Delft University of Technology

Endocrine systems modeling: Towards personalized treatment of thyroid diseases

LITERATURE REVIEW

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Abbreviations

FT3 Free triiodothyronine

FT4I Free thyroxine index

FT4 Free thyroxine

HPT Hypothalamus-pituitary-thyroid axis

LT3 Liothyronine

LT4 Levothyroxine

T3 Triiodothyronine

T4 Thyroxine

TFT Thyroid function test

TPOAb Anti-thyroid peroxidase antibodies

TRH Thyroid-releasing hormone

TSH Thyroid-stimulating hormone

Units of measure

mU/L Unit of measure of TSH, corresponding to milliunits per litre. U is the international unit, which measures the amount of a substance.

pmol/L Unit of measure of FT4 and FT3, corresponding to picomole per litre.

Contents

1 Introduction

Thyroid hormones are fundamental in the development and function of the human body. They are produced by the thyroid and their concentration is regulated by a negative feedback loop, which involves also the hypothalamus and the pituitary. This configuration of the feedback loop is called hypothalamus-pituitary-thyroid (HPT) axis [1]. Many studies have shown that each individual has a unique HPT axis set-point, which means that everyone has its own personal level of thyroid hormones. However, when the thyroid is affected by a disease, such as hypothyroidism, a change in the thyroid function modifies the levels of thyroid hormones, therefore they do not match the set-point of that individual anymore.

Hypothyroidism is a disease that affects the thyroid and it is characterised by a low level of thyroid hormones. It is one of the most common disorders in the general population and currently it is treated with tablets of levothyroxine (LT4). However, 35-60% of patients treated with levothyroxine do not reach the target range of TSH. Furthermore, it is estimated that 5-10% of patients still present persistent complaints, despite their hormone concentrations being within the normal reference ranges [2]. In particular, in the Netherlands there are already 480.000 patients taking levothyroxine and 15% of them still have symptoms, even if their thyroid hormone levels are within the target ranges. One of the reasons why this happens might be because the hormone levels of these patients do not match their HPT axis set-point. This is why this topic is an important issue and it has received increasing attention during the last years. Hence, it is fundamental to find a mathematical description of the HPT axis, together with a prediction of the individual set-point. In this way, the medication dosage can be adjusted for every patient such that each individual can reach its own set-point.

The modeling of the HPT axis started more than sixty years ago. However, not all proposed models are valid and applicable. In particular, the first models involved many parameters that could not be estimated. In the last years, the modeling of the HPT axis has focused more on population models. In fact, most of the HPT axis models developed until now are based on a statistical approach. This means that they involve and combine data from multiple patients. However, this approach implies that the hormone levels of one individual can influence the hormone values of someone else, which does not happen in reality. Furthermore, population models cannot be applied to single individuals, hence they cannot be used to estimate the specific set-point of a patient.

However, recently, a patient-specific mathematical model of the HPT axis has been developed. This is expressed as a negative exponential function between the concentrations of thyroid-stimulating-hormone (TSH) and free thyroxine (FT4). Furthermore, in this model the set-point is estimated to be the point of maximum curvature of the exponential function [3]. Thus, the purpose of modeling the HPT axis from a mathematical perspective is to gain insight into the mechanism of the negative feedback loop and improve the diagnostic process and the treatment of thyroid diseases. The set-point computed in this way can be used to adjust the therapy of thyroid disorders for each individual, such that the conditions of many patients can improve.

Therefore, the goal of this thesis project is to validate the existing exponential model for the HPT axis and, possibly, further improve and optimize it. This represents a fundamental step towards a personalized treatment of thyroid diseases. The acceptance of this theory will help to improve the condition of many thyroid patients that still present complaints or have an inaccurate diagnosis.

The remainder of this literature review is structured as follows. Section 2 provides a medical background about the HPT axis, with an explanation of all the terms needed to understand its functioning. This also includes a focus on hypothyroidism and on its treatment. Furthermore, a description of the measurements details of the hormones involved will also be provided. In

Section 3, the mathematical modeling of the HPT axis based on a patient-specific approach will be presented. This section presents the model based on a negative exponential function and the representation of the HPT axis through control theory. Finally, this section includes a different modeling approach as well, which is still valid on an individual level. Section 4 presents different population models, which are based on a statistical approach. A study that applies these models on single individuals is also presented. Finally, the last section presents the discussion, conclusion and the research questions that will lead the thesis project.

2 Medical background

2.1 General concepts

The thyroid gland is located below the larynx, anterior to the trachea. It is divided into two lobes, one on each side of the trachea [1, 4]. It is one of the largest endocrine glands and one of its main functions is to produce two major hormones, thyroxine (T4) and triiodothyronine (T3). These hormones increase the metabolic rate of the body and without them the chemical reactions of the body would become very slow [1]. Thyroid hormone is fundamental for a correct development, therefore a lack of T4 would cause an inhibited growth [4]. Another important effect of thyroid hormones is to facilitate the growth and development of the brain [1]. 93% of the hormones produced by the thyroid is T4, while the remaining 7% consists of T3. However, both hormones are functionally important because a significant portion of T4 is converted to T3. In order to produce normal quantities of T4, it is needed to ingest enough iodine. About half of T4 is then slowly deiodinated to form additional T3 [1]. Only 20% of the circulating T3 is produced by the thyroid gland, the remaining amount is produced by peripheral conversion of T4 [5]. The production of these thyroid hormones is controlled by the thyroid-stimulating hormone (TSH), also called thyrotropin, which is produced by the anterior pituitary.

The pituitary is a small gland situated in a cavity at the base of the brain. It is connected to the hypothalamus and it is divided into anterior and posterior pituitary. The anterior pituitary produces TSH whose function is to stimulate the synthesis and secretion of the thyroid hormones T4 and T3. The hypothalamus is a small region in the brain, located close to the pituitary gland. Despite its small size, it is responsible for many fundamental functions, including the release of hormones. In particular, the hypothalamus produces thyrotropin-releasing hormone (TRH), whose major function is to stimulate the secretion of TSH [1].

A feedback mechanism through the hypothalamus and the pituitary is operated in order to control the secretion of thyroid hormones. This is essential to guarantee the correct level of thyroid hormones needed to maintain a normal metabolic activity. TSH is produced by the anterior pituitary and it increases the secretory activities of the thyroid cells. The first early effect of TSH is to cause the release of T4 and T3 in the blood stream within the next minutes. All the other effects require hours or days to develop completely. The secretion of TSH by the anterior pituitary is controlled by a hormone produced by the hypothalamus, the TRH [1]. This hormone is delivered to the anterior pituitary in order to increase the synthesis and release of TSH [4]. An increased level of thyroid hormones in the body decreases the production of TSH. When the rate of secretion of thyroid hormones is around 1.75 times more than the normal rate, the secretion rate of TSH becomes almost zero. An increased level of thyroid hormones inhibits the production of TSH by affecting the anterior pituitary directly. The goal of the feedback is to keep almost a constant concentration of free thyroid hormones [1]. Figure (1) shows a representation of the hypothalamus-pituitary-thyroid (HPT) axis with its feedback loop.

One physiological aspect that affects the HPT axis is clock time. In fact, the HPT axis is regulated by a circadian cycle [7, 8]. The circadian system is an internal process that repeats every 24 hours and regulates all physiological and behavioural processes, including the release of hormones. The secretion of TSH follows a daily rhythm. In fact, during the late afternoon or early evening, the TSH concentration starts to rise, until it reaches its peak at the beginning of the sleep period. After that, TSH concentration declines again during the remaining part of the sleep period in order to reach the low daytime level [7, 8]. The 24-hours cycle of the TSH secretion is stable and robust and it is not influenced by age or sex. A diurnal variation in thyroid hormones T3 and T4, however, is not obvious since different studies report discording results [7, 8].

Thyroid hormones are transported in the blood by specific proteins. This is one of the

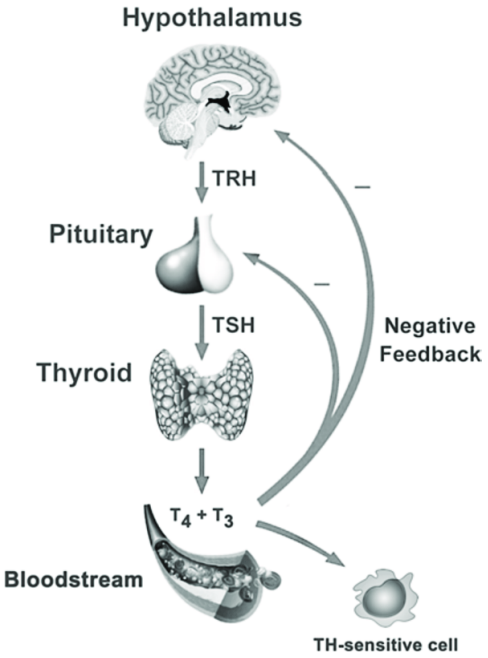


Figure 1: HPT axis negative feedback loop. Taken from [6].

reasons why total T4 and T3 are the most variable measures, making them not enough reliable measurements to study changes in the thyroid function. Free T4 (FT4) and free T3 (FT3) refer to the relative thyroid hormones not bound to serum proteins. They are considered to be more precise measures of thyroid dysfunction [4]. In order to recognise a thyroid dysfunction, a thyroid function test (TFT) is conducted. As a first screening, the level of TSH is checked and, if it is abnormal, the concentration of FT4 is then measured as well [9].

2.2 Hypothyroidism

Hypothyroidism is a pathological condition that refers to thyroid hormone deficiency [2] and it affects around 10% of the global population. Hypothyroidism affects more often women, white individuals, older people and patients with autoimmune diseases [5]. Since the symptoms and clinical manifestations can vary between different individuals, the definition of hypothyroidism is based on reference ranges of the fundamental biochemical parameters, namely TSH and FT4 [2, 10]. Reference ranges depend on the assay used and the population analyzed. An assay is the investigative procedure that can determine the presence of a substance and its amount. The reference ranges are defined between the 2.5th and 97.5th percentile of a healthy population [2]. The most common used reference range for TSH is $0.4 - 4.0$ mU/L, while for many laboratories the normal range for FT4 is $10.0 - 20.0$ pmol/L [11]. However, the reference ranges have been the matter of debate in the last years. In fact, some studies show that in particular the upper limit of the TSH reference range tends to increase in older people. Nevertheless, there is not enough data to adjust the reference ranges according to age [10].

Hypothyroidism can be divided into different categories: primary (or overt) and subclinical (or mild) hypothyroidism. Primary hypothyroidism is defined as TSH concentration above the reference range and FT4 concentration below the normal range [2], while subclinical hypothyroidism is defined as TSH above the population range and FT4 within the reference range [2, 10]. Another possible classification of hypothyroidism is into primary, secondary, tertiary and peripheral hypothyroidism. Primary hypothyroidism is caused by thyroid hormone deficiency. Secondary hypothyroidism is due to TSH deficiency, while tertiary hypothyroidism is caused by

a shortage of TRH; these two categories are usually grouped together and referred to as central hypothyroidism. Finally, peripheral thyroidism is due to extra-thyroidal causes [2].

As anticipated, clinical presentation of hypothyroidism can vary significantly between patients, ranging from life-threatening to no symptoms at all. Even though life-threatening conditions are very rare nowadays, it is still fundamental to recognise hypothyroidism early, in order to start immediately with the treatment [2]. The most common symptoms are weight gain, cold intolerance, fatigue, shortness of breath, change of voice, constipation, dry skin, hair loss, deterioration of kidney function, impaired memory and mood. However, these symptoms can vary with age and sex, therefore none of them can be used to identify patients subject to hypothyroidism [2, 10]. Hence reference ranges are the only instruments used to identify hypothyroidism.

The standard treatment of hypothyroidism is levothyroxine (LT4) monotherapy, taken in solid formulation on an empty stomach [2]. Changing different levothyroxine products is not recommended because differences in the absorption of LT4 preparations can alter the clinical outcomes and the TSH levels [5]. In particular, in older patients or in those patients with a low body weight, a small change in the medication can cause large effects on TSH concentrations [2]. This is why after the start of medication or after the adjustment of the dosage, the serum TSH concentration should be checked more frequently until it is stabilised [2, 10]. Both under-treatment and over-treatment should be avoided, because they can cause serious problems. The treatment target consists in normalizing the level of TSH and resolving all the complaints. Nevertheless, it is estimated that 35-60% of the patients does not reach the reference target for the TSH level. There could be some reasons that prevent patients from reaching their target, such as prescription of wrong dosage, non-adherence to the therapy, interaction with other medication. Around 5-10% of the patients still have persistent complaints, despite being biochemically euthyroid [2, 10]. Euthyroidism is the condition of having a thyroid gland that functions normally.

One of the reasons why this happens might be because the concentrations of circulating thyroid hormone are regulated by the HPT axis through an individual set-point, which allows a smaller intra-individual variability than the inter-individual one. The concept of HPT axis set-point will be explained further in the next sections. Therefore, the level of TSH required to reach the concentrations of thyroid hormones needed by an individual changes between different patients. This explains also why patients with similar values of TSH respond differently to the treatment [2, 10]. Population-based reference ranges are not able to define the thyroid status in an individual, because average results based on a population cannot be satisfactorily applied to all the members of the population [12]. Another possible explanation to the persistence of symptoms in some patients might rely on some flaws of the levothyroxine monotherapy itself. It should also be taken into account that a normal level of TSH represent euthyroidism at the level of the pituitary, not in all tissues [2]. From the previous considerations, it is clear that the current situation causes dissatisfaction both in patients and in doctors. One way of trying to solve this problem consists in reconstructing the individual set-point, which can give better outcomes than population-based reference ranges [12]. Hence, this will be the focus of the thesis.

2.3 Evolution of the treatment of hypothyroidism

The treatment history of hypothyroidism goes back to two thousands years ago. Already during the 6th century, Chinese treated cretins with sheep thyroid [5]. Cretinism is a condition caused by extreme hypothyroidism occurring during fetal or early life. It is characterized in particular by failure of physical growth and by mental retardation [1]. In 1888, the Clinical Society of London stated that the loss of function of the thyroid resulted in what now is called hypothyroidism. However, this was not followed by any therapeutic recommendation [13]. In 1891, the physician George Murray started to treat patients affected by myxedema, which is one of the most severe conditions of hypothyroidism, with injections of sheep thyroid extracts [5, 13]. The next year,

the physicians MacKenzie and Fox started the oral administration of fresh sheep thyroid glands [5], which was followed by many reports declaring the effectiveness of fried or ground sheep thyroid [13]. This was the first time that an effective therapy became available [13]. It was soon recognised that the preparation of thyroid extracts injections was very demanding, both in terms of time and money. This represents the reason why there was then a transition to oral preparation of thyroid extracts. However, this change carried the risk of over-dosage [5].

In 1914, Kendall was able to isolate the active principle of the thyroid extract, which in 1927 allowed Harington and Barger to find the structure of this molecule, later called thyroxine, and synthesize it. This molecule was first synthesized as an acid, which limited oral absorption [5, 13]. Hence, desiccated thyroid continued to remain the treatment of choice. Desiccated thyroid consists of dried animal thyroid glands, administered to treat hypothyroidism [13]. In 1949, a sodium salt of thyroxine, called levothyroxine, was finally synthesized in large quantities. Furthermore, in 1952, triiodothyronine (T3) was recognised as the second active thyroid hormone [5, 13]. When these synthetic preparations became available, levothyroxine was in general preferred to desiccated thyroid [13] and combination therapy with LT4 and LT3 (liothyronine) became the standard replacement therapy before 1970 [5]. However, in the 1970s, the identification of peripheral deiodinase-mediated conversion from T4 to T3 and the advent of radioimmunoassays for serum free hormone and TSH allowed to conduct specific studies regarding the different possible treatments [5, 13].

This led towards a preference for LT4 monotherapy, because it was proved that it was able to clinically normalize both T4 and T3. In fact, a relatively high incidence of side effects in patients under combination therapy was registered. Furthermore, clinicians started focusing on normalizing the level of TSH because of its ease in measurement, predictability and absence of unexpected results. It became also possible to recognise over- and under-treatment. After some changes in the quality control process of thyroid products, the quantity of LT4 contained in the tablets became more uniform. However, even after LT4 monotherapy became the treatment of choice, there still remained a subgroup of patients with persistent symptoms, despite the normalization of the TSH level [5]. In fact, 5-10% of hypothyroid patients on levothyroxine continue to present impaired well-being, decreased quality of life, increase in anxiety and depression. Hence, some doubts regarding the inadequacy of the LT4 monotherapy started to spread [13]. However, some studies conducted in the 2000s comparing levothyroxine plus liothyronine combination therapy and levothyroxine monotherapy could not prove the superiority of combination therapy. This is probably due to the fact that the subgroup of patients that can benefit from LT4-LT3 combination therapy still needs to be identified. Furthermore, combination therapy might improve if LT4 and LT3 are administered in a dose ratio that can result in normalized TSH levels and normalized FT4:FT3 concentration ratios. That is why LT4 monotherapy is still the treatment of choice and combination therapy is just an experimental modality [2, 13].

2.4 Measurements details of TSH, FT3 and FT4

Thyroid function tests are employed to distinguish hyperthyroid and hypothyroid states from the euthyroid one. In order to do this, direct measurements of the concentrations of TSH and total or free T4 and T3 are employed. However, measurement of FT3 is only used on a limited basis [14]. In fact, in hypothyroid individuals T3 is the last value to become abnormal, hence many patients still show normal levels of T3 [14]. Reference ranges of TSH and FT4 are established by each laboratory through a statistical distribution of TSH and FT4 levels, measured from a group of healthy patients belonging to the general population [15]. The measurement of free hormones (FT4 and FT3) is usually accepted as an appropriate indicator of the thyroid functional state. Hence, for diagnostic purposes, the focus should be on free hormones rather than on the total ones [16, 17].

Generally, clinical research analyzes data from a population with a statistical approach. Hence, uncertainties and measurement inaccuracies do not play a relevant role, since most of the variability is cancelled out when considering aggregated data. However, when reconstructing the hypothalamus-pituitary (HP) curve for a specific individual, only measurements from the same laboratory, conducted using the same technique and with the same calibration accuracy should be used. This is because the way of reporting laboratory results and their interpretation changes between different laboratories, causing a big impact on the reconstruction of the HP characteristic. In fact, for example, in many laboratories the level of FT4 is reported as an integer value, which implies an uncertainty of the real value. When rounding to the nearest integer, an absolute uncertainty of ± 0.5 pmol/L is expected, while, when truncating the decimal digits, the uncertainty of FT4 becomes ± 1 pmol/L. However, in other laboratories, the value of FT4 is rounded by keeping one decimal digit. In addition, it is fundamental that the measurements of TSH and FT4 of a patient are always taken at a fixed time of the day, before the daily intake of LT4, because of diurnal variations of the levels of TSH [15].

In this thesis project, data that is already available will be used, hence measurements might come from different laboratories or they may be performed with different techniques. However, for next projects, it will be important to take also into account how the data is collected, hence it is fundamental to consider measurements coming from the same laboratory, taken with the same method and at the same time of the day.

Thyroid hormones are present in the blood in extremely small quantities, hence it is very hard to measure their concentrations. However, in the 1970s, a very sensitive method for the measurement of hormones, called radioimmunoassay, was developed [1]. A radioimmunoassay consists of making a known quantity of an antigen radioactive and then use it to detect the amount of the same antigen in the patient's blood sample. The radioimmunoassay method was first introduced in 1959 by Yalow and Berson to measure the level of insulin in the blood. After that, methods for measuring the concentrations of TSH, T4 and T3 were soon developed [16]. Since then, there have been many improvements in assays for TSH, FT4 and FT3 [9]. Nowadays, immunoassays are the most common methods to measure the levels of TSH, FT4 and FT3 [16, 18]. An immunoassay measures the concentration of a substance by using an antibody or an antigen. A problem with immunoassays is specificity. In fact, for example, it can happen that when measuring the concentration of FT4, also a small amount of FT3 can be included in the measurement because the specificity of immunoassays is not optimal. Furthermore, this technique might have an impact on the diagnosis and treatment of hypothyroidism. In fact, sometimes it can happen that samples from hypothyroid patients have thyroid hormone levels below the detectable limit of immunoassays [18].

Recently, research has focused on mass spectrometry methods for the simultaneous analysis of TSH, T4 and T3, so they now represent an alternative to immunoassays since mass spectrometry instrumentation is becoming widespread in clinical laboratories [18]. A mass spectrometry can measure the mass of a molecule after having transformed it into a gas-phase ion. Mass spectrometry methods have successfully dealt with problems related to many immunoassays for thyroid hormones because they present higher specificity and accuracy of thyroid hormone measurements. This can improve diagnostic capabilities because measurements of thyroid hormones are more reliable. Therefore, mass spectrometry methods are now regarded as the new gold standard. In the near future, mass spectrometry has the potential to be applied in clinical assessment routine, in particular for FT4 and FT3 [17].

3 Mathematical modeling of the HPT axis

3.1 General overview

As described in the previous section, the well-being of many patients is still suboptimal, despite their TSH and FT4 values are within the reference ranges. This explains the need for individualised treatment [3] and it is the reason why, in the last years, the mathematical modeling of the HPT axis set-point has received increasing attention.

The first model was elaborated in 1956 by Danziger and Elmegreen [19]. Their contribution is fundamental because it points out the importance of mathematical modeling in endocrine control system. The authors implemented a system of non-linear differential equations, which can be linearized and eventually solved, if the parameters of the system are known or can be estimated. Furthermore, the authors emphasised the difficulty in obtaining measurements, hence the parameters are not known or are known with little accuracy [19]. Another important contribution was given by DiStefano and Stear in 1968 [20]. They improved the previous model and presented it in the framework of feedback control system theory. They developed a system with two coupled differential equations with 11 parameters and variables. However, not all of them are measurable, which makes their model not usable in practice [20]. Next, the publication of Wilkin et al. in 1977 [21] finally mentioned the importance of the loop gain in the representation of the HPT axis through control-loop theory. The paper from Leow [22], published in 2007, pointed out the necessity of a simple mathematical model, where only measurable parameters are involved. Furthermore, this study finally led the way in the implementation of an exponential model between TSH and FT4 [22]. In 2010, Hoermann et al. published a study [23] in which they compare the linear model between log(TSH) and FT4 with a non-linear model based on the error function (erf) between log(TSH) and FT4. This new non-linear model proved to fit better the data. However, the models were tested on aggregated data and not on single patients, so this implies a mutual influence between all the individuals included in the population. Finally, in 2014, Goede et al. [3] implemented a negative exponential model between TSH and FT4 and tested it on datasets belonging to single individuals, not on population data. This is because their model is valid on an individual level and differs from one patient to another. This model will be explained further in the next section.

Table (1) shows an overview of the main mathematical models proposed in the last decades. The first models that were developed assumed an inverse linear relationship between TSH and FT4. However, after more studies, the relationship between TSH and FT4 started to be considered log-linear and this has remained the standard in particular since 2007, with the study of Leow.

There are probably many ways to model the HPT axis in a more complex way, however simpler mathematical models are more attractive because easier to understand. Furthermore, some highly accurate models may not be applicable in practice, because they might require values of quantities, like TRH, whose measure is either not available or not reliable. In addition, even these accurate and complicated models cannot include all the factors influencing the level of hormones. That is why a minimal model including only measurable and observable variables is to be preferred. Any model including many variables might be too complicated for normal use, despite being definitely more accurate. On the contrary, a simpler model would be less realistic, but more understandable and easier to apply, even by non-mathematicians. Hence, it is not necessary that a mathematical model includes all the relevant factors under consideration, as long as the assumptions and the limitations are correctly understood and taken into account [22].

Author	Year of publication	Regression
Danziger and Elmergreen	1956	Linear
Roston	1959	Linear with basal secretion
Norwich and Reiter	1965	Linear
DiStefano and Stear	1968	Linear with basal secretion
DiStefano and Chang	1969 and 1971	Linear with basal secretion
Saratchandran et al.	1976	Log-linear
Wilkin et al.	1977	Restricted maximum secretion
Hatakeyama and Yagi	1985	Power law and linear
Cohen	1990	Exponential
Spencer et al.	1990	Log-linear
Li et al.	1995	Non-linear polynomial
Dietrich et al.	1997, 2002, and 2004	Michaelis–Menten kinetics, non-competitive inhibition and first-order time constants
Sorribas and González	1999	Power laws
Leow	2007	Log-linear
Degon et al.	2008	Non-linear
McLanahan et al.	2008	Michaelis–Menten kinetics, non-competitive inhibition and first-order time constants
Eisenberg et al.	2008 and 2010	Adopted from DiStefano
Benhadi et al.	2010	Log-linear
Hoermann et al.	2010 and 2014	Erf (modulated log-linear) and polynomial
van Deventer et al.	2011	Log-linear
Clark et al.	2012	Polynomial
Midgley et al.	2013	Segmented log-linear
Hadlow et al.	2013	Polynomial
Jonklaas et al.	2014	Segmented
Goede et al.	2014	Exponential and loglinear with Michael–Menten-type feedforward path

Table 1: Overview of the mathematical models for HPT axis. Taken from [24].

3.2 TSH-FT4 exponential model

The relationship between TSH and FT4 has been modelled as a negative exponential in 2014 by Goede et al. [3] and this has remained the standard until now.

Even though T3 is the main active hormone, this mathematical model only includes the relationship between TSH and FT4. In fact, since a model with two degrees of freedom is adopted, the influence of FT3 can be subsumed within the two model parameters [3]. Furthermore, TFTs generally require the measurements of FT4 and TSH, rarely of FT3. Hence, a more comprehensive model including also FT3 would definitely be more accurate, but it would lose its applicability in real life, since FT3 levels are usually not available [25].

In this model, the hypothalamus-pituitary (HP) complex is considered as a master regulator unit, which calibrates its level of TSH according to the concentration of FT4. The HP curve should be analyzed in an open loop, without the influence of a healthy operating thyroid [3]. In fact, in an euthyroid individual, the closed feedback loop is operating correctly, so every measurement of TSH and FT4 represents the HPT axis set-point. Therefore it is not possible

to derive the HP characteristic. However, this is not happening in patients affected by thyroid diseases since their feedback loop is not working properly, so their values of FT4 and TSH change after every adjustment of their medication dosage.

It can be noticed that TSH varies inversely with FT4, in a non-linear way. In particular, small changes in FT4 can lead to large changes in TSH. When TSH and FT4 are both represented on a linear scale, the relationship between them resembles a hyperbolic, sigmoid or exponential decay curve. Hence, through the years, a log-linear model between TSH and FT4 has been developed, where TSH has been represented in a logarithmic scale and FT4 in a linear one. If both TSH and FT4 are expressed in a linear scale, then their relationship can be modelled through a negative exponential function with two independent parameters [3].

The mathematical model is as follows:

$$[\mathrm{TSH}] = Se^{-\varphi[\mathrm{FT4}]}.$$

In this literature review, the square brackets are used to represent the concentration of the hormones. The model has two degrees of freedom, S, the multiplier, and φ, the slope of the exponential coefficient. Variations of S, with fixed φ, translates the HP curve horizontally on the FT4 axis. Variations of φ folds or unfolds the shape of the HP curve around a chosen point. S and φ are a set of parameters that describes the HP curve of a specific individual. Exponential functions are completely determined by two different sets of coordinates. Therefore, it is possible to recover S and φ when two or more measured points are available and distinct. If $([\mathrm{TSH}]_1, [\mathrm{FT4}]_1)$ and $([\mathrm{TSH}]_2, [\mathrm{FT4}]_2)$ are two distinct measurements belonging to the same individual, S and φ have then the following expressions:

$$\varphi = \frac{1}{[\mathrm{FT4}]_1 - [\mathrm{FT4}]_2} \ln\left(\frac{[\mathrm{TSH}]_2}{[\mathrm{TSH}]_1}\right)$$

$$S = [\mathrm{TSH}]_1 e^{\varphi[\mathrm{FT4}]_1} = [\mathrm{TSH}]_2 e^{\varphi[\mathrm{FT4}]_2}.$$

If more than two points are available, it is possible to combine the different measurements in order to verify the computed values of S and φ. It is then possible to compute the averages of all the S and φ values obtained and use them as model parameters [3].

The validation of the model is based on individual application of the model. This is fundamental, since the HPT axis physiology of every individual is uniquely defined by S and φ. Therefore, this model should not be applied on aggregated random FT4-TSH data from a population. In particular, this model has been validated with two datasets from two different hospitals. Its validity ranges are $5 - 40$ pmol/L for FT4 and $0.05 - 100$ mU/L for TSH. Values outside of these ranges are considered outliers. The model validation is performed on the dataset available for each individual and then repeated for every patient. This is because the HPT axis is uniquely defined for each person [3].

Figure (2) shows four different HP curves, belonging to four different patients from one of the hospital datasets used in [3]. It is clear from these plots that the HPT axis is unique in every individual and can clearly differ from one patient to another.

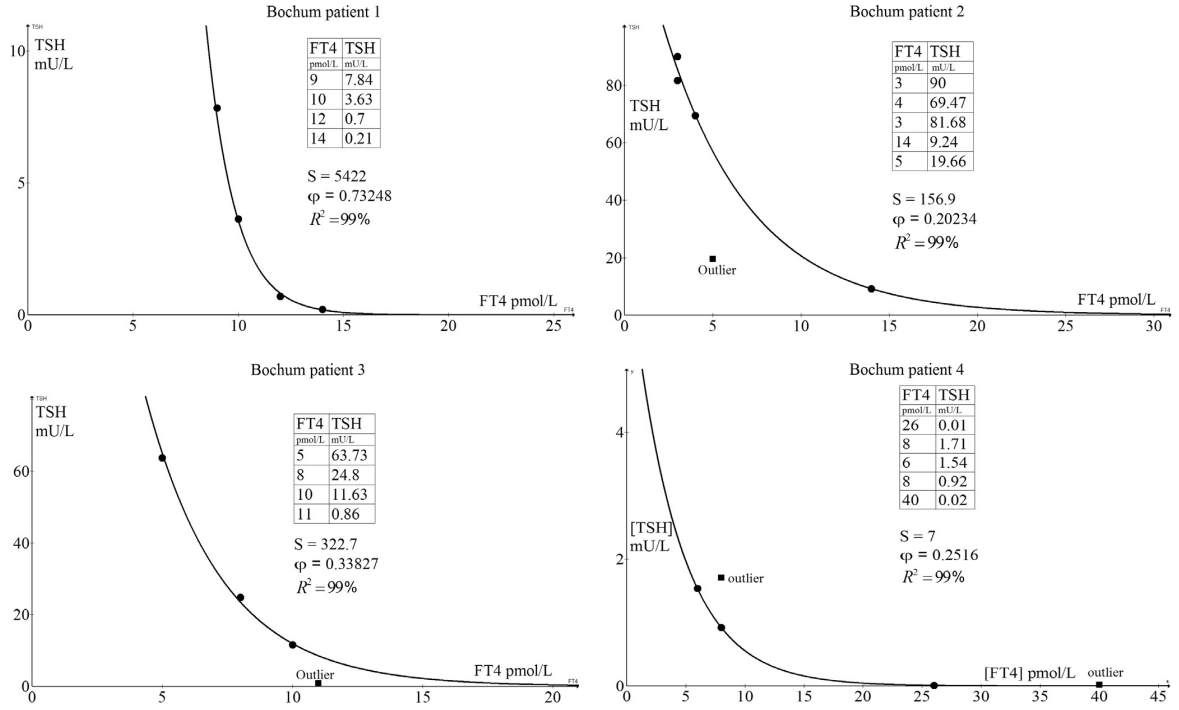


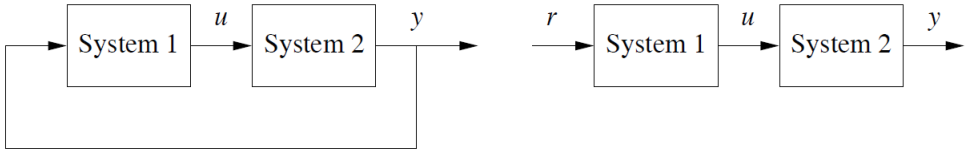
Figure 2: HP curve of 4 different patients. Taken from [3]

3.3 Control theory background

The term control can have different meanings. According to [26], control refers to the use of algorithms and feedback in engineered systems. A modern controller measures the output of a system, compares it to the desired behaviour, computes the corrections needed and actuates the system in order to carry out the desired changes. This basic feedback loop is the fundamental concept in control theory [26]. The term feedback refers to a situation in which two or more dynamical systems (systems whose behaviour is changing over time) are connected together in such a way that each system can influence the other [26]. Hence, the main idea is that the output of a dynamical system can be measured, fed back to a controller and then used to influence the system itself [27].

Control systems can be classified in closed loop and open loop systems. Figure (3) shows how these two different kinds of systems can be represented. A closed loop system is a system in which the components are interconnected in a cycle, so, according to Figure (3a), the output of system 1 is the input of system 2 and the output of system 2 is the input of system 1 [26]. Hence, in a closed loop system, the controlled output signal is measured and fed back in the control computation. A closed loop system can also be called feedback control [27]. On the contrary, if the connection between the two systems is not present, the system is defined as open loop. According to Figure (3b), the interconnection between system 2 and system 1 is removed [26]. Therefore, in an open loop system, the controller does not use the system output in control computation [27].

Figure (4) shows a simple representation of a feedback loop. P represents the plant, which consists of the central component of the feedback system, whose output is controlled. C is the controller, which is the component that actually computes the desired control signal. The controller computes the difference between the reference signal and the controlled output signal and uses it as a measure of the system error [27]. The output of the system y is fed back to a comparator, together with the reference value r. After that, the controller uses e, defined as the



(a) Closed loop (b) Open loop

Figure 3: Representation of a closed loop system (a) and an open loop system (b). Taken from [26]

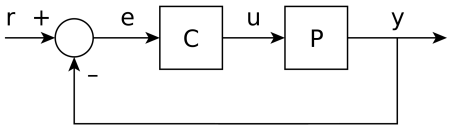


Figure 4: Simple feedback loop

difference between the reference value r and the output y, in order to change the input u of the plant P, which is the system under control. If the plant P and the controller C are linear and time-invariant then the system can be analysed using the Laplace transform on the variables, so the following relations hold:

$$\begin{aligned} Y(s) &= P(s)U(s) \\ U(s) &= C(s)E(s) \\ E(s) &= R(s) - Y(s). \end{aligned}$$

The first two relations can be re-written as

$$\begin{aligned} E(s) &= \frac{U(s)}{C(s)} \\ U(s) &= \frac{Y(s)}{P(s)} \end{aligned}$$

and, if combined, they yield to

$$E(s) = \frac{Y(s)}{P(s)C(s)}.$$

This expression of $E(s)$ can be substituted in the last relation of $Y(s)$, obtaining

$$\begin{aligned} \frac{Y(s)}{P(s)C(s)} &= R(s) - Y(s) \\ \Rightarrow Y(s) &= \frac{P(s)C(s)}{1 + P(s)C(s)} R(s). \end{aligned}$$

$|P(s)C(s)|$ is called loop gain. When $|P(s)C(s)| \gg 1$, then $Y(s) \simeq R(s)$. This is why the loop gain should be greater than 1, because in this case the output is close to the reference input. This concepts is fundamental in the next section, where the HPT axis is modelled as a closed loop system.

In the following section, the HPT axis will be represented through a closed-loop system. In that case, the controller and the plant, respectively the HP unit and the thyroid, will be

time-invariant but not linear. Hence, it will be needed to linearize the characteristics in order to compute and study the loop gain. The system function blocks will then be described through linear relations, which will be valid over a limited range for the input and output [11]. In fact, when the devices are nonlinear, the input can be considered only over a small range of values, such that the output can be assumed linear.

3.4 HPT feedback control

The HPT axis can be modelled through control theory, in particular using a negative feedback loop configuration. The system loop is divided into function blocks, such that every block is distinguished by its own nonlinear transfer characteristic valid over the total range of the input and output signals. In this way, the HPT negative feedback loop can be analyzed through mathematical considerations. Hence, the main components of the loop, HP and thyroid blocks, are both characterised by distinct relationships between TSH and FT4 [11]. According to the terms introduced in the previous section, the HP is the controller, while the thyroid is the plant, because it just satisfies the secretory demands [28]. Figure (5) shows the negative feedback loop of the HPT axis. S_{FT4} is the internal set point value of FT4. In fact, the normal operation of a negative feedback loop implies the existence of a set-point intrinsic to the system. Hence, any alteration of TSH and FT4 causes a disequilibrium that influences the HP block in order to restore the system towards the set-point [28].

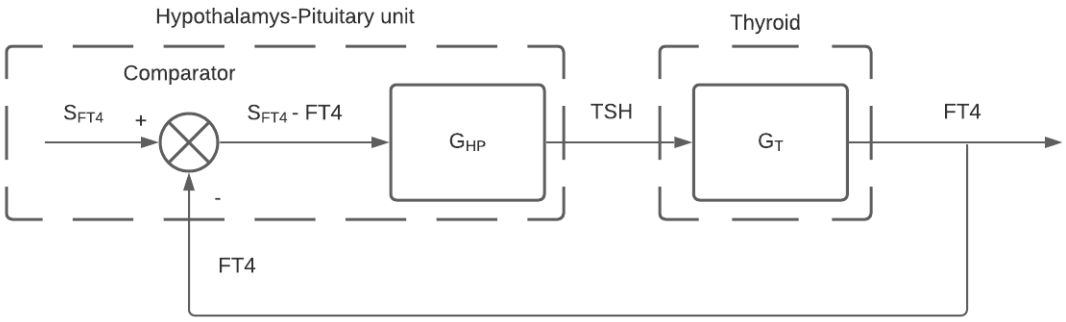


Figure 5: Generalized feedback loop of the HPT axis [11]

The HP complex is modelled with FT4 as the primary input signal and TSH as the output one. As explained previously, TSH can be expressed as a negative exponential function of FT4

$$[\mathrm{TSH}] = Se^{-\varphi[\mathrm{FT4}]},$$

where, given at least two distinct measurements of TSH and FT4, S and φ can be computed as:

$$\varphi = \frac{1}{[\mathrm{FT4}]_1 - [\mathrm{FT4}]_2} \ln\left(\frac{[\mathrm{TSH}]_2}{[\mathrm{TSH}]_1}\right)$$

$$S = [\mathrm{TSH}]_1 e^{\varphi[\mathrm{FT4}]_1} = [\mathrm{TSH}]_2 e^{\varphi[\mathrm{FT4}]_2}.$$

The HP gain factor G_{HP} is defined as the derivative of TSH with respect to FT4 [11, 28]:

$$G_{HP} = \frac{d[\mathrm{TSH}]}{d[\mathrm{FT4}]} = \frac{-\varphi S}{e^{\varphi[\mathrm{FT4}]}} = -\varphi[\mathrm{TSH}].$$

The thyroid characteristic can be modelled according to the Michaelis-Menten function, which is very popular in enzyme kinetics, and it results in:

$$[\text{FT4}] = \frac{K[\text{TSH}]}{a + [\text{TSH}]},$$

where a determines the steepness of the thyroid characteristic and K represents the maximum secretory value of T4 and T3, and consequently of FT4. a and K are specific for each individual. Figure (6) shows several thyroid characteristics, obtained with different combinations of the values a and K [11]. The thyroid gain factor G_T is defined as the first derivative of FT4 with

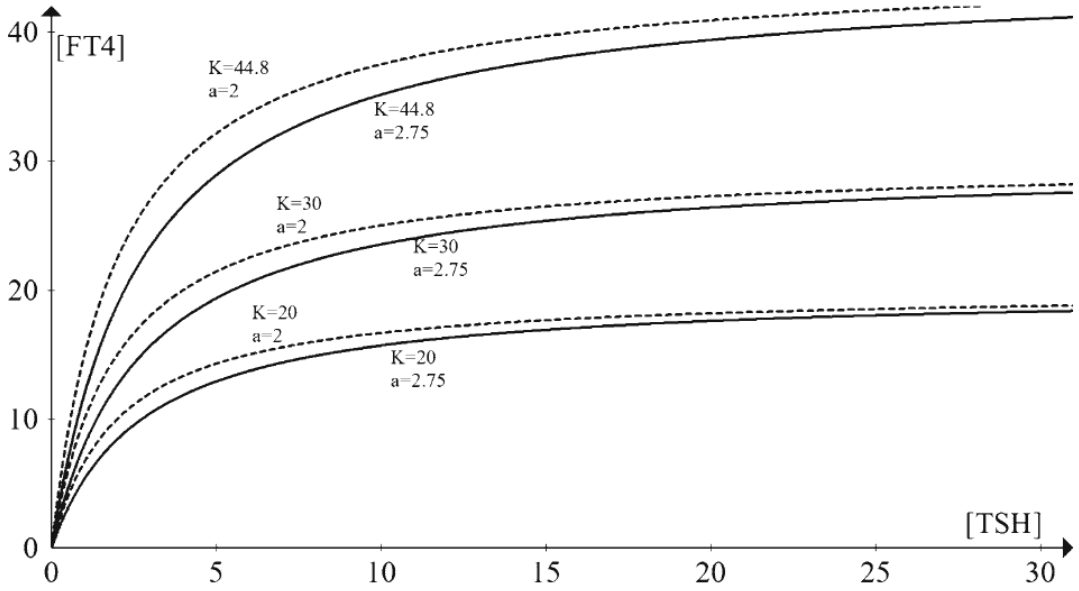


Figure 6: Thyroid characteristics, obtained with different values of a and K. Taken from [11]

respect to TSH [11]:

$$G_T = \frac{d[\text{FT4}]}{d[\text{TSH}]} = \frac{K(a + [\text{TSH}]) - K[\text{TSH}]}{(a + [\text{TSH}])^2} = \frac{aK}{(a + [\text{TSH}])^2}.$$

The loop gain G_L is given by [11, 28]:

$$G_L = |G_{HP} G_T|,$$

so its expression is [11]:

$$G_L = \left| \frac{aK\varphi[\text{TSH}]}{(a + [\text{TSH}])^2} \right|.$$

For an optimal and stable control, the loop gain G_L should always be greater than 1. When G_L becomes smaller than 1, the interaction between the HP unit and the thyroid is lost, resulting in an open loop situation [11]. The loop gain is a function of TSH, thus it is possible to study its maximum by computing the derivative of G_L with respect to TSH and set it equal to 0:

$$\frac{d\, G_L}{d[\text{TSH}]} = \frac{K\varphi(a^2 - a[\text{TSH}])}{(a + [\text{TSH}])^3} = 0.$$

The maximum value of the loop gain is obtained only when $a = [\text{TSH}]$. So, when the set-point value of TSH is known, it is possible to define

$$a = [\text{TSH}]_{\text{setpoint}}.$$

In that case, using the expression for the thyroid, the set-point value of FT4 is

$$[\text{FT4}]_{\text{setpoint}} = \frac{K}{2}$$

and the loop gain becomes

$$G_{L_{\max}} = \frac{K\varphi}{4}.$$

It is clear that the thyroid parameters depend on the set-point values [11]. Furthermore, the thyroid operates in such a way that the loop gain is at its maximum value at the set-point [11, 28].

According to [28], the thyroid function can be better formulated as:

$$[\text{FT4}] = A\left(1 - e^{-\alpha[\text{TSH}]}\right).$$

This model is still based on the Michaelis-Menten kinetics, but it shows a better fit with the data. α represents the stiffness, similarly to a in the previous model, while A represents the maximum secretory capacity of the thyroid, similarly to K. A and α are specific for each individual as well. The thyroid gain factor for this model is:

$$G_T = \frac{d[\text{FT4}]}{d[\text{TSH}]} = A\alpha e^{-\alpha[\text{TSH}]}$$

and the loop gain becomes:

$$G_L = \varphi[\text{TSH}]A\alpha e^{-\alpha[\text{TSH}]}.$$

Also in this case the loop gain is only a function of TSH, hence it is possible to compute the derivative of G_L with respect to TSH and set it equal to 0 in order to study its maximum:

$$\frac{d\ G_L}{d[\text{TSH}]} = \frac{\varphi\alpha A - \varphi\alpha^2 A[\text{TSH}]}{e^{\alpha[\text{TSH}]}} = 0.$$

This is verified only when $[\text{TSH}] = \dfrac{1}{\alpha}$, so if the set-point value of TSH is known, it is possible to set

$$\alpha = \frac{1}{[\text{TSH}]_{\text{setpoint}}}.$$

According to the thyroid model, the set-point value of FT4 is then

$$[\text{FT4}]_{\text{setpoint}} = A\left(1 - e^{-1}\right)$$

and the maximum loop gain becomes:

$$G_{L_{\max}} = \frac{\alpha\varphi}{e}.$$

3.5 HPT-axis setpoint

The term homeostasis refers to the maintenance of almost constant conditions in the internal environment. All organs and tissues of the body perform functions in order to maintain these conditions unchanged [1]. For the HPT axis, which can be represented as a closed loop system with negative feedback, the point of equilibrium or homeostasis is found at the intersection of the HP and thyroid characteristics [3]. Hence, the set-point can be found numerically by using the two curves. Figure (7) shows the set-point of the HPT axis as the intersection of the HP and thyroid curves. When the thyroid characteristic is plotted on the same graph of the HP curve, it should be inverted in order to have TSH as a function of FT4:

$$[\text{TSH}] = \frac{a[\text{FT4}]}{K - [\text{FT4}]}$$

or

$$[\text{TSH}] = -\frac{1}{\alpha} \ln\left(\frac{A - [\text{FT4}]}{A}\right),$$

according to which thyroid function is used, as explained in the previous section.

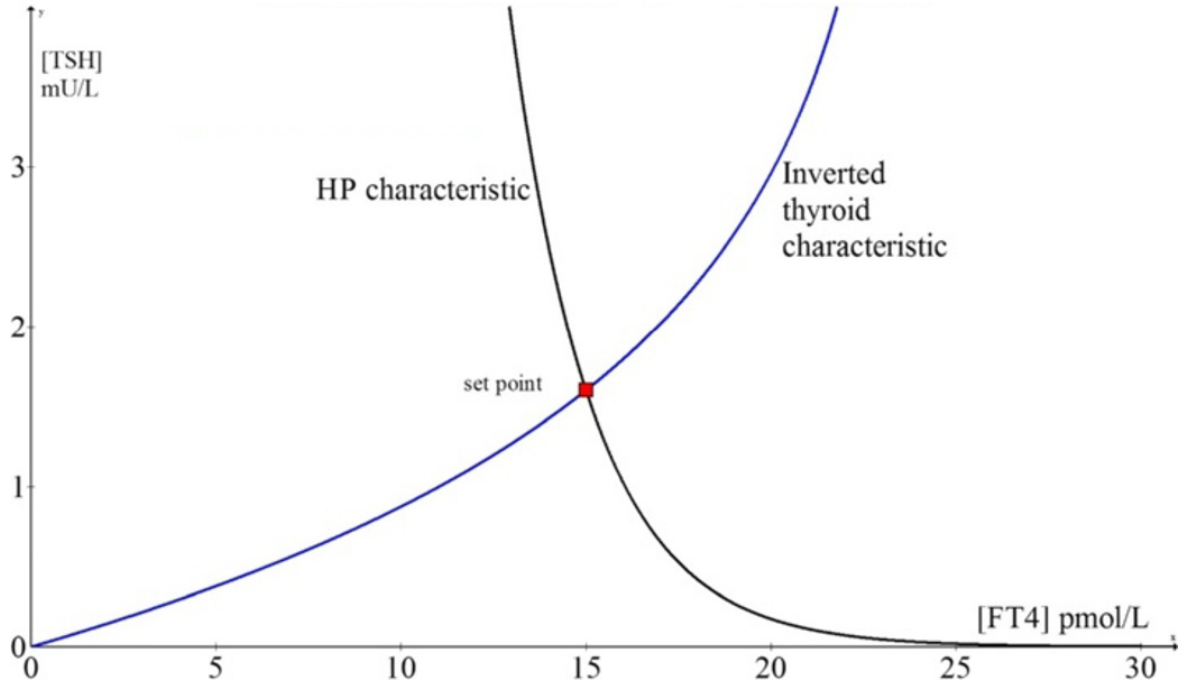


Figure 7: HP and thyroid curves intersecting in the set-point. Taken from [28]

The HP characteristic contains a set of possible points of homeostasis [3]. In fact, the normal reference ranges of TSH and FT4 fall within the knee region of the HP curve, which corresponds to the most pronounced bend of the negative exponential curve, hence this leads to think that the set-point should be in that interval [28]. The knee region of the HP function includes also the point of maximum curvature, which is the point characterised by the minimum radius of curvature [3]. Thus, it can be assumed that the set-point of the HPT axis corresponds to the point of maximum curvature of the HP function [28]. Figure (8) shows the same HP curve represented in Figure (7) with its setpoint. The red lines are the limits of the reference ranges for TSH and FT4, which are used in the graph in order to delimit the knee region of the exponential

curve. It can be noticed that the set-point is located within the knee region of the HP curve, as expected. Furthermore, it should be noted that this graph was realized by keeping the same scale on both the TSH and FT4 axes, in order to clearly identify the knee region.

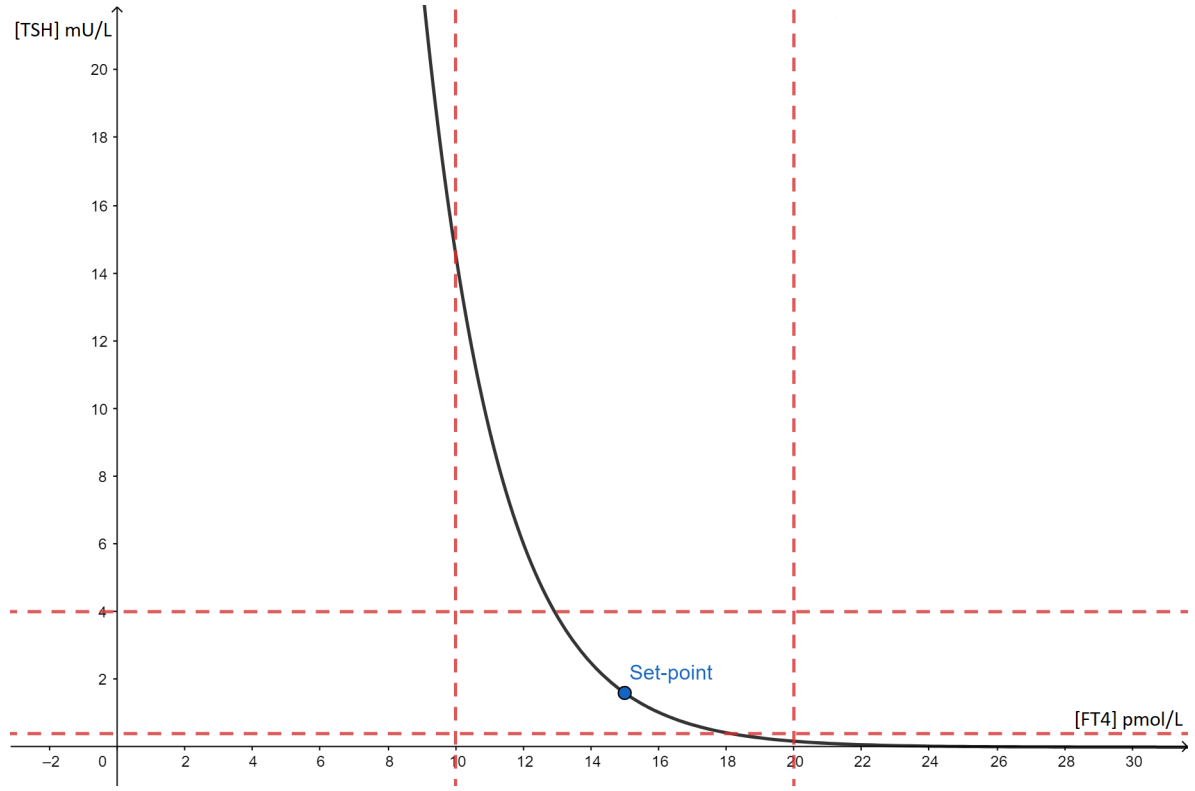


Figure 8: The black solid line represents the exponential HP curve, the same as in Figure (7). The red dashed lines represent the limits of the reference ranges of TSH and FT4, corresponding to the knee region of the exponential curve.

The point of homeostasis, defined as the intersection between the HP and thyroid curves, corresponds to the point of maximum curvature of the HP function [3]. The curvature K is defined as $K = \dfrac{1}{R}$, where R is the radius of the curvature circle. Hence, for the HP curve the curvature K is

$$K = \frac{\dfrac{d^2[\mathrm{TSH}]}{d[\mathrm{FT4}]^2}}{\left(1 + \left(\dfrac{d[\mathrm{TSH}]}{d[\mathrm{FT4}]}\right)^2\right)^{3/2}}.$$

When computing the derivatives, the curvature becomes

$$K = \frac{\varphi^2 S e^{-\varphi[\mathrm{FT4}]}}{\left(1 + \varphi^2 S^2 e^{-2\varphi[\mathrm{FT4}]}\right)^{3/2}}.$$

In order to study when K is maximum, it is possible to compute the derivative of K with respect to FT4 and set it equal to 0:

$$\frac{dK}{d[\mathrm{FT4}]} = \frac{\varphi^3 S e^{-\varphi[\mathrm{FT4}]} \left(1 + \varphi^2 S^2 e^{-2\varphi[\mathrm{FT4}]}\right)^{1/2} \left(2\varphi^2 S^2 e^{-2\varphi[\mathrm{FT4}]} - 1\right)}{\left(1 + \varphi^2 S^2 e^{-2\varphi[\mathrm{FT4}]}\right)^3} = 0.$$

This leads to

$$2\varphi^2 S^2 e^{-2\varphi[\mathrm{FT4}]} - 1 = 0,$$

which results in

$$[\mathrm{FT4}] = \frac{\ln\left(\varphi S\sqrt{2}\right)}{\varphi}.$$

The corresponding value of TSH is

$$[\mathrm{TSH}] = \frac{1}{\varphi\sqrt{2}}.$$

Hence, these are the coordinates corresponding to the set-point of the HPT axis [28].

3.6 Another attempt in modeling the individual HPT axis

In 2011, Pandiyan et al. proposed a different mathematical model that analyses the negative feedback loop of the HPT axis in patients affected by the Hashimoto disease [29]. The Hashimoto thyroiditis, also called autoimmune thyroiditis, is a disease that affects the size and function of the thyroid, which is gradually destroyed [30]. The model proposed by Pandiyan et al. is another attempt to describe the HPT axis from an individual perspective, hence it can be applied to each single patient.

This model involves four clinical variables: TSH, FT4, anti-thyroid peroxidase antibodies (TPOAb) and the functional size of the thyroid. In general, anti-thyroid antibodies are targeted against one or more components of the thyroid. Anti-thyroid peroxidase antibodies are directed against TPO, which is a protein involved in the synthesis of thyroid hormones. This kind of antibodies is mainly detected in patients affected by Hashimoto thyroiditis [30]. The functional size of the thyroid refers to the size of the active and operating part of the thyroid [30]. Three of the variables involved in the model, namely TSH, FT4 and TPOAb, are commonly measured when investigating the thyroid status. The functional size of the thyroid, however, cannot be measured, hence it will be determined through a relationship involving the other variables.

The mathematical model developed by Pandiyan et al. [29, 30] consists of a system of four differential equations describing how the four variables change in time. The model is the following:

$$\begin{aligned}
&\frac{d[\mathrm{TSH}]}{dt} = k_1 - \frac{k_1[\mathrm{FT4}]}{k_a + [\mathrm{FT4}]} - k_2[\mathrm{TSH}], && [\mathrm{TSH}](t_0) = [\mathrm{TSH}]_0,\\
&\frac{d[\mathrm{FT4}]}{dt} = \frac{k_3\mathrm{T}[\mathrm{TSH}]}{k_d + [\mathrm{TSH}]} - k_4[\mathrm{FT4}], && [\mathrm{FT4}](t_0) = [\mathrm{FT4}]_0,\\
&\frac{d\mathrm{T}}{dt} = k_5\left(\frac{[\mathrm{TSH}]}{\mathrm{T}} - N\right) - k_6[\mathrm{TPOAb}]\mathrm{T}, && \mathrm{T}(t_0) = \mathrm{T}_0,\\
&\frac{d[\mathrm{TPOAb}]}{dt} = k_7[\mathrm{TPOAb}]\mathrm{T} - k_8[\mathrm{TPOAb}], && [\mathrm{TPOAb}](t_0) = [\mathrm{TPOAb}]_0,
\end{aligned}$$

where each differential equation has its own initial condition. [TSH], [FT4] and [TPOAb] clearly represent the concentration of TSH, FT4 and TPOAb respectively, while T indicates the functional size of the thyroid gland. Furthermore, it should be pointed out that the following holds:

$$\begin{aligned}
&[\mathrm{TSH}](t) \geq 0\\
&[\mathrm{FT4}](t) \geq 0\\
&\mathrm{T}(t) > 0\\
&[\mathrm{TPOAb}](t) \geq 0.
\end{aligned}$$

The first differential equation expresses the rate of change of TSH as the difference between the secretion rate and excretion rate of TSH. Secretion refers to the release of a substance, while excretion refers to the process of waste removal from the body. The secretion rate of TSH is expressed by two terms, where the first term k_1 represents the maximum secretion rate of TSH, while the other term, $\frac{k_1[\text{FT4}]}{k_a + [\text{FT4}]}$, describes the inhibition rate of TSH and it is modelled through Michaelis-Menten kinetics. The excretion rate of TSH is proportional to the concentration of TSH itself, hence it is modelled as $k_2[\text{TSH}]$ [29]. Similarly, the differential equation for FT4 models the rate of change of FT4 concentration as the difference between the secretion rate and the excretion rate of FT4. The secretion rate of FT4 is modelled through Michaelis-Menten kinetics and it is considered proportional to the functional size of the thyroid. The excretion rate of FT4 is considered proportional to the concentration of FT4 itself, as done for the previous differential equation [30]. The rate of change of the functional size of the thyroid is modelled as the difference between the growth rate and the destruction rate of the thyroid. Finally, the last differential equation describes the rate of change of the anti-thyroid peroxidase antibodies as the difference between the production rate and the loss rate of TPOAb [30].

The variables present a different time scale. In fact, TSH changes on the order of one hour, FT4 on the order of days while the thyroid's functional size and the anti-thyroid peroxidase antibodies change on a slower scale, on the order of weeks or years. However, even though the variables of the model have different time scales, the model is constructed on a slower time scale, hence the time t is measured in days. This mathematical model presents 11 parameters, however only k_7 is the parameter that describes the progression of hypothyroidism for patients affected by Hashimoto thyroiditis, as explained in the following paragraphs [30].

Pandiyan et al. analyzed then the steady states of the proposed model. The steady states are obtained by setting the differential equations equal to 0. In this way, two steady states are obtained. From the last differential equation it is possible to notice that one steady state is characterized by $[\text{TPOAb}] = 0$, while the other one is characterized by $\text{T} = \frac{k_8}{k_7}$. The steady state with $[\text{TPOAb}] = 0$ corresponds to the euthyroid state. In fact, the anti-thyroid peroxidase antibodies are not present in healthy individuals. The euthyroid state is characterised by

$$
\begin{aligned}
[\text{TSH}] &= \frac{k_1 k_a}{k_2(k_a + [\text{FT4}])} \\
[\text{FT4}] &= \left(-\frac{b}{2} + \sqrt{\frac{b^2}{4} + \frac{a^3}{27}}\right)^{1/3} + \left(-\frac{b}{2} - \sqrt{\frac{b^2}{4} + \frac{a^3}{27}}\right)^{1/3} - \frac{k_a}{3}\left(2 + \frac{k_1}{k_2 k_d}\right) \\
\text{T} &= \frac{[\text{TSH}]}{N} \\
[\text{TPOAb}] &= 0,
\end{aligned}
$$

where

$$
\begin{aligned}
a &= -\frac{k_a^2}{3}\left(\frac{k_1^2}{k_2^2 k_d^2} + \frac{k_1}{k_2 k_d} + 1\right) \\
b &= \frac{k_1^2 k_a^3}{9 k_2^2 k_d^2} + \frac{2 k_1^3 k_a^3}{27 k_2^3 k_d^3} - \frac{k_3 k_1^2 k_a^2}{k_4 N k_d k_2^2} - \frac{2 k_a^3}{27} - \frac{k_1 k_a^3}{9 k_2 k_d}.
\end{aligned}
$$

The euthyroid state depends on the values of the model parameters, except for k_5, suggesting that this state is unique in each individual [29].

The other steady state is defined as

$$
\begin{aligned}
[\mathrm{TSH}] &= \frac{k_1 k_a}{k_2(k_a + [\mathrm{FT4}])} \\
[\mathrm{FT4}] &= \frac{-\left(k_a + \frac{k_1 k_a}{k_2 k_d}\right) + \sqrt{\left(k_a + \frac{k_1 k_a}{k_2 k_d}\right)^2 + \frac{4 k_1 k_3 k_a k_8}{k_d k_2 k_7 k_4}}}{2} \\
\mathrm{T} &= \frac{k_8}{k_7} \\
[\mathrm{TPOAb}] &= \frac{k_5 k_7}{k_6 k_8}\left(\frac{k_7[\mathrm{TSH}]}{k_8} - N\right).
\end{aligned}
$$

k_7 is a bifurcation parameter for all the individuals. This means that the value of k_7 is unique for each individual and it helps to describe the course of the Hashimoto disease. In fact, by studying this second steady state, it can be derived that, if $k_7 > \frac{N k_8}{[\mathrm{TSH}]}$, then the patient will develop overt or subclinical hypothyroidism as a consequence of Hashimoto thyroiditis, hence the second steady state represents a diseased state in this case. However, if $k_7 < \frac{N k_8}{[\mathrm{TSH}]}$, then the patient will not develop any consequence related to the Hashimoto disease [30]. Therefore, the goal of this model is to predict whether a patient will progress to subclinical or overt hypothyroidism.

4 Population models

4.1 General overview

The majority of models for the HPT axis proposed until now present a statistical approach. A population curve is obtained from a cross-sectional study, involving multiple patients, and it is the result of simultaneous plots of TSH and FT4 values of a large number of individuals [31]. Thus, cross-sectional studies include data from different individuals, where each of them presents a different HPT axis set-point [32]. HP and thyroid curves of single individuals, as described in previous sections, are independent from each other. However, in a population context, different HP and thyroid curves can influence each other [31]. Therefore, since population models describe the behaviour of a population from a statistical perspective, individual measurements in a population context are not relevant. Thus, population models cannot describe the behaviour of single individuals, because they are valid over the entire population.

Population models are widespread in clinical research and biomedicine [33]. However, this approach considers that all the individuals in a population have an influence on each other. In particular, in this case it means that the TSH concentration of an individual can affect the FT4 concentration of someone else and vice versa, which is not reasonable [34]. Biomedicine relies on advanced statistical techniques, even though a statistical approach is not always adequate to describe physiological processes and, on the contrary, its results could even be misleading [33]. In fact, population-based analysis, which relies on a statistical approach, is subject to amalgamation problems, so it is better to adopt a patient-specific approach instead [35]. Despite this, in the following sections some population models that have been developed during the years will be described.

4.2 Log-linear model

In 1990 Spencer et al. introduced a population-based model where the relationship between TSH and FT4 is considered log-linear [36]. This model was derived by analysing a population of individuals with different states of the thyroid function, ranging from hypo- to hyperthyroidism. It was possible to derive this relationship because of some improvements in the immunoassays used to measure TSH and FT4 [36]. In fact, the increased sensitivity of the new TSH assay allowed them to grasp new insights regarding the mechanism of the HPT axis. Therefore, Spencer et al. were able to confirm some previous studies regarding the log-linear relationship between TSH and FT4 and extend this result also to subnormal levels of TSH [36].

The study involved a population of 505 patients, that could be divided in five groups. Some of the individuals were normal subjects, without any thyroid disease, others were clinically hyperthyroid patients. Other two groups of patients consisted of individuals taking T4 and T3, respectively. Finally, the last group of individuals considered remaining ambulatory patients, whose thyroid status was evaluated for different thyroid-related issues [36]. The samples of the patients were used to determine the relationship between TSH and FT4, which was reflected by free thyroxine index (FT4I). FT4I is defined as the ratio between T4 and thyroxine binding capacity [36].

The relationship found by Spencer et al. is in the form

$$\log[\text{TSH}] = a + b[\text{FT4I}]$$

and for the specific dataset used in their study it has the following expression [36]:

$$\log[\text{TSH}] = 2.56 - 0.022[\text{FT4I}].$$

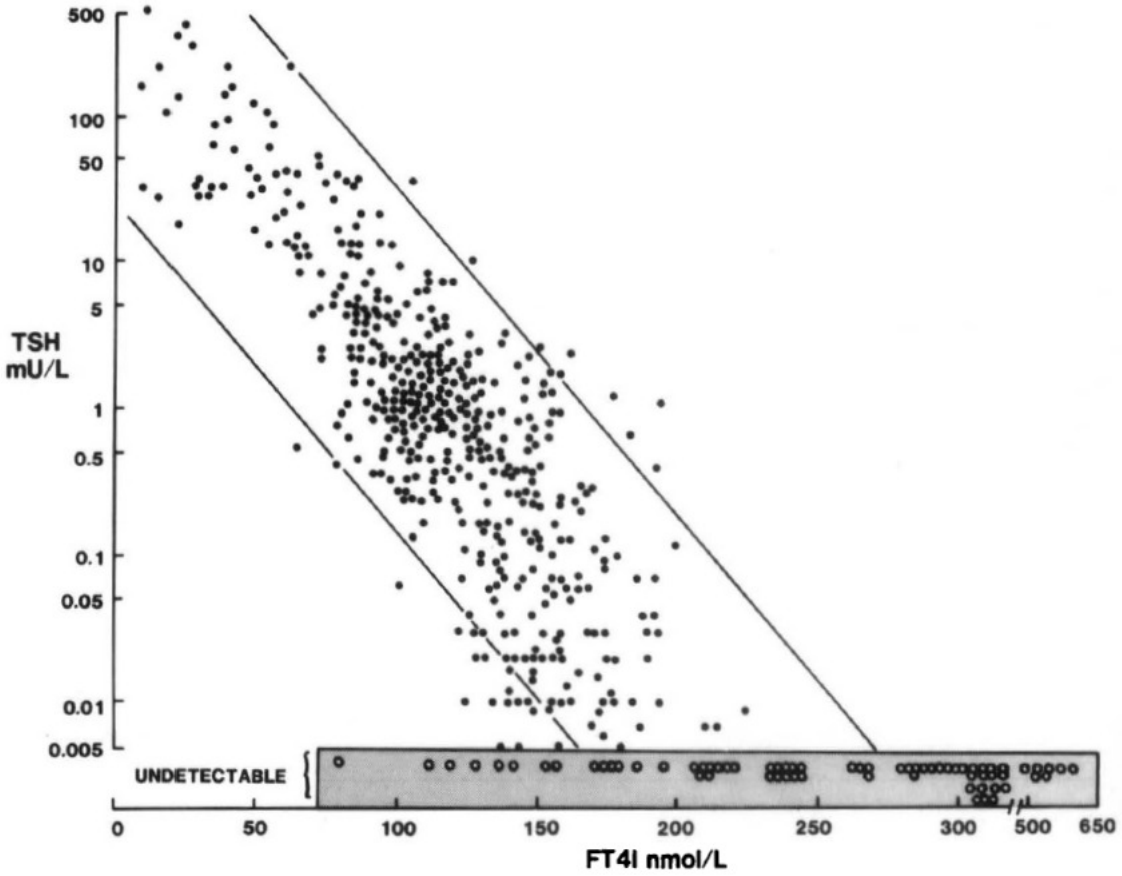


Figure 9: Relationship between log(TSH) and FT4I. The solid lines represent the 95% confidence limits of the relationship found by Spencer et al. Taken from [36]

Figure (9) shows the relationship between TSH and FT4I, together with its 95% confidence interval.

With the log-linear relationship between TSH and FT4 it was possible to notice the sensitivity of the pituitary to small alterations of circulating FT4. Furthermore, the fact that this log-linear relationship was found to be valid also at subnormal levels of TSH allowed to highlight the importance and usefulness of TSH measurements when analysing the level of hypothyroidism [36]. Hence, from this study, the population model of the HPT axis started to be considered log-linear. However, some years ago, new cross-sectional studies analyzed the relationship between log(TSH) and FT4 and came to the conclusion that it can be better described by non-linear models. This is probably due to the improvements in TSH and FT4 measurements, which are now more precise and provide more reliable results.

4.3 Non-log-linear models

Even though the relationship between TSH and FT4 has always been considered log-linear in a population approach, there have been some recent cross-sectional studies that show that the log-linear model is actually not the best fit for TSH-FT4 data. Therefore, some studies have proposed more complex models, based in particular on the error function, on negative sigmoid functions and on higher order polynomials.

In 2010, Hoermann et al. proposed a population model between log(TSH) and FT4 based on the error function [23]. This new model was compared with the common linear one in order

to show its superior accuracy. The linear model is

$$\log[\text{TSH}] = a[\text{FT4}] + b,$$

while the non-linear one based on the error function [23] is

$$\log[\text{TSH}] = \frac{\sqrt{\pi}k}{2q}\,\text{erf}(q([\text{FT4}] - a)) + d([\text{FT4}] - a) + b,$$

where erf represents the error function, which has the following expression

$$\text{erf}(z) = \frac{2}{\sqrt{\pi}}\int_0^z e^{-t^2}dt.$$

When fitting the linear model to the available dataset, Hoermann et al. noticed that the data could be divided into three distinct segments, so that the linear model could be fitted on each segment separately. The results of this approach are shown in Figure (10). It is clear from the graphs that the regression lines of the three segments are very different from each other and also from the regression line of the total data, shown in Figure (11a). This led Hoermann et

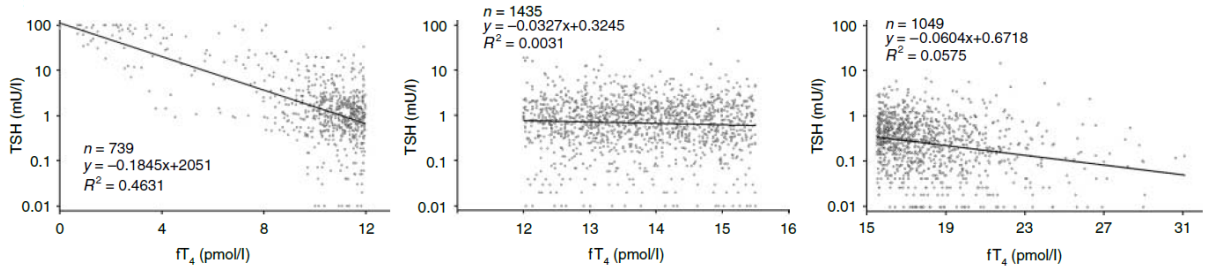
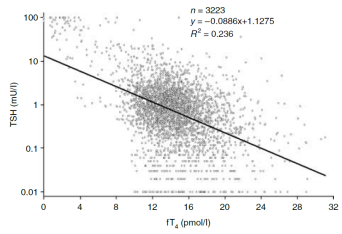


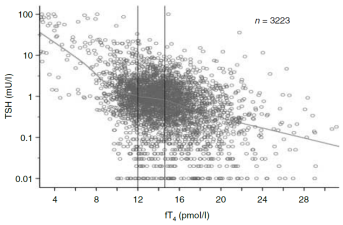
Figure 10: Regression lines of the log-linear model in each data segment. In all the three segments, TSH has been transformed in a logarithmic scale. Taken from [23]

al. to think that a different model, more complex and non-linear, would fit the data in a better way. Thus, a model based on the error function was introduced. Figure (11b) shows how the regression line based on the error function model fits the data. Furthermore, Figure (11c) shows a comparison between the two models analysed by Hoermann et al.

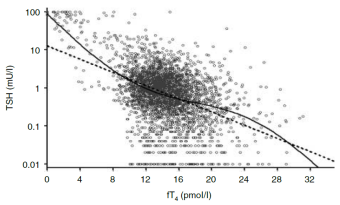
The error function model was also validated on a second dataset. A statistical comparison between the two models showed a superior performance for the error function model. Thus, the population model proposed by Hoermann et al. is supposed to be more accurate than the linear



(a) Log-linear model applied to the total data



(b) Error function model applied to the total data



(c) Log-linear and error function models plotted on the same graph

Figure 11: Comparison between the log-linear model and the error function model of TSH-FT4. In all the three graphs, TSH has been transformed in a logarithmic scale. Taken from [23]

one. Furthermore, according to the authors, the log-linear model was derived from a limited number of experiments, using old assay techniques. Hence, they claim that the log-linear model between TSH and FT4 represents now a rough estimate, which can be refined through new non-linear models [23].

In 2012, Clark et al. conducted a cross-sectional study of the thyroid function in an older population and found that the relationship between log(TSH) and FT4 is better described by a fourth order polynomial [37]. The authors investigated the relationship between log(TSH) and FT4 with a linear model, but they also considered non-linear models based on higher order polynomials, up to the fourth power of FT4. In fact, Clark et al. found that the relationship between log(TSH) and FT4 is non-linear and that it can be better described by a fourth order polynomial of FT4. Figure (12) shows the comparison between the log-linear model and the quartic one. Clark et al. suggest that a more complex model for the relationship log(TSH)-FT4 may be needed.

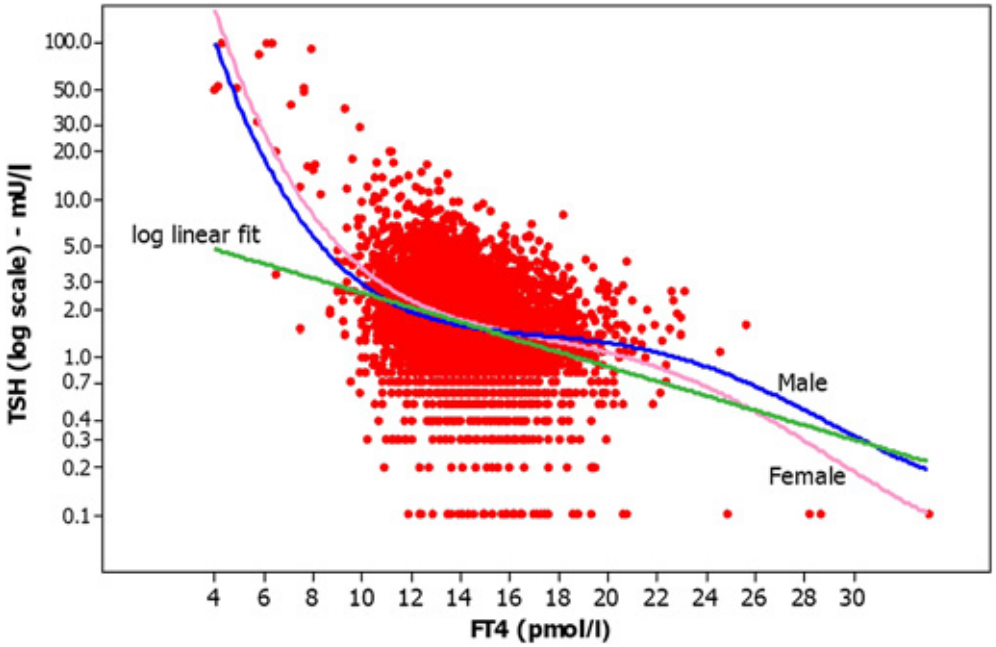


Figure 12: The graph shows a comparison between the linear model and the non-linear model based on a fourth order polynomial. The linear log(TSH)-FT4 model is showed in green, while the pink and blue lines represent the quartic models applied to the female and male populations respectively. Taken from [37]

In 2013, Hadlow et al. proposed a different non-linear model, based on two sigmoid curves, in order to describe the relationship between log(TSH) and FT4 [38]. In this study, the relationship between TSH and FT4 presented non-linear properties even after the logarithmic transformation of TSH. Hence, a negative sigmoid curve of the following form

$$\log[\text{TSH}] = A + \frac{B}{1 + e^{-(C-[\text{FT4}])/D}}$$

was adopted. In particular, the sigmoid curve was used in two stages. This means that the relationship between log(TSH) and FT4 can be described by two sigmoid curves. Thus, according

to their dataset, for [FT4] $\leq$ 12 pmol/L, the relationship is

$$\log[\text{TSH}] = 1.4 + \frac{3.5}{1 + e^{-(7.0-[\text{FT4}])/1.0}},$$

while for [FT4] $>$ 12 pmol/L the relationship becomes

$$\log[\text{TSH}] = -3.7 + \frac{5.3}{1 + e^{-(20.6-[\text{FT4}])/3.0}}.$$

The threshold value of 12 pmol/L for the concentration of FT4 was chosen as a suitable split point, because it is located midway along the section of the median TSH curve that showed the least change. This threshold area corresponds to the lower part of the reference range for FT4 [38]. Figure (13) shows the result derived from regression analysis with the sigmoid curves presented before.

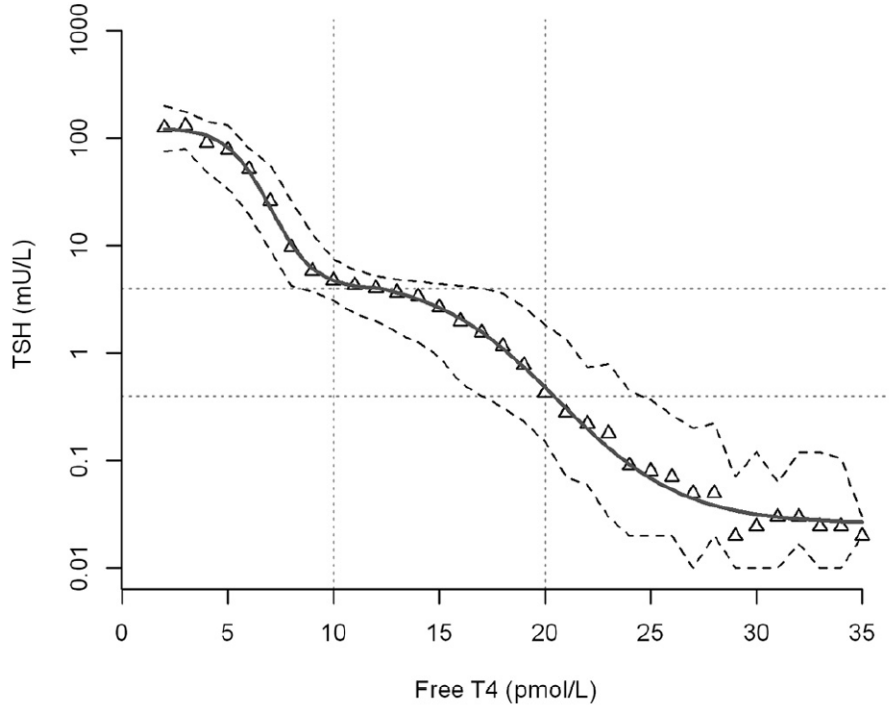


Figure 13: The solid line represents the result of the regression analysis with the sigmoid curves, the dashed lines represent the lower and upper quantiles and the small triangles represent the medians of TSH for each integer value of FT4. Taken from [38]

4.4 Population models applied to single patients

The relationship between TSH and FT4 has always been considered as inverse log-linear from a population perspective, however, as presented in the previous sections, some recent cross-sectional studies proved that the relationship between log(TSH) and FT4 is non-linear and more complex than it was thought previously .

The first study presented a nonlinear model based on the error function and proved that this was a better fit than the log-linear model [23]. A second study reported that the relationship between log(TSH) and FT4 was better described by a fourth order polynomial [37]. Finally, another study represented the relationship between log(TSH) and FT4 as two overlapping sigmoid functions [38].

However, it is not clear how population models can be applied to single individuals, since each person has different HP and thyroid functions, with a different set-point for the HPT axis [32]. Rothacker et al. compared six different models for the log(TSH)-FT4 relationship. They considered population models and applied them to single individuals. In every model, TSH was transformed using the natural logarithm, such that all the models expressed the relationship between log(TSH) and FT4. The models taken into account are the linear, quadratic, cubic and quartic ones plus the models based on the error function and on a negative sigmoid curve [32].

The six different models were compared with the null model, which consists of an horizontal line fitting the data, implying that TSH remains constant as FT4 changes. The tool used to carry out the comparison is the likelihood ratio, which is a statistical test that assesses the goodness of fit of two models, where one of them is usually more complex than the other. At first, the comparison included all the six different models. Then, least favored models were sequentially eliminated until only two non-null models remained for the final comparison. As shown in Figure (14), the models were discarded in the following order: first the error function model, then the sigmoid one, followed by the quadratic and cubic models. The two non-null models that remained until the last comparison are the linear model and the quartic one. It should be noted that the null model was always taken into account as an option. Figure (14) also shows the proportion of individuals for whom each model was the best fit. Since the least favoured models were eliminated sequentially, the proportions of best fit were computed again using the remaining models. In the last comparison, the linear model achieved best fit in 42% of the patients, while the quartic model in 43% of the individuals. The remaining 15% of cases was characterised by a superior fit of the null model.

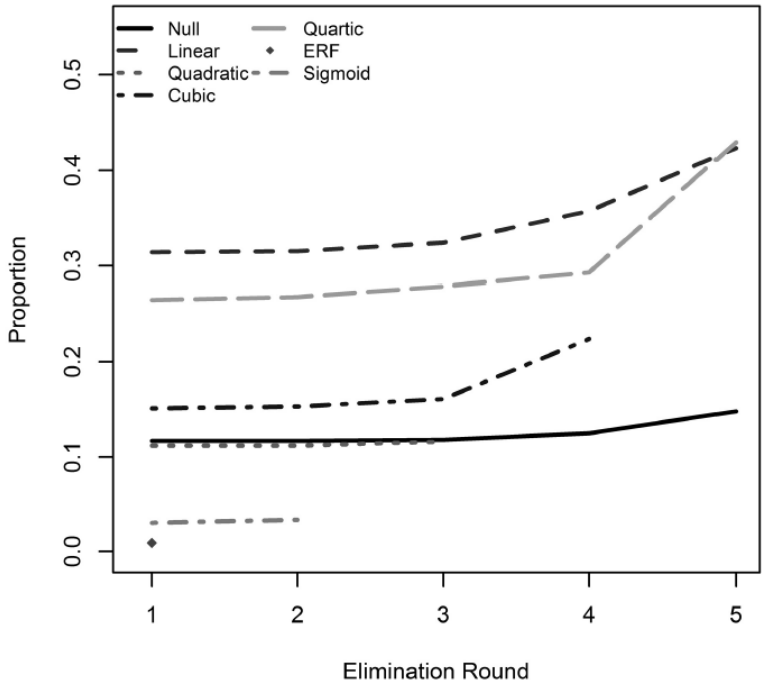


Figure 14: The graph shows in which order the models were eliminated from the comparison. It can be noticed that the null model was taken into account during all the stages of the comparison. On the vertical axis it is measured the proportion of patients for whom each model represented the best fit. This proportion was computed again after a model had been discarded. Taken from [32]

In a patient-specific approach, individuals with the highest number of measurements of TSH and FT4 are likely to be more informative. Hence, if adopting this perspective, it can be noted that the number of individuals for which the linear model was the best fit increased as the number of measurements per patient grew. This is shown in particular for the final comparison between the null, linear and quartic models in Figure (15). Therefore, it can be concluded that the log-linear model is an adequate description of the relationship between TSH and FT4 specific for a single individual [32].

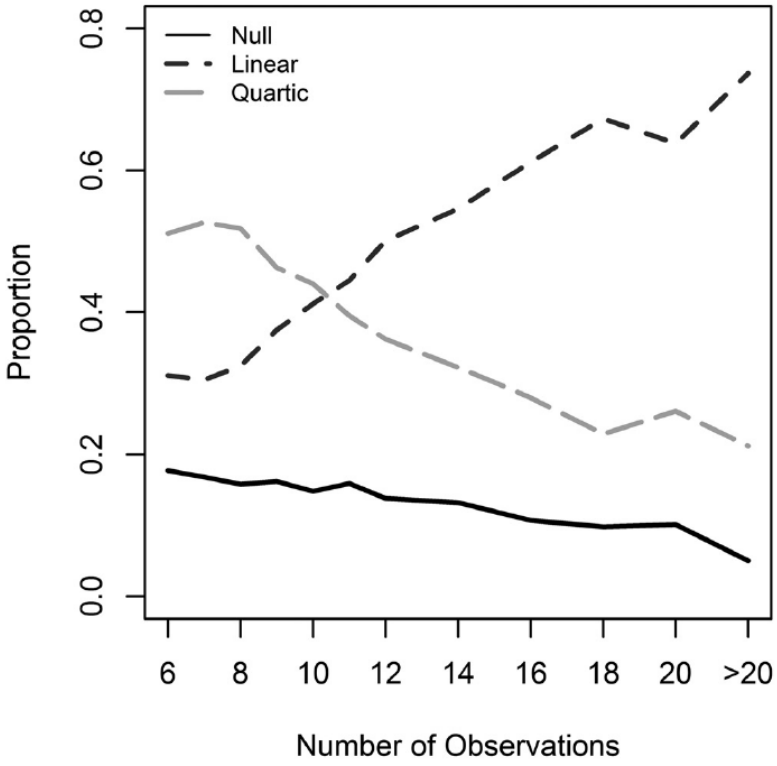


Figure 15: The graph shows in which order the model were eliminated from the comparison. It can be noticed that the null model was taken into account during all the stages of the comparison. Taken from [32]

5 Concluding remarks

5.1 Discussion

This literature review provides the necessary medical background to understand the mechanism of the HPT axis. Furthermore, it presents an overview of different modeling approaches for the HPT axis that were developed especially in the last decade. In particular, the distinction between patient-specific and population-based models is explained, with a particular focus on patient-specific models. In fact, these models are the ones of interest for this research, because they can be applied to each individual, allowing to predict the specific set-point of that patient.

This literature review underlines also the importance of implementing a mathematical model for the HPT axis and its set-point. In fact, as it is explained in the medical background, there are still patients whose symptoms do not improve even if they are under treatment. Hence, being able to predict the set-point of an individual represents an important step towards personalized diagnosis and medication for patients suffering from a thyroid disease.

Regarding patient-specific models, the model by Goede et al. [3], which expresses the relationship between TSH and FT4 as a negative exponential function, is the most reliable one. Furthermore, each exponential curve has a specific point, called the point of maximum curvature, that is used as a prediction for the set-point value. This model has been tested on distinct individuals and it has always provided satisfactory results.

The other approach presented, developed by Pandiyan et al. [29, 30], is a different attempt to model the HPT axis in patients affected by the Hashimoto disease. It should be noted that the authors understood the importance of developing a patient-specific model, which is already a big step in the HPT axis modeling. However, their model still presents some pitfalls. In particular, their model consists of a system of four differential equations, where the variables considered are the concentration of TSH, FT4 and TPOAb and the functional size of the thyroid. Nevertheless, the thyroid's functional size, as specified also by the authors, cannot be measured, hence the result obtained for this variable cannot be verified. Furthermore, the model includes 11 parameters, and it is not clear how they can be computed. Finally, the endocrine system cannot be represented with a dynamical model because the individual dynamical flow cannot be measured in real time and the relationship between TSH and FT4 is not considered time-dependent. However, since the authors focused on the steady states and one of them corresponds to the euthyroid state, it would be interesting to somehow compare it with the set-point of the exponential model.

The other models presented in the literature review are population-based models. The major flaw of population-based models is the implication that the hormone levels of one patient can influence the hormone values of another individual. This is not reasonable, because it does not happen in reality. Furthermore, these models are supposed to fit the data of the entire population, hence individual results are not considered important in this approach. Therefore, population models are of no use in the path towards personalized treatment of thyroid disorders. However, the study from Rothacker et al. [32] presents interesting results. In fact, in this study, the most common population models are applied on single patients, in order to understand if they are still valid on an individual level. It is shown that the two models with the best fit are the log-linear model and the quartic one. The log-linear model is actually nothing more than the exponential one developed by Goede et al. [3]. It might be of interest to still consider the quartic model and compare it to the exponential model using a different dataset. Furthermore, it would be interesting to see how the set-point could be estimated when using a fourth-order polynomial model.

5.2 Research questions

The research questions for this thesis will be:

- How can the HPT axis be modelled from a mathematical perspective? How can the existing model be improved?

In order to answer these questions, the exponential model by Goede et al. [3] will be considered as the starting point. It will be implemented and tested with the available data. After that, it would be possible to determine if the model is a good fit for the available datasets or if it can be somehow improved. This exponential model might be compared to the model based on the quartic polynomial, as suggested in the previous sections.

- How can the set-point of an individual be predicted?

Once the relationship between TSH and FT4 has been modelled, a prediction of the set-point should be found. If the model is the exponential one, then it should be verified that the set-point corresponds to the point of maximum curvature. Otherwise, if the exponential model has been modified and improved, it should be determined which point of the curve represents the HPT axis set-point. It could also be proved why, from a mathematical perspective, it is reasonable to assume that that specific point of the curve corresponds to the set-point.

- Once a prediction of the set-point is available, how can it be proved that it corresponds to the actual set-point?

If any data from the pre-disease period is available, it should be verified if the predicted set-point matches the real one. This question might be answered using data of patients that underwent thyroidectomy, since in most of the cases a couple of measurements for pre-surgery TSH and FT4 are available. However, in this case it is important to interpret the data in the correct way. It should be noted that it might not be possible to verify this, it depends on the available data.

- How can the optimal path leading to the desired HPT set-point be found? How much time is needed to reach the set-point?

A healthy person is in a situation of dynamic equilibrium, hence the measurements of TSH and FT4 will not vary much during time. The situation is completely different in case of a hypothyroid patient, when the concentration of FT4 decays in time. According to the current guidelines, it can take several months before the concentrations of TSH and FT4 reach again normal levels. Therefore, these last two questions regard the study of the instationary situation. Since time in the treatment of a disease is important, it is fundamental to study the optimal path to reach the new desired HPT state. Hence, the goal is to predict how a patient can reach a new equilibrium, corresponding to the set-point, and how long this process will take.

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