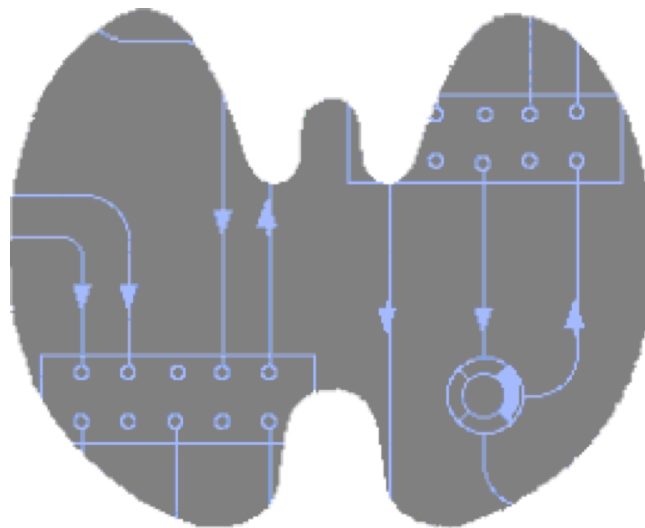


SimThyr 4.0

Handbook and Reference



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Preface

Thyroid hormones act on virtually any cell of the vertebrate 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 1936, only seven years after the discovery of the thyrotropic hormone TSH by Aron in the year 1929, Karl Fellingner suggested a negative feedback effect of thyroid hormones to thyrotropic cells of the pituitary [2]. W. T. Salter probably independently postulated the existence of a control loop linking the pituitary and thyroid gland in 1940. His 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 [3-6].

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, 7-11]. However, due to nonlinear interactions, none of these cybernetic models can 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.

One of the more popular simulation programs for the pituitary thyroid feedback control is SimThyr. Based on a parametrically isomorphic model of the overall system [1, 12-15] SimThyr looks back on more than 20 years of continued development and a plethora of publications cited in PubMed and Web of Science [11-16]. Today, SimThyr is a user-friendly “virtual thyroid” program for modern desktop and server operating systems. Applications of SimThyr cover research, including development of hypotheses, and education of students in biology and medicine, nurses and patients.

Software, source code 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 macOS (Mac OS X), Mac OS Classic, Windows and ReactOS, but it can also be compiled for popular Linux distributions. SimThyr was developed with Lazarus / Free Pascal (macOS, Linux, Windows and ReactOS) 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

macOS / Mac OS X

SimThyr 4.0 for Mac supports Mac OS X 10.4 (Tiger) or newer on systems with either Intel or PPC processors.

Windows

SimThyr 4.0 for Windows has been developed for Windows XP and was successfully tested also on Windows 2000, Windows 7, Windows 10 and ReactOS.

Mac OS Classic

Mac OS Classic (6.0.7 or newer) 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 disk image 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 on the settings of your browser). This may have advantages e.g. for CBT labs and other computer resource centres.

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 can be easily done by dragging the file representation to the trash can icon).

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

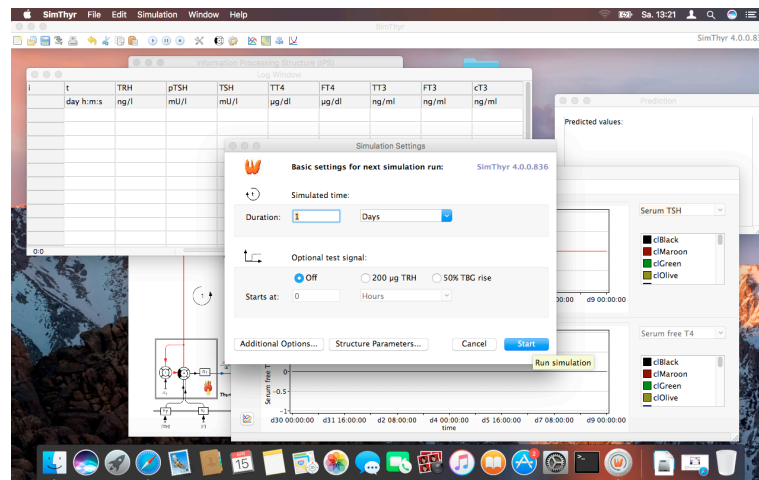
Source Code

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

SimThyr Guided Tour

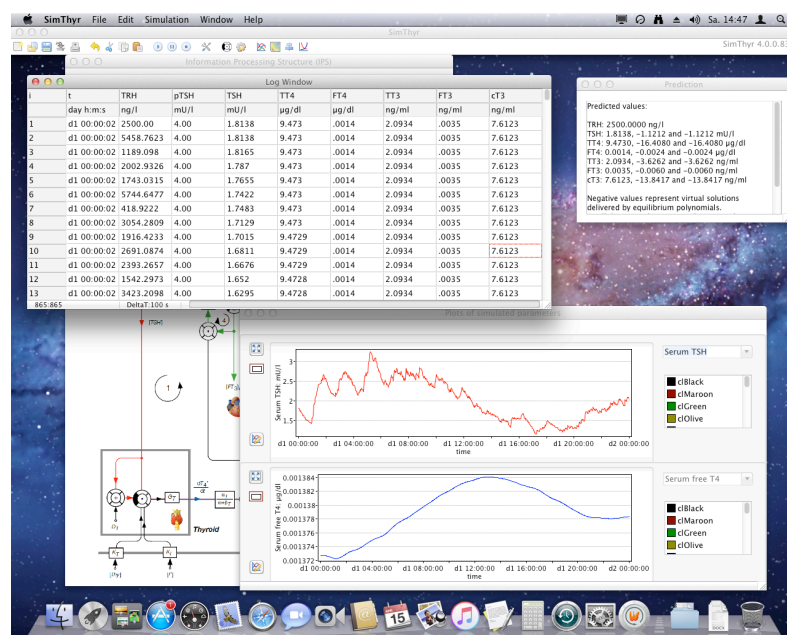
Starting SimThyr

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 run 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 as time series. 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.

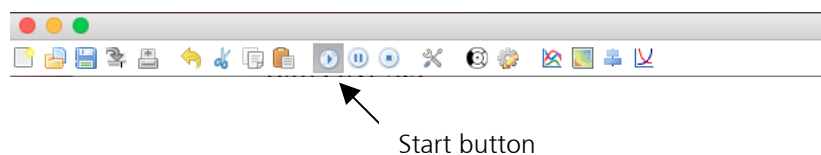
Experiment 1

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

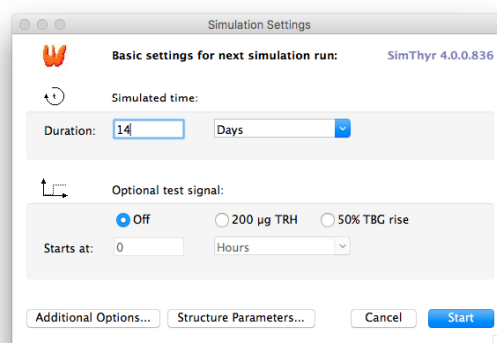
In order to do this, first click the stop and reset button in the toolbar:



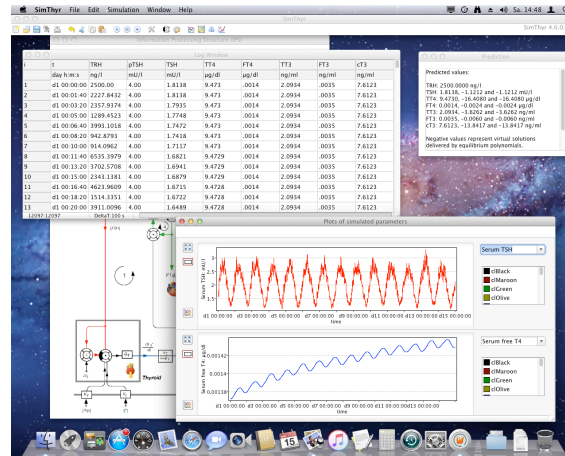
This will delete all simulated values and set the time to zero. Then, start a new simulation over 14 days. Press the start button:



and enter 14 days in the simulation settings dialog:



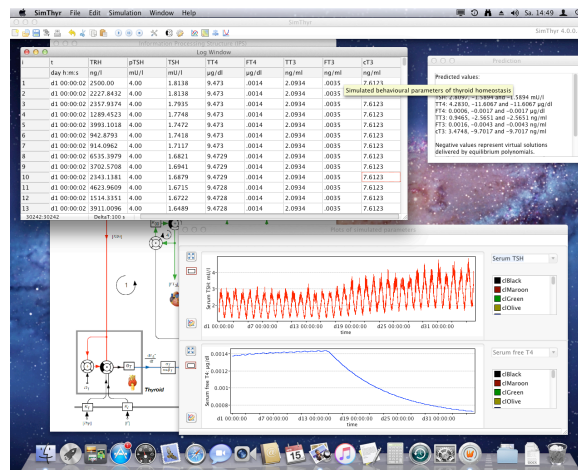
After clicking “Start” you will obtain the result of 14 days in normal conditions that may be similar but not necessarily identical as depicted below.



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. Rather click 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.

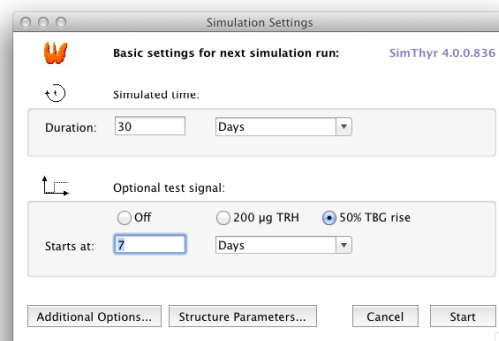
In the structure parameters window you may change virtually every constant structure parameter of thyroid homeostasis including volumes of distribution, time constants and dissociation constants. Useful starting points for experimentation may be the sum activity of peripheral deiodinases (GD) and the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

Experiment 2

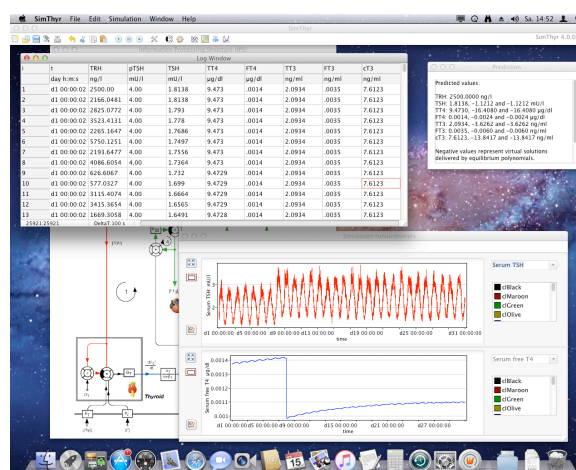
This simulates the effects of modifications in plasma proteins, e.g. in pregnancy or on contraceptive medication.

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 the radio box titled 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.



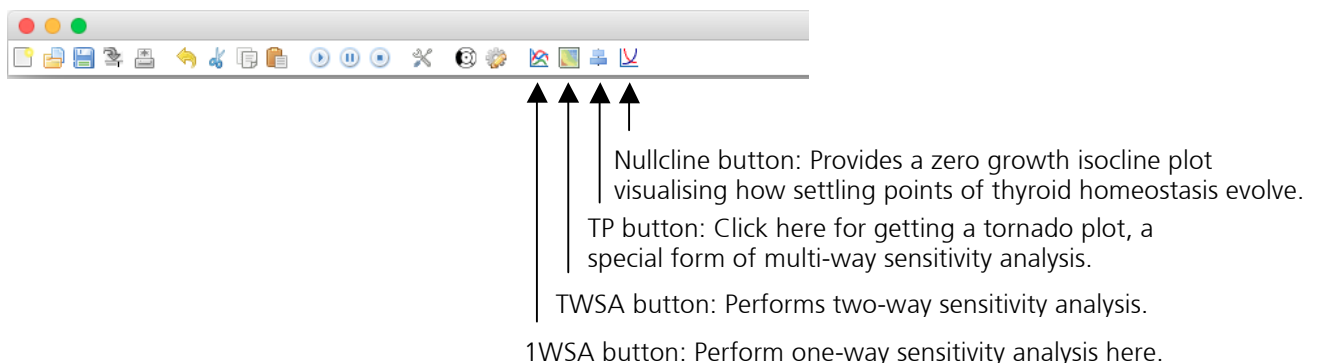
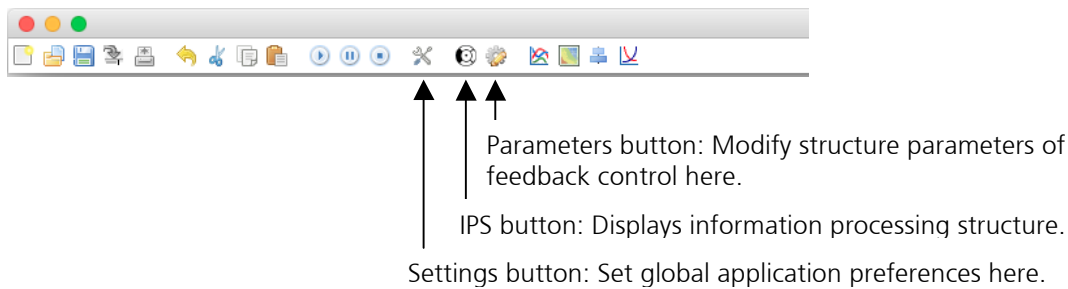
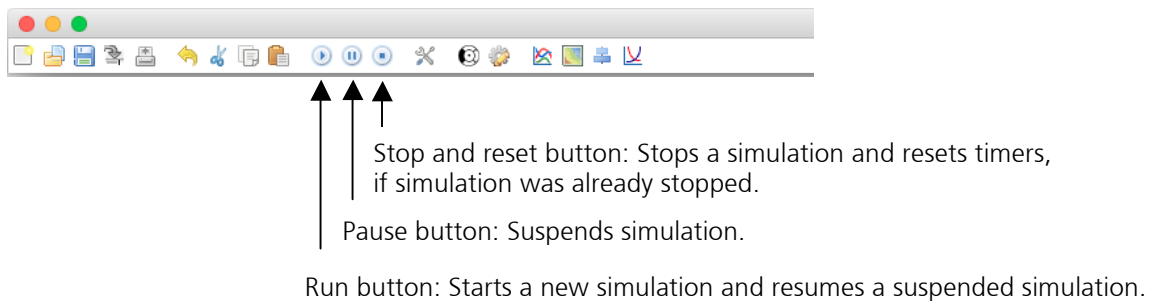
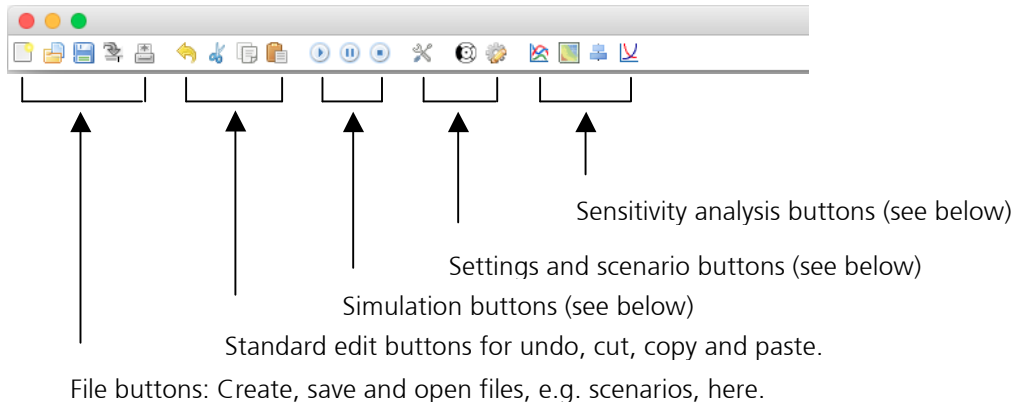
The results should be similar as depicted above, showing a decrease of FT4 levels in the beginning of the effect, than a short increase in TSH levels and a consecutive slight TSH decrease as FT4 rises in the achievement of a new equilibrium point.

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: Standardised editing options like cut, copy and paste.

Simulation menu: Options for starting, stopping and suspending simulations as well as for changing structure parameters and for editing model annotations.

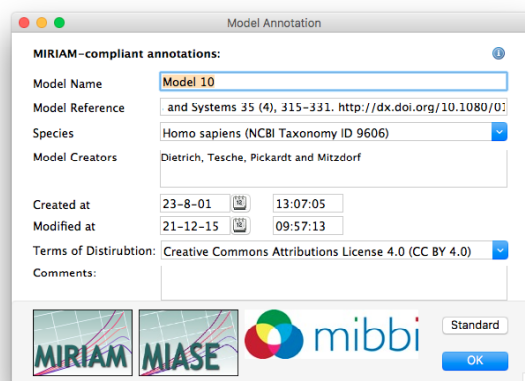
Window menu: Select background or hidden windows here.

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

Saved scenarios are also an excellent medium to make *in-silico* experiments better reproducible. An increasing number of journals requires submission of open scientific data as a supplement to submitted manuscripts. SimThyr supports this endeavour by delivering the foundations of a simulation experiment in form of an XML file, which is readable by both humans and machines. In order to make the files compliant to MIRIAM and MIASE statements, the required information may be entered in the model annotations window.



The screenshot shows a 'Model Annotation' dialog box. It has a title bar with standard window controls. The main area is titled 'MIRIAM-compliant annotations:' and contains several input fields: 'Model Name' with the text 'Model 10'; 'Model Reference' with a URL; 'Species' with a dropdown menu showing 'Homo sapiens (NCBI Taxonomy ID 9606)'; 'Model Creators' with the text 'Dietrich, Tesche, Pickardt and Mitzdorf'; 'Created at' and 'Modified at' with date and time pickers; 'Terms of Distribution' with a dropdown menu showing 'Creative Commons Attributions License 4.0 (CC BY 4.0)'; and a 'Comments:' text area. At the bottom, there are logos for 'MIRIAM', 'MIASE', and 'mibbi', a 'Standard' button, and an 'OK' button.

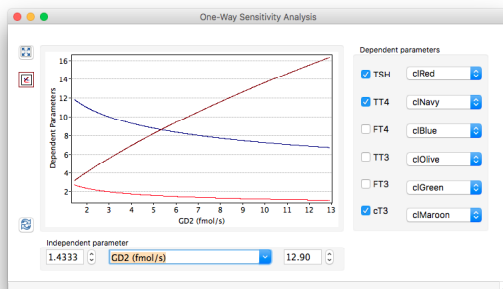
Save a scenario by selecting the entry Save from the File menu and make sure that the format Scenario (XML) is selected in the save dialog.

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

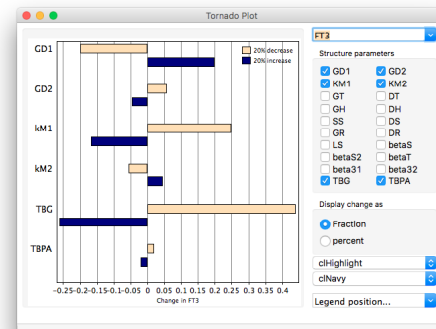
Sensitivity Analysis

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.

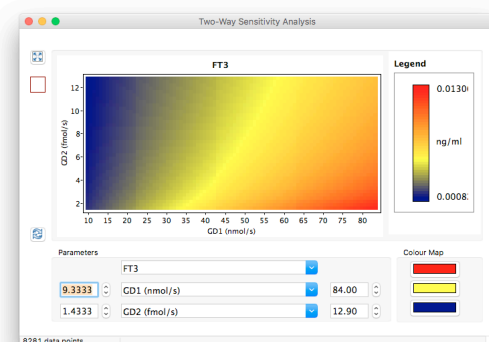
Sensitivity analysis systematically varies a structure parameter and investigates resulting behavioural variables. This helps to study the influence of certain marginal conditions on relevant output variables and to define factors that are critical for definite wanted (or unwanted) results. Additionally,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



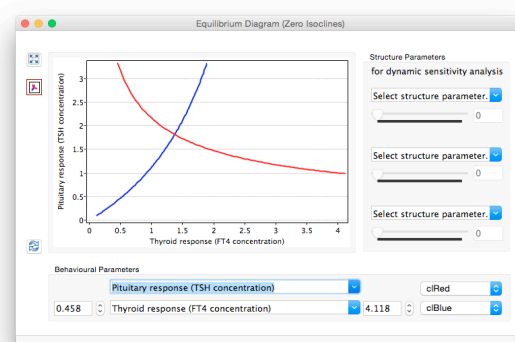
One-way sensitivity analysis



Tornado Plot



Two-way sensitivity analysis



Zero growth isocline plot

One-way sensitivity analysis, two-way sensitivity analysis, tornado plots and nullcline plots (equilibrium diagrams) may be accessed from the Simulation menu. Usage should be self-explanatory. In any case of classical sensitivity analysis select independent structure parameter(s) and dependent behavioural parameter(s) (i.e. hormone levels). In null isocline plots select two hormones, whose interaction is of interest. The resulting plots may be modified with

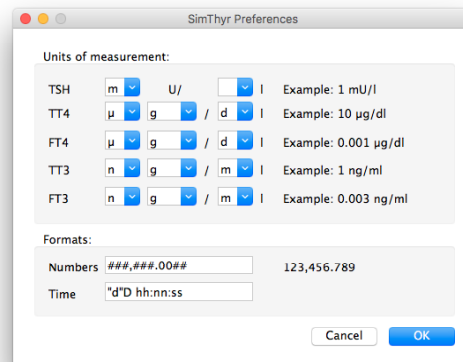
respect to colour and (for one-way and two-way sensitivity analysis) for lower and upper boundaries of structure parameters.

Table 1: Forms of sensitivity analysis provided by SimThyr

Form of sensitivity analysis	Kind of relation	Comments
One-way	Multivariate (one independent and n dependent variables)	Maps selected hormone concentrations to one structure parameter of feedback loop.
Two-way	Bivariable (two independent and one dependent variables)	Maps a selected hormone concentration to two structure parameters of feedback loop...
Tornado plot	Multivariable (n independent and one dependent variables)	Maps a selected hormone concentration to an arbitrary number of structure parameters.
Nullcline plot	Bivariable and bivariate	Maps the interaction of two hormone concentrations to visualise the evolution of an equilibrium point. Also referred to as interaction plot, null isocline plot or zero growth isocline plot.

Preferences

Global application preferences allow for setting units of measurement 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:

###,###.00##:	1,234.50
#####.0:	1234.5
#.###E+:	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 points in time are delimited by carriage return or linefeed symbols (depending on 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, with some restrictions, scalable vector graphic (SVG).

Scenarios and preferences are saved as XML files.

Appendix

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