

Bayesian hierarchical model of oscillatory cortisol response during drug intervention

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Background and motivation

Oscillating biomarker response-time courses challenge modelling of drug intervention. A periodically recurring pattern is typically seen for the stress hormone cortisol. This pattern can be captured by mechanism-based turnover models. Bayesian hierarchical modelling allows for full quantification of parameter uncertainty while also capturing the population aspects typical to nonlinear mixed effects modelling. Inter-occasion variability (IOV) is incorporated in addition to inter-individual variability (IIV). Finally, the adjusted model is used to predict specificity of a clinical test.

Key findings

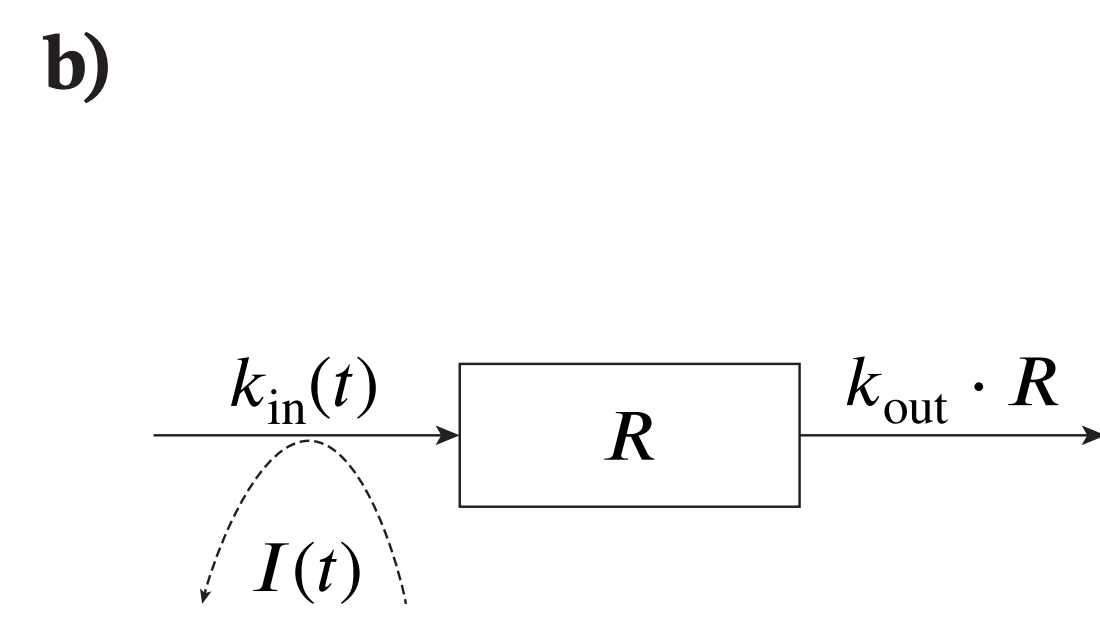
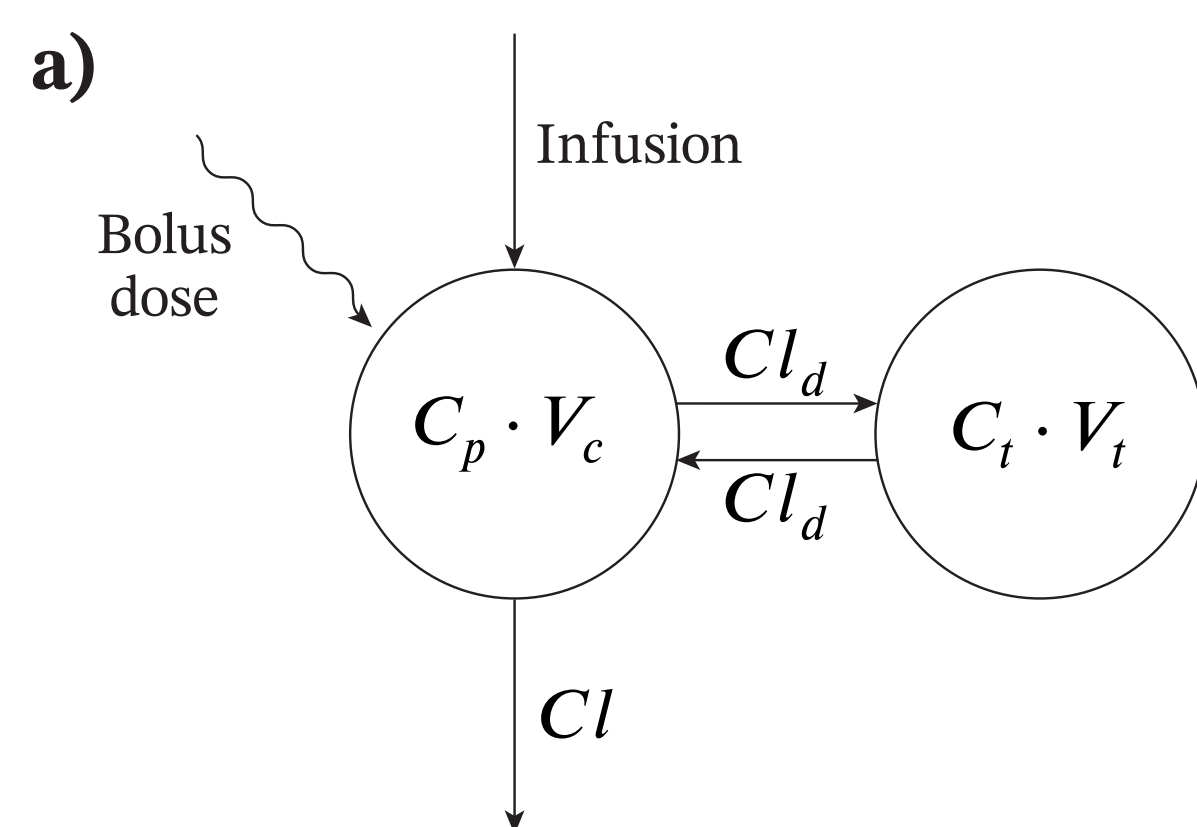
- New techniques were developed for graphical analysis of the oscillatory cortisol response
- A predictive hierarchical model was successfully constructed and applied to equine cortisol data after dexamethasone intervention
- Oscillatory behaviour and level of variability had great impact on the sparse-sample DST-design

Dexamethasone exposure and cortisol response

a) Two compartment model with bolus dose and 3h constant-rate infusion
Data were collected for four different dosing regimens (bolus + total infusion amount)
Control (saline solution), 0.1 + 0.07 µg / kg, 1.0 + 0.7 µg / kg, 10 + 7 µg / kg

b) Turnover model with oscillating turnover rate and drug-induced suppression

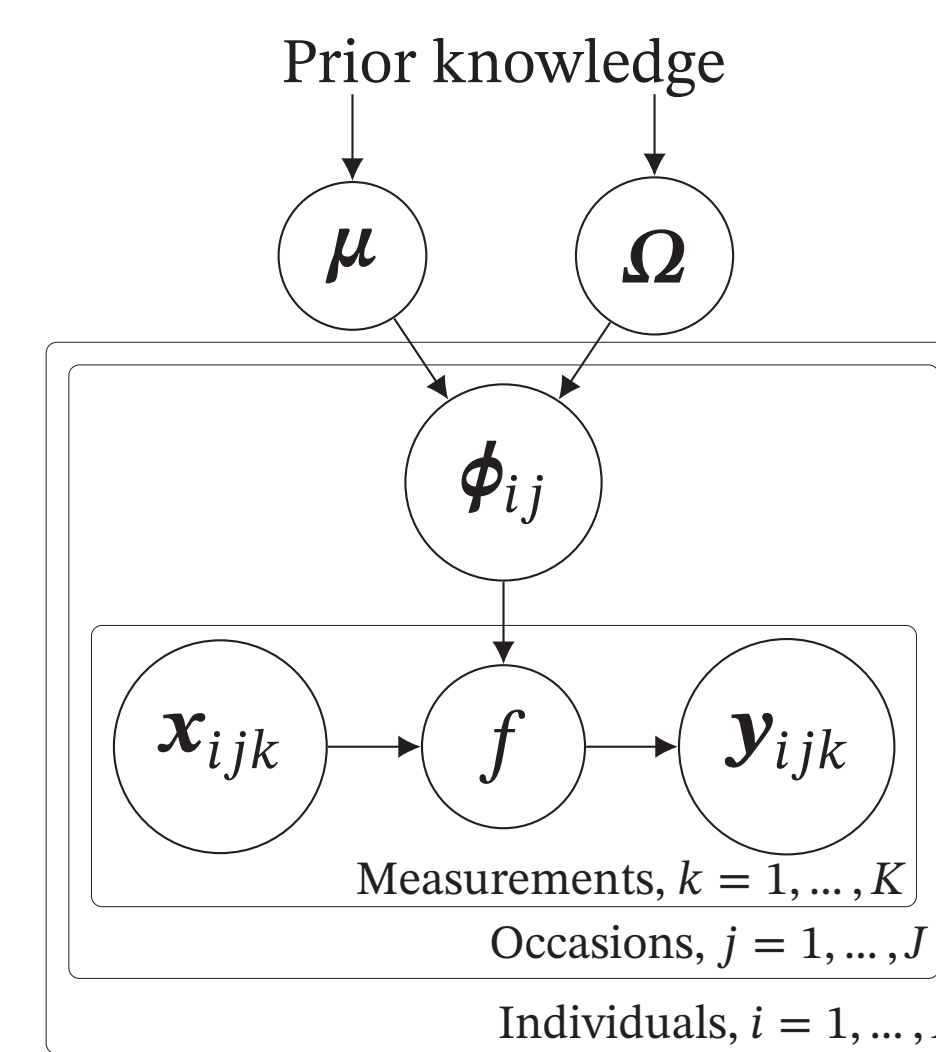
$$\frac{dR(t)}{dt} = \underbrace{\left(k_{\text{avg}} + \alpha \cos\left(\frac{2\pi}{24}(t - t_0)\right)\right)}_{\text{Oscillating turnover rate}} \cdot \underbrace{\left(1 - \frac{I_{\text{max}} C_p^n(t)}{IC_{50}^n + C_p^n(t)}\right)}_{\text{Suppression}} - \underbrace{k_{\text{out}} R(t)}_{\text{Elimination}}$$



Data previously published and model adapted from [1].

Bayesian hierarchical model

- Incorporation of IIV and IOV
- Conceptually similar to nonlinear mixed effects modelling
- Inclusion of prior knowledge allows for regularisation of the estimation



Analytic Solution

For a fixed drug concentration C_p
 $R(t, C_p) = A + B \cos\left(\frac{2\pi}{24}(t - C)\right)$

where

$$A = \frac{k_{\text{avg}}}{k_{\text{out}}} \cdot \left(1 - \frac{I_{\text{max}} C_p^n}{IC_{50}^n + C_p^n}\right)$$

$$B = \frac{\alpha}{\sqrt{k_{\text{out}}^2 + \left(\frac{2\pi}{24}\right)^2}} \cdot \left(1 - \frac{I_{\text{max}} C_p^n}{IC_{50}^n + C_p^n}\right)$$

$$C = \frac{24}{2\pi} \arctan\left(\frac{k_{\text{out}} \sin\left(\frac{2\pi}{24} t_0\right) + \frac{2\pi}{24} \cos\left(\frac{2\pi}{24} t_0\right)}{k_{\text{out}} \cos\left(\frac{2\pi}{24} t_0\right) - \frac{2\pi}{24} \sin\left(\frac{2\pi}{24} t_0\right)}\right)$$

Used to

- Calculate initial values
- Establish drug-response equilibrium curves

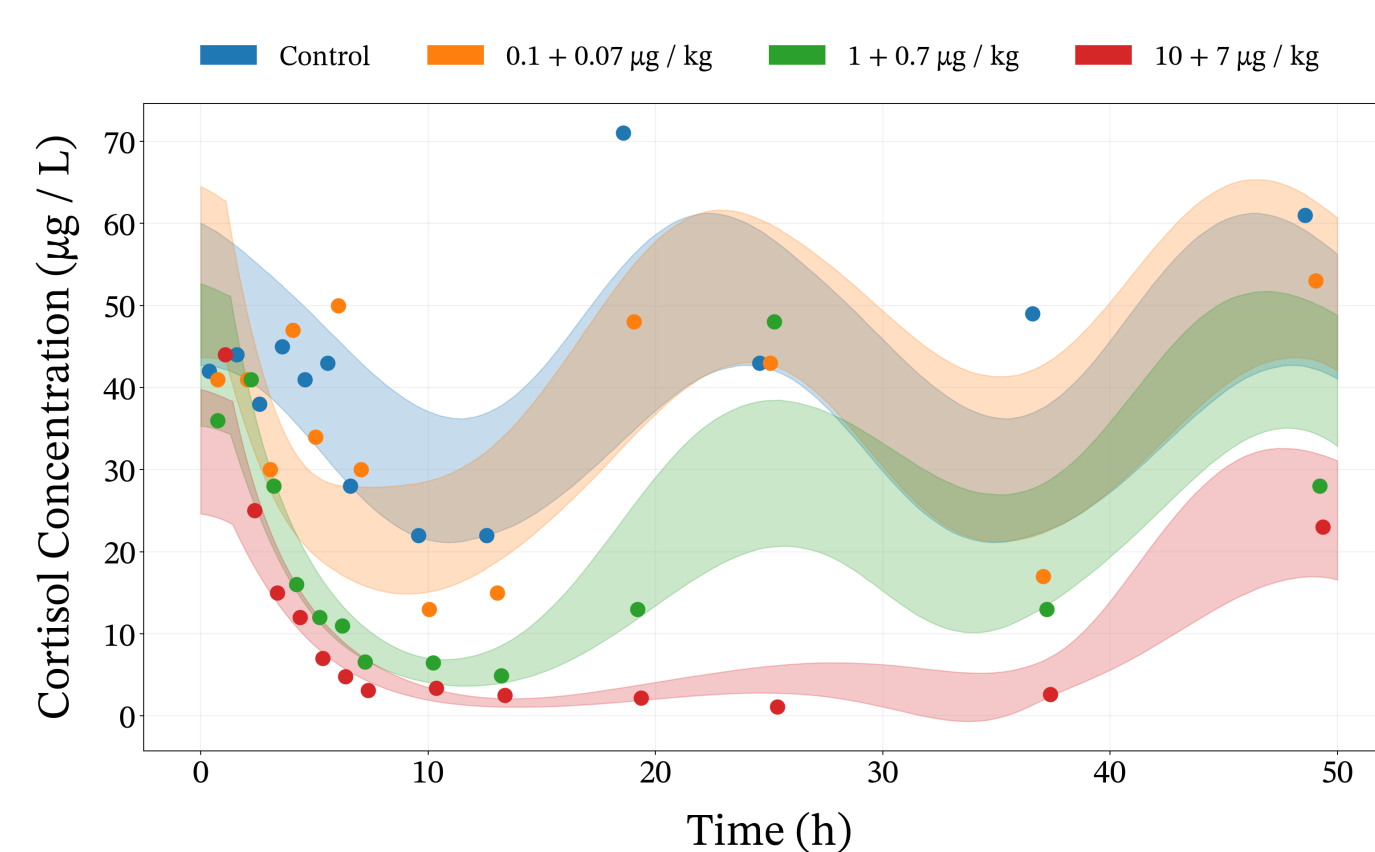
Parameter estimates, uncertainty and model predictions

Parameter estimates

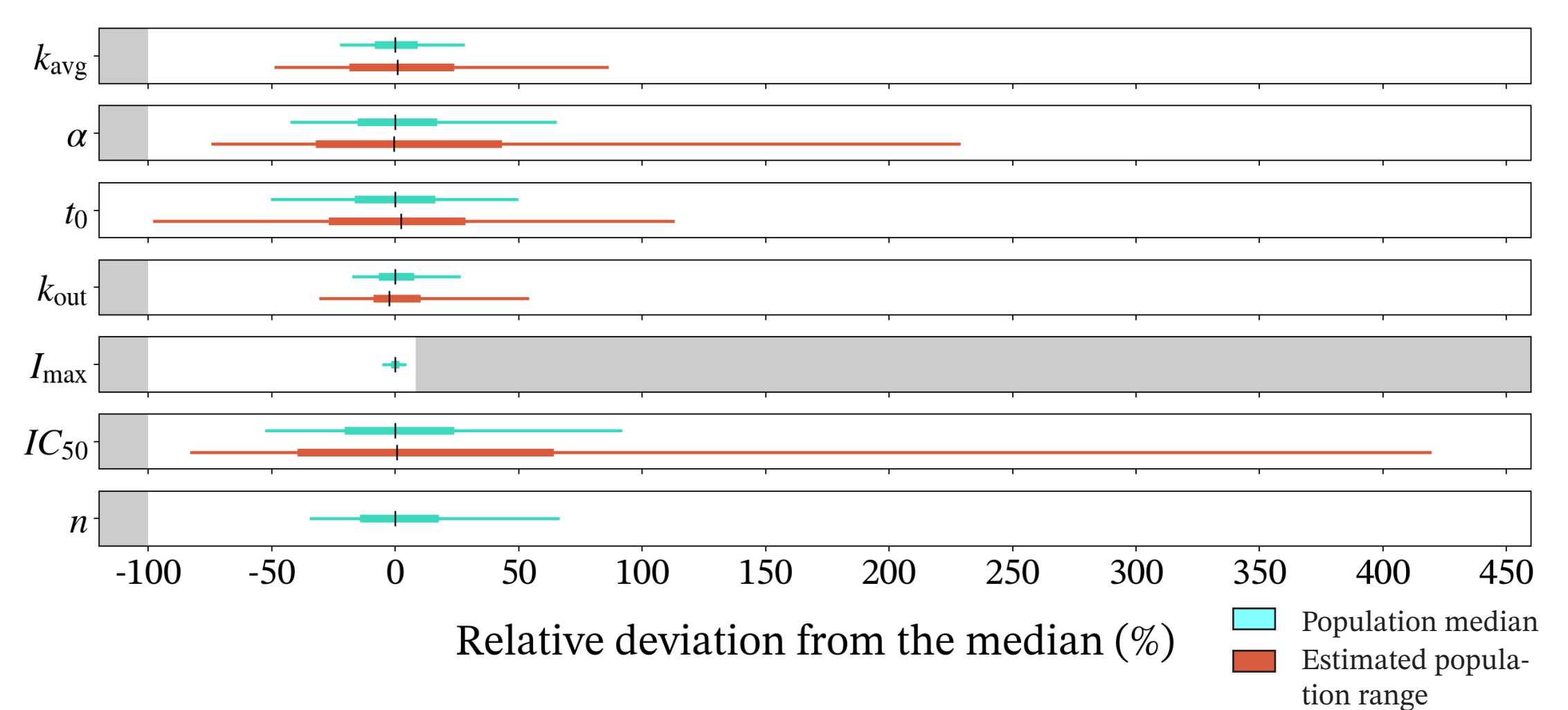
- Parameters were estimated in a Bayesian framework. Samples from the joint probability model were simulated with the Hamiltonian Monte Carlo algorithm implemented in Stan [2].
- Priors for hyperparameters were chosen by a meta-analysis of a previous study [1].
- Estimated ranges including IIV and IOV for parameters of the cortisol response model are shown
- Bayesian estimation allows estimation of three sources of variability and uncertainty
 - Uncertainty in typical values
 - Uncertainty in estimated variance components
 - Model uncertainty/Residual variance
- Variance components were hard to identify (data from $N = 6$ horses), regularisation with priors aided the parameter estimation

Model predictions

- 95% credible intervals for the predicted time-courses are shown
- Oscillation and suppression are being captured
- Reduction of variability for increasing drug doses is visible.

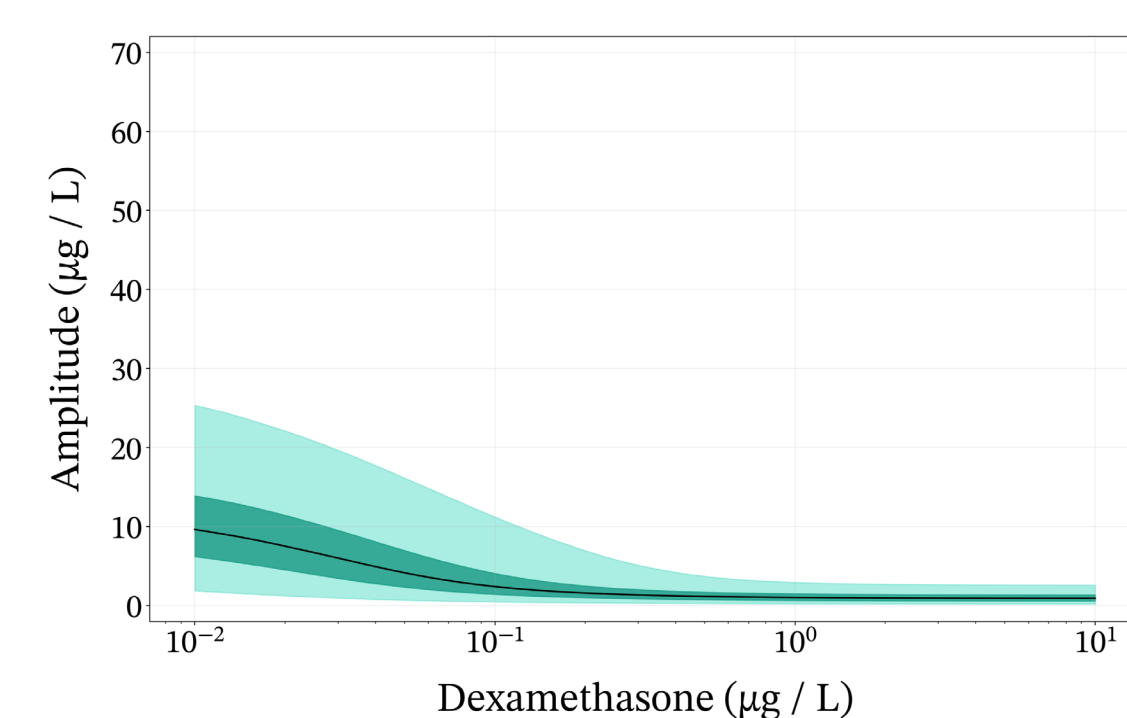
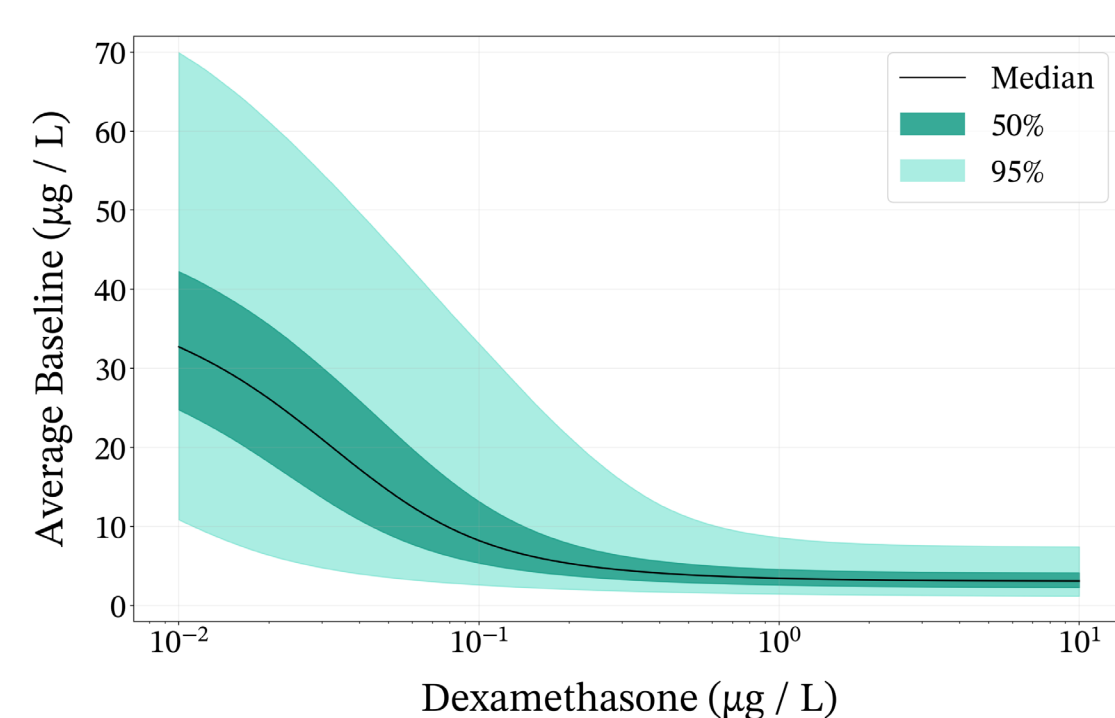


Parameter	Estimated range including IIV/IOV (quantiles)				
	2.5%	25%	50%	75%	97.5%
k_{avg}	6.44	9.22	12.7	17.2	23.5
α	1.38	3.00	5.40	9.38	17.9
t_0	-7.54	-5.44	-3.71	-2.17	0.494
k_{out}	0.221	0.272	0.315	0.378	0.493
I_{max}	0.874	0.900	0.923	0.944	0.965
IC_{50}	0.00490	0.0136	0.0298	0.0628	0.155
n	1.03	1.26	1.57	2.00	2.61



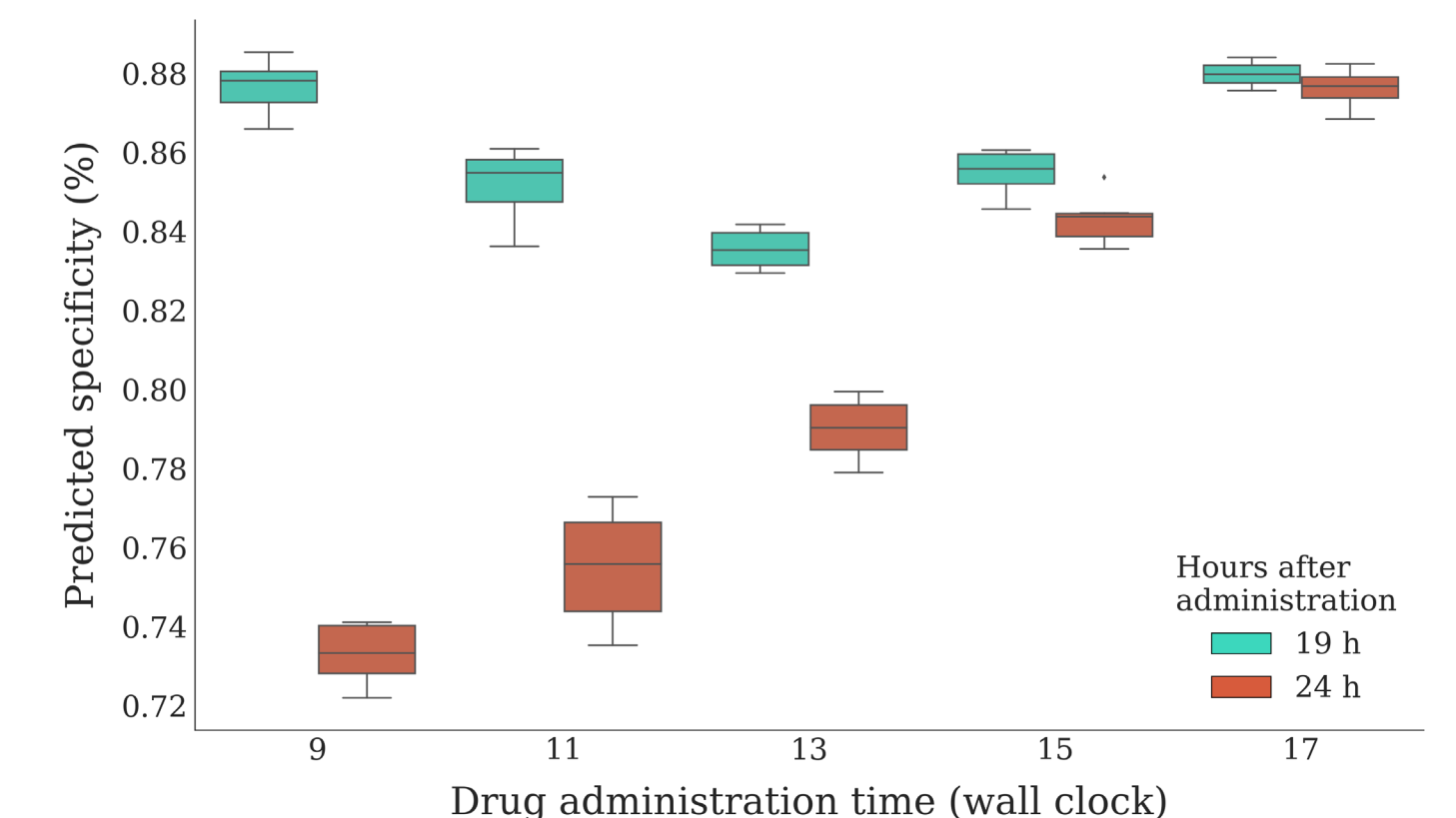
Variability of oscillation parameters

- Through Monte Carlo simulations, the average baseline A and amplitude B , as described above, were simulated.
- Average baseline is subject to both IIV and IOV resulting in higher variability
- Both parameters are suppressed in magnitude and variability for increasing drug concentration



Predicted specificity of a dexamethasone suppression test (DST)

- Two previously published protocols were evaluated. Both stated specificity.
 - Protocol 1 in [3]: 100% specificity
 - Protocol 2 in [4]: 76% specificity
- Intravenous administration of 40 µg / kg of dexamethasone at 9.00 (protocol 2) or 17.00 o'clock (protocol 1)
- Cortisol sample R_{after} taken after 19 hours (protocol 1) or 24 hours (protocol 2)
- DST indicates healthy subjects for $R_{\text{after}} < 10 \mu\text{g} / \text{L}$
- Clear dependence on “administration time” and “hours after administration”



References

- [1] C. Ekstrand et al., J. Vet. Pharmacol. Ther. 39, 255–263 (2016).
- [2] B. Carpenter et al., J. Stat. Softw. 76 (2017), doi:10.18637/jss.v076.i01.
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