

## **A study in which I could not help, not even with Bayesian hierarchical models**

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Pharmaceutically induced individual nonlinear associations were recorded under two different experimental conditions.[1] Theory predicts a shift of the inflection points. Analysis of data from historical control groups is meant to provide posteriors that may be used for priors in the future. Sigmoidal curves were fitted in a hierarchical model describing the within-subject effects. Correlations between parameter estimates within and between subjects were kept manageable by taking logarithms of parameters. Unit information priors were aimed at. Parameters of the prior distributions were chosen after looking at descriptive statistics of the data. Borrowing across curves was explored by varying the prior distributions from univariate to multivariate. Estimation employed rstan for MCMC sampling. Convergence was checked by r-hat, effective sample size, and proportion of divergent iterations. Model fit was checked by RMSE and visually.

Convergence was difficult to achieve and sampling took long. Models with higher numbers of hyperparameters achieved a better fit to the data sometimes, while too many effect parameters led to convergence problems. The theory could neither be verified nor disproven clearly, as different assumptions led to different shifts or a lack thereof.

One explanation would focus on the data. Few curves were experimentally extended to the asymptote, maybe just two of them. This limits drastically the number of parameters we can estimate. There was a great variance in asymptotes, so that learning these from other curves would either be misleading or uninformative. Correlation with steepness parameters was of little help either because of great variance among those.

Another explanation would focus on functional form. The logistic function with fixed lower asymptote is symmetrical. When the upper asymptote is uncertain, the curvature near the other end fixes it to some value that may be far off the highest observed value. Such a curve may not reflect an experiment, in which blood pressure is increased by ever higher doses of another compound than is used to lower it.

As a consequence, it is understandable that published analyses of such data [2] either approximated the curved lines by straight lines or did not reflect the hierarchical nature of the data or used just baseline data (no infusion) as a proxy for inflection points.

We have not yet used the posterior correlations to specify priors.

[1] Sayk, F., C. Becker, C. Teckentrup et al. (2007). To dip or not to dip: On the physiology of blood pressure decrease during nocturnal sleep in healthy humans. *Hypertension*. doi: 10.1161/HYPERTENSIONAHA.106.084343.

[2] Sayk, F., C. Twesten, I. Adametz et al. (2020). Angiotensin II-mediated nondipping during sleep in healthy humans: effects on baroreflex function at subsequent daytime. *Am J Physiol Regul Integr Comp Physiol*. doi: 10.1152/ajpregu.00355.2019