outer knots to zero (making them linear outside the outer knots). This is termed a *natural cubic spline* [6].

To reduce the risk of overfitting, splines can be *penalised* according to their wiggliness (by default defined as the integral of the squared 2nd derivative). A penalised spline is fitted to optimise the tradeoff between goodness of fit (e.g. high likelihood) and complexity (measured by the wiggliness of the function) (see Fig. 1b). The relative weight of fit and wiggliness in this tradeoff is controlled with a *smoothing parameter*. This smoothing parameter can be automatically optimised to prevent overfitting (e.g. using a *restricted maximum likelihood* approach [7]) or be chosen manually. A manual smoothing parameter can be useful if there is prior knowledge about the smoothness of one or more splines in the model (e.g. the effect of ventilation is expected to be very smooth).

1.1.2 Modelling interaction between variables

Interaction terms can be included in two principal ways. In the simplest case, one term is continuous (X_1) and one is categorical (X_2). Individual smooth functions are then fit for each category [$f(X_1)$ for each X_2]. If both terms are continuous, the interaction can be represented as $f(X_1, X_2)$: a function that takes two values and returns one value. This can be visualised as a smooth plane where each combination of X_1 and X_2 corresponds to an output (the elevation of the plane) (see Fig. 5e.1).

1.1.3 Modelling cyclic data

Some variables repeat cyclically without a marked distinction between the end of one cycle and the beginning of the next. An example is compass direction, where $0° \equiv 360°$. Likewise, we expect CVP at the end of one respiratory cycle to continue smoothly into the next cycle. We can model the effect of a cyclic variable with a *cyclic cubic spline*. A cyclic cubic spline is a special case of the cubic spline where the first and last knot are treated as one. The beginning and end are effectively adjacent, and the respective splines match up to the 2nd derivative (see Fig. 1a).

2 Examples

Examples are analysed using R 4.1.0 [8] with packages: *mgcv* 1.8–36 [7], *gratia* [9] and *tidyverse* [10]. While the paper aims to be language agnostic, sample data and annotated R code are supplied in Online Resource 1 (https://doi.org/10.5281/zenodo.6375221).

2.1 Example data

The data for these demonstrations are recorded during abdominal surgery from three consenting patients on pressure control ventilation (recorded as part of a project registered on ClinicalTrials.gov, NCT04298931 with regional ethical committee approval, case: 1-10-72-245-19). Haemodynamic waveforms (125 Hz) were recorded from a Philips MX550 using Vital Recorder [11] and ventilator data (timestamps for each inspiration start) were recorded from a Dräger Perseus A100 using VSCaputureDrgVent [12].

2.2 Example 1: Pulse pressure

In recent years, more complex waveform analysis is being implemented in the monitors. One example is ventilator-induced pulse pressure variation (PPV): a measure commonly used to predict fluid responsiveness [13]. While it is possible to manually calculate PPV from an arterial pressure waveform, it is neither trivial nor reproducible. Also, manually calculated PPV may differ substantially from the PPV automatically calculated by the monitor. This is due to a sophisticated analysis of the arterial waveform that takes multiple respiratory cycles into account [14, 15]. The PPV calculated automatically by, e.g., Philips monitors is robust to noise and outliers [14], but the steps between the ABP waveform and the automatically calculated PPV are probably unclear to most clinicians.

In the individual, pulse pressure (PP = systolic pressure − diastolic pressure) is highly correlated with stroke volume; and like stroke volume, PP varies between heart beats. The main cause of the short-term variation in PP is respiration, and the effect is especially pronounced during controlled mechanical ventilation. A beat's position in the respiratory cycle is associated with a specific effect on PP (see Fig. 2c). Around the end of the inspiration, PP is above average; and during expiration, it drops below average (the phase depends on respiratory cycle length).

Variation in pulse pressure (PP) can be understood as the sum of three separate effects. First, the effect of ventilation: with each breath, PP rises and then decreases. This is caused by the breath's combined effect of both preload and afterload on both ventricles [13]. It is the size of this effect that is related to the response to fluid therapy. Second, PP varies over longer periods, e.g. with changes in vascular tone. Third, there is also a fast, effectively random, variation in PP: e.g. measurement noise and subtle 'random' fluctuations in cardiac contractility). This decomposition of PP into three separate effects can be described with the equation:

$$PP = \alpha + f(pos_{ventilationcycle}) + f(time) + \epsilon.$$