KTH Computer Science
and Communication

Prediction of peptide retention time based on Gaussian Process

XUANBIN QIU

Master's Thesis at NADA
Supervisor: Patric Jensfelt
Examiner: Stefan Carlsson

TRITA 2015-3-19

Abstract

This thesis presents a alterative machine learning methods to predict the retention time of a set of peptide in hand. In order to address the precision and computational cost problem, we introduce Gaussian Process.

Contents

1 Introduction **1**
- 1.1 Background . . . 1
- 1.2 Problem Statement . . . 2
- 1.3 Outline . . . 2

2 Related Work **3**
- 2.1 Models / Methods . . . 3
- 2.2 Features . . . 5

3 Gaussian Process **7**
- 3.1 Standard Bayesian linear Regression . . . 7
- 3.2 Gaussian Process Regression . . . 9
- 3.3 Property of Gaussian Process . . . 11

4 Feature selection **13**
- 4.1 Bag of Word . . . 14
  - 4.1.1 Theory . . . 14
- 4.2 Property . . . 15
- 4.3 Alignment Analysis . . . 16
  - 4.3.1 Theory . . . 16
- 4.4 Property . . . 17

5 Optimization **19**
- 5.1 The Conjugate Gradient . . . 19
  - 5.1.1 Principle . . . 19
  - 5.1.2 Strength and Drawbacks . . . 21
- 5.2 The Particle Swarm Optimization . . . 22
  - 5.2.1 Principle . . . 22
  - 5.2.2 Strength and Drawbacks . . . 23

6 Results and Evaluation **25**

7 Discussion **27**

8 Conclusion and Future Work **29**

Bibliography **31**

Appendices **32**

A RDF **33**

Chapter 1

Introduction

1.1 Background

Protein, the most essential component of all the cells and organisms, plays an irreplaceable role in people's daily lives including providing energy, strengthen immunity and catalyzing metabolic reactions within the body. Therefore, the study of the properties of protein is very necessary and considered as one of most important subject in biological field.

To analyze the protein content, one of most popular technique is Mass spectrometry(MS) based method. This technique has three main steps, firstly, the protein in the mixture of interest will be broken into peptide. Then the resulting peptides are separated according to their hydrophobicity on a liquid chromatography(LC) column. In the end, those peptide will eluted from the column and ionized by electrospray ionization. The results are a set of spectra which contain the valuable information about the proteins in the sample.

Among these three steps, the most important one is the peptide separation in the column. Retention time(RT) is the amount of time that a peptide needs to go through the column. It is a useful feature in many aspects. It may be used in experiments involving chemometric analyses of peptide mixtures. What's more, it provides us a new perspective to investigate the behavior and biological characters of the protein. An extensive amount of research has been conducted into predicting peptide retention times. The Sequence Specific Retention Calculator(SSRC) which predicts retention times based on amino acid sequences is available on-line. The main algorithm behind those applications is mostly based on either Support Vector Regression(SVR) or Artificial Neural Network(ANN).

1.2 Problem Statement

However, all of these methods have their own drawbacks and still needed to be improved. One alternative option is to implement the Gaussian Process(GPs) to build the predictive model. GPs provides a flexible framework for probabilistic regression and is widely used to solve the high-dimensional, small-sample or nonlinear problems. It seems that the properties of GPs can overcome the shortages of ANN and SVR. Yet none of the existing publications has the prediction of retention times for peptides analyzed with the use of Gaussian Process.

Therefore, the top priority of this thesis is to develop a Gaussian Process Regression model in terms of predicting the peptide retention time and investigate the performance of it before optimization and after optimization.

Besides, this thesis will also strive to find some features with less biological meaning to represent the peptide for training model and compare their performance to the biological features.

1.3 Outline

The structure of the paper is as follows, we will firstly introduce the related work of retention time prediction that have already been done by the others in section 2. Then it will be followed by the detailed description of Gaussian Process in section 3. And the theory behind Gaussian Process and detailed mathematics derivation will also be covered in this section. Section 4 introduces three different methods regarding features selections of Gaussian Process. The optimization will be covered in section 5 and two different method will be used to optimize the parameters in the previous model. Then, the experimental results and evaluation will be analyzed in section 6. Finally, we will discuss the future work and give some perspectives for it in section 7.

Chapter 2

Related Work

Prediction of the retention time for a given peptide could help to improve the confidence of peptide identifications. Therefore, developing efficient algorithms and establish proper model to generate the prediction of peptide has become more important and necessary.

However, to make the prediction successfully, there are two problems needed to be considered. Firstly, what kind of model will have better performance of the prediction. Secondly, what factors will have an great impact on the retention time. Unfortunately, both of these two questions remain unclear so far. Therefore, in order to solve the questions, a number of models based on different features have been proposed to characterize quantitatively the peptide and to predict its retention time.

2.1 Models / Methods

From the perspective of the models, there are different kinds of machine-learned models that have been implemented. One of the model is multiple linear regression(MLR) model. This model was implemented by the author of [1] to predict the peptide retention time at different HPLC conditions and shows high precision. However,the linear regression model mainly depends on the chromatographic condition and thus prediction bias could be a serious problem when the model is used under different circumstance.

Another model is the artificial neural network(ANN) proposed by Petritis K et al. in [2]. The ANN model was based on the contributions of individual amino acids taken the neighborhood effect into account and a data set of 7000 was used for the training. The large amount of experimental data provided by this approach produced high accuracy of the retention time prediction and enhance the confidence of

the peptide identification. In addition, the initial ANN model has been improved later in 2006. In [3], the author has improved the ANN model by adding more descriptors, such as peptide length, sequence, hydrophobicity as well as nearest-neighbor amino acid. Each of the peptide is characterized by 1052 features instead of 20. The new model was trained by 345,000 peptide and tested using another 1303 confidently identified peptide which reported excellent performance.

Although a great deal of effort has been made to improve the model, there are still some remained issues. One of the main weaknesses of this model is its consuming time. To be specific, in order to train this model, a large amount of training data is required which will result in a high cost in terms of both time and facilities. What's worse, its high computational cost also implies its weakness in terms of repeatability and comparability which are essential to laboratory research. It also limited its development for commercial purpose.

In order to solve this problem, another alternative machine-learned method support vector machine(SVMs) has been carried out. Klammer et al. in [4] proposed a predictor based on this method. SVMs requires fewer data to train the model than ANNs and reduce the computational cost dramatically. Besides, dynamic SVR model avoids the RT variation between different chromatographic conditions which could have better performance than the linear regression model in terms of adaptability. However, using small dataset with low complexity to train the model also leads to the poor performance in terms of accurate regression and gives lower quality prediction compared to the ANNs.

To enhance the capacity of the predictor and raise the predicted accuracy, Luminita Moruz in [5] has developed a new predictor, ELUDE, based on support vector regression. The predictor firstly derives a retention time index for the condition at hand. Then by using those indices, the predictor creates 60 peptide features which are optimally combined during a second training procedure. After that, $\epsilon - SVR$ is implemented to train the model based on the features. The resulting retention model can be subsequently used to predict the retention time of other peptides of interest.

The performance of Elude is excellent and considered as one of the state-of-the-art retention time predictors. However, one of the shortcomings of the Elude algorithm is the rather limited use of positional information. The retention index trained in-house on which many of the other features are based is calculated using only the amino acid composition. Adding positional data is likely to capture more information, and thus lead to higher prediction accuracies [6].

However, even with the proper models, the prediction could fail or the precision

could be extremely low if the selected features are improper or unrepresentative. So the features selection is also an essential part of an successful prediction.

2.2 Features

When it comes to the features, the effect of individual amino acid was firstly taken into account when building the model because evidences implied that the inclusion of this type of additional information could increase the confidence of protein identification of the peptide [1] and the chromatographic behavior of a peptide is mainly dependent on its amino acid composition [7]. A set of retention time coefficients were generated from only different amino-acid composition by using iterative regression methods.[8] [9] [10]

However, the author of [9] pointed out that the relative location of different amino acid in a peptide could affect the behavior of the peptide too. The author of [11] has also emphasized the relation between the chromatographic behavior of peptides and their amino acid composition. It is for sure that different values of retention coefficients of the same amino acid need to be assigned according to different peptides and different neighborhoods. Besides, the other biological characters, such as hydrophobicity [12], ion-pairing reagents [13], stationary phase [14] and even the length of the peptide could influence the peptide retention behavior.

Thus, in [15], O.V. Krokhin, R. Craig have developed an improved model, Sequence-Specific Retention Calculator(SSRC), for prediction of retention times in ion pair reversed-phase based on a database of 346 peptides. The ability of this model for prediction can assist detailed peptide mapping significantly, thus increase confidence in peptide identification and the protein characterization. However, the model is not completed and has not included amino acid modification that may occur during the sample preparation. In addition, the prediction capacity becomes worse for experimental condition which is diverging from the setup.

After SSRC, there are several different kinds of factors have been used. One of them is the structural descriptors. The author has employed the Quantitative structure-retention relationships with the information of the peptide's chemical characters and its structure in article [16]. The predictor implemented in article [1] is also based on three types of chemical structural descriptors and both of them showed good results with the experimental data.

In general, most of the features that are widely used now have strong biological meaning, such as amino acid composition, hydrophobicity of the peptide and some other chemical structural descriptors and the performance of these features is really

good and can fulfill the requirement. However, these features are mostly limited within the biological field and few of the less-biological meaning features have been tried so far.

Since from the perspective of computer science, anything that can represent an object could be considered as a feature of this object, it might be worth to believe that some less-biological meaning features could also be used and even have better performance in this case. Therefore, this thesis would like to utilize some representative features with less biological meaning and compare their performance to the features mentioned above.

Chapter 3

Gaussian Process

Gaussian Process is an supervised machine learning method based on the context of Bayesian theory and statistical learning. In order to understand the theory behind and build a appropriate Gaussian Process model, this chapter starts with a brief introduction of the supervised learning method as well as the specification of Standard Bayesian linear Regression. Then we will specify the Gaussian Process in our case along with the detailed mathematical derivation. Finally, we will make a comparison between Gaussian Process and the other two methods: ANNs and SVR so that we could see the strengths of Gaussian Process.

3.1 Standard Bayesian linear Regression

Let's first consider a set of input $x = \{(x_i, y_i)|i = 1, 2...n\}$ along with some noise ϵ. In the regression setting, the targets are real values but the observations are with additive noise. We are interested in inferring the relationship between inputs and targets, i.e. the conditional distribution of the targets given the inputs.

In supervised learning, one way to decide this relationship is using parametric regression which is determine a set of w as the best descriptors of the model between the inputs and outputs. Now, the problem comes to how to define if the model is good enough.

To solve this problem, two possible methods have been carried out. Loss Function Method and Maximum Likelihood Method. The first one is achieved by optimizing the parameters w that minimizing the predefined loss function, such as minimal squared error function(MSE). However, one of the obvious shortages of this method is the over-fitting. To minimize the error of the model, one would increase the complexity of the model that might easily result in the over-fitting problem. Even though the precision of model in terms of training data could be high enough, its predictive capacity for unknown data could be really bad and unacceptable. In

addition, making a simpler model by ignoring the noise could avoid the over-fitting problem but could also lead to lower accuracy for prediction.

An alternative way to identify the quality of model is Maximum Likelihood, also known as Bayesian regression. The idea of this method is replacing the loss function by the jointly probability distribution with predefined noise (Likelihood function) and search for the parameters w that maximize the likelihood function to build the model.

Let's consider the dataset $x = \{(x_i, y_i)|i = 1, 2...n\}$ mentioned before as the input. The Bayesian analysis of the linear regression model can be written as 3.1:

$$f_x = x^T w, \quad y = f_x + \epsilon, \tag{3.1}$$

where x is the input vector, w is the parameters(weights) of the input for the linear model. The function value is represented by $f(x)$ and an bias (noise) is included. We assume that the ϵ is the independent identically distributed Gaussian noise with the zero mean and variance σ_n^2.

$$\epsilon \sim N(0, \sigma_n^2), \tag{3.2}$$

The likelihood function, the probability density of the observation given the parameters, will then have the following form:

$$p(y|x, w) = \prod_{i=1}^{n} p(y_i|x_i, w) = \prod_{i=1}^{n} \frac{1}{\sqrt{2\pi}\sigma_n} exp(-\frac{(y_i - x_i^T w)^2}{2\sigma_n^2}) \tag{3.3}$$

The idea of Bayesian linear model is mainly based on the posterior distribution computed by Bayes' rule:

$$p(w|y, x) = \frac{p(y|x, w)p(w)}{p(y|x)} \tag{3.4}$$

To calculate the posterior, we also need a prior over the parameters. The prior is usually considered as to represent our prior beliefs over the distribution of the parameters we expect to observe before seeing any data. Therefore, we put a zero mean Gaussian prior with covariance matrix Σ on the weights:

$$w \sim N(0, \Sigma) \tag{3.5}$$

Another essential part is the marginal likelihood function $p(y|x)$. The marginal likelihood,(normalizing constant), gives the likelihood of the output by considering only one specific kind of input and is independent of the other factors. To be specific, the marginal likelihood of expected output here only consider the effect of

the input x without taking the effect of the weights w into account. Therefore, it is given by

$$p(y|x) = \int p(y|x,w)p(w)dw \tag{3.6}$$

By now, combine the likelihood function in 3.3 with the prior in 3.5 and marginal likelihood function in 3.6, we could obtain the actual form of the posterior $p(w|x,y)$ in 3.4

$$p(w|y,x) = \frac{p(y|x,w)p(w)}{p(y|x)} \propto exp(-\frac{1}{2}(w-\bar{w})^T(\frac{1}{\sigma_n^2}xx^T + \Sigma^{-1})(w-\bar{w})) \tag{3.7}$$

From 3.7, it can be seen that the posterior is actually another Gaussian distribution with the new mean and new covariance matrix.

$$\begin{aligned} \bar{w} &= \sigma_n^{-2}(\frac{1}{\sigma_n^2}xx^T + \Sigma^{-1})^{-1}xy \\ \Sigma_{new} &= \frac{1}{\sigma_n^2}xx^T + \Sigma^{-1} \end{aligned} \tag{3.8}$$

For Bayesian linear regression, the prediction is made by all possible parameters along with corresponding posterior probability. Thus, we could conclude the predictive jointly distribution of the output f_{new} of an new data point x_{new} based on the training dataset x along with their weights w and their outputs y as follows :

$$\begin{aligned} p(f_{new}|x_{new},y,x) &= \int p(f_{new}|x_{new},w)p(w|x,y)dw \\ \sim N(\frac{1}{\sigma_n^2}x_{new}^T(\sigma_n^2xx^T + \Sigma^{-1})^{-1}xy, & x_{new}^T(\sigma_n^2xx^T + \Sigma^{-1})^{-1}x_{new}) \end{aligned} \tag{3.9}$$

3.2 Gaussian Process Regression

A Gaussian process, a distribution over a set of functions, is fully specified by its mean function and covariance function as 3.10

$$f(x) \sim GP(m(x), k(x,x')) \tag{3.10}$$

where the mean function m(x) and the covariance function $k(x,x')$ are:

$$m(x) = E[(f(x))] \tag{3.11}$$

$$k(x,x') = E[(f(x)-m(x))(f(x')-m(x'))] \tag{3.12}$$

Normally, for the sake of simplicity, we will take the mean function to be zero and only consider the effect of covariance function. In fact, the problem of learning in Gaussian Process is the problem of finding suitable properties for the covariance

functions.[**?**]

Since the Bayesian linear regression model has a natural disadvantages in terms of expressiveness and the relationship between our input and targeted value is barely linear, we take the advantage from Gaussian Process in terms of dealing nonlinear problem by utilizing the kernel function.

The principle of a kernel function is to project the original nonlinear input data into a higher dimensional space where they become linear separable so that the linear model could be implemented directly in that space. The Fig3.1 shows ideal of the kernel function

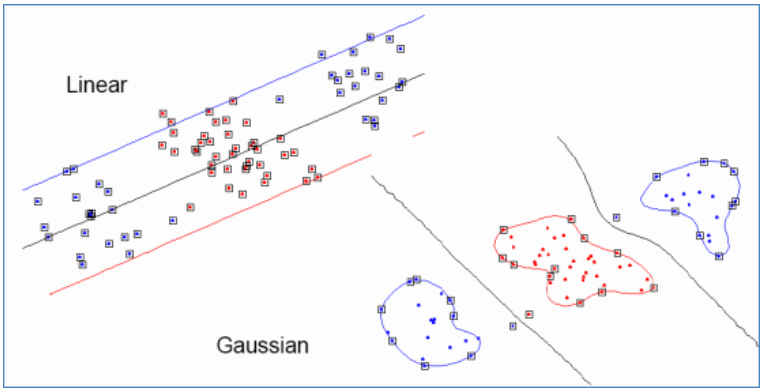


Figure 3.1. Projection of data from low-dimensional space into higher dimensional space by Radius Basis Function makes inseparable data separable

To be more specific, the Gaussian Process specifies the covariance function as the kernel function which takes the inner dot product between a pair of random variables and we assume the observations have independent identically distributed Gaussian noise, then the prior of the observations becomes:

$$cov(f(x_a), f(x_b)) = k(x_a, x_b) + \sigma_n^2 \delta_{ab} \tag{3.13}$$

where the $k(x_a, x_b)$ is a general form of kernel function.[1] and δ_{ab} is a Kronecker delta which is one iff $a \equiv b$ and zero otherwise.

Then, we could generate the joint distribution of the observations y and the predicted value f_{new} under the prior as

$$\begin{bmatrix} y \\ f_{new} \end{bmatrix} \sim N\left(0, \begin{bmatrix} k(x,x) + \sigma_n^2 I & k(x, x_{new}) \\ k(x_{new}, x) & k(x_{new}, x_{new}) \end{bmatrix}\right) \tag{3.14}$$

[1]There are many different kinds of kernel functions such as Radius Basis Function, Polynomial Function and Sigmoid Function. Linear function is also one of the simplest kernel function.

Deriving the conditional distribution, we finally arrive at the key predictive equations for Gaussian process regression

$$f_{new}|x, y, x_{new} \sim N(\bar{f}_{new}, cov(f_{new})), \quad where \tag{3.15}$$

$$\bar{f}_{new} = k(x_{new}, x)[k(x, x) + \sigma_n 2I]^{-1} y \tag{3.16}$$

$$cov(f_{new}) = k(x_{new}, x_{new}) - k(x_{new}, x)[k(x, x) + \sigma_n 2I]^{-1} k(x, x_{new}) \tag{3.17}$$

This equations give us the corresponding mean value and covariance value of the predictive point which is used to represent the predicted point. A graphical model of Gaussian Process is can be seen in Fig3.2.

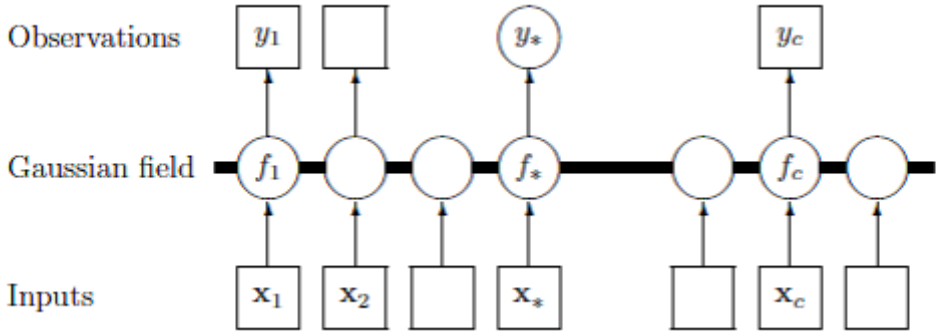


Figure 3.2. Graphical model for a GP for regression.[18]

3.3 Property of Gaussian Process

As a supervised learning algorithm, the Gaussian Process are also based on the idea that similar input give result in the similar outputs or output distributions. But it also have its unique strengths compare with ANN (Backpropagation (BP) algorithm as example) and SVR.

When it comes to BP algorithm, firstly, Since BP algorithm is based on the Empirical risk minimization, it is minimizing the expected error of the model by minimizing the differences between the output of training data and their corresponding true value. This will lead to a serious overfitting problem and poor generalization for new data since it only optimizes the parameters based on training set without considering the test set. Secondly, for a particular BP model, the number of layers of hidden units and the number of units in each layers play an irreplaceable role in ANN algorithm but how to decide these value still remain as a series problem and need to solved. Besides, the BP model adjusted the weights by iteratively calculating the difference between the predicted value and the true ones and giving

feedbacks to the system, this principle is in fact similar to the idea of gradient descending. As a result, it will have a low convergence rate and could not guarantee to find the global optima every time.

As for the SVR, it improves this situation by using structure risk minimization and introducing the penalty coefficient. The structure risk minimization describes the minimization of the sum of the empirical risk and VC confidence which is caused by the complexity of the function space. These principles could avoid the overfitting problem efficiently and allow the model to have a better generalization capacity. However, the SVR still has many obvious problems such as the choice of the type of kernel function and its parameters and the proper value for the penalty coefficient. In addition, the output of SVR is lack of probabilistic meaning.

The Gaussian Process is based on the Gaussian distribution and Bayesian theory which implies a solid foundation of probabilistic and statistic. For example, the Gaussian Process not only give the predicted value but also the uncertainty of the prediction. This property makes the prediction easier to interpret and understand. What's more, in terms of the choice of hyperparameters, the Gaussian Process is self-adaptive. In other words, the Gaussian Process choose the optimal hyperparameters during its process of training a model while SVR could only choose them by using cross-validation method or based on the pervious experiences.

Chapter 4

Feature selection

Another key point of this thesis is the feature selection. As mentioned in section 2, most of the state-of-art features have strong connection with the biology aspect. However, few of the so-called less-biological meaningful features have been implemented and investigated so far. Therefore, in this chapter, we will introduce some methods of feature selection that the selected features have less biological meaning and explain the theory behind each of them. The performance of these features will be compared with some benchmarks and fully discussed in the chapter 6.

Before introducing the methods, we will briefly describe a few concepts that we will involve latter so that one could understand the method easier.

- Peptide: Short sequence(chain) of amino acid connected by peptide bonds as Fig. 4.1 It's distinguished from proteins on the basis of size which only contain approximately 50 or fewer amino acid.

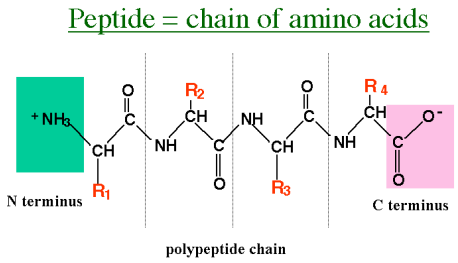


Figure 4.1. Peptide model

- Amino acid: Biologically important organic compounds composed of amine (-NH2) and carboxylic acid (-COOH) functional groups, along with a side-chain specific to each amino acid. There are approximately 20 basic types and Fig. 4.2 is an example of one of them. They are the basic unit composed

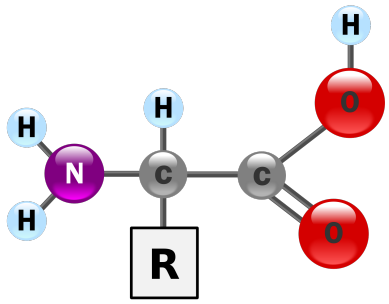


Figure 4.2. Alpha Amino Acid

of protein, giving protein their specific structural form so that they could have biological activity.

- Hydrophobicity: A physical property of a molecule that is seemingly repelled from a mass of water. It has a great impact in terms of interaction between different proteins, the structure of the protein. And more importantly, in this case, the peptide retention time has a strong relationship with it.

- Substitution matrix: a matrix that gives the score for a pair of amino acid which is using for forming the feature matrix later.

4.1 Bag of Word

4.1.1 Theory

The idea of feature selection by Bag of Word method is implement comparison of strings by embedding sequential data in a vector space.[17].

To be more specific, the peptide sequence is characterized by a predefined set of strings which is considered as the embedding language L and each of the strings in this set is the word w of L. In general, there are two ways to define the embedding language L and its words w. Here we only discuss one method called $n-grams$.

The $n-grams$ method is simply shift a small window with fixed length n along all of the peptide sequences to extract substrings with length n. The language L is then consist of all the possible substrings that have been extracted.

After establishing the embedding language L, we try to project each peptide p_i into a vector space spanned by the words of L using a function ϕ defined as

$$\phi : p_i \rightarrow \phi_w(p_i), \quad w \in L \tag{4.1}$$

where the return of $\phi_w(p_i)$ is defined as frequency for the occurrences of w in p_i.

In our case, we use $2-grams$ method to build our embedding language L then each w in L is a 2-amino-acid group and since we have 20 different amino acid in total, each of the peptide will be represented by the frequencies of occurrences of 400 words. A graphical flow of the bag-of-word method can be seen as Fig.4.3:

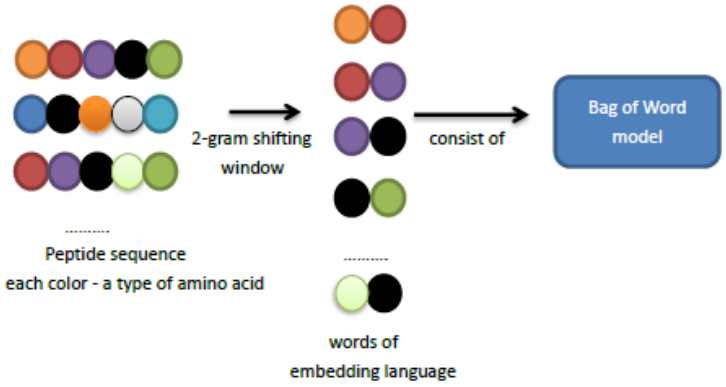


Figure 4.3. Bag of Word

Since the number of the words w in L is directly related to the length of the peptide sequence, the length of the peptide will be used as a feature to characterize the peptide.

In addition, knowing that the hydrophobicity has influenced the retention time of the peptide greatly, it is reasonable to include the hydrophobicity of the peptide in the feature set too.

4.2 Property

The advantages of the Bag-of-Word method are mainly showed in two aspects: complexity and flexibility.

In terms of complexity, the most popular features that have been used nowadays are biological features, such as amino acid number, amino acid relative position, secondary structure of peptide, peptide bond and so on. However, in order to calculate these features, a large amount of time is required. What's worse, some particular facilities are needed to calculate some of them, such as the secondary structure. Comparing with these features extraction methods, the computational cost of our method is very low. According to [17], the run-time complexity of Bag-of-Word is

$O(|x| + |y|)$ when it is $O(|x| \cdot |y|)$ for another benchmark method.

When it comes to the flexibility, since the embedding language L is constituted by the words that are directly and simply extracted from the samples, this method could easily change the language set L for particular context of the task which might imply a wider applicability in other field of biological research.

4.3 Alignment Analysis

Another alternative method is called alignment analysis. The alignment techniques are widely used in biology analytical field. Different alignment methods have been created for different purposes.

4.3.1 Theory

The idea of our alignment analysis is firstly establishing a 20×20 scoring matrix as Fig 4.4 for each potential pair of amino acid. We use Blosum 50 matrix here as one of the most popular scoring matrix in biology.

	Ala	Arg	Asn	Asp	Cys	Gln	Glu	Gly	His	Ile	Leu	Lys	Met	Phe	Pro	Ser	Thr	Trp	Tyr	Val
Ala	4																			
Arg	-1	5																		
Asn	-2	0	6																	
Asp	-2	-2	1	6																
Cys	0	-3	-3	-3	9															
Gln	-1	1	0	0	-3	5														
Glu	-1	0	0	2	-4	2	5													
Gly	0	-2	0	-1	-3	-2	-2	6												
His	-2	0	1	-1	-3	0	0	-2	8											
Ile	-1	-3	-3	-3	-1	-3	-3	-4	-3	4										
Leu	-1	-2	-3	-4	-1	-2	-3	-4	-3	2	4									
Lys	-1	2	0	-1	-3	1	1	-2	-1	-3	-2	5								
Met	-1	-1	-2	-3	-1	0	-2	-3	-2	1	2	-1	5							
Phe	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	6						
Pro	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-3	-1	-2	-4	7					
Ser	1	-1	1	0	-1	0	0	0	-1	-2	-2	0	-1	-2	-1	4				
Thr	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	1	5			
Trp	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	1	-4	-3	-2	11		
Tyr	-2	-2	-2	-3	-2	-1	-2	-3	2	-1	-1	-2	-1	3	-3	-2	-2	2	7	
Val	0	-3	-3	-3	-1	-2	-2	-3	-3	3	1	-2	1	-1	-2	-2	0	-3	-1	4

Figure 4.4. The Blosum 50 scoring matrix of a pair of amino acid

The element of the matrix is the score between each pair of amino acid. Similar with the bag of word model, we extract $2 - gram - words$ as representative features in this case. But instead of counting the frequencies of occurrences of each pair of amino acid, we compute the score based on the scoring matrix.

As a result, we could assign each pair of amino acid a score, and build one matching matrix for each peptide and one feature. After building up the matching matrix, we find the maximal value in the matrix to build the feature matrix since the score

means the similarity between the peptide and the feature.

Therefore, we could have a feature matrix that each element is the maximal score for each peptide and one feature. Then we could use these feature to train the model and make the prediction. The hydrophobicity and the length of each peptide are also included in this case.

4.4 Property

The alignment analysis method is developed based on the biological theory and using some biological scoring matrix to measure the similarity and further form the features. Therefore, compared with the bag of word model, it has more biological meaning and easier for biologists to understand and interpret. But since to gain the features we need to calculate a lot of different matrices, the computational cost could be a potential drawback of this method.

Chapter 5

Optimization

In the Gaussian Process model, the most important part is the covariance function of the model since the Gaussian Process consider it as the kernel function. The value of the covariance function along with the value of mean function are known as the hyperparameters in this case. Initially, we need to determine the hyperparameters manually. However, since we do not know the best combination of these hyperparameters beforehand, therefore, we have a group of parameters $[w, \sigma, \mu]$ where w is the weighted factor of kernel function and σ is the value of covariance function and μ represent the value of mean function that need to be optimized for the best performance.

As for the definition of optimizing the model, we simply aim at minimizing the error between the predicted retention time and the true one. Thus, the objective function in this case is the negative log marginal likelihood of Gaussian Process as 5.1

$$minf(x) = -logp(y|x, \theta) = \frac{1}{2}y^T(C)^{-1}y + \frac{1}{2}log|C| + \frac{n}{2}log(2\pi) \tag{5.1}$$

where $C = k(x, x) + \sigma_n^2 I_n$

Here, we will implement two different optimization method that based on different principles. The first one is Conjugate Gradient method and the second one is Particle Swarm Optimization method. The principle of each method will be explained in detail along with their own strengths and drawbacks towards this case.

5.1 The Conjugate Gradient

5.1.1 Principle

Since we want to optimize the hyperparameter group $[w, \sigma, \mu]$, we will try to find the minimum value of the objective function. The conjugate gradient method is one

of widely used method and is developed based on the gradient descending method and Newton Method.

In CG theory, we have two important assumptions: (1)Linearity: the k_{th} search direction d_k is the linear combination of all the previous directions. (2)Conjugation: all the search direction are conjugated with some positive definitive matrix A.

The first assumption allow as to have the follow equation:

$$d^k = -g^k + \beta_{k-1} d^{k-1} \tag{5.2}$$

whereg^{k+1} is the gradient of current point and β_k is some coefficients that need to be calculated. The second assumption is actually used to allow us calculating the β_k

The process of Conjugate Gradient(CG) method could be described as Fig.5.1

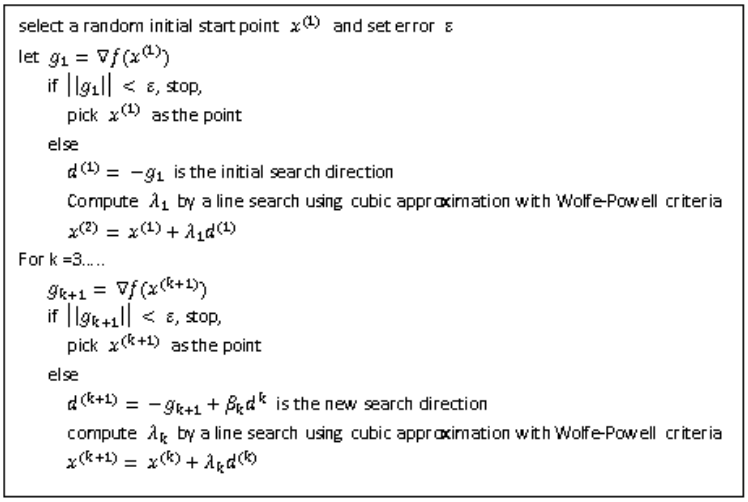


Figure 5.1. Conjugate Gradient algorithm

From the algorithm above, we could see the CG method firstly finds a descent direction along which the objective function 5.1 will be reduced and then computes a step size that determines how far should we move along the direction, aiming at find a local minimum of the objective function.
Therefore, the problem could approximately be divided into two parts: Searching the descending direction and determining the step size iteratively. To be more specific, find the proper value for parameters β_k and λ_k respectively.

When it comes to the search direction, due to the second assumption of CG method, we could know that

$$\beta_j = \begin{cases} = 0 & j = 0....k-1 \\ \neq 0 & j = k \end{cases}$$

Therefore, we are able to compute the β_k by some methods. In fact, we have many different ways to calculate the parameters β_k and each of them based on different principles. Here, we implement the Polak-Ribiere method[19] that compute the parameter β_k as 5.3.

$$\beta_k = \frac{g_{k+1}^T(g_{k+1} - g_k)}{g_k^T g_k} \tag{5.3}$$

After getting the new search direction $d^{(k+1)}$, the problem comes to define the step size λ_k. Here, we use cubic approximation to compute the new step size as 5.4

$$\begin{aligned} \lambda_k &= \lambda_{k-2} - \frac{(-d^{(k-2)}d^{(k-2)}) * (\lambda_{k-1} - \lambda_{k-2})^2}{(B + \sqrt{(B*B - A*(-d^{(k-2)}d^{(k-2)})) * (\lambda_{k-1} - \lambda_{k-2})})} \\ A &= 6*(f(x_{k-2}) - f(x_{k-1})) - 3*(-d^{(k-1)}d^{(k-1)} + (-d^{(k-2)}d^{(k-2)})) * (\lambda_{k-1} - \lambda_{k-2}) \\ B &= 3*(f(x_{k-1}) - f(x_{k-2})) - (2*(-d^{(k-2)}d^{(k-2)}) + (-d^{(k-1)}d^{(k-1)})) * (\lambda_{k-1} - \lambda_{k-2}) \end{aligned} \tag{5.4}$$

We will then calculate the objective function value $f(x_k + a_k d_k)$ and new slope $g_{k+1}^T d_k$ based on this new step size λ_k and judge it by using the Wolfe-Powell conditions as 5.5

$$\begin{aligned} f(x_k + \lambda_k d_k) &\leq f(x_1) + \lambda_1 \rho g_1^T d_1 \\ g_{k+1}^T d_k &\geq \sigma g_1^T d_1 \qquad \sigma \in (\rho, 1), \quad \rho \in (0, \frac{1}{2}) \end{aligned} \tag{5.5}$$

If the current point objective function value and slope fulfill the Wolfe-Powell conditions, we could claim we find the proper step size that is calculated by the cubic extrapolation and stop searching.

By doing these iteratively, we could minimize the objective function and eventually have the set of hyperparameters $[w, \sigma, \mu]$ that gives the minimum value of the objective function or fulfills the required accuracy.

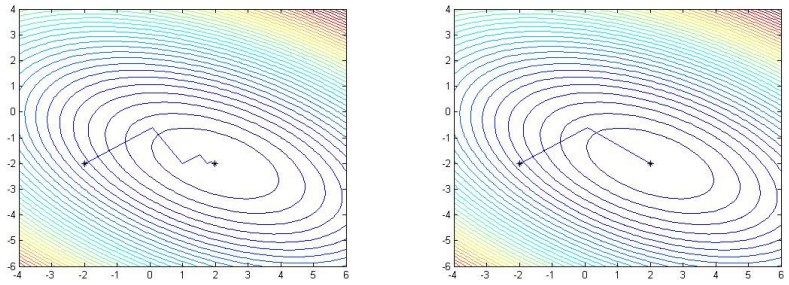
5.1.2 Strength and Drawbacks

The CG method is based on the gradient descent and Newton method. It only uses the information provided by the first order derivative which means it does not need

any further information and could be easily implemented in many aspects.

This property also implies that it does not need to compute and store the Hesse Matrix as well as its inverse. As a result, it could reduce the computational cost significantly compared with the Newton method.

What's more, since the traditional gradient descent method will slow down the searching rate dramatically when it is getting closer to the minimal value, the CG manage to overcome this drawback of the gradient descent by using the conjugation which could speed up the convergence rate. The following plots show the convergence rate of two different methods



(a) Gradient Descent (b) Conjugate Gradient

Figure 5.2. Comparison of convergence rate

However, one of the most limitation of the CG method is its dependency on the initial point which would have a great influence on the final result. The CG method could not ensure to converge to the minimum value in the whole search space.

5.2 The Particle Swarm Optimization

5.2.1 Principle

The Particle Swarm Optimization (PSO) method is one of the new iterative methods for problem optimization. It improves the solution by iteratively searching for the best result in current circumstance.

Initially, we have a branch of separated particles that represent the potential solution by their position, a group of parameters $[w, \sigma, \mu]$ in our case. And for each parameter in the one particle, we assign different velocity for them. In each iteration, the particle updates its position simply by its velocity of each parameter. Then we using these parameter to calculate the model and evaluate the result by some predefined loss functions. After that, we record the best position for each particle(local

optimal value) as well as the best position in the whole search space(global optimal value).

The wisest part of this method is the update of the velocity of each particle. The individual velocity for each particle is influenced not only by its local best known position (local optimal value) but also the best known positions in the search-space (global optimal value), which are updated as better positions are found by other particles. This is expected to move the swarm toward the best solution.

In the end, the iteration will be terminated by some criterion, such as the maximal number of iterations or a solution that gives the adequate loss function value is found. The following Fig. 5.3 shows the basic algorithm of Particle Swarm Optimization

5.2.2 Strength and Drawbacks

PSO is a heuristic search algorithm based on swarm intelligence since it makes no assumptions about the problem being optimized and can search very large spaces. Therefore, PSO can also be used on optimization problems that are partially irregular, noisy, change over time, etc. What's more, since it uses swarm intelligence which means each of the particle is related to the others and the final result is depended on the contribution of all particles, the robustness of system is strong and will not be be dramatically influenced by some outliers. In addition, its strengths in terms of convergence, global search capacity and practicability also make it one of the most popular optimization algorithm in the world.

However, as one of the main weakness of all the heuristic algorithm, PSO do not guarantee an optimal solution is ever found. More specifically, PSO does not use the gradient of the problem being optimized, which means PSO does not require that the optimization problem be differentiable as is required by classic optimization methods such as gradient descent and quasi-newton methods. As a result, it might find the local optimal value instead of the optimal value in the whole search space and consider it as the "global optimal value" due to the its convergence.

To overcome the shortages of the PSO method, a number of different methods based on the original PSO have been carried out, such as Gray-PSO, Chaos-PSO and so on. Each of these method has combined PSO with some other method so that it could overcome the problem of the original PSO and has its own advantage when dealing with some specific tasks. In this thesis, since the top priority is not given to the optimization part, we will simply use the original PSO method instead of the other methods.

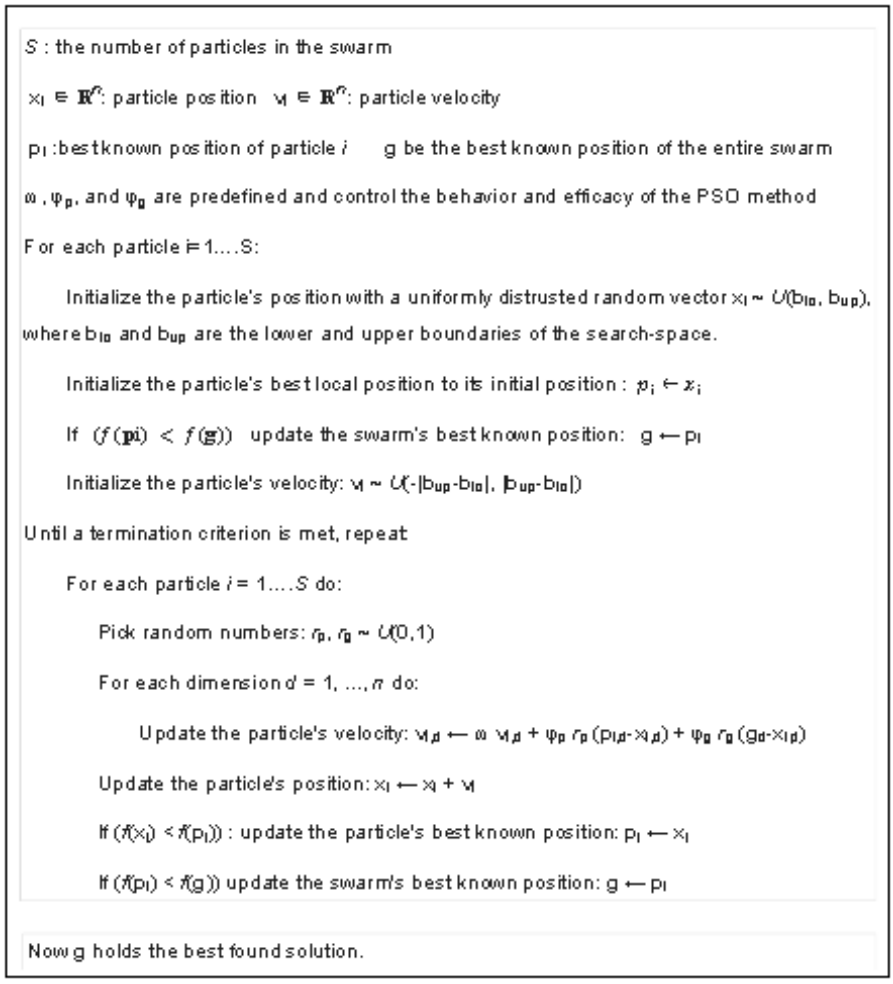


Figure 5.3. Particle Swarm Optimization

Chapter 6

Results and Evaluation

In this section, we will firstly describe the experimental setup for the evaluation and then benchmark the prediction of Gaussian Process with the two other methods. After that, a few comparison in terms of different parameters and different optimization methods will be covered. Before introducing the experimental setup, we will introduce two main concepts which we will use for evaluation later: Pearson Correlation Coefficient and minimal time window.

- Pearson Correlation Coefficient:
  In statistic theory, Pearson correlation coefficient is used to identify the linear correlation between two variables X and Y. The formula is as follow:

$$\rho = Cor(X, Y) = \frac{Cov(X, Y)}{\sqrt{Var(X)Var(Y)}} \tag{6.1}$$

  The value of Pearson Correlation Coefficient is between -1 and 1. A value of 1 (or -1)implies that a linear equation describes the relationship between X and Y perfectly, the sign implies whether the relationship is positive or negative. A value of 0 implies that there is no linear correlation between the variables. The closer the value is to 1, the stronger the linear relation they have, otherwise, the weaker the relation they have.

- Minimal Time Window:
  The minimal time window is a time window including the deviations between observed and predicted retention times for 95% of the peptides ($\Delta t95\%$). Given the time window, we could know the expected range of observing time in advance and thus enhanced paralleling generating ability of the retention time of peptide. In this case, the smaller the time window is, the more peptide we could generating at the same time.

Chapter 7

Discussion

Chapter 8

Conclusion and Future Work

sfklesjlksjflkesklfjksjfkls sjeflkjleskfjlesflkesjlskef lsefjl;seflkejfkl jfeiwjoiew sjeflkjselkfjkleiowjiojvopwioepwj 'sjf;lefji[ioj;fw weojfopjjfejpcjl

Bibliography

[1] Baczek T, Wiczling P, Marszall M, et al. (2005). "Prediction of peptide retention at different HPLC conditions from multiple linear regression models." Journal of Proteome Research, 4(2):555¨C63

[2] Petritis K, Kangas LJ, Ferguson PL, et al. (2003). "Use of artificial neural networks for the accurate prediction of peptide liquid chromatography elution times in proteome analyses." Analytical Chemistry, 75(5):1039¨C48

[3] Petritis K, Kangas LJ, Yan B, et al. (2006). "Improved peptide elution time prediction for reversed-phase liquid chromatography-MS by incorporating peptide sequence information." Analytical Chemistry, 78(14):5026¨C39.

[4] Klammer AA, Yi X, MacCoss MJ, et al. (2007). "Improving tandem mass spectrum identification using peptide retention time prediction across diverse chromatography conditions." Analytical Chemistry, 79(16):6111¨C8

[5] Luminita Moruz, Daniela Tomazela, Lukas Kall,(2010). "Training, Selection, and Robust Calibration of Retention Time Models for Targeted Proteomics"

[6] Luminita Moruz,(2013). "Chromatographic retention time prediction and its applications in mass spectrometry-based proteomics".

[7] Mant, C. T., and Hodges, R. S. (2002). "Analytical HPLC of peptides, in HPLC of Biological Macromolecules" (Gooding, K. M., and Regnier, F. E., eds) pp. 433¨C511, Marcel Dekker, New York.

[8] Meek JL (1980). "Prediction of peptide retention times in high-pressure liquid chromatography on the basis of amino acid composition." Proceedings of the National Academy of Sciences of the United States of America, 77(3):1632¨C6.

[9] Houghten RA and DeGraw ST (1987). "Effect of positional environmental domains on the variation of high-performance liquid chromatographic peptide retention coefficients." Journal of Chromatography, 386:223¨C8.

[10] Browne CA, Bennett HP, and Solomon S (1982). "The isolation of peptides by high-performance liquid chromatography using predicted elution positions." Analytical Biochemistry, 124(1):201¨C8.

[11] Zhou NE, Mant CT, and Hodges RS (1990). "Effect of preferred binding domains on peptide retention behavior in reversed-phase chromatography: amphipathic alpha-helices." Peptide Research, 3(1):8¨C20.

[12] Mant CT and Hodges RS (2006). "Context-dependent effects on the hydrophilicity/hydrophobicity of side-chains during reversed-phase high-performance liquid chromatography: implications for prediction of peptide retention behaviour." Journal of Chromatography A, 1125(2):211¨C9.

[13] Guo DC, Mant CT, and Hodges RS (1987). "Effects of ion-pairing reagents on the prediction of peptide retention in reversed-phase high-performance liquid chromatography." Journal of Chromatography,386:205¨C22.

[14] Gilar M, Xie H, and Jaworski A (2010). "Utility of retention prediction model for investigation of peptide separation selectivity in reversed-phase liquid chromatography: impact of concentration of trifluoroacetic acid, column temperature, gradient slope and type of stationary phase." Analytical Chemistry, 82(1):265¨C75.

[15] Krokhin OV, Craig R, Spicer V, et al. (2004). "An improved model for prediction of retention times of tryptic peptides in ion pair reversed-phase HPLC:its application to protein peptide mapping by off-line HPLC-MALDI MS." Molecular Cellular Proteomics, 3(9):908¨C19.

[16] Kaliszan R, Baczek T, Cimochowska A, et al. (2005). "Prediction of high-performance liquid chromatography retention of peptides with the use of quantitative structure-retention relationships." Proteomics, 5(2):409¨C15.

[17] Konrad Rieck.(2011)"Similarity measures for Sequential data"

[18] C. E. Rasmussen C. K. I. Williams,(2006) "Gaussian Processes for Machine Learning", the MIT Press.

[19] B. T. Polyak. (1969) "The conjugate gradient method in extreme problems." USSR Comp Math Math Phys, 9(4): 94-112.

Appendix A

RDF

And here is a figure

Figure A.1. Several statements describing the same resource.

that we refer to here: A.1