Dynamic Generation of Physiological Model Systems

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Abstract— **A versatile software for dynamic generation of physiological model systems is proposed. Via a graphical user interface the user can choose and combine models of varying abstraction level and complexity from the following three model families: respiratory mechanics, gas exchange and cardiovascular dynamics. Tests of different simulation runs showed results and model delay times consistent with human physiology.**

Keywords— **Physiological simulation, MATLAB, cardiovascular dynamics, respiratory mechanics, gas exchange.**

I. Introduction

Mathematical models are widely used to simulate physiological processes in the human body and can be exploited for diagnostic purpose or the automation of therapeutical measures [1]. The standard models described in literature usually assume the organs to be isolated mechanisms and therefore lack of any interaction with other physiological processes in the human body. But in model based diagnosis or therapy the interaction of different physiological systems is mandatory. These interactions can include e.g. cardiovascular response to intrathoracic pressure or reaction of body gas exchange to variations in cardiac output. Complex models with interaction between different physiological processes are usually not consisting of interchangeable submodels, so that any adaption of the submodels' abstraction level or extension of the model requires time consuming redesign. We therefore designed a versatile software based on MATLAB with dynamically exchangeable subsystems within the three model families of respiratory mechanics, gas exchange and cardiovascular dynamics. This model system is part of the Autopilot-BT system devoted to the partial automation of respiratory therapy [1].

In model based diagnosis and therapy the model system has to be individualized to patient specific physiological behaviour. Therefore parameter identification is required to fit all model parameters such that the patient characteristics are reproduced by the model system. This parameter identification will as well profit from this modular approach.

II. Methods

A. Model Families and Submodels

To allow interchangeability and interaction between the submodels, important parameters were extracted from the corresponding literature. Common interfaces were defined for each model family based on these parameters to ensure interchangeability within the same model family. For the simulation of human body gas exchange we used a 2-compartment model described by Chiari et. al. [2] with the carbon dioxide dissociation curve as found by Sharan et al. [3]. Their gas exchange model assumes laminar, continuous blood and gas flow. To integrate their model and at the same time to ensure interaction with respiratory mechanics the tidal breathing model introduced by Benallal et al. [4] was added to the alveoli model equation. The model family of cardiovascular dynamics consisted of a 3-compartment model by Parlikar et. al. [5] as well as a serially connected 14-compartment model by Danielsen and Ottesen [6] and a parallel connected 19-compartment model with CNS controller by Leaning et. al. [7]. Moreover both the cardiovascular models by Danielsen and Ottesen and Leaning et al. were extended to respond to intrathoracic pressure. The respiratory mechanics were based on a 1st order RC-model and a 2nd order RC-model. All described models have been coded in MATLAB software following the model descriptions in literature and have been tested separately to assure operability within physiological limits.

In Fig. 1 the model interactions are shown. Starting with the lungs the first interface is located between the respiratory mechanics and the ventilator settings. Both models are connected by the following parameters: applied airway pressure (P_{aw}), the positive end-expiratory pressure (PEEP) and the ventilation frequency (fR). The second interface between respirator and human physiology is concerned with gas exchange processes. It includes as parameters the inhaled gas fractions of oxygen (FiO_2) and carbon dioxide ($FiCO_2$) directly influencing the end-capillary partial pressures of these gases. As mentioned above a separate tidal breathing model had to be added, which in the MATLAB

P.D. Bamidis and N. Pallikarakis (Eds.): MEDICON 2010, IFMBE Proceedings 29, pp. 25–28, 2010.
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representation is separated from the body gas exchange. This block called "lung gas exchange" is moreover influenced by alveolar volume (V_A), air flow ($\dot{V}_A$) and inspiration/expiration ratio (I/E) given by respiratory mechanics. Both lung and body gas exchange are also influenced by cardiac output (CO) which is determined by the cardiovascular dynamics. The last interface is located between cardiovascular dynamics and respiratory mechanics where intrathoracic pressure (P_{th}) influences cardiac output.

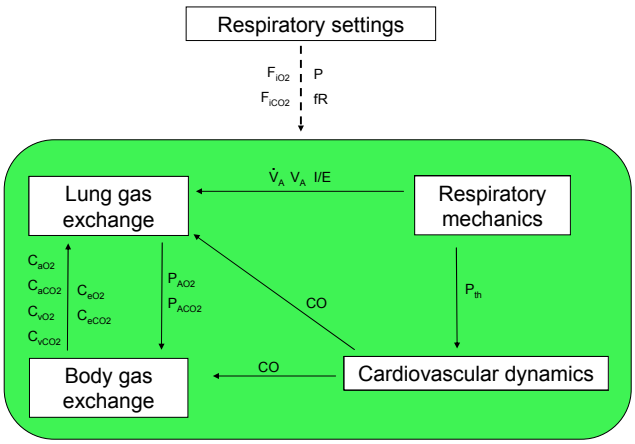

Fig. 1 Model interfaces setup

B. *MATLAB Source Code Setup*

Since the MATLAB differential equation solver needs the model system to provide all state signals at the same time step, consecutively solving of the separate submodels is not possible. One approach to sorting out this problem would be incorporating all chosen submodels into one file to allow MATLAB to call all ODEs at the same time. This on the other hand would compromise simple interchanging of several submodels.

The solution to the just mentioned dilemma is given by using a dedicated caller algorithm. This invokes all chosen submodels at the same time step and creates the vector containing all state signal derivatives. Afterwards this vector is handed over to the ODE solver which calculates the corresponding state signal vector. The caller program is created in such a way that it can combine an arbitrary number of submodels as it is most flexible using the powerful "eval" command in MATLAB. To allow communication between the different submodels all exchangeable parameters are part of a global parameter struct, being updated when the corresponding submodel is invoked.

To allow parameter alteration during the simulation, a stepwise solving of the differential equations has been introduced. Via the graphical user interface described below the user can change parameters while the simulation is running. Upon the next pause and continue phase of the simulation there will be a check if the actual breath or heartbeat is finished (this depends on the chosen parameter). If the result is positive, the new parameter value is saved and the simulation is continued using the last calculated result as new starting conditions. Otherwise the remaining time of the actual breath/heartbeat is simulated before changing the parameter value (Fig. 2).

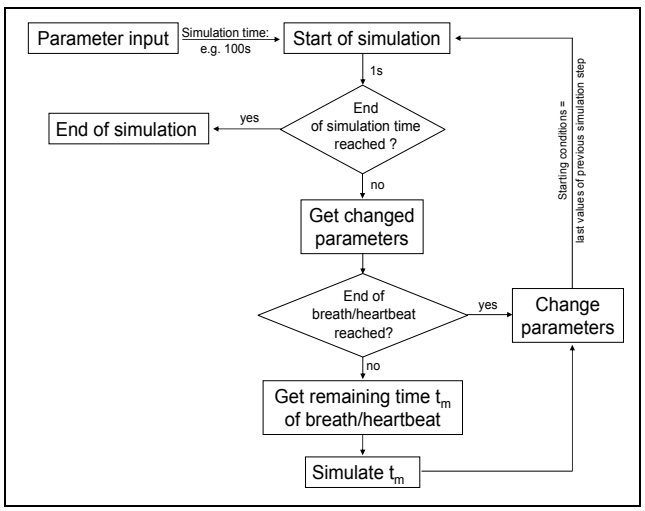

Fig. 2 Algorithm for parameter alteration

C. *Graphical User Interface*

To allow user friendly handling of the various submodels a graphical user interface (GUI) has been created (see Fig. 3). The GUI was coded using MATLAB GUIDE software which allows easy arrangement of user interface elements such as buttons, graphs and pop-up menus in a graphical programming environment.

The GUI is basically divided into two parts: simulation settings and plotting options. In the simulation settings the user can select one submodel from each model family to be combined to the model system. Via the plotting options the user can plot graphs of the simulation data directly from the GUI. The options allow plotting of alveolar gas partial pressures, tidal volume, aortic and venous pressures as well as arterial and venous gas concentrations.

Upon pressing of the "Simulate" button, it gets disabled to avoid repetitious starting of parallel simulation runs which would slow down calculation speed of the simulation massively. Also plotting options are disabled before first simulation and during simulation runs.

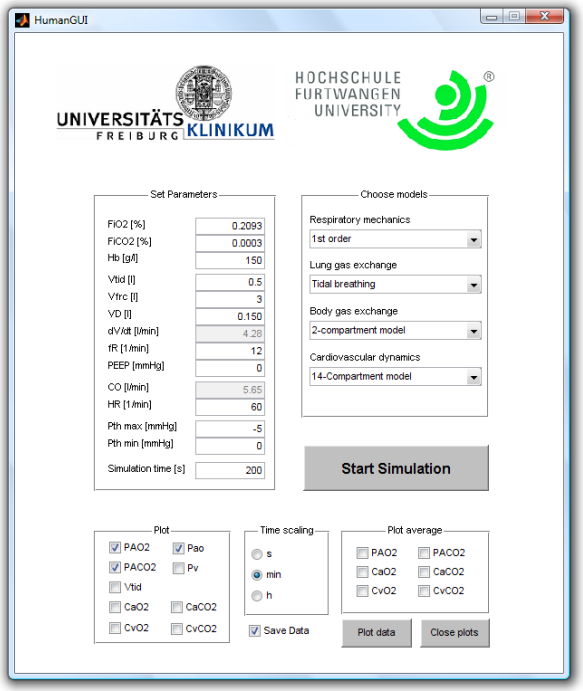

Fig. 3 Graphical user interface

III. Results

Simulations showed distinct differences in simulation output depending on the chosen submodels (Fig. 4). Combination of respiratory mechanics, tidal breathing, gas exchange and 14-compartment cardiovascular dynamics showed direct influence of intrathoracic pressure (P_{th}) on cardiac output and thereby on arterial and venous gas concentrations. Simulation results also showed pronounced influence of P_{th} on aortic and venous pressures as superimposed oscillations can be seen in the output. When applying mechanical ventilation, aortic pressure clearly drops because the chest is not expanding actively anymore and positive intrathoracic pressure is pressing on the pulmonary vessels and cardiac muscles (Fig. 5). This phenomenon also leads to a decrease in oxygen blood concentration (from 0.1932 [l(STPD)/l] to 0.1927 [l(STPD/l]). Although application of PEEP causes even larger decrease in aortic pressure, change in oxygen concentration was buffered by increase in tidal volume. Venous pressure showed only slight reaction to PEEP.

The unphysiological reaction of cardiac output to intrathoracic pressure is due to lack of a cardiovascular controller in the 14-compartment model. Using the 19-compartment model by Leaning et al. with its implanted controller was less sensitive to intrathoracic pressure.

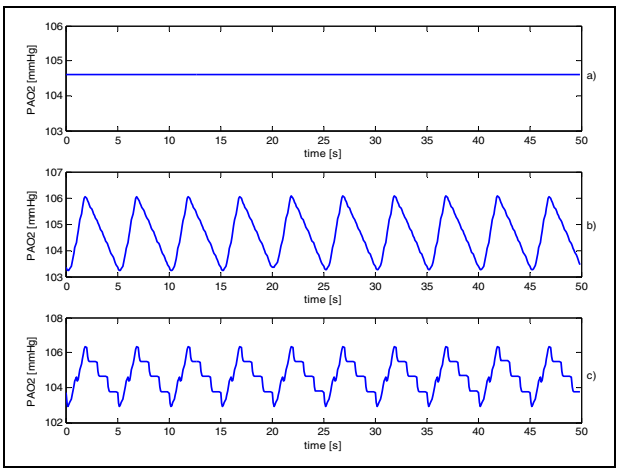

Fig. 4 Comparison of results for alveolar oxygen partial pressure from three different model combinations. a) 3-compartment gas exchange with continuous air flow and cardiac output. b) 2-compartment body gas exchange with tidal breathing 2-compartment lung gas exchange. c) 2-compartment body gas exchange with tidal breathing 2-compartment lung gas exchange and 14-compartment cardiovascular dynamics

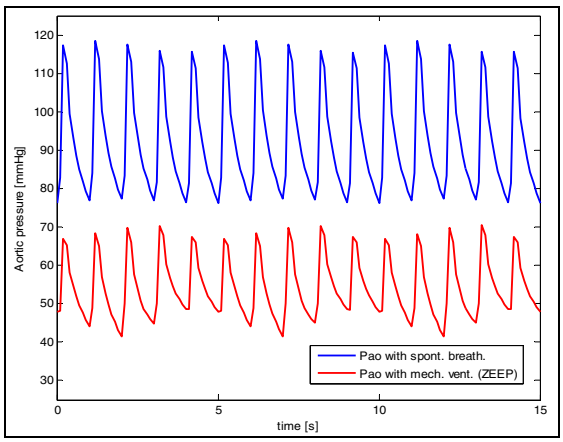

Fig. 5 Comparison of aortic pressure with spontaneous breathing and mechanical ventilation (ZEEP)

In order to test model delay time with respect to changes in simulation parameters, alterations in ventilation frequency were applied to a model combination consisting of no respiratory mechanics (sinusoidal flow assumption), tidal breathing in the lungs, 2-compartment gas exchange and continuous cardiac output. The simulation results were compared to the data collected by Jensen et al. [8]. In this experiment changes in end-tidal CO_2 ($etCO_2$) following alterations in ventilation frequency were measured on patients undergoing general anaesthesia in endotracheal intubation. Ventilation was started with 12 or 14 breaths per minute and was altered following the protocol shown in Fig. 6 when $etCO_2$ had

reached a new equilibrium. Simulation was performed using a predefined sequence of ventilation frequencies in sinusoidal form following the protocol specified in the publication. Thus ventilation frequency changed in the following order: 12/min – 14/min – 10/min – 16/min – 8/min.

Results (Fig. 6) showed that model delay time is mostly consistent with the data collected by Jensen et al. [8].

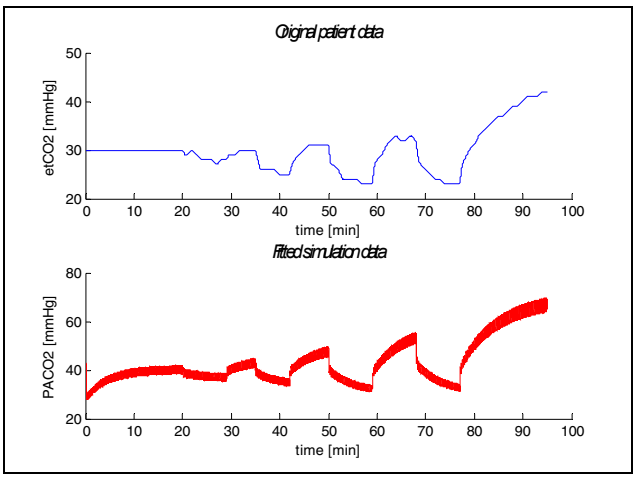

Fig. 6 Alveolar partial pressure of CO2 following alteration in ventilation frequency compared with etCO2 data taken by Jensen et al. [8]

IV. Conclusions

As demonstrated in the results section the pursued way of combining the separate submodels is working as expected. All submodels are invoked at the same time step so that chronological inaccuracies are avoided. Furthermore the model combinations show a simulation output that is consistent with physiological data and time delay. The interface arrangement can always be extended easily by more detailed submodels and parameters or even new model families. Via the graphical user interface the user is able to select the desired submodels and specify basic parameters easily.

Despite the promising results concerning modelling of complex physiological systems one must also keep in mind that parameter identification is even more difficult to achieve. Due to interactions, each submodel as an integral part of the complete model system may show different behaviour to the same input stimulus than if it is run separately. Nevertheless the fitting process may profit from fitting the submodels separately. The parameters derived from the separate fitting can be valuable for choosing the initial values for the final fitting process.

Another disadvantage is the temporal complexity of simulation runs which rises rapidly with increasing model detail. This may be a handicap in its use as a prediction tool for finding the optimal ventilation strategy.

To improve simulation speed the source code set up has to be re-evaluated and optimized. One aspect for optimization could be the applied ODE solver. As all submodels are invoked at the same time step, one submodel with stiff behaviour can slow down the simulation of the overall model system. If adaption of the simulation step size for every submodel could be done individually, simulation speed would increase significantly.

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