# A Quantitative Model of the Human Thyroid: Development and Observations

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*Abstract*—**A qualitative dynamical model of a human thyroid is derived using known intrathyroidal processes and pathways. It includes iodide transports from plasma into the thyroid and from the cell to the colloid, thyroid-stimulating hormone signaling pathways, organification, endocytosis, proteolysis, and hormone synthesis. Using mainly Michaelis-Menton kinetics, a quantitative model is derived at nominal values of internal concentrations. Simulations at different conditions demonstrate the ability of this model to predict several types of known thyroid behavior such as the Wolff-Chaikoff effect.**

## I. INTRODUCTION

The Hypothalamus-Pituitary-Thyroid (HPT) axis is a complex feedback system that uses hormones as signals to regulate activities such as synthesis, release, transport, metabolism and delivery of thyroid hormones to target cells. Adding to this complexity, this system is tightly coupled with the nervous and immune systems. The thyroid gland[6], the largest gland in the endocrine system, secretes hormones that promote normal growth and development and regulate certain homeostatic functions such as metabolism and energy. In response to various hormonal and neural signals, neurons in the hypothalamus secrete thyroid-releasing hormones, which stimulate the pituitary to secrete thyroid stimulating hormones. Thyroid-stimulating hormones then bind to their receptors on the thyroid gland, stimulating synthesis and release of thyroid hormones that affect virtually all body cells. The HPT-axis control system relies on an intricate system of endocrine, paracrine and autocrine feedback loops.

Much of the medical research on the HPT-axis has focused on discovering pathways, i.e., that a gene or protein affects certain functions. Such pathways essentially relate input and output signals at equilibrium. A recent research direction, often called *system biology*, aims at deriving mathematical models for biological processes in sufficient detail so that accurate predictions can be made on expected transient behavior. In a series of pioneering research, Distefano and colleagues have attempted to develop models, based on feedback control ideas and specialized clinical studies, for whole-body regulation of thyroid hormones (e.g., [23]-[24]). A dynamical model of the HPT axis was developed in [2] based on published clinical data. Recently, based on expected kinetics and dynamical relations, [3] developed a more refined model for the Pituitary-Thyroid axis which includes additional feedback loops. Our focus is on the thyroid alone, where in contrast to [2], [3], [23], and [24], we explicitly model intratyriodal processes necessary to study, for example, plasma iodide effects on hormone secretion and thyroid dysfunction.

In the past two decades, many of the internal mechanisms of hormone synthesis in the thyroid have been discovered. As knowledge of molecular biology grows, new pathways within the thyroid are revealed, while old pathways are explained. However, little has been done to integrate all of these pathways. The thyroid succeeds at regulating hormone synthesis despite the fact that iodine, a primary component used in synthesis, is relatively scarce in the environment and has significant day-to-day fluctuations. Obviously, a robust control system must be in place to regulate this biosynthesis.

The dynamical model developed in this paper strives to integrate a patchwork of clinical and laboratory observations and show quantitatively how hormone is secreted in a normal thyroid. In the future, we would like to predict the mechanisms contributing to thyroid dysfunction, and ultimately, reach the point where the model can be used in the design of drugs that mimic, enhance, diminish or block thyroid activities. Thyroid research is an important biomedical venue for which the control system approach may provide important insights that can be translated into better atient care. And, from a controls engineering perspective, the thyroid offers an excellent example of achieving robustness in ways different than those found in engineering implementations of feedback systems.

This paper is organized as follows. Section 2 introduces known pathways in the thyroid. Section 3 presents qualitative relations for connecting input and output signals in these pathways. Section 4 expands on the qualitative arguments by using clinical data to derive a quantitative model. This model is used in Section 5 for several simulations along with relevant observations. Conclusions and references follow.

## II. SIGNAL PATHWAYS

In this section we describe various known pathways from extrathyriodal signals, iodide ($I_P$) and thyroid stimulating hormone ($TSH$), to the thyroid outputs, 3,5,3'-Triiodothyronine and Tetraiodothyronine hormones ($T_3$ and $T_4$), as well as key intratyriodal pathways. A schematic depicting these pathways is shown in Figure 1.

The path of iodine flow through the thyroid begins with the raw material being transported from the plasma across the basolateral membrane into the cytoplasm by the Sodium/Iodide Symporter ($Na^+/I^-$ Symporter or $NIS$). The iodide is rapidly transported toward and then across the apical membrane and into the colloid by the putative Pendrin or AIT protein ($AIT$). In the colloid, in a process catalyzed by Thyroidal Peroxidase ($TPO$), iodide ($I^-$) is oxidized by hydrogen peroxide ($H_2O_2$) and incorporated into thyroglobulin, ($Tg$). The iodinated residues within the thyroglobulin molecule are then coupled to form the mature molecule, in a second processes catalyzed by $TPO$. The iodinated thyroglobulin (in all stages of maturation) undergoes *endocytosis* (carrying colloid material into the follicular cell) and *proteolysis* (cleaving the thyroglobulin molecule to release thyroid hormone and waste material). Iodine is either carried out into the plasma with thyroid hormones, $T_3$ and $T_4$, or recycled with hormone precursors, Di-iodinated Tyrosyl and Mono-iodinated Tyrosyl ($DIT$ and $MIT$). If it is recycled, it is incorporated back into the pool in the thyroid follicle. Completing the iodine flow within the thyroid, intrathyroidal iodine leaks back down its concentration gradient into the plasma [1]. The iodine pathways described above are illustrated in Figure 2.

A key input signal is $TSH$, which via its receptor, $TSH$-$R$, stimulates every aspect of thyroid hormone synthesis. It does this through two secondary messenger pathways, the adenylyl cyclase pathway and the phospholipase C pathway [4] (for brevity, we adopt the less-oft used terminology of $PKA$ and $PKC$). The $PKA$ pathway is known to stimulate $NIS$ activity [5], as well as transcription of $NIS$ [6], $TPO$, $Tg$, and $TSH$ receptor [7]. It also stimulates the endocytosis of $Tg$-containing colloid, and its stimulatory effect on lysosome synthesis promotes the proteolysis of $Tg$ [7]. The $PKC$ pathway stimulates the synthesis of Hydrogen Peroxide ($H_2O_2$) [4]. These two pathways are not entirely decoupled, and at low levels of $[TSH]$ ($[\bullet]$ denotes concentration of $\bullet$) there can be some overlapping influences [7]. For the purposes of this model, however, $TSH$ levels are assumed to be sufficient such that the predominate behavior of the respective signal pathway is observed. $[TSH]$ has a number of other effects within the thyroid, but these mostly serves to compensate for the increased energy and nutrients required for hormone synthesis and are not included in our model. These stimulatory effects of $TSH$ are shown in Fig. 1. Various inhibitory effects are also present within the thyroid. High intrathyroidal iodide ($I_T$) content is known to inhibit iodine organification, a phenomenon known as the *Wolff-Chaikoff effect* [8]. The mechanism for this effect is thought to be the decrease in $H_2O_2$ synthesis, due to the inhibitory effects of intrathyroidal iodide [8].

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[6] There are numerous books on this topic; however, [1] serves as a comprehensive reference that is reasonably accessible to engineers.
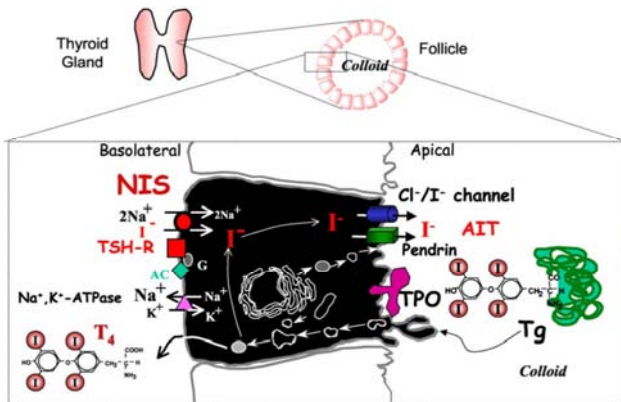
Figure 1. Schematic the hormone synthesis pathways within the thyroid follicle. (Reprinted from [6])

The mechanism for this effect is thought to be the decrease in $H_2O_2$ synthesis, due to the inhibitory effects of intrathyroidal iodide [8]. Intracellular iodide also inhibits other thyroidal processes, and this effect is thought to allow the thyroid to eventually escape from the Wolff-Chaikoff blockage. High intracellular iodide inhibits transcription of $NIS$ [9], and it may also increase $NIS$ protein turnover [10]. Transcription of various proteins has been recently suggested to also be regulated by $Tg$. Working via the asialoglycoprotein receptor $(ASPGR)$, $Tg$ can negatively inhibit $NIS$, $Tg$, $TPO$, and $TSH$-$R$ transcription [11]. These pathways are shown in Fig. 2.

In the model shown in Figure 2, there are two external inputs, $TSH$ and $I_P$ (We assume raw materials needed for synthesis of internal states such as $NIS, Tg,$ and $TPO$ exist in sufficient quantities). The thyroid outputs principally $T_4$, along with lesser amounts of $T_3$ and 3,3',5'-Triiodothyronine ($rT_3$). The role of $I_P$ is not the same as that of the reference signal. Rather, it is a necessary ingredient for synthesis that in future developments will be modeled as a time-varying parameter in the thyroid model.

## I. QUALITATIVE THYROID MODEL

The foundation of our thyroid model rests with a patchwork of published clinical and laboratory observations. In each of the following sections, relevant observations will be presented along with the justification for arriving at a description of the process.

**Iodide Movement within the Thyroid.** The principal entry point of plasma iodine into the thyroid follicle cells is through the membrane glycoprotein $NIS$ (see Figure 1). It uses the concentration gradient of $Na^+$ (high outside, low inside) to drive $I^-$ up its concentration gradient into the thyroid, creating a concentration 20-40 times that in the plasma [5]. $Na^+$ is then returned to the outside via $Na^+ - K^+$ ATPase. The $NIS$ protein is stimulated by $TSH$ [5] (via $PKA$ pathway), which will increase its transport rate for a given $NIS$ and substrate concentration. It does not appear that the concentrations of $Na^+, K^+$, and $Na^+ - K^+$ ATPase change in response to either of the two inputs $TSH$ and $I_P$, hence, it is assumed to be constant. The $NIS$ transport rate of $I^-$, termed *basolateral influx*, is therefore a function of the extracellular iodide concentration, $(I_P)$, the concentration of the transport protein $NIS$, and the concentration of $PKA$ pathway signal.

Inorganic iodine is also brought into the follicle cells through breakdown of the waste products, $MIT$ and $DIT$, of thyroglobulin proteolysis. This breakdown (and the subsequent influx of inorganic iodine), termed *recycling influx*, is catalyzed by an iodotyrosine-specific deiodinase [8], and is dependant upon the concentration of $MIT$ and $DIT$ within the cell. The proportion between the two molecules is assumed to be constant, as is the iodotyrosine-specific deiodinase concentration.

Inorganic iodine leaves the cell through the basal membrane by flowing down its concentration gradient, back into the plasma [1]. This rate, termed *basolateral efflux,* is dependant on the concentration of inorganic iodine within the thyroid cell. Under



Figure 2. Schematic of iodine flow in the thyroid, with stimulatory and inhibitory pathways shown (transport is represented by solid/blue arrows, iodine states are represented by circles, TSH related input states by squares and other intrathyroidal states by ovals; green/dashed lines going into a process/state indicate a stimulatory effect while red/dotted lines going into a process/state ending with a thick "-" sign indicates an inhibitory effect).
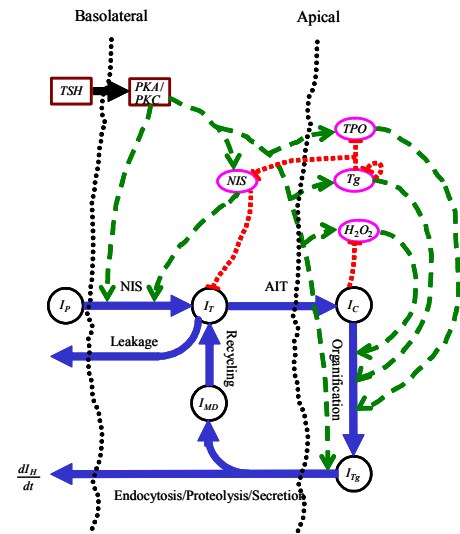
physiological conditions, the rate of basolateral iodide influx is greater than the rate of efflux [1].

Inorganic iodine also leaves the cell through the apical membrane via a yet-unconfirmed process, termed *apical flux*. Two transport mechanisms have been proposed, one via a protein known as Apical $I^-$ Transporter $(AIT)$ [12], and the other via a protein known as Pendrin [13]. Both proteins are assumed to be transport proteins that transport iodide as a function of intrafollicular iodide concentration. As mentioned later in the model development, excess intrathyroidal iodide has an inhibitory effect on a number of processes. In order for the iodide within the follicular cell to have any inhibitory influence, apical membrane transport must be slowed down in the event of high iodide levels in the colloid. Without this effect, excess iodide would continue to accumulate in the colloid. The apical transport function, therefore, must include a term to slow down in the event that inorganic iodine in the colloid ($I_C$) increases. Whether this inhibition is due to a loss of the electrochemical gradient between the follicle and the colloid or a negative feedback on the transport protein does not matter for the purposes of this model, although it does raise some interesting questions about the nature of the as-yet-unknown transport protein. Summing the above, the net flow of iodide through the thyroid follicle is $dI_T/dt =$ *basolateral influx + recycling influx – basolateral efflux – apical efflux.*

Upon arriving in the colloid, iodide is oxidized (by $H_2O_2$ and catalyzed by $TPO$) and incorporated into the tyrosyl residues within $Tg$ (by $TPO$) [1]. This entire reaction - organification of iodine - cannot proceed without the raw materials, $I^-$ and $Tg$, and the compounds that operate on the raw material, $H_2O_2$ and $TPO$. There are a finite number of iodine binding sites within each molecule of $Tg$, however, and as $Tg$ becomes more and more iodinated, it becomes increasingly difficult to organify iodine. Organification is therefore inhibited by high levels of organic iodine in the colloid ($I_{Tg}$), and the rate must include a term to account for this. Summing the above, the net flow of inorganic iodine through the thyroid colloid can be found $dI_C/dt =$ *apical flux – organification.*

**TSH, TSH-R, and resulting pathways.** $TSH$ reacts with its membrane-bound receptor, $TSH$-$R$, activating the two secondary messenger pathways. The first pathway $PKA$ involves adenylyl cyclase-cyclic AMP protein kinase, and the second $PKC$ involves $Ca^{2+}$-protein kinase C [4]. The formation of these secondary messengers is a function of $TSH$. The decay of the signal (note that decay is used here to indicate the degradation and/or clearance of the signal from within the intracellular environment) is modeled using an exponential (first order) decay function. The rate equations for the secondary messengers are given by $d[PKA/C]/dt =$ *formation –decay.*

The $PKA$ pathway affects many areas of the thyroid follicular cell. One of its principle effects is to increase $NIS$ transcription.

Excess intrathyroidal iodide inhibits *NIS* synthesis [9], and increases the degradation of *NIS* [10]. *Tg* is fed back via the *ASGPR* to inhibit transcription of *NIS* [11]. The *NIS* rate equation has a standard form of *formation – decay*. Note that the decay rate varies as a function of $I_T$. *PKA* pathways also increases the transcription of *TPO*, *Tg*, and *TSH-R* [4]. This transcription is inhibited by *Tg*, via the *ASGPR* [11]. The *TPO*, *Tg* and *TSH-R* rate equations have a standard form of *formation – decay*.

Thyroglobulin is assumed to be lost through endocytosis at a much fast rate than it degrades, due the long-term storage capabilities of *Tg* in the colloid. A secondary messenger pathway increases the synthesis of lysosomes $(Lys)$ [4]. Modeled with a first order decay rate for the digestive enzymes inside, the rate equation for *Lys* is *formation – decay*.

*PKC* pathway increases synthesis of $H_2O_2$ while $H_2O_2$ is consumed by the organification of iodine [5]. Excess intrathyroidal iodide is known to inhibit $H_2O_2$ synthesis, a phenomenon known as the Wolff-Chaikoff effect [8]. $H_2O_2$ is assumed to be affected by high $I_C$, due to its location at the apical membrane surface and that the effects of Wolff-Chaikoff are felt acutely ($I_C$ rises before inorganic iodine in cytoplasm of thyroid follicular cell, $I_T$). This results in $dH_2O_2/dt$ = *formation – organification*.

**Organification/Endocytosis/Proteolysis**. Iodine moves from the follicular cell, through the apical membrane, and is incorporated into the tyrosyl residues with the *Tg* molecule [1]. Thyroglobulin is a polypeptide matrix where the resulting thyroid hormones are formed. It resides in the colloid until it is absorbed by the follicle cell (through endocytosis) and thyroid hormones are cleaved from its branches through proteolysis. The rate of *organification* term is the same as in the $I_C$ rate equation. A thyroglobulin molecule is still not mature after incorporating iodine, however. In a reaction catalyzed by *TPO*, the iodinated residues within *Tg* are "coupled" to form thyroid hormone precursors. This coupling is a function of $I_{Tg}$ *Tg*, and *TPO*. Outflow from the colloid (Figure 1, lower right) is stimulated via the PKA pathway, which stimulates endocytosis of *Tg*-containing colloid. The colloid has a variable composition depending on the level of uniodinated *Tg*, the level of immature iodinated *Tg*, and the level of mature iodinated *Tg*. The endocytosis term is a function of *PKA* and maturity of *Tg*. Combining the above terms, the net flow of organified iodine is given by can be written as $dI_{Tg}/dt$ = *organification –endocytosis*.

Endocytosis forms vacuoles of colloid within the follicular cell, and the formation of these vacuoles is similar to the disappearance of the thyroglobulin through endocytosis. These vacuoles of colloid fuse with lysosomes, and the products are thyroid hormone and waste. This proteolysis is a function of the lysosome and the vacuole concentrations. The flow of this entire process, from vacuole to secretion can be modeled by $dVac/dt$ = *endocytosis – proteolysis*.

**Hormone Synthesis and Recycling**. Once cleaved from the *Tg* molecule by lysosomal enzymes, the hydrophobic thyroid hormones, $T_4, T_3$, and $rT_3$, and iodotyrosines, *DIT* and *MIT*, easily diffuse through their vacuole membrane and into the cytoplasm. $T_4, T_3$, and $rT_3$ then diffuse through the cellular membrane, into the plasma. In fact, as thyroid hormone is cleaved from the parent *Tg* molecule, it enters an environment that is virtually continuous with the cytoplasms of every other cell in the body, owing to the hydrophobic nature of thyroid hormone. As such, hormone synthesis is similar to proteolysis and is modeled by a nonlinear function of *Lys, Vac,* and the maturity of the *Tg*.

Following proteolysis, *DIT* and *MIT* are immediately attacked by cytoplasmic enzymes that reclaim their iodine and tyrosyl residue for future use in hormone synthesis, which can be modeled as a nonlinear function of *Lys*, $Vac$, and maturity of *Tg* minus the *recycling* term.

## II. QUANTITATIVE THYROID MODEL

In quantification of the model in the previous section, we rely on a multitude of published clinical and laboratory research, with primarily Michaelis-Menten kinetics used to describe many of the non-linear transport, promotion, and inhibition processes. Without loss of generality, when there is no clinical data on a particular internal state values, a generic value of "1" is used to indicated the normal – or 100% - level of a particular compound. Given that this paper focuses on modeling a normal thyroid all volumes are assumed to be fixed (this assumption is invalid in, for example, a goiterous thyroid) and many concentrations are taken in units of "(compound mass)/(thyroid volume)." Unknown Michaelis constants are set by using a standard assumption that many biological processes take place at substrate concentrations close to their Michaelis constant [14, Section 4.3]. The Michaelis constants are then adjusted from there to achieve the observed or expected dynamics. Further explanation of Michaelis-Menton kinetics and development of the following equations can be found in [15]

**Iodine Transport from Plasma to Organification.** Due to the ease of using its radioactive isotopes, the flow of iodine in and around the thyroid is perhaps the best understood of all the chemicals discussed thus far. An average human ingesting 500μg of iodine a day can typically expect to have about 150μg of iodine circulating in his or her bloodstream and store about 8000μg of iodine in the thyroid [1]. With this concentration of iodine in the bloodstream and a normally functioning HPT axis, the thyroid uptakes about 115μg/day of iodine via *NIS* [1]. The thyroid releases through leakage 40μg/day as inorganic iodine and 75μg/day is incorporated into thyroid hormone [1]. Of the 8000μg of iodine in the thyroid, less than 0.25% is inorganic and unbound [8]. This 20μg is assumed to be evenly split between the follicular cell (waiting to be transported to the colloid) and the colloid (waiting to be organified). Although the fractions of this split are unknown, the amount of iodide is significantly smaller than the organic iodine amount and the daily iodine flow rates, such that how the iodide is apportioned between the colloid and the follicular cell probably is negligible. Additionally, 0.5μg of organic iodine is assumed to exist in vacuoles, waiting to be digested by lysosomes and 29.5μg of organic iodine is calculated to exist as *MIT* and *DIT*, waiting to be recycled (A very small fraction is assumed in order to make the current output responsive to current *TSH* inputs). This leaves 7950μg of iodine attached to thyroglobulin in the thyroid.

The remaining iodine flow rates in the thyroid are computed from an analysis of the composition of a typical thyroglobulin molecule. Following proteolysis, it can be calculated from [1] that for every 1μg of hormonal iodine, 1.16μg of iodotyrosyl iodine is recycled. For a normal flow rate of hormonal iodine of 75μg/day, the flow rate of recycled iodine can be found to be 87μg/day. To achieve flow rate balance, the transport across the apical membrane must be equal to the net flow across the basolateral membrane plus the recycling flow rate, or 162μg/day.

The flow of inorganic iodine through the follicular cell is modeled using Michaelis-Menten kinetics to describe basolateral influx, recycling influx, apical flux and first-order rate for leakage. The promotion of turnover by the secondary messenger signal is captured by a saturable term influencing the maximum velocity term, while $\big[NIS\big]$ is assumed to linearly influence maximum velocity. The inhibition of apical transport by $I_C$ is modeled as non competitive inhibition. Using iodine flow values above, we arrive at the following model

$$\frac{dI_T}{dt} = \frac{\left(\frac{115}{6}\right)\left(\frac{[PKA]}{1+[PKA]}\right)[NIS][I_p]}{150+[I_p]} + \frac{\left(\frac{87}{12}\right)[I_{MD}]}{29.5+[I_{MD}]}$$

$$-\left(\frac{1}{6}\right)[I_T] - \frac{\left(\frac{162}{6}\right)\left(\frac{10}{10+[I_c]}\right)[I_T]}{10+[I_T]}.$$

Movement of inorganic iodine within the colloid involves the *organification* term where the enzyme *TPO* forms a complex with the $I^-$ and *Tg* prior to organification of the iodine. We assume that the enzyme concentration linearly affects the velocity parameter $V_{max}$, and that $I^-$ and *Tg* act as substrates, the required materials that are present in the product. $H_2O_2$ is consumed in the reaction, so it too acts as a substrate.

The entire *Tg* molecule is not available for organification reaction, however. Only selective binding sites are available for iodination, and the maximum number of atoms of iodine that a single *Tg* molecule can accommodate has been measured to be

around 55 atoms per molecule. Thyroglobulin can have iodine content as high as 1% [16] or as low a 0% in newly synthesized $Tg$. Converting $I_{Tg}$ from μg/thyroid to units of mg/mL of colloid and dividing by $[Tg]$, the percent iodiniation of $[Tg]$ is found to be

$$\frac{[I_{Tg}]\left(\frac{mg}{1000\mu g}\right)\left(\frac{thyroid}{7.95mL\ colloid}\right)}{[Tg]}\times100 = \%\ iodination\ .$$

At a nominal values of $I_{Tg}$ =7950μg/thyroid and $Tg$ =200mg/mL, iodination level of $[Tg]$ is 0.5%.

This saturation has the same effect as classical inhibition on the organification process. At 0% organification, there are plenty of binding sites and organification readily occurs. At 1% organification, there are essentially no binding sites available to incorporate iodine, and inhibition is at a maximum. A new variable, $Tg_{eff}$, is introduced to account for the effective amount of thyroglobulin that is reacting in the organification process. The effective concentration of thyroglobulin can be found from

$$[Tg_{eff}] = [Tg]\big(1 - \%\ iodination\big)\ .$$

Adding this effective term to the organification process in the flow of $I_C$ gives the following model:

$$\frac{dI_C}{dt} = \frac{\left(\frac{162}{6}\right)\left(\frac{10}{10+[I_C]}\right)[I_T]}{10+[I_T]}$$
$$-\frac{\left(\frac{162}{3}\right)[TPO][I_C][Tg_{eff}][H_2O_2]}{\big(10+[I_C]\big)\big(100+[Tg_{eff}]\big)\big(2.7+[H_2O_2]\big)}\ .$$

**Organification/Endocytosis/Proteolysis.** Endocytosis is a fluid transport process, rather than the strictly chemical transport previously discussed. Material from the colloid is brought into the follicular cell, and it is not thought that there is any selectivity in this process [16]. Calculating the fluid transport requires iodine flow rates and thyroglobulin concentrations. For an iodine flow rate out of the colloid of 162μg/day, $Tg$ flow rate was calculated to be 32.4mg/day. Using an approximate concentration of 200mg/mL of $Tg$, 0.162mL/day of colloid fluid is brought out of the colloid. This fluid transport is constant for a fixed $[TSH]$ level, but the chemical transport of $Tg$ and organic iodine is variable, depending on the chemical makeup of the colloid. Furthermore, the eventual hormone yield depends on the maturity of $Tg$ undergoing endocytosis. The rate of fluid transport flow is dependent on the secondary messenger as follows

$$fluid\ transport\ rate = \frac{\left(\frac{0.162}{12}\right)[PKA]}{\big(1+[PKA]\big)}\ .$$

The $PKA$ pathway controls transcription of $Tg$ and this process is inhibited by $Tg$ in the colloid. Thyroglobulin is very densely packed into the colloid, and concentrations of $Tg$ are usually greater than 100mg/mL [17], ranging from about 100mg/mL to 400mg/mL [18]. Here we use a nominal concentration of 200mg/mL. The normal iodine content in the colloid is 7950μg of iodine, implying 1590mg of $Tg$ in the colloid and a colloid volume of 7.95mL. At normal iodine flow rate from the colloid of 162μg/day, the flow rate of 0.5% iodinated $Tg$ is 32.4mg/day. As shown earlier, $Tg$ transcription is a function of the $PKA$, self-inhibited, and the outflow of $Tg$ from the colloid is dependant on the rate of fluid transport by endocytosis. The rate equation is:

$$\frac{d[Tg]}{dt} = \frac{\left(\frac{32.4}{6}\right)[PKA]}{(200+[Tg])(1+[PKA])} - \frac{\left(\frac{0.162}{12}\right)[PKA]}{\big(1+[PKA]\big)}[Tg]\ .$$

The stimulatory influence of the $PKA$ can be seen to have the same effect on both of the above terms on the right, meaning that the increase in transcription of thyroglobulin is designed to compensate for the increased rate of endocytosis.

The flow of iodine through the colloid takes on the form (the concentration must first be converted to μg/mL)

$$\frac{dI_{Tg}}{dt} = \frac{\left(\frac{162}{3}\right)[H_2O_2][TPO][I_C][Tg_{eff}]}{\big(10+[I_C]\big)\big(100+[Tg_{eff}]\big)\big(2.7+[H_2O_2]\big)}$$
$$-\frac{\left(\frac{0.162}{12}\right)[PKA]}{\big(1+[PKA]\big)}[I_{Tg}]\left(\frac{thyroid}{7.95mL\ colloid}\right)\ .$$

**TSH, TSH-R, and Resulting Pathways.** $[TSH]$ is time varying and pulsatile in nature: an average plasma level in humans of 1.8mU/dL, around 13 pulses a day of amplitude 0.6mU/dL [19], and a circadian component. Once bound to its receptor $TSH$-$R$, the signal propagates very fast within cell pathways relative to other intracellular dynamics modeled here. The half life of $cAMP$ (in the $PKA$ pathway), for example, is less than 29 seconds [20]. Given that our model is focused primarily on the time-scale of hours, secondary messenger signal levels are approximated by a saturable, non-linear gain of $[TSH]$. Since the nominal value of $[TSH]$ is 1.8mU/dL and the desired signal level in the cell at this nominal value is set to be 1, the following equations model intracellular secondary signaling

$$[PKA] = \frac{2[TSH\text{-}R][TSH]}{1.8+[TSH]}\ \ \text{and}\ \ [PKC] = \frac{2[TSH\text{-}R][TSH]}{1.8+[TSH]}\ .$$

These secondary messenger signals control a variety of processes in the thyroid. $NIS$ transcription is known to be activated by $PKA$. Its decay is assumed to be first order and nonlinear to account for the decreased half-life that occurs when $NIS$ is exposed to high levels of intracellular iodine. Given that the $NIS$ half life is about 5 days under normal conditions [6], a transcription rate is created that matches the decay rate at equilibrium

$$\frac{d[NIS]}{dt} = \frac{110\left(\frac{\ln(4)}{3}\right)[PKA]}{(1+[I_T])(200+[T_g])(1+[PKA])}$$
$$-\frac{\ln(2)}{\left(\frac{11}{1+[I_T]}\right)120}[NIS]\ .$$

Although synthesis and decay of $TPO$, $Lys$, and $TSH$-$R$ are similar to that of $NIS$, their decay rates under physiological conditions are not known. As a result, their states are assumed to be saturable, non-linear relations of the secondary messenger signal. $TPO$ and $TSH$-$R$ also include a term for $Tg$ inhibition

$$[TPO] = \frac{2[PKA]}{1+[PKA]}\left(\frac{400}{200+Tg}\right)$$
$$[TSH\text{-}R] = \frac{2[PKA]}{1+[PKA]}\left(\frac{400}{200+Tg}\right)$$
$$[Lys] = \frac{2[PKA]}{1+[PKA]}\ .$$

The $PKC$ pathway is also involved in controlling the synthesis of $H_2O_2$, a process inhibited by high levels of inorganic iodine in the colloid. Hydrogen peroxide is then consumed by the organification of iodine at a rate calculated by using the rate of organification of iodine. Normally, 162μg/day of iodine is organified; if 1 mole of $H_2O_2$ is consumed for every mole of $I^-$ that is organified, a 1:1 molar ratio exists between $H_2O_2$ and $I^-$. The molar masses of $I^-$ and $H_2O_2$ are 127g/mol and 34g/mol, respectively, and with a fixed ratio the consumption rate of $H_2O_2$ is found to be 43.3μg/day. The concentration is unknown, but assumed to be around the same concentration as the normal value of $I_C$ (10μg/thyroid) which works out to 2.7μg/thyroid. This small value (compared to the daily throughput) makes sense, as $H_2O_2$ is a highly corrosive molecule and excess amount could be destructive. Matching the synthesis rate with consumption results in

$$\frac{d[H_2O_2]}{dt} = \left(\frac{20}{10+[I_C]}\right)\frac{\left(\frac{43.4}{12}\right)[PKC]}{1+[PKC]}$$
$$-\frac{\left(\frac{43.4}{3}\right)[H_2O_2][TPO][I_C][Tg_{eff}]}{\big(10+[I_C]\big)\big(100+[Tg_{eff}]\big)\big(2.7+[H_2O_2]\big)}\ .$$

Proteolysis is dependent upon the fusion of vacuoles of colloid materials with lysosomes. The total volume of these vacuoles in

the thyroid follicle is unknown, but assumed to be around 8 minutes worth of flow, or 500nL, in order to respond to $[TSH]$ input in a timely manner. The size of all these vacuoles is assumed to be uniform, and therefore can be modeled as individual molecules acting in a reaction. These vacuoles are consumed by the process of proteolysis, and therefore the rate of disappearance of these vacuoles is equal to the rate of proteolysis. Modeling the flow rate gives

$$\frac{d[Vac]}{dt} = \frac{\left(\frac{0.162}{12}\right)[PKA]}{\left(1+[PKA]\right)} - \frac{\left(\frac{0.162}{6}\right)[Lys][Vac]}{\left(1+[Lys]\right)\left((.0005)+[Vac]\right)}.$$

**Hormone Synthesis and Iodotyrosine Recycling.** The flow rate of thyroid hormone from proteolysis is dependent upon the rate of proteolysis, but as with endocytosis, the rate depends upon the composition of the contents of the vacuoles. The composition is more complex in proteolysis, however, because not only is the concentration of $Tg$ and its iodine content a factor, but also the maturity of the $Tg$ molecule. Freshly iodinated thyroglobulin will have very few thyroid hormones embedded in its branches, but with time the $DIT$ and $MIT$ in the branches of $Tg$ will - when catalyzed by $TPO$ - couple and form $T_3$ and $T_4$ precursors. To effectively model this dynamic, two new states are created: $I_{MD*}$ and $I_{H*}$. These iodine levels reflect the iodine levels of the various precursor residues within the thyroglobulin molecule. $I_{MD*}$ is destined to become $I_{MD}$ following proteolysis, where it will be recycled back into the follicular iodine pool $I_T$. $I_{H*}$ is destined to become $I_{T_4}$ and $I_{T_3}$ and be secreted as part of thyroid hormones. The nominal ratio of iodotyrosyl iodine $I_{MD}$ to hormonal iodine $I_H$ is 14:12.1 which is expected to match the precursors. When combined, $I_{MD*}+I_{H*}=I_{Tg}$.

The influx of iodine to the state $I_{MD*}$ is exactly equal to the rate of organification of iodine. The rate of disappearance is more complicated, however. $I_{MD*}$ disappears in a coupling reaction that is catalyzed by $TPO$, dependent upon the concentration of iodine within the thyroglobulin molecule. Thyroglobulin in the coupling reaction is acting as an enzyme in the coupling reaction in that it is not consumed, but its presence increases the rate of reaction. $I_{MD*}$ also disappears during endocytosis, as immature thyroglobulin is absorbed along with mature thyroglobulin. The rate of disappearance due to endocytosis is dependant upon the concentration of $I_{MD*}$ in the colloid. Using the nominal organification rate and calculating the endocytosis rate from the expected ratio of $I_{MD*}$ to $I_{H*}$, the velocity of the coupling term was chosen so that the net flow was zero. And using $I_{MD*}+I_{H*}=I_{Tg}$, the rate equation can be found

$$\frac{dI_{MD*}}{dt} = \frac{\left(\frac{162}{3}\right)[H_2O_2][TPO][I_C][Tg_{eff}]}{\left(10+[I_C]\right)\left(200+[Tg_{eff}]\right)\left(2.7+[H_2O_2]\right)}$$
$$-\frac{\left(\frac{75.1}{2400}\right)[TPO][Tg_{eff}](\%iodination)}{\left(.05+(\%iodination)\right)}$$
$$-[I_{MD*}]\frac{\left(\frac{0.162}{12}\right)[PKA]}{\left(1+[PKA]\right)}\left(\frac{thyroid}{7.95mL\ colloid}\right).$$

The flow of hormonal precursor iodine is similar, but simpler. The appearance rate is the coupling rate, and the disappearance rate is the rate of endocytosis. The model is given by

$$\frac{dI_{H*}}{dt} = \frac{\left(\frac{75.1}{2400}\right)[TPO][Tg](\%iodination)}{\left(.05+(\%iodination)\right)}$$
$$-[I_{H*}]\left(\frac{thyroid}{7.95mL\ colloid}\right)\frac{\left(\frac{0.162}{12}\right)[PKA]}{\left(1+[PKA]\right)}.$$

Having described the composition and maturity of the thyroglobulin, the process of hormone secretion can be modeled. Once cleaved from the $Tg$ molecule by lysosomal enzymes, the hydrophobic thyroid hormones $(T_4, T_3, rT_3)$ and iodotyrosyls $(DIT, MIT)$ easily diffuse through their vacuole membranes and into the cytoplasm. $T_4$, $T_3$, and $rT_3$ then diffuse through the cellular membrane, into the plasma. As thyroid hormone is cleaved from the parent $Tg$ molecule, it enters an environment that is

continuous with the cytoplasms of every other cell in the body. As such, hormone synthesis is the same as the rate of proteolysis, multiplied by the concentration of hormonal precursors. While there is a very slight delay between the vacuole composition and the colloid composition (vacuole composition can be up to 8 minutes behind the colloid composition), the effect is assumed to be negligible due to the slow speed that the thyroid composition changes. Hormonal iodine synthesis is modeled by

$$\frac{d[I_H]}{dt} = \frac{\left(\frac{0.162}{6}\right)[Lys][Vac]}{\left(1+[Lys]\right)\left((.0005)+[Vac]\right)}[I_{H*}]\left(\frac{thyroid}{7.95mL\ colloid}\right).$$

At a fixed ratio between $I_{T_3}$ and $I_{T_4}$ of 2.1:10, the synthesis of each can be found by multiplying by their fractional composition in $I_H$. Actual hormone secretion is easily found by multiplying the iodine rate by another conversion factor

$$\frac{dT_4}{dt} = \left(\frac{1\mu mol\ T_4}{508\mu g\ iodine}\right)\frac{dI_{T_4}}{dt} = \left(\frac{1}{508}\right)$$

$$\frac{dT_3}{dt} = \left(\frac{1\mu mol\ T_4}{381\mu g\ iodine}\right)\frac{dI_{T_3}}{dt} = \left(\frac{1}{381}\right)\left(\frac{2.1}{12.1}\right)\frac{dI_H}{dt}.$$

Upon reaching the cytoplasm, $DIT$ and $MIT$ are immediately attacked by cytoplasmic enzymes that reclaim their iodine and tyrosyl residue for future use in hormone synthesis. The recycling of iodine by an iodothyrosine-specific deiodinase is modeled by

$$\frac{dI_{MD}}{dt} = \frac{\left(\frac{0.162}{6}\right)[Lys][Vac]\left(\frac{1}{7.95}\right)}{\left(1+[Lys]\right)\left(.0005+[Vac]\right)}[I_{MD*}] - \frac{\left(\frac{87}{12}\right)[I_{MD}]}{29.5+[I_{MD}]}.$$

The size of the $I_T$ pool causes a brief delay between the recycled iodine being freed of its tyrosyl residue to when it would appear in the colloid, ready for organification. This matches with laboratory observations [8].

## III. SIMULATIONS AND OBSERVATIONS

Here we test the model's ability to support clinical observations. In the first test, $[TSH]$ has a normal mean of 1.8mU/dL, pulses every 30 minutes with an amplitude of .7mU/dL, and cycles with a circadian (24hr) rhythm. This was constructed to resemble observed patterns [18]. Plasma iodine levels $[I_P]$ were set to a normal level of 150μg/body [1]. To better model actual fluctuating iodide concentrations we added noise [21]. The model predicts expected $T_4$ secretion rates in terms of average, pulsatile and circadian components (Figure 3).

Note that $T_4$ secretion rate appears to track the reference signal $[TSH]$, but that secretion of $T_4$ is invariant to fluctuation of $[I_P]$. Our conjecture is that this is due to $I_{Tg}$ remaining relatively constant even as $[I_T]$ and $[I_C]$ fluctuate with the varying iodine level. In future work, we will model iodide fluctuations around equilibrium as a time-varying model parameter. Control system analysis should show system robustness against such parametric variations.

The second test focuses on the effect of increasing the amount of iodide intake on the thyroid – the so called Wolff-Chaikoff effect. It constitutes a classic demonstration of the dynamical nature of this system. In this test, $[TSH]$ is held fixed at its nominal value (1.8mU/dL), while at hour 24 $[I_P]$ was surged from its nominal value (150μg/body) to 367% of its nominal value (550μg/body); the results are shown in Figure 4. We observe that organification is initially inhibited but resumes its normal rate within 48 hours. The increased $[I_P]$ causes a sudden rise in $[I_C]$ (and $[I_T]$ in a similar time scale) which due to its acute inhibitive effect, decreases $H_2O_2$ synthesis and $[H_2O_2]$ in short duration – resulting in reduced organification. The thyroid escapes from this transient, however, by decreasing $[NIS]$ in the basolateral membrane ([22] reports that both $NIS$ mRNA and protein are reduced). This is due to the high $[I_T]$ level. Our interpretation of the Wolff-Chaikoff effect is that it simply a transient behavior of a normal thyroid internal regulatory system adapting to a changing environment. Moreover, our test suggests the thyroid is still able to regulate $dT_4/dt$ as required by the reference signal $[TSH]$.

The final simulation studies the effect of a sharp drop at hour 24 then return to normal at hour 144 in plasma iodide $[I_P]$ level

under similar $\lceil TSH \rceil$ levels in the previous test; the results are shown in Figure 5. We observe that the thyroid control system adapts to the iodine-deficient levels, and then when normal iodine levels were reintroduced, there were slight indications of the Wolff-Chaikoff effect. This agrees with clinical results showing the threshold of Wolff-Chaikoff effect lowered at iodine-deficient environment [8]. This was due to the fact that $\lceil NIS \rceil$ level has adapted to the new iodine environment, and reintroducing the previous environment resulted in the Wolff-Chaikoff transients. This test illustrates once again the robustness of the thyroid control system which is able to maintain the correct thyroid output $dT_4/dt$ in the face of changing environment.
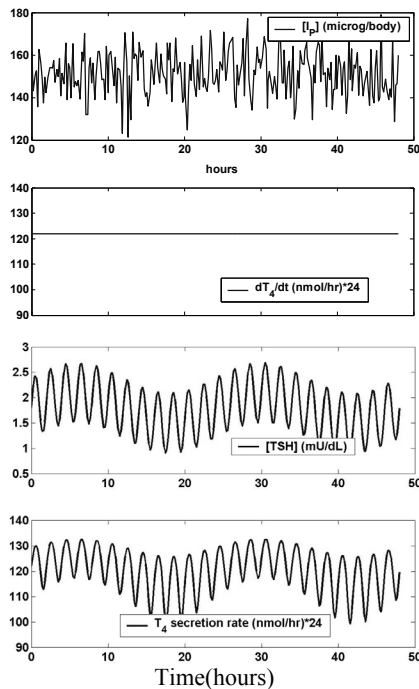


*Figure 3. Thyroid output under normal conditions.*

## IV. CONCLUSIONS

The structure of the thyroid control system exhibits strong robustness with respect to plasma iodide day-to-day fluctuation which is achieved by tight regulation of the colloid's composition. We conjecture that the large, 3-month supply of thyroid hormone within the colloid as well as the cascading feedback loops provide this robustness. This tight regulation of internal composition is a necessary characteristic of the thyroid system due to its open-loop relation between the control input signal and the thyroid hormone output. The Wolff-Chaikoff effect is shown to be a transient of this nonlinear system. Our model shows, as observed in recent clinical studies, that the mechanisms allowing the thyroid to adapt to high and low serum iodide concentration involves regulating $\lceil NIS \rceil$ levels. Future work will analyze the nonlinear system from a control viewpoint in order to study the observed robustness. We are also interested in studying the model's ability to predict intrathyroidal dynamics in hyper- and hypothyroidism.

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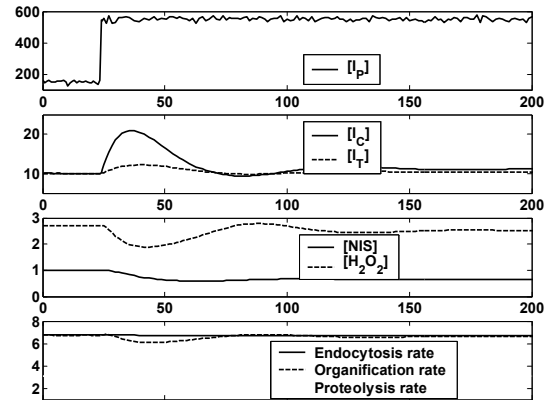
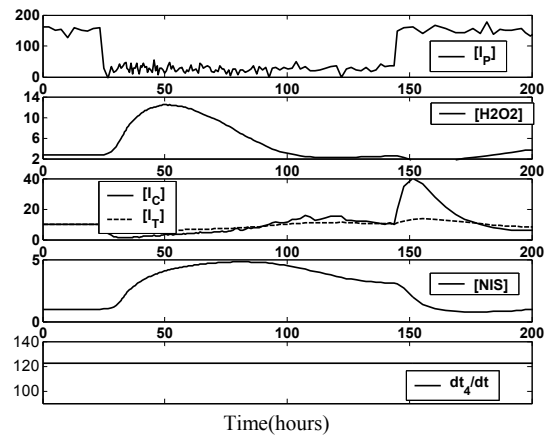*Figure 4. Wolff-Chaikoff block as a transient dynamic in the thyroid.*



*Figure 5. Thyroid response during serum iodide deficiency.*

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