Large-scale proteomic analysis is emerging as a powerful technique in biology and relies heavily on data acquired by state-of-the-art mass spectrometers. As with any other field in Systems Biology, computational tools are required to deal with this ocean of data. iTRAQ (isobaric Tags for Relative and Absolute quantification) is a technique that allows simultaneous quantification of proteins from multiple samples. Although iTRAQ data gives useful insights to the biologist, it is more complex to perform analysis and draw biological conclusions because of its multi-plexed design.

One such problem is to find proteins that behave in a similar way (i.e. change in abundance) among various time points since the temporal variations in the proteomics data reveal important biological information. Distance based methods such as Euclidian distance or Pearson coefficient, and clustering techniques such as k-mean etc, are not able to take into account the temporal information of the series. In this paper, we present an linear-time algorithm for clustering similar patterns among various iTRAQ time course data irrespective of their absolute values. The algorithm, referred to as Temporal Pattern Mining (TPM), maps the data from a Cartesian plane to a discrete binary plane. After the mapping a dynamic programming technique allows mining of similar data elements that are temporally closer to each other. The proposed algorithm accurately clusters iTRAQ data that are temporally closer to each other with more than 99% accuracy. Experimental results for different problem sizes are analyzed in terms of quality of clusters, execution time and scalability for large data sets. An example from our proteomics data is provided at the end to demonstrate the performance of the algorithm and its ability to cluster temporal series irrespective of their distance from each other.

1 Introduction

Mass spectrometry is a fundamental part of any modern proteomics research platform for accurate protein identification and quantification [1] [2] [3]. Mass spectrometers measure the mass-to-charge ratio (m/z) of ionized particles [4]. In the case of a typical LC-MS/MS proteomic experiment, the ionized particles (i.e. peptides) are introduced into a mass spectrometer at the ion source in the form of liquid solutions, then desolvated and transferred into the gas phase as gas phase ions. A variety of search algorithms are then used to match the peptide spectra to sequences in online databases in order to identify the proteins in the mixture [5] [6].

iTRAQ (isobaric tags for relative and absolute quantification) is a technique used to identify and quantify proteins from different sources in one single experiment. It uses isotope coded covalent tags and is used to study quantitative changes in the proteome [7] [8]. The method is based on covalent labeling of the N-terminus and lysine side chains from protein digestions with tags of various masses for distinction. Up to 8 different tagging reagents (8-plex kit) are used to label peptides from different samples. The samples are then pooled together as a single sample and analyzed by mass spectrometer. The fragmentation of the attached tag generates a low molecular mass reporter ion which is useful in quantifying relative peptide abundance between the different iTRAQ channels.

The iTRAQ technique allows analysis of samples in a more sophisticated and accurate manner in turn giving more relevant biological information such as phosphorylation of peptides or the effect of vasopressin at different time points in the mass spec. Although the technique allows greater accuracy in quantitation, it raises many com-
putational problems. One such problem is to identify the peptides that behave similarly for a given external agent e.g. dDAVP over the time course study. Time course measurements from iTRAQ data are becoming a common procedure in many systems biology experiments [9] [10] [11].

If the experiment is subject to variations in time, the conventional methods to cluster and analyze the similarity such as Euclidean distance, Hamming distance have significant limitations. Likewise the clustering mechanisms that use distance based measures such as k-means [12], or hierarchical clustering [13] do not always succeed when responses are highly variable in magnitude. Other methods such as fuzzy clustering of short time-series [14] are not computationally efficient after a certain number of time courses due to the combinatorial explosion in possibilities. A facilitating characteristic of successful scalable clustering is still to find a linear algorithm that involves a small number of passes over the database [15].

In this paper we present a near-linear time clustering algorithm that finds temporal patterns in a given large iTRAQ labeled dataset using one or small number of passes over the data and without compromising the quality of the clusters. Our algorithm draws its motivation from mapping problems in the parallel processing community [16] [17] and quantization in information theory [18] [19]. The proposed algorithm allows us to map the time points of a Cartesian plane into a discrete plane. The mapping then produces a predictable number of clustering possibilities that are then binned using an efficient dynamic programming technique to extract the patterns.

The paper is organized as follows. In section 2 we provide the biological experimental details and the associated computational problem. Section 3 discusses the proposed clustering algorithm and complexity analysis. Section 4 discusses the experimental results and illustrative examples for our clusters. Finally, conclusions are presented in section 5 of the paper.

## 2 Problem Statement

The objective of the study was to perform a quantitative comparison of protein phosphorylation under vasopressin(dDAVP) treatment using iTRAQ labels for different time points. LC-MS/MS [20] phosphoproteomics analysis was performed and the time course clusters that would be obtained from the study provides the basis for modeling the signaling network involved. The flow diagram for the experiment is shown in Fig.1.

In computational terms, the problem that we wish to solve is as follows. We are given a set of peptides with time points \( t_1, t_2, \ldots, t_n \) with each time point having a certain real value which in our case is the iTRAQ ratio. Given the peptides with time points and real values, we want to be able to cluster the peptides that give a similar pattern over the time course. An example of such is shown in the figure 2.

The first column in figure 2 shows peptide sequences followed by 4 columns of iTRAQ ratios corresponding to the change in peptide abundance between the vasopressin and vehicle control samples (“dDAVP/vehicle”), each corresponding to a different time point. Of course the number of columns would be dependent on the time courses that are considered and can increase or decrease depending on the particular experiment. Our objective is to determine the data points that have similar temporal patterns. It can be seen in the figure that peptide VYEPLK and LEVAK have similar patterns over the time course because both increase from point \( t_1 \) to \( t_2 \), decrease from \( t_2 \) to \( t_3 \) and increase from \( t_3 \) to \( t_4 \). The peptide IHIDPE on the other hand increases for all the time points. Hence, the peptides VYEPLK and LEVAK must be clustered together.

![Figure 1: The Flow diagram for the experiment](image.png)

![Figure 2: The peptides with corresponding time scales and their values. The first and third peptides belong to the same cluster](image.png)
Now let us formally define the problem. Let there be \( N \) data points with each data point having \( K \) time course values and \( X \) represents the peptide name. Then, let \( U \) present the set such that \( U_i = \{X_i, (t_1, \cdots, t_K)\} \) where \( 1 \leq i \leq N \). Also, let the number of clusters be \( Q \). Then, cluster set \( C = \{c_1, c_2, \cdots, c_Q\} \) where each \( c_j \in U_i \) such that \( 1 \leq i \leq N \) and \( 1 \leq j \leq Q \). Then each of the cluster \( c_j \) has the set of data points that have the same temporal pattern with time.

The temporal similarity is defined as follows. Let \( c_{pq} \) represent \( q \)th data point in cluster \( p \) where \( 1 \leq p \leq Q \) and \( 1 \leq q \leq N \). Now let \( c_{pq}(x) \) represent the mapped data point at point \( x \). Let there be another mapped data point \( c_{pq}(y) \) at point \( y \) and \( \forall x < y \). Now define an array \( r_h \) where \( 1 \leq h \leq K \). Each point in array

\[
 r_h = c_{pq}(y) - c_{pq}(x) \tag{1}
\]

Then, the data points that have strictly equal \( r_h \) would be considered temporally similar.

3 Proposed Mining Algorithm

In this section, we present details of the proposed mining strategy, referred to as Temporal Pattern Mining (TPM). We also analyze the computational complexities of the proposed algorithm.

The proposed algorithm TPM draws its motivation from the mapping problem in parallel and distributed computing \cite{16, 21, 17} and information theory \cite{18, 19}. The mapping problem in parallel computing and mapping for our mining algorithm share a similar characteristic. In mapping for parallel processing, two sets of nodes are considered: problem modules and processor modules. The objective is to map the problem modules on to processor modules in an efficient manner. In mapping for the mining algorithm we are seeking a mapping such that the Cartesian plane of the data points are mapped onto a discrete plane(e.g. binary plane) of finite possibilities. The discrete plane is defined by using the Nyquist sampling technique that allows conservation of the information from a continuous signal (or a data set with real numbers). These finite possibilities, which can grow exponentially with increasing time courses, are then mined using our efficient dynamic programming technique. Algorithm 1 gives an intuitive description of the strategy.

3.1 Mapping from Cartesian to discrete plane

The proposed algorithm TPM can be classified as a feature extraction algorithm \cite{22}. As defined in the problem statement in the section above we have a number of peptides with associated iTRAQ ratio values and we are inter-

| Data: A set \( U_i = \{X_i, (t_1, \cdots, t_K)\} \) of peptides and their time courses |
| Result: Compute the cluster set \( C = \{c_1, c_2, \cdots, c_Q\} \) such that the clusters have temporal similarity within the distinct clusters |
| for \( i = 1 \) to \( K \) do |
| Compute \( A[i] = mapping(U_i) \) from Cartesian to discrete plane |
| end |
| while there are values in \( A \) that are not null do |
| pick a random value from \( A \) call it \( A^R \) |
| count++ |
| for \( j = 0 \) to \( N \) do |
| distance = EditDistance(\( A^R \), \( A[j] \)) |
| if distance == 0 then |
| \( c_{count} \leftarrow A[j] \) |
| /* This is to eliminate values from \( A \) that have already been assigned to a cluster */ |
| \( A[j] \leftarrow NULL \) |
| end |
| end |
| end |

Algorithm 1: Mapping based temporal pattern mining algorithm

| Data: A data point in the Cartesian plane |
| Result: Return the discrete plane representation of the data point |
| mapping(datapoint \( U_w \)) |
| Vector \( V_w \leftarrow \emptyset \) |
| for \( w = 0 \) to \( U_w \), length() do |
| if \( w = 0 \) then |
| /* save as name of the peptide */ |
| else |
| if \( U_{w+1} - U_w \geq 0 \) then |
| \( V_w = a \) |
| end |
| else |
| \( V_w = b \) |
| end |
| end |
| return \( V \) |

Algorithm 2: Mapping function
Data: Two strings of length m and n
Result: LevenshteinDistance between the two string is returned

```c
/* d is a table with m+1 rows and n+1 columns */

int EditDistance(char s[1..m], char t[1..n])
int d[0..m, 0..n] ← ∅
for i from 0 to m do
    d[i, 0] := i /* deletion */
end
for j from 0 to n do
    d[0, j] := j /* insertion */
end
for j from 1 to n do
    for i from 1 to m do
        if s[i] = t[j] then
            d[i, j] := d[i-1, j-1]
        else
            d[i, j] := minimum( d[i-1, j] + 1, d[i, j-1] + 1, d[i-1, j-1] + 1)
        end
    end
end
return d[m,n]
```

Algorithm 3: Dynamic programming cluster extraction subroutine

Clustered in extracting clusters of the peptides that give similar expression levels (falling or rising) at different time points. However, k-means or hierarchical clustering cannot be used because the time points may be closer to each other in Euclidean distance, but may not be close in temporal changes over the time course.

Clustering using the real values from the Cartesian plane, however, is not feasible because of its continuous nature (infinite values). Therefore, with Cartesian coordinates the number of possible cluster combinations will be infinite in nature and clustering for all possible combinations is not computationally feasible. Thus, a Cartesian plane coordinates has to be mapped to a more discrete plane coordinates to restrict the number of combinations. The mapping function should be such that it would allow us to quantify the variations in the data with respect to time and also make the values discrete enough such that the number of combinations that are possible would decrease drastically.

To address these challenges, the mapping function that is presented allows us to make the values more discrete and also conserves the important information of expression levels between the time periods. Using the same notation that we presented in the previous section. Let $U_i$ be the set of values such that $U_i = \{X_i, (t_1, \ldots, t_K)\}$ where $1 \leq i \leq N$. $X_i$ represents the peptides and $t_1, \ldots, t_K$ represents the values of the expression level from 1 to $K$. The mapping from the Cartesian plane would be accomplished as follows:

$$[M(x, y) = \begin{cases} 
  a & \text{if } (t_x < t_y) \text{ and } (x < y) \text{ and } (y - x = 1); \\
  b & \text{o.w.} 
\end{cases}]$$

The assumption in the mapping function is that the first value is zero. However, this is an assumption that is appropriate for our data but is a not a generalized rule and can be changed accordingly. The mapping function in its functionality is simple and does the following. It looks for the data points at the next time point. If the current data point is below the previous value it is assigned ‘a’. Otherwise it is assigned ‘b’. Therefore, after the mapping has been completed, each of the time series would be a sequence of a’s and b’s with each of the characters representing the rise or fall in the expression level. The number of discrete levels can change according to the biological system under consideration.

The mapping function has been defined in a way that makes a clear distinction between the data points that have similar temporal patterns and the ones that don’t. Figure 3 shows that data points A(red) and B(black) are very close to each other in distance. However, in our mining scenario we are more interested in the pattern of the expression levels over time and in consideration of our criterion, the data point C(blue) is closer to B(black). If a naive k-means
3.2 Efficient Extraction of Clusters

Once the mapping is complete, the next step is to mine the clusters that are present in the data set. An efficient way is needed to extract the clusters from the mapped data because the number of clusters can increase exponentially with increase in the time points as well as the number of discrete levels desired. Consider, for example, two discrete levels are considered as in our case. The number of clusters would be upper bounded by the order of $Z^N$ (for $Z$ states or $2^N$ for two states), but may or may not be present in the data [23]. Even for a moderately large $N$ the number of combinations are huge and for each data point going through all of the possible combinations is waste of precious computing resources. For TPM we developed an efficient technique that allows us to keep the search space confined to the clusters that are present in the dataset. Therefore, using our technique the exponential search space of possible clusters is minimized to the set of clusters that are present in the dataset. An efficient technique that allows us to keep the search space confined to the clusters that are actually present in the data is far less than the possible number of clusters. Thus, the computational complexity is greatly decreased and makes the system more efficient.

Algorithm 3. The crux of the technique is based on a dynamic programming edit distance algorithm that allow us to calculate the 'distance' of a particular data point from another. We randomly pick a data point from the mapped data values. The randomly mapped data point is then used to calculate the levenshtein distance with other data points. The data values that have zero distance with one another belong to the same cluster, because they would have the same pattern. The technique is very efficient in practice because for large number of time points, the number of clusters that are actually present in the data is far less than the possible number of clusters. Thus, the computational complexity is greatly decreased and makes the system more efficient.

Figure 3: The mapping of a Cartesian plane to a discrete mapped plane

Figure 4: Extraction of clusters after mapping is complete
a two-state dataset. However, it can be further improved by using kd-tree data structure for extraction of clusters for higher dimensional states [24] [25] [26]. The k-d tree is a multidimensional binary search mechanism that represents a recursive subdivision of the data space into disjoint subspaces by means of d-dimensional hyper planes. The root of the tree then represents all the patterns, while the children of the root represents subsets of patterns in the subspaces. Searching for the clusters for the algorithm can then be performed in $O(N^{(1-1/No.of.states)})$. Note that as the number of states increase, the searching time would reduce correspondingly because of the division of subspaces using the hyper planes.

### 3.3 Complexity Analysis

The time complexity of the algorithm can be broken down into two parts. The first part is for the mapping and the second part for the extraction of the clusters. The mapping part has complexity of $O(KN)$ since there are $N$ data elements and each is of length $K$. The second part of the algorithm is for the extraction of the clusters. This part run $Q$ times where $Q$ is the number of clusters present in the data. For each run, dynamic programming algorithm is executed, which runs in $O(K^2)$ time; assumption is that both of the data points that are being compared are equal in length. This procedure runs for $Q$ times giving the complexity of $O(QK^2)$. Thus the total time complexity of the algorithm is $T(.) = O(QK^2) + O(KN)$.

### 4 Performance Evaluation

Performance evaluation was done for the quality of the clusters that were extracted as well as the efficiency of the technique. We tested the algorithm with data from a large-scale quantitative phosphoproteomics experiments done as follows: Inner medullary collecting duct (IMCD) samples were incubated in the presence or absence of 1nM dDAVP (vasopressin) for 0.5, 2, 5, and 15 minutes (N=3) followed by LC-MS/MS-based phosphoproteomic analysis. Quantification used 8-plex iTRAQ and commercially available software. These phosphopeptides were analyzed with our algorithm in order to identify groups that changed in abundance with similar temporal responses after exposure to vasopressin. The algorithm identified 16 clusters of phosphopeptides with distinct temporal profiles. These time-course clusters provide a starting point for modeling of the signaling network involved. The algorithm has been implemented in Java(TM) SE Runtime Environment (build1.6.0). The experiments were conducted on a Dell server consisting of 2 Intel Xeon(R) Processors, each running 2.40 GHz, with 12000 KB cache and 64GB DRAM memory. The operating system on the server is Linux RedHat enterprise version with kernel 2.6.9-89.Ellarge.smp.

For the timing experiments we used the same data that we got from our biological experiments. In order to access the timing for the algorithm, we generated the data as follows. The complexity analysis suggested that the algorithm must exhibit a linear time with increasing data points. Therefore, we wanted to access the timing by keeping other variables relatively constant i.e.

\[ T(.) = O(QK^2) + O(KN) \]

The timings for the algorithm with increasing number of data points is shown in Fig.5 for up to 80000. The timings observed have a linear trend with increasing number of data points as predicted by our complexity analysis. Even for up to 80000 elements the timings observed are no more than 3 seconds. Observe, as the number of clusters decrease, the times observed for the same number of data points have a decreasing trend. The rea-
The quality of the clustering was then compared with other algorithms such as k-means [10] [12], Self organizing maps [11] [27], and Hierarchical clustering [9] [28] [29]. A brief summary of the results from these experiments are in table 1. The assessment of the quality was done as follows. The standard algorithms used as described in [10] [11] [9] on our dataset which are the same iTRAQ labeled data that has been described in the literature. For the clusters that were identified by these algorithms, if there were more than 1% of data points that were incorrect it is labeled as incorrect cluster. Although there are many data points in the cluster that are similar to one another; data points that are incorrectly clustered can have a serious impact on the quantification of the proteins. As shown in the table, the number of clusters that were identified varied according to the algorithm used because of the high variability in the data. For the cluster that were identified, above mentioned criteria was used to distinguish the correct clusters from the incorrect one. The results obtained matched well with the previous studies e.g. In [11] the authors using self organizing maps(SOM) were only able to use 9 clusters that were sufficiently accurate to be used for quantification studies thus limiting the biological meaningful data analysis. Using our algorithm, it can be seen that the number of clusters observed were in agreement with our theoretical analysis. All of the data points that were included in the clusters didn’t had a variation more than 1% making it a highly accurate clustering algorithm for iTRAQ labeled protein quantification analysis.

Table 1: Number of correct clusters with different algorithms

| Algorithm  | Clusters Identified | Correct Clusters |
|------------|--------------------|------------------|
| K-means    | 16                 | 3                |
| Hierarchical | 18              | 6                |
| SOM        | 20                 | 10               |
| TPM        | 16                 | 16               |

Figure 7: Timing with increasing number of time points

Figure 8: Example of clustered data points

Figure 9: Example 2 of clustered data points

We were able to identify 16 distinct clusters for phosphopeptides with distinct temporal profiles. We also performed sub-
clustering of the data purely for biological analysis i.e. for quantification we wanted separate clusters for the ratios that are negative all over the time course, the ones that were positive and the ones that crossed from positive to negative or negative or positive over the length of the experiment. Some examples of the clusters are shown in Figs. 8, 9 and 10 each line presenting a peptide. As shown in Fig. 8 even though the data points have high variability in terms of distance of the points, the points have been clustered accurately with respect to the pattern of the response. For all of the data points that were clustered in Fig. 8 the ratios first decreased then increased and decreased further in the last time point. Same can be observed for Fig. 9 and 10 that even though the points have a lot of variability in terms of distance of the points, they are clustered correctly in terms of patterns over the time.

5 Conclusion

We developed a new algorithm called TPM for clustering time-course patterns following step-inputs in biological systems for iTRAQ labeled phosphopeptides. We tested the algorithm with data from large-scale quantitative phosphoproteomics experiments for up to 80,000 data points and up to 100 time point intervals. Quantification used 8-plex iTRAQ and commercially available software. These phosphopeptides were analyzed with our algorithm in order to identify groups that changed in abundance with similar temporal responses after vasopressin addition. The algorithm maps the data from a Cartesian plane to a discrete binary plane and uses an efficient dynamic programming technique to mine similar patterns after mapping. The mapping allows clustering of similar time courses that are temporally closer to each other. The algorithm identified 16 clusters of phosphopeptides with distinct temporal profiles in response to vasopressin. The algorithm was also compared for quality to other standard clustering techniques that have been used for similar experiments in the literature. It was shown that the proposed algorithm performed with significantly better accuracy (at least 99% of clusters were assigned correctly) with the ability to handle large data sets. These time-course clusters provide a starting point for modeling of the signaling network. We believe that the proposed algorithm will prove useful to the computational biology and mass spectrometry community.

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