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From fetus to neonate: A review of cardiovascular modeling in early life

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Abstract

Computational modeling has well-established utility in the study of cardiovascular hemodynamics, with applications in medical research and, increasingly, in clinical settings to improve the diagnosis and treatment of cardiovascular diseases. Most cardiovascular models developed to date have been of the adult circulatory system; however, the perinatal period is unique as cardiovascular physiology undergoes drastic changes from the fetal circulation, during the birth transition, and into neonatal life. There may also be further complications in this period: for example, preterm birth (defined as birth before 37 completed weeks of gestation) carries risks of short-term cardiovascular instability and is associated with increased lifetime cardiovascular risk. Here, we review computational models of the cardiovascular system in early life, their applications to date and potential improvements and enhancements of these models. We propose a roadmap for developing an open-source cardiovascular model that spans the fetal, perinatal, and postnatal periods.

This article is categorized under:

Cardiovascular Diseases > Computational Models

Cardiovascular Diseases > Biomedical Engineering

Congenital Diseases > Computational Models

KEYWORDS

birth transition, computational modeling, fetal circulation, hemodynamics, modeling standards, neonatal circulation, preterm birth

Abbreviations: DA, ductus arteriosus; DV, ductus venosus; FGR, fetal growth restriction; FO, foramen ovale; PDA, patent ductus arteriosus; PFO, patent foramen ovale.

1 | CHALLENGE AND SCOPE

The application of computational modeling techniques to cardiovascular physiology has been an active field of research for the past six decades, with great strides taken in understanding and simulation of human cardiovascular hemodynamics. Computational modeling has well-established utility in the study of cardiovascular hemodynamics for medical research purposes and is increasingly being translated into clinical settings to improve the diagnosis and treatment of cardiovascular diseases (Morris et al., 2016). During the same period, there have been remarkable advances in perinatal medicine, leading to a reduction in mortality and improved outcomes for infants, particularly those born preterm (defined as birth before 37 completed weeks of gestation). However, there are still several open questions in perinatal medicine that would benefit from the insights into hemodynamics that cardiovascular models can provide. To date, perinatal cardiovascular models are limited in number and most of the existing cardiovascular models have been built targeting the adult circulatory system.

In this article, we propose a roadmap for developing an open-source cardiovascular model that spans the fetal, perinatal, and postnatal periods. Desirable features for a model of the developing cardiovascular system are:

- The model should be complex enough to be individualized using image-based anatomical measurements, while also being simple enough for real-time computational simulation.
- The model should have a fully conservative formulation for mass and momentum.
- The model should be adaptable to unique circulatory conditions of early life, e.g., the preterm circulation.
- The model should be able to be implemented using modeling standards where these are available (e.g., CellML), and open-source software should be available to run the model via a graphical user interface (GUI). This interface should enable annotations of three-dimensional (3D) vascular structure.

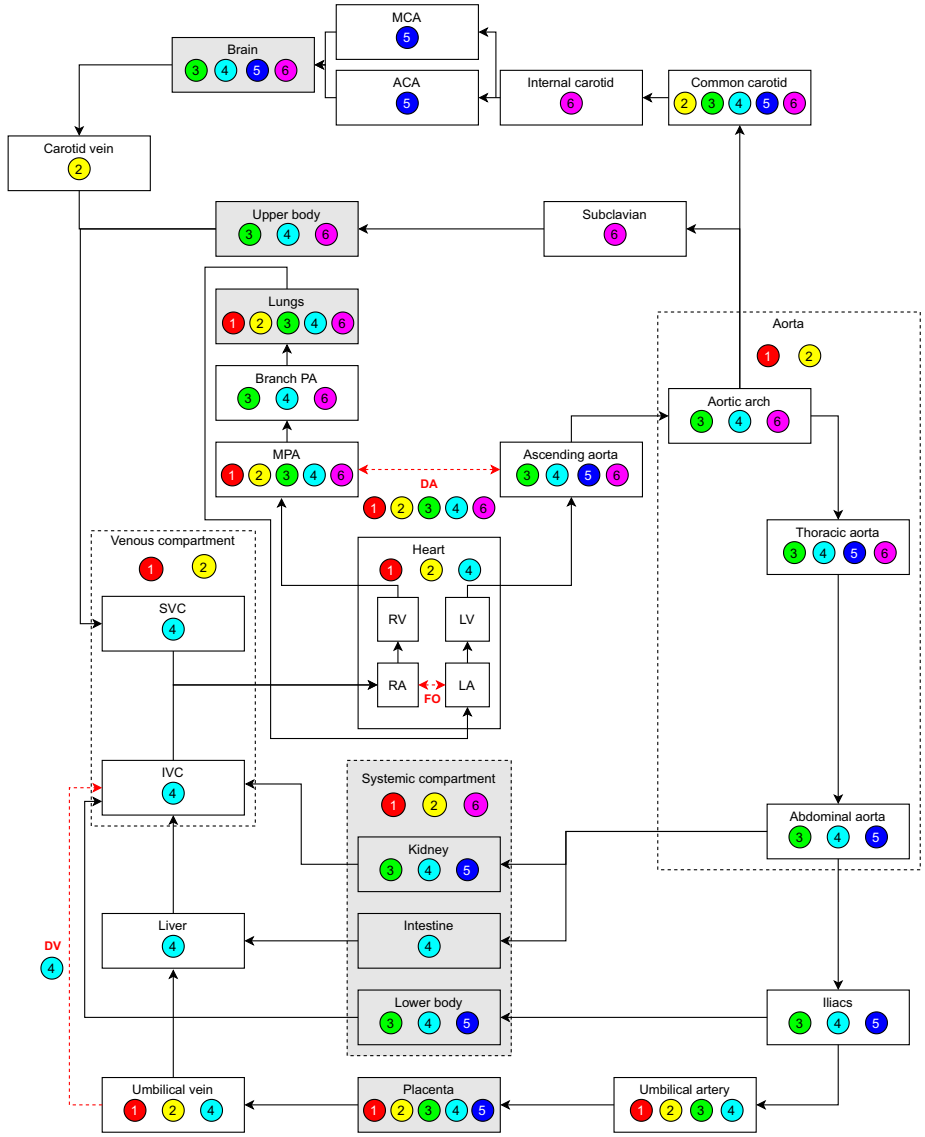
Here, we highlight influential models of the fetal circulation, transitional circulation at birth, neonatal circulation, and a postnatal growth model. Next, we discuss potential improvements and enhancements of early-life cardiovascular modeling and approaches to model customization and parameter estimation. Finally, potential clinical applications and the roadmap and rationale for developing an early-life cardiovascular model are presented.

2 | REVIEW OF EXISTENT MODELS

2.1 | Fetal models

Various computational models of fetal cardiovascular function have been proposed, with applications focused primarily on understanding the role of unique components of this circulation in early life (e.g., the role of the ductus arteriosus [DA]) or understanding fetal responses to stressors via baroreceptor function or autonomic control systems.

Zero-dimensional (0D) or lumped parameter models are hydraulic/electric analogs that have been widely implemented in modeling cardiovascular physiology. These models assume that a blood vessel (or a network of blood vessels within an organ) can be represented by parameters defining its resistance, compliance (capacitance), and inertance (inductance), which may be defined based on anatomical or functional knowledge or simply by fitting parameters to hemodynamic data measurements. One of the first 0D models of the fetal circulation was developed by Morris et al. (1965) and refined by Morrison et al. (1970); (see Figure 1). The Morris et al. (1965) model consisted of a four-chamber heart model coupled to pulmonary, systemic, and placental compartments with a unidirectional foramen ovale (FO) shunt and a bidirectional DA shunt. The major organs were represented as lumped systems, via representative resistance and compliance. The heart model was driven by asynchronous sinusoidal volume changes in the ventricles at a constant heart rate with purely resistive valves that prevented backflow. An improvement in the Morrison et al. (1970) model was the addition of a carotid sinus compartment that simulated carotid baroreception and allowed investigating the pathophysiology of carotid occlusion. These models were validated with experimental observations in fetal lambs and the results suggested that baroreceptor reflexes in the fetus may be dampened by the low-resistance placental circulation. These models have been extended, including consideration of oxygen transport in response to changes in maternal utero-placental blood flow (Huikeshoven et al., 1985). Ovine models are frequently used to investigate fetal function, and lamb data were used to parameterize early fetal circulation models. However, the models are not necessarily directly transferable to human data or validated in humans. These early models omitted the ductus



Key					
Model	**0D/1D**	**Open/closed loop**	**Time/Frequency domain**	**Normal/abnormal physiology**	**Other modelling details**
1 Morris (1965)	0D	Closed	Time	Normal	Closed loop 0D model with four-chamber heart model and 3 lumped compartments
2 Morrison (1970)	0D	Closed	Time	Normal	Based on Morris 1965; Included carotid baroregulation
3 Guettouche (1992)	1D	Open	Time	Normal	16 segments from heart to placenta and and 8 vascular beds
4 Pennati (1997)	0D	Closed	Time	Normal	19 compliant vascular compartments
5 van den Wijngaard (2006)	1D	Open	Frequency	Both	Included the umbilico-placental circulation and the fetal arterial tree
6 Garcia-Canadilla (2014)	0D	Open	Time	Both	14 arterial segments and 8 vascular beds

Fetal shunts | Blood vessel segments | Peripheral vascular beds

FIGURE 1 Schematic of existing fetal circulatory models.

venosus (DV), as their focus was predominantly on the function of the DA. The DV is an important feature to include in fetal circulatory models, as half of the umbilical venous return bypasses the portal circulation through this shunt, which connects the fetal umbilical vein directly to the inferior vena cava (Phelps et al., 2019). This shunting has

metabolic and other consequences, with DV flow patterns playing an important role in the clinical assessment of fetal cardiovascular function, particularly in response to fetal growth restriction (FGR) (Fratelli et al., 2020; Lees et al., 2020).

Pennati, Bellotti, et al. (1997) developed a more complete 0D fetal model using human Doppler ultrasound data, representing a near-term 3 kg fetus. The model featured a four-chamber heart model, which comprised a pressure generator, a time-varying elastance function to capture the elastic characteristics of the myocardium, and a resistance component to capture its dissipative characteristics with 19 compliant compartments that represented the vascular territories that could be directly investigated by ultrasound (see Figure 1). Parameter values for these compartments were based on these ultrasound measurements and anatomical data when available. The study aimed to provide a personalized assessment of fetal hemodynamics to complement existing clinical practice, that is, comparing measured Doppler flow in the major arteries with population norms. Simulations suggested that the DA shunt leads to similar pressures in the left and right circulation, despite different impedances in the pulmonary and systemic vascular beds. It also found that the flow in the DA is always directed into the descending aorta due to the high inertial flow, even during the period just before the aortic valve closure when the pressure drop across the DA is negative. A strength of this study was its validation against in vivo human Doppler measurements. However, the Pennati, Bellotti, et al. (1997) model did not include any circulatory control mechanisms, so that responses to fetal stressors could not be evaluated.

There are only a few one-dimensional (1D) models of the fetal systemic arterial circulation with notable examples including the Guettouche et al. (1992, 1993) open-loop models composed of 16 segments from the heart to the placenta. The 1D network model was derived by assuming axisymmetric laminar flow within the major arteries. The flow waveforms of the fetal Doppler measurements were the input to the model and the resistive vascular beds provided the distal boundary conditions (see Figure 1). Detailed anatomical vascular measurements in human fetuses were used to parameterize these models. The Guettouche et al. (1992) model approximated a 27.5 week fetus weighing 1.25 kg, parameterized using measurements taken between 25 and 30 weeks of gestation, while the Guettouche et al. (1993) model of a third-trimester fetus used measurements taken between 30 and 38 weeks of gestation to approximate a 34 week fetus. The comparison of these two models suggested that peripheral resistance values decreased with gestational age. Good agreement was found between the modeling blood flow predictions and the empirical Doppler flow measurements and important differences (e.g., in total placental umbilical flow rate) were noted from the fetal lamb data reported previously. The anatomical data collected to parameterize these models have been influential in many subsequent fetal modeling studies (Garcia-Canadilla et al., 2014; Myers & Capper, 2002; Mynard, 2011; Pennati, Bellotti, et al., 1997; van den Wijngaard et al., 2006). However, like previous fetal sheep models, the focus on the arterial circulation limits its applicability to clinical problems.

Some fetal cardiovascular models have been adapted from models of adult circulation (Mynard & Smolich, 2015; van den Wijngaard et al., 2006) (see Figure 2). van den Wijngaard et al. (2006) examined a wide range of gestational ages (15–40 weeks) by scaling a 1D adult model (Westerhof, 2005). This model included umbilicoplacental circulation and the fetal arterial tree, but did not include heart, venous circulation, or right-to-left fetal shunts (FO and DA; see Figure 1). The 1D model accounted for viscoelasticity in the arterial wall and was solved in the frequency domain. This open-loop model used a flow waveform from the literature as input to the model and three-element Windkessel circuits at the output representing peripheral vascular beds. The purpose of this model was to investigate common fetal pathophysiology that is associated with adverse pregnancy outcomes, which it sought to do by varying a range of parameters and observing the resulting changes in the pulsatility index of the arteries. For example, blood viscosity was increased or decreased to simulate fetal polycythaemia or anemia, respectively. Other parameters investigated included placental resistance (an increase is commonly associated with FGR as has been explored in later modeling studies Saw et al., 2018; Tun et al., 2019), vessel stiffness (through modification of Young's modulus), and vascular resistance in the fetal brain. This model has been extended to study the hemodynamics of twin-to-twin transfusion syndrome (van den Wijngaard et al., 2007).

Mynard (2011) developed a closed-loop 1D model of the entire adult, neonatal, and fetal cardiovascular systems (see Figure 2). The adult model (later further refined in Mynard & Smolich, 2015) incorporated all major vascular territories, with 396 1D segments representing the systemic and pulmonary arteries and veins, including coronary, cerebral, and portal vascular trees. The 0D heart model used a time-varying elastance function and accounted for mechanical interactions between heart chambers arising from pericardial constraint, inter-ventricular septal motion, and atrio-ventricular plane motion. 0D models were used for peripheral vascular beds, and vascular beds for the heart, liver, and brain were customized based on anatomical considerations. The results compared well with the characteristic waveforms in the literature. Wave intensity analysis was used to study the mechanisms underlying the shape of pressure and flow

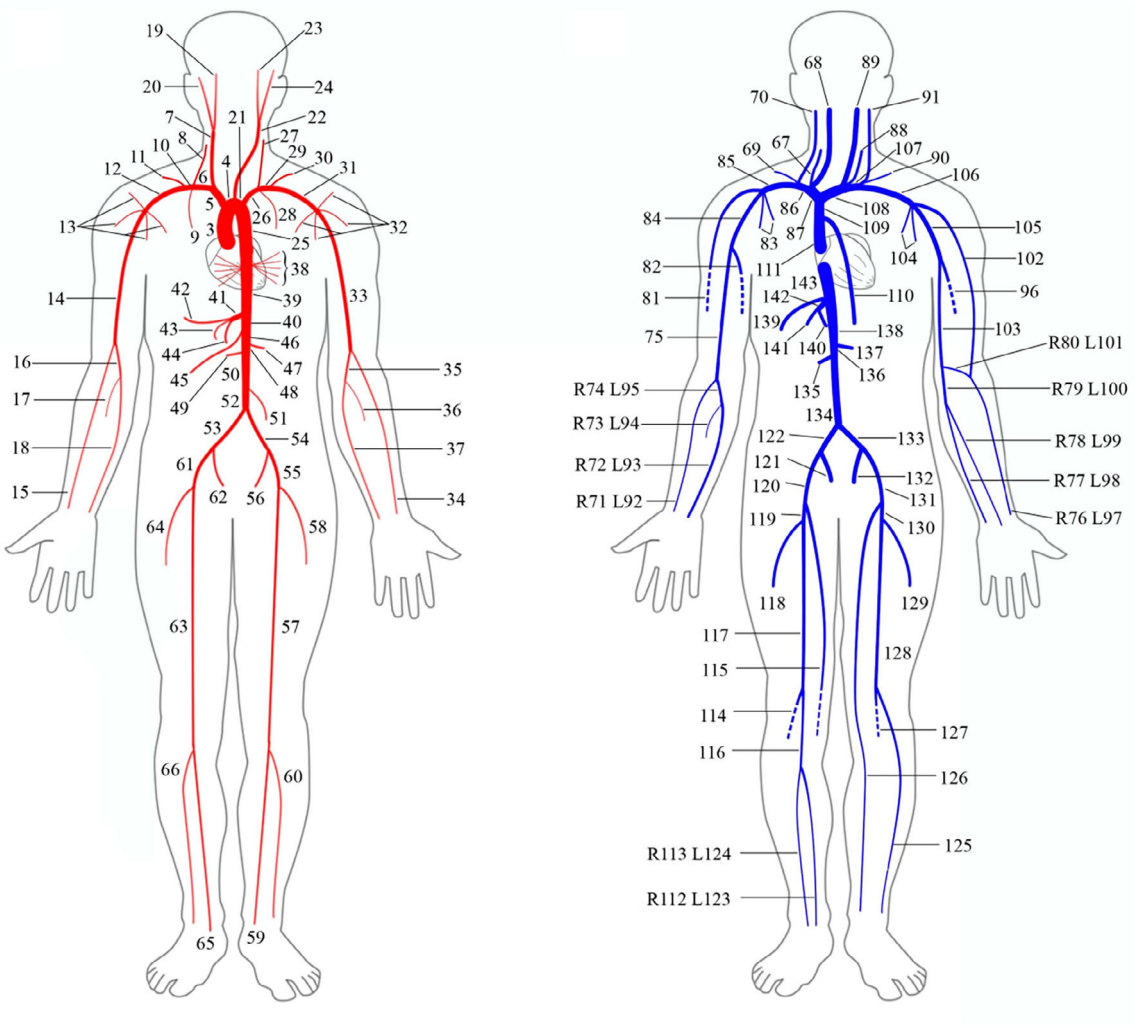


FIGURE 2 Major arteries and veins included in the Mynard and Smolich (Mynard & Smolich, 2015) adult model, all included in the adaptation to both fetal and neonatal circulations (Mynard, 2011).

waveforms and the interaction between cardiac function, mechanics, and vascular waves. Positive and negative wave intensities correspond to forward and backward traveling waves (with respect to the direction of mean blood flow), and compression and decompression waves indicate whether a wave has a pressure-increasing or pressuring-decreasing effect, respectively. This work is notable for simulating wave propagation effects in an anatomically detailed closed-loop circulation. A limitation is that, while it included detailed venous anatomy, it did not include venous valves. The adult model was allometrically scaled, and further adapted based on literature data, to produce a model of neonatal circulation. A fetal model based on the neonatal model was then developed by incorporating umbilico-placental circulation, fetal vascular shunts, and differences in flow distribution and cardiac function. In addition to studying normal fetal hemodynamics, the parameter for placental resistance in the fetus was varied with and without brain-sparing to study this important pathological condition associated with negative pregnancy outcomes. The models were validated by comparison with published literature, as well as experimental studies in lambs conducted by the Heart Research Group at the Murdoch Children's Research Institute.

The Garcia-Canadilla lumped parameter model of the fetal circulation focused on pathophysiology, in particular, cardiovascular remodeling as a result of FGR (Garcia-Canadilla, 2015; Garcia-Canadilla et al., 2014). The model aimed to investigate the brain-sparing phenomenon found in FGR where the fetal brain preferentially receives blood flow in the face of placental insufficiency, by quantifying blood redistribution in growth-restricted fetuses. The model was initially developed using clinical hemodynamic measurements from one healthy human control fetus and then further modified for FGR using Doppler flow measurements from three fetuses with varying degrees of growth restriction at

different gestational ages. Based on the Guettouche et al. (1992) model, the open-loop model was made up of 14 arterial segments and 8 vascular beds, as illustrated in Figure 1. Boundary conditions were provided by clinical arterial and pulmonary Doppler flow data at the inlet and a grounded outlet. Finally, the values of cerebral, peripheral, and placental vascular resistances were varied to simulate the effects of vasoactivity in response to FGR. The main findings of the model suggest that cerebral perfusion in growth-restricted fetuses is maintained through a decrease in vascular resistance in the brain, while preferential blood flow redistribution to the brain, quantified by blood flow through the aortic isthmus, is determined by a combination of increased peripheral-placental and decreased cerebral vascular resistance. This model is a good example of the application of individual patient data to investigate pathophysiology. However, a disadvantage of this model is that it represents a simplified anatomy, omitting the fetal heart and other fetal shunts.

Most of the fetal models discussed above include the placental circulation (often simplified). This represents a highly complex vascular branching anatomy that evolves during pregnancy. The human placenta (or parts thereof) has been modeled using 0D and 1D techniques similar to those of the fetal circulation, as well as 3D computational fluid dynamics (Bernad et al., 2016; Byrne et al., 2021; Clark et al., 2015; Gordon et al., 2007; Guiot et al., 1992; Mirbod, 2018; Todros et al., 1992; Tun et al., 2019). However, it is important to note that the placenta and its function are not entirely dependent on fetal factors. On the surface of the placenta, the maternal and fetal circulations are in close contact (but do not mix). Models of the pregnant uterus (or parts thereof; Clark et al., 2018; James et al., 2018; Saghian et al., 2019; Talbert, 1995), uterine circulation coupled with the maternal cardiovascular system (Carson et al., 2019), the materno-placental interface (Lecarpentier et al., 2016; Roth et al., 2017; Saghian et al., 2017), and the feto-placental interface (Chernyavsky et al., 2011; Erlich et al., 2019; Gill et al., 2011; Lin et al., 2016; Pearce et al., 2016; Plitman Mayo et al., 2016; Serov, Salafia, Brownbill, et al., 2015; Serov, Salafia, Filoche, & Grebenkov, 2015) have been developed that look at the details of the circulation at high spatial resolution, with a focus on the exchange capacity of the placenta. There are also a small number of sheep models that assess maternal–fetal interactions, using simplified anatomy (Wang et al., 2015). However, there are as yet no anatomical models that account for both maternal and fetal systemic circulations simultaneously, and there is a need for multiscale modeling linking the highly anatomically detailed uteroplacental models with the relatively simple lumped parameter fetal (and maternal) circulatory models. Clark et al. (2021) provide an in-depth review of this modeling in this area.

2.2 | Fetal-to-birth transitional models

One of the earliest closed-loop lumped parameter models of the fetal circulation was also used to study the transition from fetal to neonatal circulation (Morris et al., 1965). The transition was simulated through three events: lung expansion, umbilical cord cutting, and gradual closure of the DA. Lung expansion was simulated by decreasing pulmonary vascular resistance and increasing pulmonary vascular compliance. A switch was placed in the electrical circuit model such that the placenta component could be removed from the circuit to simulate cutting the umbilical cord. The DA was narrowed by increasing its resistance to flow. The results of this model suggested, contrary to the conventional wisdom at the time, that there was still right-to-left shunting across the DA even when the pressure gradient was negligible or there was a negative pressure gradient. Although these findings were validated with physiological studies in lambs, several factors in the experimental methodology of these validation studies should be taken into account: the fetus was completely exteriorized; early model constrictive electromagnetic flow probes were used; the lungs were ventilated with either 100% oxygen (which dilates their vasculature) or room air, but no further details were provided about whether all animals received only one or both; the very long interval of 30 min between cord cutting and pulmonary inflation was non-physiological and would not occur in real life (see Section 3.2 for discussion of implications).

The Sá-Couto et al. (2010) model is an extension of the earlier educational neonatal models discussed in the following section (Goodwin et al., 2004; Zijlmans et al., 2009) (see Figure 3). The aspects of the transitional circulation in this model include the onset of breathing, cord clamping, and a number of other parameter changes to mimic the transitory phase up to the first 24 h after birth. This model consists of a four-chamber heart with time-varying elastances, 7 vascular compartments, and connections to mimic the three fetal shunts (DA, DV, and FO). Onset of breathing was simulated by decreasing intrathoracic pressure from 0 mmHg in the fetal model to −3 mmHg in the newborn model and gradually decreasing pulmonary vascular resistance in the first 24 h. Cord clamping was simulated with a doubling of

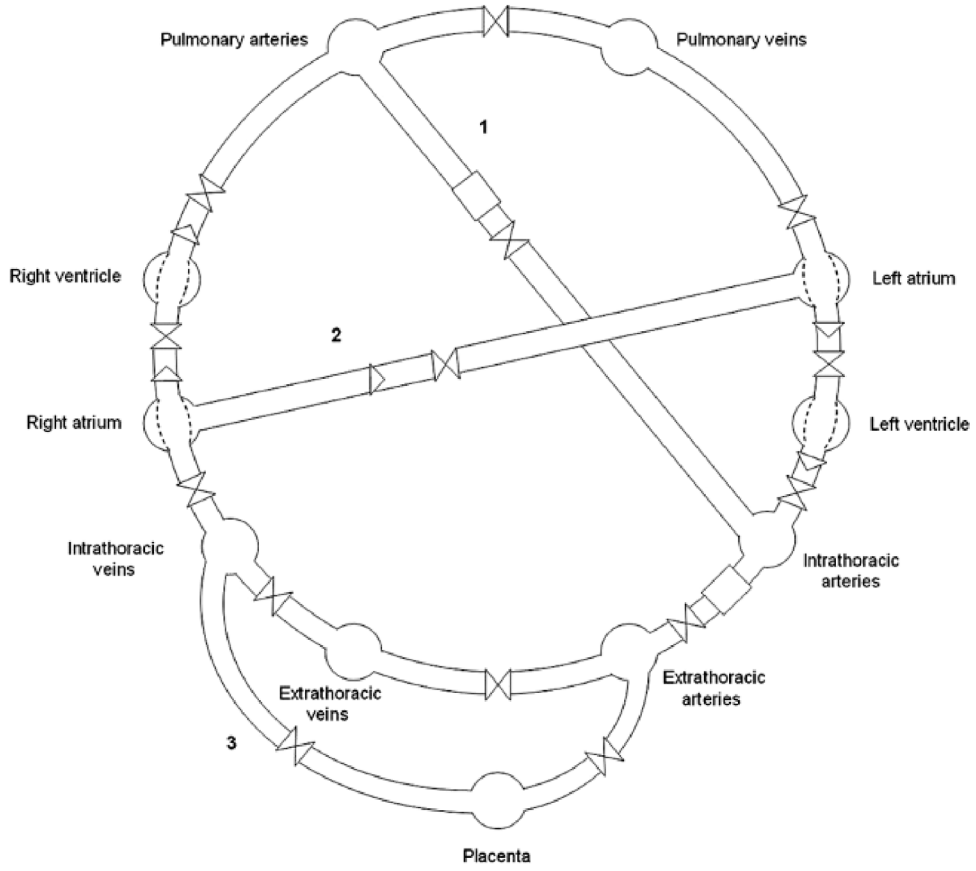


FIGURE 3 Hydraulic analogue of Sá-Couto et al. (2010) model of the transitional circulation; (1) ductus arteriosus (DA); (2) foramen ovale (FO); (3) ductus venosus (DV).

total systemic resistance followed by a slower rise over the next day. An exponential formula for the closure of the DA was derived from experimental data, with the vascular resistance being inversely related to the DA diameter to the fourth power. The model could also be used to simulate pathophysiology, for example, a patent ductus arteriosus (PDA) with left-to-right shunt and myocardial depression by modifying the ventricular time-varying elastances. The model did not include any control mechanisms. The assumption of zero intrathoracic pressure in the fetal model may also be a limitation, as intrathoracic pressure is positive in the fetus (approximately 2 mmHg; Vilos & Liggins, 1982) which is likely to have a constraining effect on ventricular function (Grant, 1999; Grant et al., 1992; Grant & Walker, 1996).

Building further on the Sá-Couto et al. (2010) model of the transitional circulation, Soleymani (2015) combined it with Ursino's baroreceptor reflex model (Ursino, 1998; Ursino & Magosso, 2000). This model was applied to study the sudden closure of the DA as would occur when a PDA is repaired surgically. It was based on a 3.5 kg neonate 2–3 days after birth. Consistent with the experimental data in lambs (Clyman et al., 1987), modeling results suggested that after DA closure, there is a sudden decrease in left ventricular output and stroke volume, but an increase in systemic blood flow since blood is no longer diverted to the pulmonary circulation. Soleymani (2015) suggested that increased systemic blood flow leads to an increase in blood pressure, triggering a baroreceptor reflex response that, in turn, decreases systemic vascular resistance; These short-lived hemodynamic changes in the modeling (e.g., an initial immediate post-closure rise in systemic blood flow followed by a subsequent decrease in systemic blood flow due to a decrease in preload) have not been reported in the clinical literature; however, this may be due to limitations in hemodynamic monitoring in neonates.

Adapted from the Pennati et al. (1997) model of fetal circulation, the Yigit et al. (2015) model aimed to study the hemodynamic consequences of immediate versus delayed cord clamping in the transition from fetal to neonatal life. This lumped parameter model shown in Figure 4 also incorporated gas exchange. The fetal shunts were simulated to close over the first 10 min after birth, with immediate cord clamping simulated as a jump to infinite umbilical vascular

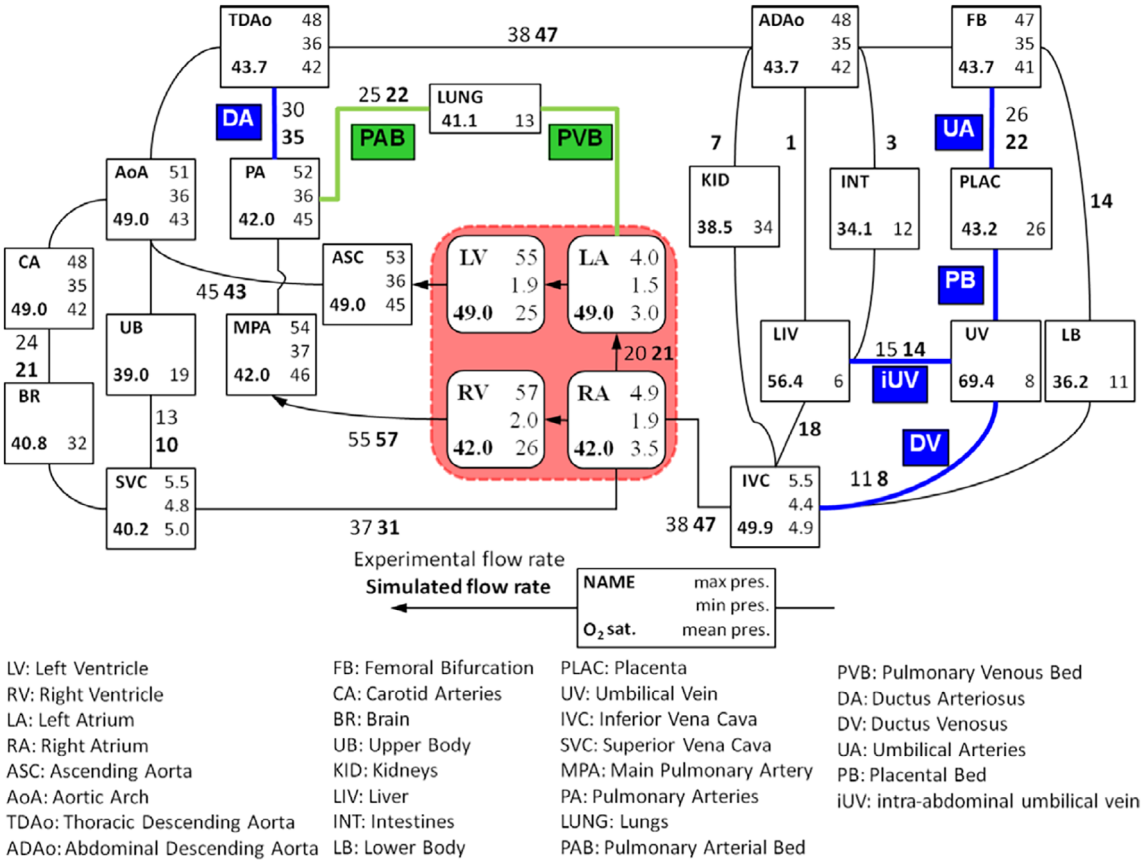


FIGURE 4 Network schematic of the Yigit et al. (2015) transitionary fetal cardiovascular model.

resistance at the start of the transition, whereas delayed cord clamping was simulated as slow closure of the umbilical arteries during the transition period of 10 min while the umbilical vein remained open to allow placental transfusion. The result was a 30 mL increase in neonatal blood volume in delayed versus immediate cord clamping scenarios (10% of total neonatal blood volume), leading to a 20% increase in cardiac output and a better maintenance of oxygen saturation level when pulmonary respiration was delayed or impaired. These results were validated against clinical findings from the literature (Bhatt et al., 2013; Sommers et al., 2012). A subsequent Yigit et al. (2019) model expanded on this work by examining the effect of the timing of cord clamping at different gestational ages and in a variety of pathological scenarios (respiratory distress syndrome, PDA, and FGR). Allometric scaling was used to scale the model to a range of gestational age at birth from 20 to 40 weeks. The results of the modeling suggested the adverse effects of immediate cord clamping at all gestational ages, with the severity of these adverse effects related to increased prematurity and the presence of respiratory distress syndrome, PDA, or FGR.

The Munneke et al. (2022) model aimed to overcome limitations of previous transitional circulation models by adding oxygen metabolism, homeostatic control mechanisms, and a one-fiber model for myocardial contraction (as opposed to the time-varying elastance cardiac model used elsewhere; see Figure 5). It was adapted from the CircAdapt model of adult cardiovascular circulation (Arts et al., 2005; Lumens et al., 2009). A time- and event-based script simulated the birth transition with several changes, including an abrupt increase in umbilical vascular resistance to infinity to mimic cord cutting, gradual aeration of the lungs that leads to higher levels of oxygen saturation during the first minute after birth, and a gradual decrease in pulmonary vascular resistance and DA diameter over the first 24 h. The model was validated against fetal and animal data from the literature. The impact of changes in the resistance of compartments in these models has been assessed primarily as a model sensitivity analysis, rather than based on data on changes in a specific organ function with pathology or the birth process. For example, there are detailed models describing how the resistance of the lungs change in the transition liquid-to-air breathing at birth, but few details of the mechanics of these processes are integrated into whole-organ/body models (Suki et al., 1998).

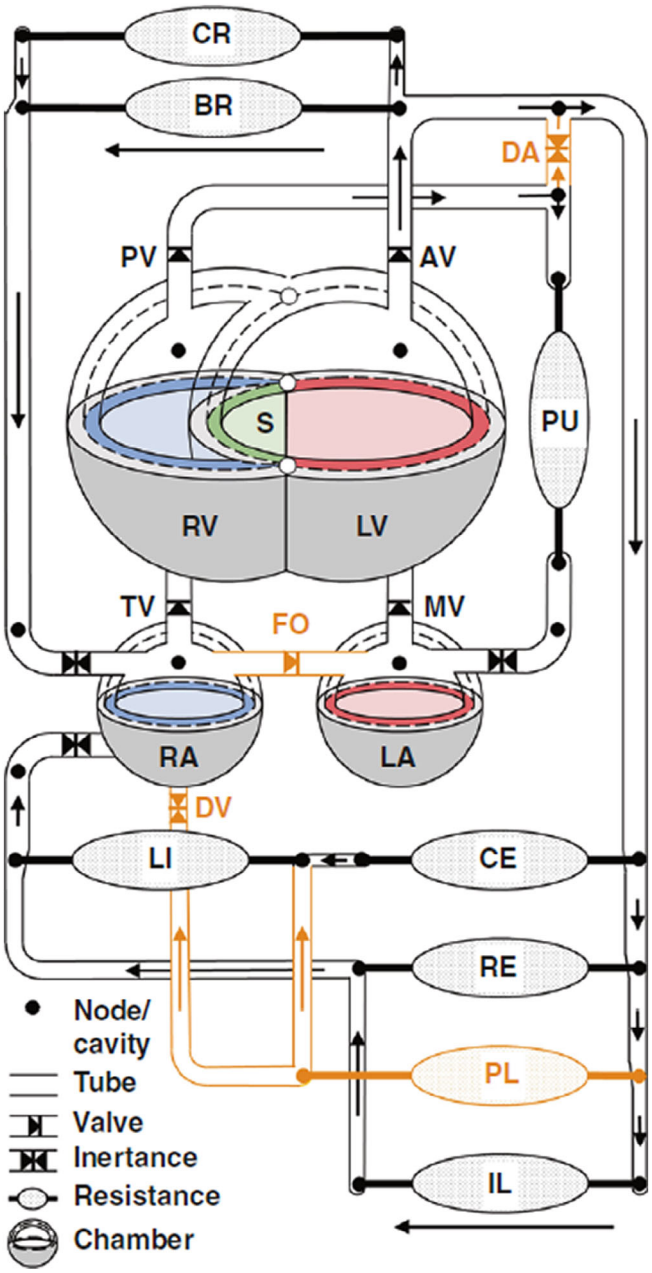


FIGURE 5 CircAdapt model of the fetal cardiovascular system with transitional segments in orange. For abbreviations, see (Munneke et al., 2022).

2.3 | Neonatal models

2.3.1 | Term neonatal models

The Goodwin et al. (2004) model was designed as an educational simulator for acute perinatal care for clinicians, to be used for medical training with the ultimate goal of contributing to patient safety. The infant model was adapted from an existing adult cardiovascular model (Beneken, 1965), which is also the basis for the commercially available simulators from CAE Healthcare. To support a wide range of clinical simulation scenarios, an uncontrolled model of relatively reduced complexity was selected. The model is illustrated in Figure 6. Due to the lumped nature of this model, with the arterial network represented by two elements (intra- and extra-thoracic arteries) and the venous network similarly represented by two elements (intra- and extra-thoracic veins), a precise vascular geometry was not required. The results were in line with the target hemodynamic variables, and realistic pressure waveforms and

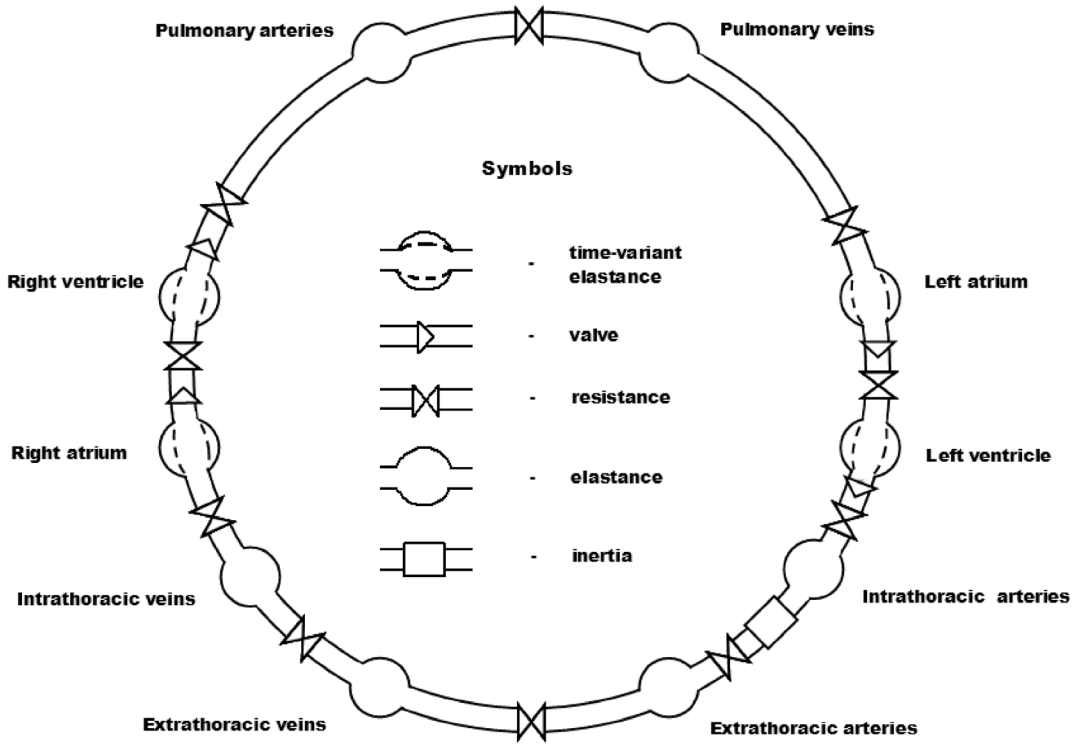


FIGURE 6 Goodwin et al. (2004) hydraulic analogue for the neonatal cardiovascular model.

pressure volume loops were achieved. The system could also be perturbed to simulate blood loss and the administration of fluids and drugs that influence hemodynamics.

This simple model has since been improved upon in several iterations and lends itself to adaptation by others due to its clear model parameters based on physiological values available in the literature. Sá Couto et al. (2006) improved the parameterization of the heart model for more realistic ventricular pulsations. It also included a baroreflex model and was adapted to simulate four congenital heart defects in a one-week-old term neonate: PDA, tetralogy of Fallot, coarctation of the aorta, and transposition of the great arteries (see Figure 7). Some corrections and improvements to parameterization were published by Zijlmans et al. (2009) with the resulting simulations closer to the target hemodynamic data.

As discussed in the review of fetal models, the work of Mynard (2011) also extends to a closed-loop neonatal model, which was applied to study one congenital heart disease: pulmonary atresia with intact ventricular septum (Mynard, 2011; Mynard et al., 2010). A particular strength of this work is the high degree of anatomical fidelity compared to most of the other simplified neonatal models discussed in this section. A natural limitation was the paucity of detailed anatomical data available for neonates, which required the use of allometric scaling techniques to adapt the adult circulatory model. Similarly to the fetal model, the model was validated by comparison with the published literature and lamb studies.

Some of the models discussed so far were adapted to various congenital heart diseases, but all are still modeling a biventricular heart. In contrast, other models have been developed to simulate hypoplastic left heart syndrome, where the underdevelopment of the left ventricle leads to a univentricular circulation (Di Molfetta et al., 2016; Jalali et al., 2015; Migliavacca et al., 2001; Pennati, Migliavacca, et al., 1997). An example of a 0D model is shown in Figure 8. Hypoplastic left heart syndrome is surgically corrected in a step-wise manner during the first 2 years of life, leading to Norwood, Glenn, and Fontan circulations, which can also be simulated using these models (see, e.g., the Di Molfetta et al. (2016) model). Although these 0D models use a highly simplified cardiovascular anatomy, they nonetheless provide useful information for treatment planning.

2.3.2 | Preterm neonatal models

The Dat (2010) and Jennekens et al. (2011) publications reported a neonatal model (Sá Couto et al., 2006) scaled down to a 28 week, 1 kg preterm neonate. The baroreflex control of Ursino et al. was added to the model with

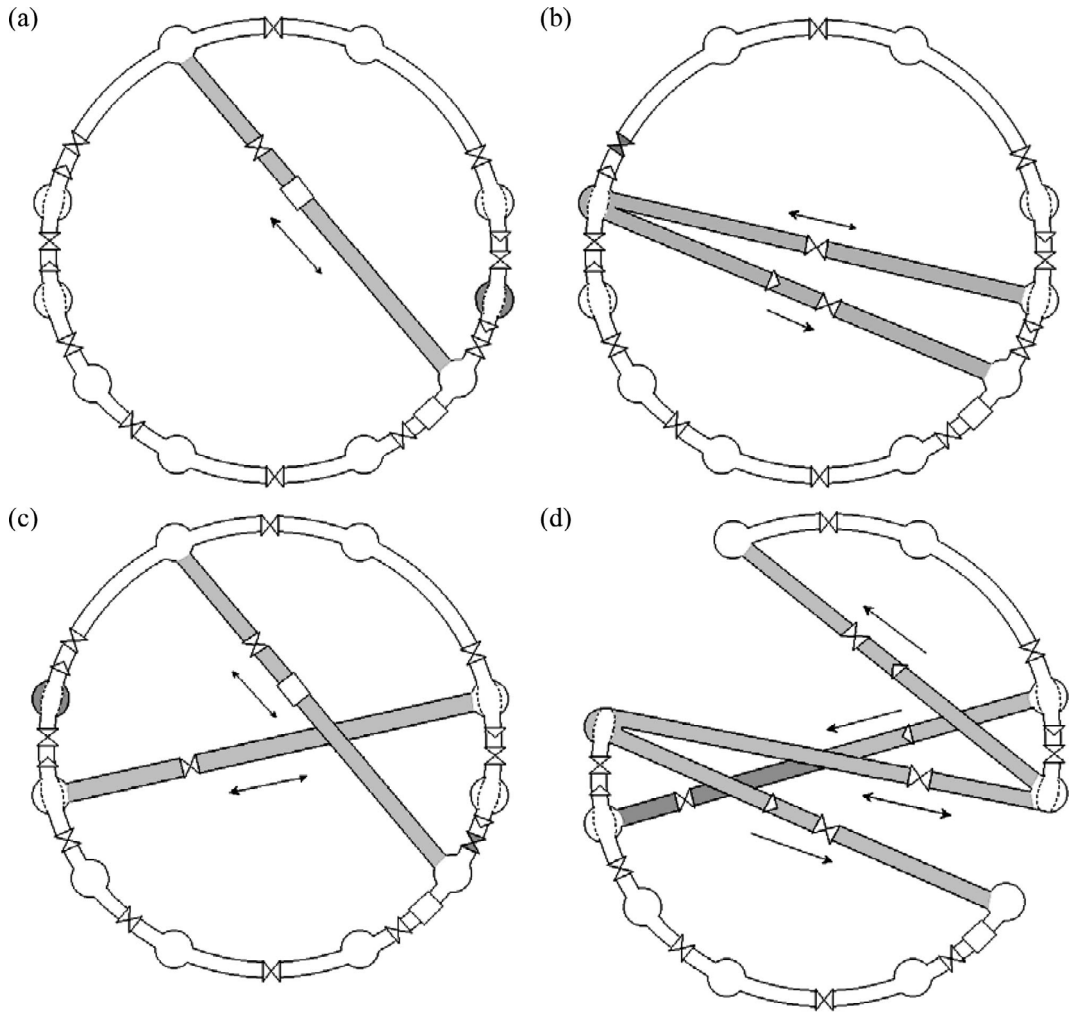


FIGURE 7 Hydraulic analogs of congenital heart disease (Sá Couto et al., 2006); (a) patent ductus arteriosus (PDA); (b) tetralogy of Fallot; (c) coarctation of the aorta with patent foramen ovale (PFO) and a small patency of the ductus arteriosus (DA); (d) transposition of the great arteries with septal defects.

interactions between heart rate, blood pressure, and respiration (Ursino, 1998; Ursino & Magosso, 2003). This model assumed that the DA would close at the end of the first week and was validated against preterm data from the literature, in particular, reference ranges for blood pressure and spectral analysis of heart rate traces. This model shows promise for clinical translation by suggesting that it may be possible to quantify baroreflex maturation in preterm infants and to simulate clinically relevant interventions, for example, vascular expansion for the treatment of hypotension. The limitations of the model are that it used parameter values from a variety of human and animal data and did not include the chemoreceptor control mechanisms of the feedback system.

2.3.3 | Postnatal growth models

The ambitious Westerhof et al. (2020) cardiovascular model is a developmental model that simulates the full age range from newborn to adult. Based on previous adult models (Stergiopulos et al., 1992; Westerhof et al., 1969), it is an open-loop model of the arterial system with 121 segments. The output boundary condition is provided by three-element Windkessel models representing the distal circulation. Standard percentile charts of height, length, and weight were used to determine the proportional volumes of six different body divisions (head, neck, thorax, abdomen, legs,

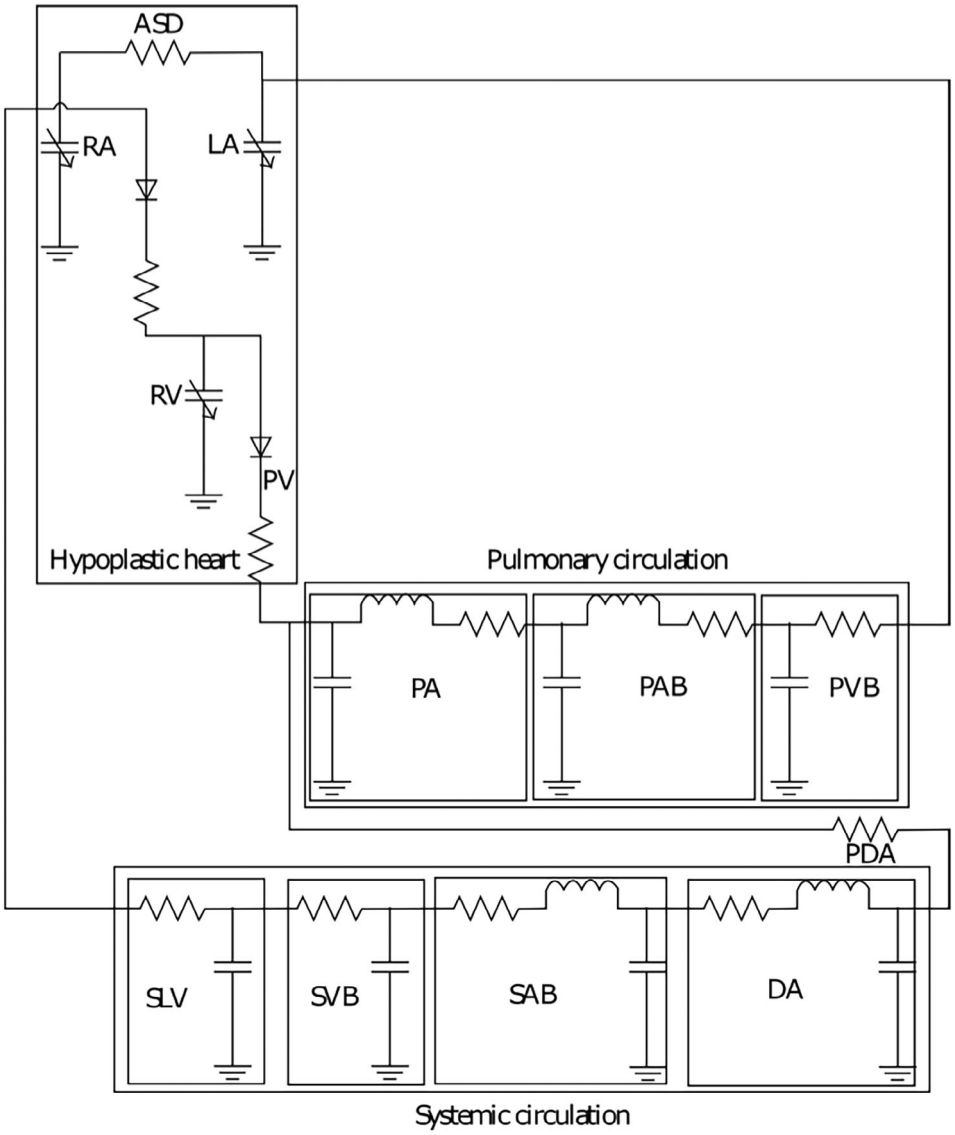


FIGURE 8 Lumped parameter model of hypoplastic left heart syndrome (Jalali et al., 2015). ASD, atrial septal defect; DA, descending aorta; LA, left atrium; PA, pulmonary artery; PAB, pulmonary arterial bed; PDA, patent ductus arteriosus; PV, pulmonary valve; PVB, pulmonary venous bed; RA, right atrium; RV, right ventricle; SAB, systemic arterial bed; SLV, systemic large veins; SVB, systemic venous bed; TV, tricuspid valve.

and arms), which were then used to determine the dimensions of arterial segments at different ages. For peripheral vascular beds, Windkessel compliances increased proportionally to the volume of body division and Windkessel resistances were inversely proportional to the volume. This model was analyzed in the frequency domain and aimed to provide central to peripheral transfer functions (i.e., a description of changes in the shape of the pressure wave as it travels distally in the arterial system), which could be useful, for example, in determining cardiac output from peripherally measured pressures. The strength of this model is the wide range of ages it covers, providing insight into cardiovascular physiological development over time. For example, the findings showed that peripheral pressure waveforms in children have a close resemblance to central pressure waveforms than in adults. They also found that the velocity of pulse waves in the aorta increases with age. However, a limitation is that the cardiovascular geometries were based on growth curves and not experimentally measured in individuals of different age groups, and aging is driven by typical changes in the size of the vascular bed, rather than by a mechanism of growth and remodeling.

3 | POTENTIAL IMPROVEMENT AND ENHANCEMENT OF EARLY LIFE CARDIOVASCULAR MODELING

3.1 | Cardiorespiratory interactions in the birth transition

The lungs are the organs that undergo possibly the most dramatic change in physiology in the birth transition. During gestation, they are fluid-filled and their vasculature is constricted; as breathing transitions from fluid to air, the blood volume in the lungs also increases dramatically, with a reduction in resistance as the vasculature relaxes. The resistance of the pulmonary vasculature is affected by changes in air pressure, since airways and blood vessels are structurally and functionally intertwined. Conditions such as surfactant deficiency related to preterm birth affect lung expansion and, in turn, blood and air pressure within the pulmonary space (Halpern et al., 1998).

Fetal and birth transition models should address these complex cardiorespiratory interactions. The fluid-filled fetal lungs have two important mechanical effects on cardiovascular function. The first is extravascular compression of the pulmonary microvasculature, which contributes to the high pulmonary vascular resistance in the fetus. A reduction in lung liquid volume, which occurs during labor and birth transition, reduces this constraint and can have a substantial effect on cardiac output and systemic arterial blood flows (Smolich, 2014; Smolich et al., 2021; Smolich & Mynard, 2019). The second is that the fluid-filled lungs constitute an external constraint on the heart itself. The reduction of lung liquid volume at birth reduces the degree of cardiac constraint, also resulting in increased ventricular output via the Frank-Starling mechanism (Grant, 1999; Grant et al., 1992; Grant & Walker, 1996). Other sources of thoracic constraint in the fetus include the pressure arising from the amniotic fluid and the maternal intra-abdominal contents. Delivery of the fetus at birth removes these sources of thoracic constraint, which may also increase cardiac output after birth.

Cardiorespiratory interactions at this stage in life are relatively understudied in mathematical and computational models, in part because the physics of the system at this time in life is complex and difficult to observe in real time. However, improvements in models in this regard would be of great benefit to understanding how cardiovascular function evolves at this stage of life, and which are the ulterior consequences in the adult circulation of subtle and quick abnormal conditions experienced during birth transition.

3.2 | Cord clamping in birth transition models

For examination of the circulatory effects of delayed and immediate cord clamping, models should have considerable flexibility in terms of the time point where cord clamping or the onset of ventilation can occur. The duration of delay in delayed cord clamping is another important consideration, as there is no standard time used clinically; the delay can range from 30 s to 8–10 min after delivery of the infant. The start of ventilation may also occur at different times within the delay period of cord clamping, since a baby could breathe immediately after delivery or breathing could also be delayed (e.g., in a preterm infant or an infant who has experienced prolonged periods of hypoxemia or asphyxia during the birth transition; Hooper et al., 2015). Similarly, for immediate cord clamping, models should be able to deploy varying intervals between cord clamping and the start of ventilation/breathing, as the duration of this interval is crucial for the type of hemodynamic changes that occur after birth (Smolich et al., 2015, 2017, 2020), with a brief non-asphyxial interval displaying relatively minor perinatal differences in hemodynamics and blood flow patterns compared to delayed cord clamping (Smolich & Kenna, 2022). Furthermore, the interaction between the timing of cord clamping and the onset of ventilation determines the newborn's circulating blood volume. If the cord is cut after pulmonary inflation and the drop in pulmonary pressure, blood from the low-resistance placental reservoir is returned to the pulmonary bed compared to the scenario in which the cord is cut before the pulmonary resistance drops and blood is sequestered in the placenta (Katheria et al., 2017). Physiological-based cord clamping, defined as cord clamping after the onset of ventilation, has been shown to stabilize heart rate and improve oxygen saturation during the birth transition in both lamb and human preterm studies (Brouwer et al., 2019; Polglase et al., 2015). This once again highlights the need for appropriate clinical data for model validation and the need for models to incorporate more physically derived processes to allow the time course of changes at birth to be explored.

3.3 | Location and directionality of the FO

In the fetus, the FO is usually modeled as a connection between the right and left atria; however, both ovine (Rudolph, 2009) and human (Kiserud et al., 1992) fetal experiments have shown that this is not anatomically correct. Although the entrance of the inferior vena cava is separated from the left atrium by the inferior margin of the atrial septum, the superior portion of the atrial septum (the crista dividens) overlies the inferior vena cava (Rudolph, 2009). This means that the posterior left portion of the inferior vena cava connects directly to the left atrium through the FO. As the heart beats, the eustachian (inferior vena cava) valve and the lower portion of the atrial septum move as one to direct blood either to the left through the FO to the left atrium or to the right through the right atrium to the tricuspid valve (Rudolph, 2009). This facilitates preferential streaming of highly oxygenated blood from the DV to the inferior vena cava through the FO into the left atrium and ventricle and to the ascending aorta. Blood with lower oxygen saturation is preferentially distributed into the right ventricle and the main pulmonary artery. Few models can account for the anatomical detail of the FO or for these preferential streaming patterns in blood flow.

In most models, the FO is modeled as a one-way valve. However, ultrasound data suggest that FO shunting is bidirectional, even in the fetus, although predominantly from right to left (Feit et al., 1991). After birth, the umbilical cord is clamped and blood flow through the inferior vena cava to both atria suddenly decreases. At the same time, the initiation of breathing increases the pulmonary return to the left atrium. These changes result in the left atrial pressure exceeding the right atrial pressure, causing a valve-like flap at the entrance to the left atrium to occlude the FO (Phelps et al., 2019). This is a functional closure and can take several months before fibrous closure occurs (Phelps et al., 2019). Before anatomic closure, there may be some degree of left-to-right shunting within a bidirectional shunt pattern (Evans & Iyer, 1994) and any rise in right atrial pressure to the point that it equals or exceeds left atrial pressure will result in a right-to-left shunt across the FO (Phelps et al., 2019).

3.4 | Cardiovascular effects of control systems

Adequate circulatory function to provide sufficient delivery of oxygen and nutrients to meet the metabolic needs of the body and the clearance of waste products depends on a cardiovascular control system that can adjust blood pressures and flows according to changing systemic requirements in response to environmental stimuli. This is achieved through the complex interplay of neural, hormonal, and metabolic mechanisms and reflex pathways.

Fetal cardiovascular responses to autonomic antagonists increase through gestation as the system matures. The fetal response to stressors, such as a change in maternal blood supply or hypoxia is typically monitored by assessing fetal heart rate. Several models have been proposed to describe fetal cardiovascular control via modeling that includes simplified 0D representations of the fetal circulation, in many cases the maternal circulation (or a variable representing maternal utero-placental blood flow), and a control system model (Jongen et al., 2016, 2017; van der Hout et al., 2012). These models often follow similar models proposed in the literature for cardio-respiratory system function in the adult human, and focus on late gestation/labor and experimental interventions in sheep such as uterine artery or umbilical cord compression/ligation.

While some of the fetal and birth transition models have incorporated baroreceptor function and oxygen delivery, none have incorporated the cardiovascular effects of sympathoadrenal activation and high levels of circulating catecholamines that can occur in fetal hypoxemia (either acute or chronic) and fetal asphyxia (Cohen et al., 1984; Comline et al., 1965; Simonetta et al., 1997; Smolich & Esler, 1999), or as part of the birth process (Lagercrantz & Slotkin, 1986; Padbury & Martinez, 1988; Smolich et al., 2017). Early-life cardiovascular models will need to be expanded to include both oxygen and carbon dioxide gas exchange and transport alongside hemodynamics for physiological control systems to be successfully deployed. These models will need to take into account the newborn infant; many aspects of the complex cardiovascular control system mature at different rates. This is particularly relevant to the preterm infant, where immaturity may impact the normal function of these systems.

3.5 | Role of antenatal corticosteroids

Antenatal corticosteroids administered to women at risk of preterm birth increase the chances that their infant will survive and significantly reduce infant and childhood morbidity, and are recommended best practice worldwide

(Roberts et al., 2017). However, they may also alter the distribution of central arterial blood flows and alter the function of the right ventricular pump in fetuses (Smolich & Mynard, 2018, 2021), augment the increases in pulmonary arterial blood flow at birth (Smolich et al., 2019) and may be associated with neonatal hypertension (Mildenhall et al., 2006). Steroids may also be administered to preterm babies after birth to prevent or treat chronic lung disease; however, postnatal steroids have an associated risk of hypertension and hypertrophic cardiomyopathy, among other adverse effects, where the magnitude of these effects are related to the postnatal steroid dose and treatment algorithm (Bloomfield et al., 1998; Halliday, 2017). Future modeling efforts could shed light on the mechanism and consequences of cardiovascular changes due to corticosteroid administration.

3.6 | Capturing phasic flow waveforms

Simplified models that are validated against mean flow may not accurately represent fetal hemodynamic events, which are more fully represented by specific features of phasic flow waveforms. For example, the fetal pulmonary arterial waveform is characterized by a large and abrupt mid-systolic drop in flow due to the presence of an extremely large backward-running compression wave arising from the lungs (Mynard, 2011; Smolich et al., 2009), which has not be captured in most existing models (see Figure 9), with the exception of the detailed investigation of this phenomenon by Mynard (2011) using 1D modeling techniques. A similar issue pertains to the fetal ductal flow profile, which frequently displays a two-component systolic increase in flow, the first component due to an initial right ventricular forward-running compression wave, and the second component related to a portion of the large pulmonary arterial backward-running compression wave turning the corner into the ductus and becoming a forward-running compression wave (Mynard, 2011; Smolich et al., 2009). Cardiovascular magnetic resonance imaging techniques have provided additional information not only on the phasic characteristics of blood flow contours within the arterial and venous compartments of the fetal circulation (Schrauben et al., 2019), but also regional oxygen saturation, delivery, and consumption (Saini et al., 2020, 2021).

3.7 | Arterial reservoir function

The reservoir properties of large elastic arteries are an important component of fetal and neonatal cardiovascular function that are often overlooked in fetal and birth transition circulation models. However, this reservoir function is responsible for some of the characteristic features of fetal arterial waveforms (e.g., the large positive flow offset in umbilical arterial waveforms), and also some of the changes in waveforms that occur after the birth transition (e.g., the rapid switch in the direction of ductal shunting from right-to-left in the fetus to left-to-right in the newborn, and the appearance of a large positive offset in the pulmonary arterial flow waveform; Adamson, 1999; Smolich et al., 2016; Smolich & Mynard, 2016).

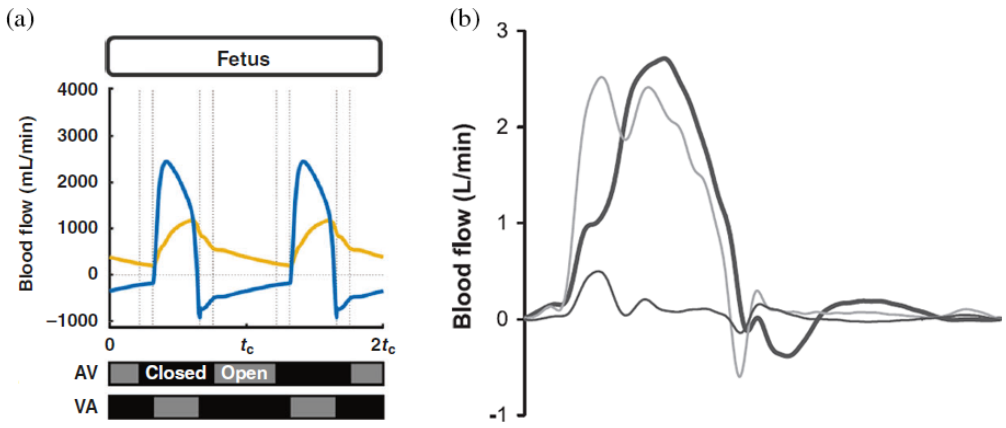


FIGURE 9 (Left) Simulated flow in the DA (yellow) and pulmonary artery (blue) (Munneke et al., 2022) and (right) experimental blood flow recording in lambs in the DA (thick line), left pulmonary artery (thin black line) and pulmonary trunk (thin gray line) (Smolich et al., 2009).

3.8 | Validation of birth transition models

Some birth transition models (e.g., Munneke et al., 2022; Sá-Couto et al., 2010) have used data from in utero ventilation experiments on fetal lambs (Teitel et al., 1987, 1990) for validation purposes. However, while these experiments provide information on the sequential effects of ventilation, oxygenation, and umbilical cord occlusion on hemodynamics and blood flow, they do not mimic the rapidity or sequence of events that occur in birth transition studies (Bhatt et al., 2013; Polglase et al., 2015). Hemodynamic parameters at birth that could be used to validate (and parameterize) models are typically acquired noninvasively (Pichler et al., 2014) and thus may have a lower spatial or temporal resolution than the desired model function. However, models should be tested where possible via appropriate "time of birth" data in the species of interest with data acquired experimentally or across species appropriately acknowledged.

4 | MODEL CUSTOMIZATION AND PARAMETER ESTIMATION

4.1 | Model personalization from medical data

Efficient and accurate personalization of computational models is widely recognized as the crucial next step for the successful translation of simulation technology into clinical applications (Corral-Acero et al., 2020; Hose et al., 2019; Morris et al., 2016; Nguyen et al., 2020; Safaei et al., 2016; Van Laere et al., 2018). Model personalization involves the definition of two groups of parameters that determine the function of the mathematical model. These are geometric parameters determined by cardiovascular anatomy and physiological parameters determined by cardiovascular function. For geometric (anatomical) personalization, models may be parameterized using patient-specific cardiovascular geometry (vessel length and radius) extracted from medical imaging (ultrasound, CT, or MRI)—also referred to as image-based modeling (Nguyen et al., 2020). A few geometric parameters (e.g., vessel thickness) can be computed by allometric laws where technical challenges preclude their acquisition (vessels too small to be seen, time required for image acquisition too long, or inaccessibility). For physiological (functional) personalization, functional parameters that capture the dynamic behavior of the cardiovascular system are needed. Examples of these functional parameters include the elastance of cardiac chambers, the compliance of arterial and venous vessels, the resistance of peripheral beds, and the time constants in the afferent and efferent components of the central nervous system (Caiazzo et al., 2017; Lal et al., 2017).

Some parameters that condition the response of the model are readily measurable, for example, volume of the cardiac chambers or the radius of large thoracic blood vessels. In contrast, other parameters, such as the elastance of cardiac chambers, or the terminal resistance and compliance of a peripheral vascular bed, are not known or readily measurable. In this section, we introduce data assimilation techniques that may be used to determine the latter type of parameters.

Data assimilation is defined as "the process of combining different sources of information to produce the best possible estimate of the true state of a physical system" (Xiao, 2014). In the context of cardiovascular modeling, data assimilation combines predictions from a mathematical model, which approximates the dynamical behavior of the cardiovascular system, with real-world physiological signals to produce an estimate of the current physical state of the cardiovascular system. This data-model integration yields a more accurate representation than one obtained either with the model or with the experimental measurements in isolation (Xiao, 2014). Data assimilation methods may be broadly categorized as variational approaches (optimization) and sequential approaches (filtering) (Xiao, 2014). Cardiovascular modeling has benefited from the application of both variational approaches (Lagrée, 2000; Martin et al., 2005; Perego et al., 2011; Stålhand, 2009) and sequential approaches (Bertoglio et al., 2012; Bertoglio et al., 2014; Maso Talou et al., 2018; Moireau et al., 2008, 2009; Muller et al., 2019). Moreover, the increasing amount of data, either acquired from experiments or from mathematical models, has allowed the application of data-driven methods to accomplish similar tasks. Examples of this are Bayesian methods (Larson et al., 2019; Paun et al., 2020) and more data-intensive machine learning algorithms (Kissas et al., 2020).

In the following sections, the Kalman filter, both in the time and frequency domain, is presented as a useful approach for parameter estimation.

4.2 | Time-domain Kalman filter for parameter estimation

The classical Kalman filter is based on recursive least-squares estimation with the inclusion of a linear dynamical model that describes the evolution of state variables, in particular, how the mean and variance of the variables of interest

propagate over time (Simon, 2006; Xiao, 2014). The extended Kalman filter extends this estimation to nonlinear dynamical systems by using a tangent linear model to approximate the nonlinear forward operator, although with limited success when systems are highly nonlinear (Xiao, 2014). An alternative to the extended Kalman filter is the unscented Kalman filter which instead uses the mean and covariance of a deterministically generated set of states (called sigma points) to approximate the true probability distribution of the estimation error (Julier & Uhlmann, 1997; Xiao, 2014). The estimation process as described so far is applied to all states and parameters (namely, the augmented state) in the system. As the augmented state grows, the computational cost will also increase. In an application such as cardiovascular modeling, we are only interested in a small subset of the augmented state, that is, the unknown cardiovascular parameters that we are trying to estimate. The reduced-order unscented Kalman filter (originally proposed by Moireau & Chapelle, 2011) fulfills this need by only targeting part of the augmented state for estimation, thus improving the computational efficiency.

The Kalman filter was first applied to cardiovascular modeling using the entire state of the system (pressure and flow signals everywhere) as observations (Lombardi, 2014), which poses several practical problems for clinical use. More recently, Caiazzo et al. (2017) evaluated the performance of Kalman-based data assimilation for measurements likely to be found in medical practice, such as sparse flow and pressure measurements. In such a scenario, it was shown that parameter identification based on a reduced number of signals remains an extremely challenging problem.

4.3 | Frequency-domain Kalman filter for parameter estimation

While some functional (physiological) parameters can be directly measured, many cannot and require the application of effective data assimilation techniques. This is challenging, in part, because physiological signals are often collected in a non-synchronized manner, and in different physiological states of the system. For example, blood flow (measured by ultrasound or MRI) may not be acquired at the same time as blood pressure measurements. This implies that these measured quantities may suffer horizontal (time) and vertical shifts depending upon the time of acquisition and, for instance, the level of pressure or the respiratory phase. Moreover, there is an intrinsic complexity in the architectural conformation of pressure and flow signals, which are the result of traveling waves arriving from different parts of the system (see Section 3.6 for examples). This poses a challenge in terms of sequential filtering, as modifications in the model parameters dictated by the sequential filter (according to error measures) have a delayed effect upon the assessed signals.

Furthermore, typically available data in cardiovascular applications comprise maxima, mean, and minima of signals, or pressure-volume loops, pulse wave velocity, amplification indices, among other atemporal data. Integrating such heterogeneous data with mathematical models is also a challenge to classical sequential filtering techniques.

Muller et al. (2019) adapted the classical Kalman filter approach to be able to deal with observations in the frequency domain. This allows for holistic assimilation of available measured quantities and/or signals and consideration of only a few structural parameters (i.e., a fixed number of harmonic components in the model signals). The filter modifies the parameters in an attempt to minimize the difference between a user-defined subset of measurement harmonics and those model predictions. In this approach, model parameters are updated after the frequency analysis is performed, which implies that the parameters are updated once per cardiac cycle (at the time boundary between one cycle and the subsequent). Therefore, these parameters remain unchanged during the whole cardiac cycle. Figure 10 shows the steps involved in the time-domain and in the frequency-domain data assimilation procedures.

Compared to the time-domain approach, the frequency-domain approach is more robust, since changes in parameter values are taken into account throughout the cardiac cycle, improving computational performance.

In addition, the frequency domain approach enables the estimation of temporal parameters. For example, the time activation constants in an elastance model of cardiac chambers cannot be estimated using the time-domain approach, but can be handled naturally using the frequency-domain version of the Kalman filter.

5 | APPLICATIONS

There remain numerous areas of controversy and uncertainty regarding cardiovascular function in the preterm neonate which could be advanced through sophisticated cardiovascular modeling. Relatively low numbers of patients, with approximately 0.8% of all births occurring at extremely preterm gestations, and the small size of patients (typically with

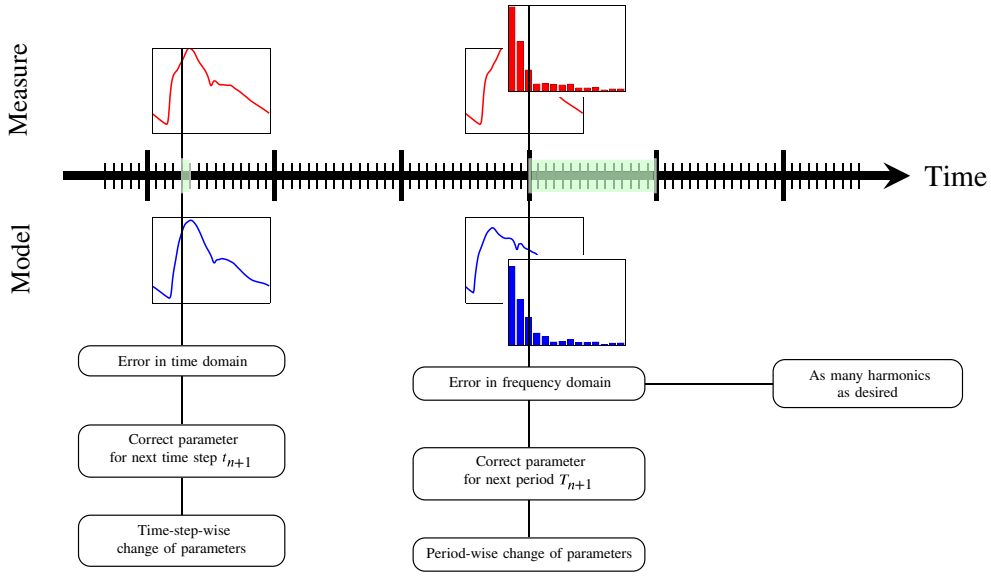


FIGURE 10 Data assimilation in the time domain (Caiazzo et al., 2017), and in the frequency domain (Muller et al., 2019).

a birthweight less than 1 kg for extremely preterm babies) make it challenging to obtain clear evidence from randomized controlled trials or instrumented studies (Dempsey et al., 2021). The following common, yet complex, fetal and neonatal problems are difficult to investigate in vivo due to challenges with imaging and direct measurement of cardiovascular parameters in the fetus and preterm neonate.

Hypotension is common in preterm babies and can lead to inadequate perfusion of the brain at a time when cerebral autoregulation is not fully developed (Thewissen et al., 2021). Although hypotension in preterm babies is associated with short-term brain injury, such as intraventricular hemorrhage, and worse long-term outcomes (Dempsey, 2017), there is insufficient evidence to demonstrate that hypotension is causative or that treatment alters the outcome. Therefore, there is controversy over whether hypotension in an otherwise stable preterm neonate should be treated and, if so, the threshold at which treatment is required (Dempsey, 2017). Computational cardiovascular models specific to the preterm circulation that could add additional hemodynamic insights into the likely causes and consequences of hypotension would be a useful clinical adjunct in this setting.

In future, another potential application of computational digital twins is for the development of perinatal life support systems for extremely premature neonates. A perinatal life support system is a novel liquid-filled incubator which would create an environment similar to that in utero, allowing maturation of the fetal lungs and other organ systems and supporting nutrition and waste elimination through an artificial placenta. Van Willigen et al. (2022) provide an example of such an application and a review of relevant fetal cardiovascular modeling techniques.

The presence of persistent fetal circulation, in particular, a hemodynamically significant PDA but also a patent foramen ovale (PFO), further complicates the interpretation of low blood pressure and the assessment of ventricular output in preterm infants (Rios et al., 2018, 2021). Observational studies report strong associations between the presence of a PDA in preterm babies and adverse outcomes, with more significant shunts associated with greater comorbidity (el-Khuffa et al., 2015; Sehgal et al., 2013). However, no clinical trial has shown that PDA closure improves outcomes (Mitra et al., 2020) and many trials fail to recruit the planned sample size (Dempsey et al., 2021). Computational models (e.g., Sá Couto et al., 2006, 2010; Soleymani, 2015; Yigit et al., 2019) can add value in the diagnosis and management of PDAs.

Congenital heart disease is common, accounting for nearly one-third of all congenital birth defects, and while it is a global problem, nine-tenths of those born with congenital heart disease live in parts of the world with little to no care and mortality remains high (Zimmerman et al., 2020). A number of the models discussed in this review have shed additional insights into the pathophysiology of various congenital heart diseases (Di Molfetta et al., 2016; Jalali et al., 2015; Migliavacca et al., 2001; Mynard, 2011; Pennati, Migliavacca, et al., 1997; Sá Couto et al., 2006). In certain centers, patient-specific computational modeling is now routinely used in the surgical planning stages of congential heart repair (Hess et al., 2019; Lin et al., 2020).

Premature birth is associated with a particular cardiac phenotype that persists into young adulthood and is associated with increased lifetime cardiovascular risk, including heart failure, atrial fibrillation, and stroke. This phenotype consists of concentric hypertrophy, reduced left ventricle volume and stroke volume, and impaired systolic and diastolic function (Huckstep et al., 2018; Telles et al., 2020). Although this observed pattern of adverse remodeling appears to be influenced by perinatal factors including degree of prematurity, requirement for intensive respiratory support, and the use of glucocorticoids (Cox et al., 2019), the etiology is yet to be fully understood. After birth, the systemic afterload increases and the left ventricle becomes the sole contributor to the systemic stroke volume. It may be that the developmentally immature myocardium is less able to adapt, but these changes are also likely to be related at least in part to the ventricular–vascular interaction. Hypertension is prevalent among children and adults born prematurely and its severity is directly related to the degree of prematurity (Markopoulou et al., 2019). The mechanism remains unclear; arrested angiogenesis has been postulated (Bertagnolli et al., 2016), and varying degrees of large artery hypoplasia and increased arterial stiffness have been reported (Bonamy, 2005; Sehgal, 2013; Sehgal, 2018). The significance of these findings is difficult to interpret in the context of atypical somatic growth and hypertension (Lewandowski et al., 2020).

The long-term consequences of premature birth and altered fetal and neonatal hemodynamics may take decades to manifest. Cardiovascular computational modeling specific for the fetus and neonate provides an opportunity to address important questions such as these and has the potential to provide a better understanding of the factors that contribute to cardiovascular maladaptation. The information gained may form the basis of therapeutic interventions to reduce the lifetime burden of disease facing premature and unwell term infants.

6 | NEXT STEPS

The purpose of this article is to present a roadmap for the development of a whole-body cardiovascular model in early life that could become a community resource for a wide range of projects that depend on knowledge of the hemodynamic environment in various tissue beds. Depending on the nature of the research question being addressed, the model may need to be subject-specific, where appropriate anatomical data are available.

- *The model should be complex enough to be individualized using image-based anatomical measurements, while also being simple enough for real-time computational simulation*. Readily personalizable neonatal circulatory models would be of great value in a clinical setting, for example, the neonatal intensive care unit, to provide additional hemodynamic insights to aid clinical decision-making and surgical planning. Ideally, these models would run in real-time on a desktop computer, suggesting 0D lumped parameter models as a computationally efficient modeling strategy.
- *The model should have a fully conservative formulation for mass and momentum*. Physics-based biological models must ensure energy conservation if they are to be accurate. An example of a modeling approach that would ensure this requirement is met is the bond graph modeling approach proposed by Safaei et al. (2018). An additional strength of this approach is that it can be readily extended to other domains, for example, the chemical domain to include cellular metabolic processes and gas exchange.
- *The model should be adaptable to unique circulatory conditions of early life, for example, preterm circulation, as well as congenital heart diseases*. This has been achieved by many of the models discussed in this review.
- *The model should be implemented using modeling standards where these are available and open-source software should be available to run the model* via *a graphical user interface. This interface should enable annotations of the vascular structure*. For biological computational models to be accessible, comprehensible, reusable, and discoverable, standardized semantic model annotation is required (Sarwar et al., 2019). Examples of freely available resources are CellML, an open standard for encoding ODE and algebraic models (Miller et al., 2010) and OpenCOR, an open-source GUI for running the model and viewing the results (Garny & Hunter, 2015). Open-source models are an important consideration to ensure feasibility of translation into clinical settings.

The computational models of early life described by this review could be directly applicable in clinical practice and also contribute to further translational research, for example, preventative strategies to address the risks of cardiovascular remodeling related to preterm birth. Should these findings translate into clinical practice, there would be substantial benefits for the future cardiovascular health of newborn babies everywhere.

AUTHOR CONTRIBUTIONS

Robyn W. May: Conceptualization (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Gonzalo Maso Talou:** Conceptualization (equal); investigation (equal); methodology (equal); resources (equal); software (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Alys Clark:** Conceptualization (equal); investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Jonathan P. Mynard:** Conceptualization (equal); writing – original draft (equal); writing – review and editing (equal). **Joseph J. Smolich:** Conceptualization (equal); writing – original draft (equal); writing – review and editing (equal). **Pablo J. Blanco:** Conceptualization (equal); writing – original draft (equal); writing – review and editing (equal). **Lucas O. Müller:** Conceptualization (equal); writing – original draft (equal); writing – review and editing (equal). **Thomas L. Gentles:** Conceptualization (equal); writing – original draft (equal); writing – review and editing (equal). **Frank H. Bloomfield:** Conceptualization (equal); writing – original draft (equal); writing – review and editing (equal). **Soroush Safaei:** Conceptualization (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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