

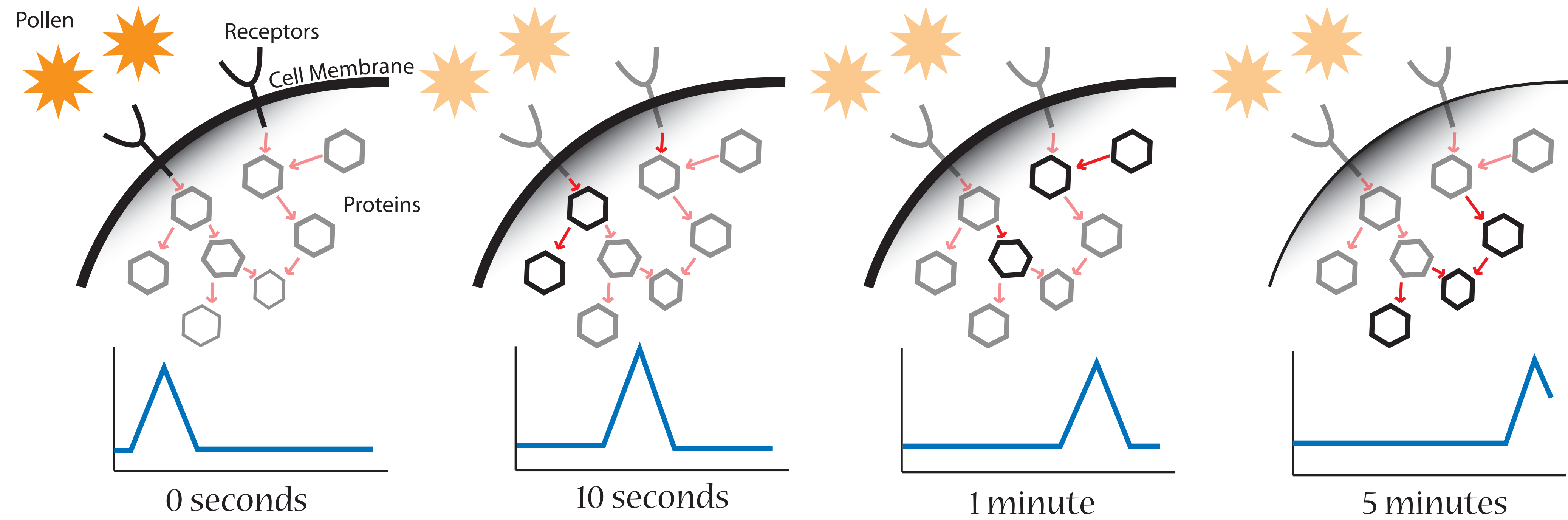
Temporal Clustering of Protein Phosphorylation Networks

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Brown University, CCMB Student Poster Session 2007

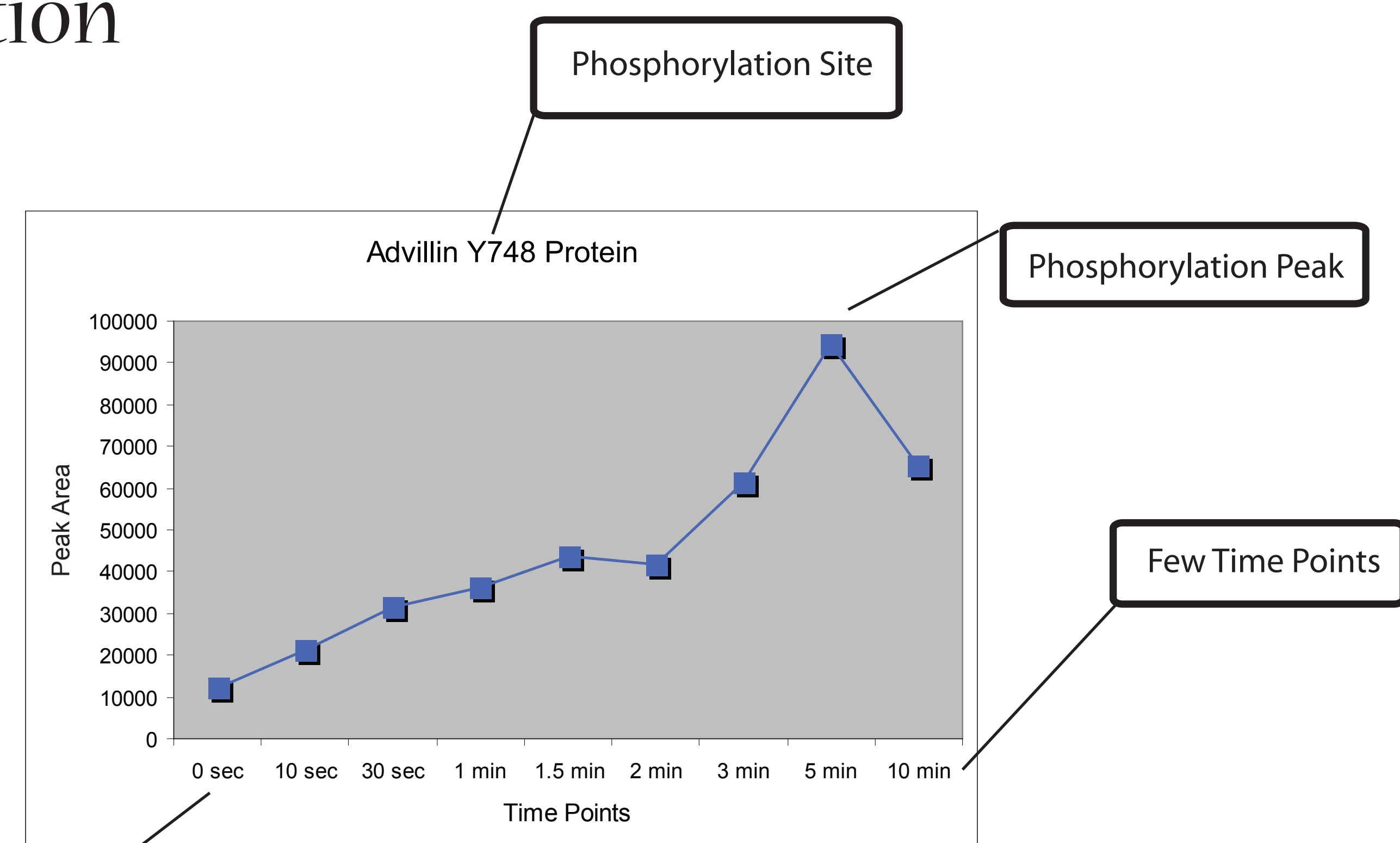
Introduction

Proteins perform many functions of the cell. In one context, proteins act as "message passers" that mediate the cell's response to a stimulus. Phosphorylation (the addition of a phosphate group) acts as an "on-off" switch. Mass spectrometry allows us to measure many phosphorylated proteins simultaneously. Performing mass spectrometry at multiple time intervals following a stimulus results in time series of phosphorylation sites. The challenge is to interpret this time series data given the complex organization of signalling pathways.



Objective: We want to group phosphorylation sites by similar temporal patterns in order to obtain insight into the organization of the signalling pathway.

Data Description



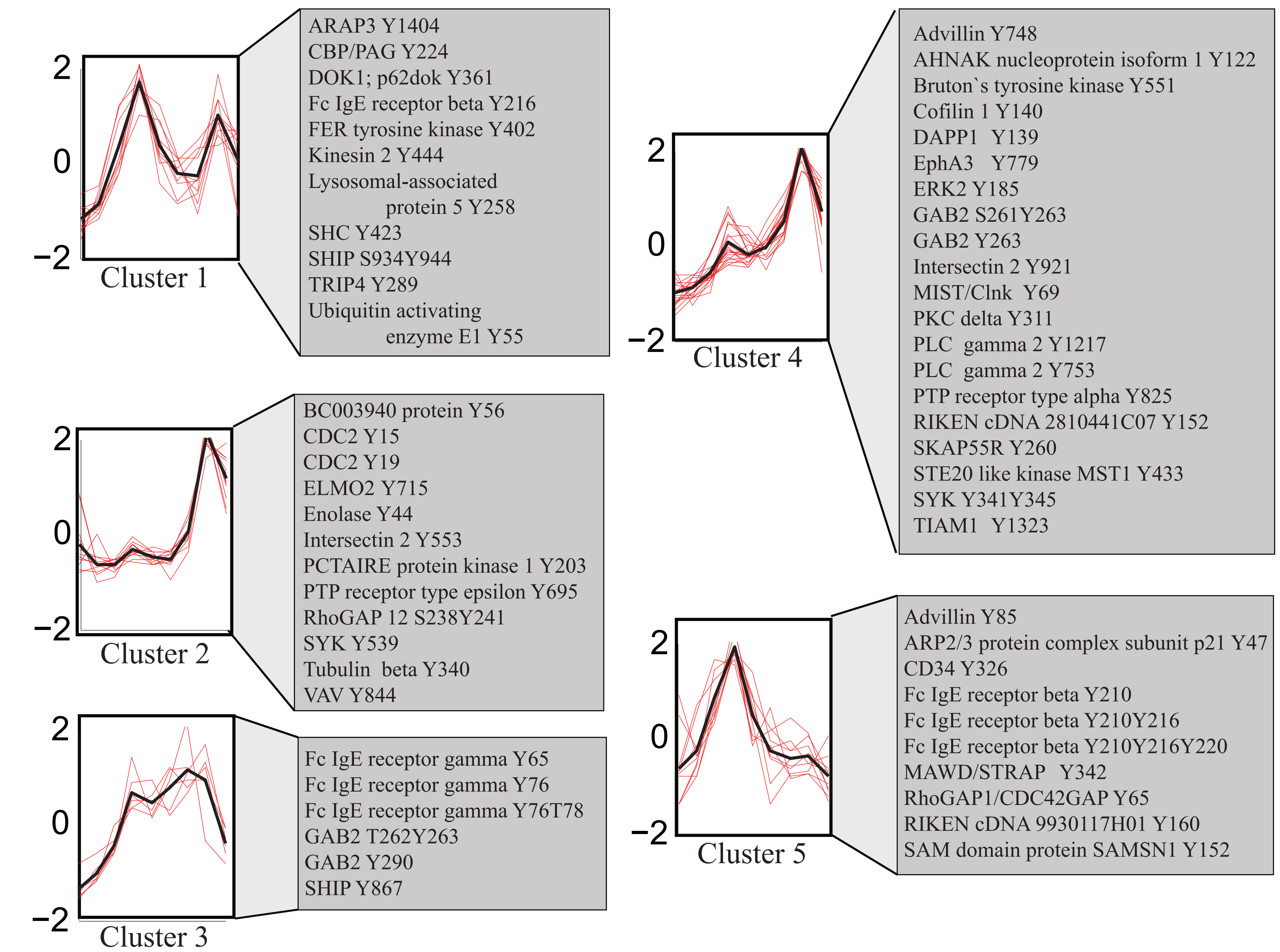
Non-Uniform Time Measurements

Each phosphorylated residue corresponds to a nine-dimensional vector $\mathbf{x} = (x_{0\text{sec}}, x_{10\text{sec}}, \dots, x_{10\text{min}})$.

One Approach: Fuzzy K-Means Clustering

K-Means clustering groups vectors into a specified number of clusters by minimizing the (euclidean) distance of each vector to the mean of all vectors in that cluster. Fuzzy clustering allows a point to be shared by many clusters, blurring the rigid cluster boundaries. This approach has been used to analyze gene expression time series.

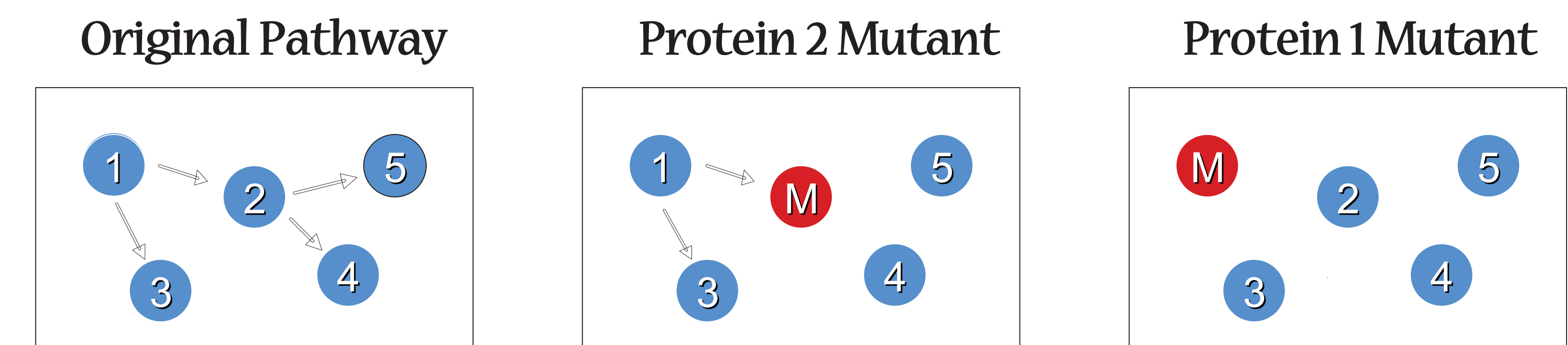
Results



The clusters above show fuzzy K-Means run with 7 clusters. Two of these clusters contained a total of five peptides, and are not shown. The peptides (labeled in the gray box) are shown in red, with the cluster average shown in black. Many of these clusters agree with the known topology of the pathway - for example, the Fc IgE receptors are grouped together, with the gammas (in Cluster 3) and the betas (in Cluster 5) both phosphorylated early. Interestingly, Cluster 1 is bimodal, capturing proteins that are phosphorylated twice over the course of the experiment. There is some evidence that SHC behaves in this way, but further experimental validation is needed.

Future Work

Art Salomon's lab is currently generating time series with mutant cells. The pathway will be measured with different members missing, and interpreting these "knock-out" experiments is nontrivial.



References

This poster is based on the paper

Lulu Cao, Kebing Yu, Cindy Banh, Vinh Nguyen, Anna Ritz, Ben Raphael, Yuko Kawakami, Toshiaki Kawakami, and Arthur R. Salomon. *Quantitative Time-Resolved Phosphoproteomic Analysis of Mast Cell Signaling*. Accepted to the Journal of Immunology, 2007.