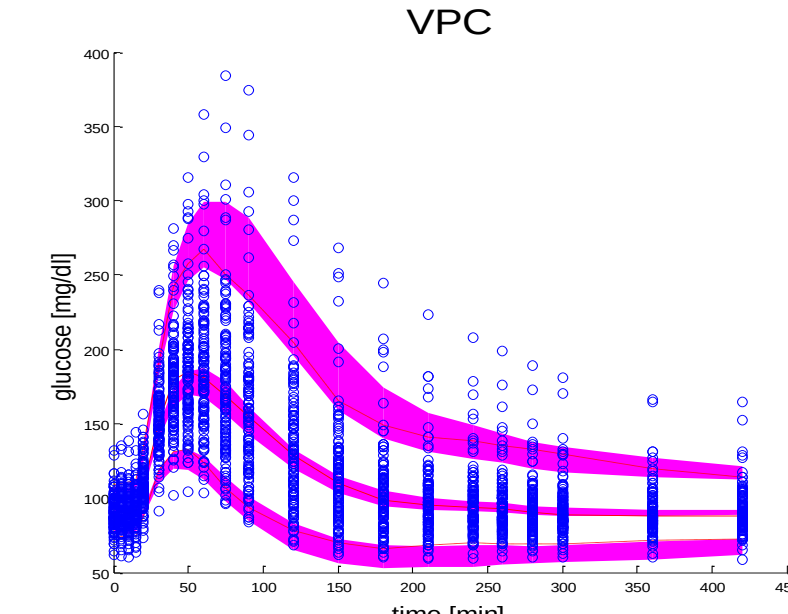


Figure 5. The VPC with MD in a simulated dataset obtained using a clustering analysis.

CONCLUSIONS

This work proposes a refinement of the simulated based diagnostic VPC which is relevant for a particular subset of models. Despite the simplicity of the method, the results show an evident improvement of VPC that it translates into a correct evaluation of models with FF.

REFERENCES

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