ILLUMINATIONS

Teaching physiology within a system dynamics framework

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INTRODUCTION

Function in living organisms is inherently dynamic, and behavior of dynamic systems is complex and, in many cases, counterintuitive.

To gain an in-depth understanding of these systems generally requires the development of mathematical models: sets of differential equations that describe changing systems.

Few undergraduate physiology students have the requisite background in advanced calculus to develop mathematical models of this type. Indeed, mathematical limitations have been recognized, among many other causes, as a reason for students experiencing difficulties in physiology (1). Wehrwein (10) mentions a movement to bring quantitative sciences into life sciences, and there is a growing recognition that quantitative skills are needed in the training of life science students (8).

However, quantitative literacy is a broad term and may not include fluency in differential equations, which is widely regarded as a prerequisite for modeling dynamic systems.

This may, at first, seem to be an insurmountable obstacle to achieving a truly deep understanding of complex systems, where the modeling techniques require competency in differential equations. Fortunately, an approach to modeling, known as system dynamics, facilitates advanced modeling without the need to work directly with differential equations.

System dynamics is a modeling framework in which the underlying differential equations are represented in a highly visual/graphical format in terms of just two constructs, termed rates (also known as flows) and levels (also known as stocks).

System dynamics modeling involves the creation of computer-based diagrams comprising these rates and levels within a system dynamics software environment, and then running simulations to show the behavior of the modeled system. These rate-level diagrams are actually nothing more than graphical (and thus highly intuitive) representations of differential equations.

These so-called rate-level diagrams are consistent with everyday notions, such as filling bathtubs and operating bank accounts, and are thus accessible to students without a mathematical background in differential equations. Despite their simplicity, these diagrams can model a surprising range of phenomena.

The underlying constructs are each individually so simple that they can be universally understood. The power of the model arises from the coupling of these individually simple constructs to form a model of arbitrary complexity.

Given this representational simplicity, system dynamics facilitates modeling of complex dynamic phenomena, retaining the pedagogical advantages of modeling, while dispensing with the need to work with the underlying mathematics. Indeed, many students do not appreciate that these simple, easily understandable constructs are nothing more than differential equations in another, far more comprehensible language.

In this paper, we discuss the use of system dynamics to teach physiological principles to undergraduate students in the Faculty of Health Sciences. The physiological examples are taught in a course called Health System Dynamics, which is not restricted to physiology and includes a wide range of health science topics, such as pharmacokinetics, epidemiology, public health, and others (7). However, in this paper, we will restrict the discussion to the modeling of physiological systems.

Physiological examples in our course include heat, mass and energy transfer, feedback loops in homeostasis, examples of dynamic equilibrium, cardiovascular modeling (such as Windkessel representations), metabolism, water balance, hematopoiesis, oscillatory systems, and many others. We also plan to introduce a wide range of pathophysiology examples, such as Cheyne-Stokes respiration and other abnormal breathing patterns, immune system behavior, and blood coagulation.

We provide a brief overview and introduction to the principles of system dynamics as well as the software used in this course. We present an applied physiology example that was given to our students under examination conditions and briefly discuss their performance. We conclude with some reflections on the utility of this approach in the teaching of physiology.

Why learn to model in physiology? A fundamental aspect of physiology is that it deals with systems and thus includes concepts such as accumulations, rate constants, half-lives, negative and positive feedback, and delays. Indeed, the principle of homeostasis, which requires at least one negative feedback loop, is regarded as a core concept in physiology (5).

The value of models as an instructional tool in physiology has been recognized. Modell (6) proposed that as few as seven general models are sufficient to cover a very wide range of phenomena in an undergraduate physiology course. He discusses the thought processes around modeling and describes the provision of general models to students.

We argue that providing students with the tools, in the form of system dynamics, to independently develop their own computational models represents a natural extension to this approach.

The qualitative description of feedback in homeostatic systems is generally regarded as simple. However, the reality is
that the specific structure of a system’s feedback loops can give rise to behaviors that are not predictable without a detailed model of the system.

For example, systems may respond to a disturbance by developing oscillations, with the frequency of the oscillation being dependent on the specific characteristics of the system. An example of this is the pulsatile secretion of insulin by the pancreas.

To explore these behaviors, it is necessary to develop a mathematical model of the system that can then be tested by varying the model structure or its numerical parameters. These models are generally constructed in the language of differential equations.

Causal loop diagrams. Causal loop diagrams represent a technique to facilitate understanding and visualization of feedback in systems (2). It may be regarded as a pre-quantitative step, and, strictly speaking, it constitutes a systems technique in its own right. However, it is often performed before, or in parallel with, system dynamics modeling and is thus frequently viewed as part of the system dynamics methodology.

A causal loop diagram can be drawn when variation in one variable influences another variable in such a way that the relative direction of the isolated effect is known. The magnitude of the effect is not considered in this analysis.

For example, glucose concentration is known to affect insulin concentration. An increase in glucose concentration causes an increase in insulin, and a decrease in glucose causes a decrease in insulin. The two variables can be linked by a causal arrow, pointing from the causal variable to the responding variable. As these two variables move in the same direction in the absence of any other influences, we assign a positive (+) sign at the arrowhead to indicate that they both move in the same direction.

We also know that insulin has an effect on glucose, where insulin is now the causal variable and glucose is the responding variable. In this case, an increase in insulin results in a decrease in glucose, and a decrease in insulin allows glucose to increase in the presence of absorption of dietary glucose and gluconeogenesis. We draw an arrow from insulin (now the causal variable) to glucose (now the responding variable), but this time, a negative (−) sign is placed at the arrowhead, because the two variables move in opposite directions in the absence of any other influences.

We can now combine the two effects into a single diagram, where glucose affects insulin and insulin affects glucose, as shown in Fig. 1. It is clear that, by combining the two influences, we have produced a closed-loop system, which indicates that there is feedback.

To indicate the nature of the feedback, we simply trace the flow around the loop, being certain to only move in the direction of the arrows, and multiply the signs on the arrowheads. In this case, there are only two signs, so it is a “+” multiplied by a “−”, which gives an overall “−” sign.

The resulting “−” sign indicates that the loop exhibits negative feedback behavior and is often called a balancing loop or regulating loop.

Finally, we can introduce glucagon by defining its interactions with glucose in the same way as we did for insulin. The resulting causal loop diagram for the overall glucagon, insulin, and glucose system shown in Fig. 1 represents a limited model of glucose homeostasis. This constitutes an adequate model for the restricted circumstances described in this example; however, extension and modification of the model would be required to capture other aspects of glucose homeostasis.

Note that there are now two loops, and, if we follow the same rules to determine the nature of the feedback, we see that this loop also exhibits negative feedback behavior. Thus the insulin, glucagon, and glucose system has two negative feedback or regulating loops.

System dynamics. System dynamics is a quantitative approach to modeling that was developed at the Massachusetts Institute of Technology by Forrester (2). Initially, the approach was intended to model business scenarios, but was soon extended to include social systems and other applications.

The approach requires that system variables be classified as either rates (also known as flows) or levels (also known as stocks). A rate is simply a time-based process, such as the rate of insulin formation or degradation, or the rate at which people become ill or recover from an illness. It has a time-varying numerical value.

A level is an accumulation of a quantity, such as the amount of insulin, given its rate of production and degradation. The numerical value of a level at a specific time is dependent on the accumulated quantity that results from the net rate, i.e., the inflow rate minus the outflow rate, and the initial value of the level before the simulation.

A number of software packages are available for system dynamics analysis, and our students use Vensim PLE (Personal Learning Edition) from Ventana Systems. This software facilitates model development, after which the simulation can be run. The software performs numerical computations to determine the model behavior, and the user can then present the output graphically for any of the variables in the model.

A simple fluid balance model in a human serves as an excellent illustrative example of the simplicity of system dynamics. A person consumes water at a given rate (which may be variable) and eliminates water via urine production, the gastrointestinal tract, and sweating. In this case, we will make the physiologically naive assumption that urine output occurs as a simple first-order process, such that its rate is proportional to the total body water and a rate constant K.

A mathematician would model the time rate of change of total body water, dW/dt, in terms of intake rate (i), urine loss rate (u) = KW, gastrointestinal loss rate (g), and sweat loss rate (s), as follows:

$$\frac{dW}{dt} = i - KW - g - s$$
In system dynamics, this differential equation would simply be drawn as a level as shown in Fig. 2, which accumulates the total body water \( W \), as a result of the inflow \( i \), and outflows \( u \), \( g \), and \( s \).

This highly intuitive depiction of a differential equation, termed a level-rate diagram, is accessible to a wide range of students with varying, and often very limited, backgrounds in mathematics.

There is more to system dynamics and the use of Vensim PLE than has been explained above, and it is not possible to include a tutorial on these topics. However, it may be helpful for readers to understand how students interact with the software, and this is briefly described below in the context of this example.

In this example, students would select a level icon from the top menu bar in Vensim PLE and click to place the rectangular box on the screen. Right-clicking the box allows the students to enter their chosen name for the level, “water” in this example, the initial value of the variable, and specify the inflows and outflows.

The student then selects the rate icon in the top menu bar and places it, names it, and assigns values to the rates in the same way as for the level. When the diagram is complete and populated with numerical values, the student can then click the “simulate” option, which runs the simulation and allows the student to view the output graphically.

Unlike the qualitative causal loop diagrams, level-rate diagrams essentially represent the equations. Thus standard system dynamics practice does not include the “/” and “–” signs on arrowheads in level-rate diagrams, as these are implicit in the structure.

An applied physiology example: peritoneal dialysis. Peritoneal dialysis illustrates the principles of diffusion across a membrane in a clinically relevant way and is representative of one of the seven general models proposed by Modell (6).

Below is a problem given to our first-year medical students under examination conditions. During the examination, the students had access to the software Vensim PLE, and the examination was conducted under closed-book conditions. The model and numerical constants were obtained or adapted from Fournier (3).

The objectives of this and other assignments include encouraging systems thinking in our students in a way that facilitates deep understanding of the interplay between physiological variables. By developing the model themselves and experimenting with the system’s behavior in a virtual environment, we anticipate that students would acquire a deep appreciation for the mechanistic aspects of physiology. In contrast to this, simply learning from the textbook or lecture slides and viewing predrawn graphical material is less likely to engender the depth of understanding that we are hoping to achieve.

To the extent that these objectives are met, modeling may be expected to hold some, although by no means all, of the benefits of laboratory-based work, and it facilitates rapid virtual experimentation with a wide range of physiological phenomena.

Patients in kidney failure may be treated with peritoneal dialysis. As shown in Fig. 3, it involves running a fluid (the dialysate) into the peritoneal cavity via a surgically inserted catheter, allowing the dialysate to remain there for a period (dwell time), and then removing it again through the catheter. During the dwell time, metabolic wastes in the blood (e.g., urea) diffuse into the dialysate due to a concentration gradient and are thus removed from the body. This process can be repeated frequently. The peritoneal membrane, which covers abdominal organs and lines the peritoneal cavity, is thin and has a rich blood supply, making it useful for this procedure. The drawing alongside shows a schematic of the process for introducing and removing the dialysate.

Consider a patient in kidney failure with plasma urea of 45 mmol/l (equivalent to a blood urea nitrogen of 126.21 mg/dl). Assume 2.5 liters of dialysate are introduced into the peritoneal cavity and remains there for 4 h before being removed. The initial concentration of urea in the dialysate is zero. Assume urea diffuses from the blood to the dialysate according to a simplified model, such that the rate is given by the equation

\[
R = PA(C_b - C_d)
\]

where \( R \) is the rate of urea transfer per unit time, \( P \) is a permeability constant, and \( A \) is the effective surface area of the peritoneum.

![Fig. 3. Schematic of peritoneal dialysis showing the dialysate being introduced into the peritoneal cavity. The drainage catheter is also shown. [Adapted from plate 1035 of Henry Gray’s Anatomy of the Human Body.]](http://advan.physiology.org)
Modeling allows students to explore the dynamics of diffusion rather than a static snapshot, which provides a sense of the process. As the urea concentration increases in the dialysate and decreases in plasma, the driving force due to the concentration gradient diminishes, which changes the dynamics.

The model shown in Fig. 4 has two levels representing the amount of urea in the dialysate and plasma. The concentrations in each of these compartments are determined in the model by dividing the levels by the respective volumes. Finally, the permeability-area product, $PA$, multiplies the concentration difference to produce the urea transfer rate.

The simulation results in Fig. 5 show the decrease in plasma urea (which is the same as the total body water urea in this well-mixed, single-compartment model), and an increase in dialysate urea, with the two urea concentrations approaching each other as they move toward equilibrium.

The questions asked in the examination test a number of skills in addition to modeling, such as unit conversion. However, for the purposes of this study, the authors, who are all part of the system dynamics teaching team, graded the student responses in two categories, i.e., model development and graphical output. The grading was performed by consensus.

For both categories, student responses were graded at three levels: Good, Minor Deficiencies, and Inadequate.

The category Good represented a competent and essentially complete model development, and, in the case of the graph, it represented the correct shape of the curves, with an approach toward equilibrium at the appropriate value.

The Minor Deficiencies category was awarded to models that had the basic elements of the correct structure, indicating that the student understood the general model architecture, but had one or more flaws that would yield incorrect results on simulation. In the case of the graph, this category was assigned when the shape of the curves was essentially correct, but there were incorrect amplitudes or times.

The Inadequate category showed misunderstanding of key aspects of the model and/or graphical output.

Taking the categories of Good and Minor Deficiencies together, it was evident that 86.5% and 74.4% of students were able to demonstrate meaningful understanding of the model and graphical output, respectively. These results are summarized in Table 1 and Fig. 6.

Reflections on student and teacher experiences. One of the problems in running a course of this nature for a very large
class is the logistics of providing suitable venues with computer facilities. We run the course in two large computer laboratories, each with ~80 workstations. Our large class sizes makes it essential to run multiple modeling sessions, which requires substantial coordination and management. Encouraging students to install Vensim PLE on their laptops does help in mitigating this problem.

Student attitudes and motivation varies. We view system dynamics as a way of doing modeling without the need for advanced mathematics. Nonetheless, some students still feel that the level of quantitative analysis required in this course is excessive.

At the other extreme, some students find the quantitative nature of the course to be exciting, and express the view that the course comprises far too little mathematics.

We have partially managed the problem of explaining difficult concepts to students by introducing voluntary, interactive tutorial sessions led by experienced teachers. In these sessions, the students are encouraged to ask any questions they have in relation to the course. This has proven to be highly efficient, as, more often than not, the problems and concerns raised by students are shared by their peers. As our students begin to appreciate this, they develop the confidence to ask questions freely.

Interestingly, we often encounter students who have completed the course within the last few years, who express the view that, while they did not appreciate it at the time, they have since found the systems thinking that they developed in the course to be invaluable. We plan to formally study these attitudes in our former students.

We have data from a student cohort in a prior year of study who took an online survey near the end of the course. A sample of six questions that relate to attitude and motivation are shown below. There were 222 responses to the survey, representing a response rate of >80%.

The questions, labeled A–F for ease of reference on the chart, are shown below.

A. The course has exposed me to an entirely new approach to understanding ideas.
B. I believe that the knowledge and thought processes that I am acquiring in the course will be of benefit in my medical thinking throughout my studies and career.
C. The course helps me to make sense of difficult concepts.
D. I find that I’m starting to think about many things in terms of systems concepts.
E. I find the ideas in the course exciting and useful.
F. The course helps me see the relationships between many apparently unrelated phenomena.

Students were required to respond by choosing one of five options, i.e., strongly agree, agree, neutral, disagree, or strongly disagree.

As can be seen in Fig. 7, in all questions other than E, “agree” is the most frequent response on all but one question.

The questions, labeled A–F for ease of reference on the chart, are shown below.

Table 1. Performance of 207 students on model development and graphical output of the peritoneal dialysis problem

|              | Good   | Minor Deficiencies | Inadequate |
|--------------|--------|--------------------|------------|
| Model development | 153 (73.9) | 26 (12.6) | 28 (13.5) |
| Graphical output    | 70 (33.8)   | 84 (40.6)    | 53 (25.6)  |

Values are the no. of students (with % in parentheses), who were graded into the following categories: Good, Minor Deficiencies, or Inadequate.
appreciation of their behavior requires the development of models using differential equations.

Students in our health sciences programs typically do not have sufficient mathematical skills to perform modeling. We have found that system dynamics provides an excellent and accessible alternative to the use of differential equations, empowering our students to perform modeling.

The example of the use of system dynamics to model transperitoneal diffusion of urea demonstrates, albeit in a simplified model, which excludes ultrafiltration, the relative success that most of our students achieved with this form of modeling.

While at its core modeling in a system dynamics framework is equivalent to using differential equations, its use holds important advantages over the mathematical approach. Its visual nature makes dynamic modeling easily accessible to students who have not been formally trained in mathematics at this level. Moreover, we propose that the system dynamics approach takes the mystery out of differential equations, making it possible for students to gain deep understanding of modeling.

We go further and argue that, even for students who have the requisite mathematical modeling skills, the visual nature of system dynamics may provide them with deeper insight than formulating the problem as a set of differential equations.

In summary, system dynamics provides a highly intuitive, widely accessible approach to modeling, and we propose its adoption as a methodology in undergraduate and graduate level courses in physiology.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.M.R. conceived and designed research; D.M.R., R.F.R.L., and X.L.R. analyzed data; D.M.R. prepared figures; D.M.R. drafted manuscript; D.M.R., R.F.R.L., and X.L.R. edited and revised manuscript; D.M.R., R.F.R.L., and X.L.R. approved final version of manuscript.

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