PopPK and Bayesian Review

### “Population pharmacokinetics and Bayesian estimation of cyclosporine in a Tunisian population of hematopoietic stem cell transplant recipient”

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| Eljebari, Hanene, et al. "Population pharmacokinetics and Bayesian estimation of cyclosporine in a Tunisian population of hematopoietic stem cell transplant recipient." *European journal of clinical pharmacology* 68.11 (2012): 1517-1524. |
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### Mentions “therapeutic drug monitoring” in the first line of the abstract

*“Population pharmacokinetics (PopPK) modeling and Bayesian estimation seem to be the best way to predict cyclosporine disposition and dose requirements to achieve the therapeutic target in an individual patient”*

* Uses NONMEM for estimation. Mention using “two compartment model with first-order absorption and *a lag time*…”.
* Mention using “nonlinear regression analysis” – doesn’t specifically mention using Bayes to model the pharmacokinetics.
* Mention that covariates were “entered in the model using a linear model”. Not really sure what that means.
* They add a “random effect” in the following way

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Here, theta is a PK parameter and eta is a parameter for interperson variability. This is similar to how I would have approached this. Authors write “where θi is the typical value of the parameter and ηθi is the associated interindividual variability parameter with mean and variance ω2.”

* Model fit assessed with “NONMEM’s objective function value using the likelihood ratio test and by visual examination of the plots”.
* “Bayesian estimation” only appears when talking about estimating AUC from sparse data. Leads me to believe pharmacokinetic model is not Bayesian.

### “Ciclosporin Population Pharmacokinetics and Bayesian Estimation in Thoracic Transplant Recipients”

Fruit, Dorothée, et al. "Ciclosporin population pharmacokinetics and Bayesian estimation in thoracic transplant recipients." *Clinical pharmacokinetics* 52.4 (2013): 277-288.

* This paper seems to have the same goals as us. Namely “To optimize the pharmacological response of ciclosporin (i.e. minimizing adverse effects without increasing the risk of rejection) “
* Authors mention “In parallel, maximum a posteriori probability Bayesian estimators, characterized by their flexibility with respect to sampling times and their ability to estimate simultaneously ciclosporin pharmacokinetic parameters and exposure indices, have been proposed in heart [9] and lung [12] transplantation.” – potential to do full Bayesian analysis (averaging over uncertainty rather than taking max a posteriori)
* Again, Bayesian estimation of AUC rather than full Bayesian model of pharmacokinetics.
* Uses NOMEM (first order conditional estimation) – see paper I found on the topic
* Two compartment model with random effects and possible lag. Model evaluation seems fucky since it is based on sequentially nested models, meaning there is likely an erroneous decision. Better to do full Bayesian inference and continuous model expansion?
* Model evaluation seems fucky “The accuracy and robustness of the final population model were assessed by a bootstrap method. Briefly, 1,000 boot- strap sets were obtained by re-sampling from the original dataset, each providing population pharmacokinetic parameter estimates. The median and 95 % confidence interval values of each pharmacokinetic parameter esti- mated from the 1,000 bootstrap sets were compared with the corresponding mean population values obtained with the original dataset. This procedure was performed using Wings for NONMEM”. They do something similar to get confidence intervals. Taking a more principled approach sounds better.
* Assessment of Bayesian estimators is odd to, employing frequentist techinuqes. See section 2.8.
* All in all, the approach does not seem very principled.