

Design, implementation and evaluation of data integration methods for biomedical cancer data

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Voorafgaande schriftelijke toestemming van de promotor is eveneens vereist voor het aanwenden van de in deze masterproef beschreven (originele) methoden, producten, schakelingen en programma's voor industrieel of commercieel nut en voor de inzending van deze publicatie ter deelname aan wetenschappelijke prijzen of wedstrijden.

Preface

I would like to thank everybody who kept me busy the last year, especially my promotor and my assistants. I would also like to thank the jury for reading the text. My sincere gratitude also goes to my wife and the rest of my family.

Michiel Ruelens

Contents

Preface	i
Abstract	iv
Samenvatting	v
List of Figures and Tables	vi
List of Abbreviations and Symbols	vii
1 Introduction	1
1.1 The need for data integration methods	1
1.2 Goals	1
1.3 Modus operandi	1
2 Generalized Linear Models	3
2.1 Introduction	3
2.2 Classical linear models	3
2.3 Training a model	4
2.4 Overfitting	8
2.5 Regularization	11
2.6 Validation	13
2.7 Conclusion	14
3 Integration Strategies	17
3.1 Introduction	17
3.2 The setup	17
3.3 Early integration	18
3.4 Late integration	18
3.5 Intermediate integration	19
3.6 Conclusion	20
4 Evaluation of integration strategies	23
4.1 Introduction	23
4.2 Case details	23
4.3 Evaluating a logistic regression model	24
4.4 Predicting stage outcome	26
4.5 Evaluating a cox proportional hazards model	26
4.6 Predicting survival curves	26
4.7 Conclusion	26

5	Tool for automated evaluation	29
5.1	Introduction	29
5.2	Technologies	29
5.3	Demonstration	30
5.4	Conclusion	32
6	Conclusion	33
A	The First Appendix	37
A.1	More Lorem	37
A.2	Lorem 51	38
B	The Last Appendix	39
B.1	Lorem 20-24	39
B.2	Lorem 25-27	40
	Bibliography	41

Abstract

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Samenvatting

In dit **abstract** environment wordt een al dan niet uitgebreide Nederlandse samenvatting van het werk gegeven. Wanneer de tekst voor een Nederlandstalige master in het Engels wordt geschreven, wordt hier normaal een uitgebreide samenvatting verwacht, bijvoorbeeld een tiental bladzijden.

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List of Figures and Tables

List of Figures

3.1	Scheme for early integration	19
3.2	Scheme for late integration	20
3.3	Scheme for intermediate integration	21
4.1	Example ROC curve	27
5.1	The input tab of the tool	30
5.2	An example model description	31
5.3	An example interactive ROC curve	32

List of Tables

List of Abbreviations and Symbols

Abbreviations

LoG	Laplacian-of-Gaussian
MSE	Mean Square error
PSNR	Peak Signal-to-Noise ratio

Symbols

42	“The Answer to the Ultimate Question of Life, the Universe, and Everything” according to [?]
c	Speed of light
E	Energy
m	Mass
π	The number pi

Chapter 1

Introduction

The first contains a general introduction to the work. The goals are defined and the modus operandi is explained.

1.1 The need for data integration methods

1.2 Goals

1.3 Modus operandi

Chapter 2

Generalized Linear Models

2.1 Introduction

In this chapter I will explain the current standard in machine learning when it comes to generalized linear models. This term indicates a generalization of simple linear regression that allows for a wide range of output variables.

First I will go over the basics of linear models, gradually building up to the definition of generalized linear models. Next, I will describe what actual data looks like and how this data is transformed into a useful model.

After that I will tackle the more recent innovation of regularization that will greatly improve our previous models by exploiting the bias-variance trade-off to reduce overfitting. Lastly I will outline the validation method that will be used to test the performance of the models.

2.2 Classical linear models

When we think of classical linear models, we can imagine a set of numeric explanatory (or input) variables and a numerical dependent (or output) variable. By making a linear combination of the explanatory variables we attempt to estimate a value for the dependent variable. Depending on the type of dependent variable the linear method gets a different name. In the following sections I will outline several of them.

2.2.1 Linear Regression

The simplest version of a linear model is called linear regression. In this case the input variables are combined using a linear combination, and the result of this calculation is immediately used as the final estimate.

//TODO MATH

For the other linear methods we will define a function each time that is applied to the result of the linear combination. We could do the same for linear regression and say that the applied function is the identity function. We could schematize this computation as follows:

//TODO SCHEMA

2.2.2 Linear Classification

The next method is called linear classification. The difference with linear regression is that we have a different type of output variable. In a classification task we want to predict a class from a list of potential classes. For instance, we could try to predict whether tomorrow will be a sunny day or not. Notice that there are only 2 possible outcomes: 'sunny' or 'not sunny' and we could represent these outcomes as 0 and 1 in our model. This form would be called binary classification because we have 2 possible classes. It is very easy to extend this method to multi-class classification. The computation in this method starts out exactly the same, combining the input variables using a linear combination. Next, we have to define a threshold to indicate which examples belong to one class or another. In the case of binary classification we would define 1 threshold, and if the result of the linear combination is higher than the threshold we would predict one class. If it is lower, we would predict the other class. The function used here would be called a sign function, which maps real values onto one of 2 possible outcomes. We could represent this computation with the following formula and schema:

//TODO MATH AND SCHEMA

2.2.3 Logistic Regression

The third method I want to present is called logistic regression. In this case, the output variable we want to predict comes from a binomial distribution. This means that they are the result of a probabilistic event. An example would be tossing a coin and checking whether the result is heads or tails. While the outcome is binary (heads or tails) we know that there is an underlying probability for the coin to be heads or tails, and we would like to know this probability.

The idea is still the same. We will make a linear combination of the input variables. However this time we will use a logistic function to produce our estimate. The logistic function is a function that maps real numbers onto the range $[0, 1]$. This result can then be interpreted as an estimate for the probability. We can schematize logistic regression as follows:

//TODO MATH AND SCHEMA

The logistic regression method is the one that will be most widely used throughout this thesis.

2.3 Training a model

In order to understand the integration strategies that will be explained later on, it is useful to know how exactly the models come to be. This section will explain what

the input data for our linear models actually looks like, and how we get from this data to a model that we can use for future predictions.

2.3.1 The data

The data we use consists of two parts: the input data, which can be seen as a matrix where the columns are the explanatory variables and each row is an example (or patient). And secondly the output data, which can be seen as a vector where each value indicates the value of the dependent variable for a single example.

It is easy to see that the length of the output vector has to be equal to the amount of rows in the input matrix, indeed there should be one output value for each example. This amount is often called the size of the dataset and we would like it to be as big as possible. Especially when we are dealing with a large number of explanatory variables, it is essential to have a reasonably amount of examples aswell. This will be discussed in more detail later on //TODO REFERENCE.

2.3.2 Gradient descent

In this section I will explain how we get from the input data to the model. The idea here is that we have some for of error measure. The error measure is a sort of rating for our current model as it indicates how big the mistakes are that our current model is making. There are many different error measures we could use. The one that is used in logistic regression is explained in more detail in the following section.

Once we have a way of computing the error that our current model makes, we can try to minimize this error to obtain our 'best' possible model.

Error measure

In logistic regression the error measure we use is called the cross-entropy error. The formula for this error is the following:

$$E_{in}(w) = \frac{1}{N} \sum_{n=1}^N \ln(1 + e^{-y_n w^T x_n})$$

where

- x_n is the vector of values for the explanatory variables for example n .
- y_n is the value of the dependent variable for example n .
- w^T is the transpose of the weights vector. These are the parameters of our model that we can adjust.
- N is the size of our dataset.
- $E_{in}(w)$ is the in-sample error. This is the cross-entropy error that we make on the examples in our dataset. It is a function of the weights w .

The origin of this function is explained in appendix //TODO ADD APPENDIX AND REFERENCE. We can however easily notice that this is a reasonable error measure. It is an averaged sum over all examples, where for each example we compute an individual error made on that example.

Notice that $w^T x_n$ is the linear combination of the input variables that our current model suggests. This is the prediction that our current model would make for example n and is a real valued number. On the other hand y_n is the actual correct prediction for example n and has a value of 0 or 1.

If the signs of $w^T x_n$ and y_n agree then our current model actually makes a correct prediction for this example. We can see that in this case the exponential becomes close to 0, making our error for example n very small, as we would expect.

If however their signs are opposite, the exponential becomes larger as our incorrect prediction becomes larger. This in turn will increase the error, again as we would expect.

Thus we can see that if we were to minimize this error, we are moving towards a model that tries to make correct predictions.

The gradient descent method

When trying to minimize a function, a general approach would be to try and compute the derivative of the function, and find the spot where this derivative equals zero. In the case of linear regression it is actually possible to compute this minimum in one step. More details about this can be found in appendix //TODO ADD AND REFERENCE APPENDIX.

In the case of logistic regression however it is not possible to find an analytic solution to this problem. The best we can do is put ourselves somewhere on the error curve and try to move towards the minimum in small steps. This is called an iterative approach.

Remember that our error function looks like this:

$$E_{in}(w) = \frac{1}{N} \sum_{n=1}^N \ln(1 + e^{-y_n w^T x_n})$$

We can now compute its derivative with respect to w :

$$\nabla E_{in}(w) = -\frac{1}{N} \sum_{n=1}^N \frac{y_n x_n}{1 + e^{y_n w^T x_n}}$$

The problem is to find the set of weights w for which the derivative becomes 0 (or that minimizes the error). We can start out with an initial set of weights $w(0)$ and then iteratively update these weights so we move towards the minimum. Let's call the direction in which we update our weights v . The update we make to w then becomes:

$$w(t+1) = w(t) + \eta v$$

where

- $w(t+1)$ are the updated weights for this iteration.
- $w(t)$ are the current weights before we make a move.
- v is a unit vector pointing in the direction we want to move.
- η is a number that indicates how big the move is that we make, also called the step size.

Remember that the gradient of a function at a certain point always points towards the steepest slope upwards. In our case we would like to find the minimum, so it is a good idea to move our weights in the direction of steepest descent. The direction v that we are moving towards then becomes the normalized opposite direction of the gradient:

$$v = -\frac{\nabla E_{in}(w(t))}{\|\nabla E_{in}(w(t))\|}$$

We can now summarize the gradient descent method as follows:

```
Data: x, y
initialize weights  $w(0)$ 
while Stopcondition is not met do
    | Compute gradient  $\nabla E_{in}(w(t))$ 
    | Compute update direction  $v$ 
    | Update weights  $w(t+1) = w(t) + \eta v$ 
end
```

Algorithm 1: Gradient Descent algorithm

There are two more non-trivial issues in this computation: the initialization of the weights and the stopcondition.

Weight initialization is sometimes a very tricky thing to do, in the case of logistic regression however it is acceptable to set $w(0)$ equal to the zero-vector as this corresponds to no correlation between any of the input variables and the output variable, and the result of the sigmoid function would be 0.5 or 50% meaning the model has no preference for either outcome.

The stopcondition however is a bigger issue and usually the way to go here is to make a combination of several stop criteria. One criteria would be to simply limit the amount of iterations to a fixed number. This could avoid endlessly overfitting. Another criteria is to set up a target error we want to achieve (a small number), and stop when we have reached this target. This however raises the question of picking the target error, and this is mostly an application dependent choice.

In the version of logistic regression explained here, it can however be shown that the error surface we are dealing with is a very nice convex surface. This makes it very easy to find its minimum and we don't need very complex initialization and stopping criteria to get good results. In other machine learning methods however these surfaces aren't always as nice, and the issue of local minima versus global minima becomes a big deal. There has been much research on this topic however and many sophisticated methods have been developed to deal with this issue.

2.4 Overfitting

Now that we have established a method of computing our models, it is time to deal with an issue known as overfitting. Overfitting points to the fact that there are several mechanisms at work when we are building a model that prevent us from reaching the perfect model (a model that predicts correctly at all times). These mechanisms essentially originate from noise and uncertainty in many aspects of the learning process (the input data, choice of model, choice of algorithm, ...). We can however try to decompose this noise into several components and then attempt to influence them by making changes to our model computation. I will present two ways in which overfitting can be tackled: regularization and validation.

2.4.1 The problem of overfitting

Let's introduce some notation. From now on I will refer to the notion of 'in-sample error' or in symbolic notation E_{in} as the error that a model makes on the examples in our training set. The training set consists of the examples that were used to train (compute) the model in the first place.

Similarly I will define 'out-of-sample error' or E_{out} as the error we make on examples that were not used for training the model. Notice that E_{in} is something we could compute because we have access to the training data, but E_{out} is a quantity we cannot exactly compute but we could try to estimate it if we have some examples left that we did not use for training. Notice also that it is E_{in} that we minimize during our model computation, but it is E_{out} that we actually want to minimize! Indeed, E_{out} corresponds to the error that we get when we are going to deploy our model in practice and use it on examples we have never seen before. We can do this because we believe that E_{in} tracks E_{out} to a certain degree. And thus if we manage to minimize E_{in} we also minimize E_{out} to some extent.

We can only speak of overfitting when we are comparing two models. We say that one model, call it model A, is overfitting with respect to another model, model B, when model A managed to get a lower E_{in} than model B, but model B has a lower E_{out} .

Another way of looking at it is during the learning process. Let's have model A be the model that we computed when we started from model B and performed one more iteration of the training algorithm. Thus model A is 'more trained' than model B. Now let's suppose model A is overfitting:

$$E_{in}^{modelA} < E_{in}^{modelB} \quad (2.1)$$

$$E_{out}^{modelA} > E_{out}^{modelB} \quad (2.2)$$

The additional iteration has decreased the in-sample error, and thus we are able to fit our training data better, but the out-of-sample error has increased, meaning that our model doesn't generalize as well to other examples outside the training set. This means that we are actually fitting our training data too well, while we are not really getting a better grasp of the underlying pattern that we wish to learn. We are

overfitting the training data.

2.4.2 The bias and variance trade-off

There are several ways of looking at overfitting and pointing out its origins. I will introduce the notions of bias and variance and how they can describe the noise in our system.

Average hypothesis

First, let me explain the playing field. We are in a situation of learning, where we are given a set of examples that are produced by some target function f . It is this target function f that we wish to learn (or in other words model). In order to do this we have to decide on the type of functions that we will use to model. In machine learning this is called the hypothesis set. It is the set of all functions that we consider possible candidates to fit our target f . And we will use the examples x in our dataset D to decide which hypothesis we will pick.

Next, let's introduce the notion of average hypothesis \bar{h} . Imagine we have a very large number of datasets. For each of these datasets we apply the learning process and we will pick a certain hypothesis h from our hypothesis set. The average hypothesis is then equal to the average of all the hypothesis' just learned. Or in a formula:

$$\bar{h} = \mathbf{E}_D[h^{(D)}]$$

where

- \bar{h} is the average hypothesis.
- \mathbf{E}_D is the expected value over an infinite number of datasets
- $h^{(D)}$ is the hypothesis that was learned for a specific dataset D

We can also look at this average hypothesis as sort of the best we can do with the given hypothesis set. Indeed, when we imagine having an infinite number of datasets we would end up cancelling out much of the variation in the learned hypothesis' and end up with a very good one.

Bias

We can now define the bias as the distance between the average hypothesis \bar{h} and our target function f .

$$bias = (\bar{h} - f)^2$$

We can see the bias as an error we make due to our own choices. Namely our choice of hypothesis set. If we choose a very simple hypothesis set, we cannot expect to

be able to find a fit for a very complex function. The target function simply isn't contained in our hypothesis set. There exists no function in our hypothesis set that exactly fits our target.

Therefore we introduced the notion of average hypothesis. We can view this as the best we can do given our current hypothesis set, and the distance to the target is what we call the bias.

Variance

This however is not the full story. In a real learning situation we generally never find this average hypothesis, because remember it required a large amount (or even infinite amount) of datasets. We never have this luxury! In reality we always have only one dataset and that is all we can use to navigate through the hypothesis set. This is where the notion of variance comes in. We can define variance as the error we get from not having the best hypothesis possible in our hypothesis set. Or in other words as the distance between the hypothesis set that we actually found by learning from our dataset and the average hypothesis.

$$variance = (h^{(D)} - \bar{h})^2$$

Error due to variance mainly comes from two sources: the first is our finite dataset, the second is the complexity of the hypothesis set.

In reality we are given a dataset of N examples and that's all you've got. Most of the time this dataset is not sufficient to find the best hypothesis and thus there will be a variance error made.

Secondly, as we increase the complexity of the hypothesis set, it becomes increasingly difficult to navigate through this set. There are simply many more hypothesis to choose from. Again this makes it harder for our learning process to find the optimal hypothesis and as such will introduce a variance error.

The tradeoff

Having both bias and variance defined we can see that they are not disconnected, there is a tradeoff. If we look purely at bias we could think that simply choosing a super complex hypothesis set is always optimal. Indeed our bias will be zero since the target function will always be inside our hypothesis set.

However, an increasingly complex hypothesis set makes it harder to actually find the optimal hypothesis. We know that the optimal hypothesis is there, but we just cannot find it. The take-away message here is that we have to choose a hypothesis set complexity based on the resources that we have. In this case the resource is our dataset. The larger the dataset that we can learn from, the more complex hypothesis sets we can afford, and the better our results will be. But there is no gain in choosing overly complex hypothesis sets when you don't have the resources to afford them. This will simply cause you to find hypothesis' that fit your training data very well (imagine fitting 3 datapoints with a 7th order polynomial, you would get an exact fit) but this model will not generalize to anything in the real world, it is a complete overfit.

2.5 Regularization

Now that we have the concepts of bias and variance, let's use this information to try and improve our models. The first method is called regularization. In very simple terms this method will add a very small amount of bias in order to greatly decrease the amount of variance, reducing the overall error we make.

2.5.1 Adding bias

Remember that bias is defined as the distance between the average (or best) hypothesis \bar{h} and our target function f . Adding bias effectively means we are going to make another choice, which will impact the average hypothesis. The choice we are about to introduce is based on the following observation: when confronted with a set of similarly performing models, the simplest model is usually the best. Or in other words we should try to prefer simple models over very complex ones.

This observation does not have a mathematical proof, it is rather an observation from experience and reason. One good argument is the fact that noise is usually of high frequency. Meaning that distortions of our dataset (for instance measurement errors) will often be very scattered and random, while the underlying pattern that really makes up the data will be rather smooth. A similar argument can be made for the error due to bias, when we choose a hypothesis set that does not contain the target function, the error due to bias will be mostly random and of high frequency. Therefore if we want to reduce the impact of this noise in our final model, we should prefer models that are not able to fit these high frequencies exactly. Lastly we can remark that if we look at our current understanding of nature (let's say at a larger scale), systems almost always have smooth transitions. The most important laws of nature that we find are all written down in small, simple formulas. Nature doesn't work with instantaneous changes (high frequency), but rather it has smooth functions that govern the basic principle, and then it adds random noise and fluctuations on top of it. This principle is what we try to extrapolate here to machine learning.

Thus, the choice we will make is that we will prefer simple models over complex ones by adding a constraint to the weights.

2.5.2 Regularization types

There are many kinds of constraints that we could add to the weights and, depending on the constraint we choose, the regularization gets a different name and it will have a different effect. One of the most famous regularizers is called ridge or weight-decay. The constraint for this regularizer is the following:

$$\sum_{i=1}^N w_i^2 \leq C$$

where

- w_i is the weight (model parameter) for the i 'th explanatory variable.

- C is the constraint value

Using this regularizer will result in a preference for models with smaller weights. This keeps certain weights from getting out of control. This form of regularization is also often called the L_2 penalty.

Another popular regularizer is called the lasso penalty (or L_1 penalty). The constraint in this case is:

$$\sum_{i=1}^N |w_i| \leq C$$

In addition to keeping the weights small, this form of regularization also performs parameter selection. This means that instead of just keeping the weights small it will also prefer to make weights actually zero. This will cause the resulting model to have fewer parameters, but the parameters that do survive the penalty are sure to be very important. This regularizer is often used when there is a huge number of explanatory variables, and we wish to find only those that are really descriptive. Later in the thesis I will use datasets that contain gene expression information about cancer patients, these datasets often have thousands of explanatory variables and will provide a good example for using the lasso regularization.

The last form of regularizer I wish to demonstrate is called the elastic net penalty. This regularizer is simply a linear combination of the ridge and lasso penalties and provides a way of balancing the two. It has the following constraint:

$$\alpha \sum_{i=1}^N w_i^2 + (1 - \alpha) \sum_{i=1}^N |w_i| \leq C$$

2.5.3 Lambda

Using a regularizer introduces a constraint, this means that we now have to deal with a constrained optimization problem which is much harder to solve than an unconstrained problem. Fortunately, through some clever mathematics it is possible to convert the constrained minimization problem to an unconstrained one by incorporating the regularization constraint in the formula for the error itself. //TODO ADD APPENDIX WITH FULL DERIVATION OR NOT ... The formula for the error with regularization then becomes:

$$E_{in}(w) = \frac{1}{N} \sum_{n=1}^N e(x_n, y_n, w) + \lambda R(w)$$

where

- $E_{in}(w)$ is the in-sample error.
- $e(x_n, y_n, w)$ is the individual error made on example n . In the case of logistic regression this would be a cross-entropy error term $\ln(1 + e^{-y_n w^T x_n})$.
- λ is the regularization parameter that will be explained below.

- $R(w)$ is the regularization term dependent on the type of regularization used. For instance: $\sum_{i=1}^N |w_i|$ for lasso, $\sum_{i=1}^N w_i^2$ for ridge, ...
- x_n is the n 'th sample in the dataset.
- y_n is the outcome for the n 'th sample in the dataset.
- w is the vector of weights, our model parameters that we are trying to find.

Notice that we now again have an error measure that we want to minimize, and it is an unconstrained optimization problem. The important new part is λ . This is the amount of regularization we want to use. It is a new form for the constraint constant C that was earlier introduced in the types of regularization. The higher λ the tighter the constraint (lower C) and vice versa. The value of λ will prove to be critical in getting good models. The way to calculate it is through validation.

2.6 Validation

In this section I will explain the method of validation which is used to estimate the out-of-sample error. I will first explain the issue of sample size and then present a method to work around this limitation.

2.6.1 The sample size dilemma

Remember that when we are training a model we use the in-sample error to navigate the hypothesis space. We do this because we believe that the in-sample error is a valid surrogate for the out-of-sample error (which is the error we actually want to minimize). A valid question to ask is: why don't we just estimate the out-of-sample error and minimize it directly? Consider the following situation:

We are given a dataset of N samples. I will use K samples of the dataset to train my model, this leaves me with $N - K$ samples that are not used for training. Since K samples were used for training, if I would compute the error the model makes on these samples I would be computing the in-sample error. If I want to estimate the out-of-sample error I have to use the $N - K$ samples that were not used for training. This sample set of $N - K$ samples is often called the validation set.

We can now make the following observations:

- The larger we choose K , the more samples are available for training and thus the better our model can be (due to lower variance!)
- The larger we choose K , the less accurate our out-of-sample error estimate is, because we have fewer datapoints for the estimation

So now it is clear that we have a tradeoff to make. We would like K to be as large as possible so that we have a large amount of samples to train a model from. On the other hand we would like K to be as small as possible so that we have enough samples to estimate the out-of-sample error. The solution to this apparent contradiction will be cross-validation.

2.6.2 Cross-validation

Cross-validation is a technique that allows us to have plenty of samples left for training, while still getting a pretty good estimate for the out-of-sample error. The method is as follows: divide the dataset of N samples into K equal parts (often called folds). Each fold now has N/K samples. Train a model on $K - 1$ folds and use the remaining fold to estimate the out-of-sample error. Repeat this process K times, one time for each of the K folds, each time leaving out a different fold. In the end we have K estimates of the out-of-sample error and we can average them to get a final result.

Notice that we are really using all samples for validation and training, but never both at the same time. It feels a bit like cheating, but in practice this method works wonderfully. Validation is often used to determine parameters of the learning process, for instance the λ parameter for regularization. We simply try several values for λ , compute the out-of-sample error using validation, and pick the λ that gives the lowest error. Once we have decided this λ we can then train a model on the full dataset of N points and use the λ we have just calculated to be optimal.

We have to remark however that when we use validation to calculate a value for λ as described above, we are really using the validation to help train the model. In this case we can no longer make the statement that the validation samples are not used for training. This is called data pollution. We are using the same data to train training parameters as well as training the model itself and it is obvious that this will give rise to additional correlations in the data. However in practice it is generally accepted that if you use this technique to decide on just a few learning parameters (often just λ), and you have a big enough dataset, the data pollution is minimal and the results and estimates you get are still reliable.

Cross-validation is not only used to estimate learning parameters. It can also be used to simply test the performance of the model. In this case the fold that is not used for training is usually not called a validation set, but rather a test set. Because samples in this set will be used to test the models performance.

2.7 Conclusion

We have now covered the basis of Generalized Linear Models. We have described the gradient descent method that we can use to navigate the hypothesis space by minimizing an error function. We have seen that overfitting is a serious issue that is caused by noise at different levels of the learning process. We have broken down this noise into bias and variance and shown that we can have an impact on this process. We can use regularization to add a slight bias in order to greatly decrease the error due to variance and we have based this on the principle that we should prefer simple and smooth models. Lastly we have covered the method of validation. A method

that we can use to estimate the out-of-sample error and which gives us the ability to choose learning parameters like λ and also test the performance of our model.

Chapter 3

Integration Strategies

3.1 Introduction

Current advancements in technology are leading to increasingly larger datasets. This is a trend that is becoming very apparent in many different fields of research. One of these is the biomedical field. Technology is about to reach the point where we are able to sequence anyones DNA at a very low cost. Secondly, we have a range of highly advanced imaging instruments creating massive amounts of imaging features. And on top of that, there are big discussions going on about researchers having to make their datasets open to the public to help other researchers around the world. All of these trends lead to huge amounts of data from different sources becoming available for analysis. This raises the question of how we have to integrate data from these different sources to get the most information out of them. In this chapter I will first explain the general setup that we are dealing with, followed by three different integration strategies that show how we can combine datasets from different sources.

3.2 The setup

We have a set of D datasets, each dataset can be represented by a matrix where the rows are the samples and the columns are the explanatory variables. Each dataset can have a different number of explanatory variables, but they all have the same amount of rows such that samples can be linked across datasets. For instance: imagine we have a set of 200 cancer patients. Each of these patients has had images taken of the cancer by different machines: an MRI scan, a PET scan, ... and they also had a bloodtest done measuring different proteïne levels in the blood (an ELISA test). Each of these methods will yield a dataset: one for each imaging scan and one for the blood test. The explanatory variables are obviously different for each dataset: the imaging datasets will have image features like blobs and pixel intensities, while the bloodtest will have values that represent the proteïne levels in the blood. Each dataset will however have 200 rows, one for each patient.

Now that we have our input data, we need a target function (dependent vari-

able). In the example case this could be whether the patient fully recovers from the treatment or not. This variable has a binomial distribution and thus we could use logistic regression to try and estimate this variable. The task of integration is now the following: how do we combine the samples across the different datasets to come up with a model that uses the information in all the datasets? In the following sections I will present three ways to do this: the early integration method which is the current standard, the late integration method that is based on an ensemble of models, and the intermediate integration method that takes advantage of variable selection present in the lasso regularization.

3.3 Early integration

The first integration method is called early integration and it is the method that is most widely used at the time. It is also the easiest way of dealing with different data sources as we are simply going to concatenate the data for each sample. Figure 3.1 shows the schema for early integration of data sources. A new large dataset is constructed by concatenating the individual datasets by matching sample. The number of samples obviously stays the same, the number of explanatory variables is equal to the sum of explanatory variables of all individual datasets. This integrated dataset can then be used to train the final model directly.

3.4 Late integration

In late integration, as the name suggests, we will combine the different datasets at the end of the learning process. The schema for late integration is shown on figure 3.2. First, a model is learned for each dataset individually. This gives rise to D different models. When we want to make a prediction using this set of models, we will ask each model to provide an output individually and then combine them using a linear combination. If we have no preference for any model we could simply compute the average output. This average would then be our final output for the integrated model. In this case we cannot represent the final model by some model parameters (weights) but rather we have to view the full set of D models as well as the linear combination we chose as the full integrated model.

There is an analogy between late integration and the ensemble averaging technique in machine learning. Ensemble learning means that instead of just building one model for a dataset, we build several models for the same dataset and then average their outcomes. Late integration takes this idea but applies it to a set of data sources instead of just one.

The thought behind this model is that we try to learn as much as possible from each dataset individually, before we combine them. An example of this is that the variable selection by the lasso regularization now has the opportunity to select the best variables for each dataset individually. While in the case of early integration, all

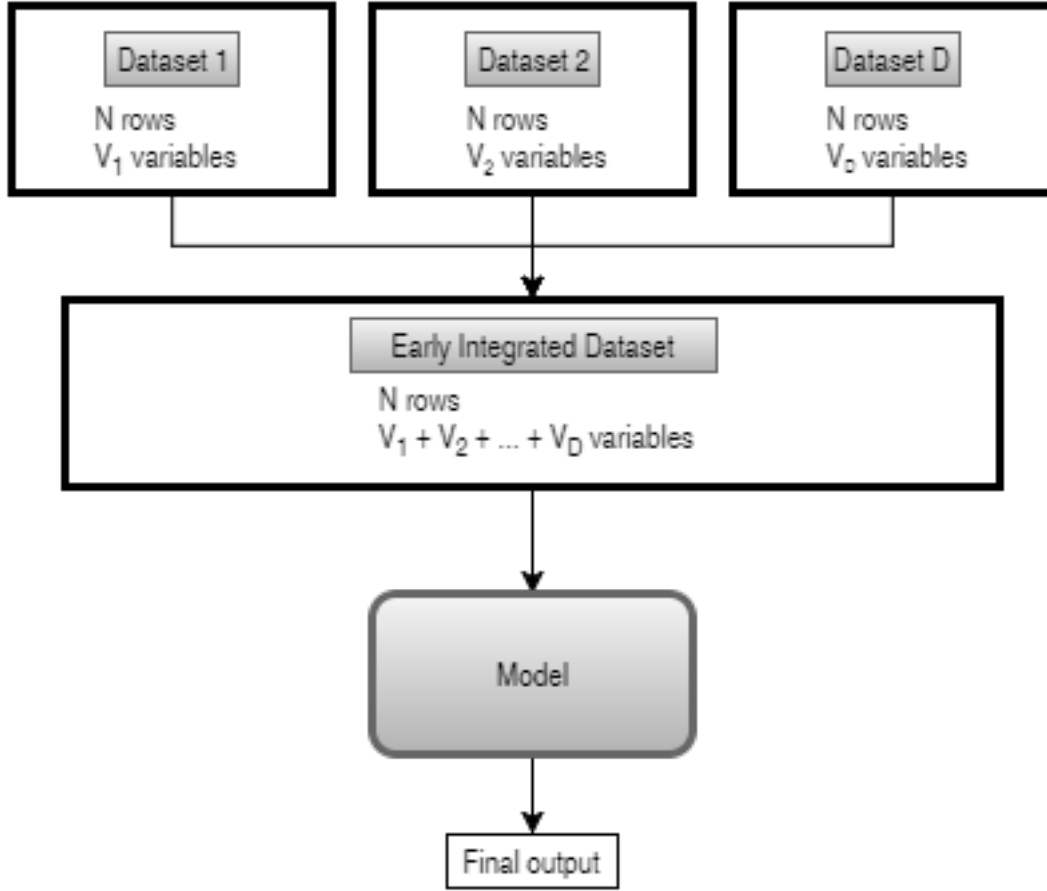


FIGURE 3.1: Scheme for early integration

the variables from the datasets are competing against each other at the same time to make it into the final model.

3.5 Intermediate integration

Intermediate integration is possibly the most advanced integration method presented. It tries to take advantage of the variable selection when using a lasso penalty. The schema for intermediate integration is shown on figure 3.3. It starts out the same way as late integration, for each dataset we compute an individual model. However, instead of using the output of these models we will simply look at the variables that were chosen by each model to be informative. We will then go back to the original datasets and extract only those explanatory variables and concatenate them together into a new integrated dataset. Lastly, we use this integrated dataset to learn a final model.

The intermediate integration can be seen as a two-step learning process. First we preprocess the datasets by computing individual models and we extract only the

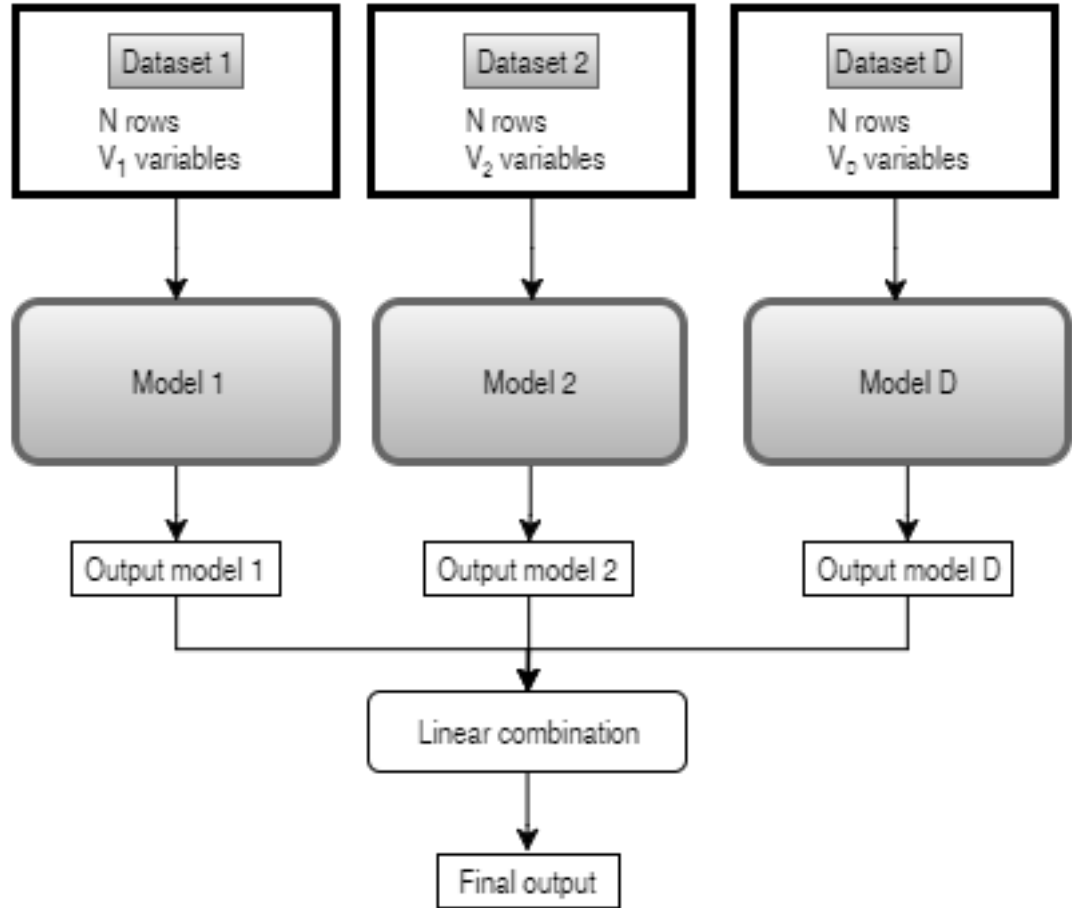


FIGURE 3.2: Scheme for late integration

informative variables. Then we will train our final model on the reduced dataset. This is very advantageous if the initial datasets have a huge amount of explanatory variables, as the preprocessing step will reduce this amount drastically while still keeping as much useful information as possible.

3.6 Conclusion

In this chapter I have shown the issue of large and high-dimensional datasets that we are currently facing. I have presented three different strategies to deal with this issue. The early integration method is the naïve method that simply concatenates the datasets together. The late integration method uses an analogous technique to ensemble learning in order to extract as much information as possible. Lastly, the intermediate integration technique introduces a two-step learning method that takes advantage of variable selection to reduce the dimensionality of the datasets.

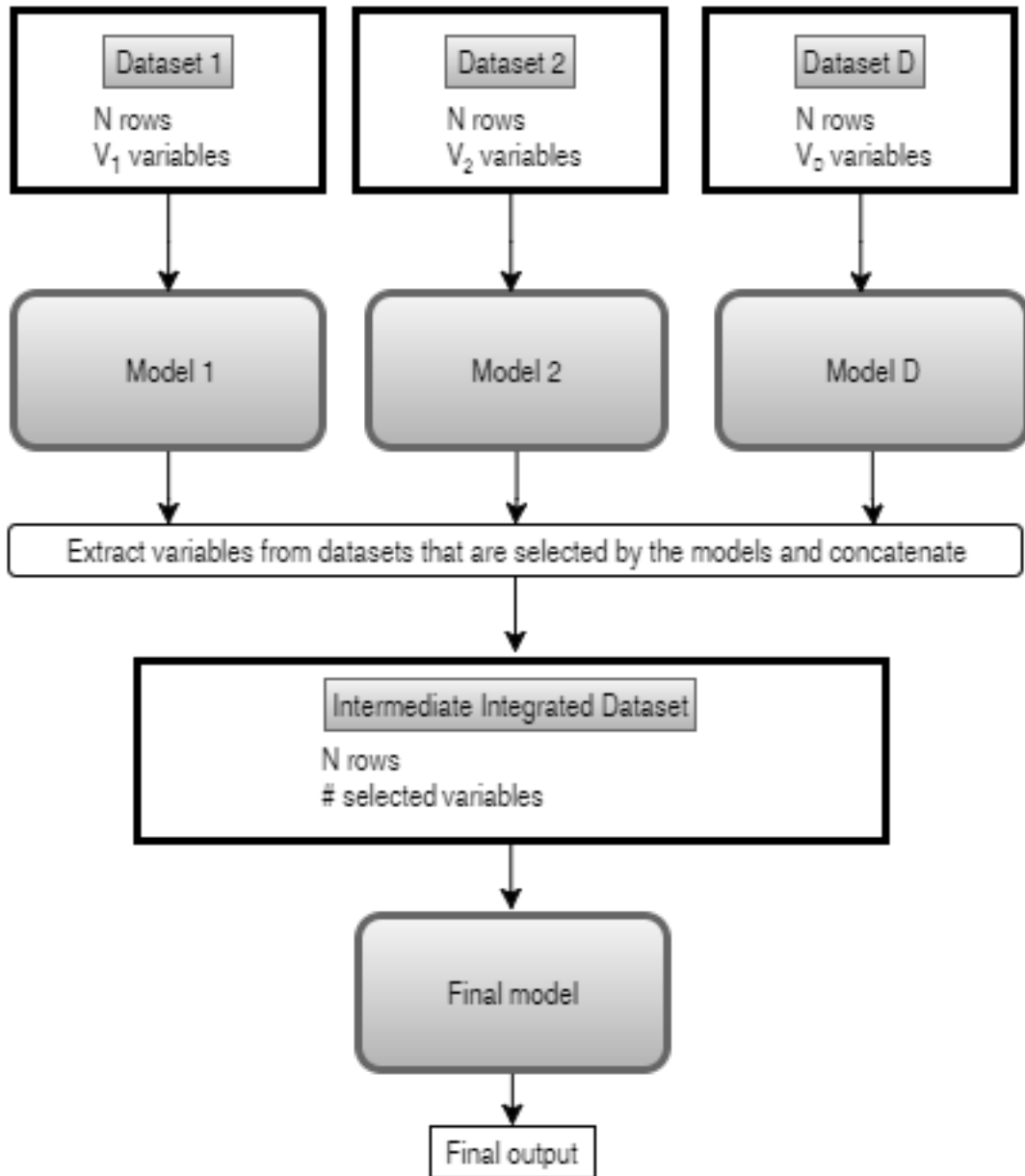


FIGURE 3.3: Scheme for intermediate integration

Chapter 4

Evaluation of integration strategies

4.1 Introduction

In this chapter I will show that different integration strategies can have better performance in different situations. I will do this by computing a model using each strategy and then comparing their performance using an appropriate metric.

4.2 Case details

The case I am showing here uses datasets created by the University Hospital of Leuven in a study on colorectal cancer patients. There are three source datasets that all contain imaging data: a dataset from MRI (Magnetic Resonance Imaging) scans, a dataset from DWI (Diffusion Weighted Magnetic Resonance Imaging) scans, and a dataset from PET (Positron Emission Tomography) scans. It is important to note that these scans were taken 3 times per patient at different periods in their treatment: one in the beginning, one roughly in the middle, and one near the end. This means that there is some temporal information present in the datasets, but this has simply been encoded in the explanatory variables. For instance: there is a variable in the MRI dataset that shows the size change of the tumour between the first and second scan. In this way we can simply treat this as a regular explanatory variable and we don't have to worry about the temporal aspect.

The dependent variable is a binary outcome based on whether the patient got a pathologically complete response. For a more in-depth explanation on what this means see appendix //TODO EXPLAIN STAGE SYSTEM IN APPENDIX. For now, we can view a positive outcome as a patient who has recovered from the cancer, and a negative outcome as a patient that has not. The aim is now to build a model that gets the variables from the scans as input, and predicts the outcome for that patient.

4.3 Evaluating a logistic regression model

The first evaluation will be made using a logistic regression model. This is a model computed for a dependent variable that has a binomial distribution. To evaluate such model, a common technique used is called Receiver-Operating-Characteristic analysis or ROC analysis for short. Remember that when we are using a logistic regression model to predict outcomes, we have to define a threshold to separate positive from negative cases. An ROC curve shows the performance of the model for any possible threshold, using metrics such as sensitivity and specificity. This gives a very good general impression of the performance of the model.

4.3.1 Predictions using validation

What we really want to do is estimate the out-of-sample error for our model. To do this we have seen that we can use the technique of cross-validation. In this case we are not going to compute any learning parameter but we are going to use the validation set as a test set. We will split our dataset into K folds. We will train a model on $K - 1$ folds and we will use this model to predict the outcomes of the remaining samples in the test fold. By repeating this process for each folds we obtain a predicted outcome for each sample in the dataset. Notice however that we also have the real outcome of the samples in our dataset, and thus we can compare our predictions with the real values to estimate our out-of-sample error.

4.3.2 Metrics

When we compare our predictions with the real outcomes, there are four possible scenario's:

- True Positive (TP): we predicted positive and this is correct
- True Negative (TN): we predicted negative and this is correct
- False Positive(FP): we predicted positive and this is wrong (type 1 error)
- False Negative (FN): we predicted negative and this is wrong (type 2 error)

Notice that this gives us more information than just registering whether we are right or wrong. It also tells us the type of mistake we made. This is a very important distinction because depending on the application there is usually a different cost attached to making type 1 or type 2 errors. And as we will see later on, there is a tradeoff between the two and we can tune our system to be more resistant towards making one type of error.

Now that we have established the notion of typed errors, there are several ways in which these numbers are combined to form evaluation metrics. Depending on your field of research these often get different names, I will use the ones applicable to the biomedical field.

Sensitivity

Sensitivity measures the proportion of the real positive samples that our model correctly predicted as positive. It can be calculated with the following formula:

$$Sensitivity = \frac{\sum TP}{\sum P}$$

where

- $\sum TP$ is the number of true positives
- $\sum P$ is the number of real positive cases in the dataset

Sensitivity can be thought of, as its name suggests, as how sensitive the model is to detecting positive cases. If the model gets a real positive sample, what is the probability that it will detect it as such. A sensitivity of 1 means that our model is capable of correctly identifying all positive cases in the dataset. This means that the higher the sensitivity, the lower the type 2 error rate.

Specificity

Specificity is the analogous metric to sensitivity, but for negative cases. It measures the proportion of the real negative samples that our model correctly predicted as negative.

$$Specificity = \frac{\sum TN}{\sum N}$$

where

- $\sum TN$ is the number of true negatives
- $\sum N$ is the number of real negative cases in the dataset

A specificity of 1 means that our model is capable of correctly identifying all negative cases in the dataset. This means that the higher the specificity, the lower the type 1 error rate.

The tradeoff

At this point it is obvious that we would like to maximize both sensitivity and specificity. Indeed, if both metrics are 1 then we make no errors and we have a perfect model. In practice however this is nearly impossible to achieve. It is easy to see that there is a tradeoff between the two metrics: when we try to increase the sensitivity, we will lose out on specificity and vice versa.

Consider the totally useless model that has a threshold lower than the smallest possible output. Meaning that this model will always predict a positive outcome regardless of the input. This model will have a sensitivity of 1, as we will get all positive cases correct. But it will also have a specificity of 0 because we get none of

the negative cases correct. As we gradually increase the threshold we will cross critical values where some sample inputs will now produce an output below the threshold and thus be classified as negatives. If this happens to be a correct prediction our specificity will go up and sensitivity will remain unchanged. If it happens to be an error, specificity is unchanged and sensitivity will go down. The gradual increase of the threshold will thus cause sensitivity to drop and specificity to increase, up to the point where we reach the other extreme. The threshold is now bigger than the biggest possible output and the model always predicts negative regardless of the input. This threshold gives us a sensitivity of 0 and a specificity of 1.

4.3.3 Receiver Operating Characteristic curve

The ROC curve is a way of showing exactly this gradual increase of the threshold. The typical way of constructing a ROC curve is to put $(1 - \textit{specificity})$ on the X-axis and *sensitivity* on the Y axis. The values for these metrics are then plotted for values of the threshold ranging from the all-positive model to the all-negative model. An example ROC curve is shown on figure 4.1. The metric I will use to evaluate the performance of different models is the area under the ROC curve (AUC). This metric works because it indicates how far we can optimize both sensitivity and specificity for different thresholds. It shows how close we can get to the upper left corner of the plot, which indicates the perfect model. The AUC metric ranges from 0 to 1, but in fact its value is only informative in between 0.5 and 1. Imagine a model that makes completely random predictions, this model will get a correct prediction 50% of the time. If we would create an ROC curve for this model we would on average get a straight diagonal line from the bottom left to the top right. This line is therefore considered a lower bound for the performance of a model. In a more realistic setting we can view models with an AUC of 0.7 and above as decent models. //TODO CHANGE FIGURE TO ROC CURVE

4.4 Predicting stage outcome

4.5 Evaluating a cox proportional hazards model

4.6 Predicting survival curves

4.7 Conclusion

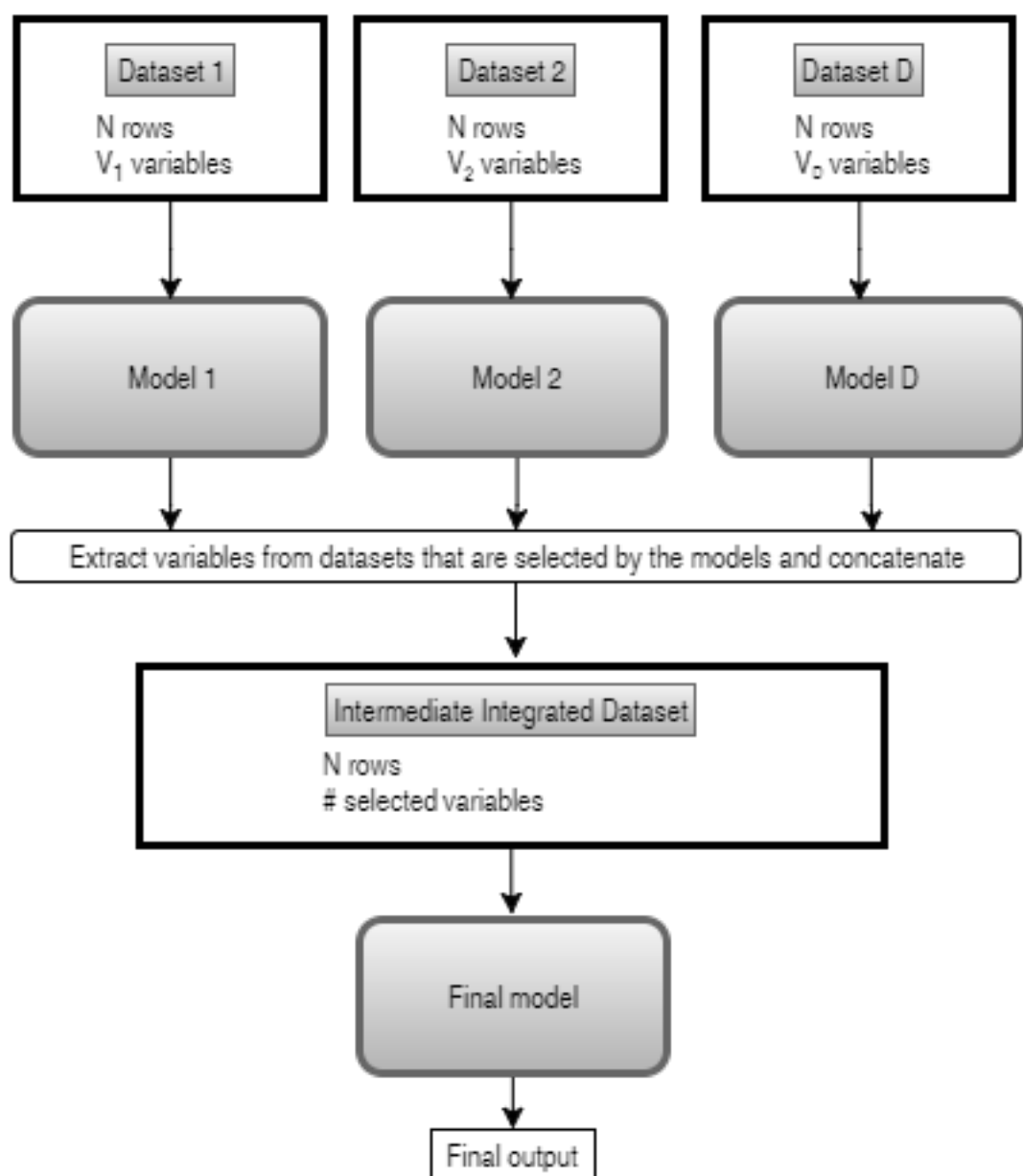


FIGURE 4.1: Example ROC curve

Chapter 5

Tool for automated evaluation

5.1 Introduction

In the previous chapter I have shown that different integration strategies do make a difference for the performance of the resulting model. However I have taken it one step further and developed a tool that allows the user to very easily compute all the integrated models and compare them.

5.2 Technologies

To develop this tool I needed a programming language that provided a lot of support for statistical algorithms, and I also wanted to create a very user-friendly interface to make an abstraction of the complicated methods.

5.2.1 The R language

The language I used to create the tool is R. R is a very popular language for statistical research as it provides many state-of-the-art algorithms in statistics. R has a huge repository with packages for all kinds of purposes. The package that I used to compute models is `glmnet`. It is developed by researchers at the Stanford University and provides very fast implementations to compute the generalized linear models explained in chapter 2.

5.2.2 Web interface

I wanted to offer a very easy-to-use interface to the application. Therefore I chose to work with shiny. Shiny is a package for R that allows you to create a web-based front-end (using html, css, javascript, ...) that can also run R code in the back-end. This provided me with exactly what I needed to create my tool.

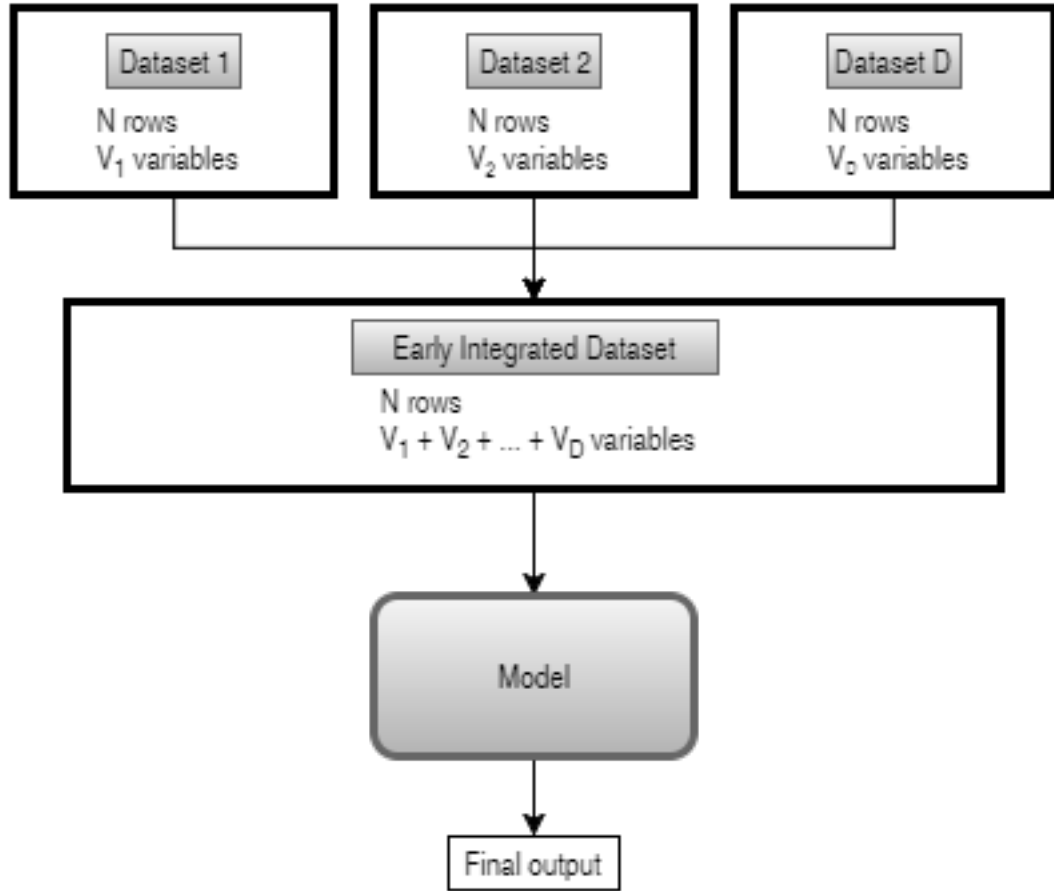


FIGURE 5.1: The input tab of the tool

5.3 Demonstration

The tool is basically divided into three sections: an input section where the user can upload their datasets, a section that computes and evaluates models for each dataset individually, and an integration section where all of the integrated models previously explained can be computed and evaluated. Currently the tool supports logistic regression models and cox proportional hazard models.

The input tab

The first tab allows the user to either use a preloaded dataset or upload their own datasets to the application. It is possible to define multiple dependent variables in one file, the tool then gives you the option to select which variable has to be modeled.

When datasets are uploaded, the tool gives a small overview of the dimensions of each dataset so the user can verify everything works correctly. Figure 5.1 shows the input page where a user has uploaded some datasets.

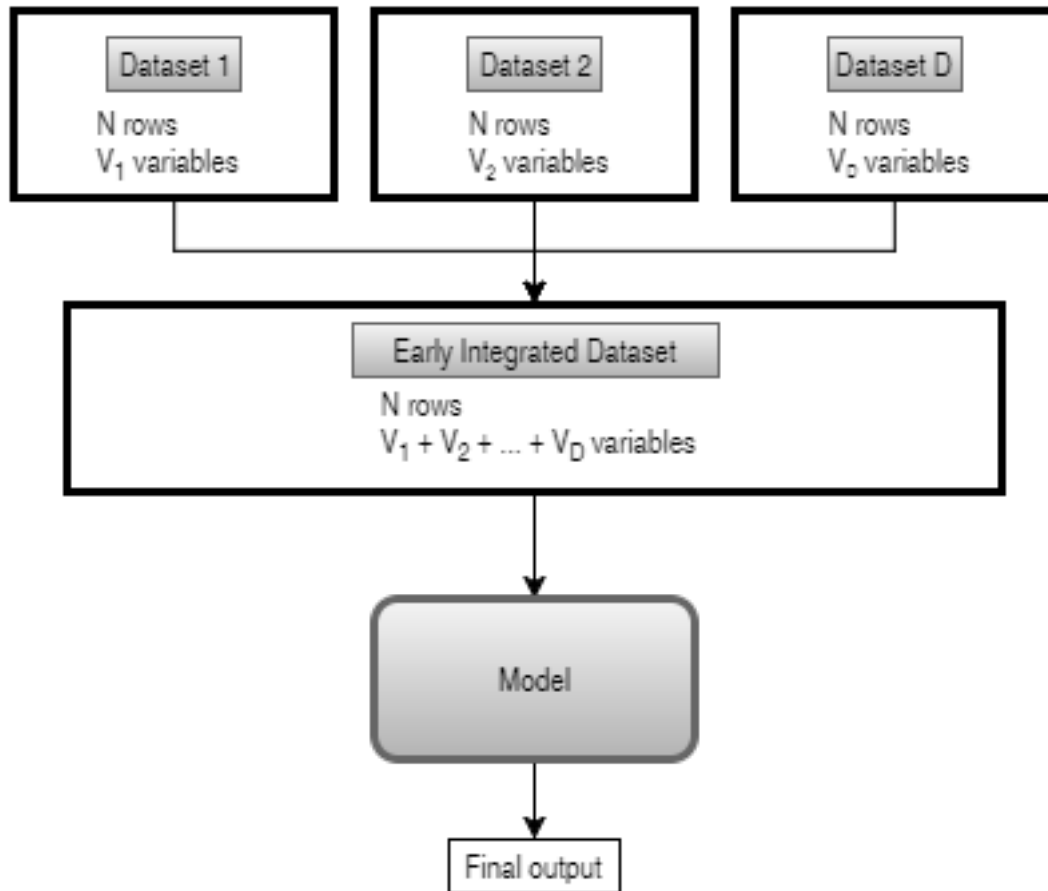


FIGURE 5.2: An example model description

The individual models tab

Once a user has uploaded their datasets they can compute a model for each dataset individually. The tool will give a concise overview of the model parameters for each model, and show an evaluation of the model. In case of logistic regression, the evaluation would be a ROC curve. Notice that the evaluation is interactive: the user can use the slider to see the performance metrics for different thresholds. Figure 5.2 shows an example model description, figure 5.3 shows an example ROC curve.

The integration tab

The integration tab is the most important part of the application, as it allows the user to compute and evaluate integrated models for their datasets. The integration tab is further split up into early-, late- and intermediate integration tabs. Each tab will allow computation and evaluation for its respective integration method. The results will look exactly the same as shown for the individual models tab as can be seen on figures 5.2 and 5.3.

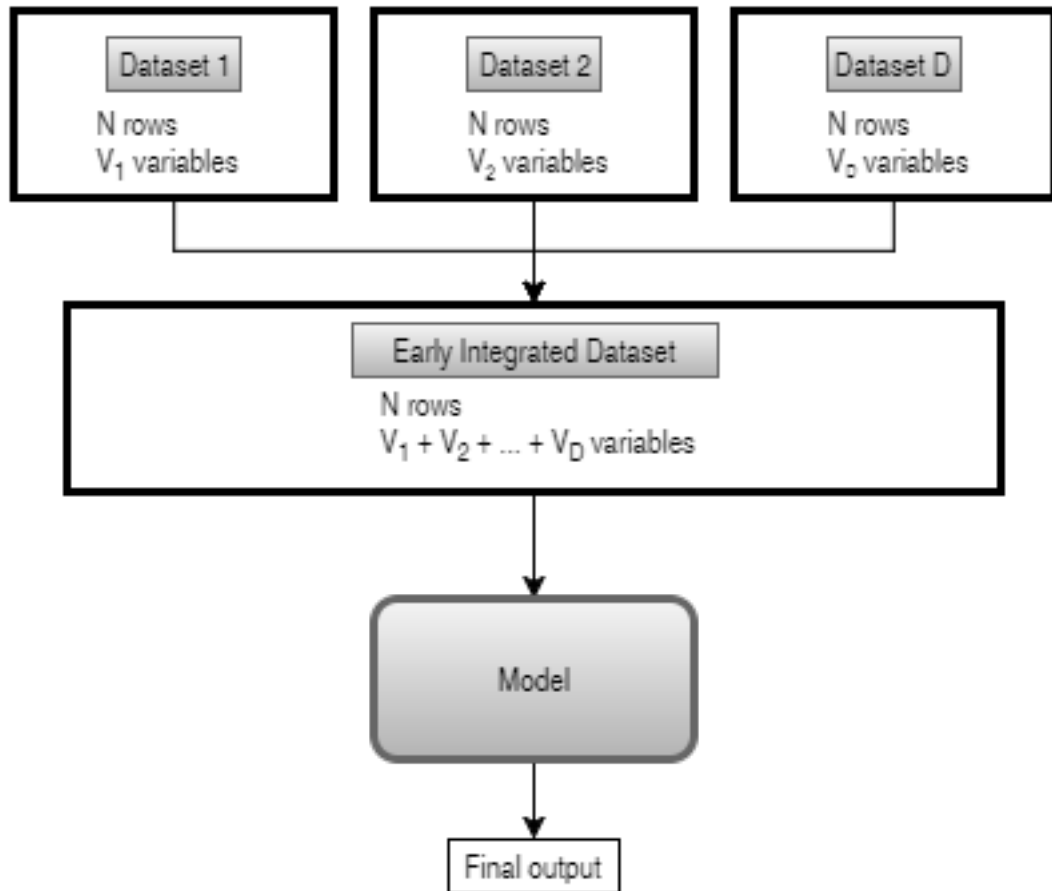


FIGURE 5.3: An example interactive ROC curve

5.4 Conclusion

Chapter 6

Conclusion

The final chapter contains the overall conclusion. It also contains suggestions for future work and industrial applications.

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Appendices

Appendix A

The First Appendix

Appendices hold useful data which is not essential to understand the work done in the master thesis. An example is a (program) source. An appendix can also have sections as well as figures and references[?].

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A.1.2 Lorem 18–19

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Nulla non mauris vitae wisi posuere convallis. Sed eu nulla nec eros scelerisque pharetra. Nullam varius. Etiam dignissim elementum metus. Vestibulum faucibus, metus sit amet mattis rhoncus, sapien dui laoreet odio, nec ultricies nibh augue a enim. Fusce in ligula. Quisque at magna et nulla commodo consequat. Proin accumsan imperdiet sem. Nunc porta. Donec feugiat mi at justo. Phasellus facilisis ipsum quis ante. In ac elit eget ipsum pharetra faucibus. Maecenas viverra nulla in massa.

A.2 Lorem 51

Maecenas dui. Aliquam volutpat auctor lorem. Cras placerat est vitae lectus. Curabitur massa lectus, rutrum euismod, dignissim ut, dapibus a, odio. Ut eros erat, vulputate ut, interdum non, porta eu, erat. Cras fermentum, felis in porta congue, velit leo facilisis odio, vitae consectetur lorem quam vitae orci. Sed ultrices, pede eu placerat auctor, ante ligula rutrum tellus, vel posuere nibh lacus nec nibh. Maecenas laoreet dolor at enim. Donec molestie dolor nec metus. Vestibulum libero. Sed quis erat. Sed tristique. Duis pede leo, fermentum quis, consectetur eget, vulputate sit amet, erat.

Appendix B

The Last Appendix

Appendices are numbered with letters, but the sections and subsections use arabic numerals, as can be seen below.

B.1 Lorem 20-24

Nulla ac nisl. Nullam urna nulla, ullamcorper in, interdum sit amet, gravida ut, risus. Aenean ac enim. In luctus. Phasellus eu quam vitae turpis viverra pellentesque. Duis feugiat felis ut enim. Phasellus pharetra, sem id porttitor sodales, magna nunc aliquet nibh, nec blandit nisl mauris at pede. Suspendisse risus risus, lobortis eget, semper at, imperdiet sit amet, quam. Quisque scelerisque dapibus nibh. Nam enim. Lorem ipsum dolor sit amet, consectetur adipiscing elit. Nunc ut metus. Ut metus justo, auctor at, ultrices eu, sagittis ut, purus. Aliquam aliquam.

Etiam pede massa, dapibus vitae, rhoncus in, placerat posuere, odio. Vestibulum luctus commodo lacus. Morbi lacus dui, tempor sed, euismod eget, condimentum at, tortor. Phasellus aliquet odio ac lacus tempor faucibus. Praesent sed sem. Praesent iaculis. Cras rhoncus tellus sed justo ullamcorper sagittis. Donec quis orci. Sed ut tortor quis tellus euismod tincidunt. Suspendisse congue nisl eu elit. Aliquam tortor diam, tempus id, tristique eget, sodales vel, nulla. Praesent tellus mi, condimentum sed, viverra at, consectetur quis, lectus. In auctor vehicula orci. Sed pede sapien, euismod in, suscipit in, pharetra placerat, metus. Vivamus commodo dui non odio. Donec et felis.

Etiam suscipit aliquam arcu. Aliquam sit amet est ac purus bibendum congue. Sed in eros. Morbi non orci. Pellentesque mattis lacinia elit. Fusce molestie velit in ligula. Nullam et orci vitae nibh vulputate auctor. Aliquam eget purus. Nulla auctor wisi sed ipsum. Morbi porttitor tellus ac enim. Fusce ornare. Proin ipsum enim, tincidunt in, ornare venenatis, molestie a, augue. Donec vel pede in lacus sagittis porta. Sed hendrerit ipsum quis nisl. Suspendisse quis massa ac nibh pretium cursus. Sed sodales. Nam eu neque quis pede dignissim ornare. Maecenas eu purus ac urna tincidunt congue.

Donec et nisl id sapien blandit mattis. Aenean dictum odio sit amet risus. Morbi purus. Nulla a est sit amet purus venenatis iaculis. Vivamus viverra purus vel

magna. Donec in justo sed odio malesuada dapibus. Nunc ultrices aliquam nunc. Vivamus facilisis pellentesque velit. Nulla nunc velit, vulputate dapibus, vulputate id, mattis ac, justo. Nam mattis elit dapibus purus. Quisque enim risus, congue non, elementum ut, mattis quis, sem. Quisque elit.

Maecenas non massa. Vestibulum pharetra nulla at lorem. Duis quis quam id lacus dapibus interdum. Nulla lorem. Donec ut ante quis dolor bibendum condimentum. Etiam egestas tortor vitae lacus. Praesent cursus. Mauris bibendum pede at elit. Morbi et felis a lectus interdum facilisis. Sed suscipit gravida turpis. Nulla at lectus. Vestibulum ante ipsum primis in faucibus orci luctus et ultrices posuere cubilia Curae; Praesent nonummy luctus nibh. Proin turpis nunc, congue eu, egestas ut, fringilla at, tellus. In hac habitasse platea dictumst.

B.2 Lorem 25-27

Vivamus eu tellus sed tellus consequat suscipit. Nam orci orci, malesuada id, gravida nec, ultricies vitae, erat. Donec risus turpis, luctus sit amet, interdum quis, porta sed, ipsum. Suspendisse condimentum, tortor at egestas posuere, neque metus tempor orci, et tincidunt urna nunc a purus. Sed facilisis blandit tellus. Nunc risus sem, suscipit nec, eleifend quis, cursus quis, libero. Curabitur et dolor. Sed vitae sem. Cum sociis natoque penatibus et magnis dis parturient montes, nascetur ridiculus mus. Maecenas ante. Duis ullamcorper enim. Donec tristique enim eu leo. Nullam molestie elit eu dolor. Nullam bibendum, turpis vitae tristique gravida, quam sapien tempor lectus, quis pretium tellus purus ac quam. Nulla facilisi.

Duis aliquet dui in est. Donec eget est. Nunc lectus odio, varius at, fermentum in, accumsan non, enim. Aliquam erat volutpat. Proin sit amet nulla ut eros consectetur cursus. Phasellus dapibus aliquam justo. Nunc laoreet. Donec consequat placerat magna. Duis pretium tincidunt justo. Sed sollicitudin vestibulum quam. Nam quis ligula. Vivamus at metus. Etiam imperdiet imperdiet pede. Aenean turpis. Fusce augue velit, scelerisque sollicitudin, dictum vitae, tempor et, pede. Donec wisi sapien, feugiat in, fermentum ut, sollicitudin adipiscing, metus.

Donec vel nibh ut felis consectetur laoreet. Donec pede. Sed id quam id wisi laoreet suscipit. Nulla lectus dolor, aliquam ac, fringilla eget, mollis ut, orci. In pellentesque justo in ligula. Maecenas turpis. Donec eleifend leo at felis tincidunt consequat. Aenean turpis metus, malesuada sed, condimentum sit amet, auctor a, wisi. Pellentesque sapien elit, bibendum ac, posuere et, congue eu, felis. Vestibulum mattis libero quis metus scelerisque ultrices. Sed purus.

Bibliography

Fiche masterproef

Student: Michiel Ruelens

Titel: Design, implementation and evaluation of data integration methods for biomedical cancer data

Nederlandse titel: Design, implementatie en evaluatie van data integratie methoden voor biomedische data

UDC: 621.3

Korte inhoud:

Hier komt een heel bondig abstract van hooguit 500 woorden. L^AT_EX commando's mogen hier gebruikt worden. Blanco lijnen (of het commando `\par`) zijn wel niet toegelaten!

Nam dui ligula, fringilla a, euismod sodales, sollicitudin vel, wisi. Morbi auctor lorem non justo. Nam lacus libero, pretium at, lobortis vitae, ultricies et, tellus. Donec aliquet, tortor sed accumsan bibendum, erat ligula aliquet magna, vitae ornare odio metus a mi. Morbi ac orci et nisl hendrerit mollis. Suspendisse ut massa. Cras nec ante. Pellentesque a nulla. Cum sociis natoque penatibus et magnis dis parturient montes, nascetur ridiculus mus. Aliquam tincidunt urna. Nulla ullamcorper vestibulum turpis. Pellentesque cursus luctus mauris.

Thesis voorgedragen tot het behalen van de graad van Master of Science in de ingenieurswetenschappen: computerwetenschappen, hoofdspecialisatie Mens-machine communicatie

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