In silico modelling of physiologic systems

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In silico modelling, in which computer models are developed to model a pharmacologic or physiologic process, is a logical extension of controlled in vitro experimentation. It is the natural result of the explosive increase in computing power available to the research scientist at continually decreasing cost. In silico modelling combines the advantages of both in vivo and in vitro experimentation, without subjecting itself to the ethical considerations and lack of control associated with in vivo experiments. Unlike in vitro experiments, which exist in isolation, in silico models allow the researcher to include a virtually unlimited array of parameters, which render the results more applicable to the organism as a whole. In silico modelling is best known for its extensive use in pharmacokinetic experimentation, the best-known example of which is the development of the three-compartment model. In addition, complex in silico models have been applied to pathophysiologival problems to provide information which cannot be obtained practically or ethically by traditional clinical research methods. These experiments have led to the development of significant insights in subject matters ranging from pure physiology to congenital heart surgery, obstetric anaesthesia airway management, mechanical ventilation and cardiopulmonary bypass/ventricular support devices.

The utility of these models is based on both the validity of the model framework as well as the corresponding assumptions. In vivo experimentation has validated some, but not all of the in silico strategies employed. We present a review illustrating by example how in silico modelling has been applied to a number of cardio-respiratory problems in states of health and disease, the

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Introduction

Classically, scientific research has been divided into two types – *in vivo* (‘within the living’) and *in vitro* (‘within glass’). The development of *in vitro* techniques was a response to several considerations, including the ethics of experimenting on live subjects, the cost (time and resources) associated with experimenting on live subjects and the inability to control conditions properly.

*In vitro* experiments can be more tightly controlled than *in vivo* experiments, and can generally be undertaken more quickly and with fewer resources. However, a major criticism of *in vitro* experiments is that they do not accurately represent the organism as a whole. Modern biomedical literature is littered with tales of therapeutic agents that exhibited great promise in the controlled setting of the basic science laboratory, only to fail miserably when applied to animal or human subjects.

The invention of the microprocessor and subsequent development of the personal computer has led to numerous scientific advances. One of the most exciting, and least developed, is in the field of *in silico* (‘in silicon’) research. *In silico* research, in which mathematical models of a physiologic or pharmacologic system are developed and tested on a computer, are a hybrid of *in vivo* and *in vitro* techniques.

Like *in vivo* techniques, *in silico* experiments are designed to mimic the behaviour of organisms in their entirety. However, like *in vitro* experiments, they do not require actual experimentation on animal subjects. Furthermore, conditions can be controlled with exquisite detail, because the investigator defines them as part of the model employed.

*In silico* techniques, thus, offer the clinician-scientist the opportunity to answer questions that, for a variety of reasons, could not otherwise be easily addressed. Most readers are familiar with the major advances in pharmacokinetics that have resulted from the development and application of sophisticated *in silico* techniques, most notably the addition of the third (‘effect site’) compartment to pharmacokinetic models and the subsequent improvement in their predictive abilities (for an outstanding introduction, see the work of Shafer). These techniques need not be limited to the field of pharmacology, however.

The purpose of this review is to introduce the reader to a few of the arenas of *in silico* experimentation, to describe the physiologic insights that have been gained thus far and to provide a brief introduction into the techniques themselves. Because of the varied nature of the models employed by different investigators, it is not possible to describe the technical details of each approach with sufficient clarity to allow for reproduction. Our goal is not to ‘recreate’ these models but to direct the reader towards this groundbreaking work.

Physiologic experimentation

Ventricular interdependence

Santamore and Burkhoff used an electrical circuit–based analogue of the cardiovascular system to study the haemodynamic effects of left (LV) and right ventricular (RV) interaction. In this haemodynamic model, both the systemic and pulmonic vascular systems were modelled using a five-element system – three resistors, which represented ventricular outflow impedance, resistance to arterial flow and resistance to venous return, respectively, and two capacitors, which represented arterial and venous capacitance.

Ventricular contraction was modelled using time-varying elastance (‘stiffness’, abbreviated E) equations (in which $\Delta V/\Delta P$ changes with time) as well as incorporation of diodes to restrict regurgitant valvular flow. For the purposes of this experiment, maximal elastance ($E_{\text{max}}$) was considered to be
a marker of ventricular contractility. During systole and diastole, elastance was modelled as sine wave and an exponential decay (with a time constant of relaxation, $\tau$), respectively.

A series of four equations relating intracardiac pressure and volume were then created, based on assumptions regarding the shape of the RV and LV pressure–volume curves. Interventricular dependence was modelled by incorporating an additional six equations relating pressure, volume and elastance of one ventricle to pressure, volume and elastance of the other. In all, 10 equations were generated. Twenty-one physiologic constants were defined for the non-interacting model (in which the ventricles did not interact) and 27 were defined for the interacting model.

After incorporating this system of equations and constants into a computer model (programmed in BASIC), two comparisons were made. First, RV and LV elastance was compared with and without incorporation of ventricular interaction into the haemodynamic model. Second, four haemodynamic 'interventions' were made – isolated changes in pulmonic arterial resistance, systemic arterial resistance, RV elastance and LV elastance (all other haemodynamic constants remained stable), and the results observed.

Increases in LV and RV end-systolic pressure increased $E_{\text{max}}$ of the companion ventricle. Quantification of these changes revealed that RV pressure-generating capacity increases by 60% above its intrinsic ability due to interaction with the left ventricle. By contrast, LV pressure-generating capacity increases only 10% above its intrinsic ability due to interaction with the right ventricle. Interestingly, while ventricular interdependence attenuated decreases in LV stroke volume associated with isolated increases in systemic arterial vascular resistance, ventricular interdependence enhanced decreases in RV stroke volume associated with isolated increases in pulmonic arterial vascular resistance, although the magnitude of these haemodynamic changes was small.

**Acute LV failure**

One important haemodynamic scenario which would be physiologically difficult (not to mention ethically challenging) to study in a controlled fashion is severe acute LV dysfunction. To assess the relative contribution of changes in heart rate, arterial resistance, venous compliance and contractility to increasing pulmonary venous pressure, Burkhoff and Tyberg attempted to simulate LV dysfunction using a variation of a previously developed haemodynamic model.

In this *in silico* experiment, Burkhoff and Tyberg manipulated heart rate, arterial resistance, venous compliance and ventricular function independently, and in various combinations. An isolated 66% decrease in ventricular contractility led to 33% reductions in mean arterial pressure and cardiac output ($\text{CO}$), and a 33% increase in pulmonary venous pressure. Increasing systemic arterial vascular resistance by over 450% led to a 65% decrease in $\text{CO}$, a 46% increase in mean arterial pressure, but only a 14% increase in pulmonary venous pressure. Increasing the heart rate from 80 to 160 beats per minute resulted in a 36% increase in $\text{CO}$ and mean arterial pressure, and a 50% fall in pulmonary venous pressure.

Importantly, models such as these are highly dependent on the parameters and initial conditions, in addition to the design of the model itself. Magder *et al.*, who have a long-standing interest in venous function, believe that values for venous resistance and capacitance used by Burkhoff and Tyberg were too low. Magder *et al.* therefore replicated Burkhoff and Tyberg's simulations, using different values for arterial and venous resistance and capacitance, as well as slightly modified left and right end-diastolic pressure–volume relationships. They then performed five experiments in the setting of decreased contractility: (1) increasing ventricular contractility alone, (2) converting unstressed to stressed volume, (3) increasing systemic arterial vascular resistance, (4) increasing systemic venous vascular resistance and (5) increasing heart rate.

The results of their initial experiment were markedly different from those of Burkhoff and Tyberg – as LV elastance (a surrogate for contractility) fell from 6 mmHg ml$^{-1}$ to 0.4 mmHg ml$^{-1}$, pulmonary venous pressure rose from 10 to 34 mmHg using Magder's parameters (as opposed to increasing from 12 to 23 mmHg using Burkhoff and Tyberg's). Also in distinction from Burkhoff and Tyberg's results, increases in arterial systemic vascular resistance using the parameters of Magder *et al.* led to a significant increase in pulmonary venous pressure (19–28 mmHg). In both scenarios, systemic venous pressures increased significantly, suggesting that the predominant cause of elevated pulmonary
venous pressures is volumetric shifts from the extrathoracic to the thoracic compartments. Increases in systemic venous resistance led to substantial decreases in CO using the parameters of Magder et al., whereas Burkhoff and Tyberg’s results suggested that CO was relatively independent of systemic venous resistance.

Adult cardiovascular surgery and anaesthesia

Vascular system

Bauernschmitt et al. hypothesised that modelling the adult vascular system might give insight into the interaction between the native vasculature and vascular prostheses. They developed a 128-branch model of the arterial tree (as proposed by Avolio), where each segment of which was ascribed values for resistance, capacitance, and inductance. The model ‘input’ was a standard aortic flow waveform. Notably, this model neglects any potential interaction with the systemic venous system, as well as the pulmonic arterial and venous systems.

To simulate replacement of the native aorta with a synthetic graft, the characteristics of specific segments were changed from native values to values consistent with an aortic graft, and the impact on the resultant pressure waveforms was analysed. So as to simulate replacement of the aortic arch, segments 1, 2 and 5 were replaced.

Replacement of the aorta with a non-compliant graft led to increases in systemic blood pressure and pulse pressure, the amount of which was proportional to the elasticity (stiffness) of the graft as well as its length. This phenomenon has previously been described in multiple animal models. Interestingly, ‘virtual replacement’ of the aortic arch increased the modulus of the first harmonic of the impedance spectrum, an indicator of ventriculoarterial impedance matching and, thus, of ventriculoarterial efficiency. Bauernschmitt et al. concluded that ‘virtual replacement’ of the aorta might be a viable means by which the haemodynamic implications of potential grafts could be elucidated, pointing out that the intra-operative environment, which allows for direct testing, is burdened by the effects of surgery and anaesthesia, both of which make interpretation difficult.

Subsequently, Bauernschmitt et al. adapted this 128-branch model to simulate the effect of extracorporeal circulation on the human vascular system during pulsatile cardiopulmonary bypass. To do this, they incorporated a means of maintaining constant flow to the brain and kidneys over a particular range of haemodynamic variables (based on published data), as well as modifications designed to characterise oxygen consumption as a function of temperature and anaesthetic depth.

Four perfusion models were tested – low flow, pulsatile, pH-stat; low flow, pulsatile, alpha-stat; high flow, pulsatile, alpha-stat; high flow, non-pulsatile, alpha-stat. In all four models, the percentage of flow to both the brain and the gastrointestinal (GI) tract was increased as compared with baseline, whereas the percentage of flow to the extremities was decreased. The percentage of flow to the kidneys, by contrast, was relatively unchanged. Actual organ flow decreased in all organs for all models, with the exception of intestinal blood flow in the high flow, pulsatile, alpha-stat state (18.75–25.6 ml s⁻¹). Cerebral blood flow decreased maximally in the low flow, pulsatile, alpha-stat state (11.4–6.2 ml s⁻¹), and was best preserved in the high flow, non-pulsatile, alpha-stat state (unchanged at 11.4 ml s⁻¹).

Mitral valve

The mitral valve (MV) is a complex structure that profoundly affects human haemodynamics. When it functions suboptimally, haemodynamics, quality of life and longevity may be impaired. Several attempts to better understand its impact on haemodynamics have been undertaken.

Sun et al. attempted the study of the impact of MV on left atrial–ventricular interaction. Flow across the MV was described by the Bernoulli principle (in which the pressure drop is related to the square of the velocity of blood flow and an inertial term related to flow acceleration or deceleration). A time-varying elastance model was used to describe atrial and ventricular contraction. An electrical analogue, which incorporated both the MV model as well as the time-varying elastance model of the left atrium and left ventricle, was then used to model the vascular system starting with the pulmonary veins and ending with the systemic peripheral arteries. The model solution required the simultaneous solving of 10 differential equations (via numerical integration).
Sun’s model accurately predicted the effects of ageing and decreased LV compliance on both pulmonary venous and transmitral flow. These same waveforms were closely related to pulse wave Doppler (PWD) recordings in both normal and post-infarction patients.

Szabó et al. attempted to describe MV haemodynamic using a slightly different approach. They developed a system of three first-order, nonlinear ordinary differential equations, the first describing flow as a function of intertance, flow acceleration and pressure gradients, the second describing atrial pressure change as a function of flow and atrial compliance and the third relating \( dp/dt \) as a function of the ratio of pressure at MV opening to the minimum diastolic ventricular pressure, the time constant, chamber stiffness and ventricular volume. The flow through the MV was separately modelled with a differential equation that incorporates physical characteristics of the valve itself as well as the forces acting on the valve.  

Model performance was validated by performing MV replacements on six pigs and comparing actual recorded intracardiac haemodynamic data to predicted values. Measured and simulated pressure and flow curves were also nearly identical. To further test this model, vena cava occlusion was performed both in vivo and in silico, and again, there was good agreement between the measured and simulated pressure and flow curves.

Szabó et al.’s model was significant because it was one of the first to incorporate a means of modifying the mitral valve area, which theoretically allows one to predict the haemodynamic effects of different orifice sizes.

To assess the impact of MV prosthesis size on prosthesis–patient mismatch, Tanné et al. used a similar approach to Sun et al., developing an electrical analogue-based model of the pulmonary arteries (Pas) and veins, left heart and systemic circulation. They simulated the effect of applying valves of varying sizes, standardising by body surface area under four CO loads to simulate exercise. Their model demonstrated the thresholds’ ratios of valve to body surface area of 1.16 cm\(^2\) m\(^{-2}\) for moderate patient–prosthesis mismatch and 0.94 at rest, which would result in significant rise in PA pressure or valve pressure gradient. These values compare favourably with observed raised long-term mortality when the ratio falls below 0.9.

Congenital cardiovascular surgery and anaesthesia

Univentricular physiology

Children born with univentricular circulation require a Norwood procedure as part of a series of operations required for survival. During the Norwood procedure, the aorta and the PA are sewn together so that blood ejected from the single ventricle perfuses the systemic circulation. A systemic-to-pulmonary shunt is then required to ensure that some blood reaches the pulmonary vascular system (for oxygenation and redistribution to the heart, and ultimately, systemic circulation). There are several anatomic options for this systemic-to-pulmonary shunt, and it is not always obvious which will afford the most haemodynamic stability. Furthermore, anaesthetic management of these patients, which necessarily entails a trade-off between systemic and pulmonic blood flow (since both originate from the same ventricle), is complex.

To study the effects of systemic and pulmonary vascular resistance (PVR), heart rate and shunt size on haemodynamics, Migliavacca et al. built a lumped-parameter electrical analogue model of the post-Norwood circulatory system. The heart, systemic circulation and pulmonic circulation were all modelled separately. Interactions between the atria and univentricle were modelled using simple resistors, and a time-varying elastance model (in which elastance \( \Delta P/\Delta V \) changes with both time and volume) was used to describe the systolic function of the univentricular heart. The pulmonic and systemic circulations were described using multi-compartmental models, each of which was made up of resistive, capacitance, and in some cases, inductive components. The systemic-to-pulmonic shunt was modelled with a flow-dependent resistor.

Variations in shunt diameter, as well as haemodynamic parameters, led to several important observations. Enlarging the shunt diameter was associated with an increase in cardiac index (CI) and the ratio of pulmonic to systemic flow (Qp/Qs), which ultimately led to increased arterial, but not venous, \( O_2 \) saturation. \( O_2 \) delivery (DO\(_2\)) increased when shunt diameter increased from 3 to 3.5 mm but sharply decreased for larger shunts, as Qp increased substantially, suggesting that the relationship between DO\(_2\) and shunt diameter is nonlinear.
Changes in systemic vascular resistance (SVR) seemed to affect haemodynamics more than changes in pulmonary vascular resistance (PVR). In fact, increasing PVR and SVR over the normal range had oppositional effects, the former increasing DO$_2$ (as blood was preferentially shunted to the systemic tissues) and the latter decreasing DO$_2$ (as blood was preferentially shunted to the pulmonary vasculature). Over the normal range of values, CI and Qp/Qs were strongly affected by changes in SVR, and minimally affected by changes in PVR.

DO$_2$ appeared to be more closely related to ‘venous’ O$_2$ saturation than arterial O$_2$ saturation, a clinically useful finding because in this population, DO$_2$, which requires assessment of CO, cannot be readily measured in the intra-operative setting. Lastly, optimal DO$_2$ was achieved by maintaining a Qp/Qs ratio of 1, regardless of shunt size.

Barnea et al. examined the effect of blood flow distribution on systemic oxygen availability$^{21}$ in patients with hypoplastic left heart syndrome. They developed a series of equations to define oxygen availability as a function of several cardiopulmonary physiologic parameters. Oxygen delivery (DO$_2$) from the systemic circulation to the right ventricle (RV) was defined as systemic DO$_2$ minus oxygen consumption. DO$_2$ to the RV from the pulmonary circulation was defined as DO$_2$ to the pulmonary system plus oxygen uptake (from the lungs). CO was defined as systemic flow plus pulmonary flow, and steady state conditions were assumed (in which oxygen consumption was equal to uptake). Combining all of these equations, Barnea et al. created an equation defining systemic oxygen availability as a function of CO, the ratio of pulmonic to systemic blood flow (Qp/Qs ratio), whole-body oxygen consumption and pulmonary venous blood oxygen content. Using a computer to conduct the analysis, they formed a theoretic basis for using systemic arterial and venous saturations to estimate the pulmonary-to-systemic flow (Qp/Qs) ratio to optimize systemic oxygen availability.

Building upon the mathematical model they created in their prior work, Barnea et al. used a computer simulation to calculate ‘DO$_2$ as a function of systemic arterial (SaO$_2$) and venous (SvO$_2$) oxygen saturation, arteriovenous oxygen difference (Sa-vO$_2$) or Qp/Qs ratio’.$^{22}$ Their prior mathematical model relied upon an estimate of pulmonary venous oxygen saturation, which can lead to substantial error. They also incorporated a new term they call the ‘oxygen excess factor’, SaO$_2$/Sa-vO$_2$, as an index of oxygen delivery to oxygen consumption. Using computer simulation to test the effect of manipulating key variables, the authors found that several variables can lead to low systemic DO$_2$: small increases in SaO$_2$, low SvO$_2$ and a Qp/Qs ratio greater than 4. They discovered that there is a linear relationship between SaO$_2$/Sa-vO$_2$ and systemic oxygen delivery. As demonstrated by this work by Barnea et al., in silico studies can help develop new strategies for managing complex congenital heart lesions, lessening the need to learn by trial and error.

**Surgical correction: the Norwood procedure and its variants**

To compare different anatomical configurations of systemic-to-pulmonic shunts placed in Norwood procedures (as opposed to simply examining shunt size), Lagana et al. built a three-dimensional (3D) mathematical model of the paediatric central vasculature using the finite volume method (FVM, which, in this case, was used to solve mass and momentum conservation equations for an incompressible fluid). FMV relies on evaluation of partial differential equations that relate individual ‘cells’ (composed of nodes) which have a specific location in space and are related to neighbouring cells. In this case, up to 130 000 cells were used to model the various shunts. Blood flow itself was modelled using a lumped parameter model (similar to Migliavacca above), in which the univentricular heart was described by time-varying elastances as well as resistance to inflow and outflow, and the systemic, pulmonic and coronary circulations were described by multi-compartment models, each with their own values for resistance, capacitance and inductance.

The 3D geometric model of the central vasculature was interfaced with the lumped parameter model of the circulation to examine the differences between two shunts – the central shunt (CS), in which a conduit is placed between the aorta and the PA, and a modified Blalock–Taussig shunt (MBTS), in which the conduit is placed between the innominate artery and the PA.

Lagan et al. made several interesting discoveries – average shunt flow (i.e., pulmonary perfusion) appeared to be higher for the CS as compared with the MBTS, and total CO was higher for the CS as compared with the MBTS. The CS distributed a smaller percentage of aortic flow to the coronary circulation as compared with the MBTS.
Migliavacca et al. then adapted this technique to compare a novel systemic-to-pulmonic shunt, the Sano shunt, to the classical Norwood shunts. In the Sano shunt, a conduit is used to connect the univentricle (rather than the aorta or innominate artery) directly to the PAs, leading to more pulsatile blood flow to the pulmonic vasculature and decreasing pulmonic diastolic blood pressure. Indeed, combination of the finite volume method and lumped parameter modelling revealed that the Sano modification to the original Norwood procedure leads to higher aortic diastolic blood pressure (and hence higher coronary perfusion pressure), decreased pulmonary arterial pressures, lower pulmonary-to-systemic flow ratios and increased ventricular efficiency.23

This approach has recently been extended to describe the haemodynamics associated with both the Glenn (superior vena cava to PA) and Fontan (inferior vena cava to PA) procedures.24

Pulmonary physiology and pharmacology

Transpulmonary drug delivery

To better understand the transpulmonary route of drug delivery, Martonen et al. developed a series of mathematical models describing the deposition patterns of aerosols in the human airway.25–27 They described clinical applications in which their models could potentially be beneficial, including targeting inhaled drug delivery for both systemic absorption and diseases of the respiratory tract such as asthma or cystic fibrosis.

Martonen’s 3D model of the human airway was based upon a mathematical concept of topology know as Delaunay tessellation.28 In Delaunay tessellation, a collection of points are connected to form a series of triangles in such a way that no point resides inside the circumcircle (circle which passes through all vertices of a polygon) of any triangle. This strategy maximises the minimum angle of the triangles in the triangulation.

Delaunay tessellation can be used to define the relationship of points in space to their nearest neighbours. These connections can be expanded into complex 3D networks that model human airways. Using this concept, Martonen et al. defined the distal portions of the airway using X, Y and Z coordinates to represent alveolar sacs. The surface was modelled by creating boundaries reflective of human lung. Using their lung model in conjunction with data from single-photon emission computed tomography (SPECT) imaging,29 the team created a simulation to predict inhaled drug deposition in asthmatic patients.

Martonen et al. developed a model that simulates the airway-related changes inflicted by asthma including bronchoconstriction, inflammation and mucus thickening, which result in narrowing of the bronchial lumen.30 Large, central and small airways were affected in varying degrees of severity in reflection of the heterogeneity of asthma. The authors also incorporated the variability that occurs in ventilation over a large range of tidal volumes and respiratory rates. Fluid dynamic analyses were used to recreate airflow through the airway network,27 and different-sized drug particles were tested. Martonen et al. demonstrated that multiple variables influence the delivery of inhaled drugs, including disease-related airway changes, individual ventilation characteristics and drug particle size. More importantly, they demonstrated that one might be able to predict the effects of these changes on drug deposition and design delivery systems for inhaled medications tailored to the diseases that they are meant to treat.

Martonen et al. went to considerable lengths to account for the variability of disease manifestations and severity as well as ventilation characteristics that are likely to be found in asthmatic patients and report the results of their simulations to be very predictive of data obtained from real human subjects. In silico models such as these could be used to design delivery systems for inhaled drugs that are targeted for the treatment of increasingly prevalent diseases such as asthma. Targeted therapy could lead to increased efficacy of the drug and better overall disease treatment outcomes with less systemic side effects. Alternatively, if systemic delivery is desired, inhaled medications could be directed to the appropriate regions of the lung for maximal systemic uptake while minimising local effects.

Mechanical ventilation

In intensive care unit (ICU) and perioperative settings, ventilator settings are often adjusted based upon physiologic measurements. To assess the effect on airway pressures, oxygenation and ventilation,
data are gathered from the ventilator and blood gas measurements before and after the intervention. Uttman et al. studied the ability of a computer simulation to predict the effects of ventilator changes. They used a series of nine linear, logarithmic and integral equations describing compliance, pressures (e.g., endotracheal tube), conductance and $V_{CO2}$, to help characterise lung function.

Using these formulae, Uttman et al. created a unique physiologic profile for ventilated pigs based upon recordings of flow, pressure, CO₂ levels, recoil and resistance at various times. They then used this profile to predict airway pressures and CO₂ elimination with changes in ventilator settings. In this study, the simulated results were predictive of measured pressures within less than 1 cmH₂O and CO₂ levels within less than 6%.

In a later study, Uttman et al. applied these findings in a clinical environment. Specifically, they investigated the ability of a simulation to predict changes in airway pressures and CO₂ elimination after incremental changes in positive end-expiratory pressure (PEEP) in patients with acute lung injury or acute respiratory distress syndrome. Prior to changes in PEEP, a unique physiologic profile was created for each patient by recording their compliance, resistance, CO₂ elimination and tidal volumes. This profile was then used in a computer simulation to predict the effects of changes in PEEP. The authors reported that simulated measurements were overall very predictive of those obtained in vitro. Differences became more significant when increasing PEEP to greater than 10 cm H₂O or when maintaining PEEP levels from 30 s to 10 min.

Uttman et al. stated that one likely reason for the differences in simulated versus measured pressures is changes in lung compliance. Overdistension could cause a decrease in lung compliance; however, sustained PEEP levels could result in recruitment of previously atelectatic lung units, leading to an increase in lung compliance. In addition, the simulation overestimated CO₂ levels at PEEPs of 7.5, 10 and 15 cmH₂O by 4%, 8% and 10% respectively. The authors asserted that the difference in simulated versus measured levels could be due to increased dead space and changes in regional blood flow at increasing PEEP levels. This study illustrates how simulation can accurately predict the effects of changes in a complex system while being limited by the unavoidable simplifications involved in creating a physiologic model.

**Physiologic control of respiration**

In 1983, Tehrani and Fincham created a mathematical model of the pulmonary system, focussing on the elements that regulate respiration. They incorporated the role of central and peripheral chemoreceptors as well as physiologic concepts such as the Hering–Breuer reflex, which prevents overdistension of the lungs and allows expiration. Tehrani designed the model to maximise respiratory efficiency. He tested the response of this model in various physiologic states, simulating hypercapnia, hypoxia, periodic breathing and exercise.

In a later study, Tehrani adapted this model to simulate the neonatal pulmonary system. He incorporated the effects of differences in neonatal physiology including anatomical shunts and the immature function of chemoreceptors. He assumed an A-a gradient of 20 mmHg. A ‘controller’ adjusted the level of ventilation, respiratory rate and dead space volume. This model was then tested in different physiologic states including hypercapnia, hypoxia and rest. The authors compared the results of the model with measured values and reported them to be very similar. Such physiologic models could be adapted to simulate various pathologic states to study respiratory disorders within adults and neonates.

**Combined cardiopulmonary models**

**Effects of preoxygenation and apnoea**

Although the majority of surgeries performed in parturients are conducted under neuraxial block, a significant number must be performed under general anaesthesia. Pregnant patients develop changes in their pulmonary and airway physiology that can make securing the airway more difficult and increase their risk of rapid desaturation. Preoxygenation increases the amount of time it takes for an individual to desaturate during the period of apnoea immediately following anaesthetic induction. To better understand these crucial concepts, McClelland et al. developed a computer simulation designed specifically to study preoxygenation and apnoea in the pregnant population.
For their investigations, the authors used the Nottingham Physiology Simulator, a computer simulation based on an iterative model of the cardiopulmonary system, which describes the lungs, pulmonary veins, arterial bloodstream, tissues and venous blood in a series of related equations (Hardman et al. provide an excellent description of this model in a validation study). The lung model includes dead space, humidification of inhaled air with variable composition of alveolar gases based upon characteristics of inhalation and exhalation. Blood gas composition was designed to equilibrate with that of alveolar gas and to be influenced directly by temperature and partial pressure. Tissues use O2 and produce CO2 based upon the metabolic rate and respiratory quotient, and then the resulting venous blood pH, CO2 and O2 levels are calculated.

McClelland et al. adapted this model for use in pregnant women and examined altered respiratory physiology in three separate studies. In their first study, to determine the optimal method of preoxygenation in parturients either by vital capacity breaths or normal tidal breathing, the authors first generated six virtual subjects to simulate a range of pulmonary physiology in both non-pregnant and full-term, non-labouring pregnant females. These simulated subjects then "breathed" 100% oxygen in the supine position with tidal breaths for 10 min, with PEO2 being measured periodically. Based upon the time required to reach 95% of maximum change in PEO2, the authors reported that the pregnant subjects took less time to preoxygenate than non-pregnant subjects using tidal breathing. They attributed this to the decrease in functional residual capacity of pregnant patients.

However, when using vital capacity breaths, they found that pregnant women required more breaths than the non-pregnant patients to preoxygenate to the same level. Using these results, they recommended that pregnant patients be preoxygenated using tidal breathing for 2 min to ensure 95% preoxygenation.

Further, they focussed on apnoea in pregnant patients. In this study, they subjected six virtual patients (pregnant and non-pregnant) to apnoea after they were preoxygenated at increasing levels of PEO2. To simulate the most common conditions present during apnoea after induction, they incorporated the physiologic effects of a rapid sequence induction into their model. Compared with non-pregnant subjects, pregnant patients took approximately 2.5 min less time to desaturate to below 90% when apnoeic. Once at below 90% saturation, pregnant patients also took less time (35 s) to fall to 40% saturation compared with non-pregnant patients (45 s).

Next, they used the methods described above to examine preoxygenation and apnoea in various clinical scenarios including labour, obesity, sepsis, pre-eclampsia, haemorrhage and multiple gestation. Models were created using multiple sources, including direct physiologic measurements, prior studies on non-pregnant patients and basic physiologic principles. Sepsis was represented by using a hyperdynamic circulation in a febrile environment. Haemorrhage was studied using two models – one incorporating hypovolaemia and a second anaemia. The model for pre-eclampsia was created using a cardiovascular system with low CO and high resistance.

Pre-eclamptic patients took a longer time to preoxygenate and to desaturate. Obesity, labour and sepsis were found to accelerate preoxygenation and desaturation. The authors explored the physiologic concepts that could explain their findings. Hyperventilation, which is often present in labour and septic patients, can accelerate preoxygenation and also increase oxygen consumption. Obesity can lead to increased oxygen consumption and reduced functional residual capacity. Overall, they found that obesity caused the greatest reduction in the amount of time a pregnant patient could tolerate apnoea before rapid desaturation. Other scenarios had less of an effect. In this article, the authors demonstrated how physiologic modelling of in silico systems can be useful in investigating specific clinical scenarios that would otherwise be difficult or unethical to study in vivo.

Mechanical circulatory support in context of mechanical ventilation

De Lazzari et al. performed in silico studies to examine the effects of mechanical circulatory and ventilatory support on cardiovascular parameters including haemodynamics and energy consumption. The authors used a physiologic model called CARDIOSIM. This simulation models the cardiopulmonary system by placing the pulmonary venous circulation, left heart, systemic arterial circulation, systemic venous circulation, right heart and pulmonary arterial circulation in series (electrical circuit analogue). Resistance of the systemic and pulmonary vasculature, compliance of the atrial chambers
and systemic and pulmonary vasculature, pressures within the heart chambers and systemic and pulmonary vasculature, blood flow and thoracic pressure are all incorporated in the model. CARDIOSIM also provides the ability to integrate mechanical assist devices such as Left ventricular assist devices (LVADs) and intra-aortic balloon pump (IABPs) into the simulation.

De Lazzari et al. examined the effect of mechanical ventilation on energetic parameters, comparing results obtained by in silico methods with those obtained in vivo in eight cardiosurgical patients. The authors used the CARDIOSIM model to measure variables such as blood pressures, CI and LV stroke work. They tested three different modes of ventilation, including conventional, lung-protective and high-frequency, each of which are postulated to result in different effects on intrathoracic pressure, haemodynamics and energy consumption. Overall, De Lazzari et al. demonstrated that the increasing levels of positive pressure created by mechanical ventilation caused a corresponding decrease in ventricular energetic variables. They found the in silico measurements to be close to those measured in vivo. Specifically, results for CI and LV stroke work differed by less than 10%, although other variables were found to have a great difference in some patients. They demonstrated that their simulation model could predict the influence of mechanical ventilation on energy use by the cardiovascular system.

In addition, De Lazzari et al. conducted a series of in silico studies concerning the effect of mechanical ventilation on cardiovascular parameters in the context of advanced circulatory support devices such as LVADs and IABPs. For these experiments, they again used the cardiopulmonary simulation model mentioned above. They tested the influence of using a rotary blood pump in league with mechanical ventilation on ventricular energetic parameters, and measured changes in ventricular energetic parameters, including external work, pressure volume area and ventricular efficiency with increasing levels of circulatory support with the rotary pump. Mean airway pressures were incorporated into the CARDIOSIM model at increasing levels of positive pressure to simulate the effects of mechanical ventilation. An increase in thoracic pressure in the context of rotary blood pump use caused an increase in right ventricular efficiency, minimal effect on LV efficiency and a decrease of external work and pressure–volume area.

Clinically, studies such as those by De Lazzari et al. can be used to adjust modes of circulatory and ventilatory support to optimise the energy requirements of the cardiovascular system in pathologic states and potentially lead to improved patient outcomes. It is impossible to simulate the true complexity of all of the interactions at play in vitro; however, in silico studies have the advantage of allowing researchers to isolate individual variables and test their effect within a complex system.

### Practice points

*In silico* studies suggest the following:

- Thirty-eight percent of right ventricular pressure-generating capacity is attributable to left-ventricular contraction, whereas only 9% of left-ventricular pressure-generating capacity is attributable to right-ventricular contraction.
- Cardiac output is profoundly affected by systemic ‘venous’ resistance.
- Changes in pulmonary venous pressure are highly dependent on the movement of fluid between the thoracic and extrathoracic compartments.
- Cerebral perfusion during cardiopulmonary bypass is maximised by high flow, non-pulsatile, alpha-stat management, and decreased maximally by low flow, pulsatile, alpha-stat state management.
- Increasing levels of positive pressure ventilation cause a decrease in ventricular energetic variables.
- When apnoeic, pregnant patients take approximately 2.5 min less time to desaturate to below 90% than non-pregnant females do. Once below 90% saturation, pregnant patients also take less time (35 s) to fall to 40% saturation, compared with non-pregnant patients (45 s).
In silico modelling techniques, which are primarily known for their contributions to our understanding of pharmacodynamics and pharmacokinetics, have provided significant insight into cardio-pulmonary physiology. Several in silico models (but not all) have been validated using in vivo experimentation. These techniques offer an exciting alternative to in vivo (resource-intensive and ethically complex) and in vitro (questionable clinical relevance) techniques. Future work will focus on broadening the applicability of these modelling techniques, as well as using them in the intra-operative environment, where they may serve as useful predictive tools for the anaesthesia provider faced with multiple complex decisions and incomplete information.

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Conflict of interest

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Disclaimers

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