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A novel minimal mathematical model of the hypothalamus–pituitary–thyroid axis validated for individualized clinical applications

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ABSTRACT

The hypothalamus–pituitary–thyroid (HPT) axis represents a complex, non-linear thyroid hormone system in vertebrates governed by numerous variables. The common modeling approach until now aims at a comprehensive inclusion of all known physiological influences. In contrast, we develop a parsimonious mathematical model that integrates the hypothalamus–pituitary (HP) complex as an endocrinologic unit based on a parameterized negative exponential function between free thyroxine (FT4) as stimulus and thyrotropin (thyroid stimulating hormone, TSH) as response. Model validation with clinical data obtained from geographically different hospitals revealed a goodness-of-fit largely ranging between $90\% < R^2 < 99\%$, each HP characteristic curve being uniquely defined for each individual akin to a fingerprint. Specifically, the HP model represents the afferent feedback limb of the HPT axis while the efferent limb is mathematically depicted by TSH input to the thyroid gland which responds by secreting T4 as its chief output. The complete HPT axis thus forms a closed loop system with negative feedback resulting in an equilibrium state or homeostasis under defined conditions illustrated by the intersection of the HP and thyroid response characteristics. In this treatise, we demonstrate how this mathematical approach facilitates homeostatic set points computation for personalized dosing of thyroid medications of patients to individualized euthyroid states.

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1. Introduction

As we enter into this present era of personalized medicine, there has never been a greater need for an individualized model governing the [FT4]–[TSH] relationship [1,2]. This is supported by an increasingly recognized observation that the wellbeing of many patients remains suboptimal despite having achieved "euthyroidism" defined by thyroid function within the normal population ranges of [FT4] and [TSH] [3].

For the purposes of this modeling strategy, we consider the hypothalamus–pituitary (HP) complex as one master regulator unit, calibrating its thyrotropin ([TSH]) response as a function of circulating free thyroxine ([FT4]). In order to elicit purely the properties of the HP response, we analyze the HP function in an open loop situation independent of the simultaneous confounding influence of the thyroid.

Although triiodothyronine [T3] is the main active hormone, the response characteristics analysis will be confined to the relationship between [FT4] and [TSH] [4]. This is valid as [TSH] is determined by the negative feedback action of the summation of [FT3] and [FT4] combined. Using a model with two degrees of freedom allows the contributory factor exerted by [FT3] to be completely subsumed within the two structural parameters such that only [FT4] remains the stimulus variable connecting [TSH] as the response.

Provided that the hypothalamus and pituitary are normal and not influenced by drugs or diseases, [TSH] varies inversely with [FT4] in a non-linear fashion whereby small changes in [FT4] can lead to fold-changes in [TSH] over several orders of magnitude [5,6]. When the [TSH] axis is presented using a linear scale, the non-linear inverse characteristic between [TSH] and [FT4] is apparent and resembles a hyperbolic, sigmoid or exponential decay function which motivated the development of the log-linear

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standard model of thyroid homeostasis more than 40 years ago [5,6]. Interestingly, the normal reference interval of [TSH] and [FT4] values falls within the "knee" region of the HP curve encompassing the greatest curvature (i.e. minimum radius of curvature) on such a graphical plot. The HP characteristic thus contains a set of possible points of homeostasis over a certain range of [FT4] and [TSH] in which the normal [TSH]–[FT4] homeostatic euthyroid set point is coincidentally also found here, suggesting an evolutionary survival advantage conferred by nature for organisms to respond and calibrate their [TSH] output robustly to achieve tight homeostasis of their [FT4] levels within a narrow physiological window [7].

Recently, a modeling example of the [TSH]–[FT4] relationship [8] succeeded to constitute the well-known standard logarithmic model from a fundamental mathematical basis. The logarithmic model of thyrotropic HP response is consistent with existing data in the literature which show that this relationship is generally depicted graphically by the [TSH] axis plotted on a logarithmic scale and the [FT4] axis plotted on a linear scale. Such a log-linear plot still shows a hyperbolic or logistic decline curve that may be approximated by a straight line with a negative gradient using semi-log scales on a Cartesian grid [8]. As such, [TSH] may be expressed as a negative exponential function of [FT4]. Based on these fundamental considerations, we devise an *a priori* negative exponential asymptotic model with two independent model parameters. The validation of the model is based on individual [FT4]–[TSH] measurements (observation space), related mode selection and belonging model identification [9].

According to non-linear curve fitting algorithm from Johansen [10] the validation results of the model are presented. In order to illustrate the derivation of euthyroid homeostasis, we introduce a thyroid hormone secretion model [11] with parameterized secretory rates such that area of homeostasis is found from the intersection of the thyroid curves with the HP curves.

2. Modeling strategy

Many HPT axis models are based on physiological measurements and observations containing numerous model parameters that finally will result in a modeling representation [12–16] based on coupled differential equations. Because only a limited set of physiological characterizations can be observed, most other relevant factors on HPT dynamics and homeostasis cannot be included for practical use. Except for DiStefano et al. [14], none of the models were validated on individual cases. All models were hampered by a set of unknown physiological parameters that could not translate into individualized applications. Also the use of simulations cannot replace real and specific patients. In the same vein, statistical modeling generates results that poorly reflect actual physiology and are also irrelevant at the individual level. The introduction of perturbation and statistical methods is an attempt to adapt the model to noisy data and/or imprecise measurements. In the final analysis, a physiologically accurate model is best constructed by reliable and reproducible thyroid function tests (TFT) (i.e. [TSH]–[FT4] paired data) [17,18].

With this knowledge, we only use the integral effects of the HPT homeostatic response from individual [FT4] and [TSH] measurements. This approach delivers a successful and applicable model, verified by individual series of TFT to construct the individual HP characteristic.

The model has two degrees of freedom, respectively S (the multiplier) and φ (the slope of the exponential coefficient) as shown:

$$[\mathrm{TSH}] = S\exp(-\varphi[\mathrm{FT4}]) \tag{1}$$

In the following, the implications and consequences of various choices for all parameters involved will be discussed. The factor S, a linear component of the thyrotropic system, is related to the [FT4] range. Variation of S, with a fixed value for φ, horizontally translates the HP characteristic curve along the [FT4] axis as shown in Fig. 1.

When φ is fixed, we can appreciate from the first derivative of (1) to [TSH]

$$\frac{d[\mathrm{TSH}]}{d[\mathrm{FT4}]} = -\varphi S\exp(-\varphi[\mathrm{FT4}]) = -\varphi[\mathrm{TSH}] \tag{2}$$

This implies that the first derivative will not change at fixed φ with variation of S.

When φ assumes a fixed known value, the value of S may be inferred from different [FT4]–[TSH] coordinates as given by:

$$S = [\mathrm{TSH}]\exp(\varphi[\mathrm{FT4}]) \tag{3}$$

The second model parameter φ represents the exponential factor. Variation of φ folds or unfolds the shape of the HP characteristic centered on a chosen set of coordinates. Notably, φ and S are inter-related accordingly to any [FT4]–[TSH] coordinate on the HP characteristic:

$$\varphi = \left(\frac{1}{[\mathrm{FT4}]}\right)\ln\left(\frac{S}{[\mathrm{TSH}]}\right) \tag{4}$$

In Fig. 2, the folding effect of the variation of φ is shown, while the HP curves 'rotate' around a defined point P.

Figs. 1 and 2 depict the theoretical range of values that φ and S can possibly assume under most clinical circumstances. Additionally, φ and S always form a parameter set describing a specific curve for a specific person. From Eq. (2), it can be readily appreciated that the first derivatives at the intersecting point, P, are only dependent on the value of φ.

Evidently, in general, a single point measured in the [FT4]–[TSH] plane cannot be used to generate a valid characteristic of the HP. Exponential functions have the property that such a function is completely defined by two different coordinates. With a set of at least two [FT4]–[TSH] measurements of a single person in the process of treatment for hypothyroidism or hyperthyroidism, measured over an interval of several weeks, the characteristic is completely determined by solving the simultaneous equations for the model parameters S and φ, provided that the thyroid function test results are not repeatedly identical and the effect of hysteresis is negligible. Based on these considerations, it is possible to obtain a reliable calculation of the HP function from [FT4] to [TSH] pairs obtained during changing treatment conditions in an open-loop situation [17].

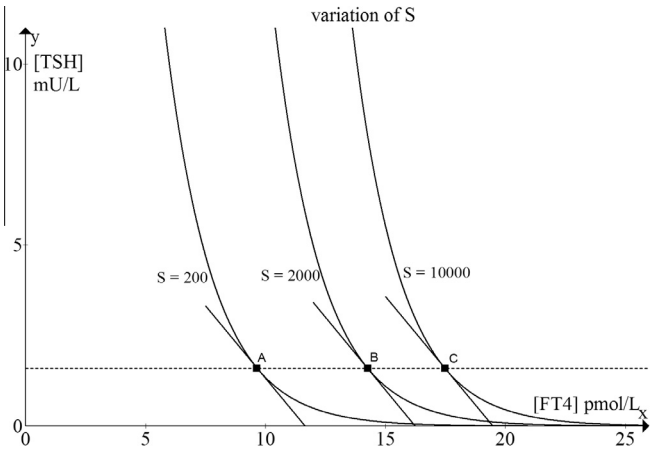

Fig. 1. Shifting the HP curve along the [FT4] axis as a function of S with a fixed value for φ. The values of S, $200 < S < 10{,}000$ are here only used as an example in practice S can be as small as 10 and in the higher regions can reach values of 10E+6.

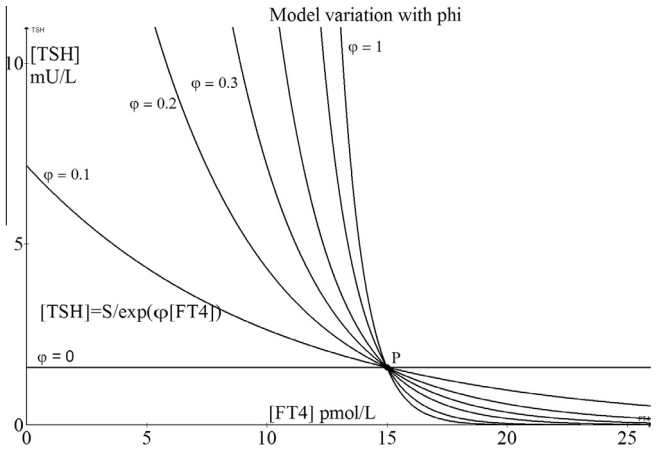

Fig. 2. Different HP curves intersecting at [FT4] = 15 pmol/L and [TSH] = 1.6 mU/L. Here the array of curves is shown with theoretical values of $0 < \varphi < 1$. Notably, in practice φ can assume values up to 10.

3. Method for calculating the HP characteristic from two or more distinct [FT4]–[TSH] measurements of a single patient

When two (or more) measured points (i.e. $([FT4]_1, [TSH]_1)$ and $([FT4]_2, [TSH]_2)$) from an individual are distinctly separated, found during the process of treatment, in the [FT4]–[TSH] plane, it is possible to plot the HP characteristic based on parameters S and φ:

$$\varphi = \left(\frac{1}{([FT4]_1 - [FT4]_2)}\right) \ln\left(\frac{[TSH]_2}{[TSH]_1}\right) \tag{5}$$

$$S = [TSH]_1 \exp(\varphi[FT4]_1) = [TSH]_2 \exp(\varphi[FT4]_2) \tag{6}$$

With the availability of additional points, i.e. $([FT4]_3, [TSH]_3)$, $([FT4]_4, [TSH]_4)$, etc., it is possible to verify the value of the parameters, S and φ, just by iterating the same calculation procedure between the third point and the other two points.

4. Clinical validation of the HP model

The model validation is based on the results of the observation space [9] and the *a priori* model form, using two independent data sets from the Tan Tock Seng Hospital in Singapore (cohort 1) and the Bergmannsheil University Hospitals in Bochum, Germany (cohort 2), both with different laboratory-specific reference ranges for [TSH] and [FT4], measured in mU/L and pmol/L, respectively.

Set 1 was obtained from Tan Tock Seng Hospital of Singapore (ethical approval from the National Healthcare Group Domain Specific Review Board (DSRB 'C') ethics committee, file number: C/2011/02012).

Set 2 stems from a subpopulation of the NOMOTHETICOS trial at the Bergmannsheil University Hospitals in Bochum, NRW, Germany (UTN U1111-1122-3273, ClinicalTrials.gov: NCT01145040, approved by the ethics committee of the Ruhr University of Bochum with file number 3718-10).

Levels for TSH and FT4 in set 1 were assayed in the clinical chemistry laboratory of Tan Tock Seng Hospital using manufacturer-supplied standard reagents, calibrators and controls from Beckman Coulter, Krefeld, NRW, Germany, on two Beckman Coulter DxI800 automated immunoassay analyzers. The intra-assay and inter-assay CVs for both these analyses vary with concentrations but are approximately less than 10%. The normal reference range for FT4 is 8–21 pmol/L while that for TSH is 0.34–5.6 mIU/L based on the Singapore normal population.

In cohort 2, these same hormone levels were similarly determined with competitive immunoassays based on direct chemoluminescence technology for both TSH and FT4. Hormones were also determined in patients' sera with a fully automated DxI800 platform by Beckman Coulter, Krefeld, NRW, Germany. For TSH, the dynamic range is 0.004–150 mU/L while the healthy reference range is 0.3–4 mU/L. The dynamic range for the FT4 assay is

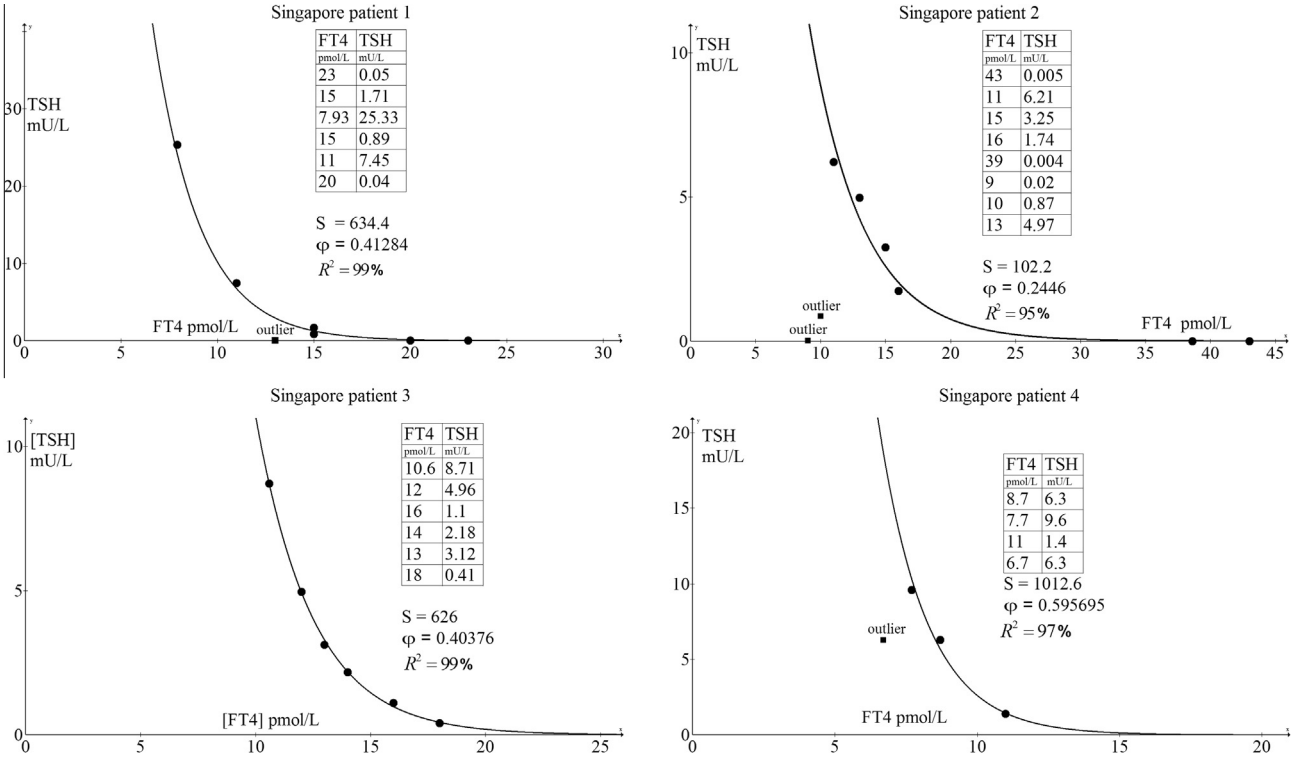

Fig. 3. (a)–(d) Calculated HP curves from 4 patients from dataset 1 (Tan Tock Seng Hospital, Singapore).

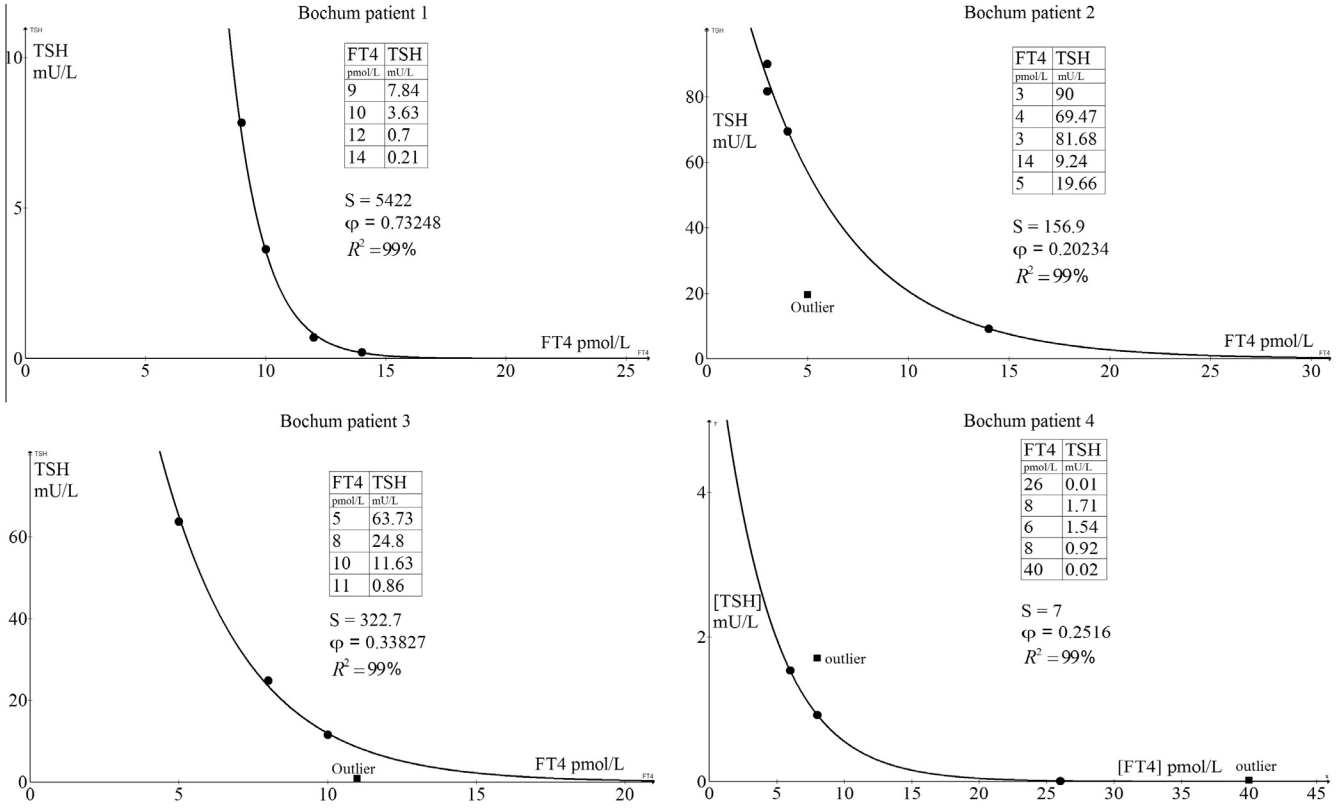

Fig. 4. (a)–(d) Calculated HP curves from 4 patients from dataset 2 (Bergmansheil University Hospitals, Bochum).

1–120 ng/L (1.54–184.8 pmol/L) while the healthy reference range is 7–20 ng/L (10–30 pmol/L). All blood samples were taken before noon. Levels for TSH and FT4 were determined from the same specimen.

For our validation, we use the following definitions. The model validity range of [FT4] is defined as 5 < [FT4] < 40 pmol/L. The model validity range of [TSH] is defined as 0.05 < [TSH] < 100 mU/L. The data points which transgress the model's conditions, such as positive derivatives between two consecutive points or values beyond the expected range of the model selection or outside the average expected model trajectory are considered outliers and are removed from the observation space. [9] Sources of possible variability in the observation space include diurnal variations of [TSH] [18], effects of disease or drugs on either [TSH] or [FT4], laboratory-specific approximation procedures such as rounding/truncating of decimals of the values of [FT4] to yield integers and inter-conversion of raw data from one measurement units to another (see Tables 1 and 2).

It should be emphasized that the model validation is performed on the dataset from a single individual each time and repeated for the entire patient sample on an individualized basis. This is crucial as the HPT axis physiology of every person is uniquely defined by S and φ akin to a fingerprint. This validation is therefore based on the individual application of the model selection [9] which resulted from previous research on the log-linear relationship between [TSH] and [FT4]. Hence, the model should not be applied on aggregated random [FT4]–[TSH] data from a population as widely disparate values of unrelated individuals diminish the signal-to-noise ratio and lead to erroneous conclusions when analyzed using inferential statistical techniques.

The following plots show the validation results:

5. Results

At every instance, the calculated curves from the accompanying dataset show a goodness-of-fit of 95% < R^2 < 99% to the measured points with exclusion of the outliers. Based on these findings and the fact that these data have been obtained from hospitals of different geographical locations, measured using the same methodology of laboratory assays but with slightly different reference ranges,

Table 1
Data points Singapore patients.

Patient 1 Fig. 3a		Patient 2 Fig. 3b		Patient 3 Fig. 3c		Patient 4 Fig. 3d	
FT4 pmol/L	TSH mU/L	FT4 pmol/L	TSH mU/L	FT4 pmol/L	TSH mU/L	FT4 pmol/L	TSH mU/L
23	0.05	43	0.005	10.8	8.71	8.7	6.3
11	7.45	11	6.21	12	4.96	7.7	9.6
15	1.71	15	3.25	16	1.1	11	1.4
8	25.33	16	1.74	14	2.18	6.7	6.3
13	0.05	39	0.004	13	3.12		
15	0.89	9	0.02	18	0.41		
20	0.04	10	0.87				
		13	4.97				

Table 2
Data points of Bochum (Germany) patients.

Patient 1 Fig. 4a		Patient 2 Fig. 4b		Patient 3 Fig. 4c		Patient 4 Fig. 4d	
FT4 pmol/L	TSH mU/L	FT4 pmol/L	TSH mU/L	FT4 pmol/L	TSH mU/L	FT4 pmol/L	TSH mU/L
9	7.84	3	90	5	83.73	26	0.01
10	3.63	4	69.47	8	24.8	8	1.71
12	0.7	3	81.68	10	11.63	6	1.54
14	0.21	14	9.24	11	0.86	8	0.92
		5	19.66			40	0.02

we proved that this model is valid for the locally related observation space of different populations. This indicates a general applicability of the parameterized model for the derivation of the HP characteristic curve.

6. Description of the thyroid transfer characteristic

The point of homeostasis (i.e. equilibrium position) occurs at the intersection of the HP and thyroid transfer characteristic curves which can be numerically solved and graphically localized on a 2-dimensional Euclidean plane defined by [TSH] and [FT4] concentrations along the respective orthogonal axes. Its coordinates explain both the phenotype of primary and central hypothyroidism, in the latter case with an intact normal thyroid that fails to operate due to missing stimulation by hypothalamus or pituitary that carry a 'master' control function.

Here, we adapt Michaelis–Menten kinetics as they are well founded in physiological and biochemical grounds as previously shown. [11] With [TSH] as the input signal, the system output is represented by [FT4] secreted by the thyroid according to the Michaelis–Menten-Hill kinetics in the form of:

$$[\mathrm{FT4}] = \frac{K_T[\mathrm{TSH}]}{D_T + [\mathrm{TSH}]}\ \mathrm{pmol/L} \tag{7}$$

From alterations in maximum [T4] yield K_T, corresponding to different thyroid's secretory capacity [11], different thyroid response characteristics can be plotted as shown in Fig. 5. D_T, the damping constant (EC_{50}) of [TSH] at the thyroid is set to 2.75, according to results of empirical research [11].

K_T is found to be 41 pmol/L for a thyroid secretion rate of about 100 nmol [T4] per 24 h from

$$K_T = \frac{G_T\alpha}{\beta\gamma} \tag{8}$$

with constant structure parameters from Table 3.

Accordingly, we find K_T = 70 pmol/L for a higher thyroid secretion rate > 100 nmol [T4] per 24 h (corresponding to G_T = 1.9 pmol/s) and K_T = 25 pmol/L for a lower thyroid secretion rate

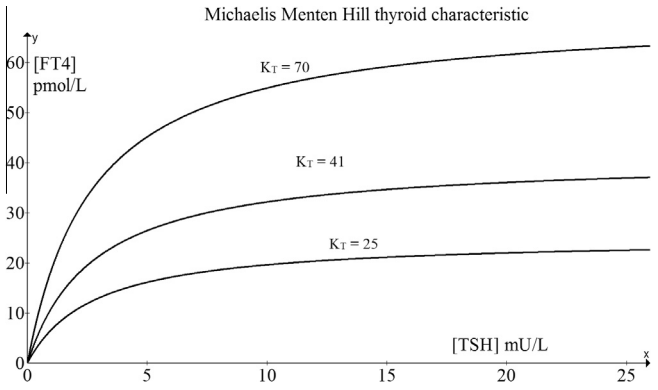

Fig. 5. Three thyroid characteristics based on Michaelis–Menten-Hill model with different maximum [T4] yield K_T.

< 100 nmol [T4] per 24 h (corresponding to G_T = 5.3 pmol/s). This leads to a distinct [TSH] for any given [FT4] level as a function of thyroid secretory capacity. In an individual patient G_T can be estimated from equilibrium levels of [TSH] and [FT4] as previously described [21,22].

Transposing [FT4] with [TSH], we get the inverted expression of the thyroid function:

$$[\mathrm{TSH}] = \frac{D_T[\mathrm{FT4}]}{K_T - [\mathrm{FT4}]}\ \mathrm{mU/L} \tag{9}$$

In this way we can express the inverted thyroid function in the same axis presentation as is done for the HP characteristic to show the effect of intersection. Thus, taking the instance when [FT4] = 15 pmol/L, a common value as shown in Fig. 6, we have:

$$[\mathrm{TSH}] = \frac{D_T[\mathrm{FT4}]}{70 - [\mathrm{FT4}]} \quad [\mathrm{T4}]\ \text{secretion rate} > 100\ \text{nmol per 24 h} \tag{10}$$

$$[\mathrm{TSH}] = \frac{D_T[\mathrm{FT4}]}{41 - [\mathrm{FT4}]} \quad [\mathrm{T4}]\ \text{secretion rate} > 100\ \text{nmol per 24 h} \tag{11}$$

$$[\mathrm{TSH}] = \frac{D_T[\mathrm{FT4}]}{25 - [\mathrm{FT4}]} \quad [\mathrm{T4}]\ \text{secretion rate} > 100\ \text{nmol per 24 h} \tag{12}$$

At equilibrium, the feedback control system fulfills both the conditions that are defined by the responses of the HP unit and the thyroid. Therefore, the equilibrium point (i.e. point of homeostasis) is illustrated by the point where the thyroid secretion characteristic curve intersects the HP characteristic curve. As an example, a common point of normal euthyroid homeostasis is hereby presented (Fig. 7), and the coordinates of P can be calculated using the HP characteristic and the thyroid characteristic equations.

The intersection point P seems to be somewhat skewed to the left side of what appears in Fig. 7 as the maximum upward concavity, or knee of the HP curve.

This is an optical illusion in the plot of Fig. 7 because of the different axis scaling.

The interception point is found at the point of strongest curvature of the HP function as described in calculus:

$$K = \frac{1}{R} \tag{13}$$

where R represents the radius of the curvature circle.

When we substitute from (1) [TSH] = y then the curvature K of y is defined as

$$K = \frac{d^2y/dx^2}{\left(1 + (dy/dx)^2\right)^{3/2}} \tag{14}$$

The theoretical considerations will be subject of future research.

Table 3
Parameters for Eq. (7) and for calculating K_T from structure parameters [11,21,22].

Symbol	Explanation	Standard value
D_T	Damping constant (EC50) of TSH at the thyroid gland	2.75 mU/L
G_T	Thyroid's secretory capacity (maximum production per second)	3.1 pmol/s
α	Dilution factor for T4	9
β	Clearance exponent for T4	1.1 e^{-6} s^{-1}
γ	Coefficient for plasma protein binding of T4	9601

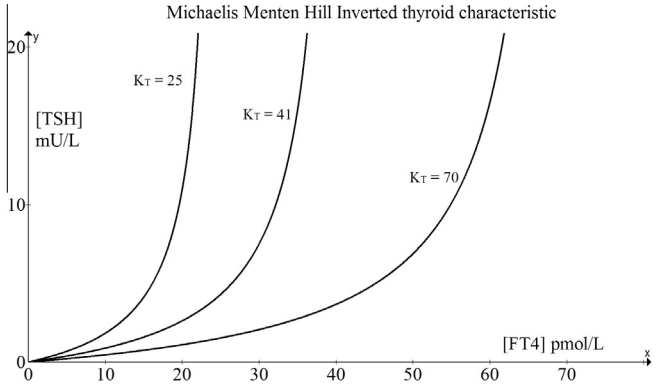

Fig. 6. Three inverted thyroid characteristics with different secretion factors K_T.

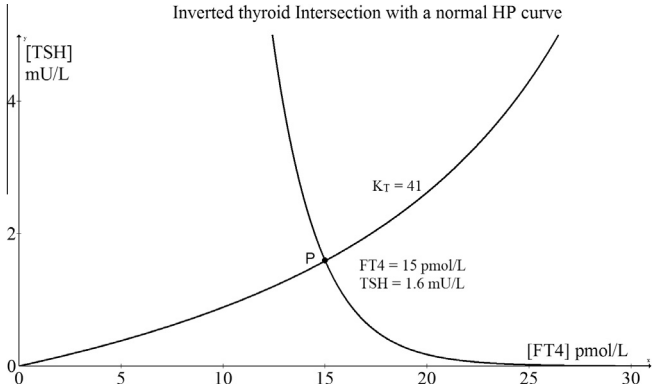

Fig. 7. Intersection of the thyroid and HP curves at point *P*.

7. Discussion

In this paper, the relationship between [TSH] and [FT4] is investigated using a non-linear HP model. The model validation for the [TSH] is valid for the range of 0.01 < [TSH] < 50 mU/L; for [FT4], we find the valid operating range of the model to extend between 5 < [FT4] < 40 pmol/L. The model shows a pronounced "knee curvature" corresponding to the area of the so-called 'normal euthyroid reference values' of [TSH] and [FT4]. There are practical diagnostic implications arising from this property of the HP response curve. First, accurate measurements of [TSH] in the highest range of [FT4] are possible but riddled with technical challenges due to the infinitesimally miniscule circulating [TSH] concentrations that tend to escape detection [17,19]. In general, low [TSH] probably implies a relatively high [FT4] with the rare exception of central hypothyroidism [20]. Conversely, measurements of [TSH] in the higher ranges are less susceptible to biochemical assay precision error limitations because the concentrations to be detected are sufficiently large to exceed the coefficient of variation of the assay techniques to yield accurate laboratory results [17].

It is imperative that the measurements are done with patients at either extreme of dysthyroid states (e.g. from a hypothyroidism state, at intervals of 4–8 weeks while the patient is replaced with levothyroxine, or starting from a thyrotoxic state and monitored over similar intervals while the patient is medicated with antithyroid drugs. Notably, the common practice among physicians of merely aiming for [FT4]–[TSH] values within the laboratory reference ranges is conceptually flawed as such "stabilized [FT4]–[TSH]" might depart significantly from the true euthyroid set points of different patients. It could also facilitate the basis for improved dosing schemes in L-thyroxine substitution therapy or accurate titration of anti-thyroid drugs.

This novel approach could potentially contribute towards improved diagnostics of thyroid heterostasis in future, given that patients whose thyroid function tests results fall within any given laboratory reference range may in fact be cases of subclinical hypothyroidism or hyperthyroidism deserving further medical attention. The methodology for elucidation of the area of homeostasis as described above is further developed into a new theory to be published in a future paper relating to this specific subject. Notably, in the clinical application of this formula, both the multiplier S and φ are only related to the specific patient under investigation. It cannot be overemphasized that [FT4] and [TSH] are coupled numbers characteristic for the specific individual insomuch as the euthyroid set point is uniquely defined for any given individual. The reference range values for [FT4] and [TSH] should therefore be tailored and interpreted for a specific person and not simply extrapolated to another individual. The clinical utility of such a technique is that the euthyroid area of homeostasis as determined can serve as a rational and more accurate therapeutic target.

8. Conclusion

In this model validation of the HP complex of the HPT axis, the HP function is analyzed and characterized as a standalone master regulator unit, with [FT4] as input signal and [TSH] as output signal, controlling the secretory behavior of the thyroid. In this way we came to the determination of an individualized [FT4]–[TSH] relationship via our proposed mathematical approach. This allows us to deduce if the [TSH]–[FT4] values of a patient are close to an acceptable possible position of homeostasis, or whether the values are relatively more 'hypothyroid' or 'thyrotoxic' for the individual.

The acquired HP characteristic is theoretically the mathematical sample space [9] of possible equilibrium points of the investigated individual. This model forms the foundation of future research to develop a theory for the determination of the characteristic unique homeostatic set point situated on the HP curve corresponding to normal euthyroid physiology appropriate to the individual person. It remains for future studies to assess if such a methodology will prove superior to current heuristic therapeutic paradigms and facilitates a more accurate, targeted treatment based on HPT axis physiology, and most importantly, if it improves patients' clinical outcomes and quality of life.

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