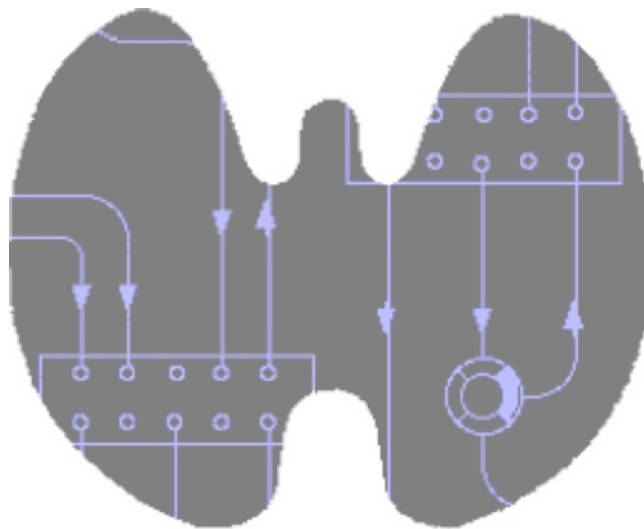


# SimThyr 3.3

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## Handbook and Reference



Johannes W. Dietrich

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## Preface

Thyroid hormones act on virtually any cell in the organism. They play a central role in metabolic coordination and differentiation. 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 then 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 enabled by improved mathematical modelling methodology as well as 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, 10-13].

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

Software and additional documentation of SimThyr are available from <http://simthyr.sf.net>.

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## Introduction

SimThyr is a continuous simulator for pituitary-thyroid homeostasis. Pre-compiled Software is available for Mac OS X, Mac OS Classic and Windows. SimThyr was developed with Lazarus / Free Pascal (Mac OS X and Windows) or THINK Pascal (Mac OS Classic), respectively. Source code is provided for all supported platforms and may also be used in order to compile SimThyr for additional platforms.

## System Requirements

### *Mac OS X*

SimThyr 3.3 for Mac supports Mac OS X 10.4 or newer on systems with either Intel or PPC processors.

### *Windows*

SimThyr 3.3 for Windows has been developed for Windows XP and was successfully tested also on Windows 2000 and Windows 7.

### *Mac OS Classic*

Mac OS Classic is supported by the legacy version SimThyr 2.0 only.

### *Linux*

In order to use SimThyr on Linux please download the source code and compile it for your processor and operating system with Lazarus / Free Pascal.

## Installation

For installing the program on Mac computers, simply drag the application file from the zip or BinHex package to the desired location on your file system. SimThyr for Mac doesn't come with and doesn't require an installer.

The recommended way to install SimThyr on Windows-based computers is to use the provided installer. For special requirements, e.g. for installation on computers without administrative rights, a portable application is available, too. In order to install the portable version simply drag the application file from the archive to the desired location on your file system. You may also start SimThyr portable directly from a USB stick, a CD and even a web server (depending from the settings of your browser). This may have advantages e.g. for CBT labs and other computer resource centers.

On Linux, please download the source code and compile it for your processor and operating system with Lazarus / Free Pascal.

## Uninstalling SimThyr

Before uninstalling SimThyr make sure that the application is not running. Then follow the directions of your operating system to delete the application file (on most platforms this is performed by dragging the file representation to the trash can icon).

As required you may also want to delete scenarios and preferences files.

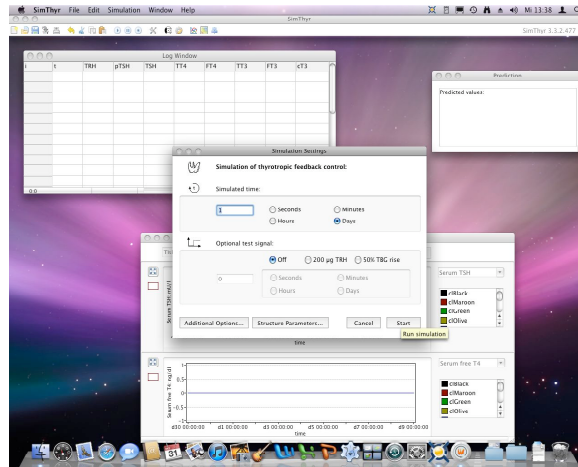
## Source Code

Source code is available from <http://sourceforge.net/projects/simthyr>. For compiling SimThyr from source please follow the directions given there.

## SimThyr Guided Tour

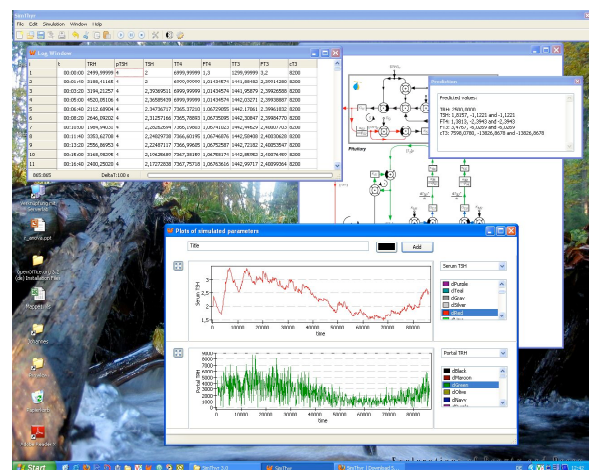
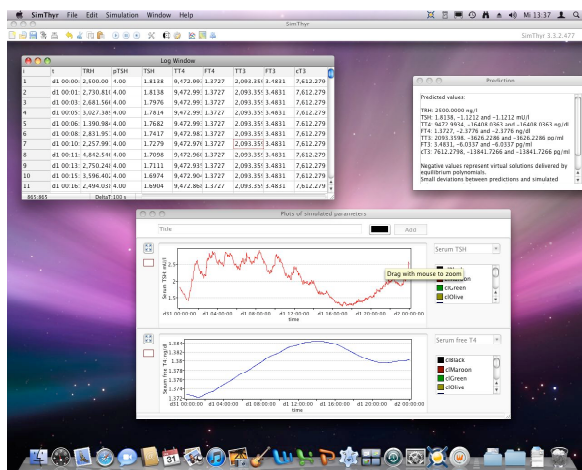
### Starting SimThyr

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.

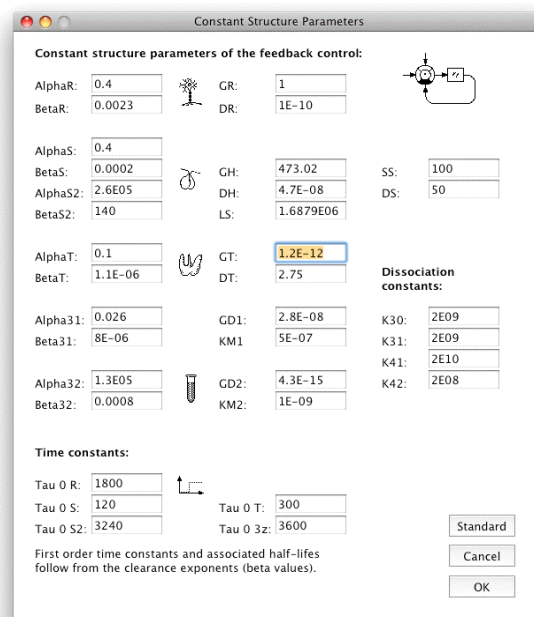
Small deviations from the depicted results above may ensue from simulated random effects.



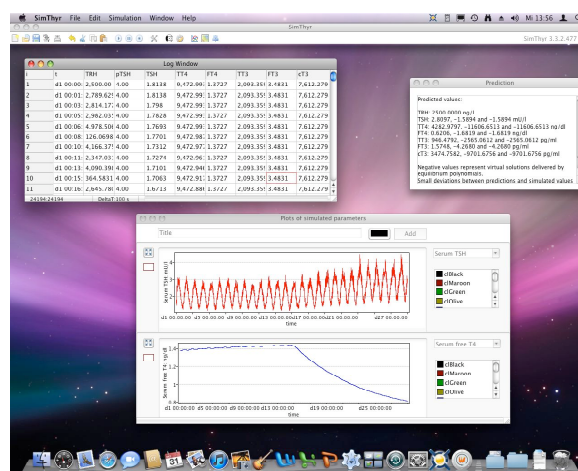


Now, let's develop subclinical hypothyroidism. In order to achieve this, click the start button again *without* hitting the stop button first. This will cause the subsequent simulation results to be appended to the previous results.

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.

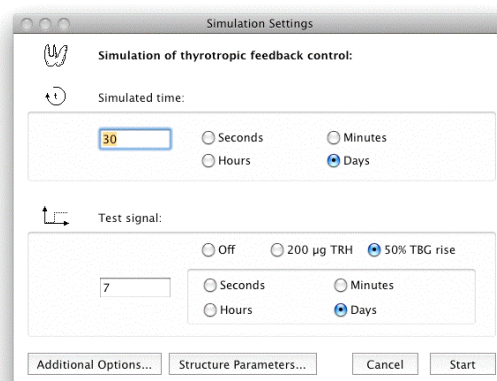
In the structure parameters window you may change virtually all constant structure parameters of thyroid homeostasis including volumes of distribution, time constants and dissociation constants. Useful starting points for experimentation may be sum activity of peripheral deiodinases (GD) and the secretory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

## Experiment 2

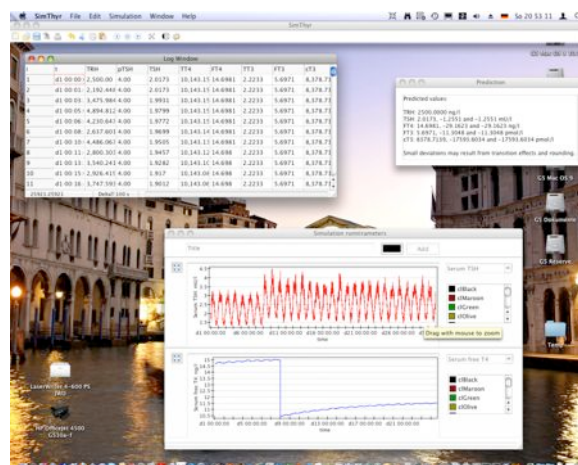
This simulates the effects of modifications in plasma proteins, e.g. in pregnancy or on contraceptive medication.

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.



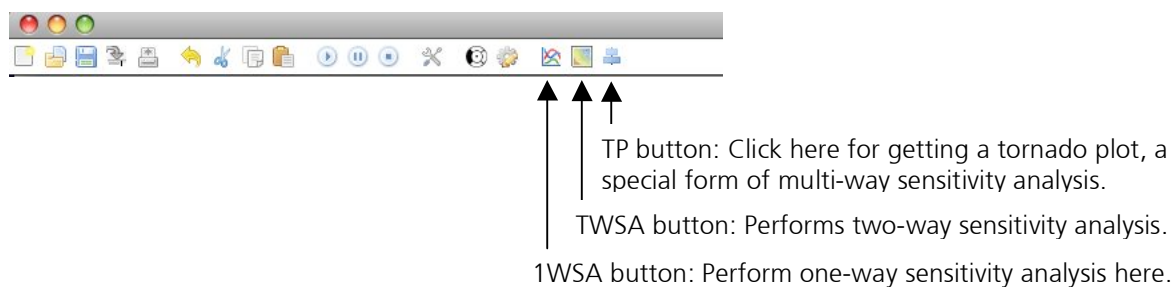
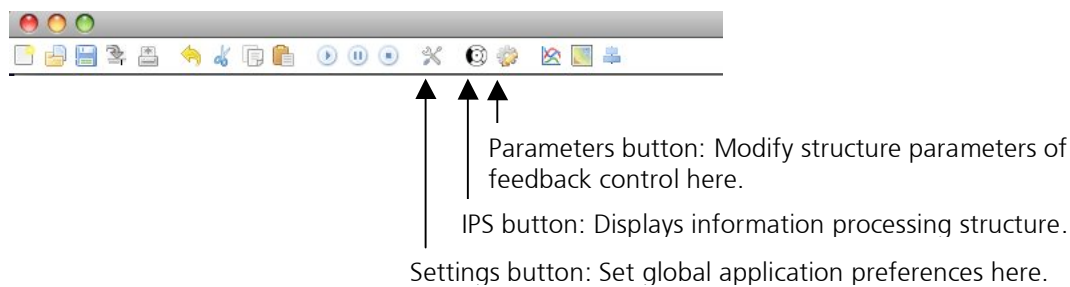
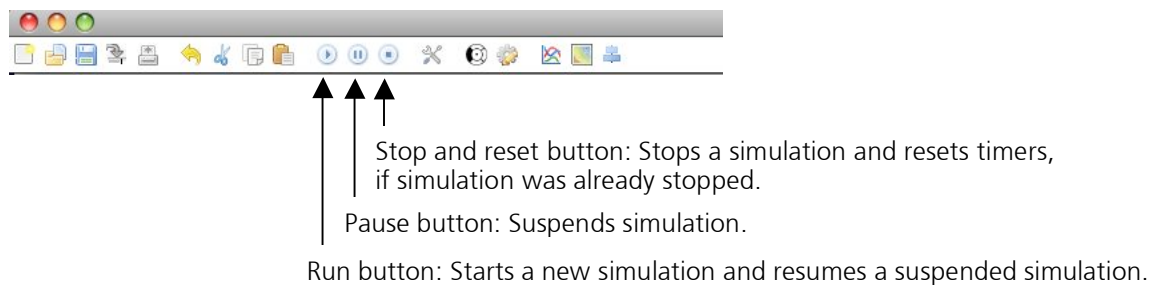
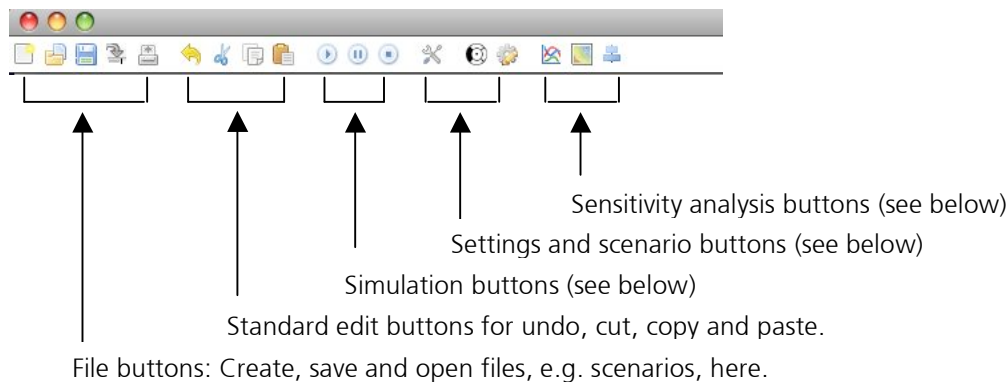
The results should be similar as depicted above, showing a decrease of FT4 levels in the beginning of the effect, than a short increase in TSH levels and a consecutive slight TSH decrease as FT4 rises in the achievement of a new equilibrium point.

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

## User Interface

### Toolbar

Most functions of SimThyr are accessible from the toolbar. If you move the mouse cursor to a button and leave it there for a second without clicking, a small tool tip is displayed explaining its function.



## Main Menu

Additional options are available from the main menu. It will look slightly different on Mac OS, Mac OS X, Windows and Linux. However, the principal functions are identical.



SimThyr menu: Application-wide options, e.g. Preferences and Services (Mac OS X only)

File menu: File- and scenario-wide options, e.g. for opening and saving files.

Edit menu: Standard editing options like cut, copy and paste.

Simulation menu: Options for starting, stopping and suspending simulations and for changing structure parameters.

Window menu: Select background or hidden windows here.

Help menu: Help and additional information.

## Scenarios

Simulation scenarios, e.g. containing a set of structure parameters in certain thyroid disorders, may be stored as XML files and reused. This may be a useful option for talks or educational purposes (SimThyr 3.0 or newer only).

Examples for useful scenarios are sets of structure parameters in certain thyroid disorders and influencing factors in some conditions like pregnancy or critical illness.

In order to save a scenario, select the entry **Save** from the **File** menu and make sure that the format **Scenario (XML)** is selected in the save dialog.

You can open and reuse an existing scenario by selecting **Open Scenario...** from the **File** menu.

## Sensitivity Analysis

In its essence, cybernetic modelling maps a system's structure onto its behaviour. This applies to both mathematical descriptions and simulation. A more methodical implementation of this approach is sensitivity analysis, a very powerful method in systems science.

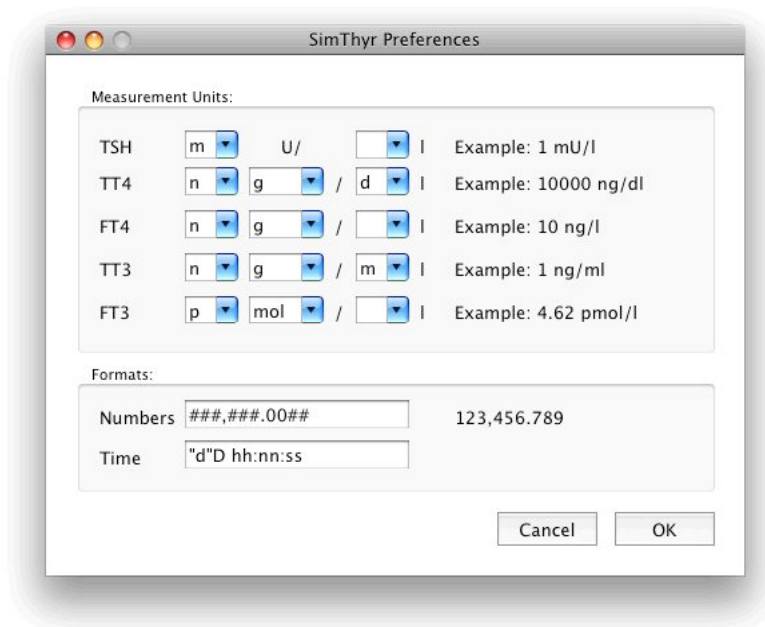
Sensitivity analysis systematically varies a structure parameter and investigates resulting behavioural variables. This helps to study the influence of certain marginal conditions on relevant output variables and to define factors that are critical for definite wanted (or unwanted) results. Additionally, this method allows assessing how the uncertainty of behavioural variables can be apportioned to different sources of uncertainty in model input.

Sensitivity analysis is available with SimThyr 3.1 (Hyperborea) and above, two-way sensitivity analysis was introduced with SimThyr 3.3 (Gaia).

One-way sensitivity analysis, two-way sensitivity analysis and tornado plots may be accessed from the **Simulation** menu. Usage should be self-explanatory. In both windows select independent structure parameters and dependent behavioural parameters (i.e. hormone levels). The resulting plots may be modified with respect to colour and (for one-way sensitivity analysis) for lower and upper boundaries of structure parameters.

## Preferences

Global application preferences allow for setting measurement units and number formats for all your simulations.



The flexible modular menu structure enables you to compose virtually every imaginable measurement unit. Your entry is parsed and automatically converted to correct conversion factors.

Number formats are also very flexible. You may specify Free Pascal - style format-strings to set the number of digits and type of notation:

**0**: Digit place holder. The digit of the corresponding place in the number will replace **0**, otherwise a missing digit is filled with **0**.

**#**: Digit place holder. A digit in the value will replace the corresponding **#**, a missing digit is replaced by a space.

**.**: Location of decimal separator

**,**: Location of thousands separator

**E+**, **e+**, **E-** and **e-**: Scientific notation. **#** signs after **E+** denote the number of places.

**;** Separates positive, negative and zero numbers, respectively.

*Examples:*

<code>###,###.00##:</code>	1,234.50
<code>#####.0:</code>	1234.5
<code>#.###E+:</code>	1.235E+5

Date formats may be specified with format strings, too:

D: day  
dd: day with leading zero  
h: hour  
n: minute  
s: second

*Examples:*

```
"d"D hh:nn:ss:           d1 03:31:40  
hh:nn "h":              03:31 h
```

## Supported File Formats

SimThyr supports export of simulation results in various formats including tab-delimited, CSV and DIF files. Both tab delimited and CSV are simple table formats, where columns (i.e. different simulated parameters) are separated by tabulator or comma signs and time points are delimited by carriage return or linefeed symbols (depending from platform conventions). DIF (data interchange format) is a standard for a neutral representation of contents that facilitates the transfer of data among various applications.

All of the mentioned formats are supported by a wide range of database, statistics and spreadsheet applications.

Plots may be saved in multiple varieties of image formats including bitmap (BMP), pixmap (XPM), portable pixmap (PPM), joint picture expert group (JPEG) format, tagged image file format (TIFF), portable network graphic (PNG) and, still experimentally in SimThyr 3.3, scalable vector graphic (SVG).

Scenarios and preferences are saved as XML files.



## Appendix

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## Contact

Dr. Johannes W. Dietrich, M.D., Bergmannsheil University Hospitals, Ruhr University of Bochum, Bürkle-de-la-Camp-Platz 1, D-44789 Bochum, NRW, Germany

<http://simthyr.sf.net>