# Generalized Additive Models To Describe Heart-Lung Interactions During Open Thoracic Surgery

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## Problem statement

During open thoracic surgery, the physician will often let the intravenous (IV) drip fluid run into the patient's bloodstream. The anesthesia causes the blood vessels to "relax", and the IV drip fluid can therefore be seen as a way of compensating both vascular relaxation and true fluid loss (perspiration, urine, bleeding). The IV drip fluid thereby ensures that the heart is well filled before each heartbeat.
However, fluid administration is also associated with side effects such as edema, and it is important to make sure that the required amount of blood circulates around the body, while avoiding high blood pressure, as it leads to overhydration. Some effective methods for guiding fluid infusion utilizes the effect of ventilation on the heart (heart-lung interaction). The issue of when and how much fluid to infuse is, however, far from settled – especially in settings with exceptional physiological conditions. Our contribution to this, is to investigate how the effect of the heart-lung interaction on the central venous pressure (CVP) changes during open thoracic surgery.

## Introduction

The connection between the overall problem and the specific assignment, that we are handling, is that through monitoring of CVP there could potentially be a more streamlined guidance for the process of injecting fluids. To create some sort of reliable guide, we need to better understand how the CVP dynamically changes throughout a surgery. What effect do the lungs and heart have, and what effect does their interaction have? For surgeries in the thoracic cavity, there is further reason to investigate this – sometimes it is necessary to cut

open the sternum to conduct the surgery. Therefore, there is a change in the environment surrounding the heart and lungs, and perhaps this could have an influence on how the CVP behaves. This is an important aspect that is not physiologically well-understood, and a better physiological description or visualization of the hemodynamics in the open-thorax condition vs. the closed condition, may found the basis for a better understanding of this physiological environment. A possible hypothesis is that when the environment surrounding the heart and lungs is closed, the lungs are limited in the ways in which they can expand, and may therefore put more pressure on the veins. Now, when the thorax is opened, the lungs would put less pressure on the veins, and therefore have less impact on the CVP. Further, there could possibly be a change in the effect of the heart-lung interaction on the CVP.

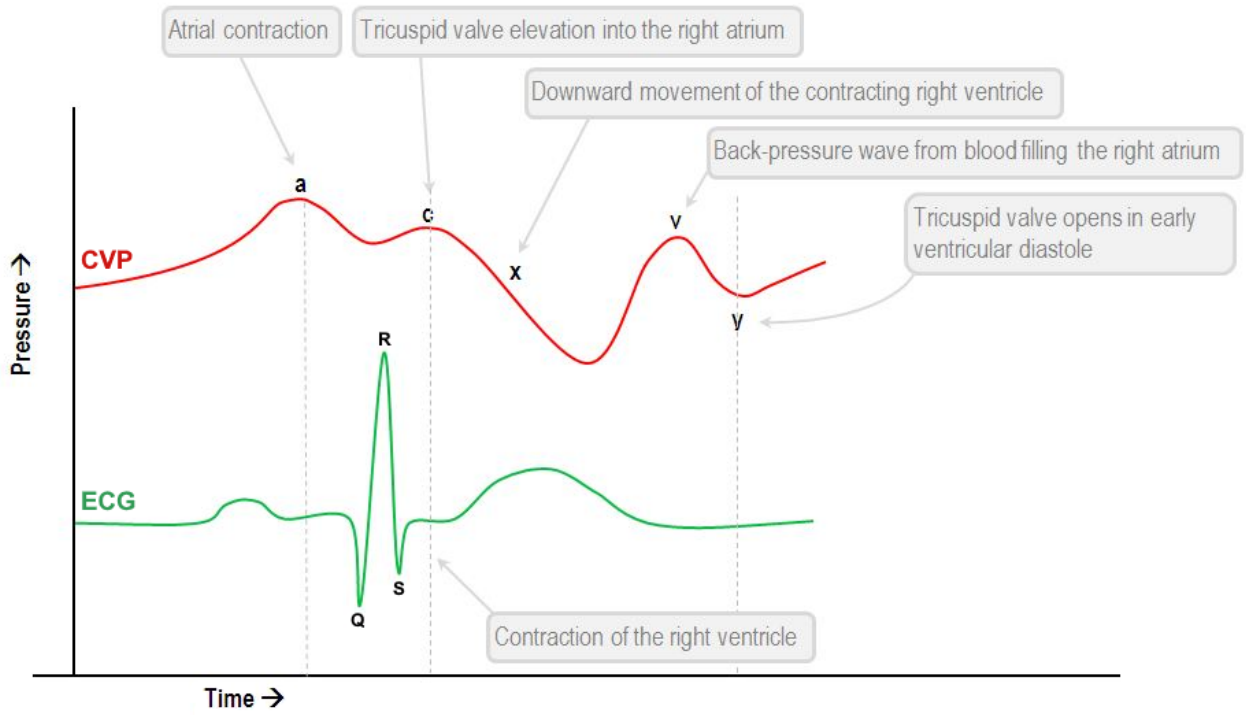


**Fig. 1** CVP waveform and electrocardiogram (ECG). On the ECG we are mostly focusing on the QRS complex, which we utilize as a reference point.

# Report

## Data

Our data is obtained from 61 patients undergoing open thoracic surgery, and consists of two data sets for each of the patients. One data set for when their chest is closed and after they have received fluids, and another data set for when their chest is opened and before they have

received another fluid. The fluid was part of the original experiment, but is not relevant for the current analysis. The two data sets contain the following recorded information:

- **Electrocardiogram** (ECG), which is a graph of voltage versus time of the electrical activity of the heart. An important part of the ECG is the QRS complexes that identify when in time that the ventricles initiates their contraction, i.e. the onset of the systolic cardiac cycle.
- **Arterial blood pressure** (ABP), which is the blood pressure in the arteries.
- **Central venous pressure** (CVP). This is the blood pressure in the superior vena cava, which is near the right atrium of the heart recorded at 125 Hz. CVP is influenced by the amount of blood returning to the heart, and by the ability of the heart to pump the blood back into the arterial system. This is measured in millimeters of mercury.
- **QRSmarker_ecg_index**. This is the position of each QRS complex (initiation of ventricular contraction) in the ECG vector.
- **QRSmarker_ms**. This is the occurrence of the QRS complex in milliseconds from start.

We also have information about the rate of ventilation for each patient, measured in cycles per minute.

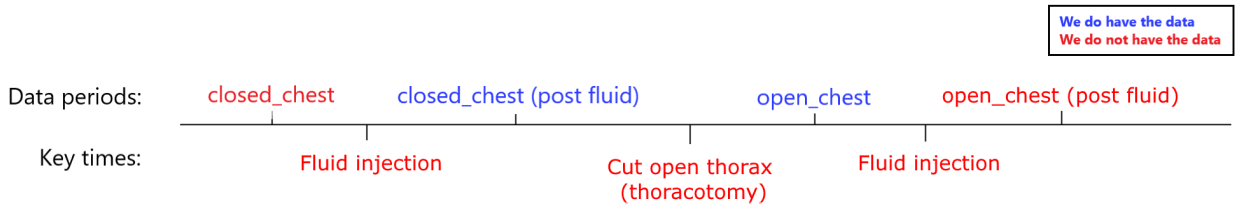


**Fig. 2** Timeline for the different data windows. We have data from the periods marked with blue. The geometrical mean time between each of the blue windows is approximately 10 to 15 minutes.

## Model creation

When creating a model for a data set, we started by choosing an appropriate time slot. For this process we visually inspected the data, and chose a continuous time period where the amount of noise was minimal. This means that some data that actually could be useful has been excluded from the training of our model. For the data sets where thorax was closed, we chose time periods as late as possible, and for the data sets where thorax was open, we

chose time periods as early as possible. This was done in an attempt to maintain ceteris paribus i.e. we wanted the only difference to be the opening of thorax. Therefore, the data was chosen in a way to minimize the noise, while also having time periods as close to each other as possible for the open and closed data sets for each patient.
CVP is a cyclic, non-linear time series and therefore, fitting such time series requires an approach that can approximate these properties.

To do this we use a generalized additive model (GAM)[1] which uses smooth terms made, in our model, through cyclic cubic regression splines. Cyclic was chosen because our variables of interest (QRS cycle and inspiration cycle) are cyclic. There were only two splines that offered the cyclic effect, of which cubic splines produced a better result, and at the same time are computationally more efficient. To put it simple, the fit of a GAM is the sum of individual smooth predictors (e.g. splines). This can be fit as a linear model by representing each smooth function as the sum of basis functions (basis expansion). An important thing about GAM modelling is to select the number of basis functions. When choosing a high number of basis functions you add more wiggliness to your smooth term, and therefore get a better fit – this can end up being computationally cumbersome, and there is a risk of overfitting. Consequently, we tested multiple values for the number of basis functions, and ended up with values that generalized well for different patients. To estimate the coefficients we use Restricted Maximum Likelihood (REML) because of its computational efficiency in GAM modelling. Moreover, it implements an automatic optimization of the penalty given to high wiggliness, reducing the risk of overfitting despite a high number of basis functions.
The individual observations in our model is a measure of CVP, the relative position in the heartbeat cycle (measured through relative position since last QRS complex), the relative position in the respiratory cycle (we do not know exact timing of this), and time since first observation for this surgery. Because we are interested in the heart-lung interaction on CVP, we create a model explaining CVP by the individual effects of the heart and the lungs, the interactive effect of the heart and the lungs, and a time effect. The time effect is included to control for the natural change in CVP over time. The individual effects are added to further distinguish between individual effects and interactive effects. The model also includes an intercept, which ensures that the mean of each effect is equal to 0, avoiding identifiability issues.
Since our IV is CVP recorded 125 times per second, an intuitive thought is that autocorrelation must be present in this data, eaning that we expect that an observation is heavily correlated with the observation right before it. However, the amount of autocorrelation in

[1] In-depth explanation: `https://www.youtube.com/watch?v=sgw4cu8hrZM`

terms of lag varies from patient to patient, but the important thing is that it is extremely heavy (see Figure 3). This is something we can account for in our GAM, which we do by including a $\rho$-term (the correlation coefficient in an AR(1) model of the residuals). Once again, we found an appropriate value which generalized well for all patients. This reduced the models' overconfidence caused by high autocorrelation in the data, effectively widening the confidence intervals.

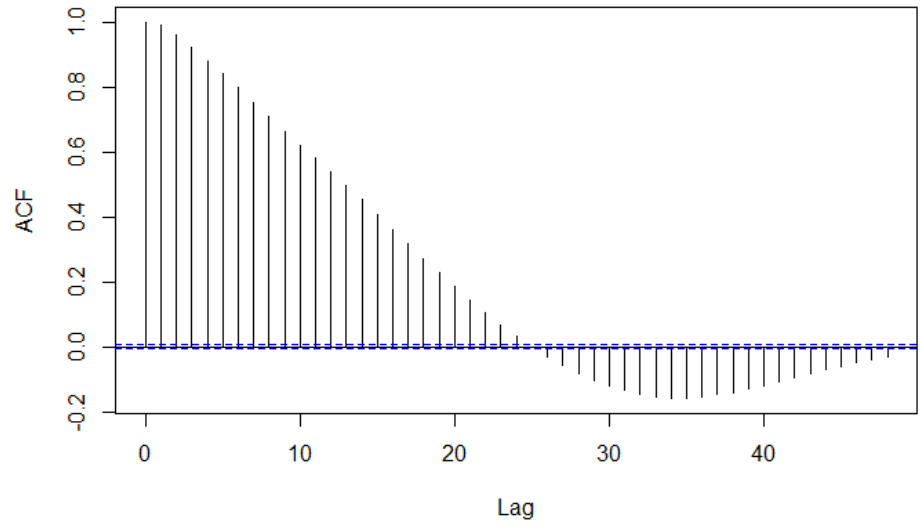


**Fig. 3** Lags of autocorrelation for a selected patient.

### Missing data

There were some occurrences of missing data; either because the data was simply not present, or because our data contained too much noise.
In the case of missing data, we had two scenarios. Either there were no data for one time period, or both time periods were missing. For such patients, we chose to exclude them altogether. Consequently, no models were created for those particular patients.
In the case where there were too much noise in the data, which could happen due to external factors in the operation room (e.g., if someone touched the lines to the pressure transducer), we also chose to exclude the respective patients, and their associated model from the Shiny application.
Due to these exclusions, we end up with 38 patients having a fully usable data set, out of a total of 61 patients.

We also face an issue of not knowing the exact time that a respiration cycle starts. We only know the settings of the ventilator. This does not change the effect that we associate

with the respiration cycle, but it changes our interpretation of the exact time that this effect takes place. To make the interpretation of the effect of the heart-lung interaction easier, we have decided to make the placement of the respiratory cycle modifiable. Meaning that it is possible to slide the x-axis related to the effect of the relative position of the respiratory cycle. This makes it more convenient to translate general domain knowledge into conclusions based on the visualizations. Even more importantly, this also ensures that it is possible to synchronize the effect of the respiratory cycle for the closed and the open models for each patient. This makes the interpretation of the effect of the heart-lung interaction on CVP cleaner.

## Model validation

An important aspect of this project was to validate our models. We might have gotten interesting results, but why should we trust our model? First off, we can take a look at a plot of our observed values, predicted values, and the residuals, shown in Figure 4. We see that the model fits the observed values extremely well. The residuals are minimal, and the small spikes are most likely caused by noise. This is a good sign, but it gives us an immediate worry; is our model overfitted to the data? Will this model generalize well? More on that later, but initially we are happy that our model is good at fitting the data that we have trained it on. This indicates that, through GAM modelling, our explanatory variables are good at explaining change in CVP.

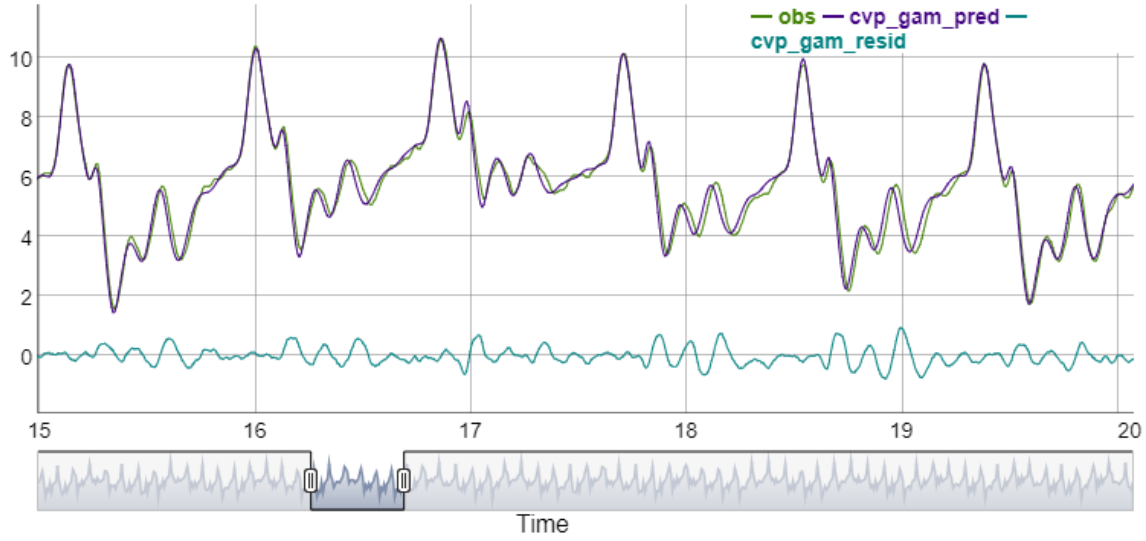


**Fig. 4** Observed (green) and predicted (purple) CVP values during a 5 second window of a given patient. Residuals (blue) are seen oscillating around 0.

Back to the worry of overfitting. Generally we want a model to generalize well, in order to be more confident of its performance. The aim with these models is to represent only physiological variation in CVP in a specific patient at a specific time while disregarding noise. Each model will not generalize to other patients, but we can still validate the model within the setting it is designed to represent. We do not want to make false conclusions based on an overfitted model. In our case, we have a slight issue when validating; the amount of clean data for each model we wish to create is fairly limited, and we wish to use as much of it as possible. To do this, we have decided to use cross validation. We split the data set into smaller parts, use most of it for training the model, and the rest for testing our model. In this project, we randomly split the data set into 80% training and 20% testing. We then train the model and evaluate it based on Mean Absolute Error (MAE). This process is then repeated 10 times. Finally, we take the average of the MAE of the 10 simulations, and use this as a measure of the generalizability of our model. A possible issue with this process is the high autocorrelation that is present in the data. There is a risk that our training and test data set are too similar, which naturally would yield a good cross validation result.
To evaluate whether or not our average cross validation MAEs are any good, we use the model trained on the entire data set as a reference.

| Patient# | Closed/open chest | Average CV MAE | Actual Model MAE |
|---|---|---|---|
| 3 | Closed | 0.227 | 0.215 |
| 4 | Closed | 0.481 | 0.478 |
| 5 | Closed | 0.168 | 0.160 |
| 7 | Closed | 0.098 | 0.087 |
| 9 | Closed | 0.170 | 0.166 |
| 10 | Open | 0.234 | 0.222 |
| 11 | Open | 0.228 | 0.215 |
| 12 | Open | 0.216 | 0.202 |
| 14 | Open | 0.179 | 0.169 |
| 15 | Open | 0.215 | 0.205 |

**Table 1** The average cross validation MAEs and MAEs for models trained on the entire data set shown for selected data sets.

The MAEs generated through cross validation are very similar to the MAEs derived from our actual models. This indicates that the models we produce generalize quite well, and that we do not have an issue with overfitting. The models are good at explaining the change in CVP without losing their generalizability. The lack of overfitting signifies more confidence in the results produced by our models – meaning more confidence in drawing conclusions

from the numbers. This is a satisfying result, which we will explore more in-depth in the *findings*-section.

**Comparison with other models**

In order to know whether the GAMs perform well, we also need to compare with other types of models. The MAEs from our GAMs may seem like good scores, but we need to interpret the values in the context of other scores. How well does a GAM fit compared to for example a linear or a polynomial model?
We try to explain the change in CVP through other complex models, and compare the MAE with the MAE created by GAM. We also present the Bayesian Information Criterion (BIC), which is a score used for model selection. BIC is similar to the Akaike Information Criterion (AIC), which can be thought of as an indication of how much information is lost by our model. BIC differentiates from AIC by penalizing models based on their complexity, which is done to avoid overfitting. Generally when choosing models, we want to pick the model that produces the lowest BIC value.

Explanation of models, which we compare to the GAM:

- Linear Regression Model (LM): A linear regression model modelling how the responsive variable, **CVP**, is effected by the interaction between the **qrs relative index** and the **inspiration relative index**, and then adding the marginal effects of **qrs relative index**, **inspiration relative index** and **time**.

$$\begin{aligned}\widehat{CVP} = &\alpha + \beta_0(\text{qrs\_rel\_index} \cdot \text{insp\_rel\_index}) + \\ &\beta_1 \text{qrs\_rel\_index} + \beta_2 \text{insp\_rel\_index} + \beta_3 \text{time} + \epsilon.\end{aligned} \tag{1}$$

- Polynomial Regression Model 1 (Poly1): Because our data is more complex than just a linear relationship, we try to use a polynomial regression model modelling how the responsive variable, **CVP**, is effected by the marginal **qrs relative index** up to degree 12, and then adding the marginal **inspiration relative index** up to degree 8, and then adding the marginal **time** component up to degree 3. The mathematical model can be described as:

$$\widehat{CVP} = \alpha + \sum_{i=1}^{12} \beta_i \cdot \text{qrs\_rel\_index}^i + \sum_{j=1}^{8} \gamma_j \cdot \text{insp\_rel\_index}^j + \sum_{k=1}^{3} \zeta_k \cdot \text{time}^k + \epsilon. \tag{2}$$

- Polynomial Regression Model 2 (Poly2): A polynomial regression model modelling how the responsive variable, **CVP**, is effected by the marginal **qrs relative index** up to

degree 23, **inspiration relative index** up to degree 23, and the **time** component up to degree 23. The mathematical model can be described as:

$$\widehat{CVP} = \alpha + \sum_{i=1}^{23} \beta_i \cdot \text{qrs\_rel\_index}^i + \sum_{j=1}^{23} \gamma_j \cdot \text{insp\_rel\_index}^j + \sum_{k=1}^{23} \zeta_k \text{time}^k + \epsilon. \quad (3)$$

The above model types have been trained on all of the data sets. We use MAE and BIC to compare the different models to the GAMs. A comparison for selected patients can be seen in Table 2 and Table 3.

| Patient# | Closed/open chest | GAM MAE | LM MAE | Poly1 MAE | Poly2 MAE |
|---|---|---|---|---|---|
| 3 | Closed | 0.215 | 0.821 | 0.286 | 0.245 |
| 4 | Closed | 0.478 | 0.768 | 0.498 | 0.381 |
| 5 | Closed | 0.160 | 0.678 | 0.235 | 0.205 |
| 7 | Closed | 0.087 | 0.835 | 0.199 | 0.149 |
| 9 | Closed | 0.166 | 0.976 | 0.339 | 0.303 |
| 10 | Open | 0.222 | 0.909 | 0.303 | 0.243 |
| 11 | Open | 0.215 | 0.676 | 0.282 | 0.240 |
| 12 | Open | 0.202 | 1.012 | 0.323 | 0.235 |
| 14 | Open | 0.169 | 0.861 | 0.271 | 0.211 |
| 15 | Open | 0.205 | 0.717 | 0.281 | 0.226 |

**Table 2** Comparison of how different models performed on selected data sets, measured using MAE.

| Patient# | Closed/open chest | GAM BIC | LM BIC | Poly1 BIC | Poly2 BIC |
|---|---|---|---|---|---|
| 3 | Closed | -18817 | 29919 | 10415 | 8332 |
| 4 | Closed | -13408 | 14998 | 10372 | 8323 |
| 5 | Closed | -27440 | 27146 | 5300 | 3140 |
| 7 | Closed | -11225 | 9676 | 651 | -872 |
| 9 | Closed | -27387 | 35975 | 13820 | 11751 |
| 10 | Open | -6558 | 13750 | 5030 | 3501 |
| 12 | Open | -29292 | 41138 | 14254 | 7901 |
| 14 | Open | -19808 | 24614 | 6305 | 2552 |
| 15 | Open | -13655 | 20624 | 6842 | 4361 |

**Table 3** Comparison of how different models performed on selected data sets, measured using BIC.

It is quite clear from the MAEs in Table 2 that the models produced as GAM perform better than the other models – the average error is smaller for GAMs in every data set, when

compared to the other models.
We will not put too much interpretation into each BIC value, but in general, we see that GAM produces a much better BIC score than the other models. The amount of information lost through GAM must be relatively small, while through the other models, the amount of information lost is relatively large. This indicates that GAMs are good at explaining the change in CVP, compared to other models. Once again this gives us more confidence in the results produced by our GAMs.

# Findings

## Explanatory variables

We are interested in extracting meaningful information from our models. More precisely, we are interested in inspecting how the effects of the explanatory variables change, when comparing the model created before thorax is opened to the model created after thorax is opened. To do this, we visualize the effect of each explanatory variable as well as their interaction.

### Marginal effects

The marginal effects describe how the relative position in the heartbeat cycle and the relative position in the respiratory cycle affect the CVP. For the heartbeat cycle, we often see a pattern of a lower CVP immediately after the QRS complex followed by a rise, then a slight drop and a rise again. Immediately after the QRS complex, systole takes place and the heart pumps blood into the arteries, it makes sense for CVP to be lowered here. Afterwards, diastole takes place and blood is flowing from the superior vena cava into the heart.
For the marginal effect of the relative position in the respiratory cycle, we often see one peak that lasts around 20% to 50% of the respiration cycle while the rest of the cycle has an effect of about 0 on CVP. The ascend of the peak represents the inspiration phase, and the descend represents the exhalation phase. When air is inhaled into the lungs, the lungs are enlarged, which increases pressure inside the thorax. The superior vena cava resides in the thorax, and thus, the CVP is increased during inspiration. It would be expected that this increase in pressure is reduced or even completely removed when thorax is opened, but this is not the result we are seeing in our models (See Figure 5). The effect of the respiratory cycle remains almost identical when thorax is opened, which is a surprising result for our clinical supervisors, as well as other clinicians with expertise in the field. It is important to emphasize that we have data from 38 patients, and therefore, general conclusions should not be made from

these specific models – but for these 38 patients, it seems like the effect of the respiratory cycle remains the same when thorax is opened.

For Figure 5, we have first synchronized the respiration cycles for closed and open chest, making the visual comparison easier. We see no significant change in the morphology of neither the respiration nor the QRS cycle effect.


**Fig. 5** The marginal effects of the respiration and QRS cycle, respectively, on CVP for patient 2.

To see where the differences between closed and open chest lies, we have created a plot containing the difference between the closed and open chest values (open minus closed). In Figure 6, for example, we see that at 0.5 QRS cycle we have the biggest difference in effect between closed and open chest.

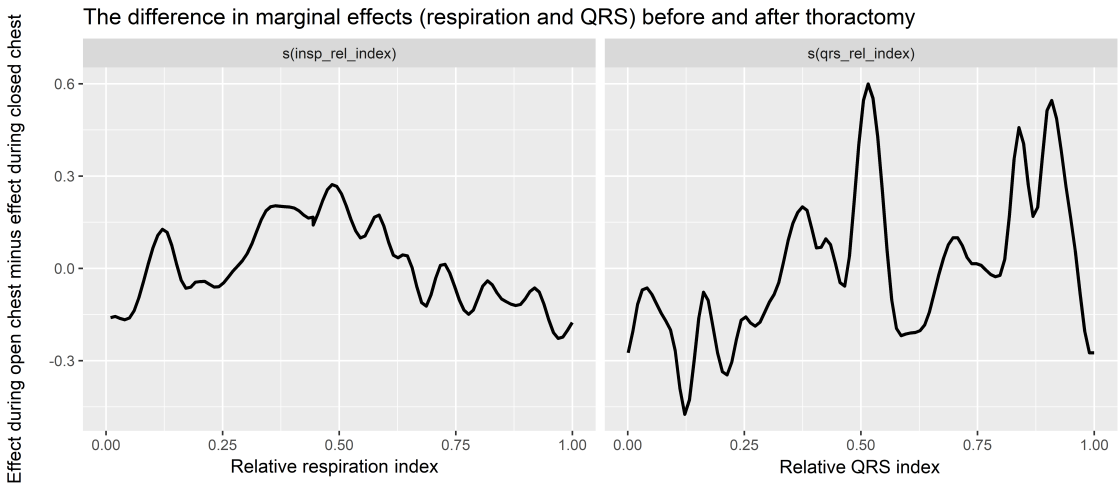


**Fig. 6** Difference in the marginal effects of the respiration and QRS cycle, respectively, before and after thoracotomy on CVP for patient 2.

### Contour Plots

The contour plots are visual representations of the effect of the interaction term. The contour plots are difficult to draw conclusions from – for the inexperienced eye it can be tough (and sometimes impossible) to distinguish between an actual interactive effect and an effect created by noise. It can be beneficial to compare the before and after contour plots to do the distinguishing. We would advice to be cautious when trying to draw conclusions from the contour plots, but if you wish to find interesting information, you should generally compare the before and after plot. In isolation it is unreasonable to draw conclusions from them.
Initially, for the interactive effect between the relative position in the QRS cycle and the relative position in the respiratory cycle, we present a contour plot for when the chest is closed and open. This can be seen in Figure 7.

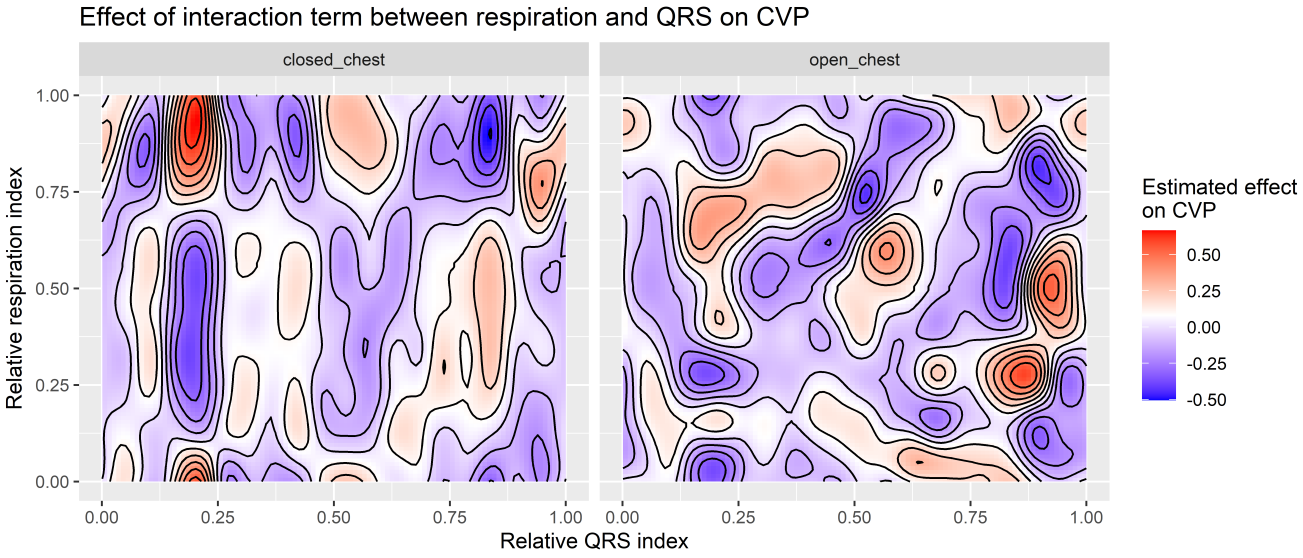


**Fig. 7** Visualization of the interaction effect between the QRS cycle and respiration cycle. The figure shows the effect during both closed and open chest for patient 2.

If we inspect Figure 7, we see quite a few dissimilarities between the effect during closed chest and during open chest. When the chest is closed, there is a rise in effect on CVP of about 0.5 at index 0.25 in the QRS cycle and index 0.9 in the respiration cycle. This positive effect does not seem to be existent when the chest is opened – quite the opposite, we see a negative effect. Furthermore, during closed chest, the vast majority of the (negative) interaction effect is present when the QRS index is approximately 0.2 and respiration index is between 0.2 and 0.7. This effect is greatly reduced when the thorax is opened. The trend of positive effects at the end of the QRS cycle and around index 0.3 to 0.5 in the respiration cycle seems, however, to be consistent between the two plots.

To make the comparison between the two contour plots more sensible, we present a contour plot showing the difference between closed and open chest (calculated as open minus closed). In Figure 8, at position 0.2 in the QRS cycle and position 0.4 to 0.6 in the respiration cycle, we can see that there is a positive change of about 0.4 CVP when thorax is opened. Similarly we see a negative change in effect of around 0.8 CVP at position 0.2 in the QRS cycle and position 0.9 to 1.0 in the respiration cycle.

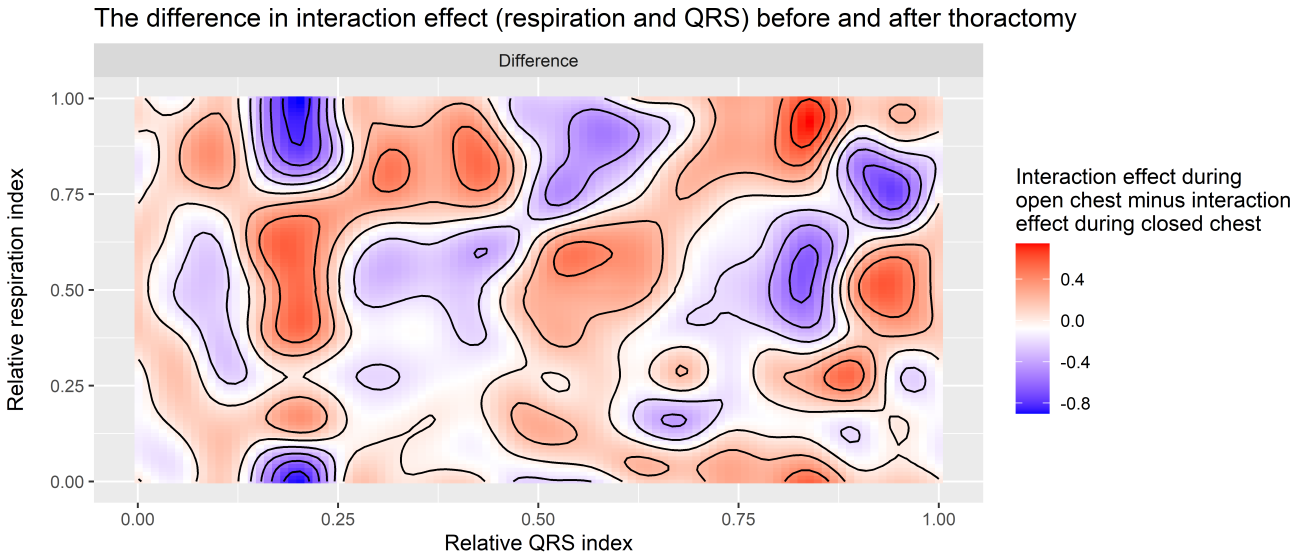


**Fig. 8** Visualization of the difference in interaction effect between the QRS cycle and respiration cycle before and after thoracotomy for patient 2. A positive (red) difference indicates a larger effect during open chest, while a negative (blue) difference indicates a larger effect during closed chest.

### Snapshots

Comparing contour plots between models (closed and open thorax) is not straightforward, and as a result, we create another two-dimensional graph showing the effect of both QRS cycle, respiration cycle and interaction. These graphs show CVP as a function of the position in the QRS cycle. Furthermore, the respiration cycle has been locked at different values. Thus, the graphs can be thought of as snapshots taken at different times in the respiration cycle. For each data set, we have taken 10 snapshots, evenly distributed throughout the respiration cycle, of CVP as a function of the QRS cycle. This procedure yields 10 line graphs all plotted in the same coordinate system. During this procedure, we suppress the effect of time. This makes the comparison simpler, and we can look directly at the change in morphology. Examples of this can be seen in Figure 9 and Figure 10.

First of all, the snapshots (Figure 9 and Figure 10) are a combination of the marginal effects of the relative position in the two cycles and their interaction. The two marginal effects are fairly simple to spot by having the relative position in the QRS cycle on the x-axis, and the relative position in the respiration cycle as the color legend. If the lines are on top of each other, there is no marginal effect from the relative position in the respiration cycle. The interaction can be seen in the morphology of each graph. If all the lines are parallel, there appears to be no interactive effect, but if the lines possess different morphology, there appears to be an interactive effect. This interactive effect can for example be seen by comparing the top line and the bottom line for closed chest CVP in Figure 9, and seeing that the valley at position 0.2 in the QRS cycle appears different.

Figure 9 and Figure 10 can be utilized to make an interpretation of how opening thorax during surgery might affect the effect of the heart-lung interaction on CVP. For patient 2 (Figure 9), around position 0.875 in the QRS cycle, there is a peak, which we can inspect further by comparing the closed chest to the open chest graph. We see that the the peak is flatter after the thorax has been opened than it was before. This could be an indication that the effect of the interaction has changed, after thorax was opened. During open chest, the CVP, at the peak, varies from 17 to almost 19, while during closed chest, the CVP varies from only 17 to 18. To be more specific, just before the QRS complex appears, there is a peak in CVP which seems to be influenced by the opening of thorax. We also see a variance in the width of this peak during open chest, which does not seem to be of significance when the thorax is closed.
Furthermore, in the contour difference plot for patient 2 (Figure 8), we see a change in the effect of the interaction term around position 0.2 in the QRS cycle when thorax is opened. This can also be seen in the snapshots (Figure 9) by noticing that the 10 lines during open chest are close to being parallel around position 0.2 in the QRS cycle. This indicates that there is almost no interaction effect taking place at that specific QRS cycle position.

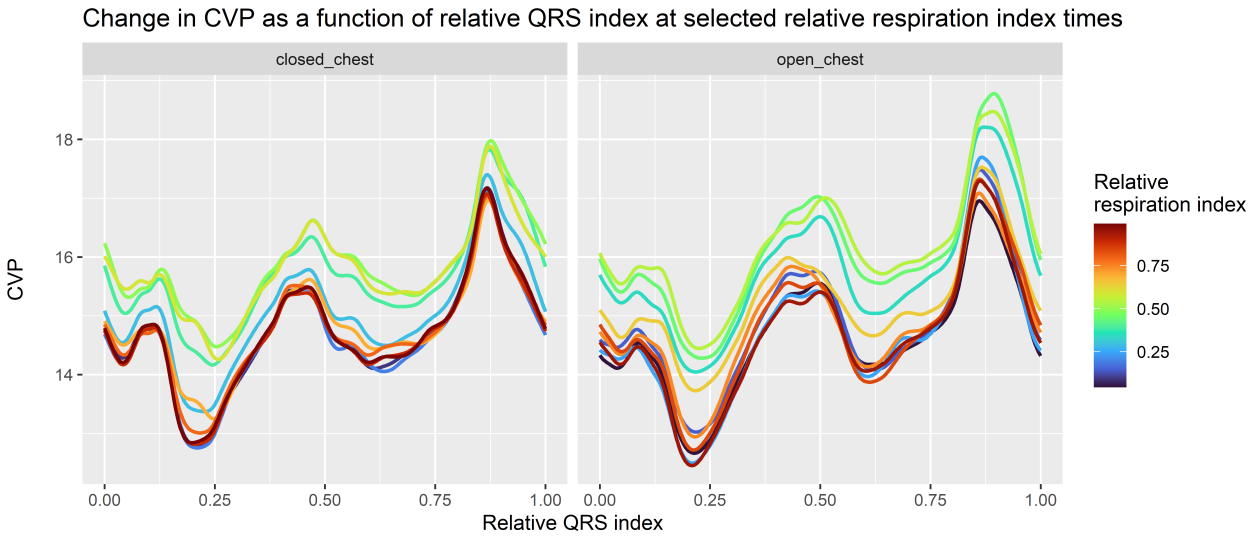


**Fig. 9** Snapshot plot showing both marginal effects and interaction effects on CVP for patient 2. The model intercept has been added for better interpretation.

For patient 7 (Figure 10), around position 0.25 in the QRS cycle, there is a valley which appears deeper after the thorax has been opened. The valley has been shifted about 0.5 CVP further down. To be more specific, just after the QRS complex has occurred, there seems to be a change in how much the CVP drops. Furthermore, before the chest is opened, the valley is much steeper – a more smooth valley is present after the chest has been opened, which indicates a change in interaction effect.

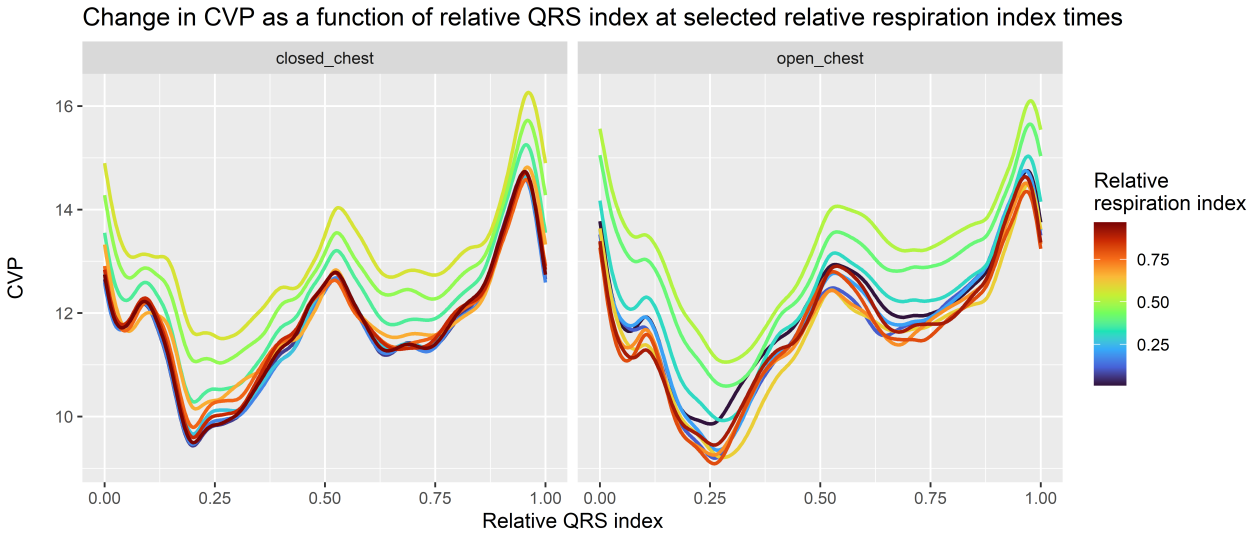


**Fig. 10** Snapshot plot showing both marginal effects and interaction effects on CVP for patient 7. The model intercept has been added for better interpretation.

Once again, we present a plot of the difference in effects between closed- and open chest (Figure 11). With the more comprehensible plot of differences, we can precisely point to when the changes take place. There is a clear difference in morphology between the light-orange line and the light-blue line which indicates a change in the effect of the interaction. Furthermore, the difference in the width of the peak at around position 0.9 QRS-cycle is easier to spot in this plot.

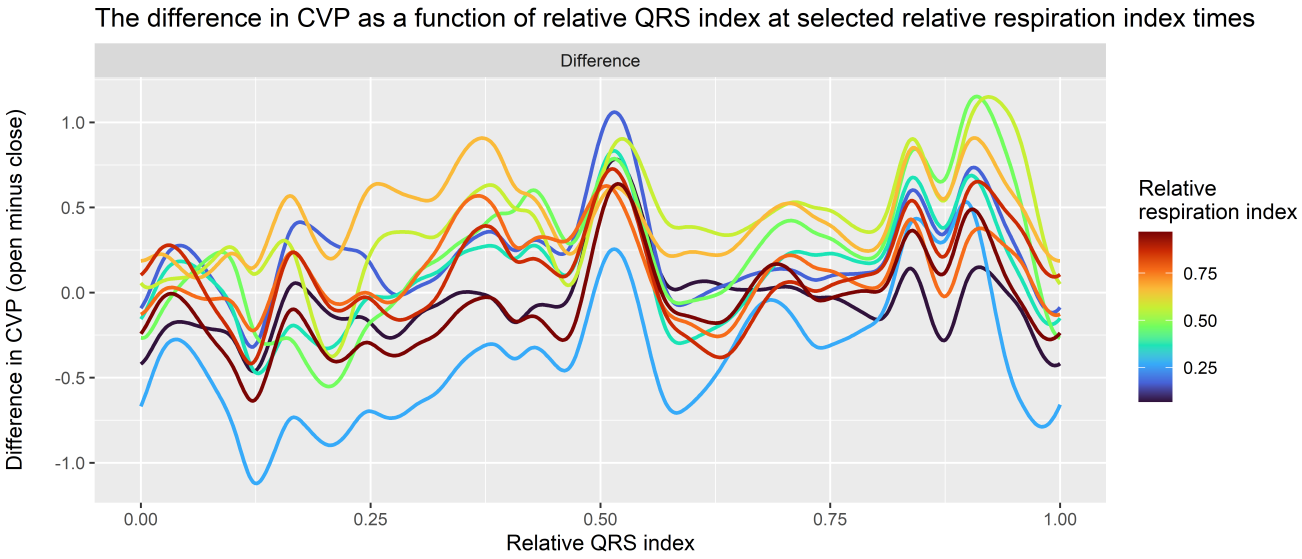


**Fig. 11** Difference between snapshot plots for closed and open chest for patient 2. Calculated as open minus closed.

# Conclusion

In this project, we set out to model and visualize heart-lung interactions in CVP using GAM modelling. The overall result is that GAM is a very suitable modelling technique to fit the CVP waveform and, in turn, identify – with a high level of physiological detail – the heart-lung interactions. Based on our observations and discussion with clinical and physiological researchers, the most interesting result we have seen in our models describing the 38 patients, is that when thorax is opened, there does not seem to be a change in the effect of the respiratory cycle on CVP. This is an unanticipated result and could reveal a different perspective of the environment of the thoracic cavity. Furthermore, there seems to be a slight change in the effect of the heart-lung interaction just before and just after the QRS complex.

First and foremost, our results seem to be quite robust across most of the 38 patients, but we need to emphasize that we are dealing with a group of cardiac surgery patients that could

have different hemodynamics from that of other patients on ventilators. This means, that while these results might seem robust, we would expect some ventilator patients to have a fundamentally different heart-lung interaction with regards to CVP – at least when thorax is closed. E.g., for COVID-19 patients, our results would be difficult to apply because of the different behavior of the lung mechanics.

## Potential

To research this further, the first step could be to gather data of better quality, e.g. a couple of minutes where we are certain that there is no noise. This would bring even more confidence to the analysis, and thereby to the conclusions drawn from the models.

Thereafter, researching further by creating a multi-level model that tries to incorporate the data from all patients, both before and after thoracotomy, could be a way to illustrate general tendencies. In order to do this in a satisfying way, it would be desirable to guarantee a homogeneous group of patients.

The surprising result from our models, that the effect of the lungs on CVP seems unchanged when thorax is opened, should be researched further. Perhaps the effect from the lungs is not due to the actual expansion of the lungs, but something else? The right ventricle pumps against the pressure inside the lungs. The respiratory variation in CVP may be caused by variation in emptying of the right ventricle, which in turn affects the flow of blood from the superior vena cava into the heart. Is the unchanged effect of the respiratory cycle due to a retrograde pressure from the right ventricle?

Another interesting feature, which could be researched more in-depth, is the higher variation in the width of the peak just before the QRS complex, caused by the atrial contraction, which could be due to a change in the heart-lung interaction. What change in the heart-lung interaction could cause this?

Furthermore, these models could be presented to domain experts. They could possibly provide essential knowledge about the field, which could explain both the expected and unexpected results.