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

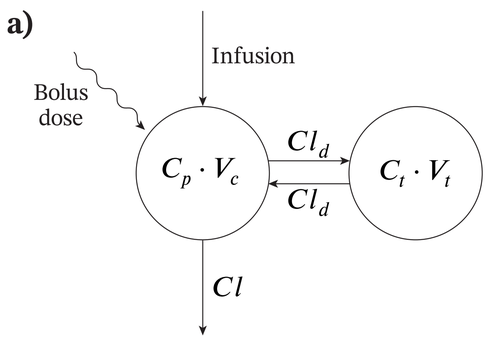
- New techniques were developed for graphical analysis of the oscillatory cortisol response
- A predictive hierarchical model was successfully constructed and applied to equine cortisol data after dexamethasone intervention
- Oscillatory behaviour and level of variability had great impact on the sparse-sample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

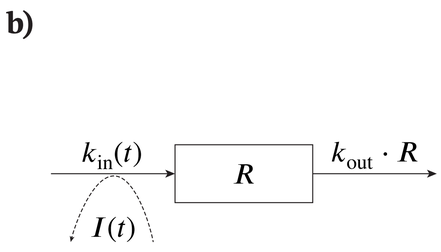
Dexamethasone exposure and cortisol response

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

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

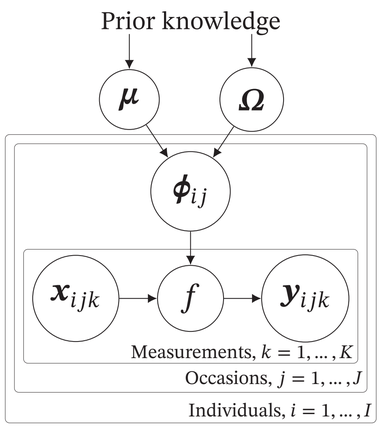




Data previously published and model adapted from [1].

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

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

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

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

Used to
- Calculate initial values
- Establish drug-response equilibrium curves

Parameter estimates, uncertainty and model predictions

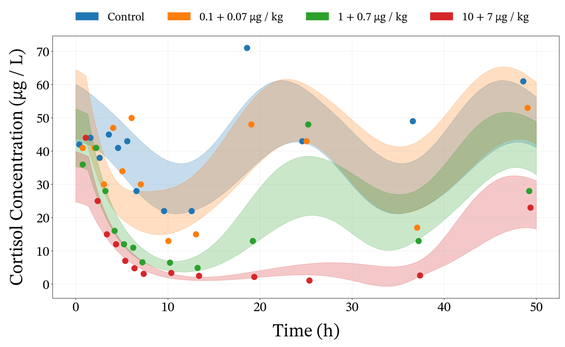
Parameter estimates

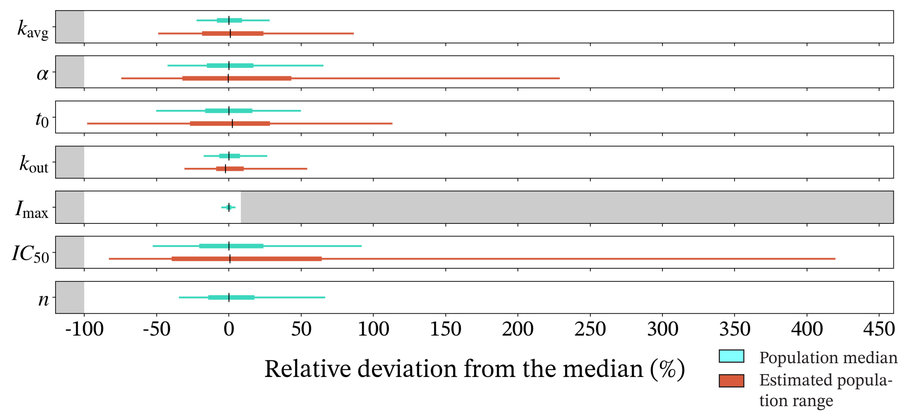
- Parameters were estimated in a Bayesian framework. Samples from the joint probability model were simulated with the Hamiltonian Monte Carlo algorithm implemented in Stan [2].
- Priors for hyperparameters were chosen by a meta-analysis of a previous study [1].
- Estimated ranges including IIV and IOV 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

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}	0.004 90	0.0136	0.0298	0.0628	0.155
n	1.03	1.26	1.57	2.00	2.61

Model predictions

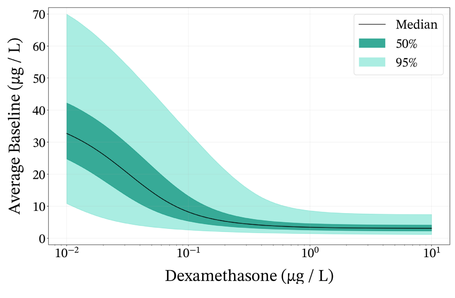
- 95% credible intervals for the predicted time-courses are shown
- Oscillation and suppression are being captured
- Reduction of variability for increasing drug doses is visible.

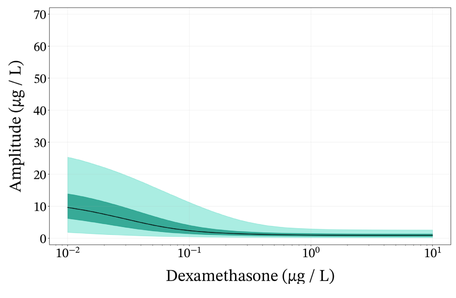




Variability of oscillation parameters

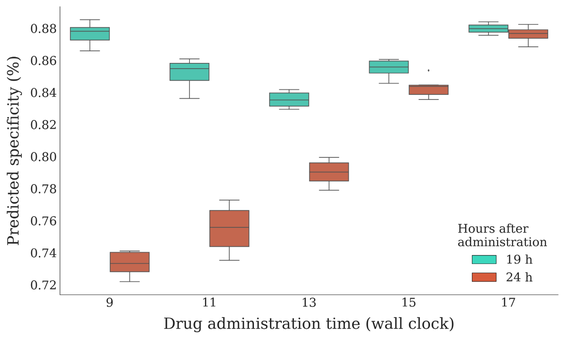
- Through Monte Carlo simulations, the average baseline A and amplitude B, as described above, were simulated.
- Average baseline is subject to both IIV and IOV resulting in higher variability
- Both parameters are suppressed in magnitude and variability for increasing drug concentration





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 $R_{\text{after}} < 10$ µg / L
- Clear dependence on "administration time" and "hours after administration"



References

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