Analysis of Ordinary Differential Equation Models Representing the Dynamics of Hormone Axis

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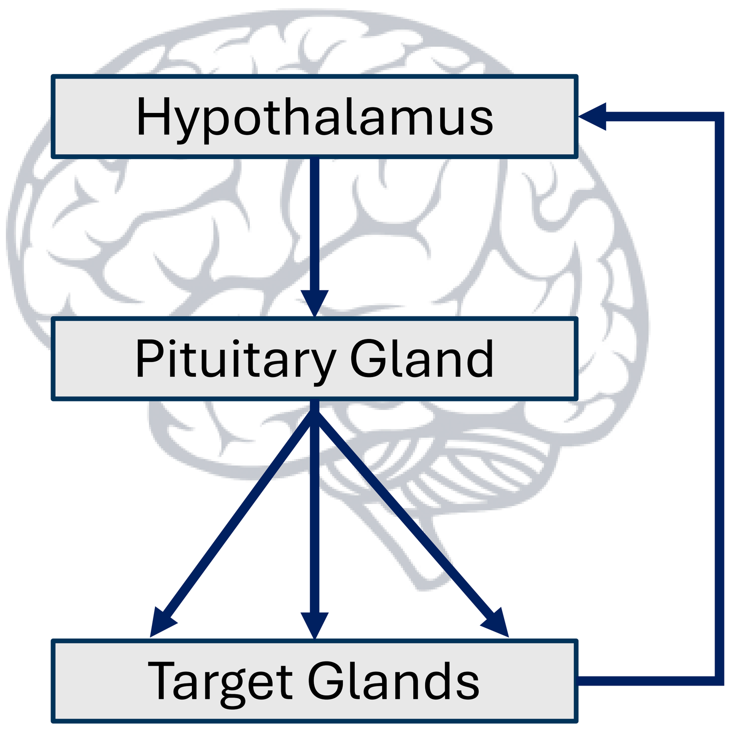
Introduction

The endocrine system is essential for maintaining overall health by regulating metabolism, reproductive function, and early brain development. Central to these regulations are hormonal axes – network of interactions where the hypothalamus releases regulatory hormones that act on the pituitary gland. This interaction triggers the secretion of tropic hormones, which in turn stimulate target organs, establishing a complex, feedback-driven system vital for physiological balance.



Objective

This study is dedicated to the mathematical modeling and analysis of two key endocrine axes:

- Hypothalamus-Pituitary-Thyroid (HPT) axis
- Hypothalamus-Pituitary-Ovary (HPO) axis

Mathematical Modeling

- Type of Equations: Ordinary Differential Equations
- Goal: To describe the dynamics and regulatory feedback loops of the endocrine system[1,2]

Exemplary Model [2] below describes the course of the autoimmune disease Hashimoto's thyroiditis.

FT4	$\frac{\mathrm{d}x}{\mathrm{d}t} = k_1 - \frac{k_1 y}{k_a + y} - k_2 x,$	$x(t_0) = x_0,$
TSH	$\frac{\mathrm{d}y}{\mathrm{d}t} = \frac{(k_3 z)x}{k_d + x} - k_4 y,$	$y(t_0) = y_0,$
Functional Size	$\frac{\mathrm{d}z}{\mathrm{d}t} = k_5 \left(\frac{x}{z} - N\right) - k_6 z w,$	$z(t_0) = z_0,$
TPOAb	$\frac{\mathrm{d}w}{\mathrm{d}t} = k_7 z w - k_8 w,$	$w(t_0) = w_0.$

Analysis

HPT-Axis[1]

Stability Analysis

- Asymptotically stable equilibrium
- The system returns to a steady state regardless of small perturbations in the model parameters

HPT- and HPO-Axis[2]

Local Sensitivity

$$\frac{\partial z(t,\theta)}{\partial t} = f(t, z(t,\theta), \theta)$$

Model Parameters (θ)

$$z\colon I \times G \to \mathbb{R}^n,\; z = z(t,\theta),\; I \subseteq \mathbb{R},\; G \subseteq \mathbb{R}^m$$

$$\left.\frac{\partial z_k(t,\theta^*)}{\partial \theta_j}\right|_{\theta=\theta^*} \qquad \theta^* \in \mathbb{R}^m \text{ Fixed Parameter Vector}$$

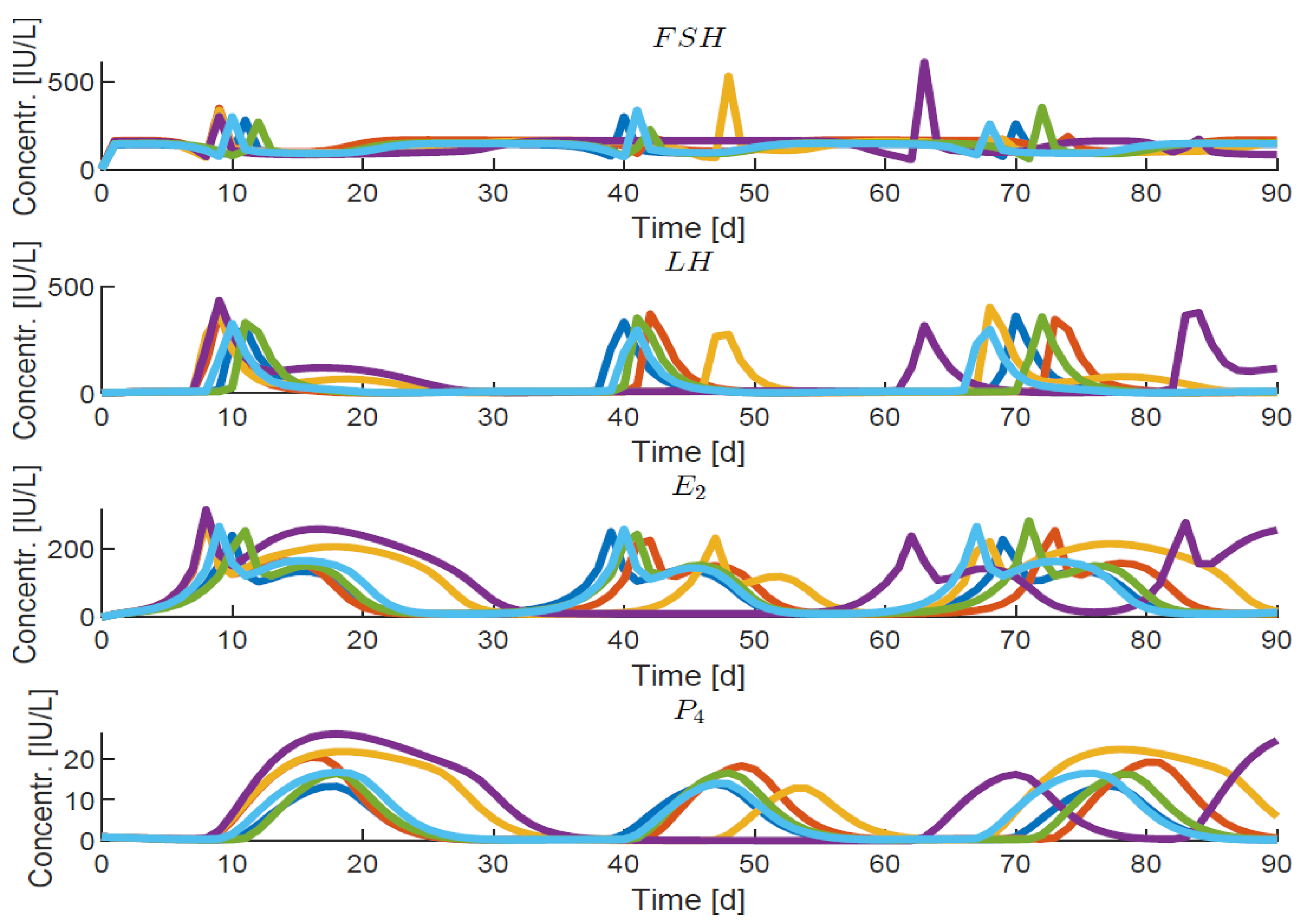
Global Sensitivity[3]

The following methods were employed:

- Latin Hypercube Sampling
- Partial Rank Correlation Coefficient
- Extensive Fourier Amplitude Sensitivity Testing
- Sobol' indices

Calibration

- Utilized clinical measurements to calibrate model parameters
- Model validation to assess applicability to depict physiological dynamics



Outlook

HPT-Axis

- Model refinement and improvement
- Further validation with clinical data

HPO-Axis

- Local and global stability analysis of selected models
- Calibration of model parameters

Main References

[1] Balamurugan Pandiyan, Stephen J. Merrill, and Salvatore Benvenga. A patient-specific model of the negative-feedback control of the hypothalamuspituitary-thyroid (hpt) axis in autoimmune (hashimoto's) thyroiditis. Mathematical medicine and biology: a journal of the IMA, 31 3:226–58, 2014

[2] Graham, E.J., Elhadad, N., and Albers, D. (2023). Reduced model for female endocrine dynamics: Validation and functional variations. Mathematical Biosciences, 358, 108979

[3] Marino, S., Hogue, I.B., Ray, C.J., and Kirschner, D.E. (2008). A methodology for performing global uncertainty and sensitivity analysis in systems biology. Journal of Theoretical Biology, 254(1), 178–196