

Effect of weight and age in drug dosing

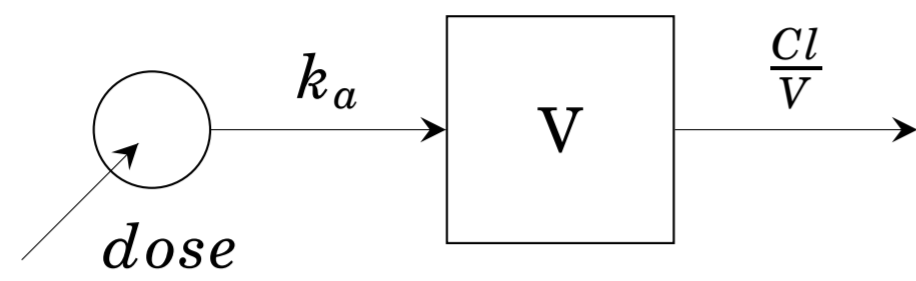
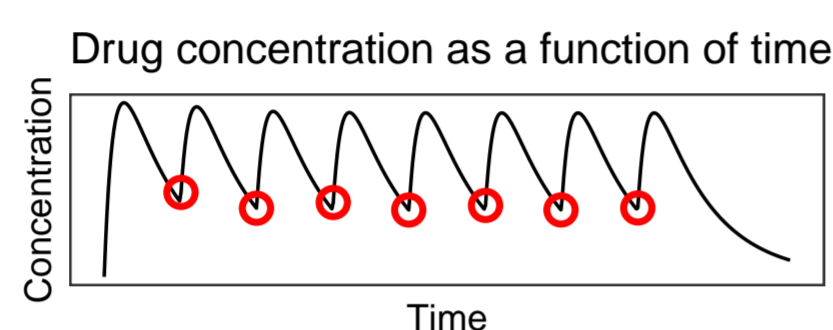


Figure 1: Linear one compartment pharmacokinetic model with first order absorption is sufficient for steady-state kinetics as often only collected. The model consists of three patient dependent parameters:

Absorption (k_a): How fast drug goes to the body from stomach.

Volume (V): Apparent volume of the central compartment.

Clearance over volume $\frac{Cl}{V}$: How fast the body gets rid of the drug.



- Adult PK model is used to extrapolate to pediatric population and define an adjusted dosing regimen which maintains drug concentration in the target therapeutic window.

- Clearance of individuals is modeled in presence of age-dependent effects as (and similarly for volume)

$$\log(Cl_i) = \log(Cl_{ref}) + A(\text{weight}_i) + M(\text{age}_i) + \eta_i.$$

- Population average, Cl_{ref} , is used for the average effect.

- **Allometric scaling**, $A(\text{weight}_i)$, is used to take weight into account.

- **Kids are not small adults**, organs are not fully developed. Especially clearance, which affects dosing, may have **additional age dependent maturation effect**, $M(\text{age}_i)$, which may have not been considered during prospective planning of pediatric trial.

Can we detect a deviation from the adult extrapolation model with the collected sparse pediatric data which may lead to dose regimen adjustments?

Modeling maturation effect with Gaussian Processes

- Pediatric data is very sparse due to ethical and operational constraints.

- Some authors propose learning the maturation effect with parametric functions. These methods are never derived from the first principles and make extra assumptions about the shape of the maturation.

- We propose setting a zero mean Gaussian Process (GP) prior on the maturation effect, $M(\text{age}) = f$.

Here $f \sim \text{GP}(\mathbf{0}, \mathbf{K})$, and $\mathbf{K}_{i,j} = k_{\text{squared_exp}}(\log(\text{age}_i), \log(\text{age}_j)) * k_{\text{linear}}(\log(\text{age}_i), \log(\text{age}_j))$ is a combination of squared exponential and linear covariance functions.

- It is known a-priori, that the younger the patient is, the smaller the maturation effect, meaning that **the maturation of log clearance is monotonic**. Using Riihimäki and Vehtari (2010), the monotonicity can be taken into account to better accommodate data sparsity.

Results

The ground truth which was used to generate the data is shown in red, true individual (maturation) parameters of patients shown as red dots and the maturation detected by GP is shown in blue as median, 68.27 and 98.45 posterior predictive intervals.

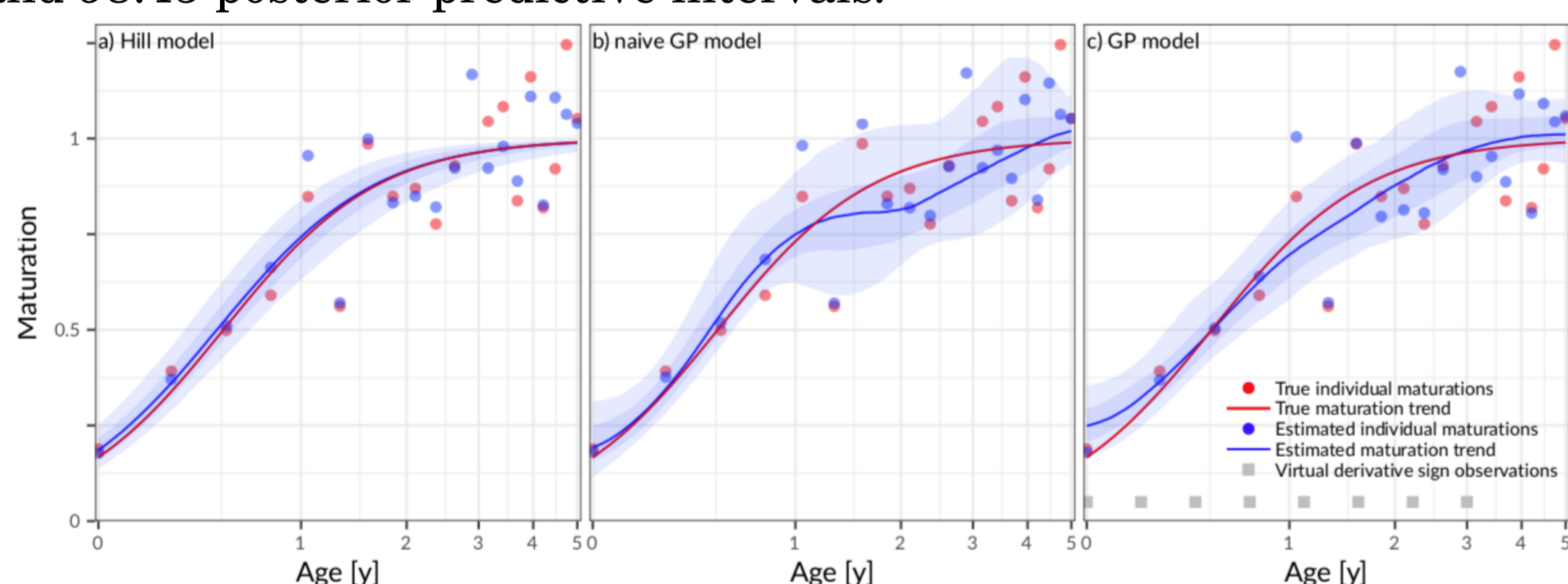


Figure 2: Maturation effect, signal case

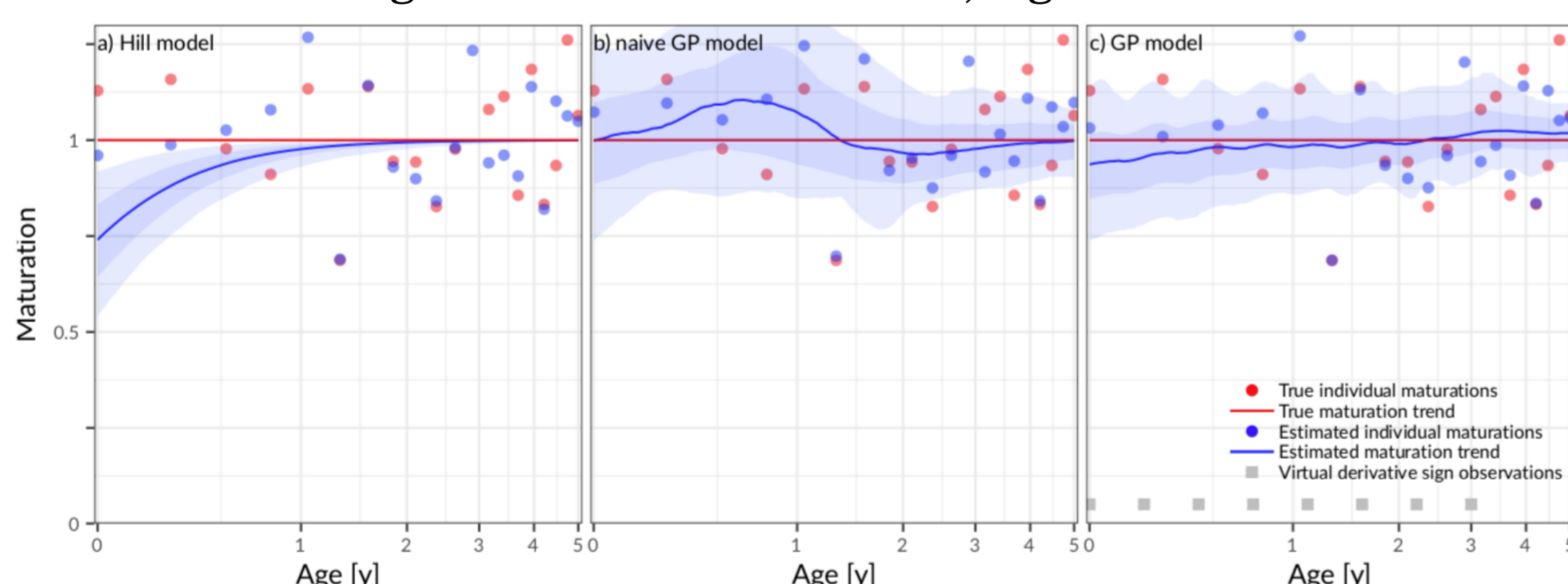


Figure 3: No maturation effect, no signal case

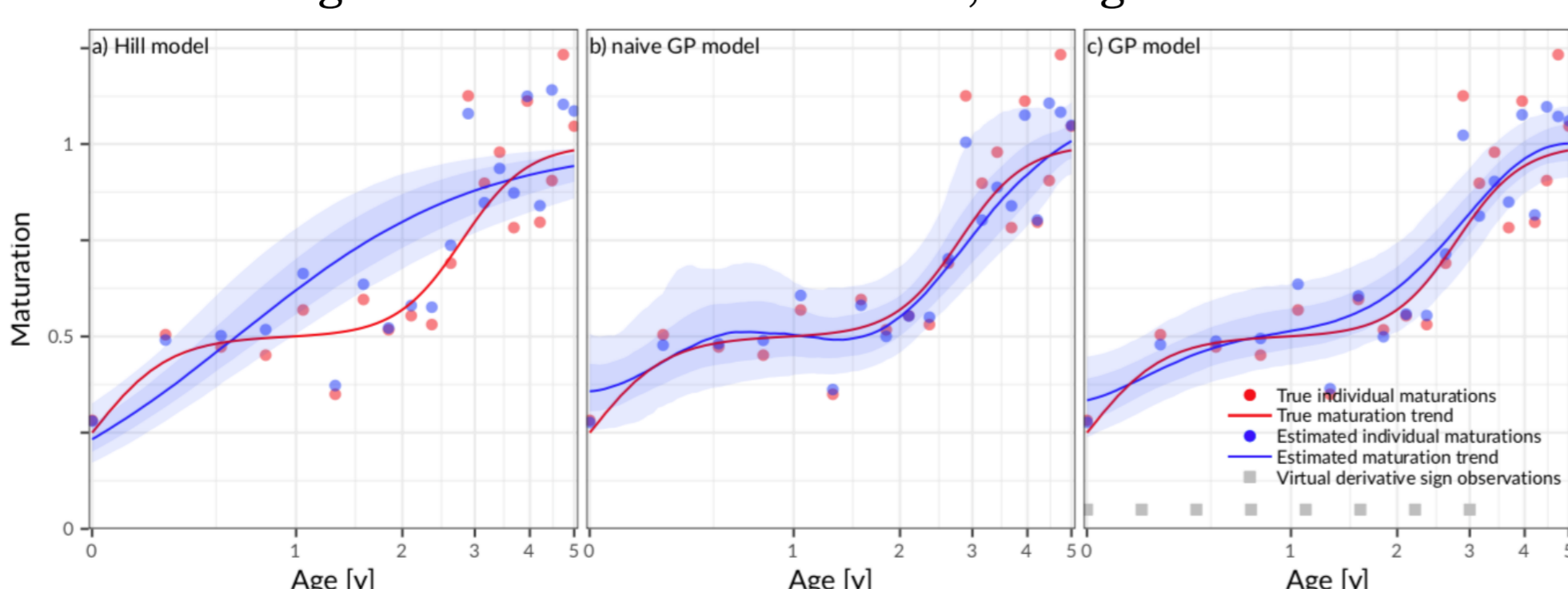


Figure 4: Double hill type maturation effect, double signal case

Simulation: Signal, No Signal & Double Signal

- We simulate 20 patients between 0 to 5 years old and assume a design which collects 10 trough concentration per patient.

- The assumed adult dosing regimen for 75kg is set to a loading dose of 1500 mg and then 10 maintenance doses of 10 mg once daily.

- For assigning doses to the pediatric patients, the adult model with standard allometric scaling only ($A(\text{weight}_i) = \alpha \log\left(\frac{\text{weight}_i}{75 \text{ kg}}\right)$, $\alpha = \frac{3}{4}$ for clearance and $\alpha = 1$ for volume) is assumed to be correct in all scenarios. Thus, the administered doses are weight adjusted using standard allometric scaling to attain the same steady-state as a 75kg adult.

- Standard population curves were used for conversion of age to weight.

- We simulate 3 scenarios with different maturation function $M(\text{age}_i)$:

Signal case: Hill type maturation, $M(\text{age}_i) = \log\left(\frac{\text{age}_i^h}{K_{age}^h + \text{age}_i^h}\right)$, with $h = 2.94$ and $K_{age} = 1.21$ years.

No signal case: No maturation, $M(\text{age}_i) = 0$.

Double signal case: Double Hill type maturation equally weighted, $K_{age,1} = 0.7$ years, $h_1 = 6$, $K_{age,2} = 3.5$ years and $h_2 = 7$.

- $Cl_{ref} = 0.58$ l/h and $V_{ref} = 10$ l

- A moderate variability of $\omega_V = 0.21$ and $\omega_{CL} = 0.21$ was used

- We analyze the pediatric data with 3 models: (a) with parametric Hill maturation, (b) naive GP without monotonicity constraints and (c) GP with monotonicity prior

Conclusion

- A non-parametric approach, the Gaussian Process (GP), is able to detect maturation effects from sparse pediatric data.

- The monotonicity prior assumption can improve precision of posterior estimates.

- The use of a GP avoids bias as no prior function shape is assumed and prevents overfitting through a-priori smoothness constraints.