Title
THYROSIM: A Web Application for Human Thyroid System Regulation Education and Research

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THYROSIM: A Web Application for Human Thyroid System Regulation Education and Research

A thesis submitted in partial satisfaction

of the requirements for the degree Master of Science

in Biomedical Engineering

by

Simon Xian He Han

2013

ABSTRACT OF THE THESIS

THYROSIM: A Web Application for Human

Thyroid System Regulation Education and Research

by

Simon Xian He Han

Master of Science in Biomedical Engineering

University of California, Los Angeles, 2013

Professor Joseph J. DiStefano III, Chair

Computer simulation tools for education and research are making increasingly effective use of the internet. To facilitate these activities in neuroendocrinology, we implemented a sophisticated and well-validated simulator of the dynamics of human thyroid hormone and thyrotropin regulation as a web-based application. A major goal was to accommodate access to this tool from virtually anywhere, on modern handheld devices as well as desktop computers and laptops. Development was done using well-established open source software components that together provide a simple and intuitive user interface platform for doing simulated "what-if" experiments. User-selectable "experimental" test-input stimuli (oral, IV-pulse, IV-infusion inputs) are represented by animated graphical icons. Familiar graphs of simulated time-dependent T_3, T_4 and TSH dynamic responses are provided on the same interface. Various disease states, e.g. hypo- and hyperthyroidism and malabsorption, are simulated by optionally changing thyroid gland secretion rates and gut absorption rates. To facilitate comparative analysis, two sets of simulated experimental results can be superimposed on the same graph.

The thesis of Simon Xian He Han is approved.

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University of California, Los Angeles

2013

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Introduction

Thyroid hormones (TH) triiodothyronine (T_3) and thyroxine (T_4) are secreted by the thyroid gland and their concentrations in blood and tissue are regulated by the pituitary gland and hypothalamus in the brain - a negative feedback system called the hypothalamic-pituitary-thyroid (HPT) axis. The hypothalamus produces thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary to produce thyroid-stimulating hormone (TSH), which stimulates the thyroid to secrete T_3 and T_4. The hypothalamus and pituitary detect increases (decreases) in T_3 or T_4 and in turn decrease (increase) TRH and TSH (1). An underactive thyroid results in hypothyroidism and an overactive one results in hyperthyroidism, two serious endocrine disorders with broad consequences on metabolism and growth (2,3).

Our laboratory has previously developed and implemented a sophisticated model of human thyroid hormone (TH) regulation in blood, tissues and the hypothalamo-pituitary-thyroid axis and validated it for several normal and abnormal conditions in adults and children (4-7). The model structure was built based on known physiological and biochemical knowledge, and where possible, parameters were based on previously published works. Certain simplification was achieved through aggregating components that cannot be further deduced because of lack of data. Ultimately, unknown variables and model validity were determined through fitting existing TH clinical data. Assumptions made in the development of the model are summarized in Table 1. In its earlier form, the model consisted of a TH submodel that dealt with hormone binding, distribution, interconversion and elimination (D&E for short), a TH secretion submodel, a gut submodel that was concerned with absorption of exogenous TH and later was refined to also incorporate dynamics in the brain and pituitary. The model was used in a variety of simulated bioequivalence and treatment studies.

Table 1. Summary of assumptions in model development.

Assumption	Ref.
Conversion from T_4 to T_3 in fast tissue is all through deiodinase type 1 (D1). Conversion from T_4 to T_3 in slow tissue is 20% through D1 and 80% through deiodinase type 2.	(4)
Ultradian, 1-2 hours TSH oscillations are not significant for TH signals downstream.	(5)
TH secretion after thyroidectomy is zero.	(7)
TH given orally exists in the gut in two possible states: solid (undissolved) and aqueous (dissolved).	(8)
Dissolution in the gut is complete and only aqueous TH can be excreted.	(8)

This moderately complex model is represented by 25 ordinary differential equations (ODEs), 9 additional equations describing various terms in the ODEs, 3 output equations and more than 50 parameters (9). Working numerically with it normally requires higher-level mathematical expertise. In this paper, we describe an internet-accessible simulation platform (web application) for interacting with and experimenting with this model, using only pictures, graphs and familiar biological science language and quantitative ideas – no higher math. It's designed as a tool for research and teaching – including patient education – on the dynamical regulation of this multi-feedback system in health and disease.

THYROSIM has a scientific-user-friendly animated cartoon interface from which various normal and abnormal thyroid states – including hypo- and hyperthyroidism and malabsorption – can be explored interactively and dynamically by adjusting T_3 and T_4 secretion and absorption rates. T_3, T_4 and TSH temporal dynamics are illustrated graphically in response to a variety of simulated what-if experimental inputs, including oral, IV-pulse and IV-infusion hormone treatment options. For easy comparisons, the interface includes facility for superimposing two sets of simulation results – a key enhancement for what-if experimentation.

The THYROSIM web application is implemented as a worldwide web application, available via a variety of web browsers. These include Google Chrome, Mozilla Firefox, Apple Safari and Amazon Silk (10-13), making THYROSIM available on a variety of handheld devices (iPhone, iPad, Android, Kindle etc) as well as laptop and desktop computers. It is accessible on our website at: http://biocyb1.cs.ucla.edu/thyrosim/.

Methods

Web Client-Server Implementation and Interactions

In distinction with applications that run independently on a single computer, different components of web application THYROSIM are distributed over two computers: the client-user machine – via the client browser – and on a remotely located server accessible only via the client browser, where the actual simulation computations are run. Interaction among the different open-source application software components listed in Table 2 is summarized in the Figure 1 flowchart – illustrating what runs where and how components communicate.

To begin a simulated experiment, users enter input simulation experiment conditions into their (client) web browser. User (client) input is validated and the web application on the client machine alerts the user to make corrections, if needed, or requests the server to begin simulating the model-experiment. A program on the server parses the input from the client and generates commands to execute the model solver on the server. When simulation is complete, results are sent back to the browser and graphed on the user interface screen.

Table 2. Software components used in programming and hosting the web application

Component	Version	Description	Ref.
Client-side			
HTML		Markup language for writing web pages.	www.w3.org/TR/html401/
CSS		Style sheet language *that* describes the visual representation of HTML.	www.w3.org/TR/CSS2/
JavaScript (JS)		Language for dynamic content, such as adding or deleting inputs.	www.w3schools.com/jsref/
jQuery	1.9.1	JS library that simplifies programming in JS.	jquery.com
jQuery UI	1.10.1	JS library for user interface interactions, such as scrollbars.	jqueryui.com
Protovis	3.3.1	JS library for graphing.	mbostock.github.io/protovis/docs/
Ajax		Protocol for sending user-input asynchronously to the server and receive calculation results.	www.adaptivepath.com/ideas/ajax-new-approach-web-applications
JSON		Data format used to transfer calculation results between the server and browser.	tools.ietf.org/html/rfc4627
Server-side			
Linux OS	Ubuntu 12.04 LTS	Operating system on the server.	help.ubuntu.com/12.04/
Apache HTTP Server	2.2.22	Web server software that delivers the web page to the user.	httpd.apache.org/docs/2.2/index.html
Perl	5.14.2	Language used to process user-inputs, execute the ODE solver, receive solver results, convert results to display units and send results back to the browser.	www.perl.org/about.html
JSON::Syck	1.21	Perl package (library) to convert Perl data structures to JSON.	search.cpan.org/~toddr/YAML-Syck-

			1.27/lib/JSON/Syck.pm
CGI	3.52	Perl package that handles HTTP requests.	perldoc.perl.org/CGI.html
CPAN	1.57	Perl package repository where the above mentioned packages are retrieved.	www.cpan.org
Octave	3.2.4	Language for numerical computations.	www.gnu.org/software/octave/
odepkg	0.8.2	Octave plugin for solving ODEs.	octave.sourceforge.net/odepkg/

HTML, CSS and JavaScript are browser-dependent and version numbers are omitted. Ajax and JSON do not have version numbers.

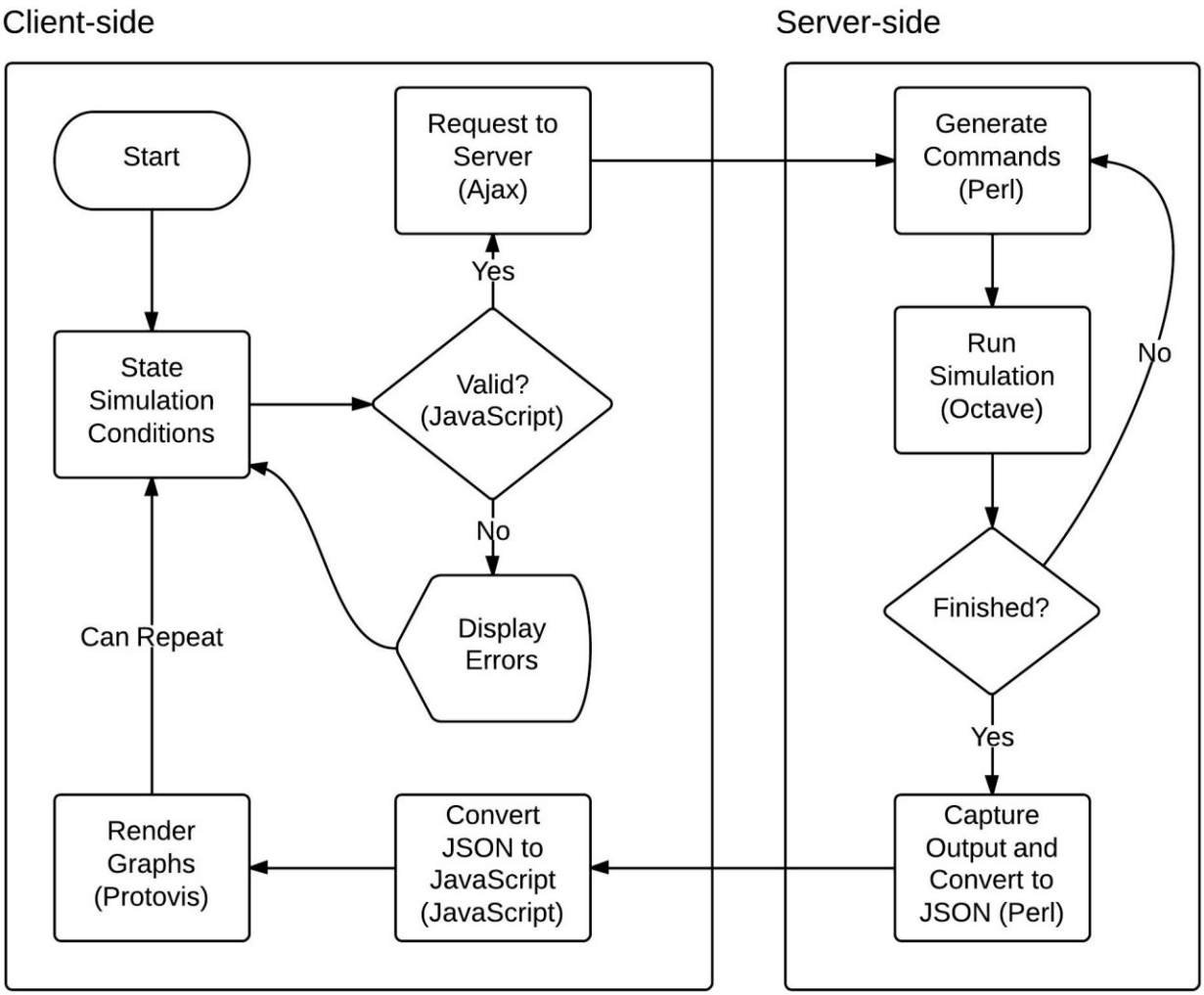

FIG. 1. Flowchart of the simulation process.

Model-Simulation Implementation

The model differential equations (ODEs) are solved numerically using the freely available ODE solver OCTAVE (14). Computations are done in molar units and hormonal output results are converted to μg/L or mU/L for T_4, T_3 and TSH time-course plotting. Euthyroid (default) conditions are defined as 100% (T_4 secretion), 88% (T_4 absorption), 100% (T_3 secretion) and 88% (T_3 absorption) (4,5) and simulation initial conditions (ICs) are precomputed to quicken the numerical solution process. When T_4/T_3 secretion/absorption values are changed, the dynamics of the system are different and default behavior is to recalculate ICs, although the user has the option to use euthyroid values. This is often useful for simulating a change in a patient condition, e.g. for simulating hormone dynamics after thyroidectomy. If no exogenous inputs are given, simulation is simply extended to the user-set simulation time.

Implementation of Exogenous Inputs

THYROSIM allows single or multiple exogenous inputs at user-specified doses and times. Added inputs (e.g., T_4 or T_3 doses) are arranged in chronological order based on these times. The simulation is then partitioned into intervals using these times as boundaries. ICs for each interval are adjusted by the amount of exogenous input at the specific time point and each interval is then executed as a separate simulation increment. For IV-infusion inputs, the end point is also used as a boundary. Results from each interval are aggregated and all are displayed as a continuum and as a single experimental outcome – on graphs of T_4, T_3 and TSH dynamic responses, as described below.

User Interface

A screenshot of the user interface (UI) is shown in Figure 2. The top-left is where exogenous T_3 and T_4 inputs are specified. Each TH has an oral input (pill icon), IV-pulse (syringe icon) and IV-infusion (IV bag icon). Inputs are color coded (T_3 is blue and T_4 is green)

so they are easily differentiated from each other. Oral inputs, by default, require dose, dosing interval, start day and end day values. An IV-pulse input requires dose and start day. IV-infusion inputs require dose, start day and end day values.

The cartoon image represents the whole-body and negative feedback system components, including absorption through the gut. When an input is added, an appropriate animation is shown.

The top-right contains graph placeholders. T_4, T_3 and TSH are in separate graphs because of differences in unit scale and dynamics can be better visualized. When hovering the mouse over graphed results, a label containing the numerical value of the nearest point is shown. The label typically shows up to the right-hand side of the cursor, but changes location to prevent running into the border of the graph.

Controls for T_4/T_3 secretion/absorption rate changes are located beneath the center image. These can be adjusted to simulate disease states, by changing these values directly or via scrollbars – by clicking on the orange-white "+".

Simulation time and pill quantity and frequency adjustments are made further down on the interface, populated as users adds inputs. Controls for deleting, enabling and disabling inputs are also provided.

Users select the color of the line used to plot results. Two color options are presented (default blue) and users can switch between them to plot two sets of results on the same graph, for comparison purposes.

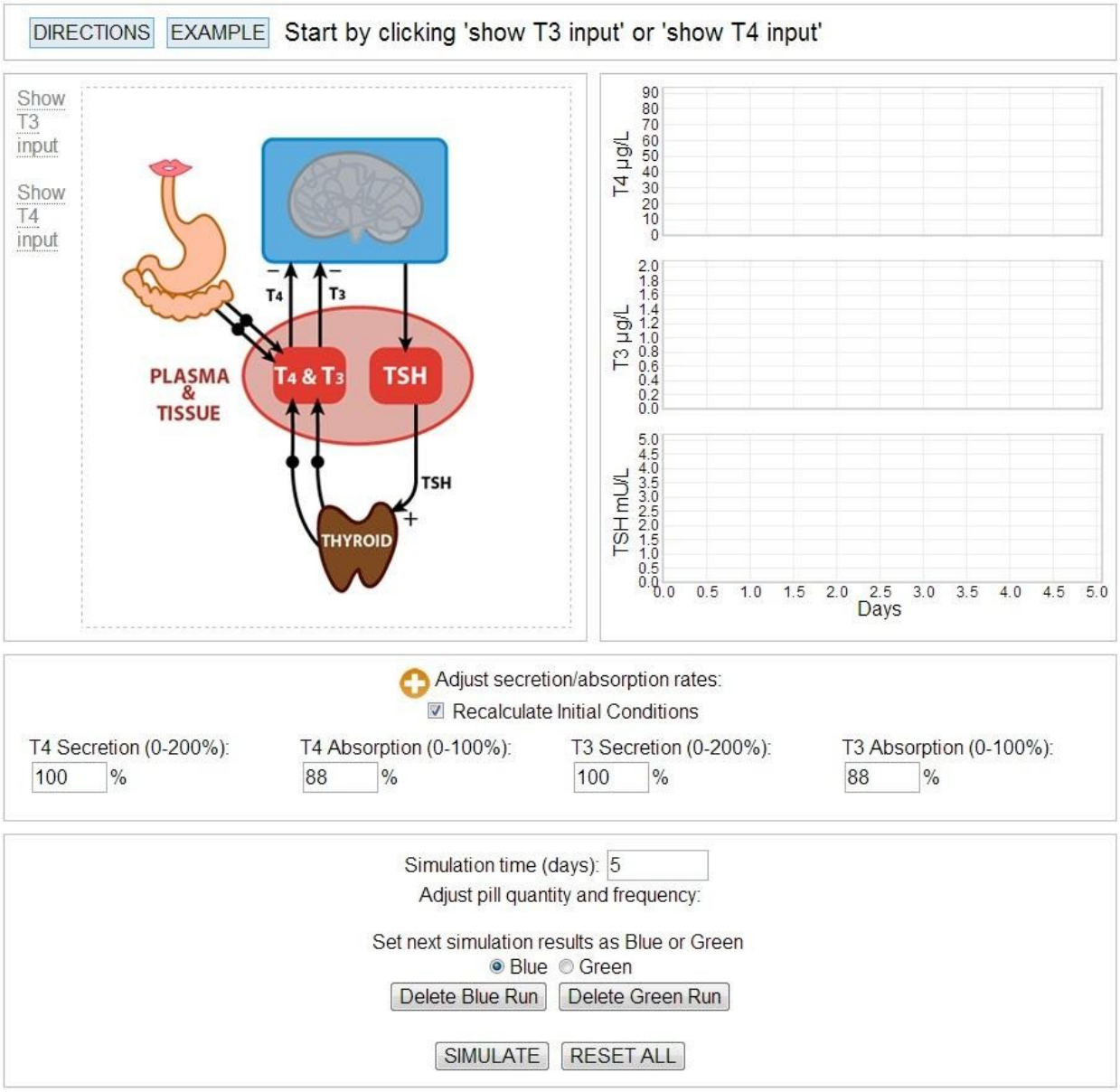

FIG. 2. Screenshot of the web application.

Usage and Sample Results

Directions for Usage

These are shown in Figure 3. In Figure 4, hovering the mouse over 'EXAMPLE' and clicking 'RUN' shows normal steady state T_4, T_3 (TH) and TSH temporal response simulated to 5 days. TH secretion rates and absorption rates can be changed and inputs (oral, IV-pulse and IV-infusion) can be added or removed to explore responses to different experimental inputs.

Simulation time can be extended to a maximum of 100 days. As noted earlier, when TH secretion or absorption are changed from default values, ICs are readjusted. However, if desired, users can uncheck “Recalculate Initial Conditions” to start the simulation with euthyroid ICs.

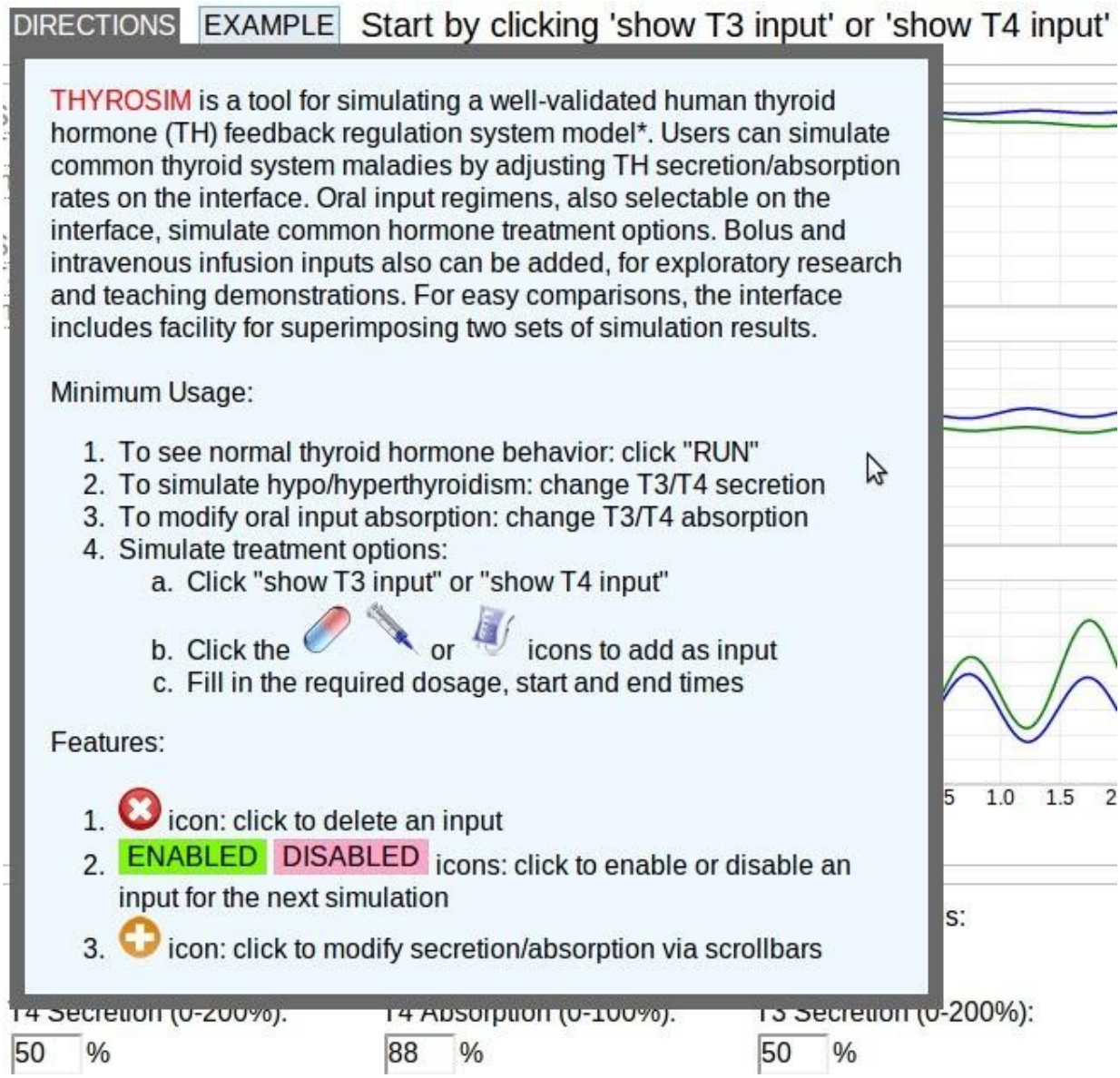

FIG. 3. Screenshot of directions.

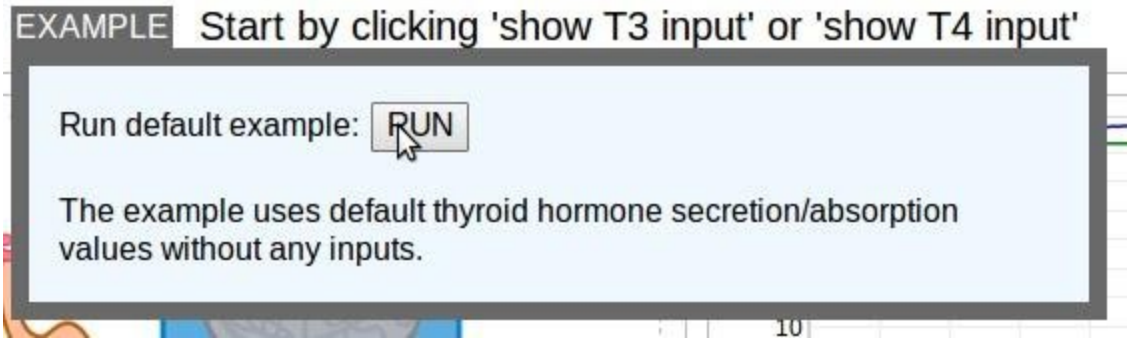

FIG. 4. Screenshot showing the example run button.

Examples

Results of two what-if experiments are shown in Figure 5. The blue line shows euthyroid responses simulated to 5 days (x-axis). TH secretion rates were then both adjusted to 50%, with results shown in green. "Recalculate Initial Conditions" was unchecked for the hypothyroid condition, so both sets of results used euthyroid ICs; the experimental goal was to observe the dynamical responses following sudden hemi-thyroidectomy.

The graphs display T_4, T_3 and TSH, dynamical responses to the experiment in three separate graphs. In the T_4 graph, the blue line shows small oscillations. The green line decreases at first, but stabilizes by the 2nd day. T_3 shows similar behavior, but T_3 levels continue to approach the blue SS line slowly. For TSH, the blue oscillations are stable whereas the green ones show bigger oscillations with a bigger mean value. Oscillations here also appear to be stable by the 3rd day. Hormone concentration values continue to change slowly until steady state is reached (4-7).

This hypothyroid experiment can be extended with other what-if conditions. For example, a user can explore different T_4 and/or T_3 dosages that might be given orally to reestablish euthyroid conditions over different time intervals.

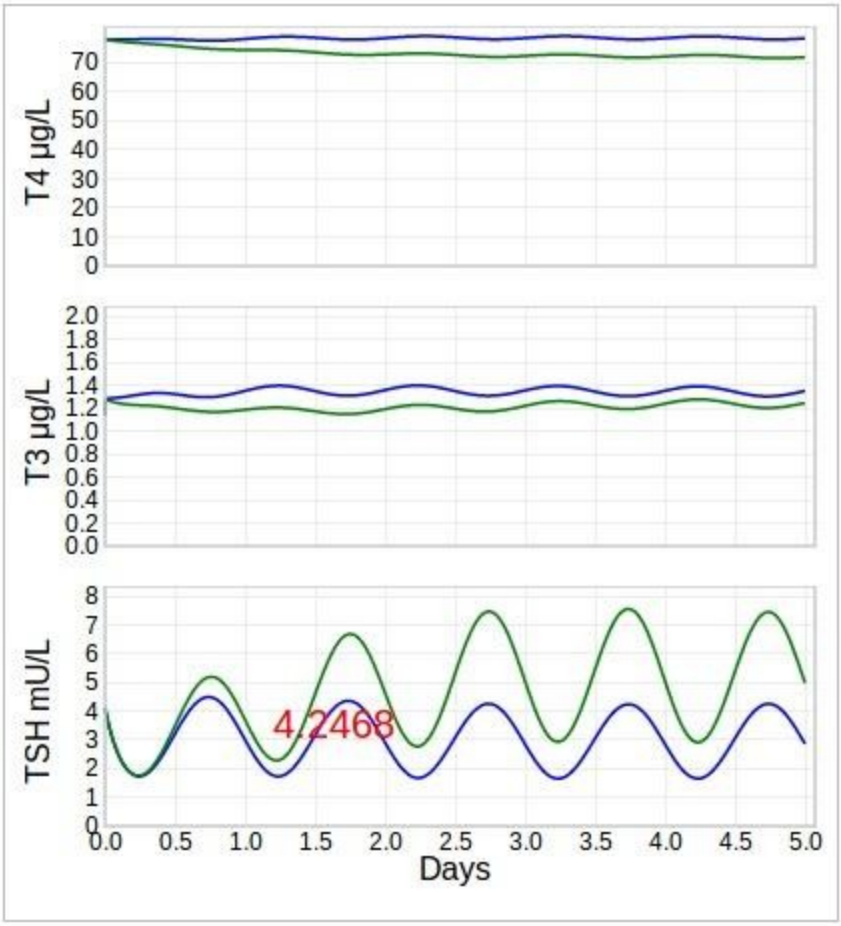

FIG. 5. Comparison of two experimental simulations. The blue line represents euthyroid conditions and the green line represents hypothyroidism with T_4 and T_3 secretion set to 50%. The number in red appears as the dynamic location of the value on the graph where users can hover the mouse.

Model Qualification

Comparison between model results and simulator results are shown in Figure 6. The model results were fitted to clinical data with patients given oral dosages of levothyroxine (L-T_4) at day 1 in 400, 450 and 600 µg in a, c and e respectively. To validate these results, the simulator was set to the same conditions. While units are different, the scales shown are equivalent (120 hours = 5 days, 8 µ/dL = 80 µg/L). As expected, T_4 levels jump when L-T_4 is given and then slowly heads toward SS. Figure 6 shows model results and simulator results match well.

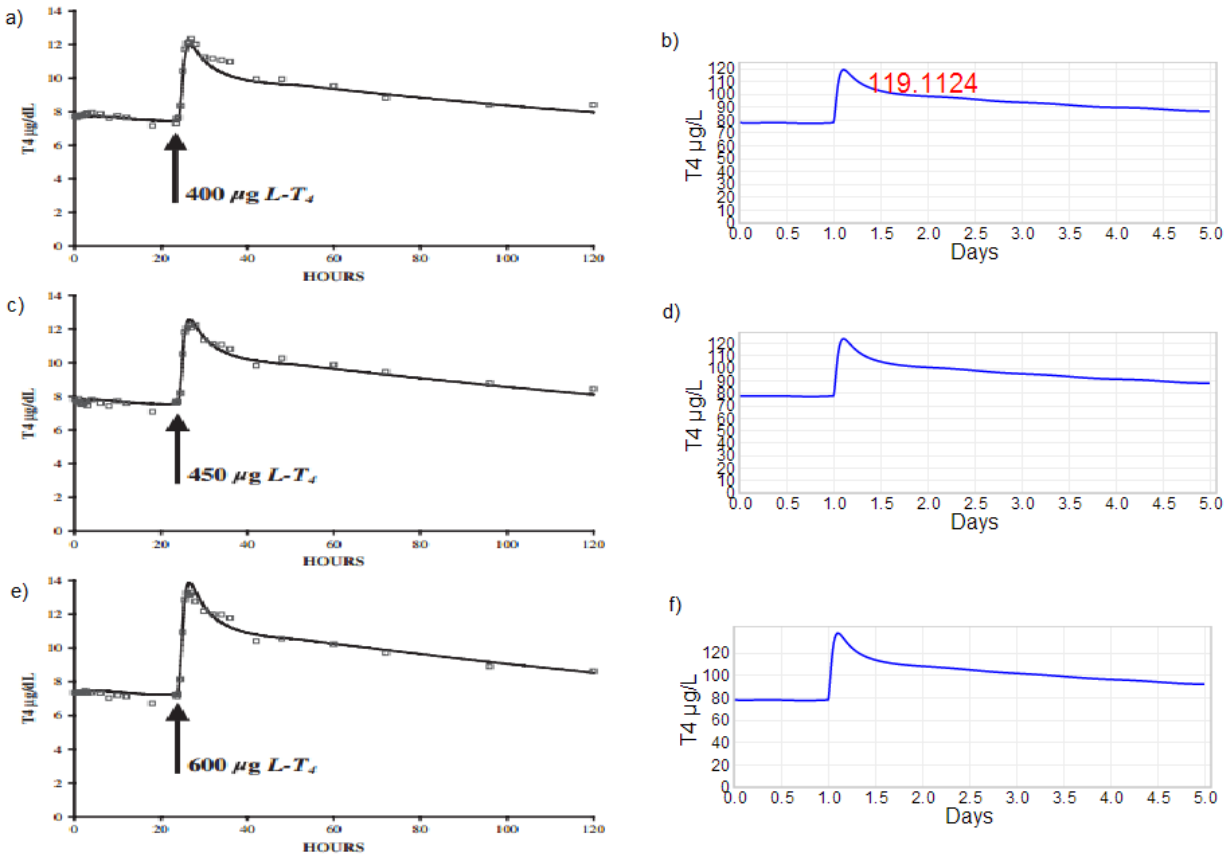

FIG. 6. Comparison between T_4 model results and simulator results. Results are for L-T_4 given at day 1 in different amounts: a,b) 400 μg, c,d) 450 μg and e,f) 600 μg. Figures a, c and e are adapted from Eisenberg 2008 (5). Simulator and model results correlate well.

Portable SBML Simulation Model Provided

SBML (Systems Biology Markup Language) is a portable programming format for representing computational models in a common language (15,16). To give others the opportunity for working with, modifying or extending this simulation model on their own computers, we have provided the basic model – without the web interface – as SBML code – downloadable freely from our website: *http://biocyb1.cs.ucla.edu/thyrosim/sbml/thyrosim.xml*. This model can be read and run in many popular software, including Matlab (17) and COPASI (18).

Discussion

We have created an intuitive and friendly user interface for a sophisticated TH feedback regulation simulator, functioning as a freely accessible web application, for use by anyone with an internet connection. THYROSIM has the basic tools to set up numerous what-if simulation experiments – useful primarily for better understanding and teaching human thyroid hormone regulation. Users can simulate oral dosing, IV-pulse and IV-infusion inputs, or combinations thereof, with options to delete, edit or temporarily disable/enable any input. Oral hormone inputs can be simulated as either single doses, or daily doses of T_4, and/or T_3, etc, simulating typical therapeutic dosing regimens. Simulation of disease state and abnormal conditions are accomplished by simply adjusting percentages of TH secretion (0-200%) and gut absorption (0-100%), e.g. secretion for completely thyroidectomized patients can be set to 0%. For these simulated patients, it is possible to see how thyroidectomy changes TH levels by not recalculating ICs and setting the simulation to start at euthyroid values. For simulated hypo/hyperthyroid patients, recalculating ICs would likely be preferred to setting them to start from euthyroid steady state conditions, since they might have been in their respective abnormal states for some time.

The comparison feature can be used to visually check predicted hormone dynamics in different thyroid states or under different treatment protocols. For example, the first run simulates euthyroid TH levels and the second run simulates a hypothyroid patient on a repeating oral dosing schedule. These controls provide broad flexibility in designing numerous what-if experiments – simulated studies that sharpen intuition as well as knowledge about neuroendocrine system dynamics.

SimThyr 3.2.2 (19) is a desktop application that also simulates TH dynamics. As a desktop application it lacks some of the inherent mobility of a web application. Dissimilar to

traditional desktop softwares, SimThyr comes with an executable that does not require installation. SimThyr has a more complex UI compared to THYROSIM, offering dozens of configurable parameters. The standard run is very easy to achieve (by pressing the start button), although the results are unexpected. Initial T_4 oscillates around 95 µg/L and falls toward 90 µg/L over a period of 25 days, indicating the default run does not start in SS. SimThyr offers artificial noise in the model input, but it does not appear to be well tuned because T_4 values drift towards 100 µg/L and not the 90 µg/L indicated in the standard run. To simulate hypo/hyperthyroidism, the correct parameter must be located among the many in the UI, potentially confusing to users. Overall, these results suggest the model behind SimThyr is not perfected and could use additional tuning, but the software does offer useful features such as data export and sensitivity analysis. However, one shortcoming is that SimThyr does not have the ability to simulate treatment options, limiting its role in research and education.

THYROSIM reproduces all experimental results published in the several papers that include the models on which it is based (4-7,9). It also has been (so far) briefly viewed by several endocrinologists, who found it easy to understand and consistent with their expectations in several simulated experimental runs. It is important to note that the data the model derives from are averages from their respective studies and cannot reflect physiological variations in individuals. The simulator should only be used to quantify general TH trends in adult populations and not in a clinical setting to guarantee any outcomes. In addition, basic understanding of endocrine function may be required to correctly interpret results. For example, while the simulator can simulate a completely thyroidectomized patient for prolonged period of time, such a case is certainly invalid in reality.

By distributing THYROSIM as a web application, we offer access to the widest possible audience. It's designed for use as a research and teaching tool, requiring minimal quantitative

skills. It can be useful as a patient education tool, as suggested by one endocrinologist who tried the application. Users only need a compatible browser and internet connection. It has been successfully tested with Google Chrome, Apple Safari, Amazon Silk and Mozilla Firefox browsers. It therefore is functional on handheld devices like the Google Android, Apple iPhone/iPad/iPod and Amazon Kindle – as well as laptop and desktop computers running any of these browsers. It does not currently work with the Microsoft Internet Explorer (IE) browser (20) because a particularly facile graphing component *Protovis* is not currently supported in IE (21).

Acknowledgments

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Appendix - SBML Code

```
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      <parameter id="u4" value="0" constant="true"/>
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              <ci> p6 </ci>
            </apply>
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   <apply>
    <times/>
    <apply>
     <plus/>
     <ci> p4 </ci>
     <apply>
```

```
          <divide/>
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          <apply>
            <plus/>
            <ci> p16 </ci>
            <ci> q_3 </ci>
          </apply>
        </apply>
        <apply>
          <divide/>
          <ci> p17 </ci>
          <apply>
            <plus/>
            <ci> p18 </ci>
            <ci> q_3 </ci>
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        </apply>
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      <ci> q_3 </ci>
    </apply>
  </apply>
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        <plus/>
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          <times/>
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          <ci> q_5 </ci>
        </apply>
        <apply>
          <times/>
          <ci> p21 </ci>
          <ci> q_6 </ci>
        </apply>
      </apply>
      <apply>
```

```
          <times/>
          <apply>
            <plus/>
            <ci> p22 </ci>
            <ci> p23 </ci>
          </apply>
          <ci> q4F </ci>
        </apply>
      </apply>
      <apply>
        <times/>
        <ci> p28 </ci>
        <ci> q_13 </ci>
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      <ci> u4 </ci>
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        <apply>
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          <ci> q4F </ci>
        </apply>
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          <divide/>
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            <times/>
            <ci> p13 </ci>
            <ci> q_2 </ci>
          </apply>
          <apply>
            <plus/>
            <ci> p14 </ci>
            <ci> q_2 </ci>
          </apply>
        </apply>
      </apply>
      <apply>
```

```
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        <plus/>
        <apply>
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          <ci> p22 </ci>
          <ci> q4F </ci>
        </apply>
        <apply>
          <divide/>
          <apply>
            <times/>
            <ci> p15 </ci>
            <ci> q_3 </ci>
          </apply>
          <apply>
            <plus/>
            <ci> p16 </ci>
            <ci> q_3 </ci>
          </apply>
        </apply>
        <apply>
          <divide/>
          <apply>
            <times/>
            <ci> p17 </ci>
            <ci> q_3 </ci>
          </apply>
          <apply>
            <plus/>
```

```
          <ci> p18 </ci>
          <ci> q_3 </ci>
        </apply>
      </apply>
    </apply>
    <apply>
      <times/>
      <ci> p21 </ci>
      <ci> q_6 </ci>
    </apply>
  </apply>
 </math>
</rateRule>
<rateRule variable="q_7">
 <math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply>
   <minus/>
   <ci> SRTSH </ci>
   <apply>
    <times/>
    <ci> fdegTSH </ci>
    <ci> q_7 </ci>
   </apply>
  </apply>
 </math>
</rateRule>
<rateRule variable="q_8">
 <math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply>
   <minus/>
   <apply>
    <plus/>
    <apply>
     <times/>
     <apply>
      <divide/>
      <ci> f4 </ci>
      <ci> p38 </ci>
     </apply>
     <ci> q_1 </ci>
    </apply>
    <apply>
     <times/>
     <apply>
```

```
          <divide/>
          <ci> p37 </ci>
          <ci> p39 </ci>
         </apply>
         <ci> q_4 </ci>
        </apply>
       </apply>
       <apply>
        <times/>
        <ci> p40 </ci>
        <ci> q_8 </ci>
       </apply>
     </apply>
   </math>
</rateRule>
<rateRule variable="q_9">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <ci> fLAG </ci>
      <apply>
        <minus/>
        <ci> q_8 </ci>
        <ci> q_9 </ci>
      </apply>
    </apply>
  </math>
</rateRule>
<rateRule variable="q_10">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <apply>
        <minus/>
        <ci> p43 </ci>
      </apply>
      <ci> q_10 </ci>
    </apply>
  </math>
</rateRule>
<rateRule variable="q_11">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <minus/>
```

```
      <apply>
        <times/>
        <ci> p43 </ci>
        <ci> q_10 </ci>
      </apply>
      <apply>
        <times/>
        <apply>
          <plus/>
          <ci> p44 </ci>
          <ci> p11 </ci>
        </apply>
        <ci> q_11 </ci>
      </apply>
    </apply>
  </math>
</rateRule>
<rateRule variable="q_12">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
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      <apply>
        <minus/>
        <ci> p45 </ci>
      </apply>
      <ci> q_12 </ci>
    </apply>
  </math>
</rateRule>
<rateRule variable="q_13">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <minus/>
      <apply>
        <times/>
        <ci> p45 </ci>
        <ci> q_12 </ci>
      </apply>
      <apply>
        <times/>
        <apply>
          <plus/>
          <ci> p46 </ci>
          <ci> p28 </ci>
```

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        </apply>
        <ci> q_13 </ci>
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  </math>
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  <math xmlns="http://www.w3.org/1998/Math/MathML">
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      <apply>
        <times/>
        <apply>
          <minus/>
          <ci> kdelay </ci>
        </apply>
        <ci> q_14 </ci>
      </apply>
      <ci> q_7 </ci>
    </apply>
  </math>
</rateRule>
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  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <ci> kdelay </ci>
      <apply>
        <minus/>
        <ci> q_14 </ci>
        <ci> q_15 </ci>
      </apply>
    </apply>
  </math>
</rateRule>
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  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <ci> kdelay </ci>
      <apply>
        <minus/>
        <ci> q_15 </ci>
        <ci> q_16 </ci>
```

```
      </apply>
    </apply>
  </math>
</rateRule>
<rateRule variable="q_17">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <ci> kdelay </ci>
      <apply>
        <minus/>
        <ci> q_16 </ci>
        <ci> q_17 </ci>
      </apply>
    </apply>
  </math>
</rateRule>
<rateRule variable="q_18">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <ci> kdelay </ci>
      <apply>
        <minus/>
        <ci> q_17 </ci>
        <ci> q_18 </ci>
      </apply>
    </apply>
  </math>
</rateRule>
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  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <ci> kdelay </ci>
      <apply>
        <minus/>
        <ci> q_18 </ci>
        <ci> q_19 </ci>
      </apply>
    </apply>
  </math>
</rateRule>
<assignmentRule variable="q4F">
```

```
  <math xmlns="http://www.w3.org/1998/Math/MathML">
   <apply>
    <times/>
    <apply>
     <plus/>
     <ci> p24 </ci>
     <apply>
      <times/>
      <ci> p25 </ci>
      <ci> q_1 </ci>
     </apply>
     <apply>
      <times/>
      <ci> p26 </ci>
      <apply>
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       <ci> q_1 </ci>
       <cn type="integer"> 2 </cn>
      </apply>
     </apply>
     <apply>
      <times/>
      <ci> p27 </ci>
      <apply>
       <power/>
       <ci> q_1 </ci>
       <cn type="integer"> 3 </cn>
      </apply>
     </apply>
    </apply>
    <ci> q_4 </ci>
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  </math>
</assignmentRule>
<assignmentRule variable="q1F">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
   <apply>
    <times/>
    <apply>
     <plus/>
     <ci> p7 </ci>
     <apply>
      <times/>
      <ci> p8 </ci>
```

```
        <ci> q_1 </ci>
       </apply>
       <apply>
        <times/>
        <ci> p9 </ci>
        <apply>
         <power/>
         <ci> q_1 </ci>
         <cn type="integer"> 2 </cn>
        </apply>
       </apply>
       <apply>
        <times/>
        <ci> p10 </ci>
        <apply>
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         <ci> q_1 </ci>
         <cn type="integer"> 3 </cn>
        </apply>
       </apply>
     </apply>
     <ci> q_1 </ci>
    </apply>
  </math>
</assignmentRule>
<assignmentRule variable="SR3">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <ci> p19 </ci>
      <ci> q_19 </ci>
      <ci> d3 </ci>
    </apply>
  </math>
</assignmentRule>
<assignmentRule variable="SR4">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <ci> p1 </ci>
      <ci> q_19 </ci>
      <ci> d1 </ci>
    </apply>
  </math>
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</assignmentRule>
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  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <plus/>
      <cn type="integer"> 1 </cn>
      <apply>
        <times/>
        <apply>
          <minus/>
          <apply>
            <divide/>
            <ci> p32 </ci>
            <apply>
              <times/>
              <ci> p31 </ci>
              <apply>
                <exp/>
                <apply>
                  <minus/>
                  <ci> q_9 </ci>
                </apply>
              </apply>
            </apply>
          </apply>
          <cn type="integer"> 1 </cn>
        </apply>
        <apply>
          <divide/>
          <cn type="integer"> 1 </cn>
          <apply>
            <plus/>
            <cn type="integer"> 1 </cn>
            <apply>
              <exp/>
              <apply>
                <minus/>
                <apply>
                  <times/>
                  <cn type="integer"> 10 </cn>
                  <ci> q_9 </ci>
                </apply>
                <cn type="integer"> 55 </cn>
              </apply>
```

```
          </apply>
        </apply>
      </apply>
    </apply>
  </apply>
 </math>
</assignmentRule>
<assignmentRule variable="SRTSH">
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   <apply>
    <plus/>
    <ci> p30 </ci>
    <apply>
     <times/>
     <ci> p31 </ci>
     <ci> fCIRC </ci>
     <apply>
      <sin/>
      <apply>
       <minus/>
       <apply>
        <times/>
        <apply>
         <divide/>
         <pi/>
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        </apply>
        <csymbol encoding="text" definitionURL="http://www.sbml.org/sbml/symbols/time">
         t
        </csymbol>
       </apply>
       <ci> p33 </ci>
      </apply>
     </apply>
    </apply>
   </apply>
   <apply>
    <exp/>
    <apply>
     <minus/>
     <ci> q_9 </ci>
    </apply>
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```
      </apply>
    </apply>
  </math>
</assignmentRule>
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  <math xmlns="http://www.w3.org/1998/Math/MathML">
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      <plus/>
      <ci> p34 </ci>
      <apply>
        <divide/>
        <ci> p35 </ci>
        <apply>
          <plus/>
          <ci> p36 </ci>
          <ci> q_7 </ci>
        </apply>
      </apply>
    </apply>
  </math>
</assignmentRule>
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  <math xmlns="http://www.w3.org/1998/Math/MathML">
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      <ci> p41 </ci>
      <apply>
        <divide/>
        <apply>
          <times/>
          <cn type="integer"> 2 </cn>
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            <power/>
            <ci> q_8 </ci>
            <cn type="integer"> 11 </cn>
          </apply>
        </apply>
        <apply>
          <plus/>
          <apply>
            <power/>
            <ci> p42 </ci>
            <cn type="integer"> 11 </cn>
          </apply>
```

```
            <apply>
              <power/>
              <ci> q_8 </ci>
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            </apply>
          </apply>
        </apply>
      </apply>
    </math>
  </assignmentRule>
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            <times/>
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          </apply>
          <apply>
            <plus/>
            <cn type="integer"> 1 </cn>
            <apply>
              <exp/>
              <apply>
                <minus/>
                <apply>
                  <times/>
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                </apply>
                <cn type="integer"> 7 </cn>
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            </apply>
          </apply>
        </apply>
      </apply>
    </math>
  </assignmentRule>
 </listOfRules>
</model>
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</sbml>

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