

Development of a semi-population deconvolution method for the analysis of growth hormone profiles

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Study highlights

- ✓ Endogenous pulsatile 24h growth hormone profiles were modelled.
- ✓ Deconvolution analysis and non-linear mixed effects modelling techniques were combined to provide a tool for quantifying drug effects targeting growth hormone secretion.
- ✓ Simulations were performed to provide an example of the application of this method on the quantification of secretion stimulating or inhibiting drug effects.

Introduction

- Secretion of endogenous growth hormone (GH) is pulsatile.
- GH secretion is inhibited by somatostatin and stimulated by growth hormone releasing hormone, released from the hypothalamus.
- Feedback mechanisms, circadian rhythmicity, ghrelin and other factors impact the complexity of GH regulation.
- Currently, structural information is lost when summarizing a pulsatile profile in a single value (AUC, mean) or by comparing the number of peaks between groups (using deconvolution) in the identification of drug effects.
- These factors highlight the need for a quantitative method to analyse pulsatile profiles, follow drug effects over time and incorporate pulsatile profiles in PK/PD models.

Method

Endogenous GH profiles were modelled following 5 steps:

- I) Deconvolution analysis of individual GH profiles with AutoDecon^[1]
- II) Inform NONMEM model with pulse locations derived from deconvolution results
- III) Implement pulses as separate Gaussian shaped events^[1]:
 - $Secretion(t) = e^{\log(Amplitude) - \frac{1}{2} \left(\frac{t - Pulse\ location}{SecretionWidth} \right)^2}$
- IV) Estimate population parameters in NONMEM:
 - Pulse amplitude
 - Pulse secretion width
 - Baseline secretion rate
 - Elimination rate
- V) Identify covariate relationships

PK/PD simulations

- Quantify drug effects targeting growth hormone secretion.
- Two simulated proportional drug effects are depicted in Figure 2:
 - 1) Stimulating pulse amplitude
 - 2) Inhibiting pulse amplitude
- Effects were simulated using a sigmoid EMAX relationship on the pulse amplitude parameter.
- This semi-population deconvolution method can be implemented using:
 - All PK/PD relationships
 - Targeting the different population parameters of GH secretion

Conclusions

- ✓ Ability to analyse highly variable endogenous pulsatile data
- ✓ Follow GH secretion over time
- ✓ Individuals retain their individual pulse interval + frequency
- ✓ Study concentration-effect relationship on GH secretion
- Can be extended with:
 - Different pulsatile hormones (FSH, GnRH, LH)
 - Implement circadian rhythm on population parameters

Traditional deconvolution

- AutoDecon^[1]: A fully automated deconvolution software
 - Implements pulses using the Nelder-Mead algorithm using a fitting, triage and insertion module to determine optimal pulse locations.

Table 1. Example of deconvolution results, adapted from Pijl et al.^[2]

Parameter description	Mean (± SD)
Pulse frequency	18.1 (3.6)
Pulse amplitude (mU/LV _d /d)	0.37 (0.2)
Half-life (min)	15.6 (2.4)
Secretion pulse width (min)	30 (4)
Pulse interval (min)	79 (14)

- Limitations exist in the reporting of traditional deconvolution results:
 - Limited knowledge on the actual secretion profile over time is reported
 - Circadian effects on secretion are neglected
 - Drug effects can only be studied by comparing the mean (±SD) between groups

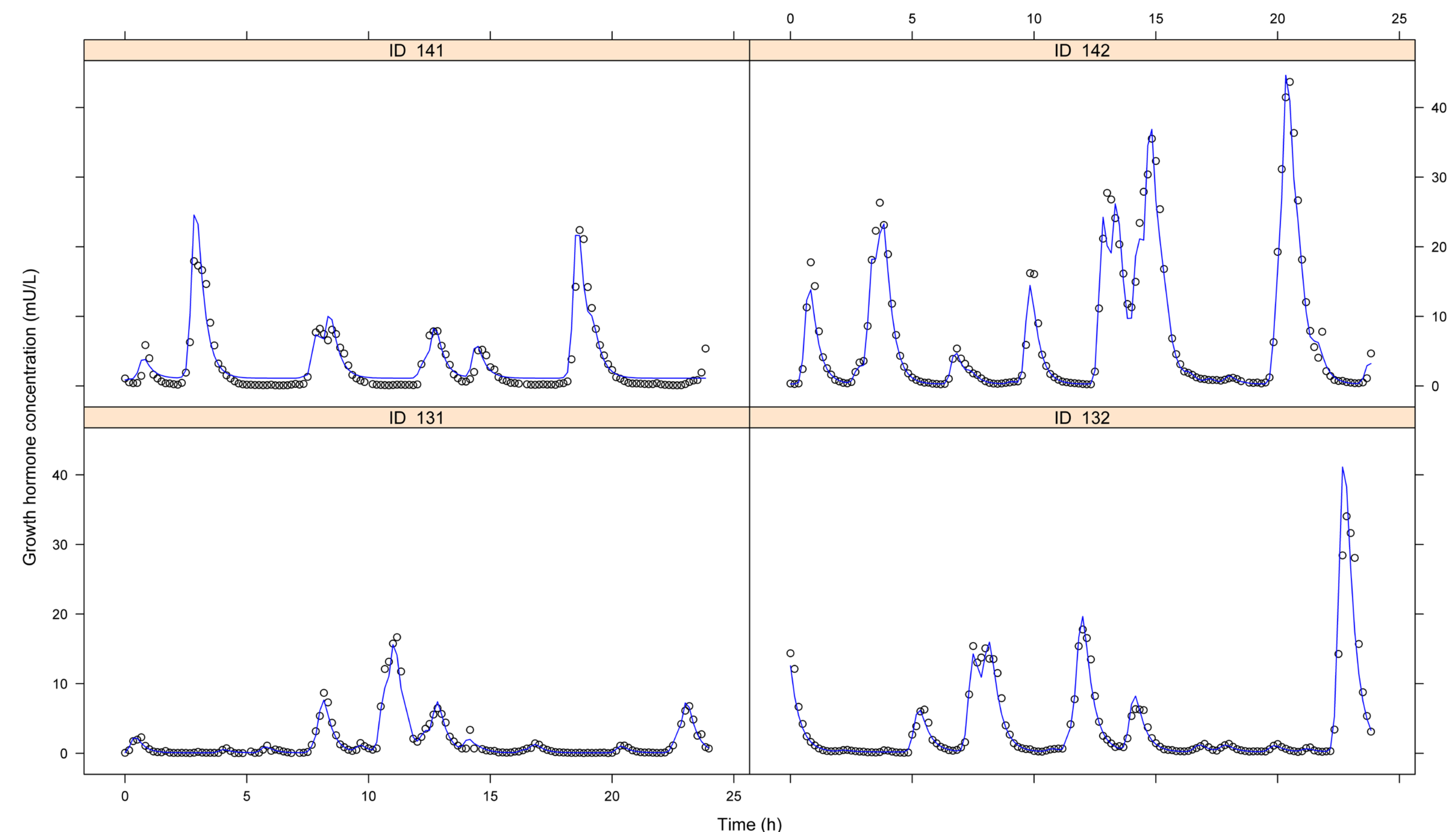


Figure 1. Endogenous growth hormone 24h concentration-time profile model fits for 4 individuals. Black open circles: observations. Blue line: Individual model predictions.

(1) Stimulation

(2) Inhibition

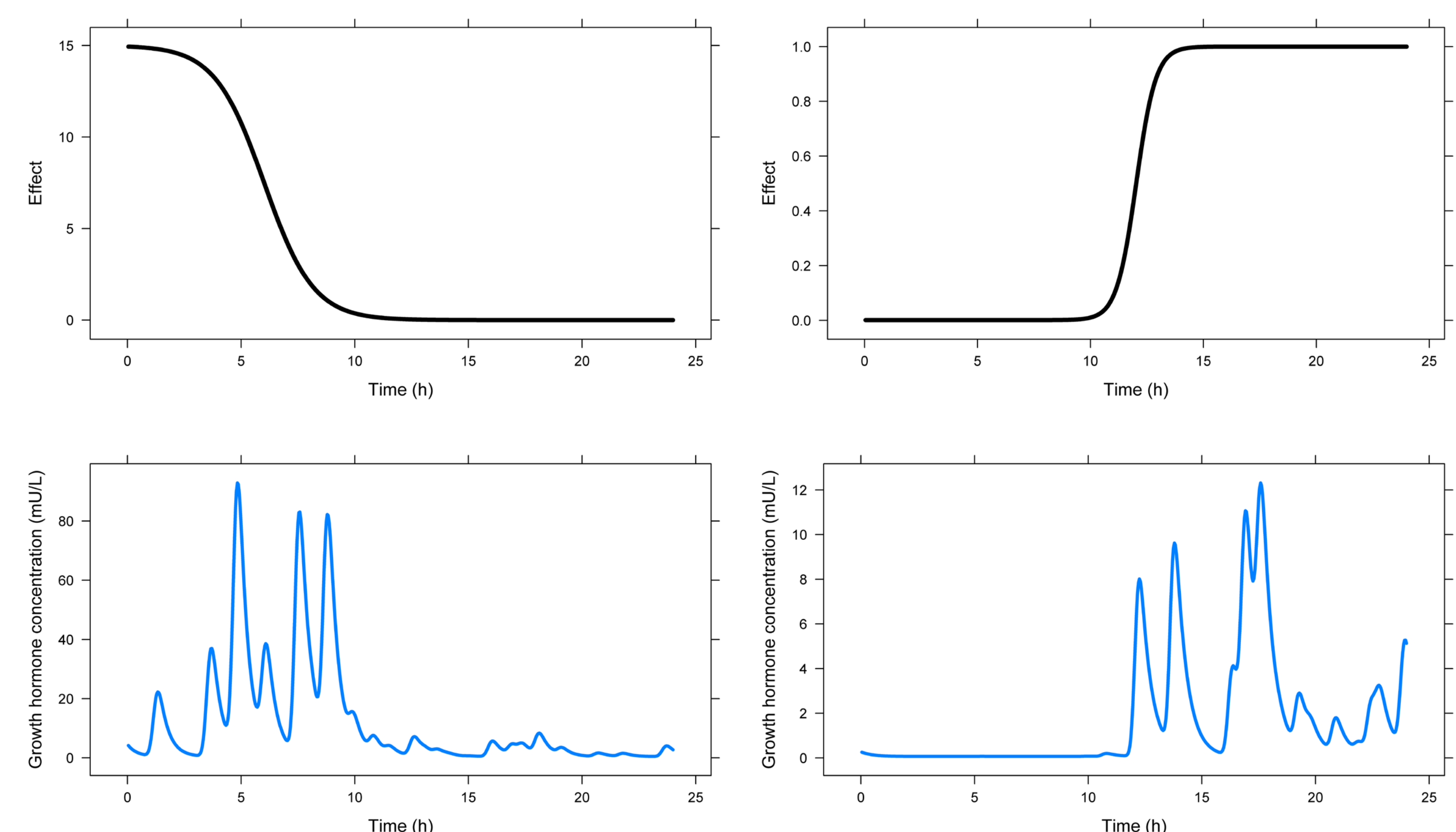


Figure 2. Simulated drug effects that stimulate (1) or inhibit (2) growth hormone secretion. Top row: Proportional drug effect over time. Bottom row: Simulations of growth hormone concentrations.

References

- [1] Johnson ML, Pipes L, Veldhuis PP et al. AutoDecon: A Robust Numerical Method for the Quantification of Pulsatile Events. *Methods Enzymol.* 2009. 454: 367-404
- [2] Pijl H et al. Altered Neuroregulation of GH Secretion in Viscerally Obese Premenopausal Women. *The Journal of Clinical Endocrinology & Metabolism.* 2001. 86(11):5509-5515