生物信息学：导论与方法
Bioinformatics: Introduction and Methods

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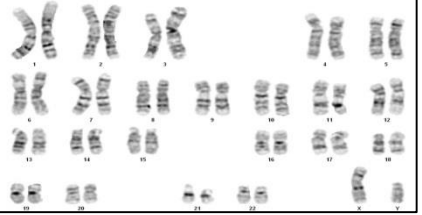
Center for Bioinformatics, Peking University

https://www.coursera.org/course/pkubioinfo



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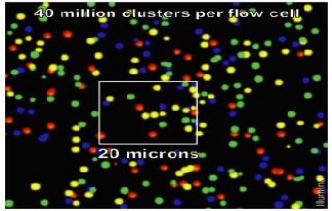

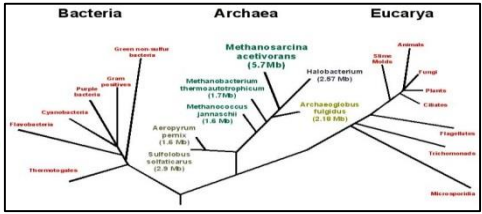

Week 6: Functional prediction of genetic variations

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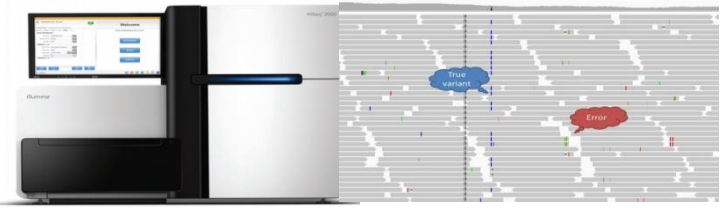

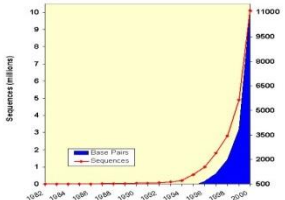

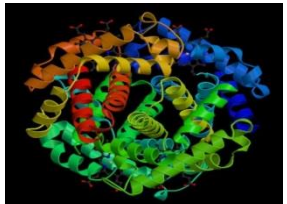

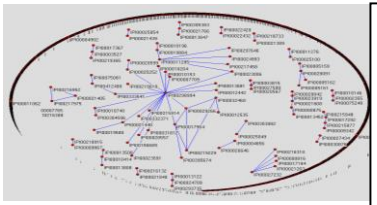

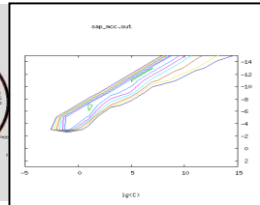

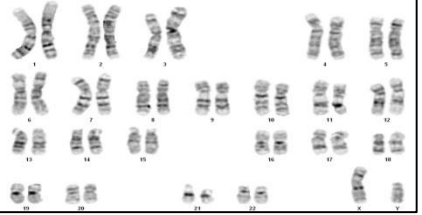

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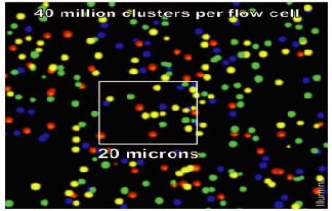

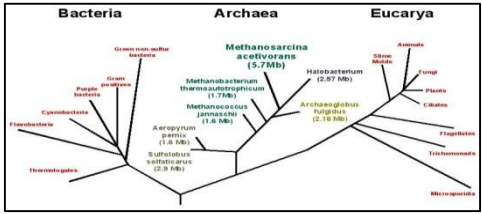

Week 6 Unit 4: Classifier-based methods: SAPRED

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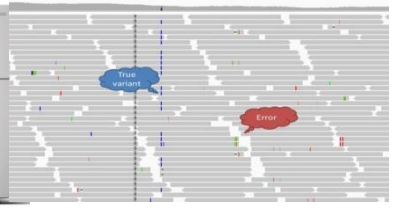
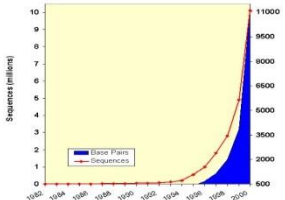
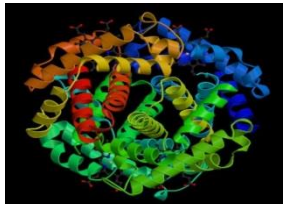
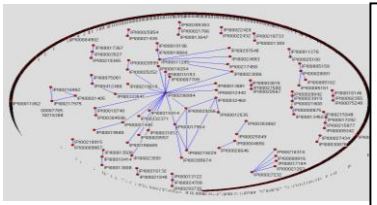
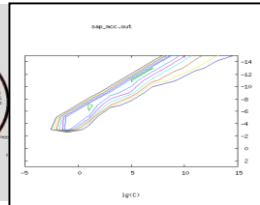






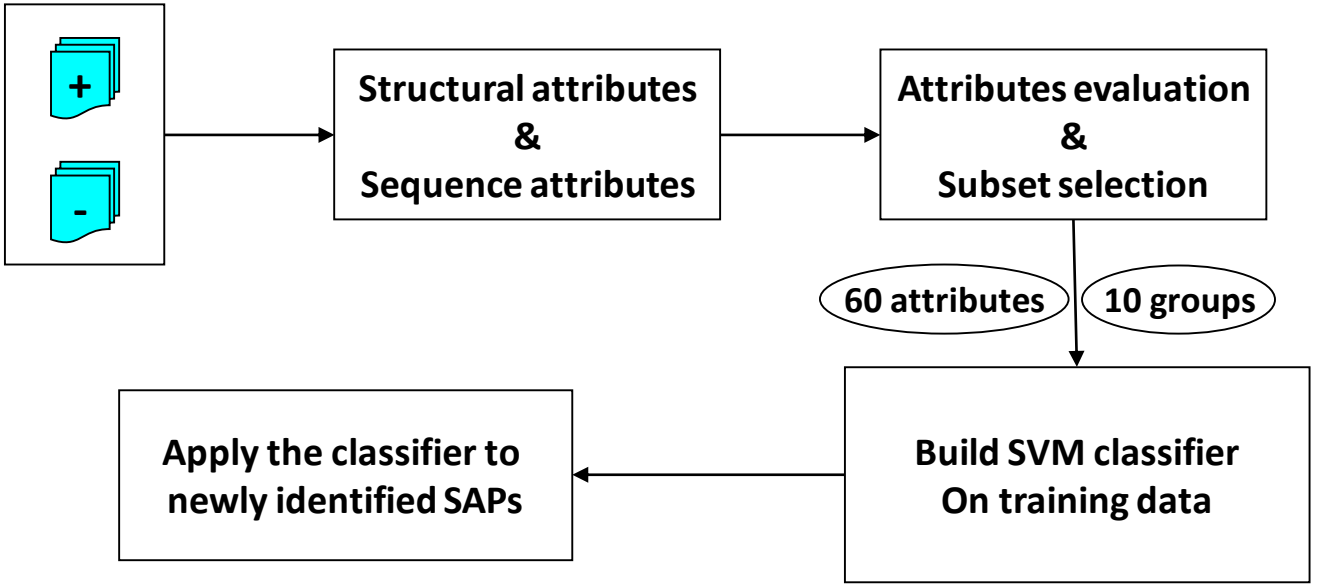




Single Amino acid Polymorphisms disease-association Predictor (SAPRED)

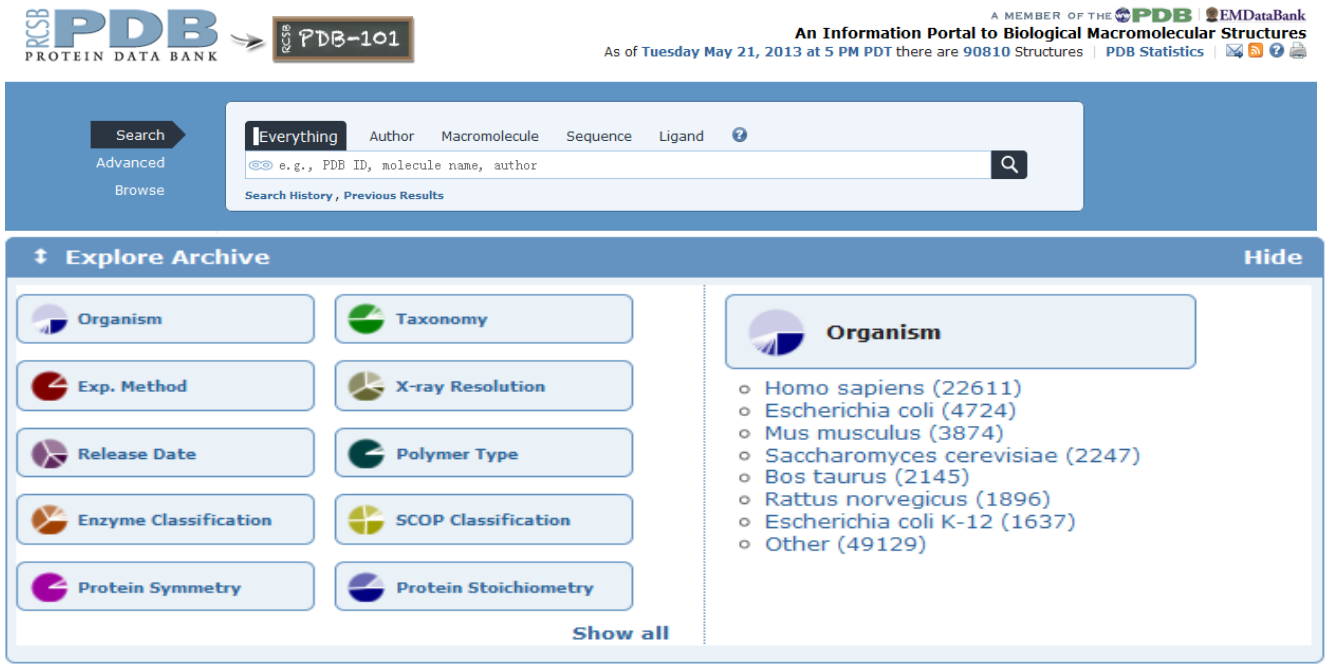
www.sapred.cbi.pku.edu.cn

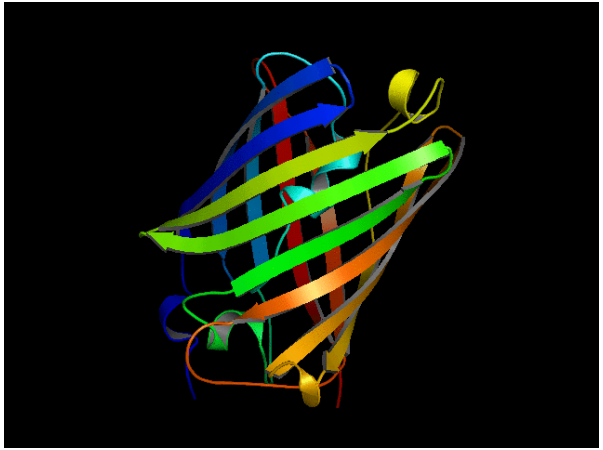
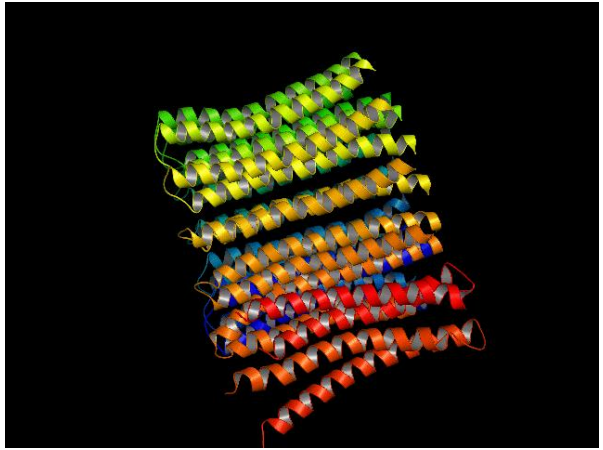
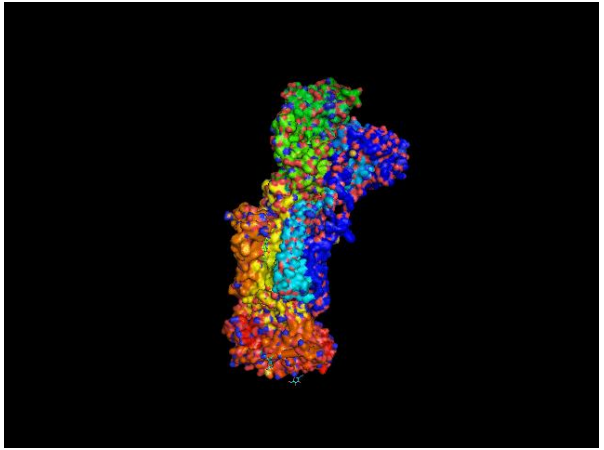
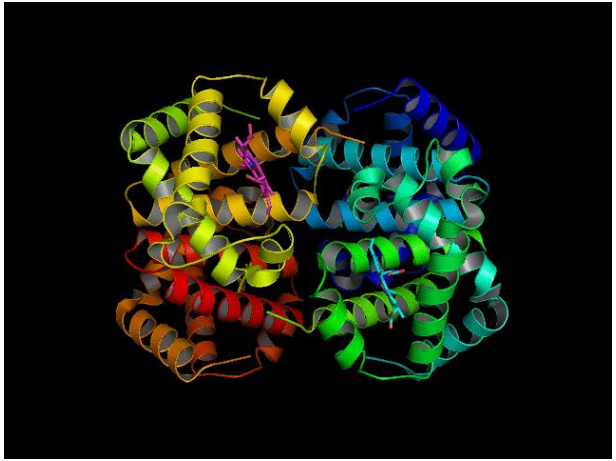
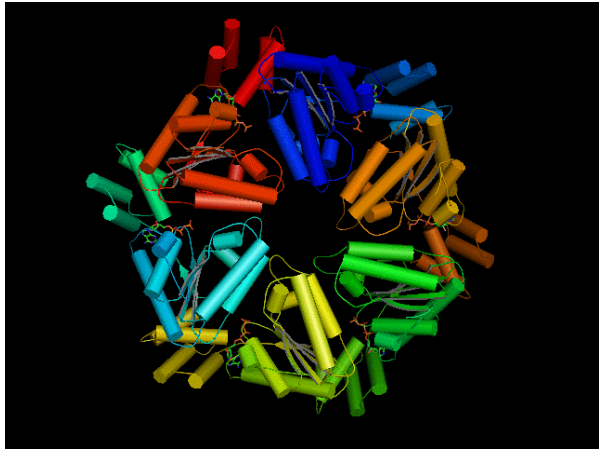
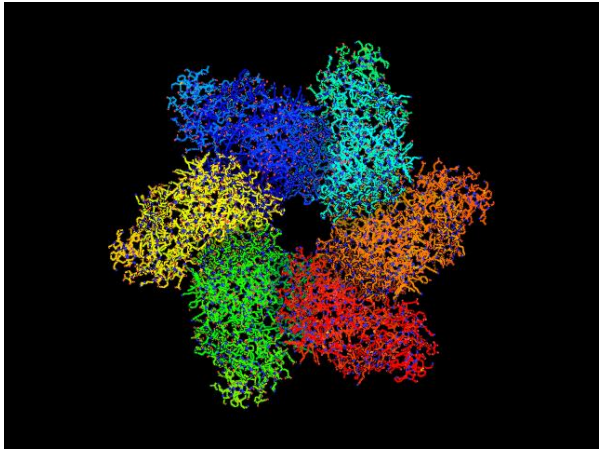
Formulate as a supervised classification problem



PDB – get protein 3D structure

- http://www.rcsb.org/pdb/home/home.do

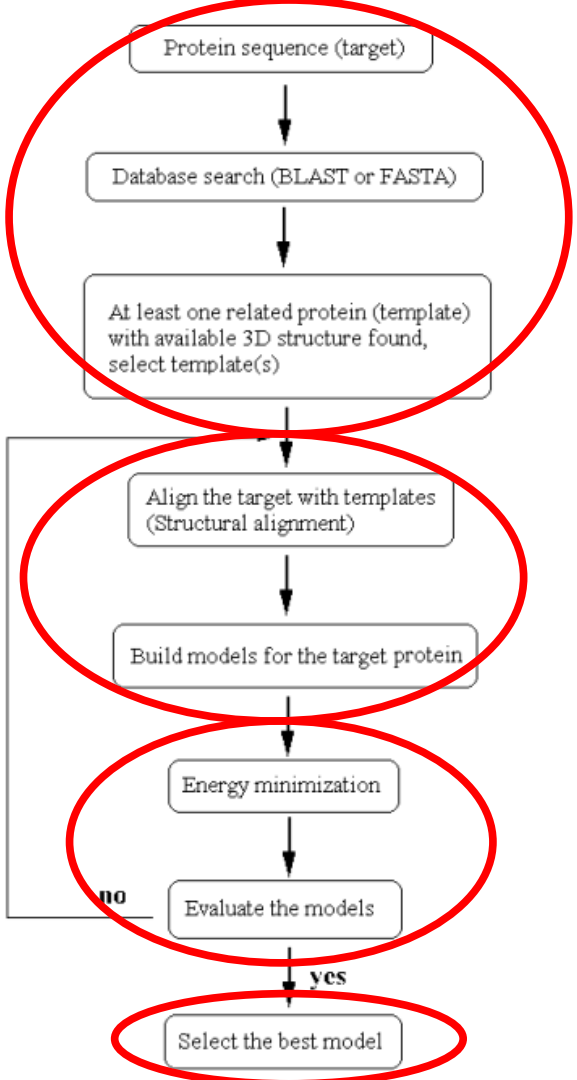


Homology Modeling

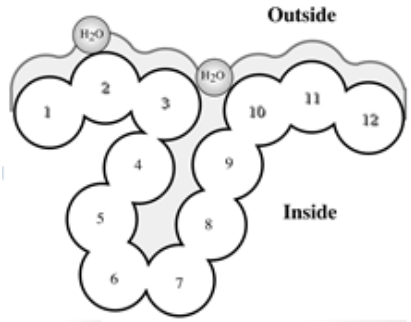
- http://swissmodel.expasy.org/

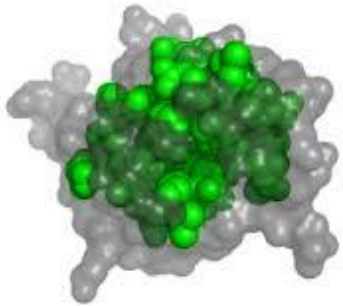
SWISS-MODEL



Biologically-Intuitive features

- Residue frequencies, conservation scores
- Solvent accessibilities and C_β density, secondary structure...





New attributes:

- Structural neighbor profile
- Nearby functional sites
- Disordered regions
- Hydrogen bonds change
- β-aggregation
- HLA family

Structural neighbor profile

- Definition:
  - A 20-D vector: take the C_α of the variant residue as the center, draw a sphere with a specific radius. The residues inside are counted to get the number for each of the 20 kinds of residues. Each number is a component of the vector.

$$\left[N_{R,a_i}\right] = \sum_{j=1}^{L} X_j$$

where $X_j = 1$ if $X_j = a_i$ & $r_{X_{j,c}} < R$;

otherwise, $X_j = 0$

R: radius

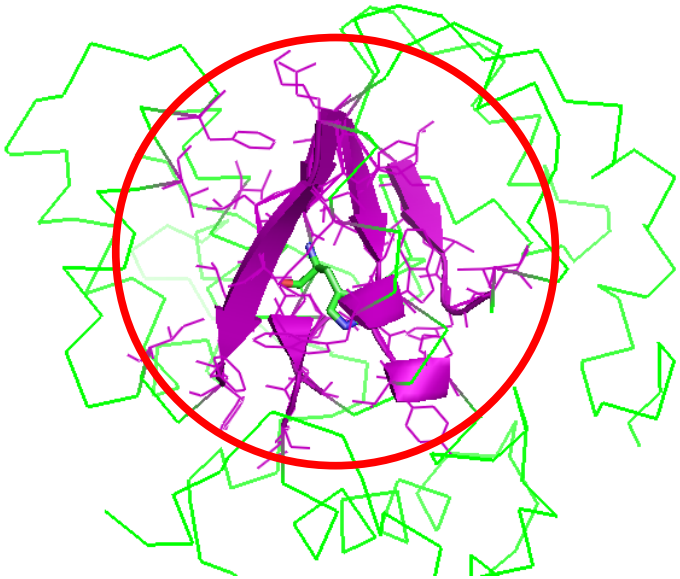
L: protein length

a_i: a specific residue type

r: distance between a residue and the center residue

Ye, ZQ, *et al.*, 2007, Bioinformatics, 23(12):1444

Structural neighbor profile



The variant site is H128, radius is 10 Angstroms. Neighbors are:

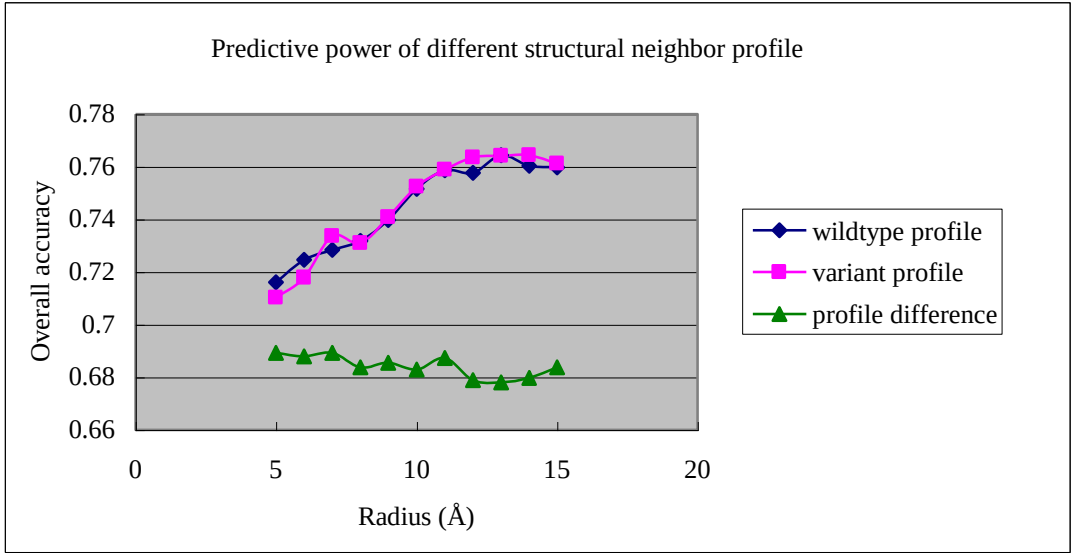
42-47: LLICTY
50-52: AGT
55: I
59: V
106-110: LKTHL
112: T
125-127: KFL
129-131: VAR
176-177: HV
180-181: WW
184: K
188-194: QILFLFY
197: I
208: V
211: F

Structural neighbor profile: vector

a.a.	A	C	D	E	F	G	H	I	K	L
N	2	1	0	0	4	1	2	4	3	7

a.a.	M	N	P	Q	R	S	T	V	W	Y
N	0	0	0	1	1	0	4	4	2	2

Structural neighbor profile



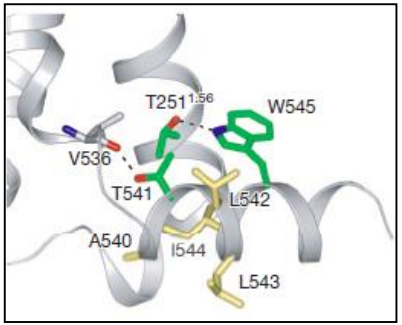
- Different radius had different predictive power.
- We selected 13 Angstroms as the optimal radius.

Ye, ZQ, *et al.*, 2007, Bioinformatics, 23(12):1444

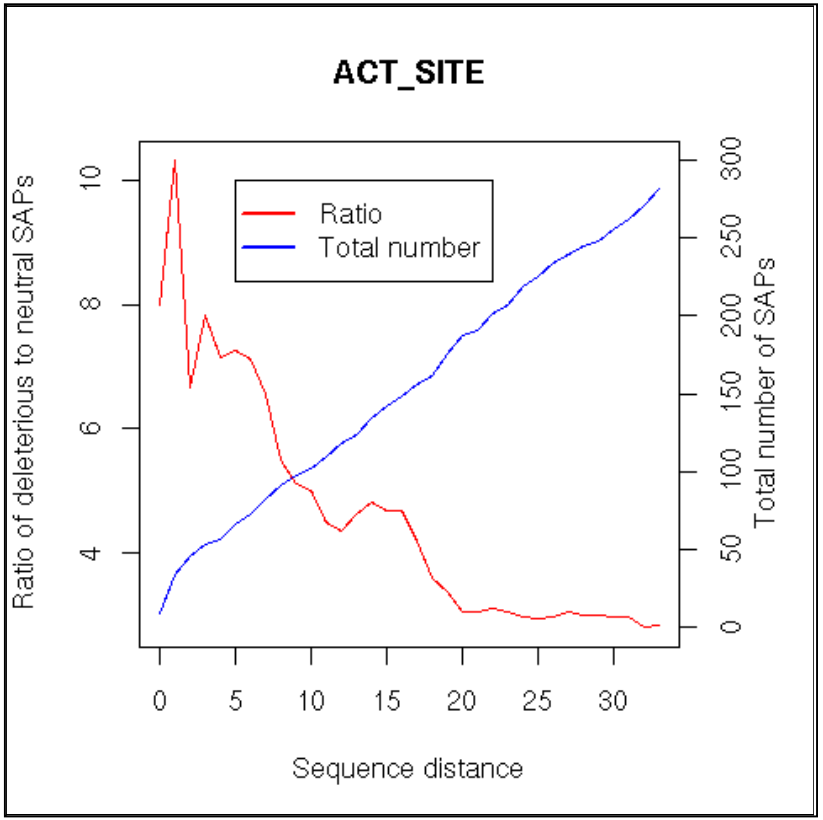
Nearby functional sites

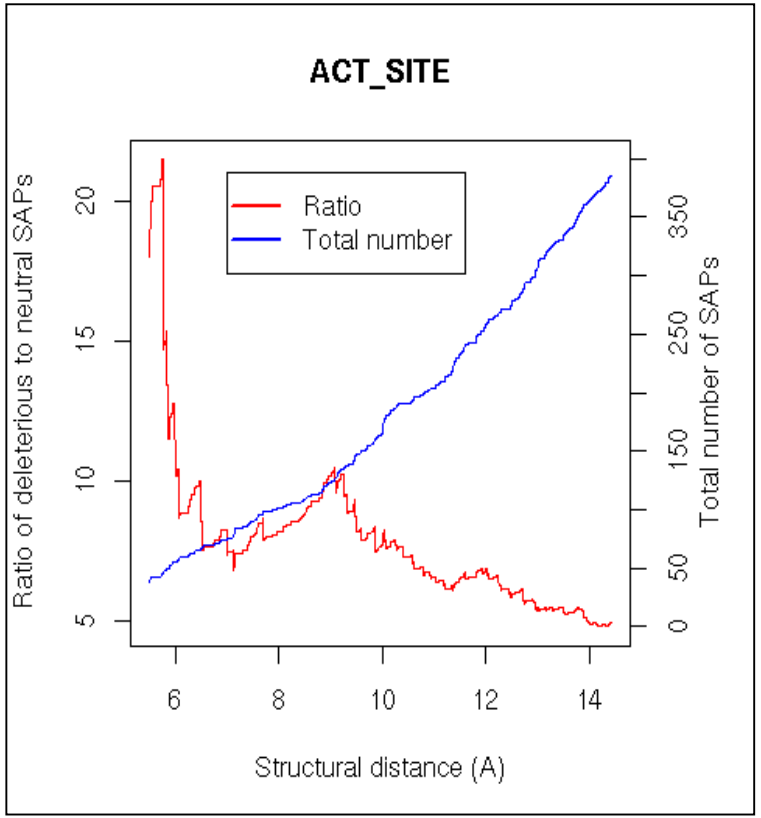
- Amino acid variations located exactly on functional, active, and binding sites tend to have large effect on protein function.
  - But coverage is low.

- We considered that variations **<u>in the vicinity of important sites</u>** could also affect protein function.
  - Significantly increased coverage.



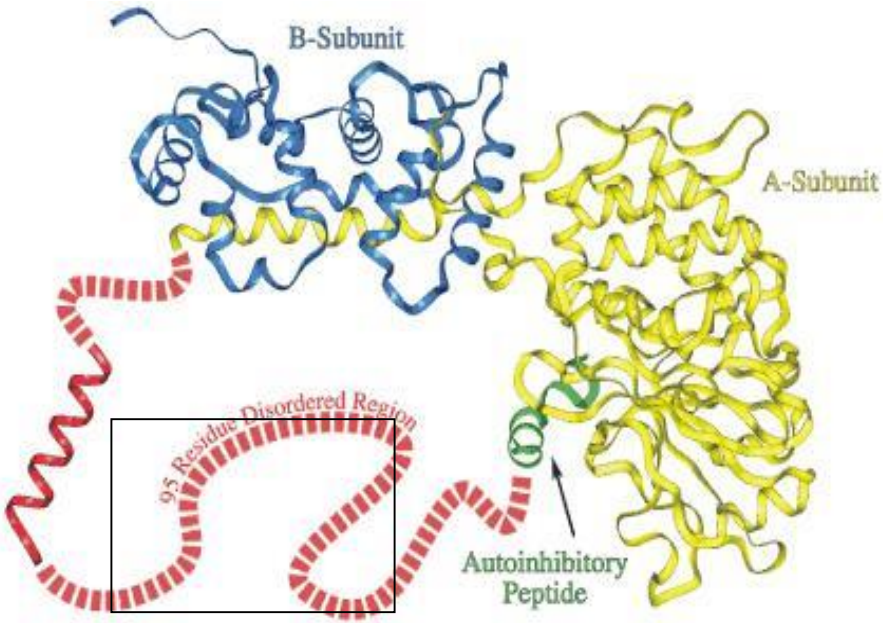
Nearby functional sites





Ye, ZQ, *et al.*, 2007, Bioinformatics, 23(12):1444

Disordered Region

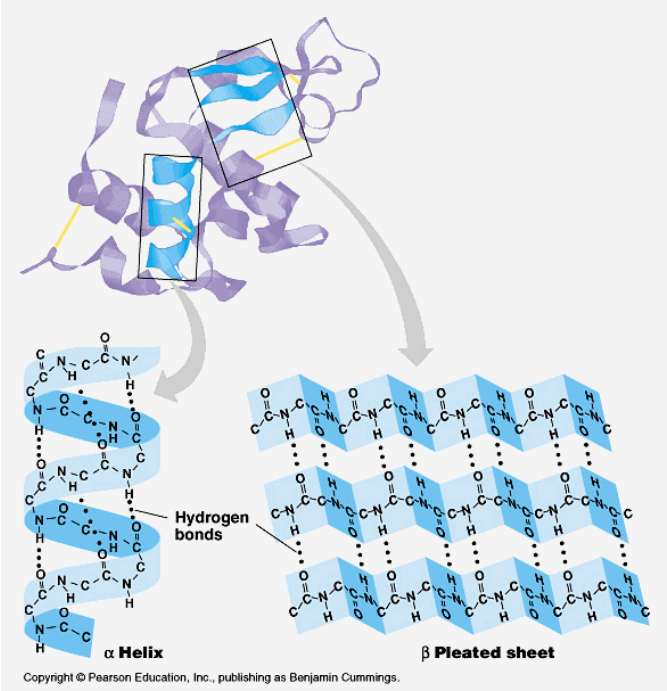


(Image adapted from: Kissinger CR, et al. 1995. "Crystal structures of human calcineurin and the human FKBP12-FK506-calcineurin complex." Nature 378:641-4.)

122 SAPs in disordered regions,
114 (93%) are disease-associated.

From: http://ist.temple.edu/disprot/index.php

Hydrogen bond change



Changed Hydrogen bond	Disease	Polymorphism	ratio
-6	1	0	1/0
-5	12	1	12
-4	44	2	22
-3	114	16	7.25
-2	230	55	4.18
-1	403	213	1.89
0	1142	716	1.59
1	224	142	1.58
2	68	36	1.89
3	11	4	2.75
4	0	2	0
5	0	2	0

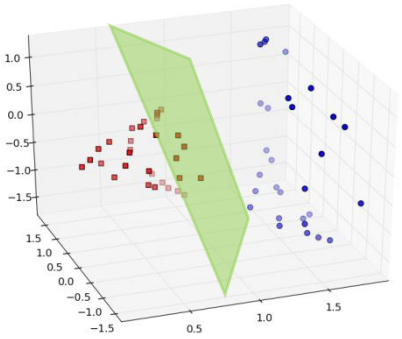
Other attributes

- 52 variants in **transmembrane** regions, 49 (94%) are disease-associated
- 194 variants altered β-aggregation properties, 169 (87%) are disease-associated
- 435 variants from HLA families, all except one are “polymorphism”.

SVM classifier

- **SVM – support vector machine**

  Separate transformed data with a hyper plane in a high-dimensional space



- **Kernel function – Radial Basis Function(RBF)**

- **Grid-search to select proper values of parameter**

Five-fold cross-validation

Part	Total proteins	Total SAP	Deleterious SAP	Neutral SAP
1	105	686	449	237
2	104	688	450	238
3	105	688	450	238
4	105	688	450	238
5	103	688	450	238
Total	522	3438	2249	1189

Ye, ZQ, *et al*., 2007, Bioinformatics, 23(12):1444

Accuracy: ACC and MCC

SAP status	Predicted as disease-association (+)	Predicted as polymorphism (-)
Disease-association (+)	TP	FN
Polymorphism (-)	FP	TN

Overall accuracy:

$$ACC = \frac{TP + TN}{TP + TN + FP + FN}$$

Matthew correlation coefficient:

$$MCC = \frac{(TP \times TN - FP \times FN)}{\sqrt{(TN + FN)(TN + FP)(TP + FN)(TP + FP)}}$$

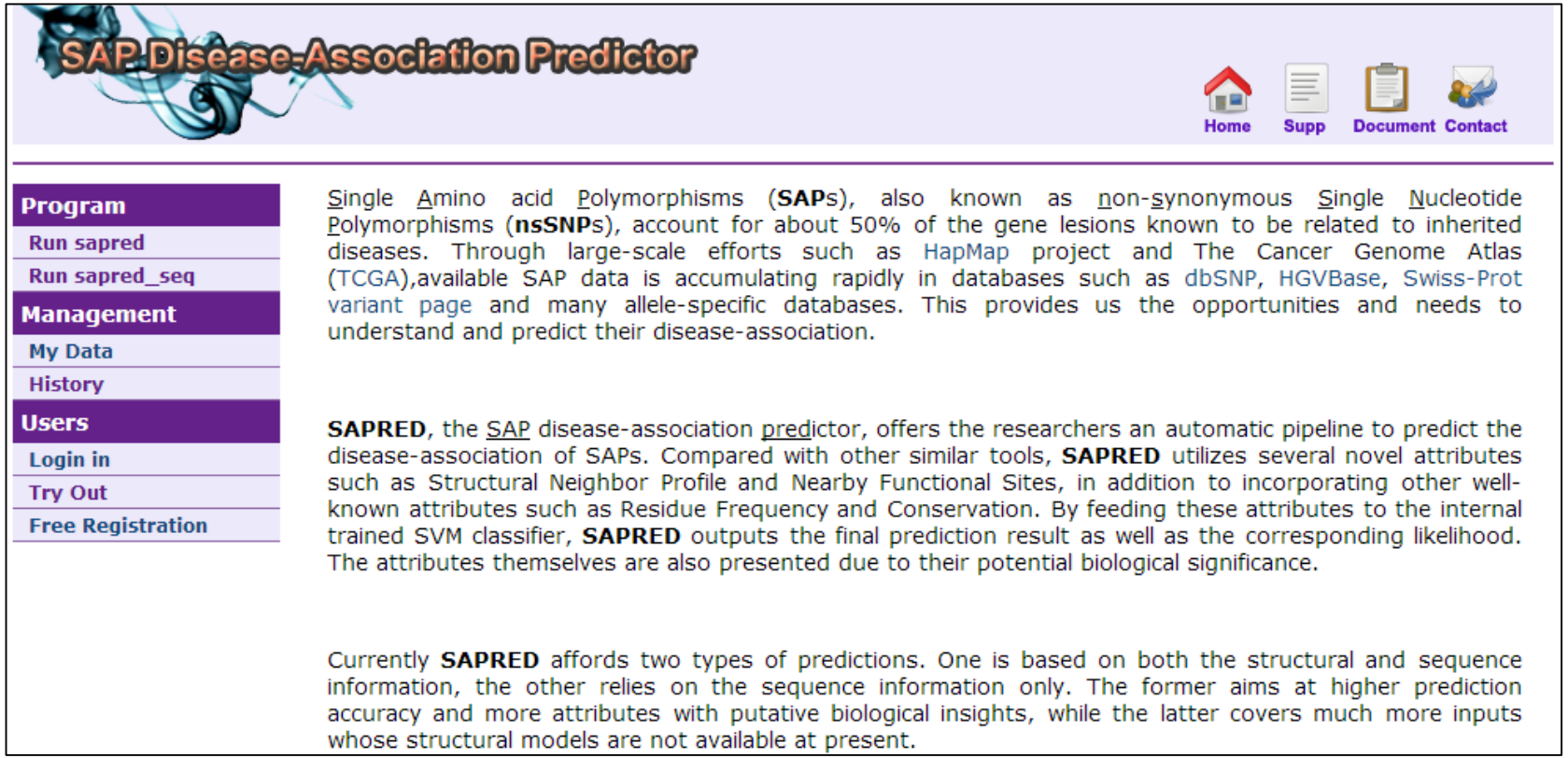
Predictive power

Attribute groups	ACC (%)	MCC
Residue frequencies	77.5	0.489
13 Å structural neighbor profile	76.4	0.467
Conservation scores	74.8	0.425
Nearby functional sites	69.3	0.246
Solvent accessibilities	68.0	0.232
C_β density	67.0	0.190
Final attribute set	82.6	0.604

Ye, ZQ, *et al*., 2007, Bioinformatics, 23(12):1444

SAPRED web server

http://sapred.cbi.pku.edu.cn/



Run SAPRED

SAP Disease-Association Predictor

Currently SAPRED supports only one substitution each time. The user should also supply the PDB files of the wildtype and variant protein with enough quality for extracting structural information. Make sure the PDB file contains only one chain and its residue numbering system is consistent with the FASTA sequence. Such PDB file can be prepared using Swiss-Model or Modeller. If the structure model is unavailable, the user can switch to sapred_seq instead, whose accuracy is a little lower. The users can try these demos first: demo1 demo2 demo3

Input

* input fasta file: ----------

* mutation name:

* wildtype pdb file: ----------

* variant pdb file: ----------

Output

* save result in directory: Work Directory

* prediction result: (bio:sapred:sapred) Untitled.sapred

Run

Results

Prediction Result

Prediction	Disease Likelihood	Neutral Likelihood
Disease	0.88069	0.11931

Explanation of Results: Structural features

Structure-derived attributes

13A structural neighbor profile	A	0	G	1	M	1	S	3
	C	4	H	1	N	2	T	2
	D	2	I	3	P	3	V	0
	E	0	K	8	Q	2	W	0
	F	1	L	5	R	1	Y	0

Structurally Nearby Functional Sites	ACT_SITE	14
	BINDING	14
	METAL	14
	MOD_RES	14
	DISULFID	14
Solvent Accessibilities	Side-chain absolute	88.44
	Side-chain relative	48.5
C-beta density	16	
Secondary structures	Secondary structure	C
	No alteration of secondary structure	Y
	No alteration of 3-mer secondary structure	Y
Dihedrals	|Phi Difference|	1.350
	|Psi Difference|	1.530
	|Chi1 Difference|	0.914
Changed Hydrogen Bonds	0	
Changed Disulfide Bonds	0	
RMSD	0.07358	
Difference between energy	2.1752	

Explanation of Results: sequence features

Sequence-derived attributes

Residue frequencies	Frequency of widetype residue	0.8591
	Frequency of variant residue	0.0052
	Difference residue frequency	-0.8539
Conservation Scores	neibor3L	0.7586
	neibor2L	1.0534
	neibor1L	0.7201
	conserv	1.1102
	neibor1R	0.1574
	neibor2R	0.1906
	neibor3R	1.0747
Sequentially Nearby Functional Sites	ACT_SITE	30
	BINDING	30
	METAL	30
	MOD_RES	30
Aggregation Properties	tango_wt	0.00
	diff_tango	0
	frag_equal	Y
BLOSUM Score	-3	
GRANTHAM Score	116	
In TRANSMEM Region	N	
In Disordered Region	N	
In HLA Family	N	

Results using SAPRED_Seq

ACC=81.5%

MCC=0.577

Prediction Result

Prediction	Disease Likelihood	Neutral Likelihood
Disease	0.871749	0.128251

Sequence-derived attributes

Residue frequencies	Frequency of widetype residue	0.8591
	Frequency of variant residue	0.0052
	Difference residue frequency	-0.8539
Conservation Scores	neibor3L	0.7586
	neibor2L	1.0534
	neibor1L	0.7201
	conserv	1.1102
	neibor1R	0.1574
	neibor2R	0.1906
	neibor3R	1.0747
Sequentially Nearby Functional Sites	ACT_SITE	30
	BINDING	30
	METAL	30
	MOD_RES	30
Aggregation Properties	tango_wt	0.00
	diff_tango	0
	frag_equal	Y
BLOSUM Score	-3	
GRANTHAM Score	116	
In TRANSMEM Region	N	
In Disordered Region	N	
In HLA Family	N	

The New York Times

May 14, 2013

My Medical Choice

By ANGELINA JOLIE

LOS ANGELES

MY MOTHER fought cancer for almost a decade and died at 56. She held out long enough to meet the first of her grandchildren and to hold them in her arms. But my other children will never have the chance to know her and experience how loving and gracious she was.

Angelina Joli has a genetic variation in *BRCA1*

Do you think she had made the right decision to remove her breasts?

Lots of factors to consider in making this complicated decision

- Given her genetic mutation, what is the likelihood of her getting breast cancer?
  - P(cancer|mutation)
  - P(cancer-free|mutation)
- Even after she got mastectomy, what is the likelihood of her getting breast cancer?
  - P(cancer|mutation, mastectomy)
- If she didn't get mastectomy, what could her outcome be?
  - P(early detection|mutation, cancer)
  - P(cure|mutation, cancer, early detection)
  - P(new treatment before cancer develops)
- What is the risk of death from the procedure of mastectomy?
  - P(death from surgery|mastectomy)

- Age of onset of cancer
- Emotional stress: fear of cancer *vs.* distress over loss of breasts
- Cost of mastectomy

Using family history to increase prediction power

- Strong family history
  - Jolie's mother, Marcheline Bertrand, died from ovarian cancer at 56 after a 10 year battle.
  - Her aunt, 61-year-old Debbie Martin, is dying of breast cancer after a 9 year battle.
  - Her grandmother, Lois Bertrand, died of cancer at 45.
  - Her great-grandmother, Virginia Gouwens, died of ovarian cancer at 53.
  - Her uncle, Raleigh, also died of cancer in 2009.

- Strong family history, early-onset, poor prognosis

- Has the causal mutation been identified in her affected relatives and does it co-segregate with cancer in her family?
- Does Jolie carry the same mutation?

Lots of remaining challenges

- Prediction accuracy
- Integration of multiple sources of evidence
- Noncoding variants
- More training data
- Ethical issues

Wherever there are challenges, there are opportunities.

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