Identifiability as a Crucial Step For Using 0D Models To Derive Deeper Physiological Insights: An Application to Neonatal Cardiovascular Modelling

Robyn May[1,2], Gonzalo Maso Talou[1], Finbar Argus[1]

[1] Auckland Bioengineering Institute, University of Auckland, Auckland, New Zealand
[2] Liggins Institute, University of Auckland, Auckland, New Zealand

Abstract

Models which are identifiable both replicate clinical data and have well-determined parameters and predictions. In the context of model personalisation to patient-specific data, identifiability is crucial if estimated parameters are to be representative of the individual. We collected ultrasound data for term and late preterm babies at two time points to inform personalised 0D closed-loop cardiovascular models. Models were reduced in an iterative manner until all estimated parameters were identifiable, as demonstrated by sensitivity analysis and Markov Chain Monte Carlo analysis. There were no differences in ultrasound measures of cardiovascular structure or function between the term and preterm groups. Although estimated model parameters were similar for the term and preterm group at birth, by three to six weeks of age, the preterm group had significantly higher lower body resistance compared to the term group. As this parameter was shown to be practically identifiable, it is valid to use it to make inferences about the underlying physiology and suggests possible impaired vascular elastogenesis in those born preterm. This provides an example of the way in which identifiable computational modelling can provide further insight into underlying pathophysiological mechanisms in cardiovascular remodelling related to prematurity.

1. Introduction

1.1. Identifiability in cardiovascular modelling

Computational modelling has well-established utility in the study of cardiovascular haemodynamics for medical research purposes and is increasingly being translated into clinical settings to improve the diagnosis and treatment of cardiovascular diseases [1]. These modelling techniques use parameter estimation methods that are capable of producing good models, in the sense that Wieland (2021) defines a good model as one that describes the data with reasonable accuracy. For good models to also be useful, they also need to explain the data, make falsifiable predictions that can be tested experimentally and provide insight into the biological system [2]. In contrast, bad models cannot explain the data, may be overparameterized such that they overfit the data and their parameters and predictions are not well determined [2]. Identifiability is crucial to produce good models that describe the data and also have well-determined parameters and predictions. A model is defined as being structurally identifiable if the combination of model structure and measured model output has inherently determinable parameters and a unique parameterisation exists for any given model output [2]. This stands in contrast to practical identifiability, where the combination of the model and data (and, importantly, the noisiness of the ground truth data) together are sufficiently informative for parameters to be estimated with finite confidence intervals [2]. Several methods have been developed to determine whether models are practically identifiable, including profile likelihood analysis and Markov Chain Monte Carlo (MCMC) analysis. Using these methods in iterative modelling approaches, model complexity can be reduced or additional data added to achieve practically identifiable models that meet the definition of good, useful models [2]. In the context of model personalisation to patient-specific data, this is particularly important because estimated parameters should be identifiable if they are to be in any way representative of the individual. Furthermore, if the ultimate aim of patient-specific modelling is to provide clinical insights, that implies that any patient-specific parameters need to be identifiable and model predictions need to also have acceptably small uncertainties.

1.2. Application to cardiovascular remodelling following preterm birth

Most cardiovascular models developed so far have been from the adult circulatory system; however, there are a

number of open questions in perinatal medicine that would benefit from the insight into haemodynamics that these models can provide. Globally, one in ten children are born preterm (defined as birth before 37 completed weeks of gestation). Preterm birth is associated with a particular cardiovascular phenotype that persists into young adulthood and is associated with an increased lifetime cardiovascular risk, however, the mechanisms of cardiovascular remodelling in those born preterm are complex, multifactorial and poorly understood [3].

We hypothesise that early remodelling of the cardiovascular system may predict later cardiovascular structure and function and aimed to develop identifiable computational models of the cardiovascular system for term and preterm newborns, personalisable using ultrasound data.

2. Methods

2.1. Data Collection

Single-centre, prospective, observational cohort study recruiting term (born $\geq 37^{+0}$ weeks' gestation) and late preterm (born between 34^{+0} and 36^{+6} weeks' gestation) healthy babies. Ultrasound data were collected within 48 hours of birth and again three to six weeks later. We collected structural (vessel radii and lengths) and functional (Doppler blood flow, time varying cardiac chamber volumes) cardiovascular ultrasound data, blood pressure, heart rate and oxygen saturation. Ethical approval for this data collection was obtained from the Northern A Health and Disability Ethics Committee (20/NTA/187).

2.2. Computational Modelling

A 0D bond graph model of the newborn cardiovascular system was developed and presented previously [4], which is parameterised using patient-specific arterial measurements and included patent fetal shunts unique to the preterm circulation. To summarise briefly, models were parameterised using fixed values where these are well established or for which patient-specific values were not feasibly obtainable (e.g. blood density and viscosity, cardiac dead space volumes), patient-specific data (e.g. arterial radii, heart rate) and unknown parameters (e.g. terminal resistance and compliance) optimised by fitting model outputs to the functional data with a genetic algorithm (freely available from `https://github.com/FinbarArgus/circulatory_autogen/releases/tag/Version_0_2`) [5]. The cost function $C(X)$ used was:

$$C(X) = \frac{\sum_{x_i \in X} w_{x_i} \frac{|x_i - \hat{x_i}|}{\sigma_{\hat{x_i}}}}{n} \quad (1)$$

where X is a vector of ground truth data, w_{x_i} is a weight assigned to each ground truth measurement, x_i is the model predicted value, $\hat{x_i}$ is the measured value, $\sigma_{\hat{x_i}}$ is the standard deviation of the measured value (assumed to be 10% of the measured value for all measurements) and n is the number of ground truth measurements provided in X.

Models were reduced in an iterative manner until all estimated parameters were practically identifiable, as demonstrated by cost sensitivity analysis and MCMC. For the cost sensitivity analysis, the genetic algorithm's parameter estimates were varied by a 10% and 20% increase and decrease, the model was re-run with the updated parameter and the cost recalculated and reported as a percentage difference. For the MCMC identification of parameter identifiability, the genetic algorithm parameter estimation was rerun and repeat parameter estimates plotted as posterior distributions. Models were validated using an 80/20 split of available data and by omitting a subset of flows in the calibration process to determine the fitted model's ability to predict that flow.

3. Results

3.1. Clinical data

We assessed 15 term and 10 preterm babies on day 2 of life and 12 (80%) term and 7 (70%) preterm babies underwent a second assessment at median post-menstrual age 295 days (25 days old for term group and 38 days old for preterm group). There were no differences in ultrasound measures of cardiovascular structure or function between the term and preterm groups.

3.2. Computational modelling outputs

The personalised models compared extremely well to clinically measured blood pressures and left ventricular volumes, with a median error of -0.1% (IQR 2.2, 1.4) for mean blood pressure, 1.8% (IQR 0.5, 7.4) for end-systolic volumes and -9.3% (IQR -19.8, -0.7) for end-diastolic volumes. Across the whole cohort, predicted left ventricular maximum, minimum and stroke volumes matched the measured volumes very closely in most cases where parameter estimation was successful (Figure 1).

Figure 2 is an exemplar of the cost sensitivity analysis and demonstrates that any change in model parameters affected cost in a meaningful manner. Figure 3 is an exemplar of the posterior parameter distributions from the MCMC method which exhibits clear peaks for all parameters except the terminal resistance in the arm modules, suggesting that these parameters are practically identifiable.

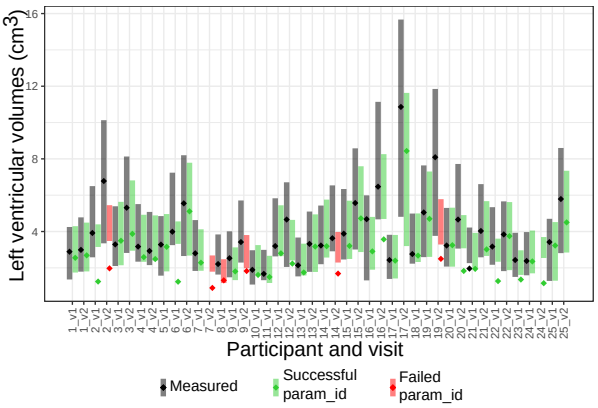

Figure 1. Measured vs predicted left ventricular volumes for all participants. Line segments for each participant link the end-systolic and end-diastolic left ventricular volumes. Stroke volume is indicated by a diamond.

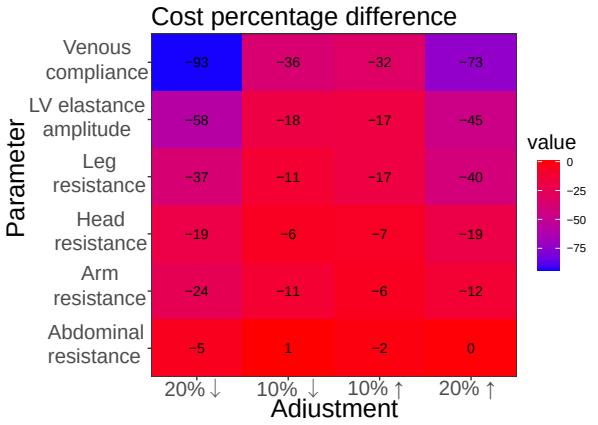

Figure 2. Heat map of an exemplar model cost sensitivity to variations in all parameters.

3.3. Parameter estimation

Although estimated parameters were similar for the term and preterm group at birth (Table 1), by three to six weeks of age, the preterm group had significantly higher lower body resistance compared to the term group (Table 2). Growth may influence venous compliance for the term group but not for those born preterm.

4. Discussion

This work represents one of the largest patient-specific computational modelling studies and the first in early life. If the ultimate aim of patient-specific modelling is clinical translation, that implies that any patient-specific parameters need to be identifiable and model predictions need to also have acceptably small uncertainties. It may not be necessary for all model parameters to be identifiable, as

Table 1. Term vs preterm parameter estimates for assessment at birth.

Parameter	Term (n=15)[1]	Preterm (n=10)[1]	p-value[2]
Left ventricular elastance amplitude (J/m^6)	6.9e+09 (5.8e+09, 8.4e+09)	6.6e+09 (5.3e+09, 9.4e+09)	0.8
Leg resistance (Js/m^6)	5.9e+09 (3.8e+09, 8.7e+09)	4.9e+09 (3.2e+09, 8.3e+09)	0.5
Arm resistance (Js/m^6)	2.6e+10 (1.7e+10, 6.9e+10)	2.3e+10 (1.2e+10, 2.9e+10)	0.3
Head resistance (Js/m^6)	9.2e+09 (6.6e+09, 1.3e+10)	7.8e+09 (5.3e+09, 1.4e+10)	0.7
Abdominal resistance (Js/m^6)	4.0e+10 (2.5e+10, 6.2e+10)	5.4e+10 (2.2e+10, 6.4e+10)	0.8
Venous compliance (m^6/J)	1.2e-07 (1.1e-07, 1.4e-07)	1.1e-07 (9.5e-08, 1.4e-07)	0.6

[1]Median (IQR)

[2]Wilcoxon rank sum test

Table 2. Term vs preterm parameter estimates for assessment at 3-6 weeks of age.

Parameter	Term (n=12)[1]	Preterm (n=7)[1]	p-value[2]
Left ventricular elastance amplitude (J/m^6)	5.3e+09 (3.9e+09, 6.7e+09)	5.7e+09 (4.2e+09, 6.4e+09)	>0.9
Leg resistance (Js/m^6)	3.8e+09 (2.6e+09, 5.0e+09)	2.6e+10 (1.0e+10, 4.7e+10)	0.043
Arm resistance (Js/m^6)	1.1e+10 (1.0e+10, 1.8e+10)	2.5e+10 (5.9e+09, 4.4e+10)	0.8
Head resistance (Js/m^6)	6.4e+09 (5.4e+09, 8.2e+09)	4.5e+09 (4.2e+09, 8.4e+09)	0.6
Abdominal resistance (Js/m^6)	5.1e+10 (1.8e+10, 7.1e+10)	6.3e+10 (4.0e+10, 6.5e+10)	0.8
Venous compliance (m^6/J)	8.7e-08 (7.6e-08, 1.0e-07)	1.2e-07 (9.2e-08, 1.7e-07)	0.081

[1]Median (IQR)

[2]Wilcoxon rank sum test

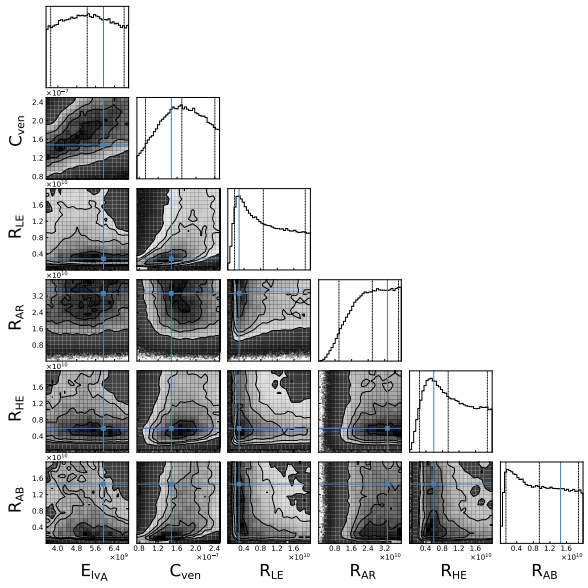

Figure 3. MCMC method's parameter distributions for an exemplar model.

long as models are validated and conclusions are not drawn on the unidentifiable parameters.

In this study, we have shown that terminal resistance for the "leg" module is practically identifiable and shows a significant increase with age for those born preterm compared to those born at term. This lumped module comprised a large vascular territory - essentially, the lower half of the body. This trend towards increasing vascular resistance in a significant proportion of the vasculature in the preterm group does have a mechanistic explanation. The mechanically relevant vascular components of blood vessels are elastin, collagen, and vascular smooth muscle; of these, in physiological pressure ranges, elastin is the highly extensible component primarily responsible for vessel elasticity. Elastin accumulates in the vessel walls in late gestation and its synthesis declines quickly after birth [6]. It also has an extremely slow turn-over rate and a long half-life of 40 years [6]. Impaired vascular elastogenesis in those born prematurely leads to increase in the ratio of collagen and smooth muscle to elastin, changing the viscoelastic properties of the vasculature and resulting in stiffer arteries [6, 7]. This may lead to higher blood pressure and increased risk of cardiovascular disease later in life for those born preterm [6, 7]. Despite no differences in ultrasound measurements between the term and preterm groups, by augmenting our clinical dataset with computational modelling, we have provided evidence of a potential pathophysiological mechanism of cardiovascular remodelling.

5. Conclusions

We have demonstrated an automated model calibration workflow to produce practically identifiable 0D cardiovascular models and applied and validated these in a rich clinical dataset. This provides an example of the way in which identifiable computational modelling can provide further insight into underlying pathophysiological mechanisms in cardiovascular remodelling related to prematurity and an important step in clinical translation of cardiovascular computational modelling.

Acknowledgments

Robyn May thanks the Auckland Medical Research Foundation for their support through a Doctoral Scholarship.

References

[1] Morris PD, Narracott A, von Tengg-Kobligk H, Soto DAS, Hsiao S, Lungu A, Evans P, Bressloff NW, Lawford PV, Hose DR. Computational fluid dynamics modelling in cardiovascular medicine. Heart 2016;102(1):18–28.

[2] Wieland FG, Hauber AL, Rosenblatt M, Tönsing C, Timmer J. On structural and practical identifiability. Current Opinion in Systems Biology 2021;25:60–69.

[3] Bavineni M, Wassenaar TM, Agnihotri K, Ussery DW, Lüscher TF, Mehta JL. Mechanisms linking preterm birth to onset of cardiovascular disease later in adulthood. European Heart Journal 2019;40(14):1107–1112.

[4] May RW, Maso Talou GD, Argus F, Gentles TL, Bloomfield FH, Safaei S. An image-based computational model of the newborn cardiovascular system with term and preterm applications. In International Conference on Functional Imaging and Modeling of the Heart. Springer, 2023; 475–484.

[5] Argus F, Zhao D, Gamage TPB, Nash MP, Talou GDM. Automated model calibration with parallel MCMC: Applications for a cardiovascular system model. Frontiers in Physiology 2022;13.

[6] Ligi I, Grandvuillemin I, Andres V, Dignat-George F, Simeoni U. Low Birth Weight Infants and the Developmental Programming of Hypertension: A Focus on Vascular Factors. Seminars in Perinatology 6 2010;34(3):188–192.

[7] Martyn C, Greenwald S. Impaired synthesis of elastin in walls of aorta and large conduit arteries during early development as an initiating event in pathogenesis of systemic hypertension. The Lancet 1997;350(9082):953–955.

Address for correspondence:

Robyn May
The University of Auckland
Private Bag 92019
Auckland
New Zealand
1142
r.may@auckland.ac.nz