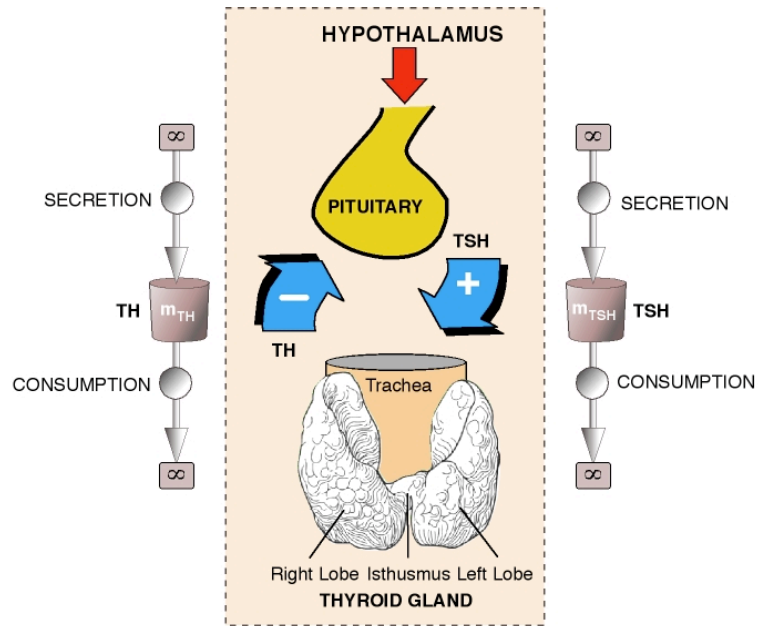
Lesson 6. FEEDBACK REGULATION IN THYROID-PITUITARY SECRETION

OBJECTIVES

1. To study feedback interactions.
2. To simplify a complex system to a 2-tank model.
3. To estimate model parameters.



PROBLEM

Simulate the regulation of the thyroid gland secretion, which is dependent on thyroxine feedback on TSH secreting cells of the anterior pituitary gland.

Background

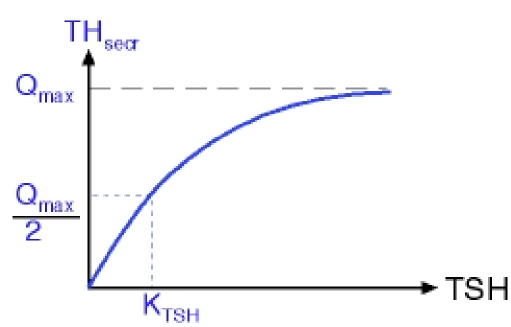
This simulation will only consider two hormones, thyroxine (TH) and thyroid stimulating hormone (TSH). Thus we will neglect most of the intricacies of iodine metabolism.

Stimulation of thyroid secretion by TSH

$$TH_{Secr} = \frac{Q_{max} \cdot [TSH]}{K_{TSH} + [TSH]} \qquad (1)$$

where:

- Q_{max} = maximal rate of TH secretion
- K_{TSH} = concentration of TSH required for 50% maximal TH secretion



Removal of TH

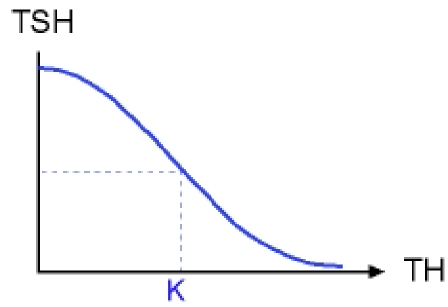
(metabolic and/or renal) is assumed to be proportional to [TH}. By [TH}, we mean the concentration of free TH and the concentration of TH bound to plasma protein. Since [TH] is proportional to m_{TH}, the total mass of TH, we can write

$$TH_{removal} = R_{TH}\, m_{TH} \qquad (2)$$

where R_{TH} is a rate constant i.e. 1/time constant(day^{-1}).

Inhibition of TSH secretion by TH:

$$TSH_{SECR} = \frac{S_{max}(K_{TH})^n}{(K_{TH})^n + [TH]^n} \qquad (3)$$



where:

S_{max} = the rate of TSH secretion in the absence of TH

K_{TH} = the concentration of TH required for 50% maximal TSH inhibition.

Removal of TSH

Removal of TSH is assumed to be proportional to [TSH] which is proportional to m_{TSH}

$$TSH_{removal} = R_{TSH}\, m_{TSH} \qquad (4)$$

where R_{TSH} is the TSH rate constant [day^{-1}].

Parameters

Because the bound TH and the free TH are proportional to each other, assuming a steady state is not a serious compromise. For normal humans in a steady state:

TH_{secr} = 80 μg/day	TSH_{secr} = 110 μg/day
$[TH]_{ss}$ = 80 μg/liter	$[TSH]_{ss}$ = __________
$[TH]_{half\ life}$ = 6.5 days	$[TSH]_{half\ life}$ = 1 hour
Volume of distribution of thyroid hormone = 10 liters. (This includes the TH bound to plasma protein—which soaks up the hormone as if there were an additional volume available.)	
Volume of distribution for TSH = 3 liters. (This is the volume of plasma—a guess—TSH is a protein, not bound to other plasma proteins)	

Estimate the remaining parameters for this simulation:

- R_{TH}: compute the value from $[TH]_{half\ life}$
- R_{TSH}: compute the value from $[TSH]_{half\ life}$
- $[TSH]_{ss}$: Use the known value of TSH_{Secr} (see Table) and compute the steady state value, $[TSH]_{SS}$, using the steady state condition (Secr = Removal)
- S_{max} and K_{TH}: assume K_{TH} is the steady state value of [TH] and compute S_{max}
- Q_{max} and K_{TSH}: assume K_{TSH} = steady state value of [TSH] and compute Q_{max}
- **Assume:** n = 3

Exercises

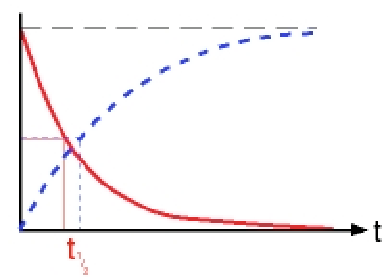
1. Run the simulation for 50 days using initial values of [TH] = 30 μg/liter, and [TSH] = 1 μg/liter. Plot both [TH] and [TSH] and determine their "normal" steady state values. Are they consistent with the data? Note how fast the feedback system operates. Compare with different values of n. [Hint: $[TH]_{ss}$ = 80 μg/l; if you don't get this, check your parameter values carefully.
2. A patient suspected of chronic hypothyroidism has blood samples taken every few days and the averaged measured levels of [TH] = 36.7 μg/L and [TSH] = 4.6 confirm the original suspicion. [TH] level is low, but because [TSH] is too high, the thyroid deficiency may be due to a reduced affinity of the TSH receptor (increased K_{TSH}), or a deficiency of the total number of TSH receptors, or of TH secretion (a decreased Q_{max}). Show that the latter assumption (defective Q_{max}) will account for the data.
3. A physician wants to compensate for low levels of TH (in the patient described above) by administering daily doses of TH. What dose should he use? (Simulate the daily dose with the pulse function).

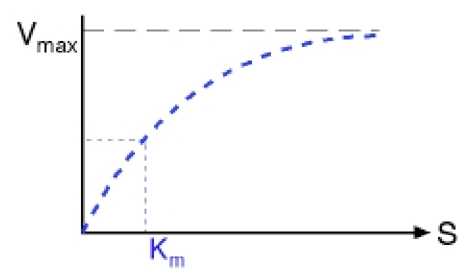
Appendix: 'Guesstimating' parameters from data

1. Assume the process is 'first order' (i.e. exponential rise or decay):

   Rate constant $k \sim 0.69/t_{1/2}$

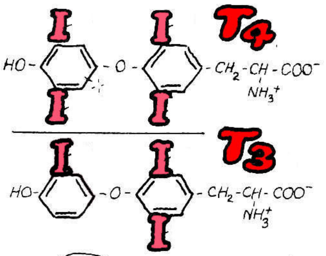
2. Assume a steady state ($dx/dt \equiv 0$) and use the resulting algebraic equation to eliminate one parameter.
3. If S is a 'regulated' quantity, then assume that at steady state $\bar{S} \sim K_m$ (this 'rule of thumb' is expected to be accurate only to an order of magnitude).

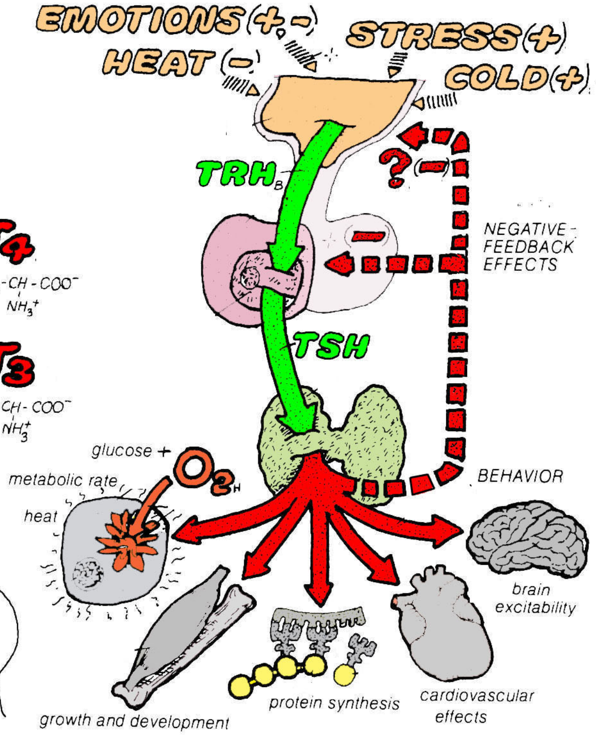


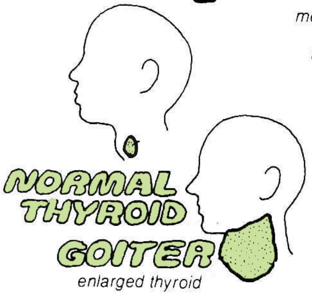


HYPOTHALAMUS A
THYROID-RELEASING H. (TRH)
ANTERIOR PITUITARY

THYROID-STIMULATING H. (TSH)
THYROID GLAND
THYROXINE T4
TRI-IODOTHYRONINE T3 F²
TARGET TISSUE



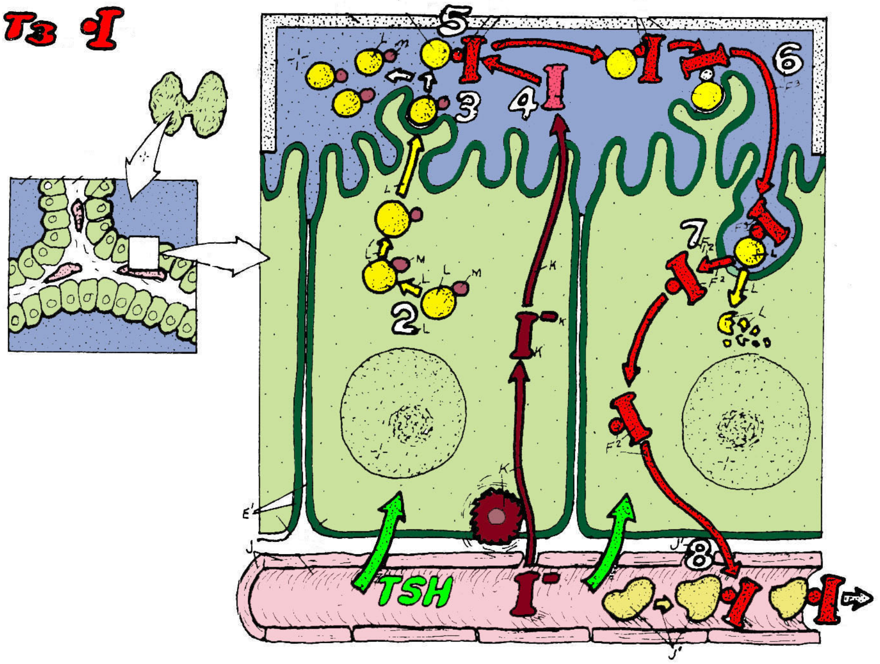




THYROID HORMONE: T4 F¹ T3 •I

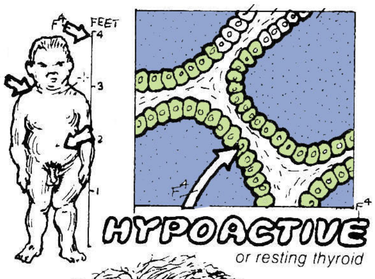
(MANUFACTURE, STORAGE & RELEASE)

FOLLICLE CELL
COLLOID (CAVITY)
CAPILLARY
BLOOD PROTEIN
IODIDE I⁻
IODINE I
THYROGLOBULIN
TYROSINE



HYPOTHYROIDISM

CHILDREN
CRETINISM



ADULTS
MYEXEDEMA

HYPERTHYROIDISM