Endocrine systems modeling

Towards personalized treatment of thyroid diseases

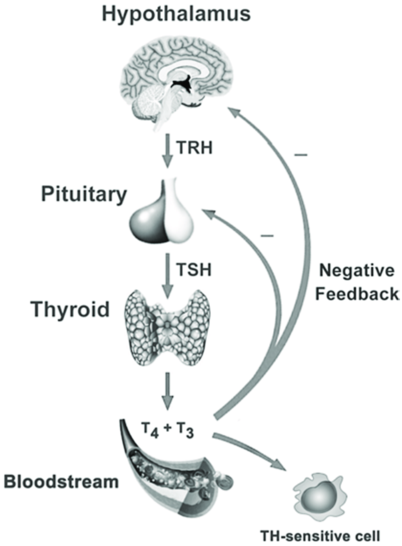
Benedetta Bonfanti

Supervisors: K. Vuik, M. Medici, S. L. Goede

Delft University of Technology, The Netherlands

4th June 2021

HPT axis


Hypothalamus
TRH
Pituitary
TSH
Thyroid
Negative
Feedback
–
–
$T_4 + T_3$
Bloodstream
TH-sensitive cell

Hypothyroidism

- Pathological condition that refers to thyroid hormone deficiency
- Affects 10% of the global population
- Definition based on reference ranges:

$$0.4 \text{ mU/L} < [\text{TSH}] < 4.0 \text{ mU/L}$$
$$10.0 \text{ pmol/L} < [\text{FT4}] < 20.0 \text{ pmol/L}$$

- Standard treatment is LT4 monotherapy
- Many patients do not reach their treatment targets
- Some patients still present complaints

Measurements of TSH, FT4, FT3

- Reference ranges for TSH and FT4 are established by each laboratory with statistical techniques
- Use measurements taken at the same time, in the same laboratory, with the same technique
- Immunoassays
  → Specificity is not optimal
- Mass spectrometry
  → Solve successfully problems of immunoassays
- Important to take into account that measurements have a certain accuracy
  → It might influence the results

Erasmus MC

TU Delft

Importance of the topic

Need for a mathematical model of the HPT axis

- 35-60% of patients do not reach reference target for TSH
- 5-10% of patients still have complaints despite their values being in the target ranges
- Personalized treatment for thyroid disorders
- Optimal path towards the set-point

Patient-specific models and population models

Two classes of models

Population models

- Statistical approach
- Different individuals have influence on each other
- Cannot be applied on single individuals

Patient-specific models

- Models of interest for this thesis
- Can be applied on single individuals
- Importance of simple and testable models

Exponential model

- HP curve analyzed in an open loop situation
- Mathematical model

$$[\mathrm{TSH}] = Se^{-\varphi[\mathrm{FT4}]}$$

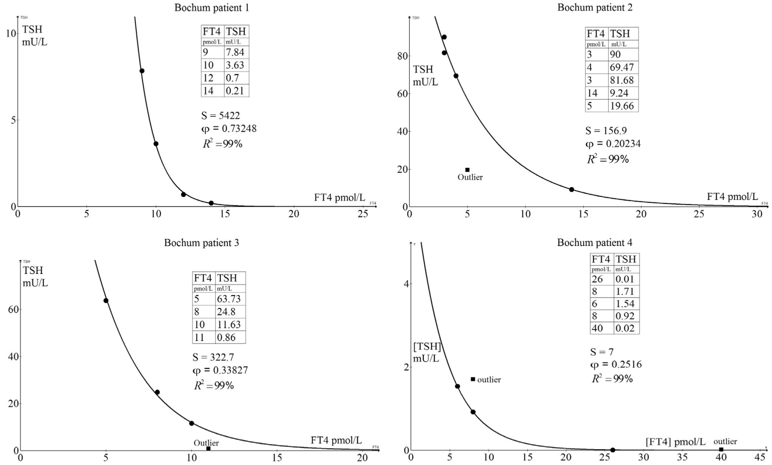
- At least two measurements for TSH and FT4 are needed to compute S and φ:

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

$$S = [\mathrm{TSH}]_1 e^{\varphi[\mathrm{FT4}]_1} = [\mathrm{TSH}]_2 e^{\varphi[\mathrm{FT4}]_2}$$

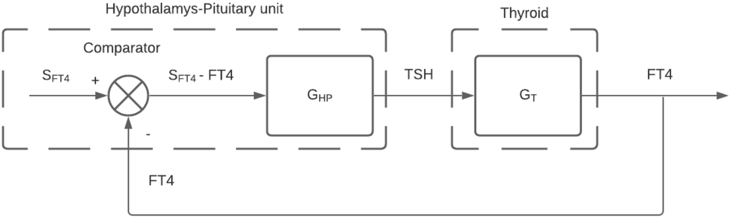
- S and φ are unique for every individual

Exponential model



Simon L Goede, Melvin Khee-Shing Leow, Jan WA Smit, and Johannes W Dietrich. A novel minimal mathematical model of the hypothalamus–pituitary–thyroid axis validated for individualized clinical applications. *Mathematical biosciences*, 249:1–7, 2014

HPT negative feedback loop



HPT negative feedback loop

- HP characteristic:

$$[\mathrm{TSH}] = Se^{-\varphi[\mathrm{FT4}]}$$
$$\Rightarrow G_{HP} = \frac{d[\mathrm{TSH}]}{d[\mathrm{FT4}]} = -\varphi[\mathrm{TSH}]$$

- Thyroid characteristic:

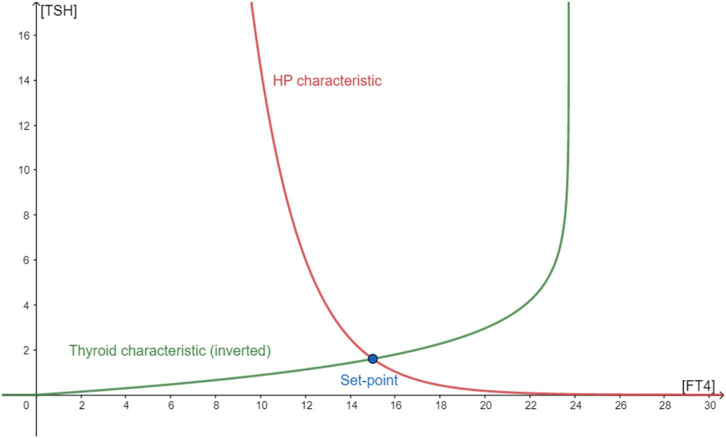
$$[\mathrm{FT4}] = A\left(1 - e^{-\alpha[\mathrm{TSH}]}\right)$$
$$\Rightarrow G_T = \frac{d[\mathrm{FT4}]}{d[\mathrm{TSH}]} = A\alpha e^{-\alpha[\mathrm{TSH}]}$$

- Loop gain larger than 1:

$$G_L = |G_T G_{HP}| = \varphi[\mathrm{TSH}]A\alpha e^{-\alpha[\mathrm{TSH}]} > 1$$

HPT axis set-point

Intersection between HP and thyroid curves



HPT axis set-point

Point of maximum curvature of the exponential function:

$$K = \frac{\frac{d^2[\mathrm{TSH}]}{d[\mathrm{FT4}]^2}}{\left(1 + \left(\frac{d[\mathrm{TSH}]}{d[\mathrm{FT4}]}\right)^2\right)^{3/2}} = \frac{\varphi^2 S e^{-\varphi[\mathrm{FT4}]}}{\left(1 + \varphi^2 S^2 e^{-2\varphi[\mathrm{FT4}]}\right)^{3/2}}$$

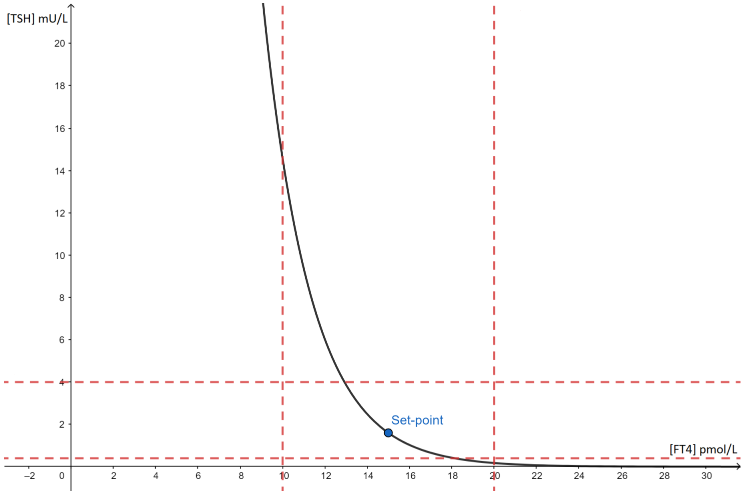
$$\Rightarrow \frac{dK}{d[\mathrm{FT4}]} = 0$$

$$\Rightarrow [\mathrm{TSH}] = \frac{1}{\varphi\sqrt{2}}, \qquad [\mathrm{FT4}] = \frac{\ln\left(\varphi S \sqrt{2}\right)}{\varphi}$$

Erasmus MC

TUDelft

HPT axis set-point



Erasmus MC

TU Delft

Model for Hashimoto thyroiditis

$$\frac{d[\mathrm{TSH}]}{dt} = k_1 - \frac{k_1[\mathrm{FT4}]}{k_a + [\mathrm{FT4}]} - k_2[\mathrm{TSH}]$$

$$\frac{d[\mathrm{FT4}]}{dt} = \frac{k_3 \mathrm{T}[\mathrm{TSH}]}{k_d + [\mathrm{TSH}]} - k_4[\mathrm{FT4}]$$

$$\frac{d\mathrm{T}}{dt} = k_5\left(\frac{[\mathrm{TSH}]}{\mathrm{T}} - N\right) - k_6[\mathrm{TPOAb}]\mathrm{T}$$

$$\frac{d[\mathrm{TPOAb}]}{dt} = k_7[\mathrm{TPOAb}]\mathrm{T} - k_8[\mathrm{TPOAb}]$$

Erasmus MC

TUDelft

Model for Hashimoto thyroiditis

Drawbacks

- Functional size of the thyroid cannot be measured
- Too many parameters
- Dynamic models cannot be applied

Positive aspects

- Focus on steady states
  → One of them corresponds to the euthyroid state
- Importance of a patient-specific model

Erasmus MC

TUDelft

Population models

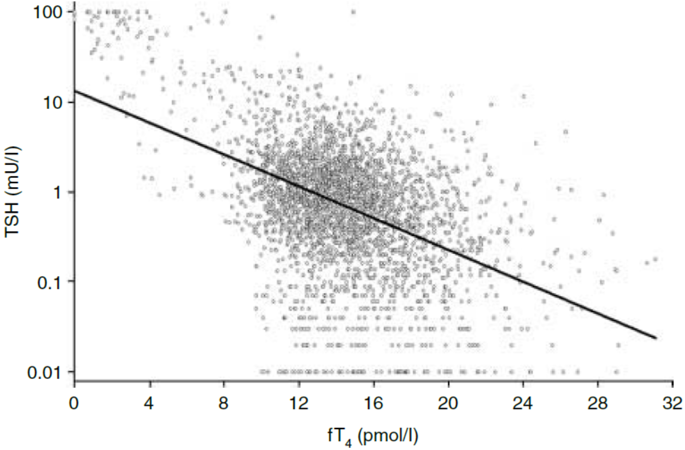
- Most of the models are population models
- Population models are widespread in clinical research
  → however they are not always adequate
- Statistical approach
  → individual results are not relevant
- FT4 of one patient influences TSH of someone else

Erasmus MC

TU Delft

Log-linear model

$$\log[\mathrm{TSH}] = a + b[\mathrm{FT4}]$$



Non-log-linear models

- Error function

$$\log[\mathrm{TSH}] = \frac{\sqrt{\pi}k}{2q}\,\mathrm{erf}(q([\mathrm{FT4}] - a)) + d([\mathrm{FT4}] - a) + b$$

- Fourth order polynomial

$$\log[\mathrm{TSH}] = a[\mathrm{FT4}]^4 + b[\mathrm{FT4}]^3 + c[\mathrm{FT4}]^2 + d[\mathrm{FT4}] + e$$

- Negative sigmoid curve

$$\log[\mathrm{TSH}] = A + \frac{B}{1 + e^{-(C-[\mathrm{FT4}])/D}}$$

Erasmus MC

TU Delft

Population models applied to individuals

- Error function and sigmoid models are not good fits for single individuals
- Log-linear and quartic models show the best fit
- Log-linear model is equivalent to exponential model $\rightarrow$ it shows the best fit for patients with the highest number of measurements

Erasmus MC

TUDelft

Conclusion

- Exponential model is well justified and provides satisfactory results
- Model for Hashimoto thyroiditis presents some pitfalls, like functional size of the thyroid, dynamic model, too many parameters
- Population models are not useful in the path towards personalized treatment of thyroid disorders

Erasmus MC

TUDelft

Research questions

- How can the HPT axis be modelled from a mathematical perspective? How can the existing model be improved?
- How can the set-point of an individual be predicted?
- Once a prediction of the set-point is available, how can it be proved that it corresponds to the actual set-point?
- How can the optimal path leading to the desired HPT set-point be found? How much time is needed to reach the set-point?