

Population modeling of the synergistic effects of morphine and gabapentin in the rat: A Response surface approach

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Introduction

- Combination pharmacotherapy is an important modality for the treatment of postoperative pain.
- Synergistically acting drugs may lead to improvement of analgesic efficacy or reduction in side effects.
- Combination of morphine and gabapentin leads to synergistic interactions in a postoperative pain model in the rat (1).
- PKPD modelling can be used to identify the optimal concentration effect relationship of combinations.

Methods

- Blinded, randomized, 16 arms study with s.c administration of morphine (1, 3 and 7 mg/kg), gabapentin (10, 30 and 100 mg/kg) or their combination.
- PD was evaluated in a rat plantar incision model using an electronic von Frey device (2).
- Population PKPD modelling was performed in NONMEM 7.3 with PsN, Piraña, Xpose4 and ggplot2 libraries for R (4).
- Interaction model: parameter θ describes the concentration ratio. The effect model was extended by making the model parameters dependent on θ (3).
- M3 method for data above the LOQ. Laplacian estimation with Importance sampling.

Interaction Model

$$U_M = \frac{C_{Mor}}{C_{100,Mor}} \quad U_G = \frac{C_{Gab}}{C_{100,Gab}} \quad \theta = \frac{U_{Mor}}{U_{Mor} + U_{Gab}}$$

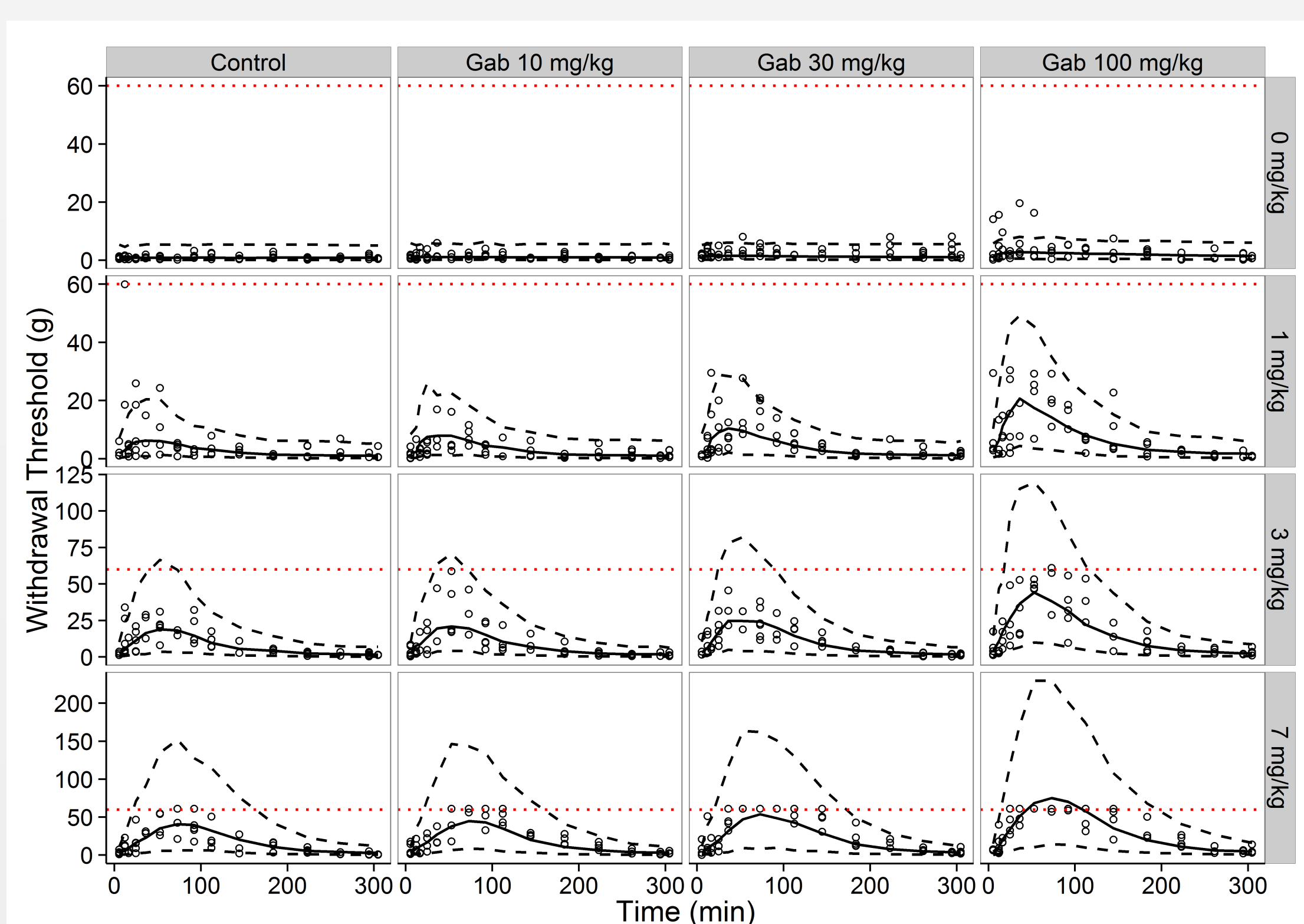
$$E = E_0 + \left(\frac{U_M + U_G}{U_{100}(\theta)} \right)^{\gamma(\theta)}$$

$$U_{100}(\theta) = \begin{cases} U_G, & \theta = 0 \\ U_{comb}, & 0 < \theta < 1 \\ U_M, & \theta = 1 \end{cases} \quad \gamma(\theta) = \begin{cases} \gamma_G, & \theta = 0 \\ \gamma_{comb}, & 0 < \theta < 1 \\ \gamma_M, & \theta = 1 \end{cases}$$

$$U_{100}(\theta) = 1 + (-\beta_1 - \beta_2) \cdot \theta + \beta_1 \cdot \theta^2 + \beta_2 \cdot \theta^3$$

$$\gamma(\theta) = \gamma_G + (\gamma_M - \gamma_G - \beta_3 - \beta_4) \cdot \theta + \beta_3 \cdot \theta^2 + \beta_4 \cdot \theta^3$$

Results



Visual predictive check of the final interaction model, stratified by combination dose, with observations (points), model predicted population median (solid lines), 90% confidence intervals of the median (dashed lines) and upper limit of quantification (red dotted lines).

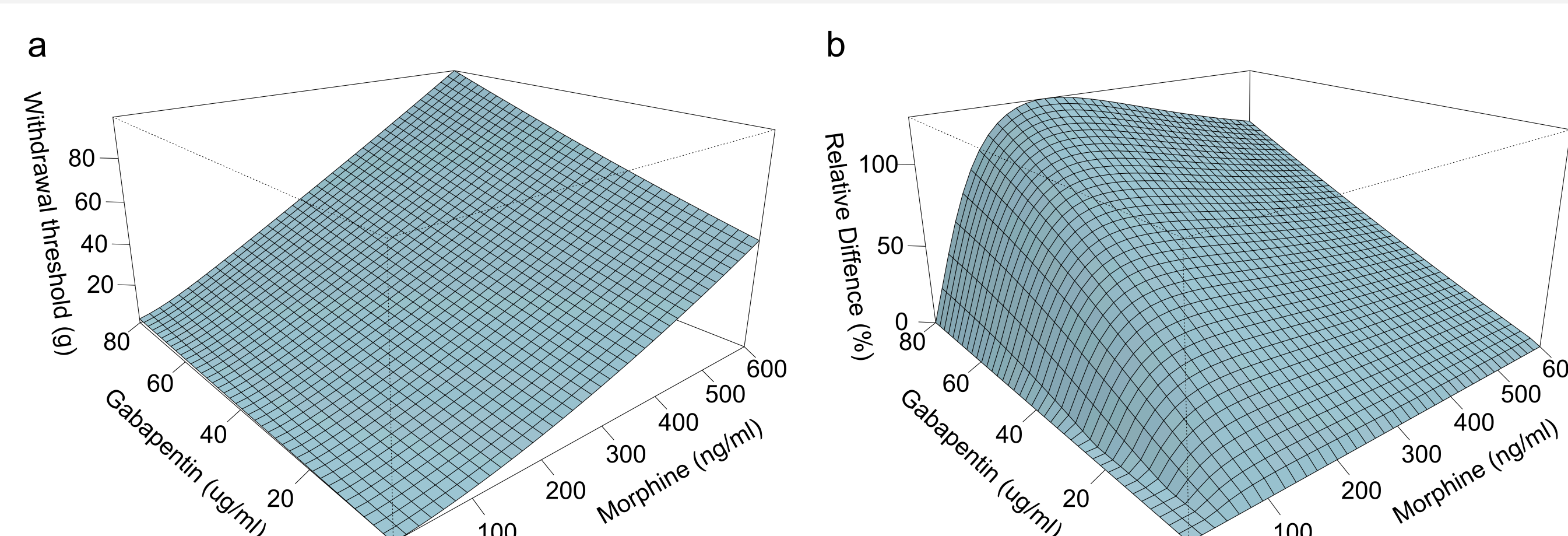
Parameter	Estimate (RSE%)	IIV(RSE%)
E_0 (g)	1.02 (19)	99.6 (11.2)
$C_{100,Mor}$ (ng/ml)	42.3 (22)	34.2 (15.9)
γ_{Mor} (unitless)	1.47 (22)	-
$k_{E0,max,Mor}$ (min ⁻¹)	0.0543 (22)	50.3 (23.3)
$k_{M,Mor}$ (ng/ml)	290 (25)	-
$C_{100,Gab}$ (µg/ml)	42.4 (13)	-
γ_{Gab} (unitless)	1(FIX)	-
β_3 (unitless)	-2.25 (30)	-
σ_{prop} (%)	0479 (3)	-

Individual and interaction effect parameters for the final combination model. The negative interaction parameter for the shape factor denotes asymmetric synergy (3).

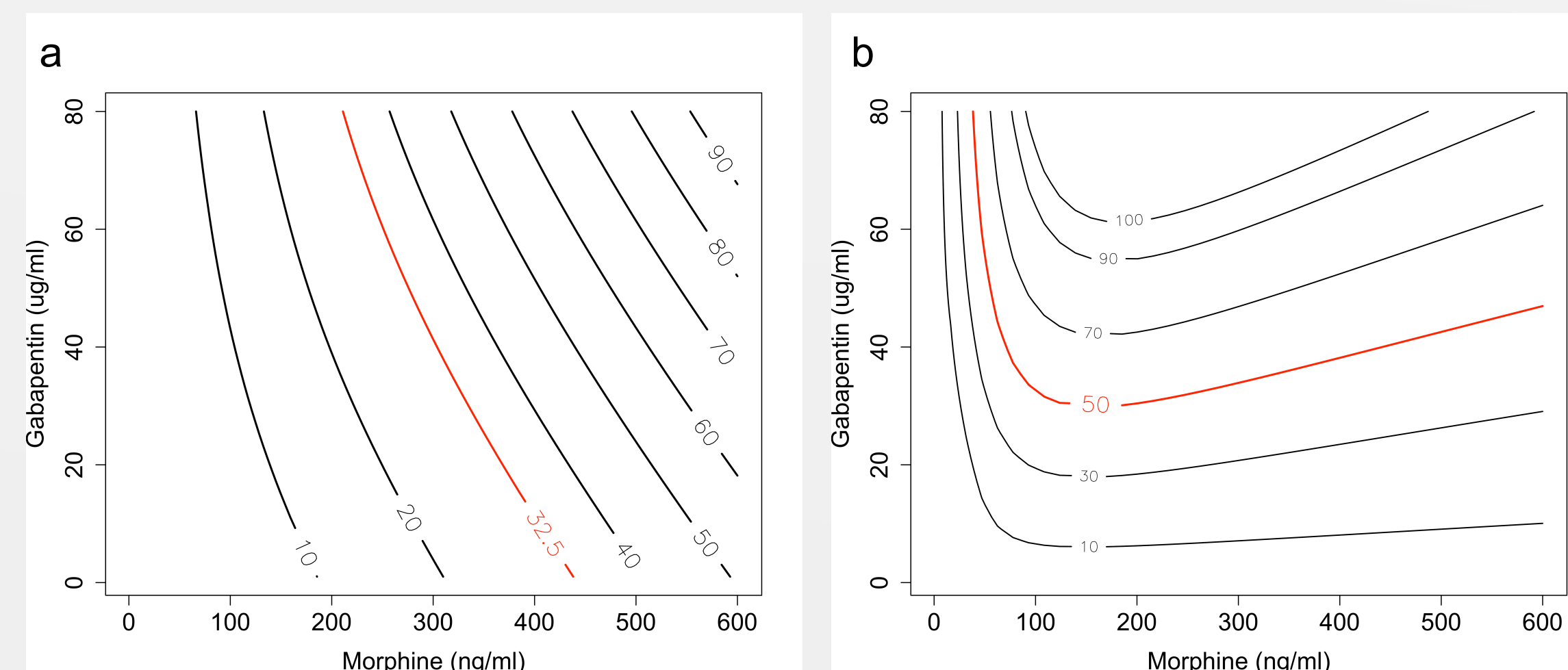
Aim

The aim of this study was to develop a population pharmacokinetic-pharmacodynamic model describing the synergistic interaction of morphine and gabapentin and to identify the optimal concentration effect relationship of the combination

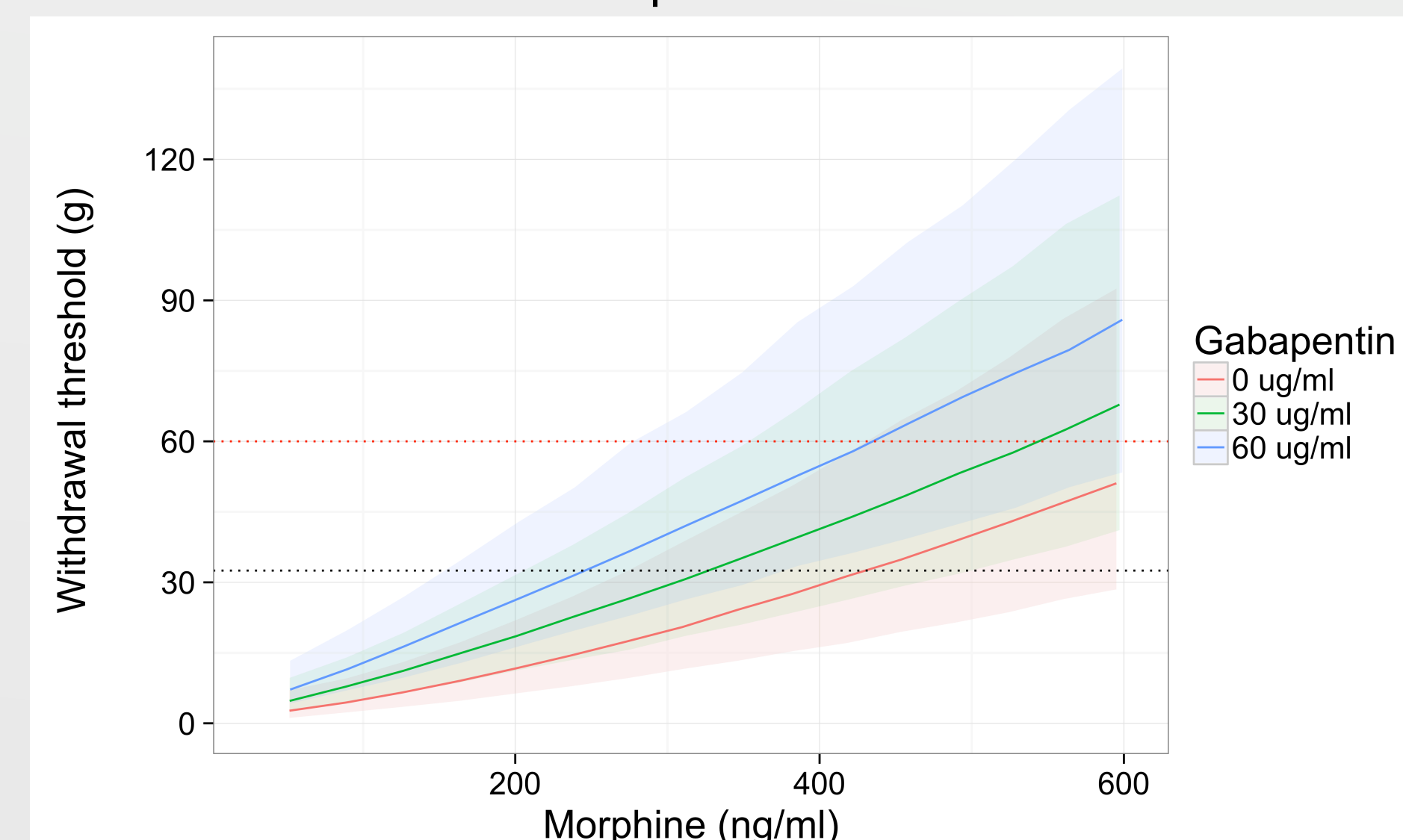
Synergistic Interactions and Response Surface



(a) Estimated paw withdrawal thresholds versus the concentrations of morphine and gabapentin and (b) the relative difference between the model predictions and the theoretical additive response (derived by setting all interaction parameters equal to zero).



Contour plots of the response surfaces presenting the (a) effect levels and (b) relative to additive response differences being as solid lines. Full reversal of withdrawal thresholds for the pain stimulation was estimated at a morphine effect compartment concentration of 430 ng/ml. Co-administration of up to ~40 µg/mL of gabapentin led to reduction of the needed morphine concentration down to 300 ng/ml (~ 25% reduction). The red contours present the (a) withdrawal thresholds equal to mean pre-surgery baseline and (b) the 50% increase of effect relative to the additive response.



Concentration-effect relationship of morphine alone or in combination with gabapentin. Solid lines and shaded areas: Population median and 90% CI. Red dotted line: Upper limit of quantification (60 g). Black dotted line: Mean withdrawal baseline prior to surgery.

Conclusion

- Morphine and gabapentin lead to concentration dependent reversal of hyperalgesia but with significantly different potency.
- Combination of morphine and gabapentin leads to concentration-dependent synergistic anti hyperalgesic effects in a preclinical model of postoperative pain.
- This study highlights the importance of finding the right combination in multimodal analgesia and the developed model might help in guiding clinical studies for the selection of appropriate doses.

References

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