A NOVEL APPROACH TO ESTIMATE ONTOGENIES FOR PBPK APPLICATIONS – FROM LITERATURE DATA TO SIMULATIONS

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Objectives

Application of physiologically based pharmacokinetic (PBPK) modelling in pediatric and geriatric populations requires a detailed understanding of age-dependent physiological processes (ontogenies). Important examples include the expression of certain proteins (e.g. plasma proteins, metabolic enzymes or transporters) or functional measures (e.g. glomerular filtration rate). The aim of this study was to develop a novel approach informed by ontogenetic information from literature that allows
(1) to cover the complete age range (including maturation and ageing) with one generic ontogeny function and
(2) to integrate individual and aggregated (e.g. mean and standard deviation) data.
Resulting ontogenies will be populated in PK-Sim® as part of the Open Systems Pharmacology (OSP) suite [1].

Methods

Combining aggregated and individual data

Markov Chain Monte Carlo (MCMC) methods, which allow the usage of aggregated data in combination with individual data, are used to estimate the parameters of a function describing the typical course of the ontogeny as well as the variability around it.
For each aggregated data point a set of virtual individual data points with the following properties is generated
- Age uniformly distributed in reported range
- Measurements log-normally distributed based on reported aggregated data.

The resulting simulated data points are combined with the originally reported individual data points to constitute the analysis dataset. This procedure is repeated 1000 times and for each analysis dataset one MCMC run is performed. Finally, all MCMC chains are combined to obtain the posterior distribution. The posterior distribution allows an assessment of the general trend of the ontogeny, its population variability and parameter uncertainty.
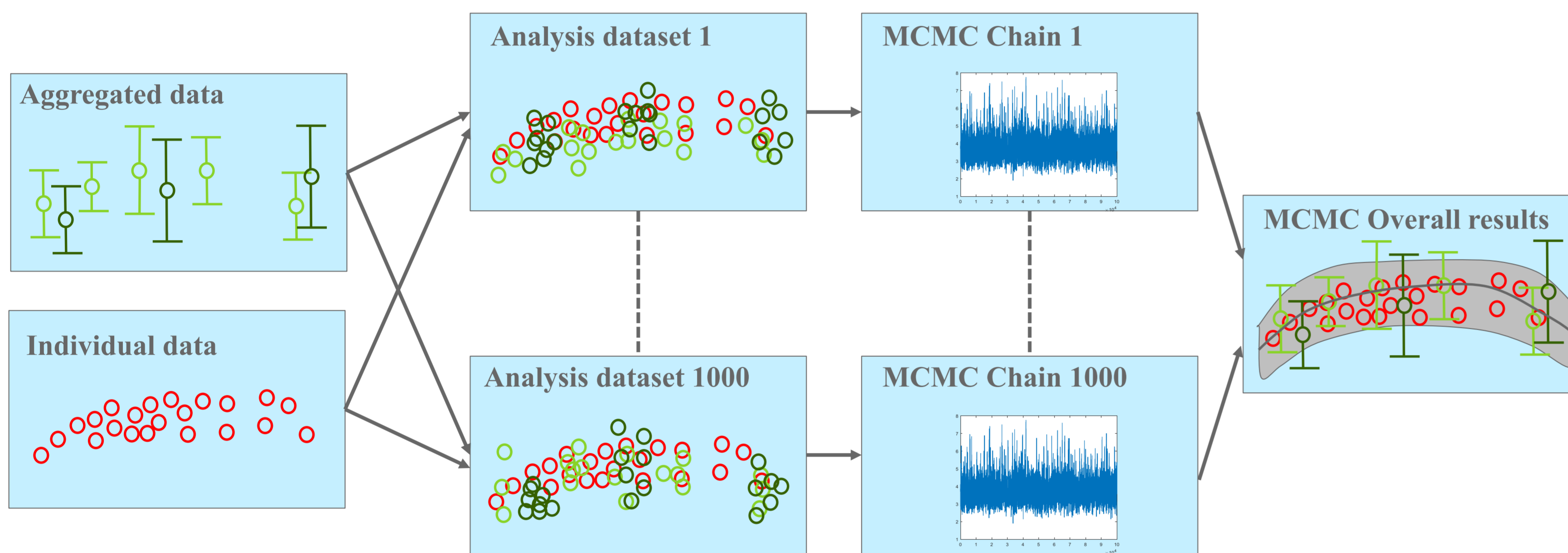
Figure 1: Schematic representation of the workflow for using aggregated and individual data simultaneously.

Functional approach

The typical course of the ontogeny is described using a piecewise defined function in combination with a flexible estimation of the transition points between the different pieces. The pieces are connected in such a way that the function is continuously differentiable at each point. As default there are three parts:
- The first one describes an increase during the maturation phase similar to a Hill function,
- the second one refers to a constant level in (healthy) adults and
- the third one describes a decrease during ageing similar to a Hill function.

All parameters of this function have a biological meaning such as the time indicating the end of maturation or the maximal level reached in adults. The variability may be modelled in an age-dependent manner making use of the continuously differentiable function.
This function can be extended by including further pieces describing additional phases of increase or decrease.

Applications

Based on the results of the MCMCs the relevant quantities can be simulated in future applications taking into account the age of the simulated individual as well as variability and uncertainty for this particular age. As a first feasibility assessment the approach was applied to learn ontogenies for alpha-acid glycoprotein (AAG), Human Serum Albumin (HSA) and Hematocrit (HCT). In cases of differences with respect to gender or ethnicity separate ontogenies are fitted for each subgroup.

Results

A general applicability of the proposed approach with its flexible properties was demonstrated by an application to AAG, HSA and HCT (Fig. 2 and 3). For example, the following properties shown in the data could be well described: there is no age-dependent decline for AAG, HSA levels in men are elevated compared to those in women and the decline of HCT levels in elderly is more pronounced for men than for women. The ontogenies for the plasma proteins HSA and AAG can be qualified by a comparison of measured and predicted fraction unbound values in children and adults.
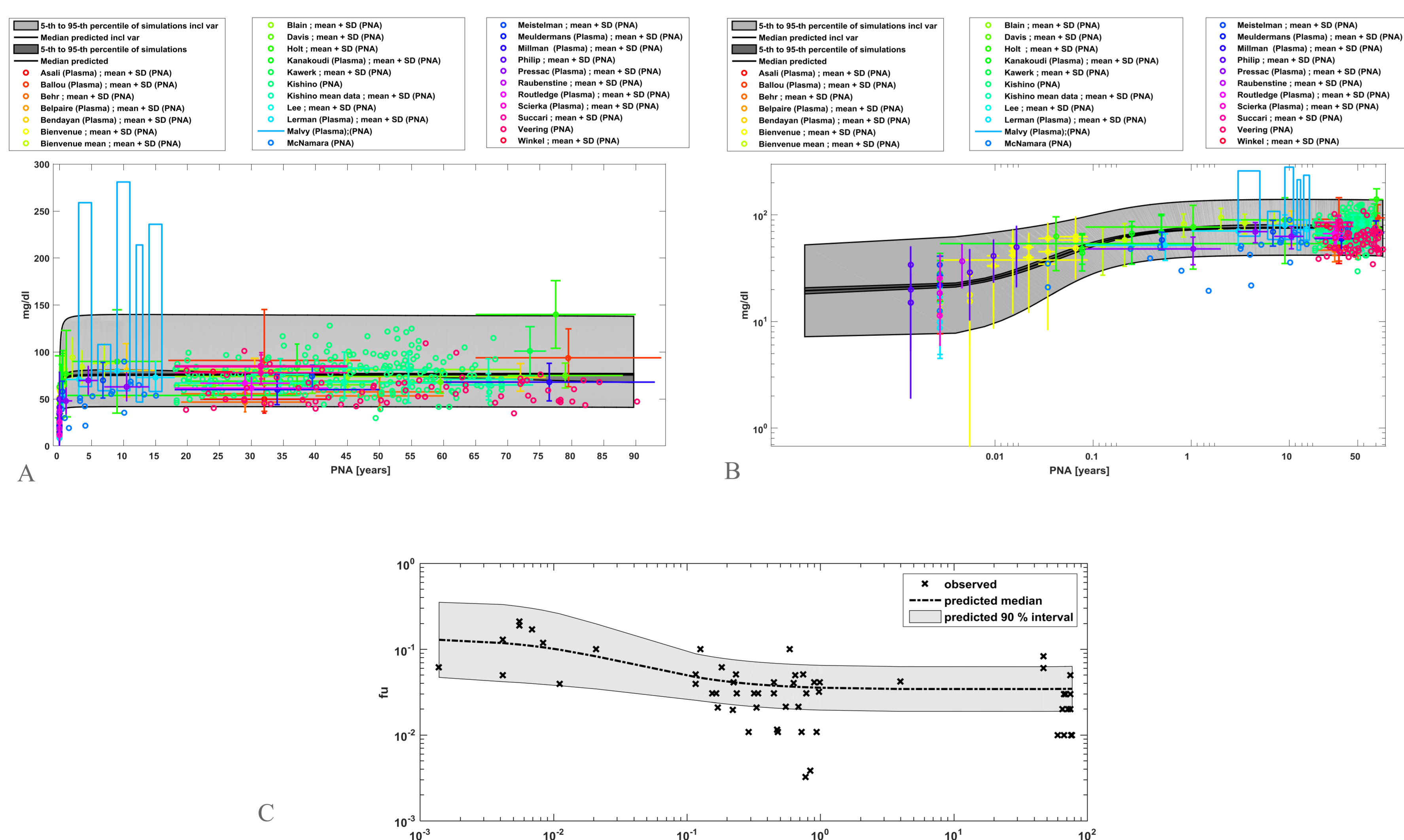
Figure 2: Ontogeny for AAG based on 1000 MCMC runs and informed by literature data on a linear scale (A) and a double logarithmic scale (B). The graphs show the uncertainty of the median as well as 90 % prediction range including variability. (C) Comparison of measured and predicted fraction unbound is shown for qualification.
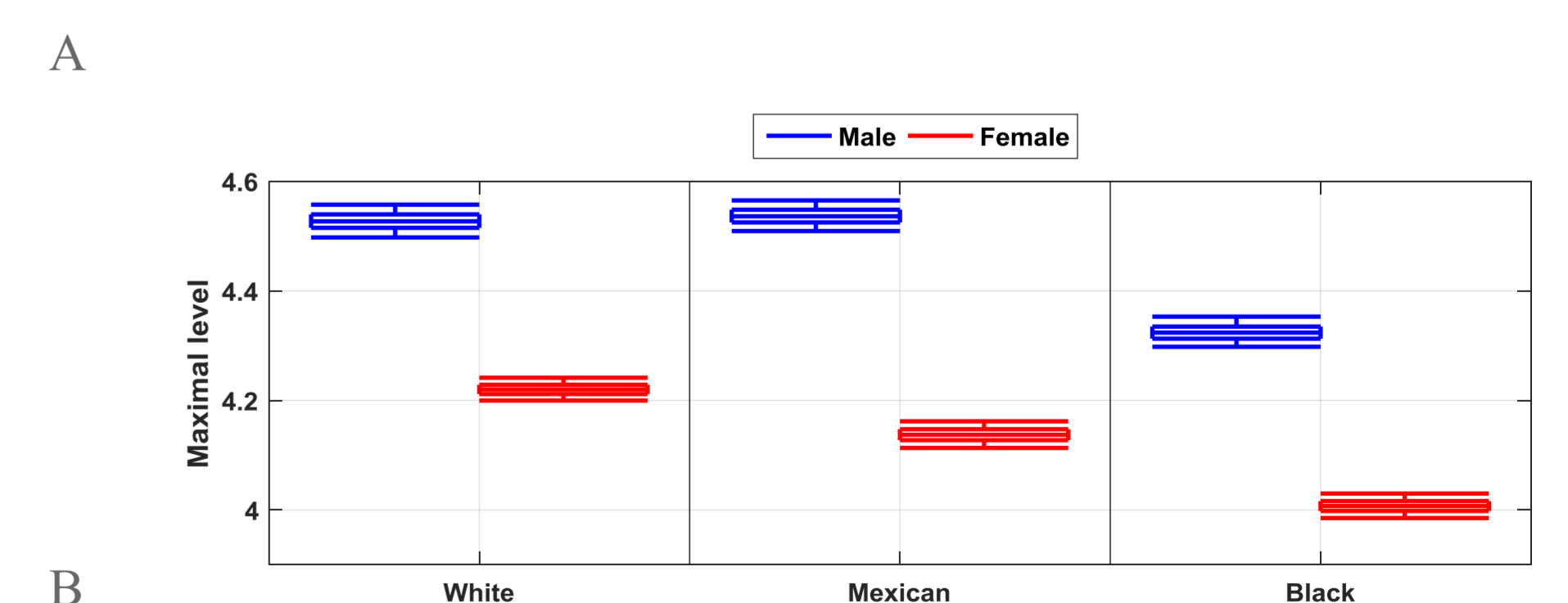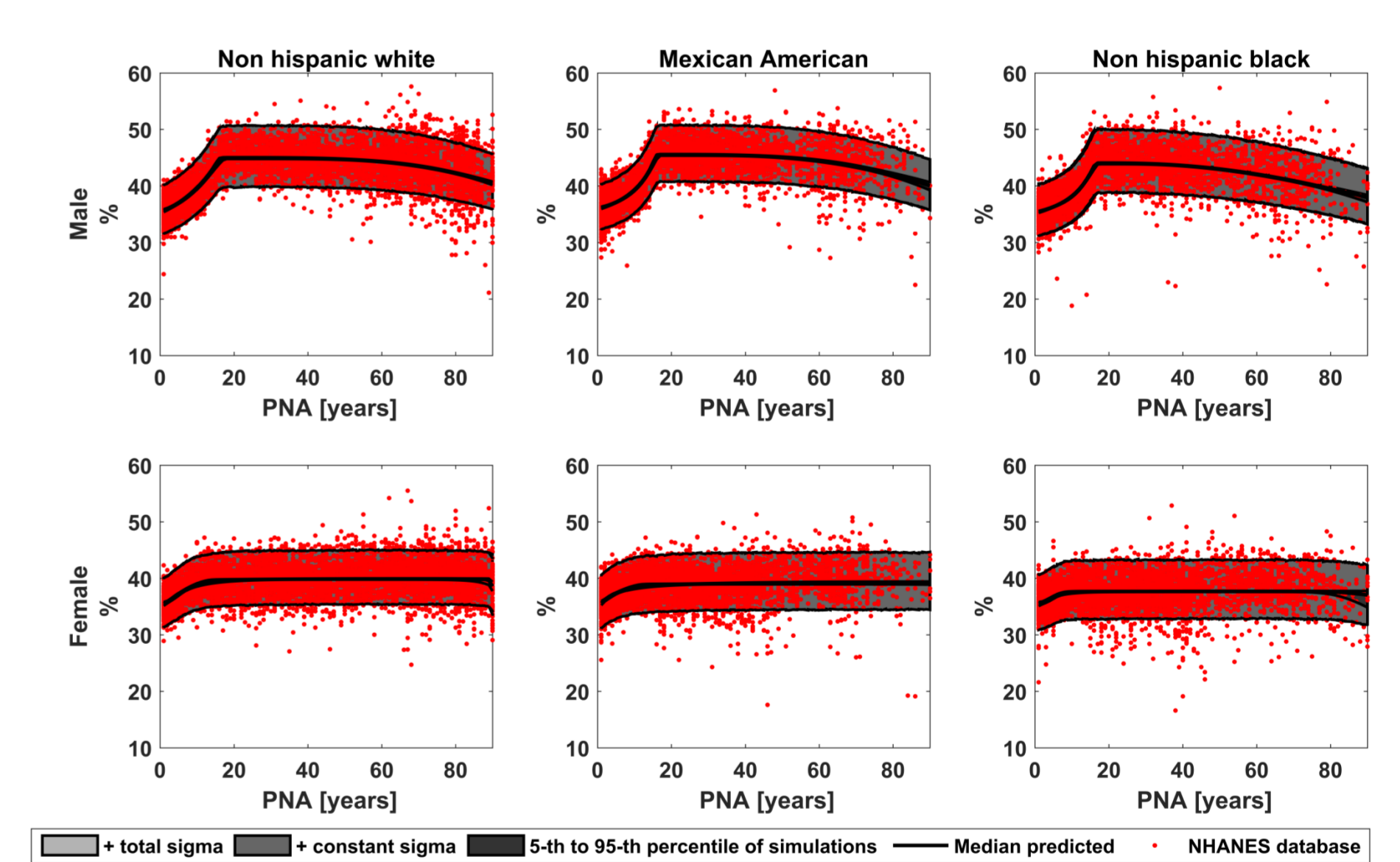
Figure 3: (A) Resulting ontogenies for HCT based on NHANES data (only subjects older than one year) split by gender and ethnicity. (B) Boxplots showing the posterior distribution of the parameter representing the maximal level for ALB.

Conclusion

The newly developed approach can adequately describe ontogenies over the complete age range and reflects the observed variability. It comprises a hill-function-like increase during the maturation phase and a hill-function-like decrease during the ageing phase. This approach could be applied to derive ontogenies for PBPK applications in pediatric and geriatric populations.

References

[1] http://www.open-systems-pharmacology.org/

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