Mathematical Modeling and Dynamical Analysis of the Operation of the Hypothalamus - Pituitary - Thyroid (HPT) Axis in Autoimmune (Hashimoto's) Thyroiditis

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MATHEMATICAL MODELING AND DYNAMICAL ANALYSIS OF THE OPERATION OF THE HYPOTHALAMUS – PITUITARY – THYROID (HPT) AXIS IN AUTOIMMUNE (HASHIMOTO'S) THYROIDITIS

by

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ABSTRACT
MATHEMATICAL MODELING AND DYNAMICAL ANALYSIS OF THE OPERATION OF THE HYPOTHALAMUS – PITUITARY – THYROID (HPT) AXIS IN AUTOIMMUNE (HASHIMOTO'S) THYROIDITIS

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This thesis is a mathematical modeling study of the operation of the negative feedback control through the hypothalamus-pituitary- thyroid (HPT) axis in autoimmune (Hashimoto's) thyroiditis. Negative feedback control through the HPT axis is a mechanism in which the high levels of thyroid hormone; free thyroxine (FT4) in the blood inhibits the secretion of the pituitary hormone, thyroid stimulating hormone (TSH) into the blood. Similarly, the low levels of free thyroxine (FT4) sensed by the pituitary gland and then it secretes thyroid stimulating hormone (TSH) into the blood. Autoimmune (Hashimoto's) thyroiditis is a disease in which the immune system turns against the thyroid follicle cells and destroys them slowly for a long period of time. This in turn interrupts the operation of the negative feedback control, in fact, the HPT axis. The half-life of thyroid stimulating hormone (TSH) and free thyroxine (FT4) is one hour and seven days respectively in the blood. This implies that thyroid stimulating hormone (TSH) changes in a faster time scale than free thyroxine (FT4) both in the healthy and diseased thyroid gland. Thus, the operation of negative feedback control is at least in two different time scales. The normal reference range for TSH and FT4 is used in this thesis are$(0.4 - 2.5)\ mU/L$ and $(7 - 18)\ pg/mL$ respectively. In thyroid clinics, in general, physicians see three different kinds of patients with autoimmune (Hashimoto's) thyroiditis with or without goiter (enlarged thyroid gland).

i) Patients with euthyroidism (normal FT4 and TSH levels).
ii) Patients with subclinical hypothyroidism (normal FT4 but TSH above normal levels).
iii) Patients with overt (clinical) hypothyroidism (low FT4 and TSH above normal levels).

Usually patients with euthyroidism progress to subclinical hypothyroidism and then progress to overt hypothyroidism. This is a sequential event, but in some patients' cases, it is not true.

To describe the operation of the feedback control in autoimmune (Hashimoto's) thyroiditis, we developed a mathematical model in this thesis involving four clinical (state) variables, thyroid stimulating hormone (TSH), free thyroxine (FT4), anti-thyroid antibodies (TPOAb and TGAb), and the functional size of the thyroid gland (T). The first three variables are regularly measured in thyroid clinics to determine the function of negative feedback control and the status of the thyroid gland in autoimmune thyroiditis. The last variable is determined through relationships between the other three variables and is required for this work to accurately track the output of the gland. The problem of two different time scales is addressed using singularly perturbation theory. Also, the analysis of the mathematical model establishes stability and conditions under which the diseased state can be maintained the slow movement of the functioning of the negative feedback control toward the diseased state equilibrium.

In this thesis, the purpose of modeling the operation of negative feedback control is to describe the natural history of autoimmune (Hashimoto's) thyroiditis. This means to describe the natural course of euthyroidism, subclinical hypothyroidism or overt hypothyroidism for every

patient with autoimmune thyroiditis. Although, we have used four variables in modeling the feedback control through the HPT axis, the end product depends on the levels of thyroid stimulating hormone (TSH) and free thyroxine (FT4). In addition, the clinical chart is developed based on the levels of thyroid stimulating hormone (TSH) and time. To validate the model description, patient's dataset are employed in chapter 5. For this thesis, the dataset is obtained from Sicilian adult population, Italy through our clinical collaborator.

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LIST OF ABBREVIATIONS

HT – Hashimoto's Thyroiditis

AT – Autoimmune Thyroiditis

TSH – Thyroid Stimulating Hormone

T3 – Triiodothyronine (three iodine molecules attached to tyrosine molecules)

T4 – Thyroxine (four iodine molecules attached to tyrosine molecules)

FT4 – Free thyroxine

TPO – Thyroid peroxidase (enzyme)

TG – Thyroglobulin (protein)

TPOAb – Thyroid peroxidase Anti-thyroid antibodies

TGAb – Thyroglobulin Anti-thyroid antibodies

TSHR – Thyroid Stimulating Hormone Receptors

TBG – Thyroglobulin Binding Globulin

T – The functional size of the Thyroid gland

1d – One dimensional

2d – Two dimensional

3d – Three dimensional

4d – Four dimensional

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INTRODUCTION TO A MEDICAL PROBLEM

The thyroid stimulating hormone (TSH), a key hormone, is synthesized and secreted into the blood by the pituitary gland. In response to TSH, the thyroid gland secretes thyroxine (T4) into the blood, in which 99% of T4 binds to proteins in blood serum such as thyroxine binding globulin, albumin and the remaining 1% circulates as free thyroxine (FT4). This in turn inhibits the secretion of TSH in the pituitary gland. This mechanism is called a negative feedback control through the hypothalamus-pituitary-thyroid (HPT) axis. The existence of the negative feedback control is to maintain the adequate levels of free thyroxine (FT4) in the blood, which, in the clinical setting, referred to a set point of the HPT axis. The set point of the HPT axis varies greater between individuals than in the same individual sampled repeatedly over time (Andersen et al. 2002).

Autoimmune (Hashimoto's) thyroiditis is a complex disorder in which the immune system attacks the thyroid gland with both proteins and immune cells such as T cells, and cytokines for long periods. More precisely, as one aspect of autoimmune thyroiditis, the immune system produces proteins (thyroid peroxidase antibodies, TPOAb and thyroglobulin antibodies, TGAb) against the thyroid follicle cell membrane proteins (thyroid peroxidase, TPO and thyroglobulin, TG) in the blood. These proteins (TPOAb and TGAb) induce thyroid follicle cell lysis by binding with TPO and TG respectively. Thus, autoimmune thyroiditis interrupts the normal thyroid operation and eventually disrupts feedback control. Consequently, one develops symptoms (like, goiter),signs (like, hyperactivity), and some clinical conditions, like, euthyroidism (normal FT4and TSH levels in the blood), subclinical hypothyroidism (normal FT4, but TSH above normal levels),overt (clinical) hypothyroidism (underactive thyroid gland- low FT4 levels and TSH above normal levels) or hashitoxicosis (transient hyper to hypothyroidism). Hashitoxicosis is a life-threatening abnormal clinical condition. It is one of the rare presentations of autoimmune thyroiditis, approximately 5% of all autoimmune thyroiditis patients.

From the clinical viewpoint, the presence of anti-thyroid antibodies in blood serum is the hallmark of this disease and has been considered as a diagnostic tool of autoimmune thyroiditis in healthy and asymptomatic individuals. Their presence in normal individuals is the risk factor for overt hypothyroidism and also believed that, antibodies induce thyroid damage for long periods until hypothyroidism is clinically become evident. As a result, the set point of the HPT axis changes for long periods along with damaging thyroid gland. So, in this thesis, a mathematical model will be constructed to track the changes of the set point, in other words, the development of overt hypothyroidism. On the other hand, the absence of anti-thyroid antibodies is strong evidence against autoimmune thyroiditis (Shoenfeld et al 2007). Therefore, individuals with anti-thyroid antibodies (TPOAb and TGAb) considered being autoimmune (Hashimoto's) patients in the clinical setting.

In clinical practice, in general, physicians see three different kinds of patients with autoimmune (Hashimoto's) thyroiditis with or without goiter.

a) Patients with euthyroidism (normal FT4 and TSH levels).
b) Patients with subclinical hypothyroidism (normal FT4 but TSH above normal levels).
c) Patients with overt (clinical) hypothyroidism (low FT4 and TSH above normal levels).

Usually patients with euthyroidism progress to subclinical hypothyroidism and then progress to overt hypothyroidism. This is a sequential event in most patients. But, euthyroidism in some patients may persist for many years even lifelong. This means to say that overt hypothyroidism is not an obligated evolution of the autoimmune thyroiditis. Similarly subclinical hypothyroidism in some patients may persist for many years even lifelong. It means to say that again overt hypothyroidism is not an obligated evolution of the autoimmune thyroiditis. Overt hypothyroidism is the end stage of the course of autoimmune thyroiditis where patients need thyroid hormone replacement treatment. Levothyroxine (synthetic free thyroxine) is commonly used drug as thyroid hormone replacement. The half-life of thyroid stimulating hormone (TSH)

and free thyroxine (FT4) is one hour and seven days respectively in the blood. This implies that TSH changes in a faster time scale than FT4. Thus, the operation of negative feedback control is at least in two different time scales.

To describe the operation of negative feedback control, that is, the HPT axis, in autoimmune thyroiditis, patient-specific mathematical model is required and will be developed in this thesis. The model is patient-specific since all autoimmune patients are different. Modeling is done with ordinary differential (rate) equations. Moreover the problem of two different time scales is addressed using singularly perturbation theory.

Outline of Thesis

Chapter 1 provides the background materials required for this thesis, such as, physiology of the thyroid gland, the HPT axis, autoimmune thyroiditis, and clinical staging. In autoimmune thyroiditis, the clinical evidence suggests that the hypothalamus-pituitary function is intact and the thyroid-pituitary function is interrupted. That is, to say that one part of the operation of negative feedback control is normal and the other part is abnormal (see Figure 1.3). To observe this phenomenon in the dataset, we presented several graphs showing the abnormal behavior of the HPT axis. As a final result of the Chapter 1, we established the patient-specific clinical staging criterion for patients with autoimmune thyroiditis. The staging criterion has three general cases, namely euthyroidism → euthyroidism, euthyroidism → subclinical hypothyroidism and euthyroidism → subclinical → clinical hypothyroidism.

Chapter 2 provides a four dimensional (4d) non-linear model for patients with autoimmune thyroiditis. To construct this model, we used four clinical variables. Out of four, three of them are clinically measurable quantities, thyroid stimulating hormone (TSH), free thyroxine (FT4), and anti-thyroid antibodies (TPOAb and TGAb) and the other, the functional

size of the thyroid gland (T) [1] can be measured through relationships with other three variables. The model takes the form of a singularly perturbed initial value problem due to the presence of at least two-time scales. Singular perturbation theory is the main tool for the analysis of a model, which is elaborated in this chapter. The model has eleven parameters - some parameters are available from the literature and most are estimated through the equilibrium arguments. But three parameters, namely, k_5, k_6 and k_7 turned out to be the governing parameters of the system. Through further investigation in Chapter 4, we noticed that k_7 is an important parameter and with that we could describe the dynamics of all autoimmune thyroiditis patients.

Chapter 3 provides the special case of the four dimensional (4d) non-linear model. That is, investigate the 4d model in the aspect of absence of anti-thyroid chronic immune response. This resulted in the three dimensional (3d) non-linear model. We found that 3d model has one steady state (set point of the HPT axis) in the positive octant, in fact, inside the trapping rectangular box. In Chapter 3, we referred the steady state to euthyroid state and the arguments for constructing rectangular box have elaborated. Through linear stability analysis, we proved that euthyroid state is always stable in the box. Using singular perturbation arguments, we showed that all solutions are attracted to this euthyroid (steady) state.

Chapter 4 provides the analysis of the dynamics of the 4d model. We constructed a rectangular box in 4d space such that the euthyroid (steady) state is trapped inside the box. Furthermore, through local stability analysis, we found that k_7 is an important parameter in the system, in fact, a bifurcation parameter. As k_7 changes from zero to the larger range of values, we obtained two critical values, one k_7^* and another k_7^{**}. When $k_7 < k_7^*$, the box contains only one steady state which is the euthyroid state and the diseased steady state located in the negative orthant. As k_7 changes in the system, the diseased steady state moves towards the box and when $k_7 = k_7^*$, the diseased steady state merges with the euthyroid (steady) state. When $k_7 > k_7^*$, the

[1]The clinical variable T means the functional size of the thyroid gland as opposed to the thyroid size

diseased steady state emerges into the rectangular box and becomes stable – we showed that through local stability analysis. But when k_7 reaches the value of k_7^{**}, free thyroxine (FT4) concentrations goes below the lower reference range 7 pg/mL which means clinical hypothyroidism. Therefore, we conclude that, when k_7 is below the critical value k_7^* , patients with autoimmune thyroiditis do not develop the consequences of autoimmune thyroiditis. When k_7 is in between k_7^* and up to k_7^{**}, patients with autoimmune thyroiditis develop subclinical hypothyroidism. When k_7 is greater than k_7^{**}, then patients develop subclinical hypothyroidism and eventually become clinical hypothyroidism.

Chapter 5 implements the results of Chapter 4 through clinical staging criterion described in Chapter 1. This in turn results in clinical staging charts. It is the main result of this thesis. The charts are mainly based on TSH because test results of TSH are more reliable in autoimmune thyroiditis. We have given the discussion of how one could use the clinical chart in thyroid clinics for all autoimmune patients to describe the natural history and to predict the eventual TSH value of particular patient. In addition to clinical chart, we presented the dynamics in two dimensional (TSH versus FT4) phase plane parameterized by k_7. Also, we validated the mathematical model using patient's dataset in order to verify the model's ability to describe the natural history of autoimmune thyroiditis.

CHAPTER 1 – BACKGROUND MATERIAL

In this chapter, we introduce the background material required for this mathematical modeling work. The background material mainly focuses on the operation of the hypothalamus-pituitary-thyroid (HPT) axis both under healthy and diseased thyroid gland. The healthy thyroid gland preserves the normal operation of the HPT axis while the diseased thyroid gland interrupts the normal operation of the HPT axis with the thyroid unable to produce adequate amounts of thyroid hormones. The diseased thyroid gland in this work is the consequence of autoimmune (Hashimoto's) thyroiditis.

1.1 Introduction to Thyroid Physiology

General Anatomy

The thyroid is the largest endocrine gland, located in front of the neck just below the larynx or above the collar bones (see Figure 1.1). The thyroid gland is butterfly-shaped and consists of two wings, called lobes and attached through a middle part called the isthmus. In healthy state, the normal adult thyroid gland weighs approximately 10 - 20 g and each lobe of thyroid measures about 2.5 - 4 cm in length, 1.5 - 2 cm in width, and 1 - 1.5 cm in thickness, but in diseased state, the thyroid weight and size are variable (see Greenspan and Gardner, 2001).

Function of the Thyroid Gland

Thyroid stimulating hormone (TSH) is synthesized and secreted into blood from the pituitary gland. In response to TSH, the thyroid gland produces triiodothyronine (T3) and thyroxine (T4) and secretes them into the blood. This is the main function of the thyroid gland. These hormones in turn control the metabolic rate in human body. The main thyroid hormone is thyroxine (T4), which contains four iodine molecules, whereas triiodothyronine (T3) contains three iodine

molecules. In the healthy state, the daily thyroid gland production of T4 is about $100\ \mu g$. The daily production of T3 is about $30\ \mu g$, of which about 20% is produced by the thyroid gland and 80% by deiodination of T4 in extra thyroidal tissues (Bunevicius et al. 1999). T4 molecules are active longer in the blood than T3, but T3 molecules are more biologically active at the cellular level. Further, approximately 99.98% of T4 in blood binds with plasma proteins (such as thyroxine binding globulin (TBG) (60-75%), prealbumin/transthyretin (15-30%), and albumin (~10%)(Werner et al. 2005; Robbins and Rall, 1960)) and circulates as bound T4 - the remaining 0.02% circulates as free (unbound) T4. Similarly, (~ 99.7%) of T3 in blood binds with plasma proteins, specifically, TBG. In the clinical setting, free T4 and TSH are considered to be the most reliable measure to determine the status of the thyroid gland (Surks et al. 1990). Their normal reference ranges for adult populations for free T4 and TSH are usually between $(7-18)\ pg/mL$ and $(0.4-4.0)\ mU/L$ (Baloch et al. 2003) respectively. Note that TSH upper reference limit is $4.0\ mU/L$. But TSH upper reference limit is a controversial subject, so nowadays, researchers suggest to decrease the upper normal range of TSH to $2.5\ mU/L$ (Surks et al. 2005) due to the clinical observation that patients with TSH between 2.5 to $4\ mU/L$ have increased risk of progression to hypothyroidism (underactive thyroid gland).

Thyroid Follicles

The functional unit in the thyroid gland is the follicle. The follicle consists of thyroid follicle cells surrounding colloid. Colloid is the central region in the follicle, and contains the raw materials for thyroid hormone production such as thyroglobulin (TG), iodine, thyroid-peroxidase (TPO), and other proteins. The microscopic findings indicate that the shapes and sizes of the follicles are irregular (Greenspan and Gardner, 2001), but for modeling purposes, one typically assume follicles are roughly spherical in shape (Degon et al. 2004) (see Figure 1.2). But, in our model, the shape and size do not matter. Furthermore, blood vessels, lymphatics, parafollicular cells (C-

cells) and fibrous tissues all surround the follicles and they are completely covered by a network of capillaries.

Thyroid Follicle Cells

The follicle cells controls the secretion of thyroid hormones in blood based on the level of stimulation from the pituitary gland by TSH. The follicle cells become columnar (i.e., elongated and rectangular) when stimulated by TSH and are flat when resting. These follicle cells are the victims in Hashimoto's thyroiditis. Charles et al. (1996) noted that the size of the follicles depends on the number of follicle cells and the amount of colloid. If the follicle cells die under the diseased state, then it causes the size of the follicles to shrink significantly and results in decreased thyroid hormone production from that follicle.

In the diseased state, the immune cells infiltration a region of the thyroid gland and their destructive action makes that region non functional or not active. Thus, the affected region is unable to respond to TSH and produce thyroid hormones. Therefore, for our work, we consider the active part of the gland (the functional part of the thyroid gland) which is able to respond to TSH and produce thyroid hormones. The size of this active part of the gland we call the functional size of the thyroid gland.

1.2 The Hypothalamus - Pituitary - Thyroid (HPT) Axis

If the blood levels of free thyroid hormones (T3 and T4) become too low (below a set point), then the hypothalamus senses the reduction of free thyroid hormones and secretes thyrotrophic releasing hormone (TRH) which stimulates the pituitary gland to make and secrete TSH into the blood. This in turn stimulates thyroid follicle cells to secrete thyroid hormones (T3 and T4) into the blood. If the blood levels of free thyroid hormones become too high, and then the hypothalamus and/or pituitary gland senses the high levels of free thyroid hormones and reduces its secretion of TRH and TSH, which in turn slows down the production of thyroid hormones in

thyroid follicle cells. This type of control mechanism is a negative feedback loop the control through hypothalamus - pituitary - thyroid axis (see Figure 1.3) (Brown-Grant, 1957; Zoeller et al. 2007).

The principal purpose of the existence of the HPT axis is to maintain the set point of TSH, and free thyroid hormones (T3 and T4) within the normal reference range. The set point and normal reference range changes from person to person and it depends on many factors such as age, gender, genes, body weight and race (Panicker et al. 2008). For instance, in children, the HPT axis undergoes progressive maturation and modulation until puberty resulting in continuous changes in the set point and normal reference range (Nelson et al. 1993). In general, children have higher TSH and lower thyroid hormone levels. On the other hand, higher TSH levels and lower thyroid hormones are reported in the elderly people (Surks and Hollowell, 2007), suggesting that elderly people have different normal set points for TSH and free thyroid hormones (T3 andT4). In general, in healthy people, variability in TSH, and free thyroid hormones (T3 and T4), is greater between individuals than in the same individual sampled repeatedly over time, suggesting that different people have different set points for the function of HPT axis (Andersen et al. 2002).

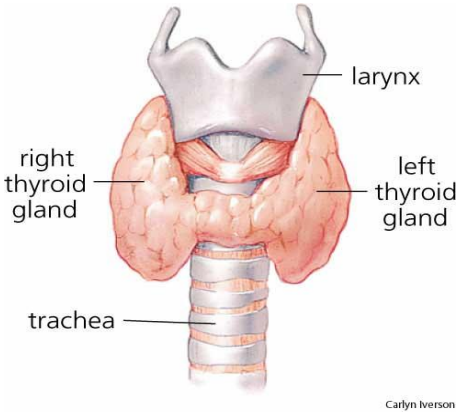


Figure 1.1: The Thyroid Gland

(see http://nursingninjas.com/nursingschoolblog/2010/05/medical-surgical-rotation/functions-of-thyroid-hormones/)

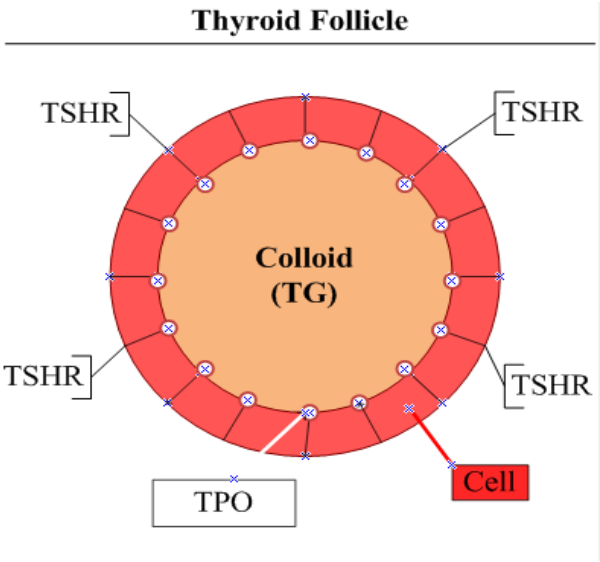


Figure 1.2: This figure shows a typical follicle from the thyroid gland. It is roughly spherical in shape with normal follicle cells, thyroid receptors (TSHR), thyroid peroxidase (TPO) and thyroglobulin (TG) in the colloid.

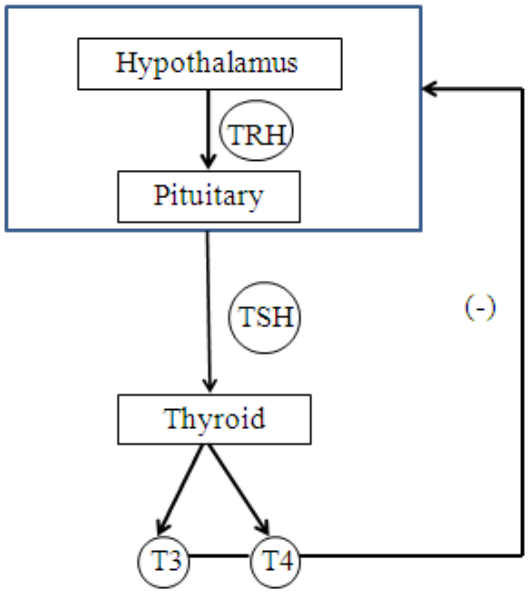


Figure 1.3: This figure shows the HPT axis. The sign (-) indicates the existence of a negative feedback loop. Note that free thyroid hormones (T3 and T4) are sensed by the pituitary gland and the hypothalamus.

1.3 Hypothyroidism and its Types

Hypothyroidism is an underactive thyroid gland, which means the thyroid gland does not produce enough thyroid hormones to stay in the reference range (Silverman and William, 1997; Ord, 1878). The result of hypothyroidism is the slowing down many bodily functions, most importantly, metabolism. Hypothyroidism is also known as myxoedema. For the hypothyroidism condition, the patients are treated clinically with synthetic thyroxine pills, called Levothyroxine, which they must take every day for their entire life (Papapetrou et al. 1972). There are three main types of hypothyroidism, namely primary, secondary and tertiary, which result from the dysfunction of the thyroid gland, the pituitary, and the hypothalamus respectively.

Primary Hypothyroidism

An individual is said to have primary hypothyroidism if the thyroid gland does not produce enough of thyroid hormones, but the pituitary and hypothalamus are normal. Primary hypothyroidism occurs mainly due to autoimmune (Hashimoto's) thyroiditis or due to lack of dietary iodine. We discuss primary hypothyroidism in detail in next section after the introduction of autoimmune (Hashimoto's) thyroiditis.

Secondary Hypothyroidism

An individual is said to have secondary hypothyroidism if the pituitary gland does not produce enough of TSH which stimulates the thyroid gland to produce the thyroid hormones, but the thyroid and hypothalamus are normal. Secondary hypothyroidism occurs in pituitary tumors, radiation and after surgery.

Tertiary Hypothyroidism

An individual is said to have tertiary hypothyroidism if the hypothalamus does not secret thyrotropin releasing hormone (TRH) which stimulates the pituitary gland to produce TSH, but the thyroid and pituitary are normal.

Symptoms

The general symptoms of hypothyroidism are fatigue, drowsiness, forgetfulness, difficulty with learning, dry and itchy skin, puffy face, constipation, sore muscles, weight gain and heavy menstrual flow. The symptoms are variable among patients; so the only way to know for sure whether the patient has hypothyroidism is via blood tests. We will discuss the thyroid function test below.

1.4 Autoimmune (Hashimoto's) Thyroiditis

Hashimoto's thyroiditis or autoimmune thyroiditis, also called chronic lymphocytic thyroiditis, is caused by the abnormal immune response to components of the thyroid gland by means of both the cellular and humoral response (Chistiakov, 2005). This cellular and humoral immune response results in production of T-cells, helper T-cells, B-cells, killer cells, macrophages, and cytokines specifically against the thyroid gland (Dayan and Daniels, 1996). These immune cells then infiltrate into the thyroid gland and induce damage to thyroid follicles, more precisely follicle cells, size and thereby structure, which in turn interferes with the production of thyroid hormones, triiodothyronine (T3) and thyroxine (T4). Autoimmune thyroiditis is characterized as a complex disease due to a strong involvement of genetic and environmental contributors to the pathogenesis of disease (Burek, 2009). The pathogenesis of autoimmune thyroiditis remains unclear to this date and the subject of controversy, although there are many animal models published since the mid-1950s demonstrating autoimmune thyroiditis, with different hypothetical mechanisms (Nishikawa and Iwasaka, 1999; Rose and Burek, 2000; Kong, 2007).

The B-cells responsible for the humoral antibody response produce anti-thyroid antibodies, mainly thyroid peroxidase and thyroglobulin antibodies (TPOAb and TGAb), which in turn attack the specific thyroid proteins, thyroid peroxidase and thyroglobulin (TPO and TG) in the thyroid tissue. Although only one aspect of the immune response, in the clinical setting, these anti-thyroid antibodies are considered to be the bio-markers of the level of the immune response activity in autoimmune thyroiditis (McLachlan and Rapoport, 1995; Fink and Hintze, 2010). Usually, these anti-thyroid antibodies are measured from the patient blood serum in order to evaluate the level of intensity of immune response to the thyroid gland.

Overall, autoimmune thyroiditis induces a slow destruction of the thyroid gland over many years, which results in the disruption of function of the HPT axis that controls the thyroid physiology. As a result of this progressive destruction of the thyroid, autoimmune thyroiditis patients may experience various clinical forms, such as euthyroidism, subclinical or clinical hypothyroidism and/or hashitoxicosis (transient form characterized as from hypothyroidism to hyperthyroidism or from hyperthyroidism to hypothyroidism – experienced by some at the onset of the autoimmune thyroiditis, according to some researchers) (Mazokopakis, 2007) with or without diffuse goiter (an enlarged thyroid gland).

Autoimmune thyroiditis is more common in women than in men and it can occur at any age (including, children and adults), but usually shows up in middle-aged women. In 1912, Hashimoto, a Japanese physician (Hashimoto, 1912), described this disease with hypothyroidism and goiter (symptom), referred to a classical form. However, some patients do not develop a goiter but have hypothyroidism – atrophic form; some patients do develop a goiter but switch to atrophic form as the disease progress over time. Little is known about the connection, if any, between two forms. Researcher's suspect that apoptosis (programmed cell death) plays an important role at the late stage of the disease that causes atrophy (Kotani et al. 1997). Overall, a complicated phenomenon involved in the course of the disease that makes the size of the thyroid gland unpredictable.

Primary Hypothyroidism

Primary hypothyroidism results from the destruction of thyroid gland by autoimmune thyroiditis. Some people develop this type of hypothyroidism quickly over a few months and some develop it slowly over several years – this different behavior depends on the aggression of the immune response to the thyroid gland (Tunbridge et al. 1981; Karmisholt et al. 2011).

Primary hypothyroidism is a graded phenomenon in which the thyroid status changes from euthyroid (non-diseased) state to subclinical hypothyroidism and may progress to the overt hypothyroidism state. For this transient situation, TSH values are used to monitor the disease progression (see Hall and Evered, 1973). We will now give the clinical definitions of subclinical and overt hypothyroidism based on TSH and free T4 values.

Subclinical (Mild) Hypothyroidism

Elevated blood levels of TSH($> \ (2.5 - \ 4)\ mU/L$ and $< \ 10\ mU/L$), but normal free T4($7 - 18$) pg/mL.

Clinical (Overt) Hypothyroidism

Elevated blood levels of TSH($> \ (2.5 - \ 4)\ mU/L$) with low free T4 ($< \ 7\ pg/mL$).

Goiter

Goiter means an enlarged thyroid gland. It can be treated by a thyroid hormone replacement, Levothyroxine (Schmidt et al. 2008). There is no consensus explanation available for the appearance of goiter in Hashimoto's thyroiditis, some hypothesize that either that high blood levels of TSH induce a goiter or inflammation of thyroid gland induce a goiter.

Hashitoxicosis

Hashitoxicosis is an autoimmune thyroid condition in which the patient experiences transient hyperthyroid episodes. According to some researchers, Hashitoxicosis is most likely to be encountered in the early stages of autoimmune (Hashimoto's) thyroiditis (Mazokopakis, 2007).

Since the chronic immune response is activated against the thyroid gland at early stages of Hashimoto thyroiditis, the thyroid gland releases its stores of thyroid hormones (both T3 and T4) and the raw materials for thyroid hormone production into the blood. This sudden burst of thyroid hormones, especially T3, is responsible for the transient symptoms of hyperthyroidism.

1.5 Clinical Tests

Thyroid function tests are designed to identify the diseased states (hypothyroidism and hyperthyroidism) from the healthy state of the thyroid gland (Dunlap, 1990). Here, we will discuss a few tests that are necessary for our study.

TSH Test

Thyroid stimulating hormone (TSH) is measured through the simple blood test by using a modern method of non-isotope immunometric assay (IMA) with highly enhanced sensitivity and specificity. The IMA is capable of achieving a functional sensitivity ≤ 0.02 mU/L, which is the necessary sensitivity for detecting the full range of TSH values observed between hypothyroidism and hyperthyroidism (Baloch et al. 2003). As stated before, the normal reference range for TSH for adult population is $(0.4 - (2.5 - 4.0))\ mU/L$. If TSH test results in values that are outside the reference range, then thyroid status is not stable. Suppose thyroid status is stable and hypothalamic – pituitary function is normal, then serum TSH test is more sensitive and preferred test than free T4 test (as discussed below) for detecting subclinical (mild) thyroid hormone excess or deficiency. Therefore, the TSH measurement is considered to be the main tool for the detection of various degrees of diseased states (such as subclinical hypothyroidism and hyperthyroidism).

Free T4 Test

Thyroxine (T4) in blood is available in two forms. One is bound T4 and the other free T4. There is approximately 99.98% bound T4 and 0.02% free T4 in the blood. There are some physical methods exist to separate free T4 from bound T4 that are equilibrium dialysis, ultra filtration and gel filtration. Unfortunately, they are technically demanding, inconvenient to use and relatively expensive for routine clinical laboratory to use. There are other methods that most clinical laboratories employ, that is, indexes and immunoassay, to get an estimate of free T4. The Index method requires two separate measurements - one is a total hormone measurement and the other is an assessment of thyroid binding protein concentration using an immunoassay for thyroxine-binding globulin (TBG) or a T4 uptake test called thyroid hormone binding ratio (THBR) (Baloch et al. 2003).

Anti-thyroid Antibodies (TPOAb and TGAb) Test

The anti-thyroid antibodies (TPOAb and TGAb) can be measured either by hemagglutination assay or radioimmunoassay (RIA). The summary of these assays are discussed in (Merrill, 1998). These methods have been commonly used in thyroid clinics to quantify the anti-thyroid antibodies.

Ultrasound

Ultrasound can detect thyroiditis because a hypoechoic ultrasound pattern indicates lymphocytic infiltration (Rosario et al. 2009; Premawardhana et al. 2000). In addition, ultrasound can detect nodules, lumps, and enlargement of the thyroid gland. In a study of over 3000 prospective ultrasounds ordered for a variety of reasons, nearly 15% of subjects displayed evidence of hypoechogenicity.

1.6 The Operation of the HPT Axis in Hashimoto's Thyroiditis

The normal function of the HPT axis depends on the function of the hypothalamus, the pituitary, and the thyroid gland. If something goes wrong with any one of these organs, then the function of axis is typically interrupted. In our setting, autoimmune thyroiditis destroys the thyroid gland, which affects the operation of the HPT axis (see Figure 1.4). As a consequence, autoimmune thyroiditis patients become euthyroid, subclinical, or clinical hypothyroidism with or without goiter. But, most patients successfully regulate free T4 for several years before they become hypothyroidism – suggesting that the dynamics of TSH may be interesting in the clinical setting. Our primary interest here is to track the development of euthyroidism, subclinical or clinical hypothyroidism with or without goiter, using the measurable quantities in blood, TSH, free T4, and anti-thyroid antibodies (Ab) along with the other quantity, the functional thyroid size in the autoimmune thyroiditis. We also want to demonstrate some known and unknown clinical results using a mathematical model.

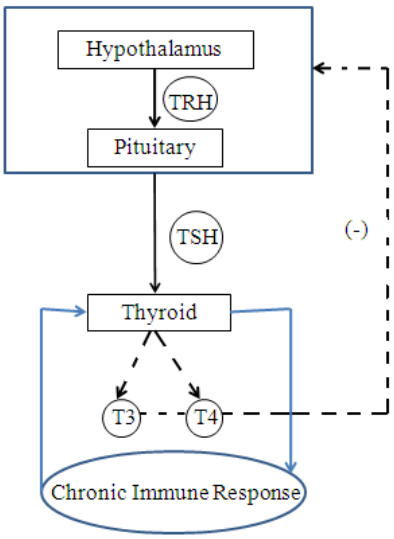


Figure 1.4: In autoimmune thyroiditis, there exists a chronic immune response against the thyroid gland. Due to immune response, the gland's hormone production may decrease and this cause the interpretion of the operation of the HPT axis. The dotted lines represent the dormant part of the HPT axis. The solid line from hypothalamus to pituitary to thyroid gland is the active part of the axis.

TSH and Free T4 Relationship

An understanding of the normal relationship between the blood levels of TSH and free T4 is useful when interpreting thyroid function test results. If TSH measurements are to be used to evaluate primary thyroid dysfunction (such hypothyroidism/ hyperthyroidism), then it is a prerequisite that the function of the hypothalamus – pituitary axis is intact. When hypothalamus – pituitary axis function is normal and thyroid status is stable (meaning free T4 normal), then there is an inverse log/linear relationship between TSH and free T4 (Spencer et al. 1990). We will show this log/linear relationship in our dataset and as a consequence of our model later.

1.7 Dataset

We have received a dataset of 119 patients with autoimmune thyroiditis from our clinical collaborator, Dr. Salvatore Benvenga, Professor of Medicine, Section of Endocrinology, Department of Clinical and Experimental Medicine, University of Messina, Messina, Sicily, Italy. This dataset consists of blood serum levels of thyroid stimulating hormone (TSH), free T4 (FT4), anti-thyroid antibodies (TPOAb and TGAb) and/ or Levothyroxine (L-T4) taken at different time points for every patient. The unit for time is month. The first measurement of those values for a patient is considered time zero (month). Half of our patients received treatment with L-T4 from the first visit to thyroid clinic in Sicily (those patients are referred to treated patients from time zero). The anti-thyroid antibodies column has missing values for almost all patients. For this research, we have received Institutional Review Board (IRB) approval from Marquette University.

To be more specific about the dataset, 46 patients with autoimmune thyroiditis received no treatment (group1- always untreated, see Figures 1.5 and 1.6) because the levels of free T4 within laboratory reference range, 51 patients with autoimmune thyroiditis received treatment with L-T4 from time zero (group2- treated patients from time zero, see Figures 1.6 and 1.7) and

the remaining patients received no treatment initially and then received treatment with L-T4 after they developed clinical hypothyroidism (group3, see Figures 1.8 and 1.9). For these groups, the duration of follow-up is varied up to some extent. In group1, the average duration of follow-up is approximately 24.5 months. In group2, the average duration of follow-up is approximately 32 months. In group3, the average duration of follow-up is approximately 28.5 months. To gain insight into patient's progression toward subclinical hypothyroidism or euthyroidism, we pick patient's data from group1 (see Figure 1.11(M)). To gain insight into patient's progression toward clinical hypothyroidism, we pick patient's data from group3 (see Figure 1.11(N)). Also, we separated group3 patient's data into two parts, before treatment and after treatment in order to observe the course of the disease (see Figure 1.9). Overall, we observed that patients with autoimmune thyroiditis showed high variability in developing subclinical or clinical hypothyroidism. In addition, we observed that the untreated patients mimic the abnormal function of the axis and treated patients mimic the normal operation of the axis as we expected.

The data was collected from different laboratories across Sicily population under the approval of government of Italy. These different laboratories had established slightly different normal reference ranges and set points of the HPT axis according to the local adult population and the measurements are not comparable. So, in order to utilize the entire data set for analysis, it is important to scale TSH and FT4 values within the normal reference range adopted for this project. For that, we introduce a simple proportion formula,

$$x = (2.5 - 0.4) * \frac{y - a}{b - a} + 0.4$$

$$x_1 = (18 - 7) * \frac{y_1 - c}{d - c} + 7$$

where x and y are referred to TSH values in the reference interval $(0.4 - 2.5)$ and $(a - b)$ mU/L respectively and x_1 and y_1 are referred to free T4 values in the reference interval $(7 - 18)$ and $(c - d)$ pg/mL respectively. Note a and b are referred to lower and upper reference limit of TSH. Similarly c and d are referred to lower and upper reference limit of free T4. For an

example of scaling, see Table 1.1 and 1.2 below. Let us consider a patient (#103) with normal reference range and measured TSH and free T4 values used in the lab. We will now employ the above formula to scale TSH and free T4 values into a standard range $(0.4 - 2.5)$ mU/L and $(7 - 18)$ pg/mL. Note: For patient 103, $a = 0.35, b = 5.5, c = 7$ and $d = 17$.

Table 1.1

Patient ID Number	**Normal Range**	**TSH**	**Standard Normal Range**	**TSH** $\boldsymbol{x = (2.5 - 0.4) * \frac{y - 0.35}{5.5 - 0.35} + 0.4}$
103	0.35 – 5.5	1.4	0.4 – 2.5	0.8282
103	0.35 – 5.5	1.65	0.4 – 2.5	0.93
103	0.35 – 5.5	2.26	0.4 – 2.5	1.178

Table 1.2

Patient ID Number	**Normal Range**	**Free T4**	**Standard Normal Range**	**Free T4** $\boldsymbol{x_1 = (18 - 7) * \frac{y_1 - 7}{17 - 7} + 7}$
103	7 – 17	13.5	7 – 18	14.15
103	7 – 17	13	7 – 18	13.6
103	7 – 17	11.8	7 – 18	12.28

2d and 3d-Scatter Plots

We use two and three dimensional (2d and 3d) scatter plots to explore the autoimmune thyroiditis patients dataset. More precisely, for group1 and group3 (untreated) patients, we use 2d and 3d scatter plots to see the abnormality in the function of the HPT axis, nonlinear relationships

between clinical variables and inter and intra - variability in developing hypothyroidism. For group2 patients, we use scatter plots to see the normal operation of the HPT axis.

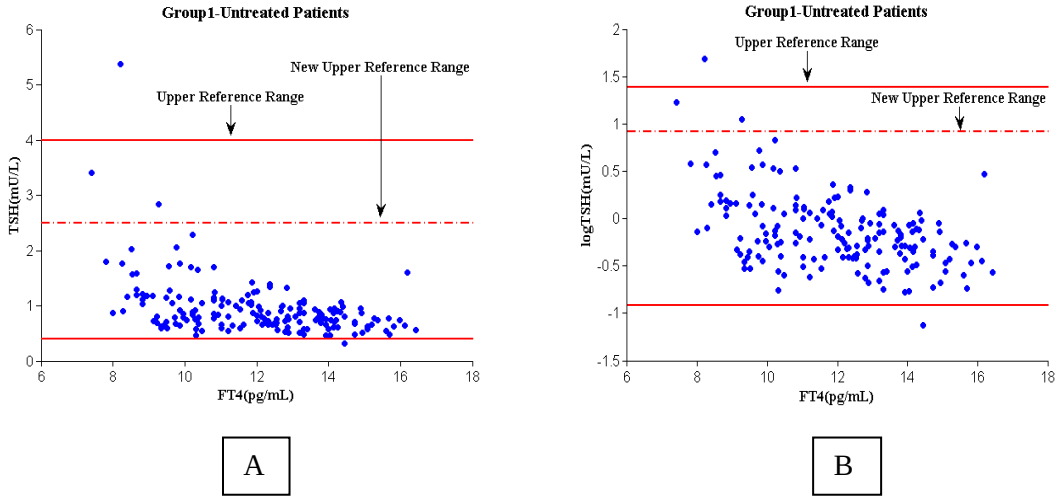


Figure 1.5: The figures (A and B) show 45 patients with autoimmune thyroiditis from group1. Figure A shows all patient's TSH versus free T4 values taken at different time points. Figure B shows patient's log (TSH)(mU/L) versus free T4(pg/mL). All patients have anti-thyroid antibodies but untreated clinically because free T4 levels are normal. 2d plots show how each patient is different in the dataset. The solid red lines indicate the reference range of TSH. The dotted red line indicates the new upper reference limit of TSH. Note: Temporal component is not shown here.

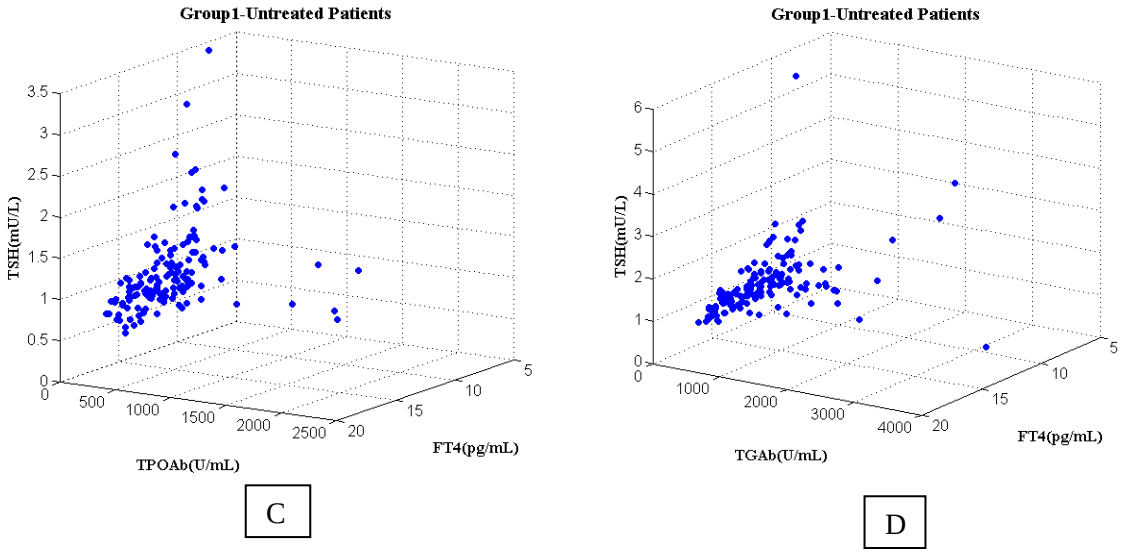


Figure 1.6: 3d plots (C and D) show that all patients from group1 have anti-thyroid peroxidase (TPOAb) and/or anti-thyroglobulin (TGAb) in their blood serum. Group1 patients are monitored but do not receive L-T4. Figure C shows patient's free T4 (pg/mL), TPOAb (U/mL) and TSH (mU/L). Figure D shows patient's free T4 (pg/mL), TGAb(U/mL) and TSH(mU/L).

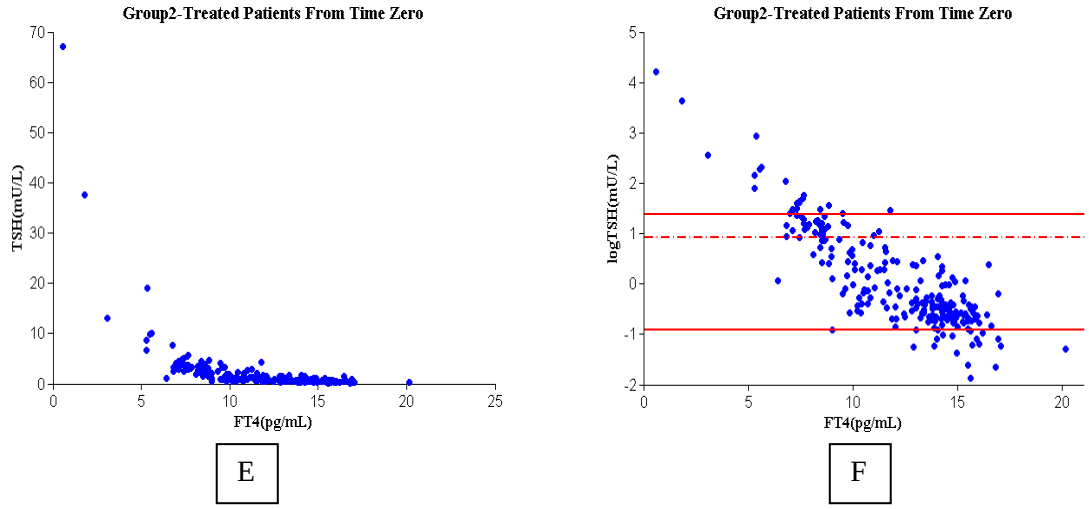


Figure 1.7: 2d plots (E and F) show treated patients with L-T4 from group2. Group2 contains 51 patients (treated from first visit to thyroid clinic – referred to treated patients from time zero). Figure E shows patients TSH versus free T4 taken at different time points. Figure F shows patient's log (TSH) versus free T4. Comparing Figures F and B, we see that group2 patients has better inverse log/linear relationship between log (TSH) (mU/L) and FT4(pg/mL) than group1 patients.

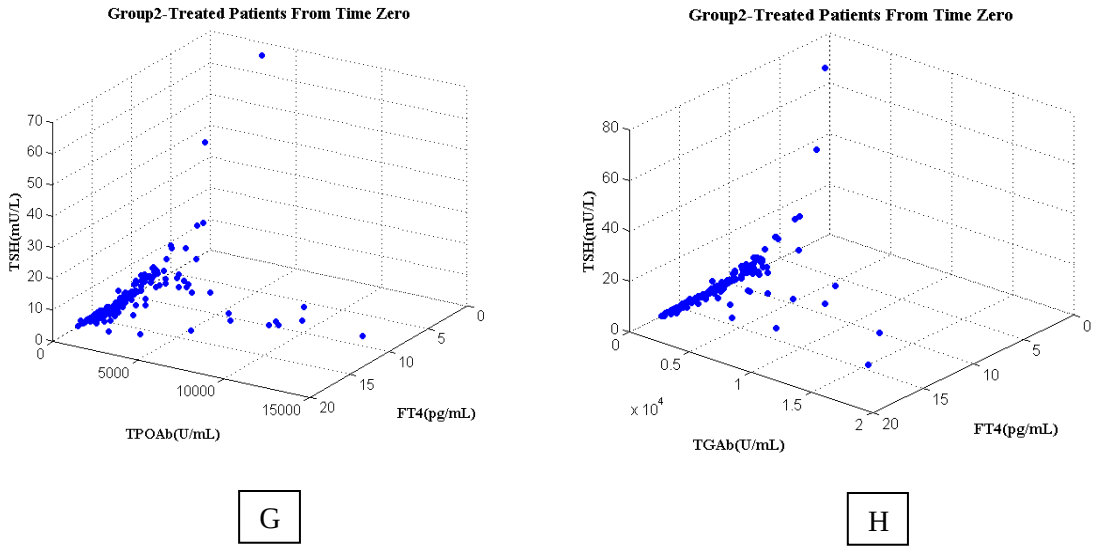
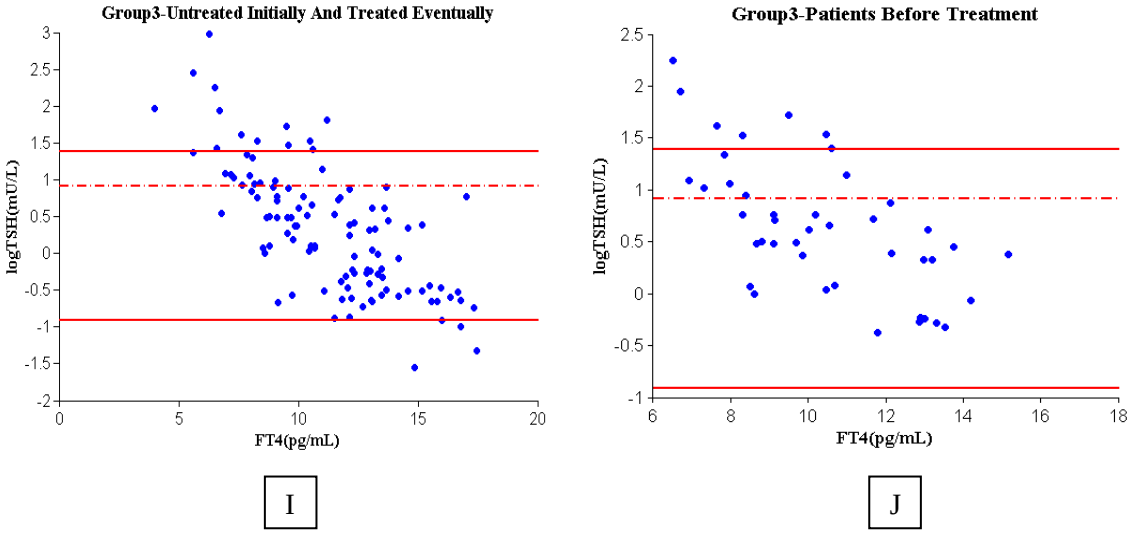
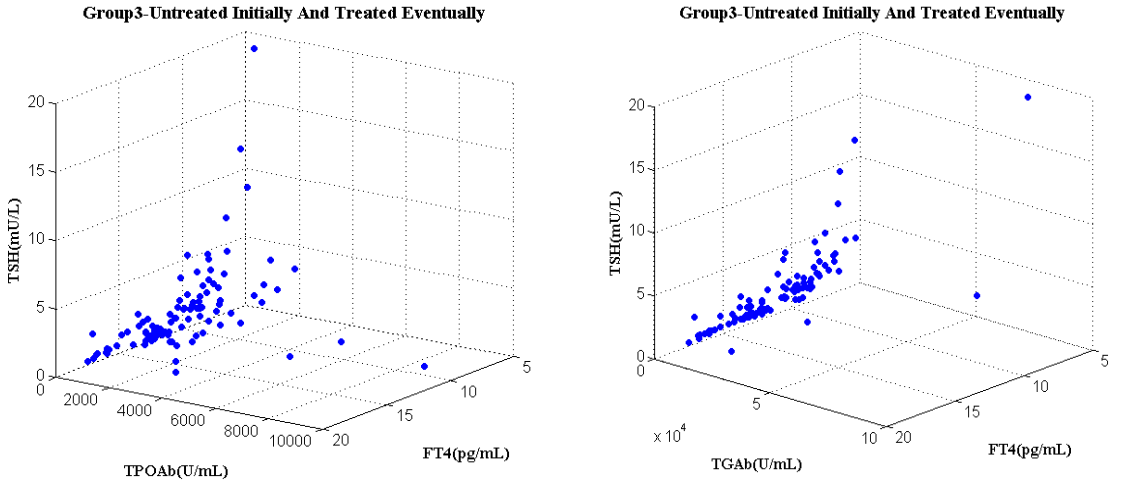


Figure 1.8: 3d plots (G and H) show treated patients from time zero from group2. All treated patients live with anti-thyroid peroxidase (TPOAb) and/or anti-thyroglobulin (TGAb) in their blood serum. Figure G shows patient's free T4 (pg/mL), TPOAb (U/mL) and TSH(mU/L). Figure H shows patient's free T4(pg/mL), TGAb(U/mL) and TSH(mU/L).



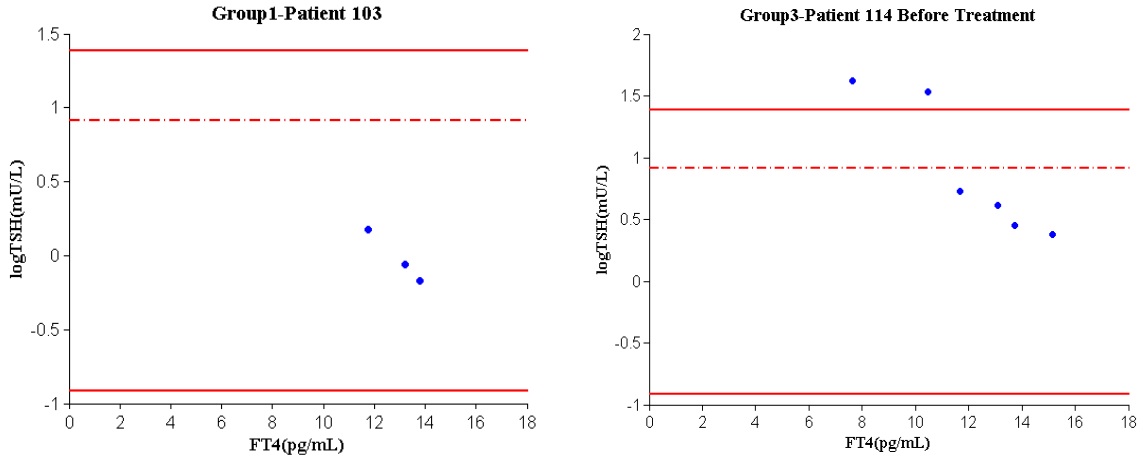
I J

Figure 1.9: 2d plots (I and J) show patients from group3. Group3 contains 22 patients with autoimmune thyroiditis. Figure I shows how patient's progress from euthyroidism to hypothyroidism both in terms of TSH and free T4. Figure J shows the data of 22 patients from group3 before treatment. All patients in Figure J progress from euthyroidism to hypothyroidism while free T4 within laboratory reference range adopted for this project.



K L

Figure 1.10: 3d plots (K and L) show patients from group3. It appears that group3 patients contain more anti-thyroid peroxidase antibodies rather than anti-thyroglobulin antibodies. Figure L shows group3 patients with TPOAb(U/mL) taken at different time points. Figure L shows group3 patients with TGAb(U/mL) taken at different time points.



M N

Figure 1.11: 2d plots (M and N) show a patient from group1 and group3. Figure M shows patient 103 from group1 while Figure N shows patient 114 (before treatment) from group3.

Statistical Test for Nonlinearity

We will now investigate an inverse log/linear relationship in our dataset through a statistical test or model. For that, we first transform TSH values into logarithmic scale, which we call log (TSH). And then, we will construct a linear regression model to evaluate the relationship between log (TSH) and free T4. If this model produces a linear relationship, then we conclude that there is a non-linear relationship between TSH and free T4. For more details such as how to construct a linear regression model, see (Montgomery et al. 2006). We will use group1 patients and group3 patients before treatment dataset for this statistical test.

We will employ Matlab curve fit toolbox to construct a linear regression model, and investigate the statistical quantity R^2 which measures the proportion of explained variation in a dataset. In statistics, R^2 is a descriptive measure between 0 and 1. If R^2 is close to 1, then the linear regression model fits the sample dataset better. If R^2 is close to 0, then the linear regression model fits the sample dataset poorly. On the other hand, the population measure, the Pearson's correlation ρ measures the degree of linear relationship between two variables in the dataset. It ranges between -1 and +1. A correlation of +1 means a perfect positive linear

relationship between two variables and -1 means a perfect inverse linear relationship. Note r is the estimate of ρ and the real connection between R^2 and r is $R^2 = r^2$.

Figure 1.12 shows the linear regression model for group1 patients and group3 patients before treatment. We found $R^2 = 0.3243$, $r = -.569$ and this implies $R^2 = r^2$. Also we found p-value of t-test < 0.001. Thus, the statistical test confirms a linear relationship between log TSH and free T4. Hence, TSH and free T4 have a non-linear relationship.

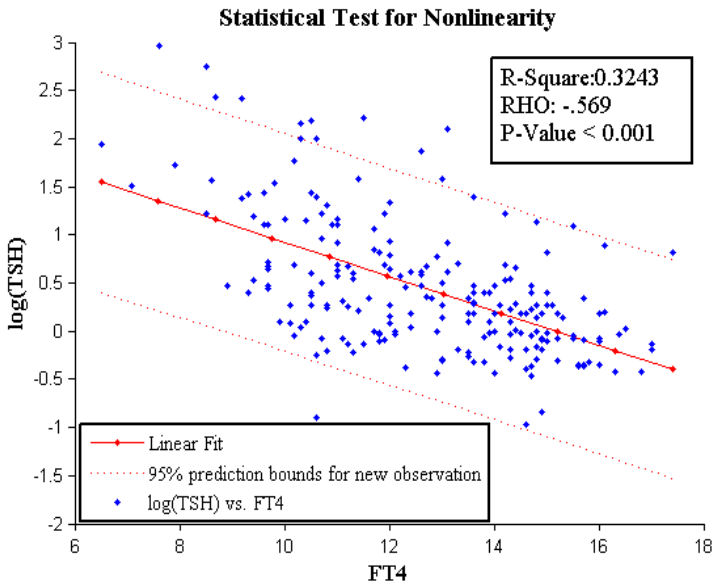


Figure 1.12: The 2d scatter plot showing a linear regression model and the statistical quantities (R^2 and ρ). It seems $R^2 = 0.3243$, ($p < 0.001$) and Pearson's correlation $r = -.569$ negative. This indicates that there is a linear relationship between log (TSH) (mU/L) and free T4 (FT4) (pg/mL). Thus, TSH and free T4 have a non-linear relationship.

1.8 Clinical Staging and Disease Progression

In autoimmune thyroiditis the immunologic attack is very aggressive and destructive and the pathogenesis of the disease is strongly associated with some suspected genes (for instance, non-MHC class II genes) and environmental factors (for instance, high levels of iodine) (Chistiakov, 2005). Every individual is likely to born with one of the predisposition genes in their body which

determines whether the individual will develop the clinical states, such as, subclinical or clinical hypothyroidism or euthyroidism (none) given an environmental stimulus. We will now discuss **patient-specific clinical staging** for autoimmune thyroiditis. The staging is important and useful to plan treatment.

Case1:

Suppose patients with autoimmune thyroiditis (anti-thyroid antibodies are consistently present in the blood) do not develop any clinical consequences such as subclinical or clinical hypothyroidism, then the staging will be,

Euthyroidism → Euthyroidism

Case2:

Suppose patients with autoimmune thyroiditis develop subclinical hypothyroidism, then the staging will be,

Euthyroidism → Subclinical Hypothyroidism

Case3:

Suppose patients with autoimmune thyroiditis develop subclinical hypothyroidism and eventually become clinical hypothyroidism, then the staging will be,

Euthyroidism → Subclinical→ Clinical Hypothyroidism

1.9 Summary

In this chapter, we introduced the background material required for modeling the operation of the HPT axis in autoimmune thyroiditis. The background material includes thyroid physiology, the normal operation of hypothalamus-pituitary-thyroid (HPT) axis, autoimmune (Hashimoto) thyroiditis, and the operation of the HPT axis in autoimmune thyroiditis, clinical tests and clinical staging. In addition, we discussed autoimmune thyroiditis patient's dataset used in this thesis. The dataset was obtained from Sicilian adult population, Italy through our clinical collaborator, Dr. Benvenga. We separated the dataset into three groups, namely, group1-always untreated

patients, group2-treated patients with L-T4 (from the first visit to thyroid clinic (time zero)), and group3-untreated initially but treated after developed hypothyroidism and presented scatter plot analysis. We observed that group1 and group3 patients showed the abnormal operation of the HPT axis whereas the group2 patients showed the normal operation of the HPT axis. Finally, we established patient-specific clinical staging criteria for patients from group1 and group3 in order to describe their natural history of autoimmune thyroiditis.

CHAPTER 2 – A MATHEMATICAL MODEL OF THE HPT AXIS

We devote this chapter mainly to the construction of a mathematical model of the operation of the HPT axis in autoimmune (Hashimoto's) thyroiditis. Recall from the previous Chapter that in autoimmune thyroiditis the status of the thyroid gland and the normal function of the HPT axis are interrupted. This model is primarily aimed at the middle - age women or adult patients group since most of these patients regulate free T4 successfully for several years in spite of an increase in TSH and the presence of anti-thyroid antibodies (TPOAb and TGAb) in their blood serum. We will first review other models of the thyroid- pituitary system aimed for regulating free thyroxine (T4).

2.1 Literature Review

One of the remarkable properties of the thyroid gland is to maintain the amount or concentration of free T4 within a stable range $(7-18)\ pg/mL$. For that, control mechanisms exist within the thyroid gland. Here, we review some mathematical models from literature describing the regulation of thyroid hormones. In 1954, Danziger and Elmergreen (Danziger and Elmergreen, 1954) developed a mathematical model based on thyroid and pituitary hormones in order to explain the mental disorder called periodic relapsing catatonia. They proposed a set of nonlinear differential equations using Langmuir adsorption isotherm, i.e.,

$$\frac{d\pi}{dt} = c - \frac{k_2 n\theta}{(1+n\theta)} - g\pi, \qquad \pi \geq 0$$

$$\frac{d\theta}{dt} = \frac{k_1 m\pi}{(1+m\pi)} - b\theta, \qquad \theta \geq 0$$

where π and θ are concentrations of TSH and thyroid hormone respectively at time t and $c, b, g, k_1, k_2, m,$ and n are positive real constants. This system of equations describes most of normal and malfunctions of the thyroid - pituitary system but the system fails to produce the

sustained oscillations of the hormone levels, which was believed to be the reason for periodic relapsing catatonia.

In 1956, Danziger and Elmergreen (Danziger and Elmergreen, 1956) proposed another mathematical model to account for the sustained oscillations of the thyroid hormone levels, in addition to explaining the normal and abnormal operations of thyroid-pituitary system. They assumed the pituitary gland secretes TSH, which activates an enzyme in the thyroid gland. The rate of production of thyroid hormone is considered to be proportional to the concentration of that enzyme. Their second mathematical model was as follows,

$$\frac{d\pi}{dt} = \begin{cases} (c - h\theta) - g\pi & \text{when } \theta \leq c/h \\ -g\pi & \text{when } \theta \geq c/h \end{cases}$$

$$\frac{dE}{dt} = m\pi - kE$$

$$\frac{d\theta}{dt} = aE - b\theta$$

where π, E and θ are concentrations of TSH, an enzyme and thyroid hormone at time t. The system is simply referred to thyroid-pituitary regulator. There are two notable observations from this model apart from producing sustain oscillations, firstly they linearized the nonlinear terms and added a third differential equation and secondly, by varying specific model parameters, they explained the clinical conditions such as hyper - and hypothyroidism.

In 1959, S. Roston (Roston, 1959) presented a mathematical model of endocrinological homeostasis. The model had no enzymatic reaction terms and periodic solutions but had the autonomous secretion term for both TSH and thyroid hormones (T3 and T4) from the pituitary and the thyroid. In addition, he assumed i) thyroid hormones bound to serum proteins such as (thyroid binding globulin (TBG) and albumin), ii) the physiological volumes V_p , V_x in which TSH and thyroid hormones are dissolved are constant over a short period of time, and iii) the rate of secretion of thyroid hormones is proportional to the rate at which TSH passes through the thyroid gland. A mathematical model of S. Roston was as follows,

$$\frac{dP}{dt} = k_2 - k_1\left(\frac{x}{V_x} - x_1\right) - \frac{k_3 P}{V_p},$$

$$\frac{dx}{dt} = k_5 + \frac{k_4 F}{V_p} P - \frac{k_6 x}{V_x}$$

The notable features of this model are all the equations are stated in terms of ***amounts*** of TSH and thyroid hormones, which distributed homogeneously and instantaneously throughout the physiological volumes V_p , V_x and the parameter k_1 represents the sensitivity of the pituitary gland to thyroid hormones inhibition. Note x_1 is a physiologically standard value of thyroid hormones (in concentration units). In other words, the effect of the hypothalamus on the secretion of TSH from pituitary can be expressed by changes in the value of a model parameter (k_1).

In 1964, N. Rashevsky (Rashevsky, 1964) published a heterogeneous model of thyroid hormone regulator in a discussion of a mathematical theory of the effects of cell structure and diffusion processes on the homeostasis and kinetics of the endocrine system. The author kept all the basic assumptions of Danziger and Elmergreen (1956) and added the effects of the highly heterogeneous assumption of thyroid hormone regulator system.

In 1965, Norwich and Reiter (Norwich and Reiter, 1965) published a homogenous model of thyroid hormone regulation involving a set of linear differential equations expressing the relationship between the rates of secretion of thyroxine and of TSH. Using their model, they were able to replicate the known behavior of thyroxine and TSH and made certain predictions which are amenable to experimental verification or disproval by existing techniques.

In 1968, Joseph J. Distefano and Edwin B. Stear (DiStefano and Stear, 1968) published a model of thyroid hormone regulation including the hypothalamus. In 1976, P. Saratchandran, E.R. Carson and J. Reeve (Saratchandran et al. 1976) published an improved mathematical model of thyroid hormone regulation by the anterior pituitary gland which accounted for experimental data of TSH and thyroid hormones. In 2008, Mike Degon (Degon et al. 2008) published a computational model of the human thyroid gland based on the clinical observation of changes in

the dietary iodine and the molecular-pathways in the thyroid gland. This model captures the known aspects of thyroid physiology.

In the next section, we construct a nonlinear model of the operation of the HPT axis in autoimmune thyroiditis. Note that this model is the first mathematical model in the literature to study the function of the HPT axis with abnormality in the thyroid gland.

2.2 Construction of the model

The model is constructed primarily for patients (especially middle-aged women, or adults) with autoimmune thyroiditis. To construct a model, we first identify the key players in the disease. Second, we make assumptions about those key players. Third, we use those assumptions to construct the rate equations, which is our model. For patients with autoimmune thyroiditis, the key players are thyroid stimulating hormone, free T4, (unbound) anti-thyroid antibodies and the functional (active) size of the thyroid gland. Note thyroid stimulating hormone (TSH), free T4 (FT4), anti-thyroid antibodies (Ab) and the functional size of the thyroid gland (T) varies with time in the presence of autoimmune thyroiditis. Also TSH, FT4 and Ab are measurable quantities in the clinical setting to diagnose autoimmune thyroiditis but not the functional size of the thyroid gland (T). The functional size can be computed using other key players which will be discussed later in this Chapter. We now make the following assumptions,

Assumptions:

1. Anti-thyroid antibodies attack the thyroid follicle cells whereby the gland stimulates more activity of the immune response.
2. The damaged part of the gland is no longer functional (active) in secreting thyroid hormones.
3. TSH stimulates the functional (active) part of the thyroid gland for growth and hormonal secretion.

4. TSH disappears from the blood through a non-specific excretion mechanism.
5. TSH distributes uniformly throughout the functional part of the gland.
6. The hypothalamus – pituitary function is intact.
7. The blood concentration of iodine is sufficient for synthesis of hormonal production.
8. The total TSH receptor concentration in the gland is approximately constant since the anti-thyroid antibodies (TPOAb and TGAb) do not attack the TSH receptors (Tamaki, 1990).

Let us now define the key players in autoimmune thyroiditis in terms of function of time and followed by the rate equations,

$TSH\ (t)\ =$ Concentration of thyroid stimulating hormone (mU/L) at time t in blood

$FT4\ (t)\ =$ Concentration of free thyroxine (pg/mL) at time t in blood

$T\ (t)\ =$ the functional size of thyroid gland (active part of the gland) (L) at time t

$Ab\ (t)\ =$ Concentration of (unbound) anti-thyroid antibodies (U/mL) at time t in blood

Rate Equation 2.1

The rate of change of concentration of TSH is equated to the secretion rate of TSH minus the excretion rate of TSH. That is,

$$\frac{dTSH}{dt} = g_1(FT4) - g_2(TSH) \tag{2.1}$$

where $g_1(FT4)$ and $g_2(TSH)$ are the secretion and excretion rate of TSH respectively. Although, it seems appropriate to include the interaction rate of TSH and the functional size of thyroid gland on the right hand side of equation (2.1), however we ignore this term by considering the physical nature of the problem that active areas in the thyroid gland getting smaller and smaller as the disease progress in the gland.

We will first model the secretion rate with two terms; one accounts for the maximum secretion rate and another for inhibition rate. That is,

$$g_1(FT4) = k_1 - \frac{k_1\, FT4}{k_a + FT4}$$

The term k_1 represents a maximum secretion rate of TSH in the absence of $FT4$ in the blood (Utiger, R.D. 1987). The next term represents the inhibition of maximum secretion rate of TSH. It depends on plasma concentration of $FT4$. This term is modeled by using Michaelis – Menten kinetics, which made use of a simple mechanism

$$FT4 + \ FT4R \rightleftharpoons \text{FT4}\sim\text{FT4R} \rightarrow TSH$$

where *FT4, FT4R*, and *FT4~FT4R* represents the concentration of free T4, free T4 unbound receptors on the surface of the pituitary gland and/or the hypothalamus (as we remarked before, we considered the hypothalamus-pituitary gland as one unit for our work (see Figure 1.3)), and free T4-free T4 receptor bound molecules respectively.

In general, Menten kinetics describes the relationship between the affinity constant (k_a) and total number of receptors (k_1) on the surface of the pituitary gland and/or the hypothalamus (see (Matthews, 1993)). The affinity constant (k_a) can be described as the concentration of $FT4$ required for 50% of maximal TSH inhibition. Also note that total number of receptors corresponds to the maximum secretion rate of TSH.

Properties of $g_1(FT4)$

Since

$$\frac{\partial g_1}{\partial FT4} = -\frac{k_a k_1}{(k_a + FT4)^2} < 0 \text{ for all } FT4 \geq 0$$

Then,

$$g_1(FT4) = k_1 - \frac{k_1\, FT4}{k_a + FT4} \leq 0 \text{ for all } FT4 \geq 0$$

Remark

$i)\ g_1(0) = k_1$

$ii)\ g_1(k_a) = \frac{k_1}{2}$

$iii)\ \lim_{FT4\to\infty} g_1(FT4) = 0\ \ or\ \ \lim_{FT4\to 0} g_1(FT4) = k_1$

$iv)\ g_1(FT4)$ is at least twice continuously differentiable

Therefore the secretion rate decreases/increases as concentration of $FT4$ increases/decreases.

We will now model the excretion rate of TSH. By assuming that the excretion rate of TSH decreases at a rate proportional to the concentration of TSH in blood serum (i.e., to say TSH excrete through non-specific mechanism - assumption 4). Thus, we write

$$g_2(TSH) = k_2\, TSH$$

Remark:

$i)\ g_2(0) = 0$

$ii)\ \lim_{TSH\to\infty} g_2(TSH) = \infty\ \ or\ \ \lim_{TSH\to 0} g_2(TSH) = 0$

Thus,

$$\frac{dTSH}{dt} = k_1 - \frac{k_1\, FT4}{k_a + FT4} - k_2\, TSH \qquad (2.2)$$

Rate Equation 2.2

We first derive the rate equation for thyroxine (T4) and then later convert $T4$ into free T4 in the equation using the fact that bound T4 and free T4 are proportional to each other. The rate of change of concentration of thyroxine $(T4)$ is equated to the secretion rate of $T4$ minus the excretion rate of $T4$. That is,

$$\frac{dT4}{dt} = f_1(TSH, T) - f_2(T4) \qquad (2.3)$$

where $f_1(TSH, T)$ and $f_2(T4)$ represents the secretion and excretion rate of $T4$ respectively. We will first model the secretion rate of $T4$ in equation(2.3). To formulate the secretion rate term, we consider the active region of the thyroid gland (assumption 3). So, let the thyroid functional size

be T and size of a follicle S (constant). Let the number of follicles be $\frac{T}{S}$. Let F_0 be the number of follicle receptors per follicle (constant, assumption 8). Then total number of follicle receptors is $\frac{T}{S}F_0$. Let $TSHR$ and $TSH{\sim}TSHR$ be the free (unbound) receptors and bound receptors concentrations. Then $TSHR * V =$ number of unbound receptors and $TSH{\sim}TSHR * V =$ number of bound receptors, where V is the volume of the blood. Also, observe that,

$$(TSHR + TSH{\sim}TSHR) * V = \text{number of (bound + unbound)receptors}$$

$$(TSHR + TSH{\sim}TSHR) = \frac{T}{VS}F_0 \tag{2.4}$$

Using stoichiometry,

$$TSH + TSHR \underset{k_q}{\overset{k_b}{\rightleftharpoons}} TSH{\sim}TSHR \overset{k_p}{\rightarrow} T4 + TSHR$$

k_b, k_q and k_p are binding, dissociation and production rate constants affiliated with this reaction. For this stoichiometry, the rate equations of $TSH{\sim}TSHR$ and $T4$ are,

$$\frac{d\,TSH{\sim}TSHR}{dt} = k_b TSH * TSHR - k_q\,TSH{\sim}TSHR - k_p\,TSH{\sim}TSHR \tag{2.5}$$

$$\frac{dT4}{dt} = k_p TSH{\sim}TSHR \tag{2.6}$$

Furthermore, using on equilibrium assumption on (2.5), we get

$$TSH{\sim}TSHR = \left(\frac{k_b}{k_p + k_q}\right) TSH * TSHR \tag{2.7}$$

Substitute (2.4) into (2.7), we get

$$TSH{\sim}TSHR = \left(\frac{k_b}{k_p + k_q}\right) TSH \left(\frac{T}{VS}F_0 - TSH{\sim}TSHR\right)$$

That is,

$$TSH{\sim}TSHR = \frac{\left(\frac{TF_0}{VS}\right) TSH}{\left(\frac{k_q + k_p}{k_b} + TSH\right)} \tag{2.8}$$

Substitute (2.8) into (2.6), we get

$$\frac{dT4}{dt} = k_p \frac{\left(\frac{TF_0}{VS}\right) TSH}{\left(\frac{k_q + k_p}{k_b} + TSH\right)}$$

Thus,

$$f_1(TSH, T) = \text{Secretion rate of } T4$$

$$= \frac{k_r T\, TSH}{k_d + TSH}$$

where,

$k_d = \frac{k_q + k_p}{k_b}, k_r = \frac{k_p F_0}{VS}$

Properties of $f_1(TSH, T)$

i) Suppose $TSH = T = 0$ or $TSH = 0$ or $T = 0$, then $f_1(TSH, T) = 0$

ii) Since $\frac{\partial f_1}{\partial T} = \frac{k_r TSH}{k_d + TSH} \geq 0$ or $\frac{\partial f_1}{\partial TSH} = \frac{k_r k_d T}{(k_d + TSH)^2} \geq 0$, then $f_1 \geq 0$ for all $TSH, T \geq 0$

We will now model the excretion rate of $T4$ in equation(2.3). By assuming that the blood serum concentration of $T4$ excreted on the basis of first order kinetics, we get this term,

$$f_2(T4) = k_4 T4$$

Thus,

$$\frac{dT4}{dt} = \frac{k_r\, T\, TSH}{k_d + TSH} - k_4\, T4 \qquad (2.9)$$

Since physicians measure free T4 ($FT4$) to monitor thyroid $T4$ secretion in patients with autoimmune thyroiditis, we describe (2.9) in terms of $FT4$. By utilizing the fact that bound T4 ($BT4$) is proportional to free T4($FT4$). That is,

$$T4 = BT4 + FT4$$

$$= (a + 1)FT4$$

where a is proportionality constant.

We obtain,

$$\frac{dFT4}{dt} = \frac{k_3\, T\, TSH}{k_d\, +\, TSH} -\, k_4 FT4 \tag{2.10}$$

where $k_3 = \frac{k_r}{1+a}$.

Rate Equation 2.3

The rate of change of the functional size (active part) of thyroid gland is equated to the growth rate minus the destruction rate of functional thyroid gland.

$$\frac{dT}{dt} = h_1(TSH, T) - h_2(Ab, T) \tag{2.11}$$

where $h_1(TSH, T)$ and $h_2(Ab, T)$ represent the growth rate and destruction rate of functional thyroid gland respectively.

We will model the growth rate of the functional thyroid gland using two terms; one accounting for when TSH is available in the blood serum and another, when TSH is not available in the blood serum. When TSH is available in the blood serum, we assume that the growth rate is the proportion of concentration of TSH in blood serum to total number of receptors in the functional region.

That is,

$$\frac{TSH}{\text{total number of receptors in the functional region}} \tag{2.12}$$

Furthermore, we will assume that the total number of receptors in the functional region of the thyroid gland is directly proportional to the functional size of the gland. That is,

$$\text{total number of receptors in the functional region} = \mathrm{r} * T \tag{2.13}$$

Substitute (2.13) into (2.12), we get,

$$\frac{TSH}{r *\, T} \tag{2.14}$$

Now, we let $k_5 = \frac{1}{r}$. Therefore (2.13) becomes,

$$k_5 \frac{TSH}{T}$$

When TSH is not available in the blood serum (and from assumption (6)), we assume that the growth rate of the gland decreases at a physiologically standard constant rate N, that is,

$$-k_5 N$$

Thus, the growth rate of the functional gland is,

$$h_1(TSH, T) = k_5\left(\frac{TSH}{T} - N\right)$$

where k_5 represents the sensitivity of the thyroid gland to TSH stimulation.

Properties of $h_1(TSH, T)$

$i)$ $h_1(TSH, 0) =$ does not exist. This implies that there is a singularity at $T = 0$.

$ii) h_1(0, T) = -k_5 N$.

We will now model the destruction rate of the functional size of the thyroid gland. The destruction rate of the functional thyroid gland depends on the aggression of the anti-thyroid immune response. To model this term, we use anti-thyroid antibodies (TPOAb and TGAb) to stand in for immune response (assumption 1) and the functional size (T) for the active part of the gland. Therefore, the destruction rate of Ab is assumed to be the interaction rate of anti-thyroid antibodies and the functional size of the gland. So, we write

$$h_2(Ab, T) = k_6\, Ab\, T$$

Properties of $h_2(Ab, T)$

$i)$ if $Ab = 0$ or $T = 0$ then $h_2 = 0$.

The rate equation of the functional size of the thyroid gland is,

$$\frac{dT}{dt} = k_5\left(\frac{TSH}{T} - N\right) - k_6 Ab\, T \qquad (2.15)$$

Rate Equation 2.4

The rate of change of concentration of unbound anti-thyroid antibodies is equated to the production rate of anti-thyroid antibodies due to the destruction of the functional size of thyroid gland *minus* the aging rate of anti-thyroid antibodies respectively. That is,

$$\frac{dAb}{dt} = m_1(Ab, T) - m_2(Ab) \tag{2.16}$$

where $m_1(Ab, T)$ and $m_2(Ab)$ represents the production rate of anti-thyroid antibodies due to the destruction of the functional size of thyroid gland and the aging rate of anti-thyroid antibodies respectively. We will model the production rate of anti-thyroid antibodies using the interaction term, that is, $m_1(Ab, T) = k_7 Ab\, T$ [Note – this is an important point in defining Hashimoto's as an autoimmune disease, because it reflects our assumption 1 that anti-thyroid immune response attacks the thyroid follicle cells whereby the gland stimulates more activity of the immune response and that antibody acts as a marker of immune activity]. We will model the aging term using the first order kinetics, that is, anti-thyroid antibodies concentration decreases at a rate proportional to the levels of anti-thyroid antibodies in the blood ($m_2(Ab) = k_8\, Ab$).

Thus,

$$\frac{dAb}{dt} = k_7 Ab\, T - k_8\, Ab \tag{2.17}$$

Hence, the four dimensional model (4d) is as follows,

$$\frac{dTSH}{dt} = k_1 - \frac{k_1\, FT4}{k_a + FT4} - k_2\, TSH \qquad TSH(t_0) = TSH_0 \tag{2.2}$$

$$\frac{dFT4}{dt} = \frac{k_3\, T\, TSH}{k_d + TSH} - k_4 FT4 \qquad FT4(t_0) = FT4_0 \tag{2.10}$$

$$\frac{dT}{dt} = k_5\left(\frac{TSH}{T} - N\right) - k_6 Ab\, T \qquad T(t_0) = T_0 \tag{2.15}$$

$$\frac{dAb}{dt} = k_7 Ab\, T - k_8\, Ab \qquad Ab(t_0) = Ab_0 \tag{2.17}$$

with initial conditions associated with the model and the parameters are all positive, that is, $k_1, k_2, k_3, k_4, k_5, k_6, k_7, k_8, k_a k_d, N > 0$. The equations (2.2), (2.10), (2.15) and (2.17) will be referred to as (2.2) – (2.17).

Remark

The right hand sides of the model $(2.2) - (2.17)$ are continuous except when $T = 0$ and satisfy a local Lipschitz condition in R_+^4.

Existence and Uniqueness Theorem

We will now state the general theorem of existence and uniqueness for the initial value problem (Robinson, 2004, page 71).

Theorem

Consider the differential equation

$$\dot{\mathbf{x}} = \mathbf{F}(\mathbf{x})$$

where $\mathbf{x}$ is a point in R^n and $\mathbf{F}(\mathbf{x})$ is a vector field in R^n. Assume that both $\mathbf{F}(\mathbf{x})$ and $\frac{\partial \mathrm{F_i}}{\partial \mathrm{x_j}}(\mathbf{x})$ are continuous for $\mathbf{x}$ in some open set U in R^n, and that $\mathbf{x}_0$ is a point in U.

Then there exists a solution $\mathbf{x}(\mathbf{t})$ defined for some time interval $-\tau < t < \tau$ such that $\mathbf{x}(\mathbf{0}) = \mathbf{x}_0$**.** Moreover, the solution is unique in the sense that if $\mathbf{x}(\mathbf{t})$ and $\mathbf{y}(\mathbf{t})$ are two such solutions with $\mathbf{x}(\mathbf{0}) = \mathbf{y}(\mathbf{0}) = \mathbf{x}_0$, then they must be equal on the largest interval of time about $t = 0$ where both solutions are defined. Let $\phi(t; \mathbf{x}_0)$ be this unique solution with $\phi(0; \mathbf{x}_0) = \mathbf{x}_0$. The solution $\phi(t; \mathbf{x}_0)$ depends continuously on the initial condition $\mathbf{x}_0$**.** Moreover, let T > 0 be a time for which $\phi(t; \mathbf{x}_0)$ is defined for $0 \leq t \leq T$. Let $\epsilon > 0$ be any bound on the distance between solutions. Then, there exists a $\delta > 0$ which measures the distance between allowable initial conditions, such that if $\left|\left|\boldsymbol{y}_0 - \boldsymbol{x}_0\right|\right| < \delta$, then $\phi(t; \mathbf{y}_0)$ is defined for $0 \leq t \leq T$ and

$$||\phi(t; \mathbf{y}_0) - \phi(t; \mathbf{x}_0)|| < \epsilon$$

for $0 \leq t \leq T$. In fact, the solution $\phi(t; \mathbf{x}_0)$ is differentiable on the initial condition, $\mathbf{x}_0$.

Proof: see (Robinson, 2004, page 86 - 89)

■

Let us now compare the necessary assumptions needed for the existence and uniqueness theorem to satisfy in our 4d model. In our model, we have,

$$\mathbf{x} = \begin{pmatrix} TSH \\ FT4 \\ T \\ Ab \end{pmatrix} \qquad \text{and} \qquad \mathbf{F}(\mathbf{x}) = \begin{pmatrix} k_1 - \frac{k_1\, FT4}{k_a + FT4} - k_2\, TSH \\ \frac{k_3\, T\, TSH}{k_d + TSH} - k_4 FT4 \\ k_5\left(\frac{TSH}{T} - N\right) - k_6 Ab\, T \\ k_7 Ab\, T - k_8\, Ab \end{pmatrix}$$

Note $\mathbf{F}(\mathbf{x})$ and $\frac{\partial \mathrm{F_i}}{\partial \mathrm{x_j}}(\mathbf{x})$, $i, j = 1,2,3,4$ are a continuous functions except possibly when $T = 0$. Thus, we require a non-negative open region in R^4 without $T = 0$ in order for the existence and uniqueness theorem to work in our 4d model and of course all the initial conditions are non-negative, $\mathbf{x}_0$ contained within the open set $U = \mathrm{R}^4_+$.

We will now employ the model in an adult population, since they are the ones who develop this autoimmune thyroiditis most frequently. For a given adult group, the clinical variable normal values, ranges, units and sources are listed in Table 2.1. Note that the normal value of TSH, FT4 and the functional size varies with person to person. So, we arbitrarily picked normal values from the reference ranges adopted for this dissertation. The normal value of anti-thyroid antibodies is zero.

Table 2.1: Variable Normal Values, Ranges, Units and Sources

Name	Normal Value	Normal Range	Source	Unit
TSH	1	$0.4 - (2.5 - 4)$	Literature(Baloch et al. 2003)	mU/L
$FT4$	13	$7 - 18$	Literature(Baloch et al. 2003)	pg/mL
T	0.015	$0.005 - 0.125$	Literature(Carle et al. 2009)	L
Ab	0	$0 - < 200$	Dataset	U/mL

2.3 Singularly Perturbed Structure to 4d Model

We have observed that thyroid stimulating hormone (TSH) changes on the order of days in the blood, free T4 (FT4) changes on the order of weeks in the blood, and the functional size of thyroid gland (T) and anti-thyroid antibodies (Ab) changes either on the order of weeks or years, possibly depending on the person, the degree of the disease, age, gender, race and so many unknown factors. Thus, there exists at least two different time-scales in the model. We impose this assumption of two time-scales present in our 4d model. We will call TSH a fast state variable since it changes on the faster time scale and the rest of the variables (FT4, T, and Ab) are slow state variables since they change on the slower (common) time scale. This in turn gives rise to a singularly perturbed structure to our model and also helps us to analyze the model effectively by reducing a dimension (see below for the introduction of singularly perturbed initial value problem). The presence of this structure is seen in Chapter1 in the log-linear relationship between TSH and free T4.

Divide (2.2) with k_2, then we get,

$$\frac{1}{k_2}\frac{dTSH}{dt} = \frac{k_1}{k_2} - \frac{k_1\, FT4}{k_2(k_a + FT4)} - TSH \qquad TSH(t_0) = TSH_0 \qquad (2.18)$$

$$\frac{dFT4}{dt} = \frac{k_3\, T\, TSH}{k_d + TSH} - k_4 FT4 \qquad FT4(t_0) = FT4_0 \qquad (2.19)$$

$$\frac{dT}{dt} = k_5\left(\frac{TSH}{T} - N\right) - k_6 Ab\, T \qquad T(t_0) = T_0 \qquad (2.20)$$

$$\frac{dAb}{dt} = k_7 Ab\, T - k_8\, Ab \qquad Ab(t_0) = Ab_0 \qquad (2.21)$$

Let

$$\varepsilon = \frac{1}{k_2} << 1$$

Then, we obtain a singularly perturbed structure of our 4d model,

$$\varepsilon \frac{dTSH}{dt} = \frac{k_1}{k_2} - \frac{k_1\, FT4}{k_2(k_a + FT4)} - \; TSH \qquad TSH(t_0) = TSH_0 \qquad (2.18)_\varepsilon$$

$$\frac{dFT4}{dt} = \frac{k_3\, T\, TSH}{k_d \; + \; TSH} - \; k_4 FT4 \qquad FT4(t_0) = FT4_0 \qquad (2.19)$$

$$\frac{dT}{dt} = k_5 \left(\frac{TSH}{T} - N\right) - k_6 Ab\, T \qquad T(t_0) = T_0 \qquad (2.20)$$

$$\frac{dAb}{dt} = k_7 Ab\, T - \; k_8\, Ab \qquad Ab(t_0) = Ab_0 \qquad (2.21)$$

Note: the singularly perturbed model equations numbers are all renamed ((2.18) – (2.21)). The singularly perturbed 4d model is described on the order of intermediate slower time scale, more precisely, in terms of weeks (see parameter estimation section in Chapter 4). Also, we could have chosen k_1 to define ε instead of k_2. If k_1 was our chosen candidate, the singularly perturbed model will be on the order of years (slower time scale).

Introduction to Singularly Perturbed Initial Value Problem

Let x denote the "slow" variables and y denote the "fast" variables, then standard autonomous singularly perturbed initial value problems are given as,

$$\begin{aligned} \frac{dx}{dt} &= f(x, y, \varepsilon), \qquad x(t_0) = x_0 \\ \varepsilon \frac{dy}{dt} &= g(x, y, \varepsilon), \qquad y(t_0) = y_0 \end{aligned} \qquad (2.22)$$

where ε a real parameter near a zero and $x, f \in R^n$ and $y, g \in R^m$. Because of the presence of fast and slow states in the model, singular perturbation problem shows multi-time-scale behavior; therefore it is reasonable to analyze the slow and fast state variables on the order of different time scales. The original model breaks down into two related sub models, the reduced and boundary layer models. We will now show this analysis (see Tihonov, 1952; Hoppensteadt, 1966, and 1971).

First, by setting $\varepsilon = 0$, we see that the dimensions of state equations reduce from $n + m$ to n. Thus, the differential equation (2.22) will change to:

$$\begin{aligned} \frac{dx}{dt} &= f(x, y, 0), \qquad x(t_0) = x_0 \\ 0 &= g(x, y, 0) \end{aligned} \tag{2.23}$$

after dropping the initial condition $y(0) = y_0$. We call problem (2.23) the reduced model. Second, by introducing the stretching transformation $\tau = \frac{t}{\varepsilon}$ to the problem (2.22) results in,

$$\begin{aligned} \frac{dx}{d\tau} &= \varepsilon f(x, y, \varepsilon), \qquad x(t_0) = x_0 \\ \frac{dy}{d\tau} &= g(x, y, \varepsilon), \qquad y(t_0) = y_0 \end{aligned} \tag{2.24}$$

Furthermore, by setting $\varepsilon = 0$ yields $\frac{dx}{d\tau} = 0$ which in turn results in $x(\tau) = \theta$, a constant solution. We will now let $\theta = x_0$ to obtain the following differential equation,

$$\frac{dy}{d\tau} = g(x_0, y, 0), \qquad y(t_0) = y_0 \tag{2.25}$$

We call problem (2.25) the boundary layer model. Thus, in summary, analysis of a singularly perturbed initial value problem involves two sub models: the reduced model, and the boundary layer model. The former is related to dynamics of the slow variables while the latter model reveals the dynamics of the fast variables where $x(\tau)$ becomes constant.

For our work, we focus on the reduced model of the singularly perturbed initial value problem. Thus, we will now discuss an important theorem of Hoppensteadt (applied to autonomous system), where he proved that the solution of singularly perturbed model for small $\varepsilon > 0$ approximates the solution of the reduced model on the time interval $t_0 \leq t < \infty$ if certain conditions on the functions f and g are satisfied.

Hoppensteadt Theorem (Hoppensteadt, 1966)

Preliminaries:

Norm of a vector: (required to measure the distances between the solutions of the system)

$$|x| = |x_1| + |x_2| + \cdots + |x_n| = \sum |x_i|$$

$$|y| = |y_1| + |y_2| + \cdots + |y_n| = \sum |y_i|$$

Let $I = [0, \infty), R > 0$ such that $S_R = \{(x, y) \in \mathrm{E}^{k+j}: |x| + |y| \leq R\}$ and let $S_{R|x}$ and $S_{R|y}$ represent the restriction of S_R to E^k and E^j respectively. Let us assume that f and g satisfy the following conditions.

1) The reduced model (2.23) has a solution$(x(t), y(t))$ for all time $t \geq t_0 > 0$.
2) The functions$f, g, f_x, f_y, g_x, g_y \in C(S_R \times [0, \varepsilon_0])$. Here f_x denotes the matrix with components $\frac{\partial f_i}{\partial x_l}$, $i, l = 1, \ldots, k,$ and similarly for f_y, g_x and g_y.
3) There exists a bounded, twice continuously differentiable function $y = h(x)$ such that $g(x, h(x)) = 0$ for all $x \in S_{R|x}$. Furthermore assume $h(x)$ is isolated in the sense that if $z_1 \neq h(x_1)$ and $g(x_1, z_1) = 0$ for some $x_1 \in S_{R|x}$ imply $|z_1 - h(x_1)| > R$.
   With this assumption, the reduced model can be written in the more convenient form
   $$\frac{dx}{dt} = f(x, h(x), 0), \qquad x(t_0) = x_0 \qquad (*)$$
4) The function f is continuous at $y = 0, \varepsilon = 0$ uniformly in $x \in S_{R|x}$ and $f(x, 0, 0)$ and $f_x(t, x, 0, 0)$ uniformly asymptotically stable solution. In this assumption, Hoppensteadt translated the equilibrium to the origin, but it can be applied to any equilibrium.
5) The function g is continuous at $\varepsilon = 0$ uniformly in $(x, y) \in S_R$ and $g(x, y, 0)$ and its derivatives with respect to t and the components of x any y are bounded on S_R.
6) Let $\mathcal{R}$ be the class of all continuous, strictly increasing, real-valued functions $d(r)$, $r \geq 0$ with $d(0) = 0$; and let $\wp$ be the class of all nonnegative, strictly decreasing, continuous, real-valued functions $\sigma(s)$, $0 \leq s < \infty$. Let the zero solution of $(*)$ is asymptotically stable. That is, if $x = \phi(t_0, x_0)$ is the solution of $(*)$, there exist $d \in \mathcal{R}$ and $\sigma \in \wp$ such that $|\phi(t_0, x_0)| \leq d(|x_0|)\sigma(t - t_0)$ for $|x_0| \leq R$ and $t \geq t_0$.

Theorem:

Let the conditions (1) through (6) be satisfied. Then for sufficiently small $|x_0| + |y_0|$ and $\varepsilon > 0$ the solution of the original model exists for $t \geq 0$ and this solution converges to the solution of the reduced model as $\varepsilon \to 0^+$ uniformly on all closed subsets of $t \geq t_0 > 0$.

Remark

If we remove the uniform condition from (4) and replace $t \geq t_0 > 0$ by $a \leq t \leq b$ from Hoppensteadt theorem, we obtain a similar theorem from Tikhonov (1952).

Now, from $(2.18) - (2.21)$, we have a reduced model,

$$0 = \frac{k_1}{k_2} - \frac{k_1\, FT4}{k_2(k_a + FT4)} - \ TSH \qquad TSH(t_0) = TSH_0 \qquad (2.18)_0$$

$$\frac{dFT4}{dt} = \frac{k_3\, T\, TSH}{k_d\ +\ TSH} - \ k_4 FT4 \qquad FT4(t_0) = FT4_0 \qquad (2.19)$$

$$\frac{dT}{dt} = k_5\left(\frac{TSH}{T} - N\right) - k_6 Ab\, T \qquad T(t_0) = T_0 \qquad (2.20)$$

$$\frac{dAb}{dt} = k_7 Ab\, T - \ k_8\, Ab \qquad Ab(t_0) = Ab_0 \qquad (2.21)$$

Since the algebraic equation has a unique root,$TSH = \frac{k_1 k_a}{k_2(k_a+FT4)}$, so we can write our model in the more convenient form,

$$\frac{dFT4}{dt} = \frac{k_3\, k_1 k_a T}{k_1 k_a + k_2 k_a k_d\ + k_2\, k_d\, FT4} - \ k_4\, FT4 \qquad FT4(t_0) = FT4_0 \qquad (2.26)$$

$$\frac{dT}{dt} = k_5\left(\frac{k_1\, k_a}{k_2 k_a T + k_2 T FT4} - N\right) - k_6 Ab\, T \qquad T(t_0) = T_0 \qquad (2.27)$$

$$\frac{dAb}{dt} = k_7 Ab\, T - \ k_8\, Ab \qquad Ab(t_0) = Ab_0 \qquad (2.28)$$

The reduced model, (2.26) – (2.28) defines the vector field on the algebraic surface, also called slow manifold $\left(\frac{k_1 k_a}{k_2(k_a+FT4)} - TSH = 0\right)$. So, the solution of the reduced model stays on the surface $\left(\frac{k_1 k_a}{k_2(k_a+FT4)} - TSH = 0\right)$. We will use the reduced model in Chapter 4 for the stability analysis and the numerical simulations.

2.4 Summary

This chapter focused on the construction of a nonlinear model of the operation of the HPT axis in autoimmune (Hashimoto's) thyroiditis. Followed by the construction of the model, we stated and compared the existence and uniqueness theorem in non-negative region of four dimensional spaces. For this thesis, we chose an adult population and listed their normal values, ranges, units

and sources in a tabular format for all model variables, since patients with autoimmune thyroiditis are normally from adult populations rather than other populations. The model contains eleven parameters and four initial conditions. The model has singularly perturbed structure to it since the system has at least two different time scales, which in turn enables one to reduce a dimension of the 4d model.

CHAPTER 3 – NORMAL AXIS OPERATION

In the previous chapter, we formulated a model which encompasses both normal and abnormal operation of the HPT axis. In this chapter, we will look at the normal operation of the HPT axis operation. For that, we assume there are no anti-thyroid antibodies in the system. This can be done by setting the initial condition (state) of anti-thyroid antibodies to be zero in the singularly perturbed model in Chapter 2, solutions starting with $Ab(0) = 0$ will always have $Ab(t) = 0$. Thus, the four dimensional (4d) singularly perturbed model becomes a 3d model. The 3d model is,

$$\varepsilon \frac{dTSH}{dt} = \frac{k_1}{k_2} - \frac{k_1\, FT4}{k_2(k_a + FT4)} - \ TSH \qquad TSH(t_0) = TSH_0 \qquad (2.29)$$

$$\frac{dFT4}{dt} = \frac{k_3\, T\, TSH}{k_d \ + \ TSH} - \ k_4 FT4 \qquad FT4(t_0) = FT4_0 \qquad (2.30)$$

$$\frac{dT}{dt} = k_5\left(\frac{TSH}{T} - N\right) \qquad T(t_0) = T_0 \qquad (2.31)$$

3.1 Mathematical Analysis of the Singularly Perturbed (3d) Model

Remark

i) The vectorfield $\boldsymbol{F}$ becomes a 3d vector, $\boldsymbol{F} = \begin{pmatrix} \frac{k_1}{k_2} - \frac{k_1\, FT4}{k_2(k_a + FT4)} - \ TSH \\ \frac{k_3\, T\, TSH}{k_d \ + \ TSH} - \ k_4 FT4 \\ k_5\left(\frac{TSH}{T} - N\right) \end{pmatrix}$

ii) the 3d initial value problem has a unique solution if $T_0 > 0, FT4_0 \geq 0$ and $TSH_0 \geq 0$ (see Chapter 2).

Steady states

For any $\varepsilon > 0$, one can solve for steady states by setting the right hand sides of each equation in the model, $(2.29) - (2.31)$ equal to zero. If we now solve for steady states which yields, a cubic polynomial for $FT4_1$ suggesting that the model could predict three meaningful steady states.

$$TSH_1 = \frac{k_1 k_a}{k_2(k_a + FT4_1)}$$

$$T_1 = \frac{TSH_1}{N}$$

$$FT4_1^3 + k_a\left(2 + \frac{k_1}{k_2 k_d}\right)FT4_1^2 + \left(k_a^2 + \frac{k_a^2 k_1}{k_2 k_d}\right)FT4_1 - \frac{k_3 k_1^2 k_a^2}{k_4 k_2^2 k_d N} = 0$$

In Appendix B, we applied Descartes' sign rule to the cubic polynomial and noticed that the cubic polynomial has one sign change and so therefore, the model has exactly one positive real steady state and other two steady states are either negative real or complex depending upon the model parameter values. The existence of positive real steady state is a biologically meaningful state; we call this steady state the euthyroid state. The existence of other two steady states either in the negative orthant or complex space is biologically meaningless. For steady state analysis, we only consider the euthyroid state which is as follows (see Appendix B for solving the cubic polynomial),

Let

$$a = \frac{-k_a^2}{3}\left(\frac{k_1^2}{k_2^2\, k_d^2} + \frac{k_1}{k_2 k_d} + 1\right)$$

$$b = \frac{k_1^2 k_a^3}{9k_2^2 k_d^2} + \frac{2k_1^3 k_a^3}{27k_2^3 k_d^3} - \frac{k_3 k_1^2 k_a^2}{k_4 N k_d k_2^2} - \frac{2k_a^3}{27} - \frac{k_1 k_a^3}{9k_2 k_d}$$

Then

$$FT4_1 = \left(\frac{-b}{2} + \sqrt{\frac{b^2}{4} + \frac{a^3}{27}}\right)^{\frac{1}{3}} + \left(\frac{-b}{2} - \sqrt{\frac{b^2}{4} + \frac{a^3}{27}}\right)^{\frac{1}{3}} - \frac{k_a}{3}\left(2 + \frac{k_1}{k_2 k_d}\right)$$

$$TSH_1 = \frac{k_1 k_a}{k_2(k_a + FT4_1)}$$

$$T_1 = \frac{TSH_1}{N}$$

Note: the euthyroid state depends on the model parameter values suggesting that this state is unique for each individual in the adult population. Also, the euthyroid state is independent of the parameter k_5.

Let

$$TSH1 = \frac{k_1\, k_a}{k_2(k_a + FT42)}, TSH2 = \frac{k_1\, k_a}{k_2(k_a + FT41)}, FT41 = \frac{k_3\,(T1)(\,TSH1)}{k_4(k_d\, +\, TSH2)},$$

$$FT42 = \frac{k_3(TSH2)(T2)}{k_4(k_d\, +\, TSH1)}, T1 = \frac{TSH1}{N} \text{ and } T2 = \frac{TSH2}{N}$$

Then for

$$D = \left\{(TSH, FT4, T)\middle| \begin{matrix} TSH1 \le TSH \le TSH2 \\ FT41 \le FT4 \le FT42 \\ T1 \le\ T \le T2 \end{matrix}\right\}$$

We have the following theorem.

Theorem 3.1 (Boundedness)

The solutions of $(2.29) - (2.31)$ with initial conditions in $D \subset \mathrm{R}^3_+$ are bounded for all $t > 0$.

Proof

First, let us determine six faces, $T = T1,\ T = T2,\ FT4 = FT41,\ FT4 = FT42,\ TSH = TSH1$ and $TSH = TSH2$ in R^3_+ such that the faces trap solutions within a rectangular box D and $\boldsymbol{n} \cdot \boldsymbol{F} < 0$ where, $\boldsymbol{n}$ the unit outward normal vector to D. The 3d rectangular box is represented as follows,

$$T1 \le\ T \le T2, \qquad FT41 \le FT4 \le FT42\,, \qquad TSH1 \le TSH \le TSH2$$

Second, let $\boldsymbol{i}, \boldsymbol{j}$, and $\boldsymbol{k}$ be the unit normal vectors in the positive $T, FT4$ and TSH directions. On $TSH = TSH1$, $\boldsymbol{n} = -\boldsymbol{k}$ and $\boldsymbol{n} \cdot \boldsymbol{F} < 0$ requires

$$-\boldsymbol{k}\cdot\boldsymbol{F}]_{TSH=TSH1} = -\varepsilon\frac{dTSH}{dt}\Big]_{TSH=TSH1}$$

$$= -\frac{1}{\varepsilon}\left(\frac{k_1\,k_a}{k_2(k_a+FT4)} - \ TSH1\right) \le 0 \text{ and } = 0 \text{ if } FT4 = FT42$$

Along the edge $TSH = TSH1$ and $FT4 = FT42$ for any solution of $(2.29) - (2.31)$ on that edge,

$$\frac{d^2TSH}{dt^2} = \frac{-k_1k_a\left(\frac{dFT4}{dt}\right)}{(k_a+FT4)^2} - k_2\frac{dTSH}{dt}, \text{using } \varepsilon = \frac{1}{k_2}$$

$$= \frac{-k_1k_a\left(\frac{dFT4}{dt}\right)}{(k_a+FT4)^2}$$

since $\frac{dTSH}{dt} = 0$ on edge $TSH = TSH1$ and $FT4 = FT42$. So the sign of the second derivative of TSH is determined by $\frac{dFT4}{dt}$ on that edge.

$$\frac{dFT4}{dt} = \frac{k_3\,T\,TSH1}{k_d\ +\ TSH1} -\ k_4FT42$$

$$= \frac{k_3\,T\,TSH1}{k_d\ +\ TSH1} - \frac{k_3(TSH2)(T2)}{k_d\ +\ TSH1} < 0$$

since $FT42 = \frac{k_3(TSH2)(T2)}{k_4(k_d+TSH1)}$ and $TSH1 < TSH2$. Thus, $\frac{d^2TSH}{dt^2} > 0$ and TSH increases on that edge. So the solution would move back into $TSH1 \le TSH \le TSH2$.

On $TSH = TSH2$, $\boldsymbol{n} = \boldsymbol{k}$ and $\boldsymbol{n}\cdot\boldsymbol{F} < 0$ requires

$$\boldsymbol{k}\cdot\boldsymbol{F}]_{TSH=TSH2} = \varepsilon\frac{dTSH}{dt}\Big]_{TSH=TSH2}$$

$$= \frac{1}{\varepsilon}\left(\frac{k_1\,k_a}{k_2(k_a+FT4)} - \ TSH2\right) \le 0 \text{ and } = 0 \text{ if } FT4 = FT41$$

Along the edge $TSH = TSH2$ and $FT4 = FT41$ for any solution of $(2.29) - (2.31)$ on that edge,

$$\frac{d^2TSH}{dt^2} = \frac{-k_1k_a\left(\frac{dFT4}{dt}\right)}{(k_a+FT4)^2}$$

So the sign depends on $\frac{dFT4}{dt}$. On $TSH = TSH2$ and $FT4 = FT41$

$$\frac{dFT4}{dt} = \frac{k_3\, T\, TSH2}{k_d\, +\, TSH2} -\, k_4 FT41$$

$$= \frac{k_3}{k_d\, +\, TSH2}(\, T\, TSH2 - T1\, TSH1) > 0$$

Thus $\frac{d^2TSH}{dt^2} < 0$ and TSH decreases on that edge. So the solution would move back into $TSH1 \leq TSH \leq TSH2$.

Therefore, the faces $TSH1 = \frac{k_1\, k_a}{k_2(k_a + FT42)}$ and $TSH2 = \frac{k_1\, k_a}{k_2(k_a + FT41)}$, where

$$TSH1 \leq\, TSH \leq TSH2$$

Consider now the faces $FT4 = FT41$ and $FT4 = FT42$, where $FT41 \leq FT4 \leq FT42$.

On $FT4 = FT41$, $\boldsymbol{n} = -\boldsymbol{j}$ and $\boldsymbol{n} \cdot \boldsymbol{F} < 0$ requires

$$-\boldsymbol{j} \cdot \boldsymbol{F}]_{FT4=FT41} = -\frac{dFT4}{dt}\Big]_{FT4=FT41} = -\left(\frac{k_3\, T\, TSH}{k_d\, +\, TSH} -\, k_4 FT41\right) < 0$$

if and only if,

$$\frac{k_3\, T\, TSH}{k_4(k_d\, +\, TSH)} > FT41 \text{ for all } TSH1 \leq TSH \leq TSH2 \text{ and } T1 \leq T \leq T2$$

We can now obtain the lower bound for $FT4$ by choosing $FT41$ as,

$$FT41 = \frac{k_3\, T_{min}\, TSH_{min}}{k_4(k_d\, +\, TSH_{max})} = \frac{k_3\, (T1)\, (TSH1)}{k_4(k_d\, + TSH2)}$$

On $FT4 = FT42$, $\boldsymbol{n} = \boldsymbol{j}$ and $\boldsymbol{n} \cdot \boldsymbol{F} < 0$ requires

$$\boldsymbol{j} \cdot \boldsymbol{F}]_{FT4=FT42} = \frac{dFT4}{dt}\Big]_{FT4=FT42} = \frac{k_3\, T\, TSH}{k_d\, +\, TSH} -\, k_4 FT42 < 0$$

if and only if,

$$\frac{k_3\, T\, TSH}{k_4(k_d\, +\, TSH)} < FT42 \text{ for all } TSH1 \leq TSH \leq TSH2 \text{ and } T1 \leq T \leq T2$$

We can now obtain the upper bound for $FT4$ by choosing $FT42$ as,

$$FT42 = \frac{k_3\, T_{max}\, TSH_{max}}{k_4(k_d\, +\, TSH_{min})} = \frac{k_3\, (T2)\, (TSH2)}{k_4(k_d\, +\, TSH1)}$$

Therefore, the faces $FT41 = \frac{k_3\, (T1)\, (TSH1)}{k_4(k_d + TSH2)}$ and $FT42 = \frac{k_3\, (T2)\, (TSH2)}{k_4(k_d + TSH1)}$ where

$$FT41 \leq FT4 \leq FT42$$

Finally let us consider the faces $T = T1$ and $T = T2$ where $T1 \leq\ T \leq T2$. On $T = T1$, $\boldsymbol{n} = -\boldsymbol{i}$ and $\boldsymbol{n} \cdot \boldsymbol{F} < 0$ requires

$$-\boldsymbol{i} \cdot \boldsymbol{F}]_{T=T1} = -\frac{dT}{dt}\Big]_{T=T1} = -k_5\left(\frac{TSH}{T1} - N\right) \leq 0 \text{ and } = 0 \text{ if } TSH = TSH1$$

Along the edge $T = T1$ and $TSH = TSH1$ for any solution of $(2.29) - (2.31)$ on that edge,

$$\frac{d^2T}{dt^2}\Big]_{\substack{T=T1 \\ TSH=TSH1}} = k_5\left(\frac{T\left(\frac{dTSH}{dt}\right) - \left(\frac{dT}{dt}\right)TSH}{T^2}\right)\Bigg]_{\substack{T=T1 \\ TSH=TSH1}}$$

$$= k_5\left(\frac{\frac{dTSH}{dt}}{T1}\right)$$

So the sign is determined by $\frac{dTSH}{dt}$. On the edge $T = T1$ and $TSH = TSH1$,

$$\frac{dTSH}{dt} = \frac{k_1 k_a}{k_a + FT4} - k_2 TSH1$$

$$= \frac{k_1 k_a}{k_a + FT4} - \frac{k_1 k_a}{k_a + FT42}$$

This is equal to zero if, in addition $FT4 = FT42$, otherwise $\frac{dTSH}{dt} > 0$, so T is increasing back into the range $T1\ \leq T \leq T2$ except in one case. To examine the remaining case, if $T = T1, TSH = TSH1$ and $FT4 = FT42$, as $\frac{dT}{dt} = 0$ and $\frac{d^2T}{dt^2} = 0$. We look at

$$\frac{d^3T}{dt^3} = k_5\left(\frac{\frac{d^2TSH}{dt^2}}{T}\right)$$

$$\frac{d^3T}{dt^3}\Big]_{\substack{T=T1 \\ TSH=TSH1 \\ FT4=FT42}} = k_5\left(\frac{\frac{d^2TSH}{dt^2}}{T}\right)\Bigg]_{\substack{T=T1 \\ TSH=TSH1 \\ FT4=FT42}}$$

So the sign of $\frac{d^3T}{dt^3}\Big]_{\substack{T=T1\\TSH=TSH1\\FT4=FT42}}$ is determined by $\frac{d^2TSH}{dt^2}$. Consider the second derivative of TSH at $T = T1, TSH = TSH1$ and $FT4 = FT42$.

$$\frac{d^2TSH}{dt^2} = \frac{-k_1k_a\left(\frac{dFT4}{dt}\right)}{(k_a + FT4)^2} - k_2\frac{dTSH}{dt}, \text{since } \varepsilon = \frac{1}{k_2}$$

From the previous case, $\frac{dFT4}{dt} < 0$ and $\frac{dTSH}{dt} = 0$ on $TSH = TSH1$ and $FT4 = FT42$. So $\frac{d^2TSH}{dt^2} > 0$ at that point this means that T is increasing back into the range $T1 \le T \le T2$.

On $T = T2$, $\boldsymbol{n} = \boldsymbol{i}$ and $\boldsymbol{n} \cdot \boldsymbol{F} < 0$ requires

$$\boldsymbol{i} \cdot \boldsymbol{F}]_{T=T2} = \frac{dT}{dt}\Big]_{T=T2} = k_5\left(\frac{TSH}{T2} - N\right)$$

$$= k_5N\left(\frac{TSH}{TSH2} - 1\right) \le 0 \text{ and } = 0 \text{ if } TSH = TSH2$$

On the edge $T = T2, TSH = TSH2$,

$$\frac{d^2T}{dt^2}\Big]_{\substack{T=T2\\TSH=TSH2}} = k_5\left(\frac{\frac{dTSH}{dt}}{T2}\right)$$

From the previous work, $\frac{dTSH}{dt} < 0$ when $TSH = TSH2$, except when $FT4 = FT41$. Examining that case,

$$\frac{d^3T}{dt^3}\Big]_{\substack{T=T2\\TSH=TSH2\\FT4=FT41}} = k_5\left(\frac{\frac{d^2TSH}{dt^2}}{T2}\right)$$

Again from a previous case, we found $\frac{d^2TSH}{dt^2} < 0$ and as a result, T is decreasing at the point back into the range $T1 \le T \le T2$.

Therefore, the faces $T1 = \frac{TSH1}{N}$ and $T2 = \frac{TSH2}{N}$ where

$$T1 \le T \le T2$$

Thus,

$$D = \left\{(TSH, FT4, T)| \frac{k_1\, k_a}{k_2(k_a + FT42)} \leq TSH \leq \frac{k_1\, k_a}{k_2(k_a + FT41)}, \frac{k_3\,(T1)(\,TSH1)}{k_4(k_d\, +\, TSH2)} \leq FT4 \right.$$

$$\left. \leq \frac{k_3\,(T2)\,(TSH2)}{k_4(k_d\, +\, TSH1)}\ , \frac{TSH1}{N} \leq T \leq \frac{TSH2}{N}\right\}$$

Hence the proof

■

Corollary

As D in R_+^3 is compact and invariant, there will be a steady state in D (Srzednicki, 1985). Since D lies in the positive region and there is only one steady state in the positive region, it must be in D.

Before we begin the analysis of the 3d model$(2.29) - (2.31)$, we will analyze the reduced model by setting $\varepsilon = 0$ to gain insight into the dynamics on the algebraic surface $\frac{k_1}{k_2} - \frac{k_1\, FT4}{k_2(k_a+FT4)} -\ TSH = 0$.

3.2 Mathematical Analysis of the Reduced (2d) Model

Let us consider the reduced model from $(2.29) - (2.31)$

$$\frac{dFT4}{dt} = \frac{k_3\, k_1 k_a T}{k_1 k_a + k_2 k_a k_d\, + k_2 k_d FT4} -\ k_4 FT4 \qquad FT4(t_0) = FT4_0 \qquad (3.1)$$

$$\frac{dT}{dt} = k_5\left(\frac{k_1\, k_a}{k_2 k_a T + k_2 TFT4} - N\right) \qquad T(t_0) = T_0 \qquad (3.2)$$

Notice that the reduced (2d) model describes its dynamics on the algebraic surface (also called slow manifold for the reduced model in the literature of singular perturbation theory), B, which is as follows,

$$B = \left\{(TSH, FT4, T)\middle| \frac{k_1}{k_2} - \frac{k_1\, FT4}{k_2(k_a + FT4)} -\ TSH = 0\right\}$$

One could imagine B (2d manifold) embedded in 3d space for ε equal to zero. Thus, we will first start with the mathematical (phase plane) analysis of (3.1) – (3.2) in the bounded region D

contained on the algebraic surface, $B(ie., D \cap B)$ and second, we will present the numerical simulations of the reduced model to support the analysis.

Qualitative Behavior of the Trajectories

Here, we are concerned about the qualitative behavior of the trajectories with initial conditions within the bounded region($D \cap B$). We will first start with an array of mathematical definitions that are required to construct trajectories within $D \cap B$.

Consider the autonomous initial value problem,

$$\begin{aligned} \frac{dx}{dt} &= f(x,y) \qquad x(t_0) = x_0 \\ \frac{dy}{dt} &= h(x,y) \qquad y(t_0) = y_0 \end{aligned} \tag{3.3}$$

where $F: D \cap B \rightarrow \mathrm{R}^2$ is continuously differentiable function and $F(x,y) = \begin{pmatrix} f(x,y) \\ h(x,y) \end{pmatrix}$ as a vector field in R^2.

Definition: Forward trajectory

The forward trajectory through $\boldsymbol{x}_0$ is the set

$$\gamma^+(\boldsymbol{x}_0) = \bigcup_{\tau \geq 0} \phi(\tau; \boldsymbol{x}_0)$$

where $\phi(\tau; \boldsymbol{x}_0)$ is the unique solution with initial condition $\boldsymbol{x}_0$ (see Chapter2 for general construction of ϕ).

Definition: Positively Invariant Set

A set D is said to be a positively invariant set if $\boldsymbol{x}_0 \in D$ then $\gamma^+(\boldsymbol{x}_0) \in D$

Definition: $\boldsymbol{\omega - limit\ set}$

The $\omega - limit\ set$ of $\gamma^+(\boldsymbol{x}_0)$ is

$\omega(\gamma^+(\boldsymbol{x}_0)) = \{y \in \mathrm{R}^n \mid \text{there exists } \{\tau_n\} \text{ with } \tau_n \rightarrow \infty \text{ and } \phi(\tau; \boldsymbol{x}_0) \rightarrow y \text{ as } n \rightarrow \infty\}$.

Definition: Stable Manifold

For an equilibrium state x^*, the stable manifold of the equilibrium state is given by

$$W^s(x^*) = \left\{\gamma^+(\boldsymbol{x}_0) \mid \omega\left(\gamma^+(\boldsymbol{x}_0)\right) = \{x^*\}\right\}$$

Before we use all the above definitions; we will do linear stability analysis of the euthyroid state.

Linear Stability Analysis

This section is concerned with the stability of an equilibrium (euthyroid) state for the system (3.1) – (3.2). First, note that the euthyroid steady state stays on the slow manifold within the bounded region $D \cap B$. Second, we will test the local and global nature of this state on the slow manifold using the reduced system. Recall again from Chapter 2, the reduced system defines the vector field only on the slow manifold.

Consider the reduced system,

$$\frac{dFT4}{dt} = \frac{k_3 k_1 k_a T}{k_1 k_a + k_2 k_a k_d + k_2 k_a FT4} - k_4\, FT4 = f(FT4, T) \tag{3.1}$$

$$\frac{dT}{dt} = k_5\left(\frac{k_1\, k_a}{k_2 k_a T + k_2 T FT4} - N\right) = h(FT4, T) \tag{3.2}$$

Lemma 3.1

The euthyroid state $(FT4_1, T_1)$ of $(3.1) - (3.2)$ is locally asymptotically stable on the slow manifold.

Proof

We linearize the model, $(3.1) - (3.2)$ near the euthyroid state $(FT4_1, T_1)$. The Jacobian matrix at a general point $(FT4, T)$ is,

$$J(FT4, T) = \begin{bmatrix} \dfrac{\partial f}{\partial FT4} & \dfrac{\partial f}{\partial T} \\ \dfrac{\partial h}{\partial FT4} & \dfrac{\partial h}{\partial T} \end{bmatrix}$$

$$= \begin{bmatrix} -\frac{k_3 k_1 k_a k_2 k_d T}{(k_1 k_a + k_2 k_a k_d + k_2 k_a FT4)^2} - k_4 & \frac{k_3 k_1 k_a}{k_1 k_a + k_2 k_a k_d + k_2 k_d FT4} \\ \frac{-k_a k_1 k_5}{k_2 T (k_a + FT4)^2} & \frac{-k_a k_1 k_5}{k_2 (k_a + FT4) T^2} \end{bmatrix}$$

Evaluating the Jacobian at $(FT4_1, T_1)$, we get

$$J(FT4_1, T_1) = \begin{bmatrix} -\frac{k_3 k_2 k_d N^2 T_1^3}{k_1 k_a (k_d + NT_1)^2} - k_4 & \frac{k_3 N T_1}{k_d + NT_1} \\ -\frac{k_2 T_1 N^2 k_5}{k_1 k_a} & \frac{-N k_5}{T_1} \end{bmatrix}$$

Thus, the linearized system can be written as,

$$\begin{pmatrix} \frac{du}{dt} \\ \frac{dv}{dt} \end{pmatrix} = J(FT4_1, T_1) \begin{pmatrix} u \\ v \end{pmatrix}$$

Observe that,

$$trace\, J = -\left(\frac{N k_5}{T_1} + k_4 + \frac{k_3 k_2 k_d N^2 T_1^3}{k_1 k_a (k_d + NT_1)^2} \right) < 0$$

and

$$det\, J = \frac{k_3 k_2 k_d N^3 T_1^2 k_5}{k_1 k_a (k_d + NT_1)^2} + \frac{N k_5 k_4}{T_1} + \frac{k_3 k_2 k_5 {T_1}^2 N^3}{k_1 k_a (k_d + NT_1)} > 0$$

Thus, the linear system is asymptotically stable. Hence the euthyroid state $(FT4_1, T_1)$ is locally asymptotically stable. Furthermore, since the eigenvalues of matrix $J(FT4_1, T_1)$ are the roots of the characteristic equation

$$\lambda^2 - traceJ\, \lambda + detJ = 0$$

and the roots are

$$\lambda_{1,2} = \frac{traceJ \pm \sqrt{(traceJ)^2 - 4\, detJ}}{2}$$

We have three cases,

Case1:

Suppose $(traceJ)^2 - 4\,detJ > 0$, then the eigenvalues of J are real. However,

$$(traceJ)^2 > (traceJ)^2 - 4\,detJ \qquad \text{since } detJ > 0$$

$$\lambda_{1,2} = \frac{traceJ \pm \sqrt{(traceJ)^2 - 4\,detJ}}{2} < 0$$

Thus, the euthyroid state is a stable node.

Case2:

Suppose $(traceJ)^2 - 4\,detJ < 0$, then the eigenvalues of J are complex with negative real part, therefore the euthyroid state is a stable focus.

Case3

Suppose $(traceJ)^2 - 4\,detJ = 0$, then the eigenvalues of J are equal with negative real part $\frac{traceJ}{2}$ therefore the euthyroid state is a degenerate stable node.

Remark

For our system,

$$(traceJ)^2 - 4\,detJ = \left[\left(\frac{Nk_5}{T_1} - k_4\right) - \frac{k_3k_2k_dN^2T_1^3}{k_1k_a(k_d + NT_1)^2}\right]^2 - \frac{4k_3k_2k_5{T_1}^2N^3}{k_1k_a(k_d + NT_1)}$$

We call the left hand side as $p = (traceJ)^2 - 4\,detJ$ for simplicity. For illustration, we use parameter values from Table A2 (see Appendix A – parameter estimation) except for k_5. If $k_5 > 1.3 * 10^{-4}$ then, $p > 0$ and then the euthyroid state is a stable node. If $0 < k_5 < 1.3 * 10^{-4}$, then $p < 0$, and then the euthyroid state is a stable focus. If $k_5 \cong 0$ or $k_5 = 1.3 * 10^{-4}$, p is approximately zero, therefore the euthyroid state is a degenerated stable node (see Figure 3.1).

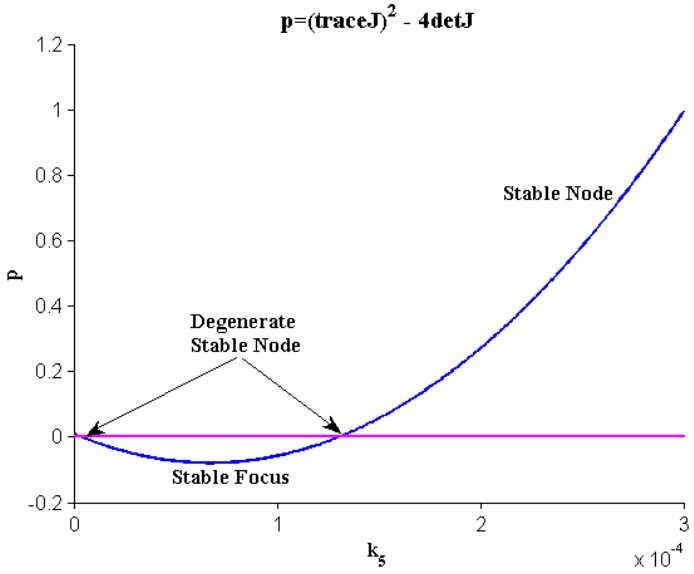


Figure 3.1: For the values in Table A2, but with k_5 varying, the figure shows how k_5 changes the changes the nature of the euthyroid steady state. Note that the euthyroid state is independent of k_5.

■

Basin of Attraction for the Euthyroid State

In this section, we will show that the euthyroid state is an attractor for the set of points on the slow manifold. We show this by employing Dulac's Criterion and the Poincare - Bendixson theorem on the slow manifold. Recall that the euthyroid state is located within the bounded region,$D \cap B \subset B$.

Dulac's Criterion (Robinson, 2004)

This method is based on Green's theorem, which rules out the possibility of closed orbit in the planar region. This method works only in 2d space (manifold). In our case, the planar region is the algebraic surface (slow manifold) and the reduced (2d) model $(3.1) - (3.2)$ is defined at all points on the slow manifold.

Theorem: (Dulac's Criterion)

Consider the differential equation (3.3) where $F(x,y) = \begin{pmatrix} f(x,y) \\ h(x,y) \end{pmatrix}$ be a continuously differentiable vector field defined on simply connected subset $A \subset \mathrm{R}^2$ in the plane. If there exists a continuously differentiable, real-valued function $g(x,y)$ such that $div(gF) = \frac{\partial(gf)}{\partial x} + \frac{\partial(gh)}{\partial y} > 0\ (< 0)$ has one sign throughout A, then there are no closed orbits lying entirely in A.

Theorem (Poincare-Bendixson) (Robinson, 2004)

Consider a differential equation (3.3) on R^2. Assume that F is defined on all of R^2. Assume that a forward trajectory $\{\phi(\tau; \boldsymbol{x}_0)\colon \tau \geq 0\}$ is bounded. Then $\omega(\boldsymbol{x}_0)$ either (i) contains a steady state or (ii) is a periodic orbit.

Remark

Let R^2_+ and B be two open sets in R^3_+. A homeomorphism u from R^2_+ to B is a continuous map onto B, which has a continuous inverse v from B to R^2_+. It follows that u is one to one (i.e., if $u(x_1) = u(x_2)$ then $x_1 = x_2$.

Remark

We will first use Dulac's criterion to rule out the possibility of closed orbit in the bounded region on the slow manifold and next, by using the Poincare-Bendixson theorem (on the slow manifold), we conclude all trajectories of the system (3.1) – (3.2) converge to the euthyroid state.

Lemma 3.2

The euthyroid state $(FT4_1, T_1)$ of the reduced system $(3.1) - (3.2)$ is an attractor for the set of points$(D \cap B)$ contained in the slow manifold(B).

Proof

Let $F =< f, h >$ and $g = 1$. We already have constructed the bounded region $D \cap B \subset B$ (slow manifold) for our reduced (2d) model.

$$div(F) = \frac{\partial f}{\partial FT4} + \frac{\partial h}{\partial T}$$

$$= -\left(\frac{k_3 k_1 k_a k_2 k_d T}{(k_1 k_a + k_2 k_a k_d + k_2 k_d FT4)^2} + k_4 + \frac{k_a k_1 k_5}{k_2 (k_a + FT4) T^2}\right) < 0 \text{ for all } (FT4, T) \in D \cap B$$

This implies there are no closed orbits in the bounded region $D \cap B \subset B$(slow manifold). Since the bounded region $D \cap B$ is compact and positive invariant, therefore, we conclude from the Poincare-Bendixson theorem that all trajectories of the system (3.1) – (3.2) converge to the euthyroid steady state.

■

Theorem 3.2

For any given initial condition $(FT4(t_0), T(t_0))$ in $D \cap B$ is on the slow manifold, there exists a unique trajectory starting at the initial state which approaches the euthyroid steady state $(FT4_1, T_1)$ as $t \to \infty$. That is,

$$\lim_{t \to \infty} ((FT4(t), T(t)) = (FT4_1, T_1) \text{ or } W^s(FT4_1, T_1) = D \cap B.$$

Proof

We have shown in Theorem 3.1, D is a bounded region, so $D \cap B$ is a bounded region on the slow manifold. This means any trajectories of reduced (2d) model (3.1) – (3.2) starting in $D \cap B$ at time t_0 will stay there for all future time $(t > t_0)$ and we have also shown that there are no closed orbits in $D \cap B$ but the euthyroid state by using Dulac's criterion. From Lemma 3.1, and 3.2, we see that the euthyroid state is locally asymptotically stable and attracts all trajectories starting in $D \cap B$. Thus, $W^s(FT4_1, T_1) = D \cap B$.

■

Theorem 3.3

For any $\varepsilon > 0$ and initial condition $\left(TSH(t_0), FT4(t_0), T(t_0)\right) \in D$, there exists a unique trajectory starting at the initial state which approaches to the euthyroid state $(TSH_1, FT4_1, T_1)$ in D.

That is,

$$\lim_{t \to \infty} (TSH(t), FT4(t), T(\mathrm{t})) = (TSH_1, FT4_1, T_1) \text{ or } W^s(TSH_1, FT4_1, T_1) = D.$$

Proof

We prove this theorem by relating the trajectories of the reduced (2d) model $(3.1) - (3.2)$ and the 3d model $(2.29) - (2.31)$ through the Hoppensteadt theorem (see Chapter 2). Hoppensteadt's theorem says that for sufficiently small $\varepsilon > 0$ and initial condition $\left(TSH(t_0), FT4(t_0), T(t_0)\right)$ in D, the trajectory of the 3d model $(2.29) - (2.31)$ exists for $t \geq t_0$ and that trajectory converges to the trajectory of the reduced 2d model $(3.1) - (3.2)$ as $\varepsilon \to 0^+$ uniformly on all closed subsets of $t \geq t_0$. Note: in our case, $\varepsilon = \frac{1}{\mathrm{k}_2} = 0.06 \ll 1$ is a fixed small number and does not converge to zero, so the trajectories of the 3d model and 2d model do not converge. But, the $\omega - limit\ set$, must be the euthyroid steady state for both the reduced (2d) and 3d model (see Figure 3.9). This means that the distance between the trajectories of the reduced (2d) model and the 3d model in D must be decreasing in order to share the same $\omega - limit\ set$. In addition, D is positively invariant and contains the euthyroid steady state which is locally asymptotically stable (see Chapter 4). Thus, our result follows $W^s(TSH_1, FT4_1, T_1) = D$.

3.3 Numerical Simulations of the Reduced (2d) Model

We have done the mathematical analysis of the two dimensional reduced system in the bounded region on the slow manifold. In this section, we will present the numerical simulations of the

reduced 2d model to confirm our mathematical analysis (see Figures 3.2, 3.3, 3.4, 3.5, 3.6 and 3.7). For numerical simulations, we pick an imaginary normal individual, whose normal TSH, free T4 and the functional size are given in Table A1, in other words, euthyroid state of this individual is given in Table A1(see Appendix A). For this individual, the parameter values are estimated and listed in Table A2 (see Appendix A) however, we use $k_5 = 0.8 * 10^{-4}\ \frac{L^3}{mU*day}$ in order to confirm our analysis. We start the 2d system with different clinical initial states and investigate the dynamics of our imaginary individual. For all our simulations, we use ode15s solver from Matlab suite (see Chapter 4 for specific details).

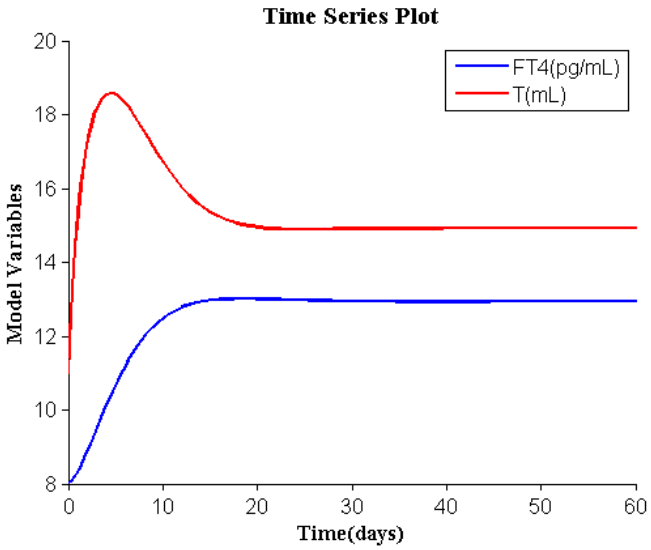


Figure 3.2: The plot of free T4 and the thyroid functional size (T) as a function of time of a simulated individual. Note the thyroid functional size (T) is in milliliters. We start the reduced (2d) model at the initial state $(FT4, T) = (8\frac{pg}{mL}, 0.011\ L)$, having free T4 and T within the reference range (normal), and using parameter values from the Table A2 in Appendix A except for k_5. Here $k_5 = 0.8 * 10^{-4}\ L^3/mU * day$. The 2d reduced system predicts that the imaginary individual probably develops a goiter before the monitored values asymptotically approaches the euthyroid state $(13\frac{pg}{mL}, 0.015\ L)$ in approximately 60 days.

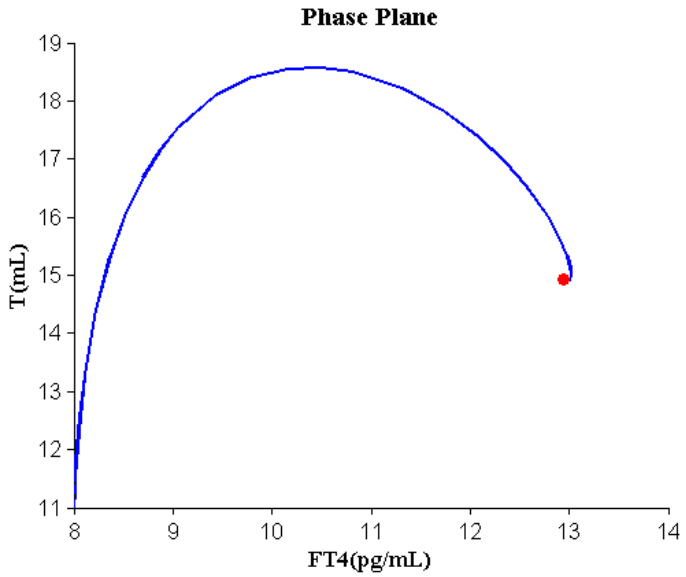


Figure 3.3: The phase plane view of the previous time series plot. Note the thyroid functional size (T) is in milliliters. Here $k_5 = 0.8 * 10^{-4}\ L^3/mU * day$. The reduced 2d system asymptotically approaches the euthyroid state $(13\frac{pg}{mL}, 0.015\ L)$.

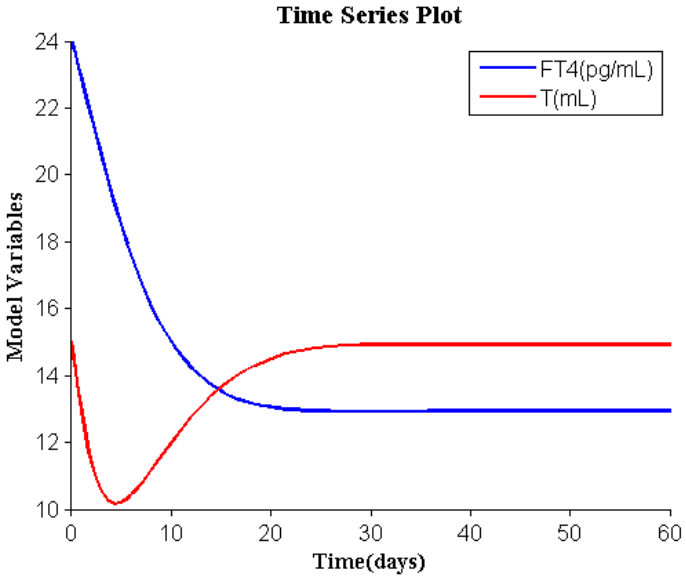


Figure 3.4: Note the thyroid functional size (T) is in milliliters. We start the reduced (2d) model at the initial state $(FT4, T) = (24\frac{pg}{mL}, 0.015\ L)$, having free T4 above the upper reference limit of free T4 and T normal (hashitoxicosis), and using parameter values from the Table A2 in Appendix A except for k_5. Here $k_5 = 0.8 * 10^{-4}\ L^3/mU * day$. The 2d reduced system predicts that the imaginary individual asymptotically approaches the euthyroid state $(13\frac{pg}{mL}, 0.015\ L)$ in approximately 60 days.

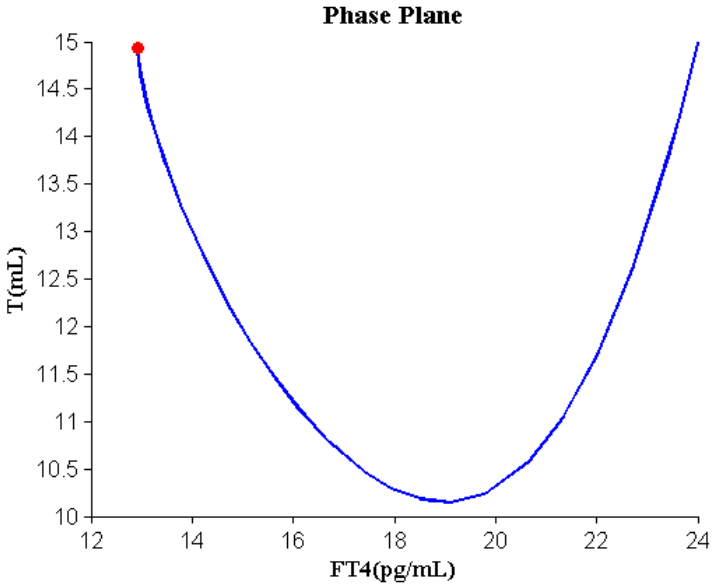


Figure 3.5: The phase plane view of Figure 3.4. Note the thyroid functional size (T) is in milliliters and $k_5 = 0.8 * 10^{-4}\ L^3/mU * day$. The reduced 2d system asymptotically approaches the euthyroid state $(13\frac{pg}{mL}, 0.015\ L)$ from hashitoxicosis state $(24\frac{pg}{mL}, 0.015\ L)$.

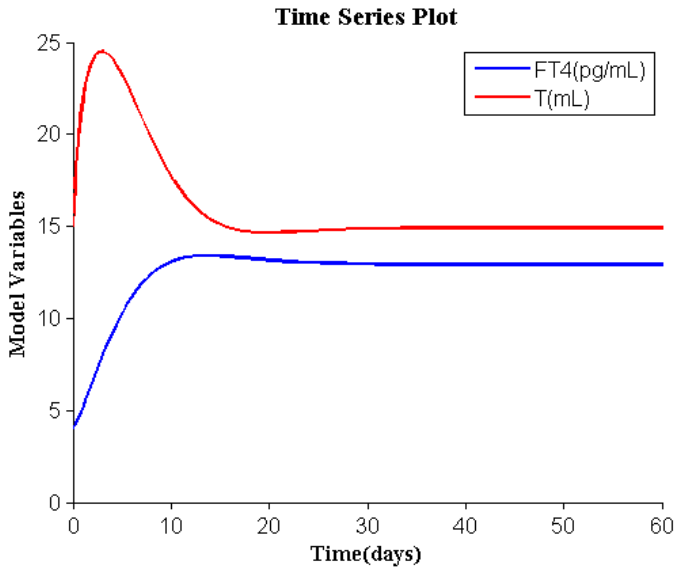


Figure 3.6: Note the thyroid functional size (T) is in milliliters. We start the reduced (2d) model at the initial state $(FT4, T) = (4\frac{pg}{mL}, 0.015\ L)$, having free T4 below lower reference limit of free T4 and T normal (clinical hypothyroidism), and using parameter values from the Table A2 in Appendix A except for k_5. Here $k_5 = 0.8 * 10^{-4}\ L^3/mU * day$. The 2d reduced system predicts that the imaginary individual asymptotically approaches the euthyroid state $(13\frac{pg}{mL}, 0.015\ L)$ in approximately 60 days.

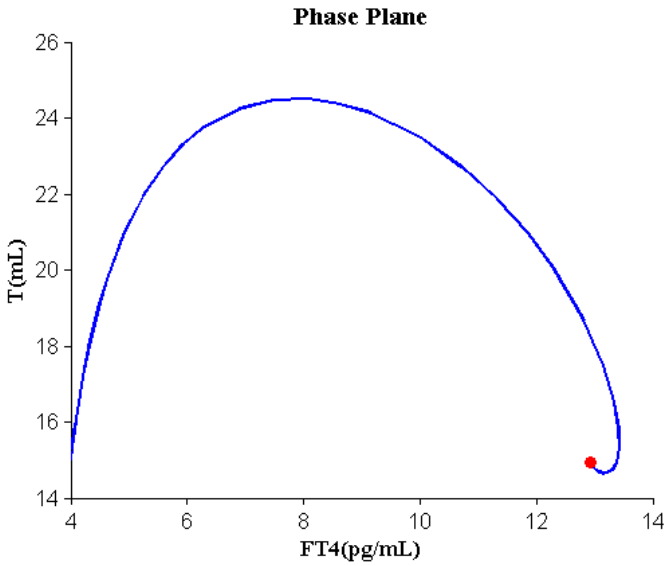


Figure 3.7: The phase plane view of Figure 3.6. Note the thyroid functional size (T) is in milliliters and $k_5 = 0.8 * 10^{-4}\ L^3/mU * day$. The reduced 2d system asymptotically approaches the euthyroid state $(13\frac{pg}{mL}, 0.015\ L)$ from clinical hypothyroidism state $(4\frac{pg}{mL}, 0.015\ L)$.

3.4 Numerical Simulations of the Singularly Perturbed (3d) Model

To present numerical simulations of the 3d model, we will use the original 4d model, (2.2) – (2.17) by setting the initial condition of anti-thyroid antibodies to be zero (that is, $Ab_0 = 0$). We use ode15s from Matlab suite for all our simulations (see Chapter 4 for specific details). We illustrate the mathematical analysis of the 3d model through our simulations. For that, we use our imaginary individual's variable and parameter values from Table A1 and Table A2 in Appendix A. Also, we use $k_5 = 0.8 * 10^{-4}\ \frac{L^3}{mU*day}$.

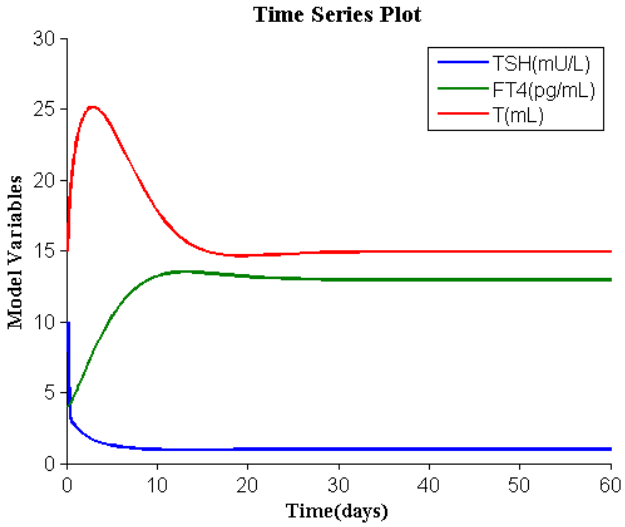


Figure 3.8: Note the thyroid functional size(T) is in milliliters. We start the original (4d) model at the initial state $(TSH, FT4, T, Ab) = (10\ \frac{mU}{L}, 4\ \frac{pg}{mL}, 0.015\ L, 0)$, having TSH, free T4 outside the reference range (clinical hypothyroidism), T and Ab normal, plus using the parameter values from Table A2 in Appendix A except for k_5. Here $k_5 = 0.8 * 10^{-4}\ L^3/mU * day$. The 4d system predicts that the imaginary individual asymptotically approaches the euthyroid state $(1\ \frac{mU}{L}, 13\frac{pg}{mL}, 0.015\ L, 0)$ in approximately 60 days. Also, observe that TSH quickly approaches the euthyroid state suggestive of the existence of a fast-time-scale for TSH.

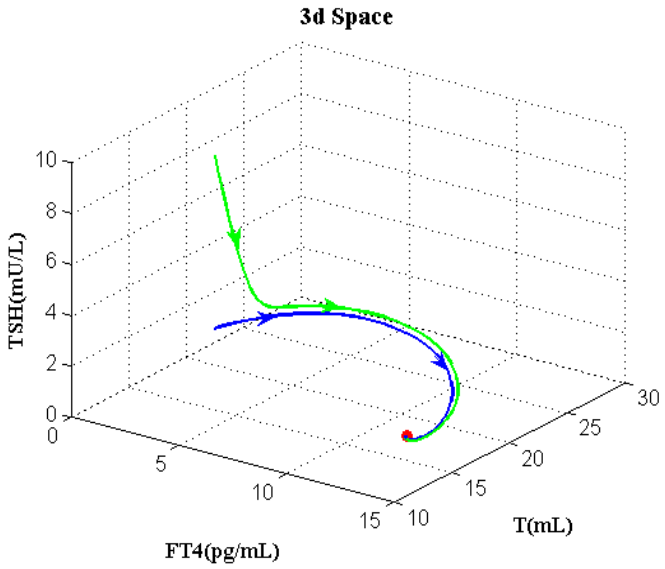


Figure 3.9: 3d phase space view of Figure 3.8. Note the thyroid functional size (T) is in milliliters and $k_5 = 0.8 * 10^{-4}\ L^3/mU * day$. The reduced 2d system asymptotically approaches the euthyroid state $(13\frac{pg}{mL}, 0.015\ L)$ from clinical hypothyroidism state $(4\frac{pg}{mL}, 0.015\ L)$. Using the algebraic equation, $g = 0$, TSH is computed for the 2d system. The 4d system asymptotically

approaches the euthyroid state $(1\ \frac{mU}{L}, 13\frac{pg}{mL}, 0.015\ L, 0)$ from clinical hypothyroidism state $(10\ \frac{mU}{L}, 4\ \frac{pg}{mL}, 0.015\ L, 0)$. Note: the reduced 2d system approximates the 4d system. Also, $\varepsilon = \frac{1}{k_2} = 0.06 \ll 1$ is a small fixed value.

3.5 Summary

This chapter focused on the dynamics of the normal operation of the HPT axis. For that, we have excluded the anti-thyroid antibodies (stand in for anti-thyroid immune response) from the system which gave rise to the 3d model. We used the singularly perturbed 3d model in order to reduce a dimension of the 3d model and to study the dynamics of the HPT axis on the algebraic surface (plane) in an effective manner. Thus, the reduced 2d model described all its dynamics in the plane, in fact, the algebraic surface (also called slow manifold). In addition, we constructed a bounded region in the slow manifold so that if a solution starts within the bounded region at time t_0, it stays there for all future time $t > t_0$. Finally, we proved that the euthyroid state is locally asymptotically stable on the algebraic surface and an attractor for the set of values in the bounded region (*D*). This is the main result for this Chapter. We have also presented numerical simulations of reduced 2d model $(3.1) - (3.2)$ and original 4d model, $(2.2) - (2.17)$ to confirm the mathematical analysis of this Chapter.

CHAPTER 4 – ANALYSIS OF DYNAMICS OF 4d MODEL

In this chapter, we present an analysis of the full 4d model which includes investigating the local stability of euthyroid state and diseased steady state. Along with this, we present numerical simulations to support stability analysis of the full 4d model. In addition, we present bifurcation analysis to determine the qualitative behavior of the system, that is, the structural stability of the model as a parameter changes in the system.

The 4d model is as follows,

$$\varepsilon \frac{dTSH}{dt} = \frac{k_1}{k_2} - \frac{k_1\, FT4}{k_2(k_a + FT4)} - \ TSH \qquad TSH(t_0) = TSH_0 \qquad (2.18)_\varepsilon$$

$$\frac{dFT4}{dt} = \frac{k_3\, T\, TSH}{k_d \ + \ TSH} - \ k_4 FT4 \qquad FT4(t_0) = FT4_0 \qquad (2.19)$$

$$\frac{dT}{dt} = k_5\left(\frac{TSH}{T} - N\right) - k_6 Ab\, T \qquad T(t_0) = T_0 \qquad (2.20)$$

$$\frac{dAb}{dt} = k_7 Ab\, T - \ k_8\, Ab \qquad Ab(t_0) = Ab_0 \qquad (2.21)$$

Remark

i) The vectorfield $\boldsymbol{F}$ is a 4d vector, where $\boldsymbol{F} = \begin{pmatrix} \frac{k_1}{k_2} - \frac{k_1\, FT4}{k_2(k_a + FT4)} - \ TSH \\ \frac{k_3\, T\, TSH}{k_d \ + \ TSH} - \ k_4 FT4 \\ k_5\left(\frac{TSH}{T} - N\right) - k_6 Ab\, T \\ k_7 Ab\, T - \ k_8\, Ab \end{pmatrix}$

ii) Note that the 4d initial value problem has unique solutions if $T_0 > 0, FT4_0 \geq 0, TSH_0 \geq 0$ and $Ab_0 \geq 0$ (see Chapter 2).

4.1 Mathematical Analysis of the Singularly Perturbed (4d) Model

We begin the analysis of 4d model by examining the steady states of the system. For every $\varepsilon > 0$, we can find equilibrium states. Setting the left hand side of (2.21) equal to zero yields $Ab = 0$ or $T = k_8/k_7$. When $Ab = 0$, we obtain the euthyroid state (steady state – see Chapter 3 and Appendix B), that is,

$$Ab_1 = 0$$

Let

$$a = \frac{-k_a^2}{3}\left(\frac{k_1^2}{k_2^2\, k_d^2} + \frac{k_1}{k_2 k_d} + 1\right)$$

$$b = \frac{k_1^2 k_a^3}{9k_2^2 k_d^2} + \frac{2k_1^3 k_a^3}{27k_2^3 k_d^3} - \frac{k_3 k_1^2 k_a^2}{k_4 N k_d k_2^2} - \frac{2k_a^3}{27} - \frac{k_1 k_a^3}{9k_2 k_d}$$

Then

$$FT4_1 = \left(\frac{-b}{2} + \sqrt{\frac{b^2}{4} + \frac{a^3}{27}}\right)^{\frac{1}{3}} + \left(\frac{-b}{2} - \sqrt{\frac{b^2}{4} + \frac{a^3}{27}}\right)^{\frac{1}{3}} - \frac{k_a}{3}\left(2 + \frac{k_1}{k_2 k_d}\right)$$

$$TSH_1 = \frac{k_1 k_a}{k_2(k_a + FT4_1)}$$

$$T_1 = \frac{TSH_1}{N}$$

The euthyroid state is located in a hyper plane ($Ab_1 = 0$), reasonable initial conditions for the system of differential equations are $\mathrm{TSH}(t_0) = TSH_1, FT4(t_0) = FT4_1, T(t_0) = T_1, Ab(t_0) = Ab_1 + (\text{some antibody value})$ in numerical simulations to investigate the local stability of euthyroid state in patients with autoimmune thyroiditis.

Next, consider a possible equilibrium when $Ab \neq 0$. This requires $T = k_8/k_7$ and substitution of this equilibrium value into the right hand sides of the equation $(2.18)_\varepsilon$, (2.19) and (2.20), that leads to a steady state in the system, which we call a diseased state,

$$T_2 = \frac{k_8}{k_7}$$

$$FT4_2 = \frac{-\left(k_a + \frac{k_1 k_a}{k_d k_2}\right) + \sqrt{\left(k_a + \frac{k_1 k_a}{k_d k_2}\right)^2 + \frac{4\, k_1 k_3 k_a k_8}{k_d k_2 k_7 k_4}}}{2}$$

$$TSH_2 = \frac{k_1 k_a}{k_2(k_a + FT4_2)}$$

$$Ab_2 = \frac{k_7 k_5}{k_6 k_8}\left(\frac{k_7 TSH_2}{k_8} - N\right)$$

Remark

If the expression $\left(\frac{k_7 TSH_2}{k_8} - N\right) < 0$ is true, then the diseased (steady) state is located in the negative orthant, that is, $Ab_2 < 0$.

Positively Invariant (Bounded) Region

We constructed a bounded region in the previous chapter using TSH, $FT4$ and T when the initial state of anti-thyroid antibodies is set to zero ($Ab = 0$). But, now we will establish a bounded region in 4d space for the full model when the initial state of anti-thyroid antibodies is not set to zero. Recall the definitions of $TSH1$ and $TSH2$ from the previous chapter – the particular faces of the rectangular box D.

Let

$$TSH1 = \frac{k_1\, k_a}{k_2(k_a + FT42)}, TSH2 = \frac{k_1\, k_a}{k_2(k_a + FT41)}, FT41 = \frac{k_3\,(T1)(\,TSH1)}{k_4(k_d\, +\, TSH2)},$$

$$FT42 = \frac{k_3(TSH2)(T2)}{k_4(k_d\, +\, TSH1)}, T1 = \frac{-k_5 N + \sqrt{(k_5 N)^2 + 4k_6 k_5 (Ab2)(TSH1)}}{2k_6(Ab2)}, T2 = \frac{TSH2}{N},$$

$Ab1 = 0$ and $Ab2 = Ab(t_0)$.

Then for

$$D^+ = \left\{ (TSH, FT4, T, Ab) \middle| \begin{matrix} TSH1 \le TSH \le TSH2 \\ FT41 \le FT4 \le FT42 \\ T1 \le\ T \le T2 \\ 0 \le Ab \le Ab2 \end{matrix} \right\}$$

Theorem 4.1

If $T2 = \frac{TSH2}{N} < \frac{k_8}{k_7}$, the solutions of $(2.18)_{\varepsilon}-$ (2.21) that start in D^+ at t_0 will remain in D^+ for all time $t > t_0$.

Proof

We construct eight hyper planes in R_+^4 such that the planes trap solutions within a rectangular box D^+ and $\boldsymbol{n} \cdot \boldsymbol{F} < 0$ where, $\boldsymbol{n}$ the unit outward normal vector to D^+ on seven of the hyper plane faces of the box D^+. That is,

$T1 \le\ T \le T2, \quad FT41 \le FT4 \le FT42\,, \quad TSH1 \le TSH \le TSH2, \quad Ab1 \le Ab \le Ab2$

In autoimmune thyroiditis, we can choose the lower bound for anti-thyroid antibodies (Ab), that is, $Ab1 = 0$ (the hyper plane). If a trajectory reaches $Ab = 0$, then an argument similar to that in Chapter 3 where shows the trajectory stays within the following box,

$$T1 \le\ T \le T2, \quad FT41 \le FT4 \le FT42\,, \quad TSH1 \le TSH \le TSH2$$

where $T1 = \frac{TSH1}{N}$. Second, let $\boldsymbol{i}$, $\boldsymbol{j}$, $\boldsymbol{k}$, and $\boldsymbol{l}$ be the unit normal vectors in the positive $T, FT4, TSH$ and Ab directions. In the third case, we established bounds for $TSH, FT4$, and T in Chapter 3, but the lower bound for T is affected in the presence of anti-thyroid antibodies (Ab) in the system. Thus, we construct a new lower bound for T and upper bound for Ab,

On $T = T1$, $\boldsymbol{n} = -\boldsymbol{i}$ and $\boldsymbol{n} \cdot \boldsymbol{F} < 0$ requires

$$-\boldsymbol{i} \cdot \boldsymbol{F}]_{T=T1} = -\frac{dT}{dt}\Big]_{T=T1} = -\left(k_5\left(\frac{TSH}{T1} - N\right) - k_6 Ab\, T1\right) < 0$$

if and only if

$0 < T1 < \dfrac{-k_5 N + \sqrt{(k_5 N)^2 + 4k_6 k_5 (Ab)(TSH)}}{2k_6 (Ab)}$ for $TSH1 \le TSH \le TSH2$ and

$$0 < Ab \leq Ab2$$

By choosing $TSH = TSH1$ (minimum value) and $Ab = Ab2$ (maximum value), we can obtain the lower bound for T, that is,

$$T1 = \frac{-k_5 N + \sqrt{(k_5 N)^2 + 4k_6 k_5 (Ab2)(TSH1)}}{2k_6 (Ab2)}$$

But, note that solutions on the edge, $T = T1, TSH = TSH1$ and $Ab = Ab2$ have

$$\frac{dT}{dt} = 0$$

So, along the edge, $T = T1, TSH = TSH1$ and $Ab = Ab2$ for any solution of $(2.18)_\varepsilon$ – (2.21) on that edge,

$$\left.\frac{d^2T}{dt^2}\right]_{\substack{T=T1 \\ TSH=TSH1 \\ Ab=Ab2}} = k_5 \left(\frac{T\left(\frac{dTSH}{dt}\right) - \left(\frac{dT}{dt}\right) TSH}{T^2} \right) - k_6 T \frac{dAb}{dt} - k_6 Ab \frac{dT}{dt} \Bigg]_{\substack{T=T1 \\ TSH=TSH1 \\ Ab=Ab2}}$$

$$= k_5 \left(\frac{\frac{dTSH}{dt}}{T1} \right) - k_6 (T1) \frac{dAb}{dt}$$

So the sign $\left.\frac{d^2T}{dt^2}\right]_{\substack{T=T1 \\ TSH=TSH1 \\ Ab=Ab2}}$ is determined by $\frac{dTSH}{dt}$ and $\frac{dAb}{dt}$. We see $\frac{dAb}{dt} = k_7 Ab\left(T - \frac{k_8}{k_7}\right) < 0$ and $Ab > 0$. On that edge $TSH = TSH1$, and $\frac{dTSH}{dt} = 0$ if $FT4 = FT42$, otherwise $\frac{dTSH}{dt} > 0$ for $FT41 \leq FT4 \leq FT42$. For $FT4 = FT42$, suppose $\frac{dTSH}{dt} = 0$ and

$$\left.\frac{d^2T}{dt^2}\right]_{\substack{T=T1 \\ TSH=TSH1 \\ Ab=Ab2}} > 0$$

Therefore, when $T = T1$, $TSH = TSH1$ and $Ab = Ab2$, $T(t)$ is increasing back into the range $T1 \leq T \leq T2$. Thus,

$$\frac{-k_5 N + \sqrt{(k_5 N)^2 + 4k_6 k_5 (Ab2)(TSH1)}}{2k_6 (Ab2)} \leq T \leq \frac{TSH2}{N}$$

Consider now the hyper plane $Ab = Ab2$ where $0 \leq Ab \leq Ab2$.

On $Ab = Ab2$, $\boldsymbol{n} = \boldsymbol{l}$ and $\boldsymbol{n} \cdot \boldsymbol{F} < 0$ requires

$$\boldsymbol{l} \cdot \boldsymbol{F}]_{Ab=Ab2} = \frac{dAb}{dt}\Big]_{Ab=Ab2} = Ab2(k_7 T - k_8) < 0$$

if and only if,

$$T < \frac{k_8}{k_7} \text{ for all } T1 \leq T \leq T2$$

By choosing $T = T2 = \frac{TSH2}{N}$ (maximum value), we know for sure that the anti-thyroid antibodies (Ab) are bounded as long as the following inequality satisfies,

$$\frac{TSH2}{N} < \frac{k_8}{k_7}$$

Thus, we conclude that $Ab2 = Ab(t_0)$.

Hence the proof

■

Corollary

As D^+ in R^4 is compact and invariant, there will be a steady state in D^+ (Srzednicki, 1985). Since D^+ lies in the positive region and there is only one steady state (euthyroid state) in the positive region, it must be in D^+. Also, the diseased state is not in the positive region as long as the expression $\left(\frac{k_7 TSH_2}{k_8} - N\right) < 0$ is true. Thus, the model suggests that the necessary condition for the diseased steady state to emerge into the positive region, in fact in the box, is $\left(\frac{k_7 TSH_2}{k_8} - N\right) > 0$. In addition, we observed that necessary condition becomes true as k_7 (positive parameter) changes in the system (see bifurcation analysis below).

Theorem 4.2

When $Ab = 0$ there is only one steady state (euthyroid state) in the positive octant.

Proof

The proof of this theorem follows from the following definition which relates the euthyroid state and diseased steady state.

Definition

When $\frac{k_7 TSH_2}{k_8} - N = 0$, the second steady state (diseased state) of the system $(2.18)_\varepsilon$ – (2.21) has $Ab = 0$. So it must coincide with the euthyroid state in the positive quadrant if

$$k_7 = \frac{Nk_8}{TSH_2} = \frac{Nk_8}{TSH_1}$$

Let k_7^* be the unique value of k_7 where,

$$k_7 = \frac{Nk_a k_2(k_a + FT4_2)}{k_1 k_a}$$

In addition, we have observed $k_7 = k_7^*$,

$$k_7^* = \frac{k_8}{T_1} \quad \text{since } T_1 = \frac{TSH_1}{N} \text{ for those values.}$$

Note: This critical parameter can be uniquely determined for every individual in the adult population.

Remark

k_7^* is independent of the parameters k_5, and k_6 because the euthyroid state is independent of those parameters.

Local Stability of Euthyroid State

To prove the euthyroid state is locally stable in 4d space. We need Lemma 4.1.

Lemma 4.1

Let $\alpha < \beta$ be real roots of $x^2 + bx + c = 0$. If $x > \beta$ then $x^2 + bx + c > 0$ (quadratic inequality)

Proof

Since $x^2 + bx + c = (x - \alpha)(x - \beta)$,

If $x > \beta$, both $(x - \alpha) > 0$ and $(x - \beta) > 0$ then $x^2 + bx + c > 0$.

■

Theorem 4.3

The euthyroid state is locally asymptotically stable in $(2.18)_\varepsilon$ – (2.21) if

$$k_7 < k_7^* \quad \text{and} \quad \frac{Nk_5k_7^*}{k_8} > \frac{-(k_2 + k_4) + \sqrt{(k_2 + k_4)^2 - 4k_2k_4 - 4w}}{2}$$

where

$$w = \frac{\left(k_2^2k_3k_dN^2k_8^3(k_2 + k_4) - k_2^2k_3k_5N^3k_8^2(k_dk_7^* + Nk_8)\right)}{k_1k_ak_7^*(k_2 + k_4)(k_dk_7^* + Nk_8)^2}$$

Proof

We will prove this theorem by using the Routh-Hurwitz criteria on our 4d model. We first state the Routh-Hurwitz theorem, along with the stability condition for 3d case and then prove our claim.

Routh-Hurwitz Theorem (see Hurwitz, 1895; Routh, 1877; Edelstein-Keshet, 1988)

Given a characteristic polynomial $\lambda^k + a_1\lambda^{k-1} + a_2\lambda^{k-2} + \cdots + a_k = 0$, define k matrices as follows:

$$H_1 = (a_1), \qquad H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix}, \qquad H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix}, \cdots$$

$$H_j = \begin{pmatrix} a_1 & 1 & 0 & 0 & \cdots & 0 \\ a_3 & a_2 & a_1 & 1 & \cdots & 0 \\ a_5 & a_4 & a_3 & a_2 & \cdots & 0 \\ a_{2j-1} & a_{2j-2} & a_{2j-3} & a_{2j-4} & \cdots & a_j \end{pmatrix}$$

$$H_k = \begin{pmatrix} a_1 & 1 & 0 & \cdots & 0 \\ a_3 & a_2 & a_1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & \cdots & \ldots & a_k \end{pmatrix}$$

where the (l, m) term in the matrix H_j is

$$\begin{Bmatrix} a_{2l-m} & \text{for } 0 < 2l - m < k \\ 1 & \text{for } 2l = m \\ 0 & \text{for } 2l < m \text{ or } 2l > k + m \end{Bmatrix}$$

Then the real parts of the roots are negative if and only if the determinants of all Hurwitz matrices are positive:

$$\det H_j > 0 \quad (j = 1,2, \ldots, k).$$

May (1973) summarizes these conditions for the cases $k = 2, \ldots, 5$. For our problem, we will use the case $k = 3$, which is as follows,

$$a_1, a_3 > 0;\ a_1 a_2 - a_3 > 0$$

Let us now consider the Jacobian matrix of full 4d model of (2.18) – (2.21) at euthyroid state

$$\mathrm{J}_1 = \begin{pmatrix} -\frac{1}{\varepsilon} & \frac{-k_1 k_a}{\varepsilon k_2 (k_a + FT4_1)^2} & 0 & 0 \\ \frac{k_3 k_d T_1}{(k_d + TSH_1)^2} & -k_4 & \frac{k_3 TSH_1}{(k_d + TSH_1)} & 0 \\ \frac{k_5}{T_1} & 0 & -\frac{k_5 TSH_1}{T_1^2} - k_6 Ab_1 & -k_6 T_1 \\ 0 & 0 & k_7 Ab_1 & k_7 T_1 - k_8 \end{pmatrix}$$

By utilizing $\varepsilon = \frac{1}{k_2}$ and evaluating $Ab_1 = 0, \frac{TSH_1}{T_1} = N,$ and $TSH_1 = \frac{k_1 k_a}{k_2 (k_a + FT4_1)}$, then the Jacobian becomes,

$$J_1 = \begin{pmatrix} -k_2 & \frac{-k_2^2 TSH_1^2}{k_1 k_a} & 0 & 0 \\ \frac{k_3 k_d T_1}{(k_d + TSH_1)^2} & -k_4 & \frac{k_3 TSH_1}{(k_d + TSH_1)} & 0 \\ \frac{k_5}{T_1} & 0 & -\frac{k_5 N}{T_1} & -k_6 T_1 \\ 0 & 0 & 0 & k_7 T_1 - k_8 \end{pmatrix}$$

For this Jacobian matrix, the eigenvalues can be found by solving the characteristic equation $\det(J_1 - \lambda I) = 0$. Note that the euthyroid state is asymptotically stable if and only if all the eigenvalues of Jacobian matrix have negative real parts. For this Jacobian matrix, the characteristic equation is,

$$(\lambda + k_8 - k_7 T_1)\left[(\lambda + k_2)(\lambda + k_4)\left(\lambda + \frac{k_5 N}{T_1}\right) + \frac{k_2^2 TSH_1^2}{k_1 k_a}\left(\frac{k_3 k_d T_1}{(k_d + TSH_1)^2}\left(\lambda + \frac{k_5 N}{T_1}\right) + \frac{k_5 k_3 N}{(k_d + TSH_1)}\right)\right] = 0$$

We can immediately see that if

$$k_7 < \frac{k_8}{T_1} = \frac{N k_8}{TSH_1} = k_7^*$$

then one of the eigenvalues $\lambda = -(k_8 - k_7 T_1)$ has negative real part and clearly if $k_7 = k_7^*$, there is a zero eigenvalue in the direction of anti-thyroid antibodies.

Let us now consider the equation in the square bracket,

$$\left[(\lambda + k_2)(\lambda + k_4)\left(\lambda + \frac{k_5 N}{T_1}\right) + \frac{k_2^2 TSH_1^2}{k_1 k_a}\left(\frac{k_3 k_d T_1}{(k_d + TSH_1)^2}\left(\lambda + \frac{k_5 N}{T_1}\right) + \frac{k_5 k_3 N}{(k_d + TSH_1)}\right)\right] = 0$$

Rewriting the above,

$$\lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3 = 0$$

where

$$a_1 = k_4 + k_2 + \frac{k_5 N}{T_1}$$

$$a_2 = k_2k_4 + (k_2 + k_4)\frac{k_5N}{T_1} + \frac{k_2^2k_3k_dT_1}{k_1k_a\left(\frac{k_d}{TSH_1} + 1\right)^2}$$

$$a_3 = \frac{k_2k_4k_5N}{T_1} + \frac{k_2^2k_3k_dk_5N\,TSH_1^2}{k_1k_a(k_d + TSH_1)^2} + \frac{k_2^2k_3k_5N\,TSH_1^2}{k_1k_a(k_d + TSH_1)}$$

Substituting $k_7^* = \frac{Nk_8}{TSH_1} = \frac{k_8}{T_1}$,

$$a_1 = k_4 + k_2 + \frac{Nk_5k_7^*}{k_8}$$

$$a_2 = k_2k_4 + (k_2 + k_4)\frac{Nk_5k_7^*}{k_8} + \frac{k_2^2k_3k_dk_8^3N^2}{k_1k_ak_7^*(k_dk_7^* + Nk_8)^2}$$

$$a_3 = \frac{Nk_2k_4k_5k_7^*}{k_8} + \frac{k_2^2k_3k_dk_5N^3k_8^2}{k_1k_a(k_dk_7^* + Nk_8)^2} + \frac{k_2^2k_3k_5N^3k_8^2}{k_1k_ak_7^*(k_dk_7^* + Nk_8)}$$

Note that $a_1 > 0, a_2 > 0$ and $a_3 > 0$ since all the parameters are positive and the euthyroid state is located in non-negative orthant R_+^4. By Routh-Hurwitz condition, the remaining three roots of characteristic equation will have negative real parts if and only if

$$a_1, a_3 > 0 \text{ and } a_1a_2 - a_3 > 0$$

Clearly $a_1 > 0$ and $a_3 > 0$ are true, since all parameters are nonnegative. We will now examine the condition $a_1a_2 - a_3 > 0$. Consider,

$$a_1a_2 - a_3 = \left(\frac{Nk_5k_7^*}{k_8}\right)^2(k_2 + k_4) + \frac{Nk_5k_7^*}{k_8}(k_2 + k_4)^2 + k_2k_4(k_2 + k_4)$$
$$+ \frac{k_2^2k_3k_dN^2k_8^3(k_2 + k_4)}{k_1k_ak_7^*(k_dk_7^* + Nk_8)^2} - \frac{k_2^2k_3k_5N^3k_8^2}{k_1k_ak_7^*(k_dk_7^* + Nk_8)}$$

Divide by $(k_2 + k_4)$,

$$\frac{a_1a_2 - a_3}{(k_2 + k_4)} = \left(\frac{Nk_5k_7^*}{k_8}\right)^2 + \frac{Nk_5k_7^*}{k_8}(k_2 + k_4) + k_2k_4$$
$$+ \frac{k_2^2k_3k_dN^2k_8^3(k_2 + k_4) - k_2^2k_3k_5N^3k_8^2(k_dk_7^* + Nk_8)}{k_1k_ak_7^*(k_2 + k_4)(k_dk_7^* + Nk_8)^2}$$

We want $a_1 a_2 - a_3 > 0$. By Lemma 4.1, this inequality becomes true if

$$\frac{N k_5 k_7^*}{k_8} > \frac{-(k_2 + k_4) + \sqrt{(k_2 + k_4)^2 - 4k_2 k_4 - 4w}}{2} \tag{4.1}$$

where

$$w = \frac{\left(k_2^2 k_3 k_d N^2 k_8^3 (k_2 + k_4) - k_2^2 k_3 k_5 N^3 k_8^2 (k_d k_7^* + N k_8)\right)}{k_1 k_a k_7^* (k_2 + k_4)(k_d k_7^* + N k_8)^2}$$

Hence the proof

■

Remark

For the given parameters values in Table A2, we see that the above inequality (4.1) is satisfied and thus $a_1 a_2 - a_3 > 0$.

Observation

If $k_7 < k_7^*$ and inequality (4.1) are true, then all four eigenvalues of euthyroid state have negative real parts. If $k_7 = k_7^*$ but inequality (4.1) is true, then the eigenvalue of euthyroid state in anti-thyroid antibodies (Ab) direction becomes zero. Therefore, the euthyroid steady state loses its stability to the diseased steady state. In fact, in general, when $k_7 = k_7^*$ the euthyroid and diseased states merge with each other and exchange stability in the direction of anti-thyroid antibodies (see bifurcation analysis section below). Thus, there is a bifurcation at $k_7 = k_7^*$, but we do not know exactly what kind of bifurcation it is at this point.

If $k_7 > k_7^*$ but inequality (4.1) holds, then the eigenvalue of euthyroid state in anti-thyroid antibodies direction will have positive real part and the other eigenvalues of euthyroid state have negative real parts and therefore the euthyroid state becomes unstable only in the direction of anti-thyroid antibodies. Thus, we conclude that k_7 is a bifurcation parameter for the euthyroid steady state. Next, we will study the local stability of the diseased state for $k_7 > k_7^*$.

4.2 Mathematical Analysis of the Reduced (3d) Model

Recall that, for $k_7 > k_7^*$, the necessary condition $\left(\frac{k_7 TSH_2}{k_8} - N\right) > 0$ for the diseased steady state emerge into the box D^+ becomes true. Thus, we have a diseased state in the positive orthant, R_4^+, in fact in D^+. We will use Routh – Hurwitz criterion to study the local stability of the diseased state. But, for this, we will use the reduced model from singularly perturbed 4d system – since we focus on the operation of the HPT axis in autoimmune thyroiditis and the active part of the axis (the hypothalamus-pituitary function is intact) let us reduce a dimension of the 4d model (see Chapter 2). Thus, the reduced (3d) model defines the problem of interest and of course we assumed that ε is zero, although it is $\varepsilon = \frac{1}{k_2} = 0.06 \ll 1$. Note that the reduced (3d) model is the approximation of the singularly perturbed 4d model in a slower time scale. By setting $\varepsilon = 0$, we obtained the reduced (3d) model (see Chapter 2), which is as follows,

$$\frac{dFT4}{dt} = \frac{k_3\, k_1 k_a T}{k_1 k_a + k_2 k_a k_d + k_2\, k_d\, FT4} - k_4\, FT4 \qquad FT4(t_0) = FT4_0 \qquad (2.26)$$

$$\frac{dT}{dt} = k_5\left(\frac{k_1\, k_a}{k_2 k_a T + k_2 T FT4} - N\right) - k_6 Ab\, T \qquad T(t_0) = T_0 \qquad (2.27)$$

$$\frac{dAb}{dt} = k_7 Ab\, T - k_8\, Ab \qquad Ab(t_0) = Ab_0 \qquad (2.28)$$

Notice that the reduced model describes all its dynamics on the algebraic surface (slow manifold). We will call this slow manifold as $B1$, that is,

$$B1 = \left\{(TSH, FT4, T, Ab)\,\middle|\, \frac{k_1}{k_2} - \frac{k_1\, FT4}{k_2(k_a + FT4)} - TSH = 0\right\}$$

One could imagine $B1$ (3d manifold) embedded in 4d space for ε equal to zero (see Figure 4.3 and 4.4).

Theorem 4.4

If $k_7 > k_7^*$, the necessary condition $\left(\frac{k_7 TSH_2}{k_8} - N\right) > 0$ for the diseased state in D^+ becomes true and then the diseased state in system $(2.26) - (2.28)$ is locally asymptotically stable.

Proof

We will now apply Routh-Hurwitz criteria and analyze the local stability of the diseased state. As a first step, let us compute the Jacobian matrix at the diseased state, which is,

$$J_2 = \begin{pmatrix} \frac{-k_3 k_1 k_a k_2 k_d T}{(k_1 k_a + k_2 k_a k_d + k_2 k_d FT4)^2} - k_4 & \frac{k_1 k_3 k_a}{(k_1 k_a + k_2 k_a k_d + k_2 k_d FT4)} & 0 \\ \frac{-k_1 k_a k_5}{k_2 T (k_a + FT4)^2} & \frac{-k_1 k_a k_5}{k_2 (k_a + FT4) T^2} - k_6 Ab & -k_6 T \\ 0 & k_7 Ab & k_7 T - k_8 \end{pmatrix}$$

Evaluate J_2 with $T_2 = \frac{k_8}{k_7}$, $Ab_2 = \frac{k_7 k_5}{k_6 k_8}\left(\frac{k_7 TSH_2}{k_8} - N\right)$, and $TSH_2 = \frac{k_1 k_a}{k_2 (k_a + FT4_2)}$,then the Jacobian becomes

J_2

$$= \begin{pmatrix} \frac{-k_3 k_1 k_a k_2 k_d k_8}{k_7 (k_1 k_a + k_2 k_d (k_a + FT4_2))^2} - k_4 & \frac{k_1 k_3 k_a}{(k_1 k_a + k_2 k_d (k_a + FT4_2))} & 0 \\ \frac{-k_1 k_a k_5 k_7}{k_2 k_8 (k_a + FT4)^2} & \frac{-k_1 k_a k_5 k_7^2}{k_2 (k_a + FT4_2) k_8^2} - \frac{k_7 k_5}{k_8}\left(\frac{k_7 TSH_2}{k_8} - N\right) & -\frac{k_6 k_8}{k_7} \\ 0 & \frac{k_7^2 k_5}{k_6 k_8}\left(\frac{k_7 TSH_2}{k_8} - N\right) & 0 \end{pmatrix}$$

Substituting $(k_a + FT4_2) = \frac{k_1 k_a}{k_2 TSH_2}$

$$J_2 = \begin{pmatrix} \frac{-k_3 k_2 k_d k_8 TSH_2^2}{k_1 k_a k_7 (k_d + TSH_2)^2} - k_4 & \frac{k_3 TSH_2}{(k_d + TSH_2)} & 0 \\ \frac{-k_2 k_5 k_7 TSH_2^2}{k_1 k_8 k_a} & \frac{-TSH_2 k_5 k_7^2}{k_8^2} - \frac{k_7 k_5}{k_8}\left(\frac{k_7 TSH_2}{k_8} - N\right) & -\frac{k_6 k_8}{k_7} \\ 0 & \frac{k_7^2 k_5}{k_6 k_8}\left(\frac{k_7 TSH_2}{k_8} - N\right) & 0 \end{pmatrix}$$

Remark

If $k_7 = \frac{Nk_8}{TSH_2}$ then $\det(\mathrm{J}_2) = 0$.

The eigenvalues of the diseased state can be found by solving the characteristic equation $det(\mathrm{J}_2 - \lambda I) = 0$, which is,

$$\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 = 0$$

where,

$$b_1 = k_4 + \frac{k_3k_2k_dk_8TSH_2^2}{k_1k_ak_7(k_d + TSH_2)^2} + \frac{k_5k_7}{k_8}\left(\frac{k_7TSH_2}{k_8} - N\right) + \frac{k_5k_7^2}{k_8^2}TSH_2$$

$$b_2 = \frac{k_4k_5k_7}{k_8}\left(\frac{k_7TSH_2}{k_8} - N\right) + \frac{k_5k_3k_2k_dTSH_2^2}{k_1k_a(k_d + TSH_2)^2}\left(\frac{k_7TSH_2}{k_8} - N\right) + \frac{k_7^2k_5k_4TSH_2}{k_8^2}$$
$$+ \frac{k_5k_7TSH_2^3k_3k_2k_d}{k_8k_1k_a(k_d + TSH_2)^2} + \frac{k_2k_5k_7TSH_2^3k_3}{k_8k_1k_a(k_d + TSH_2)} + k_5k_7\left(\frac{k_7TSH_2}{k_8} - N\right)$$

$$b_3 = k_5k_7k_4\left(\frac{k_7TSH_2}{k_8} - N\right) + \frac{k_3k_2k_5k_dk_8TSH_2^2}{k_1k_a(k_d + TSH_2)^2}\left(\frac{k_7TSH_2}{k_8} - N\right)$$

Since$\left(\frac{k_7TSH_2}{k_8} - N\right) > 0$, $b_1 > 0$ and $b_3 > 0$. We will now check May's remaining condition $b_1b_2 - b_3 > 0$.

$$b_1b_2 - b_3 = \frac{k_5k_7{k_4}^2\left(\frac{k_7TSH_2}{k_8} - N\right)}{k_8} + \frac{2k_3k_2k_dk_5k_4TSH_2^2\left(\frac{k_7TSH_2}{k_8} - N\right)}{k_1k_a(k_d + TSH_2)^2} + \frac{k_5k_4^2k_7^2TSH_2}{k_8^2}$$
$$+ \frac{k_2k_3k_dk_4k_5k_7TSH_2^3}{k_1k_8k_a(k_d + TSH_2)^2} + \frac{k_2k_3k_4k_5k_7TSH_2^3}{k_1k_8k_a(k_d + TSH_2)}$$
$$+ \frac{k_3^2k_2^2k_d^2k_5k_8TSH_2^4\left(\frac{k_7TSH_2}{k_8} - N\right)}{k_1^2k_a^2k_7(k_d + TSH_2)^4} + \frac{k_7k_3k_2k_dk_5k_4TSH_2^3}{k_1k_ak_8(k_d + TSH_2)^2}$$
$$+ \frac{k_3^2k_2^2k_d^2k_5TSH_2^5}{k_1^2k_a^2(k_d + TSH_2)^4} + \frac{k_3^2k_2^2k_5k_7k_8k_dTSH_2^5}{k_1^2k_a^2k_7k_8(k_d + TSH_2)^4} +$$

$$+k_4\left(\frac{k_5k_7\left(\frac{k_7TSH_2}{k_8}-N\right)}{k_8}\right)^2+\frac{k_3k_2k_dk_7k_5^2\,TSH_2^2\left(\frac{k_7TSH_2}{k_8}-N\right)^2}{k_8k_1k_a(k_d+TSH_2)^2}$$

$$+\frac{2k_7^3k_5^2k_4TSH_2\left(\frac{k_7TSH_2}{k_8}-N\right)}{k_8^3}+\frac{2k_3k_2k_dk_5^2k_7^2TSH_2^3}{k_8^2k_1k_a(k_d+TSH_2)^2}\left(\frac{k_7TSH_2}{k_8}-N\right)$$

$$+\frac{k_5^2k_7^2k_2k_3TSH_2^3}{k_1k_8^2k_a(k_d+TSH_2)}+\frac{k_5^2k_7^2}{k_8}\left(\frac{k_7TSH_2}{k_8}-N\right)^2+\frac{k_4k_5^2k_7^4TSH_2^2}{k_8^4}$$

$$+\frac{k_3k_2k_dk_5^2k_7^3TSH_2^4}{k_8^3k_1k_a(k_d+TSH_2)^2}+\frac{k_3k_2k_5^2k_7^3TSH_2^4}{k_8^3k_1k_a(k_d+TSH_2)}+\frac{k_7^3k_5^2TSH_2\left(\frac{k_7TSH_2}{k_8}-N\right)}{k_8^2}$$

Notice that $\left(\frac{k_7TSH_2}{k_8}-N\right)>0$. Therefore, the condition $b_1b_2-b_3>0$ is true for any given a set of positive model parameter values and thus the diseased state is always locally asymptotically stable once it appears in the positive orthant.

■

4.3 Numerical Simulations

The numerical simulations of the four dimensional (4d) system results in trajectories in 4d state space (actually 5d with time). In order to visualize the trajectories of the 4d system, when plotting we suppress time and the results of two or more of the four variables. For numerical simulations, we will use the original 4d system(2.2) – (2.17), unless there is a need to use the singularly perturbed system $(2.18)_\varepsilon$ – (2.21) or the reduced system (2.26) – (2.28).

$$\frac{dTSH}{dt}=k_1-\frac{k_1\,FT4}{k_a+FT4}-\,k_2\,TSH \qquad TSH(t_0)=TSH_0 \qquad (2.2)$$

$$\frac{dFT4}{dt}=\frac{k_3\,T\,TSH}{k_d\,+\,TSH}-\,k_4FT4 \qquad FT4(t_0)=FT4_0 \qquad (2.10)$$

$$\frac{dT}{dt} = k_5\left(\frac{TSH}{T} - N\right) - k_6 Ab\, T \qquad T(t_0) = T_0 \qquad (2.15)$$

$$\frac{dAb}{dt} = k_7 Ab\, T - k_8\, Ab \qquad Ab(t_0) = Ab_0 \qquad (2.17)$$

Since the system $(2.2) - (2.17)$ contains two different time scales, the Runge - Kutta methods such as ode23, ode45 in Matlab suite may not be the best choice for numerical approximations. Recall from Chapter 2 that the two-time scale issue was due to the presence of fast and slow variables in the 4d system. This means that a portion of the trajectory varies rapidly and the remaining portion of the trajectory varies slowly in 4d state space. Also, if we use the singularly perturbed system $(2.18)_\varepsilon - (2.21)$ for simulations in Matlab, again Runge-Kutta methods do not work well since it contains a small parameter (ε) in front of the derivative of TSH. These systems $(2.2) - (2.17)$ and $(2.18)_\varepsilon - (2.21)$ are referred to stiff systems in the numerical analysis literature. Therefore, we will now introduce the concept of stiff systems, the definition of stiffness, and a possible way to avoid stiffness using the ordinary differential equation solver in Matlab suite. Next, we will discuss some existing mathematical methods to eliminate stiffness in the singularly perturbed system.

Stiffness

Stiffness is an important concept in the numerical solution of ordinary differential equations which depends on the differential equation, the initial condition, and the numerical method. Basically, it affects efficiency, accuracy and graphical output of a computed solution. Generally speaking, whenever there involves a quickly changing dynamics in some components but not the others, there is stiffness.

Definition: Stiff Systems

Let $A \in R^{n\times n}$ be a constant matrix and $x, \phi \in R^n$. A linear differential system

$$\frac{dx}{dt} = Ax + \phi(t)$$

is said to be *stiff* if and only if

1. For all i, the real part of each eigenvalue λ_i of A, $\Re\lambda_i$ is negative
2. (Stiffness ratio) $\frac{\max |\Re\lambda_i|}{\min |\Re\lambda_i|} \gg 1$

Remark

A general nonlinear problem

$$\frac{dx}{dt} = f(t,x),$$

is said to exhibit stiffness if the eigenvalues of the Jacobian matrix $J(x) = \frac{\partial f}{\partial x}$ behave in a similar fashion. This is because near a particular solution $x = u(t)$ we may regard

$$f(t,x) = f\big(t,u(t)\big) + \frac{\partial f\big(t,u(t)\big)}{\partial x}\big(x - u(t)\big) + O(\|x - u(t)\|^2).$$

Define $z(t) := x(t) - u(t)$. Then z solves the system

$$z' = J(x)z + O(\|z\|^2)$$

To tackle stiffness in differential equations using the Matlab suite, we employed the standard differential equation solver ode15s. ODE15s can solve both non-stiff and stiff initial value problems, and differential algebraic equations (DAEs). ODE15s is a variable order method solver (Shampine and Reichelt, 1997) – it changes the step size when stiff solutions are encountered. Note that the code ode15s is a quasi-constant step size implementation of the numerical differentiation formulas in terms of backward differences. The quasi-constant step size means that the formulas used are those for a constant step size and the step size is held constant during an integration step. The syntax of this solver for an initial value problem is,

$$[t,y] = ode15s(\text{'}xdot\text{'}, tspan, x0, options);$$

Here $xdot$ is the name of a function that defines the differential equation. The interval of integration is $tspan = [t0, tfinal]$ and the initial conditions are $x0$. The code obtains the number of equations by measuring the length of the vector $x0$. The vector $options$ is optional

and it is built by means of the function $odeset$ that accepts name-value pairs. The most commonly used options are relative ($rtol$) and absolute ($atol$) tolerances associated with the error control. The default value of relative and absolute error tolerances are 10^{-3} and 10^{-6} respectively. Throughout our simulations, the default values of relative and absolute error tolerances are used.

Next, we will discuss some mathematical methods to solve stiff systems. Suppose the assumptions of Hoppensteadt theorem are satisfied, particularly assumption (3), that is, the algebraic system $g = 0$ has a unique root $y = h(x)$ with the Jacobian matrix remains strictly stable (see Chapter 2), then the reduced problem should be computationally simple since complications of stiffness have been eliminated (Dahlquist 1969; Dahlquist and Soderlind, 1982 ; Aiken 1985). In our case, the reduced system is as follows,

$$\frac{dFT4}{dt} = \frac{k_3\, k_1 k_a T}{k_1 k_a + k_2 k_a k_d\, + k_2\, k_d\, FT4} - \, k_4\, FT4 \qquad FT4(t_0) = FT4_0 \qquad (2.26)$$

$$\frac{dT}{dt} = k_5 \left(\frac{k_1\, k_a}{k_2 k_a T + k_2 T FT4} - N \right) - k_6 Ab\, T \qquad T(t_0) = T_0 \qquad (2.27)$$

$$\frac{dAb}{dt} = k_7 Ab\, T - \, k_8\, Ab \qquad Ab(t_0) = Ab_0 \qquad (2.28)$$

This reduced system (2.26) – (2.28) can be simulated in Matlab using Runge-Kutta methods because the solutions of the reduced system are on the same time scale (slow). But we found that using ode15s reduces the computational time. Thus, we prefer using ode15s in this system to present simulations in $(FT4, T, Ab)$ phase space.

Next, we will discuss another interesting alternative procedure described in (O'Malley, R.E, 1988). Consider the algebraic system $g = 0$ from problem (2.23) from Chapter 2. That is,

$$\begin{aligned} \frac{dx}{dt} &= f(x, y, 0), \qquad x(0) = x_0 \\ 0 &= g(x, y, 0) \end{aligned} \qquad (2.23)$$

Differentiate $g = 0$ with respect to t. Then, we get,

$$g_x \frac{dx}{dt} + g_y \frac{dy}{dt} = 0$$

That is,

$$\frac{dy}{dt} = -\frac{g_x}{g_y} f(x, y, 0)$$

Thus, we have a new set of $(n + m)$ differential equations with initial conditions,

$$\frac{dx}{dt} = f(x, y, 0), \qquad x(0) = x_0$$

$$\frac{dy}{dt} = -\frac{g_x}{g_y} f(x, y, 0), \qquad g(x_0, y_0, 0) = 0$$

Note that these equations eliminated the stiffness because the initial condition has been chosen on the algebraic surface, $g(x_0, y_0, 0) = 0$ which in turn eliminated the fast dynamics of the problem (2.22). Moreover, the trajectories of this system lie completely on the surface (slow manifold). Therefore Runge-Kutta methods work well on this system.

Now, let us rewrite our singularly perturbed system, $(2.18)_\varepsilon - (2.21)$. First, consider the algebraic system

$$g(FT4, TSH, T, Ab, 0) = \frac{k_1}{k_2} - \frac{k_1\, FT4}{k_2(k_a + FT4)} - TSH = 0$$

Differentiate with respect to t,

$$g_{FT4} \frac{dFT4}{dt} + g_{TSH} \frac{dTSH}{dt} + g_T \frac{dT}{dt} + g_{Ab} \frac{dAb}{dt} = 0$$

This yields,

$$\frac{dTSH}{dt} = -\frac{g_{FT4}}{g_{TSH}} \frac{dFT4}{dt}$$

Thus,

$$\frac{dTSH}{dt} = -\frac{k_1 k_a}{k_2(k_a + FT4)^2}\left(\frac{k_3\, T\, TSH}{k_d\, +\, TSH} -\, k_4 FT4\right) \qquad g(FT4_0, TSH_0, T_0, 0) = 0 \qquad (4.2)$$

$$\frac{dFT4}{dt} = \frac{k_3\, T\, TSH}{k_d\, +\, TSH} -\, k_4 FT4 \qquad FT4(t_0) = FT4_0 \qquad (4.3)$$

$$\frac{dT}{dt} = k_5\left(\frac{TSH}{T} - N\right) - k_6 Ab\, T \qquad T(t_0) = T_0 \qquad (4.4)$$

$$\frac{dAb}{dt} = k_7 Ab\, T -\, k_8\, Ab \qquad Ab(t_0) = Ab_0 \qquad (4.5)$$

Note that we could use this system, (4.2) – (4.5) instead of $(2.18)_\varepsilon$ – (2.21) for initial condition chosen on the algebraic surface, $g(FT4_0, TSH_0, T_0, 0) = 0$. This one requirement actually avoids the fast dynamics of the singularly perturbed system and also forces the trajectories to stay on the manifold for all $t > 0$. But as we remarked in the introduction of the numerical simulations that we use the original system, (2.2) – (2.17) wherever it is possible, so let us choose the initial condition of TSH from the algebraic surface and use the original system instead of (4.2) – (4.5). Also from Hoppensteadt theorem, we know that the trajectories of the original system stay near or on the algebraic surface, $g = 0$ for all $t > t_0 > 0$. That is,

$$\frac{dTSH}{dt} = k_1 - \frac{k_1\, FT4}{k_a + FT4} -\, k_2\, TSH \qquad g(FT4_0, TSH_0, T_0, 0) = 0 \qquad (2.2)$$

$$\frac{dFT4}{dt} = \frac{k_3\, T\, TSH}{k_d\, +\, TSH} -\, k_4 FT4 \qquad FT4(t_0) = FT4_0 \qquad (2.10)$$

$$\frac{dT}{dt} = k_5\left(\frac{TSH}{T} - N\right) - k_6 Ab\, T \qquad T(t_0) = T_0 \qquad (2.15)$$

$$\frac{dAb}{dt} = k_7 Ab\, T -\, k_8\, Ab \qquad Ab(t_0) = Ab_0 \qquad (2.17)$$

We use this model to present numerical simulations in $(TSH, FT4, Ab)$ and $(TSH, FT4, T)$ state space.

4.3.1 Numerical Simulations of the 4d Model, (2.2) – (2.17)

All numerical simulations are done using parameters from the Table A2 in Appendix A– we will just alter the parameter k_7. For the parameter values from Table A2, we obtained $k_7^* = 2.3421\ \frac{1}{L*day}$. We will first look at the case when $k_7 < k_7^*$ and investigate the behavior of anti-thyroid antibody concentrations (Ab) by choosing the initial state exactly at the euthyroid state except for anti-thyroid antibodies, that is, $(TSH_1, FT4_1, T_1, Ab) = (1, 13, 0.015, 16)$. Note: in euthyroid state, $Ab_1 = 0$ but we chose $Ab = 16$ in order to use the 4d model. We present simulations both through time series plots and phase-space diagrams in 3d space. For phase-space diagrams, we mainly use Hoppensteadt's theorem that the trajectories of the model stay near the slow manifold (surface) $g = 0$ for all time $t > 0$ if we take initial states near or on the surface. We use $(FT4, T, Ab)$, $(TSH, FT4, T)$ and $(TSH, FT4, Ab)$ phase space diagrams to illustrate the results.

We arbitrarily pick the value of $k_7 = 1.3421 < k_7^*$ and fix it in the 4d system and then simulate the model for approximately 2 years. In all our Figures below, the red dot represents the euthyroid steady state, the green dot represents diseased steady state, the black dot represents the initial state of the system, and the yellow surface represents slow manifold for $\varepsilon = 0$. Figure 4.1 illustrates the 4d system time series plot in which we can see that anti-thyroid antibody concentration decreases from the initial state $(1, 13, 0.015, 16)$ and approaches zero in approximately 350 days while other variables remain at the steady state. Figures 4.2, 4.3 and 4.4 illustrate the 4d system in $(FT4, T, Ab)$, $(TSH, FT4, T)$ and $(TSH, FT4, Ab)$ phase space. As we see in Figure 4.2, 4.3 and 4.4, the 4d system moves from the initial state to the euthyroid state for $k_7 < k_7^*$ and the parameter values from Table A2. Note that in Figure 4.3 and 4.4, the dynamics of 4d system is shown near the slow manifold. In addition, Figure 4.3 and 4.4 shows, the red and

black dots on the slow manifold, but not the green dot for $k_7 < k_7^*$ and the parameter values from Table A2.

Next, we arbitrarily pick the value of $k_7 = 3.3421 > k_7^*$ and fix it in the 4d system and then simulate the model for approximately 2 years. This will help us to demonstrate the euthyroid steady state is no longer attracting the trajectories, but the diseased steady state will emerge into the rectangular box for that particular k_7 and attract all trajectories with any initial conditions in the box or positive orthant. Figures 4.5, 4.6, 4.7 and 4.8 illustrate the 4d system moves from the initial state to the diseased steady state. Figure 4.5 and 4.6 shows the red and green dots on the slow manifold for $k_7 > k_7^*$. Note in Figures 4.5 and 4.6, the initial state and euthyroid state $(1,13,0.015,16)$, is taken to be the same but not in Figures 4.7 and 4.8. Again, as we noted before, we used parameter values from Table A2 to generate all figures 4.5, 4.6, 4.7 and 4.8. To generate Figure 4.8, we used the reduced (3d) model, (2.26) – (2.28) instead of the 4d system, (2.2) – (2.17).

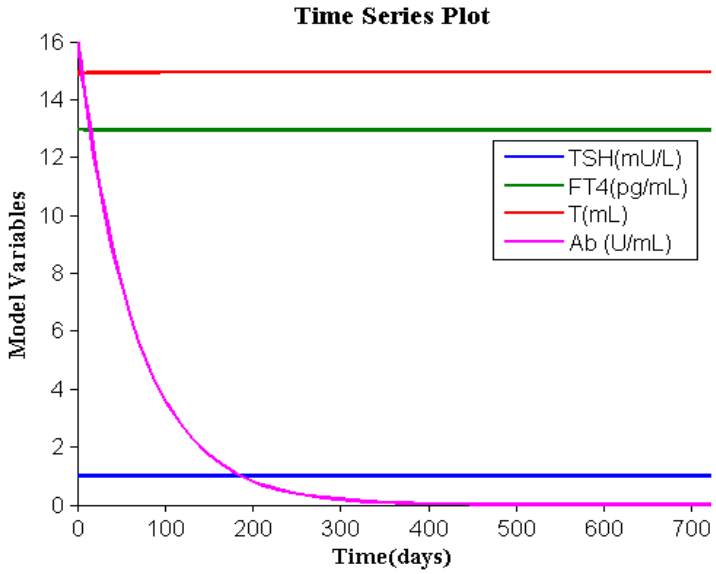


Figure 4.1: Note the thyroid functional size (T) is in milliliters. The 4d system, (2.2) – (2.17) with the initial condition $(1, 13, 0.015, 16)$ for the parameter values from Table A2, predicts that Ab concentration asymptotically approaches zero in approximately 350 days while other variables remain at steady state. This means that the anti-thyroid antibodies did not affect the function of the HPT axis.

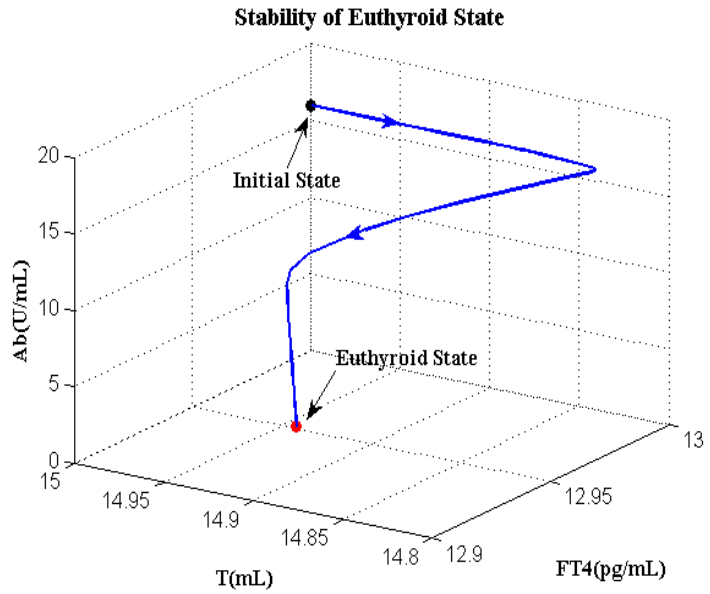


Figure 4.2: For $k_7 = 1.3421 < k_7^*$ and the parameter values from Table A2, the 4d system, (2.2) – (2.17) moves from the initial state $(TSH, FT4, T, Ab) = (1, 13, 0.015, 16)$ to euthyroid steady state $(1, 13, 0.015, 0)$. Note the thyroid functional size (T) is in milliliters.

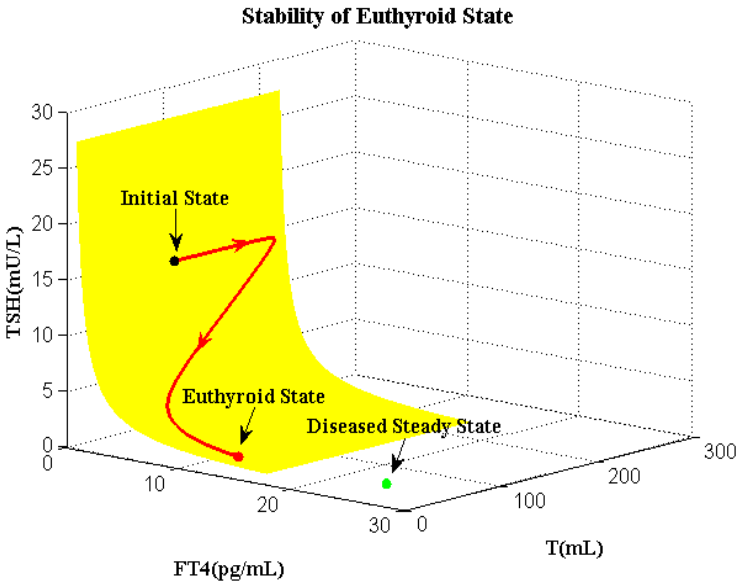


Figure 4.3: If the initial state $(TSH, FT4, T, Ab) = (14.312, 1, 100, 16)$ is taken on the slow manifold, not at euthyroid state, then the 4d system, (2.2) – (2.17) for the parameter values from Table A2, predicts that the trajectory converges to euthyroid state. This suggests the euthyroid state is asymptotically stable. Since $k_7 < k_7^*$, the diseased steady state is not on the surface. Note the thyroid functional size (T) is in milliliters.

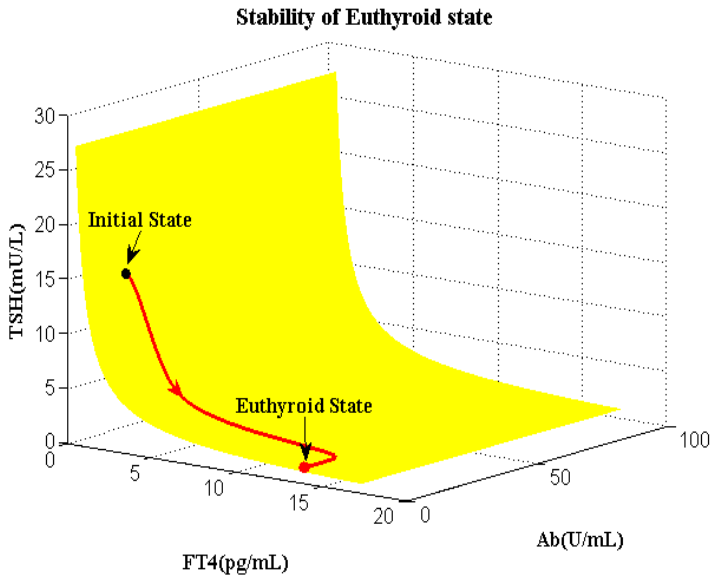


Figure 4.4: We started the 4d system, (2.2) – (2.17) from $(TSH, FT4, T, Ab) = (14.312, 1, 100, 16)$ and the numerical solutions of the system approaches euthyroid state. Since $k_7 < k_7^*$, the diseased steady state is located in the negative octant, so we did not plot the green dot (representing diseased state).

We will now investigate the dynamics of the 4d system, (2.2) – (2.17) by arbitrarily choosing $k_7 > k_7^*$ $\left(\text{say } k_7 = 3.3421 \frac{1}{L*day}\right)$.

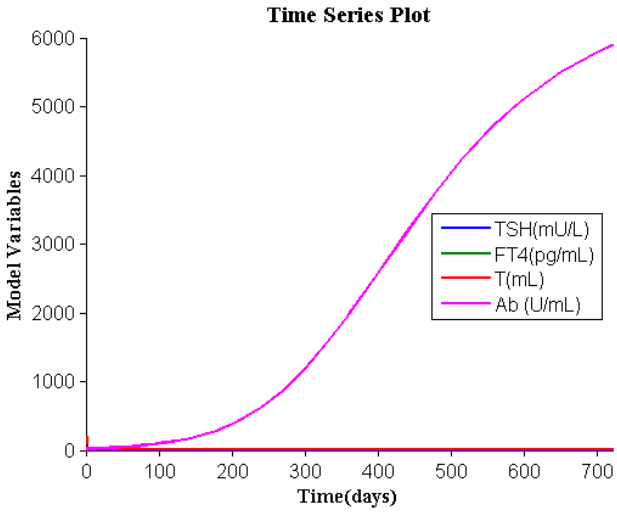


Figure 4.5: For the initial state (1,13,0.015,16), the 4d system (2.2) – (2.17) for the parameter values from Table A2 predicts that Ab concentration asymptotically approaches 6800 in approximately 2 years while other variables start at euthyroid state. Note the thyroid functional size (T) is in milliliters.

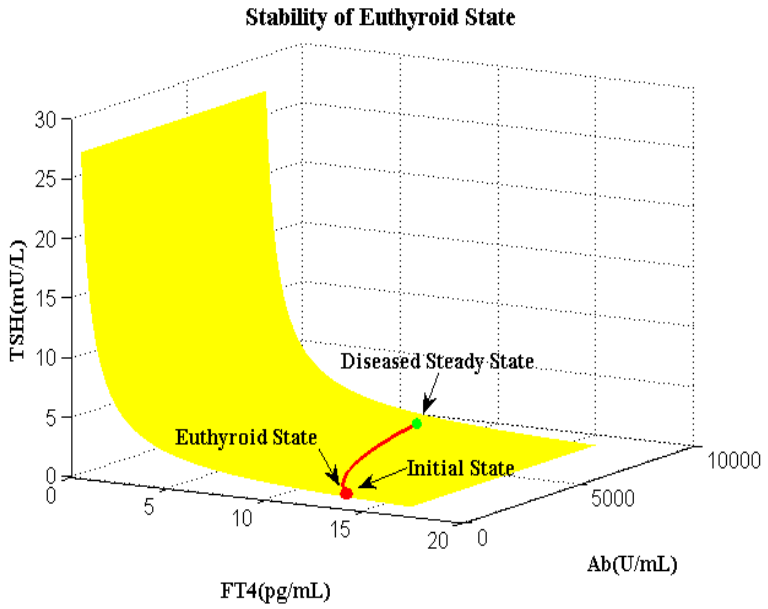


Figure 4.6: For the initial state (1,13,0.015,16) and $k_7 = 3.3421 > k_7^*$, the 4d system (2.2) – (2.17) for the parameter values from Table A2 predicts that euthyroid state becomes unstable, and the trajectory approaches the diseased state.

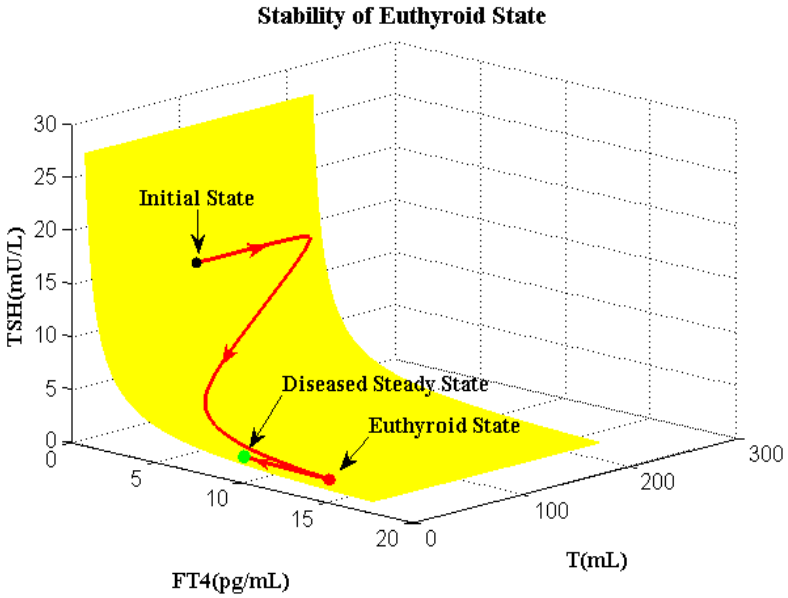


Figure 4.7: If the initial state $(TSH, FT4, T, Ab) = (14.312, 1, 100, 16)$ is taken on the level curve, not at euthyroid state, then the 4d system, (2.2) – (2.17) for the parameter values from Table A2, predicts that the trajectories approaches the diseased state (subclinical hypothyroidism) while euthyroid state becomes unstable and shows saddle-type behavior. Note the thyroid functional size (T) is in milliliters.

4.3.2 Numerical Simulation of the Reduced (3d) Model

Stability of Diseased Steady State

We now present the numerical simulations to support that the diseased steady state is stable when it is in the positive orthant. For this simulation, we use the reduced system, (2.26) – (2.28) with parameter values from Table A2 and visualize the trajectories in $(FT4, T, Ab)$ phase space.

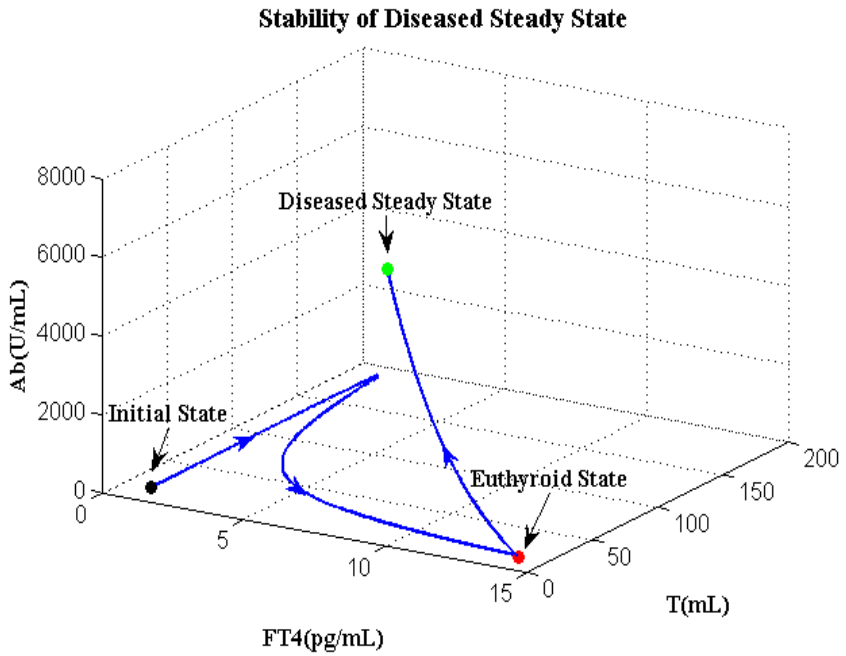


Figure 4.8: This figure shows the stability of diseased steady state, the initial state was chosen at $(FT4, T, Ab) = (1, 0.015, 16)$. The reduced system, (2.26) – (2.28) approaches the diseased state via euthyroid state. Note the saddle-like behavior near the euthyroid state. Here, $k_7 = 3.3421 > k_7^*$. Note the thyroid functional size (T) is in milliliters.

4.4 Bifurcation Analysis

General Introduction

Bifurcation analysis is in general used for analyzing the qualitative behavior of steady states, periodic orbits or some other invariant objects, such as a homoclinic or hetroclinic orbit, as parameters are varied in the system. The usual definition of bifurcation is that a qualitative

change occurs in the topological nature of the solution, when a parameter passes through a critical value. That is, the phase portraits or vector field of the dynamical system before and after the bifurcation are not topologically equivalent. There are two important classes of bifurcations in literature, namely local and global. Local bifurcations focus on changes that take place near a steady state or periodic orbit. This is what we will describe here. In our 4d system, we analyze the qualitative behavior of the steady states as k_7 changes in the system – local bifurcation. There are several types of local bifurcations that exist in the literature (Strogatz, 1994, Perko, 1991). Qualitative behavior of the system is typically visualized via a bifurcation diagram. A bifurcation diagram is a plot which gives a steady state solution as a function of a control parameter. This plot consists of branches that are either solid or dotted lines representing the locations of stable or unstable steady states of the system. Importantly, this diagram shows the long-term system behavior as a control parameter is varied. Next, we will discuss the transcritical bifurcation since our 4d system undergoes this bifurcation.

Definition: Transcritical Bifurcation

A transcritical bifurcation is a local bifurcation in which two steady states of a model involves in exchange of stabilities between them.

Example

Consider the 1d system $\dot{x} = rx - x^2$. This 1d system has two steady states $x = 0$ and $x = r$. For $r < 0$, the steady state $x = 0$ is stable and $x = r$ is unstable. For $r = 0$, there is only one steady state $x = 0$ which is structurally unstable. For $r > 0$, there are two steady states, but $x = 0$ is unstable and $x = r$ is stable (see Figure 4.9).

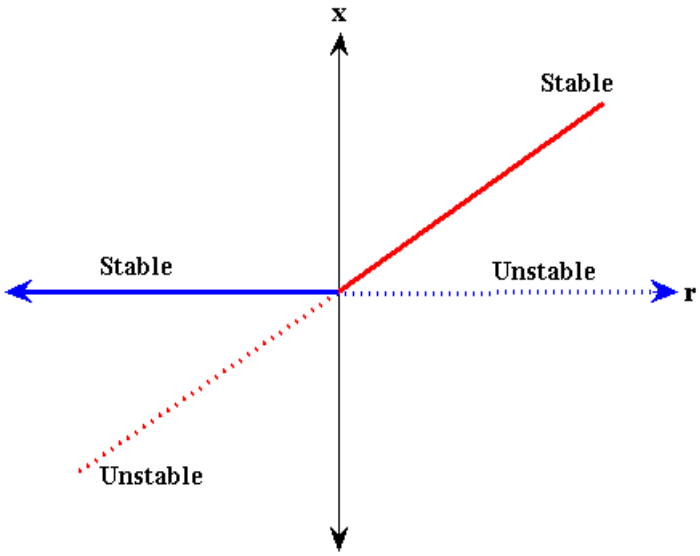


Figure 4.9: A bifurcation diagram shows a transcritical bifurcation for a range of values r. The local bifurcation takes place at $(r, x) = (0,0)$.

4.4.1 Bifurcation Analysis of the 4d Model – Varying the Parameter k_7

Why k_7 is a control parameter?

The parameter k_7 in the model is chosen to be a control parameter since the stability analysis of the 4d system and the biology of the autoimmune thyroiditis suggested this control parameter. From the biological point of view, the parameter k_7 is involved in the production rate of anti-thyroid antibodies and it is one of the suitable candidates to choose for bifurcation analysis. Also, the biology of the autoimmune thyroiditis suggests that parameters k_5 and k_6 are potential candidates for bifurcation analysis.

Bifurcation Diagrams

We will now present the bifurcation diagrams of our 4d system which will help us to see the long - term system behavior as k_7 varied. Basically, the bifurcation diagrams depict the complete picture of all possible states of the system for large range of values for k_7. For our 4d system, the bifurcation diagrams are drawn by plotting the euthyroid steady state and the diseased steady state

for range of values for k_7. We observed that when we solve for the steady states in the introduction of Chapter 4, the euthyroid state is independent of k_7 and the diseased steady state dependent of k_7. Furthermore, we observed that the stability nature of the steady states changes as k_7 varied.

Figures 4.10, 4.11, 4.12 and 4.13 shows how the steady states change as the parameter k_7 is varied. Stable and unstable steady states are drawn as solid and dotted lines respectively. In particular, Figure 4.10 shows how the anti-thyroid antibodies steady state changes as k_7 varies in the model from 0 to 7. Figure 4.11 shows how free T4 steady state changes as k_7 varies in the model from 0 to 7. Figure 4.12 shows how TSH steady state changes as k_7 varies in the model from 0 to 7. Figure 4.13 shows how the functional size of the thyroid gland steady state changes as k_7 varies in the model from 0 to 7. All these figures illustrates that the euthyroid state is stable for the range of values of k_7 from 0 up to k_7^*. More precisely, when $0 < k_7 \leq k_7^* = 2.3421$, the euthyroid state is stable. That is, the real parts of the eigenvalues of euthyroid state are negative between 0 and up to k_7^*. When $k_7 > k_7^*$, the euthyroid state is unstable. That is, when k_7 is bigger than k_7^*, the real parts of the eigenvalues of euthyroid state are negative except in the direction of anti-thyroid antibodies for the parameter values in Table A2. Note k_7^* is the bifurcation point where the system undergoes an exchange of stability. In other words, the trajectories of the 4d system before and after k_7^* are different. A further important clinical value, k_7^{**}, will be defined in this discussion. All pictures are drawn with parameter values from Table A2, except for k_7 is varied.

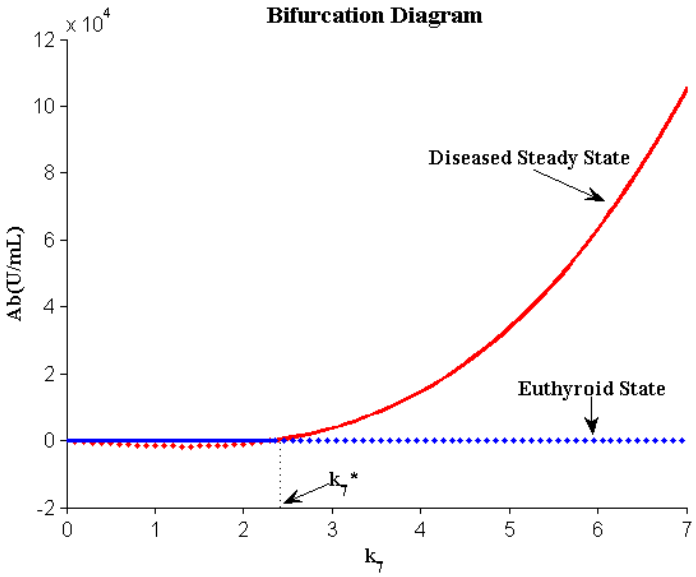


Figure 4.10: This bifurcation diagram illustrates how the anti-thyroid antibodies steady state concentrations(Ab) changes as k_7 varies in the model from 0 to 7. Note that the bifurcation occurs at $k_7 = k_7^* = 2.3421$.

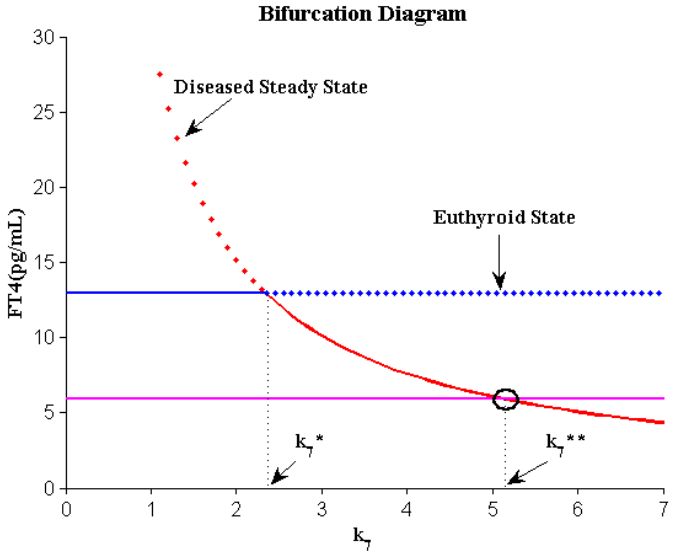


Figure 4.11: This bifurcation diagram shows how free T4($FT4$) steady state concentrations changes as k_7 varies from 0 to 7. Observe that the bifurcation occurs at $k_7 = k_7^*$ and when $k_7 > k_7^{**} = 5.2$, we see a patient would have clinical hypothyroidism (see the baseline value of free T4, shown as a solid magenta line).

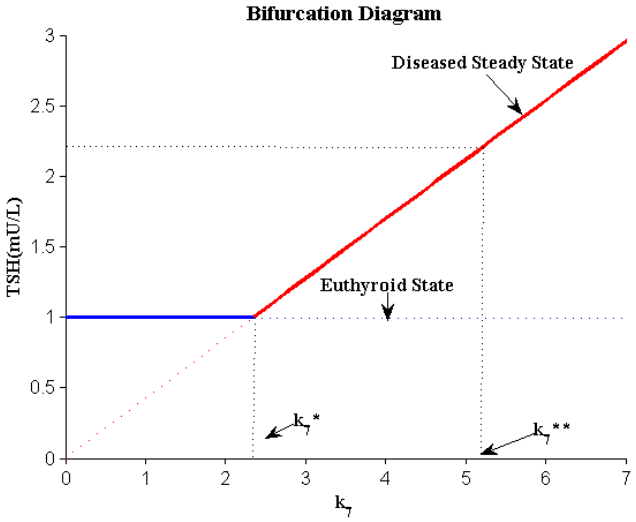


Figure 4.12: This bifurcation diagram shows how TSH steady state concentrations changes as k_7 varies from 0 to 7. Also, observe that the bifurcation occurs at $k_7 = k_7^*$ and when $k_7 > k_7^{**}$, resulting in clinical hypothyroidism. Thus, the model suggests that at k_7^{**}, TSH upper reference limit is 2.3 mU/L (approximately). The diseased steady state is still inside the box.

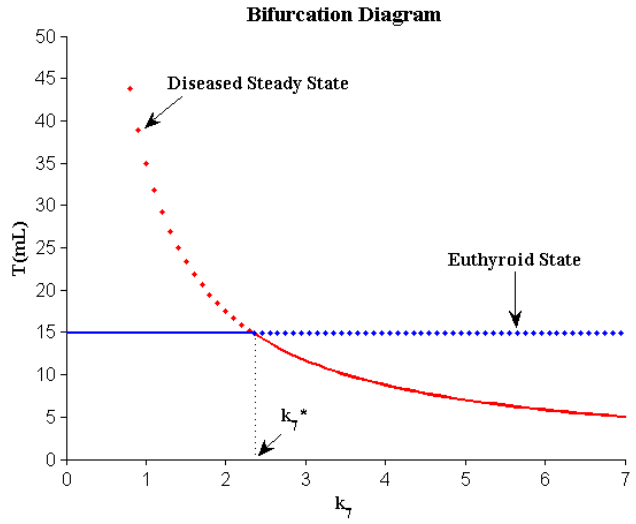


Figure 4.13: This bifurcation diagram shows how the functional size of thyroid gland (T) changes as k_7 varies from 0 to 7. Also, observe that the bifurcation occurs at $k_7 = k_7^*$.

The bifurcation diagrams depicted the qualitative behavior of our 4d model as k_7 varied in the system. We found that bifurcation occurred at the numerical value of $k_7^* = 2.1738 \frac{1}{L*day}$ for the parameter values from Table A2. In addition, we found that when k_7 increases above the value 5.2 results in transition to clinical hypothyroidism. Thus, we called this critical value k_7^{**} and it would be where hypothyroidism takes place. In summary, for $k_7 < k_7^*$, the euthyroid state is stable and therefore patients with autoimmune thyroiditis do not develop the consequences of autoimmune thyroiditis (such as subclinical and clinical hypothyroidism). For $k_7 = k_7^*$, bifurcation occurs, meaning, the disease steady state and euthyroid state merge each other, so the patients with autoimmune thyroiditis likely to develop the consequences of the disease in the future as k_7 changes further. Finally, for $k_7 > k_7^*$, the euthyroid state becomes unstable and patients with kinetic parameter in Table A2 with $k_7 > k_7^*$ have autoimmune thyroiditis and eventually develop hypothyroidism. More precisely, we found that when k_7 is between k_7^* and k_7^{**} results in subclinical hypothyroidism and $k_7 > k_7^{**}$ results in clinical hypothyroidism. Also, we observed that the bifurcation diagrams predicted the proper upper limit for TSH (2.3) mU/L, which indicates the validation of the 4d system for Table A2 values.

4.5 Summary

This chapter mainly focused on the stability and bifurcation analysis of 4d system. We derived conditions for the euthyroid steady state to be stable and unstable in 4d space in the presence of anti-thyroid chronic immune response. We found that k_7 is a bifurcation parameter. The 4d system undergoes a transcritical bifurcation as k_7 changes in the system which results in diseased steady state to emerge in a rectangular box. We have proved that this disease steady state is locally asymptotically stable. Next, in order to find out the nature of the diseased steady state, whether subclinical or clinical hypothyroidism, we preformed bifurcation analysis in the 4d system. This analysis showed that if $k_7 \leq k_7^*$, the patients with autoimmune thyroiditis do not

develop any consequences of the disease and if $k_7^* < k_7 \leq k_7^{**}$ the patients with autoimmune thyroiditis develop subclinical hypothyroidism. If $k_7 > k_7^{**}$, the patients with autoimmune thyroiditis and eventually develop clinical hypothyroidism. This is our main result for this chapter. In addition, through bifurcation analysis, we found that the upper TSH reference limit is 2.3 mU/L by using the parameter values from Table A2. Note that for numerical simulations and bifurcation analysis, we used the parameter values from Table A2. This means to say that each patient's k_7^* and k_7^{**} is different because patient's euthyroid steady state (set point) is different.

CHAPTER 5 – CLINICAL STAGING AND DISEASE PROGRESSION

The goal of this project is to provide a patient-specific description of the natural history of autoimmune thyroiditis through a mathematical model. What does this mean? It means to determine the natural course of subclinical or clinical hypothyroidism through a model for each patient. By using a staging criterion for autoimmune disease patients, we can describe this natural clinical course. We will first start this chapter with the summary of results of analyzing the operation of the HPT axis from the previous chapters.

- In Chapter 1, we have observed that the hypothalamus-pituitary function is intact and the thyroid-pituitary function is interrupted in diseased patients. We have used the dataset to show the motivation of this mathematical modeling project and, in addition, established a patient-specific clinical staging criterion for diseased patients. The staging criterion has three cases, namely euthyroidism → euthyroidism, euthyroidism → subclinical hypothyroidism and euthyroidism → subclinical → clinical hypothyroidism.
- In Chapter 2, we have constructed a higher dimensional non-linear model for patients with autoimmune thyroiditis. The model takes the form of a singularly perturbed initial value problem. This is the main tool for the analysis of a model, which is elaborated in this chapter.
- In Chapter 3, we looked at the special case of the model, that is, the absence of anti-thyroid chronic immune response in a singularly perturbed initial value problem– it mimics the normal axis operation.
- In Chapter 4, we have presented the stability analysis of a singularly perturbed initial value problem. We found that k_7 is a bifurcation parameter. As this parameter changes up to the critical value k_7^* , the individuals with autoimmune thyroiditis do not develop the consequences of autoimmune thyroiditis, but above the critical value, k_7^* , the individuals

with autoimmune thyroiditis develop subclinical hypothyroidism. Furthermore, we found another critical value k_7^{**}, where patients eventually develop clinical hypothyroidism.

We will now use k_7 values to relate clinical staging defined in Chapter 1 and along with that, the numerical simulations are presented to support our staging both via time series plots and phase space. In time series plots, we will show TSH values since the hypothalamus-pituitary function are normal and therefore, TSH values are more reliable in autoimmune thyroiditis patients. But, in phase-space both TSH and free T4($FT4$) will be presented unless there is a need for other clinical variables (T and Ab). The main reason for presenting only TSH and free T4($FT4$) in phase-space is because these two hormones are measured regularly in the clinical setting and for treating patients. Thus, after presenting numerical simulations the dataset will be used subsequently for validating the model prediction.

Case 1

Suppose $k_7 \leq k_7^*$, then patients with autoimmune thyroiditis do not develop any clinical consequences (subclinical or clinical hypothyroidism) and thus a staging will be,

Euthyroidism → Euthyroidism

Case 2

Suppose $k_7^* < k_7 \leq k_7^{**}$, then patients with autoimmune thyroiditis develop the subclinical hypothyroidism. Thus, a staging will be,

Euthyroidism → Subclinical Hypothyroidism

Case 3

Suppose $k_7 > k_7^{**}$, then patients with autoimmune thyroiditis develop subclinical hypothyroidism and eventually become clinical hypothyroidism. Thus, a staging will be,

Euthyroidism → Subclinical→ Clinical Hypothyroidism

5.1 Numerical Simulations for Clinical Charts

For numerical simulations, we use a full model with Ode15s solver in Matlab 7.1.1.0 suite.

Case 1: Let us pick arbitrarily ten different k_7 values, less than k_7^* and the initial state of the system is at the euthyroid state except for anti-thyroid antibodies, that is, $(TSH, FT4, T, Ab) = (1, 13, 0.015, 16)$.

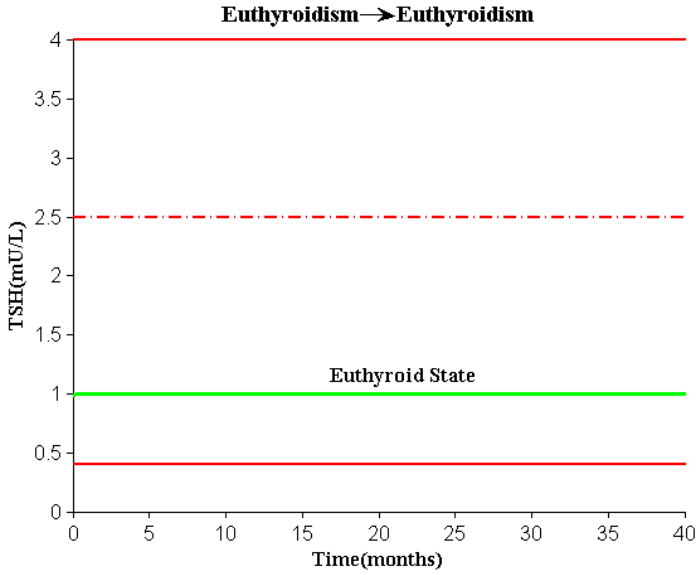


Figure 5.1: This figure shows Case 1: euthyroidism → euthyroidism chart. Note: The solid red lines illustrate the normal reference range for TSH. The dotted red line chosen for this project as an upper TSH reference limit. The green solid line indicates that the 4d system, (2.2) – (2.17) approaches the euthyroid (steady) state for ten different k_7 values less than k_7^*. The initial state of the 4d system is $(TSH, FT4, T, Ab) = (1, 13, 0.015, 16)$. The parameter values are all from Table A2 in Appendix A.

Case 2: Let us arbitrarily pick six different k_7 values $(2.44, 2.76, 3.39, 4.03, 4.6, 5.2)$ between k_7^* (2.3412) and up to $k_7^{**}(5.2)$ and the initial state of the system is at the euthyroid state except for anti-thyroid antibodies, that is,$(TSH, FT4, T, Ab) = (1, 13, 0.015, 16)$. We use parameter values from Table A2 to generate the euthyroidism → subclinical hypothyroidism chart (see Figure 5.2).

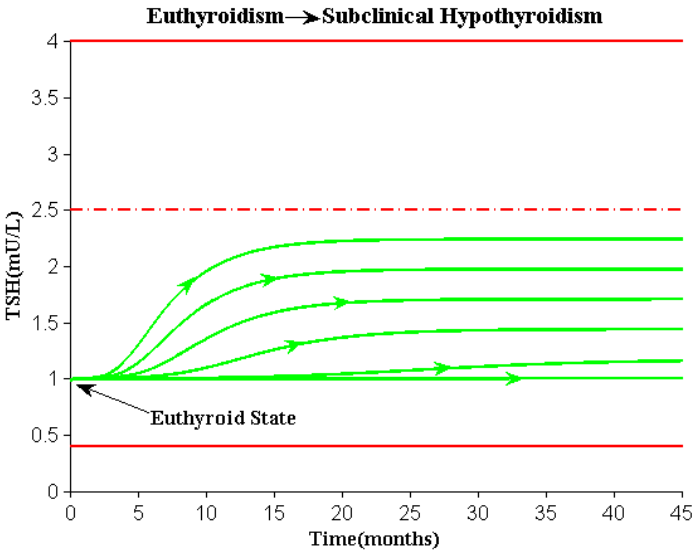


Figure 5.2: This figure shows euthyroidism → subclinical hypothyroidism chart. Note that all TSH solutions go to subclinical diseased steady state. We simulated the 4d system, (2.2) – (2.17) with the initial state $(1, 13, 0.015, 16)$ and the parameter values from Table A2 with six different k_7 values between k_7^* =2.3412 and up to $k_7^{**} = 5.2$.

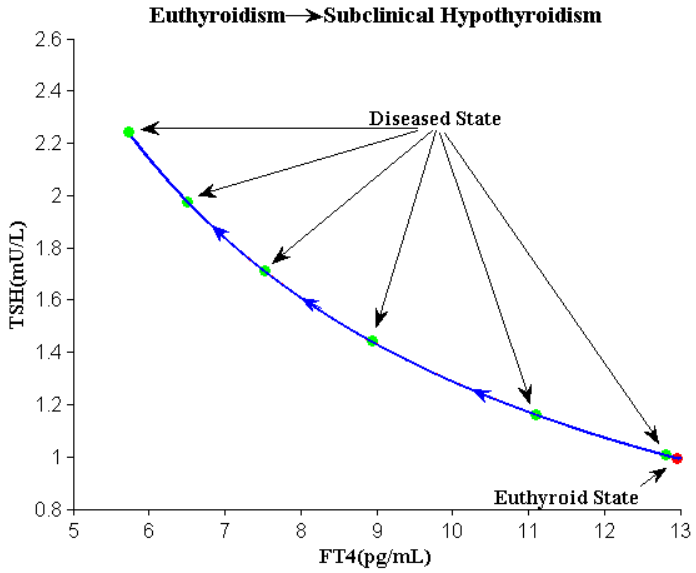


Figure 5.3: 2d view of euthyroidism → subclinical hypothyroidism chart. We simulated the 4d system with the initial state $(1, 13, 0.015, 16)$ and the parameter values from Table A2 but different k_7 values, between k_7^* =2.3412 and up to $k_7^{**} = 5.2$. The curve in this picture is parameterized by six different k_7 values, that is,(2.44, 2.76,3.39,4.03,4.6,5.2). For every $k_7 > k_7^*$, we have a diseased steady state (subclinical), that is shown in the picture with a green dot. The euthyroid state is shown in the picture with a red dot.

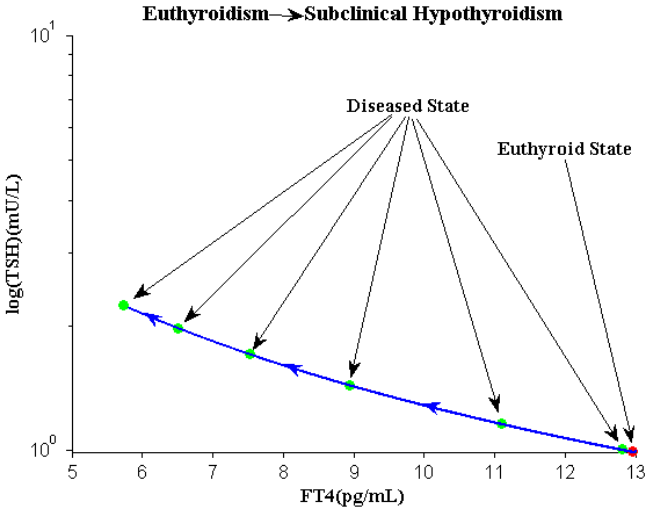


Figure 5.4: log(TSH) versus freeT4($FT4$) view of the previous Figure 5.3.

Case3: Let us pick arbitrarily eleven different k_7 (5.5, 6.8, 8.14, 9.4, 10.7, 12.1, 13.4, 14.7, 16, 17.3, 18.7) values greater than $k_7^{**} = 5.2$, and the initial state of the system is at the euthyroid state except for anti-thyroid antibodies, that is, $(TSH, FT4, T, Ab) = (1, 13, 0.015, 16)$. We use parameter values from Table A2 to generate the euthyroidism → subclinical → clinical hypothyroidism chart (see Figure 5.4).

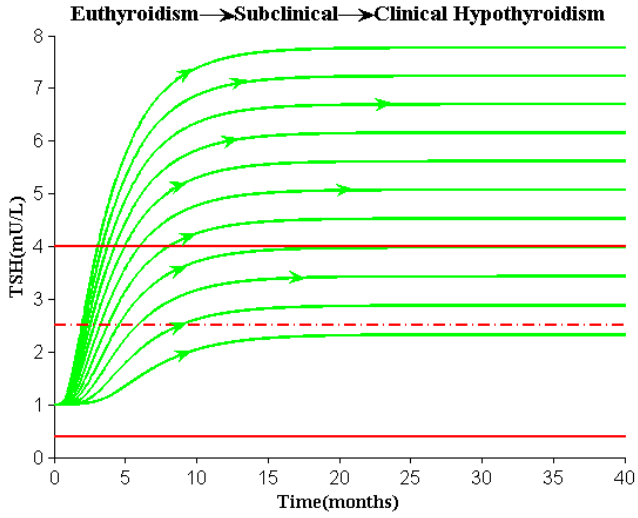


Figure 5.5: This figure shows the euthyroidism → subclinical → clinical hypothyroidism chart. To generate this picture, we picked eleven different k_7 values greater than k_7^{**} and then simulated the 4d system with initial condition $(1, 13, 0.015, 16)$. The parameter values are all from Table A2.

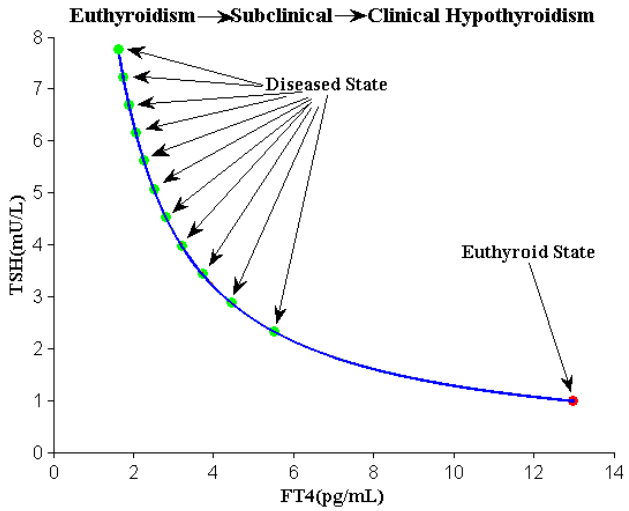


Figure 5.6: 2d view of euthyroidism → subclinical → clinical hypothyroidism chart. We simulated the 4d system with the initial state $(1, 13, 0.015, 16)$ and the parameter values from Table A2 but different k_7 values. The curve in this picture is parameterized by eleven different k_7 values greater than k_7^{**}. For every $k_7 > k_7^{**}$, we have a diseased steady state (clinical hypothyroidism), that is shown in the picture with a green dot. The euthyroid state is shown in the picture with a red dot. Note an individual progress to clinical hypothyroidism via subclinical hypothyroidism.

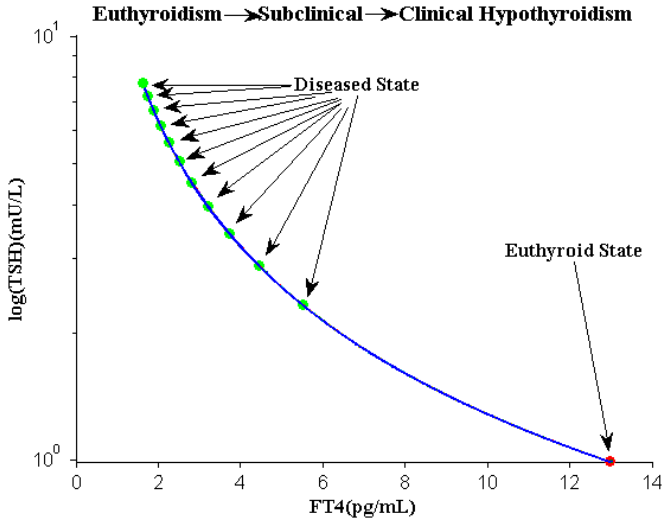


Figure 5.7: log(TSH) versus freeT4($FT4$) view of the previous Figure 5.6.

We will now combine euthyroidism → subclinical hypothyroidism and euthyroidism → subclinical → clinical hypothyroidism charts and present it as one complete chart.

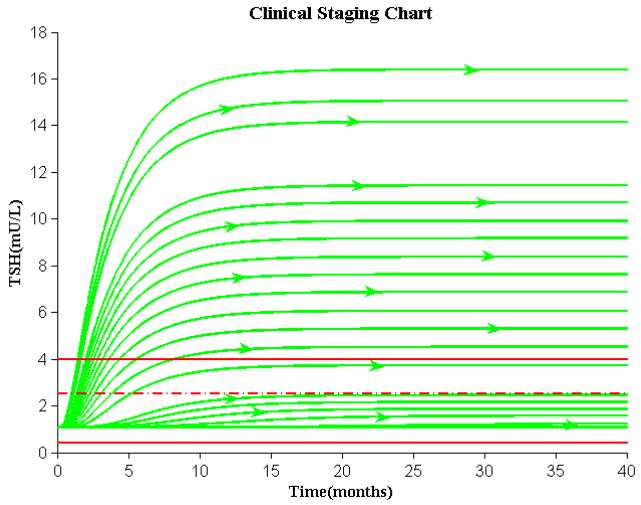


Figure 5.8: Clinical staging chart. This chart can be used to determine the natural course of subclinical or clinical hypothyroidism or euthyroidism by moving the graph up and down according to the patient's set point (see Validation of Model with Data Section). Note we simulated all these curves with different k_7 values in the 4d system using an imaginary individual's table parameter values from Appendix A.

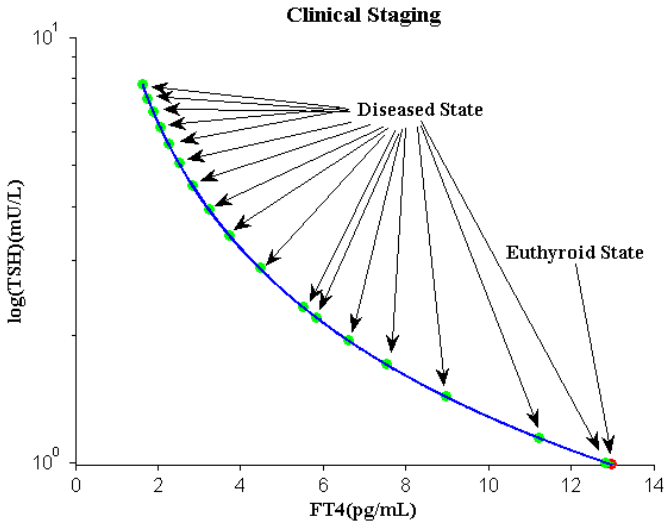


Figure 5.9: Combing Figures 5.7 and 5.4 yields the above parameterized curve. This parameterized curve belongs to an imaginary individual that we picked for this project (see Appendix A). Since the model (2.2) – (2.17) is patient-specific, each patient has their own curve depending on their parameter values and the normal value of the HPT axis. The euthyroid state is shown in the picture with a red dot and diseased steady states are shown with green dots.

5.2 Discussion of using Patient's Dataset

We will first discuss how one could determine the euthyroid steady state from patient's dataset and next, we will depict how many data points of a patient are required to describe the natural clinical course of subclinical, clinical hypothyroidism or euthyroidism. Euthyroid steady state means the set point (normal value) of the HPT axis in the clinical setting. The clinical definition of the set point is a value of TSH and free T4, within the normal reference range of TSH $((0.4 - (2.5 - 4))\ mU/L$ and free T4 $(7 - 18)\ pg/mL$. Normally, the set point varies between individuals due to inter and intra variations in the adult population. Suppose if a patient has several values for TSH and free T4 (of course at different time points) within the reference range, then our best guess for the euthyroid steady state (set point) is the first data point.

Needless to say, with one data point (say just euthyroid state or set point) of TSH and free T4, it will be very hard to describe the patient's clinical course of subclinical, clinical hypothyroidism or euthyroidism. With two data points of TSH and free T4 at different time points, one could describe the clinical course using the chart but may not be the better description. With three or more data points of TSH and free T4 at different time points, one could provide a better description of patient's clinical course of subclinical, clinical hypothyroidism or euthyroidism using the chart. Therefore, we need at least three or more data points in order to use the chart effectively and make some conclusion about the eventual value (diseased steady state) of TSH.

In section 5.1, we generated clinical charts using an imaginary individual's table values from Appendix A. Recall that our imaginary individual's euthyroid steady state (set point) is $(TSH, FT4) = (1,13)$. Although the euthyroid steady state varies between individuals, the dynamics of the clinical variables (TSH and free T4) do not change (see Figure 5.11 and 5.12) so instead of calculating the parameter values for every patient and simulate their own dynamics. We will just move the clinical chart up and down according to the euthyroid steady state (first

data point) of the patient (see Figure 5.11) in order to describe the patient's natural history of autoimmune thyroiditis.

5.3 Validation of Model with Dataset

Let us consider a patient (#99) from group1 (always untreated patients dataset) for model validation. We will use euthyroidism → euthyroidism chart for this patient. Patient's initial (euthyroid) state is taken to be the first data point of TSH. That is, $TSH = 1.06$.

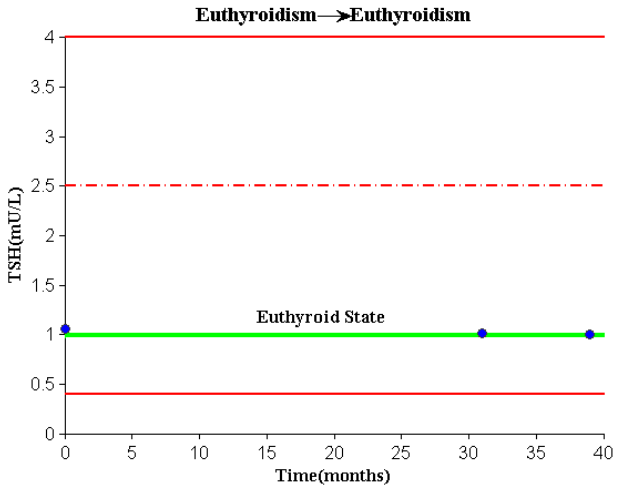


Figure 5.10: This figure illustrates patient (#99) natural history of euthyroidism in euthyroidism → euthyroidism chart. It seems patient's TSH value remains at the euthyroid steady state for 40 months. This patient's euthyroid state for TSH value is 1.06 mU/L.

Let us now consider a patient (#103) from group1 (always untreated patients) and a patient (#114) from group3 (untreated initially and then received treatment after developed hypothyroidism, see Chapter1) for model validation. For patient (#103), we will use euthyroidism → subclinical hypothyroidism chart. For patient (#114), we will use the complete clinical staging chart from Figure 5.8. In practice, one could move the clinical staging chart up and down according to the initial (euthyroid) state of the patient, but for numerical simulation one cannot. So, we will choose the initial state of both patient (#103 and #114) and compute all the parameters as outlined in Appendix A and simulate the 4d system. The initial state for patient (#103 and #114) is taken to be the first data point of TSH, free T4, anti-thyroid antibodies and the functional size of the

thyroid gland. The functional size is chosen in the manner of Appendix A. So, the initial state for patient (#103) is $(TSH, FT4, T, Ab) = (0.828, 14.15, 0.015, 50.92)$. Similarly the initial state for patient (#114) is $(TSH, FT4, T, Ab) = (1.4634, 15.164, 0.015, 176)$. The model parameter values are listed in the following Table 5.1 to generate the charts (see Figures 5.11, 5.12). Also Figure 5.13 and 5.14 illustrate the 2d curve of the patient (#103 and #114) respectively. From Figures 5.11, and 5.13, we could see that the patient (#103) developed subclinical hypothyroidism. From Figures 5.12 and 5.14, we could see that the patient (#114) eventually developed clinical hypothyroidism via subclinical hypothyroidism.

Table 5.1: Parameter Estimated Values, and Units

Name	Patient (#103) Estimated Value	Patient (#114) Estimated Value	Unit
k_1	5000	5000	$\frac{mU}{L * day}$
k_2	16.6355	16.6355	$\frac{1}{day}$
k_3	100	100	$\frac{pg}{mL * L * day}$
k_4	0.099021	0.099021	$\frac{1}{day}$
k_5	1	1	$\frac{L^3}{mU * day}$
k_6	1	1	$\frac{mL}{U * day}$
k_8	0.035	0.035	$\frac{1}{day}$
k_a	0.039	0.074034	$\frac{pg}{mL}$
k_d	0.0083	0.0147	$\frac{mU}{L}$
N	58.516	96.505	$\frac{mU}{L^2}$

Note: the parameters $k_1, k_2, k_4,$ and k_8 are the same numbers as in Appendix A. To generate the chart, Figure 5.11, we used six different k_7 values $(2.44, 2.76, 3.39, 4.03, 4.6, 5.2)$ between k_7^* (2.485) and k_7^{**}(5.3). Note k_7^* and k_7^{**} values changed a bit for patient (#103). Similarly to

generate the complete clinical chart in Figure 5.12, we used fourteen different k_7 values, $(0.1, 0.6, 1.4, 2.2, 2.44, 3.39, 4.6, 5.2, 6.8, 8.14, 9.4, 10.7, 12.1, 13.4)$. For patient (#114), $k_7^* = 2.3195$ and $k_7^{**} = 5.22$.

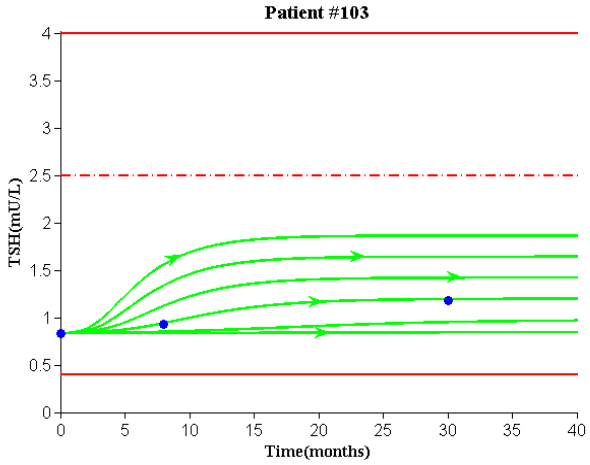


Figure 5.11: This figure illustrates patient (#103) natural course of subclinical hypothyroidism in euthyroidism → subclinical hypothyroidism chart. It seems this patient's TSH value continuously increases as time increases. By looking at 3 data points in this chart, we could predict that TSH cannot go beyond 2.5 mU/L at least for 40 months. Thus, this patient may have chance to become subclinical hypothyroidism throughout his life time unless there is some triggering event that changes the nature of the immune response and thus k_7.

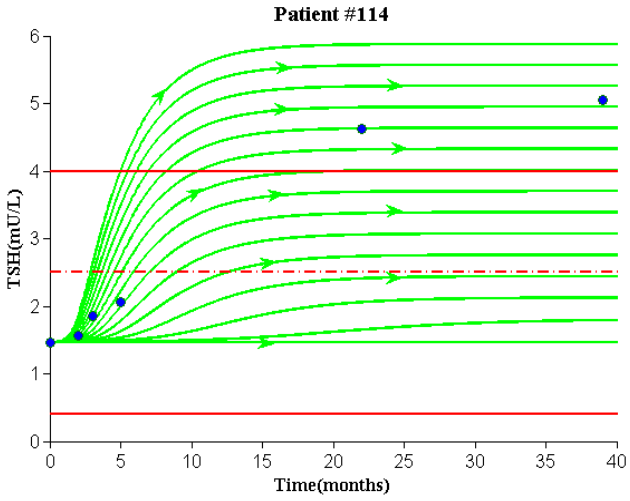


Figure 5.12: This figure shows the natural history of patient (#114). This patient reaches clinical hypothyroidism via subclinical hypothyroidism. Note this patient's TSH value increases continuously but did not exceed 6 mU/L in 40 months.

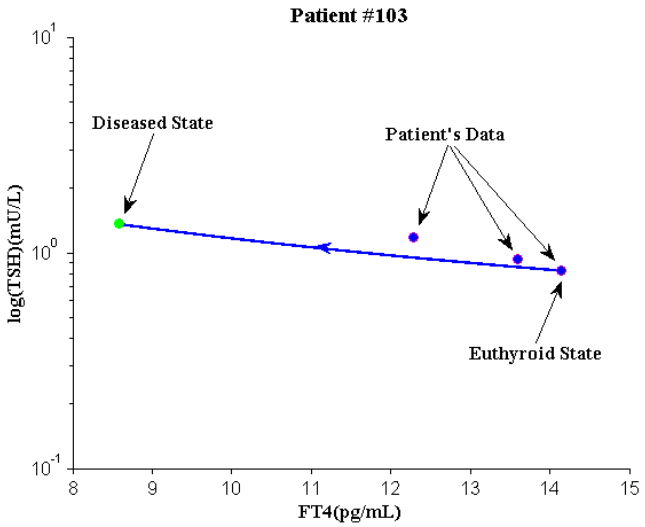


Figure 5.13: To generate this 2d picture, log(TSH) (mU/L) versus free T4($FT4$) (pg/mL), we simulated the 4d system with patient (#103) parameter values from Table 5.1. Here k_7 was 3.39 and the initial (euthyroid) state was $(TSH, FT4, T, Ab) = (0.828, 14.15, 0.01415, 50.92)$. Note: the diseased steady state is located within the normal free T4 reference range. So, the model predicts that the patient (#103) may remain in subclinical hypothyroidism unless the immune response of this patient changes in the future.

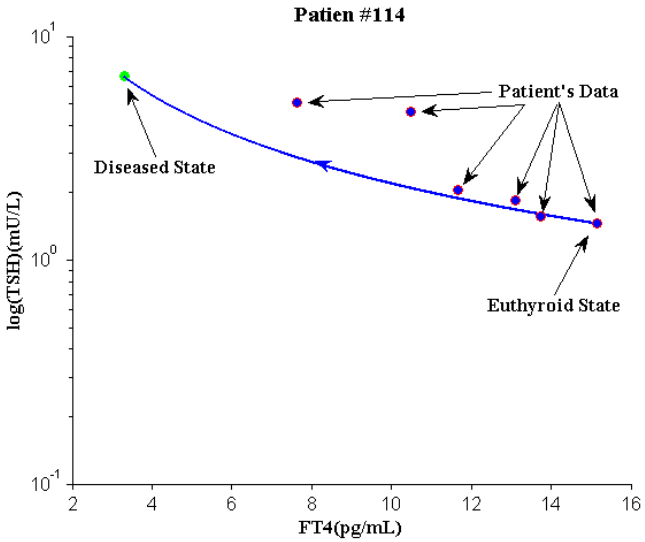


Figure 5.14: To generate this 2d picture, log(TSH) (mU/L) versus free T4 ($FT4$)(pg/mL), we simulated the 4d system with patient (#114) parameter values from Table 5.1. Here k_7 was 10.7 and the initial (euthyroid) state was $(TSH, FT4, T, Ab) = (1.4634, 15.164, 0.0151{,}176)$. Note: the diseased steady state is not located within the normal free T4 reference range. So, the model predicts that the patient (#114) will definitely become a clinical hypothyroidism patient in the future.

5.4 Results and Summary

In this chapter, we related a patient-specific clinical staging with a model. We mainly presented charts, namely, euthyroidism → subclinical hypothyroidism chart and euthyroidism → subclinical → clinical hypothyroidism chart and a combined chart involving only TSH and time (months), because in autoimmune thyroiditis, the hypothalamus-pituitary function is intact. These charts can be used in thyroid clinics to predict the natural clinical course of subclinical or clinical hypothyroidism in autoimmune patients. For that, we need at least three data points of TSH with respect to three different time points. This means, in simple language, that a doctor, using the TSH test, may be able to distinguish between those who will not develop thyroid problems and those who may become thyroid patients. Furthermore, the doctors will be able to treat sooner those destined for autoimmune thyroiditis related diseases. In addition, we presented the parameterized curve involving free T4 and TSH phase space.

From the mathematical viewpoint, the goal of this project is to identify a curve based on TSH that an autoimmune patient follows as time changes. This curve predicts whether a patient progress to subclinical or clinical hypothyroidism diseased state. If this curve is known, then patient diseased dynamics is known to physicians and thereby plans for treatment (free T4 replacement) can be developed based on TSH test results. For a physician's convenience, we simulated a lot of curves for different k_7 values in the clinical staging chart (see Figure 5.8). This may help physicians to visualize patient's TSH curve over time. This charting method for test results of TSH could be used to predict the ultimate level of thyroid destruction, and thyroid hormone production.

Future Work

- Examine the relationship between the high levels of TSH in autoimmune patients and follicular thyroid cancer initiation.
- Relating genetics of this disease to model results.

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Appendix A

Parameter used for Simulations.

To illustrate the general results in this dissertation, we would like parameter values consistent with our data and the literature. We remark in chapter 2 that the system (2.2) – (2.17) has eleven parameters, some of them are available from the literature, some are calculated, and some are determined experimentally using equilibrium value of an adult individual to match the expected behavior of a normal thyroid. We will now reveal how the example parameter values are estimated. Suppose a normal adult has an equilibrium value of $(TSH, FT4, T, Ab) = (1, 13, 0.015, 0)$, then the unknown parameter values of this adult can be computed around the equilibrium value.

Consider the equation (2.2),

$$\frac{dTSH}{dt} = k_1 - \frac{k_1\, FT4}{k_a + FT4} - \; k_2\, TSH$$

The first term accounts for the secretion rate of TSH and the second term accounts for the excretion rate of TSH. It has three parameters namely k_1, k_a, and k_2.

The parameter k_1 is available from the medical literature (Faglia, 1987). It is greater than $4000\ mU/L * day$. For this study, we will choose $5000\ mU/L * day$ and fix this number for all adults in the population. The meaning of k_1 is the largest possible secretion rate of thyroid stimulating hormone (TSH) from the pituitary in the absence of free thyroxine $(FT4)$. Biologically, this condition means clinical hypothyroidism (myxoedema).

The parameter k_2 is calculated using TSH chemical half-life (about 1 hour) in equation (2.2). The biological meaning of k_2 is the rate at which TSH disappears from the blood. Neglecting the secretion rate in (2.2), gives

$$\frac{dTSH}{dt} = -\, k_2\, TSH$$

The solution of this rate equation is,

$$TSH(t) = TSH(0)e^{-k_2 t}$$

where $TSH(0)$ is the initial value of TSH in the blood. The half-life is the time that concentration of a quantity takes to fall to 50% of the initial value in the blood. Using TSH half-life, we obtain,

$$\frac{1}{2}TSH(0) = TSH(0)e^{-k_2\,(1\ hour)}$$

That is,

$$k_2 = \frac{\ln(2)}{1\ \text{hour}} = 16.6355/day$$

The parameter value of k_a can be computed experimentally by using the equilibrium value of TSH. Thus, set

$$\frac{dTSH}{dt} = 0$$

and solve for k_a which yields $k_a = \frac{k_2 TSH\ FT4}{k_1 - k_2 TSH}$. Utilizing the equilibrium value and the parameter values, that is, $FT4 = 13\ pg/mL$, $TSH = 1\ mU/L$, $k_1 = 5000\ mU/L * day$ and $k_2 = 16.6355/day$. We determined the value of k_a, that is, $0.0434\ pg/mL$.

Consider the equation (2.10),

$$\frac{dFT4}{dt} = \frac{k_3\ T\ TSH}{k_d\ +\ TSH} -\ k_4 FT4$$

The first term accounts for the secretion rate of free $T4$ and the second one for the excretion rate of free $T4$. It has three parameters namely k_3, k_{d} , and k_4.

The parameter k_4 is calculated similar to k_2 by using the chemical half-life of free $T4$. The half-life of free $T4$ is about 7 days. Thus, k_4 is found to be $0.099021/day$.

The parameter k_3 is calculated using both the equilibrium and limiting argument. First, set

$$\frac{dFT4}{dt} = 0$$

This gives

$$FT4 = \frac{k_3\, T\, TSH}{k_4(k_d\, +\, TSH)} = \frac{k_3\, T}{k_4\left(\frac{k_d}{TSH} +\, 1\right)}$$

Since TSH quickly approaches the equilibrium value in the blood, so we will take a limit of the above equation, that is,

$$\lim_{TSH\to\infty} FT4 = \lim_{TSH\to\infty} \frac{k_3\, T}{k_4\left(\frac{k_d}{TSH} +\, 1\right)} = \frac{k_3\, T}{k_4} = 13\ pg/mL \text{ (equilibrium value)}$$

From this limiting equation, we can solve for k_3,

$$\frac{k_3\, T}{k_4} = 13$$

$$k_3 = \frac{13\, k_4}{T}$$

We can further use $T = 0.015\ L$ and $k_4 = 0.099021/day$ to obtain $k_3 = 85.8\ \frac{pg}{L*mL*day}$.

The parameter k_d is computed experimentally similar to k_a. By setting

$$\frac{dFT4}{dt} = 0 \text{ and solve for } k_d = \frac{TSH\ (k_3 T - k_4 FT4)}{k_4\, FT4}$$

Note that: if $k_3 T = k_4 FT4$, then $k_d = 0$. To avoid this situation, I picked k_3 a little bit greater than $\frac{13\, k_4}{T}$ $\left(\text{say } k_3 = 86 \frac{pg}{L*mL*day}\right)$. And then use $4 =\ 13\ pg/mL$,$TSH =\ 1\ mU/L$, $T = 0.015\ L$ and $k_4 = 0.099021/day$. This gives a value of $k_d = 0.0021\ mU/L$.

Consider the equation (2.15),

$$\frac{dT}{dt} = k_5\left(\frac{TSH}{T} - N\right) - k_6 Ab\, T$$

The first term accounts for the growth rate of the active thyroid gland and the second account for the destruction rate of the functional thyroid gland. The equation has again three parameters namely $k_5,\ k_6$ and N. Now, setting

$$\frac{dT}{dt} = 0 \Rightarrow k_5\left(\frac{TSH}{T} - N\right) - k_6 Ab\, T = 0$$

and using $Ab = 0\ U/mL,\ TSH =\ 1\ mU/L, T = 0.015\ L$. The value of $N = \frac{TSH}{T}$ is calculated to be $66.7\ mU/L^2$. Note that the euthyroid state (steady state) in Chapter 3 or Chapter 4 is independent of the parameters k_5 and k_6 . So we could pick any value for k_5 and k_6. The value of k_5 and k_6 does not change the stability of the euthyroid state. Thus, we will pick $k_5 = 1$ and $k_6 = 1$.

Consider the equation (2.17),

$$\frac{dAb}{dt} = k_7 Ab\ T -\ k_8\ Ab$$

The first term accounts for the production rate of anti-thyroid antibodies due to the destruction of active thyroid gland and second term accounts for aging rate of anti-thyroid antibodies. This equation has two parameters namely k_7 and k_8.

The parameter k_7 is an important parameter in the model. We used the value of this parameter to describe the natural clinical course of subclinical or clinical hypothyroidism in adult population. We studied this parameter in detail in Chapter 4. Thus, the reader should refer to Chapter 4.

The parameter k_8 is calculated using the half-life (about 20 days) of anti-thyroid antibodies in equation (2.17). The biological meaning of k_8 is the rate at which anti-thyroid antibodies disappears from the blood. This parameter can be calculated just like k_2 and k_4. Thus, $k_8 = \frac{\ln(2)}{20} = 0.0347/day$.

Table A1 list the imaginary individual's variable values, range, units and sources. Similarly Table A2 lists the parameter values for that particular imaginary individual.

Table A1: Variable Normal Values, Ranges, Units and Sources

Name	Normal Value	Normal Range	Source	Unit
TSH	1	$0.4 - (2.5 - 4)$	Literature(Baloch etal. 2003)	mU/L
$FT4$	13	$7\ -18$	Literature(Baloch etal. 2003)	pg/mL
T	0.015	$0.005 - 0.125$	Literature(Carle etal. 2009)	L

Ab	0	$0-<200$	Dataset	U/mL

Table A2: Parameter Estimated Values, Ranges, Units, and Sources

Name	Estimated Value	Normal Range	Source	Unit
k_1	5000	>4000	Literature (Faglia, 1987)	$\frac{mU}{L*day}$
k_2	16.6355	N/A	Literature (Greenspan and Gardner, 2001)	$\frac{1}{day}$
k_3	86	N/A	Simulation	$\frac{pg}{mL*L*day}$
k_4	0.099021	N/A	Literature(Greenspan and Gardner, 2001)	$\frac{1}{day}$
k_5	1	N/A	Simulation	$\frac{L^3}{mU*day}$
k_6	1	N/A	Simulation	$\frac{mL}{U*day}$
k_8	0.035	N/A	Literature	$\frac{1}{day}$
k_a	0.0434	N/A	Calculation/Simulation	$\frac{pg}{mL}$
k_d	0.0021	N/A	Simulation	$\frac{mU}{L}$
N	66.7	N/A	Calculation	$\frac{mU}{L^2}$

Appendix B

Solving Cubic Equation

In this Appendix, we will outline a method to solve a cubic equation (see Selby, 1969). Suppose a cubic equation is given in the form $y^3 + py^2 + qy + r = 0$, then we will solve for y by substituting

$$y = x - \frac{p}{3} \qquad (c1)$$

into the cubic equation and reduce to the form,

$$x^3 + ax + b = 0$$

where,

$$a = q - \frac{p^2}{3}$$

and

$$b = r - \frac{pq}{3} + \frac{2p^3}{27}$$

For solution let A and B

$$A = \left(\frac{-b}{2} + \sqrt{\frac{b^2}{4} + \frac{a^3}{27}} \right)^{\frac{1}{3}}$$

and

$$B = \left(\frac{-b}{2} - \sqrt{\frac{b^2}{4} + \frac{a^3}{27}} \right)^{\frac{1}{3}}$$

then the values of x will be given by,

$$x = A + B, \qquad -\frac{1}{2}(A+B) + \frac{\sqrt{-3}}{2}(A-B)\,, \qquad -\frac{1}{2}(A+B) - \frac{\sqrt{-3}}{2}(A-B)$$

Now, we can of course convert from the x solutions to the y solutions using the equation (c1).

If p, q, r are real, then:

If $\frac{b^2}{4} + \frac{a^3}{27} > 0$, there will be one real root and two conjugate imaginary roots

If $\frac{b^2}{4} + \frac{a^3}{27} = 0$, there will be three real roots of which at least two are equal

If $\frac{b^2}{4} + \frac{a^3}{27} < 0$, there will be three real and unequal roots

Descartes' Rule of Signs (Murray, 2002)

Consider the polynomial in the general form,

$$y^n + a_1 y^{n-1} + \cdots + a_n = 0 \qquad (c2)$$

where the coefficients a_i, $i = 0,1, \ldots, n$ are all real and $a_n > 0$. Let M be the number of sign changes in the sequence of coefficients $\{a_n, a_{n-1}, \ldots, a_0\}$, ignoring any which are zero. Descartes' Rule of Signs says that there are at most M roots of (c2), which are real and positive, and further, that there are M, M-2 or M-4,… real positive roots. By setting $\omega = -y$ and again applying the rule, information is obtained about the possible real negative roots. Together these often give invaluable information on the sign of all roots, which from a stability point of view is usually all we need.

Example: While solving for the euthyroid steady state, we encountered the cubic polynomial of the form,

$$FT4_1^3 + k_a\left(2 + \frac{k_1}{k_2 k_d}\right) FT4_1^2 + \left(k_a^2 + \frac{k_a^2 k_1}{k_2 k_d}\right) FT4_1 - \frac{k_3 k_1^2 k_a^2}{k_4 k_2^2 k_d N} = 0 \qquad (c3)$$

Note: M=1, because the equation $(c3)$ has only one sign change in the sequence of coefficients $\left\{1, k_a\left(2+\frac{k_1}{k_2k_d}\right), \left(k_a^2+\frac{k_a^2k_1}{k_2k_d}\right), -\frac{k_3k_1^2k_a^2}{k_4k_2^2k_dN}\right\}$. Therefore, by Descartes' rule there is exactly one real positive root. If we now set $\omega = -FT4_1$, the equation $(c3)$ becomes,

$$-\omega^3 + k_a\left(2+\frac{k_1}{k_2k_d}\right)\omega^2 - \left(k_a^2+\frac{k_a^2k_1}{k_2k_d}\right)\omega - \frac{k_3k_1^2k_a^2}{k_4k_2^2k_dN} = 0 \qquad (c4)$$

That is,

$$\omega^3 - k_a\left(2+\frac{k_1}{k_2k_d}\right)\omega^2 + \left(k_a^2+\frac{k_a^2k_1}{k_2k_d}\right)\omega + \frac{k_3k_1^2k_a^2}{k_4k_2^2k_dN} = 0 \qquad (c5)$$

There are two sign changes in the sequence of coefficients and so there are either two or zero real negative roots.

Appendix C

Data Sets

File Name	File Description
NewData.xslx	119 Hashimoto's thyroiditis patients raw dataset
NOPT.mat	This file contains patient's identification number (Id), time (Time), thyroid stimulating hormone (TSH), free thyroxine (FT4), and anti-thyroid antibodies (TPOAb and TGAb). There are 119 Hashimoto's thyroiditis patients in this dataset. It is created from NewData.xslx file.
group1scaled.mat	Always untreated patient's dataset is created from NOPT.mat file. This dataset contains Id, Time, TSH, FT4, TPOAb and TGAb. Note: group1 patient's TSH and FT4 values are all scaled to normal reference range of TSH: $(0.4 - 4)\ mU/L$ and FT4: $(7 - 18)\ pg/mL$.
group2scaled.mat	Treated patients from time zero is created from NOPT.mat file. This dataset contains Id, Time, TSH, FT4, TPOAb and TGAb. Note: group2 patient's TSH and FT4 values are all scaled to normal reference range of TSH: $(0.4 - 4)\ mU/L$ and FT4: $(7 - 18)\ pg/mL$.
group3scaled.mat	Untreated patients initially and then received treatment with Levothyroxine after developed hypothyroidism. This dataset is created from NOPT.mat file. It contains Id, Time, TSH, FT4, TPOAb and TGAb. Note: group3 patient's TSH and FT4 values are all scaled to normal reference range of TSH: $(0.4 - 4)\ mU/L$ and FT4: $(7 - 18)\ pg/mL$.
group3scaleduntreated.mat	Group3 patients' dataset before treatment. It is created from group3scaled.mat file
patient99.mat	Patient #99 data is extracted from group1scaled.mat file (always untreated patients dataset).

patient103.mat	Patient #103 data is extracted from group1scaled.mat file (always untreated patients dataset).
patient114.mat	Patient #103 data is extracted from group3scaleduntreated.mat file.

Matlab Files

File Name	File Description
scatterplots.m	This Matlab file contains codes for all scatter plots in Chapter 1.
normal_operation.m	This Matlab file contains codes for simulating the reduced 2d model in Chapter 3.
norm_operation.m	This Matlab file contains codes for simulating 3d model when Ab set to zero in Chapter 3.
Disr_feed.m	Using this Matlab file, one could generate all figures in Chapter 4. Note that $k_5 = 1$ and k_7 value changes for different arguments.
bifurcation.m	Using this file, one could generate all bifurcation diagrams in Chapter 4.
euthyroid.m	Using this file, one could generate euthyroidism → euthyroidism chart in Chapter 5.
subclinicalhypo.m	Using this file, one could generate euthyroidism → subclinical hypothyroidism chart and the parameterized curve (by k_7) in Chapter 5.
clinicalhypo.m	Using this file, one could generate euthyroidism → subclinical → clinical hypothyroidism chart and the parameterized curve (by k_7) in Chapter 5.
completechart.m	Using this file, one could generate the complete euthyroidism → subclinical → clinical hypothyroidism chart and the parameterized curve (by k_7) in Chapter 5.

patient103.m	Using this file, one could generate patient #103 clinical chart and the curve in TSH- FT4 phase plane.
patient114.m	Using this file, one could generate patient #114 clinical chart and the curve in TSH- FT4 phase plane.

All files are available in the following Url:

http://www.mscs.mu.edu/~stevem/bala_files.html