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

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Problem definition

During open thoracic surgery, the physician will often let the intravenous (IV) drip fluid run into the patient's bloodstream. The anesthesia causes the bloodstream to "relax", and the IV drip fluid can therefore be seen as a form of compensation in the volume, in order for the heart to be well filled before each heartbeat.
It is important to make sure that the required amount of blood circulates around the body, while avoiding high blood pressure. It can be challenging to know when and how much fluid to inject into the patient, which is partly due to the fact that there is currently no monitoring (central venous pressure (CVP) or other) that with a high reliability can guide the fluid treatment. Our contribution to this is to investigate how the effect of the heart-lung interaction changes on the CVP 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 heart and lungs 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 of the body, and perhaps this could have an influence on how the CVP behaves. A theory could be that, when thorax is closed, the lungs are limited in the ways that they can expand and may put more pressure on the veins. Now, when thorax is opened, the lungs would put less pressure on the veins, and therefore have less impact on the CVP. There could possibly be a change in the heart-lung interaction or at least the impact that the heart-lung interaction has on the CVP.

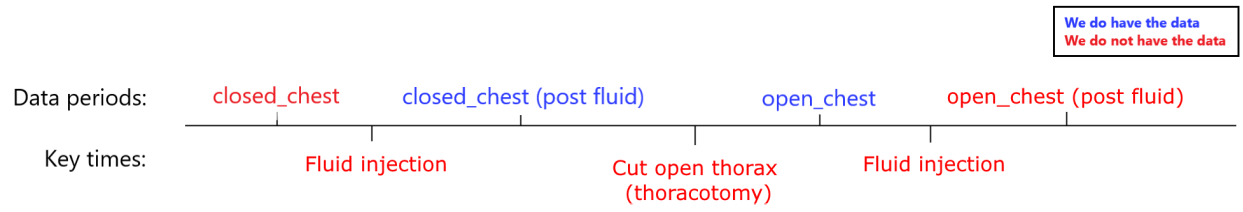
Report

Data

Our data is obtained from 61 patients undergoing open thoracic surgery, and consists of two datasets for each of the patients. One dataset for when their chest is closed and after they have received fluids, and another dataset for when their chest is opened and before they have received another fluid. In the two datasets we are then given the following recorded information:

- ECG: Electrocardiogram, which is a graph of voltage versus time of the electrical activity of the heart.
- ABP: Arterial blood pressure, the blood pressure in the arteries.
- CVP: Central venous pressure, the blood pressure in the superior vena cava, which is near the right atrium of the heart. CVP is a measurement of the amount of blood returning to the heart, and therefore an interpretation of the ability of the heart to pump the blood back into the arterial system. This is measured in mm of mercury in the blood.
- QRSmarker_ecg_index: A marker for when the QRS complex is starting the ECG.
- QRSmarker_ms: Occurrence of the QRS complex in milliseconds from start.

The window of the data is as follows:



We have data from the periods marked with blue.
We are also given information about the rate of the respirator for the surgery measured in cycles per minute.

Missing data

In the process of finding the effect of the heart-lung-interaction on the CVP during open thoracic surgery, 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, it could occur that there were no data for either one or both time-periods. Here, we chose to exclude the patients and therefore, no model was created for that particular dataset.
In the case where there were too much noise in the data - which could happen due to external factors in the operation room, eg. if someone touches the respirator hose - we also chose to exclude the respective patients and their associated model from the Shiny-application.
Because of these exclusions, we end up with 38 patients with a fully usable dataset, 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 respirator. 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 for people with knowledge about the domain to make precise conclusions about the model. This also ensures that it is possible to synchronize the effect of the respiratory cycle for the closed- and the open dataset for each patient. This makes the interpretation of the effect of the heart-lung-interaction on CVP cleaner.

Model creation

When creating a model for a dataset we started by choosing an appropriate time slot. For this process we inspected the data as a graph 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 datasets where thorax was closed, we chose time periods as late as possible, and for the datasets where thorax was open, we chose time periods as early as possible. This was done to minimize the "difference" between the two datasets - 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 having time periods as close to each other as possible for open- and closed datasets 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 Generalized Additive Models[1] which uses smooth terms made, in our model, through cyclic cubic regression splines. Cyclic was chosen because our variables of interest (heart cycle and inspiration cycle) are cyclic, and there were only two splines that offered the cyclic effect of which cubic splines produced a better result. To put it simple the linear predictor created by GAM is a sum of smooth functions. An important thing about GAM-modelling is to select the amount of basis functions. When choosing a high number of basis functions you add more wiggliness to your smooth term and therefore a better fit - this can end up being computationally cumbersome and there is a risk of overfitting. Therefore, we tested multiple values for the amount of basis functions and ended up with values that generalized well for different patients. To estimate the coefficients we use Restriced Maximum Likelihood (REML) because of its computational efficiency in GAM-modelling.

One data point for training 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 saying CVP explained 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.

An intuitive thought is that autocorrelation must be present in this data. Meaning that we expect that an observation is heavily correlated with the observation right before it - the amount of autocorrelation in terms of lag varies from patient to patient, but the important thing is that it is extremely heavy (see Figure 1). This is something we can account for in our GAM, which we do by including a rho term. Once again we found an appropriate value which generalized well for all patients. This resulted in a cleaner interpretation of the individual effects by smoothing the individual effects slightly - this is done through an increase of confidence intervals.

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

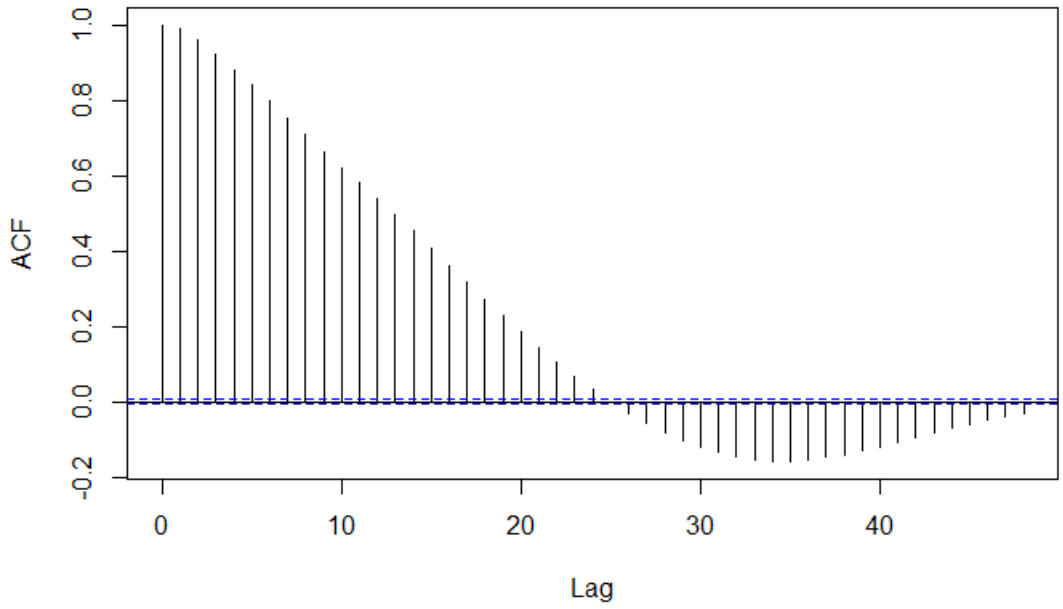


Figure 1: Lags of autocorrelation for a patient

Model validation

An important aspect of this project was to validate our models. We might have gotten interesting results, but how can we determine the accuracy of our model? We can start inspecting this by taking a look at a plot of our observed values, predicted values, and the residuals (See Figure 2). Here we can see that the model fits the observed values well. The residuals are of minimal value and the small errors are most likely caused by noise. This is a good sign, but it gives us an immediate worry; have we overfitted our model 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 points towards that through GAM-modelling our explanatory variables are good at explaining change in CVP.

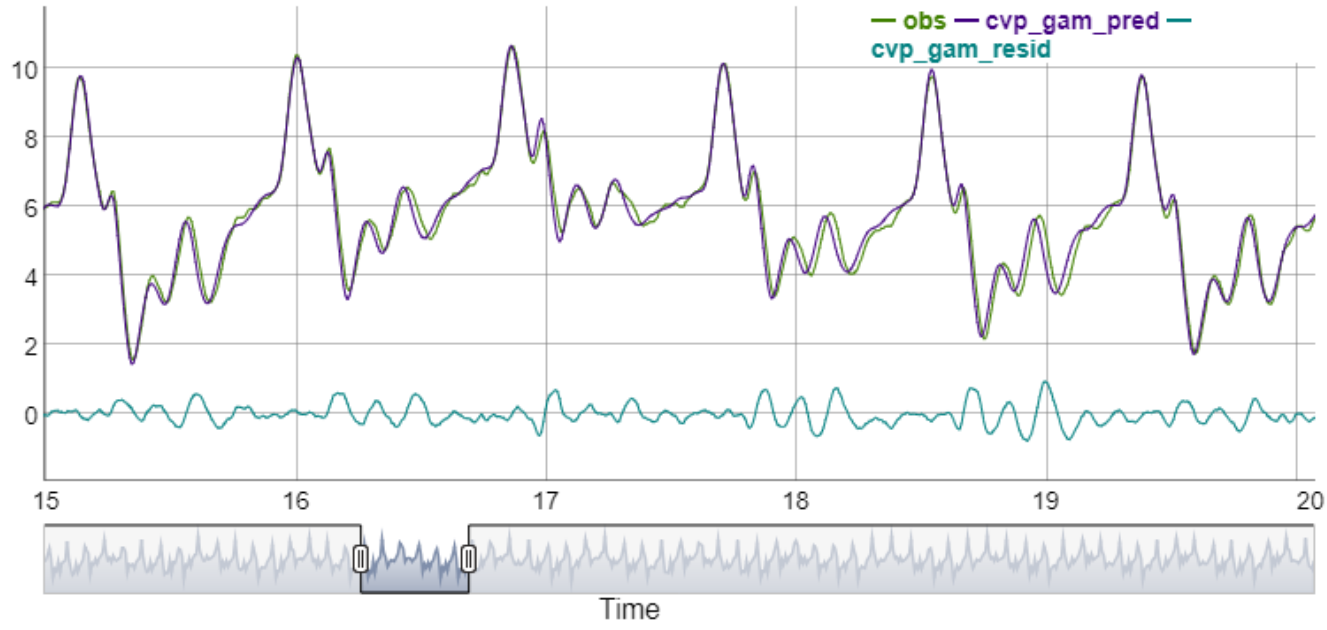


Figure 2: Plot of observed- and predicted values, as well as residuals

Back to the worry of overfitting - generally we want a model to generalize well to be more confident of its performance. We do not want to make false conclusions based on an overfitted model. In our case, we have a slight issue; 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 dataset 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 dataset into 80% training and 20% testing, train the model and evaluate it based on Mean Absolute Error (MAE), and then repeat this process 10 times. We then take the average of the MAE of the 10 simulations, and use this as a measure of the generalizability of our model. To know if we have a good MAE-value we also present the MAE of the actual model that we use for that specific dataset.

Patient	Open/Closed	Average 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

The MAEs generated through cross validation are very similar to the MAEs associated with our actual models. This points towards 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 produd 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

To know whether the models produced by GAM perform well, we also need to compare with other types of models. The MAEs from our GAM-models may seem like good scores, but we need to interpret the values in the context of other scores. How well does 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 creation. BIC is similar to 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 - this is done to avoid overfitting. Generally when choosing models, you want to pick the model that produces the lowest BIC-value.

Explanation of models that are compared with 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**.

$$\widehat{CVP} = \beta_0(\text{qrs\_rel\_index} \cdot insp\_rel\_index) + \beta_1 \text{qrs\_rel\_index} + \beta_2 insp\_rel\_index + \beta_3 \text{time} + \epsilon$$

- 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** of 12th degree, and then adding the marginal **inspiration relative index** of 8th degree, and then adding the marginal **time** component of 3rd degree. The mathematical model can be described as:

$$\widehat{CVP} = \beta_0 \text{qrs\_rel\_index}^{12} + \beta_1 \text{qrs\_insp\_index}^{8} + \beta_2 \text{time}^{3} + \epsilon$$

- Polynomial Regression Model 2 (Poly2): A polynomial regression model modelling how the responsive variable, **CVP**, is effected by the marginal **qrs relative index** of 23th degree, **inspiration relative index** of 23th degree, and the **time** component of 23th degree. The mathematical model can be described as:

$$\widehat{CVP} = \beta_0 \text{qrs\_rel\_index}^{23} + \beta_1 \text{qrs\_insp\_index}^{23} + \beta_2 \text{time}^{23} + \epsilon$$

From the above described models, we then find the following MAE and BIC values for some arbitrary patients.

Patient	Open/Closed	Actual Model 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

It is quite clear from the MAEs that the models produced by GAM perform better than the

other models - the average error is significantly smaller for GAM compared with the other models.

Patient	Open/Closed	Actual Model BIC	LM BIC	Poly1 BIC	Poly2 BIC
3	Closed	-18817.410	29918.670	10415.152	8331.862
4	Closed	-13407.840	14998.172	10372.465	8322.864
5	Closed	-27439.993	27146.212	5300.090	3139.670
7	Closed	-11224.824	9676.119	650.879	-872.237
9	Closed	-27386.677	35975.411	13819.837	11750.611
10	Open	-6558.170	13749.515	5030.215	3500.628
11	Open	-8650.277	14347.066	5463.605	4272.220
12	Open	-29291.618	41138.353	14254.302	7901.032
14	Open	-19807.675	24613.889	6305.000	2552.056
15	Open	-13654.521	20624.152	6841.798	4361.414

We will not put too much interpretation into each specific numbers, but it is quite clear that GAM produces a much better BIC score than the other models. The amount of information lost through GAM must be quite small while through the other models, the amount of information lost is relatively large. This signals that GAM is good at explaining the change in CVP through the relative position in the heart cycle and the relative position in the respiration cycle compared with other models. Once again this gives us more confidence in the results produced by GAM.

Findings

Explanatory variables

We are interested in extracting meaningful information from our models. More precisely, we are interested in inspecting how the effect of the explanatory variables changes when comparing the model created before thorax is opened and after thorax is opened. To do this, we present visualizations of the effect of each explanatory variable.

Marginal effects

The marginal effects describe how the relative position in the heartbeat cycle and the relative position in the respiratory cycle affect 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, which makes sense with regards to the rise in CVP.
For the marginal effect of the relative position in the respiratory cycle, we often see one peak that is around 0.2-0.5 *insp_rel_index* wide while the rest of the *insp_rel_index* 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 and this means more resistance for the veins - resulting in an increase in CVP. It would be expected that this resistance is reduced or even completely removed when thorax is opened, but this is not the result we are seeing in our models (See Figure **??**). The effect of the respiratory cycle remains almost identical when thorax is opened which is a surprising result. 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 3, we have first synchronized the respiration-cycles for open- and closed chest - making the comparison more tolerable. We see no significant change in the morphology of the graph describing the effect of the respiration-cycle, and neither do we see a significant change in the effect of the QRS-cycle.

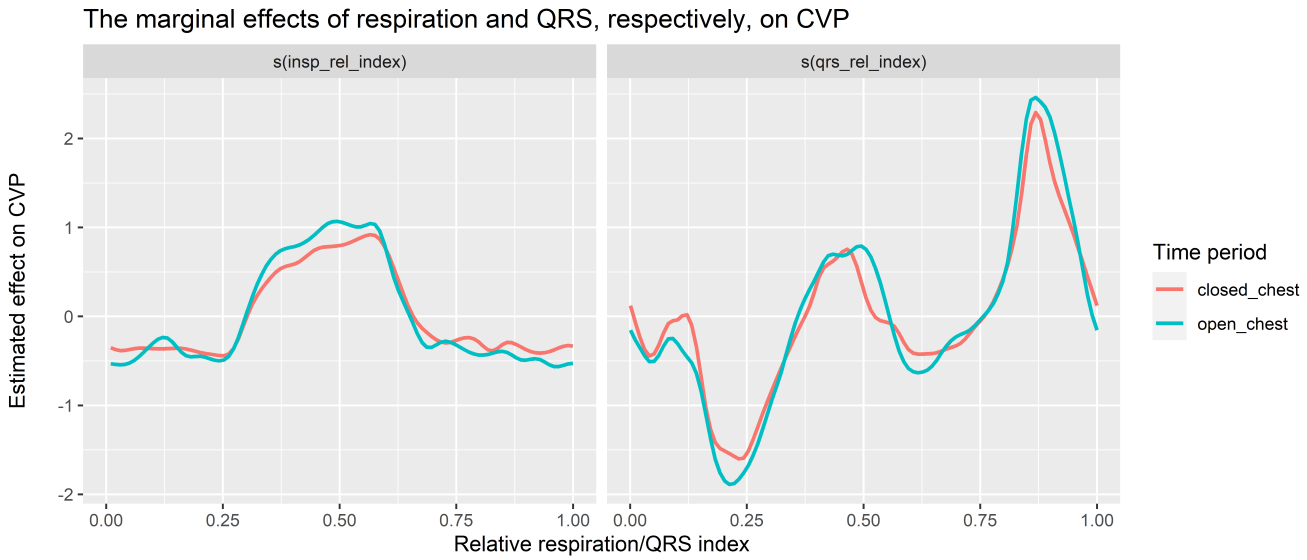


Figure 3: The marginal effects of respiration and QRS, respectively, on CVP

To make the comparison more tolerable, we have created a plot of the difference between the closed- and open chest values (open minus closed), which clearly shows where we see the biggest differences between closed- and open chest. In figure 4, we can for example see that at 0.5 QRS-cycle we see the biggest difference of the effect between closed- and open chest.

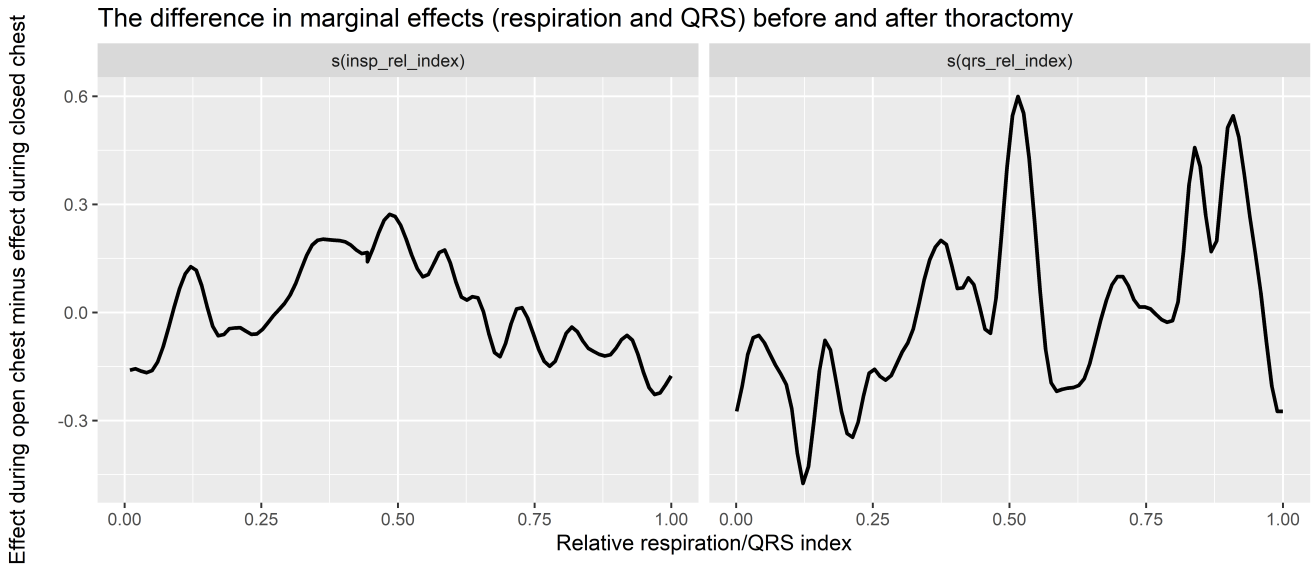


Figure 4: Difference in the marginal effects of respiration and QRS, respectively, on CVP

Contour Plots

The contour plots are a representation 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 even undesirable 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 heartbeat 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 5. If we inspect figure 5, there are quite a few dissimilarities between the effect at *closed_chest* and *open_chest*. When the chest is closed there is an effect of about a rise of 0.5 on CVP at 0.25 relative position in QRS-cycle and about 0.9 relative position in respiration cycle. This positive effect does not seem to be existent when the chest is opened - quite the opposite, we see a negative effect. The negative effect, we see at 0.2 QRS-cycle and 0.2-0.7 respiration-cycle also seems to change when the chest is opened. The trend of positive effects at the end of the QRS-cycle and around 0.3-0.5 in the respiration-cycle seems to be consistent between the two plots.

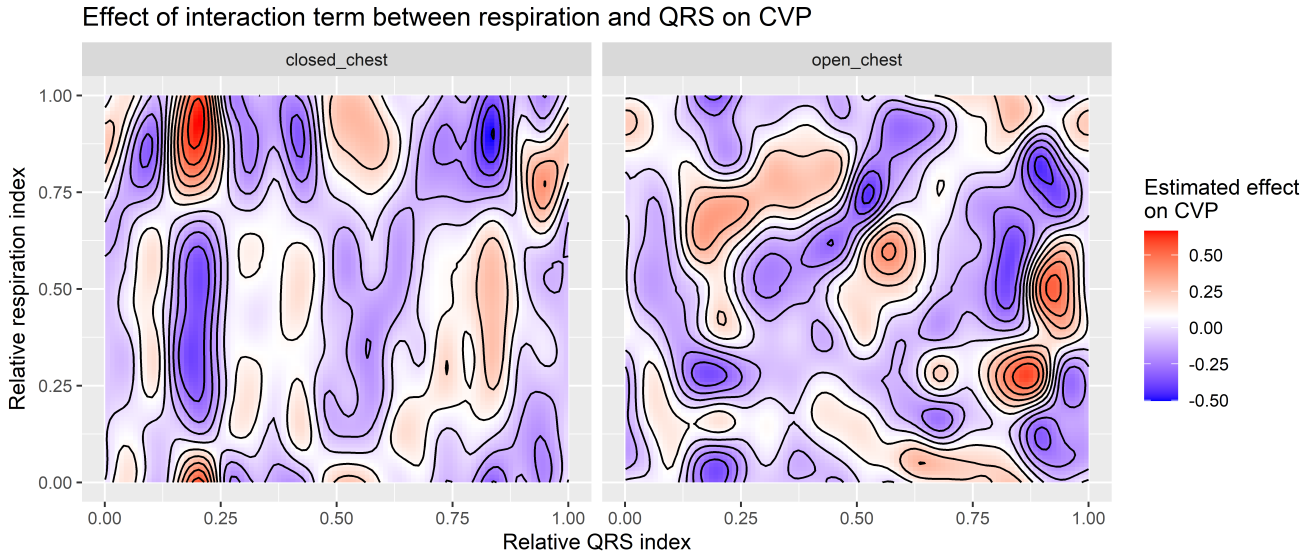


Figure 5: Contour of interaction between QRS-cycle and respiration-cycle - Patient 2 closed/Open

To make the comparison between the two contour plots more tolerable, we present a contour plot describing the difference between closed- and open chest (open minus closed). In figure

6, at position 0.2 in QRS-cycle and position 0.4-0.6 in respiration-cycle we can see that there is a positive change of around 0.4 CVP when thorax is opened. Similarly we see a negative effect of around 0.8 CVP at position 0.2 QRS-cycle and position 0.9-1.0 respiration-cycle.

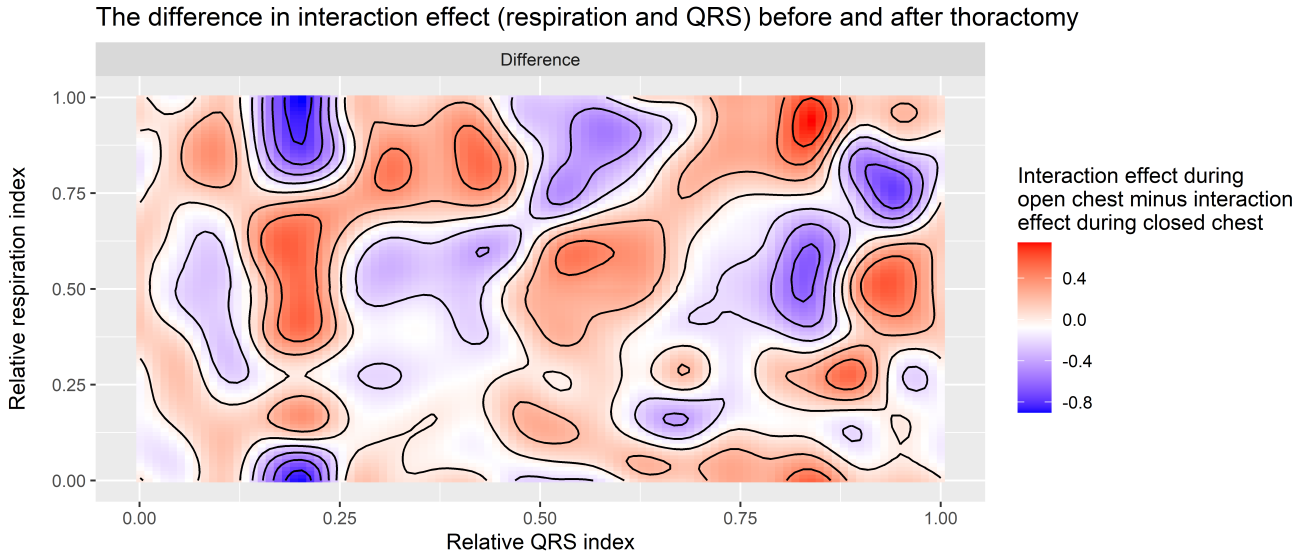


Figure 6: Difference in the interaction effects of respiration and QRS

Snapshots

The comparison of the above contour plots between the two models for the patient is not straightforward, and as a result, we create another two-dimensional graph for the relative position in the heartbeat cycle for which we lock specific values of the relative position in the respiratory cycle. If we for example choose 10 values for the relative position in the respiratory cycle, we stack 10 graphs on top of each other by predicting the actual value of CVP at each of those values - we ignore the value of *time* when doing this. This makes the comparison more tolerable, and we can directly look at the change in morphology of the graphs - this can be seen in figure 7 and figure 8.

First of all, the snapshots (Figure 7 and 8) 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 characteristics there appears to be an interactive effect. This interactive effect can for example be seen in by comparing the top

line and the bottom line for closed chest CVP for patient 2, and seeing that the valley around 0.2 qrs_rel_index appears different.

Figure 7 and figure 8 can be used to make an interpretation of the effect of opening thorax during surgery on the heart-lung-interaction's effect on CVP. For patient 2 (Figure 7), around 0.875 qrs_rel_index there is a peak which we can inspect further by comparing *closed_chest* with *open_chest*. We see that the value of the peak is more spread out after the chest is opened than before. This could be an indication that the effect of the interaction has changed after thorax was opened. For *open_chest* the CVP varies from 17 to almost 19 while for *closed_chest* the CVP varies from 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 for open chest which does not seem to be a case for when the chest is closed.

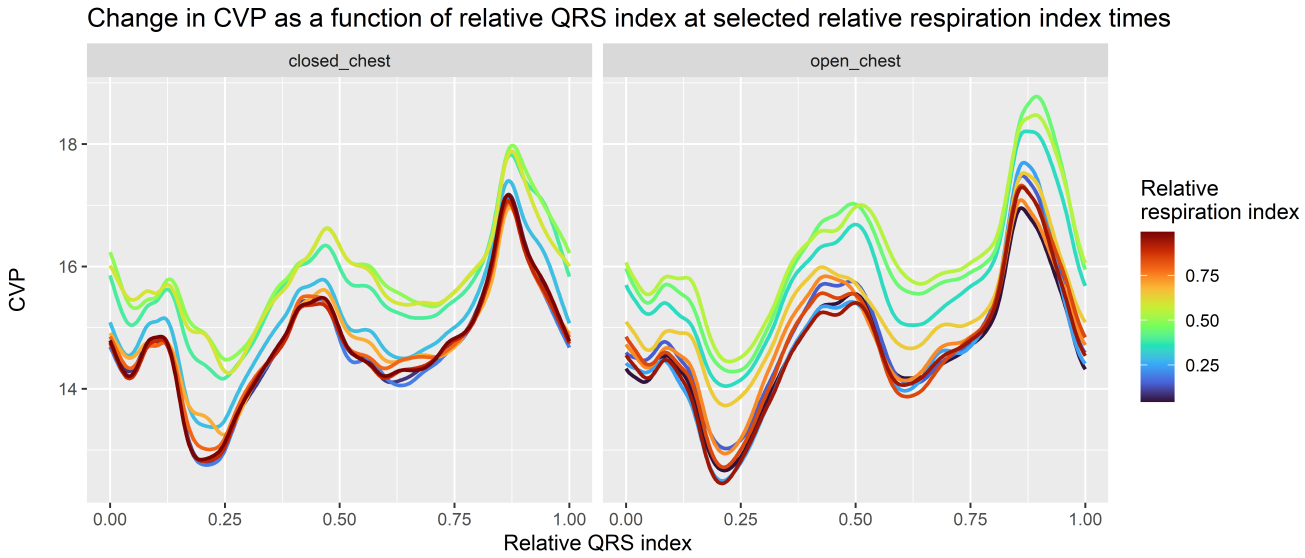


Figure 7: Snapshot of interaction between QRS-cycle and respiration-cycle (intercept added) - Patient 2

For patient 7 (Figure 8), around 0.25 qrs_rel_index there is a valley which appears deeper after the chest has been opened. The valley has been shifted about 0.5 CVP further down. To be more specific, just after the QRS-complex has occured there seems to be a change in the drop of CVP. Furthermore, before the chest is opened, the valley is much steeper - a more smooth valley is present after the chest has been opened.

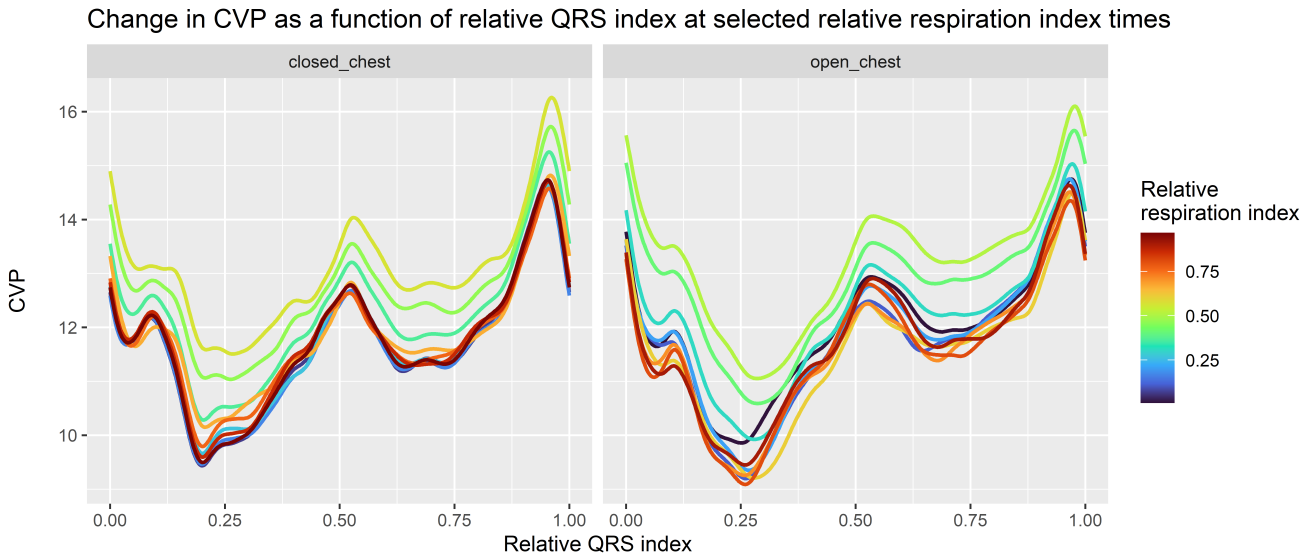


Figure 8: Snapshot of interaction between QRS-cycle and respiration-cycle (intercept added) - Patient 7

Once again, we present a plot of the difference in effects between closed- and open chest (Figure 9). 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, there the difference in the width of the peak at around position 0.9 QRS-cycle is easier to spot in this plot.

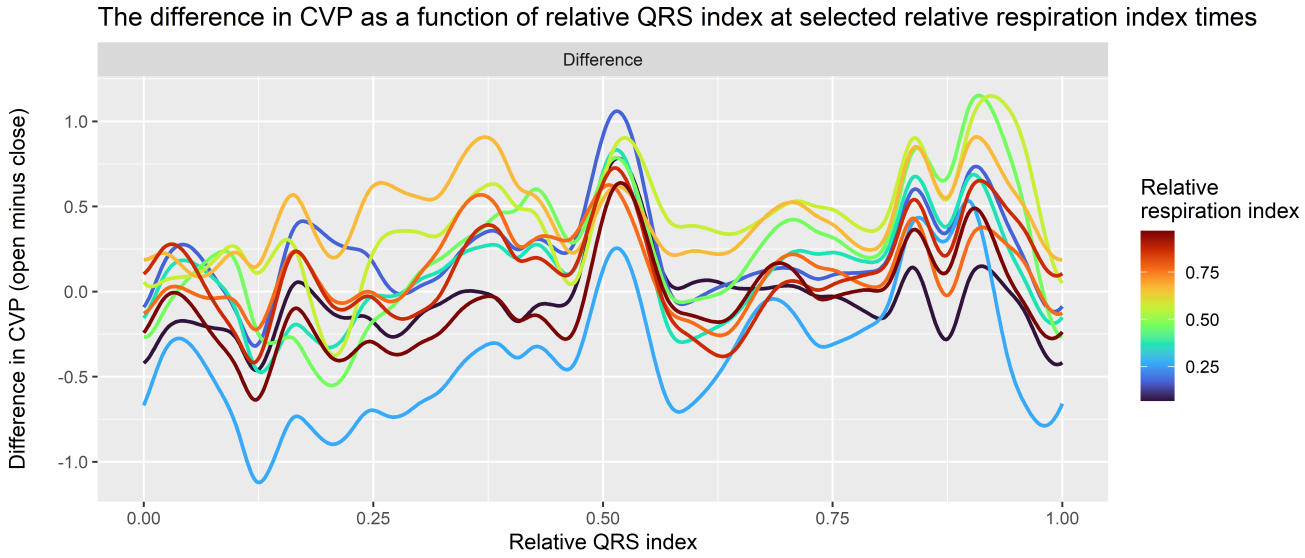


Figure 9: Difference of snapshot between closed- and open chest - Patient 2

Conclusion

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. We, once again, emphasize that we only deal with data from 38 patients, and to draw truly meaningful conclusions, it would be necessary to research even further on a larger amount of patients.

Potential

To research this further the first step could be to gather more data. This would bring more confidence to the analysis and thereby to the conclusions drawn from the models.
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 because of the actual expansion of the lungs, but due to something else? Is this unchanged effect due to a retrograde pressure from the right ventricle/atrium?
Another interesting feature which could be researched more in-depth is the higher variety in the width of the peak just before the QRS-complex 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 for domain experts that could provide essential knowledge about the field which could explain both the expected an unexpected results.