Approaches to Cardiovascular and Respiratory Systems Modelling

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'Medicine in silico' has been strongly encouraged due to ethical and legal limitations related to animal experiments and investigations conducted on patients. Computer models, particularly the very complex ones (virtual patients—VP), can be used in medical education and biomedical research as well as in clinical applications. Simpler patient-specific models may aid medical procedures. However, computer models are unfit for medical devices testing. Hybrid (i.e., numerical–physical) models do not have this disadvantage.

Keywords: modeling and simulation ; cardiopulmonary interaction ; gas exchange

1. Introduction

Several governmental agencies and non-profit organizations, such as the Avicenna Alliance, the Centre for Devices and Radiological Health of the U.S. Food and Drug Administration, and the European Union (Directive 2010/63/EU), for example, have encouraged 'in silico trials' to reduce animal experiments. In particular, there was an idea to create the Virtual Physiological Human [1]. Additionally, in silico experiments can decrease the cost of the research and development of medical devices [2]. They play also an important role in the process of developing new drugs [3] and allowing an understanding of various phenomena at the molecular level [4]. Computer models can be used in medical education, biomedical research (for example, to study particular cardiorespiratory phenomena) and in clinical applications (for example, to aid medical procedures and optimize the patient's treatment) [5]. However, although computer models may be useful in medicine and biomedical engineering, they have one great disadvantage: no possibility to interact with physical devices, e.g., with devices for organ functions support. Therefore, for 'in silico' investigation of relations between a particular device and an organ, a numerical model of this device would be necessary. Such a model, unfortunately, can be only an approximation of the real device, particularly of a new tested device, unless instead of the device, only a method of support is investigated. Physical models do not have this particular disadvantage; however, they have a number of other ones, e.g., they are uneasily modifiable and expensive, and they usually cannot mimic biological systems with the desired precision, or in most cases, cannot mimic some biological phenomena, such as O_2 and CO_2 transfer across the respiratory tract, their exchange by gas-permeable membranes in alveoli and tissues, and transport through the cardiovascular system. These phenomena can be easily implemented in numerical models.

To avoid the above problems, Pillon et al. presented the idea of connection of numerical circulatory models and a real ventricular assist device (VAD) by means of a unique interface [6]. Verbraak et al. proposed a bellows-based respiratory system simulator with a computer-controlled system mimicking the diaphragm [7]. These works led to the term 'hybrid model' or 'hybrid simulator' since such models or simulators consist of two different components: numerical and physical [8]. Certainly, there has to be a third component, i.e., a physical–computer interface, which is the crucial element in hybrid modeling.

There are a number of aspects of a biological system which are difficult to be modeled physically, such as the neural control, pharmacological agents or mentioned above membrane-based phenomena, such as gas exchange, for example. Therefore, the system element that interacts with a physical device has to be modeled physically, whereas the others can be modeled either physically or numerically, and the constructor of a hybrid simulator should determine which method should be chosen for a particular element or aspect. Such features as costs, required model flexibility as well as reliability and the accuracy of mathematical description necessary in investigation, for example, should be taken into account. In general, it is strongly recommended to minimize the number of parts modeled physically in order to maximize benefits of computer modeling. A numerical component may be either relatively simple or complex, which depends on an analyzed problem. The use of a very complex general purpose model of a biological system ('virtual patient') is another choice. A hybrid model with such a virtual patient as its numerical component can be called an 'artificial patient'.

2. Approaches to Cardiovascular and Respiratory Systems Modelling

Due to the increasing role of modeling in medicine and biomedical sciences, there have been developed thousands of models of the CVS and RS. Because of this great number of various models, only the types of approach to modeling can be discussed here. Depending on the used criteria, the models can be differently grouped.

First of all, a group of 3D models reflecting anatomical geometry of *CVS* or *RS* can be identified. Recently, physical 3D models, usually 3D-printed models, are the most frequently used to aid surgical and diagnostic procedures (e.g., [9][10][11]) or in medical education and staff training (e.g., [12]); however, some of them are used for research of a chosen phenomenon (e.g., [13]). Here, it should be mentioned a very interesting 3D model of lungs containing living cells, which were infected with real respiratory syncytial viruses [14]. There are also a number of 3D or 2D computer models, e.g., an interesting connection of 2D model of the heart with a simple 0D model of the vascular system [15].

Although 3D models constitute a group that is very useful in medicine and education, only models simulating the RS and/or CVS work are discussed below. Note, however, that there are models, which, though they simulate the work, some geometrical relations are taken into account to make it possible to simulate the ventilation–perfusion mishmash, for example, caused by gravity, pleural effusion, etc. (e.g., [16][17]). Additionally, although a CVS and/or RS model belongs to 0D models, in general, more precise simulations of gas transfer and transport with blood require 1D sub-models to simulate the propagation of changes in gas tensions with realistic, finite velocity (e.g., changes caused by altered minute ventilation [18]). For that reason, bronchi and vessels in such models require description by discrete differential equations. Additionally, simulations of elements, being both significantly resistive and significantly compliant, e.g., pulmonary capillaries or medium-sized bronchi, require a kind of 1D representations [19].

Taking into account applications, several groups of models simulating the CVS and/or RS work can be distinguished, e.g., those used in education, research or medical procedures support. The existence of educational models that are based on pure medical knowledge can be only mentioned here despite their complexity (e.g., [20][21]) because they are usually not based on a mathematical description of physical properties of the RS and/or CVS. In general, since these properties are nonlinear, they should be mathematically described by nonlinear equations rather than by simple numbers, such as ‘airway resistance’ or ‘pulmonary vascular resistance’ (additionally, the values of those resistances at a given moment depend on several factors and variables, such as pleural pressure, for example). If, however, a model is intended to be used in simulations of responses to small stimuli, simple numbers can be used. For example, forced spirometry or explanations of phenomena observed during thoracentesis [17][19] require nonlinear equations (note that airflow does not depend on the driving pressure during forced expiration and thus the Ohm’s idea of resistance loses meaning); however, simulations of tidal breathing may use simple numbers, e.g., those proposed by Arnal et al. [22].

From the technical point of view, all models can be used in education if they have a user-friendly interface (e.g., [16][23][24]). On the other hand, some simulation-based environment originally developed for learning about physiology, can be utilized in research, e.g., the educational Harvi environment [25] was utilized in a model used to investigate the optimal form of circulatory support in a ventricular septal defect [26].

A number of the CVS and RS computer models have been developed to solve only a particular problem (e.g., [27]) or to support a medical procedure in cases of individual patients. The latter models, called patient-specific models or bedside models, are of special meaning and have been used for dozens of years. Indeed, vascular or airway resistance and arterial or lung compliance, for example, are the simplest models (the RC circuits) used in medicine, in fact, despite that physicians usually do not recognize that they use simple mathematical models. Parameters of those models and such original variables as the cardiac output and arterial pressures constitute the fundamental set of quantities characterizing the patient’s state. Certainly, development of the IT technology enabled to develop more complex models, giving much more information and predictions [28][29][30][31]. Identifiability from the data available at the bedside or clinical situation is a main feature of such models; however, this is also the main limitation of those models: they cannot be too complex. For example, local pleural pressures, which have significant influence on both ventilation and the perfusion of particular lung regions, cannot be measured and, in consequence, models containing these pressures rather cannot be used as patient-specific models. Note that there are patient-specific models of the RS (e.g., [32]) but their number is far lower that the number of patient-specific models of the CVS.

Research with the use of models may concern either the average human being or a virtual/artificial population. This population can be created in two main ways, in general [33]. The first method consists of deviation of the model parameters from their values assumed for the average human being (e.g., [34]). A 1-to-1 mapping approach, in which each virtual patient corresponds to a real patient is the second method, i.e., the virtual population consists of patient-derived virtual patients. Certainly, the second approach is possible if a model is a simpler, patient-specific model rather than a more complex one.

More detailed comparison between particular CVS or RS models would be impossible due to their number. However, as an example, the following seemingly very similar works can be compared: the tests presented by Kung et al. [35] and the investigation presented by Di Molfetta et al. [36]. Both works concerned Jarvik VADs, and own hybrid models were used in those works. Thus, both the methodology and the kind of medical devices were the same. Certainly, there were also significant differences. First of all, these works concerned different VADs: the Infant Jarvik 2015 was studied by Di Molfetta et al., whereas Kung et al. used the Jarvik 2000 for adults. Moreover, Di Molfetta et al. tested the Infant Jarvik 2015 with the use of their own hybrid model, whereas Kung et al. tested their own hybrid model with the use of the Jarvik 2000.

The latter difference was caused by the fact that Kung et al. proposed a new approach to coupling the numerical and physical components, and therefore they wanted to test it. The original, hardware-in-the-loop approach proposed by Pillon et al. [6] and Verbraak et al. [7] has been commonly used by several researchers(e.g., [37][38][39][40]). According to this approach, a change in the physical component creates the corresponding reaction of the numerical component and vice versa. Therefore, numerical simulation of physiological phenomena during a time period, usually equal to 1 ms, has to take less than this period to make it possible to synchronize the real-time and simulated ones. Therefore, the hardware-in-the-loop approach requires real-time systems for numerical simulation, and computer models requiring time-consuming numerical calculations cannot be numerical components of hybrid models because the above synchronization would be impossible. Kung et al. [35] proposed another approach to overcome those limitations. According to this approach, an iterative coupling method to achieve the dynamic closed-loop feedback between the physical and numerical domains is used. This iterative algorithm modulates the common flow waveform(s) to identify their shapes, when pressure drops in the physical part (called a physical experiment) are equal to respective pressure drops in the numerical part (called computational physiology simulation). The common flow waveforms mean the flows connecting two domains and existing both in numerical and physical forms.

This new approach was further developed to enable more complex experiments [41]. As the absence of real-time calculations is the main advantage of this approach, hardware bandwidth limitations have minimal restraint. Thus, the time-consuming operations can be used in hybrid models built in accordance with Kung’s concept, whereas time-consuming 3D calculations, for example, are impossible in the case of hybrid models built in accordance with Pillon’s concept (pending a significant increase of the computers speed). Unfortunately, the Kung’s concept has one great disadvantage: it requires a kind of steady-state condition of simulations, as each change of the conditions requires new initial iterations. For that reason, this approach is not useful in simulations of changes, e.g., adaptive mechanisms in mechanical circulatory or ventilatory support devices or the left ventricular suction and the rotary LVAD speed reduction to prevent this phenomenon.

An extracorporeal membrane oxygenation (ECMO) system is reserved as a last resort of life support technology and is used when treatment by a mechanical ventilator and other strategies fail. In cases of respiratory failure ECMO may be applied for few days only while lung disaster caused by, for example, COVID-19, may require at least 4 or many more weeks to effectively help the sickest patients. ECMO is the ultimate tool to replace lungs or/and heart functions when one of these organs do not work anymore. The task of ECMO is to transfer the gas exchange from these organs to an extracorporeal membrane for oxygenation and CO_2 removal. It gives time to heal the patient’s organ or to replace it by an implant. ECMO is supportive therapy, not a disease-curing treatment. ECMO application is a complex and very costly process that requires well-trained professionals and, being the most invasive treatment, at the same time lowers risk of death due to, for example, COVID-19 in critically ill patients—both adults and children. ECMO was also successfully used at the outbreak of an influenza *A* (*H1N1*) in 2013. ECMO is a medical technology that has two applications: for cardiovascular support (by venous–arterial (*V-A*) cannulation) and for treatment of acute respiratory failure (by veno–venous (*V-V*) cannulation). An enormous increase of ECMO centers in recent years was observed [42] and in order to increase patients’ safety and to optimize ECMO efficacy, both training simulators as well as hybrid simulators are needed [43][44][45][46][47][48]. The simulators can help in ECMO system training, enabling, in some cases, high fidelity clinical scenarios [43][44] or to study the hemodynamic effect of ECMO on the left ventricular loading in a *V-A* configuration and the parasitic effect of blood recirculation in *V-V* cannulation [46]. However, these simulators usually can only mimic the hemodynamic physical effect when connected to an actual ECMO. The membrane oxygenation and CO_2 removal usually must be simulated numerically due to the fact that oxygen consumption and carbon dioxide production in cardiopulmonary physiology are difficult to simulate physically. One of exceptions is the simulator presented in [47] using the hardware-in-the-loop approach with a physiological numerical model, where a computer-controlled de-oxygenator was utilized to simulate the blood flow with a desired oxygen level entering the ECMO system.

One of the major limitations of artificial as well as virtual patients (models) is their validation. It is important especially when they are considered as a part of decision support systems when simulating the specific patient. The validation procedure of the model usually is as follows [5]. The patient's data, such as characteristic and diagnostic data and therapeutic actions are inputs for the model. The model simulates specific patients then, and its output data are compared with the outputs of real patients. However, it requires a large-scale database [5] with data from various sources of intensive-care units. An artificial intelligence could support this validation process (for example, adjusting the model's parameters), as it can be applied in clinical examinations and diagnosis [49]. If the model is not used to simulate the specific patient but rather to study phenomena or for training and education purposes, a simpler verification can be enough. An exemplary process of cardiovascular model verification in case of the left ventricular assistance in animals was presented in [50].

The CVS and RS have a common goal (oxygen delivery to tissues), and their failures have frequently common symptoms (e.g., dyspnea). To accurately test physical devices for ventilatory or cardiac support, an artificial patient has to contain an accurate model of the RS with pulmonary circulation, which can simulate such phenomena that are important for blood saturations as ventilation–perfusion mismatch or influence of obstructive lung diseases of any severity on the CVS work, for example. The artificial patient applied by the researchers has this potential [51], which led to the creation of the CARDIOSIM© simulator [28][29][48], which can be used in medical devices testing [8]. As the numerical components of this artificial patient are 0D models, in general, they cannot be used in investigations of phenomena at the microscale, such as turbulences in air and blood flows, for example. However, they are good and partly exceptional tools to investigate a wide range of phenomena at the macroscale. In particular, although physical equipment testing was the original goal of the artificial patient, the models were utilized in systems for e-learning and e-support of medical decisions and used in analyses of cardiopulmonary interaction in different cases. As, this artificial patient is the most general-purpose platform for various simulations.

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