Qualitatively Predicting Compound-Protein Interactions by Multi-Task Learning

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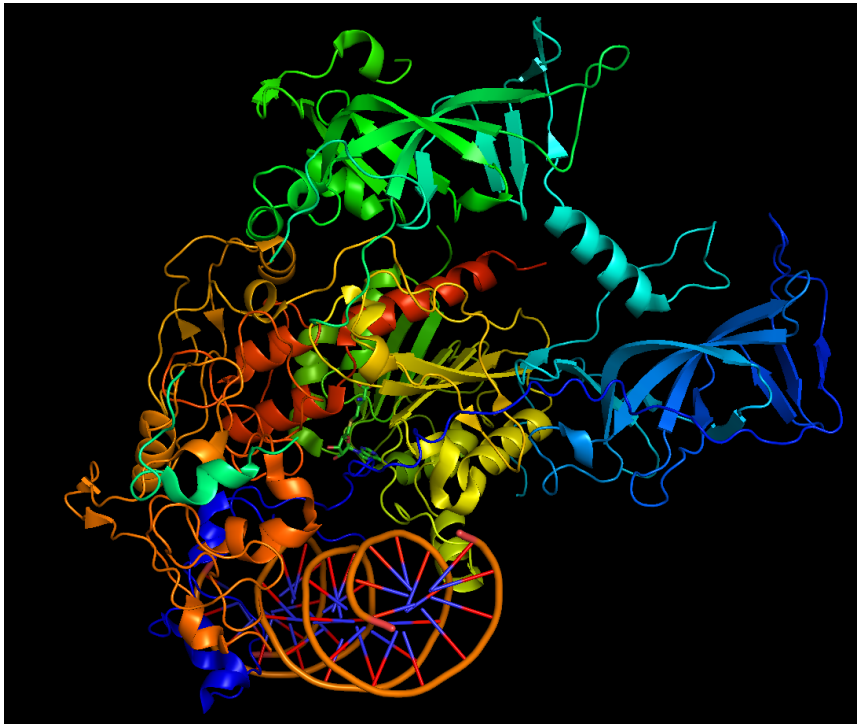
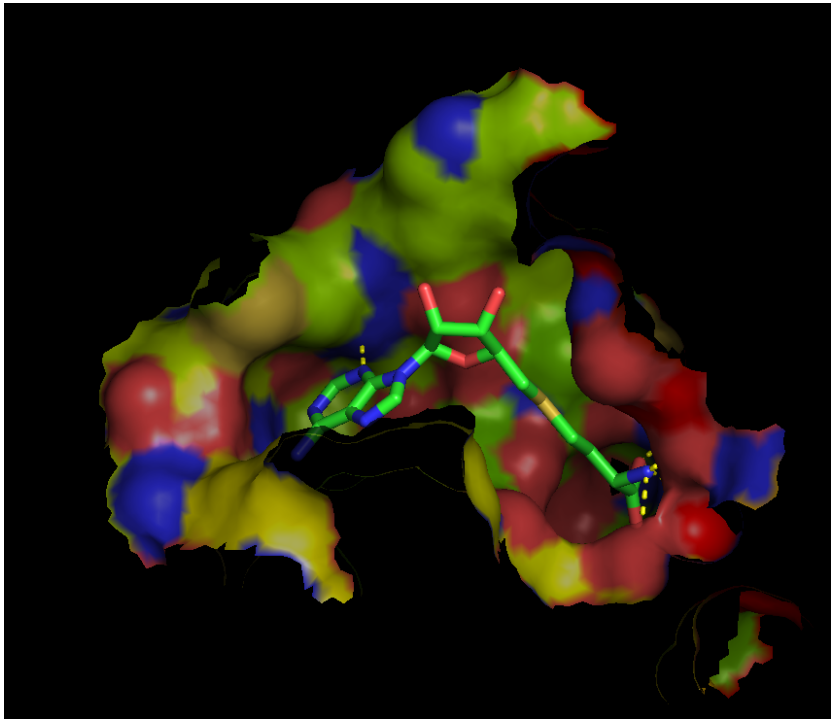
May 15, 2016

outline

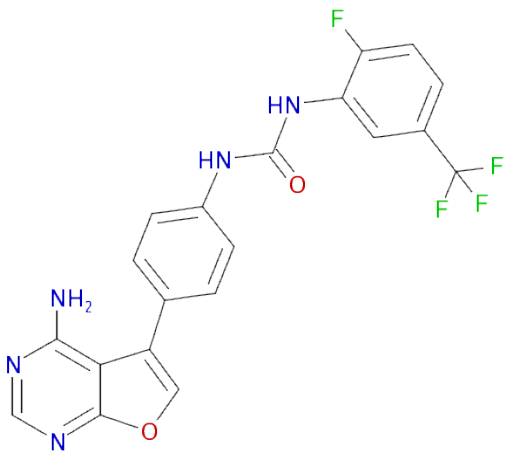
- Background:
  - Quantitative Structure-Activity Relationship (QSAR)
  - Multi-task Learning
- Method: hierarchical Bayesian model called MulTQSAR
- Result: reduce MSE on PeptideGPCR
- Discussion:
  - Sparsity and feature selection
  - Multi-task deep learning on QSAR

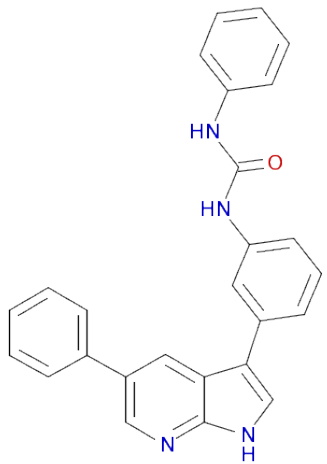
Compound-Protein Interactions (CPIs)

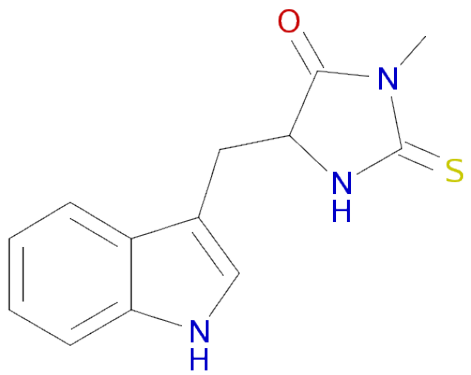




Protein Versus Multiple Compounds

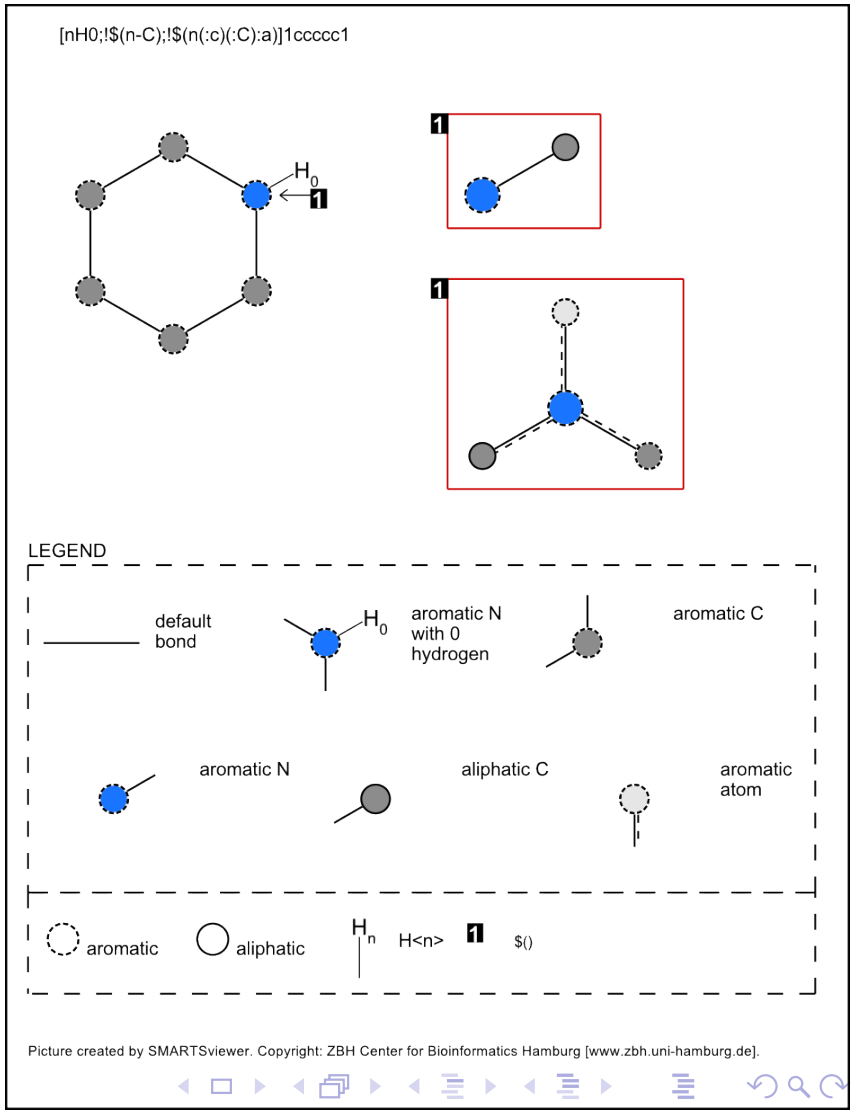






Chemical Space: Representation of Compounds

- Compounds represented by topological fingerprints. The similar as proteins.
- CPIs recorded as binary variable or continuous variables.
- Classification or regression models then are used.



Single Protein QSAR Model

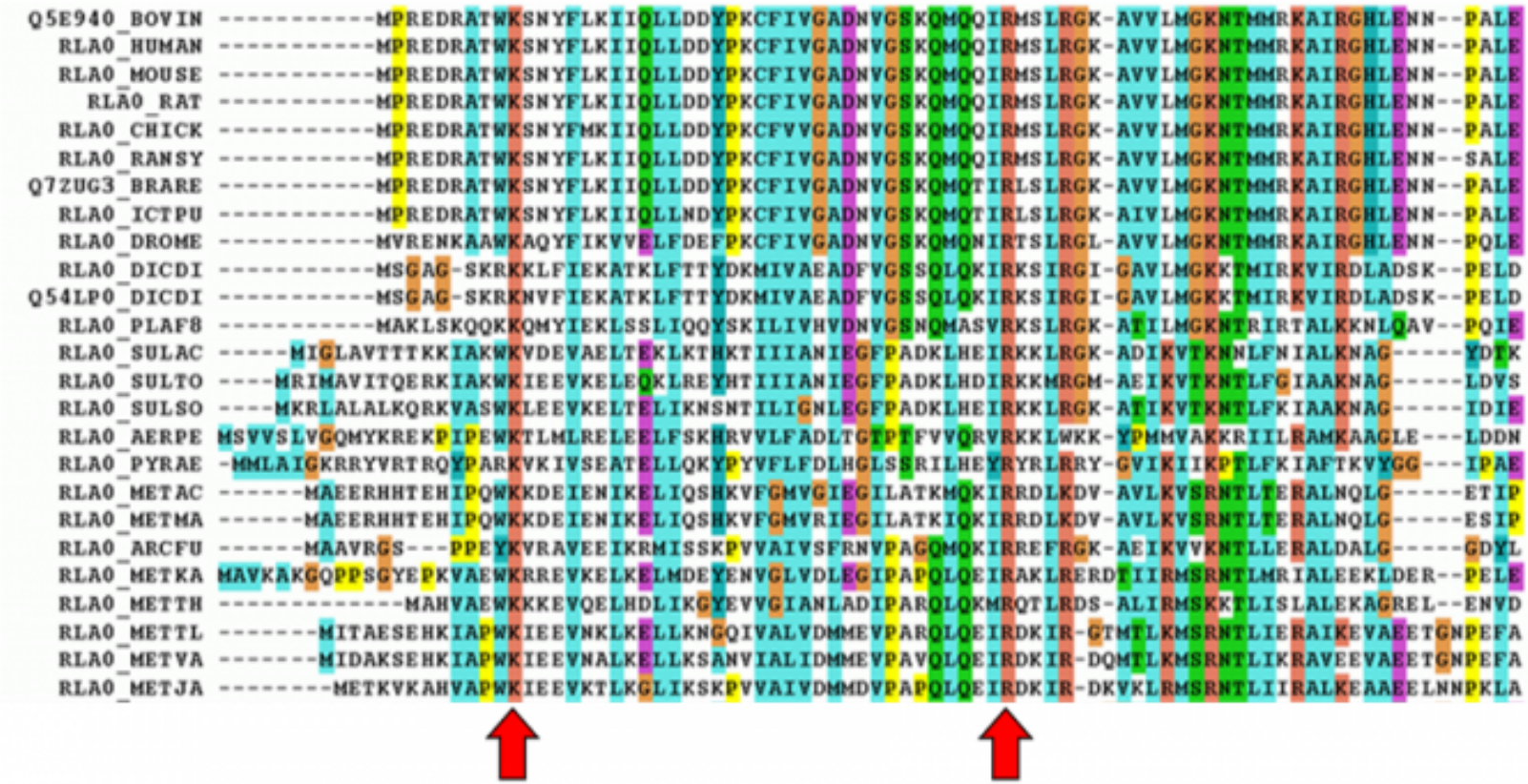
For the protein l, we have n_l compounds. Let $\mathbf{x}_i^l$ represents the compound i's features in the chemical space, and $\mathbf{y}_i^l$ represents the interaction affinity between the compound i and protein l.
QSAR is then to solve the problem:

$$f = \arg\min_f \mathcal{L}\left(\mathbf{y}^l, f(\mathbf{X}^l)\right) \tag{1}$$

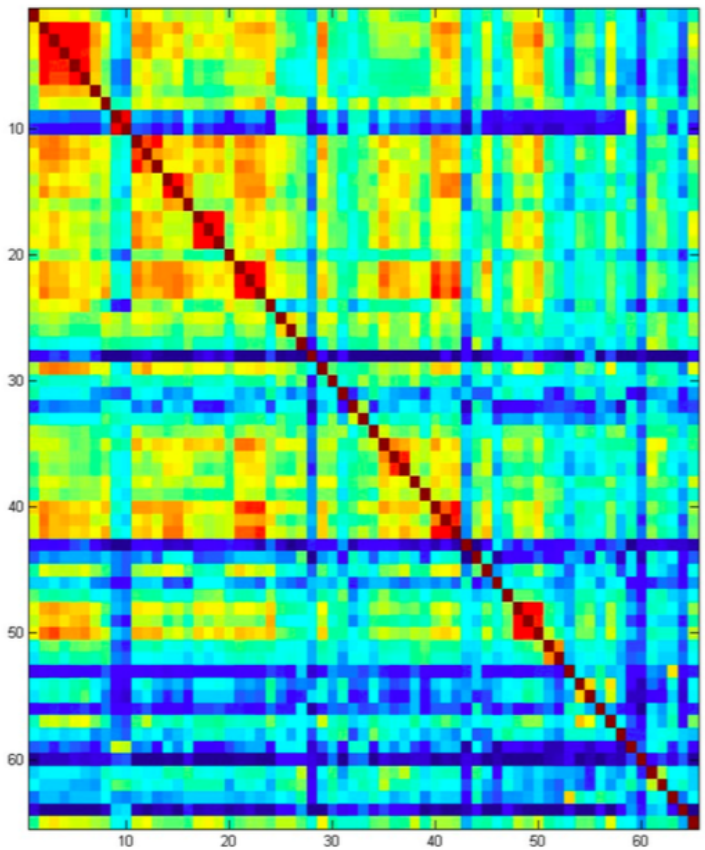
in which, $\mathbf{X}^l = (\mathbf{x}_1^l, \cdots, \mathbf{x}_{n_l}^l)^t$, $\mathcal{L}(\ ,\ )$ is the loss function. Usually we treat is as a linear regression model, *i.e.*,

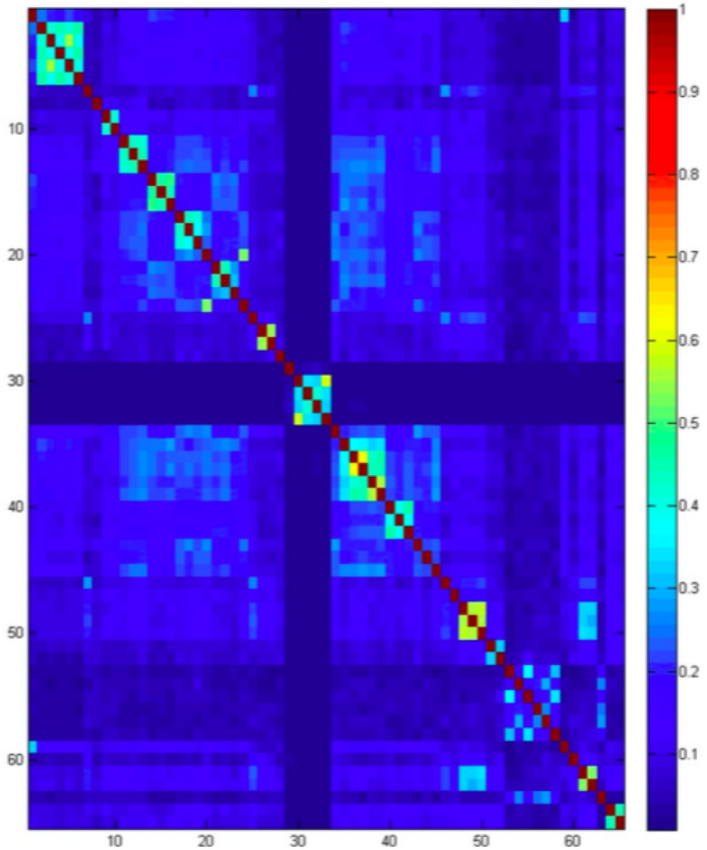
$$\omega^l = \arg\min_{\omega^l} \|\mathbf{y}^l - \mathbf{X}^l\omega^l\|^2 \tag{2}$$

Protein Family



Can We Learn QSAR Models In A Protein Family?





Learning Different But Similar Tasks

- Learning multiple tasks together, one type of transfer learning (Pan S. and Yang Q., 2010).
- Examples:
  1. Multi-task feature selection (Obozinski G., Taskar B., Jordan, M., 2006)

$$\min_{\omega} \sum_{l=1}^{L} \frac{1}{N_l} \sum_{i=1}^{N_l} \mathcal{L}(\omega^l, x_i^l, y_i^l) + \lambda \sum_{j=1}^{p} \|\omega_j\|^2 \tag{3}$$

  in which, p is the feature number, L is the task number.

  2. Adaptive multi-task LASSO (Lee S., Zhu J., and Xing E., 2010)

$$\min_{\omega} \frac{1}{2} \sum_{l=1}^{L} \|Y^l - X\omega^l\|_2^2 + \lambda_1 \sum_{j=1}^{p} \theta_j \sum_{l=1}^{L} |\omega_j^l| + \lambda_2 \sum_{j=1}^{p} \rho_j \|\omega_j\|_2 \tag{4}$$

Statistics Behind Linear Regression

Suppose $\mathcal{D}^l = \left\{\mathbf{X}^l, \mathbf{y}^l\right\}, l = 1, \cdots, L$, and $\mathbf{X}^l \in \mathbb{R}^{n^l \times p}$. Then we have

$$\mathbf{y}^l \sim \mathcal{N}\left(\mathbf{X}^l \omega^l, \sigma_y^2 \mathbf{I}\right) \tag{5}$$

$$\omega^l \sim \mathcal{N}\left(\omega_*, \sigma_l^2 \mathbf{I}\right) \tag{6}$$

$$\omega^* \sim \mathcal{N}\left(\mathbf{0}, \sigma_*^2 \mathbf{I}\right) \tag{7}$$

Here we assume that $p(\sigma_y^2) \propto 1$. Let $\Theta = \{\omega^l, l = 1, \cdots, L, \omega^*, \sigma_y^2\}$. We have

$$
\begin{aligned}
&\mathcal{L}_{hier}(\mathcal{D};\Theta) = \mathcal{L}_{orig}(\mathcal{D}|\Theta) + \log p(\Theta) \\
&= \sum_{l=1}^{L} \left(\log p(\mathcal{P}^l|\omega^l) - \frac{\| \omega^l - \omega^* \|^2}{2\sigma_l^2} \right) - \frac{\| \omega_* \|^2}{2\sigma_*^2} \\
&- \sum^{l} \frac{p}{2} \log(2\pi\sigma_l^2) - \frac{p}{2} \log(2\pi\sigma_*^2) \\
&= \sum_{l=1}^{L} \left(-\frac{\| \mathbf{y}^l - \mathbf{X}^l\omega^l \|^2}{2\sigma_y^2} - \frac{\| \omega^l - \omega^* \|^2}{2\sigma_l^2} \right) - \frac{\| \omega^* \|^2}{2\sigma_*^2} - \sum_{l=1}^{L} \frac{n^l}{2} \log(2\pi\sigma_y^2) \\
&- \sum_{l=1}^{L} \frac{p}{2} \log(2\pi\sigma_l^2) - \frac{p}{2} \log(2\pi\sigma_*^2)
\end{aligned}
\tag{8}
$$

We can use MCMC algorithm to simulate the posterior distribution of Θ. Here σ_l^2, σ_* are fixed, and L-BFGS-B is then used following the gradient below.

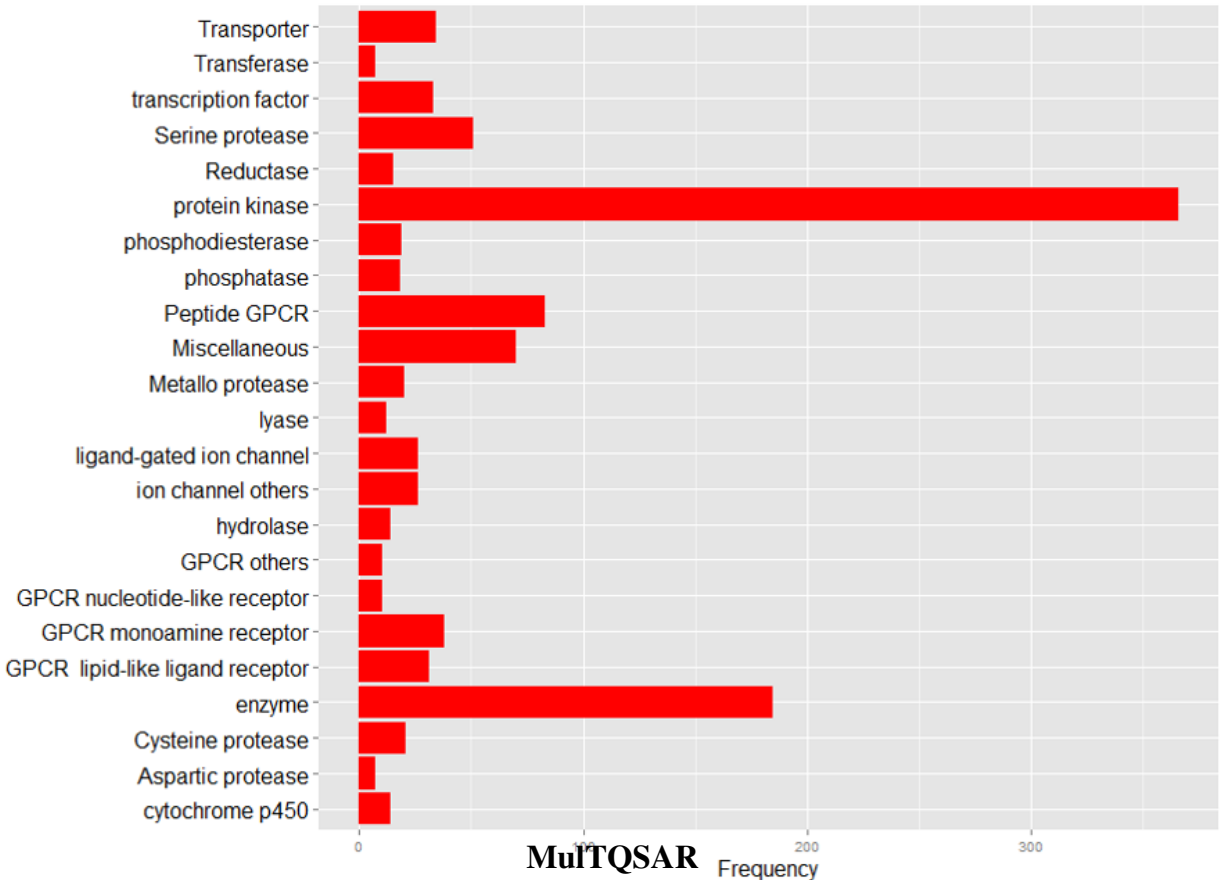
$$\begin{aligned}\frac{\partial \mathcal{L}_{hier}(\mathcal{D};\Theta)}{\partial \omega^l} &= -\frac{1}{2\sigma_y^2}\frac{\| \mathbf{y}^l - \mathbf{X}^l\omega^l \|^2}{\partial \omega^l} - \frac{1}{2\sigma_l^2}\frac{\| \omega^l - \omega^* \|^2}{\partial \omega^l} \\ &= \frac{\mathbf{y}_l{}^t\mathbf{X}^l}{\sigma_y^2} + \frac{\omega^*}{\sigma_l^2} - \left(\frac{\mathbf{X}_l{}^t\mathbf{X}^l}{\sigma_y^2} + \frac{1}{\sigma_l^2}\mathbf{I}\right)\omega^l\end{aligned} \tag{9}$$

$$\frac{\partial \mathcal{L}_{hier}(\mathcal{D};\Theta)}{\partial \omega^*} = -\sum_l \frac{\omega^* - \omega^l}{\sigma_l^2} - \frac{\omega^*}{\sigma_*^2} \tag{10}$$

$$\frac{\partial \mathcal{L}_{hier}(\mathcal{D};\Theta)}{\partial \sigma_y^2} = \frac{\sum_l \| \mathbf{y}^l - \mathbf{X}^l\omega^l \|^2}{2\sigma_y^{2^2}} - \frac{n}{2\sigma_y^2} \tag{11}$$

where n is the total number of samples in all the groups.

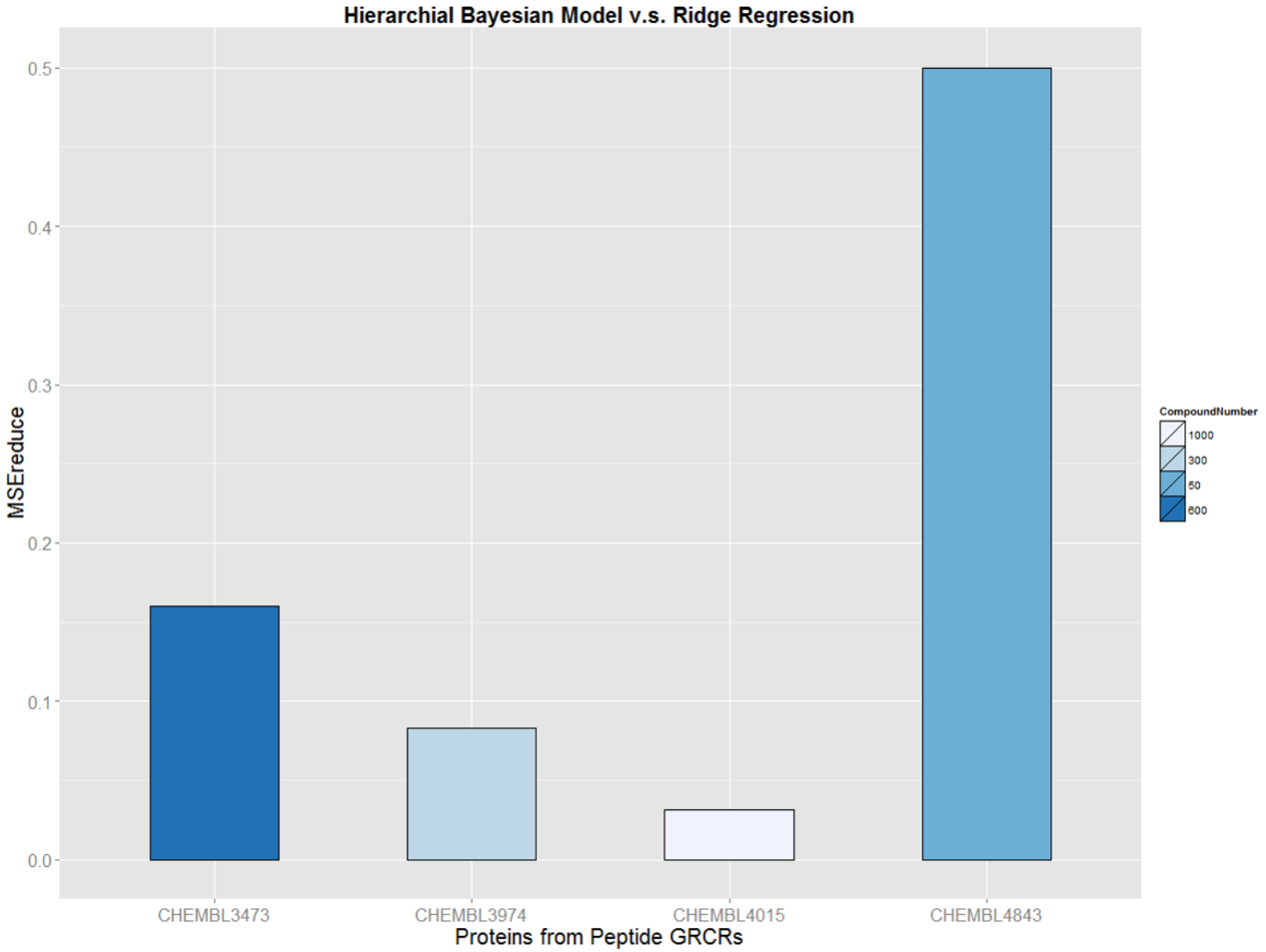
- 210,000 CPIs including more than 1,000 proteins from 20 protein families, and 150,000 compounds.
- 22 physicochemical properties and 881 chemical substructures as the compounds' features.



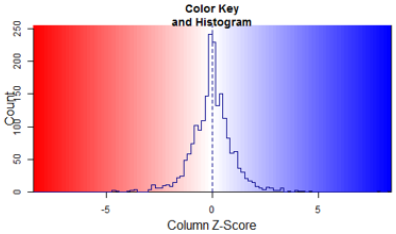
Feature Selection

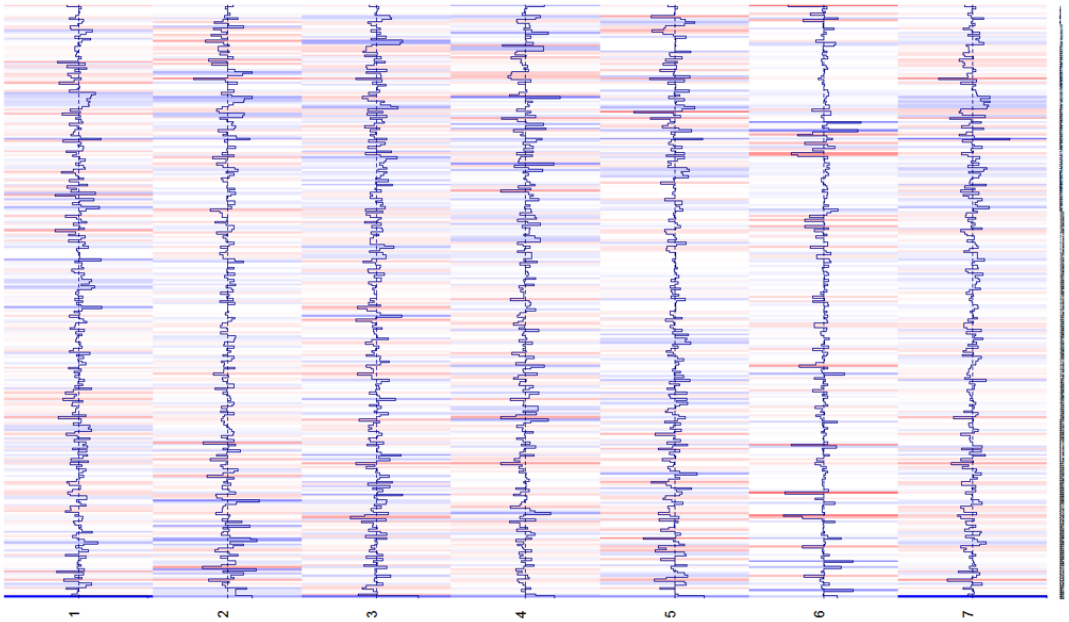
The protein family of Peptide GPCR including 85 proteins as examples.

- Based on the definitions of chemical fingerprints, SUB1-SUB115, SUB264-SUB327 are removed.
- Chemical fingerprints with too low or high frequencies are removed.
- Non-parametric dynamic slicing method for marginal feature selection.
- 284 features are finally kept.


Hierarchial Bayesian Model v.s. Ridge Regression
MSEreduce
0.5
0.4
0.3
0.2
0.1
0.0
CHEMBL3473
CHEMBL3974
CHEMBL4015
CHEMBL4843
Proteins from Peptide GRCRs
CompoundNumber
1000
300
50
600

We can involve L1 regularization for sparsity and feature selection.





How can we involve features' combinations?