Full-Body Particle Simulation of the HPA Axis: Comparison to Mathematical Models and Experimental Results

Lisa Y. Debus
Technische Universität Berlin
Berlin, Germany
debus@ccs-labs.org

Falko Dressler
Technische Universität Berlin
Berlin, Germany
dressler@ccs-labs.org

Abstract

By integrating experimental measurements and in-silico methods, health digital twins (HDTs) have huge potential for future personalized medicine applications. While current HDT approaches often fall back on mathematical models, they are not optimal for replicating detailed system characteristics. In this work, we present our current work-in-progress on the use of particle simulations in HDTs. With the hypothalamic–pituitary–adrenal axis as an example, we show that particle simulations can replicate given experimental measurements more accurately.

CCS Concepts

• **Networks** → **Network simulations**; • **Applied computing** → **Life and medical sciences**.

Keywords

Health Digital Twin, HDT, In-Body Molecular Communication, Simulation and Modeling

ACM Reference Format:
Lisa Y. Debus and Falko Dressler. 2026. Full-Body Particle Simulation of the HPA Axis: Comparison to Mathematical Models and Experimental Results. In *13th Annual ACM International Conference on Nanoscale Computing and Communication (NANOCOM '26), September 21–23, 2026, St. John's, NL, Canada.* ACM, New York, NY, USA, 2 pages. https://doi.org/10.1145/3818305.3830251

1 Introduction

Health digital twins (HDTs) are increasingly important as a basis for personalized patient and disease analysis in precision medicine [3]. They combine measurement data with in-silico approaches like mathematical models or simulations to create a patient-in-silico and enable machine learning (ML) solutions [2]. To remain computationally feasible, the used mathematical models often only consider the full system in its entirety without considering the exact behavior of single system components. Their exact movement and detailed interaction characteristics are summarized in abstractions. Although this can be enough for zoomed-out long-term analysis of the systems, it can hide important interaction parameters that could provide starting points for medical solutions.

NANOCOM '26, St. John's, NL, Canada

ACM ISBN 979-8-4007-2767-2/2026/09
https://doi.org/10.1145/3818305.3830251

One discipline, where HDTs promise great potential for new treatment solutions, is endocrinology [2]. Guided by highly complex interaction dynamics, hormones move through the body as signaling molecules creating communication axes. Collecting data that accurately represent these in-body communication systems over a long time can be challenging [4] and although there are some mathematical models to describe the dynamics of the overall system, they often lack the detail to be useful for a more in-depth analysis. Here, simulation-based approaches offer a step towards creating more realistic models while keeping the need for patient measurements to a minimum.

In this work, we take a first step towards more detailed in-silico representations of the hypothalamic–pituitary–adrenal (HPA) axis, one of the main communication axes in the endocrine system. Using the particle simulator medical holistic simulation architecture (MEHLISSA), we simulate the dynamics of the HPA axis and compare our output to an established mathematical model and experimental data. Our results show that the inclusion of particle simulations could offer a great benefit for future HDT systems.

2 Dynamics of the HPA axis

The HPA axis is a closed-loop feedback system that plays an important part in the body's response to stress [6]. While it is a complex system based on the interaction of many different elements, it can be condensed into the interaction between three main components: Adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH), and glucocorticoids, cortisol (CORT) in humans [6].

As shown in Figure 1, stress and circadian inputs trigger the release of CRH in the hypothalamus which in turn induces the release of ACTH in the anterior pituitary gland. Higher CRH and ACTH levels lead to the synthesis of CORT in the adrenal gland. The synthesis process delays the release of the CORT response. Once released it introduces a negative feedback-loop by reducing the CRH and ACTH release. Figure 2 shows the ACTH and CORT levels over time in experimental data collected by Upton et al. [4].

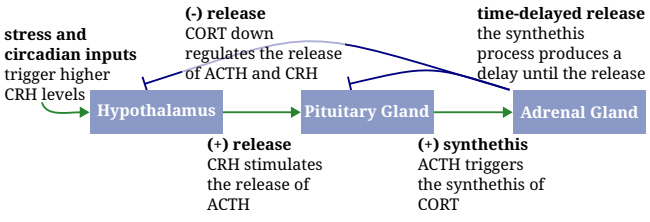

Figure 1: The HPA axis is a closed-loop feedback system that oscillates due to a delayed negative feedback loop.

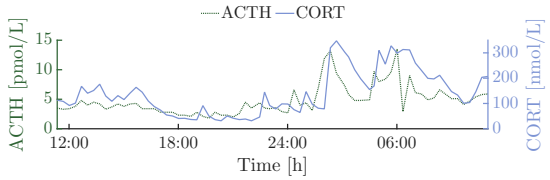

Figure 2: The ACTH and CORT levels oscillate over time [4].

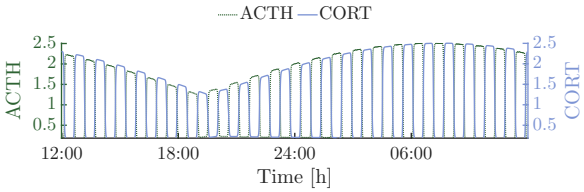

Figure 3: While the mathematical model by Walker et al. [5] replicates the general dynamics of the HPA axis, it does not accurately reproduce the actual hormone levels.

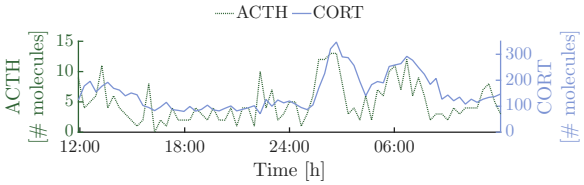

Figure 4: Using experimental ACTH measurements as an input, MEHLISSA can replicate the behavior of the HPA axis.

2.1 Mathematical Modeling

The established modeling approach for the HPA axis dynamics is via the use of delayed differential equations (DDEs). In this work, we use the three DDE system proposed by Walker et al. [5]. It expresses the circadian and ultradian oscillations of the HPA axis with each equation equaling the level of one of the involved hormones. The calculated normalized hormone levels of ACTH and CORT over 24 hours are shown in Figure 3. In the figure, the circadian oscillation was adapted from the original paper to match the hormone levels in the experimental data collected by Upton et al. [4] shown in Figure 2. While the mathematical model replicates the general dynamics of the HPA, it does not accurately reproduce the actual hormone levels.

2.2 Particle Simulation

In a first step towards a more realistic replication of the dynamics of the HPA axis, we implemented its three major signaling components and their interactions in MEHLISSA [1]. MEHLISSA is a particle simulator that enables recreating full-body flow dynamics of the human circulatory system (HCS) in-silico. To simulate the HPA axis, we added the hypothalamus, the pituitary gland, and the adrenal gland in the form of transceivers to the simulated system. They continually monitor the particles moving along their respective positions and react with the release of their own hormones following the interactions defined by Walker et al. [5]. The detection probabilities and distances, the sensitivity to detected signaling particles, the baseline intensity at the hypothalamus, and the synthesis delay at the adrenal gland can be adapted dynamically in the simulation. Based on the mathematical model by Walker et al. [5], the height of the hormone release is set via a dynamic input variable at the pituitary gland. With the experimentally collected ACTH levels from Upton et al. [4] as an input, the simulation replicates the observed CORT dynamics as shown in Figure 4.

3 Evaluation

Comparing Figures 3 and 4 with the experimental data in Figure 2, we can clearly observe that the simulation in MEHLISSA replicates the hormone dynamics much better than the mathematical model. While the mathematical models offer faster computation times, the simulation is able to recreate a higher level of detail. For this, the MEHLISSA simulation needs ACTH measurements as input. With these as a baseline, its simulation parameters are adapted to fit the exact system behavior. The approach is slower and more complex than the straight-forward and fast mathematical model, but it offers the potential for detailed customization. While the current work-in-progress model has to be customized by hand, the full parameter fitting process will be automated in future iterations. The adaptability of the simulation-based model offers the potential to run detailed parameter studies emulating medical interventions. Together with the integration of artificial intelligence, this approach can enable detailed and continuously adaptable in-silico-patients for health digital twins.

4 Conclusion

Our work-in-progress simulation of the HPA axis clearly shows the potential of using simulations in HDTs. The simulated model offers a high level of detail and customizability. In future work, we will automatize the fitting of the simulation parameters to experimental data and extend its validation with experimental data.

Acknowledgments

This work was funded by BMFTR (project IoBNT, grant 16KIS1986K) and by DFG (project NaBoCom, grant DR 639/21-3).

References

[1] Lisa Y. Debus, Regine Wendt, Stefan Fischer, and Falko Dressler. 2025. MEHLISSA 2.0: Accelerating Full-body Molecular Communication Simulations. In *ACM NANOCOM 2025, Poster Session.* ACM, Chengdu, China, 171–172. doi:10.1145/3760544.3765642

[2] Clara Mosquera-Lopez and Peter G. Jacobs. 2024. Digital Twins and Artificial Intelligence in Metabolic Disease Research. *Trends in Endocrinology & Metabolism* 35, 6 (6 2024), 549–557. doi:10.1016/j.tem.2024.04.019

[3] Christoph Sadée, Stefano Testa, Thomas Barba, Katherine Hartmann, Maximilian Schuessler, Alexander Thieme, George M. Church, Ifeoma Okoye, Tina Hernandez-Boussard, Leroy Hood, Ilya Shmulevich, Ellen Kuhl, and Olivier Gevaert. 2025. Medical Digital Twins: Enabling Precision Medicine and Medical Artificial Intelligence. *The Lancet Digital Health* 7, 7 (7 2025), 1–10. doi:10.1016/j.landig.2025.02.004

[4] Thomas J. Upton, Eder Zavala, Paal Methlie, Olle Kämpe, Stylianos Tsagarakis, Marianne Øksnes, Sophie Bensing, Dimitra A. Vassiliadi, Marianne A. Grytaas, Ileana R. Botusan, Grethe Ueland, Katarina Berinder, Katerina Simunkova, Maria Balomenaki, Dimitris Margaritopoulos, Nina Henne, Robin Crossley, Georgina Russell, Eystein S. Husebye, and Stafford L. Lightman. 2023. High-Resolution Daily Profiles of Tissue Adrenal Steroids by Portable Automated Collection. *Science Transl. Med.* 15, 701 (6 2023). doi:10.1126/scitranslmed.adg8464

[5] Jamie J. Walker, John R. Terry, and Stafford L. Lightman. 2010. Origin of Ultradian Pulsatility in the Hypothalamic–pituitary–adrenal Axis. *Proceedings of the Royal Society of London B: Biological Sciences* 277, 1688 (June 2010), 1627–1633. doi:10.1098/rspb.2009.2148

[6] Eder Zavala, Kyle C.A. Wedgwood, Margaritis Voliotis, Joël Tabak, Francesca Spiga, Stafford L. Lightman, and Krasimira Tsaneva-Atanasova. 2019. Mathematical Modelling of Endocrine Systems. *Trends in Endocrinology & Metabolism* 30, 4 (April 2019), 244–257. doi:10.1016/j.tem.2019.01.008