Bridging different perspectives of the physiological and mathematical disciplines

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Mathematical formulation of relationships between physiological quantities and analytic tools for analyzing such relationships have played an important role in physiology. A clear example of the power of mathematical computation is given by the simple arithmetic calculations (with a sophisticated viewpoint leading to its application) of William Harvey, which provided convincing evidence against the accepted view at the time of his work of how blood flow functions.

Given that mathematics is a powerful tool for quantifying complex relationships, it is important to find educational approaches that can impart to physiology, medical, and mathematics students and simultaneously act to stimulate mathematical/physiological/clinical interdisciplinary research. While physiology education incorporates mathematics, via equations and formulas, it does not typically provide a foundation for interdisciplinary research linking mathematics and physiology. Here, we provide insights and ideas derived from interdisciplinary seminars involving mathematicians and physiologists that have been conducted over the last decade. The approaches described here can be used as templates for giving physiology and medical students insights into how sophisticated tools from mathematics can be applied and how the disciplines of mathematics and physiology can be integrated in research, thereby fostering a foundation for interdisciplinary collaboration. These templates are equally applicable to linking mathematical methods with other life and health sciences in the educational process.

Interdisciplinary Seminar

Here, we provide a format for a semester-length interdisciplinary seminar involving joint presentations by mathematicians and physiologists focusing on analyzing and modeling physiological systems. This format will draw on ideas and approaches from a series of seminars that has been conducted continuously over the last 22 academic semesters (http://www.uni-graz.at/~batzel/course-info.html) developed jointly by the Institute for Mathematics and Scientific Computing at the Karl Franzens University Graz and the Institute of Physiology of the Medical University of Graz in Graz, Austria.

These seminars have been designed to develop critical thinking, to establish new insights through cross-disciplinary understanding and experience, and to provide new opportunities for collaboration by making students comfortable with interdisciplinary work. The seminars have covered physiological topics related to the cardiovascular and respiratory control systems, clinical issues in dialysis treatment, and glucose-insulin control. Seminar subjects from mathematics have included control theory, delay differential equations, sensitivity analysis, parameter estimation, and state space and input-output models.

The content of the seminars varied from semester to semester, reflecting both the interests and skills of the students. In the sections below, template examples for course design and resources for course development are provided. Each institution can draw on its own expertise in developing a unique seminar format and in choosing the appropriate course content. This development could, in principle, be done without explicit participation of mathematical or engineering researchers, using a number of freely available modeling tools (referenced below). However, our experience, based on seminar development and the organization of a number of interdisciplinary summer schools and workshops, is that mathematicians and engineers are typically interested in new applications, and, hence, an
interdisciplinary presentation of the seminars is easily achievable. The experiences of these interdisciplinary summer schools and workshops also contributed to the seminar ideas and approaches presented here.

Summarized below is the outline of a template seminar. Examples of specific semesters, including outlines and topics, can be found via links from a resource website (http://www.uni-graz.at/~batzel/course-info.html), which contains a number of curriculum development links.

**Purpose.** In this seminar, we examine the mathematical techniques needed for modeling physiological systems as well as some important concepts and systems in human physiology. These issues will be considered both from the perspective of physiologists and mathematicians, thus advancing interdisciplinary learning and research.

**Organization.** The organization of the seminar is as follows:

- The seminars are held 1.5 h/wk during a semester.
- Lectures include course material and talks given by invited mathematicians, clinicians, or life scientists.
- At the completion of the course, there may be a report on a research paper related to the topics of the seminar, a project, or a test.
- A given semester may focus more on mathematical issues, modeling physiological systems, or modeling applications and experimentation. These topics, though, could be covered across various semesters.
- Typically, students attend for two semesters. Students can obtain credit for one or both semesters.

**Semester topics.** The following topics can be introduced:

- Introduction and overview: modeling, parameter estimation, and experimental design
- Modeling issues I (mathematician)
- Cardiovascular physiology I (physiologist)
- Cardiovascular physiology modeling I (physiologist)
- Experimental design I (physiologist)
- Laboratory demonstration (physiologist)
- Experimental design II (physiologist)
- Modeling issues II (mathematician)
- Model development (mathematician)
- Parameter estimation I (mathematician)
- Parameter estimation II (mathematician lecturer)
- Parameter estimation III (mathematician)
- Discussion of final project (mathematician, physiologist)
- Presentation of individual projects I
- Presentation of individual projects II

*Figure 1 shows an overview of the main organizational elements of the seminar.*

**Integrated Content of the Seminars**

In these seminars, we emphasized two main goals:

- To develop an understanding and appreciation of the differences in the basic viewpoints and concepts found in the fields of mathematics and physiology. For example, the physiological term "homeostasis" and the mathematical term "system stability" are ideas that have a similar conceptual basis, but their effective merging requires an awareness of the technical similarities and differences.
- To present unifying and well-motivated examples illustrating how mathematical methods naturally find applications in exploring physiological systems and related clinical problems. Provided below are some examples showing the interlinking between mathematical modeling and physiological systems.

**Example 1: cardiorespiratory control.** Cardiorespiratory control interactions include the phenomenon of periodic breathing and sleep apnea. This area brings into play several important mathematical concepts related to feedback control...
loops. This includes transport delays that occur in moving system information to those sensory sites that monitor system status and influence the responses of these feedback loops. In particular, these transport delays (which, in this example, depend on blood flow) are increased in patients with congestive heart failure, who also exhibit enhanced disturbed sleep patterns and sleep apnea partly as a consequence of the impaired function of the feedback control induced by these delays. In turn, such patterns of disturbed breathing during sleep in patients with congestive heart failure cause further deterioration in heart function, leading to further problems with feedback control and disturbed sleep patterns and apnea (12, 28, 31). Hence, a natural interweaving of mathematical, physiological, and clinical issues can be developed in examining this issue (see example 5). A number of modeling examples related to this topic can be found in Ref. 3.

Example 2: kidney failure, dialysis, and fluid volume control. Aspects of mathematical modeling, physiology, clinical issues, and data acquisition can all be integrated and illustrated by considering issues related to patients with kidney failure who undergo hemodialysis. The loss of kidney function impacts many systems and states, including mid- and long-term control of blood pressure and blood volume. Compromising these controls has consequences for blood pressure and blood volume control during the dialysis sessions, which include hypovolemic and hypotensive events (6, 36). In addition, the loss of kidney function impacts control loops related to red blood cell production, resulting in the need for erythropoietin administration. However, the administration of erythropoietin is challenging, given the long time delays inherent in the blood cell production mechanisms. Complex control and clinical problems can be examined from a modeling perspective (7) and data perspective (43) with an emphasis on addressing clinical problems associated with dialysis.

Example 3: current applications in the clinical setting. The glucose tolerance test represents a simple modeling application at a similar level of complexity to the body mass index (BMI) model in example 4. In addition, signal processing approaches represent another approach to deriving information on system status using an a priori or statistical modeling approach very different from the physiology-based modeling represented in this seminar. More complex examples that can be used in the seminars using models built from physiological information include the following applications.

VOLATILE ORGANIC COMPOUNDS. Volatile organic compounds produced by the human body are often exhaled in human breath. These volatile organic compounds represent biomarkers that can reflect physiological and clinical conditions and, hence, can have diagnostic value. Given their volatility, the estimate of internal concentrations from exhaled or end-tidal breath is challenging. For example, some compounds are reabsorbed during the passage of air through the conducting airways. Typically, estimation of internal states depends on mathematical models and estimates of parameters from the data provided by exhaled air. The challenge to applying this important noninvasive source of information involves both delicate problems in measurement and in model validation and parameter estimation. This is an active area of current research, and one that has promise for providing new data about physiological and clinical states. Hence, consideration of this problem, as outlined in Ref. 30, can provide a more complex modeling example.

ESTIMATING INTRACRANIAL PRESSURE. Intracranial pressure plays an important role in many clinical conditions. The standard methods for estimating this quantity involve invasive approaches, such as sampling cerebral spinal fluid. This limits the amount of data that can be collected for dynamic modeling and also for assessing patient status. An approach has been recently proposed (26) that uses modeling to generate a continuous estimation of intracranial pressure using noninvasive (or minimally invasive) techniques based on measurements of peripheral arterial blood pressure and blood flow velocity in the middle cerebral artery. These data are then applied to a model of cerebrovascular dynamics, leading to continuous estimates of intracranial pressure.

The above two applications are somewhat complex but illustrate the form in which modeling can be used to derive noninvasive measurements in the clinical setting.

Individualized and focused strategies for teaching students with varying backgrounds. For students with a background in physiology/life sciences, the following need to be emphasized:

- Development of mathematical modeling skills
- Understanding the problem of model validation (the process of testing whether the model properly reflects the phenomenon being modeled)
- Clarification of model identifiability, which assesses if model parameters can be uniquely estimated from appropriate data. Models must fit the data and predict behavior or be able to assess system status
- The importance of matching data to model design

For students with a background in mathematics, the following points need to be emphasized:

- Understanding what clinical and experimental measurements can be taken, both noninvasively and invasively
- Understanding how to assess data quality (including the degree of error involved and whether data are directly measured or derived from measurement algorithms) and how to assess the relevance of given data for the model being developed. For example, some key quantities in hemodynamic monitors are derived via internal algorithms, and this needs to be taken into account when using data for model validation
- Recognition that effective experimental design is critical for producing data that are useful for parameter identification
- Appreciation of questions related to sample collection cost and added value of invasive measurements
- Development of hands-on experience in experimentation

In fact, all of these points will be important to all students, with any difference in the level of significance of the points reflecting more the level of experience in one’s own field.

Integrating Mathematical and Physiological Perspectives: Course Development

The seminar content should focus on students developing an appreciation of key perspectives from each discipline (physiology and mathematics) by including the following:

- Theoretical development, derivation, simulation, and validation of mathematical models
• Exploration of data acquisition: instrumentation and issues related to noninvasive versus invasive measurements
• Hands-on examples showing how measurement can be done
• Inclusion of guest speakers to supplement the core seminar teacher group: these guests, experts in mathematics and life sciences, can provide additional perspectives as well as potential contacts for further research involving the students

We now provide detail on each of these aspects and provide ideas and resources for developing them.

Theoretical development, derivation, simulation, and validation of models. Our seminars have provided classic modeling examples in physiological areas such as cardiovascular and respiratory system control. For this purpose, template models of the cardiovascular system of A. C. Guyton and colleagues (20) and the respiratory system of F. Grodins and colleagues (18, 19) were introduced as clear examples (and reference templates) of sophisticated models of significant complexity and physiological detail. However, such models, while providing a summary of current knowledge and providing a basis for theoretical studies, would be difficult to apply in the clinical setting. Hence, the process of modeling requires considerations of how to reduce model complexity.

As examples of modeling resources at the middle level of model complexity, we examined cardiovascular modeling applications provided by Ursino and colleagues (cardiovascular system control mechanisms (39–42)), Ottesen [baroreflex control with delay (33)], Cavalcanti and colleagues [cardiovascular control problems in hemodialysis (6, 7)], and Heldt and colleagues [modeling orthostatic stress (22)].

The above-mentioned spectrum of models illustrates how modeling assumptions, modeling goals, and modeling applications, together with consideration of available data, can interact. These can then be used accordingly to define the research program of the seminars.

Students need to understand the process and motivation for designing and developing midlevel and minimal models when considering patient-specific modeling applications. Such modeling is required to allow for matching the number of model parameters in a reasonable way to the type and quantity of data available from clinical tests. Model identification, validation, and application to patient-specific diagnosis are ongoing topics of research (21).

For both Life science and mathematical students, we emphasized the following:

• Numeric computer simulation begins with reasonable starting values (initial values) and values for all model parameters. Allometric scaling drawn from nominal values from the literature is an important tool for generating reasonable guesses for those parameters that are not to be estimated from data (9, 22, 32, 34, 39).
• Model validation issues are central to effective modeling. Since data comprise the key for model validation, a clear understanding of the relation between data, model design, and the level of model complexity is important for students to acquire. Here again, interdisciplinarity is critical. In our seminars, we paid particular attention to sensitivity identifiability analysis (1, 37), discussed below, since this tool can aid in adapting models to patient-specific data.

MODEL VALIDATION ISSUES. Model parameter estimation and model validation are the most difficult aspects of modeling since models of sufficient complexity to capture system dynamics and the myriad of system component interactions typically require a large number of model parameters. On the other hand, typically, data on the system states needed to estimate unknown parameters are limited because measurements are difficult (and may require invasive measurements) or, for some states, impossible to acquire. Many techniques have been developed to analyze this match of model and data. Sensitivity analysis, which describes the impact of changes in model parameters on model output, can be used to study this problem. Sensitivity analysis has been used in the past in engineering and physical science disciplines, and new tools are currently being applied to problems of model validation in physiology. Sensitivity identifiability analysis (1, 37) can be used to select the parameters best suited for estimation. This approach can provide an assessment of the impact of errors in chosen (nonestimated) parameters and help to ascertain the right combination of model detail, data, and experimental design (5, 11, 37, 38). Example 4 (below) incorporates an example of sensitivity analysis.

MODEL SIMULATION AND TEACHING TOOLS. The computational and simulation tool Matlab (a student version is available) includes basic commands for model simulation, which can easily be introduced to the students in one lecture. Other software for simulation, such as Matlab-Simulink and LabVIEW, provides a user-friendly graphical interface. In addition, cost-free highly developed teaching models are available online, such as comprehensive cardiovascular models (23, 35) and a comprehensive cardiorespiratory model [Pneuma model (8, 10)]. Finally, Physiome (http://www.physiome.org/) is a worldwide project for cataloging and coordinating the very large inventory of mathematical models that have been developed for studying physiological systems. Within this site is JSim (http://physiome.org/jsim/), a web source that allows access to models that can be run interactively over the internet.

Exploration of data acquisition: instrumentation and noninvasive measurements. It is important that both students of physiology and science and mathematics develop an appreciation of the problems and needs of each side. The areas to be covered can be adjusted according to what is available in the institution offering these seminars, especially as every physiology institute has differing areas of focus and laboratory facilities. For the seminars described in this report, major emphasis was placed on cardiovascular research, as there is access to a variety of cardiovascular assessment tools, including head-up tilt and lower body negative pressure tests. Readily available is the continuous monitoring of heart rate and arterial blood pressure using the task force monitor (TFM, CNSystems, Graz, Austria) (13–17, 24). Other quantities that are available for assessment using the task force monitor include the following:

• Total peripheral resistance index (calculated as mean arterial blood pressure/cardiac index)
• Mean arterial blood pressure
• Cardiac index, which relates heart performance to the size of the individual (calculated as cardiac output/body surface area)
• Stroke index (calculated as stroke volume/body surface area)
• Impedance cardiography, in which the changes in thoracic impedance are converted to reflect changes in thoracic fluid/volume over time
• ECG measurements, which can be used to present ideas and applications of heart rate and blood pressure variability and deductions about autonomic function

Near-infrared spectroscopy and transcranial Doppler measurements are also available for use in our seminars to investigate regional blood flow in the calf and brain, respectively. For details, see Ref. 4. These measurements illustrate the problems and challenges in data acquisition and provide students with an initial experience of working in a laboratory setting and considering the problems related to invasive versus noninvasive measurements.

Illustrating modeling skills: two template examples. The two examples described below illustrate how physiological hypotheses can be examined using minimal compartment models, which are easy to derive and simulate. Example 4 uses a compartmental model that is only a bit more complex than the model implemented in the glucose tolerance test (example 3) and hence illustrates modeling principles that are applied everyday in clinical assessment. Example 5 is a bit more complicated but easily implementable with only a couple of lessons in model simulation.

EXAMPLE 4: MODELING THE BUILD UP OF TOXINS IN PATIENTS WITH KIDNEY FAILURE AND ISSUES OF MODEL VALIDATION. Example 4 illustrates a model that can be used to examine issues related to mortality rates in hemodialysis patients in terms of BMI or body type. Research indicates that high BMI patients have a survival advantage over patients with lower BMI (25, 27). This observation seems to be related to the way that toxins, which accumulate in patients, are distributed or sequestered in muscle and fat tissue. The model, including model equations, parameters, and some data on parameters, can be found in Refs. 25 and 26. The model incorporates four compartments. The model tracks the dynamics of the levels of a toxin produced at a rate in the organ compartment and with the compartment and an adipose tissue compartment. The model simulates the intradialytic and interdialytic periods in a patient with kidney failure and can be used to test the levels of toxin in the extracellular fluid for patients with various BMIs. Figure 2A, left, shows the model block diagram, and Fig. 2A, right, shows several intra- and interdialytic phases for three levels of BMI. The structure of the model equations and terminology are provided in APPENDIX B. This model can be set up for simulation using very easy simulation techniques.

APPENDIX B also provides a sample of how sensitivity analysis proceeds as an example of a tool for model parameter estimation and model validation. Full details of the sensitivity calculations can be found in Refs. 25 and 27, and the Matlab code for sensitivity calculations can be found at the resource web-page developed for this report.

EXAMPLE 5: A MODEL OF THE CONTROL OF VENTILATION. In example 5, we describe a respiratory system control model (derived from Refs. 19 and 28). This model can be used to test various hypotheses regarding the causes of unstable breathing patterns such as periodic breathing in normal subjects and subjects with congestive heart failure. These issues were discussed above in example 1 in terms of delay in the feedback control loop. This model is somewhat more complex but follows essentially the same lines of development as in example 3. The model tracks O2 and CO2 levels in the lung and tissue compartments and models the chemoreflex control of ventilation based on these levels. The compartment inflows and outflows of O2 and CO2 are based on diffusion and blood transport (Fig. 3A). Delays exist in the transport of O2 and CO2 to the sensors, which set the ventilation rate based on the levels of these blood gases. These delays, together with ventilation control gains, can induce unstable breathing patterns similar to Cheyne-Stokes respiration. Further model details are provided in APPENDIX B. Again, this model can be implemented after a reasonably short introduction to simulation. In addition, pre-built Simulink models can be acquired and used to test various combinations of parameters (see the book resource by M. C. K. Khoo in Books and review articles). An important point to note in terms of model design in this example is that here the delay (3) is taken as a point delay (information is delayed by a–perhaps variable–discrete amount). In reality, as blood gases are transported, diffusion will dilute any impulse perturbation in blood gases at the lungs due to abrupt change in breathing. Hence, information about such an abrupt change will arrive at the sensors delayed but also spread out, which will constrain the response of the sensors and reduce the tendency to destabilize the system.

Inclusion of guest speakers in the seminars. Visitors to research institutes are an important resource for enriching the content of interdisciplinary seminars. These researchers provide valuable expertise and insights into skills related to collection, assessment, and interpretation of data and mathematical approaches for analyzing data and modeling systems. These researchers can provide students with appreciation of the current state of the art questions and problems and also provide students with contacts for future collaboration.

Books and review articles. The following resources provide a large number of mathematical models and modeling studies in physiology that could be used in the seminars:


The reviews by Khoo and Yamashiro (29) and Batzel and Kappel (2) include references to a large number of physiological models in cardiovascular and respiratory modeling that can be used.

Online resources. The semester seminars have been supplemented by a series of parallel summer workshops and summer schools. These events were designed to bring together leading experts in mathematical modeling related to physiological issues as well as physiologists with an interest in modeling (for
the various resource links, see again http://www.uni-graz.at/~batzel/course-info.html). This resource page, developed for this report, also includes sample final projects and code for the sensitivity calculations discussed in example 4.

These workshops and summer school webpages provide an extensive listing of research and course topics connected to mathematical-physiological interdisciplinary work. In particular, see the four events described at http://www.uni-graz.at/mc_training_schools/index.htm. Within this resource webpage is a virtual library with extensive notes that have been compiled from these events that can be used as templates for seminar lectures (http://www.unigraz.at/mc_training_schools/library.html).

**Websites.** Online modeling databases include PhysioNet (http://www.physionet.org/), which is designed to collect and coordinate useable data sets for physiology modeling research, and Physiome (http://www.physiome.org/; mentioned above), which is an initiative to organize/merge the very large inventory of mathematical models in physiology that have arisen and continue to appear. These two databases reflect the recognition that coordination of the accelerating body of knowledge and interdisciplinary collaboration are critical to maximize the return on scientific efforts.

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**Fig. 2.** A: diagram of the four-compartment model for the body mass index (BMI) model discussed in example 4. Exchange of toxin $x$ [with internal production rate ($G$)] produced in the organ mass compartment (OM) is only between the extracellular compartment (E) and the OM, muscle mass compartment (MT), and adipose tissue compartment (AT). Furthermore, we assume that the exchange between compartments is proportional to concentration ($C$) differences and only due to diffusive processes, $k_{E,OM}$, $k_{E,MT}$, and $k_{E,AT}$, exchange rate parameters between E and the other compartments; $k_{clear}$, clearance rate. B: several cycles of interdialytic and intradialytic periods simulated from the BMI model. Shown here are the toxin levels in the OM, E, AT, and MT ($C_{OM}$, $C_{E}$, $C_{AT}$, and $C_{MT}$) for a person of high BMI. C: sensitivity curves of relevant parameters for toxin exchange for example 4 for the output state, which is the concentration of toxin in E.
effort. JSim (Java simulation resource) within Physiome allows for user-friendly access to a large set of models and methods for analysis that can be used to illustrate modeling principles.

Evaluations From Students and Teachers

Student and teacher evaluations for the seminars and workshops are presented here. A sample form is provided in Appendix A. The impact of the seminars and summer schools has not been continuously assessed, as this was not a formal requirement previously. However, we obtained the responses of 37 students from the last 2 seminars and 3 of the most recent summer schools (Table 1). Based on the personal feedback of the students over the years, we believe that these responses are representative of the overall expectations and experiences of our students.

In addition, seminar effectiveness and student performance in the seminars have been evaluated in various ways depending on the semester. These included final reports, analysis of

Fig. 3. A: diagram of a six-compartment model for the respiratory system study discussed in example 5. The compartments in blue include a lumped tissue compartment, a brain tissue compartment, and a lung compartment, all with equations for O₂ and CO₂. V, volume; P, partial pressure (related to C and typical for respiratory quantities); subscript B, brain values; subscript a, arterial values; subscript v, venous values; subscript p, peripheral values; subscript c, central values. Subscripts p and c relate to the chemosensor control components (Vp and Vc), which represent the sensors at the carotid bodies and central sensors in the brain, which provide the input to determine Va, which represents the total ventilatory drive. A version of this model is used for the simulation problem linked in Appendix A. B: model simulation of the effects of unstable breathing patterns on the partial pressures of lung and tissue O₂ and CO₂ and brain CO₂.
Results of student evaluations of the seminars and summer schools

<table>
<thead>
<tr>
<th>Question Asked</th>
<th>Mean</th>
<th>SD</th>
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<tbody>
<tr>
<td>The seminars/courses met my expectations.</td>
<td>1.68</td>
<td>0.66</td>
</tr>
<tr>
<td>I will be able to apply the knowledge learned.</td>
<td>2.03</td>
<td>0.82</td>
</tr>
<tr>
<td>The objectives for each topic were identified and</td>
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<td></td>
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<tr>
<td>followed.</td>
<td>1.89</td>
<td>0.83</td>
</tr>
<tr>
<td>The content was organized and easy to follow.</td>
<td>1.83</td>
<td>0.73</td>
</tr>
<tr>
<td>The materials distributed were useful.</td>
<td>2.03</td>
<td>0.88</td>
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<tr>
<td>The speakers/teachers were knowledgeable.</td>
<td>1.44</td>
<td>0.64</td>
</tr>
<tr>
<td>The quality of education was good.</td>
<td>1.76</td>
<td>0.79</td>
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<tr>
<td>The speakers/teachers met the seminar/course</td>
<td>1.61</td>
<td>0.64</td>
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<tr>
<td>objectives.</td>
<td></td>
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<tr>
<td>Critical thinking and student-teacher interactions</td>
<td>1.84</td>
<td>0.85</td>
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<tr>
<td>were encouraged.</td>
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<tr>
<td>Adequate time was provided for questions and</td>
<td>1.89</td>
<td>0.81</td>
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<tr>
<td>discussion.</td>
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<tr>
<td>How do you rate the seminars/courses overall?</td>
<td>1.84</td>
<td>0.68</td>
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Responses were rated on a scale of 1–5, where 1 = strongly agree and 5 = strongly disagree.

Summary and Conclusions

With proper understanding of the physiological and mathematical principles, both physiologists and mathematicians can work together and develop aspects of modeling, which not only provide information regarding regulatory aspects of control but also could lead to the development of predictive parameters that are important in understanding disease development and outcome. We believe that such comprehensive interdisciplinary seminars are important for the development of the learning process, especially in students of varying educational and research backgrounds. Finally, such seminars also provide a foundation for interdisciplinary research while the workshops and summer schools open avenues for future collaborations and networking.

APPENDIX A

A sample simulation problem related to examples 1 and 5 in the text can be found at the following webpage: http://www.uni-graz.at/~batzel/seminar_project_2008.pdf.

All seminar outlines and links for possible seminar topics and lecture materials can be found at this webpage: http://www.uni-graz.at/~batzel/course-info.html.

A sample teacher event survey template that can be used is shown in Fig. A1.

APPENDIX B

Example 4: BMI Transport of Toxin Model Details

Figure 2A shows the BMI compartment model. Compartments include an extracellular compartment (E), an organ mass compartment (OM), a muscle mass compartment (MT), and an adipose tissue compartment (AT). The compartments are characterized by their volumes (VE, VMT, VAT, and VOM). Toxin x is produced in the OM [production rate of toxin (G)], and the exchange of toxin x occurs only between E and the other compartments (OM, MT, and AT; as denoted by the arrows in Fig. 2A). Furthermore, we assume that the exchange between compartments is proportional to concentration differences and only due to diffusive processes. The generation of model equations is carried out in a straightforward manner involving the compartmental exchange rates shown in Fig. 2A for the masses (xOM,xAT, xAT,xOM, and xOM,xAT in mg). For example, to write the differential equation [d/dt(xOM)] representing the change in xOM (in mg/min), we simply apply the mass-balance assumption based on the conservation of mass. As a result, for the OM, the change in toxin mass (or time derivative) depends on the inflow of toxin from E [proportional to the concentration of toxin x in E (xE/VE)], internal rate G, and the outflow of toxin x from the OM proportional to the toxin concentration in the OM (i.e., xOM/VOM). The exchange rate parameter is kEOM. These relations are expressed by the following differential equation:

\[
\frac{d}{dt}(x_{OM}) = G - (k_{EOM}/V_{OM})x_{OM} + (k_{EOM}/V_{E})x_{E}
\]

All other differential equations are derived similarly. Using this model, it is straightforward to choose parameters and volumes to reflect the different BMI body types and test via simulation whether over time the toxin level is higher in low BMI patients under treated by hemodialysis. To carry out this simulation, it is only necessary to assume periods of toxin removal, indicated by setting the clearance parameter (kclear) at zero for interdialytic periods and at the given dialysis clearance rate during dialysis. Figure 2B shows simulations from the model. Several cycles of interdialytic and intradialytic periods were simulated using the BMI model. Figure 2B shows toxin levels in the OM, E, AT, and MT for a person with a high BMI. See again Refs. 25 and 27 for detailed simulations produced by the model that can be reproduced by students with only a bit of training in using simulation software.

Sensitivity analysis. As discussed in Integrating Mathematical and Physiological Perspectives: Course Development under model validation, sensitivity analysis can also be done to see which parameters might have the greatest influence. The sensitivity (\(s\)) of a model output \(y = f(x,p)\) with respect to a parameter \(p\) where \(i\) is time and \(x\) is the state of the system is defined as \(dy/dp\) (for fixed \(i\)). When the sensitivity is low with respect to a given parameter, then errors in the estimate of this parameter will not greatly influence model simulations, and, in fact, this parameter will be hard to estimate and should

Teacher Evaluation Form

I am a:  O Mathematician  O Life Scientist  O Other

Please place an x next to your impressions of the items listed below:

<table>
<thead>
<tr>
<th>Question</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
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<tbody>
<tr>
<td>1. The event structure met my expectations.</td>
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<td>2. Student pool was diverse</td>
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<td>3. The school/workshop mix of research topics was well balanced</td>
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<td>4. The content I prepared was about right for the educational level</td>
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<td>5. The resources available were useful</td>
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<tr>
<td>6. The students were knowledgeable.</td>
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<td>7. The students were motivated</td>
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<td>8. I found the event useful for myself</td>
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<td>9. Students asked many interesting questions</td>
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<td>10. Adequate time was provided for questions and discussion.</td>
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<td>11. How do you rate the educational impact overall?</td>
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Fig. A1. Sample teacher event survey template.

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likely be chosen based on a priori information or group estimates. Hence, sensitivity analysis and tools built from sensitivities, such as subset selection (5) and generalized sensitivity (38), can aid in the strategy for parameter estimation, give hints on which data should be collected and how (experimental design), and can aid in model validation.

To derive, for example, the sensitivity of state $x_{OM}$ with respect to $k_{E,OM}$, note that taking $\frac{\partial}{\partial k_{E,OM}}$ on both sides of the above state equation for $x_{OM}$ produces the following equation:

\[
(\frac{\partial}{\partial k_{E,OM}})\frac{dx_{OM}}{dt} = \frac{\partial}{\partial k_{E,OM}}[G - (k_{E,OM} / V_{OM})x_{OM}]
+ \left( k_{E,OM} / V_{OM} \right) \frac{dx_{OM}}{dt}
\]

Changing the order of differentiation $[\frac{d}{dt}(\frac{\partial}{\partial k_{E,OM}})](x_{OM})$ and considering $\frac{\partial}{\partial k_{E,OM}}(x_{OM})$ as an unknown that appears on the right-hand side after partial derivatives are taken gives a new differential equation for the sensitivity of $x_{OM}$ with respect to $k_{E,OM}$. This equation, when solved with the state equations, will give the sensitivity of $x_{OM}$ with respect to $k_{E,OM}$. The Matlab model code and sensitivity code for this example can be found at the resource webpage cited in Appendix A. The output (see Ref. 27) will show the desired sensitivity over time.

**Example 5: Control of Ventilation Model Details**

In example 5, we describe a respiratory system compartmental model (based on Refs. 19 and 28) that consists of six compartments (the O2 and CO2 compartments overlap in the diagram with ordinary differential equations describing mass balances reflecting the compartment inflows and outflows of O2 and CO2; Fig. 3A).

The compartments include a lumped tissue compartment, a brain tissue compartment, and a lung compartment, all with equations for O2 and CO2. Each tissue equation includes a metabolic rate term to track O2 consumption or CO2 production as well as terms for loading or unloading of these blood gases in exchange with blood flow. For example, the equations for the changes in tissue compartment CO2 and O2 are given as follows:

\[
\begin{align*}
V_{TCO2} \frac{dc_{i,CO2}(t)}{dt} &= MR_{CO2} + F_i[c_{a,CO2}(t - \tau_i) - c_{i,CO2}(t)] \\
V_{TO2} \frac{dc_{i,O2}(t)}{dt} &= -MR_{O2} + F_i[c_{a,O2}(t - \tau_i) - c_{i,O2}(t)]
\end{align*}
\]

In the above equations, $d/dt$ is the time derivative, $c$ is concentration, $V$ is volume (in ml), $MR$ is the metabolic rate (in ml/min), $F$ is blood flow (in ml/min), $T$ is the tissue compartment, subscript $a$ indicates arterial values, and subscript $v$ indicates venous values. With these variables, for example, $V_{TCO2}$ denotes the effective CO2 volume of the general body tissue compartment. The equations are given over time $t$ (in min) with a delay ($\tau_i$) representing the time needed for arterial blood to reach the tissues. As can be seen by comparison, these are mass-balance equations completely analogous to those derived for example 4. Figure 3A shows gas concentrations in terms of partial pressures (P), which are typical in respiratory physiology. Figure 3B shows simulations of the variations in partial pressures of blood gases resulting from unstable breathing patterns. Analogous equations are derived for the lung compartment, where blood gases are exchanged with alveolar air. In these lung equations, the metabolic rates, which add or subtract tissue blood gases via metabolism, become the ventilation rate, which adds or subtracts blood gases via exchange with air.

The control mechanisms incorporate simple expressions for the peripheral chemosensor ($V_P$) and central chemosensor ($V_C$), which influence the ventilation rate ($V_T$). The peripheral chemosensors are located in the carotid bodies and respond to $O_2$ and $CO_2$ levels and sensors in brain tissue (central sensors) monitoring $CO_2$. This model can be easily extended to study many situations, including the transition to sleep, high-altitude breathing, sleep apnea in patients with congestive heart failure, and various tests for assessing ventilatory function (3, 10).

An important additional feature in this model is the incorporation of transport delays (depicted in yellow in Fig. 3B), which describe the delay in transporting blood gases from the lungs to the control sensors. As mentioned in example 1 (in Integrated Content of the Seminars), these transport delays play an important role in the stability of the feedback control of ventilation. This model is easily implemented in Matlab, which also can simulate equations with delay. In addition, the pneuma model and the modeling textbook of Khoo (see Resources and Websites for Seminar Course Development and Ref. 10) provide prewritten software to test the impact of delay on system stability. A final project based on this model, including the main model equations, is given in the link in Appendix A.

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**DISCLOSURES**

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