DegSampler: Collapsed Gibbs sampler for detecting E3 binding sites

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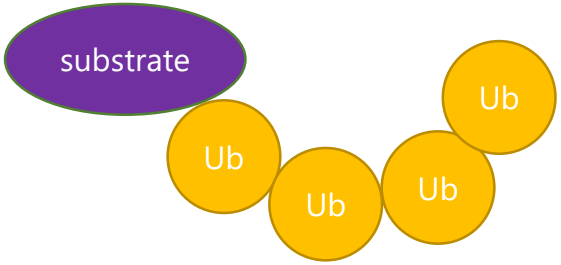
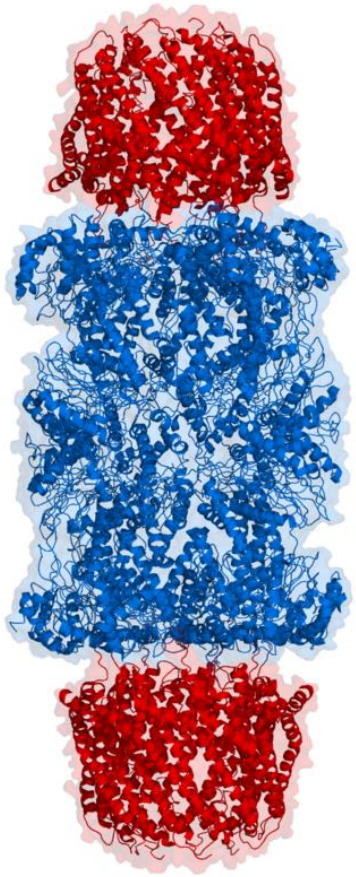
Motivation

Unneeded and damaged proteins are degraded and recycled

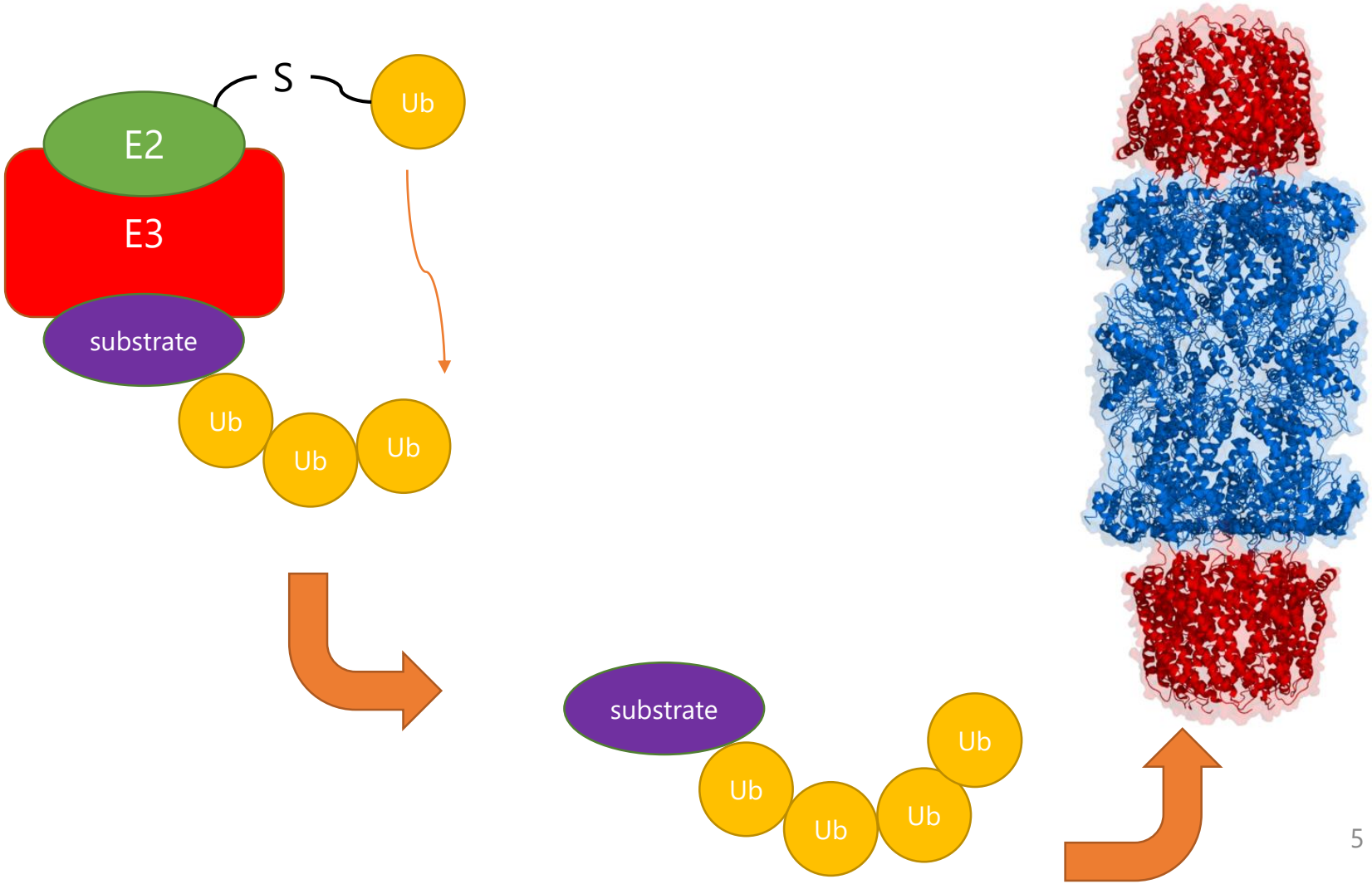


Proteasome (Wikipedia)



Ubiquitin-proseasome system

E3 ubiquitin ligase selectively recognizes a substrate protein



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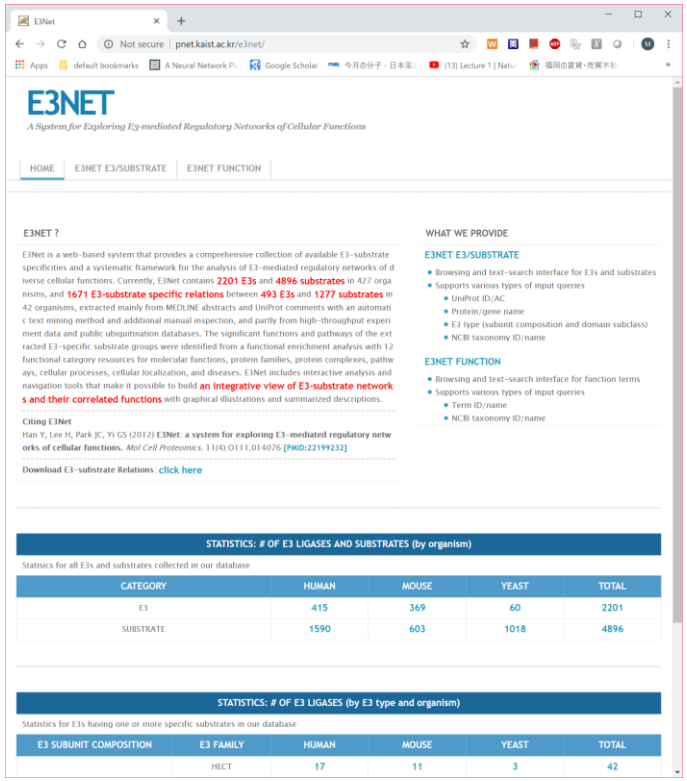
Available data sets

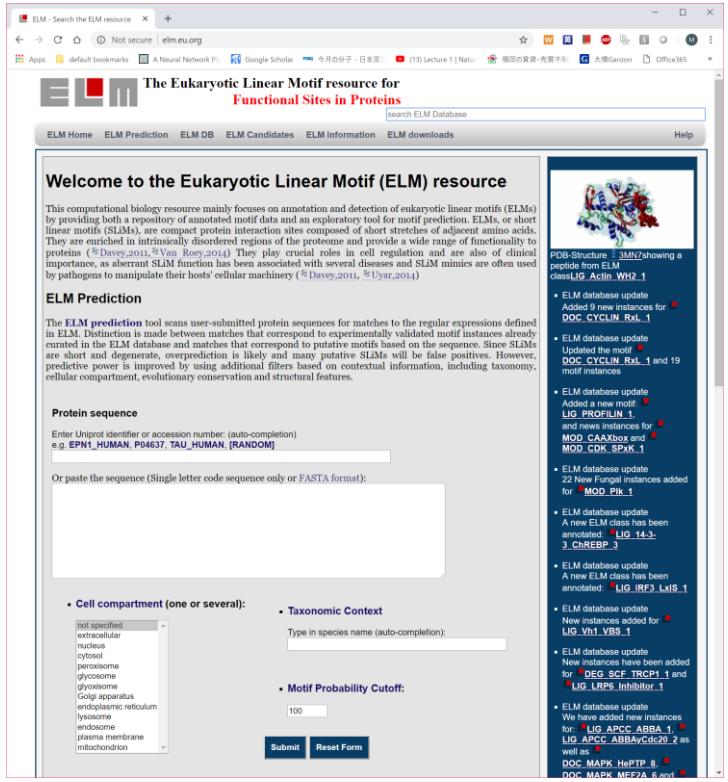
E3NET:

E3-substrate interactions



ELM: DEG class motifs:

E3 binding sites of protein sequences



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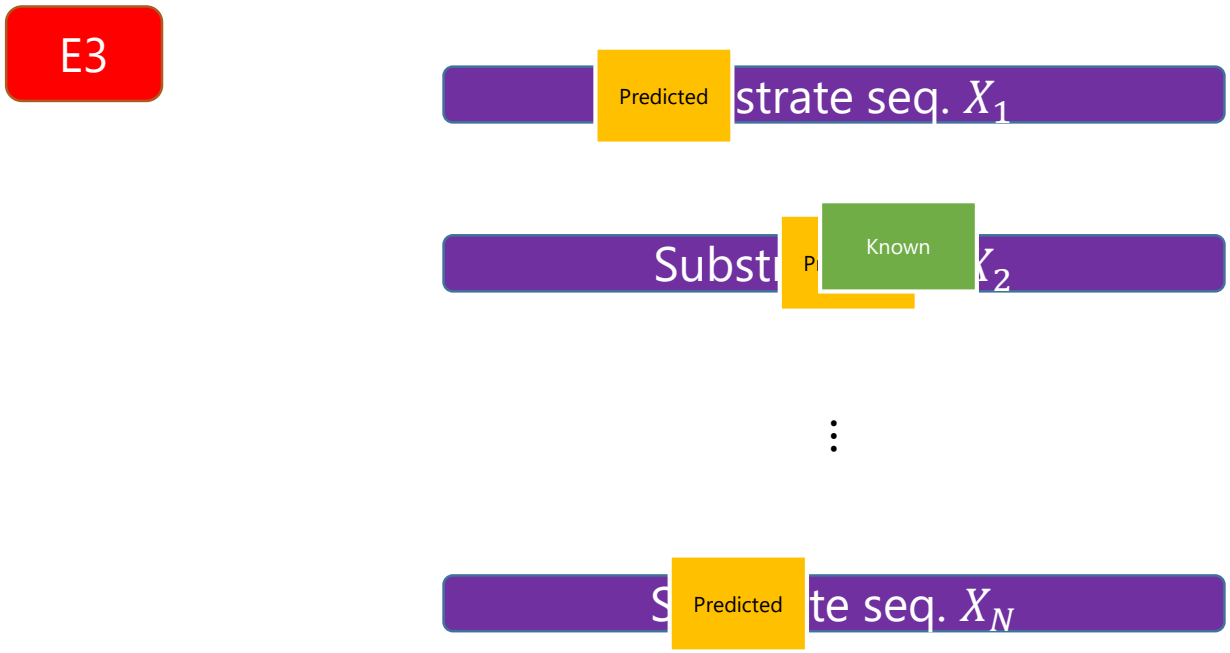
Problem: Estimate the motif of binding site of an E3



- Performance measure =#position covered by known and predicted motifs simultaneously / W (motif width)
- 36 E3-specific sets of substrate proteins, some of which have known motifs.

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Posterior probability distribution for motif identification

- $\boldsymbol{X} = (X_1, \ldots, X_N)$: N given sequences.
- $\boldsymbol{Z} = (z_1, \ldots, z_N)$: starting positions of motif occurrences.
- $\boldsymbol{\theta}_{0:W} = (\boldsymbol{\theta}_0, \boldsymbol{\theta}_1, \ldots, \boldsymbol{\theta}_W)$: $W + 1$ categorical distributions of letters.
- Posterior:

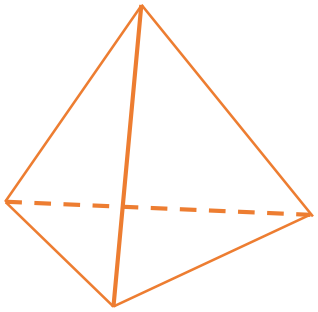
$$p(\boldsymbol{Z}, \boldsymbol{\theta}_{0:W} | \boldsymbol{X}) \propto p(\boldsymbol{X} | \boldsymbol{Z}, \boldsymbol{\theta}_{0:W}) \cdot p(\boldsymbol{Z}) \cdot p(\boldsymbol{\theta}_{0:W})$$

MEME: meme-suite.org

Gibbs Motif Sampler:

Likelihood function $L_{pssm}(\boldsymbol{Z}, \boldsymbol{\theta}_{0:W} | \boldsymbol{X})$

⋯ A C C T A C⋯
⋯ T G C T A C ⋯
⋯ A G G A A C ⋯



Symbol	Probability
A	1/10
C	2/10
G	3/10
T	4/10

$$\frac{2}{10} \cdot \frac{2}{10} \cdot \frac{3}{10}$$

Categorical distribution

Prior distributions and collapsing

$p(\boldsymbol{Z})$:

Uniform distribution

$p(\boldsymbol{\theta}_{0:W})$:

Dirichlet distribution

∵ conjugate prior of the categorical distribution.

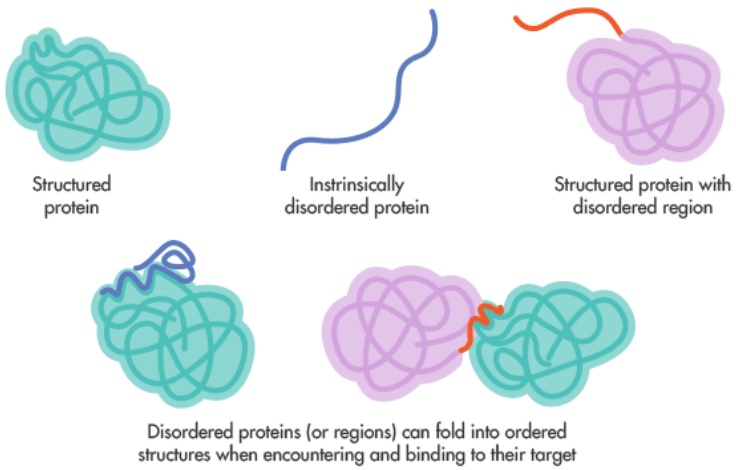
- Recall posterior:

  $p(\boldsymbol{Z}, \boldsymbol{\theta}_{0:W}|\boldsymbol{X}) \propto p(\boldsymbol{X}|\boldsymbol{Z}, \boldsymbol{\theta}_{0:W}) \cdot p(\boldsymbol{Z}) \cdot p(\boldsymbol{\theta}_{0:W})$

- Collapsed posterior:

$$p(\boldsymbol{Z}\,|\boldsymbol{X}) = \int p(\boldsymbol{Z}, \boldsymbol{\theta}_{0:W}|\boldsymbol{X}) d\boldsymbol{\theta}_{0:W}$$

Modeling: Prior knowledge



E3 binding sites are often located in disordered regions of substrates [Guharoy *et al.*, 2016]

https://www.quantamagazine.org/how-disordered-proteins-are-upending-molecular-biology-20170118/

Prior of starting position z_i

$disorder_{i,j}$: disorderness of $X_{i,j}$

$$p(z_i) \propto \left(\prod_{w=1}^{W} disorder_{i,z_i+w-1} \right)^{\frac{1}{W}}$$

$$p(\boldsymbol{Z}) \propto \prod_{i=1}^{N} p(z_i)$$

Modeling: 2nd likelihood based on amino acid indexing $L_{aai}(\boldsymbol{Z}\,|\boldsymbol{X})$

Resulting likelihood: $p(\boldsymbol{X}|\boldsymbol{Z},\boldsymbol{\theta}_{0:W}) \propto L_{pssm}(\boldsymbol{Z},\boldsymbol{\theta}_{0:W}|\boldsymbol{X}) \cdot L_{aai}(\boldsymbol{Z}\,|\boldsymbol{X})$

⋯ A P A P P V ⋯
⋯ A P P A A V ⋯
⋯ G P R A G V ⋯

Symbol	Probability
A	
R	
N	
D	
C	
Q	
E	
G	
H	
I	
L	
K	
M	
F	
P	
S	
T	
W	
Y	
V	

Symbol	Probability
A	a (non-polar)
G	
I	
L	
M	
F	
P	
W	
V	
N	b (polar)
C	
Q	
S	
T	
Y	
D	c (negatively charged)
E	
R	d (positively charged)
H	
K	

ELM DB motif:
DEG_APCC_DBOX_1
.R..L..[LIVM].

Penalize the inconsistency among the mapped symbols

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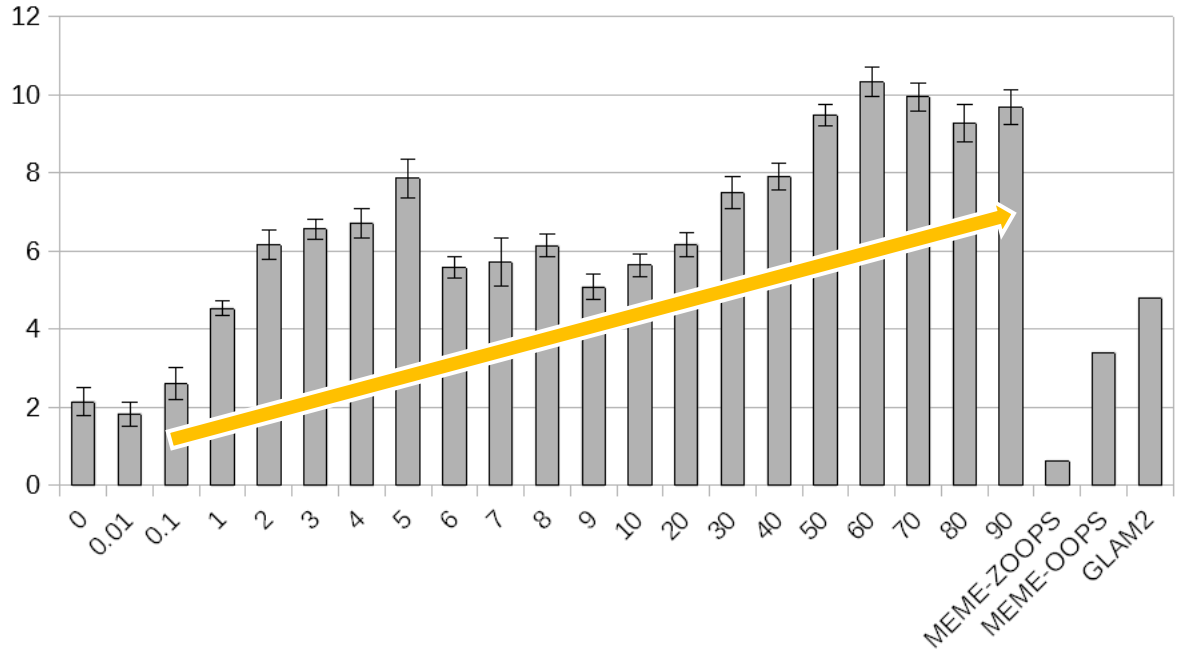
Result:
Effectiveness of disorder prior

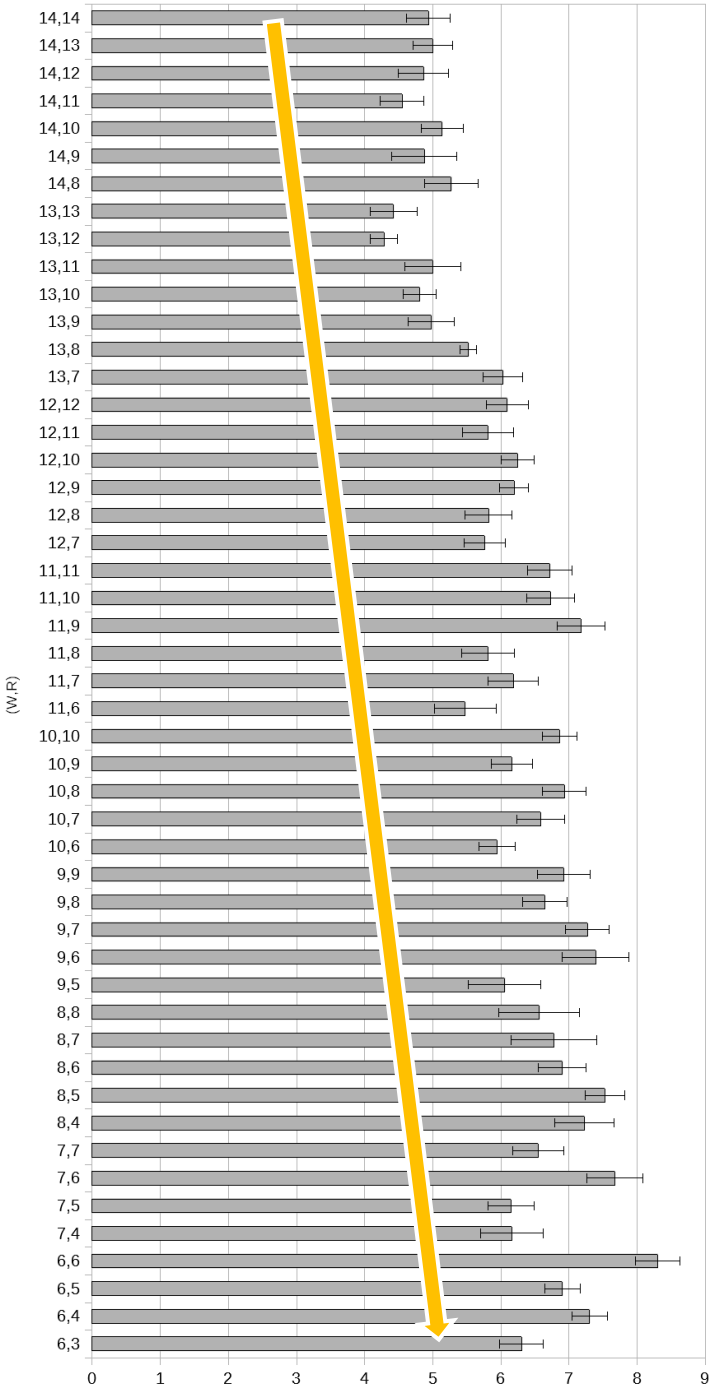


c_d: coefficient of disorder prior.
(W,R)=(9,6)

W: motif width

R: #selected columns as motif part)

Result:
Effectiveness of (W,R)



Example: E3 SIAH2_HUMAN

			.	P	.	A	.	V	.	P
Substrate	Pos	*	*	*		*		*		*
O14974	390	A	A	**P**	V	**A**	V	T	T	P
O75376	124	A	A	V	L	P	L	**V**	H	**P**
O75925	562	A	A	A	A	**A**	A	**V**	S	D
P29590	437	A	Q	**P**	M	**A**	V	**V**	Q	S
P37840	89	A	A	A	T	G	F	**V**	K	K
P43146+	1330	T	I	**P**	T	**A**	C	**V**	R	**P**
Q16633+	45	P	A	**P**	T	**A**	V	**V**	L	**P**
Q92667	284	A	A	**P**	A	P	P	**V**	A	D
Q9GZT9	77	P	A	**P**	P	**A**	A	**V**	P	**P**
Q9H6Z9	62	A	G	**P**	R	**A**	G	**V**	S	K

Contents

Future works

- Improvement of the likelihood function based on amino acid indexing.
- Simulated annealing as a postprocessing.