Event Prediction in Pharyngeal High-Resolution Manometry

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Abstract. A prolonged phase of increased pressure in the upper esophageal sphincter (UES) after swallowing might result in globus sensation. Therefore, it is important to evaluate *restitution times* of the UES in order to distinguish physiologic from impaired swallow associated activities. Estimating the event $t^\star$ where the UES has returned to its resting pressure after swallowing can be accomplished by predicting if swallowing activities are present or not. While the problem, whether a certain swallow is pathologic or not, is approached in [Mielens, 2012], the analysis conducted in this paper advances the understanding of normal pharyngoesophageal activities.

From the machine learning perspective, the problem is treated as binary sequence labeling, aiming to find a sample $t^\star$ within the sequence obeying a certain characteristic: We strive for a best approximation of label transition which can be understood as a dissection of the sequence into individual parts. Whereas common models for sequence labeling are based on graphical models [Nguyen, 2007], we approach the problem using a logistic regression as classifier, integrate sequential features by means of FFT-coefficients and a Laplacian regularizer in order to encourage a smooth classification due to the monotonicity of target labels.

1 Introduction

The work presented in this paper aims to support physicians analyzing high resolution manometry data of regular swallowing activity. The medical problem consists of estimating *restitution times* of the upper esophageal sphincter (UES) which we define as *duration after swallowing* until swallow related activities have subsided. We will denote this time stamp as the *restitution sample* $t^\star$ from which the restitution time can be inferred. Since estimation of *restitution times* is time-consuming for physicians and not standardized yet, we develop a novel semi-automatic application to assist the analysis.

1.1 Pharyngeal High-Resolution Manometry

In High-Resolution Manometry, pressures in the pharynx and UES are measured using a probe containing k equidistantly aligned pressure sensors. This probe is inserted through the patient's nose and stretches down to just below the UES. Pressures are recorded at a predefined sample rate. Resulting data can be visualized by a time-vs.-sensor plot as shown in Figure (1) [Meyer, 2012].

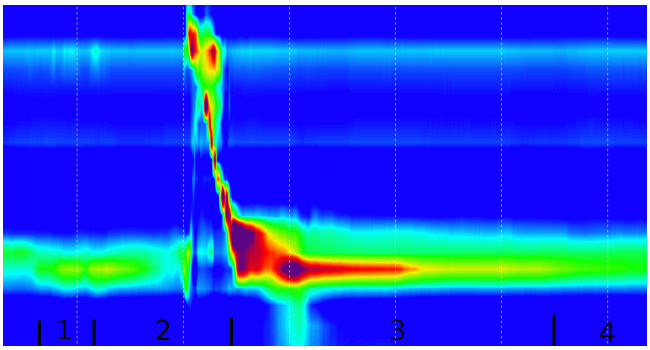

Fig. 1: Data is plotted as a time-vs.-pressure plot. Four different phases of the swallow can be identified.

1.2 Estimation of Restitution Times

Treatments of diseases such as dysphagia are expected to be enhanced by a better understanding of human pharyngeal and especially upper esophageal activities during swallowing. The UES maintains a basal pressure at rest to prevent air from entering into the gastrointestinal tract during inspiration and to protect the airways from material refluxing back from the esophagus into the pharynx. When swallowing, the UES relaxes, allowing a bolus to pass the sphincter region. This region can easily be depicted on the manometric recording (Figure (1)). The pressure decreases to a minimum and increases again to very high pressure values when the peristaltic wave passes the sphincter region during swallowing. After having reached the maximum pressure, sphincter pressures will eventually return to the resting pressure, this time interval is defined as *restitution time*. Since UES pressures decrease irregularly, it is difficult to define the exact $t^\star$.

For these reasons, it is important to develop a semi-automated method able to predict restitution times. The two main contributions of this paper are:

- To introduce the problem of estimating restitution times and regard it as a machine learning problem.

- To develop a method for estimating restitution times based on an annotated corpora of 100 swallows measured across 10 patients in two real-world medical application scenarios:
  1. *Intra-individual*: having learned the swallowing behavior of an individual patient, we apply the learned model to predict restitution times for the same patient.
  2. *Inter-individual*: having learned the swallowing behavior for several patients, we apply the learned model to predict restitution times of an unknown patient.

2 Related Work

2.1 Medical Background

Pressures in the paryngeal and esophageal tract are typically measured by HRM [Fox, 2008]. Several study groups have investigated pressure recodings associated with physiological as well as pathological swallowing, analyzing among others minimal and maximal as well as resting pressures, time intervals [Meyer, 2012], integrals and velocities [Jungheim, 2013]. In order to distinguish normal sphincter function from pathological swallowing activity, however, it is also necessary to evaluate the restitution time. Changes in restitution times could be indicative of i.e. globus sensation, impaired bolus passage or regurgitation. Since the UES pressure decreases slowly but inconstantly (not in an asymptotic solution) after swallowing, it is difficult to define the exact point in time when the resting pressure is reached again. This is probably why restitution times have not been determined yet and why it is necessary to develop a computed model to determine restitution times of the UES.

2.2 Machine Learning Background

We will cast the problem as a sequence labeling problem and define the restitution sample $t^\star$ with the aid of a labeled sequence $\mathbf{y} = (y_1, \ldots, y_{|T|})$ where labels are categorical, i.e. $y_t \in \mathcal{Y}$ and $\mathcal{Y}$ is a finite set. Predicting structured output has been researched extensively throughout recent years [Nguen, 2007], especially since problems such as part-of-speech tagging, the process of categorizing words as *noun, verb, preposition* can be modeled. Earlier work [Rabiner, 1989] employs Hidden Markov Models on speech recognition. More recently, [Lafferty, 2001] use Conditional Random Fields, a generalization of Markov Models for labeling sequence data.

Since $\mathbf{y} \in \mathcal{Y}^{|T|}$, the problem can also be understood as a multiclass problem and therefore be solved using multiclass Support Vector Machines. This approach is based on averaged perceptrons proposed in [Collins, 2002]. The earliest approaches were reported by [Altun, 2003] and [Tashar, 2003]. [Nguen, 2007] found, SVM Struct is among the most competitive methods and is therefore chosen as the competing method for the experiments.

3 Problem Definition

The data obtained by the High-Resolution Manometry forms a multivariate sequence of pressure values, as for each timestamp $t \in T$ an associated pressure vector $p_t \in \mathbb{R}^k$ exists, containing the recorded pressures by the sensors. Every swallow is assumed to have the same length to use only one finite index set T. We denote the set of all swallows of length $|T|$ by $\mathcal{P}$. Moreover, we obtain the *restitution samples* $t^\star \in T$ as ground truth.

3.1 Definition as Sequence Regression

The swallow data set contains a sequence of associated pressure vectors and the restitution sample.

$$\mathcal{D} := \left\{ \{p_t\}_{t \in T}\, ,\, t^\star \right\} \in \mathcal{P} \times T \tag{1}$$

The goal is to learn a classifier $\hat{f} : \mathcal{P} \to T$ that maps a swallow to a discrete time sample. However, one swallow corresponds to one instance, following this approach is therefore expensive since the model needs a large amount of training data. Therefore, we aim to formulate the problem as sequence labeling.

3.2 Definition as Sequence Labeling

The formulation as sequence labeling involves two steps. The first step requires a definition of labels y_t (states) for each time sample t we employ binary labels $\mathcal{Y} = \{1, -1\}$.

$$\mathcal{D} := \{(p_t, y_t) \,|\, t \in T\}. \tag{2}$$

Consequently, we try to learn a classifier $\hat{y} : \mathbb{R}^k \to \mathcal{Y}$ which gives more instances to learn a model. One state contains all time samples t where swallow related activities are present, the other state forms the converse.

The second step consists of infering $t^\star$ from a predicted sequence of labels. We segment the swallow according to these labels, which we accomplish through a derived maximum pressure p_{max} curve over the UES and additional knowledge in form of an annotated region of resting pressure before swallowing.

As the probe monitors the whole pharynx, the region of the UES is observed by a subset $I \subset \{1, \ldots, k\}$ of sensors. Over this subset, we compute a curve p_{max} of maximum pressure

$$p_{max}(t) := \max \{p_i(t) | i \in I\} \qquad t^{max} := \underset{t}{\operatorname{argmax}}\; p_{max}(t),$$

which assigns the maximum pressure in the UES region to every time sample t. Moreover, we denote its maximum position by t^{max}, using these properties

Algorithm 1 PredictRestitutionSample

1: **procedure** PREDICT
input: $\mathcal{D}^{test} \cup \{\hat{y}_t \,|\, t \in T\}$, w

2: $\forall\, x_t \in \mathcal{D}^{test}: \quad \hat{y}_t \leftarrow \hat{y}(x_t, \theta^\star)$
3: $\forall\, \hat{y}_t: \quad \overline{y_t} \leftarrow \frac{1}{2w+1} \sum_{i=t-w}^{t+w} \hat{y}_i$
4: $t^\star \leftarrow \min \{i > t^{max} \,|\, \overline{y_i} \geq 0 \wedge \overline{y_{i+1}} < 0\}$
5: **end procedure**

enables us to segment a swallow into four different phases as can be seen in Figure (1):

The first phase of the swallow describes the annotated resting pressure before swallowing. The state $y_t = -1$ is assigned. The second phase contains the beginning of activities in the velopharynx, until the t^{max} sample is reached. We will perform a supervised exclusion for phase two as it belongs to neither of the states. The third phase begins at the t^{max} sample, as from this point on swallow related activities of the UES are present we assign $y_t = 1$ for these time samples. The remaining samples are labeled $y_t = -1$, since by definition of $t^\star$ swallow related activities have subsided.

3.3 Deriving the Restitution Sample from a Labeled Sequence

For the sequence labeling techniques presented in the next section, we are required to derive the restitution sample given a labeled sequence of a test swallow. This procedure is given in Algorithm (1). Based on the segmentation presented in Figure (1), going ahead in time from the t^{max} sample, we determine $t^\star$ as the first transition of states.

$$t^\star \,=\, \min \{i > t^{max} \,|\, y_i = 1 \,\wedge\, y_{i+1} = -1\}\,. \tag{3}$$

In an ideal case, we have a classification sequence where the labels change only once for all $t > t^{max}$, when the swallowing activities have subsided. Problems may arise when the classification is not perfectly smooth, consider a change of labels for only a short time period. We will overcome this issue by smoothing the final prediction with a predefined window size w representing an additional hyperparameter.

3.4 Preprocessing and Derivation of Additional Features

As a preprocessing step, we normalize the swallows individually, as to (a) account for possible probe calibration offsets, and to (b) roughly align the value ranges for swallows of different lengths. Normalizing the swallows patient-wise hase empirically prooven to result in a weaker classification.

Furthermore, since the UES region defined by I differs interindividually, we compute derived sphincter features as follows: we calculate local pressure

maxima over the first, second, and last third of the UES region. We also repeat this process for the first and second half and for the overall UES region. Consequently, we obtain six additional sphincter features, denoted by s_t and discard the initial pressure features.

Moreover, from the maximum pressure curve p_{max}, we derive additional features by commiting a discrete fourier transformation (FFT) on every time stamp t of the p_{max} curve, using a constant window size $b = 128$. The obtained coefficients $c_t = (c_1^t, \ldots, c_b^t)$ of the fourier transform, together with the current value $p_{max}(t)$, the extracted sphincter features s_t, and the label information are then concatenated to a vector $x_t \in \mathbb{R}^n$, which leads to the following swallow data set.

$$\mathcal{D}^{train} := \{(x_t, y_t) := (p_{max}(t), c_t, s_t, y_t) \,|\, t \in T\} \tag{4}$$

4 Proposed Methods

4.1 Prediction based on Maximum Pressure Curve

The simplest prediction method is based only on the p_{max} curve. From the given resting pressure, we compute an average resting pressure p^{avg} over all resting pressure samples. Given these figures, we compute a labeled sequence as:

$$\hat{y}_t := \begin{cases} 1 & \text{if} \quad p_{max}(t) \geq p^{avg} \\ -1 & \text{else.} \end{cases} \tag{5}$$

Following equation (3), the restitution sample $t^\star$ is then estimated as the first sample $t > t^{max}$ where the p_{max} curve falls below the average resting pressure. This is a very simple method as it involves no learning and no preprocessing besides computing p_{max}, and furthermore does not take sequential information into account. Its shortcomings will be discussed in the experiment section.

4.2 Logistic Regression

We perform a logistic regression, where model parameters $\theta \in \mathbb{R}^n$ are learned from the labeled data, optimized for logistic loss and regularized by the common l^2-regularizer as to avoid overfitting:

$$\mathcal{L}_{Log}(\hat{y}(\theta), \mathcal{D}) = \sum_{x_i \in \mathcal{D}} \log\left(1 + e^{-y_i \langle \theta, x_i \rangle}\right) + \lambda \|\theta\|_2^2 \tag{6}$$

The model parameters θ are initialized randomly by a Gaussian $\mathcal{N}(0, \sigma^2)$ and iteratively optimized using gradient descent with a fixed step size η. Note that $\langle \cdot, \cdot \rangle$ denotes the scalar product in $\mathbb{R}^n$ and λ denotes a regularization parameter.

4.3 Laplacian Logistic Regression

We integrate the knowledge that a label change ($1 \rightarrow -1$) is expected only once after t^{max}. To force learned parameters to adopt this property, we penalize label changes throughout the sequence by introducing a Laplacian regularizer $\mathcal{S}(\theta)$ on neighboring samples,

$$\mathcal{S}(\theta) := \sum_{x_i \in \mathcal{D}} \sum_{x_j \in w(x_i,s)} \frac{1}{2} \Big(\sigma\Big(\langle \theta, x_i \rangle\Big) - \sigma\Big(\langle \theta, x_j \rangle\Big) \Big)^2 , \tag{7}$$

where $\sigma(\cdot)$ is a sigmoid function in order to make $S(\theta)$ differentiable, and $w(x_i, s) := \{x_{i-s}, \ldots, x_i, \ldots, x_{i+s}\}$ is the set of neighboring samples for a predefined window length s. This term will be added to the overall loss functional given in equation (6),

$$\mathcal{L}_{Lap}(\hat{y}(\theta), \mathcal{D}) := \mu \cdot \mathcal{L}_{Log}(\hat{y}(\theta), \mathcal{D}) + (1 - \mu) \cdot \mathcal{S}(\theta) \tag{8}$$

using a weighting coefficient $\mu \in [0, 1]$ to capture the tradeoff between learning an accurate solution and learning a smooth solution.

5 Experiments

We are using SVM-HMM [Altun, 2003], as a competitor method for predicting structured output by converting our data as follows: One entire swallow is treated as a sentence, while one time stamp is treated as a token. As there are only two possible states, we convert these two states into two tags. More details concerning the implementation of SVM-HMM can be found in [Joachims, 2009].

Regarding our initial questions on the performance of the proposed methods, we design two experiments as follows.

5.1 Experimental Setup

The dataset used in the experiments consists of 10 patients, who have each conducted 10 swallows. The data is split per swallow into a training and a test set according to the use case, and determine optimal hyperparameters on a validation set using grid search.

Accuracy scores are reported for the predicted sequence as well as absolute time differences between the predicted restitution sample and the true restitution sample. For the Logistic Regression, we evaluated accuracies and sample differences after every iteration, while for the SVM-HMM, we employed the model learned after convergence of the algorithm. Note that, for an accurate prediction of the restitution sample $t^\star$, the accuracy of the predicted binary sequence correlates only to a certain extent with finding the correct $t^\star$, but does not necessarily lead to a correct prediction of $t^\star$. As such, a model with a higher accuracy might predict an inaccurate $t^\star$.

5.2 Hyperparameter Optimization

As stated earlier, the hyperparameters have been optimized using grid search. The step size η was searched in $10^{-5} \cdot \{1, 0.7, 0.5, 0.1\}$, the regularization constant λ and the window size w have been searched in $\{0.001, 0.01, 0.1, 1\}$ and $\{10, 75, 150\}$, respectively. For the Laplacian Logistic Regression, μ and the window extent s were searched in $\{0.01, 0.5, 1\}$ and $\{3, 5, 11, 31\}$.

The hyperparameters concerning the SVM-HMM were searched on the following grid. C was searched in $\{10^{-4}, \ldots, 10^{3}\}$, epsilon was set to 0.5 as a suggestion of the authors, the number of transitions was between 1 and 3, the number of emission was either 0 or 1.

Patient	SVM-HMM	LogReg	LapLogReg	p_{max}	SVM-HMM	LogReg	LapLogReg
1	84.81 ± 6.3	82.75 ± 6.2	**85.49** ± 6.3	5.32 ± 3.65	9.72 ± 2.42	10.48 ± 2.83	**10.01** ± 2.45
2	81.45 ± 5.6	86.29 ± 9.0	**86.91** ± 9.2	22.84 ± 5.42	2.16 ± 1.03	1.41 ± 1.64	**0.58** ± 0.39
3	**83.20** ± 5.1	82.00 ± 4.4	80.96 ± 6.4	7.49 ± 3.42	**6.45** ± 2.74	6.66 ± 3.63	6.92 ± 3.44
4	85.86 ± 2.7	86.02 ± 3.1	**87.18** ± 4.5	5.08 ± 3.24	**3.20** ± 2.48	4.07 ± 3.78	4.12 ± 3.75
5	**88.52** ± 5.5	71.20 ± 4.1	87.20 ± 4.5	10.17 ± 4.74	2.69 ± 1.64	2.65 ± 1.34	**1.83** ± 1.27
6	**79.13** ± 5.1	68.29 ± 3.8	65.97 ± 3.2	7.19 ± 5.32	6.64 ± 1.93	3.26 ± 1.81	**2.50** ± 1.56
7	**86.51** ± 4.3	61.00 ± 1.9	61.64 ± 3.4	9.43 ± 6.05	3.90 ± 1.52	3.13 ± 1.30	**2.74** ± 1.12
8	**88.65** ± 9.4	66.85 ± 4.3	64.62 ± 3.8	3.47 ± 2.49	**4.18** ± 4.73	5.72 ± 4.92	6.46 ± 4.76
9	**78.38** ± 12.7	60.77 ± 6.2	62.24 ± 7.6	16.05 ± 5.54	8.48 ± 5.12	9.02 ± 4.58	**8.37** ± 4.82
10	**86.51** ± 4.0	63.34 ± 3.5	65.38 ± 4.6	18.12 ± 8.55	13.45 ± 9.10	**12.30** ± 10.69	14.16 ± 10.15

Table 1: Results for the Intra-Individual use case are shown. Average accuracies and 95%-confidence intervals are reported on the left. Average sample differences converted to seconds and their confidence intervals are reported on the right.

5.3 Use Case 1: Intra-Individual

We train the classifiers individually in a leave-one-out cross validation, where we omit one swallow as test swallow for which we want to predict the restitution sample. Of the remaining swallows, 2 swallows are randomly picked as validation data. Thus, we have 7 training swallows, 2 validation swallows and 1 test swallow.

Table (1) shows the results for all different methods. As can be seen clearly, SVM-HMM wins in accuracy, but the Laplacian Logistic Regression is best in predicting time differences. For all methods, we chose the model which gave the best accuracy on validation. Then, we apply the window extent that gives the best sample difference score on validation and apply the model with the chosen window extent. Note that the time differences are the target we are actually looking to optimize.

We can also see that the p_{max} method works well on Patient 1 and Patient 8. Nevertheless, the predicted $t^{\star}$ is inferior for very many other patients, such as 2,5,9 and 10.

Moreover, we observe that predicting restitution times seems to differ a lot regarding the individual patients as for instance for patient 2, the time differences are quite low, whereas especially for patient 10, the time differences are large. The confidence intervals reported are wide, since every patient conducted only 10 swallows. Nevertheless, we see that our method outperforms the SVM-HMM for the majority of patients and we also see that including a Laplacian regularizer aids in finding $t^\star$.

5.4 Use Case 2: Inter-Individual

We train the classifiers on 9 of the 10 patients (training patients) and predict the restitution times for the remaining test patient. We randomly leave 2 out of the remaining 9 swallows per training patient as validation data. Thus, we build a training set of 72 swallows, a validation set of 18 swallows and a test set consisting of one swallow of the test patient. For each patient, 10 different splits have been created.

Table (2) shows the results for the competing methods. Analogous to the first use case, we can observe that SVM-HMM outperforms our approaches with respect to accuracy, even though the margin is not that large anymore. In comparison to use case 1, predicting $t^\star$ for patient 1 seems to give better results, when the model did not learn on the same patient's swallows, which is rather surprising as for the majority of patients, the predicted $t^\star$ is worse. For this use case, adding a Laplacian regularizer seems to work best for some patients.

Patient	SVM-HMM	LogReg	LapLogReg	SVM-HMM	LogReg	LapLogReg
1	79.80 ± 8.2	83.76 ± 6.8	**83.79** ± 7.0	6.70 ± 6.70	**3.27** ± 2.32	4.24 ± 2.50
2	**87.45** ± 5.6	84.63 ± 8.2	85.10 ± 8.6	3.04 ± 1.03	1.02 ± 0.41	**0.97** ± 0.49
3	**78.48** ± 4.7	66.03 ± 9.8	65.64 ± 10.3	8.76 ± 3.17	**6.58** ± 3.12	7.19 ± 3.06
4	76.22 ± 7.3	80.02 ± 5.9	**81.29** ± 5.6	11.62 ± 2.41	5.37 ± 2.90	**4.56** ± 2.63
5	**90.26** ± 5.0	81.00 ± 8.5	80.67 ± 9.1	**2.36** ± 1.72	3.33 ± 1.79	3.29 ± 1.83
6	**88.08** ± 6.4	79.79 ± 8.1	79.99 ± 8.8	**1.87** ± 0.59	4.31 ± 3.47	4.17 ± 3.53
7	**71.29** ± 8.7	62.31 ± 8.4	68.70 ± 6.5	**4.62** ± 1.51	5.69 ± 1.53	6.11 ± 1.43
8	83.81 ± 13.4	87.94 ± 10.3	**88.47** ± 10.6	5.31 ± 4.34	3.81 ± 4.67	**3.00** ± 2.93
9	**84.20** ± 13.5	80.15 ± 8.5	80.31 ± 8.6	9.02 ± 5.54	6.17 ± 3.35	**6.13** ± 3.38
10	83.05 ± 6.3	84.10 ± 4.5	**84.78** ± 4.5	14.32 ± 8.61	10.47 ± 9.52	**10.12** ± 9.60

Table 2: Results for the Inter-Individual use case are shown. Average accuracies and 95%-confidence intervals are reported on the left. Average sample differences converted to seconds and confidence intervals are reported on the right.

6 Conclusions and Future Work

We introduced the problem of estimating restitution times and formulated it as a machine learning problem suitable for semi automation, in the sense, that still an annotated corpora of swallows is required for learning and parameters, such as the window size have to be tuned manually. Furthermore, we depicted that predicting restitution times is possible and delivers reasonable results. Among the tested methods, we empirically showed that the Laplacian Logistic Regression is the most promising method for predicting restitution times. However, as the prediction varies strongly inbetween swallows and patients, we aim for a more stable and more accurate estimation throughout future work.

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