

Accurate modeling of ACTH and cortisol dynamics for Cushing's disease treatment



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Objectives

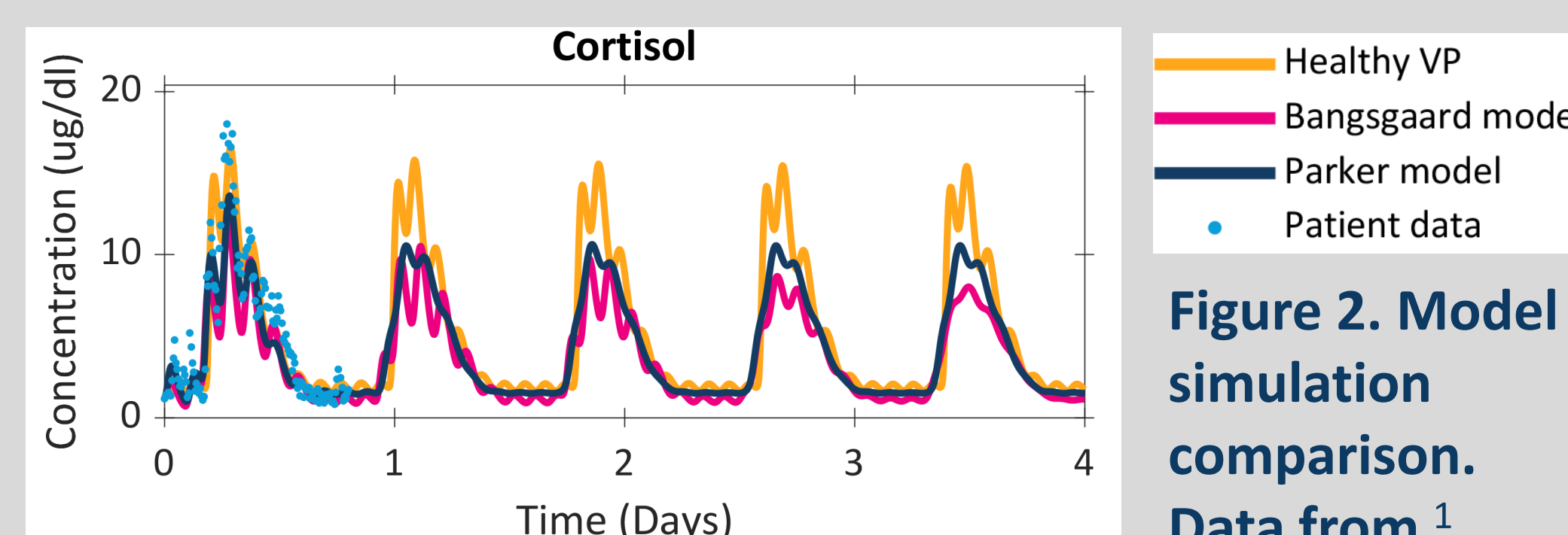
Modeling variations in ACTH and cortisol

- Cushing's disease (CD) is a rare condition that results from having too much cortisol in blood:
 - The most common cause is a pituitary noncancerous tumor (adenoma) secreting adrenocorticotrophic hormone (ACTH), which causes increased secretion of cortisol
 - The hypothalamic-pituitary-adrenal (HPA) axis regulates cortisol production
- Our Platform represents the HPA axis dynamics accurately and the effects of Cushing's disease
- ACTH and cortisol oscillations are not easy to capture; our model, however, shows stability and accuracy from hours to months, unlike previous models^{1,2}

Methods

Capturing oscillations accurately

- Hormone level peaks and ultradian oscillations rapidly decrease after the first 24 hours of simulation when previous models are used^{1,2} (Figure 2)



- Our calibration process guarantees a better fitting and a stable concentration pattern over time since it is based on:
 - Using a 72-hour dataset by repeating the original 24-hour dataset 3 times in a row
 - Assigning more weight to the high concentration datapoints

Conclusions

A powerful tool for HPA axis therapies

- The model simulations match published single-day clinical data and remain stable and accurate in long term scenarios
- The Platform simulations are in agreement with results reported in literature:
 - They replicate a healthy and a CD patient
 - Both VP responses to CRH and dexamethasone tests match clinical data
- A variety of CD treatments can be implemented for therapy development or predictive purposes:
 - Drugs targeting ACTH and/or cortisol production
 - Tumor removal
 - Adrenal glands removal or inhibition of their effect on cortisol production

Cushing's Disease Model

The HPA Axis PhysioPD® Platform

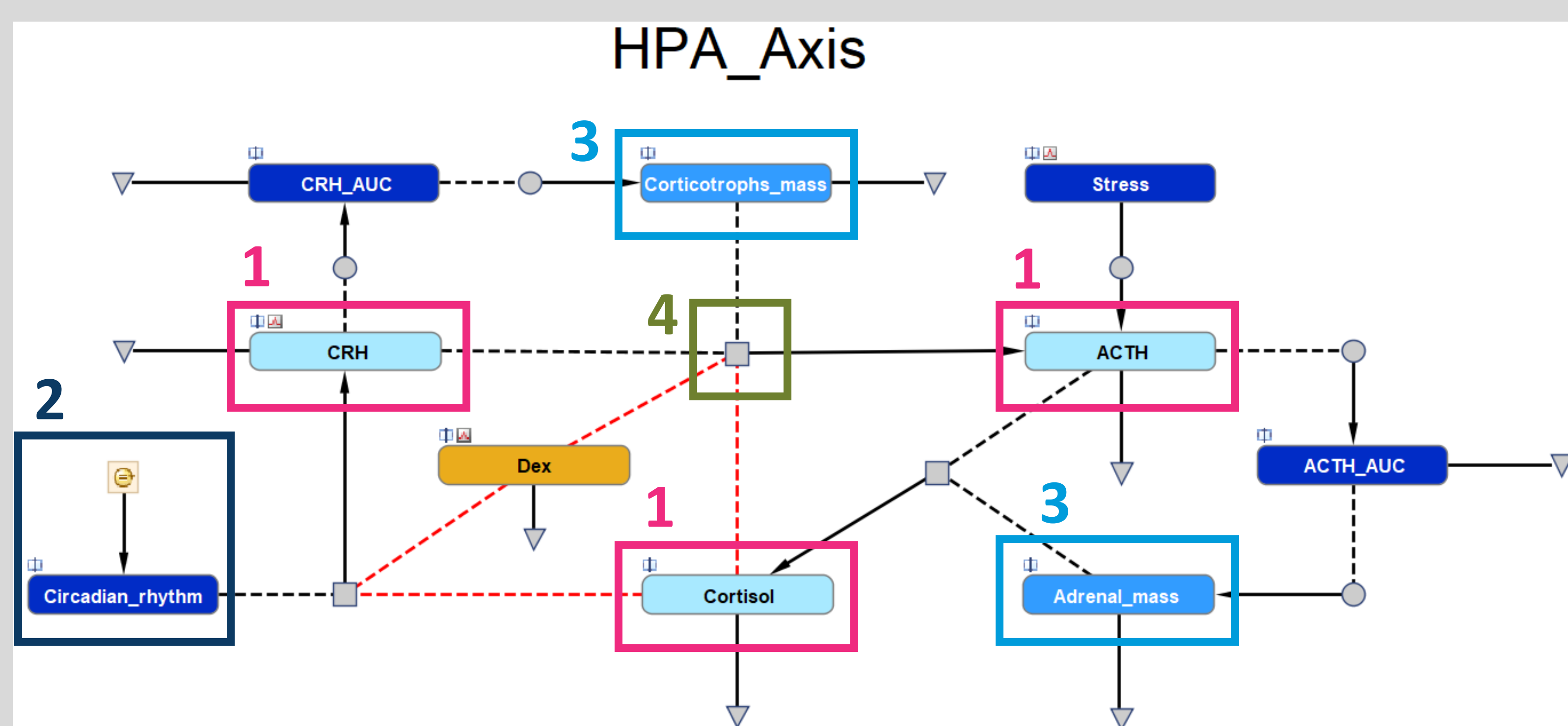


Figure 1. The HPA Axis PhysioMap® is based on Bangsgaard et al. work¹.

- Our Platform (Figure 1) represents corticotropin-releasing hormone (CRH), ACTH, and cortisol with appropriate feedback regulation of hormone production (1)
- It also includes an artificial construct for setting a circadian rhythm that has an effect on CRH production (2)
- To this structure, we have added tissue mass (corticotroph and adrenal) (3), outcome measures, and drug/hormone treatments
- A healthy VP and a Cushing's disease VP (CD VP) have been created and calibrated to simulate short- (hourly variations) to long-term scenarios (clinical trials lasting for weeks or months)
- The CD VP required the addition of a constant rate and a CRH-dependent rate to ACTH production to capture tumor effects (4)
- Dexamethasone and CRH tests, which identify the source of excess of cortisol and ACTH, respectively, and are used in the diagnosis of CD, have been implemented

Results

Testing of the healthy and Cushing's disease VPs

- The healthy VP shows circadian and ultradian rhythms and has the appropriate hormone concentrations in plasma^{3,4} (Figure 3)
- The CD VP has time-averaged hormone concentrations that are in agreement with the data^{3,4} (Table 1)
- Salivary cortisol is correlated with cortisol in plasma and it is within the range of expected values⁵ (Table 1)

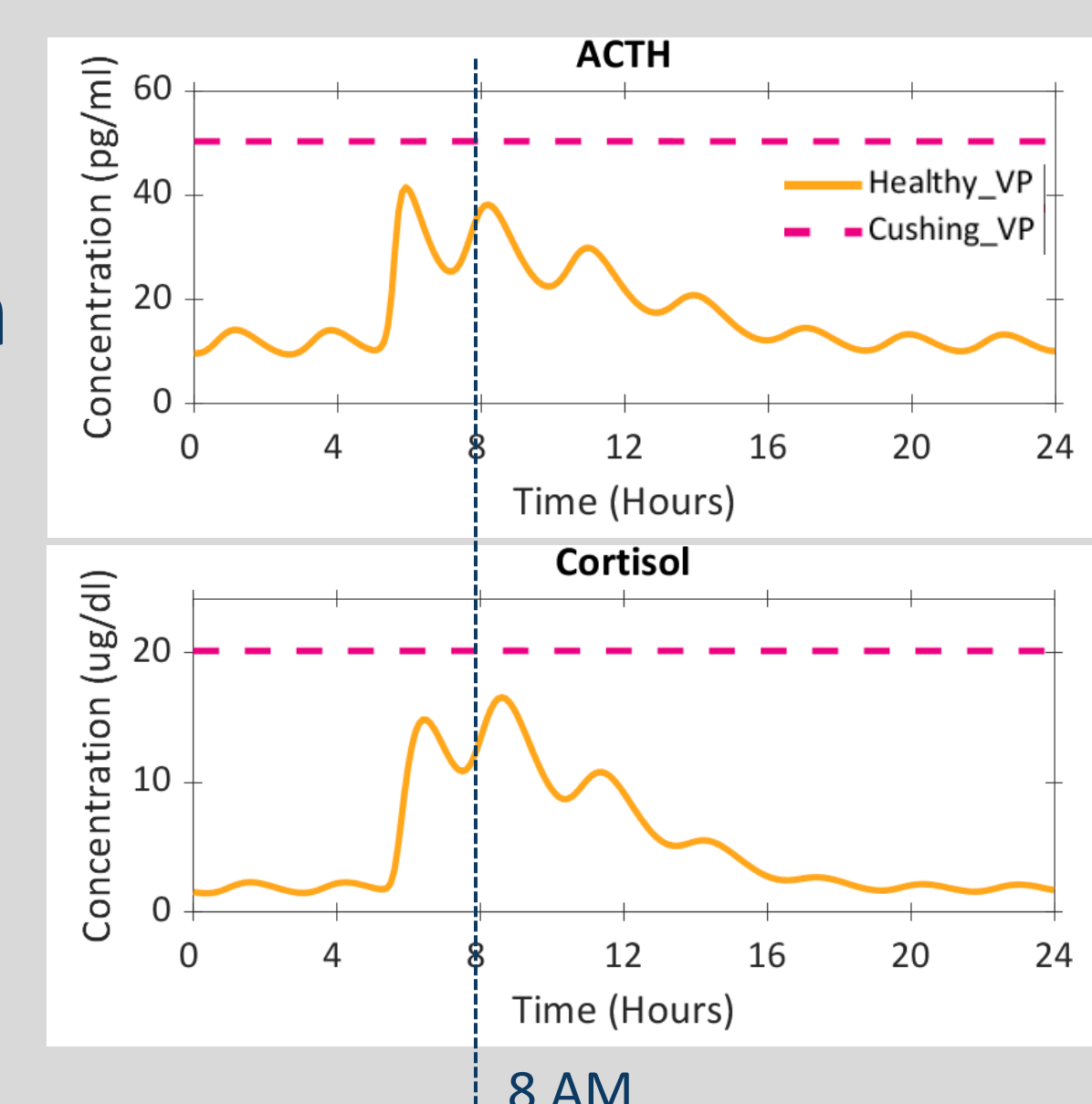


Figure 3. Single-day simulation of the healthy and CD VPs.

	Healthy VP	Expected range in healthy subjects	Cushing's disease VP	Expected range in CD patients
Cortisol (8 AM), ug/dL	13.00	5-15	20.12	15-30
ACTH (8 AM), pg/mL	37.00	5-50	50.30	40-100
CRH (8 AM), pg/mL	70.23	-	0.004	-
Salivary Cortisol (12 AM) ug/dL	0.73	0.01-2	1.73	1-30

Table 1. Healthy and CD VPs have the appropriate concentrations.

- The model reproduces and is consistent with dexamethasone (DEX) and CRH test results for both VPs:
 - For the former, the model captures a greater than 50% inhibition of cortisol concentration for an 8 mg DEX dose reported in literature^{6,7}
 - For the latter, it captures the fold change of ACTH and cortisol concentrations for a standard 8 mg ovine CRH test^{4,8} (Table 2) and predicts the fold change in human upon applying allometric scaling

	Healthy VP	Cushing's Disease VP	Expected Value in Healthy	Expected Value in CD
ACTH: Fold change concentration	3.96	2.94	3-45	2.5-4.3
Cortisol: Fold change concentration	7.35	2.27	2-7.5	1.5-2

Table 2. Ovine CRH test fold change.

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