Endocrine systems modeling:

Towards personalized treatment of thyroid diseases.

Thyroid hormone plays an essential role in development and function of virtually all human organs. Thyroid hormone is produced by the thyroid and concentrations are tightly regulated by a negative feedback loop, the so-called hypothalamus-pituitary-thyroid (HPT) axis (Figure 1). Various studies have shown that every individual has its own unique HPT-axis set point, i.e., its own unique combination of thyroid hormone levels. When the thyroid is affected by a disease, a lower thyroid function can lead to low thyroid hormone levels (hypothyroidism). Hypothyroidism is among the most common disorders in the general population, and is treated with oral tablets of thyroid hormone (levothyroxine). Currently, 480,000 patients in The Netherlands alone are treated with levothyroxine. Approximately 15% of these patients experience persistent hypothyroid complaints despite normalization of the thyroid hormone levels on levothyroxine treatment. This is likely because their blood hormone levels do not match their unique HPT-axis set point. An overview of the normal operating configuration of the hypothalamus – pituitary - thyroid (HPT) system is depicted in Figure 1.

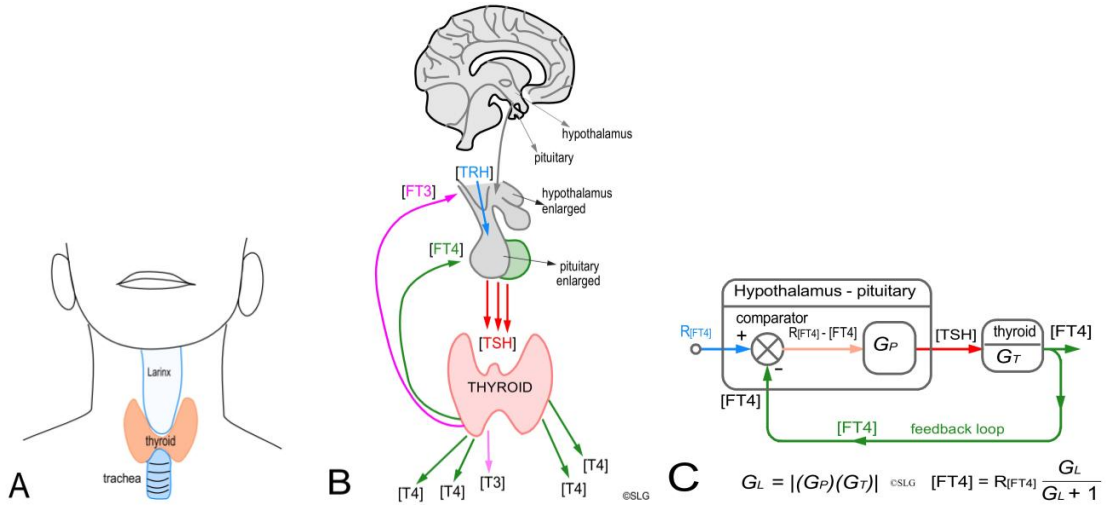

Figure 1 Panel A represents the position of the thyroid in the human body. Panel B depicts the physiological presentation where the hypothalamus, pituitary and the thyroid form a closed feedback loop system with the main hormones [TSH] as stimulating hormone concentration to initiate thyroidal hormone production of mainly [T4] and a little [T3]. The hypothalamus pituitary responds on the detected free fraction of [T4], noted as [FT4] to inhibit the generation of [TSH] from the pituitary and represents the negative (inhibiting) part of the loop. Panel C of figure 1 represents the functional feedback block diagram of the HPT system where the [FT4] output is kept close to the $R_{[FT4]}$ input reference.

Unfortunately, we currently cannot predict a patient's HPT-axis set point. However, in recent years Goede and colleagues have mathematically modeled the HPT-axis, expressed as a negative exponential function[1,2]. Every exponential function has a curvature singularity, or point of maximum curvature[3] , which is expected to represent an individual's HPT-axis set point. In the current MSc project, this model will be further optimized and tested at the Department of Applied Mathematics. This will be an important step before testing this model in patients. For these reasons, this MSc project provides the unique opportunity to work at the intersection of applied mathematics and medicine, and will be a key step towards a personalized treatment of thyroid diseases .

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