

Mathematical Modelling at the Interface of Digital Endocrinology and Wearable Sensing Technologies

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Summary:

Mathematical models are essential tools for fundamental understanding of hormonal dynamics within the Hypothalamic-Pituitary-Adrenal axis. Novel hormonal biosensing technologies from interstitial fluid require validating their dynamic fidelity against high resolution serum profiles.

Computational methods can integrate our mathematical understanding of endocrine systems with multimodal wearable device datasets to quantify individual variability. This can help identify reliable proxies of endocrine function for precision medicine applications.

Keywords: mathematical model, hormones, interstitial fluid, wearables, rhythms.

Background, Motivation and Objective

The Hypothalamic-Pituitary-Adrenal (HPA) axis is a vital neuroendocrine system that maintains homeostasis by regulating stress hormone secretion through tightly controlled circadian and ultradian rhythms. Despite misaligned hormonal rhythms being associated with morbidity [1], we still lack a quantitative understanding of their variability across sub-populations, their mechanistic origin, pathogenicity and dynamic adaptation in diseased states.

Dynamic 24-hr hormonal profiles collected via high frequency biosampling have demonstrable potential to advance precision endocrinology [2]. Currently, clinical decision making is predominantly based on single time point measurements typically collected from blood, saliva or urine. While novel technologies for minimally invasive subcutaneous biosampling of interstitial fluid are developing rapidly [2, 3], a barrier for their adoption is quantifying their fidelity versus the gold standard of serum hormone concentrations. This is particularly important for assessing dynamic responses to perturbations (e.g., stressors, diagnostic tests, physical activity) which can manifest through rapid changes in adrenal steroid hormones away from their dynamic equilibrium.

Mathematical modelling and computational data analysis can address this challenge by testing our understanding of hormonal regulation and formulating new hypotheses about endocrine function. We extend this approach to gain insight on the mechanisms governing HPA axis activity, including circadian and ultradian rhythms as well

as dynamic responses to stressors. This theoretical framework informs the analysis of non-invasive wearable device data to identify digital biomarkers for precision endocrinology [4].

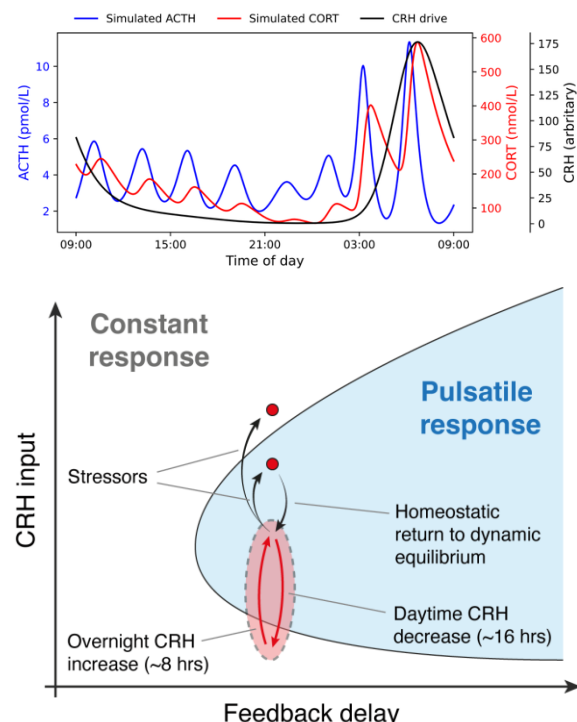


Fig. 1. Mathematical modelling of human HPA axis hormones in blood (top). The model predicts ultradian oscillations are governed by hypothalamic CRH and the delay within the pituitary-adrenal feedback loop (bottom). Figure adapted from Lombard et al. 2026 (under review).

Description of the New Method or System

We analyse 24-hour high-frequency hormonal profiles from healthy humans to quantify individual variability in HPA axis hormone rhythms. We use these profiles to develop and calibrate a mathematical model of the human HPA axis and perform computer simulations to understand the regulation of hormonal rhythms and their dynamic responses to stressors. We also analyse multimodal wearable device data in ambulatory humans to shed light on the dynamic relationship between endocrine markers and their variability across individuals.

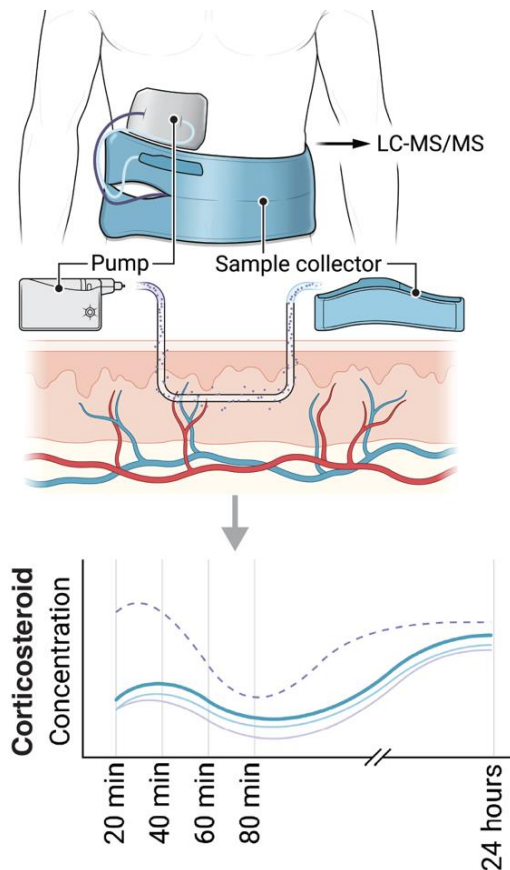


Fig. 2. Novel wearable technologies for high frequency hormonal sampling are enabling understanding of endocrine function. Computational analysis of this data allows quantification of variability, paving the way for digital endocrinology and precision medicine applications. Figure adapted from [5].

Results

The model reproduces distinct human-specific features of HPA axis dynamics, including an asymmetric circadian rhythm peaking at waking and ultradian oscillations with period and phase consistent with clinical observations. We show that the nonlinear delayed negative feedback between the pituitary and adrenal glands suffices to produce ultradian pulsatility and is critically dependent on the CRH drive and feedback delay. Computational simulations of the model predict how stressors of different intensity, duration and

timing perturb HPA axis dynamics, allowing qualitative comparisons with stress responses observed during heart surgery. We also show how combining novel biosampling techniques with mathematical and computational analysis methods can support the development of digital tools for clinical decision-making. This includes digital biomarkers that help quantify variability of daily profiles of HPA axis rhythms, define normative ranges in health, and signal endocrine dysfunction [6].

Taken together, our work provides a theoretical framework for integrating novel data from wearable sensing technologies and understanding human HPA axis regulation. Our models offer quantitative insights into the robustness, fragility and individual variability of hormonal rhythms and their role in the stress response. Computational analysis of non-invasive wearable device data can help identify surrogates of hormonal rhythm misalignment. By shifting from a qualitative to a quantitative description of endocrine function, these insights will take us a step closer to personalised clinical interventions for which timing is key.

References

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