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Dynamically generated models for medical decision support systems

Jörn Kretschmer [a,*], Alexander Wahl [b], Knut Möller [a]

[a] Furtwangen University, Institute for Technical Medicine, Jakob-Kienzle-Straße 17, 78054 Villingen-Schwenningen, Germany
[b] Furtwangen University, Department of Informatics, Robert-Gerwig-Platz 1, 78120 Furtwangen, Germany

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ABSTRACT

Doctors applying mechanical ventilation need to find the best balance between benefit and risk for the patient. Mathematical models simulating patient's reactions to alterations in the ventilation regime may be employed. A framework is introduced that is able to dynamically combine mathematical models from different model families to form a complex interacting model system. Each of these families consists of submodels differing in complexity of dynamics formulation or anatomical/geometrical resolution. The interaction of model systems reveals qualitatively varying results depending on the complexity of the involved models. Realistic overlaying of respiratory and cardiovascular rhythms can be detected in blood gas concentrations.

1. Introduction

Mechanical ventilation can aid patients in intensive care units to survive states of impaired respiratory function. Unfortunately, this intervention may cause secondary or so called "ventilator induced" lung injury (VILI) if not applied appropriately. Therefore, the best balance between benefit and risk has to be found by the treating clinician. This can be exemplified with the dilemma of mechanical ventilation therapy in ARDS (Acute Lung Distress Syndrome) patients. This disease leads to atelectasis, i.e. due to collapsing alveoli the available gas exchange surface is significantly decreased. One of the immediate goals of therapy is to re-open the collapsed alveoli ("recruitment") by providing high ventilation pressures. These however are harmful for the lung tissue and can lead to barotrauma [1]. The doctor in charge usually has neither time to stay at the bedside nor to optimize the ventilator setting according to the needs of the patient and to explore the complex interactions between ventilator and respiratory system. Therefore it is claimed that better settings adapted to each patient individually are possible. Mathematical models of the human respiratory system can help in finding these optimal settings using the simulation results in combination with individualization methods related to artificial intelligence and active exploration.

However, not only the human respiratory mechanics but a broader context is needed to accurately predict a patient's reaction to alterations in the ventilation regime. This may for e.g. include gas exchange and cardiovascular dynamics. In patients suffering from ARDS, the applied PEEP and the resulting rise in intrathoracic pressure affects the human cardiovascular system e.g. changes cardiac output [2]. Although physiological models dealing with these processes can be found in literature in various complexities, most of them are assuming the particular organs to be isolated mechanisms. Thus, interactions with other physiological processes in the human body are not considered. Complex models regarding these interactions are naturally not consisting of interchangeable submodels, so that changes in the detailing of the model or shifting the focus of simulation towards a different aspect of the human physiology lead to time consuming redesign of the model structure.

Therefore a framework for dynamic generation of complex model systems is proposed. A medical decision support system (MDSS) can employ this framework to incorporate different submodels into its reasoning processes depending on needs. Driven by the current reasoning demands, the MDSS will choose appropriate submodels from a model library (see Fig. 1). The system may then exploit the opportunity to execute several simulations to optimize parameter settings of the ventilator or other therapeutical measures. With appropriately identified model parameters these measures are adapted to the actual individual case, i.e. the particular patient would receive optimal ventilation when applying these settings. Using a model library comprising models of different complexity moreover opens up new, robust and efficient approaches for parameter identification. More simple, less detailed models are used to estimate initial parameter settings close to final values before these estimates are introduced into the identification process of advanced models [3].

2. Methods

2.1. Model families and submodels

The proposed system defines model families as groups of models that are related in terms of simulation focus.

* Corresponding author. Tel.: +49 7720 307 4370; fax: +49 7720 307 4210.
E-mail address: krj@hs-furtwangen.de (J. Kretschmer).

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Fig. 2 exemplarily shows a model family of respiratory mechanics comprising various models distinguished by different aspects like numerical order, linearity or preliminary assumptions [4–6].

The above example illustrates a potential hierarchical structure of models inside a model family. However in this paper we restrict ourselves to a subset of this model family. Three major model families have been established: respiratory mechanics, gas exchange and cardiovascular dynamics. All individual models inside a model family differ in complexity of the dynamics formulation or anatomical/geometrical resolution, i.e. the number of Ordinary Differential Equations (ODEs) that define the particular model. Below, each model family with its different models ordered from low to high complexity are explained in detail.

The model family of respiratory mechanics (Fig. 3) includes a simple 1st order RC-model as the simplest non trivial analog. To simulate time depending effects, four 2nd order RC-models have also been added to this model family. The implemented models can moreover be split up by their representation of lung and chest wall compliance. Using separate chest wall compliance is needed to calculate pleural pressure, which further increases model complexity. Shunt effects in mechanical ventilation can be simulated by using the implemented model as proposed by Khoo [4].

Next we discuss a gas exchange model family consisting of two models, which differ in respiratory flow assumptions. The less complex model was adapted from the 3-compartment model proposed by Chiari et al. [7] whereas the equations defining the carbon dioxide dissociation curve were adopted from Sharan and Selvakumar. [8]. This model assumes laminar, constant gas and blood flow; inspiration and expiration phases are not considered. To enable interaction with respiratory mechanics, alterable alveolar volume and a dead space compartment as proposed by Benallal et al. [9,10] have been added to the simple model to form a more complex representation. Now the gas exchange model is enabled to react to varying conditions of alveolar volume as delivered by the employed respiratory mechanics model. Fig. 4 illustrates the gas exchange model family as implemented in the framework.

Fig. 5 shows the model family of cardiovascular dynamics. Here, four models ranging from 3 to 19 differential equations will be considered in this paper. A simple representation has been adopted from Parlikar and Verghese. [11] who proposed a 3-compartment model that assumes a single cardiac compartment as well as two body compartments. Moreover a 6-compartment model based on Heldt et al. [12] has been added. This model is responsive to changes in intrathoracic pressure, which is required to capture blood pressure variations depending on ventilation pressure. Furthermore, a serially structured 14-compartment model by Danielsen and Ottesen [13] and a parallel connected 19-compartment model as presented by Leaning et al. [14] were added to the model family of cardiovascular dynamics. Reaction to changes in intrathoracic pressure has also been implemented into the 14-compartment model. All models contain time variant ventricular compliances to mimic heart muscle contraction and to generate cardiac pulsation.

All described models have been coded in MATLAB (R2008a, The MathWorks Inc., Natick, MA, USA) following the model descriptions in literature and have been tested separately to ensure operability within physiological limits.

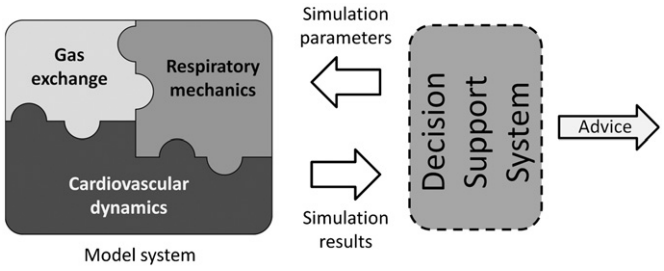

Fig. 1. Integration of interacting model families into a medical decision support system. The MDSS can run several simulations using the complex model system to find e.g. optimal ventilator settings for the particular patient.

2.2. Model interfaces and exchange parameters

To ensure interchangeability within the same model family we have specified common interfaces. Inputs to the complete system are governed by the ventilator settings. An interface connects ventilator settings with the respiratory mechanics model. Inspiratory air flow ($\dot{V}_{in}$) and respiratory frequency (f_R) are parameters exchanged via this interface. Ventilator settings also influence gas exchange by inspiratory gas fractions of oxygen and carbon dioxide (F_{i,O_2},F_{i,CO_2}). Inside the model system there are interfaces defined between each model family. Thus, respiratory mechanics influence cardiovascular dynamics via pleural pressure (P_{pl}). Gas exchange is influenced by respiratory flow ($\dot{V}$) and alveolar volume (V_A) derived from the respiratory mechanics model as well as cardiac output (CO) offered by the cardiovascular model. Fig. 6 shows the model interactions and interfaces.

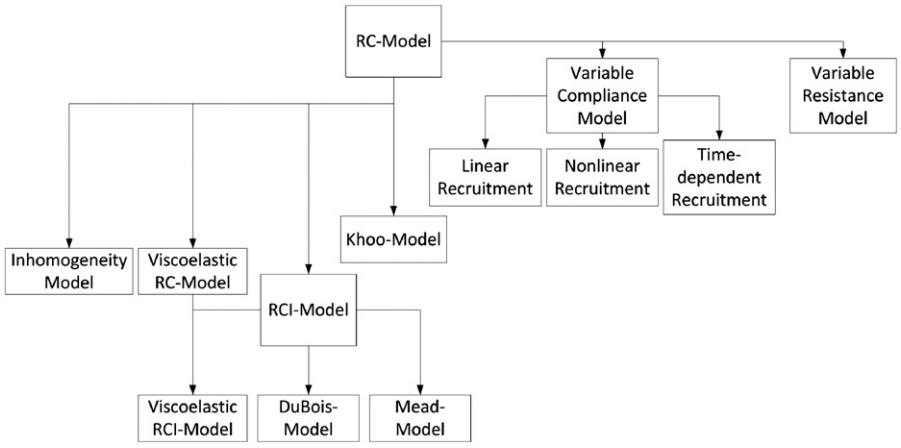

Fig. 2. Exemplary model family of respiratory mechanics comprising several models in hierarchical order. Hierarchy is based on aspects like numerical order, linearity or preliminary assumptions.

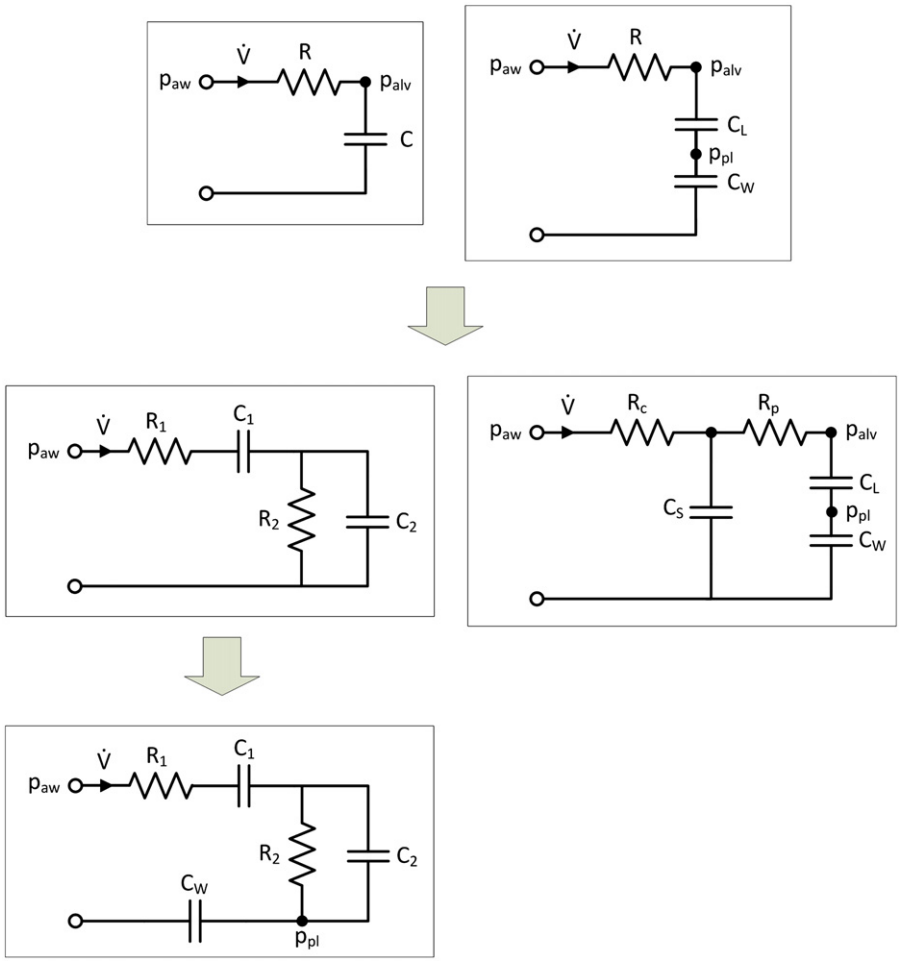

Fig. 3. Respiratory mechanics model family. Resistors (R) depict airway resistances, capacitors (C) represent compliances, p_{aw}—airway pressure, p_{alv}—alveolar pressure, p_{pl}—pleural pressure, $\dot{V}$ depicts air flow into the airways. Top models are 1st order model representations, middle row comprises models of 2nd order (model on left side assumes combined lung and chest wall compliance, right model uses separate compliances: C_L—lung compliance, C_W—chest wall compliance). C_S represents shunt compliance. Model in the lowest row is of 3rd order and comprises chest wall compliance C_W.

2.3. Runtime execution

To avoid temporal inaccuracies at the interfaces, all submodels need to be computed concurrently. Thus, solving the individual submodels independently and consecutively is not possible. To allow MATLAB to call all ODEs at the same time all submodels could be incorporated into one file. This, on the other hand, would compromise easy and dynamic interchanging of submodels, as the program code would have to be created for every model combination or all possible combinations would have to be provided in advance.

To circumvent this problem a dedicated caller algorithm was implemented, that invokes all chosen submodels at the same time step and creates a vector containing all state signal derivatives. The caller algorithm is created in such a way that an arbitrary number of submodels can be combined to form the overall model system (OMS). For interaction between the submodels a global structure is defined that comprises all the model parameters. This structure is updated after every simulation step. Fig. 7 shows the program flow of the caller algorithm.

2.4. Model combinations for evaluation

Model interaction was tested using different submodel combinations. Table 1 shows the tested combinations and the number of ODEs defining the OMS. In OMS1 pseudo models with constant air- and blood flow were used for respiratory mechanics and cardiovascular dynamics. Thus, only gas exchange was simulated dynamically. OMS 1 is computationally not demanding and requires only limited information for parameter identification. Nevertheless it is able to predict basic blood gas characteristics. In OMS2 a dynamic model to simulate lung mechanics is added. Therefore, gas exchange has to be switched to a tidal breathing model that is reactive to alternating air flow and alveolar volume. OMS2 includes effects of mechanical ventilation on gas exchange and may be more appropriate in therapy optimization. OMS3 comprises dynamic models for all model families by adding a simple dynamic cardiovascular model, which also influences gas exchange. Sudden changes in heart rate or blood pressure now impose influence on blood gases. OMS4 finally contains all possible submodel interactions, as the last interface is included into the OMS by adding a cardiovascular model reactive to pleural pressure. This model system provides a most complete picture of the patient's reactions to alterations in the ventilation regime. Ventilator settings can be optimized with respect to the patient's cardiac output as may be found necessary in patients featuring cardiovascular instability. Though most powerful, it is computationally the most expensive model combination. The large amount of parameters require a careful designed strategy for parameter identification.

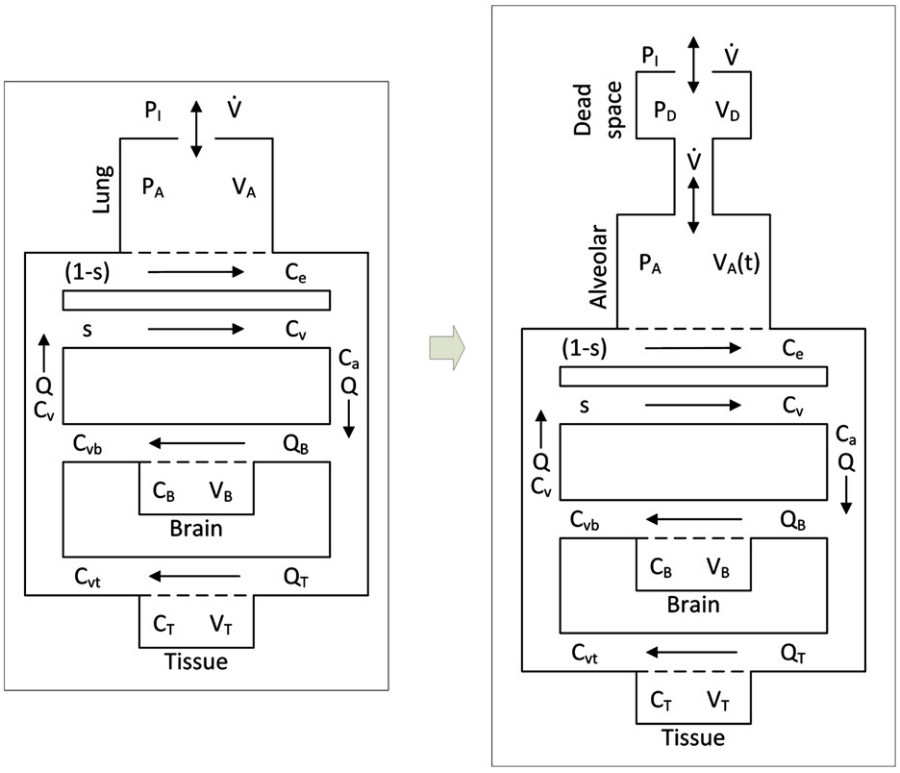

Fig. 4. Examples from the gas exchange model family. The model on left side assumes constant alveolar volume, whereas the model on the right side is more complex, i.e. including dead space volume and alterable alveolar volume. *P*—partial pressure, *V*—volume, $\dot{V}$—flow, *C*—gas concentration in blood, *Q*—cardiac output. Indices are A—alveolar, D—dead space, I—inspiratory, B—brain tissue, T—body tissue, a—arterial, v—venous, e—end-capillary, vb—venous brain tissue, vt—venous body tissue. Partial pressures and concentrations are again separated into oxygen and carbon dioxide gas. s indicates shunt.

All systems were simulated using standard physiological parameters as found in literature or in the model description. Simulation was started from an equilibrium system state.

3. Results

Simulation results for airway pressure, arterial oxygen concentration and arterial blood pressure in OMS 1–4 are shown in Fig. 8a–d. The presented results are chosen exemplarily to illustrate the submodel interactions with rising overall model system complexity.

Simulation results of OMS1 show constant arterial oxygen concentration of 0.1925 l/l (Fig. 8a). In OMS2 alveolar volume and respiratory flow is alternating dynamically as the pseudo model from OMS1 is replaced by a 1st order respiratory mechanics model. Therefore, airway pressure shows distinct inspiration and expiration phases (0–26 mmHg, Fig. 8b). Additionally, arterial oxygen concentration shows an alternating behavior (0.1955 l/l–0.1962 l/l). In OMS3 a simple model of cardiovascular dynamics is included in the model combination, thus arterial blood pressure is oscillating between 83 mmHg and 120 mmHg (Fig. 8c). The gas exchange submodel shows additional local maxima in the results for arterial oxygen concentration. OMS4 comprises 2nd order respiratory mechanics, thus airway pressure shows viscoelastic behavior (Fig. 8d). Additionally, arterial blood pressure variability comprises a respiratory related lower frequency oscillation, i.e. the pressure amplitude ranges cyclically from 23 mmHg to 32 mmHg.

4. Discussion

This paper describes a framework for the dynamic combination of physiological models from different model families. The proposed system is intended for use in medical decision support systems (MDSS) and for automated optimization of mechanical ventilation therapy [15–18]. The framework is able to dynamically create complex model systems in dependence of diagnostic or therapeutic needs. These model systems shall be exploited by an MDSS to predict the effects of alternative therapeutical strategies, e.g. to explore the usefulness of certain ventilator settings to support a specific patient on ICU [19]. In other words optimal ventilator settings with respect to some disease and patient specific objective function can be determined under the assumption that the model reflects the individual properties of the patient. Previously proposed MDSS only applied a fixed combination of models to predict patient responses [19]. However, fixed physiological models might show to be inappropriate for varying therapeutical situations [20,21]. With our proposed system, an MDSS is given the ability to choose an appropriate model combination for a given clinical situation during the reasoning process. Additionally, the proposed framework can be used for training purposes, as it is able to generate various scenarios of differing complexity and is thus adaptable to the experience of the learner. Respecting the introduced interfaces, every model family can be extended by new submodels. Moreover, new model families can be added to the framework.

Most of the implemented submodels have been checked for validity by their respective authors through comparison with data found in literature [7,12,13,22] or verification with experimental data [10,12]. Parlikar and Verghese. [11] did not validate their model, however simulation results are consistent with values found in literature. The respiratory mechanics model as proposed by Khoo [4] has been validated by Schranz et al. [3].

In the results arterial oxygen concentration interaction with respiratory mechanics is clearly visible whenever tidal breathing models were applied, i.e. concentrations alternate between

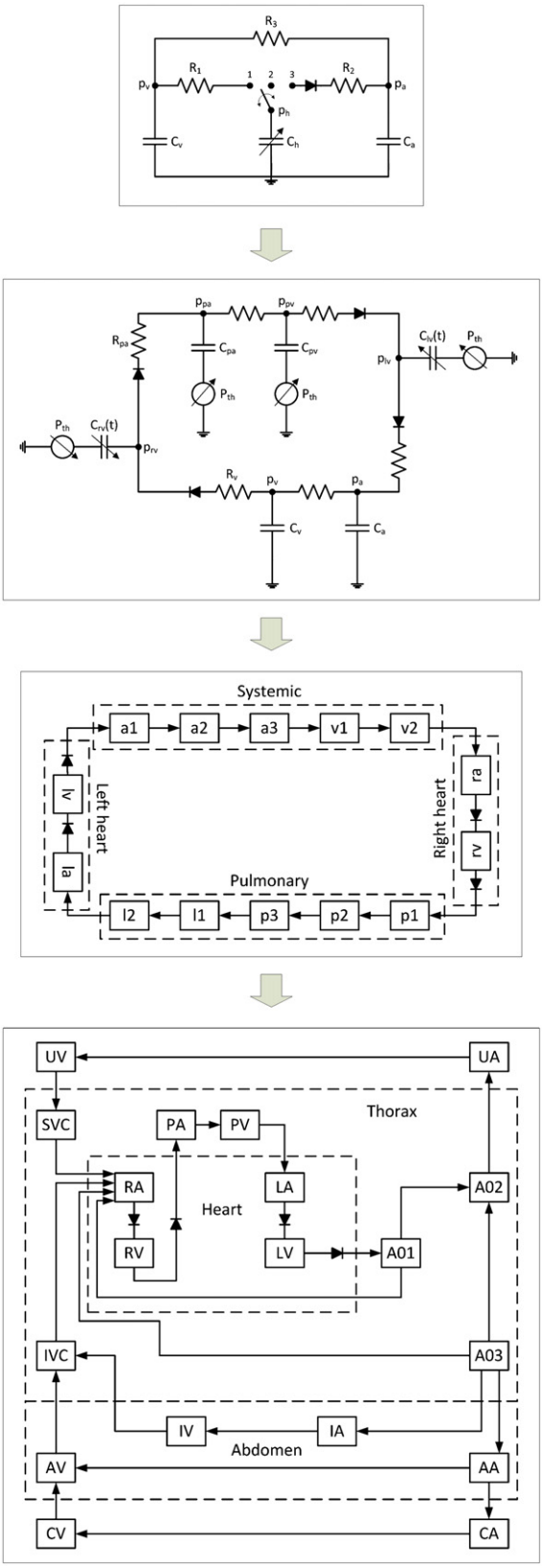

Fig. 5. Cardiovascular model family. Ordered from top to bottom a 3-compartment model, a 6-compartment model with reaction to changes in intrathoracic pressure, a serially connected 14-compartment model and a parallel connected 19-compartment model are depicted. Resistors (R) represent vascular resistances and capacitors (C) vascular compliances. P indicates pressures in the compartments and P_{th} intrathoracic pressure. Diodes depict atrial and ventricular valves, they open if $P_{n-1} > P_n$. A detailed representation of the 14- and 19-compartment models as well as symbol definition is shown in the Appendix.

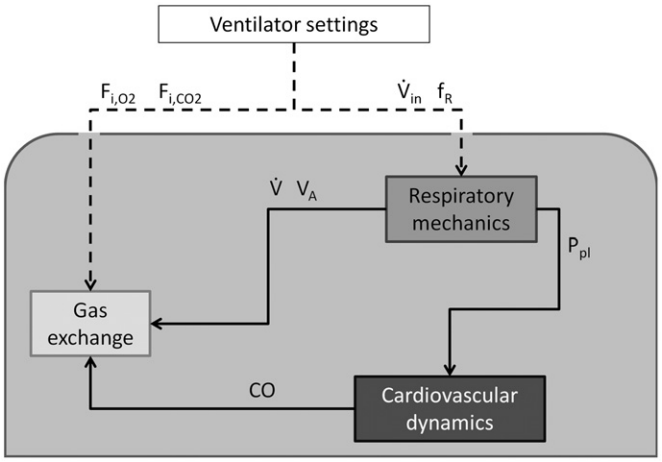

Fig. 6. Model interfaces set up. Input signals are inspiratory gas fraction of oxygen and carbon dioxide (F_{i,O_2}, F_{i,CO_2}), applied respiratory frequency (f_R) and inspiratory air flow ($\dot{V}_{in}$). Exchange parameters inside the model complex are respiratory flow and alveolar volume ($\dot{V}$, V_A), pleural pressure (P_{pl}) and cardiac output (CO).

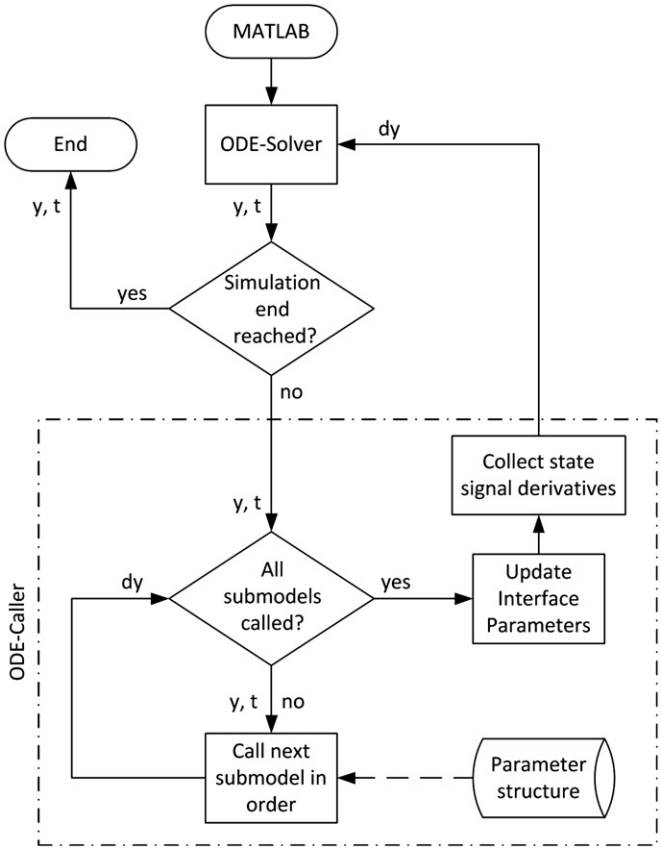

Fig. 7. Proposed dedicated caller algorithm. The figure shows the complete simulation flow from the start of the MATLAB ODE solver algorithm to the return of the simulation results. For every simulation time step the ODE-caller invokes each submodel and collects the state signal derivates that are returned by the submodel. Model interaction is achieved using a global parameter structure that is updated with every time step.

inspiration and expiration phases. This behavior can be linked to the alternating alveolar volume and respiratory flow that are derived from the respiratory mechanics model. Fig. 9 shows the simulation results for alveolar volume and respiratory flow in system 2. In moments of high alveolar volume and inspiratory flow, oxygen concentration in blood rises, whereas it decreases in the expiration phases when alveolar volume decreases. Blood

Table 1
List of tested model combinations. System complexity rises with implemented model detail. Four model combinations were tested, comprising an increasing number of ODEs and model interactions. OMS1 contains only gas exchange, pseudo models with constant air- and blood flow were used for respiratory mechanics and cardiovascular dynamics, respectively.

OMS-Nr.	Respiratory mechanics	Gas exchange	Cardiovascular dynamics	Number of ODEs
1	Continuous air flow	Continuous air flow	Continuous blood flow	6
2	1st order	Tidal breathing	Continuous blood flow	10
3	1st order	Tidal breathing	3-compartment	13
4	2nd order with pleural pressure	Tidal breathing	14-compartment	25

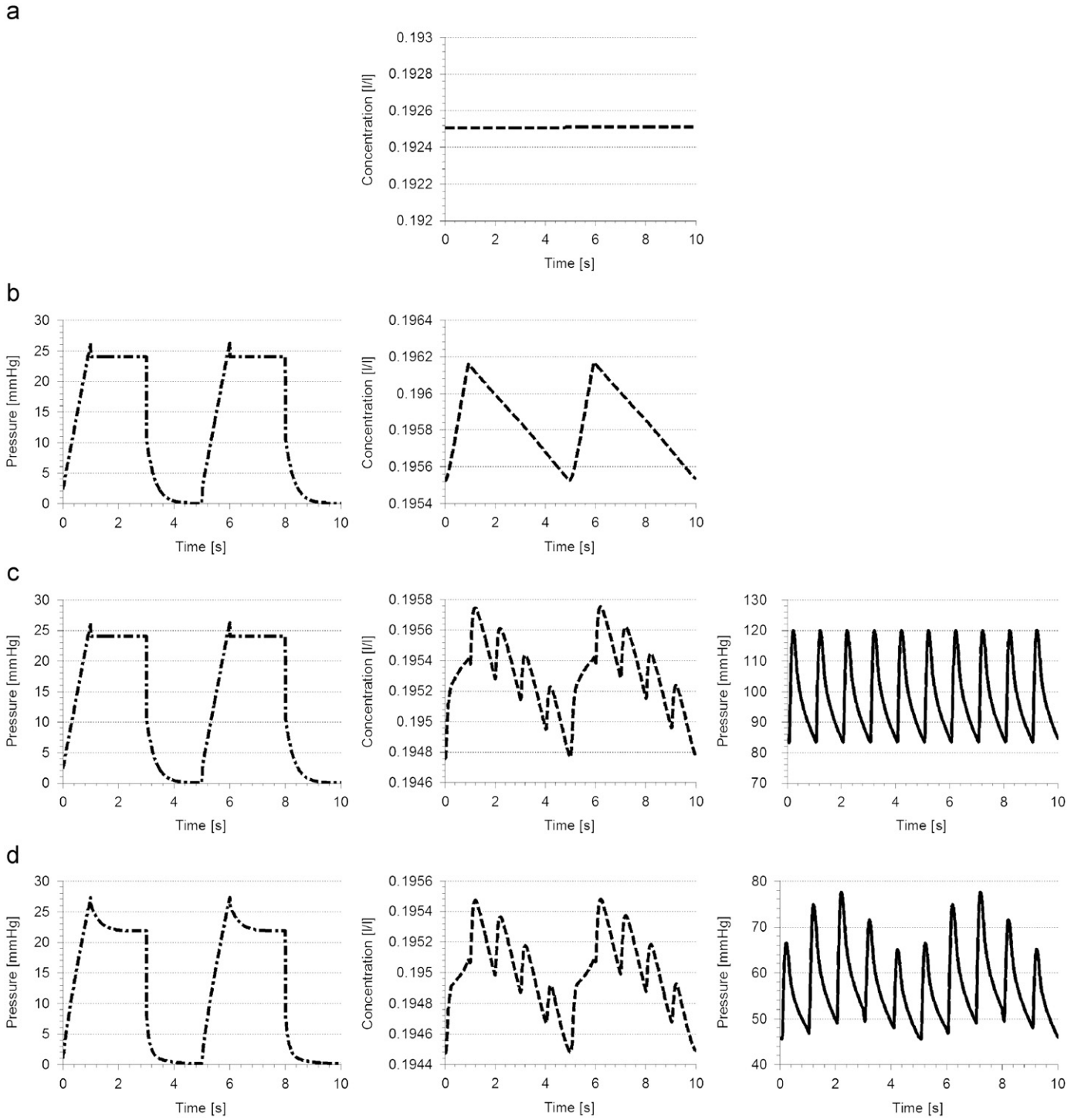

Fig. 8. Results for all evaluated model combinations OMS1(a)–OMS4(d). Airway pressure is shown as dash-dotted line; arterial oxygen gas concentration is shown as dashed line, arterial blood pressure is shown as solid line.

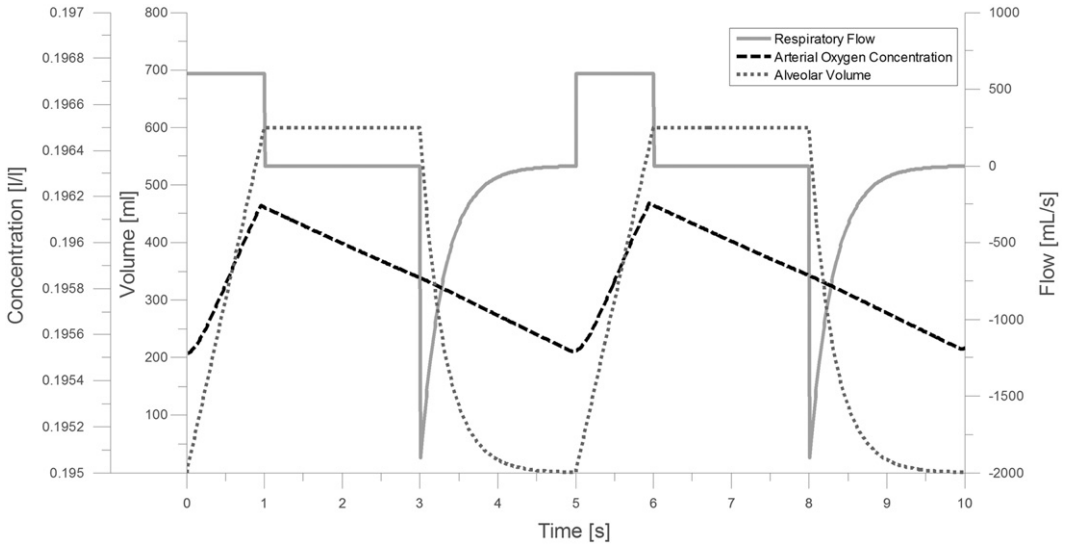

Fig. 9. Results for alveolar volume, respiratory flow and arterial oxygen concentration in OMS2. Arterial oxygen concentrations alternate between inspiration and expiration phases. In moments of high alveolar volume and inspiratory flow, oxygen concentration in blood rises, whereas it decreases in the expiration phases when alveolar volume decreases.

concentration of carbon-dioxide shows the opposite behavior. Similar findings in the animal models are reported in literature [23,24].

Additionally, reactions to changes in cardiac output can be observed when a pulsatile cardiovascular submodel is included in the OMS. They manifest themselves as local maxima in the oxygen concentration curves synchronized to cardiac output, i.e. during the cardiac ejection phase. In simple simulations models with a constant blood flow within physiological limits cardiac output has negligible influence on gas concentrations in blood. In contrast, cardiac output has a pronounced effect on the gas exchange submodel when dynamic cardiovascular models are employed, as the complete volume is ejected during the first third of the cardiac cycle, the ejection phase.

Moreover, cardiovascular dynamics showed reactions to alterations in pleural pressure. This is exhibited as superimposed variations on the arterial blood pressure results. Laude et al. reported analogous findings in a human experiment [25]. The applied 14-compartment cardiovascular model does not comprise a baroreceptor model or cardiovascular regulation. Thus, upon application of pleural pressure levels as they occur in mechanical ventilation, the mean arterial pressure decreases to 62 mmHg. Tests using the 19-compartment cardiovascular model as proposed by Leaning et al. [14] including a baroreceptor model showed results of arterial pressure within physiological limits.

The presented simulations show physiologically consistent results. Naturally, more complex model approaches like multi-scale models would show even higher physiological detail, which however is not required in this framework. The aim of this work is to create model systems that are reliably identifiable and require low computing effort. Still the proposed framework is extendable to more complex modeling approaches if this should be necessary in response to the specific clinical scenario.

A drawback that appeared during simulation tests is that computing time rises rapidly with increasing model complexity. This would compromise the application of our framework in MDSS at the actual stage, because in order to find the optimal ventilation setting an MDSS needs to run several simulations applying different simulation parameter settings. As this optimization procedure needs to be executed in a reasonable time, simulations need to be efficient and faster than real time. Fig. 10 shows the resulting computing times for all the presented model

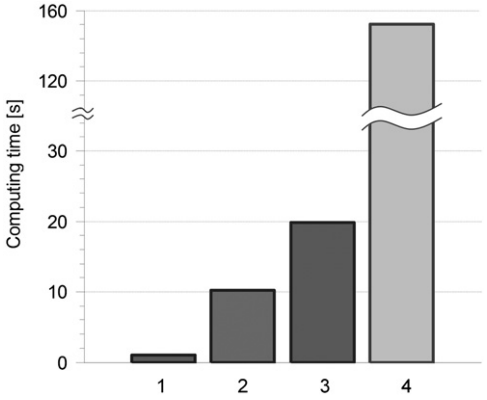

Fig. 10. Computing times using MATLAB ode113 function on OMS 1–4. Computing time rises rapidly with increasing model complexity. Simulation was executed on a standard PC (Q8200, 4 × 2.33 GHz, 4 GB RAM).

systems, using the ode113 algorithm on a standard PC (Q8200, 4 × 2.33 GHz, 4 GB RAM). However, first tests of a sophisticated integration algorithm, that is designed specifically for this application, showed promising results [26].

5. Conclusion

Preliminary tests demonstrated that the proposed framework is useful for dynamic generation of complex model systems. The system is flexibly extendable and can be adapted to many simulation scenarios. It exhibits the potential to improve medical decision support or training of medical personnel. Still, evaluation with clinical data is required and numerical algorithms need to be adapted to the complex model systems for higher efficiency.

Summary

Mechanical ventilation can aid patients in intensive care units to survive states of impaired respiratory function. Unfortunately, this intervention may cause secondary or so called "ventilator induced" lung injury (VILI) if not applied appropriately. Therefore,

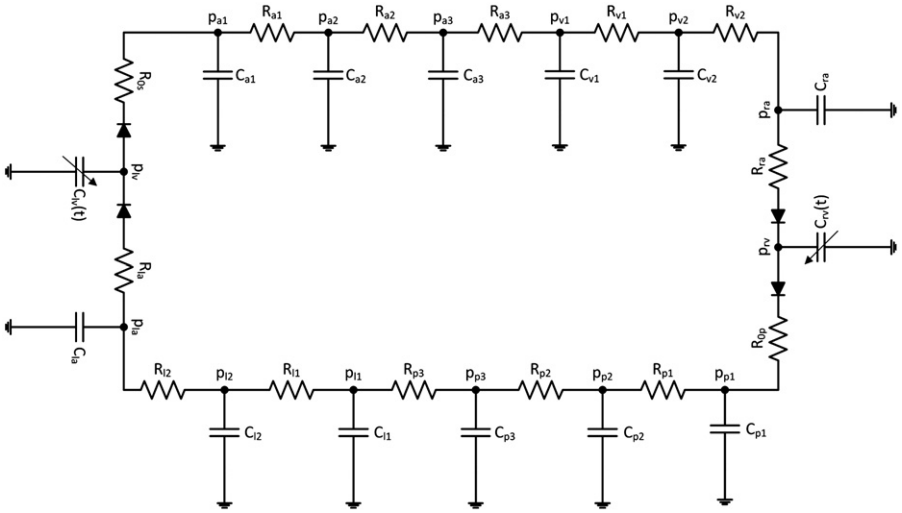

Fig. 11. 14-compartment cardiovascular dynamics model as proposed by Danielsen and Ottesen. The model comprises five systemic, five pulmonary and four cardiac compartments. It has a linear structure, i.e. no bifurcations are implemented in the model structure. Pulsatile behavior of the ventricular cavities is simulated by time-varying compliances. Atrial and ventricular valves are used to avoid blood flows in inverse direction. Symbol definition is shown in Table 2.

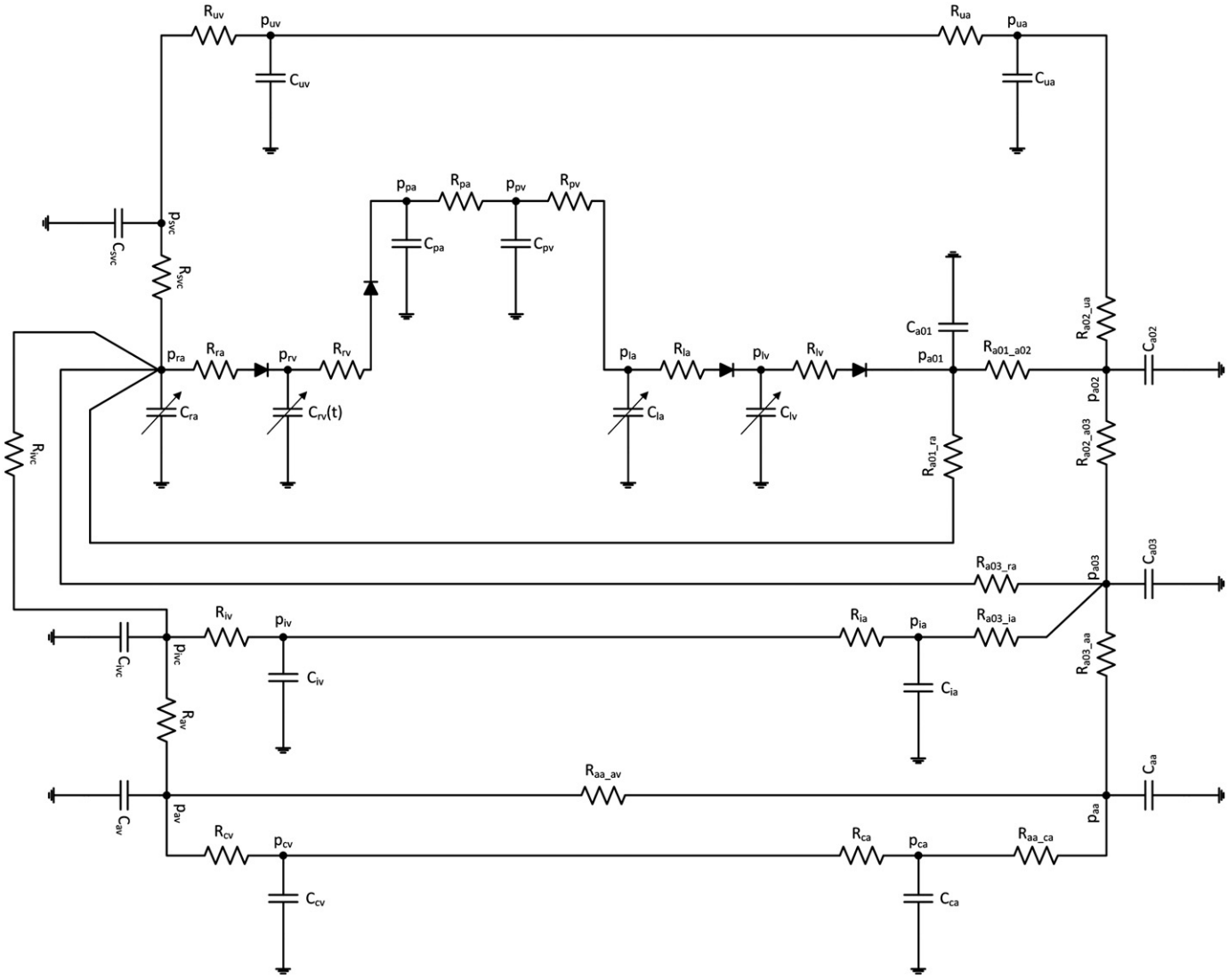

Fig. 12. 19-compartment cardiovascular dynamics model as proposed by Leaning et al. The model is divided into coronary, thoracic and abdominal cavity. Additionally there are head and arms and leg compartments. The model comprises a parallel structure, i.e. bifurcation of blood vessels is implemented in the model. Pulsatile behavior of the ventricular cavities is simulated by time-varying compliances. Atrial and ventricular valves are used to avoid blood flows in negative direction. Symbol definition is shown in Table 2.

Table 2
Symbols and definitions as used in the cardiovascular model representations (Figs. 5, 11 and 12).

Symbol	Definition	Symbol	Definition
h	Ventricular	v2	Pulmonary veins
a	Arterial	la	Left artrial
v	Venous	ra	Right artrial
lv	Left ventricular	A01	Ascending aorta
rv	Right ventricular	A02	Aortic arch
th	Thoracic	A03	Thoracic aorta
pa	Pulmonary arterial	IA	Intestinal arteries
pv	Pulmonary ventricular	IV	Intestinal veins
a1	Large systemic arteries	AA	Abdominal arteries
a2	Small systemic arteries	AV	Abdominal veins
a3	Systemic arterioles	CA	Leg arteries
v1	Systemic venules	CV	Leg veins
v2	Small systemic veins	IVC	Inferior vena cava
p1	Pulmonary arteries	UA	Head and arm arteries
p2	Pulmonary arteries	UV	Head and arm veins
p3	Pulmonary capillaries	SVC	Superior vena cava
v1	Pulmonary veins		

doctors applying mechanical ventilation need to find the best balance between benefit and risk for the patient. Mathematical models can assist in finding optimal settings for each patient individually. Thereto mathematical models simulating various physiological processes to predict patient's reaction to alterations in the ventilation regime have to be employed. However, not only the human respiratory mechanics but a broader context is needed to accurately predict a patient's reaction to alterations in the ventilation regime. This may e.g. include gas exchange and cardiovascular dynamics. Thus, these simulations should not focus on respiratory mechanics exclusively but also other model families should be included in the simulation.

To this extend a framework is introduced that is able to dynamically combine models of respiratory mechanics, gas exchange and cardiovascular dynamics to form a complex interacting model system. Each of these model families consists of submodels differing in complexity of the dynamics formulation or anatomical/geometrical resolution, i.e. the number of Ordinary Differential Equations that define the particular model. As all submodels need to be computed concurrently, a new algorithm is introduced that combines all selected submodels and handles model family interaction at runtime. This algorithm is created in such a way that an arbitrary number of submodels can be combined to form the overall model system. For interaction between the submodels a global structure is defined that comprises all the model parameters and is updated after every simulation step. Four different model combinations with an increasing number of interactions have been tested. Simulations showed physiologically consistent interaction between the model families.

Conflict of interest statement

None declared

Acknowledgments

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Appendix

Figs. 11 and 12 show detailed representations of the 14-compartment cardiovascular model by Danielsen and Ottesen [13] and the 19-compartment model by Leaning et al. [14]. Table 2 shows the symbol definitions of both the figures.

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