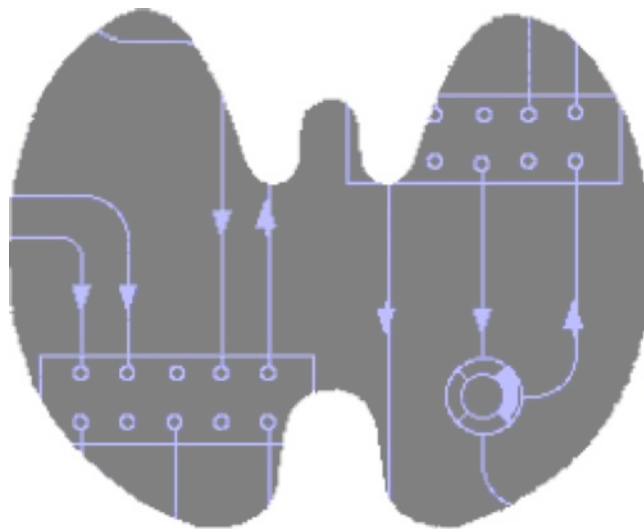


SimThyr 3.0

Short introduction



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Thyroid hormones that act on virtually any cell play a central role in metabolic coordination. Robust control of thyroid homeostasis is therefore essential for survival, differentiation and reproduction [1].

In 1940, eleven years after the discovery of the thyrotropic hormone TSH by Aron in the year 1929, W. T. Salter postulated the existence of a control loop linking the pituitary and thyroid gland. This idea was inspired by the recent description of the two gonadotropic feedback control loops. Only a few years later, Astwood and Hoskins could reveal both the existence and the pathophysiological relevance of this thyrotropic feedback control system. In 1968, Panda and Turner succeeded in a quantitative description of the interdependence of thyroxine and TSH levels, but the first mathematical models of the feedback loop had already been developed up to 12 years earlier [2-5].

Over the years, cybernetic models of thyroid homeostasis were increasingly improved, a success that was also enabled by growing empirical data. As a consequence of this continued evolution, some of the newest models are also suitable for medical decision-making [1, 6-9].

However, due to nonlinear interactions, these cybernetic models cannot simultaneously describe static and dynamic behaviour. This gap may be filled with computer simulations that additionally facilitate an intuitive insight into the dynamics of thyrotropic feedback.

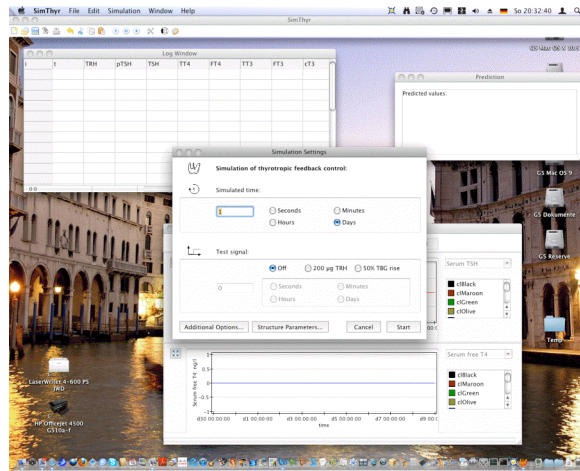
SimThyr is a simulation program for the pituitary thyroid feedback control that is based on a parametrically isomorphic model of the overall system [1, 10].

Applications of SimThyr cover research, including development of hypotheses, and education of students in biology and medicine, nurses and patients.

This is a short introduction into basic usage of SimThyr. Full documentation is available at <http://simthyr.sf.net>.

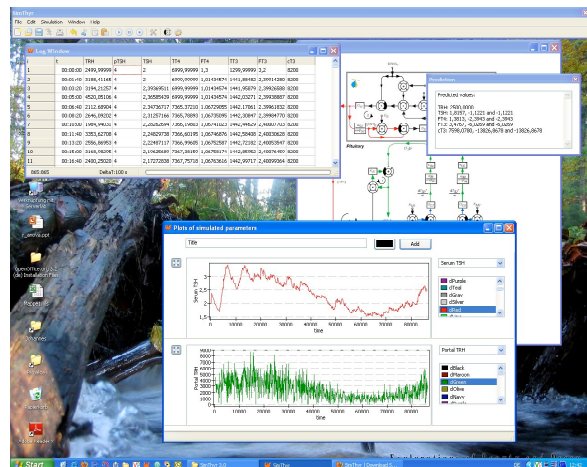
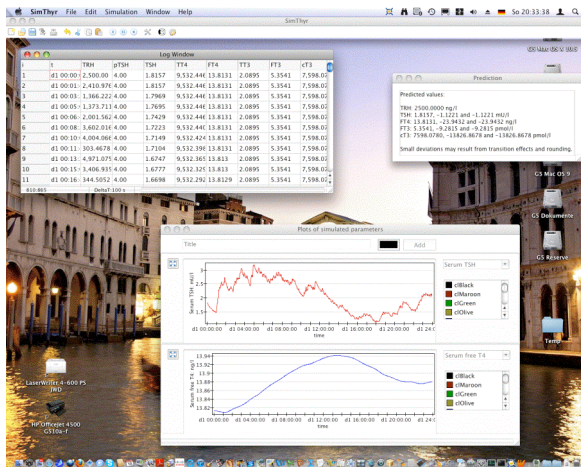
Starting SimThyr

Start SimThyr by double-clicking its icon. After a short while a dialog box asking for simulation options is presented:



First simulation

For a first simulation simply hit the **Start** button on the dialog box or press the **Enter** key on your keyboard. This will start a simulation of one day under standard conditions.



The Log window shows simulated values of time and hormone levels. In the plot window results are presented graphically. The small window titled “Prediction” displays predicted results from analytically solving the equations describing the feedback loop in a parametrically isomorphic model.

Small deviations from the depicted results above may ensue from simulated random effects.

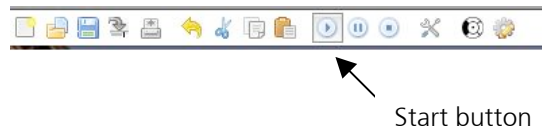
Experiment 1

The first experiment simulates the development of subclinical (latent) hypothyroidism.

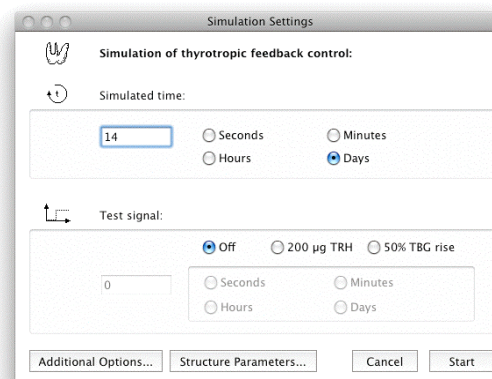
In order to do this, first click the stop and reset button in the toolbar:



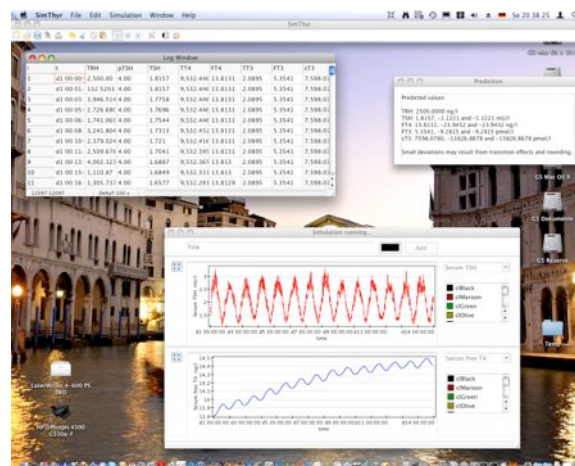
This will delete all simulated values and set the time to zero. Then, start a new simulation over 14 days. Press the start button:



and enter 14 days in the simulation settings dialog:

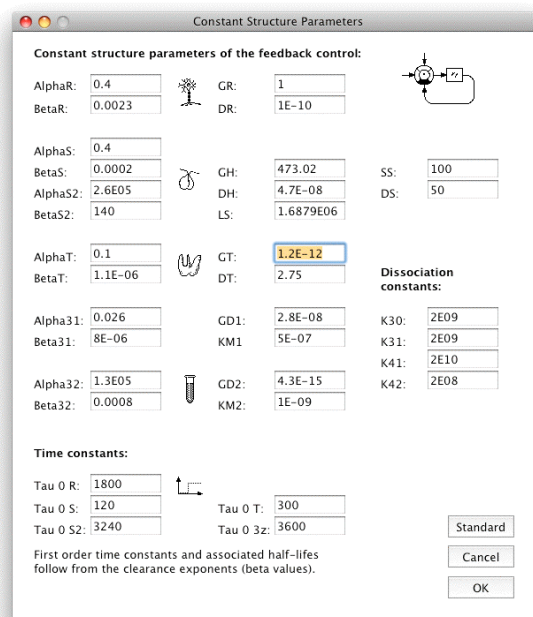


After clicking “Start” you will obtain the result of 14 days in normal conditions that may be similar but not necessarily identical as depicted below.

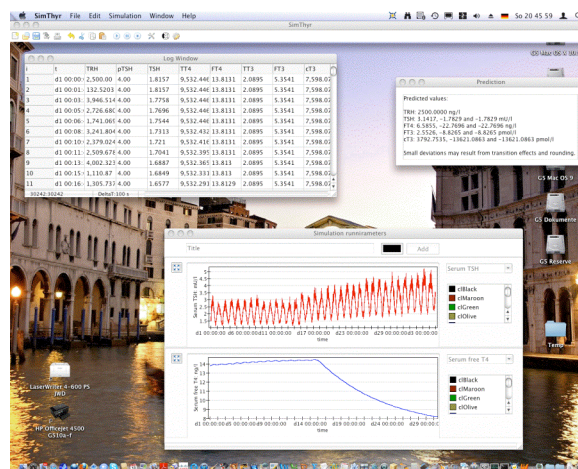


Now, let's develop subclinical hypothyroidism. In order to achieve this, click the start button again *without* hitting the stop button first. This will cause the subsequent simulation results to be appended to the previous results.

In the simulation settings dialog don't click the start button but on the button titled **Structure parameters...** in the middle of the lower part. This will open a new dialog enabling you to modify structure parameters of the overall feedback system. Here, change the thyroid's secretory capacity (GT) to 1.2 pmol/sec, i.e. you should enter $1.2E-12$ into the field depicted GT.



After clicking the **OK** button the new value for GT is stored. Then change the simulated time to 21 days to allow for enough settling time. After clicking **Start** you should receive results that are similar to the following:



Obviously, FT4 falls into the low-normal range while TSH oscillates between normal and elevated levels.

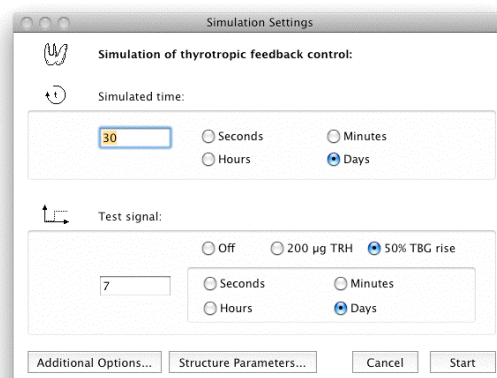
In the structure parameters window you may change virtually all constant structure parameters of thyroid homeostasis including volumes of distribution, time constants and dissociation constants. Useful starting points for experimentation may be sum activity of peripheral deiodinases (GD) and the secretory capacity of thyrotropic anterior pituitary cells (GH).

Experiment 2

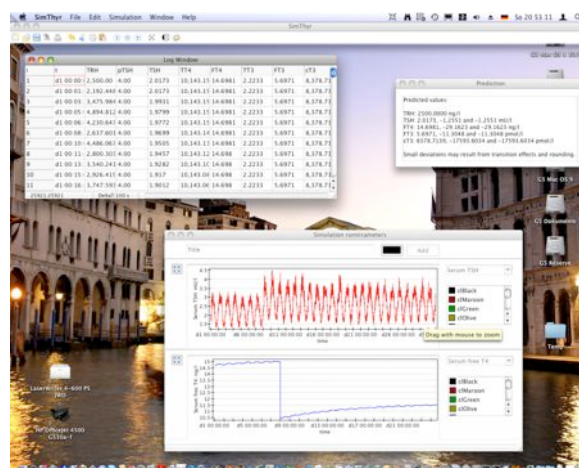
This simulates the effects of modifications in plasma proteins, e.g. in pregnancy or on contraceptive medication.

First, reconstruct standard conditions by clicking **Standard** in the structure parameters window and confirm with **OK**. Then, click the stop and reset button in the toolbar in order to delete all entries and start with time point 0.

After clicking the start button you will get the already well-known simulation settings dialog. Here click on **50% TBG rise** in the lower part of the window.



To allow for the necessary settling times enter 30 days for total simulation and 7 days as beginning of the effect.



The results should be similar as depicted above, showing a decrease of FT4 levels in the beginning of the effect, than a short increase in TSH levels and a consecutive slight TSH decrease as FT4 rises in the achievement of a new equilibrium point.

You may change the combo boxes in the plot window in order to study the effects on other hormones of the feedback loop.

References

1. Dietrich JW: **Der Hypophysen-Schilddrüsen-Regelkreis. Entwicklung und klinische Anwendung eines nichtlinearen Modells**, vol. 2. Berlin: Logos-Verlag; 2002.
2. Danziger L, Elmergreen GL: **The thyroid pituitary homeostatic mechanism**. *Bulletin of Mathematical Biology* 1956, **18**(1):1-13.
3. DiStefano JJ, 3rd, Stear EB: **Neuroendocrine control of thyroid secretion in living systems: a feedback control system model**. *Bull Math Biophys* 1968, **30**(1):3-26.
4. Norwich KH, Reiter R: **Homeostatic control of thyroxin concentration expressed by a set of linear differential equations**. *Bull Math Biophys* 1965, **27**(2):133-144.
5. Roston S: **Mathematical representation of some endocrinological systems**. *Bulletin of Mathematical Biology* 1959, **21**(3):271-282.
6. Degon M, Chipkin SR, Hollot CV, Zoeller RT, Chait Y: **A computational model of the human thyroid**. *Math Biosci* 2008, **212**(1):22-53.
7. Eisenberg M, Samuels M, DiStefano JJ, 3rd: **Extensions, validation, and clinical applications of a feedback control system simulator of the hypothalamo-pituitary-thyroid axis**. *Thyroid* 2008, **18**(10):1071-1085.
8. Leow MK: **A mathematical model of pituitary--thyroid interaction to provide an insight into the nature of the thyrotropin--thyroid hormone relationship**. *J Theor Biol* 2007, **248**(2):275-287.
9. Li G, Liu B, Liu Y: **A dynamical model of the pulsatile secretion of the hypothalamo-pituitary-thyroid axis**. *Biosystems* 1995, **35**(1):83-92.
10. Dietrich JW, Tesche A, Pickardt CR, Mitzdorf U: **Thyrotropic Feedback Control: Evidence for an Additional Ultrashort Feedback Loop from Fractal Analysis**. *Cybernetics and Systems* 2004, **35**(4):315-331.

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