Qualitative Reference Model for Learning about Melatonin Regulation

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Abstract

Learning by creating qualitative representations is a valuable approach to learning. However, modelling is challenging for students, especially in secondary education. Support is needed to make this approach effective. To address this issue, we explore automated support provided to students while they create their qualitative representation. This support is generated form a reference model that functions as a norm. However, the construction of a reference models is still a challenge. In this paper, we present the reference model that we have created to support students in learning about the melatonin regulation in the context of the biological clock.

1 Introduction

Qualitative representations are used to aid students in learning about dynamic systems [1-5]. By creating a qualitative model, students actively develop their understanding of the subject matter as well as enhance their system thinking skills. However, qualitative representations are inherently complex and therefore difficult to construct [6,7]. Students require specific guidance that is detailed enough to facilitate progress, yet sufficiently restrained to leave ample room for discovery and learning [24]. To meet this need, we use reference models that function as a standard (as a norm) on the basis of which the necessary guidance is generated automatically [8,9].

We develop these reference models together with teachers and domain experts. Meanwhile, miscellaneous models have been created, particularly for usage in secondary education [10-14]. Yet, each new model remains a challenge, mainly for two reasons. Firstly, the source documentation is often incomplete, ambiguous and sometimes even contradictory which hampers extracting the relevant details and mapping them into the qualitative representation. Secondly, to act as a reference model for norm-based support (e.g., in secondary education) the model should adhere to specific requirements, including the following:

Graceful progression. The subject matter must be broken down into units, each representing a learnable yet adequately complex subsystem, while together these units are organized into a logical sequence that incrementally encompasses the entire system.

Self-contained and manageable. Qualitative models can easily explode and generate large state-graphs, or conversely, not generate any states at all. To be suitable for learning, subsystems must generate simulations that provide correct solutions with for students manageable state-graph sizes.

Meaningful. The decomposition into units is not arbitrary, on the contrary, each subsystem should by itself address at least one, possibly a few, important, meaningful, and valuable features of the subject matter.

Intriguing and curiosity driven. Surprises may help stimulate students' curiosity and their drive to wanting to address the next challenge [23]. Simulation results can be used for this. Hence, the goal is to orchestrate modelling steps such that when simulated they regularly produce intriguing results, which then become the challenge to be addressed in the next modelling step.

In this paper, we present the reference model that we developed for aiding students in learning about melatonin regulation, as well as the decomposition of this model into a sequence of learnable units. Melatonin is a hormone that is part of the mechanism that regulates the 24-hour rhythm of the biological clock. Understanding the biological clock and how it impacts life is in principle universally relevant yet typically not deeply embedded in formal education (at least not in the Netherlands). As such, the biological clock presents an interesting and relevant case.

The content of this paper is as follows. Section 2 summarizes the subject matter. Section 3 describes the qualitative representation software we use. Section 4 presents the reference model, with subsections for each mechanism from the full system. Section 5 and 6 conclude the paper.

2 Biological clock

The biological clock, also known as the circadian clock, is a cycle that takes place roughly within 24 hours. It is an autonomous series of responses in biological species that synchronizes with the day-night cycle. Before humans invented candles and the use of electricity for lamps, organisms relied on natural light only, resulting in the internal clock being in sync with this cycle. In modern times, however, the biological clock is disrupted by the 24-hour society in which people live. Research shows this disruption

has a major impact on human, animal and plant behaviour, as well as on whole ecosystems [15,16].

For the work presented here we focus on a particular aspect of the human circadian clock, namely the hormone melatonin and how its concentration changes during 24 hours.

The main driver of the biological clock is a group of nerve cells called the Suprachiasmatic Nucleus (SCN). The SCN inhibits the inhibiting work of the Paraventricular Nucleus (PVN). This results in more Aralkylamine N-acetyltransferase (AANAT), because less AANAT is being degraded. Next, because AANAT drives the conversion of serotonin into melatonin, the latter now increases. This process has a cyclic nature, because the initial cause, the SCN, has a cyclic behaviour. Fig. 1 illustrates the mechanism in more detail.

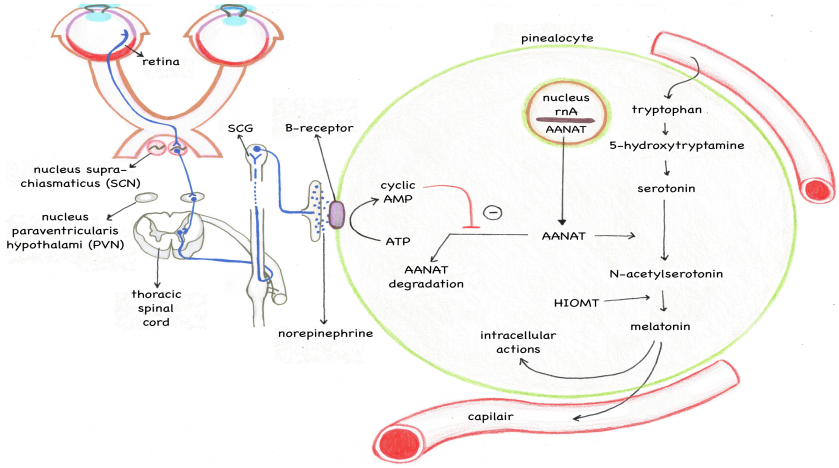

Fig. 1. Artist impression of the biological clock mechanism according to [17] (but see also [18]).

3 Qualitative Reasoning with DynaLearn

DynaLearn (https://www.dynalearn.nl) is an interactive tool that allows learners to create and simulate qualitative representations. It provides a web-based graphical user interface to Garp3 [19], facilitating online usage of the latter. The following ingredients are available via this interface to create representations. *Entities* can be used for representing physical objects and/or abstract concepts that make up the system. *Configurations* can be used for representing structural relationships between entities. *Quantities* can be used for representing changeable and measurable features of entities. Quantities have *Direction of change* (∂) (decreasing, steady, and increasing) and a *Quantity space* (a set of alternating point and interval values that the quantity can take on). *Causal dependencies* can be used for representing directed relationships between quantities. *Correspondences* can be used for representing co-occurring values and co-occurring directions of change. *In/equalities* can be used for representing order information among values and among directions of change. Finally, there is the option to represent *conditional statements*: IF *A* THEN *B*, where *A* and *B* can refer to the ingredients mentioned above.

When simulating, *Initial values* are defined for quantities, typically (but not exclusively) at the start of *Causal paths* (sequences of causal dependencies). This can be a direction of change, an initial value or an *Exogenous* behaviour. Additionally, in/equalities can be specified.

The simulation produces a *State-graph*, which consist of one or more *States* (unique qualitative behaviour of the system) and possibly *Transitions* (continuous passage) between pairs of states. The changes of system behaviour throughout the state-graph can be inspected using the *Value-history* and the *Inequality-history*.

Introducing advanced tooling in education requires a stepwise approach regarding complexity. To accommodate this, DynaLearn can be used at different levels of complexity [20]. The ideas presented in this paper are situated at level 4, which encompasses a large set of available ingredients. Importantly, this level includes the causal dependencies influence (I+/I-) and proportionality (P+/P-) [21]. Learners can thus focus on the distinction between processes (I) (initial causes) and the propagation (P) of these through the system. Positive and negative feedback loops are also available and in/equality (< ≤ = ≥ >) can be used to represent the relative impact of competing processes.

4 The Reference Model

The final version of the reference model, as we developed it, is shown in Fig. 13. We first developed the complete model, based on the required learning goals, and after that decomposed this model into units for learning.

The complete model can roughly be divided into four subsystems: the pulse generation (left), the AANAT regulation (middle), the production of serotonin (right-top), and the production of melatonin (right-bottom). Table 2 shows the simulation results focussing on the current value and direction of change for each quantity in each state. For instance, *AANAT Degradation* reaches its highest point and becomes momentarily steady in state 7 (<M, 0>) and then starts decreasing in state 8 (<M, –>). Table 3 shows the inequality information. For instance, *AANAT Degradation* and *Production* are equal in state 4 (=), while *Degradation* has become higher in state 5 (>). Notice that the behaviour of

the system is cyclic. The state transitions follow the path as show by the state-graph in Fig. 13.

4.1 Production and degradation of AANAT

It may seem logical to start the learning with the initial change at the start of the causal path. However, starting with the production and degradation of the *AANAT* is preferred. The main reason being that this combination of processes is the richest place in the whole model, with many opportunities for introducing key notions of systems thinking combined with domain knowledge. This is achieved without the added complexity of an oscillating impulse (see Fig. 13), which could lead to many states that are not yet useful for learning about this part of the mechanism.

The instruction for the lesson is given to the students via a workbook (on paper). The first assignments in de workbook thus focusses on modelling the production of *AANAT* (Fig. 2). This entity must be given two quantities: *Amount* and *Production*. The latter has a positive influence on the former (I+), while the production itself remains steady due to the exogenous influence. An influence requires a quantity space, here {0, +, Max}, because we need to know if the causing 'value' is positive or negative. In Fig. 2, this value is 0 and not causing any effect. Hence, when simulating, *Amount* remains steady. From this point, the workbook moves to the details in Fig 3, in which the value of the influencing quantity (*Production*) is set to +. Now the influence does cause an effect and hence *Amount* is increasing.

At this point in the lesson, the student is required to vary model details, run simulations, and answer question about the results. The workbook instructions guide these steps.

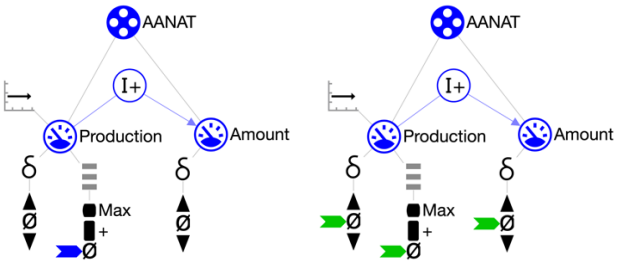

Fig. 2. AANAT production. Left side shows the model with production initially being set to 0 and steady (due to the exogenous influence ⊢). Right side shows the simulation results. Because the process is inactive, nothing changes.

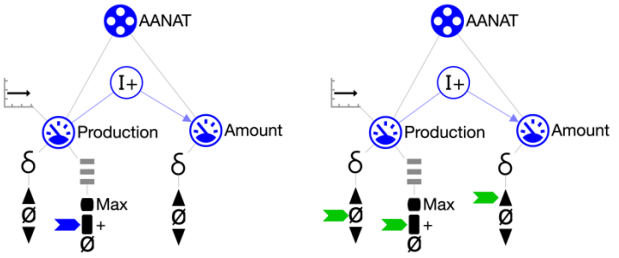

Fig. 3. AANAT production. Left side shows the model with production initially being set to + and steady (due to the exogenous influence ⊢). Right side shows the simulation results. Because the process is active, the amount of AANAT increases, while the process itself remains steady.

After production is sufficiently addressed, the next step is to add degradation as a competing process. Fig. 4 shows the result. *Degradation* has a positive current value (+) and a negative influence on *Amount* (I-). However, only specifying this information is insufficient, resulting in an ambiguous simulation with miscellaneous solutions. For instance, quantity spaces are (by definition) independent sets of ordered values, with only 0 as a universal. Hence, in Fig 4 the values *Max* for *Production* (P_{Max}) and for *Degradation* (D_{Max}) are unrelated, and all options are in principle valid (thus: $P_{max} < D_{Max}$, $P_{max} = D_{Max}$, $P_{max} > D_{Max}$) unless more information is specified. A similar situation holds for the balance between the *Production* and *Degradation* processes, all options are possible (thus: P < D, P = D, P > D).

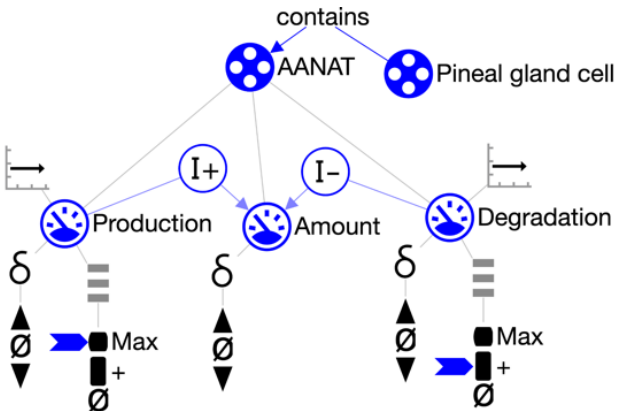

Fig. 4. AANAT production and degradation.

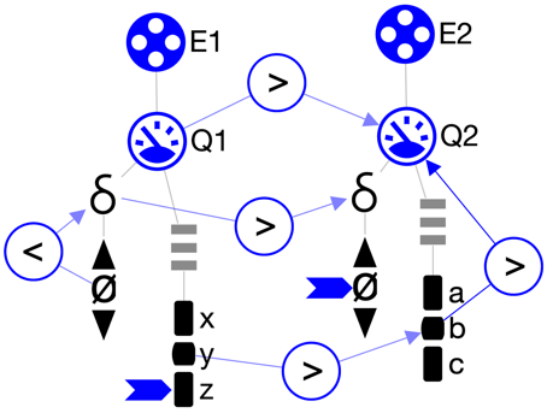

Fig. 5. Inequality information in a qualitative model.

Although ambiguity in qualitative models is typically considered to be a burden, here it provides an opportunity to intrigue students and stimulate them to further refine their understanding of the system. Let's consider an example. Fig. 5 illustrates the kinds of inequality information and their role for describing unique characteristics of systems. Let's assume that quantities Q_1 and Q_2 refer to the mutual temperatures (T) of the entities E_1 (T_{E1}) and E_2 (T_{E2}), respectively. The details in Fig 5 can then be read as follows:

- Current value of T_{E1} is z ($Q_1 = z$).
- T_{E1} is increasing ($0 < \partial Q_1$).

- Current value of T_{E2} is below b ($b > Q_2$).
- T_{E2} is steady ($\partial Q_2 = 0$).
- Current value of T_{E1} is greater than the current value of T_{E2} ($Q_1 > Q_2$).
- T_{E1} is increasing faster than T_{E2} ($\partial Q_1 > \partial Q_2$).
- If we assume that y and b are boiling points of Q_1 and Q_2, respectively, then the boiling point of Q_1 is higher than the boiling point of Q_2 ($y > b$).

When building a model, students must think explicitly about such system details and figure out the appropriate facts.

With the above-mentioned options in mind, the workbook continues by prompting students to think about additional (relevant) details regarding the two processes influencing *AANAT*. Fig 6 shows a particular situation in this context. In comparison to Fig. 4, it is now also known that the highest possible level of *Production* equals that of the highest possible level of *Degradation* ($P_{max} = D_{Max}$). It is also known that currently *Production* is higher than *Degradation* ($P > D$). Simulating this model delivers a state-graph with four consecutive states: $1 \rightarrow 2 \rightarrow 3 \rightarrow 4$. Table 1 summarises the results. It shows that there is a steady *Production* in all states. *Degradation* on the other hand is increasing. Initially it is smaller than *Degradation* (S_1), than it becomes equal (S_2), and finally it outperforms *Production* (S_3 and S_4). Due to this, *Amount* initially increases (S_1), becomes steady (S_2), and then decreases (S_3 and S_4).

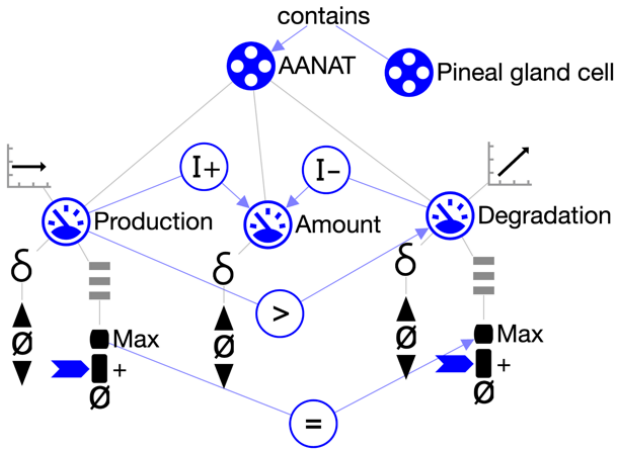

Fig. 6. Additional information regarding the two processes influencing AANAT.

Table 1. Simulation results for the model shown in Fig. 6. S refers to State, M to Max, P to Production, A to Amount, D to Degradation, and u refers to unspecified value.

	S_1	S_2	S_3	S_4
P	<+, 0>	<+, 0>	<+, 0>	<+, 0>
A	<u, +>	<u, 0>	<u, ->	<u, ->
D	<+, +>	<+, +>	<+, +>	<M, 0>
(P ? D)	P > D	P = D	P < D	P < D

To conclude this part of the lesson, the workbook asks students to draw line-graphs (on paper) of how the quantities change over time. Fig. 7 shows a graph they must complete.

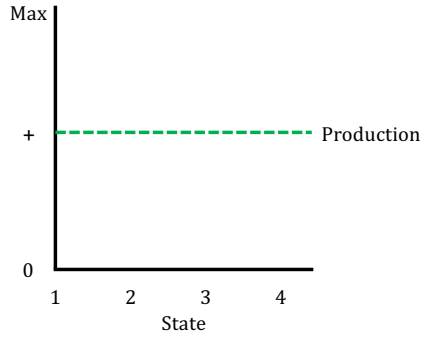

Fig. 7. Student assignment (on paper): Draw the line-graph of how AANAT changes according to the simulation results.

4.2 Regulation of AANAT degradation

The next logical step in the model is to focus on the mechanism that controls the *AANAT* degradation process. Why? Part of the reason is that correct behaviour of *AANAT* is a prerequisite before being able to discuss the other effects that follow and are subsequently controlled by *AANAT*.

The workbook introduces the topic with the visual and the textual explanation shown in Fig 8. Notice that the *SCN* influences the *Degradation* process via a double negation including the *PVN*. Hence, the *Degradation* process follows the *SCN* rhythm. Students find a double negation in a causal chain sometimes difficult.

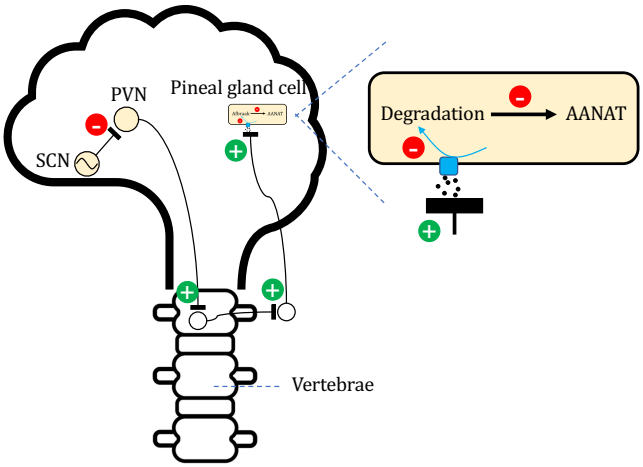

Fig. 8. Workbook information source (drawing & text). Text: 'The SCN (suprachiasmatic nucleus) is an area of the brain that contains clock genes that determine the 24-hour rhythm of many processes in the body by sending out impulses. The SCN has an inhibitory effect on the PVN (paraventricular nucleus). Through several nerve cells, the PVN has an inhibitory effect on the breakdown of AANAT.'

Fig. 9 shows the qualitative representation. The *SCN* impulses have a negative proportional influence on the *PVN* impulses, which in turn has a negative proportional influence on the *Degradation* process. By choice, some intermediate causal dependencies are not included in the representation. The *SCN* quantity *Impulse* is give an exogenous starting behaviour (type: sinusoidal) [22]. This implements the

sinusoidal behaviour of the internal clock. To ensure that *Degradation* fully follows the *SCN*, a quantity space correspondence (C) between the two quantity spaces is needed. Note that a quantity space for the *SCN* quantity *Impulse* is strictly speaking not needed. However, adding it makes the sinusoidal behaviour more visible as during the sequence the quantity now changes values.

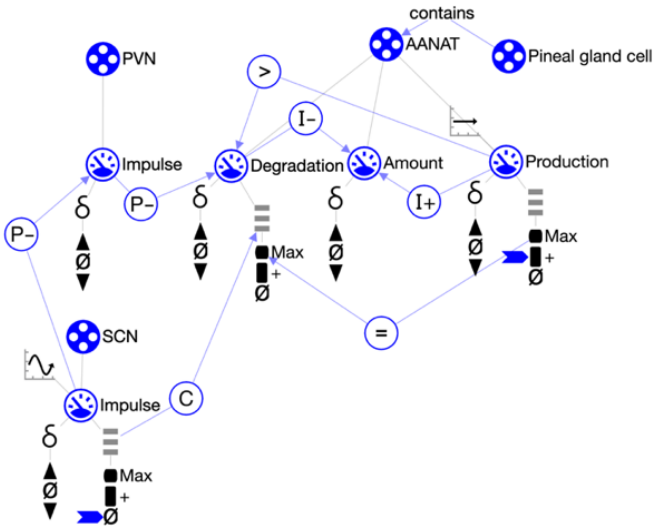

Fig. 9. AANAT production as shown in Fig 6, augmented with the SCN (and PVN) which controls the degradation process.

Fig. 10 and 11 show the simulation results. The state-graph has 10 consecutive states (Fig. 10). The *SCN Impulse* has a cycle behaviour, due to the exogenous influence. It starts at value 0 in state 1 <0, 0> (Fig. 11), increases to value Max in state 6 <Max, 0>, starts decreasing again in state 7 <Max, ->, and via state 10 <+, -> goes back to 0 and steady in state 1. The *PVN Impulse* changes opposite from this. It is also momentary steady in state 1, but then it decreases in states 2 to 5, becomes momentary steady in state 6 and increases in states 7 to 10. The *AANAT Degradation* behaves opposite from the *PVN* and hence follows the original *SCN* behaviour. *AANAT Production* is not shown in Fig. 11, but from Fig. 9 we can see that it has value + and remains steady due to an exogenous influence, hence <+,0> in all states. Because *AANAT Degradation* changes, the balance between *AANAT Production* and *Degradation* varies over the consecutive states. This is shown in the inequality history in Fig. 11 (bottom). In state 1 to 3 *Production* dominates and *AANAT Amount* increases. In state 4 the two processes reach a balance and *AANAT Amount* stops increasing. In state 5 to 8 *Degradation* dominates and *AANAT Amount* decreases. In state 9 the two processes balance again and *AANAT Amount* stops decreasing. The *Amount* increases again in state10.

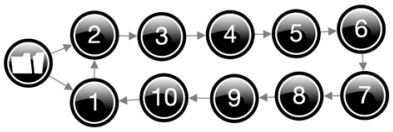

Fig. 10. State-graph when simulating the representation in Fig. 9.

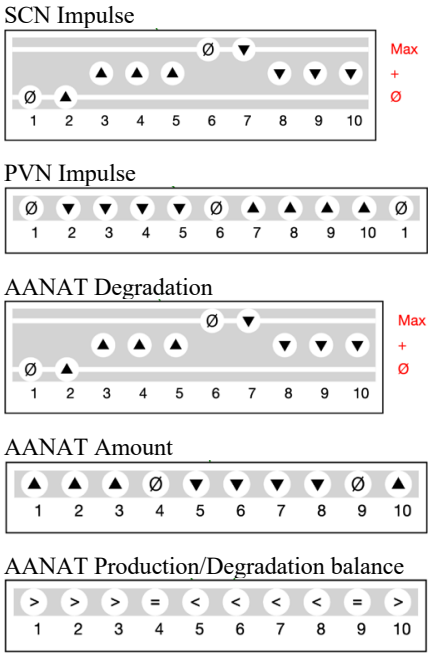

Fig. 11. Simulation results of the SCN controlling the AANAT as shown in the representation in Fig. 9.

4.3 Conversion and degradation of melatonin

Melatonin is produced in the pineal gland cells and then goes to the blood. The liver breaks it down again. The representation details are shown in Fig 12. It continues with adding the entities *Melatonin* and *Liver* (blood is not modelled). Next quantities are added. *Conversion* to the *Pineal gland cells*, *Degradation* to *Liver*, and *Amount* to *Melatonin*. The *Conversion* process is proportional to *AANAT Amount*, while *Conversion* and *Degradation* each influence *Melatonin Amount*. By placing an inequality, we can track the balance between them. Finally, there is negative feedback from *Melatonin Amount* on *Degradation* (P+).

The simulation now produces 12 states, similar to (in fact a subset of) the details shown in Fig. 13 and Table 2 and 3.

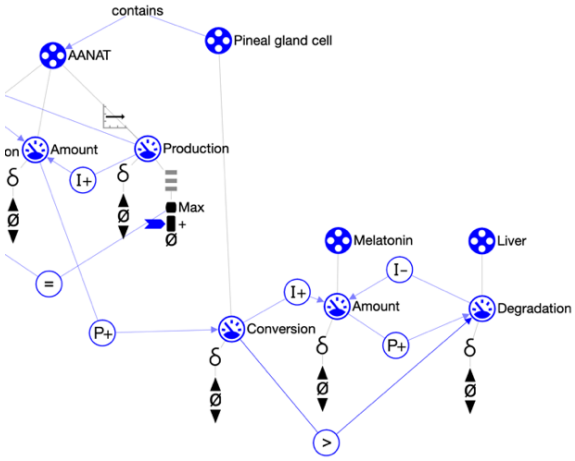

Fig. 12. Conversion and degradation of melatonin added to the representation shown in Fig 9. Note, to maintain readability we cropped the figure. See Fig. 9 for the remaining context.

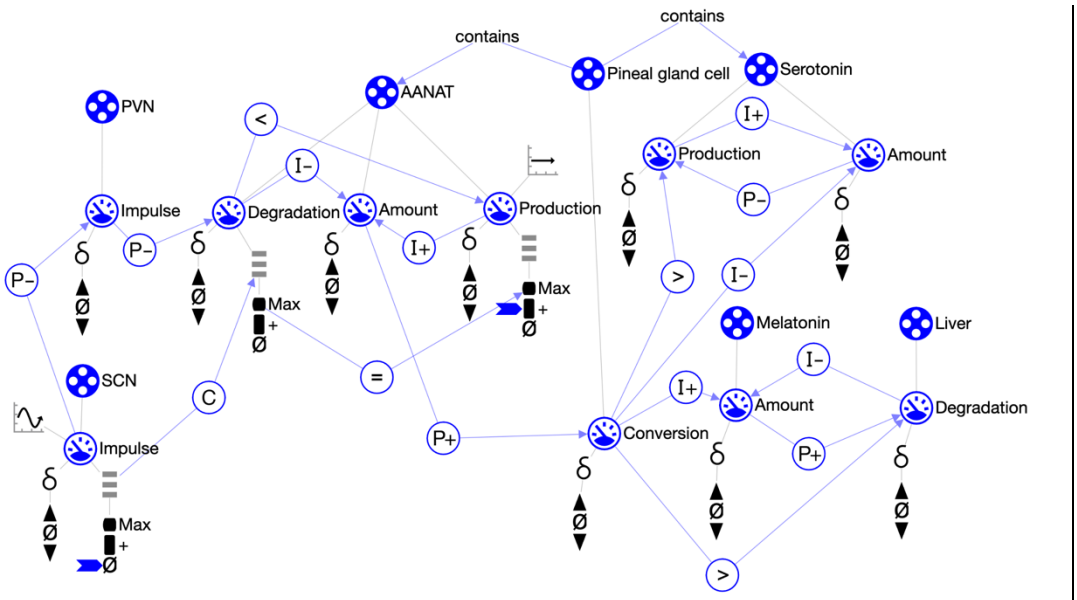

Figure 13. Qualitative reference model of melatonin regulation. Left side shows the representation. Right side shows the simulation results as a state-graph which consists of a loop of 12 consecutive states.

Table 2. Simulation results for the melatonin regulation reference model shown in Figure 13. PGC refers to Pineal gland cell, S refers to State, <v, ∂> refers to value and derivative (change), respectively, M refers to Max, and u refers to unspecified value.

Entity	Quantity	S_1	S_2	S_3	S_4	S_5	S_6	S_7	S_8	S_9	S_{10}	S_{11}	S_{12}
AANAT	Amount	<u, +>	<u, +>	<u, +>	<u, 0>	<u, ->	<u, ->	<u, ->	<u, ->	<u, ->	<u, 0>	<u, +>	<u, +>
	Production	<+, 0>	<+, 0>	<+, 0>	<+, 0>	<+, 0>	<+, 0>	<+, 0>	<+, 0>	<+, 0>	<+, 0>	<+, 0>	<+, 0>
	Degradation	<0, 0>	<0, +>	<+, +>	<+, +>	<+, +>	<+, +>	<M, 0>	<M, ->	<+, ->	<+, ->	<+, ->	<+, ->
Liver	Degradation	<u, +>	<u, +>	<u, +>	<u, 0>	<u, 0>	<u, ->	<u, ->	<u, ->	<u, ->	<u, 0>	<u, 0>	<u, +>
Melatonin	Amount	<u, +>	<u, +>	<u, +>	<u, 0>	<u, 0>	<u, ->	<u, ->	<u, ->	<u, ->	<u, 0>	<u, 0>	<u, +>
PGC	Conversion	<u, +>	<u, +>	<u, +>	<u, 0>	<u, ->	<u, ->	<u, ->	<u, ->	<u, ->	<u, 0>	<u, +>	<u, +>
PVN	Impulse	<u, 0>	<u, ->	<u, ->	<u, ->	<u, ->	<u, ->	<u, 0>	<u, +>	<u, +>	<u, +>	<u, +>	<u, +>
SCN	Impulse	<0, 0>	<0, + >	<+, +>	<+, +>	<+, +>	<+, +>	<M, 0>	<M, ->	<+, ->	<+, ->	<+, ->	<+, ->
Serotonin	Amount	<u, ->	<u, ->	<u, ->	<u, 0>	<u, 0>	<u, +>	<u, +>	<u, +>	<u, +>	<u, 0>	<u, 0>	<u, ->
	Production	<u, +>	<u, +>	<u, +>	<u, 0>	<u, 0>	<u, ->	<u, ->	<u, ->	<u, ->	<u, 0>	<u, 0>	<u, +>

Table 3. Simulation results cont. showing the inequality information for three quantity pairs in each of the states.

Compared quantities	S_1	S_2	S_3	S_4	S_5	S_6	S_7	S_8	S_9	S_{10}	S_{11}	S_{12}
AANAT: Degradation *versus* AANAT: Production	<	<	<	=	>	>	>	>	>	=	<	<
Pineal gland cell: Conversion *versus* Serotonin: Production	>	>	>	=	=	<	<	<	<	=	=	>
Pineal gland cell: Conversion *versus* Liver: Degradation	>	>	>	=	=	<	<	<	<	=	=	>

4.4 Conversion and production of serotonin

The final part of the model concerns the production and conversion of serotonin. The details are show in Fig 13 (right hand top). Serotonin is produced (from tryptophan) and then converted to melatonin using AANAT. In the representation this is slightly simplified making details kind of analogous to the mechanism for melatonin.

The *Conversion* by the *Pineal gland cells*, negatively influences the *Serotonin Amount*, because it is used to create the melatonin. The *Serotonin Production* is negative proportional to the *Serotonin Amount* (together implementing a negative feedback loop). The inequality between the *Pineal gland cells Conversion* and the *Serotonin Production* is not needed for arriving at the correct simulation results, but it helps to make the balance between these two processes visible, and thereby the mechanism potentially more insightful for students.

Note that there is no feedback from the amount of serotonin and the amount of melatonin on the conversion process *(Pineal gland cell Conversion)*. This feedback was

not included for two reasons. First, the main driver for the conversion is *AANAT Amount*. Second, such feedback loops result in extra states making the simulation harder to interpret. Adding additional information to circumvent those extra behaviours requires adding more ingredients in the representation, which would also make the lesson more complex. Together that lead to the decision to not include this feedback.

The representation is now complete. The simulation produces the results as shown in Fig. 13 and Table 2 and 3. To conclude the lesson, the workbook asks students to draw a line-graph (on paper) showing the changes of Serotonin during a full 24-hour cycle. Fig. 14 shows the graph they must complete.

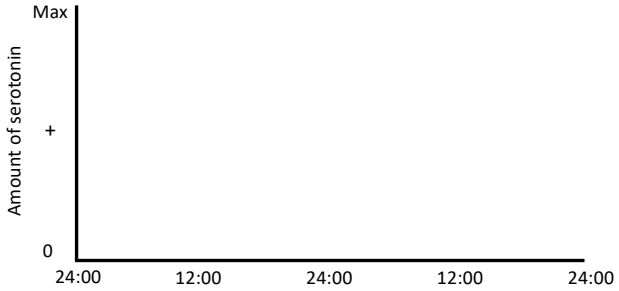

Figure 14. Student assignment (on paper): Draw a line-graph showing how the amount of serotonin changes according to the simulation results.

5 Towards evaluation

The reference model presented in this paper is part of our research effort to make 'learning by building qualitative models' a valuable approach. For this purpose, 8 students (upper secondary education), 5 teachers in training (higher education) and 4 teacher educators (higher education) have taken the lesson based on the model presented in this paper.

These users were all novices in the sense that they had no previous experience with qualitative modelling. On average they took 110 minutes to complete the lesson. Except for one subject, they all completed the lesson in the allotted time. Pre- and post-tests suggest learning effects for Systems thinking (from 6.4 to 12.4 out of 16 points) and for Melatonin regulation (from 4.8 to 8.8 out of 16 points), but these results may also indicate that the learning experience can be improved (although there is a limit to what can be learned in two hours). The users seem to have enjoyed the lesson, as they graded their experience with an 8 (on a scale of 10). However, these results are all preliminary. These lessons have been recorded and are currently being analysed to investigate the (*i*) support *use* and (*ii*) support *need* that these users have. The results will be input to further advance the learning by modelling approach.

The development of the reference model described in this paper underwent several improvements before reaching its final status. Critical expert reviews were provided by researchers who have published scientific justifications of the mechanisms (cf. [17,18]) to ensure that the model reflects the latest scientific insights on the topic.

6 Conclusion and Discussion

Reference models are an important asset in our approach to support students in learning from creating qualitative models. In this paper, we present a reference model for learning about melatonin regulation. Melatonin regulation is a particular aspect of the human circadian clock (also known as the biological clock). The model was developed in close collaboration with subject matter experts to ensure validity.

The model has four interacting processes, which together cause a serious amount of ambiguity upon simulating, easily resulting in complex state-graph consisting of 90 qualitative states with many alternative paths between those states. The shortest path algorithm hides alternative paths between two states leaving the shortest path (while ensuring certain constraints to maintain correct results [22]). By deploying the fastest path heuristic, the simulation results are simplified leaving only the behaviour relevant to explaining the quintessence of the regulation mechanism.

After development, the model was disentangled into four units that together form the system: (*i*) pulse generation, (*ii*) AANAT regulation, (*iii*) production of serotonin, and (*iv*) production of melatonin. The decomposition followed guidelines to guarantee learnability, specifying that units should facilitate (*i*) graceful progression, as well as being (*ii*) self-contained and manageable, (*iii*) meaningful, and (iv) intriguing and curiosity driven. Next, the order of the units in the overall assignment was arranged such that learning experience per unit was maximised as much as possible.

Future research focusses on advancing our automated support to aid students in learning from building qualitative models. For that purpose, seventeen users have taken the lesson build on the reference model presented in this paper. These data are currently being analysed.

Creating valuable qualitative models is still cumbersome. It requires a significant amount of craftsmanship based on experience. Future research could focus on automating this knowledge engineering endeavour and create tools that make building such models easier.

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