3.1 Possible applications of GAMs

Currently, GAMs are research tools that may aid investigation of complex, yet deterministic patterns in medical time series and waveforms. Respiratory variation in hemodynamic variables is often just regarded as a potential source of error, sometimes dealt with by reporting only end-expiatory measurements. There may be clinically relevant information in the respiratory variation of measurements and GAMs give researchers a powerful tool for visualising and describing the effects of ventilation on their measurement of interest. It would be interesting to see GAMs like those demonstrated here for the CVP waveform and its changes during a respiratory cycle correlated to echocardiographic measurements like tricuspid annular plane systolic excursion (TAPSE) or other measures of right ventricular function. In particular, one hypothesis is that the *x'* descent and its dynamics during a respiratory cycle reflect right ventricular contraction against varying afterload [23]. Another CVP feature of interest is the *y* descent, whose magnitude is related to the rate of right ventricular filling during diastole. A large *y* descent has been proposed to indicate a *non*-fluid-responsive heart [24]. This hypothesis, and the respiratory variation in the *y* descent, could be further investigated using GAMs of CVP waveforms. CVP morphology has not had a prominent place in the scientific literature for decades, although venous return and mean systemic filling pressure are gaining more interest [25, 26]. The detailed dynamics of the CVP waveform during mechanical ventilation may reflect "upstream aspects" of venous return, mean systemic filling pressure and conditions for outflow of organs such as the kidneys. These might be elucidated by the diastolic parts of the CVP waveform.

A GAM of the arterial blood pressure waveform (and not just PPs) could give a more nuanced picture of the variation in left ventricular contraction.

As a clinical tool, estimation of PPV using a GAM could be implemented in a bedside monitor. The PPV could be presented along with a visualisation of the model fit (similar to Fig. 2c and d) for a clinician to decide if, e.g., a high PPV should be interpreted as noise or a true respiratory variation. Such interpretation, however, may require more than basic understanding of the physiologic determinants of PPV.

Another intriguing use case is that by Wyffels et al. They use a GAM to separate the seemingly random PPV from patients with atrial fibrillation into variation caused by ventilation and variation caused by the atrial fibrillation [4]. In this regard, both the respiratory component as well as the atrial fibrillation component may offer insights concerning fluid responsiveness, because blood pressure changes induced by filling time changes (induced by extrasystoles) have also predicted fluid responsiveness with acceptable accuracy in the intensive care unit [27, 28].

3.2 Limitations

In the examples, we use synchronised data from both the ventilator and the bedside monitor. This is rarely available in data that is not recorded specifically to study heart–lung interactions. It is possible to fit these models if only the respiratory rate is known (by using the modulo operation of time over respiration length), though the phase of the respiratory effect will be arbitrary [4]. In many cases, the respiratory rate can be assessed by frequency analysis; fourier analysis for recordings with a constant sample rate (e.g. CVP) or Lomb-Scargle analysis for irregular time series (e.g. pulse pressure).

The models presented here assume that all respiratory cycles are equivalent. This requires deeply sedated, mechanically ventilated subjects. Therefore, the models presented here are most suitable in the setting of general anaesthesia. It is possible that the models could be extended to account for spontaneous ventilation efforts, e.g., by including esophageal- or airway pressure as independent variables in the model.

The CVP model uses a non-cyclic spline to model the effect of a cardiac cycle. We expect that the CVP at the end of one cardiac cycle continues smoothly into the following cycle, but this expectation is not enforced in our model. We cannot simply use a cyclic spline, as they require a fixed cycle length, while the cardiac cycle length varies with respiration. We could use the relative position in the cardiac cycle (from 0 to 1) as the independent variable in a cyclic spline, but this assumes that the cardiac cycle effect scales linearly with cardiac cycle length (i.e. if the cardiac cycle length is 10% longer, the time from, e.g., the '*a* peak' to the '*v* peak' should be 10% longer), which is not the case. Using non-cyclic splines to model the cardiac cycle gives the model some "unnecessary" degrees of freedom, and a better solution may exist.

It can be computationally expensive to fit GAMs, especially with large, high-resolution data sets and when interaction terms are introduced. The CVP model used in Fig. 5 takes ~ 60 s to fit on a modern laptop, currently making it infeasible for real time implementation. The quantile model used in Fig. 7 takes ~ 300 s for just 15 s of signal (1875 samples). The PP model in Fig. 2 takes only ~ 30 ms.