TECHNISCHE UNIVERSITÄT WIEN

MASTER THESIS

Finding the Homeostatic Set Point of the Hypothalamus-Pituitary-Thyroid Axis with Different Modelling Approaches

submitted to the

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Analysis and Scientific Computing
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Kurzfassung

Derzeit basiert die Behandlung von Schilddrüsenerkrankungen auf veröffentlichter Literatur, Leitfäden für die klinische Praxis sowie auf bewährten Verfahren, welche auf klinischer Erfahrung und akzeptierten Referenzbereich für die Konzentration von Schilddrüsenhormonen aufbauen. Diese Strategie führt im Regelfall zum gewünschten Ergebnis kann jedoch ebenso zu Fehldiagnosen und suboptimalen Behandlungsergebnissen führen.
Diese Arbeit handelt von einem Model des thyreotropen Regelkreises. Dieser wird auch als Hypophysen-Schilddrüsen-Achse bezeichnet und kann dazu herangezogen werden das Verständnis der Mechanismen dieses hormonalen Regelkreises sowie die Diagnostik und Therapie von Schilddrüsenerkrankungen zu verbessern. Aus diesem Grund wurde das wechselseitige Verhältnis zwischen dem Hypophysenhormon TSH und dem Schilddrüsenhormon FT4 modelliert. Weitere im thyreotropen Regelkreis involvierte Hormone wurden aufgrund von Gründen, welche im Zuge der Arbeit genauer erörtert wurden, vernachlässigt.
Der Modellansatz basiert einerseits auf einem analytischen Ansatz und andererseits auf einer Schätzung der Parameter während der Simulation. Neben einem Vergleich der beiden Modellansätze steht vor allem die Validierung des Modells mit Patientendaten, welche während einer Studie an der Medizinischen Universität Wien erhoben wurden, im Mittelpunkt dieser Arbeit. Des weiteren werden andere Versuche die Hypophysen-Schilddrüsen-Achse zu modellieren erörtert.
Die aus dieser Modellierung resultierende exponentiell fallende Kurve, welche die Beziehung zwischen dem Hypophysenhormon TSH und dem Schilddrüsenhormon FT4 grafisch darstellt, kann dazu verwendet werden das für den Patienten optimale Hormonlevel zu bestimmen. Dieser auch als Set-Point bezeichnete Wert steht in direktem Zusammenhang mit dem Erreichen des euthyreoten Zustandes beziehungsweise eines symptomfreien Zustandes. Obwohl es auf Grund von fehlenden Daten nicht möglich war die Set-Point Theorie zu validieren, wurden die auf unterschiedlichen basierenden Modellansätzen berechneten Werte verglichen um den Einfluss des Modellansatzes auf den Set-Point zu bestimmen. Dieses Modell soll bei Patienten mit einer Hypothyreose oder einer Hyperthyreose, bei denen die Hypophyse und der Hypothalamus nicht von einer Erkrankung oder Medikamenten beeinflusst wird, zum Einsatz kommen, um die Therapie zu erleichtern.

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Abstract

At the moment, the treatment of thyroid disorders is based on published literature, clinical practice guidelines and best local practice, which is based on clinical experience and accepted normal ranges of thyroid function tests. This strategy might work out in most situations, but can also lead to misdiagnosis and suboptimal treatment outcomes.
The main focus of this thesis lies on the modelling of the Hypothalamus-Pituitary-Thyroid axis. The purpose of such a model is to gain insight into the mechanism of the hormonal feedback loop and to improve the diagnostic process as well as the treatment of thyroid dysfunctions. Therefore, two different approaches of modelling were used to simulate the relationship between the pituitary hormone TSH and the thyroid hormone FT4, one analytical and the other with parameter estimation in Simulink. Other involved hormones have been neglected due to various reasons. Apart from a comparison of the different modelling approaches, the main part of this thesis is the validation of the model with medical data, which was collected during a study at the Medical University of Vienna. In addition, other attempts at modelling the HPT-axis are discussed.
The resulting exponentially decreasing curve, which depicts relationship between the pituitary hormone TSH and the thyroid hormone FT4, can be used to calculate the homeostatic set point of the Hypothalamus-Pituitary-Thyroid axis. The set point theory states that a unique set point connected to the euthyroid state exists for every human being. The calculated set point can be used to improve therapy of thyroid dysfunctions and consequently the state of many patients, who would otherwise suffer from discomforts even though their hormone levels are located in the normal range. Although, it was not possible to validate the set point theory with the available data, the influence of the modelling approach on the set point was examined. The resulting model should be used to improve the therapy of thyroid disorders and consequently the quality of life of the patient as long as the hypothalamus and pituitary are not influenced by disorders and drugs.

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On this note, I would like to thank my contact at the Medical University of Vienna, Michael Krebs, M.D., Associate Professor of Internal Medicine/Endocrinology, for his cooperation and the time he contributed to the exchange of medical data.
I am also grateful for Simon L. Goede, MSc. for his insight on thyroid systems engineering and his advice.
In addition, I would like to thank my colleague, Katharina Brunner, BSc., for proofreading this thesis and providing discussions, which helped me to improve it. Last but not least, I'd like to thank my partner and my family for their support and encouragement.

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List of Abbreviations

CSF	Cerebrospinal Fluid
FT3	Free Triiodothyronine
FT4	Free Thyroxine
HPT	Hypothalamus-Pituitary-Thyroid
HP	Hypothalamus-Pituitary
LT-3	Liothyronine or synthetic T3
LT-4	Levothyroxine or Synthetic T4
μIU/l	Micro-International-Units per Liter
mU/L	Miliunits per Deciliter
ng/DL	Nanogram per Liter
pmol/L	Pikomol per Liter
T3	$3, 5, 3'$-Triiodothyronine
T4	$3, 5, 3', 5'$-Tetraiodothyronine or Thyroxin
TFT	Thyroid Function Test
Tg	Thyroglobulin
TRH	TSH-Releasing Hormone or Thyrotropin-Teleasing Hormone
TSH	Thyroid-Stimulating Hormone

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1. Introduction

The number of people diagnosed with thyroid disease increases continuously and consequently more people have to rely on lifelong medication to treat their condition. However, state of the art of treatment of thyroid disorders is based on published literature, clinical practice guidelines and best local practice, which relies on clinical experience, and accepted normal ranges of thyroid function tests. These accepted normal ranges also vary depending on country and the respective laboratory performing a thyroid function test. Moreover, the current strategy does not perform well for every patient and can lead to misdiagnosis and suboptimal treatment outcomes, which can be attributed to the biological differences in every patient.
During the past few years the realisation that a patient's attributes influence the potency and secondary effects of medication led to the rise of individualised therapy plans regarding the dose of prescribed drugs. Consequently, the need to generate individualised treatment plans and the ability to customise application rates led to the demand of medical software, which is able to assist health care providers in this task. In most cases medical software modelling the course of a disease to calculate an individualised treatment plan is based on mathematical models.
The hormonal feedback loop of the homeostatic control system including the thyroid is very complex and its mechanisms are not fully understood to this day. Therefore, generating a model that is able to imitate and predict the function of the thyroid and its relation to the other organs of the system, namely the hypothalamus and the pituitary, would permit an insight into the mechanism of the feedback loop.

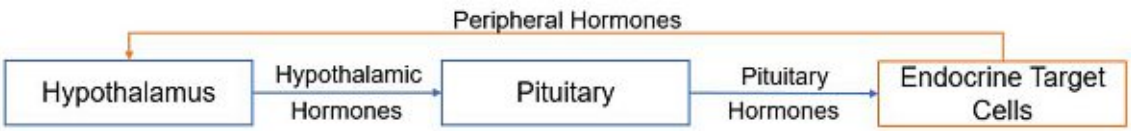

Figure 1.1: A simplified version of a hormonal feedback loop.

The field of science which covers the development of such models is interdisciplinary, including physicists, chemists, electrical engineers and mathematicians. Amongst other things, it is possible to trace the history of medical modelling back to the first epidemiological models, simulating the spread of disease in a population. Over time, researchers concluded that models describing transmission dynamics in a population can also be used to describe the transmission of a disease within a patient. During the same time,

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scientists from other fields came to the same conclusion, that it is possible and -more importantly- beneficial to apply knowledge from other fields to medical problems. Here, both mathematical and medical knowledge is needed to build a model meeting these high expectations.
The medical background needed to understand and generate a mathematical model is covered in Chapter 2. Besides discussing the different medical mechanisms of the hormone production and distribution as well as their influence on each other, the different diseases with an impact on the thyroid and consequently on the hormone production are described. Since the goal of this thesis is to improve the diagnostics and therapy of thyroid indispositions, the diagnostic process and the current treatment plan are covered in Chapter 2 as well.
In Chapter 3, an introduction to mathematical modelling is given in order to understand the modelling process and its results. At first, the advantages of mathematical models in medicine and the implementation of such models is discussed. Afterwards, the process of model building is expatiated in this chapter, to impart basic knowledge to the reader.
During the pursuit of a model able to produce these results many different mathematical approaches were used to yield a functioning model.The goal to build a precise dynamic model of this feedback-loop turned out to be especially impractical. The model's complexity and restrictions are caused by the measurability of some parameters, which influence the validation process, rendering it useless in practice.
During research one simple model stood out besides many complex ones with escapist parameters. This model, which will be discussed in Chapter 4, was first presented by Goede and Leow and simulates the relationship between the pituitary hormone TSH and the thyroid hormone FT4. To answer the thesis question of whether the model of Goede and Leow can be improved, two different approaches of modelling were used to simulate this relation, one analytical and one with parameter estimation in Chapter 4, where their performance was compared as well. Moreover, the question of why it is legitimate to neglect the other involved hormones will be answered in the same chapter taking into account, the usual process of diagnosing thyroid indispositions and the production and distribution of the different hormones.
The result of the model is an exponentially decreasing curve, which can be used to calculate the homeostatic set point of the Hypothalamus-Pituitary-Thyroid axis. The set point theory, which will be discussed in Chapter 5, states that a unique set point connected to the euthyroid state exists for every human being. From a mathematical point of view, the homeostatic set point interestingly coincides with the point of maximum curvature granting uniqueness due to the properties of exponential functions.
This is also the answer to the question of how it is possible to improve the health-related quality of life of many patients. The calculated set point can be used to improve therapy of thyroid dysfunctions and consequently the physical state of many patients, who otherwise would suffer from discomforts even though their hormone levels are located within the normal range.
To summarize, the model presented in this thesis can be used to improve the therapy of thyroid disorders as long as the hypothalamus and pituitary are not influenced by disorders and drugs. However, more validation of the model is needed before it is suitable for general use. Even though it is possible to use generated data to validate a model, the validation of a model for practical application usually relies on medical data.

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Normally, obtaining medical data is complicated by the local ethics commission, which is responsible for the protection of patient data, restrictions from different departments concerning data exchange and last but not least if it is not possible to conduct a new medical study it is often difficult to find a study providing datasets that fits the requirements of the clinical validation process. After approval from the local ethics commission, the Medical University of Vienna was able to provide an appropriate data set, which was obtained during a longitudinal, prospective pilot study. On this note, a validation of the model with clinical data from Austria is conducted in Chapter 6.

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2. Medical Background for the Mathematical Model

Thyroid hormones are responsible for the stimulation of the basal metabolic rate and therefore have an impact on many vital processes in the human body, including general cell and tissue growth according to Lecture [3] and Book [11]. They influence the fatty acid metabolism, thermogenesis, bone metabolism, especially bone growth, the cardiovascular system and the development and maturation of the brain and nervous system. The thyroid gland secrets mainly two different hormones, namely $3, 5, 3', 5'$-tetraiodothyronine or thyroxin T4 and $3, 5, 3'$-triiodothyronine T3, which have an inhibiting effect on the hypothalamus and are depicted with an red arrow in Figure 2.2.

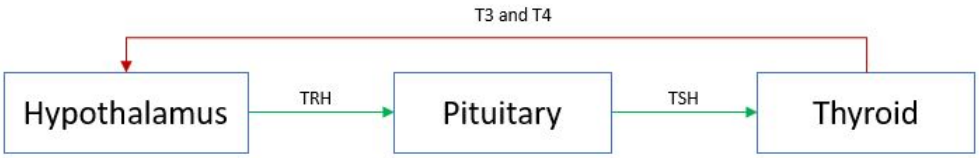

Figure 2.2: An overview of the Hypothalamus-Pituitary-Thyroid axis based on Lecture [3] and Book [11].

To regulate the secretion of T3 and T4 the hypothalamus produces TSH-Releasing-Hormone TRH stimulating the pituitary to produce Thyroid-Stimulating-Hormone TSH, which is depicted in Figure 2.2, with the green arrows indicating a stimulating effect. Together these three organs form the so-called Hypothalamus-Pituitary-Thyroid axis or HPT axis for short and are responsible for the maintenance of the euthyroid state, which describes the optimal thyroid hormonal equilibrium. The homeostatic control system of the HPT axis can achieve this by a feedback loop, which will be discussed later in this paper.

2.1 Anatomy of the Involved Glands

Even though many believe that the pituitary should be named as the master gland due to its control over the hormone production according to [5], one should keep in mind that the pituitary gland is controlled by the hypothalamus and therefore the hypothalamus should be appointed as master gland. The location of the hypothalamus is at the base of the forebrain, below the thalamus as illustrated in Figure 2.3. It is divided by the third ventricle, which is filled with cerebrospinal fluid or CSF for short.

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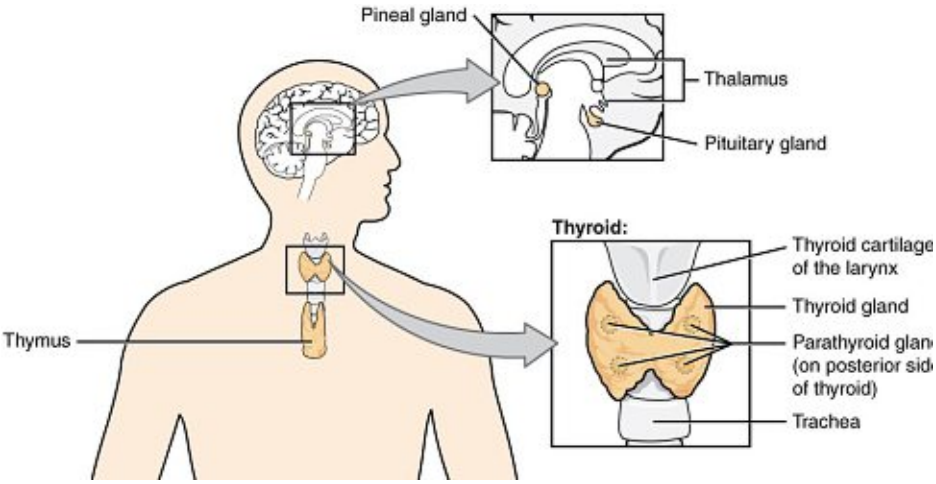

Figure 2.3: Overview of the Endocrine System, see[1] Book [1].

The hypothalamus contains many groups of nerve body cells, so called nuclei, which are paired and then distributed with one half of the pair on either side of the third ventricle. The nuclei control many important body functions like regulating the sympathetic and parasympathetic branches of the autonomic nervous system, which again control visceral functions. The hypothalamus is responsible for the temperature regulation mechanism of the body, the regulation of electrolyte balance as well as the control of emotional responses and it mediates motivational arousal and hormone secretion. The hypothalamus also contains a 'biological clock' which determines many biological rhythms.
The cells of the hypothalamus are regulated by neurotransmitters, which are released by neurons in the cerebral cortex, thalamus, other parts of the limbic system and the spinal cord and are then transported to the hypothalamus via afferent and efferent nerve fibres. The blood supply of the hypothalamus also has a big impact since the hypothalamic nuclei are influenced by a wide variety of chemical messengers, which are delivered via blood and CSF as well as neurotransmitters from other neurons.
The synthesis of the different hypothalamic hormones happens in neurosecretory (neuroendocrine) cells. They act as neuroendocrine transducers, i.e. converting neural input into hormonal output. Even though the hypothalamus is responsible for many different hormones, we are only interested in the thyrotropin releasing hormone TRH, which is also known as thyroid stimulating hormone releasing hormone TSH-RH.
According to [5] besides stimulating the pituitary to produce TSH, the hormone TRH also operates as a neuromodulator in the brain. Synthesis of this hormone primarily takes place in the paraventricular nucleus and the anterior periventricular nuclei. Smaller amounts of TRH are synthesised in several other nuclei, such as the preoptic-anterior hypothalamic area, the dorsomedial, ventromedial, and suprachiasmatic nuclei and arcuate nuclei. In addition to environmental factors, which stimulate the release of TRH like acute cold exposure and stress, the TRH synthesis is regulated by catecholaminergic neurotransmitters as well as neuropeptides, like somatostatin and opioids. Afterwards, the synthesised hormones are released to the pituitary via the capillary system.

[1]Book [1]: Unit 3: Chapter 17 — The Endocrine System: Page 734: Figure 17.2 Endocrine System.

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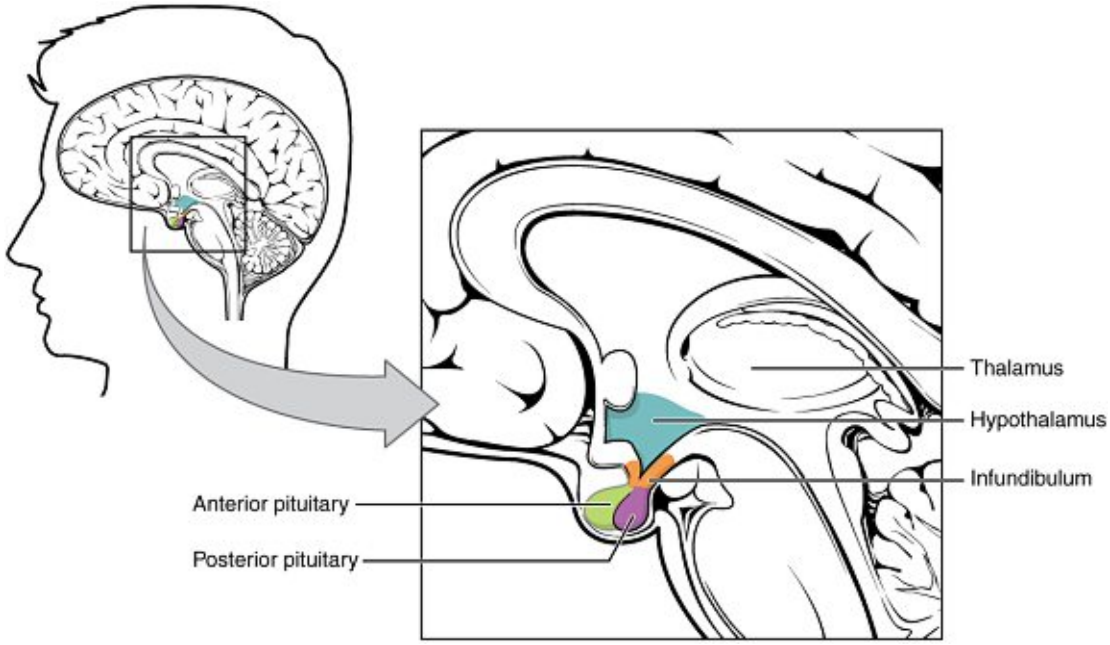

Figure 2.4: Hypothalamus–Pituitary Complex of the HTP axis, from [2] Book [1].

The pituitary gland, also known as the hypophysis, is situated in a small cavity of bone above the roof of the mouth and below the bottom of the hypothalamus at the base of the brain, which can be seen in Figure 2.4. It hangs from the bottom of the hypothalamus by the hypophyseal stalk, which is connected to the median eminence of the hypothalamus. The pituitary can be divided into three parts: the anterior lobe (pars distalis), the intermediate lobe (pars intermedia) and the posterior lobe (pars nervosa). Only the anterior and intermediate lobes form a true endocrine gland, which is called the adenohypophysis. Hormonal stimulation of the endocrine tissue of the adenohypophysis happens through the blood vessels of the hypophyseal portal system, which is situated in the pars tuberialis of the hypophyseal stalk, whereas the posterior lobe or the neurohypophysis is only an extension of the hypothalamus and consists of neural tissue.
Although the pituitary gland is responsible for the production of ten different hormones, which are all important for the body, only the production of thyroid stimulating hormone TSH is important for our cause. In thyrotroph cells of the adenohypophysis the production of TSH, alias thyrotropin or thyrotropic hormone, takes place.
The thyroid gland, as can be seen in Figure 2.5, is located in front of the thyroid cartilage of the larynx that can be found just below the Adam's apple. It is an endocrine gland consisting of two lobes that are connected by an isthmus. A very remarkable feature of the thyroid is the great variability in size and weight of the lobes, approximately 15 to 30 grams per gland and approximately 4×3 cm per lobe.

[2]Book [1]: Unit 3: Chapter 17 — The Endocrine System: Page 744: Figure 17.7 Hypothalamus–Pituitary Complex

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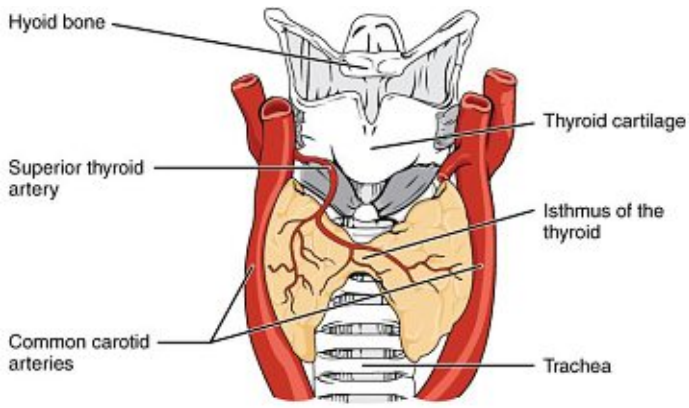

Figure 2.5: An anterior view of the thyroid gland, from[3] Book [1].

Vascularization is warranted via the superior thyroid artery, a branch of the external carotid artery, and the inferior thyroid artery, a branch of the thyrocervical trunk. Venous vascularization, where venous blood is drained from the organs, occurs via the superior and middle thyroid veins, which discharge into the internal jugular vein, and via the inferior thyroid veins, which drains to the superior vena cava.
The thyroid gland is responsible for the production of three main hormones. Two of these hormones have been mentioned before, triiodothyronine (T3) and thyroxine (T4). They are quite similar and depend on iodine for their synthesis, and based on the end product three or four iodine ions are bound to the protein thyroglobulin (Tg). This process occurs in the follicle cells of the thyroid. The hormones are stored in the colloid and then distributed to the blood via follicle cells. The ratio of T3 to T4 in human blood is 1:40, therefore T4 is much more prevalent in blood than T3. The third thyroid hormone is calcitonin, which reduces blood calcium levels and plays an important role in the calcium metabolism. The information in this part was taken from Lecture [7] as well as Lecture [3] and Book [5].

2.2 Endocrine Feedback-Loop

The synthesis and release of pituitary hormones, which influence endocrine and non-endocrine target cells, are regulated by hypothalamic hormones. These endocrine target cells release a third hormone that influences the synthesis and release of hypothalamic hormones. Consequently all three levels of hormones, hypothalamic, pituitary and peripheral act in feedback loops. In these feedback loops neurotransmitters and neuropeptides are also involved.
Thus, a medical feedback loop describes the situation in which the release of hormones by the cells of a given system regulate the secretion of the hormones, which stimulated their release in the first place and by that the secretion of hormones regulates itself. In terms of the feedback loop mechanism a distinction can be made between a positive and a negative feedback loop. In positive feedback the release of a hormone stimulates the secretion of another hormone and thus has an increasing effect on hormone production,

[3]Book [1]: Unit 3: Chapter 17 — The Endocrine System: Page 752: Figure 17.12 Thyroid Gland (a) Anterior view

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whereas in negative feedback the release of a hormone reduces the secretion of another hormone and hence has a dampening effect on the hormone production. The feedback loop of the HPT axis is a negative feedback loop because T3 and T4 inhibit the release of TRH.

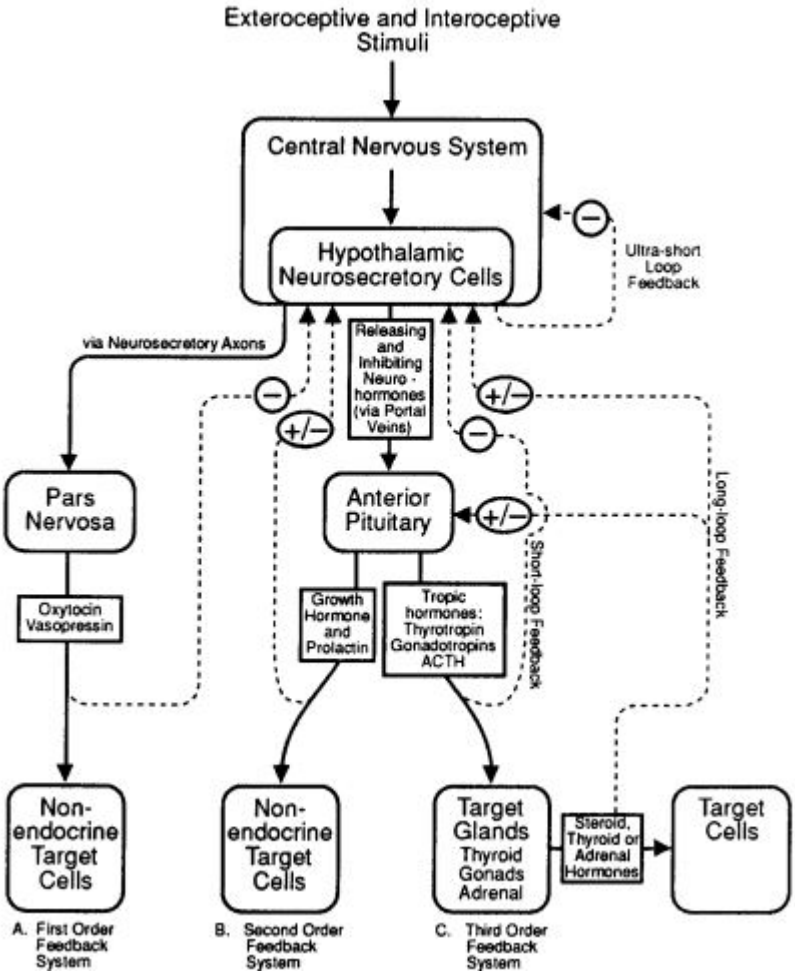

Figure 2.6: The Endocrine Feedback-loop as depicted in[4] Book [5].

In medicine and according to Book [5], one distinguishes between three orders of hormonal feedback loop based on their complexity - first, second and third order feedback systems - in regard to the number of involved hormones and involved glands. In first order systems one hypothalamic hormone is released and acts on one endocrine gland but it neither stimulates pituitary hormones nor any other endocrine target. The hormone levels in such a system are monitored by hormonesensitive nerve cells in the brain and regulate themselves.
Second order systems are a bit more complicated. They still involve hypothalamic releasing and inhibiting hormones but include pituitary hormones too. The hypothalamic hormones still do not stimulate any other endocrine target cells. The secretion of the pituitary hormones regulate themselves via feedback regulation of the hypothalamic hormones.

[4]Book [5]: Chapter 8 - Regulation of hormone levels in the bloodstream: Page 134: Figure 8.5 Endocrine Feedback-loop

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The third order feedback systems, to which the hypothalamic-pituitary-thyroid feedback system belongs, consist of three endocrine glands, the hypothalamus, the pituitary and a peripheral endocrine gland, and is the most complex feedback system. In a third order feedback loop each hormone can provide negative feedback to the hypothalamus, therefore three levels of feedback can be differentiated: long, short, and ultrashort loop feedback. The different kinds of feedback will be explained in regard to the hypothalamic-pituitary-thyroid feedback system.

Long loop feedback solely occurs within third order feedback systems and is in most cases negative and hence has an inhibitory effect. There are some exceptions which will not be discussed. In the HPT axis the long loop feedback to the hypothalamus and pituitary is provided by thyroxine. More precisely the release of TSH is inhibited by thyroid hormones and thus is controlled by a direct negative feedback on the pituitary thyrotroph cells.

A *short loop feedback* within a third order system equals a second order feedback system, with the additional restriction of occurring within an third order feedback system. In our case the pituitary hormone TSH provides such a short loop negative feedback to the hypothalamus.

A so-called *ultra-short loop feedback* is provided by hypothalamic hormones, which feedback to help to regulate themselves. This ultra-short feedback loop can be best described as a first order feedback, which is contained within a third order system and therefore two other hormones are involved in this loop.

Besides the three main hormones, which have been mentioned repeatedly, neurotransmitters play a big role in the control of thyrotropin releasing hormone TRH and thyroid stimulating hormone TSH secretion. The release of TSH from the thyrotroph cells of the anterior pituitary is not only stimulated by TRH, which is released by the neurosecretory cells in the dorsomedial hypothalamus, but is also inhibited by somatostatin, which increases with increasing stress from neurosecretory cells in the medial preoptic area.

The baseline TSH levels are mainly reduced by dopamine, but can be stimulated by adrenaline and noradrenaline. Cold-induced TRH and TSH release are also stimulated by adrenaline and noradrenaline and inhibited by dopamin in two ways, on one hand by inhibiting the release of TRH from the hypothalamus and on the other hand by inhibition of the thyrotroph cells in the pituitary.

Serotonin plays a controversial role in TSH release since some studies report that serotonin has an increasing effect on TSH levels, others a decreasing effect and some even report no effects on TSH levels. These varying conclusions can be explained by the interaction of serotonin and thyroid hormone feedback in the regulation of TSH release. Serotonin takes contrary roles in the feedback system, depending on the presence of thyroid hormones. During their absence serotonin resumes the position of a stimulator for TRH and TSH release, whereas serotonin inhibits TSH release during normal thyroid hormone levels. It could be possible that serotonin is involved in the negative feedback effects of T3 and T4 on TRH secretion.

Other neurotransmitter involved in the feedback-loop are acetylcholine, histamine, which appears to stimulate TRH release, GABA and enkephalins, which inhibit TRH and TSH release. Acetylcholine acts similar to adrenalin and noradrenalin, even though it only has little effect on the baseline release of TSH. A more detailed description of this system can be found in Book [5].

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2.3 Pathology of the Thyroid Gland

In Pathology as per Lecture [3] a distinction is made for the dysfunction of the thyroid gland between hypothyroidism, which characterizes an underactive thyroid, and hyperthyroidism, which means an excessive amount of thyroid hormones is produced.

2.3.1 Hypothyroidism

In Lecture [3] two kinds of hypothyroidism were discussed, primary and secondary hypothyroidism, depending on their cause. Primary hypothyroidism is induced by different defects affecting the thyroid gland, like genetic sources, iodine deficiency, after an operation or an inflammation of the gland, like Hashimoto's thyroiditis. In this case due to the feedback loop responsible for thyroid hormone production the TSH level is high.
Secondary hyperthyroidism is characterised by a lack of TSH and TRH. Typical symptoms are weight gain, hypercholesterolemia, myxedema of the skin, anaemia, constipation, fatigue and also a decrease in the cardiac output as well as the kidney and liver function. In children hypothyroidism can also lead to disorders of bone growth and brain development.

Pathogenesis In Article [6] a more detailed classification was presented, where depending on the cause hypothyroidism was classified as primary, secondary, tertiary or peripheral. The most common kind is primary hypothyroidism, which occurs due to a thyroid hormone deficiency. Both Articles [6] and [8] pointed out that the main cause for primary hypothyroidism, especially in iodine-sufficient areas, is chronic autoimmune thyroiditis, also known as Hashimoto's disease. Other reasons causing primary hypothyroidism include the condition after radioiodine therapy, insufficient substitution with thyroid hormones after a thyroid resection, also after neck radiation or surgery for cancer therapy. Usually a subclinical hypothyroidism evolves into an apparent hypothyroidism, during subclinical hypothyroidism especially basal TSH levels correlate with the risk of this development, which was proven by a Swiss study mentioned in Article [8]. Other environmental factors implicated in autoimmune thyroiditis according to Article [6] are vitamin D and selenium deficiency as well as moderate alcohol intake.
A study, which was done over a 10 year long observation period, monitored the development of apparent hypothyroidism in different patient groups with chronic autoimmune thyroiditis separated by TSH levels. The results according to Article [8] showed that patients with TSH values above 12 mU/l developed apparent hypothyroidism in 78% of the cases, while only 26% of the group with a TSH level between $6 - 12$ mU/l develop apparent hypothyroidism. In patients with a minor increase in TSH levels, precisely TSH values below 6 mU/l, only 7.4% develop apparent hypothyroidism. In total 34% of the monitored patients develop apparent hypothyroidism. It makes sense that the group of people with detected thyroid autoantibodies show a cumulative development of apparent hypothyroidism.
Less than 1% of cases are classified as central hypothyroidism, which affects both sexes

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equally and includes both secondary and tertiary cases and peripheral hypothyroidism, making these conditions rare. The cause for secondary hypothyroidism is TSH deficiency, while the reason for tertiary hypothyroidism is a thyrotropin releasing hormone deficiency. Central hypothyroidism is more often associated with disease of the pituitary than hypothalamic disorders but involves in some cases both. Biochemically it is characterised by low or low to normal TSH concentrations and a disproportionately low concentration of free thyroxine. In some cases TSH concentration can be mildly elevated presumably due to decreased bioactivity. The main cause for central hypothyroidism in more than half of the cases is pituitary adenomas. Other reasons include pituitary or hypothalamic dysfunction due to head trauma, pituitary apoplexy, Sheehan's syndrome, surgery, adiotherapy, genetic and infiltrative disease. Also several drugs are known to have an impact on the hypothalamic–pituitary–thyroid axis.
Peripheral hypothyroidism can be caused by consumptive hypothyroidism or by tissue-specific hypothyroidism due to decreased sensitivity to thyroid hormones. A very rare disruption of the hypothalamic–pituitary–thyroid axis known as consumptive hypothyroidism is caused by the overexpression of the deiodinase 3 enzyme in tumour tissue, which inactivates thyroid hormones and by that induces severe hypothyroidism.

Epidemiology In Article [8] various studies collecting data of the prevalence of hypothyroidism in different sections of the population were listed. The *Nixdorf-Recall-Studie* is one of them, it was done on the general public and targeted 4400 people between the ages of 45 and 74. 0.1% of the tested group have apparent hypothyroidism while 6.1% only developed subclinical hypothyroidism. Another study, which targeted people over the age of 65, called the *Birmingham Elderly thyroid study* showed that 0.4% of the tested group have apparent hypothyroidism and 2.9% have developed only subclinical hypothyroidism. The third study concentrated on Pomeranians, *Study of health in Pomerania*, and showed that 1.2% of the general public have increased TSH values and 0.7% have apparent hypothyroidism and only 0.5% have the subclinical type of hypothyroidism.
In Article [6] the effect of differences in iodine status like a relatively high iodine intake or severe iodine-deficiency on the prevalence of hypothyroidism were pointed out. According to Article[8] it was also possible to verify with different experiments that a connection between iodine supply and the occurrence of autoimmune thyroiditis in the population exists. In regions with a high iodine supply raised incidence of thyroid autoantibodies in the population as well as a cumulative prevalence of autoimmune thyroiditis, which results in an apparent hypothyroidism, could be detected compared to regions with a normal or low iodine supply.
In Article [6] it was mentioned that especially women, people over the age of 65 and -although data on ethnic differences is scarce- also white individuals are diagnosed more often with hypothyroidism. Patients with autoimmune diseases, such as type 1 diabetes, autoimmune gastric atrophy, and coeliac disease are more prone to hypothyroidism, which can occur as part of multiple autoimmune endocrinopathies. Another patient group with increased risk of hypothyroidism are individuals with Downs' syndrome or Turners' syndrome, whereas tobacco smoking and moderate alcohol intake are associated with reducing the risk.
In Article [6] the genetic epidemiology of hypothyroidism was discussed, like the her-

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itability of TSH and free thyroxine concentration in serum, which is estimated to be between 23 and 65%. Only a small proportion of thyroid function variablity could be explained by genome-wide association studies, especially since only three of them have focused solely on hypothyroidism. The identified loci possibly related to hypothyroidism include autoimmunity-related and thyroid-specific regulatory genes. Most of them could also be linked to serum TSH concentration within the reference range. Seldom, the cause of congenital hypothyroidism can be monogenetic disorders like TSH resistance, thyroid dysgenesis, and thyroid dyshormonogenesis.

Clinical Picture The different stages of clinical manifestation of hypothyroidism, which range from life threatening conditions like myxedema coma to no symptoms at all, were described in detail in Article [6]. Even though myxedema coma has become a rare condition, early recognition is vital since it is the outcome of long-standing untreated and severe hypothyroidism with a mortality rate of 40% despite treatment. It can induce altered mental status, hypothermia, progressive lethargy, and bradycardia. In severe cases it can lead to multiple organ dysfunction syndrome and even death. For that reason an early initiation of thyroid hormone therapy and other supportive measures is of utmost importance.

Typical symptoms of hypothyroidism in adults are fatigue, lethargy, cold intolerance, weight gain, constipation, change in voice, and dry skin. Still, symptoms for the diagnosis of hypothyroidism are non-specific, since the clinical presentation can include a wide variety of symptoms depending on age, sex and time between onset and diagnosis. Especially in elder patients fewer and less classical signs are found than in younger individuals.

A case study from Article [6] showed that none of 34 hypothyroidism related symptoms could be used to identify patients with hypothyroidism. It is also problematic that approximately 15% of patients with autoimmune hypothyroidism are asymptomatic or report only one hypothyroidism-associated symptom. On the other hand 70% of euthyroid controls have one or more thyroid associated complaints.

Hypothyroidism affects nearly all major organs, but the most researched system regarding influences of this disease is the cardiovascular system. An increased vascular resistance, decreased cardiac output, decreased left ventricular function, and changes in several other markers of cardiovascular contractility can be found in patients with this illness. Other conditions more common in patients with hypothyroidism than in matched euthyroid controls include Myocardial injuries and pericardial effusions as well as a higher prevalence of cardiovascular risk factors and features of metabolic syndrome, like hypertension, increased waist circumference, and dyslipidaemia. It also increases total cholesterol, low density lipoprotein, and homocysteine concentrations.

A decline in mood and quality of life can be detected especially in the context of thyroid cancer treatment. Hypothyroidism can also cause reversible dementia, even though it is not known how often that is the case and, more importantly, to what extent dementia is reversible. Hypothyroidism can affect the course of other disease and lead to neurosensory, musculoskeletal and gastrointestinal signs and symptoms.

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2.3.2 Hyperthyroidism

Hyperthyroidism can be caused by three different diseases: Morbus Basedow, toxic nodular goitres and toxic adenoma, according to Lecture [3]. Due to excessive production of thyroid hormones, the patient will suffer from one or more of the following symptoms: weight loss, bone resorption, tachycardia and other types of arrhythmia, diarrhoea or steatorrhea, tremor, muscle weakness, sleeping problems like insomnia. Thyroid storm, or thyrotoxic crisis, is a life-threatening exacerbation of the patient's condition.

Pathogenesis In Article [13] the most common cause in iodine-sufficient areas for hypothyroidism is Graves' disease or Morbus Basedow, which is an inflammation of the thyroid gland. Notwithstanding that over 80% of cases in iodine-sufficient areas are caused by Graves' disease, in iodine-deficient areas approximately 50% of diagnosed cases are caused by toxic multinodular goitre and toxic adenoma, which are more predominant in elderly people. Thyroid nodules cause hyperthyroidism by becoming autonomous and producing thyroid hormones, disregarding signals from either TSH or TSH-receptor antibodies. Other less common causes include thyrotropin-induced thyrotoxicosis and trophoblastic tumours, in which TSH receptors are stimulated by excess TSH and human chorionic gonadotropin.

Epidemiology In Article [13] it was stated that the prevalence of hyperthyroidism amounts to 0.8% in Europe and to 1.3% in the USA, whereas the prevalence of overt hyperthyroidism is between 0.5% and 0.8% in Europe and only 0.5% in the USA. The chance to get hyperthyroidism increases with age and the disease is also more common in female patients. Even though data for ethnic differences are scarce, white people seem to be more frequently affected than any other race. Cases of mild hyperthyroidism are reported more often in iodine-deficient areas than in iodine-sufficient areas. By introducing universal salt iodisation programmes, a decrease in the number of reported cases can be noted.

Clinical Picture Typical signs and symptoms include weight loss, resorption of bone, tachycardia, diarrhoea or steatorhea, tremor or myasthemia and insomnia, according to Lecture [3]. In Article [13] the different symptoms due to excess thyroid hormones were separated into differing categories assigned to different organ systems.
Symptoms regarding the constitutional system are weight loss despite increased appetite and heat related symptoms like heat intolerance, sweating, and polydipsia. The neuromuscular part shows symptoms like tremor, nervousness, anxiety, fatigue, weakness, disturbed sleep, and poor concentration, which lead to signs like tremor of the extremities, hyperactivity, hyper-reflexia, and pelvic and girdle muscle weakness.
Symptoms of the cardiovascular system are mainly palpitations, which lead to signs like Tachycardia, systolic hypertension, and irregular heartbeat like atrial fibrillation. The pulmonary system displays symptoms Dyspnoea or shortness of breath resulting in Tachypnoea. The gastrointestinal system suffers symptoms like Hyperdefecation, nausea

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and vomiting as well as signs of abdominal tenderness. An increased perspiration in patients leads to warm and moist skin. Also, the reproductive system is affected due to menstrual disturbances.

2.3.3 Inflammation

There are two kinds of autoimmune inflammation of the thyroid gland, which were discussed in Lecture [3]: Morbus Basedow, which causes hyperthyroidism, and Hashimoto's thyroiditis, which triggers hypothyroidism.
According to [8], Morbus Basedow and Hashimoto's thyroiditis can lead to the development of so-called autoimmune polyendocrine syndromes or polyglandular autoimmune syndromes, which characterize the co-occurrence of different autoimmune disease in one patient. Other illness associated with this syndrome are Addison's disease, hypoparathyroidism, pernicious anaemia, vitiligo, coeliac disease, alopecia, hypophysitis, autoimmune hypothyroidism, primary hypogonadism and myasthenia gravis.

Morbus Basedow

According to Lecture [3], Morbus Basedow or Graves' disease is an autoimmune disease, which is characterised by the production of TSH-receptor-autoantibodies. These autoantibodies bind to the TSH receptors of the follicular cells and activate them, resulting in uncontrolled growth of the thyroid and unregulated production of thyroid hormones. Therefore, these autoantibodies operate like TSH without feedback control.

Pathogenesis In Article [13] Graves' disease is depicted as a multifactorial disease caused by the loss of immunotolerance and the development of autoantibodies which stimulate thyroid follicular cells by binding to the TSH receptors. A low penetrance due to genetic predisposition could be proven by several studies. Mostly immune-regulatory genes and thyroid autoantigens such as thyroglobulin and TSH-receptor genes are involved in Graves' disease. Other non-genetic risk factors include psychological stress and smoking. Another suspected risk factor due to a higher prevalence in women are sex hormones and chromosomal factors, such as the skewed inactivation of the X chromosome. Also certain infections, vitamin D and selenium deficiency, thyroid damage and immunomodulating drugs are suspected triggers but further studies are still needed to precise the role of these factors in causing Morbus Basedow.

Clinical Picture Signs and symptoms in Graves' disease specified in Article [13] include ophthalmopathy, thyroid dermopathy, and thyroid acropachy. The uncontrolled growth of the thyroid gland leads to a multiple nodule goitre, which causes oesophageal or tracheal compression and induces symptoms and signs like globus sensation, dysphagia or orthopnoea. Anterior neck pain in painful subacute thyroiditis can also occur.

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According to Article [13], 25% of patients with Morbus Basedow develop Ophthalmopathy, also known as Graves' orbitopathy. Typical signs are Exophthalmos due to the growth of orbital adipose tissue induced by TSH-receptor-autoantibodies, periorbital oedema and diplopia. A rare extrathyroidal manifestation occurring in 1–4% of patients with thyroid ophthalmopathy and in even less patients without this symptom is thyroid dermopathy, with lesions that are characterised by slightly pigmented thickened skin occurring primarily in the pretibial area. The rarest extrathyroidal manifestation of Graves' disease is acropachy causing clubbing of the fingers and toes.

Hashimoto's Thyroiditis

As per Lecture [3] and Article [8], Hashimoto's thyroiditis or autoimmune thyroiditis is the most common autoimmune thyroid disease and is mostly diagnosed in female patients. Chronic thyroiditis is characterised by the production of autoantibodies, which attack mainly thyroid peroxidase and thyroglobulin, but also thyroid follicles, colloid components and the thyroid hormones (T4) and (T3). Patients normally suffer from subclinical hypothyroidism which develops into persistent hypothyroidism or apparent hypothyroidism with typical clinical symptoms and the need of hormonal substitution arises in succession of the lymphocytic infiltration of the thyroid.

Pathogenesis In Article [8] it is stated that the mechanism triggering this disease is not sufficiently known and research is still ongoing. But after exposure to thyroid specific autoantigens, the activity of T helper cells increases and after cytokine is released, the production of antibodies is started by B lymphocytes or B cells. Particularly with regard to the course of the disease, T helper cells seem to play a decisive role. Furthermore, there seems to be a genetic factor, i.e. autoimmune thyroiditis is associated with the expression of human leukocyte antigen (HLA) system corresponding to MHC class II, precisely DR3, DR4 and DR5. In addition to suffering from autoimmune thyroiditis, patients often develop other autoimmune disease, especially diabetes mellitus of type one. Not only index cases show susceptibility to different autoimmune disease, but also first degree relatives show a higher risk of developing an autoimmune disease.

Clinical Picture According to Article [8], there is no typical clinical picture depicting autoimmune thyroiditis, making diagnostics especially difficult. Initially a goitre can be observed. While the disease progresses the goitre changes to an atrophy of the thyroid gland. Autoimmune thyroiditis is mostly diagnosed at a later stage when the gland is already atrophic and the patient already suffers from apparent hypothyroidism.
Histologically, a lymphocytic infiltration of the thyroid can be observed. Also, the size of thyroid follicles are small and the colloid is reduced. During the course of the disease, atrophy of the thyroid follicular cells occurs. Due to the loss of the function of follicular cells which are responsible for the production of different hormones a primary hypothyroidism is developed, which is distinguished by a reduction of thyroid hormones and a raise in TSH. In the final stage, the patient suffers from apparent hypothyroidism.

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Preceding this stage, subclinical hypothyroidism can be observed where the thyroid gland supplies the body with enough thyroid hormones, but a raised amount of TSH can be detected.
During the last stage typical symptoms like bradycardia, hypotonia, tendency to constipation, general weakness, cold intolerance or mental changes like depression, which are often connected with weight gain, dominate the course of this disease. In the course of examinations dry skin, sometimes accompanied by myxoedema, and bradycardia stand out. Since the progress of autoimmune thyroiditis is very slow, symptoms and disorders tend to be overlooked, leading to a latency of the diagnostic procedure. The above mentioned symptoms and disorders of apparent hypothyroidism do not occur during subclinical hypothyroidism. Sometimes, a tendency for bradycardia and mental changes like mood swings can be observed. Besides neuromuscular weakness, a decrease in activity or a general slowdown are typical for this condition. Moreover, a connection between subclinical hypothyroidism and disorder of their fertility or a disturbance on the course of pregnancy in young women could be made.

2.3.4 Diagnostics

The measurement of serum TSH should be the first step in the diagnostic process regarding thyroid disease, due to its high sensitivity and specificity in the diagnosis of thyroid disorders, as per Article [13].
The definition of primary hypothyroidism presented in Article [6] states that the TSH concentration is above the reference range while free thyroxine concentrations is below the reference range, which depends on the used type of assay and the studied population. Besides circadian fluctuation, which causes higher concentration towards the evening, also seasonal variations have been detected, with higher TSH levels in winter and spring. Especially patients with severe hypothyroidism have irregular TSH secretion cyles.
To determine if a patient suffers from autoimmune thyroiditis Article [8] recommends the measurement of free T3 and free T4 levels as well as the levels of different thyroid antibodies. Due to reasons of cost efficiency, laboratory tests target anti-thyroid peroxidase antibodies (anti-TPO, or TPOAb) due to their prevalence of $80 - 90\%$, while levels of anti-thyroglobulin antibodies (anti-Tg) are only used when no TPOABs can be detected due to their prevalence at $60 - 70\%$. Only if clarification is needed due to atypical symptoms like present hyperthyroidism, laboratory tests are performed to measure TSH-receptor antibodies, otherwise these kind of tests are deemed unnecessary.
The thyroid gland in a patient with hypothyroidism is often described as hypoechogenic, inhomogeneous and sometimes even augmented in the absence of raised thyroid peroxidase antibody concentrations. Hypoechogenicity can be experienced in most cases of autoimmune thyroiditis and can be seen as dark areas in the sonographical picture. In later stages of hypothyroidism, the size of the organ is reduced. During colour doppler-ultrasonography a reduced perfusion of the thyroid gland can be experienced. Normally, if additional clinical indications like abnormal thyroid palpation are absent an ultrasound and other additional tests are not required.
On the other hand, if the TSH level is low the patient suffers from hyperthyroidism.

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According to Article [13], the next step is to distinguish between subclinical hyperthyroidism with a regular level of circulating hormones and overt hyperthyroidism, which is accompanied by an increased level of thyroid hormones, by measuring the serum free T4 or free T4 index as well as the free or total T3 concentration. Other disorders with increased thyroid hormone concentration and normal or only slightly raised TSH concentrations like TSH-secreting pituitary adenomas or a peripheral resistance to thyroid hormones can also be identified during this step.
The modality used to determine the cause of thyrotoxicosis vary from country to country, partly depending on different population characteristics, cultural backgrounds, and socio-economic reasons. In Europe thyroid ultrasound and assessment of TSH-receptor antibodies or TRAb, i.e. thyroid-stimulating immunoglobulins or thyroid-stimulating antibodies, are used to diagnose Graves' disease. The ultrasound spares the patient from exposure to ionising radiation in contrast to the thyroid radioactive iodine uptake test used in America and it is also more accurate in the detection of thyroid nodules as well as more cost-efficient. Furthermore, a colour-flow Dopple ultrasound can differentiate between a destruction induced thyrotoxicosis, which shows a decreased blood flow, and Graves' disease, which besides an increased blood flow also features diffusely enlarged hypoechogenicity.

2.3.5 Therapy

To treat hypothyroidism the missing thyroid hormones have to be substituted and in most cases the treatment of choice is levothyroxine monotherapy in solid formulation, which has to be taken on an empty stomach to ensure proper resorption, as per Article [6] and Article [8]. Usually in younger patients without co-morbidities the full optimal dosage of $1,5$–$1,8\mu$g per kg of bodyweight can be given but with adequate monitoring to avoid overtreatment. If for example the patients suffers from autoimmune thyroiditis, it has been shown to be beneficial according to Article [8] for younger patients to initially administer $50 - 75\mu$g levothyroxine on an daily basis. The dosage is increased every $10 - 14$ days until the individual substitution dose is reached. The aim of this process is to reach a TSH-level in the lower normal range. Especially elderly patients with a long history of hypothyroidism and patients with coronary heart disease need a therapy of moderate intensity, therefore a very low initial dosage of 12.5–25μg on a daily§ basis is used, which is gradually increased on the basis of symptoms and TSH concentrations. The aim is still to reach a TSH-level in the lower normal range by increasing the dosage every $2 - 3$ weeks. Some studies mentioned in Article [8] have shown that, concerning elderly patients, a TSH-level in the upper range or even a TSH-level slightly above the normal range have beneficial effects on the survival of patients.
After initial treatment a TSH measurement is done after $4 - 12$ weeks and then every 6 months. If no changes in the patient's condition can be observed, yearly check-ups with a determination of the TSH-levels are sufficient, otherwise the interval of regular control examinations should be increased again. Moreover, adjustment of the therapy should be made according to laboratory findings and with the patient's trait in mind, since small changes in dose for elderly or light-weighted patients can have substantial effects on serum

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TSH concentrations.
Otherwise, there is no specific therapy for autoimmune thyroiditis according to Article [8]. Because of (transient) hyperthyroidism, which is a result of the destruction of thyroid follicles due to autoimmune processes with a subsequent wash out of stored thyroid hormones in the follicular cells, a therapy with antithyroid agents is not possible. In case of distinct clinical symptoms, symptomatic therapy with β-blockers, mostly propranolol, is prescribed and is therefore the best way to deal with undesirable symptoms. Since apparent hypothyroidism in this case is the final condition due to the destruction of the thyroid gland, a lifelong permanent therapy with thyroid hormone substitution cannot be avoided.
The therapy approach at early states, especially for subclinical hypothyroidism, depends on many different factors and should be adjusted to the patient's needs. Only the condition after radioiodine therapy or thyroid resection is a mandatory therapeutic indication for the use of Levothyroxine. If a patient shows an increased TSH level, especially for values above 10 mU/l, detection of TPO-antibodies and/or a sonographically verified hypoechogenic of the thyroid is a generous indication for the use of Levothyroxine due to the high risk of developing apparent hypothyroidism. If the TSH level is below 10 mU/l, a customised therapeutical approach in agreement with the patient should be persecuted. For young patients an early decision concerning substitution is important, since the determination of positive antibodies have a big impact on the development of apparent hypothyroidism. 4.3% of patients with antibodies develop an apparent hypothyroidism in contrast to only 2.1% of patients without antibodies. Despite a proven association of subclinical hypothyroidism with hypercholesterolemia, increased levels of LDL-cholesterol and an increased level of lipoprotein are no recommendation to start a Levothyroxine substitution therapy, even if TSH levels are respected.Still, a therapy only due to an increased TSH level is not advised because available evidence only proves a low causal relation between subclinical hypothyroidism and mortality.
In Book [11] and Article [8] different approaches to hormonal therapy were discussed, especially thyroid hormone replacement by synthetic T4 and T3. The idea is to mimic normal thyroid hormone secretion in an ideal substitution therapeutic regime. Normally during L-T4 replacement therapy, intra-thyroidal T3 is largely absent because the thyroid gland failed or is completely ablated, otherwise 20% of T3 in circulation is produced by a healthy thyroid. Normally, $5'-$deiodinase acts on T4 to generate T3 peripherally in different organs to compensate for the lack of T3. There are rare cases where this mechanism is deficient and therefore the use of additional L-T3 is necessary to achieve their personalised euthyroidism. Otherwise, there is no sufficient reason to prescribe additional T3 along with T4 because only 20% of the total measurable FT3 is provided by a healthy thyroid, which can easily be compensated by the overwhelming FT3 to FT4 conversion by making the amount of FT4 sufficiently available.

To treat hyperthyroidism three options were presented in Article [13]: antithyroid drugs (ATDs), radioactive iodine ablation and surgery. Even though all three treatment options could be used to treat Graves' disease, patients suffering from toxic adenoma or toxic multinodular goitre either can be treated with radioactive iodine therapy or surgery, since they rarely go into remission.

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Currently, the used antithyroid thionamide drugs or ATDs, which are actively transported into the thyroid, are propylthiouracil, thiamazole, and carbimazole. According to Article [13], they inhibit iodide oxidation and organification in the thyroid by inhibiting thyroid peroxidase and the coupling of the iodotyrosines to synthesise T4 and T3. Comparing those drugs shows that carbimazole is converted to the active form after intake, thiamazole, with very similar properties to the drug thiamazole. On the contrary, propylthiouracil in large doses is able to decrease the conversion of T4 to T3 in peripheral tissues by inhibiting the outer ring deiodinase of T4. It is also stated in Article [13] that these drugs might have antiinflammatory and immunosuppressive effects.
Especially after reports of liver damage in patients who had received propylthiouracil as treatment for Graves' disease emerged its role was reassessed. Most notably thiamazole already had several advantages like a better efficacy, less severe side-effects as well as longer half-life and duration of action, making once-daily dosing possible while propylthiouracil has to be taken two to three times daily, therefore making thiamazole the preferred treatment for Graves' disease. The exception are patients with adverse reactions to thiamazole and women in the first trimester of pregnancy. Beside a primary treatment with ATDs, patients are additionally treated with β-blockers for relief of the symptoms of thyrotoxicosis. Definitive therapy is only used for patients with persistent or recurrent hyperthyroidism.
In patients with toxic nodular goitre ATDs are usually used to restore euthyroidism before definitive treatment with surgery or radioactive iodine. In some cases if the other two therapies are contraindicated or the patient has a short life expectancy, antithyroid thionamide drugs can be used as a long-term treatment.
More information on the treatment of both hypothyroidism and hyperthyroidism can be read in Article [6] and Article [13].

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3. Introduction to Mathematical Modelling

The field of mathematical modelling has become increasingly popular due to its large range of application in many different fields, especially when experiments are restricted due to monetary, ethical or other reasons. Here we will concentrate on medical models and the obstacles one has to conquer before a model is applicable.

3.1 Advantages of Mathematical Models in Medicine

As far as I am concerned, after listening to different Lectures on modelling, especially Lecture [2] and [4], mainly four reasons make mathematical modelling for medical purposes appealing. In particular, monetary reasons explain the tendency to use mathematical models in many fields due to expensive experiments or costly and scarce resources.
Another reason to lean towards mathematical models are ethical standards. Sometimes testing a new medical thesis, which can result in a new pharmaceutical or a new treatment plan, requires experiments on human subjects that are not justifiable. Therefore other ways for verification are needed, even though mathematical models can also be restricted by ethical standards.
The realisation that every human being reacts differently to the same treatment, since no organism is exactly the same when its characteristics are compared, resulted in the need for individualised treatment. Personalised medicine is a relatively new field, which leads to many new obstacles since a treatment plan needs to be custom-made for every patient. A mathematical model can be of use because notwithstanding that only one model was developed, the initial values like age, weight or health status can still be adapted for every individual, making the result unique to the patient. For example, a physician could use such models to calculate drug dose rates for different patients with the same condition.
Another interesting aspect is the possibility to use a mathematical model to simulate a medical test that cannot be performed on a patient due to health reasons. Such a model was introduced in Lecture [4], where a model was used to simulate the heart rate under stress. Normally, a bicycle ergometry is done to monitor the heart rate under stress, but this might not be possible due to various health reasons, although some measurements are still needed to verify the model. The two main advantages of such a model are the possibility to predict the individual behaviour of the heart rate under various types of stress and the potential to modify the parameters of the model, resulting in differing outcomes concerning for example different forms of endurance.

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3.2 Translating Medical Knowledge into Formulas

After the research question is formulated the first step in modelling is to answer a list of questions regardless of the model's purpose. The most important question is: *What do I want to model?*, which seems like an easy question but can lead to the first obstacle, since the answer depends on many factors. If we look at the Hypothalamus-Pituitary-Thyroid system for example, there are various ways to start such a model. The straightforward approach would be to look at the medical system and the different components as well as the various hormones affecting the system and use them as a basis for the model.
There are multiple problems with this approach, primarily the measurability of every component can lead to problems due to ethical reasons or technical limitations. Therefore, the values of non-measurable hormones in the system have to be estimated leading to inaccuracies in the output. Also, translating medical processes directly into a mathematical model leads in most cases to a very complicated model, which depends on many different parameters and sometimes for the model unnecessary aspects of the biological process.
The issue with biological processes is their complexity, especially if they are not yet fully understood, leading to black box approaches or models that are not based on the medical process but solely on model-related input and output parameters. This kind of model can sometimes be useful and even lead to a better understanding of the process. The most important part of modelling is to decide what part of the process is relevant to answer the research question and what parts can be simplified without a big trade-off, leading to a more understandable model. To summarise: the goal of mathematical modelling is to find a simplified model of the medical process, which results in an output as accurate as possible.

Time in Medical Models

Especially in medical processes or biological systems the concept of time-dependency seems to be ubiquitous due to the fact that state variations in a system are in most cases developing processes as a function of time. Although this concept seems straightforward, one has to keep in mind that in a human body various processes concerning biological units like organs are operating on different time scales and non-simultaneous, therefore complicating the model development further.
In mathematical models different distinctions are made concerning the time line of a model, one is made between discrete and continuous time. The observation of a medical process over a specific period of time to accumulate measurement data leads to data points, which are time-discrete in most cases, since continuous measurements are not easy due to technical or ethical restrictions. However, in most cases a time-continuous model is wanted, because medical processes are in the majority of the cases time-continuous.

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Systems Dynamics

Around 1961 Jay W. Forrester pioneered the field of System Dynamics by applying the principles of feedback and control to social systems. The outstanding feature of System Dynamics is its ability to generate qualitative models based on causalities. It is possible to transform the qualitative models by appropriate parametrisation into quantitative models to simulate the investigated system. Systems Dynamics as a field received widespread interest after it was used to build large world models like WORLD2 (World Dynamics, by Forrester in 1971), WORLD3 (The Dynamics of Growth in a Finite World, by Meadows), and WORLD3 revisited (Beyond the Limits).
Before a model based on systems dynamics can be implemented, the system variables and boundaries have to be identified. First the problem has to be analysed, therefore the purpose and use of the model has to be determined as well as a target of the simulation. The collection of information and data as well as the development of hypotheses concerning parts of the system should be started. Next, the elements of the system and causal relationships between the elements have to be determined. During the model building process, which will be discussed in the next part of this chapter, this process is separated into two steps namely definitions and systems analysis.
Afterwards, the behaviour as well as the links of and within the system by related interlinking system variables should be captured in a casual loop diagram. The behaviour of the system can be traced back to Feedback Loops, System memory or stocks, and delays in material and information delays. The main components of causal loop diagrams are links and feedback loops. A link in a causal loop diagram can either have a positive or negative effect, which is represented by a plus or a minus sign. A positive link can be seen as a positive correlation and a negative link as a negative correlation.
A feedback loop in a casual loop diagram is depicted as a closed loop of arrows. It is a key element in systems dynamics to identify all closed, causal feedback loops, because the most important causal influences are enclosed within a feedback loop. In Chapter 2 an endocrine feedback-loop was described, which describe the effect of different hormones on the production of themselves or other hormones. A feedback loop in the mathematical sense has either a positive or reinforcing effect on the system or a negative or balancing effect on the system. A distinction concerning the complexity in regard to the number of involved parameters as well as the length of the loop is not made. If the goal is to achieve a stable model, at least one negative feedback loop is needed.
The last step before modelling is to build a stock and flow diagram since not all system elements are system variables. The best solution is to distinguish between sources or sinks, levels or stocks, flows, auxiliaries, parameters and links. A source represents system variables and rates outside the boundaries of the model, which are directly fed into the model. Sinks on the other hand are used to terminate the flow outside the system. Levels, stocks or system variables are quantities that accumulate over time and change their value continuously. A flow or rate or activity or movement changes the values of the levels and to get variations in the model every level has to be connected to at least one flow. It is usually useful to work with auxiliaries, which sum up everything that can be calculated directly or analytically out of stocks and constants, consequently avoiding confusing models. Anything predefined for the whole simulation is a parameter or constant. But a parameter can be a function too, even though they usually refer to constants.

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3.3 The Process of Modelling

The definition of a mathematical model, as defined by Stachoviak in 1973, can be separated into three key words: mapping, reduction and pragmatism. Mapping specifies the attribute of a model to represent a natural or artificial object. Reduction means that a model is normally a simplified version of reality and therefore does not have all attributes of the original object. Pragmatism stresses the limitations of a model, because it was created for a certain purpose, a certain subject and a certain time span. Especially the interaction between pragmatism and reduction is very important and should always be kept in mind.
The process of model building itself can be divided into the following steps, as illustrated on Page 5 of Book [19]:

- *Definitions:*
  The problem or question that should be solved has to be defined.
  The system must be defined as well, which represents our problem or question only partially compared to reality.
- *Systems Analysis:*
  The parts of the system that are relevant for our task have to be identified.
- *Modelling:*
  A model of the system can be developed based on the findings from system analysis.
- *Simulation:*
  In this step the model is applied to our problem or question and a strategy to solve the problem or answer to the question should be derived.
- *Validation:*
  In the end it is important to know if the strategy derived in the simulation step solves the problem or answers the question of the real system.

In many cases the most time-consuming step in the list above is the systems analysis step, because an in-depth evaluation of literature has to be done. It is very common that during research reports on similar investigations are found and at best we are able to benefit from the experience of previous researchers. Another important source are experts from other disciplines, since discussions and meetings with them can help with understanding the system itself and answer in-depth questions that cannot be answered by literature alone. Especially in medicine the topic of data sets will arise during those discussion and show that in many cases new data is needed for a better understanding of the biological system and primarily for the validation of the model. Therefore, the decision on input and output measurement units is another important part of the system analysis step.
During modelling the appropriate software to solve the model has to be chosen. The selection of the software depends on the modelling approach and more importantly on the model type, which refers to the used equations of the mathematical model. In some

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cases it is necessary to write your own software if the mathematical model includes non-standard equations.
The modelling and simulation scheme above shows the essential steps, but it is a very simplified version of what really happens. Figure 3.7, which depicts the solution finding process as a circle, is closer to reality, even though it misses some points that are mentioned in the list above.

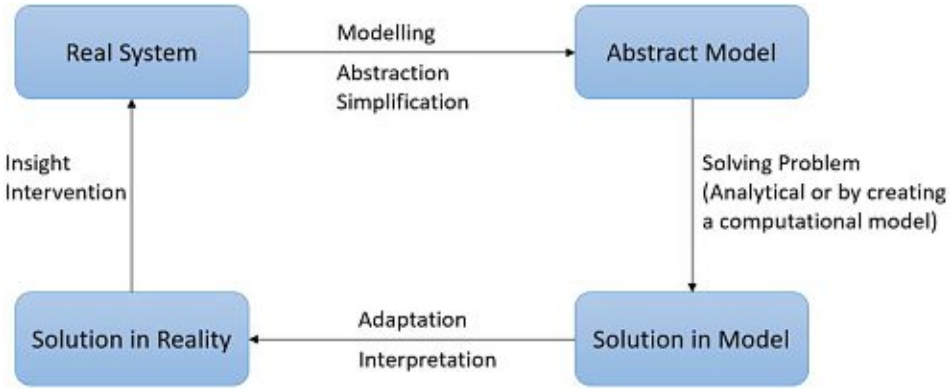

Figure 3.7: A simplified version of the solution finding process during modelling based on Lecture [2].

However, Figure 3.7 is still a simplification of the steps leading to a validated model. Figure 3.8, mostly referred to as Modelling Circle, shows the standard workflow of modelling as well as the interaction between the individual steps. The best way to enhance a model is iteratively, that is by starting at the bottom question and adding new questions as soon as the model is correct, which means running through the whole modelling circle verifying and validating the model during all steps of the model building process and every time a new question is added it assures the correctness of the model itself.

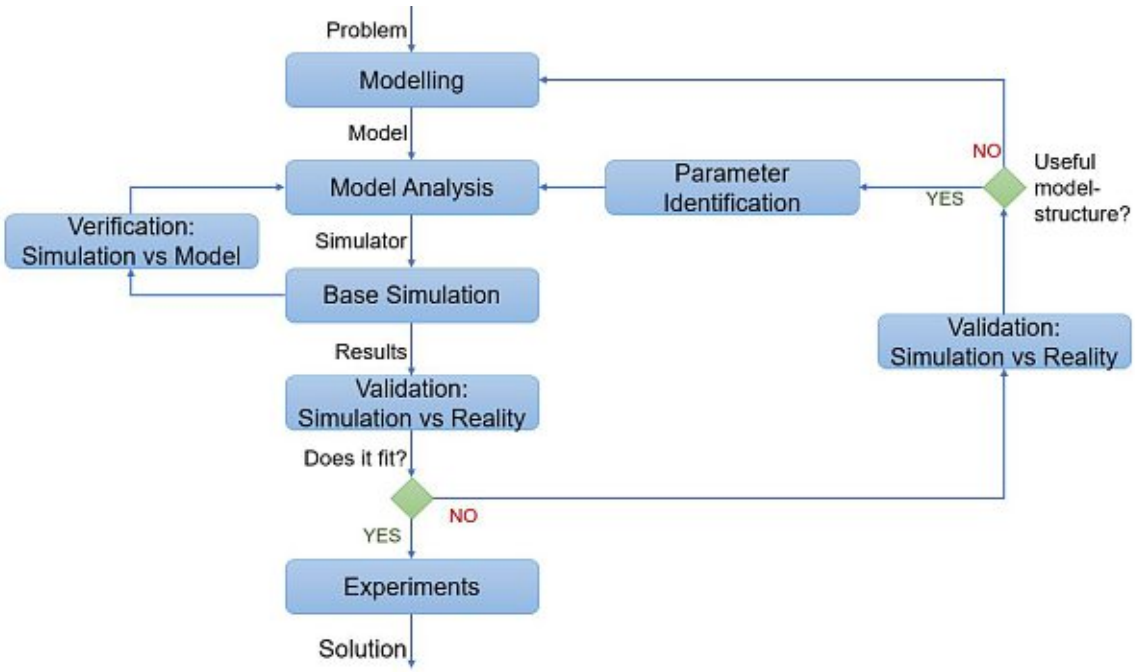

Figure 3.8: The modelling circle displaying the standard workflow of modelling based on Lecture [2].

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3.3.1 Model Verification

In Lecture [2] the process of validation and verification was discussed in great detail and it was stressed that before a model can be validated, it has to be verified to ensure that the model was implemented correctly. Some sources for errors that occur due to a failed verification process are code errors, logical errors, numerical errors, and output errors like stochastic fluctuations. Code or syntax errors arise if the programming language was used in the wrong sense or if infinity loops appear or if not all initial values have been implemented, to name a few. Logical errors can be found mostly in complex models, where a lot of cross referencing happens, or in agent based models. Numerical Errors are in most cases connected to the used solver or algorithm. There are ways to reduce errors by starting with the smallest possible running instance and by splitting up the code. The next important step to reduce errors is by coding breakpoints and executing the code stepwise. Another essential ability a modeller has to learn is reading and writing and especially being able to interpret error messages. It is also advantageous if steps in between are visualised and not only the results. Also, profiling the code to improve code parts in regard to computation time and memory usage helps to reduce errors.

3.3.2 Model Validation

During validation we assume that the model was implemented correctly and compare the model results to experimental data, either from literature or from experiments conducted specifically to validate the model. For this reason, a certain base of knowledge regarding the real system is needed. There are seven vastly different situations related to the level of knowledge. Accordingly, more known scenarios, more available data and more training data lead to a more valid result. If the outcome for all wanted scenarios is known, it is a *no need for a model* situation, which is depicted in Figure 3.9.

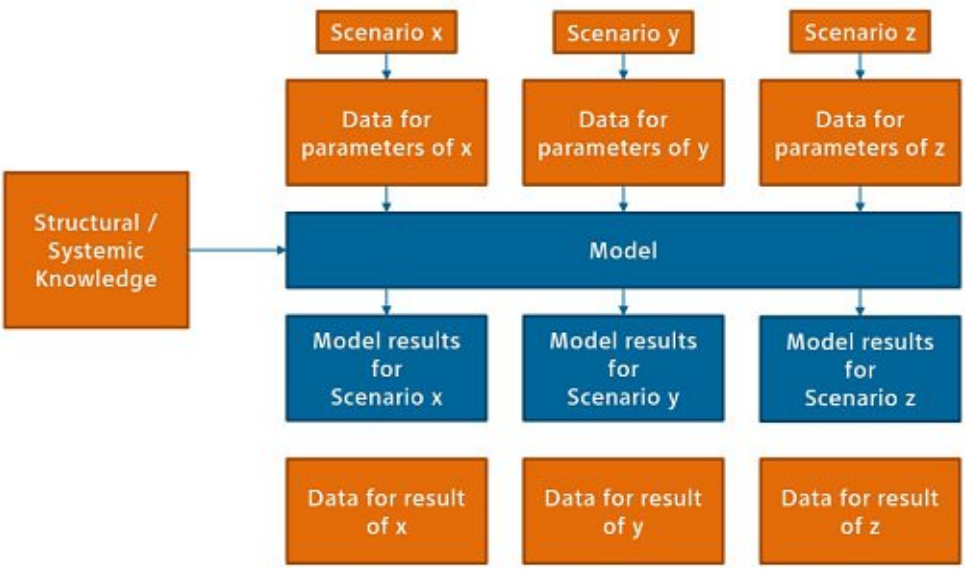

Figure 3.9: The *no need for a model* situation according to[5] Lecture [2].

[5]Lecture [2] : Validierung, Verifikation und Kalibrierung: held by Projektass. Dipl.-Ing. Dr.techn. Martin Bicher: Slide 9: The "no need for a model" situation

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The *optimal* situation would be the only missing outcome data being the one that answers the research question. Normally, the existing structural and systemic knowledge can be used for the validation process in this case. The most difficult situations to solve regarding validation are the *usual* and the *black-box* situation. In the *usual* situation we have an idea about reality and some structural and systemic knowledge but less information than in the *optimal* situation. Therefore, the model output is difficult to interpret and validate, leading to an unsharp model and fuzzy results. The *black-box* situation is a data based approach without structural and systemic knowledge to back it up. Consequently, the model mainly depends on input and output data. A black-box approach can be solved by transfer functions, using mathematical methods to model the inside of the box based on the input and output of the box.

In case no experimental data exists, which is a so-called *almost impossible* situation, the validity of the model results depend on the research field of the problem. If the structural and systemic knowledge of the field is big and well tested, the model results are comprehensible but in most cases not precise. In case of soft sciences we are not able to produce quantitative results, but in both cases we can get qualitative results. For example, qualitative results can be used to interpret the changes of the system due to changes in the initial conditions, leading to a better understanding of the system behaviour.

In the event of having neither structural and systemic knowledge nor experimental data, a validation process is not possible and there are no benefits of such a model. This kind of situation is also known as the *impossible* situation. The *calibration* situation, which seems impossible in the beginning due to missing input parameters for the scenarios with known outcome data, can be solved by parameter calibration. The process of calibration will be explained later on in more detail, but to sum it up, the model is first run with dummie parameters and calibrated to fit the known output data, which is then used with the structural and systemic knowledge in the validation process.

There are three types of validation, which can be related to three different phases in the modelling process. During the modelling phase the *conceptual model validation* happens, where the conceptual model is compared to the structure of the real system. *Data validation* during the analysis phase describes the process of analysing the given data for validity. The main part of the validation process occurs after the execution of the simulation and is called *operational validation*.

The most important parts of operational validation are plausibility checks and face validation. They check if the model output and logic is plausible and are done in most cases by domain experts, because they know a lot about the real system and can determine if the model behaviour is realistic. The next step is qualitative and quantitative validation of the model. During qualitative validation the model output data is compared to the output data of the real system to check for similarities like peaks and if trends in the model data set matches reality. Quantitative validation is done with defined error functions to evaluate the goodness of the fit. The last step is sensitivity analysis to check the different parameters of the model for their influence. This part is mostly automated to prevent errors due to bias of the programmer. The best way to avoid bias is by using the 3rd party concept, which states that it is better if a 3rd party performs validation.

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3.3.3 Model Calibration

The idea behind model calibration is that if you do not know the model parameters in advance but only the output for those scenarios, you can still achieve a correct model by adjusting the initial parameters. The two main challenges are to decide if the model fits reality and how the parameters have to be adjusted to get a better fit if it doesn't. Before a model can be calibrated, some questions have to be answered like if you get real data out of the model or if post-processing is needed and, if you deal with time series, how to combine them. Therefore, the *calibration circle* depends a lot on application.
In Figure 3.10 such a calibration circle is depicted, showing the different steps of calibration. The input in the first instance are model parameters, which are adjusted each step to reach a good fit. In the end, the most important question to answer is if the model fits. For this reason a method is needed to compare the model and its fit to reality. The goodness of fit is measured via an error function, comparing the model output to the reference data. As soon as the error is small enough, the calibration circle outputs the fitted model parameters.

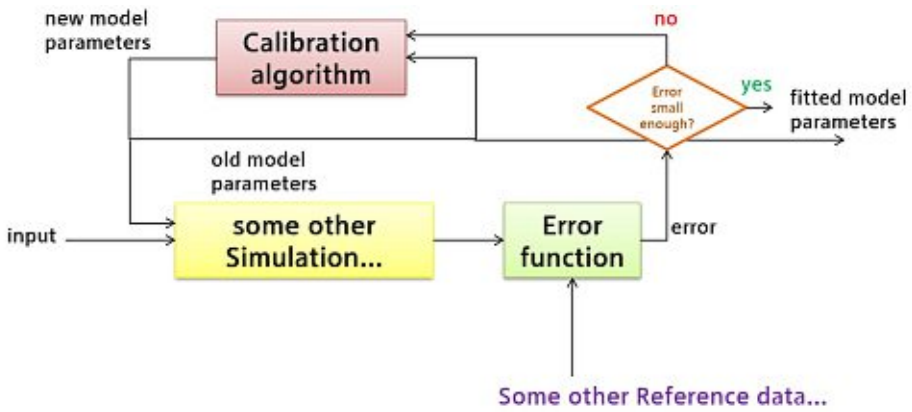

Figure 3.10: The standard workflow of calibrating a model also known as the Calibration-Circle, see[6] Lecture [2].

Error Function

The error function computes the difference between reference data and model output based on a formula that considers differences in both data sets due to non-matching time intervals. There are different methods to match time intervals, but since many calibration loop runs are needed, an approach that is not time-consuming should be favoured.
Spline interpolation is the first thing that comes to mind when data sets with different step sizes have to be compared. Interpolating only the experimental data can lead to problems if there is not an adequate amount of data available, if the data is not smooth enough or if different results of the model have varying amounts of time steps due to the used solver, for example. In other instances interpolation of the experimental data might be sufficient if there is a vast amount of data and the model uses equidistant steps.

[6]Lecture [2] : Validierung, Verifikation und Kalibrierung: held by Projektass. Dipl.-Ing. Dr.techn. Martin Bicher: Slide 36: Calibration-Circle

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Another option is to just interpolate the model results, which works well if the simulation results are smooth enough and thoroughly described by the output. But if the time steps of the simulation are much larger than the time steps of the available data, this approach won't lead to a satisfactory result. However it is the most time consuming approach. Spline interpolation of both data sets is the best way because it grants control over the comparison points.
In the end, the decision over which interpolation scheme fits the requirements of the data points best depends on the used model type as well as smoothness of the data set. Whether higher order splines should be used also depends on the differentiability of the data set, although the usage of global interpolation or compensation polynomials are in most cases not a good idea. Nevertheless, the question how errors should be added up still remains.
The idea to use either the sum of absolute errors or the sum of quadratic errors seems great in theory but how do you compare the reference data and the model results if the step size is different? Another problem is categorisation of the error, when is an error classified as big and when as small? The Reimann strategy is one possible solution to these problems, because it also considers the distance between different measurement points.The Reimann strategy is thus an inclusion of the step size into the error and thus the error is an approximation of the integral of difference functions leading to the following formula, with f_1 being the model results and f_2 is the function for the real data

$$||f_1 - f_2||_{L_1} = \int |f_1 - f_2| dt \approx \sum_{i \in I} |f_1(t_i) - f_2(t_i)|(t_{i+1} - t_i). \tag{3.1}$$

The error function based on the Reimann strategy can be computed with quadratic error instead of an absolute error, altering the equation from above into

$$||f_1 - f_2||_{L_2} = \int |f_1 - f_2|^2 dt \approx \sum_{i \in I} |f_1(t_i) - f_2(t_i)|^2(t_{i+1} - t_i). \tag{3.2}$$

Another and especially the cheapest way to calculate an error is with the maximum norm

$$||f_1 - f_2||_{L_\infty} \approx \max_{i \in I} \left(|f_1(t_i) - f_2(t_i)|\right). \tag{3.3}$$

Particularly, if there is a lot of noise in the real data some points cannot be matched to the simulation data, the maximum metric will be at the level of the biggest noise. Consequently, this method is not reasonable if a lot of noise in real data is involved. The third possible solution, which was presented in Lecture [2], was the use of relative errors. There are two main advantages to this method because it is not biased by peaks of the curve but is independent of the scale of simulation. Hence, the influence of data noise is constricted. The relative error is calculated by dividing Equation (3.3) by the maximum metric of the real data, leading to the following equation

$$\frac{||f_1 - f_2||_{L_\infty}}{||f_2||_{L_\infty}} \approx \frac{\max_{i \in I} \left(|f_1(t_i) - f_2(t_i)|\right)}{\max_{i \in I} \left(|f_2(t_i))|\right)}. \tag{3.4}$$

Another advantage is that the interpretation of the error itself is very easy, since the value of the error should always be between 0 and 1. If the error is for example 0.1 there is a 10% discrepancy between model data and real data. In conclusion, it can be said that the usage of 'real' norms is to be favoured, since methods like straightforward summation depend on the number and size of the steps and a direct comparison is not possible.

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Calibration Algorithm

The next obstacle during the calibration process is the choice of the right calibration algorithm, which improves the model parameters during every step. The calibration algorithm receives two inputs: the old parameter set and the error of the model with the old parameter set. The algorithm needs the error as an input to adjust the parameter set to get the smallest possible error.
While both Newton and gradient method seem to suggest themselves as calibration algorithms, there are some points objecting to their application. Both methods require good starting values like local optima, which cannot be granted. They are also inefficient for higher dimensions due to large parameter spaces. The different parameters might have constraints, for example in their type due to the definition of the methods. Another problem, especially for the Newton method, is the differentiability of the solution. Because solutions are not always differentiable, the Newton method is not bound to converge.
Therefore, a calibration metaheuristic, which is known as an approximate or non-traditional method, is needed. Metaheuristics aim to find optimally acceptable solutions for the optimisation problem in reasonable time by merging randomisation and rule-based theories, which are normally based on natural phenomena like evolution, characteristics of biological systems, social systems, swarm intelligence, and governing laws in different phenomena like basic physical laws. In Figure 3.11 an overview of different calibration metaheuristics is given. More detailed information on metaheuristics can be found in Book [12].

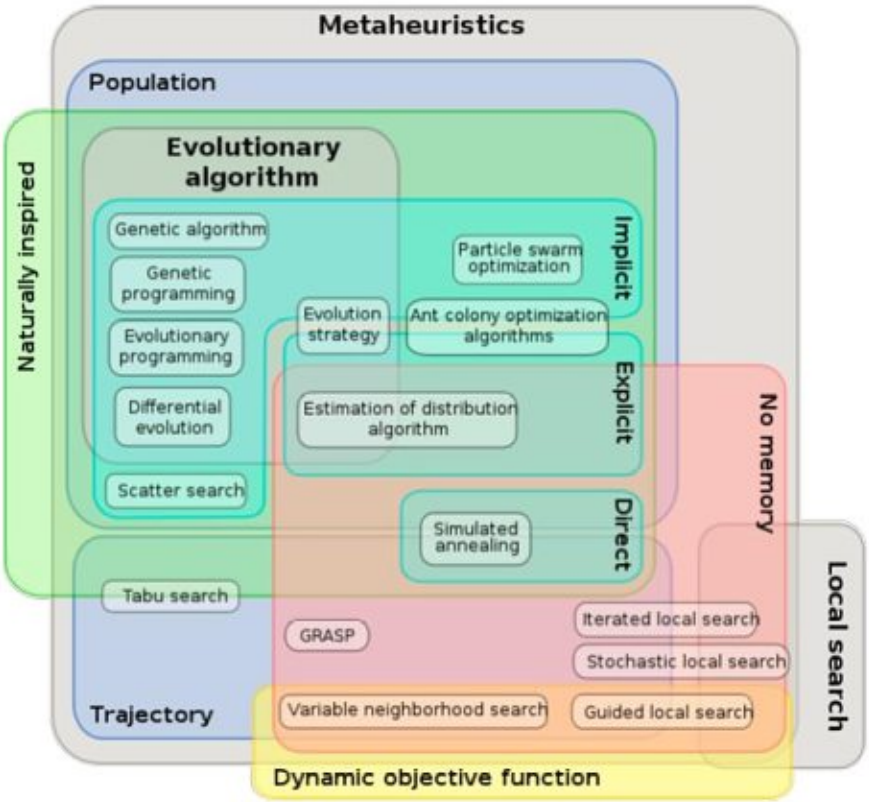

Figure 3.11: Different classifications of calibration metaheuristics, see[7] Lecture [2].

[7]Lecture [2] : Validierung, Verifikation und Kalibrierung: held by Projektass. Dipl.-Ing. Dr.techn. Martin Bicher: Slide 60: Some land map of calibration metaheuristics

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The general concept of calibration is based on the fitness level of every individual. In this concept one parameter set, which is used to parametrise the model, is termed an individual. Each individual can be weighted by the error function, dividing the individuals into different fitness levels. That's why the whole process is sensitive to the definition of the error function. On this account, a higher fitness level can be translated into a lower error, which indicates a better fitting parameter set.
The most prominent metaheuristic used for calibration is *Simulated Annealing*, which was developed circa $1983 - 1985$ and is used when no other method comes to mind. It is a trajectory-based calibration algorithm, therefore only one parameter set is optimised at a time. This method is an extension of the Metropolis Algorithm and it is motivated by the forging of metal and the process of heating and cooling iron. *Simulated Annealing* is an iterative algorithm. In the beginning a starting parameter set is chosen, of which the fitness is calculated. During each step the newly computed error is compared to the determined tolerance parameter tol and to the old error. If the new calculated Error $Error'$ fulfils the condition

$$Error' < tol, \tag{3.5}$$

the algorithm is terminated, since the optimum has already been found. Otherwise, the error of the new individual is compared to the old error. There are two possible scenarios. If $Error' < Error$, the new individual is accepted due to its higher fitness. In case $Error' \geq Error'$ is true, the new individual is accepted with probability

$$\mathrm{P}(accept) = \mathrm{e}^{\frac{Error' - Error}{T}}, \tag{3.6}$$

with a positive temperature T, which will be reduced at the end of each step. The algorithm starts with a high temperature, because if T is high it is more likely an individual with worse fitness is accepted. The case that T is small can be compared to the cool down phase, where the metal stiffens and therefore only individuals with a smaller error are chosen. The idea on which the success of the algorithm is based on is that possible local optima can be left again.

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4. Introducing a Basic Mathematical Model of the Hypothalamus-Pituitary-Thyroid Axis

This chapter is based on information taken from Article [10], Article [15] and Article [9], as well as Book [11]. *Thyroid Systems Engineering* is an interdisciplinary field where physicists, electrical engineers, chemists, biologists, endocrinologists and experts from other fields are involved to research the complex mechanisms behind the hypothalamus-pituitary-thyroid axis and improve the treatment strategies for different disorders. Chapter 5 of Book [11] states that biological models are mostly non-linear, in all cases continuous and analytic over a dynamic interval of interest. The input parameter space is always limited to definable extends.

In most biological systems, the effects of externally added substances, their pharmacokinetics and dynamics are probed and well known. Therefore, once those effects have been characterised for certain biological systems and entities, the reaction of the system to a certain amount of externally added substances can be predicted. Since it is practically impossible to obtain generalised models for dynamic processes, biological models are normally individually determined. The individualisation of a model is done through parametrisation and with investigation protocols dedicated to an individual.

Besides the restricted generalisation possibilities for biological models, differences concerning age, gender, health status, as well as fitness level and weight have an impact on treatment plans, which in turn promote the usage of personalised medicine. For those reasons the need for an individualised model presenting the FT4 and TSH relationship arose. Another argument for the usefulness of such a model is the observation that even though 'euthyroidism' was achieved, defined as thyroid function within the normal population ranges of FT4 and TSH, the well-being of many patients remained suboptimal.

In Article [14] the reason for the usage of only two hormones to diagnose thyroid dysfunctions or disease was justified. First of all, TRH, which is secreted by the hypothalamus, has a very short half-life of approximately five minutes, while TSH has a half life of one hour. Another reason why TRH is usually not measured in practice is that determining its concentrations outside a research setting is limited, due to it being riddled with significant intra-assay and inter-assay variations, as well as due to its pulsatility, diurnal fluctuations and clearance.

Therefore, model approaches that include a hypothalamic component yield models, which despite their closeness to reality, have restricted applicability due to an unknown quan-

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tity. Also disease, like experimental euthyroidism, hypothyroidism and hyperthyroidism, which alter metabolic states and thus have an impact on serum T4 and TSH levels have no significant effect on hypothalamic or peripheral blood TRH levels. Nevertheless, to evaluate thyroid function nowadays, the level of TSH is quantified, as TSH is a very sensitive and robust indicator of the thyroid hormone status.
Although T3 is the main active hormone, it is mainly derived from deiodination of T4. Consequently, T4 can be used as a clinical surrogate parameter of thyroid hormone levels, making measurements of T3 mostly unnecessary.

4.1 Hypothalamus Pituitary Function

The decision on how a model is formulated was already discussed in Chapter 3, but as was mentioned in Article [9], the common approach to model the hypothalamus-pituitary-thyroid axis is to include all known physiological influences. Earlier mathematical models of the thyroid gland concentrated on its dynamic behaviour, the size of the thyroid gland and the synthesis process of the different hormones due to the measurability of the changes and variations of these parameters as a function of time and volume. Since the thyroid hormone system in vertebrates is non-linear and very complex due to it being a result of million years of evolutionary development the resulting models were very complex and influenced by numerous variables.
The dynamics of this process make it impossible to derive a usable model. Furthermore, the time-dependent dynamics of the observed system mentioned in Chapter 2 are to complex to come to a satisfying result, because the various processes and biological units are operating on different time scales. Moreover, in most cases the goal of biological models is to give a generalised description of a certain system or phenomenon, which is not possible due to the diversity regarding biosystem characteristics and individuals. While the common approach will not result in a usable model, another property of biological systems can help to achieve a useful model, which can be described by the conditions of a defined equilibrium.
As reported in Chapter 5 of Book [11], a distinction between dynamics can be made as a result of sudden changes in conditions, acceleration, resulting in a transient situation or the state maintained over a longer period, continuous speed, and can thus be identified as a dynamic equilibrium or homeostasis. Alternatively, the final results of complex systems can be analysed in the form of states of dynamic equilibrium. Instead of equilibrium models, the transient behaviour can also be modelled by means of stimulus and response, leading to a Black Box approach. But, according to Chapter 7 of Book [11], the observation and measurement of the equilibria can help to discover the underlying dynamic behaviour of the system.
However, the equilibrium or homeostatic states are the end result of the contemplated dynamic processes and -more importantly- stable according to Chapter 5 of Book [11]. As a result, a suitable approach for biological modelling is the comparison of states of equilibrium as the end result of a characterised dynamic process, which is the equilibrium state of initial transients. Those systems characterised by state dependent response, are defined as state transfer functions. This kind of transfer function is considered to be time

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independent and its first derivative results in the small signal transfer function, which describe small variations around a defined operating point on the transfer curve.
On this account, the following model is related to the steady state hormone currents and concentrations of the system. In Article [9], Simon L. Goede et al. presented such a new approach, which is based on only one endocrinologic unit, thus simplifying the model by concentrating on the hypothalamus-pituitary complex as a master regulator unit. The HP function is analysed in an open loop situation independent of the influence of the thyroid to determine solely the features of the HP response. Therefore, the only model parameters are the thyroid hormones T3, T4 and the pituitary hormone TSH.
While T3 is the main active hormone, it is valid to limit the response characteristic analysis to the relationship between FT4 and TSH, because the TSH level is dictated by the negative feedback action of the sum of FT3 and FT4. Still, the contributory factor of FT3 has to be considered in the model. By using a model with two degrees of freedom, the influence of FT3 can be incorporated into the two structural parameters, resulting in the desired model structure with FT4 as stimulus variable and TSH as response.

4.1.1 The Relationship between TSH and FT4

In Chapter 6 of Book [11], the scientific approach to find a relationship between [FT4] and [TSH] was to analyse the measured data individual by individual, after many mathematical modelling attempts to describe the dynamics of the HPT system failed. Therefore, the already mentioned approach to define the relationship between [FT4] and [TSH] as the collection of stable equilibrium states measured at a certain moment in a single person was used. But before the idea for an individualized model arose, the idea was to plot the measured [TSH] and [FT4] of many different people regardless of their health status, gender, weight or other characteristics and try to derive a relationship between [FT4] and [TSH] from those values.
The derived model has no mathematical relevance, since the measured [TSH] of one person has no impact on the [FT4] of another person. To understand the mechanism behind a healthy HPT system one might think that a model of the relationship between [FT4] and [TSH] of a healthy individual would be helpful. But the thyroid of a healthy person is part of a control system that maintains the specific individual level of serum-free thyroxine [FT4] at a specific value corresponding to what is defined in Chapter 5 of Book [11] as the set point value of [FT4] for the HPT system. The main task of the HPT system is to remain at the level of the specific individual's set point. Its reactions are based on the local detection and conversion of [FT4] to intracellular T3, resulting in a stable equilibrium state of concentration of FT4, which is supported by the fast reacting [TSH] equilibrium state due to its relative short half life of one hour. Consequently, the occurrence and maintenance of a certain thyroid state can be modelled as a flow of [T4] and [T3] currents from the thyroid, which is controlled by a [TSH] current flowing from the pituitary.
Furthermore, the secretion behaviour of the thyroid gland in a healthy individual can be interpreted as a pulsatile current of T3 and T4 in a specific relation, according to Chapter 7 of Book [11]. However, this pulsatility stems from small oscillations, which are a result

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of the normal feedback control situation of the hypothalamus-pituitary-thyroid system, occurring only in healthy individuals. Since the remaining thyroid activity in diseased patients is overruled by a daily compensatory dose of LT-4, this pulsatility cannot be observed in an open system. Also, a healthy hypothalamus-pituitary-thyroid system is a closed-loop feedback system, which cannot be analysed as any input signal will be cancelled out by the control mechanism, as stated by Chapter 5 of Book [11].
In 2012, Suzuki et al. were the first to identify the logarithmic-linear relationship between [TSH] and [FT4] in their Article [18]. Even though the discovered relationship was based on the wrong application of statistical methods and incorrect interpretation of the resulting scatter plots, it was correctly written by accident in a parametrised logarithmic form. If the relationship was plotted, the model resulted in straight lines. The discovered relationship can be mathematically written as

$$\log[\mathrm{TSH}] = b - a[\mathrm{FH}], \tag{4.7}$$

where [FH], later on defined as free T4 or [FT4], represents the free thyroid hormone concentration on the horizontal axis and [TSH] represents the thyroid-stimulating hormone concentration on the vertical logarithmic axis in a two dimensional plane. Without further investigation, Suzuki et al. stated that Equation (4.7) should be simplified via $a = 1$, although variations in this model parameter influences the angle of the function at a constant value of b according to Chapter 6 of Book [11]. Variations in the model parameter b were investigated and resulted in a horizontal shift of the function along the [FH] axis at a constant value of $a = 1$. However, according to Chapter 6 of Book [11] this postulated model was never investigated further or tested on individual TFTs of hypothyroid patients who were treated with L-T4 to a euthyroid state.
The logarithmic linear expression was used because of the range of the different hormones encountered in healthy and diseased individuals. While [TSH] ranges over five orders of magnitude from $0.005 < [\mathrm{TSH}] < 400\mathrm{mU/L}$, the other hormone concentration [FT4] ranges only within one order of magnitude between $1 < [\mathrm{FT4}] < 30$ pmol/L, which can be easily represented within the range of a linear scale. But since the vertical [TSH] axis was presented in a logarithmic scale, the discovery of the properties and application of a parametrised exponential function describing the equilibrium characteristics of the [FT4]-[TSH] relationship was delayed.
By modifying the [TSH] axis from a logarithmic scale to a linear one, the original featureless straight lines from which only position and angle can be obtained change to a curve. This step reveals a prominent curvature in a certain area of the [FT4]-[TSH] plane, which will play a central role in the location of the euthyroid set point. The first verification of this model was done in 2007 in Article [14] by Leow in a publication of the exponential relationship between [FT4] and [TSH]. The correct interpretation describing the relationship between [FT4] and [TSH] as a parametrisable exponential characteristic, representing the collection of all possible equilibrium conditions of [FT4] and [TSH] in an individual was published and validated with clinical data by Goede et al. in 2014 in Article [9].

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Equation (4.7) derived by Suzuki can be transformed to a representation in which the [TSH] axis is linear with the following steps

$$\log[\text{TSH}] = b - a[\text{FH}],$$
$$[\text{TSH}] = \exp(b)\exp\{-a[\text{FH}]\}$$
$$[\text{TSH}] = \frac{\exp(b)}{\exp\{a[\text{FH}]\}}, \tag{4.8}$$

according to Page 79 of Book [11]. But this log-linear relationship is only valid for equilibrium conditions in TFT during L-thyroxine dose titration from a hypothyroid situation to a euthyroid condition. Otherwise, the pair of [FT4] - [TSH] values in a normal healthy individual represent the euthyroid set point, which is except for some circadian variations in the corresponding [TSH] value relatively fixed at a stable value for [FT4].
The hypothalamus-pituitary in a person diagnosed with primary hypothyroidism caused by Hashimoto thyroiditis, post radioiodine thyroid ablation or total thyroidectomy is no longer under the influence of the thyroid. Hence, an open loop situation is encountered. Even though the HPT loop is opened by a non-functional thyroid, the HP system still operates perfectly as an [FT4] sensor and [TSH] generator over a wide input $0.1 < [\text{FT4}] < 100$ pmol/L and output $0.01 < [\text{TSH}] < 1000$ mU/L range.
As stated by Chapter 6 of Book [11], the HP system itself is a complex control unit, which becomes apparent when its properties are examined. To enable the presentation of a complete analysable model of this unit, many model parameter have to be included yielding a highly complex model without a practical solution. For this reason, it makes more sense to derive a simple model, which depends on a minimum of variables but is still able to simulate the system properties as realistic as possible.
According to Chapter 6 of Book [11], the series of TFT values of an open loop supply a sufficiently good picture of the possible curve or characteristic that connecting the dots of the different TFTs would yield, leading to a very simple model of the relationship of [FT4] and [TSH]. Moreover, Article [9] states that the normal reference interval of [TSH] and [FT4] values falls within the 'knee' region of the HP curve, encompassing the greatest curvature on such a graphical plot. Thus, it appears that the HP characteristic contains a set of possible points of homeostasis over a certain range of [FT4] and [TSH] in which the normal [TSH]–[FT4] homeostatic euthyroid set point can be found, enabling the calculation of a set point for diseased individuals.

4.1.2 Modelling Strategy

Based on the considerations above, where [TSH] was expressed as a negative exponential function of [FT4] in Equation (4.8), an a priori negative exponential asymptotic model with two independent model parameters was constructed. In Chapter 6.3 of Book [11], different functions were analysed for their goodness of fit in order to find a function to model the curved [FT4]- [TSH] characteristic, which resulted in a similar result. The third fitting attempt with an exponential relationship yielded the best results. This makes sense

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since Article [9] states that the measurement points except for some outliers in the data sets resemble a hyperbolic, sigmoid or exponential decay function when connected. In conclusion, an exponential relationship between [FT4] and [TSH] was found and validated. The discovered relationship

$$[\mathrm{TSH}] = S \exp(-\varphi[\mathrm{FT4}]) \tag{4.9}$$

is identical to the relationship in Equation (4.8) after the following substitutions are made

$$\exp(b) = S, \quad a = \varphi \quad \text{and} \quad [\mathrm{FH}] = [\mathrm{FT4}]. \tag{4.10}$$

According to Article [9], the final analysis shows that reliable and reproducible TFTs are crucial to establish a physiologically accurate model. Thus, only the integral effects of the HPT homeostatic response from one individual [FT4] and [TSH] measurements are used to yield an applicable model. Therefore, each model is verified by a series of TFTs belonging solely to one individual to achieve the unique HP characteristic.
The model has two degrees of freedom: the multiplier model parameter S and the exponential model parameter φ. The linear component S of the thyrotropic system is related to the [FT4] range. Changes in S lead to a horizontal translation of the HP characteristic curve along the [FT4] axis, as can be seen in Figure 4.12. For a fixed value of φ, the curve preserves its shape, which can be proved by calculating the first derivative of Equation (4.9) with respect to [FT4]:

$$\frac{d[\mathrm{TSH}]}{d[\mathrm{FT4}]} = -\varphi S \exp(-\varphi[\mathrm{FT4}]) = -\varphi[\mathrm{TSH}]. \tag{4.11}$$

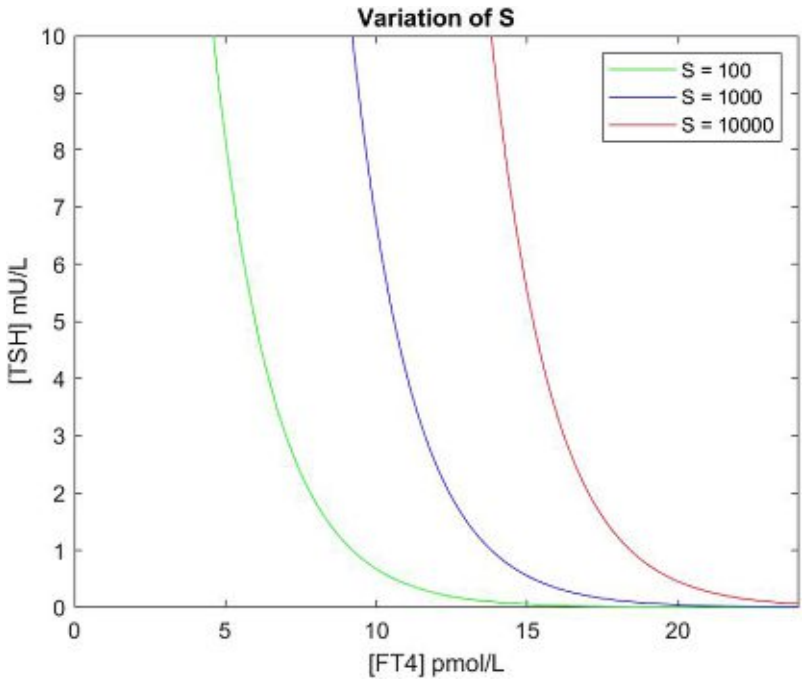

Figure 4.12: Horizontal translation along the [FT4] axis of the HP characteristic curve for varying S, with $\varphi = 0.5$.

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Since the values of [TSH] and φ are constant in this case, the value of the derivative is constant. Therefore, any variation of S in the range of $0 < S < \infty$ will have no effect on the derivative. In case of φ assuming a fixed known value, it is possible to calculate the value of S with different [FT4]–[TSH] coordinates via:

$$S = [\mathrm{TSH}] \exp(\varphi[\mathrm{FT4}]). \tag{4.12}$$

The exponential factor in the model is represented by the second model parameter φ. The shape of the HP characteristic curve centred on a chosen set of coordinates will fold or unfold with changes in the parameter φ, as can be seen in Figure 4.13. Furthermore, Equation (4.11) shows that the first derivative at the intersection P depends only on φ.

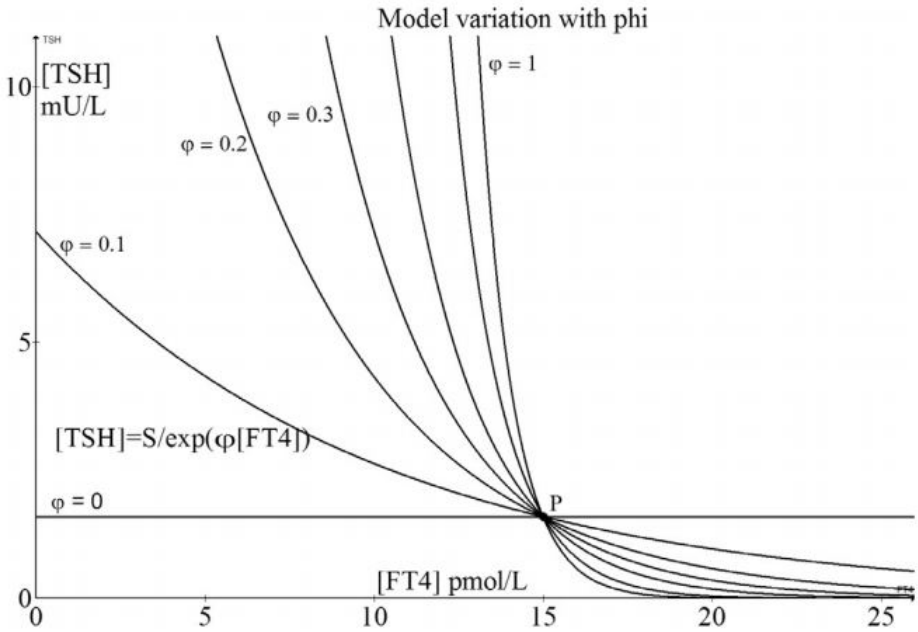

Figure 4.13: Folding effect caused by variations of the model parameter φ, which causes an intersection of different HP characteristic curves in a fixed point P as depicted in[8] Article [9].

According to Chapter 6 of Book [11], parameters S and φ are also interrelated according to the following relation

$$\varphi = \left(\frac{1}{[\mathrm{FT4}]}\right) \ln\left(\frac{S}{\mathrm{TSH}}\right), \tag{4.13}$$

which is valid for any [FT4]-[TSH] coordinate on the HP curve. Consequently, every parameter set φ and S is unique and describes a specific curve for an individual. The parameters of this relationship can be calculated with the individual TFT values of hypothyroid persons, while the dose of L-T4 is adjusted to change the hormone status from hypothyroidism to euthyroidism.

[8]Article [9]: Page 3: Fig. 2: Different HP curves intersecting at FT4 = 15pmol/L and TSH= 1.6 mU/L. Here the array of curves is shown with theoretical values of $0 < \varphi < 1$.

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4.1.3 Calculation of the Relevant Parameters

First the parameter set (S, φ) is calculated analytically, as was done in Chapter 6 of Book [11]. The HP characteristic curve can be plotted with computed parameter values, if at least two TFTs are done during the process of treatment and the resulting points $P_1 = ([\text{FT4}]_1, [\text{TSH}]_1)$ and $P_2 = ([\text{FT4}]_2, [\text{TSH}]_2)$ are distinctly separated.
For the sake of simplicity, the following substitutions are made:

$$x = [\text{FT4}] \quad \text{and} \quad y = [\text{TSH}], \tag{4.14}$$

leading to the following representation of the measured points $P_1 = (x_1, y_1)$ and $P_2 = (x_2, y_2)$ and Equation (4.9)

$$y = S \exp(-\varphi x). \tag{4.15}$$

It follows from the above that

$$y_1 = S \exp(-\varphi x_1) \quad \text{and} \tag{4.16}$$
$$y_2 = S \exp(-\varphi x_2). \tag{4.17}$$

Dividing Equation (4.16) by Equation (4.17) leads to

$$\frac{y_1}{y_2} = \frac{S \exp(-\varphi x_1)}{S \exp(-\varphi x_2)} = \exp(-\varphi x_1) \cdot \exp(\varphi x_2) = \exp(\varphi(x_2 - x_1)), \tag{4.18}$$

enabling calculation of the model parameters S and φ via

$$\varphi = \left(\frac{1}{[\text{FT4}]_2 - [\text{FT4}]_1}\right) \ln\left(\frac{[\text{TSH}]_1}{[\text{TSH}]_2}\right) \quad \text{and} \tag{4.19}$$

$$S = [\text{TSH}]_1 \exp(\varphi[\text{FT4}]_1) = [\text{TSH}]_2 \exp(\varphi[\text{FT4}]_2). \tag{4.20}$$

Based on this calculation, the MATLAB code was implemented in Appendix A using data points from Bochum patient 1 published in Article [9], which can be seen in Table 4.1.

FT4 pmol/L	TSH mU/L
9	7.84
10	3.63
12	0.7
14	0.21

Table 4.1: Table from Page 4 of Article [9] depicting TFTs of Bochum patient 1.

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Figure 4.14: Implemented model of Equation (4.9) in Simulink.

Besides using the analytical method to calculate the model parameters, the parameter estimator app of Simulink was used to generate S and φ. Hence, the model had to be implemented in Simulink, see Figure 4.14. An overview of the used parameter estimation app is given in Figure 4.15. Afterwards, the calculated parameters were used to calculate the [TSH] values using Equation (4.9), as can be seen in the MATLAB code in Appendix A. The timeseries in the code was used to import the measured data set into Simulink.

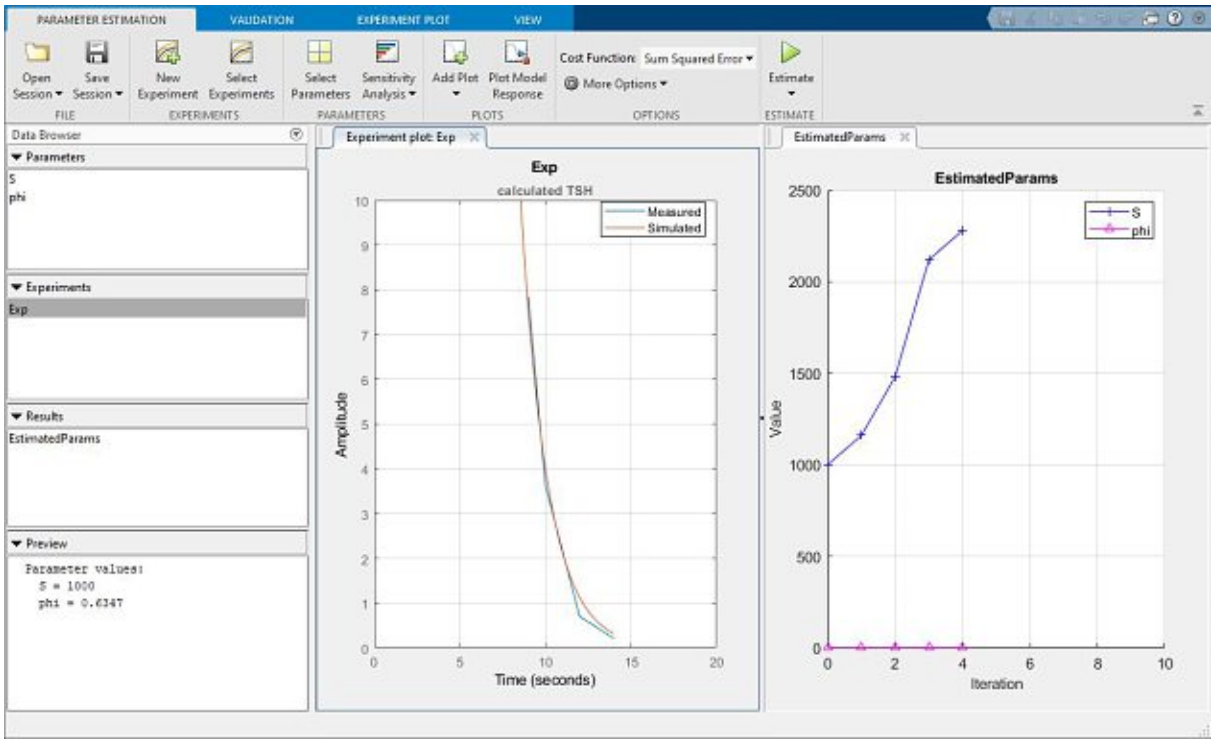

Figure 4.15: Calculation of parameter S and φ in the parameter estimation app of Simulink.

4.2 Evaluating Goodness of Fit

If a model is used to mimic real life data sets evaluating the goodness of fit is essential after fitting the model to the data, which was done following the Mathworks User's Guide for the curve fitting toolbox [16]. Since it is common in statistical literature to use one

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term for different meanings, goodness of fit was defined according to Page 44 of Chapter 7 of User's guide [16]: A 'good fit' could be

- a model that your data could reasonably have come from, given the assumptions of least-squares fitting,
- a model in which the model coefficients can be estimated with little uncertainty or
- a model that explains a high proportion of the variability in your data, and is able to predict new observations with high certainty.

Methods to evaluate the fit of a model can be divided in to two groups: graphical and numerical. The first step is to use graphical methods like plotting residuals and prediction bounds. Those methods aid visual interpretation. In Figure 4.16, the calculated curve is plotted as well as the measured data points.

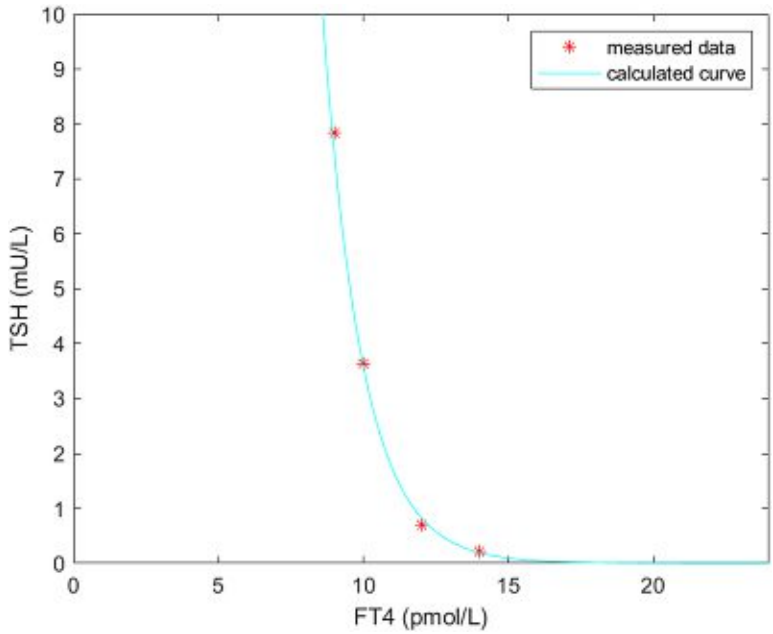

Figure 4.16: The fitted curve and the measured data points displayed in a Matlab plot for visual examination.

As shown in Figure 4.16, the calculated values for S and φ generate a curve that is close to the measured data sets. In some cases graphical measures are more beneficial than numerical measures, since they allow the viewing of the whole data set at once. It is also possible to display a wide range of relationships between the model and the data with graphical methods.
On the other hand, numerical methods that compute goodness-of-fit statistics and coefficient confidence bounds yield numerical measures that aid statistical reasoning. Numerical measures concentrate on particular aspects of the data set and in addition try to compress the obtained information into a single value. Depending on the provided data and analysis requirements to achieve the best fit, both types of evaluation are normally needed.
There is still a possibility that, based on these methods, none of the obtained fits can

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be considered suitable for the data set and therefore the selection of a different model is advisable. Other times, the goodness-of-fit measures imply that a particular fit is most suitable for the data set. However, the resulting coefficients are useless if the goal was to extract fitted coefficients which have physical meaning but the model does not reflect the physics of the data.Thus, it is of uttermost importance to also understand what the used data represents and how it was obtained.
The statistical method or goodness-of-fit statistics used here is R^2 also known as the square of the multiple correlation coefficient or the coefficient of multiple determination. The value R^2 is used to measure how successful a fit is in depicting the variation of data. In other words, it represents the square of the correlation between the response values and the predicted response values.

Definition 1. According to Pages $45-46$ of Chapter 7 of the User's Guide [16], R^2 is defined as the ratio of the sum of squares of the regression SSR and the total sum of squares or the sum of squares about the mean SST

$$SSR = \sum_{i=1}^{n} w_i(\hat{y}_i - \bar{y})^2 \quad \text{and}$$
$$SST = \sum_{i=1}^{n} w_i(y_i - \bar{y})^2,$$

or the summed square of residuals SSE, which can be calculated as follows

$$SSE = \sum_{i=1}^{n} w_i(y_i - \hat{y}_i)^2.$$

Since $SST = SSR + SSE$ applies, R^2 can be expressed as

$$R^2 = \frac{SSR}{SST} = 1 - \frac{SSE}{SST}.$$

The calculated R^2 can assume any value between 0 and 1 and a value closer to 1 indicates that a greater proportion of variance is accounted for by the model. The statistic SSE mentioned in Definition 1, which measures the total deviation of the response values from the fit to the response value, can also be used and is easier to calculate. The SSE or the sum of squares due to error with a value closer to 0 indicates that the fit will be more useful for prediction because the model has a smaller random error component. For this reason the result of R^2 is more intuitive, since it is possible to convert the results to a percentage scale. The Matlab code was implemented according to the definitions from above, see Appendix A.

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4.3 Goodness of Fit for Used Calculation Methods

In Appendices B and C Matlab code is displayed, where the goodness of fit and the percentage error of each method with a varying quantity of measurement points are compared. The percentage error was also contemplated because in some cases the goodness of fit R^2 was over 100%, even though it was apparent from the plot that the computed HP function was not a perfect fit. The percentage error was calculated via

$$E_{\%} = \frac{1}{n} \sum_{i=1}^{n} \frac{|_{calc}V_i -_{meas} V_i|}{_{meas}V_i}, \tag{4.21}$$

with n being the quantity of measurement points, $_{calc}V$ being the calculated values and $_{meas}V$ the measured values. Furthermore, the summed square of residuals SSE was compared, where a value closer to 0 indicates that the model has a smaller random error component and consequently a better fit, as stated the Mathworks User's Guide for the curve fitting toolbox [16]. At first, the quantity of measurement points was varied as per Table 4.3 using the data from Table 4.2.

Nr.	FT4 pmol/L	TSH mU/L
1	9	7.84
2	10	3.63
3	12	0.7
4	14	0.21

Table 4.2: Table from Page 4 of Article [9] depicting TFTs of Bochum patient 1.

The resulting parameter pairs $[S, \varphi]$ from analytical calculations and estimation are displayed in Table 4.3. The effects of different values on the HP function, the goodness of fit and the resulting error will be discussed here.

Sample number	TFT	analytical	estimated
1	1 to 4	$[5397.17, 0.7316]$	$[4859.97, 0.7171]$
2	1 and 3	$[11014.63, 0.8053]$	$[297939.24, 1.1794]$
3	2 and 4	$[4509.46, 0.7124]$	$[2338.70, 0.6485]$
4	1, 2 and 4	$[6315.52, 0.7412]$	$[7786.05, 0.7669]$

Table 4.3: Different used samples and their calculated and estimated $[S, \varphi]$.

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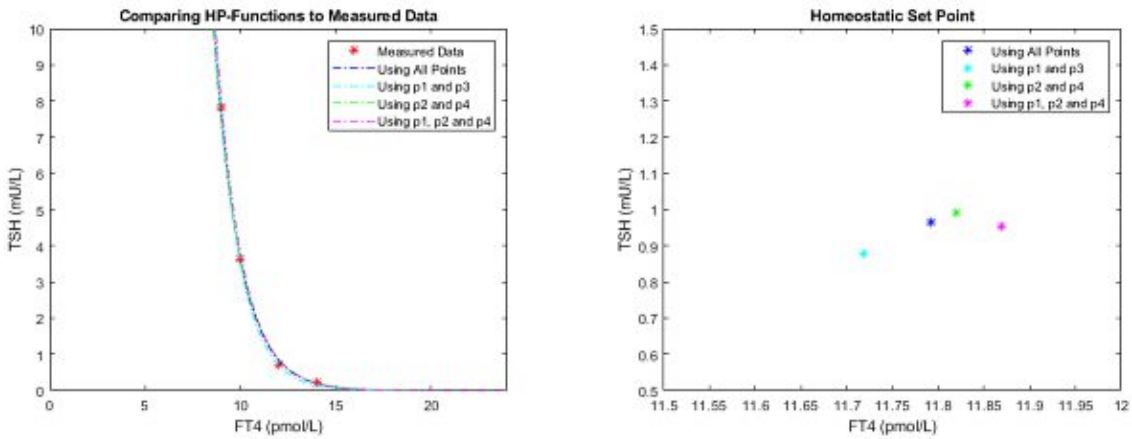
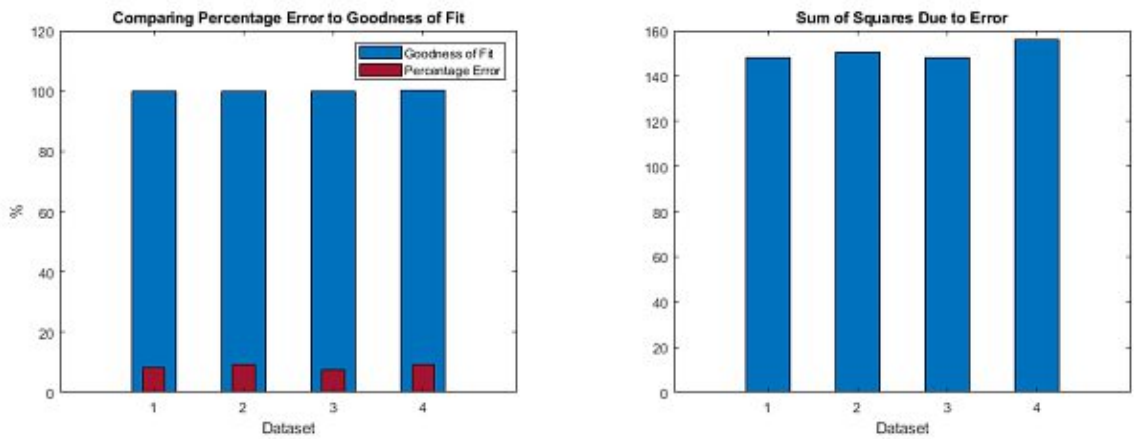
Calculating the parameter pair $[S, \varphi]$ analytically leads to Figures 4.17 and 4.18. In Figure 4.17(a) it is apparent that the quantity of measured data points used to calculate $[S, \varphi]$ does not have a big effect on the outcome. Moreover, Figure 4.17(b) shows that the variation in the calculated set point is also minimal and can be neglected especially when the impossibility to vary the medication in such a small interval is considered.



(a) HP functions. (b) Set points.

Figure 4.17: The HP functions and their set points calculated with a different quantity of measurement points and plotted in Matlab with analytically calculated $[S, \varphi]$.

For every contemplated sample the goodness of fit R^2 is surprisingly close to 100%. However, this can be due to various reasons. In the author's opinion, since the plot supports the results from R^2 in this case, we can assume a goodness of fit of over 95%, but the calculated values of R^2 have to be treated with reserve. One reason for the high values of R^2 could be the small sample size.



(a) R^2 and $E_{\%}$. (b) SSE.

Figure 4.18: Goodness of fit R^2, percentage error $E_{\%}$ and the Sum of Squares Due to Error SSE calculated for different Samples.

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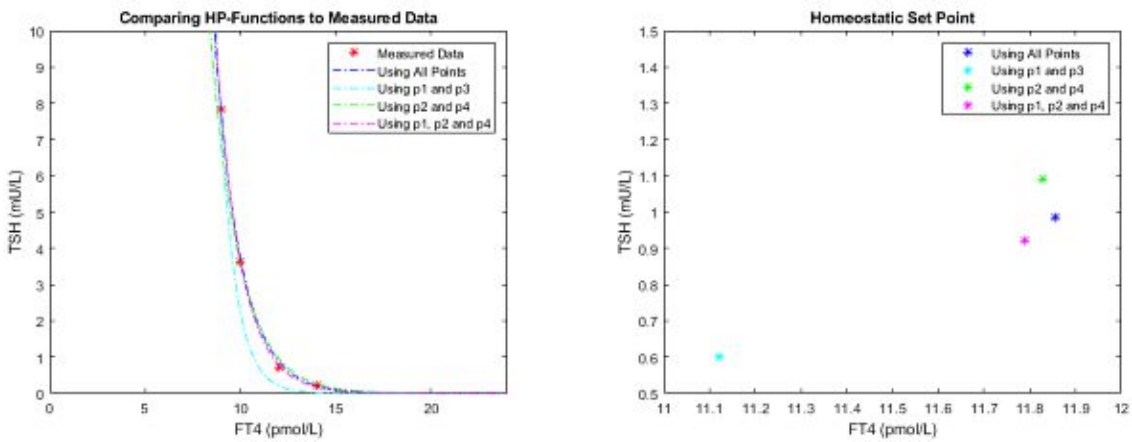
In case of $R^2 > 100\%$, it makes sense to also look at other methods of error measurement. Therefore, the percentage error as well as the SSE value were examined. The results for every sample are displayed n Table 4.4, showing that $E_{\%}$ is below 10% in all instances. Normally, a SSE value closer to 0 indicates a small random error component and therefore the calculated fit will be more useful for prediction. The SSE values displayed in Table 4.4 could also be attributive to the small quantity of the measured data.

Sample number	R^2	$E_{\%}$	SSE
1	99.93%	8.30%	148.30
2	99.98%	9.21%	150.47
3	99.94%	7.57%	147.97
4	100.09%	9.29%	156.05

Table 4.4: The calculated values of R^2, $E_{\%}$ and SSE for every sample.

Estimating the parameter pair $[S, \varphi]$ with the parameter estimator app from Simulink led to Figures 4.19 and 4.20. Every estimation was started with initial values $S = 1500$ and $\varphi = 0.5$ to enable comparable results and prevent tampering due to initial values with low error. In comparison to Figure 4.17(a), it is apparent in Figure 4.19(a) that the quantity of the samples has an impact on the fitness of the calculated HP function.



(a) HP functions. (b) Set points.

Figure 4.19: The HP functions and their set points calculated and plotted in Matlab with estimated $[S, \varphi]$

The different computed set points are depicted in Figure 4.19(b) and while the set points of Sample 1 and 4 are in the same interval as the set points calculated with the analytical method represented in Figure 4.17(b), the set point achieved with Sample 2 is far away from the other set points. This makes sense when the plot of the HP curve is consulted, since the result of Sample 2 is the only curve subtending only one data point.

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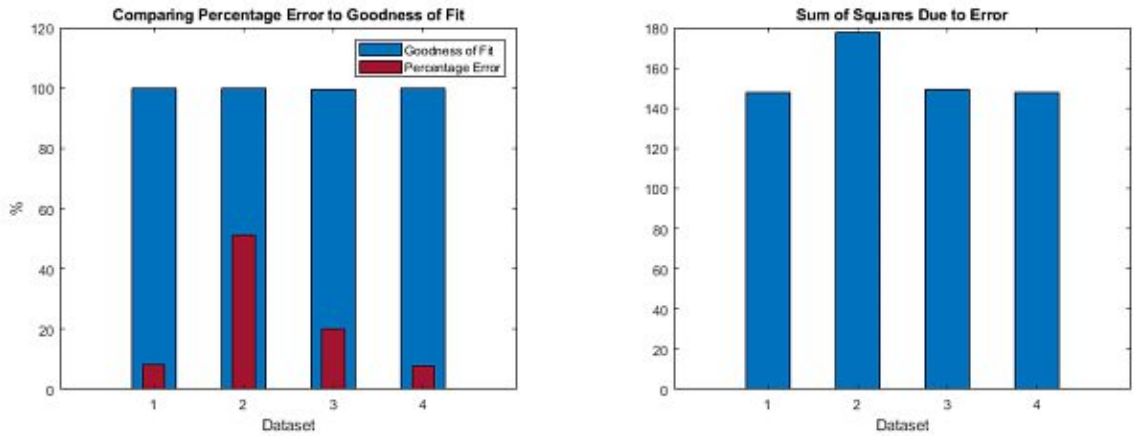

(a) R^2 and $E_{\%}$.

(b) SSE.

Figure 4.20: Goodness of fit R^2, Percentage Error $E_{\%}$ and the Sum of Squares Due to Error SSE calculated for the different samples

R^2 for the estimated values of $[S, \varphi]$ is also very close and sometimes even above 100% probably due to the same reasons why R^2 was close to 100% in the analytical case. The plot of the HP functions from Figure 4.19(a) shows that the curves for Sample 1, 3 and 4 seem to fit the measurement data visually, while Sample 2 is not a good fit.
It is also obvious when Figure 4.20(a), Figure 4.20(b) and Table 4.5 are observed, that the samples with only two measurement points, especially Sample 2, lead to a bigger percentage error and a higher SSE value. Therefore, to yield a HP function with an $E_{\%}$ below 10%, a sample has to consist of at least three measurement points.

Sample number	R^2	$E_{\%}$	SSE
1	100.03%	8.34%	147.60
2	99.98%	51.23%	177.69
3	99.69%	20.24%	149.33
4	100.01%	7.94%	147.59

Table 4.5: The calculated values of R^2, $E_{\%}$ and SSE for every sample.

4.4 Other Attempts Modelling the HPT-axis

Before I settled on the HP model from Goede and Leow, which was presented earlier in this chapter, I tried other modelling approaches. My first idea was to model the HPT axis in a healthy individual and then change it to model a diseased system. However, I learned during my research that the hypothalamus-pituitary-thyroid system is a closed loop system, which cannot be simulated. Furthermore, by changing the health status to *'diseased'*, the whole system is changed from a closed loop situation to an open loop situation. Also, changing a model that is used to represent a diseased system cannot be remodelled to simulate a functioning system, which is not possible due to the change of open loop to closed loop. On that account, I decided to try a new approach.

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Since my first idea was to use transfer functions to model hypothalamus-pituitary-thyroid system, I tried to change a model using transfer functions to my needs. For this idea I used a patient-specific model of the negative-feedback control of the HPT axis in autoimmune thyroiditis from Article [17]. For this attempt, a system of differential equations was considered. However, in the published model the size of the thyroid decreased due to the patient's autoimmune thyroiditis. This problem was bypassed by changing the system of differential equation to a system that required the size of the thyroid to be constant. The in Simulink implemented model is displayed in Figure 4.21.

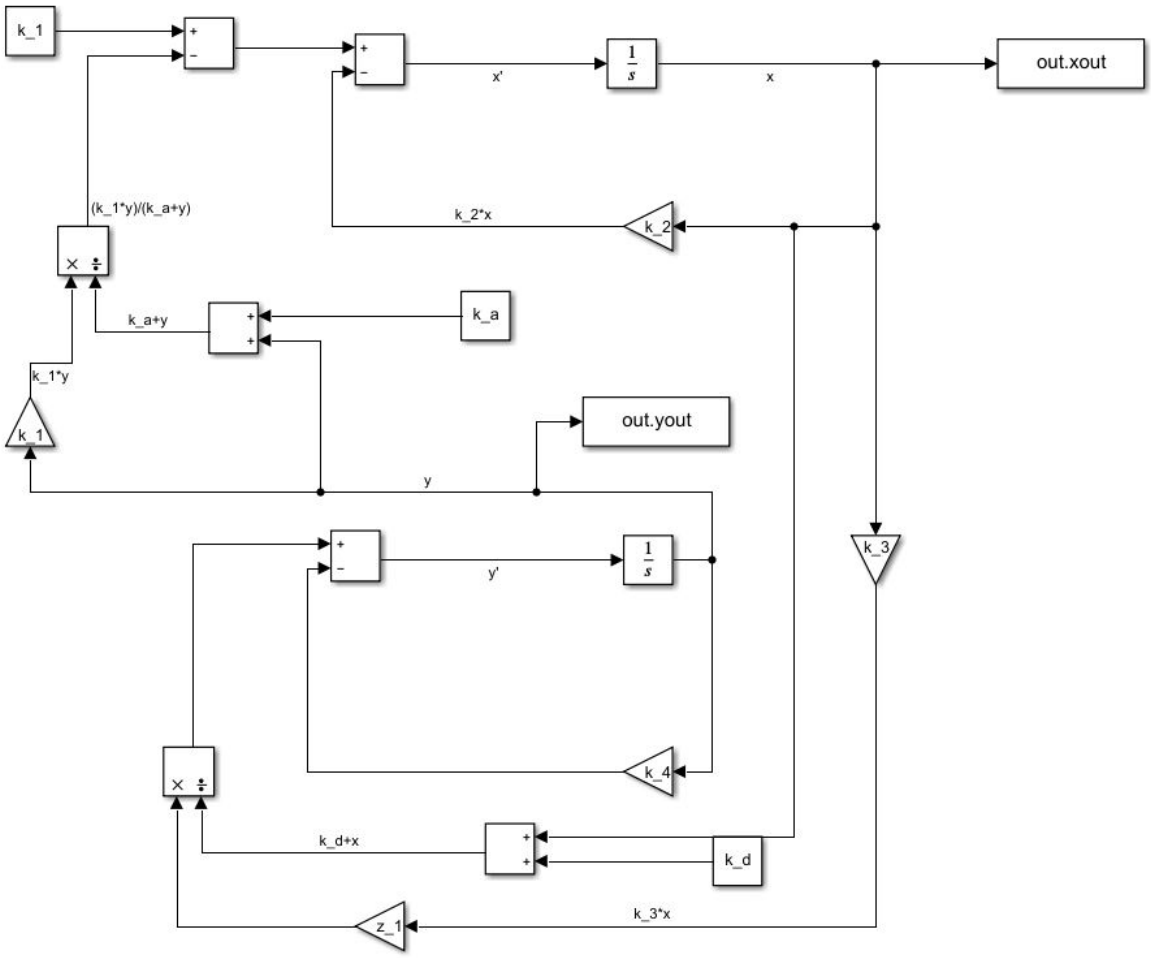

Figure 4.21: An individualised Simulink model of the hypothalamus-pituitary-thyroid system of a patient with a thyroid disease.

The first problem was to connect the measurement data to a fitting timeline, since the HP model and the data sets are independent in time. The resulting HP curve didn't match the measurement data, as can be seen in Figure 4.23. Even though it was possible to match the model to the [FT4] data, as can be seen in Figure 4.22(b), I was not able to fit the function to the [TSH] data as well. In Figure 4.22(a), it is apparent that the curve is too steep, which can be attributed to the time under which the model operates.

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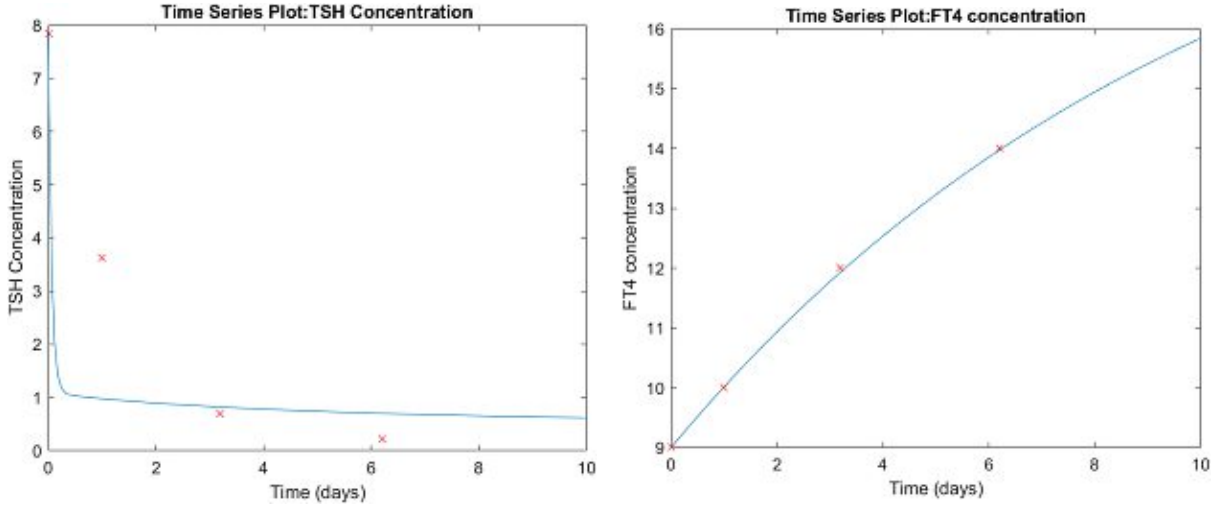

(a) TSH concentration.

(b) FT4 concentration.

Figure 4.22: Calculating the HP function with a Simulink model and comparing the result to the measured data.

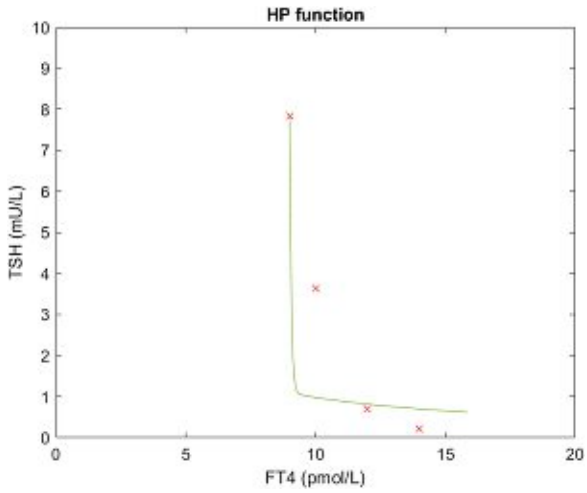

Figure 4.23: Computed HP function with a Simulink model.

In conclusion, it can be said that this idea also won't work without being able to influence the steepness of the resulting function. However, using the transfer function estimator app on the measurement data in order to generate a transfer function modelling the relationship between [TSH] and [FT4] didn't lead to a satisfying result. The resulting transfer function oscillated heavily. In my opinion, this approach didn't work because transfer functions are normally time dependent in some form, whereas the relationship between [TSH] and [FT4] is not. Also, the small sample size might cause problems. Another obstacle could be the linearity normally required for transfer functions.

Based on my findings I decided to use the same approach as Goede and Leow, which means using a negative exponential function to model the measurement data. However, I wanted to use a parameter estimation algorithm like simulated annealing to calculate the parameter set $[S, \varphi]$ for the HP function insted of the analytical solution Goede and Leow provided. This is not possible because the amount of the available measurement data is insufficient and therefore the result is not precise.

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5. The Hypothalamus-Pituitary Set Point Theory

Nowadays, increasingly more patients diagnosed with hypothyroidism have to rely on a life-long thyroid hormone replacement therapy. However, despite being 'biochemically euthyroid', these patients often express symptomatic complaints, which manifest as symptoms consistent with thyroid hormone excess or deficiency.

Definition 2. A person is said to be *biochemically euthyroid*, according to Chapter 8 of Book [11], if the TFTs show that the measured [FT4] and [TSH] values can be found within their respective reference ranges.

The application of this definition only makes sense to a certain degree, because if a patient still suffers from symptoms the range value they have obtained must be above or below the optimally paired [FT4]-[TSH] values. This leads to the assumption that the [FT4]-[TSH] coupled optimum values are unique for every patient.
Interestingly, plotting the HP function derived in Chapter 4 shows that the normal levels of [FT4] and [TSH] fall within the region where the negative exponential function displays the greatest curvature. From there on it makes sense to calculate the curvature of a two-dimensional function and determine the point of maximum curvature with standard calculus. The point of maximum curvature is unique on the exponential function. In addition, from the point of maximum curvature to the lower values of [FT4], changes in [FT4] lead to strong variations in [TSH]. Vice versa, strong variations in [FT4] at relatively small variations in [TSH] can be found below the point of maximum curvature for [TSH] values. Based on these considerations from Chapter 8 from Book [11], it makes sense that the point of maximum curvature was chosen by nature as an effective method for homeostatic control purposes in biological systems. Therefore, the properties of the HP characteristic curve have to be investigated in more detail, as was done in Chapter 8 of Book [11].
The basis for the validated parametrised negative exponential expression derived in Chapter 4 lays within the opening of the closed-feedback-loop found in healthy people. A healthy HP unit is a sensitive metabolic sensor and master controller in a closed-loop thyroid hormone control system. This closed negative feedback loop containing the HP unit and the thyroid needs a well-defined point of reference on which the narrow [FT4] range will be established and maintained. Moreover, it can be shown that the intrinsic properties of the HP characteristic actually encode this reference value and thus provide a solution to find this unique point.

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However, a closed-loop system can only be analysed with a step and/or impulse response method in the frequency and time domain, according to systems and control theory. If those methods are not applicable, the only alternative is to investigate the properties of the system in an open-loop mode. The opening of the feedback loop, which can be encountered in patients with failed thyroid hormone secretory function, facilitates the analysis of the dose response properties of the HP in an interrogative and proportional way.

The reason why the characteristics' analysis is confined purely to the relationship between [FT4] and [TSH], even though T3 is the the key active thyroid hormone of the body, can be found in the generation and distribution process of T3. Most T3 is not produced by the thyroid, but is converted from T4 in the glial cell of the hypothalamus and the thyrotrophs of the pituitary.

In the hypothalamus the, locally directly from FT4 generated FT3 suppresses TRH expression while circulating FT3 besides locally generated T3 induces TSH gene suppression in the anterior pituitary. Therefore, the inhibitory effect on the secretion of TSH caused by the local 5′-deiodination and the associated high local intracellular concentration of T3, which predominates over the one contributed by plasma [FT3], is reflected in clinical data of hypothyroid patients treated with a combination therapy using both L-T4 and L-T3. Precisely, relatively lower values of [FT4] and [TSH] can be found in patients treated with combination therapy, compared to patients who have received purely L-T4 substitution therapy.

More importantly, the measured [FT4] and [TSH] values of patients receiving only L-T4 therapy exhibit a clear exponential relationship. Also, the model that involves the observable variables of [FT4] and [TSH] has been proven to be correct by various sources. On the contrary, models including [T3] and/or [FT3] have no use, because both [T3] an [FT3] have no inhibitory impact on the secretion of [TSH] since they are mostly products of the necessary local tissue deiodination of [FT4].

The relationship based on these thoughts has already been derived in Chapter 4 and can be written as

$$[\mathrm{TSH}] = S \exp(\varphi[\mathrm{FT4}]). \tag{5.22}$$

The function written in Equation (5.22) depicts a characteristic in the two-dimensional Cartesian space with real positive parameters S and φ, which were derived from measured individual TFTs. Consequently, only one exponential function is completely defined by the coordinates of two different measured coordinate pairs ([FT4], [TSH]). According to Chapter 8 from Book [11], it can be proven with the theory of differential calculus that every exponential function thus has an unique identifiable point of maximum curvature.

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5.1 Derivation of the Point of Maximum Curvature

In Chapter 8 of Book [11] and Article [15], Goede and Leow discuss the calculation method of the point of maximum curvature. In both sources, the set point for euthyroid homeostasis in the HPT axis feedback loop is postulated to be the point of the HP function where the sensitivity for any change around this point on the curve is maximal. This is based on the perception that the exponential function has only one point of maximum curvature and thus maximum sensitivity for change on the characteristic.
The point of maximum curvature can be found according standard curvature theory. At a point P of a function, the radius of curvature is defined as R and the curvature is defined as K, leading to

$$K = \frac{1}{R}.$$

Definition 3. The curvature K of a defined function $y = f(x) = f_1$ is defined as

$$f_2 = K = \frac{\frac{\mathrm{d}^2 y}{\mathrm{d}x^2}}{\left(1 + \left(\frac{\mathrm{d}y}{\mathrm{d}x}\right)^2\right)^{\frac{3}{2}}}. \tag{5.23}$$

Using the HP function of the hypothalamic-pituitary unit from Equation (5.22) in its simplified form with [TSH] $= y$ and [FT4] $= x$, we have

$$y = S\exp(-\varphi x). \tag{5.24}$$

Calculating the curvature K using Equation (5.23) from Definition 3 and Equation (5.24) leads to

$$K = \frac{\varphi^2 S\exp(-\varphi x)}{(1 + \varphi^2 S^2 \exp(-2\varphi x))^{\frac{3}{2}}}.$$

To calculate the point of maximum curvature, the condition

$$\frac{\mathrm{d}K}{\mathrm{d}x} = 0,$$

for $f_3 = \frac{\mathrm{d}K}{\mathrm{d}x}$, has to be fulfilled, with

$$\frac{\mathrm{d}K}{\mathrm{d}x} = \frac{\varphi^3 S\exp(-\varphi x)\left[1 + \varphi^2 S^2 \exp(-2\varphi x)\right]^{0.5}\left[2\varphi^2 S^2 \exp(-2\varphi x) - 1\right]}{\left[1 + \varphi^2 S^2 \exp(-2\varphi x)\right]^3}.$$

This leads to the subsequent calculation

$$\begin{aligned}
0 &= \frac{\varphi^3 S\exp(-\varphi x)\left[2\varphi^2 S^2 \exp(-2\varphi x) - 1\right]}{\left[1 + \varphi^2 S^2 \exp(-2\varphi x)\right]^{2.5}}, \\
0 &= \exp(-\varphi x)\left[2\varphi^2 S^2 \exp(-2\varphi x) - 1\right] \\
\exp(-\varphi x) &= 2\varphi^2 S^2 \exp(-3\varphi x) \\
x &= \frac{\ln(\sqrt{2}\varphi S)}{\varphi}.
\end{aligned}$$

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The result can be summed up into

$$x = \frac{\ln(\sqrt{2}\varphi S)}{\varphi} \quad \text{and} \tag{5.25}$$

$$y = \frac{1}{\sqrt{2}\varphi}, \tag{5.26}$$

where Equation (5.25) was inserted into Equation (5.24) and from which the first derivative at the point of maximum curvature yields

$$\frac{\mathrm{d}y}{\mathrm{d}x} = -\frac{1}{\sqrt{2}}.$$

When the substitution from Equation (5.24) is reversed, the representation of the euthyroid set point changes to

$$[\mathrm{FT4}] = \frac{\ln(\sqrt{2}\varphi S)}{\varphi} \quad \text{and}$$

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

In Figure 5.24 the HP function f_1, the curvature function f_2 as well as its first derivative f_3 are depicted in one graph to show the theory behind the physiology of the homeostatic control process. For illustrative purposes a vertical line, later referred to as the *set point line*, coinciding with the set point value of [FT4] was drawn, in which the set point is depicted with a light blue asterisk in Figure 5.24.

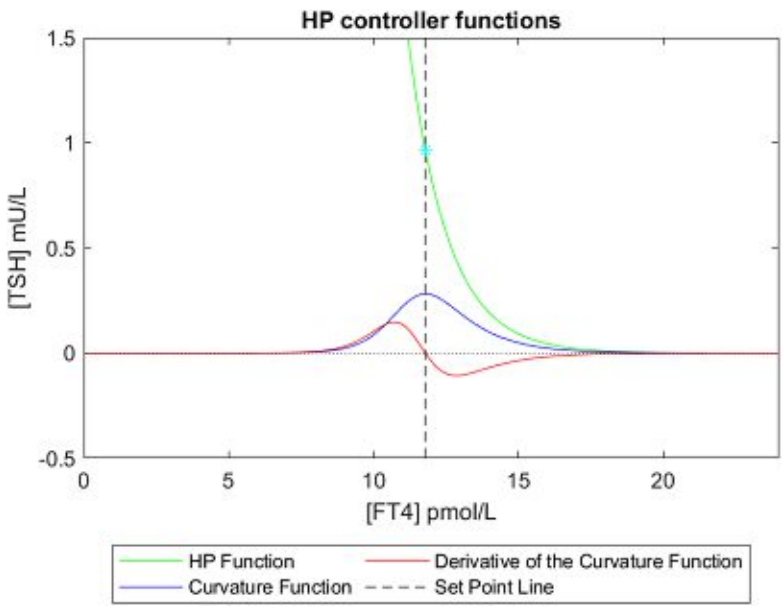

Figure 5.24: A Matlab plot of the HP function, the curvature function and its first derivative.

The [FT4] value of the set point is determined by the maximum of the curvature function, for which the first derivative of the function has to be calculated. In Figure 5.24, the

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function f_3 displays two extrema on either side of the set point line. This finding can lead to more insight into the physiological processes with the help of differential calculus. If [FT4] increases and leaves the set point towards the extrema on the right side of the set point line, the sign of f_3 is negative and thereby prepares the HP system to increase the inhibition on TSH secretion, resulting in a decreased thyroid hormone production rate. Consequently, [FT4] decreases before reaching the extrema of f_3 on the left and returns to the set point. In contrast, when [FT4] decreases beyond the extrema on the left side of the set point line, the positive gradient of f_3 is detected by the HP unit, which responds by reducing the degree of TSH inhibition to allow [FT4] to increase toward the set point. By operating as a gradient-modulated controller, the HP unit is able to maintain the value of [FT4] as close to the set point as possible.
Based on this, the set point homeostatic control was visualised in Chapter 8.4 of Book [11] as a marble based in a bowl, where the curvature is a maximum. The control of FT4 at the set point can be described as a marble resting at the bottom of a bowl, which is placed upright on its base. Since the marble has a very strong tendency to remain at its position even if it is momentarily shifted away from its location, which was also indicated by the mathematical discussion above, it makes sense that this is a point of stable equilibrium.
On the contrary, the control of TSH at set point can be pictured as a marble delicately balanced on the exterior surface of the bottom of an inverted bowl. At this point of unstable equilibrium, the marble can easily roll off the bowl in either direction, indicating that the sensitivity for change in [TSH] is highest at a point of maximum curvature. In conclusion, the site of maximum curvature of the HP characteristic can be described as having a maximum sensitivity for [TSH] changes and a maximum stability of maintenance of [FT4].

5.2 Applicability of the Set Point in Medicine

The presented maximum curvature theory, which forms the basis of the thyroid set point theory, has a rational and logical appeal that, in contrast to the current guideline, where treatment is based on the population ranges of [TSH]. Furthermore, the importance of the clinical inspection and interpretation of [FT4] is generally disregarded. Goede and Leow stress in Book [11] that individual [FT4] and [TSH] do not change very much over time in a healthy state, hence they assumed and proved in their book that the euthyroid set point is probably genetically programmed and -more importantly- unique. Moreover, when compared to the very wide normal ranges in population the set point accounts only for a significantly narrow variation in [FT4] and [TSH] for any given person.
The concept of titrating thyroid medications to a personalised set point is still largely unknown. On that account, they decided to code a software algorithm based on this theory to facilitate practising physicians access to this new treatment method. The theory on which the algorithm is based is able to predict the individualised euthyroid set points of thyroid patients with a certain level of precision. The main ideas was to enable a routine treatment of thyroid patients to their individualised set point as computed quickly using the software by their health care provider.

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However, the developed euthyroid set point algorithm, which was patented in 2013, is only licensed for use in clinics on a case-by-case basis according to each physician's best clinical judgement and with the patient's consents. The set point theory is still experimental and undergoing research evaluation. Consequently, until this strategy becomes accepted as standard treatment and integrated into medical practice guidelines, its use is restricted by a set of regulations protecting the patient from harm. Therefore, the patient has to give his fully informed consent within the context of a doctor-patient relationship and the treating doctor is bound by the Hippocratic oath and has to act in the patient's best interest, doing no harm. But even if the medical software is approved by the regulatory authorities, the use of the software has to be restricted to patients whose well-being is apparently suboptimal regardless of the patient's euthyroid state as per the standard definition.

Three clinical studies, which were conducted to show the effectiveness of their software, were mentioned by Goede and Leow in Book [11]. In the first study codenamed EQUILEBRATE, which is derived from the title 'A Prospective Randomized, Double-blind, Parallel Arm, Multi-center Clinical Trial to **E**valuate the **Qu**al**i**ty of **L**ife and **E**uthyroid **B**alance using Conventional Thyroid Hormone **R**epl**a**cement versus Se**t** Point Strat**e**gy', a formal randomised double-blind placebo controlled study to evaluate the effectiveness os the desktop version of the thyroid software *Thyroid-SPOT* was conducted.

For EQUILEBRATE, mainly patients with primary hypothyroidism treated with L-thyroxine replacement therapy were recruited. Besides their doubtful reputation in serious research methods two quality of life questionnaires, more precisely a robust questionnaire (SF−36) and a thyroid-specific questionnaire 'ThyPro', were used to evaluate the patient's quality of life during the clinical trial.

The second study called TRIBUTE, which stands for 'The Role of **T**hyroid Status in **R**egulat**i**ng **B**rown Adipose Tiss**u**e Activity. White Adipose **T**issue Partitioning and Resting **E**nergy Expenditure', concentrates on patients with hyperthyroidism from Graves' disease. The evaluation of the patient's residual thyroid symptoms as well as objective measures of fasting lipids, serum electrolytes, body weight and brown adipose tissue function was conducted while they undergo anti-thyroid drug therapy.

Meanwhile, Goede and Leow also tried to prove the accuracy of their set point prediction in a retro-perspective study codenamed PREDICT-IT from '**P**rofiling **R**etrospective Thyroid Function **D**ata **i**n **C**omplete **T**hyroidectomy Patients to **I**nversigate the Hypothalamus-Pituitary-Thyroid (HPT) Axis Set-Poin**t**.' In this study the computed set points of thyroidectomised patients on L-thyroxine replacement were compared to the TFTs pre-thyroidectomy at a time when these patients were healthy. More information on this medical app can be found in Chapter 18 of Book [11].

5.3 Error Sources

The exact measurement and correct interpretation of numerical information is a crucial step in the modelling process. Therefore, Goede and Leow discuss different error sources in Chapter 12 of Book [11]. A fundamental condition for every measurement system is a defined calibrated standard. Notwithstanding that the precision of routine automated immunoassays like TFTs is nowadays reliable and robust for clinical decision making

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with respect to diagnosis and treatment, there are still no acceptable standards for the measurements of [FT4] and [TSH], especially since normal reference ranges of [TSH] and [FT4] are defined by each clinical laboratory via the statistical distribution of [TSH] and [FT4] of a group of healthy subjects from the general population in a scatter plot.
In the scatter plot, every coupled [TSH]-[FT4] point represents the current value of the points of equilibrium of an individual thyroid status in the investigated population. It is impossible to draw any valid conclusion about the [TSH]-[FT4] relationship from these scatter plots and their related regression analyses for any given person across the spectrum of the thyroid hormone status, since different people can have widely separated positions of [TSH]-[FT4] pairs on such plots and still have a similar thyroid hormone status. The generated scatter plots can still provide an unexpected insight into modelling, leading to the negative exponential model established in Chapter 4. The derived HP characteristic curve can be viewed as the collection of all possible points of equilibrium of an individual.
The idea is to validate the model with measurements of [FT4] - [TSH] pairs of a patient with overt primary hypothyroidism treated with L-T4 over a number of months till their [FT4] and [TSH] are fine tuned to the coordinate space surrounding their original pre-disease euthyroid set point. Inaccuracies in the measured data sets can falsify the calculation of the homeostatic set point, thereby affecting the patient-specific treatment. Since many hormone systems in the body exhibit natural circadian bio-rhythms dependent on time, biological variations are expected to occur in [FT4] and [TSH].
Circadian variations in [TSH] heavily influence the measurement results between morning and evening readings. Thus, it is important to determine a time of the day to perform the TFT. Another point having to be considered is that a patient already using L-T4 has to be tested before the intake of the daily L-T4 dose. Therefore, TFTs are usually done shortly upon awakening in the early morning between 7.00 h and 10.00 h before breakfast for convenience reasons.
Besides using different normal reference ranges, there are four other error sources found in laboratories. Every laboratory can work with their preferred test equipment and use different measurement methods and different measurement standards, therefore differences are common. The preferred measurement methods to obtain [FT4] should be based on equilibrium dialysis and/or tandem mass spectrometry. Also, for consistency reasons only TFT values from the same laboratory should be used. Measurement errors also occur due to the utilisation of imprecise direct analogue immunoassay for the determination of [FT3] and [FT4] because of incomplete separation of bound and unbound fractions. Another large source of errors is the rounding of the measurement results, leading to an absolute error.

Definition 4. According to Page 160 of Book [11], an *error value* is the difference between measured result and real value. Furthermore, the relative error is defined as the relative difference between the measured value M and the true value v, leading to

$$\epsilon = \frac{M - v}{v}.$$

If the measured value M is rounded to the nearest integer above or below the value M, which can be written as $M \pm 1$, the result is an uncertainty of ± 0.5. An even bigger uncertainty of ± 1 is achieved by rounding with the use of truncation of the decimal value

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behind the primary integer. In conclusion, the determination and reporting of [FT4] should have an accuracy of up to at least one decimal value, since the consequence for the error magnitude depends highly on the value of [FT4]. More precisely, even small variations in lower values of [FT4] lead to large variations of [TSH], making accuracy for this range especially important, while readings of higher values of [FT4] are less sensitive to variations in [TSH]. Consequently, the possible deviation in [TSH] has a sensitivity dependent on [FT4].

In Chapter 12 of Book [11], two other error sources were mentioned connected to medical conditions, resulting in changes in the model parameter S. Prolonged periods of hypothyroidism and pregnancy cause an increase in S, which results in a temporary shift to the higher end of the [FT4] scale in the first case and in a shift of about 2 to 3 pmol/L to the higher end of the [FT4] scale in the second case. On the other hand, a prolonged period of hyperthyroidism leads to a decreased value of S resulting in a HP shift to the lower end of the [FT4] scale.

Another aspect to keep in mind is the sensitivity of the TFTs. While the sensitivity of [TSH] values is an order of magnitude better than the sensitivity of [FT4] values, the accuracy of both methods remains in the magnitude of $\pm 5 - 10\%$. Consequently, measured [TSH] values below 0.1 mU/L lose their validity while the validity of measured [FT4] values is given due to the range of $5 <$ [FT4] < 50 pmol/L.

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6. Clinical Validation of the Model with TFTs from Austria

There is a lot of evidence that the unique euthyroid set point found in healthy patients is constant and stable over a period of approximately two decades. In Chapter 5 it was demonstrated that the euthyroid set point has a natural and strong tendency to remain at the point of maximum curvature of the HP function. Moreover, the long term health of thyroid patients benefits massively if physiological functions driven by metabolically potent thyroid hormones are optimally regulated within feedback threshold hormonal levels. These levels encompass the euthyroid set point and its surrounding narrow neighbourhood for maximal disease-free survival.
It has been mentioned various times, but it is crucial that medical models are validated with supporting clinical data. The closed feedback loop of an intact HP loop the [FT4] and [TSH] to the set point, obscuring the unique negative exponential HP function, which is required to test the theory. Consequently, to break open the closed loop and unravel the HP characteristic for testing a pathological thyroid state is needed.
On Pages 15 to 16 in Article [15], a number of independent methods was listed, which can be used by researchers trying to validate the set point theory. However, some of these methods could be considered challenging to perform, logistically impracticably or potentially ethically untenable depending on the circumstances. The following methods of clinical validation strategies to test the set point theory are displayed in ascending order of difficulty and feasibility as per Page 15 in Article [15].

I Observing the TFTs of patients with total thyroidectomy, for example caused by thyroid cancer, who require life-long L-T4 during therapy. Their original set point, which is defined by their original euthyroid pre-operative FT4-TSH levels, can be compared to the calculated set point using the plotted HP curve.

II Patients with Graves' disease, who successfully achieved a sustained long term clinical remission after finishing antithyroid drug therapy. Their during remission newly achieved euthyroid set points are compared to the computed set point values using TFTs, which were done while the patients still received medication.

III TFTs from patients on anti-thyroid drugs for hyperthyroidism or L-T4 for hypothyroidism, where a prior historical record of previously normal euthyroid FT4-TSH data exists. This data has to date back long before the onset of thyroid disease

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required a definitive thyroid-specific treatment and consequently dose adjustments. In this case the calculated set point of their HP curve can be matched against their original normal FT4-TSH data.

IV Researching existing epidemiologic literature with published laboratory data documenting the natural history of patients screened positive for thyroid autoimmune markers associated with an euthyroid state initially, who later develop a thyroid disease requiring treatment.

V Patients who develop hypothyroidism after receiving radiation therapy of the neck for cancers, enabling the calculation of HP curves and associated set points. Here any euthyroid TFTs pre-radiotherapy can serve as a reference value for comparison with the computed set points.

VI It is also possible to use euthyroid healthy human volunteers, who are transiently rendered hypothyroid or who receive medication to induce experimental thyrotoxicosis. The hypothyroid state is achieved using thionamides. Other times and sometimes even additionally L-thyroxine (L-T4) or liothyronine (L-T3) is used to induce experimental thyrotoxicosis. All this is done according to ethically approved safe research protocols.The goal is to generate unique HP curves for set point determination which can then be compared against their own natural set points.

VII Unusual patients diagnosed with "euthyroid Graves' disease", whose TFTs are consistently within the normal ranges, could arguably be considered euthyroid set points since they are a result of equimolar mixture of TSH receptor stimulating and blocking autoantibodies leading to euthyroidism. The HP curve and the computed set point is based on the subsequent development of thyrotoxicosis or hypothyroidism due to imbalance of antibodies.

VIII Over years accumulated prospective follow-ups of euthyroid people positive for thyroid autoantibodies before a thyroid dysfunction manifests can be used. Euthyroid TFTs prior to developing thyroid autoimmunity are needed, so the calculated set points on their respective HP curves can be compared with their initial euthyroid TFTs.

Other obstacles in obtaining medical data include the local ethics commission, which is responsible for the protection of patient data and restrictions from different departments concerning data exchange. Also if it is not possible to conduct a new medical study it is often difficult to find a study providing datasets that fits the requirements of the clinical validation process.
However, I was able to gain access to a medical study, which was conducted at the Medical University of Vienna. The study is called *Effects of thyroid function on phosphodiester concentrations in skeletal muscle and liver: An in vivo NMRS study* and had the objective to measure the actions of peripheral thyroid hormones on PM and PL tissue concentration. The longitudinal, prospective pilot study gathered measurement data from nine patients with hyperthyroidism and four patients with hypothyroidism. The provided data can be found in two tables in Appendix E, where Table E.1 covers the

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measurements of patients with hyperthyroidism and Table E.2 represents the measurement data from patients with hypothyroidism.
The study states that the TSH and FT4 levels were measured at the central laboratory of the Medical University of Vienna according to standard laboratory methods and refers to the laboratories website *www.kimcl.at* for detailed informations. The method used to determine the hormone levels is called ECLIA. The measuring inaccuracy for TSH is 4% with a sensitivity of 0.01μIU/ml, the measuring inaccuracy for FT4 is between 5% and 7% with a sensitivity of 0.02ng/dl. The blood sample has to arrive at the laboratory within three hours and blood samples from external senders have to be centrifuged and only the serum should be sent to the laboratory. The sample for the laboratory has to consist of 0.3ml serum.
Before it is possible to validate the HP function the data set of each patient have to be sorted and rejected if the data set is insufficient. At first data sets with only one measurement are rejected, because at least two measurements are needed for the HP function leading to the rejection of the patients $5, 8, 11$ and 13. Especially, the [TSH] values of patients with hypothyroidism are in some cases too low for exact measurements. This phenomenon can be found in patient 2 and 3 and therefore they cannot be used for the validation of the model. After sorting out the data sets, the remaining data sets displayed in Table 6.6 can be used to validate the HP function.

Patient-Nr.	1st Measurement	2nd Measurement	3rd Measurement
1	$[4.92, 0.80]$	$[2.93, 1.06]$	$[0.01, 4.80]$
6	$[113.00, 0.11]$	$[50.94, 0.43]$	$[01.93, 0.96]$
7	$[0.90, 0.81]$	$[0.58, 0.88]$	$[0.01, 2.50]$
4	$[0.60, 0.95]$	$[0.01, 7.69]$	
9	$[0.05, 1.19]$	$[0.01, 3.61]$	
10	$[096.00, 0.65]$	$[43.24, 1.17]$	
12	$[159.40, 0.60]$	$[04.44, 1.84]$	

Table 6.6: Sorted measurement data for the validation displayed in pairs of [TSH (μIU/mL), FT4 (ng/dL)].

However, it is not possible to validate the set point theory with them. This is due to the fact that no reference set point exists to validate the calculated set point. To validate the set point theory, a study has to be conducted, where the set point of a healthy HP loop is known. Since two different methods for calculating the HP function are compared, the respective set points will be calculated and compared to each other.
At first, the data sets with three measurement points were used, including two patients with hyperthyroidism and one patient with hypothyroidism. Afterwards, the results from data sets with two measurements were analysed from two patients with hyperthyroidism and two patients with hypothyroidism. In the following analysis, Method 1 refers to the analytically calculated HP function and Method 2 refers to the estimated HP function.

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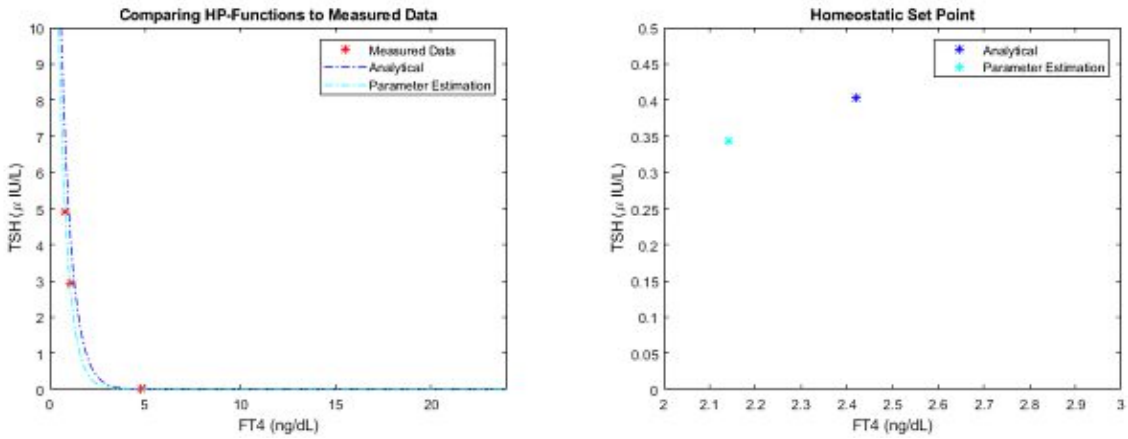
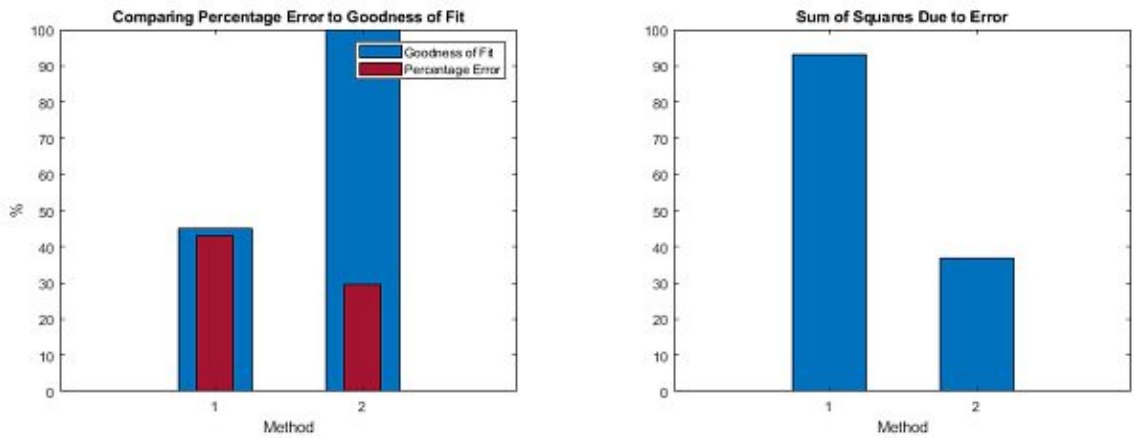
Patient 1



(a) HP functions. (b) Set points.

Figure 6.25: The HP functions and their set points calculated and plotted in Matlab with calculated and estimated $[S, \varphi]$.

Patient 1 was diagnosed with hyperthyroidism. Probably due to the low TSH and FT4 values, the estimated function is a better fit, which is obvious in Figure 6.25(a), depicting the different HP functions, and in Figure 6.26(a), representing the goodness of fit and the percentage error. In addition, the sum of squares due to error is also very low compared to the values calculated in Section 4.3.



(a) R^2 and $E_{\%}$. (b) SSE.

Figure 6.26: Goodness of fit R^2, percentage error $E_{\%}$ and the Sum of Squares Due to Error SSE calculated for different methods.

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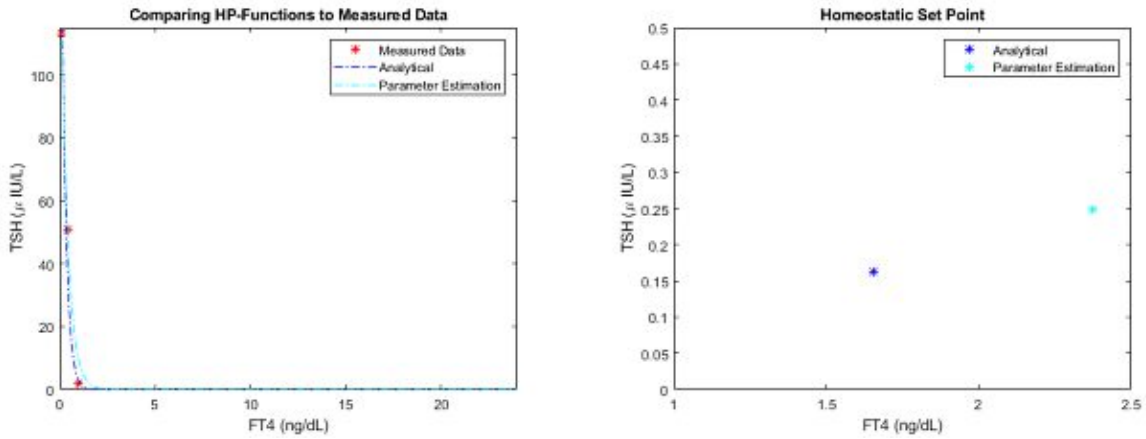
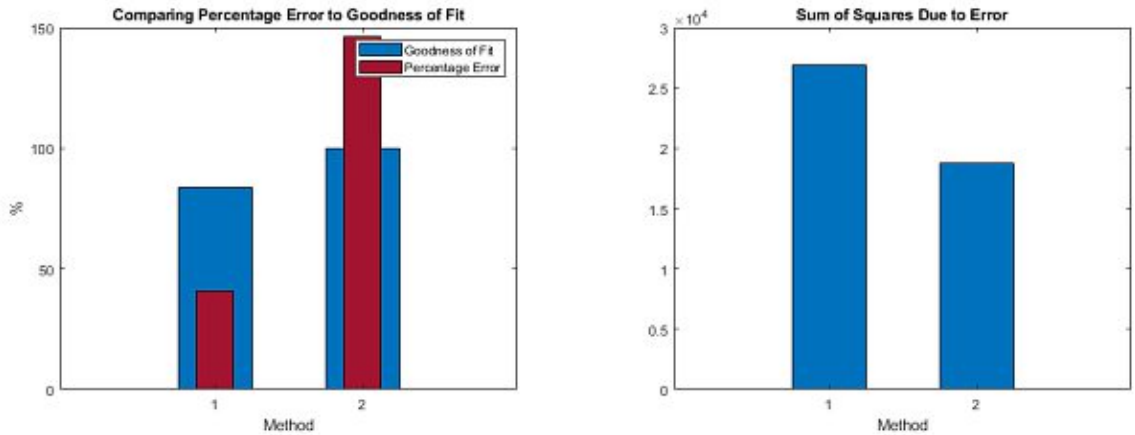
Patient 6



(a) HP functions. (b) Set points.

Figure 6.27: The HP functions and their set points calculated and plotted in Matlab with calculated and estimated $[S, \varphi]$.

From the data set in Table 6.6, it is apparent that Patient 6 suffers from hypothyroidism. As shown in Figure 6.27(a), the measured values of FT4 are located in a very small interval while the TSH values vary between 1 and 115. The HP function with calculated $[S, \varphi]$ values is a better fit according to Figure 6.27(a) and the percentage error $E_{\%}$ represented in Figure 6.28(a), while R^2 and SSE seem to indicate that the estimated HP function is a better fit. In a case like this it is advisable to use the plot of the HP function and choose the best fit with a graphical method.



(a) R^2 and $E_{\%}$. (b) SSE.

Figure 6.28: Goodness of fit R^2, percentage error $E_{\%}$ and the Sum of Squares Due to Error SSE calculated for different methods.

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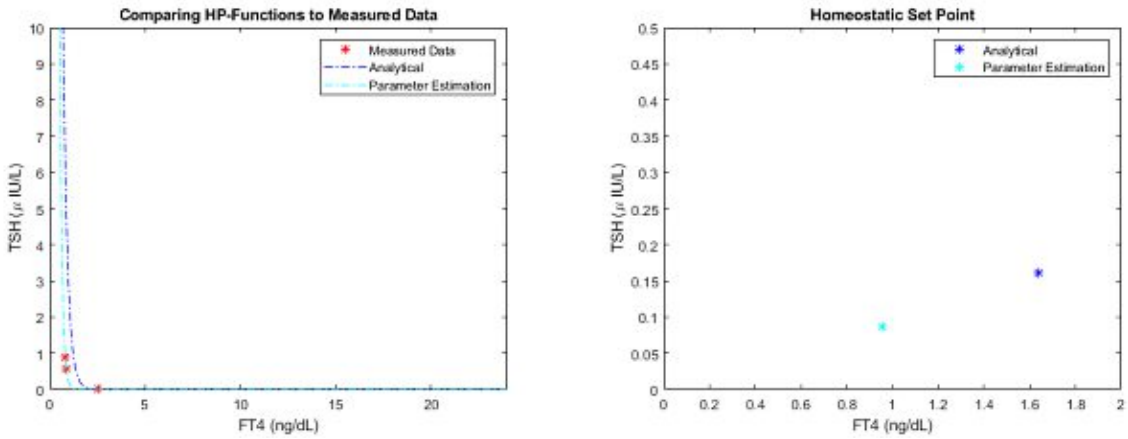
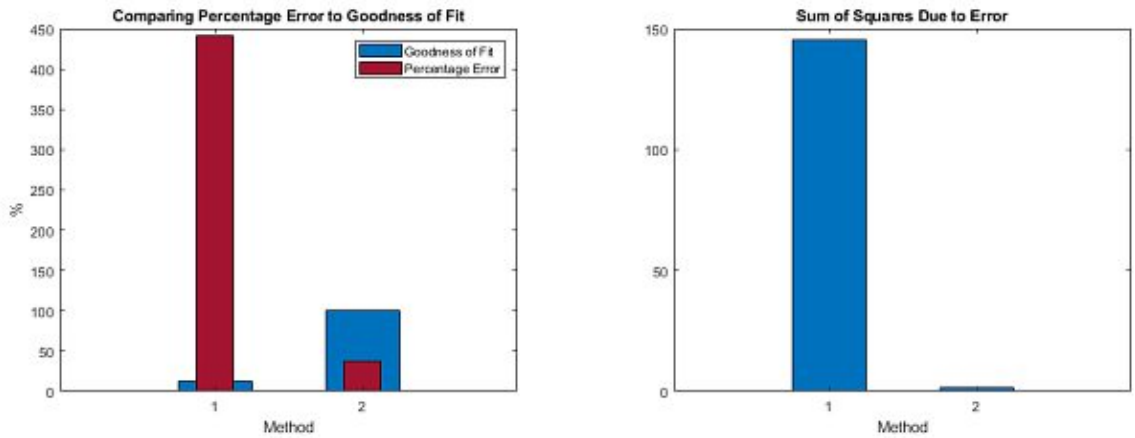
Patient 7



(a) HP functions. (b) Set points.

Figure 6.29: The HP functions and their set points calculated and plotted in Matlab with calculated and estimated $[S, \varphi]$.

The last patient with three measurement points was diagnosed with hyperthyroidism. Figure 6.29(a) shows that the estimated parameter set $[S, \varphi]$ leads to a better fit. This is also apparent in Figure 6.30, where the percentage error and the sum of squares due to error for the analytical method are very high and the goodness of fit is very low, while the opposite applies for the estimated parameter set. Furthermore, the difference between the two set points is significant.



(a) R^2 and $E_{\%}$. (b) SSE.

Figure 6.30: Goodness of fit R^2, percentage error $E_{\%}$ and the Sum of Squares Due to Error SSE calculated for different methods.

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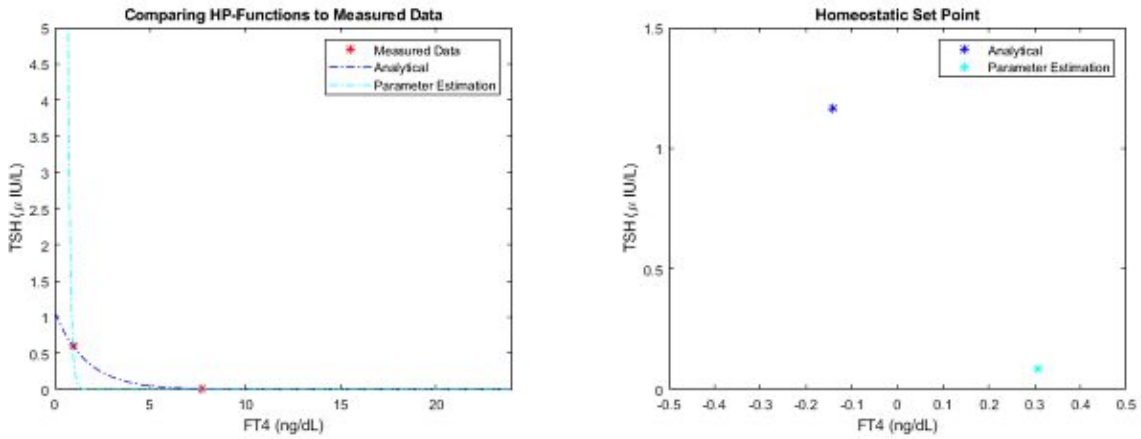
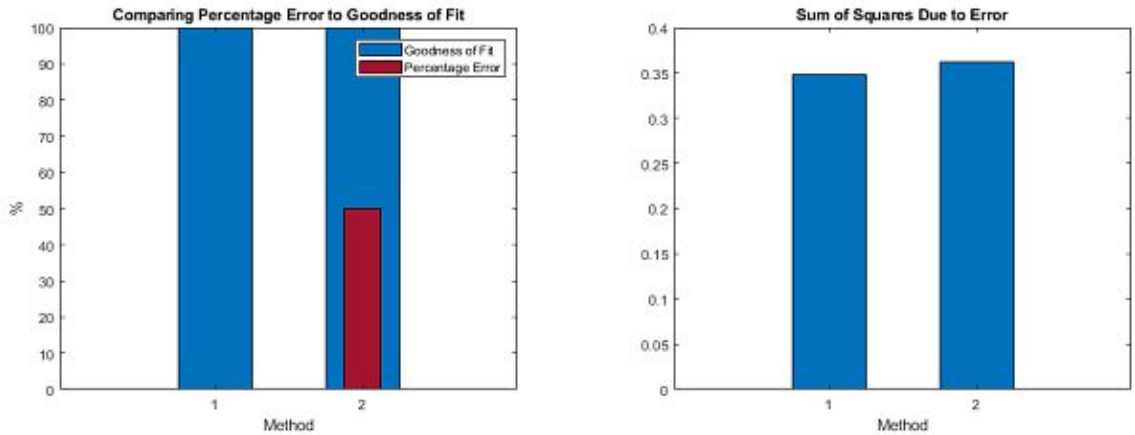
Patient 4



(a) HP functions. (b) Set points.

Figure 6.31: The HP functions and their set points calculated and plotted in Matlab with calculated and estimated $[S, \varphi]$.

The first patient were only two measurement points are available was diagnosed with hyperthyroidism. The measured TSH values are very low, which affects the HP function as can be seen in Figure 6.31(a). Consequently, the FT4 value of the calculated set point of the analytical HP function is located below zero. This result is not applicable because negative values are not possible. In this case the estimated function has a better fit, even though the percentage in Figure 6.32(a) is higher for the estimated function. However, the problem of the negative set point can be solved by conducting another TFT.



(a) R^2 and $E_{\%}$. (b) SSE.

Figure 6.32: Goodness of fit R^2, percentage error $E_{\%}$ and the Sum of Squares Due to Error SSE calculated for different methods.

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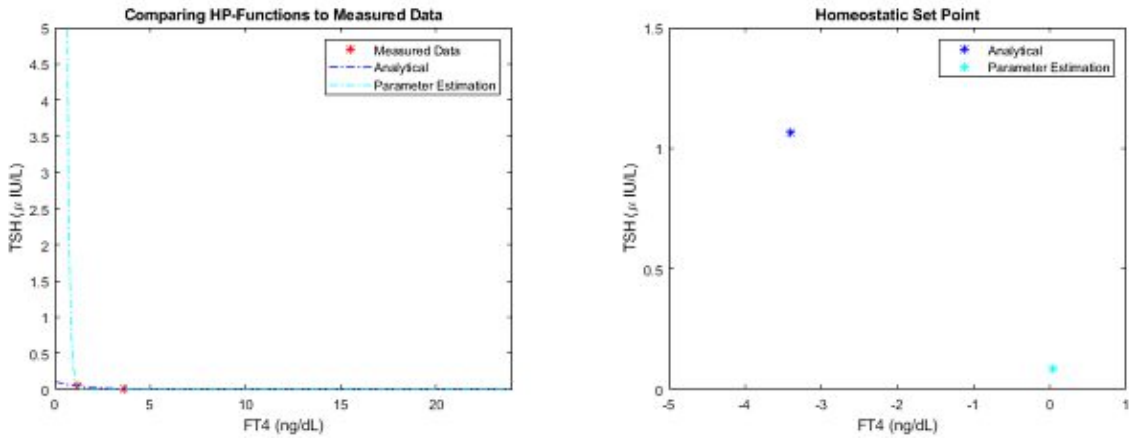
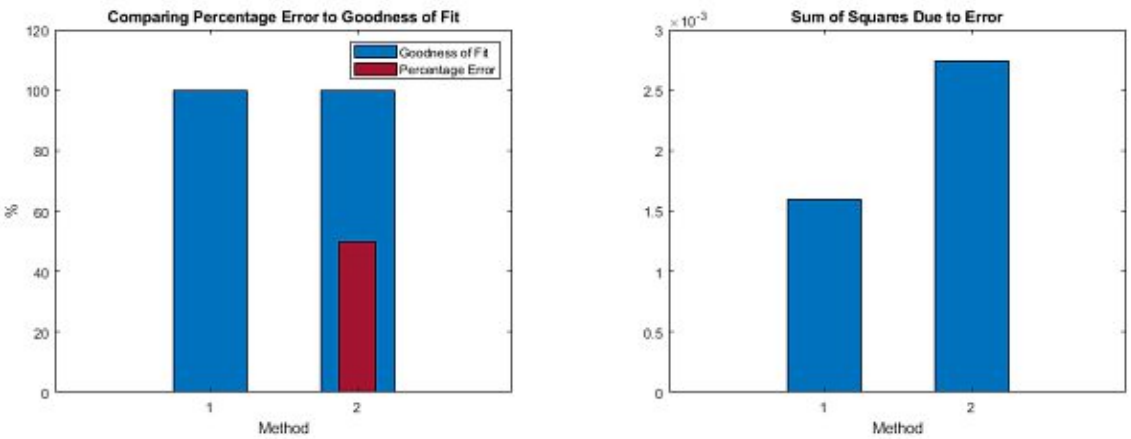
Patient 9



(a) HP functions. (b) Set points.

Figure 6.33: The HP functions and their set points calculated and plotted in Matlab with calculated and estimated $[S, \varphi]$.

Patient 9, who also suffers from hypothyroidism, possesses similar measurement results like Patient 4. In Figure 6.33(a) the characteristic form of the HP function is not observable when the parameter pair is calculated analytically because the measurement values define the function. The set point for the analytical HP function is located in the negative FT4 interval, as can be seen in Figure 6.33(b). Consequently, the estimated HP function is the better choice.



(a) R^2 and $E_{\%}$. (b) SSE.

Figure 6.34: Goodness of fit R^2, percentage error $E_{\%}$ and the Sum of Squares Due to Error SSE calculated for different methods.

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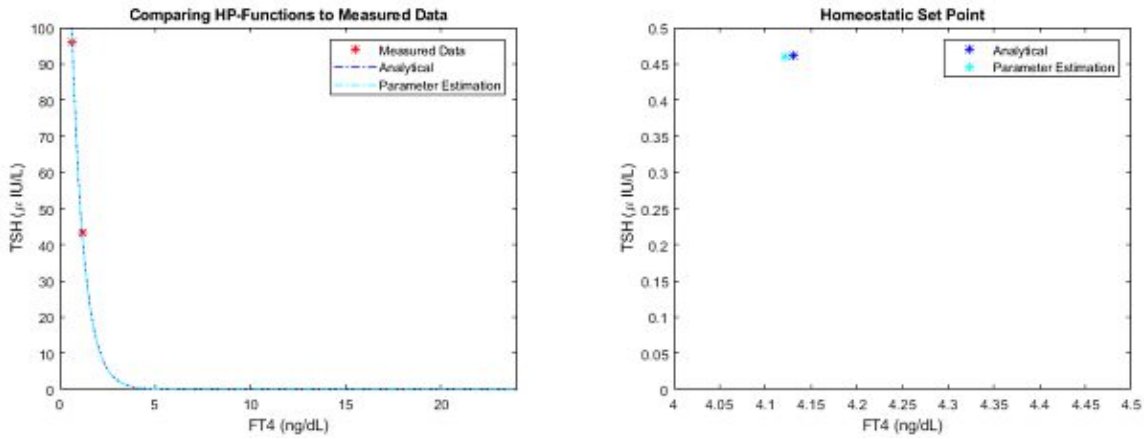
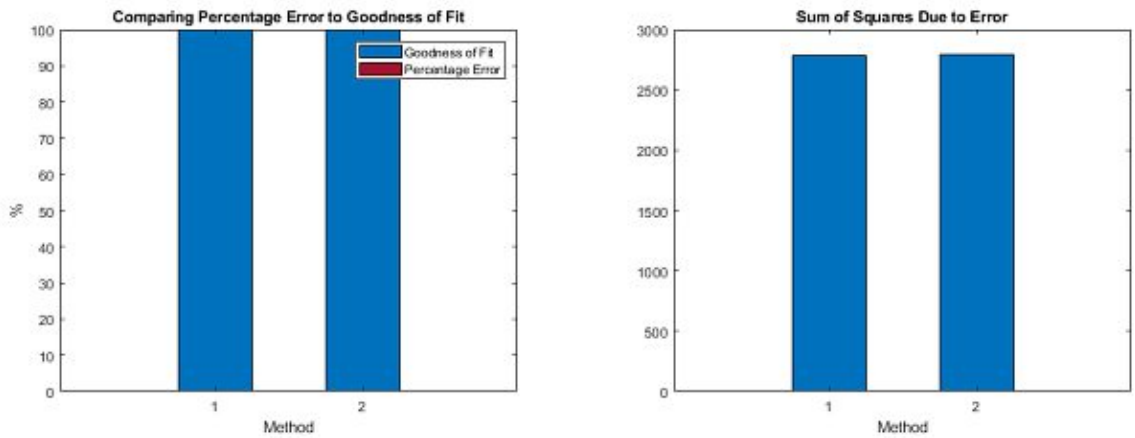
Patient 10



(a) HP functions. (b) Set points.

Figure 6.35: The HP functions and their set points calculated and plotted in Matlab with calculated and estimated $[S, \varphi]$.

The HP functions for Patient 10, who is diagnosed with hypothyroidism, as well as the calculated set points show that, in this case, both methods lead to equivalent results, as can be seen in Figure 6.35. This conclusion is supported by Figure 6.36, where the goodness of fit, the percentage error and the sum of squares due to error yield the same results for both methods.



(a) R^2 and $E_{\%}$. (b) SSE.

Figure 6.36: Goodness of fit R^2, percentage error $E_{\%}$ and the Sum of Squares Due to Error SSE calculated for different methods.

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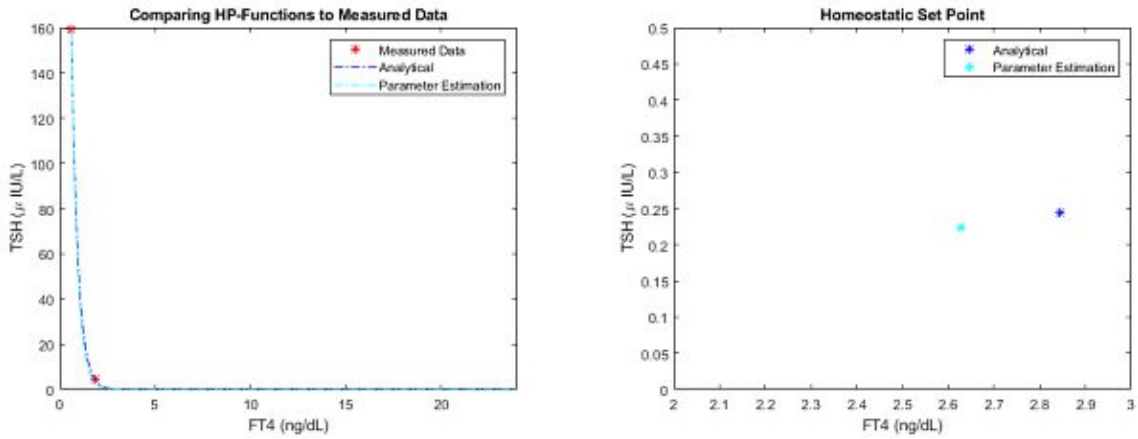
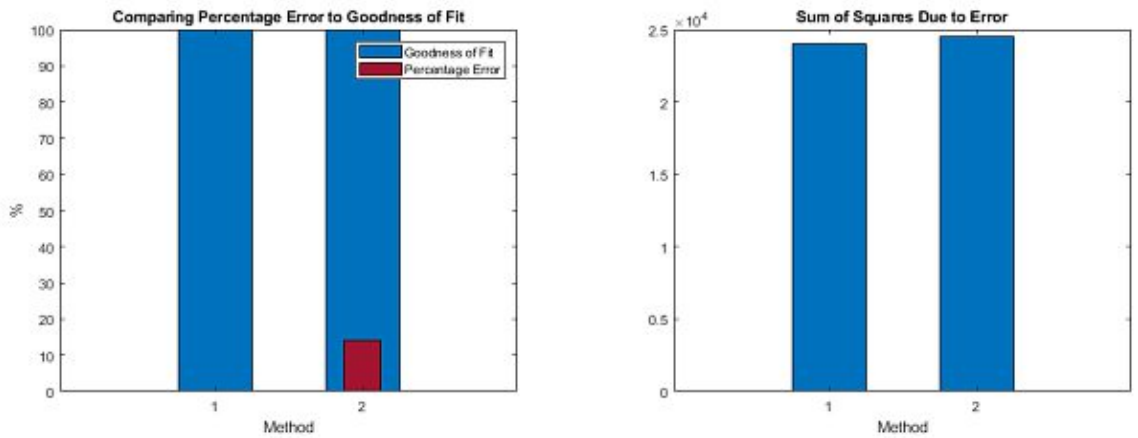
Patient 12



(a) HP functions. (b) Set points.

Figure 6.37: The HP functions and their set points calculated and plotted in Matlab with calculated and estimated $[S, \varphi]$.

Patient 12 is suffering from hypothyroidism and therefore it makes sense that the analysis shows similar results to Patient 10. It is apparent that the HP functions in Figure 6.37(a) are alike and therefore yield similar set points, shown in Figure 6.37(b). However, the percentage error of the estimated HP function is higher than the one from the analytical HP function.



(a) R^2 and $E_{\%}$. (b) SSE.

Figure 6.38: Goodness of fit R^2, percentage error $E_{\%}$ and the Sum of Squares Due to Error SSE calculated for different methods.

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In conclusion, it can be said that both methods can be used to illustrate the HP function of different patients. However, the quantity of measurement points and - more importantly- the interval of the measurement values, which rely on the type of thyroid disease, have the greatest impact on the HP function and its level of fitness. It became apparent that the estimated HP function yields better results than the analytical HP function, when the patient suffers from hyperthyroidism and the results of the TFTs are in a small interval. This can lead to a negative set point. However, for hypothyroid patients the performance of the analytical method is in some cases better and at least equal to the estimated method when the HP functions are compared. This can also be seen in the the percentage error when the HP functions appear to be equal.

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7. Conclusion and Outlook

Thyroid Systems Engineering is an interdisciplinary field. Therefore, in the beginning of this thesis, medical and mathematical knowledge was distributed to give the reader the information needed to understand and generate a mathematical model of the Hypothalamus-Pituitary-Thyroid axis. The mathematical model concentrates on the hormonal feedback loop. The examined loop connects the three organs in the following way: While the thyroid secrets T3 and T4, which have an inhibiting effect on the hypothalamus, the hypothalamus produces the hormone TRH, stimulating the pituitary to secret TSH, which in turn excites the production of T3 and T4, closing the loop.
The demands that were made on the model include the ability to simulate the hormonal feedback loop, precision and the ability to mimic nature. However, a model is always a simplified version of reality and its limitations have to be kept in mind accordingly. As a result, the definition of the model itself is a complex process when biological systems are involved. The first models of the system were precise dynamic model. The applicability of these models in medicine is not given, due to the model's complexity and restrictions caused by the measurability of some parameters.
The measurability of the different parameters leads us to the first question of why it is legitimate to neglect some of the involved hormones. The measurement of TRH is limited due to its half life and determining its concentration outside a research setting is close to impossible. Also, the hypothalamic or peripheral blood TRH levels are not affected by disease that alter the metabolic state like the levels of T4 and TSH. Consequently, despite its closeness to reality, models with a hypothalamic component have restricted applicability due to unknown quantities, for this reason the hypothalamus will not be an independent model component.
The main active hormone T3 is mainly derived from deiodination of T4, which facilitates the usage of T4 as a clinical surrogate parameter of thyroid hormone levels. Nowadays, to evaluate the thyroid function, the pituitary hormone TSH is used, because it is a very sensitive and robust indicator of the thyroid hormone status. Since the TSH level is dictated by the negative feedback action of the sum of FT3 and FT4, a contributory factor of FT3 is incorporated into the two structural parameters. This results in a simplified model concentrating on the hypothalamus-pituitary complex as a master regulator unit with FT4 as stimulus and TSH as response, which is able to determine solely features of the HP response.
The examined model, which is related to the steady state hormone currents and concentrations of the system, was discovered during the analysis of measured data individual by individual, conducted to find a relationship between [FT4] and [TSH]. It was appar-

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ent that the measurement points, except for some outliers in the data sets, resemble a hyperbolic, sigmoid or exponential decay function when connected. Thus, the discovered relationship can be represented by

$$[\mathrm{TSH}] = S\exp(-\varphi[\mathrm{FT4}]).$$

The parameter set $[S, \varphi]$ was calculated analytically and with the parameter estimator app of Simulink to enquire whether the method from Goede and Leow can be improved. The analysis of the goodness of fit and the percentage error showed that the analytical method has an advantage over the parameter estimator app, especially when only two sets of TFTs are available. In Chapter 4, other modelling attempts were discussed, which did not yield satisfactory results. In conclusion, it was not possible to improve the analytical method from Goede and Leow, which answers the question on whether it is possible.
The question of how it is possible to improve the health-related quality of life of many patients with a mathematical model leads us to the homeostatic set point theory. This theory is based on the observation that the normal levels of [FT4] and [TSH] fall within the region where the negative exponential function displays the greatest curvature. Consequently, it makes sense to investigate the point of maximum curvature further, especially since it is unique on the exponential function.
The point of maximum curvature gains in importance when its properties are investigated further, as was done in Chapter 5. In conclusion, the site of maximum curvature of the HP characteristic curve can be described as having a maximum sensitivity for [TSH] changes and a maximum stability of maintenance of [FT4]. Based on this it is logical that nature chose the point of maximum curvature as an effective method for homeostatic control purposes in biological systems.
Consequently, the point was labelled as the homeostatic set point. It can be calculated simply, using standard calculus. The idea of the homeostatic set point theory is that every human being has a unique euthyroid set point, where they do not suffer from any symptoms. Comparing the different calculation methods while varying the quantity of the measurement data showed that the calculated set points are located in a very small interval. Accordingly, it is possible to use this theory to calculate the optimally paired [FT4]-[TSH] values. Afterwards, health care providers should incorporate the calculated set point values into the treatment plan instead of targeting a normal reference interval.
However, the applicability of a medical model depends on its clinical validation and clinical studies before they receive regulatory approval and can be applied in practice. The validation process of a medical model relies on medical data obtained through studies, conducted explicitly to answer the research question or in sometimes existing data that matches the problem. The process to gain real life measurements is complicated by the local ethics commission, which is responsible for the protection of patient data, restrictions from different departments concerning data exchange and last but not least, if conducting a new medical study is not possible, a lot of research is needed to find a study providing datasets that fits the requirements of the clinical validation process.
In this thesis the validation of the HP function was done with data sets, which were obtained from a study conducted at the Medical University of Vienna. The study is called *Effects of thyroid function on phosphodiester concentrations in skeletal muscle and liver: An in vivo NMRS study* and had the objective to measure the actions of peripheral thyroid hormones on PM and PL tissue concentration. The longitudinal, prospective pilot

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study gathered measurement data from nine patients with hyperthyroidism and four patients with hypothyroidism. The provided data can be found in two tables in Appendix E, where Table E.1 covers the measurements of patients with hyperthyroidism and Table E.2 represents the measurement data from patients with hypothyroidism.
The study states that the TSH and FT4 levels were measured at the central laboratory of the Medical University of Vienna according to standard laboratory methods, in this case with ECLIA was used. The measuring inaccuracy for TSH is 4% with a sensitivity of 0.01μIU/ml and the measuring inaccuracy for FT4 is between 5% and 7% with a sensitivity of 0.02ng/dl. The blood sample has to arrive at the laboratory within three hours and blood samples from external senders have to be centrifuged and only the serum should be sent to the laboratory. The sample for the laboratory has to consist of 0.3ml serum to get valid results.
However, it was not possible to validate the set point theory with the provided data sets, because no reference set points exist to validate the calculated set points. For this case, a new study specific to the research question would have been required, where the set point of a healthy HP loop is known. Since one research question of this thesis was to improve the HP function, the resulting set points of the different functions are calculated and compared in Chapter 6.
For the validation process the patients $1, 4, 6, 7, 9, 10$ and 11 were chosen. The other data sets were rejected, because there was only one measurement or in the case of two hyperthyroid patients the values of the TSH level were below the sensitivity level of the laboratory test yielding invalid results. Besides the HP function and the set points, also the goodness of fit R^2, the percentage error $E_{\%}$ and the sum of squares due to error SSE were compared. Aside from that, the estimation of the parameter set $[S, \varphi]$ were conducted with the Simulink estimation app using the initial values $S = 1500$ and $\varphi = 0.5$ to provide equal conditions for each estimation.
It was possible to validate the usage of both methods for different patients. During the validation process, the question of whether it is possible to improve the HP function of Goede and Leow arose again. It became apparent that the quantity of measurement points and - more importantly - the interval of the measurement values, which rely on the type of thyroid disease, have the greatest impact on the HP function and its level of fitness.
When the patient suffers from hyperthyroidism, leading to low levels of TSH (and in addition the results of the TFTs are located in a small interval), the estimated HP function yielded better results than the analytical HP function. Above all, the FT4 component of the set point of the analytical HP function was below zero, which is an unrealistic result. However, for hypothyroid patients the performance of the analytical method is in some cases better and at least equal to the estimated method when the HP functions are compared. Differences in the performance of the two methods can especially be found in the level of the the percentage error, which is higher for the estimated HP function.
In conclusion, it can be said that the validation process was a success. Though it should be kept in mind that the validation was done with a small data set consisting only of 7 patients and further testing is still needed. In addition, medical software has to be approved by the regulatory authorities of a country before it is licensed for use in practice. For a licence, trials with the software should be conducted also, to show the software's performance in practice and its impact on the life of the patient.

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The presented model can improve the diagnosis and therapy of thyroid disease, if it is used correctly and has been approved. However, the model does not only impact endocrinology but also shows how mathematical models can be used to improve diagnostics and treatment plans in other medical fields. As was mentioned in the beginning of this thesis, individualised medicine is on the rise and often depends on mathematical models, which can be adapted to each patient.
Moreover, the way this model was developed also demonstrates that in some cases it is wise to neglect the physiological background to a certain extent and analyse the measurement data. Based on these findings, it can be concluded that the application of mathematical models in medical practice is still in its infancy and shouldn't be restricted by the urge to unnecessarily complicate the model for realities sake. The current research and its results are groundbreaking in many regards and will, I am sure, lead to fascinating and important scientific and medical advances in the future, improving the life of many patients.

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Appendices

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Appendix A

Primal Matlab Code

```
%-------------------------------------------------------------
%----------------Measured Points [FT4, TSH]----------------
%-------------------------------------------------------------
clearvars;
p1 = [9, 7.84];
p2 = [10, 3.63];
p3 = [12, 0.7];
p4 = [14, 0.21];
Sample = [p1;p2;p3;p4];
%-------------------------------------------------------------
%--------------Calculate S and phi Analytically------------
%-------------------------------------------------------------
phi1 = (1/(p1(1,1)-p2(1,1)))*log(p2(1,2)/p1(1,2));
phi2 = (1/(p2(1,1)-p3(1,1)))*log(p3(1,2)/p2(1,2));
phi3 = (1/(p3(1,1)-p4(1,1)))*log(p4(1,2)/p3(1,2));

phi = (phi1 + phi2 + phi3)/3;

S1 = p1(1,2)* exp(phi*p1(1,1));
S2 = p2(1,2)* exp(phi*p2(1,1));
S3 = p3(1,2)* exp(phi*p3(1,1));
S4 = p4(1,2)* exp(phi*p4(1,1));

S = (S1 + S2+ S3 + S4)/4;

%-------------------------------------------------------------
%--------------Calculate and Plot HP Function--------------
%-------------------------------------------------------------
stepsize = 0.1;
FT4 = [0.1:stepsize:30];

```

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```
TSH = S .* exp(-phi.* FT4);

figure()
plot(Sample(:,1),Sample(:,2),'r*')
hold on
plot(FT4, TSH, 'c'), axis([0 24 0 10])
xlabel('FT4 (pmol/L)')
ylabel('TSH (mU/L)')
legend('measured data', 'calculated curve')

%-------------------------------------------------------------
%---------------Evaluating Goodness of Fit-----------------
%-------------------------------------------------------------
TSHmean = sum(TSH)/length(TSH);
poi = Sample(:,1)./stepsize; %poi = point of interest
calcTSH = [TSH(poi)];
measTSH = Sample(:,2);
SSR = norm(measTSH-TSHmean, 2)^2;
SST = norm(calcTSH-TSHmean,2)^2;

Rsq = SSR/SST;
formatSpec = 'R^2 is %4.2f %%.';
fprintf(formatSpec,Rsq *100);

%-------------------------------------------------------------
%---------------Calculate and Plot Set Point---------------
%-------------------------------------------------------------
setpoint = [log(phi.*S.*sqrt(2))./phi; 1./(phi.*sqrt(2))];

figure()
plot(p1(1,1), p1(1,2),'rx')
hold on
plot(p2(1,1), p2(1,2),'rx')
hold on
plot(p3(1,1), p3(1,2),'rx')
hold on
plot(p4(1,1), p4(1,2),'rx')
hold on
plot(setpoint(1,1), setpoint(2,1),'b*')
hold on
plot(FT4, TSH), axis([0 24 0 10])
title('homeostatic set point')
xlabel('FT4 (pmol/L)')
ylabel('TSH (mU/L)')

%-------------------------------------------------------------
```

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```
%------Use Parameter Estimator to Calculate S and phi------
%-----------------------------------------------------------
in = [9; 10; 12; 14];
out = [7.84; 3.63; 0.7; 0.21];
tsout = timeseries(out, in);

estS= 4723.1; % estimated S
estphi = 0.71398; % estimated phi
estFT4 = [0.1:stepsize:30];
TSHE =  estS .* exp(-estphi.* estFT4);

%-----------------------------------------------------------
%---------------Evaluating Goodness of Fit-----------------
%-----------------------------------------------------------
TSHmeanE = sum(TSHE)/length(TSHE);
poiE = Sample(:,1)./stepsize; %poi = point of interest
calcTSHE = [TSHE(poiE)];
measTSHE = Sample(:,2);
SSR_E = norm(measTSHE-TSHmeanE, 2)^2;
SST_E = norm(calcTSHE-TSHmeanE,2)^2;
Rsq_E = SSR_E/SST_E;
formatSpec = 'R^2 is %4.2f %%.';
fprintf(formatSpec,Rsq_E *100);

%-----------------------------------------------------------
%---------------Calculate and Plot Set Point---------------
%-----------------------------------------------------------
estsetpoint = [log(estphi.*estS.*sqrt(2))./estphi;...
    1./(estphi.*sqrt(2))];

figure()
plot(p1(1,1), p1(1,2),'rx')
hold on
plot(p2(1,1), p2(1,2),'rx')
hold on
plot(p3(1,1), p3(1,2),'rx')
hold on
plot(p4(1,1), p4(1,2),'rx')
hold on
plot(estsetpoint(1,1), estsetpoint(2,1),'b*')
hold on
plot(estFT4, TSHE), axis([0 24 0 10])
title('homeostatic set point')
xlabel('FT4 (pmol/L)')
ylabel('TSH (mU/L)')
```

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Appendix B

Matlab Code Used to Calculate and Compare the Goodness of Fit for Analytical Method

```
% ----------------Comparing Goodness of fit----------------
% -----Different HP curves were calculated and compared----
% ------------------------------------------------------------
% --------------------used data set-------------------------
clearvars;
p1 = [9, 7.84];
p2 = [10, 3.63];
p3 = [12, 0.7];
p4 = [14, 0.21];

stepsize = 0.1;
FT4 = (0.1:stepsize:30);
% --------------------empty vector--------------------------
Rsqvec= zeros(4,1);
Pevec = zeros(4,1);
Setpointvec = zeros(4,2);
% ------------------------------------------------------------
% ------First methode using calculation of S and phi-------
% ----------------with 4 measurement points----------------
% ------------------------------------------------------------
Sample1 = [p1;p2;p3;p4];
phi1 = (1/(p1(1,1)-p2(1,1)))*log(p2(1,2)/p1(1,2));
phi2 = (1/(p2(1,1)-p3(1,1)))*log(p3(1,2)/p2(1,2));
phi3 = (1/(p3(1,1)-p4(1,1)))*log(p4(1,2)/p3(1,2));
fphi = (phi1 + phi2 + phi3)/3;

calcS = Sample1(:,2).*exp(fphi.*Sample1(:,1));
```


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```
S1 = sum(calcS)/length(calcS);

% --------------Calculate TSH and Set Point----------------
TSH1 = S1 .* exp(-fphi.* FT4);
setpoint1 = [log(fphi.*S1.*sqrt(2))./fphi;...
    1./(fphi.*sqrt(2))];
Setpointvec(1,:) = setpoint1;

TSHmean = sum(TSH1)/length(TSH1);
poi = Sample1(:,1)./stepsize; %poi = point of interest
calcTSH = [TSH1(poi)];
measTSH = Sample1(:,2);
% --------------------Goodness of fit----------------------
SSR = norm(measTSH-TSHmean)^2;
SST = norm(calcTSH-TSHmean)^2;
SSE1 = norm(calcTSH-measTSH)^2;
Rsq = SSR/SST;
Rsqvec(1,1) = Rsq;
formatSpec = 'R^2 is %4.2f %%.';
fprintf(formatSpec,Rsq *100);
% --------------------percentage error----------------------
pe1 = sum(abs(calcTSH'-measTSH)./measTSH)/length(measTSH);
Pevec(1,1)= pe1;
% ----------------------------------------------------------
% ----------------with 2 measurement points----------------
% ----------------------------------------------------------
Sample2 = [p1; p3];
sphi = (1/(p1(1,1)-p3(1,1)))*log(p3(1,2)/p1(1,2));

calcS = Sample2(:,2).*exp(sphi.*Sample2(:,1));
S2 = sum(calcS)/length(calcS);

% --------------Calculate TSH and Set Point----------------
TSH2 = S2 .* exp(-sphi.* FT4);
setpoint2 = [log(sphi.*S2.*sqrt(2))./sphi;...
    1./(sphi.*sqrt(2))];
Setpointvec(2,:) = setpoint2;

TSHmean = sum(TSH2)/length(TSH2);
poi = Sample1(:,1)./stepsize; %poi = point of interest
calcTSH = [TSH2(poi)];
measTSH = Sample1(:,2);
% --------------------Goodness of fit----------------------
SSR = norm(measTSH-TSHmean)^2;
SST = norm(calcTSH-TSHmean)^2;
SSE2 = norm(calcTSH-measTSH)^2;
```

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```
Rsq = SSR/SST;
Rsqvec(2,1) = Rsq;
formatSpec = 'R^2 is %4.2f %%.';
fprintf(formatSpec,Rsq *100);
% --------------------percentage error----------------------
pe2 = sum(abs(calcTSH'-measTSH)./measTSH)/length(measTSH);
Pevec(2,1)= pe2;
% ------------------------------------------------------------
% ----------------with 2 measurement points----------------
% ------------------------------------------------------------
Sample3 = [p2; p4];
tphi = (1/(p2(1,1)-p4(1,1)))*log(p4(1,2)/p2(1,2));

calcS = Sample3(:,2).*exp(tphi.*Sample3(:,1));
S3 = sum(calcS)/length(calcS);

% --------------Calculate TSH and Set Point----------------
TSH3 = S3 .* exp(-tphi.* FT4);
setpoint3 = [log(tphi.*S3.*sqrt(2))./tphi;...
    1./(tphi.*sqrt(2))];
Setpointvec(3,:) = setpoint3;

TSHmean = sum(TSH3)/length(TSH3);
poi = Sample1(:,1)./stepsize; %poi = point of interest
calcTSH = [TSH3(poi)];
measTSH = Sample1(:,2);
% --------------------Goodness of fit----------------------
SSR = norm(measTSH-TSHmean)^2;
SST = norm(calcTSH-TSHmean)^2;
SSE3 = norm(calcTSH-measTSH)^2;
Rsq = SSR/SST;
Rsqvec(3,1) = Rsq;
formatSpec = 'R^2 is %4.2f %%.';
fprintf(formatSpec,Rsq *100);
% --------------------percentage error----------------------
pe3 = sum(abs(calcTSH'-measTSH)./measTSH)/length(measTSH);
Pevec(3,1)= pe3;
% ------------------------------------------------------------
% ----------------with 3 measurement points----------------
% ------------------------------------------------------------
Sample4 = [p1; p2; p4];
fphi1 = (1/(p1(1,1)-p2(1,1)))*log(p2(1,2)/p1(1,2));
fphi2 = (1/(p2(1,1)-p4(1,1)))*log(p4(1,2)/p2(1,2));
fophi = (fphi1+fphi2)/2;

calcS = Sample4(:,2).*exp(fophi.*Sample4(:,1));
```

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```
S4 = sum(calcS)/length(calcS);

% --------------Calculate TSH and Set Point----------------
TSH4 = S4 .* exp(-fophi.* FT4);
setpoint4 = [log(fophi.*S4.*sqrt(2))./fophi;...
    1./(fophi.*sqrt(2))];
Setpointvec(4,:) = setpoint4;

TSHmean = sum(TSH4)/length(TSH4);
poi = Sample1(:,1)./stepsize; %poi = point of interest
calcTSH = [TSH4(poi)];
measTSH = Sample1(:,2);
% --------------------Goodness of fit----------------------
SSR = norm(measTSH-TSHmean)^2;
SST = norm(calcTSH-TSHmean)^2;
SSE4 = norm(calcTSH-measTSH)^2;
Rsq = SSR/SST;
%adjRsq = 1-SSE*3/(SST*(4-300));
Rsqvec(4,1) = Rsq;
formatSpec = 'R^2 is %4.2f %%.';
fprintf(formatSpec,Rsq *100);
% --------------------percentage error----------------------
pe4 = sum(abs(calcTSH'-measTSH)./measTSH)/length(measTSH);
Pevec(4,1)= pe4;
% ------------------------------------------------------------
% -------------------------plot---------------------------
% ------------------------------------------------------------
figure()
plot(Sample1(:,1),Sample1(:,2),'r*')
hold on
plot(FT4, TSH1, 'b-.'),
plot(FT4, TSH2, 'c-.'),
plot(FT4, TSH3, 'g-.'),
plot(FT4, TSH4, 'm-.'), axis([0 24 0 10])
xlabel('FT4 (pmol/L)')
ylabel('TSH (mU/L)')
legend('Measured Data', 'Using All Points',...
    'Using p1 and p3', 'Using p2 and p4',...
    'Using p1, p2 and p4')
title('Comparing HP-Functions to Measured Data')

figure()
x = [1 2 3 4];
w1 = 0.5;
bar(x,Rsqvec.*100,w1,'FaceColor',[0 0.4470 0.7410]),
w2 = .25;
```

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```
hold on
bar(x,Pevec.*100,w2,'FaceColor',[0.6350 0.0780 0.1840])
hold off
xlabel('Dataset')
ylabel('%')
legend('Goodness of Fit', 'Percentage Error')
title('Comparing Percentage Error to Goodness of Fit')

figure()
x = [1 2 3 4];
w1 = 0.5;
bar(x,[SSE1, SSE2, SSE3, SSE4],w1,'FaceColor',[0 0.4470
   0.7410])
xlabel('Dataset')
ylabel('')
title('Sum of Squares Due to Error')

figure()
plot(setpoint1(1,1),setpoint1(2,1),'b*')
hold on
plot(setpoint2(1,1),setpoint2(2,1),'c*')
hold on
plot(setpoint3(1,1),setpoint3(2,1),'g*')
hold on
plot(setpoint4(1,1),setpoint4(2,1),'m*'), axis([11.5 12 0.5
   1.5])
xlabel('FT4 (pmol/L)')
ylabel('TSH (mU/L)')
legend('Using All Points','Using p1 and p3', 'Using p2 and p4
   ',...
    'Using p1, p2 and p4')
title('Homeostatic Set Point')
```

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Appendix C

Matlab Code Used to Calculate and Compare the Goodness of Fit for Estimated Method

```
% ----------------Comparing Goodness of fit----------------
% -----Different HP curves were calculated and compared----
% ---------------------------------------------------------
% --------------------used data set-------------------------
clearvars;
p1 = [9, 7.84];
p2 = [10, 3.63];
p3 = [12, 0.7];
p4 = [14, 0.21];

stepsize = 0.1;
FT4 = (0.1:stepsize:30);
% --------------------empty vector-------------------------
Rsqvec= zeros(4,1);
Pevec = zeros(4,1);
Setpointvec = zeros(4,2);
% ---------------------------------------------------------
% ----Second methode using Simulink Parameter Estimator----
% ----------------with 4 measurement points----------------
% ---------------------------------------------------------
Sample1 = [p1;p2;p3;p4];
fphi = 0.717122792679264;
S1 = 4859.97799066342;

% --------------Calculate TSH and Set Point----------------
TSH1 = S1 .* exp(-fphi.* FT4);
setpoint1 = [log(fphi.*S1.*sqrt(2))./fphi;...
```


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```
    1./(fphi.*sqrt(2))];
Setpointvec(1,:) = setpoint1;

TSHmean = sum(TSH1)/length(TSH1);
poi = Sample1(:,1)./stepsize; %poi = point of interest
calcTSH = [TSH1(poi)];
measTSH = Sample1(:,2);
% --------------------Goodness of fit----------------------
SSR = norm(measTSH-TSHmean)^2;
SST = norm(calcTSH-TSHmean)^2;
SSE1 = norm(calcTSH-measTSH)^2;
Rsq = SSR/SST;
Rsqvec(1,1) = Rsq;
formatSpec = 'R^2 is %4.2f %%.';
fprintf(formatSpec,Rsq *100);
% --------------------percentage error----------------------
pe1 = sum(abs(calcTSH'-measTSH)./measTSH)/length(measTSH);
Pevec(1,1)= pe1;
% ------------------------------------------------------------
% ----------------with 2 measurement points----------------
% ------------------------------------------------------------
Sample2 = [p1; p3];
sphi = 1.17947924307032;
S2 = 297939.247720394;

% --------------Calculate TSH and Set Point----------------
TSH2 = S2 .* exp(-sphi.* FT4);
setpoint2 = [log(sphi.*S2.*sqrt(2))./sphi;...
    1./(sphi.*sqrt(2))];
Setpointvec(2,:) = setpoint2;

TSHmean = sum(TSH2)/length(TSH2);
poi = Sample1(:,1)./stepsize; %poi = point of interest
calcTSH = [TSH2(poi)];
measTSH = Sample1(:,2);
% --------------------Goodness of fit----------------------
SSR = norm(measTSH-TSHmean)^2;
SST = norm(calcTSH-TSHmean)^2;
SSE2 = norm(calcTSH-measTSH)^2;
Rsq = SSR/SST;
Rsqvec(2,1) = Rsq;
formatSpec = 'R^2 is %4.2f %%.';
fprintf(formatSpec,Rsq *100);
% --------------------percentage error----------------------
pe2 = sum(abs(calcTSH'-measTSH)./measTSH)/length(measTSH);
Pevec(2,1)= pe2;
```


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```
% ------------------------------------------------------------
% ----------------with 2 measurement points----------------
% ------------------------------------------------------------
Sample3 = [p2; p4];
tphi = 0.648503542469559;
S3 = 2338.70097456389;

% --------------Calculate TSH and Set Point----------------
TSH3 = S3 .* exp(-tphi.* FT4);
setpoint3 = [log(tphi.*S3.*sqrt(2))./tphi;...
    1./(tphi.*sqrt(2))];
Setpointvec(3,:) = setpoint3;

TSHmean = sum(TSH3)/length(TSH3);
poi = Sample1(:,1)./stepsize; %poi = point of interest
calcTSH = [TSH3(poi)];
measTSH = Sample1(:,2);
% --------------------Goodness of fit---------------------
SSR = norm(measTSH-TSHmean)^2;
SST = norm(calcTSH-TSHmean)^2;
SSE3 = norm(calcTSH-measTSH)^2;
Rsq = SSR/SST;
Rsqvec(3,1) = Rsq;
formatSpec = 'R^2 is %4.2f %%.';
fprintf(formatSpec,Rsq *100);
% --------------------percentage error---------------------
pe3 = sum(abs(calcTSH'-measTSH)./measTSH)/length(measTSH);
Pevec(3,1)= pe3;
% ------------------------------------------------------------
% ----------------with 3 measurement points----------------
% ------------------------------------------------------------
Sample4 = [p1; p2; p4];
fophi = 0.766940114056511;
S4 = 7786.05426270902;

% --------------Calculate TSH and Set Point----------------
TSH4 = S4 .* exp(-fophi.* FT4);
setpoint4 = [log(fophi.*S4.*sqrt(2))./fophi;...
    1./(fophi.*sqrt(2))];
Setpointvec(4,:) = setpoint4;

TSHmean = sum(TSH4)/length(TSH4);
poi = Sample1(:,1)./stepsize; %poi = point of interest
calcTSH = [TSH4(poi)];
measTSH = Sample1(:,2);
% --------------------Goodness of fit---------------------
```

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```
SSR = norm(measTSH-TSHmean)^2;
SST = norm(calcTSH-TSHmean)^2;
SSE4 = norm(calcTSH-measTSH)^2;
Rsq = SSR/SST;
Rsqvec(4,1) = Rsq;
formatSpec = 'R^2 is %4.2f %%.';
fprintf(formatSpec,Rsq *100);
% --------------------percentage error----------------------
pe4 = sum(abs(calcTSH'-measTSH)./measTSH)/length(measTSH);
Pevec(4,1)= pe4;
% ------------------------------------------------------------
% -------------------------plot----------------------------
% ------------------------------------------------------------
figure()
plot(Sample1(:,1),Sample1(:,2),'r*')
hold on
plot(FT4, TSH1, 'b-.'),
plot(FT4, TSH2, 'c-.'),
plot(FT4, TSH3, 'g-.'),
plot(FT4, TSH4, 'm-.'), axis([0 24 0 10])
xlabel('FT4 (pmol/L)')
ylabel('TSH (mU/L)')
legend('Measured Data', 'Using All Points',...
    'Using p1 and p3', 'Using p2 and p4',...
    'Using p1, p2 and p4')
title('Comparing HP-Functions to Measured Data')

figure()
x = [1 2 3 4];
w1 = 0.5;
bar(x,Rsqvec.*100,w1,'FaceColor',[0 0.4470 0.7410]),
w2 = .25;
hold on
bar(x,Pevec.*100,w2,'FaceColor',[0.6350 0.0780 0.1840])
hold off
xlabel('Dataset')
ylabel('%')
legend('Goodness of Fit', 'Percentage Error')
title('Comparing Percentage Error to Goodness of Fit')

figure()
x = [1 2 3 4];
w1 = 0.5;
bar(x,[SSE1, SSE2, SSE3, SSE4],w1,'FaceColor',[0 0.4470
   0.7410])
xlabel('Dataset')
```

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```
ylabel('')
title('Sum of Squares Due to Error')

figure()
plot(setpoint1(1,1),setpoint1(2,1),'b*')
hold on
plot(setpoint2(1,1),setpoint2(2,1),'c*')
hold on
plot(setpoint3(1,1),setpoint3(2,1),'g*')
hold on
plot(setpoint4(1,1),setpoint4(2,1),'m*'), axis([11 12 0.5
   1.5])
xlabel('FT4 (pmol/L)')
ylabel('TSH (mU/L)')
legend('Using All Points','Using p1 and p3', 'Using p2 and p4
   ',...
    'Using p1, p2 and p4')
title('Homeostatic Set Point')
```

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Appendix D

Matlab Code Used for the Validation of Both Methods

```
% ----------------Comparing Goodness of fit----------------
% -----Different HP curves were calculated and compared----
% ---------------------------------------------------------
% --------------------used data set-------------------------
clearvars;
p1 = [0.81, 0.9];
p2 = [0.88, 0.58];
p3 = [2.5, 0.01];

Sample = [p1;p2;p3];
stepsize = 0.01;
FT4 = (0.01:stepsize:30);
% --------------------empty vector--------------------------
Rsqvec= zeros(2,1);
Pevec = zeros(2,1);
Setpointvec = zeros(2,2);
% ---------------------------------------------------------
% ------First methode using calculation of S and phi-------
% ----------------with 3 measurement points----------------
% ---------------------------------------------------------
phi1 = (1/(p1(1,1)-p2(1,1)))*log(p2(1,2)/p1(1,2));
phi2 = (1/(p2(1,1)-p3(1,1)))*log(p3(1,2)/p2(1,2));
fphi = (phi1 + phi2)/2;

calcS = Sample(:,2).*exp(fphi.*Sample(:,1));
S1 = sum(calcS)/length(calcS);

% --------------Calculate TSH and Set Point----------------
TSH1 = S1 .* exp(-fphi.* FT4);
```


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```
setpoint1 = [log(fphi.*S1.*sqrt(2))./fphi;...
    1./(fphi.*sqrt(2))];
Setpointvec(1,:) = setpoint1;

TSHmean = sum(TSH1)/length(TSH1);
poi = Sample(:,1)./stepsize; %poi = point of interest
calcTSH = [TSH1(poi)];
measTSH = Sample(:,2);
% --------------------Goodness of fit---------------------
SSR = norm(measTSH-TSHmean)^2;
SST = norm(calcTSH-TSHmean)^2;
SSE1 = norm(calcTSH-measTSH)^2;
Rsq = SSR/SST;
Rsqvec(1,1) = Rsq;
formatSpec = 'R^2 is %4.2f %%.';
fprintf(formatSpec,Rsq *100);
% --------------------percentage error----------------------
pe1 = sum(abs(calcTSH'-measTSH)./measTSH)/length(measTSH);
Pevec(1,1)= pe1;
% ----------------------------------------------------------
% ----Second methode using Simulink Parameter Estimator----
% ----------------with 3 measurement points----------------
% ----------------------------------------------------------
sphi = 8.179444594878275;
S2 = 695.1548502061010;
% --------------Calculate TSH and Set Point----------------
TSH2 = S2 .* exp(-sphi.* FT4);
setpoint2 = [log(sphi.*S1.*sqrt(2))./sphi;...
    1./(sphi.*sqrt(2))];
Setpointvec(2,:) = setpoint2;

TSHmean = sum(TSH2)/length(2);
poi = Sample(:,1)./stepsize; %poi = point of interest
calcTSH = [TSH2(poi)];
measTSH = Sample(:,2);
% --------------------Goodness of fit---------------------
SSR = norm(measTSH-TSHmean)^2;
SST = norm(calcTSH-TSHmean)^2;
SSE2 = norm(calcTSH-measTSH)^2;
Rsq = SSR/SST;
Rsqvec(2,1) = Rsq;
formatSpec = 'R^2 is %4.2f %%.';
fprintf(formatSpec,Rsq *100);
% --------------------percentage error----------------------
pe1 = sum(abs(calcTSH'-measTSH)./measTSH)/length(measTSH);
Pevec(2,1)= pe1;
```

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```
% ------------------------------------------------------------
% -------------------------plot----------------------------
% ------------------------------------------------------------
figure()
plot(Sample(:,1),Sample(:,2),'r*')
hold on
plot(FT4, TSH1, 'b-.'),
hold on
plot(FT4, TSH2, 'c-.'),axis([0 24 0 10])
xlabel('FT4 (ng/dL)')
ylabel('TSH (\mu IU/L)')
legend('Measured Data', 'Analytical',...
    'Parameter Estimation')
title('Comparing HP-Functions to Measured Data')

figure()
x = [1 2];
w1 = 0.5;
bar(x,Rsqvec.*100,w1,'FaceColor',[0 0.4470 0.7410]),
w2 = .25;
hold on
bar(x,Pevec.*100,w2,'FaceColor',[0.6350 0.0780 0.1840])
hold off
xlabel('Method')
ylabel('%')
legend('Goodness of Fit', 'Percentage Error')
title('Comparing Percentage Error to Goodness of Fit')

figure()
x = [1 2];
w1 = 0.5;
bar(x,[SSE1, SSE2],w1,'FaceColor',[0 0.4470 0.7410])
xlabel('Method')
ylabel('')
title('Sum of Squares Due to Error')

figure()
plot(setpoint1(1,1),setpoint1(2,1),'b*')
hold on
plot(setpoint2(1,1),setpoint2(2,1),'c*'), axis([0 2 0 0.5])
xlabel('FT4 (ng/dL)')
ylabel('TSH (\mu IU/L)')
legend('Analytical', 'Parameter Estimation')
title('Homeostatic Set Point')
```

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```
% ----------------Comparing Goodness of fit----------------
% -----Different HP curves were calculated and compared----
% ---------------------------------------------------------
% --------------------used data set------------------------
clearvars;
p1 = [0.95, 0.6];
p2 = [7.69, 0.01];

Sample = [p1;p2];
stepsize = 0.01;
FT4 = (0.01:stepsize:30);
% --------------------empty vector-------------------------
Rsqvec= zeros(2,1);
Pevec = zeros(2,1);
Setpointvec = zeros(2,2);
% ---------------------------------------------------------
% ------First methode using calculation of S and phi-------
% ----------------with 2 measurement points----------------
% ---------------------------------------------------------
fphi = (1/(p1(1,1)-p2(1,1)))*log(p2(1,2)/p1(1,2));

calcS = Sample(:,2).*exp(fphi.*Sample(:,1));
S1 = sum(calcS)/length(calcS);

% --------------Calculate TSH and Set Point----------------
TSH1 = S1 .* exp(-fphi.* FT4);
setpoint1 = [log(fphi.*S1.*sqrt(2))./fphi;...
    1./(fphi.*sqrt(2))];
Setpointvec(1,:) = setpoint1;

TSHmean = sum(TSH1)/length(TSH1);
poi = round(Sample(:,1)./stepsize); %poi = point of interest
calcTSH = [TSH1(poi)];
measTSH = Sample(:,2);
% --------------------Goodness of fit----------------------
SSR = norm(measTSH-TSHmean)^2;
SST = norm(calcTSH-TSHmean)^2;
SSE1 = norm(calcTSH-measTSH)^2;
Rsq = SSR/SST;
Rsqvec(1,1) = Rsq;
formatSpec = 'R^2 is %4.2f %%.';
fprintf(formatSpec,Rsq *100);
% --------------------percentage error----------------------
pe1 = sum(abs(calcTSH'-measTSH)./measTSH)/length(measTSH);
Pevec(1,1)= pe1;
```

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```
% ---------------------------------------------------------
% ----Second methode using Simulink Parameter Estimator----
% ----------------with 2 measurement points----------------
% ---------------------------------------------------------
sphi = 8.178982278687112;
S2 = 1421.547140189986;
% --------------Calculate TSH and Set Point----------------
TSH2 = S2 .* exp(-sphi.* FT4);
setpoint2 = [log(sphi.*S1.*sqrt(2))./sphi;...
    1./(sphi.*sqrt(2))];
Setpointvec(2,:) = setpoint2;

TSHmean = sum(TSH2)/length(2);
poi = round(Sample(:,1)./stepsize); %poi = point of interest
calcTSH = [TSH2(poi)];
measTSH = Sample(:,2);
% --------------------Goodness of fit----------------------
SSR = norm(measTSH-TSHmean)^2;
SST = norm(calcTSH-TSHmean)^2;
SSE2 = norm(calcTSH-measTSH)^2;
Rsq = SSR/SST;
Rsqvec(2,1) = Rsq;
formatSpec = 'R^2 is %4.2f %%.';
fprintf(formatSpec,Rsq *100);
% --------------------percentage error----------------------
pe1 = sum(abs(calcTSH'-measTSH)./measTSH)/length(measTSH);
Pevec(2,1)= pe1;
% ---------------------------------------------------------
% -------------------------plot----------------------------
% ---------------------------------------------------------
figure()
plot(Sample(:,1),Sample(:,2),'r*')
hold on
plot(FT4, TSH1, 'b-.'),
hold on
plot(FT4, TSH2, 'c-.'),axis([0 24 0 5])
xlabel('FT4 (ng/dL)')
ylabel('TSH (\mu IU/L)')
legend('Measured Data', 'Analytical',...
    'Parameter Estimation')
title('Comparing HP-Functions to Measured Data')

figure()
x = [1 2];
w1 = 0.5;
bar(x,Rsqvec.*100,w1,'FaceColor',[0 0.4470 0.7410]),
```


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```
w2 = .25;
hold on
bar(x,Pevec.*100,w2,'FaceColor',[0.6350 0.0780 0.1840])
hold off
xlabel('Method')
ylabel('%')
legend('Goodness of Fit', 'Percentage Error')
title('Comparing Percentage Error to Goodness of Fit')

figure()
x = [1 2];
w1 = 0.5;
bar(x,[SSE1, SSE2],w1,'FaceColor',[0 0.4470 0.7410])
xlabel('Method')
ylabel('')
title('Sum of Squares Due to Error')

figure()
plot(setpoint1(1,1),setpoint1(2,1),'b*')
hold on
plot(setpoint2(1,1),setpoint2(2,1),'c*'), axis([-0.5 0.5 0
   1.5])
xlabel('FT4 (ng/dL)')
ylabel('TSH (\mu IU/L)')
legend('Analytical', 'Parameter Estimation')
title('Homeostatic Set Point')
```

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Appendix E

Clinical Data for Validation

The following tables display the gathered data from the study *Effects of thyroid function on phosphodiester concentrations in skeletal muscle and liver: An in vivo NMRS study.*

Patient-Nr.	1st Measurement	2nd Measurement	3rd Measurement
1	[0.01, 4.80]	[4.92, 0.80]	[2.93, 1.06]
2	[0.01, 6.92]	[0.01, 2.49]	[0.01, 1.63]
3	[0.01, 7.70]	[0.01, 1.39]	[0.01, 2.43]
4	[0.01, 7.69]	[0.60, 0.95]	
7	[0.01, 2.50]	[0.58, 0.88]	[0.90, 0.81]
13	[0.01, 2.99]		
8	[0.01, 3.95]		
9	[0.01, 3.61]	[0.05, 1.19]	
11	[0.01, 7.70]		

Table E.1: Measurement data from nine patients with hyperthyroidism displayed in pairs of [TSH (μIU/mL), FT4 (ng/dL)].

Patient-Nr.	1st Measurement	2nd Measurement	3rd Measurement
5	[089.00, 0.66]		
6	[113.00, 0.11]	[01.93, 0.96]	[50.94, 0.43]
10	[096.00, 0.65]	[43.24, 1.17]	
12	[159.40, 0.60]	[04.44, 1.84]	

Table E.2: Measurement data from four patients with hypothyroidism displayed in pairs of [TSH (μIU/mL), FT4 (ng/dL)].

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