A Brief Introduction to the Temporal Group LASSO and its Potential Applications in Healthcare

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Abstract

The Temporal Group LASSO is an example of a multi-task, regularized regression approach for the prediction of response variables that vary over time. The aim of this work is to introduce the reader to the concepts behind the Temporal Group LASSO and its related methods, as well as to the type of potential applications in a healthcare setting that the method has. We argue that the method is attractive because of its ability to reduce overfitting, select predictors, learn smooth effect patterns over time, and finally, its simplicity.

1 Introduction

The prediction of longitudinal, patient level outcomes has a wide range of potential applications in healthcare, including early safety signal detection [14], patient stratification [7], assessment of difference of treatment effects [21] over time, prediction of symptom exacerbations [8] over time, prediction of patient cost blooming [15], among many others.

There are many approaches to the modelling and prediction of longitudinal data, including mixed-effects regression models [17], covariance pattern models [3], structural equations [4] models, generalized estimating equations [1] models, as well as pharmacokinetics and pharmacodynamics based models [12], among others.

The Temporal Group LASSO was introduced by Zhou et al. [23] as a method to predict longitudinal outcomes, select most relevant predictors (and simultaneously eliminate less relevant ones), as well as obtaining effect estimates for the selected variables that vary smoothly over time.

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This paper is organized as follows: in Section 2 we introduce the reader to some of the concepts and methods that preceded the development of the Temporal Group LASSO; in Section 3 we present the Temporal Group LASSO and its differences and similarities with traditional GLMs; in Section 4 we present a brief example, applying the Temporal Group LASSO on a simulated clinical dataset; finally, we present our final thoughts and conclusions in Section 5.

2 Preliminary Concepts

Generalized linear models (GLMs) [9] are widely used in healthcare for modelling outcomes and for estimating the effects that different explanatory variables have on them. GLMs generalize ordinary linear regression to non-linear relationships by allowing the use of a link function that relates the expected value of the response to the linear predictor. When the link function is the identity, and the random component is the normal distribution, the GLM reduces to ordinary linear regression. In general, the problem of fitting a GLM can be written as

$$w^* = \arg \min_w L(w)$$

where the left side of the equation is the vector of coefficients that will be assigned to the GLM. This set of coefficients may have different interpretations depending on the GLM model class, such as odds ratios in the case of logistic regression, hazard ratios in the case of a Cox proportional hazards model, etc. The right side of the equation represents the obtention of a set of coefficients that minimize the error of the GLM. The loss function, \(L(w)\) may be the least squares in the case of linear regression, the negative log-likelihood in the case of logistic regression, etc. It is outside of the scope of this work to explain GLMs in detail, but the reader can refer to the large amount of existing literature on GLMs [9, 5, 10].

Although GLMs are effective at modelling outcomes and effects, they have some shortcomings in particular situations. For example, GLMs are prone to overfitting [2], in particular when the number of predictors considered is very large [2]. A common approach in modern regression to reduce overfitting (at the expense of more ‘shrunked’ coefficients) is the use of ridge regression [6]. In ridge regression, the loss function in 1 is modified through the addition of a penalty term, and the problem is now given by

$$w^* = \arg \min_w L(w) + \lambda \|w\|_2^2$$

where \(\|w\|_2^2\), called the squared \(L_2\) norm of \(w\), is equivalent to the sum of the squared coefficients in \(w\). Essentially, this means that the solution should minimize the error but also favor solutions with smaller coefficients (closer to zero), and the degree of tradeoff between smaller error and smaller coefficients is determined by the tuning parameter \(\lambda\), which is often chosen through cross validation.
Another shortcoming of GLMs is that they don’t allow the selection of relevant predictors, so predictors need to be selected in some other way, for example using time and computationally consuming processes, such as subset selection or step-wise selection. Although ridge regression reduces overfitting and shrinks the coefficients by taking them closer to zero, it doesn’t eliminate coefficients, and instead produces a solution with very small coefficients. A common approach from statistical learning to reduce overfitting as well as to select predictors is the use of the LASSO. Similar to the ridge regression case, in the LASSO, the loss function is modified by the addition of a penalty term, and the problem given by

\[
\mathbf{w}^* = \arg\min_{\mathbf{w}} L(\mathbf{w}) + \lambda \| \mathbf{w} \|_1,
\]

where \( \| \mathbf{w} \|_1 \) is known as the \( L_1 \) norm of \( \mathbf{w} \), and is equivalent to the sum of absolute values of the coefficients in \( \mathbf{w} \). Like in ridge regression, this formulation favors solutions with 'shrinked' coefficients, but unlike in ridge regression, it favors solutions with zero valued coefficients as well, also referred to as 'sparse' solutions. This means that the LASSO can be used to select relevant predictors, a task known as feature selection in the machine learning literature.

Although both ridge regression and the LASSO enhance the power of GLMs, each one of them has particular weaknesses, and while ridge regression doesn’t yield sparse solutions, the LASSO lacks the ability to select multiple variables from a group of correlated variables, often selecting only one of them instead. An approach often used to combine the strengths of both ridge regression and the LASSO is the Elastic Net. In Elastic Nets, the penalized regression problem is given by

\[
\mathbf{w}^* = \arg\min_{\mathbf{w}} L(\mathbf{w}) + \lambda_1 \| \mathbf{w} \|_1 + \lambda_2 \| \mathbf{w} \|_2^2,
\]

with both the \( L_1 \) and squared \( L_2 \) penalties being applied jointly. Such a model is able to achieve both the sparse solutions needed for selecting predictors, as well as preventing the selection of only one variable from groups of highly correlated variables.

Finally, one limitation of the Elastic Net is that it is unable to select (and eliminate) groups of predictors. It would be useful for an algorithm to perform a group-wise selection, for example when having diverse sources of data, such as laboratory data, vital signs, gene expression data, etc. One way to perform group-wise selection of predictors is the Group LASSO. In the group LASSO, the penalized regression problem is given by

\[
\mathbf{w}^* = \arg\min_{\mathbf{w}} L(\mathbf{w}) + \lambda \sum_{g=1}^{G} \| \mathbf{w}^{(g)} \|_2,
\]

where \( G \) is the number of groups, and \( \mathbf{w}^{(g)} \) is a vector containing the subset of elements in \( \mathbf{w} \) that belong to the \( g \)th group. Notice that the \( L_2 \) norm is not squared, and in this case is \( \| \mathbf{w}^{(g)} \|_2 \) is equivalent to the square root of the sum.
of squared elements in \( w^{(g)} \). Notice also that in the particular case where there is one group \( g \) for each element in \( w \) and having only that one element, this reduces to the LASSO.

3 The Temporal Group LASSO

The core of the Temporal Group LASSO \cite{23} is a GLM with a multivariate response. In this case, the loss function can be written as \( L(W) \), where \( W \) is a matrix of coefficients, rather than a vector. Each column of \( W \) corresponds to a specific time point in the data. For example, in the case of such a multivariate GLM with Gaussian error, the loss function would be given by

\[
L(W) = \| Y - XW \|_F^2, \tag{6}
\]

where \( Y \) is a matrix of response values with one row per patient and one column per time point, \( X \) is a matrix of predictors with one row per patient and one column per predictor variable, note that we have omitted the intercepts for simplicity. The notation \( \| \cdot \|_F^2 \) simply stands for the sum of the squares of the elements of the matrix inside the norm, and it’s referred to as the squared Frobenius norm. This formulation of the loss is equivalent to the least squares loss that is normally used in ordinary linear regression. Similar multivariate losses can be written for the other GLM classes.

This formulation has weaknesses similar to those of GLMs with a univariate response, such as susceptibility to overfitting, inability to perform feature selection, etc. In addition, there is no connection between the coefficients learned in different columns. Intuitively, a model where the coefficients for a given variable (the rows of \( W \) vary smoothly over time would be desirable. Therefore, a model that allows the prevention of overfitting, the row-wise selection of predictors, as well as smooth variation over time is desired. The Temporal Group LASSO attempts to approach this using the following a formulation given by

\[
W^* = \arg \min_W L(W) + \lambda_1 \| W \|_F^2 + \lambda_2 \| RW^T \|_F^2 + \lambda_3 \| W \|_{2,1}. \tag{7}
\]

This formulation has three penalties. The first one, \( \| W \|_F^2 \) is equivalent to the sum of the squared coefficients in \( W \), which means that this penalty induces shrinkage of the coefficients in a similar way to ridge regression.

In the second penalty term, \( R \) is a matrix \( T - 1 \times T \) matrix where \( T \) is the number of time points,

\[
R_{i,j} = \begin{cases} 
  i = j, 1 \\
  i + 1 = j, -1 \\
  otherwise, 0 
\end{cases}, \tag{8}
\]

and this means that the formulation penalizes the squared differences of the coefficients associated to adjacent time points for each predictor. This can also be interpreted as a Laplacian term \cite{22}, and essentially means that the Temporal
Group LASSO favors solutions with coefficients that vary smoothly over time. In addition, it’s possible to weight the differences using numbers other than one in order to penalize differences at different time points more than others. This may be desirable, for example, when measurements are taken at irregular intervals, or if a drastic change is actually expected at a particular timepoint.

The third penalty term, $\|W\|_{2,1}$, is called the $L_{2,1}$ norm of $W$ and is equivalent to the sum of the $L_2$ norms of each of the rows of $W$. This is equivalent to a Group LASSO penalty where the groups are the rows of $W$, and it means that the formulation will favor solutions with row-wise sparsity. Since the rows of $W$ are coefficients assigned to the same predictor but at different time points, this means that this penalty will favor the selection (and elimination) of the same predictors across multiple time points. The selection of predictors across multiple tasks is known in the machine learning literature as joint feature selection.

As a result of these three penalty terms, the Temporal Group LASSO is able to reduce overfitting, learn coefficients that vary smoothly over time, and perform joint feature selection across time points. Finally, the model is simple to implement, with most of the penalties being smooth and differentiable, and the $L_{2,1}$ penalty being row-wise separable and for which the same methods used for other LASSO type methods, such as proximal gradient methods [13], can be used.

Although Zhou et al. introduced a stability sampling based method for feature selection, here we explore a cross validation based method, more similar to approaches used with other methods, such as the LASSO. Zhou later introduced other related models, such as the Fused Sparse Group LASSO [22]. However, these models use somewhat more complex penalty schemes, and are outside of the scope of this paper.

4 Brief Example on a Simulated Clinical Dataset

In order to show an example of application of the Temporal Group LASSO, a simulated dataset has been generated based on a model that mimics the effect of 3 injections of warfarin over the course of 50 hours [18]. Using this model, data for 500 patients has been simulated, of which 350 are used as a training set, and 150 are used as a test set. A set of 300 randomly generated features following a gaussian distribution was generated for each patient, and the parameters of the simulation have been generated as linear functions of a subset of these features. In total, 170 features are involved in at least one of the simulation parameters. Thus, the relationship between the features and the effect itself is generally not purely linear. Random noise has been added in order to account for random variation not related to any of the features in a dataset. In a real dataset, these features may be variables such as baseline gene expression [11], medical imaging features [23], laboratory measurements, etc.

After selection of the optimal regularization parameters through cross-validation, the final model selects 131 (77%) of the 171 features that truly have an influence in the effect. The remaining features are not truly involved in the mechanism.
Table 1: Summary characteristics and error metrics of the effect on the test set.

| Hour | Mean (± Std. Dev.) | TGL RMSE | TGL $R^2$ | RR $R^2$ | MLR $R^2$ |
|------|--------------------|----------|-----------|----------|-----------|
| 5    | 0.500 (± 0.058)    | 0.025    | 0.810     | 0.715    | 0.382     |
| 10   | 0.278 (± 0.059)    | 0.028    | 0.773     | 0.691    | 0.405     |
| 15   | 0.241 (± 0.059)    | 0.030    | 0.749     | 0.666    | 0.446     |
| 20   | 0.275 (± 0.069)    | 0.034    | 0.753     | 0.647    | 0.413     |
| 25   | 0.287 (± 0.074)    | 0.036    | 0.761     | 0.649    | 0.408     |
| 30   | 0.165 (± 0.053)    | 0.027    | 0.733     | 0.639    | 0.395     |
| 35   | 0.134 (± 0.043)    | 0.022    | 0.723     | 0.633    | 0.391     |
| 40   | 0.155 (± 0.044)    | 0.023    | 0.739     | 0.635    | 0.387     |
| 45   | 0.192 (± 0.052)    | 0.025    | 0.756     | 0.638    | 0.362     |
| 50   | 0.178 (± 0.050)    | 0.024    | 0.758     | 0.647    | 0.384     |

governing the effect. However, the predictions of the Temporal Group Lasso (TGL) model are highly accurate, as shown in Table 1, and the model is able to explain more than 72% of the variance at all time points in this dataset despite the presence of noise and the high amount of uninformative variables. Further, the model clearly outperforms Ridge Regression (RR) and Multiple Linear Regression (MLR).

Figure 1 shows the trends and spread of both the expected and predicted effect in the test set, which are highly similar. A number of outliers can be observed for the expected effect, though, which are not completely captured by the model. This may be due to the non-linear nature of the relationship between the features and the effect. An alternative may be to model the logarithm of the effect instead, however, we don’t explore this alternative in this example.

Figure 1: Box plot of the effect at each time point for the expected (E), and predicted (P) outcomes in the test set.
5 Conclusion

We have presented here an introduction to the concepts behind the Temporal Group Lasso, a multi-task learning algorithm that can be used to predict outcomes as well as select important predictors while reducing over-fitting and achieving a smooth variation of the model coefficients over time points. We have also presented a brief example based on a simulation of a clinical treatment effect over the course of 50 hours in 500 patients. The model outperformed other linear regression methods, such as ridge regression and traditional multi-linear regression.

The ability to select the most relevant features jointly over multiple time-points, as well as to obtain coefficients that vary smoothly over time seems to result in a clear gain in performance. The Temporal Group LASSO is a simple yet powerful extension of the traditional regularized generalized linear model concept to longitudinal data, and we believe that this category of models deserves more exploration and evaluation in the future.

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