MODELING THE DYNAMICS OF THYROID HORMONES AND RELATED DISORDERS

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Abstract

In this study, a dynamic simulation model for thyroid hormone system is constructed. The objective of this work is to first generate the dynamics of the hormones involved in thyroid hormone system in healthy body, and then to adapt the model to portray the dynamics of certain common thyroid disorders. The ultimate aim is to provide a platform for scenario analysis to support medical education, training and research, without risking patients' health. Thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), thyroid hormones T3 and T4, sizes of hypothalamus, pituitary and thyroid gland are the basic variables in the model. The model structure is tested by standard structure validity tests. Scenario experiments are simulated and outputs consistent with the data in literature, both qualitative and quantitative, are obtained. The model is shown to capture well the dynamics of a particular well-known disorder, namely subacute thyroiditis. As future work, the parameter values will be more realistically calibrated and the model will be extended to cover more disorders, include drug therapy and other medical interventions.

Key Words: thyroid hormone dynamics, thyroid disorders, subacute thyroiditis, medical modeling, physiological simulation, disease simulation.

1. INTRODUCTION

The main goal of modeling physiological systems is to provide a platform to conduct experiments and subsequently propose policies, without any necessity to rehearse on humans. This study aims at modeling the thyroid system to capture the dynamics of thyroid hormones and some related diseases in order to facilitate the

recognition of these disorders. Initial goal is to generate the dynamics of key stimulating and thyroid hormones in healthy body. Next purpose is to represent some well-known thyroid disorders using the modified model. The final goal is to capture the typical dynamics of the key hormones under these disorders, hence to hopefully offer a platform for the recognition of these disorders and for scenario analysis to assist medical education, training and research.

There are mainly two systems in the regulation of the functions of the body: (1) the nervous system, and (2) the endocrine system, or the hormonal system. In this study, a hormonal system will be of interest. For the lexical meaning, the word "hormone" is derived from the Greek word *hormaein*, which means to excite, arouse or stir up. As for the biological implication, a hormone is a chemical substance responsible for conveying messages to target cells. They are secreted by a cell or gland. Through the actions of hormones, the endocrine system exerts physiological control on metabolic functions of the body. Therefore, endocrine system plays a crucial role in the regulation, integration and coordination of various physiological processes (Rhoades and Bell, 2009).

In the endocrine system, a hormone is first secreted into blood (although some other pathways exist, bloodstream is the usual way) and is free to contact almost any cell in the body; however, only the target cells act in response to that hormone (Rhoades and Bell, 2009). This mechanism is facilitated by the receptors, which are hormone-specific molecular entities located on or within the cells. When receptors are in unbound state, they are inactive. Inactivity of the receptors means that the intracellular mechanisms related to them stay passive (Guyton, 2006). Binding of a hormone to its receptor can be described as a lock-and-key interaction, key standing for the hormone and lock for the receptor. A hormone serves as the key for the receptor (the lock); it unlocks the expression of its function by binding to the receptor. After the binding of a hormone to its receptor, series of intracellular actions are triggered which eventually result in the synthesis and secretion of the hormone. In general, the number of receptors is an important determinant on how well the cell reacts to the stimulation by a hormone (Bhagavan, 2002).

A crucial point in the functioning of endocrine system is to ensure the equilibrium state in the body. This is where feedback loops come into play. Feedback loops are the principal regulators of the endocrine system. They adjust the amount of hormones released by the gland and keep them at a desired level in order to guarantee a healthy maintenance of bodily functions.

As far as the order of feedback loops is concerned, different forms of hormonal regulation exist. Rather than the systems that operate under the control of a single feedback loop, the ones involving higher order, complex feedback loops have more interesting dynamics to study. Production of thyroid hormones, which comprises the main focus in this study, is controlled by such higher order negative feedback loops. The thyroid hormones play key roles in the regulation of bodily functions. They govern the pace of metabolic functions in the body. Since these hormones affect virtually every part of the body and regulate some vital functions, the dynamics of these hormones and related disorders are worth to be investigated.

As just mentioned, the thyroid system is under a multilevel feedback regulation. Three tiers are involved; first tier is the hypothalamus, second is the pituitary, and the third one is the thyroid gland (Kronenberg *et al*., 2008). Firstly, the hypothalamus secretes *thyrotropin-releasing hormone* (TRH) which prompts the production of *thyroid-stimulating hormone* (TSH) from the pituitary. Then, TSH stimulates the thyroid gland. Upon stimulation, production of thyroid hormones, which are *triiodothyronine* (T3) and *thyroxine* (T4), is triggered. After T3 and T4 are secreted from the thyroid, they circulate in blood and reach their target tissues. Circulating hormone concentrations in blood are a function of the glandular secretion pattern and metabolic clearance rate, which is the rate of removal of the hormone from the blood. (Guyton, 2006; Kronenberg *et al*., 2008; Rhoades and Bell, 2009). Eventually, concentration of thyroid hormones in blood creates a double-armed negative feedback effect. That is, thyroid hormones in blood affect negatively both the hypothalamus and the pituitary, and consequently inhibit the secretion of TRH and TSH. Pictorially, the basic structure of the thyroid hormone system looks as follows:

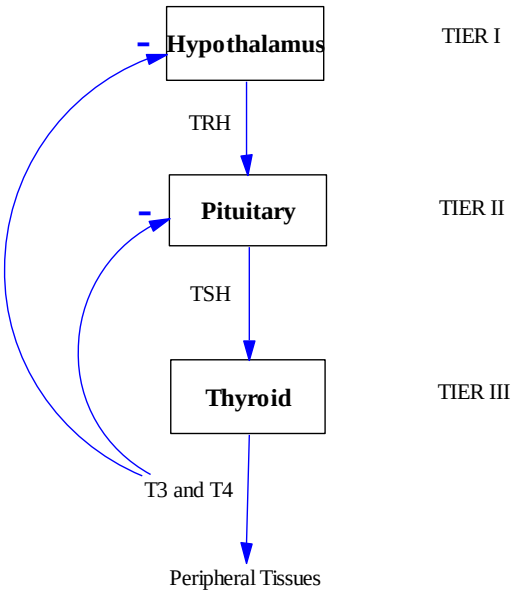

Figure 1: Basic structure of the thyroid hormone system

After the formation of T3 and T4 hormones, they are released into blood. Most of the T3 and T4 molecules become bound to plasma proteins, only less than 1% of them circulate in free form. Merely the free portion of the hormones interacts with target cells (Rhoades and Bell, 2009). And, it is the circulating free hormones that create the negative feedback effect on the hypothalamus and pituitary. Although thyroid hormones feed back negatively both hypothalamus and pituitary, the ultimate effect can be observed on the secretory rate of the pituitary, because amount of TRH secreted just affects the amount of TSH to be secreted. And since TSH is the eventual messenger in the stimulation of the thyroid gland, one may just focus on the effect of TSH on thyroid gland to make macro inferences about the thyroid gland in short and long run. As mentioned earlier, a fall in concentration of free thyroid hormones leads to an increase in TSH secretion, and vice versa. Also, it is known that activation of glandular cells happens via binding of the stimulating hormone with the associated receptor. Then,

since TSH stimulates and increases all the known activities of thyroid follicular cells (Guyton, 2006; Rhoades and Bell, 2009), a rise in TSH production will surely enhance the thyroid activity. Conversely, in case thyroid hormone levels in blood increase, TSH secretion diminishes and thyroid follicular cell activities fall off. These are the short-term impacts of TSH on thyroid gland. If the short-term effects of TSH persist for a sufficiently long time, thyroid size changes. Prolonged high TSH levels results in the enlargement of the thyroid gland due to proliferative effect of TSH. And, in case low TSH levels last for a long time, thyroid gland atrophies, in other words shrinks (Guyton, 2006; Donovan, 1966; Melmed, 2002). As an evidence to the atrophic effect of TSH on thyroid gland, *hypophysectomy*, which means the complete removal of the pituitary gland, can be considered. In case of hypophysectomy, obviously no TSH secretion takes place. This means that the thyroid gland will no longer be stimulated by TSH. As a result, substantial decrease in thyroid hormone activities and atrophy of thyroid gland because of prolonged "idling" is observed (Donovan, 1966). In short, depending on the relative levels of TSH, either enlargement or atrophy of thyroid gland may be the result over the long term.

Relying upon the fact that a hormone, which provokes or inhibits the activity of a gland, can also affect its size over the long term in certain cases (Donovan, 1966; Melmed, 2002; Guyton, 2006), TRH and thyroid hormones can also influence the size of the pituitary and hypothalamus. First, TRH acts on the pituitary in the same manner as TSH does on the thyroid gland. So, the impact of continued high levels of TRH will be an increase in the size of the specific portions of pituitary, which are in charge of the production of TSH, and vice versa. Second, since the effect of thyroid hormones on hypothalamus is negative, persistent high levels of thyroid hormones in blood would cause parts of the hypothalamus, which are responsible for the production of TRH, to shrink to some extent. Conversely, sustained low levels of thyroid hormones in blood will lead to expansion of the related portions of hypothalamus. These are the defence mechanisms of the body against the persistent disturbances from equilibrium.

One interesting characteristic of thyroid gland, in contrast to most endocrine glands, is that it has a certain capacity to store thyroid hormones in itself. In literature, it is stated that thyroid gland is able to store 2 to 3 months' supply of thyroid hormones in it. Thus, if synthesis of thyroid hormone ceases, the physiologic effects may not be recognized for a few months (Guyton, 2006; Molina, 2004). In a sense, these stores serve as buffers in the body.

2. OVERVIEW OF THE MODEL

The model consists of three subdivisions: the hypothalamus, the pituitary, and the thyroid. Each subdivision involves one gland, its related hormone(s) and hormone stores, if any, and the measures and relationships that have an effect on the gland and hormone(s). A causal loop diagram depicting the main variables in the model is shown in Figure 2. Not all the feedback loops are shown and numbered in the diagram; only the key loops are presented.

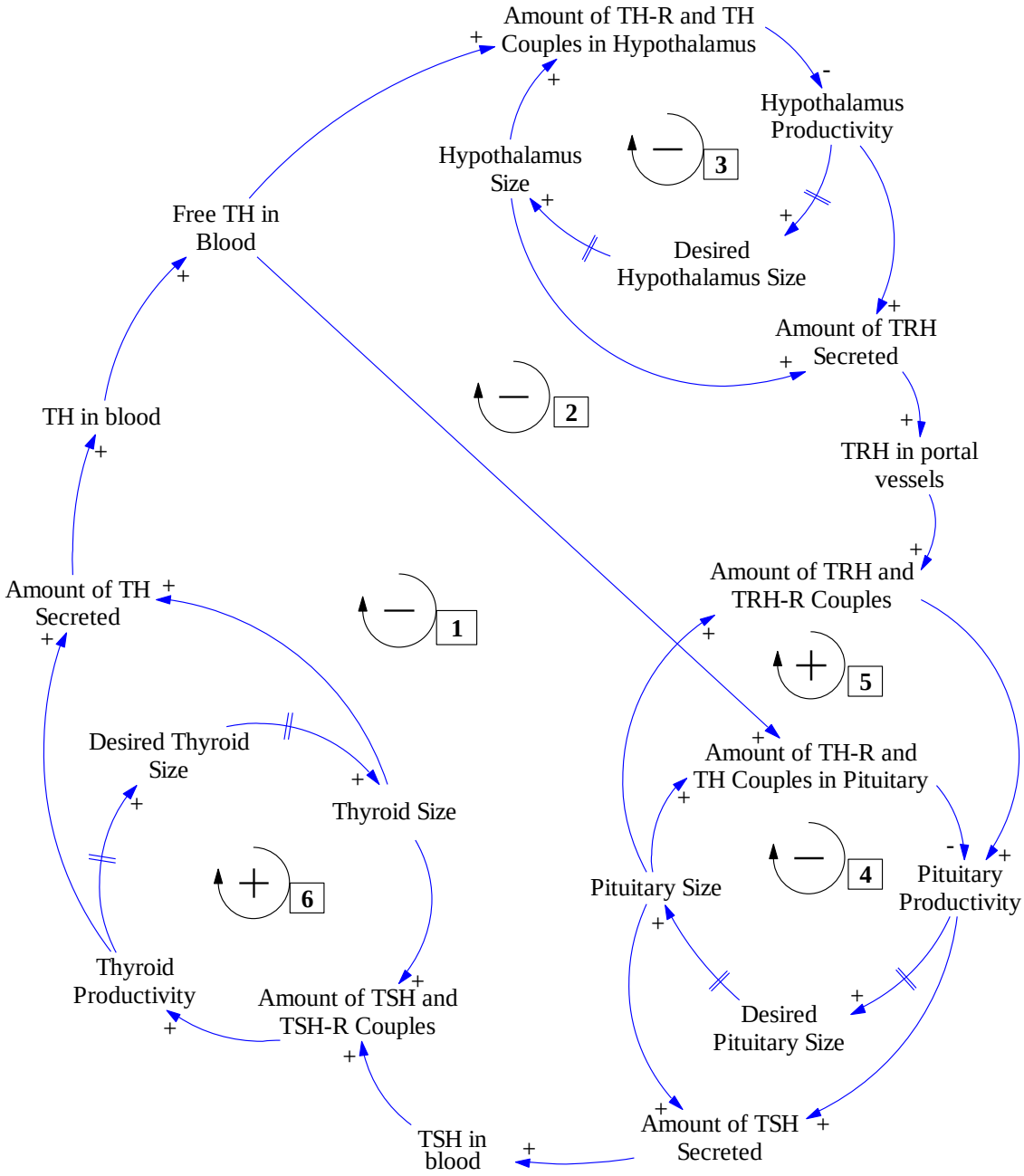

Figure 2: Causal loop diagram of the model

There are four important negative feedback loops in the model. The first one, loop no. 1, stands for the negative feedback effect of thyroid hormones on pituitary gland in short term. Formation of thyroid hormone-thyroid hormone receptor complexes in pituitary creates inhibitory effect on TSH synthesis (Melmed, 2002). As the free thyroid hormone levels in blood increase, TSH synthesis by the pituitary gland will be inhibited to maintain healthy levels of thyroid hormones in the body. Conversely, TSH synthesis will be triggered if thyroid hormone concentrations drop below the normal level. The second balancing loop, loop no. 2, depicts the negative feedback effect of thyroid hormones on hypothalamus. This feedback loop ultimately affects the amount of TRH released from the hypothalamus. Loop no. 3, again a balancing loop, illustrates the long-

term effect of thyroid hormones on the size of the hypothalamus. The last balancing loop, loop no. 4, stands for the long-term effect of TRH on pituitary size.

In addition to the negative feedback loops, two important reinforcing loops exist in the model. The first positive feedback loop, loop no. 5, depicts the long-term impact of TRH on the size of the pituitary gland. As aforementioned, prolonged over-stimulation of pituitary gland by TRH will lead to the growth of this gland over the long run. Conversely, if the pituitary gets under-stimulated for a sufficiently long time, it will shrink. Lastly, loop no. 6 represents the long-term effect of TSH on the size of the thyroid gland. As one might guess, the effect of TSH on thyroid gland is qualitatively the same as that of TRH on the pituitary gland.

The model will be elucidated in detail in the next section; but, briefly the rationale behind the model is as follows: The amount of a hormone secreted depends on two factors, the size and the productivity of the gland. Productivity can be affected by the relative amounts of hormone-receptor couples without a delay. However, changes in gland size take place in time. First, the body "decides" on a desired gland size with a delay by considering the needs of the body, which is actually imposed by the productivity levels. According to this target level, gland size is changed in the long run.

3. MODEL DESCRIPTION

There are twelve stocks in the model, four of them for the levels of hormones in the body, two of them for the thyroid hormone stores in the body, three of them for the sizes of glands, and three for explaining the mechanism of change in gland sizes. *TRH*, *TSH*, *T4 in Blood* and *T3 in Blood* represent the levels of these hormones in the body (in blood or in specific portal vessels). *Hypothalamus Size*, *Pituitary Size*, and *Thyroid Size* denote the sizes of the parts of the related glands which are responsible for the synthesis and secretion of the associated hormones. The last three stocks, *Hypo size change info* *Pit size change info* and *Thyroid size change info*, keep the information which will potentially lead to a change in the sizes of the glands. Simplified stock-flow diagram of the model is shown in Figure 3 (see Appendix for the complete version).

3.1. Assumptions

Normally, hormones are secreted in a pulsatile fashion and their concentrations in the body change very rapidly during the day. This means that they demonstrate a noisy pattern in real life. As far as the scope and the ultimate aim of this study are concerned, time unit is taken to be day and thus the natural diurnal variations of hormones are not taken into account.

Concentration of a hormone in the body may appear in slightly different units in literature. It is usually given as weight of a hormone per unit fluid volume (e.g. micrograms/dl). TSH and thyroid hormones circulate in blood; so, their concentrations are given per unit plasma volume, where plasma is the colourless liquid part of blood. TRH, however, circulates in the cerebrospinal fluid (CSF), which is a serumlike fluid that essentially circulates through the ventricles of the brain. In the model, not the amount per unit volume but the total amount of a hormone is taken as the value of the

relevant stock. This is simply done by multiplying the relative concentrations with the total fluid volume. In this model, plasma volume is taken to be 3 litres (Distefano and Chang, 1971) and the volume of CSF is approximately taken to be 150 ml (Conn, 2008). All the four stocks standing for the four hormones have units of micrograms.

In general, hormones are cleared from the blood with respect to a specific rate. The model also works according to this principle; each hormone is removed with respect to a certain fraction, which is called the metabolism fraction in the model. In literature, half-lives are commonly used to quantify the clearance rate of a hormone. Thus, removal of hormones from blood (or the related fluid) is assumed to follow a first order exponential decay in the model, and the respective metabolism fractions are calculated from their half-lives using the following equation:

$$Metabolism\ fraction = ln2/t_h$$

where t_h stands for the half-life in days. So, the metabolism fractions are in units of day^{-1}.

Relying upon the interviews with the medical doctors and real cases, it is known that changes in gland sizes do not happen immediately. Therefore, both the accumulation of information for gland size changes and the changes in the gland are subject to delays. Currently, the adjustment time for the accumulation of gland size change information is assumed to be one week, and the adjustment time for a gland size to change is taken to be two weeks. After collecting more real life data, these parameters will be calibrated further.

Lastly, in the model, the number of receptors of a gland is calculated by multiplying the number of receptors per unit size of the gland with the size of the gland. The number of receptors per unit size of a gland is taken as a constant quantity. So, it is assumed that the total number of receptors would only vary through changes in the size of the gland. In reality, the number of receptors in the tissues is highly variable. Their amounts may rise or decline even from minute to minute with the effect of the hormones interacting with them (Guyton, 2006). However, the limiting variable in real life is the amount of hormones that interact with the receptors. And, as compared to the time unit of our model, changes in the number of receptors would happen very rapidly, if they were taken as variables. As far as the aim of the study and the above-mentioned characteristics of receptors are concerned, it would be redundant to include their dynamical nature. Thus, in the model, the number of receptors per unit gland size is assumed to be at a maximal level that they could eventually reach. So, instead of allowing the number of receptors per unit gland size to be altered by the hormones to some desired level without a delay, it is assumed that a maximal number of receptors per unit gland size is available all the time.

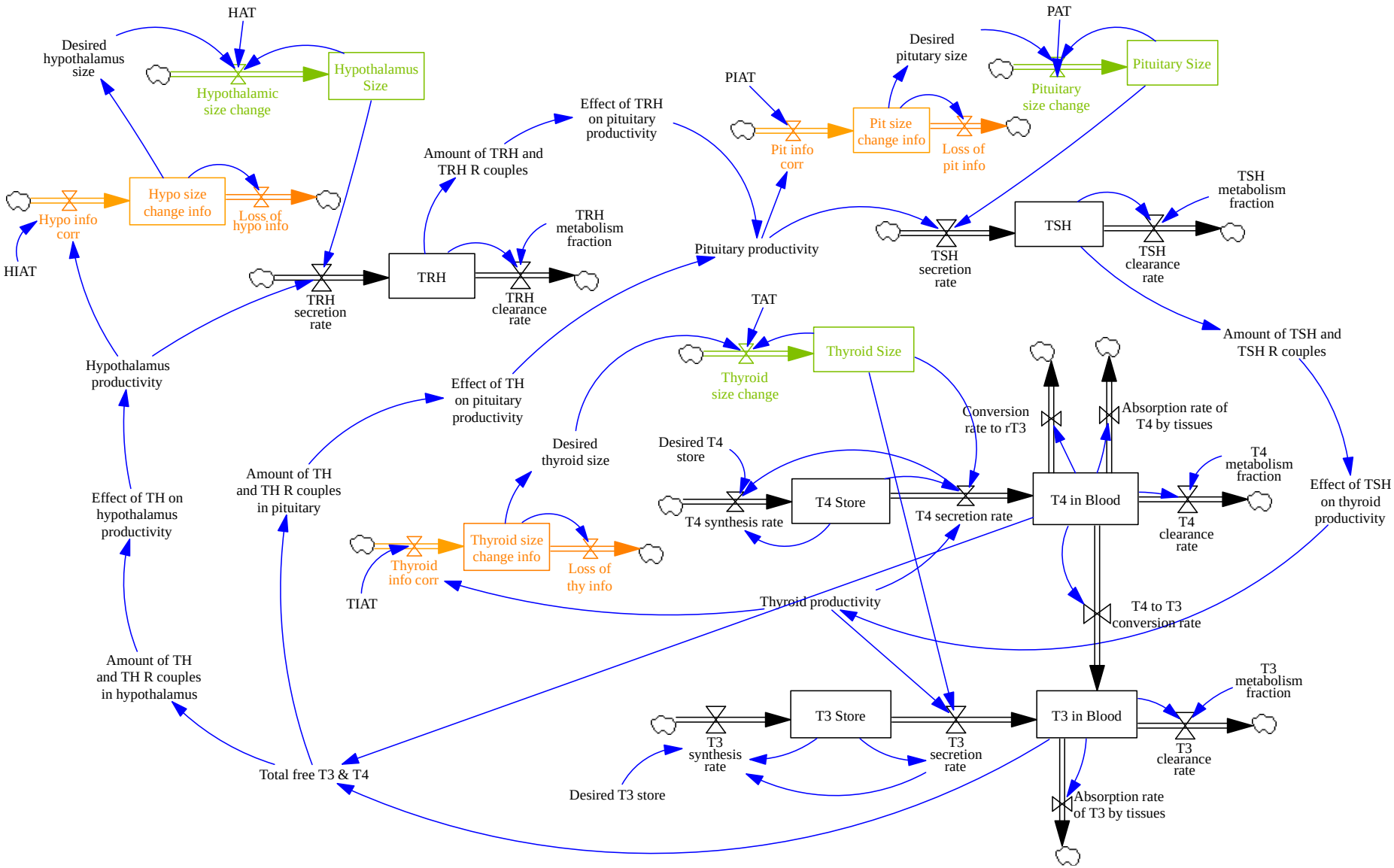

Figure 3: Simplified stock-flow diagram

3.2. Technical Description of the Model

As explained before, three tiers are involved in the control of thyroid hormone secretion. First, the short-term happenings will be explained. Everything begins with the secretion of TRH from the hypothalamus. Amount of TRH secreted (*TRH secretion rate*, the inflow to *TRH* stock) is the product of two quantities; hypothalamus productivity, which is assumed to be amount of hormone to be secreted per unit size per unit time, and the size of the hypothalamus (again, it is not the total size of the hypothalamus but just the relevant portions of it). After being released, TRH couples with its receptors, TRH R's, located on the pituitary cells. Coupling of hormones with their receptors happen on a molecular basis. Therefore, the value of *TRH* stock is divided by the molecular weight of TRH, denoted by *MW of TRH* in the model, to figure out the amount of TRH molecules that currently exist. TRH and TRH R couples, whose amount is limited to the minimum of either of these two quantities, affect the productivity of the pituitary with respect to the ratio of the current amount of couples to the normal. This ratio becomes an input to a graphical effect function in the model, called *Graph func for effect of TRH on pit prod*. The output of this function, *Effect of TRH on pituitary productivity*, is then multiplied with the *Normal pituitary productivity* and a new productivity value is calculated at each step. Since TRH affects the pituitary gland positively, its effect function on the productivity will obviously be an increasing function. The function is explicitly shown in Figure 4.

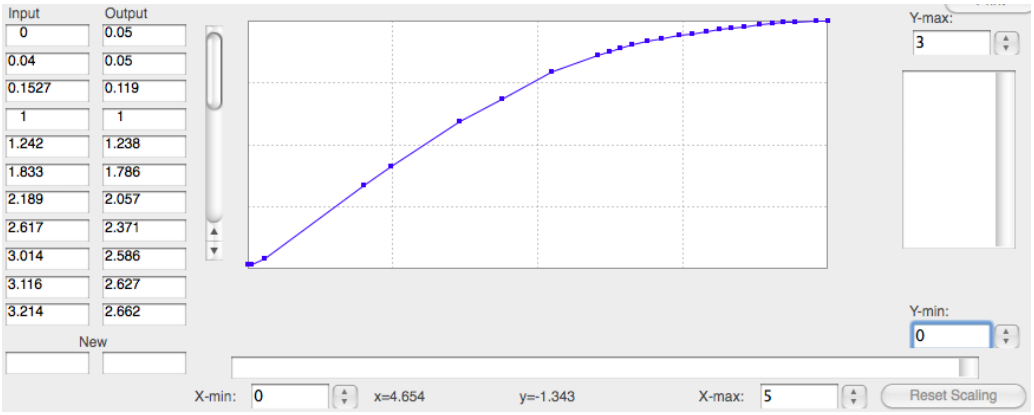

Figure 4: Function for the effect of TRH on pituitary productivity

In turn, TSH gets secreted. Again, the secretion rate is the product of the productivity and the relevant gland size. Upon secretion of TSH, things happen in the same manner as after the secretion of TRH (as the stock-flow diagram pictorially suggests), and thyroid hormones get secreted. This means that the release of TSH creates very similar effects on its receptors, couples to them, and positively influences the productivity of the thyroid gland. So, although not exactly the same, the effect functions of TSH are similar to the one shown in Figure 4.

It was previously explained that it is the freely circulating thyroid hormones that create the negative feedback effect on both hypothalamus and pituitary. The free portion 0.02% for T4 and 0.3% for T3 (Braunwald *et al*., 2001). Thyroid hormones affect hypothalamus productivity just in the opposite way that TRH and TSH act on the pituitary and thyroid productivity, respectively. Therefore, the related function is a

decreasing function. The function for the effect of thyroid hormones on hypothalamus productivity is given in Figure 5.

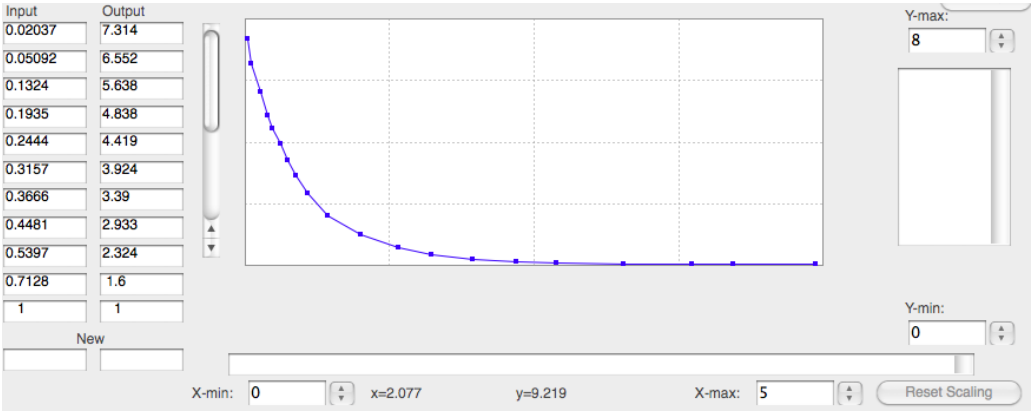

Figure 5: Function for the effect of TH on hypothalamus productivity

Up to this point, short-term effects of hormones on the glands are explained. Now, the long-term effects of hormones on the glands will be clarified. In the whole model, there are three stocks that pool the information which potentially lead to changes in gland sizes. The cells can expand their individual capacities to some extent. But, if the capacity, i.e. current productivity level, of a cell no longer suffices to respond to the needs of the body, which is imposed by the amount of hormone-receptor couples, it will tend to proliferate. To imitate this tendency, the ratio of current productivity to the normal productivity for each of the three glands are pooled in three separate stocks (*Hypo size change info*, *Pit size change info* and *Thyroid size change info*) and updated at each step. Initial values of these stocks are 1. The meaning of value "1" is that things have been operating under normal conditions. Since cells can expand their productivity to some degree, the inflow to the stocks that keep the size change information can take a nonzero value only if the ratio of current productivity to normal is outside of some limits. This illustrates the resistance of a gland to change its size immediately. Changes in gland sizes do not happen immediately. First, desired gland sizes are determined. According to these target levels, which is just the product of normal gland size with the value of the stock keeping the information, gland sizes are adjusted in time.

One last remark about this structure is that all the three stocks, which serve as the information pools, are subject to an outflow. The reason to embed this outflow to the stocks is that it may not be reasonable to assume that no information loss takes place. In a sense, the body should "forget" some information gradually. The equation for this flow is formulated as such (let us take the *Pit size change info* stock as an example):

$$Loss\ of\ pit\ info = 0.3 * (Pit\ size\ change\ info - 1)$$

This equation says that 30% of information, which creates the deviation from the normal conditions, is forgotten per unit time. Subtraction "1" from the stock value denotes the amount of deviation from the normal conditions because the value "1" symbolizes the normal conditions. If, instead, the fraction were merely multiplied with the stock value, then the desired gland sizes would change even under normal conditions.

Lastly, the parameters regarding the levels of hormones in the body, their half-lives and molecular weights, and the sizes of the glands are set consistent with literature. The parameter values regarding the three hormones that are taken from various sources (Werner *et al*., 2005; Motta, 1991; Bhagavan, 2002; Henry, 2001; Melmed, 2002; Negi, 2009; Rhoades and Bell, 2009; Guyton, 2006; Kronenberg *et al*., 2008) and used in the model are given in Table 1. When a reference interval is given, a reasonable point value is chosen. Those values are shown in parentheses in the table.

Table 1: Reference parameter values

	Average level	***Half-life***	***Molecular weight (Da)***
TRH	65-290 pg/ml (200 pg/ml)	6.2 min	362
TSH	1-4 ng/ml (2.2 ng/ml)	60 min	28000
T3	75-220 nanograms/dl (166,67 nanograms/dl)	1 day	651
T4	4-11 micrograms/dl (8 micrograms/dl)	7 days	777

4. MODEL VALIDATION

A significant portion of model validation has been done during the model building process. It is done both by verifying the structure with the existing information in literature and also through the interviews with medical doctors. In this section, after showing the base run to show the steady-state behaviour, two test runs will be given to show that the model produces expected behaviours under these conditions.

4.1. Base Run

When all stock variables are initially set to their equilibrium (normal) levels, all hormones stay constant at their equilibrium values, as expected.

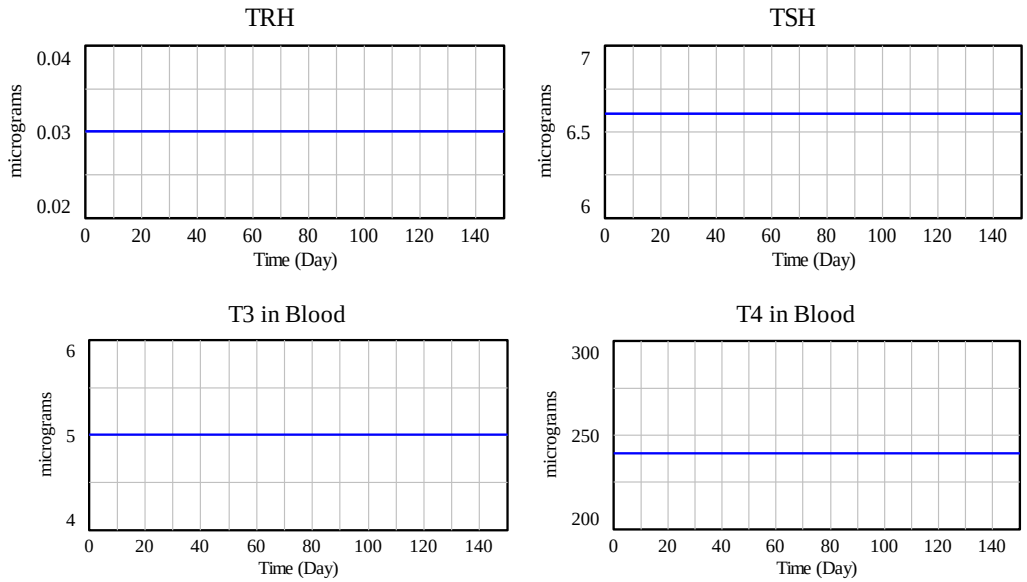

Figure 6: Base run

4.2. T4 Secretion Doubled for One Day

In literature, it is stated that if T4 secretion were doubled for one day, we would expect T4 concentration in blood to increase about 30% (Goodman, 2009). Here, it is assumed that from t=0 to t=1, *T4 secretion rate* is twice its normal value. After t=1, no external intervention is applied on T4 secretion. The behaviour of T4 under this scenario is shown separately in Figure 7.

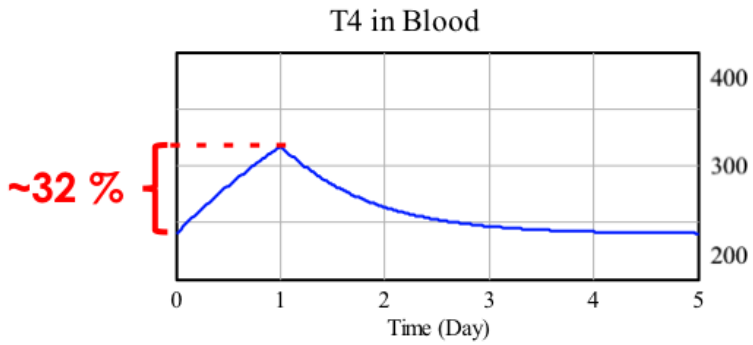

Figure 7: T4 levels in blood when its secretion is doubled for one day

Doubling of T4 secretion for one day causes T4 levels to increase until the end of the first day, as expected. The amount of increase is about 32% which is quite consistent with the data in literature. Since no component of the system is interfered with after the first day, T4 levels start to decrease thereafter, and reach equilibrium in a few days.

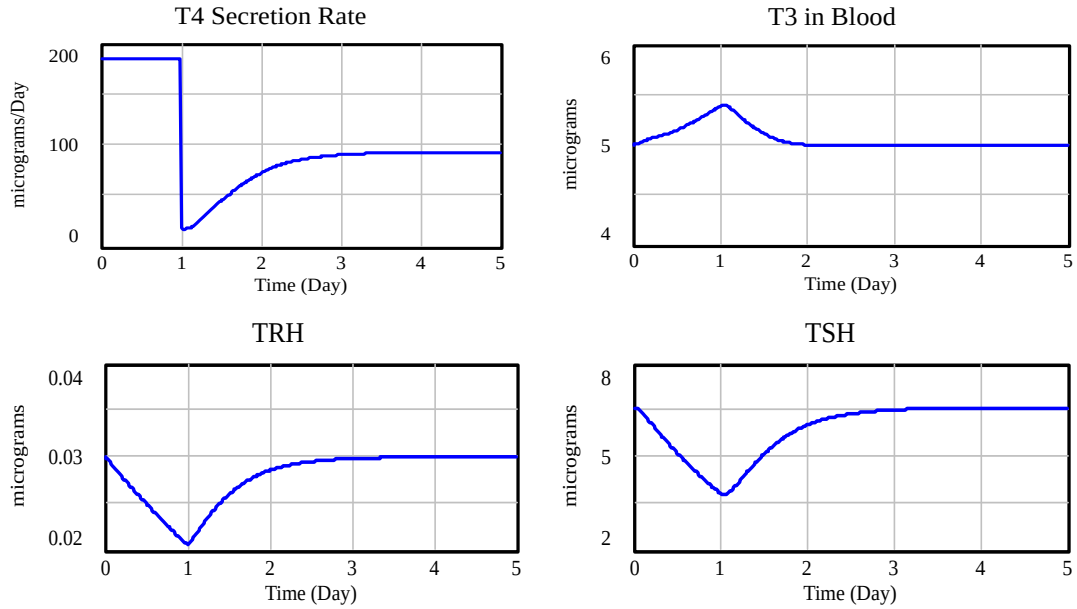

Figure 8: Hormone levels when T4 secretion is doubled for one day

Under this scenario, it is not only T4 whose value is disturbed from equilibrium. A significant portion of T3 in the body is formed via conversion T4 to T3 (see Figure 3). Because of this conversion, T3 levels also rise in this case. And, as a result of negative feedback effect of thyroid hormones on both the hypothalamus and pituitary, TRH and TSH levels decline. As the feedback effect of thyroid hormones on TRH and

TSH secretion shows itself very quickly as compared to our time unit, these changes go almost parallel with the changes in T4 levels. As seen in Figure 8, TRH and TSH levels in the body first decline and then rise so as to enable the body to restore the equilibrium state. As for the T4 secretion rate, it does not return to its normal value right after the termination of doubled secretion; since the levels of thyroid hormones are above normal, it starts at a below-normal level at t=1. And lastly, although not shown pictorially, the gland weights do not change.

4.3. Hypophysectomy

Hypophysectomy, as stated before, means the complete removal of the pituitary gland. In reality, a person cannot survive in the absence of such a critical gland without any medical intervention. However, for the sake of the validation of the model, we assume that the person continues to live. The behaviours of the glands and hormones are shown in Figure 9 and 10.

Since the pituitary is completely removed, no TSH exists in the body. And since there is no TSH in the body, only basal amounts of thyroid hormones can be secreted. This outcome is in consistency with the information that the secretion of thyroid hormones are greatly reduced in the absence of TSH but not reduced to zero (Guyton, 2006). Since the metabolic clearance rate is greater than the slight secretion rate of thyroid hormones, thyroid hormone levels in blood decline. Low levels of thyroid hormones in blood cause TRH secretion to rise. However, since the medium of communication between the hypothalamus and the thyroid gland is no longer present, thyroid hormones in blood continue to drop.

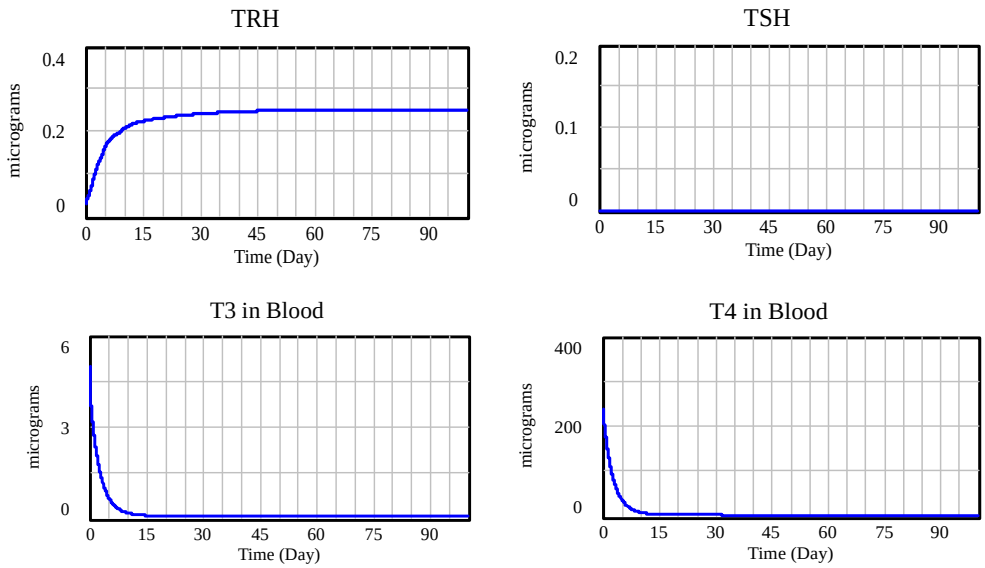

Figure 9: Hormone levels in case of hypophysectomy

As for the gland sizes, they also demonstrate the expected behaviour. Since low levels of thyroid hormones persist because of the absence of pituitary gland, the hypothalamus persistently over-functions. This, in turn, leads to an increase in the size of the hypothalamus. The opposite is seen in thyroid gland. Since no TSH exists in the

body, thyroid hormone secretion barely takes place. Due to prolonged "idling", the gland shrinks (Donovan, 1966; Melmed, 2002).

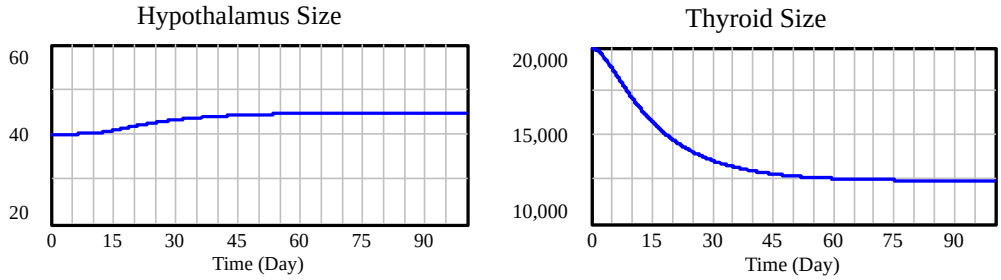

Figure 10: Gland sizes in case of hypophysectomy

5. SUBACUTE THYROIDITIS

In this part, a particular thyroid disorder, named subacute thyroiditis, will be of interest. It is the most common reason of the painful thyroid gland and may account for up to 5% of clinical thyroid abnormalities. In subacute thyroiditis, the thyroid gland is exposed to inflammation. Inflammation the response of tissues to harmful stimuli, and is commonly attributed to viral infections (Werner *et al*., 2005). Here, we are not interested in the causes of the inflammation, but rather in the consequences of it. Inflamed cells lose their ability to synthesize hormones. Also, inflammatory reaction within the thyroid gland disrupts the cells of the thyroid gland and causes release of preformed hormones into the peripheral circulation (Grossman, 1998).

Subacute thyroiditis demonstrates a triphasic clinical course of hyperthyroidism, hypothyroidism and restoration of normal thyroid functioning. Hyperthyroidism, which means an excess of thyroid hormones in the body, is a result of destruction of thyroid cells and uncontrolled release of hormone stores into the circulation. Since thyroid cells cannot synthesize hormones during the inflammation phase and leakage of preformed hormones persist due to inflammation, hormone stores get depleted after some time. As a result, hypothyroidism is observed. As the name suggests, hypothyroidism is a condition in which too little thyroid hormone is circulating throughout the body. After the gland recovers, levels of hormones restore their normal levels and hormone stores are replenished gradually (van den Berghe, 2008; Grossman, 1998).

In the model, the notion of inflammation is quantified by using a stock which is allowed to vary between 0 and 1. The name of that stock is *Inflammation Status*. *Inflammation Status* being 1 means that the gland is completely inflamed, and being 0 means that the gland is functioning properly. In a sense, this variable gives the inflamed proportion of the gland. In our case, we assume an inflammation course as shown in Figure 11. The model is run for 150 days assuming such a course of inflammation. The graph on the left-hand-side in Figure 12 is the data of a patient with subacute thyroiditis, and the one on the right-hand-side is the output of the model. Comparing the two, it can be said that the patterns of hormones obviously match.

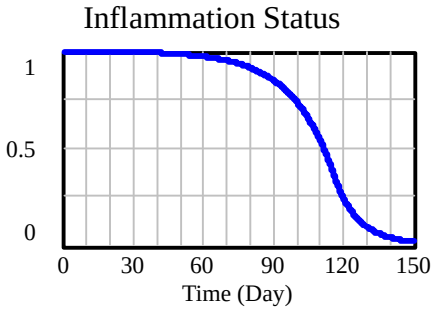

Figure 11: Presumed course of inflammation in case of subacute thyroiditis

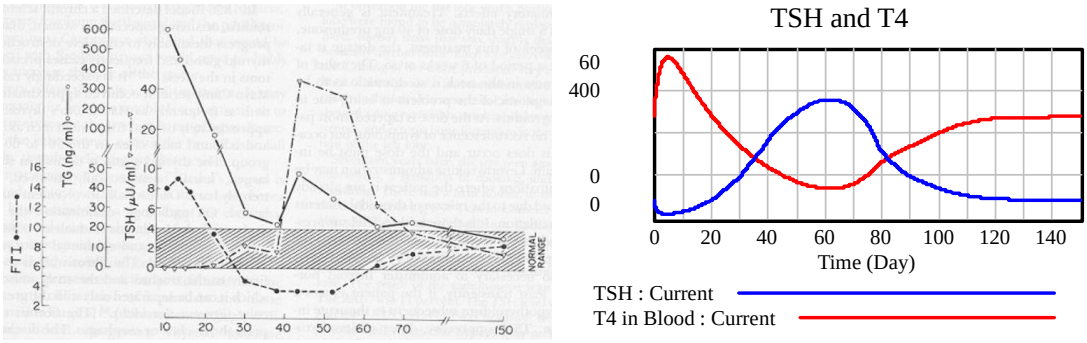

Figure 12: Real data (Lazarus, 2009) and model output in case of subacute thyroiditis

The curves depicting *FTI* and *TSH* levels in the real data are the ones that we basically compare our results to. The curve showing *TG* levels is commonly used as an indicator for thyroid damage. *TG* being high implies that the thyroid gland is damaged (Rubin, 2006). In this case, it returns to normal range (shaded region) near the end of the time horizon. This is consistent with our presumed *Inflammation Status* for this case. *FTI* is an indicator of free T4 levels in blood, but not the direct amount of it. In the model output in Figure 12, the total T4 level is shown. Since the real data uses a different measure for T4 levels in blood, the output of out model is numerically not comparable to the real data. It also uses a different unit for TSH levels in blood. In subacute thyroiditis, not the behaviour or the course, but the levels of hormones may show variability from patient to patient. So, even if the units did match, it would not be very reasonable to try to exactly match to the data points of only one patient. And, since the ultimate aim of this study is not point prediction, it can be said that the model gives reasonable results by matching the typical dynamical behaviour.

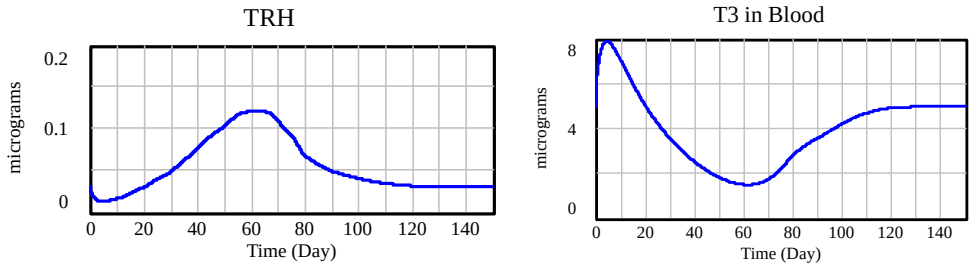

Figure 13: Model output showing TRH and T3 levels in subacute thyroiditis

6. CONCLUSION

In this study, a model for the thyroid hormone dynamics is constructed. Thyroid hormones are the primary regulators of metabolic functions in the body, and disorders related to thyroid hormone system are commonly seen. The aim of this study is to generate the dynamics of the thyroid hormones and the stimulating hormones in healthy body, then to adapt the model to portray some common abnormalities/disorders, finally to capture the characteristic dynamics of the hormones involved under these circumstances and to provide a platform to test possible scenarios.

For model validation, standard model structure and behaviour validity tests have been applied. In this article, validity tests are illustrated by two runs to demonstrate the consistency of the model outputs with the information in literature. First of all, the base run is shown to depict the equilibrium state in the body under normal conditions. Then, the model is run under a scenario where the secretion rate of T4 is doubled for one day. Finally, the effects of hypophysectomy, the complete removal of the pituitary gland, are shown. It can be said that the behaviour of the model under these scenarios reasonably matches the qualitative and quantitative data in literature.

After the validation part, a specific thyroid disorder, subacute thyroiditis, is addressed. Subacute thyroiditis is a common disorder in which thyroid gland is exposed to inflammation. The model captures well the behaviour of hormones during the typical triphasic clinical course of subacute thyroiditis comprised of hyperthyroidism, hypothyroidism and normal thyroid functioning.

As far as the information in literature and interviews with the medical doctors are concerned, the current model structure exhibits a reasonable degree of validity. But, this study is still in progress. In near future, adjustments in the parameter values and effect functions to more precisely reflect quantitative and qualitative real data, and extensions in the model structure to be able to address other disorders, to model medical interventions and drug therapy will be done.

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APPENDIX: Complete Stock-Flow Diagram