

PROTEOMIKA

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- Proteinové interakce – 18.10.
 - jak spolu proteiny interagují?
 - interaktom
- Proteinové komplexy – 25.10.
 - protein-proteinové interakce a komplexy
 - komplexom, architektura a funkce komplexů

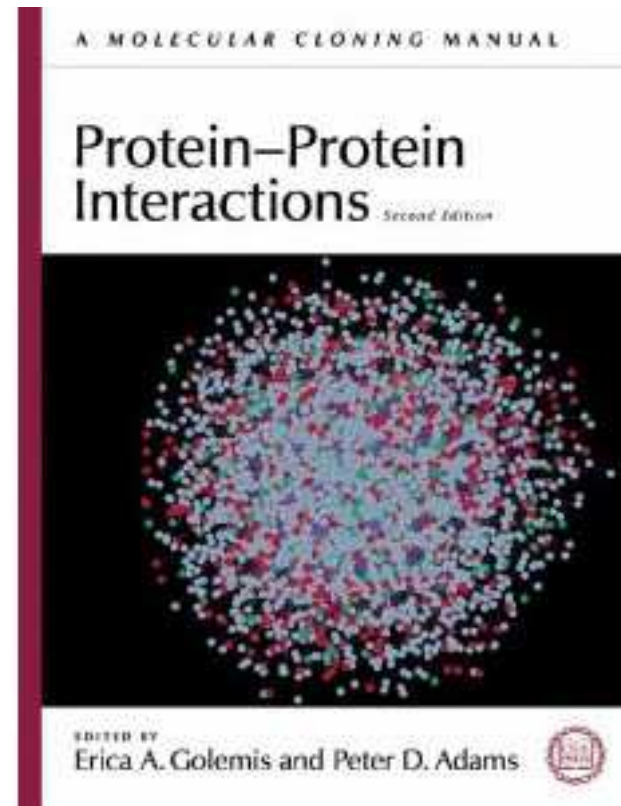
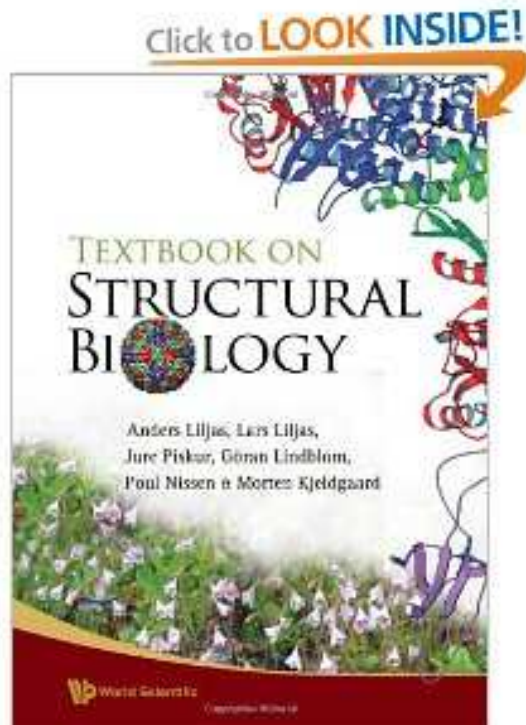
CG030 – Struktura a funkce proteinových komplexů

Informační zdroje

Alberts a spol: Molecular biology of the Cell (2008 ...)

Liljas a spol: Structural biology (2009) ...

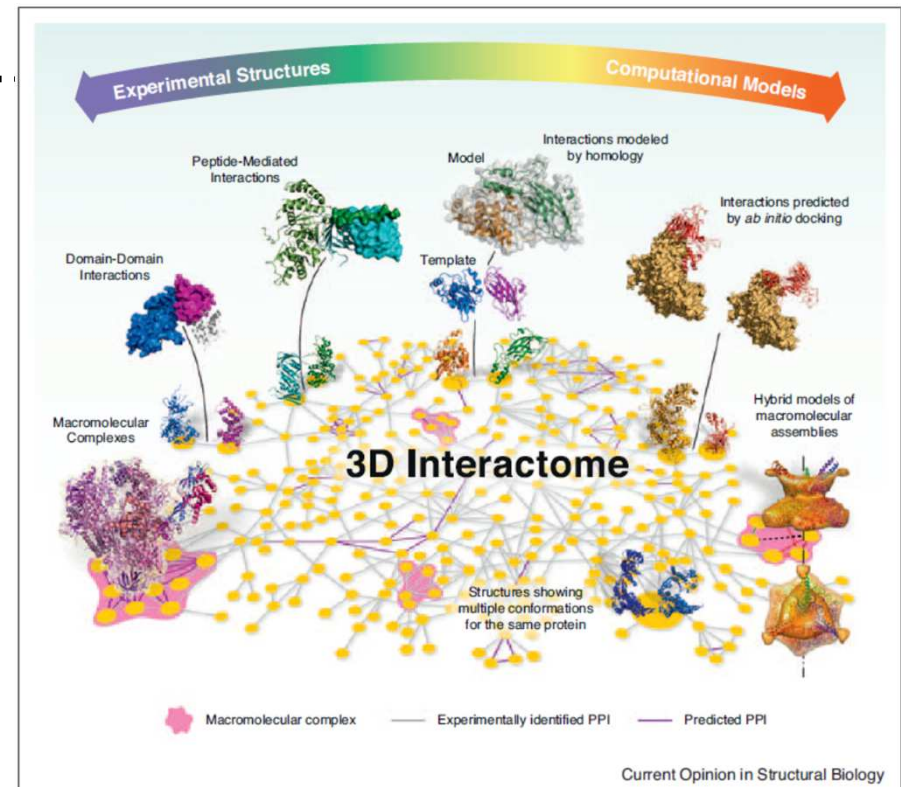
... nejnovější články z časopisů Cell, Nature, Science, PLoS ...

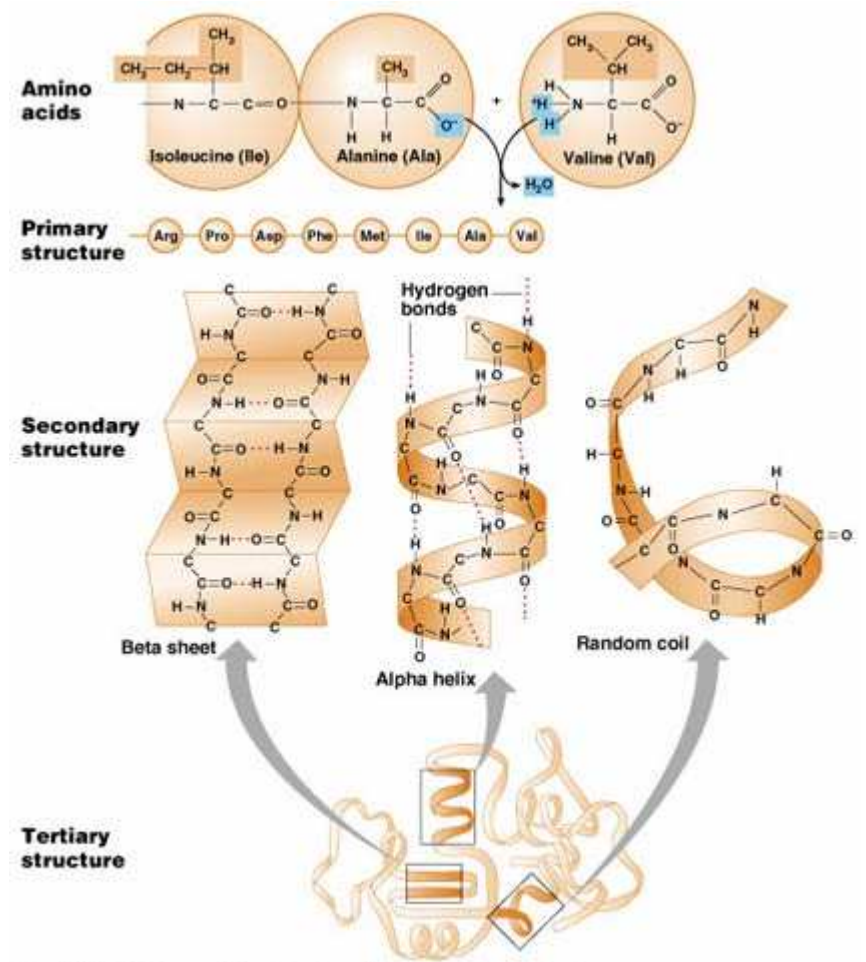
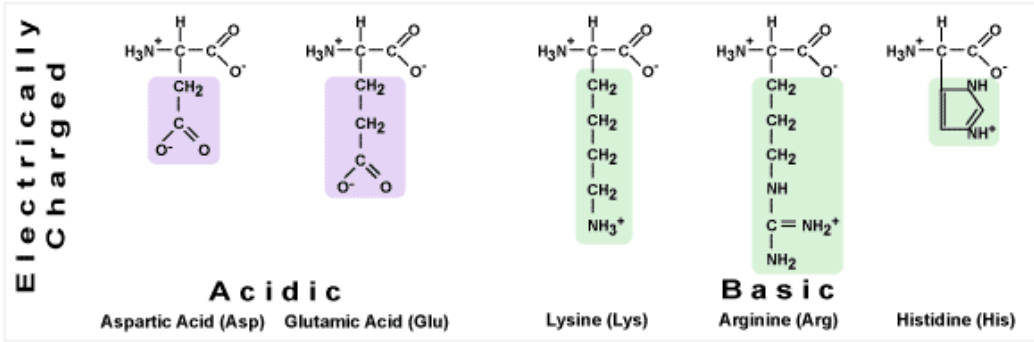
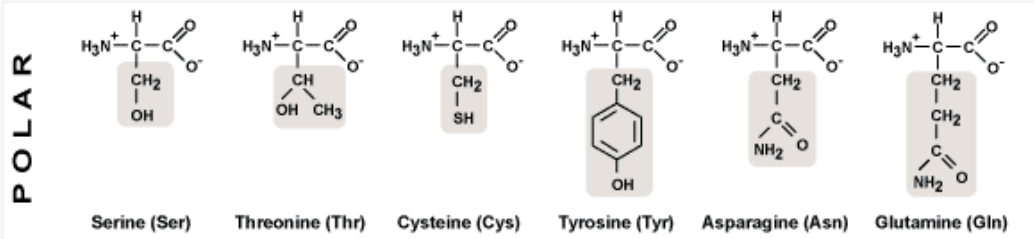
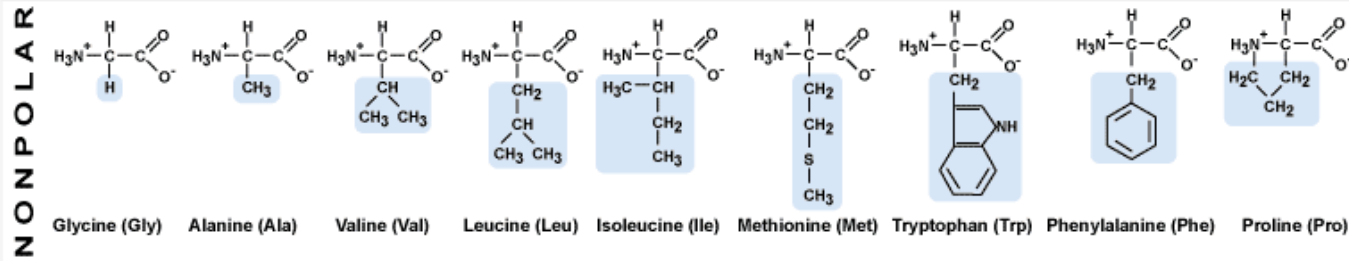


Databáze proteinových struktur: <http://www.rcsb.org/pdb/home/home.do>,
<http://www.ebi.ac.uk/pdbsum/>

Database protein-proteinových interakcí: <http://string-db.org/newstring.cgi> ...
<http://www.ebi.ac.uk/intact/?conversationContext=1>

- Proteinové interakce – 18.10.
 - Interakce: od primární po terciární strukturu
 - Typy vazeb ...
 - Informatika:
 - databáze struktur, interakcí ...
 - docking ...
 - motivy, evoluční aspekty ...
 - nástroje ...
 - interaktom ...



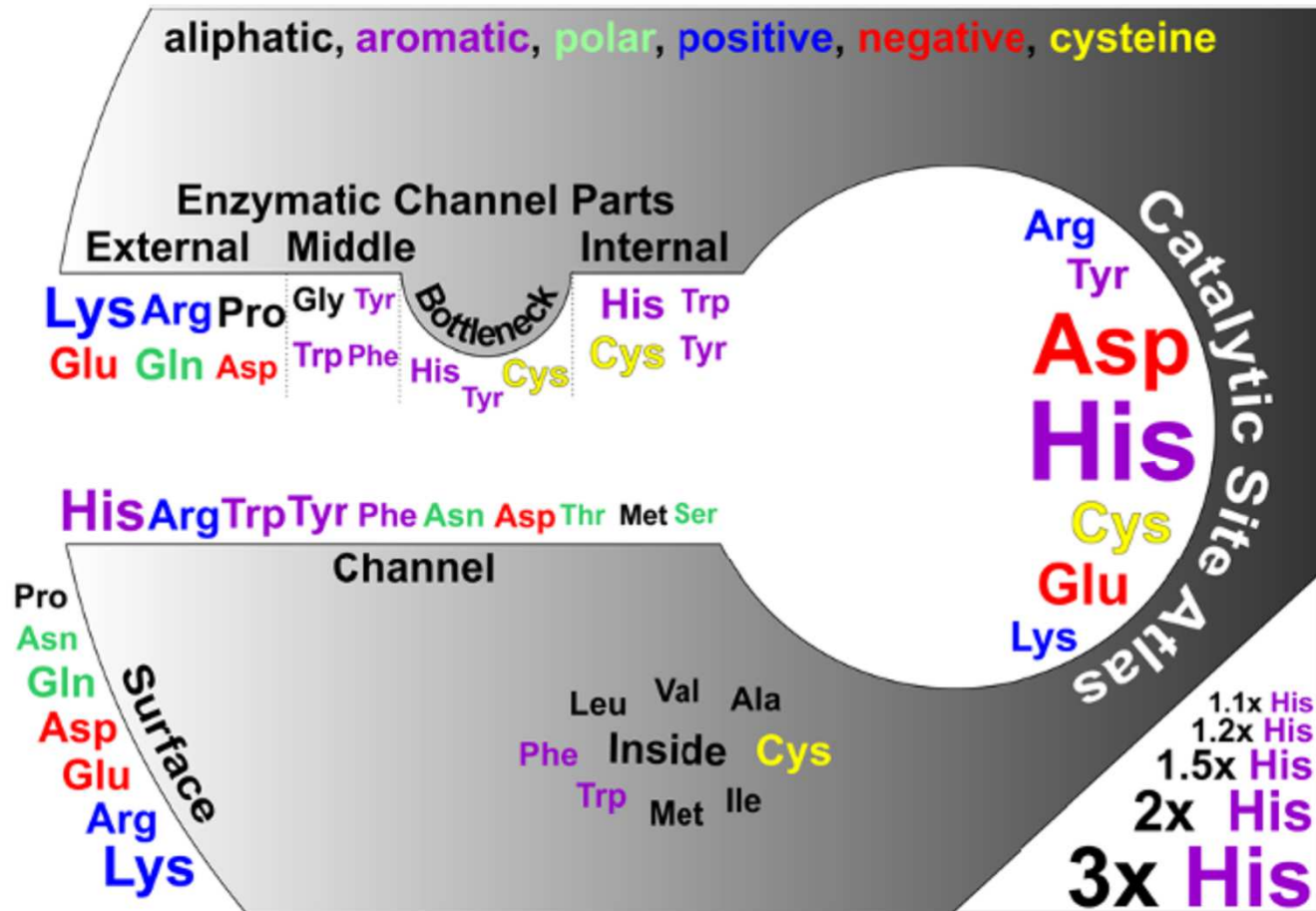


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Základní proteinové charakteristiky

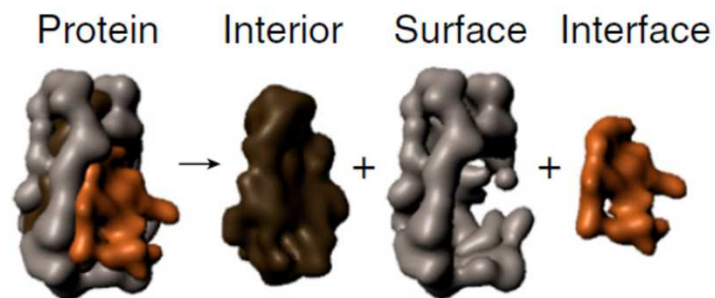
- Primární
- Sekundární
- Terciární
- Kvarterní – dva proteiny a více ...

Podíl AMK (primární struktury) na proteinových interakcích

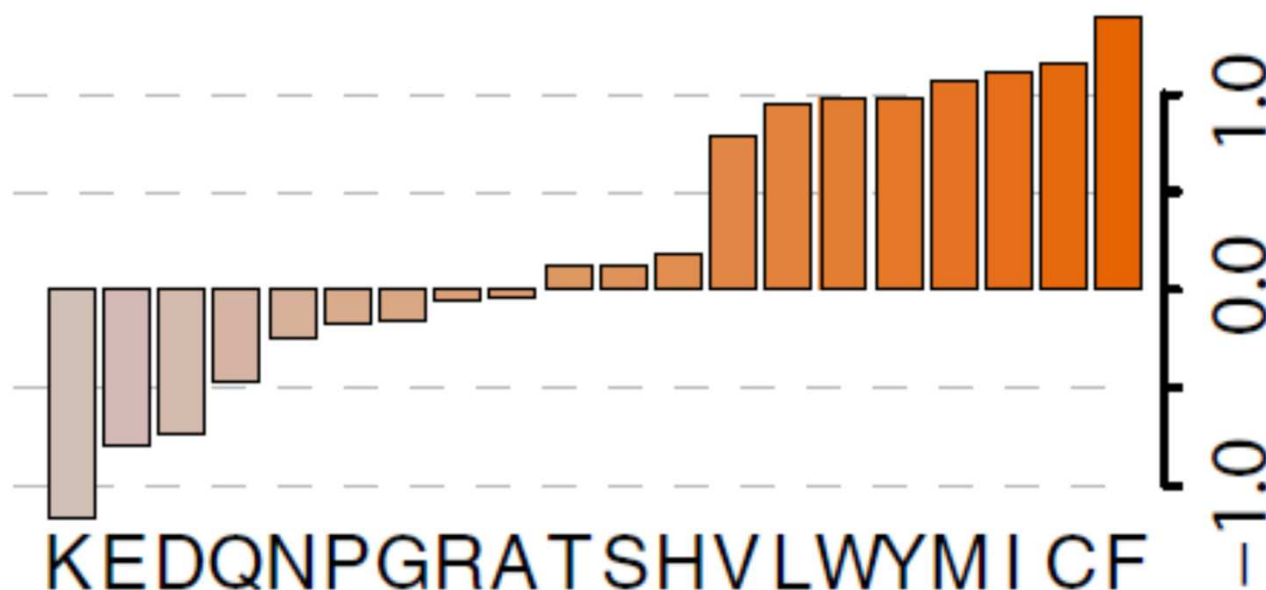


- uvnitř hydrofobní, povrch polární/nabitý (do solventu/vody), ale katalytická centra (tunely) jsou také polární a nabité (katalýza biochemické reakce)

PPI od primární struktury ...



amino acid interface propensity
 $\log\left(\frac{\text{freqAA}_{\text{interface}}}{\text{freqAA}_{\text{surface}}}\right)$
 proxy for amino acid "stickiness" scale



Eichborn et al, Genome Inf, 2009
 Levy et al.: PNAS, 2012

poměr mezi výskytem AMK na „intaktním“ povrchu a interakčním povrchu – polární a nabitě do solventu tj. povrchu - hydrofobní na povrchu nejčastěji vytváří protein-proteinové interakce

Typy vazeb v PPI

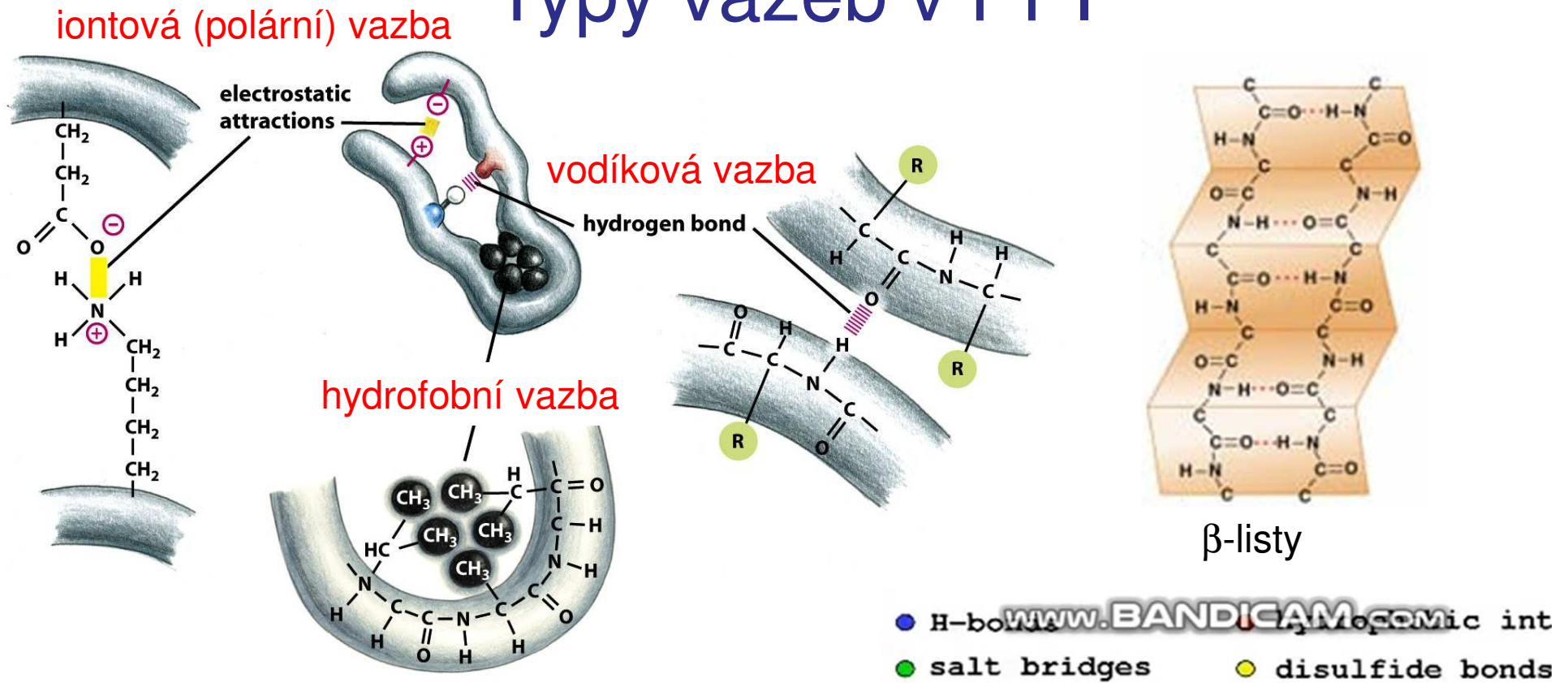
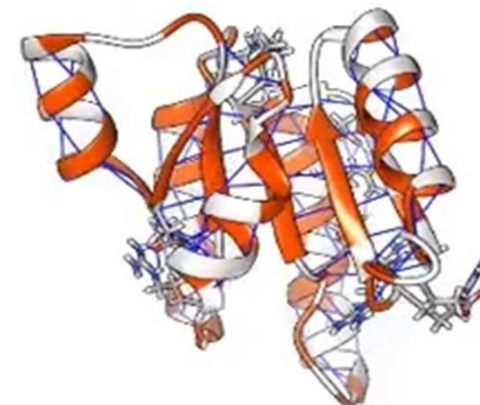


Figure 3-4 *Molecular Biology of the Cell* (© Garland Science 2008)

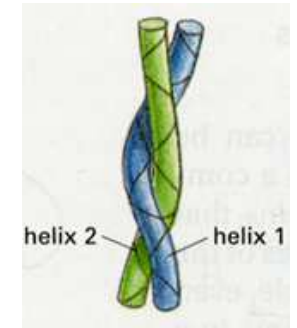
Která z těchto vazeb převažuje v PPI?

Kovalentní vazba = modifikace (nikoli PPI)
 vyjimečně např. disulfidické můstky nebo jiné
 posttranslační modifikace (ubikvitinace,
 SUMOylace)



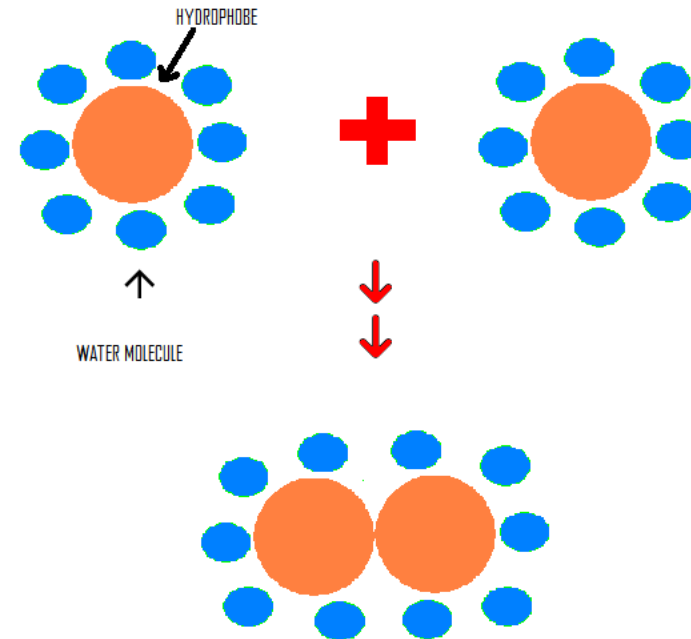
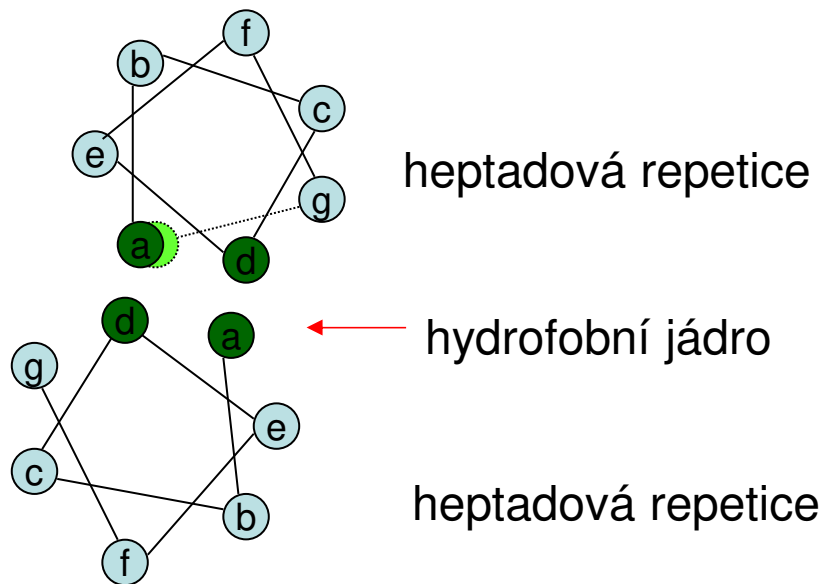
... sekundární struktury ...

- šroubovice se vůči sobě orientují různým způsobem
- skládání slabých vazeb ovlivňuje sílu a specifitu celkové vazby

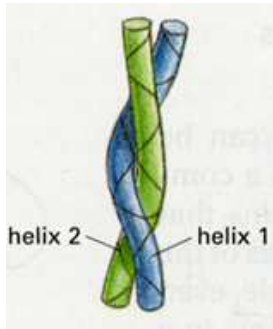


coiled-coil struktura

- dvě šroubovice s tzv. heptádovou repeticí (hxxhxxx – hydrofobní zbytky vytváří rozsáhlý povrch a tedy silnou vazbu)

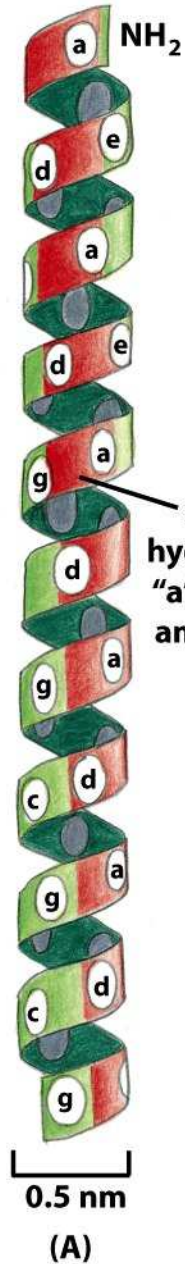


...LKS**L**HNQ**L**RD**L**EES**L**TH...

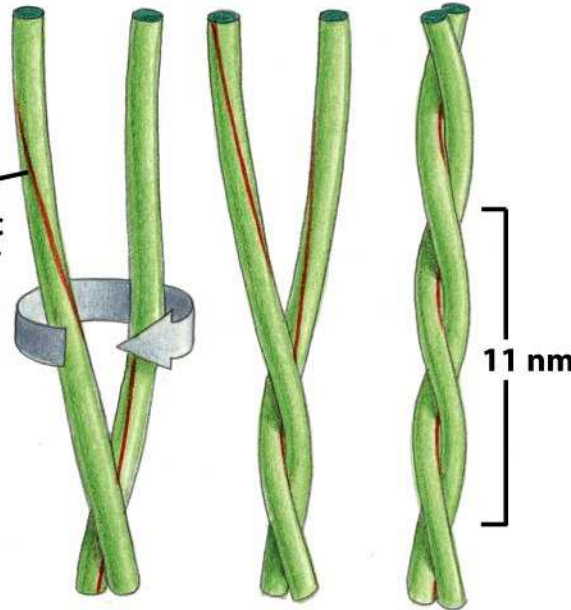


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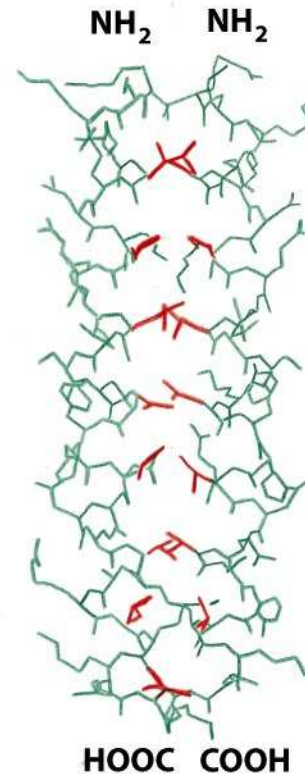


stripe of hydrophobic "a" and "d" amino acids



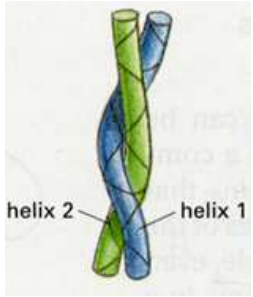
hydrofobní jádro

...LKSLHNQLRDLLEESLTH...



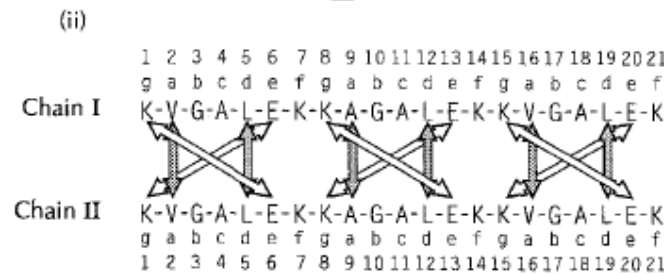
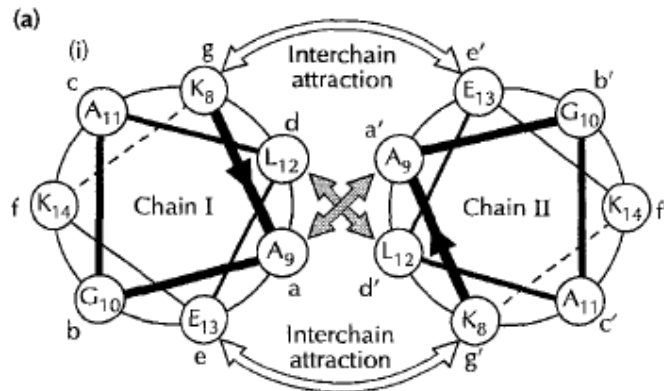
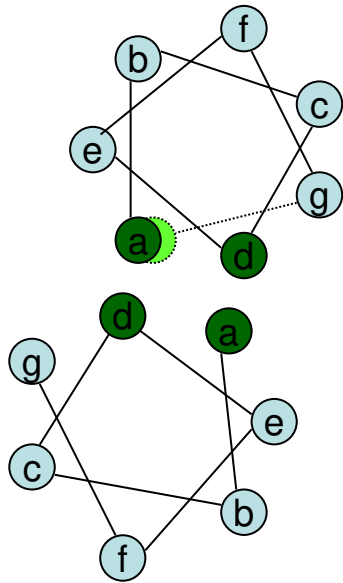
paralelní šroubovice

(C)

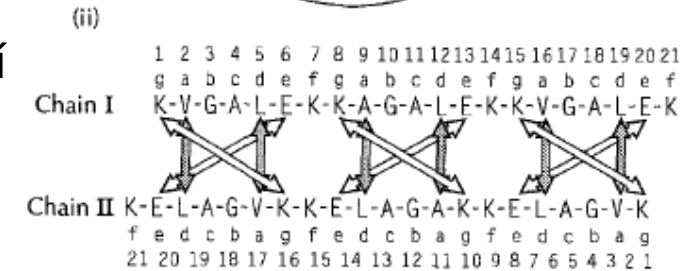
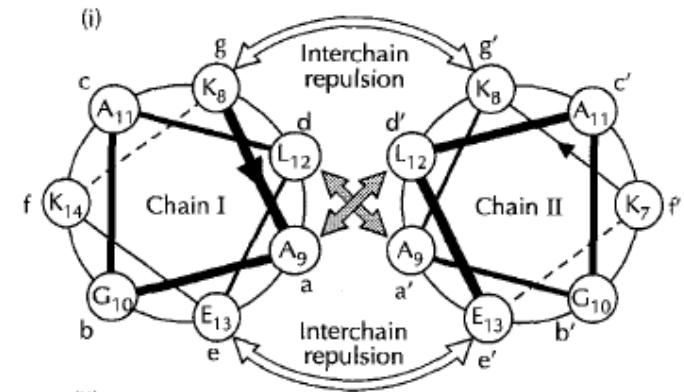


coiled-coil struktura

Síla interakce může být ovlivněna sousedními AMK

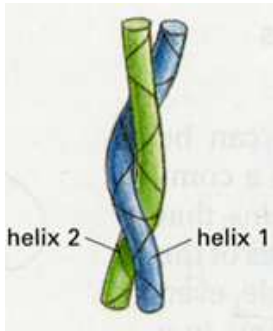


Sousední AMK stabilizují interakce šroubovic



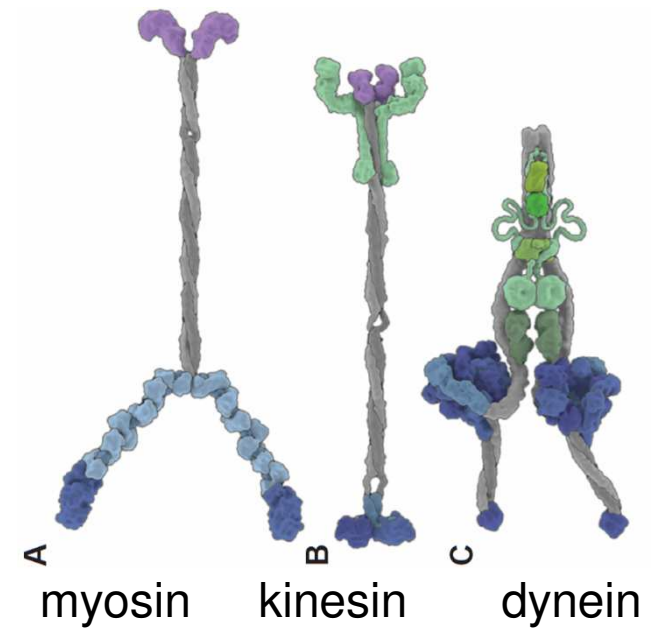
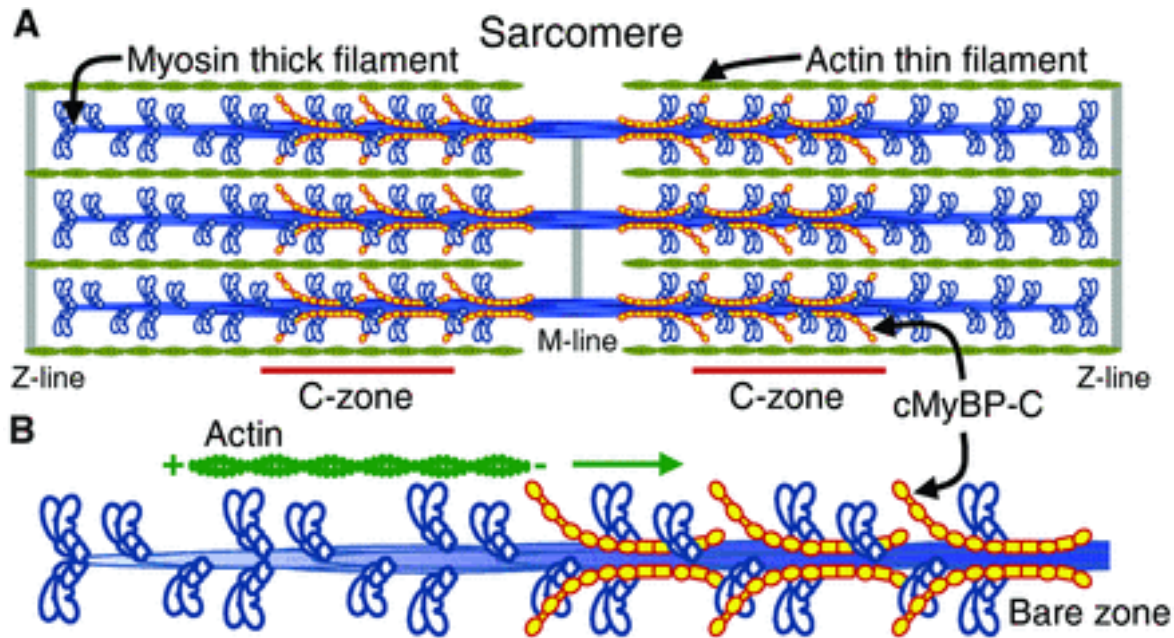
Sousední AMK destabilizují interakce šroubovic

Adamson et al.: CO in Biotech, 1993
Ivanov et al., PLoS One, 2017

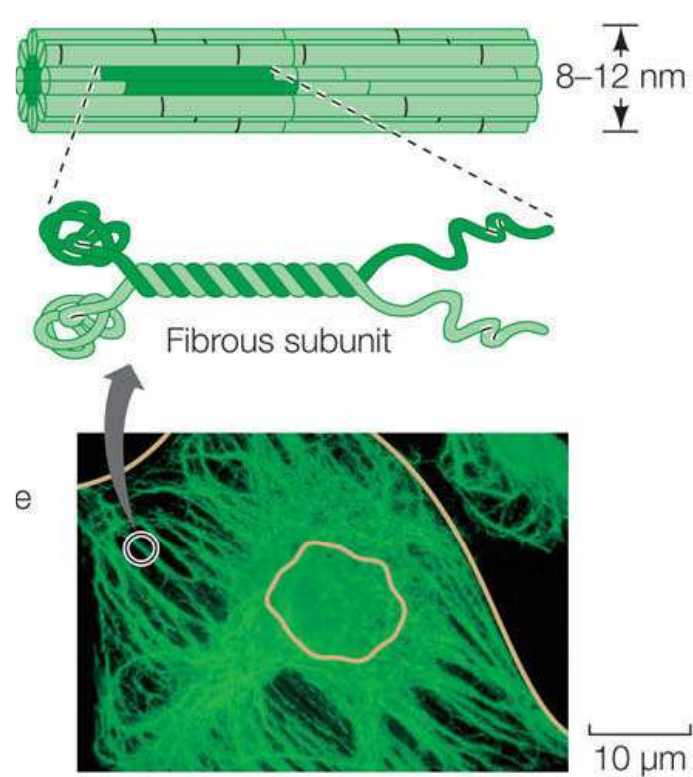


coiled-coil struktura

-dlouhé CC (>100AMK) vytváří vláknité struktury (myosin tvoří vlákna - svaly)

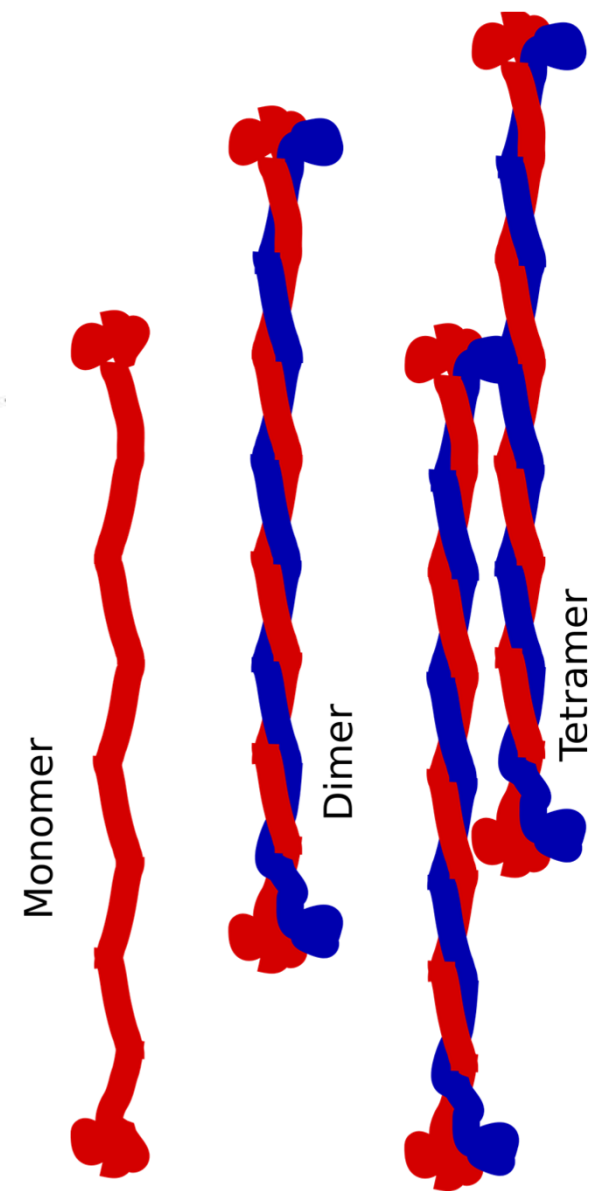


- CC v myosinu je intermolekulární (paralelní)



B) Intermediate filaments
 Made up of fibrous proteins organized into tough, ropelike assemblies that stabilize a cell's structure and help maintain its shape.

stria.

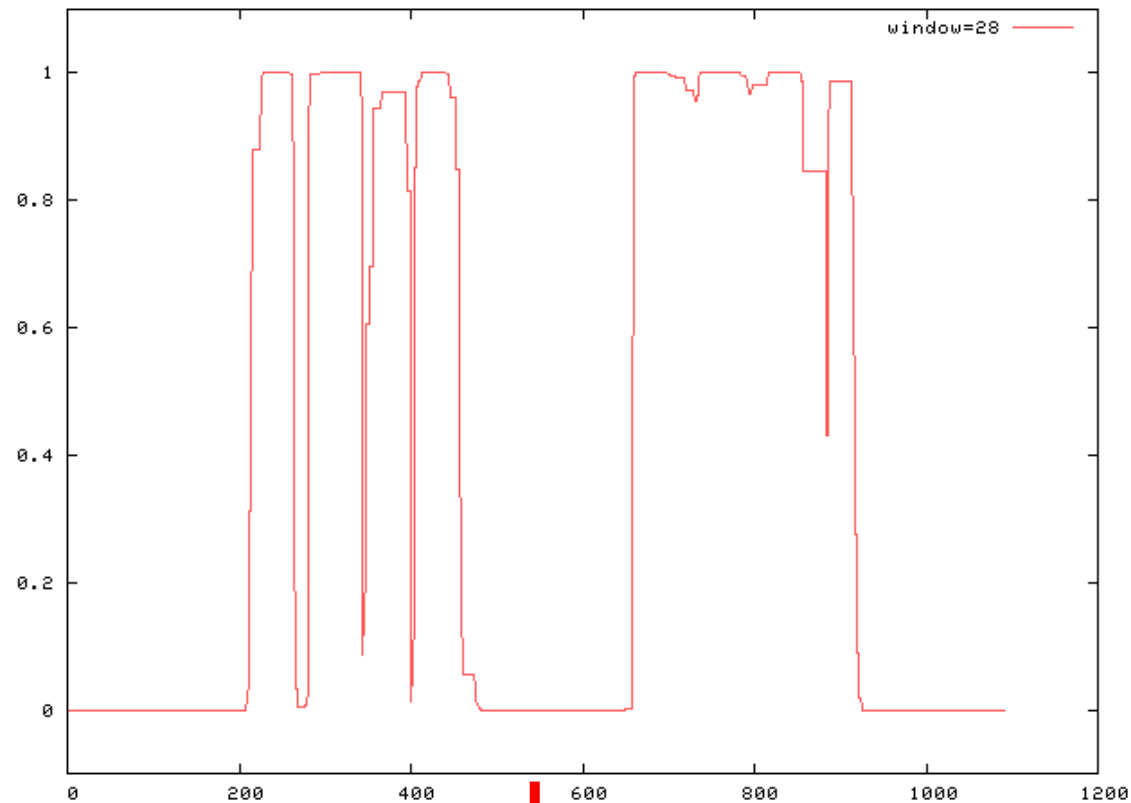


- CC v intermediárních filamentech je intermolekulární (antiparalelní)

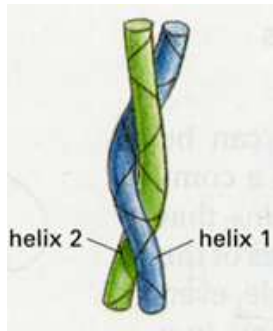
coiled-coil struktura

- program COIL: http://www.ch.embnet.org/software/COILS_form.html

profil SMC6

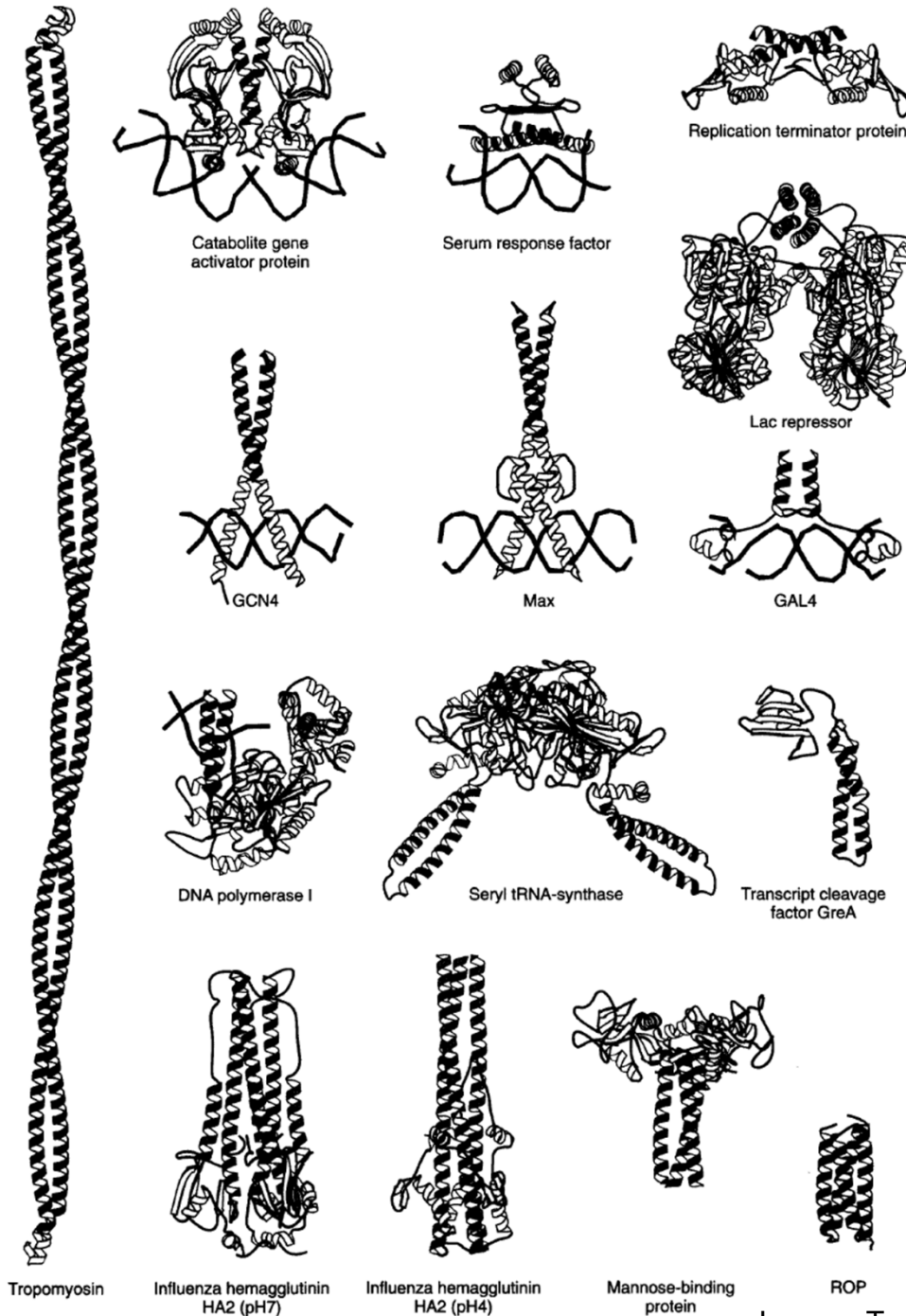


- CC v SMC proteinech jsou intramolekulární (antiparalelní)

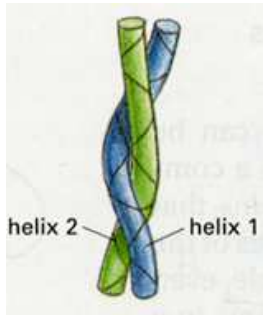


Coiled-coil doména je významným dimerizačním modulem u mnoha proteinů (GCN4, Max ...)

Intermolekulární - homo- či heterodimery (oligomery)



Interakce šroubovic

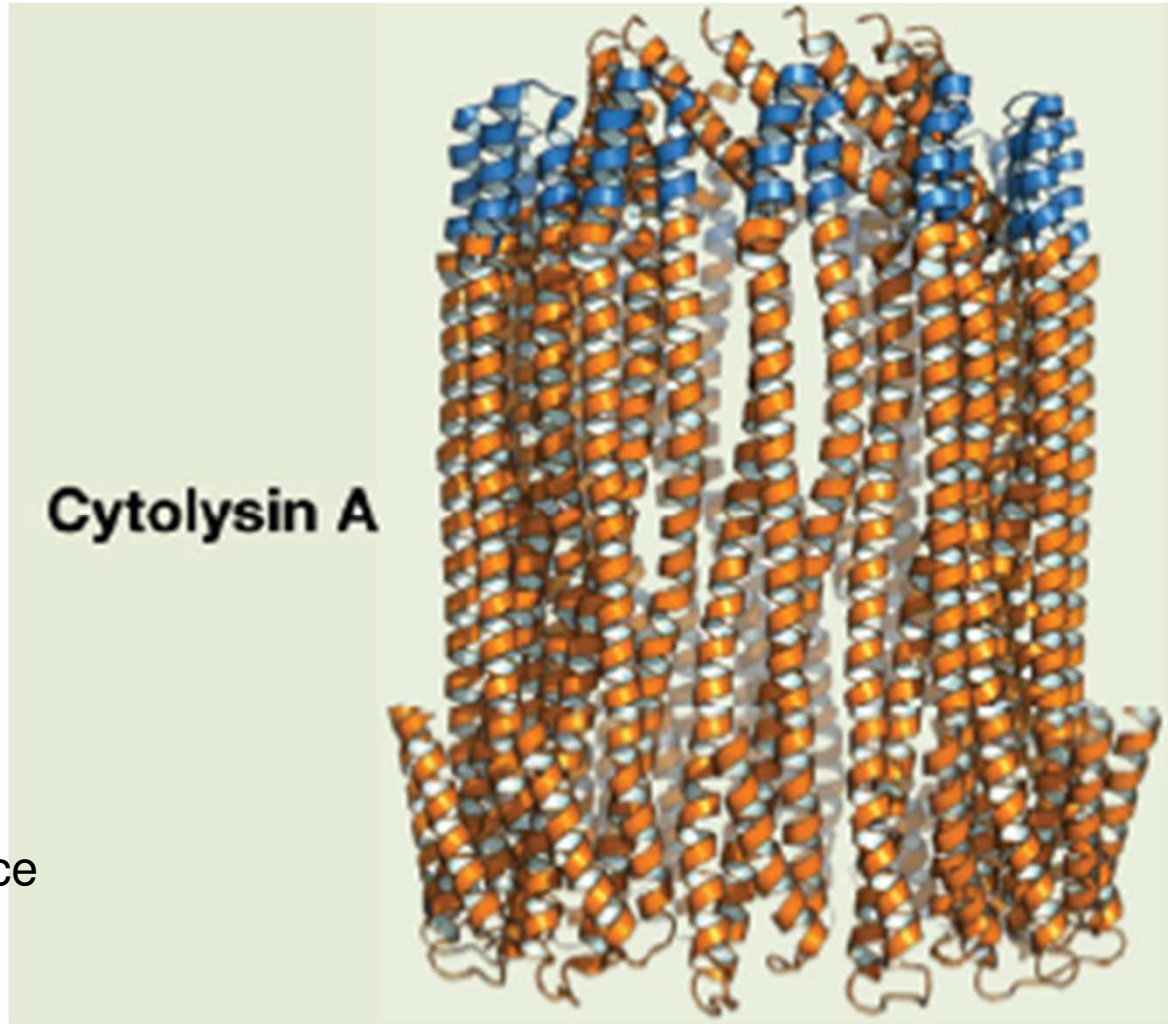


3 šroubovice



Influenza hemagglutinin

4 šroubovice

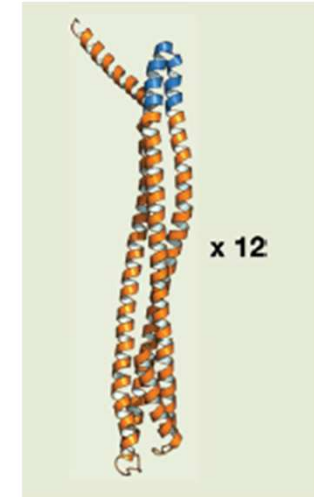


Cytolysin vytváří póry v membránách cizích buněk

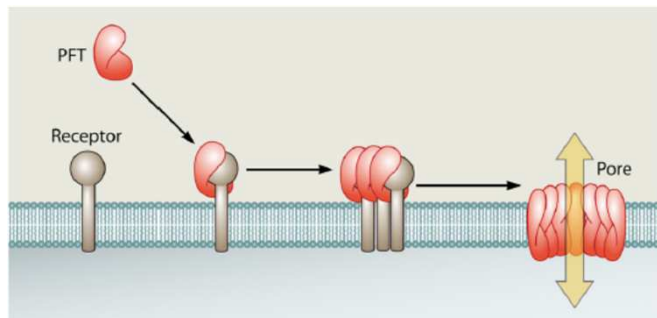
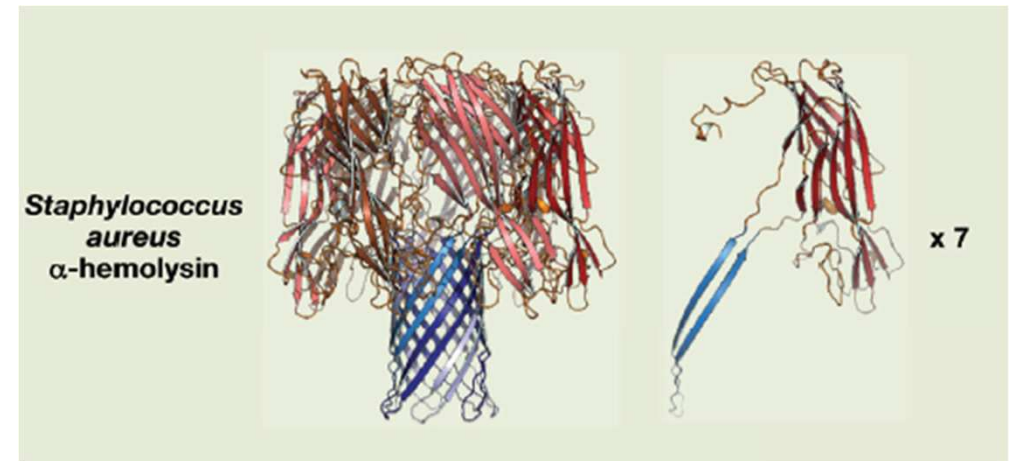
Šroubovice se pod určitým úhlem dotýkají - obtáčejí Mueller & Ban, Cell, 2010; 1QOY, 2WCD

... sekundární struktury ...

- **listy, šroubovice, smyčky**
... se podílí na protein-proteinových interakcích (PPI) podobným způsobem jako při skládání proteinu do 3D – podobné sterické faktory (listy vůči sobě, šroubovice vůči sobě)



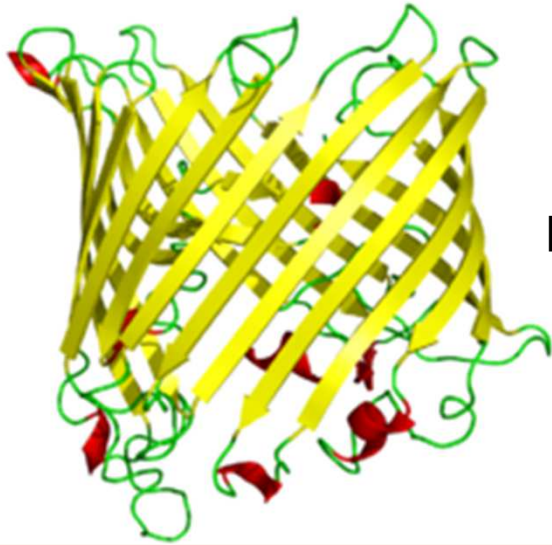
- **foldingskládání** ... struktura některých „disordered“ proteinů se utváří až v rámci interakce s druhým proteinem



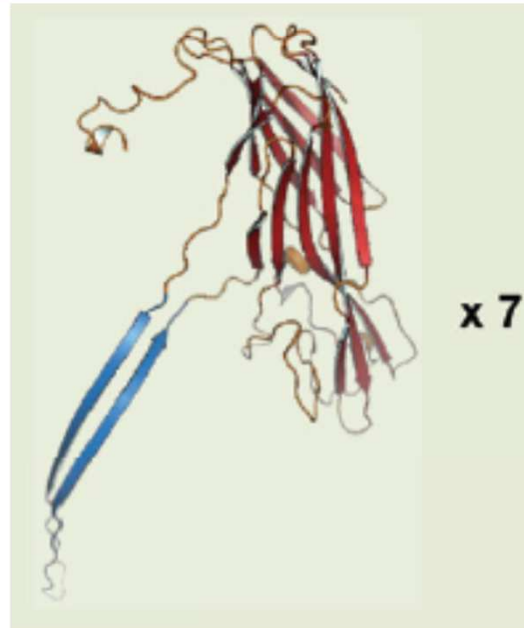
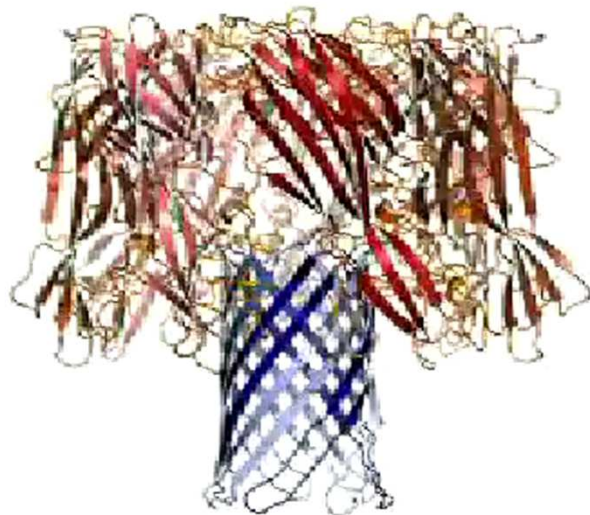
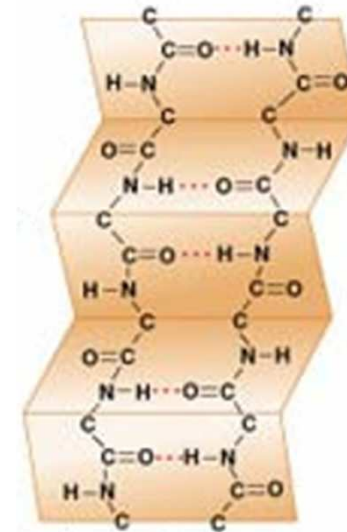
Toxiny – podjednotky se skládají tj. vytváří pór až v místě působení (neublíží původní buňce)

... sekundární struktury ...

v interakcích β -listů převažují vodíkové vazby (peptidového řetězce)

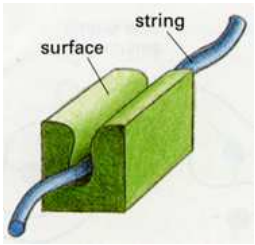


Porin
(1 ORF - polypeptid
prostup mitochondriální
membrány)



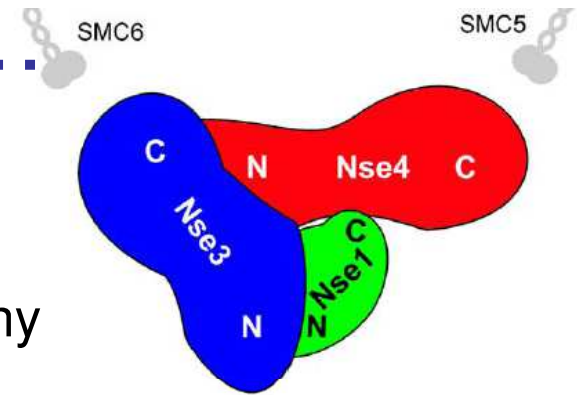
tento „pór“ vzniká interakcí
7 podjednotek

Mueller & Ban, Cell, 2010
Los a spol, MMBR, 2013

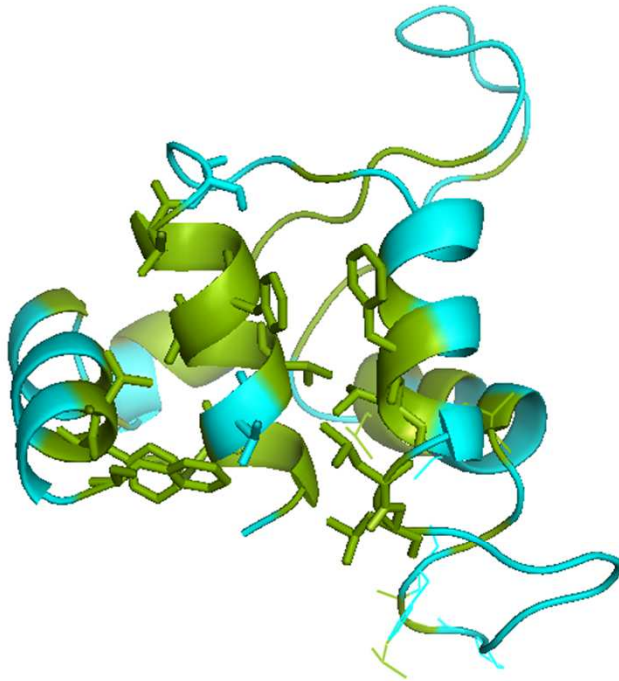


... terciární struktura ... kapsa-peptid

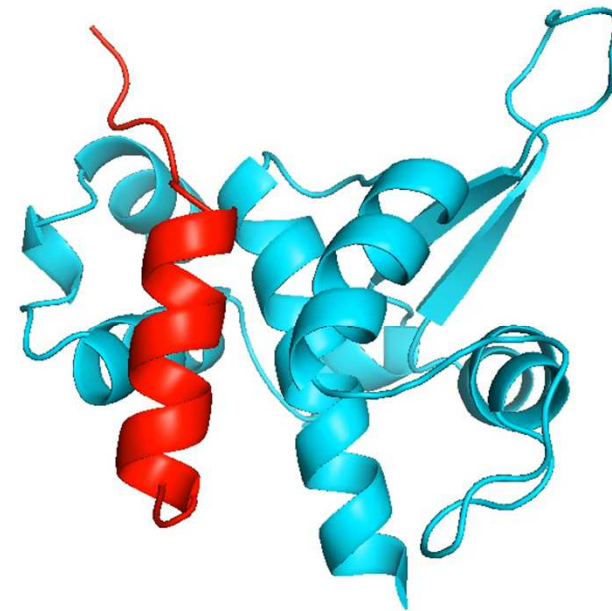
sekundární struktury (šroubovice, beta-listy)
interagují pod různými úhly a vytváří různé povrchy



hlubší prohlubně na povrchu
mohou tvořit kapsy pro vazbu
partnera (šroubovice, peptid)

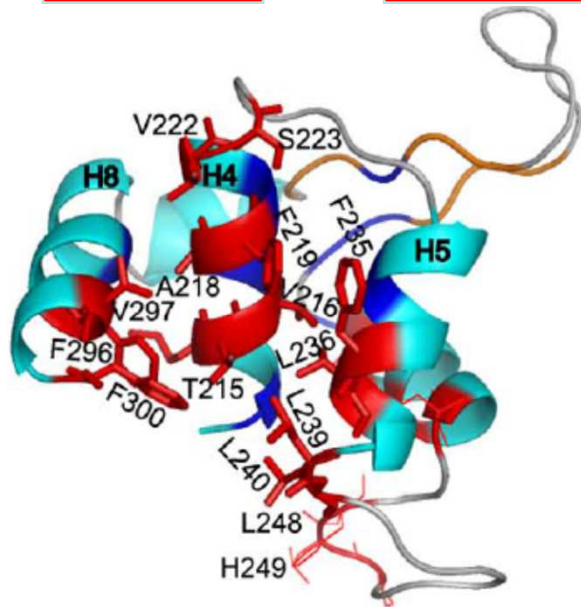
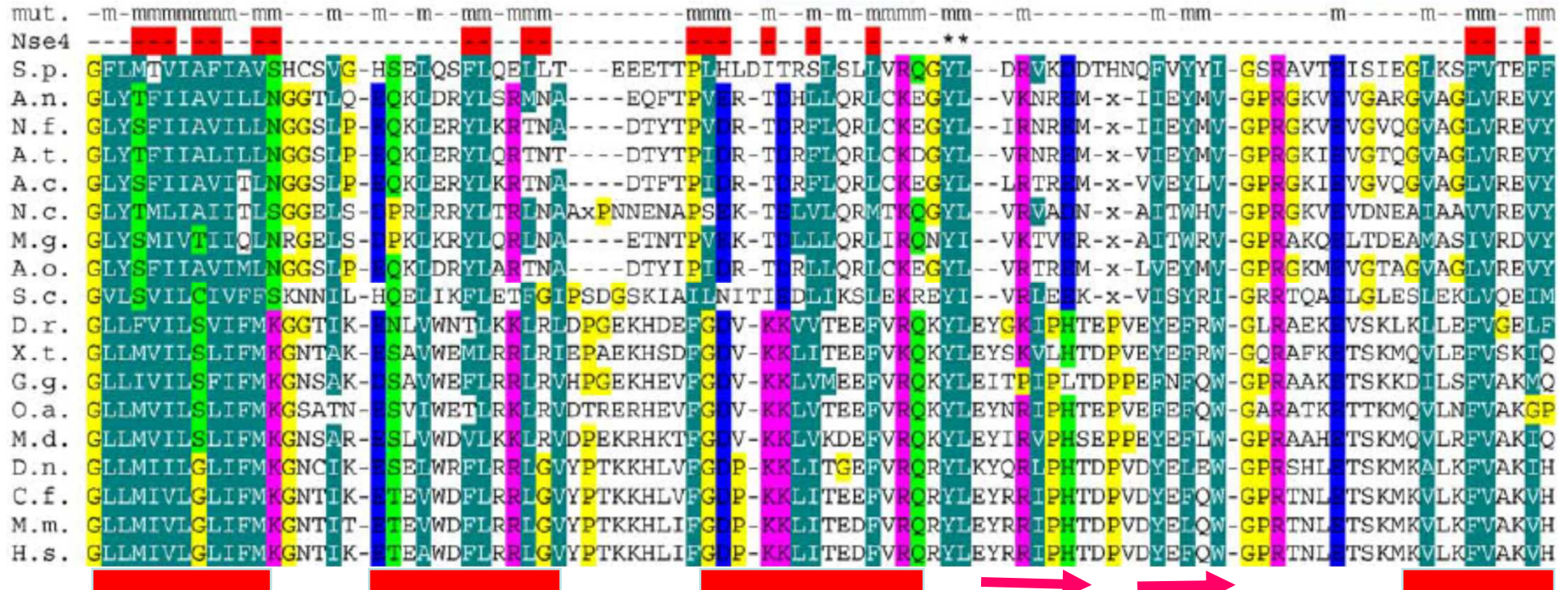


161 166 171 176 181 186 191 196 201 206 211 216 221 226 231 236 241 246 /D/107 111 116 1'
'ESAIWEMLRRLRIEFGEMHSEFGDVKLVTEEFVKQKYLEYN...KIQGKPKSMTTQYKDAQE HMTVFDPTSFTADLL'
(ining)

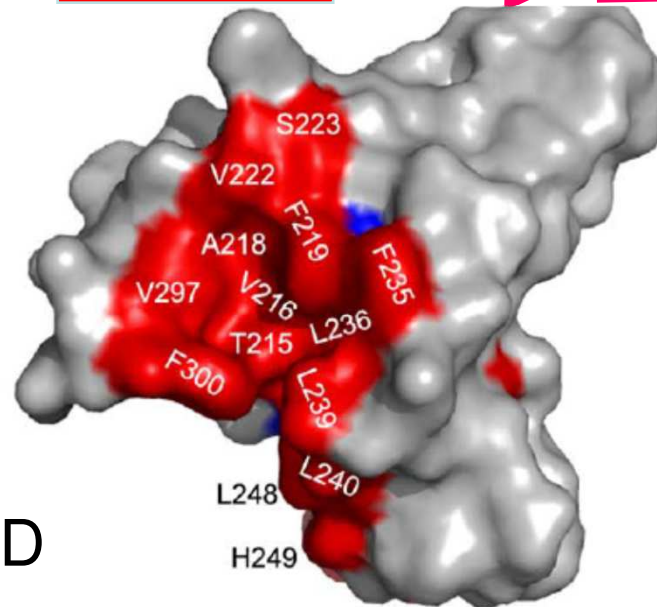


hydrofobní interakce mezi Nse3 a Nse4

Tato hydrofobní šroubovice není transmembránová, ale podílí se na protein-proteinové interakci (NSE3-NSE4)



WHD



Interakce
mapována
mutagenezí

v PDBsum můžete hledat kapsy (povrchy vhodné pro vazbu partnera) – musí mít **komplementární tvar a charakter** (terciární)

MAGEA4 – podobný Nse3

PDBsum

Go to PDB code: 2wa0 go

Top page Protein **Clefts** Tunnels Links

Cleft analysis for: 2wa0 PDB id 2wa0

WHD

View options

- Binding-site(s)
- Binding-surface(s)

Coloured by

- cleft (as in table below)
- closest atom type
- residue type
- residue conservation

Jmol RasMol

Clefts	Volume	R1 ratio	Accessible vertices	Buried vertices	Average depth	Residue type	Ligands			
1	2370.52	0.98	65.15	1	10.55	1	10.50	1	8 6 5 15 4 4 1	

největší kapsa

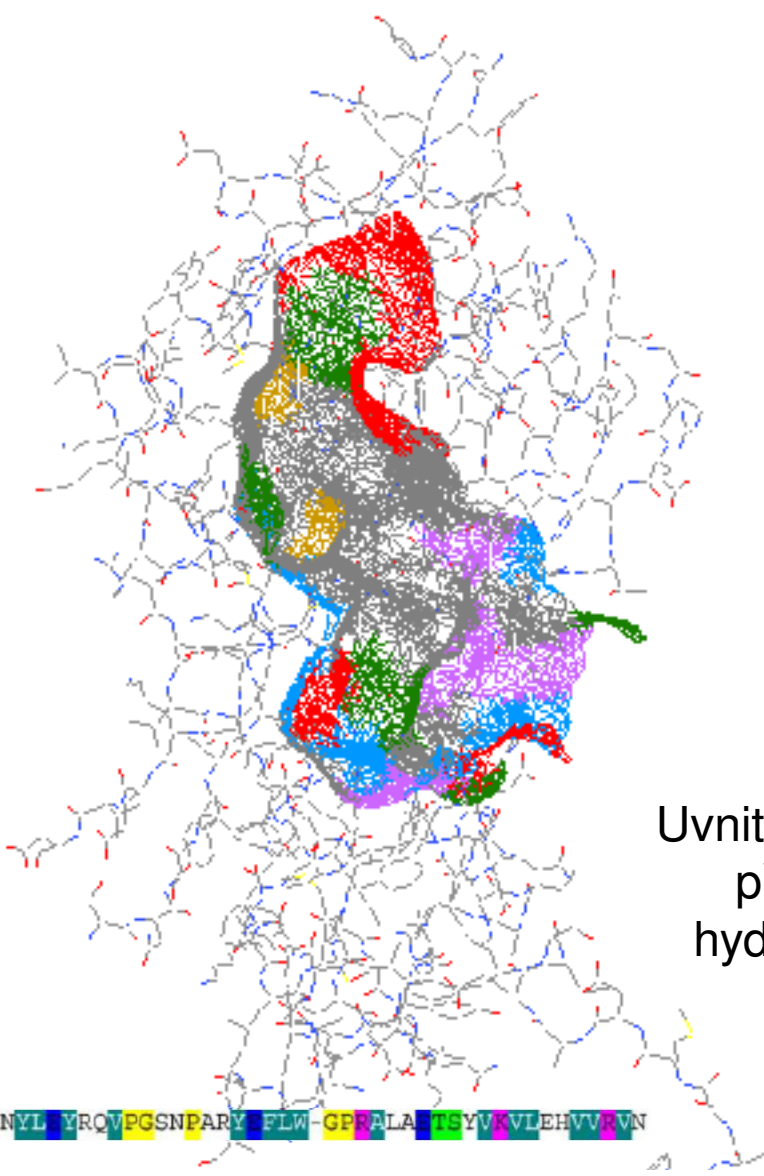
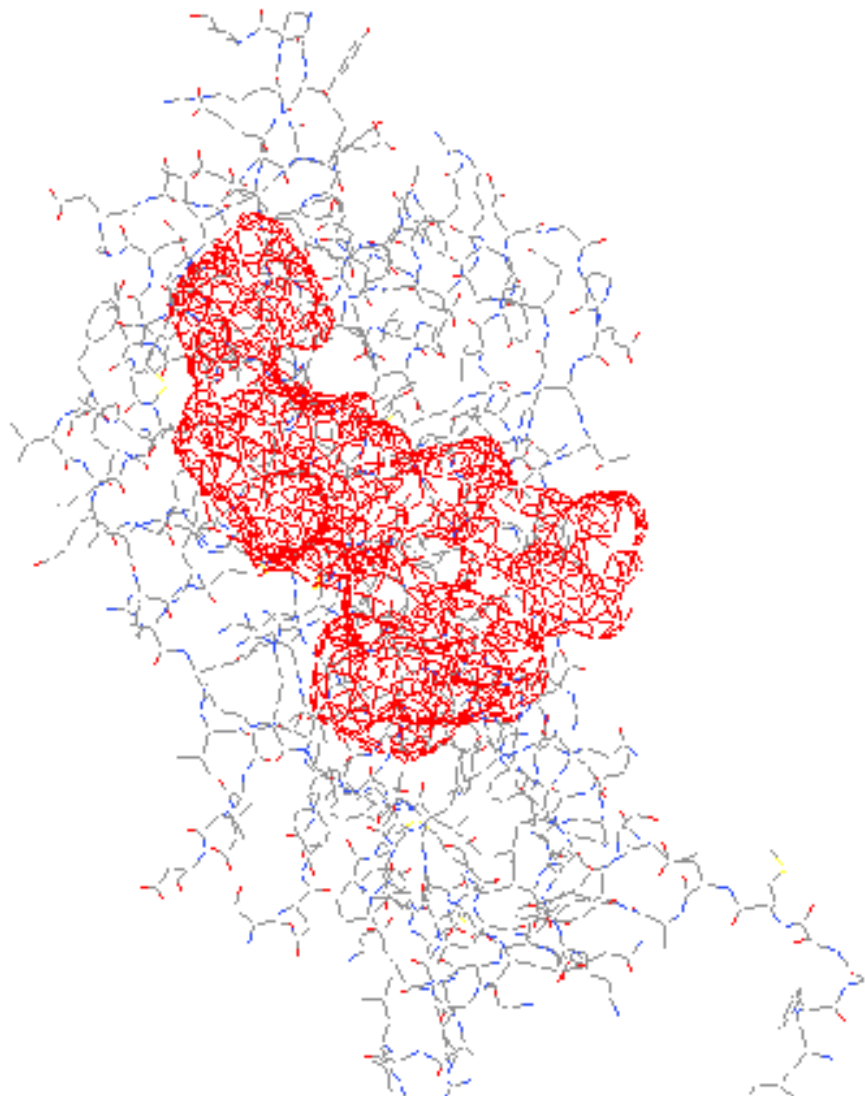
<http://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/pdbsum/>

Laskowski et al.: Prot Sci, 2018

Residue-type colouring						
Positive	Negative	Neutral	Aliphatic	Aromatic	Pro & Gly	Cysteine
H,K,R	D,E	S,T,N,Q	A,V,L,I,M	F,Y,W	P,G	C

Binding site

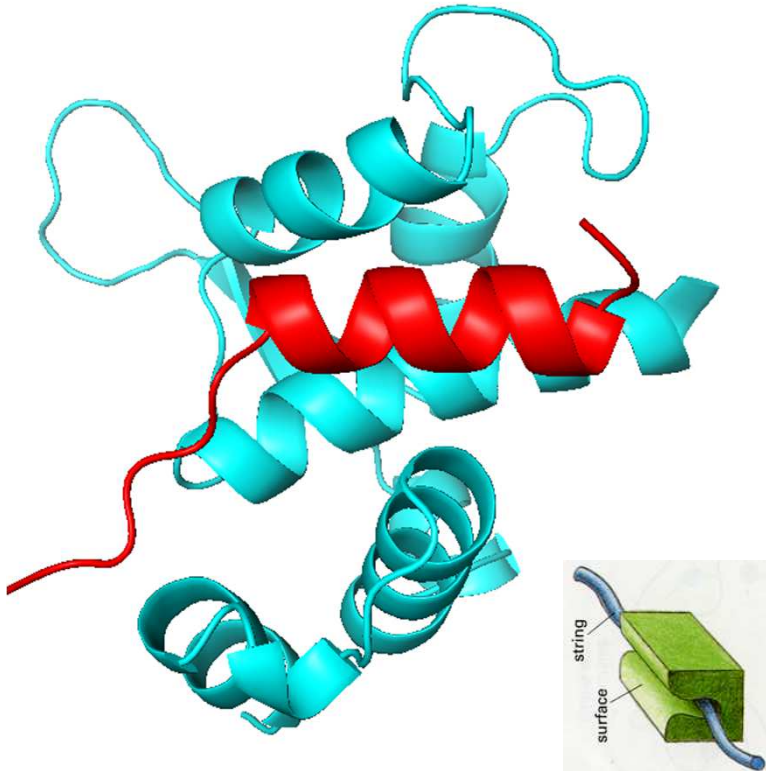
Binding surface



Uvnitř kapsy
převládá
hydrofobní
povrch

A4 GLLIIVLGTIAMEGDSAS-EEIWEELGVVGVYDGREHTVYCF-RKLLTQDWVQENYLVRQVPGSNPARYFLW-GPRALANTSYWVLEHVVRVN

Residue-type colouring						
Positive	Negative	Neutral	Aliphatic	Aromatic	Pro & Gly	Cysteine
H,K,R	D,E	S,T,N,Q	A,V,L,I,M	F,Y,W	P,G	C



HADDOCK
Software web portal

10111
01001010010010
10001010010100101
01001010010100101
01001010010100101
01001010010100101
01001010010100101

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WELCOME TO THE UTRECHT BIOMOLECULAR INTERACTION WEB PORTAL >>

Universiteit Utrecht

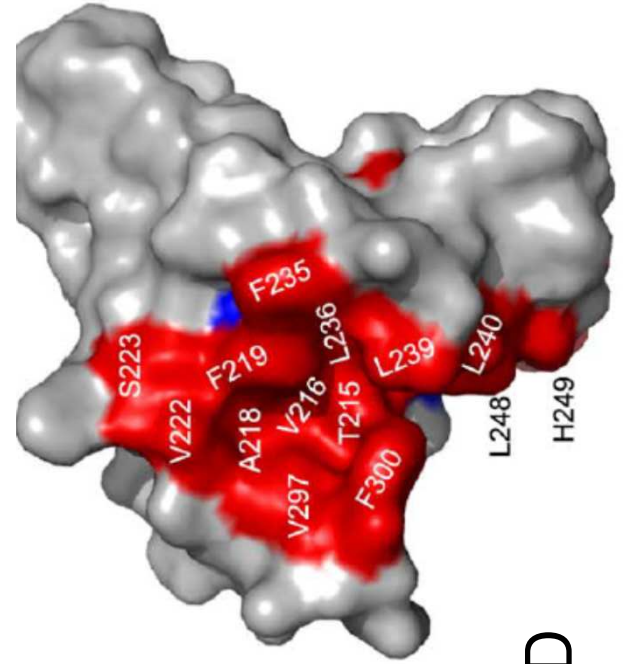
PROFILE >>

The Utrecht Biomolecular Interactions software portal provides access to software tools developed in the Computational Structural Biology group / NMR Research Group of Utrecht University with a main focus on the characterization of biomolecular interactions. Please note that this site is in active development.

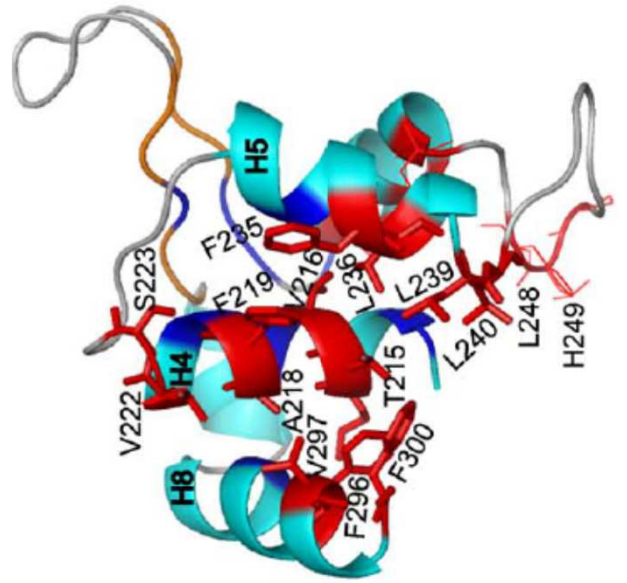
HADDOCK WEB DOCKING

HADDOCK (High Ambiguity Driven protein-protein DOCKing) is an information-driven flexible docking approach for the modeling of biomolecular complexes. HADDOCK distinguishes itself from ab-initio docking methods in the fact that it encodes

Docking

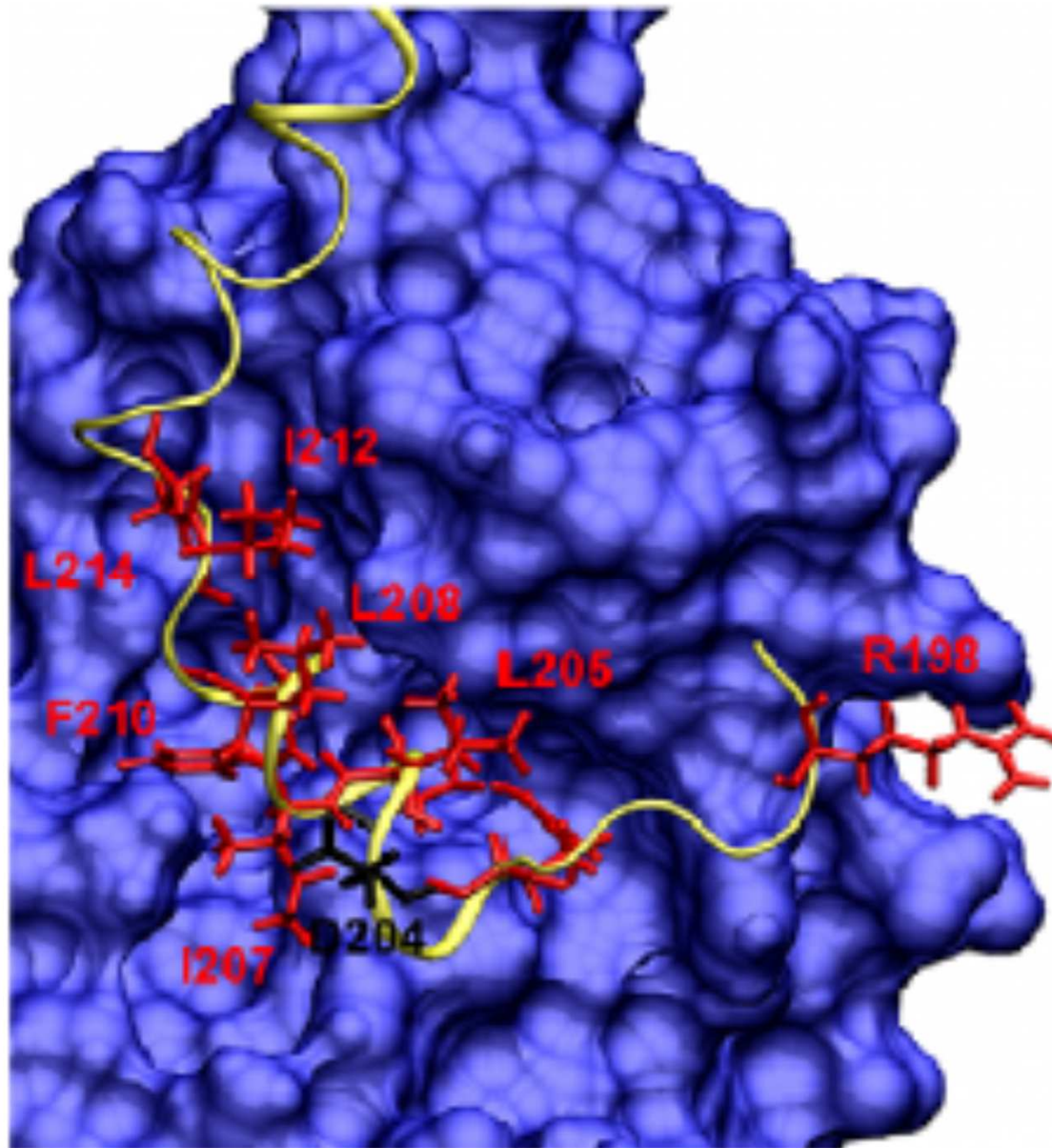
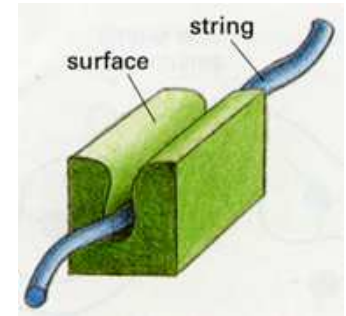


WHD



Hudson et al.: PLoS One, 2011
Guerineau et al.: PLoS One, 2012

Interakce
mapována
mutagenezí



de novo docking partnera
(HEX docking a
molekulární dynamika):
do hydrofobní kapsy
proteinu byl nadockován
„jednoduchý“ peptid (*de
novo* docking větších
povrchů je nespolehlivý)

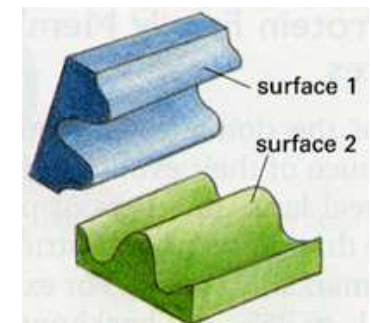
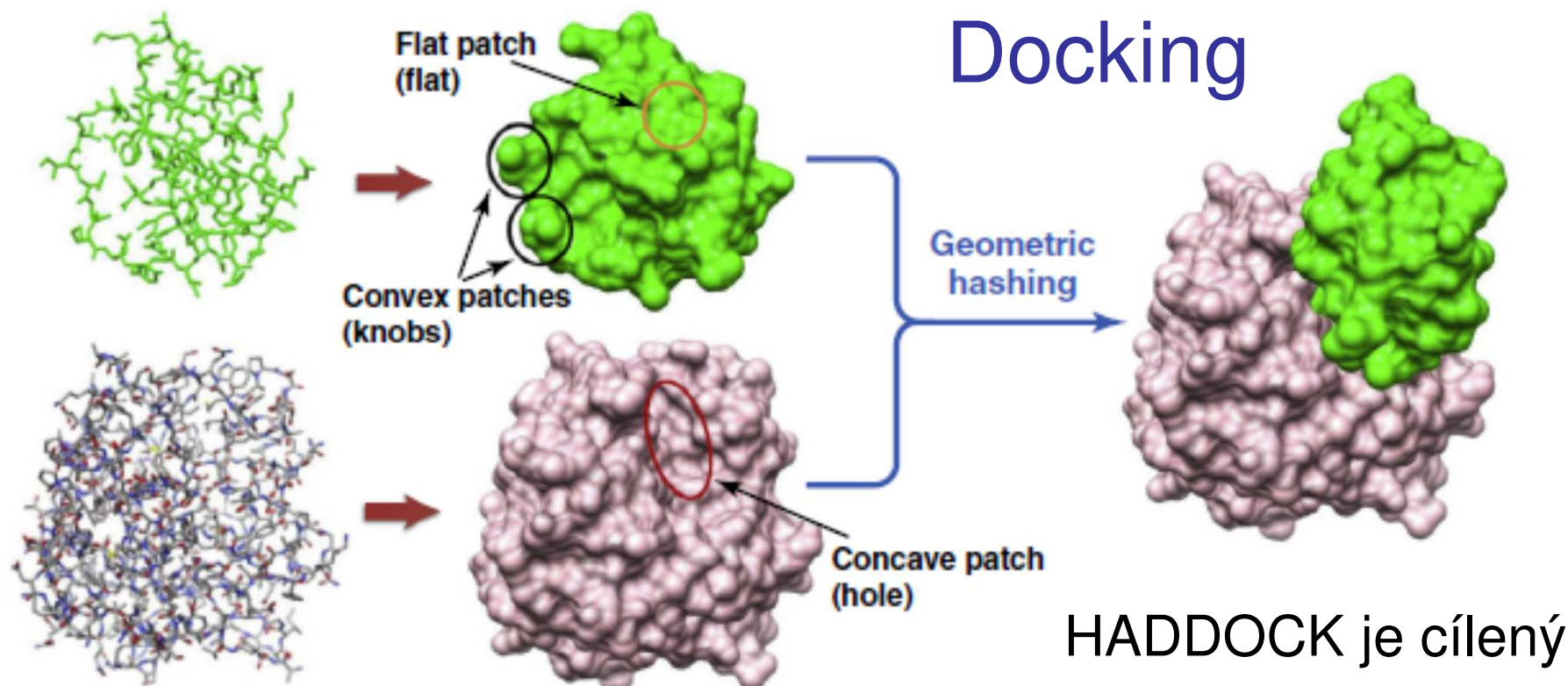
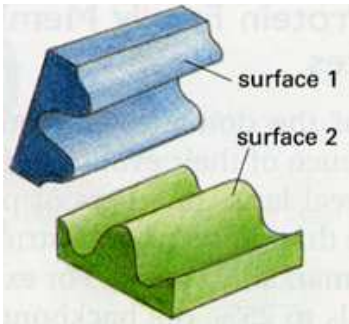


TABLE 1

Search strategies in protein-protein docking

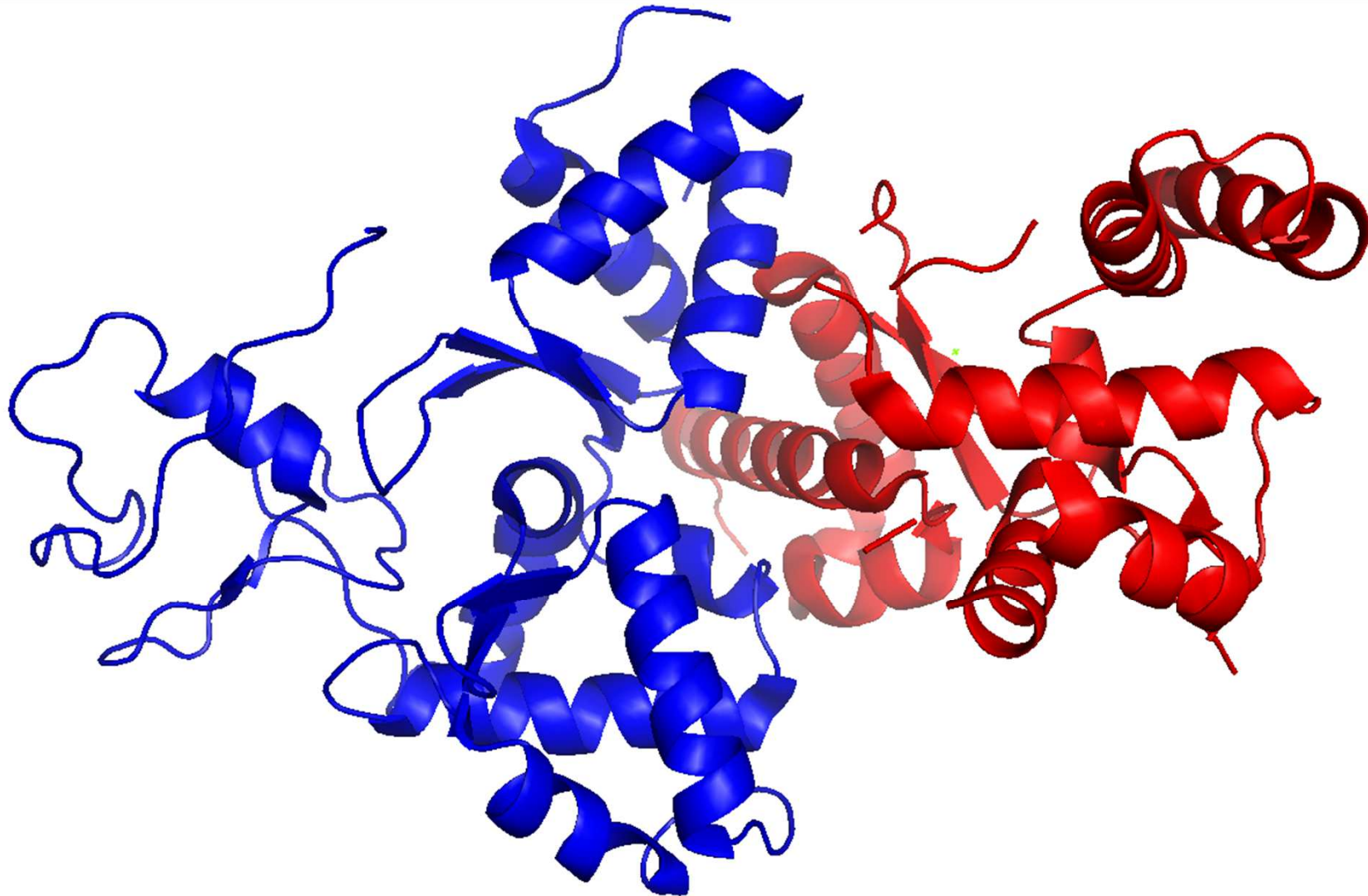
Search algorithms	Examples of docking programs	Refs
Exhaustive global search		
FFT-based search	FTDock, GRAMM, DOT, ZDOCK, MolFit, PIPER, F2DOCK, SDOCK, ASPDock, Cell-Dock	[25–41]
Spherical Fourier transform-based search	HEX, FRODOCK	[45–47]
Direct search in Cartesian space	SOFTDOCK, BIGGER, SKE-DOCK	[49–51]
Local shape feature matching		
Distance geometry algorithm	DOCK	[52]
Geometric hashing	PatchDock, SymmDock, LZerD	[53–56]
Genetic algorithm	GAPDOCK	[57]
Randomized search		
Monte Carlo search	RosettaDock, ICM-DISCO, ATTRACT, HADDOCK	[61–71]
Particle swarm optimization	SwarmDock	[72]
Genetic algorithm	AutoDock	[73]
Post-docking approach		
Using advanced scoring functions	RPScore, ZRANK, PyDock, EMPIRE, DARS, DECK, SIPPER, PIE, MDockPP, etc.	[81–94]
Considering protein flexibility	MultiDock, SmoothDock, RDOCK, FireDock, FiberDock, EigenHex, etc.	[95–104]
Other ranking protocols	SDU, CyClus, CONSRANK, etc.	[105–111]

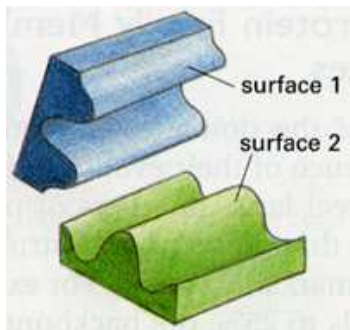




DOMÉNY - šroubovice, β -listy ... interagují pod různými úhly a vytváří různé vazebné motivy s rozsáhlými vazebnými povrchy

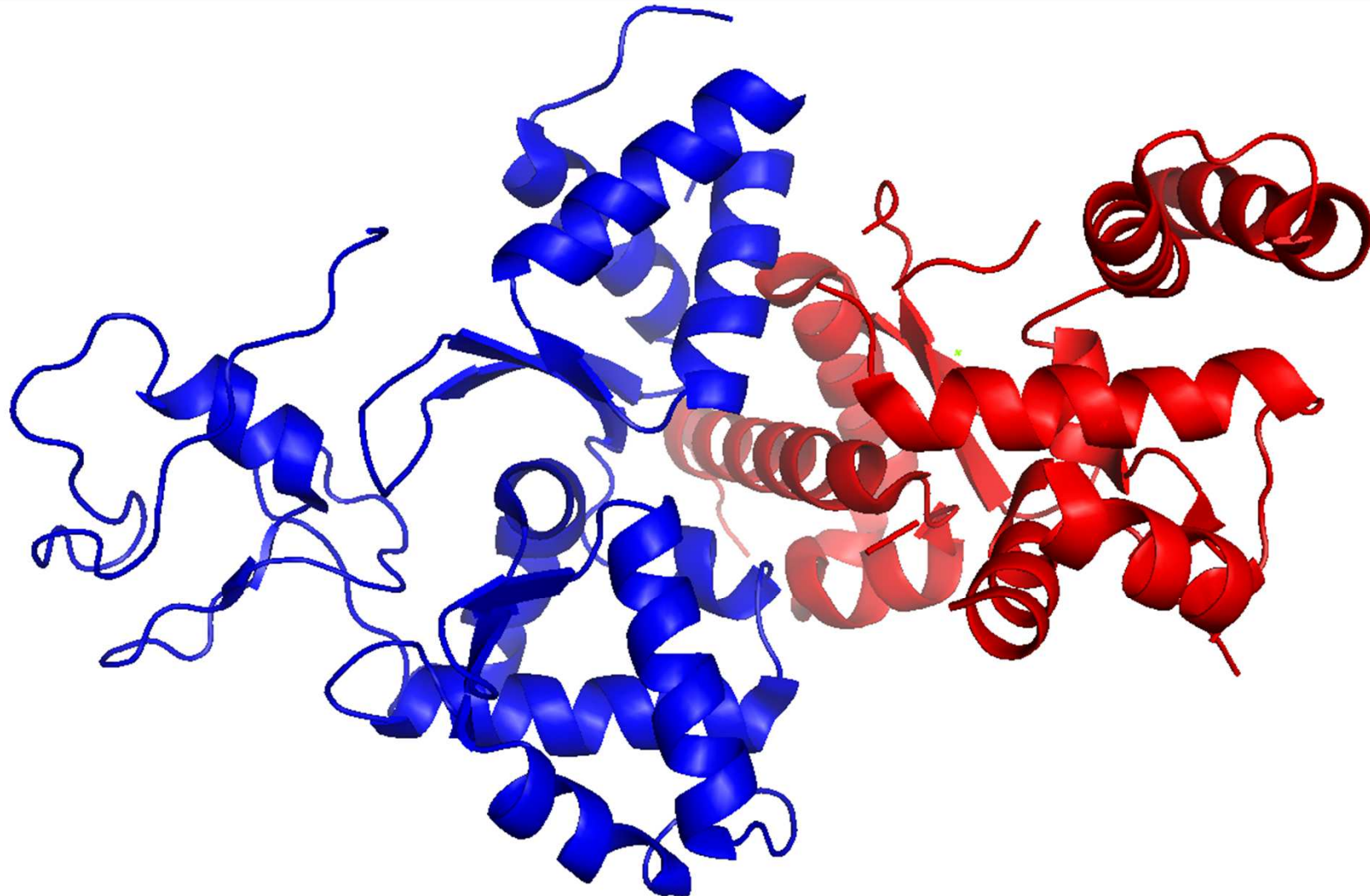
(kokrystal NSE1-NSE3 proteinů)





nejlépe lze získat info (vizuální, o typech vazby)
z vyřešených struktur (PDBsum, 3DID - databáze)

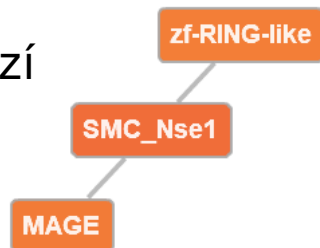
(kokrystal NSE1-NSE3 proteinů)



Domain SMC_Nse1 (Pfam: PF07574.11)

GO terms: P GO:0006281 DNA repair C GO:0030915 Smc5-Smc6 complex

integrace PDB,
PFAM a GO databází



D F C P Default color scheme

Interacting domains (2 domains)

MAGE

zf-RING-like

HMM profile interface residues in SMC_Nse1 (2 interfaces)

HMM prof. interface res.

Binding partner(s)

MAGE

zf-RING-like

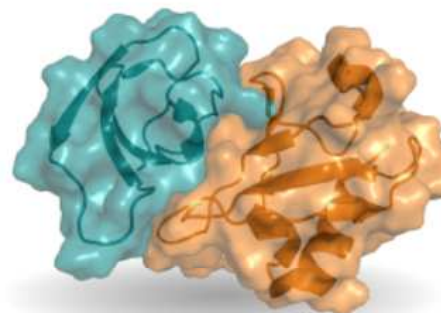
Search motif by name or keyword: ?

Motif name (e.g. SH2_LIG_0)

Search motif



<https://3did.irbbarcelona.org/>

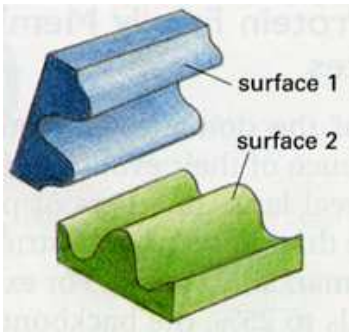


- > Overview General information on 3did
- > Getting Started Help for new users
- > Technical Information Linking to 3did
- > Download data files or MySQL tables

Statistics

Pfam version	30.0
PDB version	2017_06
Domain-domain interactions	11200
Motifs in interactions of known 3D structure	702

3DID kategorizuje doména-doména interakce z PDB (06/2017 – cca 10000 doména-doména komplexů/100000 struktur) – topologie ne detaily



PDBsum – detailní info

<http://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/pdbsum/GetPage.pl?pdbcode=index.html>

(kokrystal NSE1-NSE3 proteinů)

[Top page](#)
[Protein](#)
[Metals](#)
[Prot-prot](#)
[Clefs](#)
[Tunnels](#)
[Links](#)

Protein-Protein interface: A}B PDB id **3nw0**

Protein-protein interface: A}B
NSE1-NSE3

Chain A Chain B

16res 100 7 17res

Key: — Salt bridges — Disulphide bonds — Hydrogen bonds — Non-bonded contacts

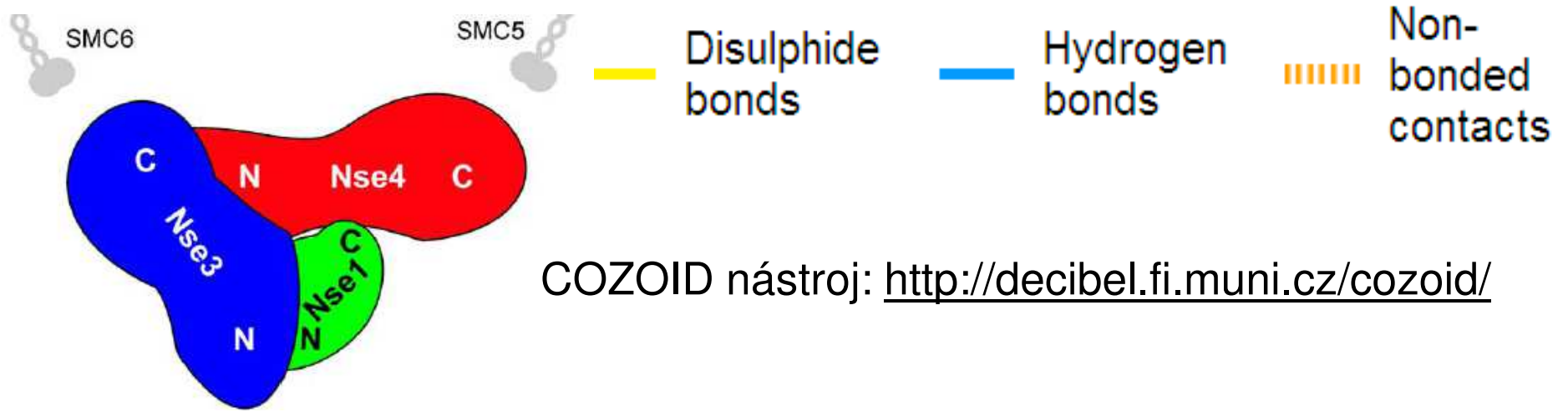
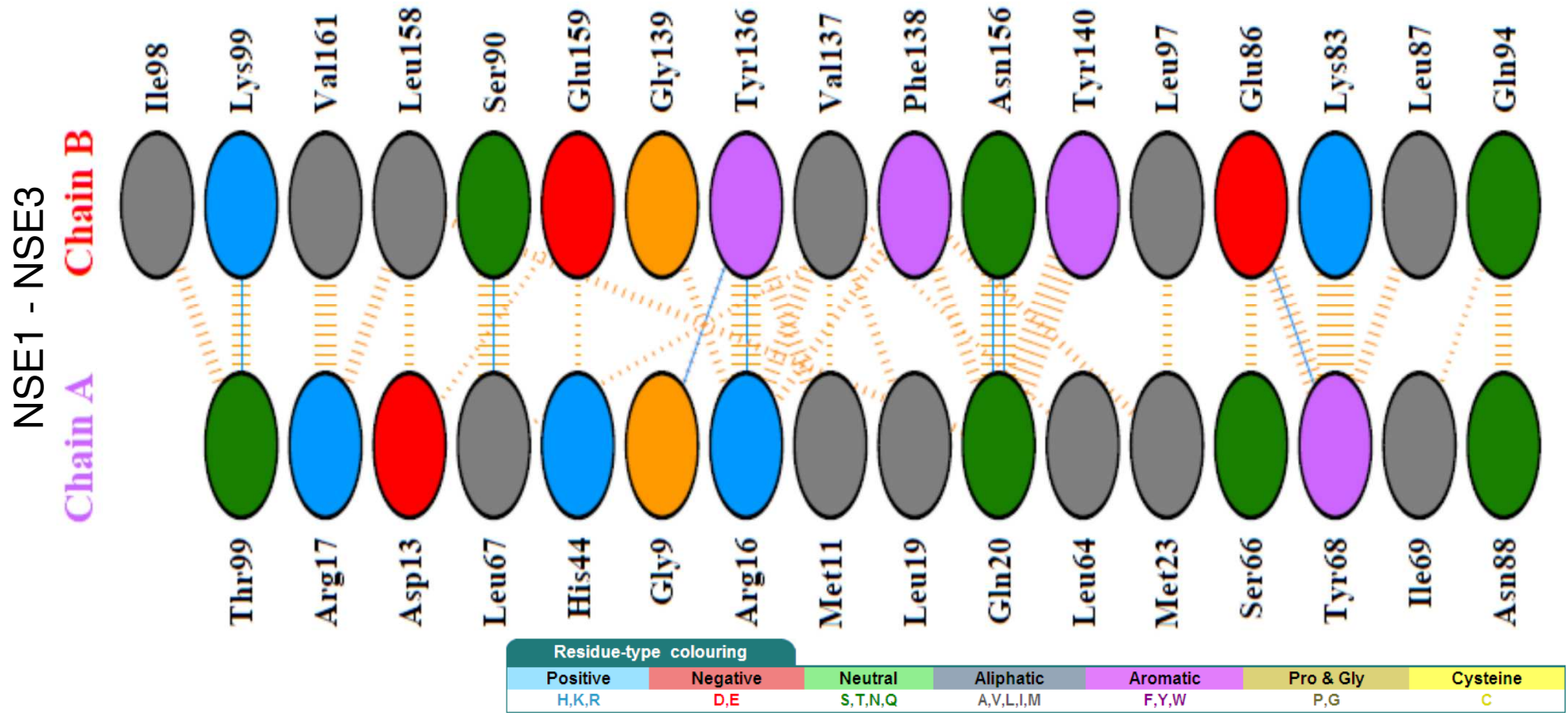
Chains A and B highlighted (click to view)

Jmol Interfaces **A}B (16:17 res)**

Interface statistics

Chain	No. of interface residues	Interface area (Å ²)	No. of salt bridges	No. of disulphide bonds	No. of hydrogen bonds	No. of non-bonded contacts
A	16	1015	-	-	7	100
B	17	1003	-	-		

Silná interakce mezi NSE1 (chain A) a NSE3 (chain B)



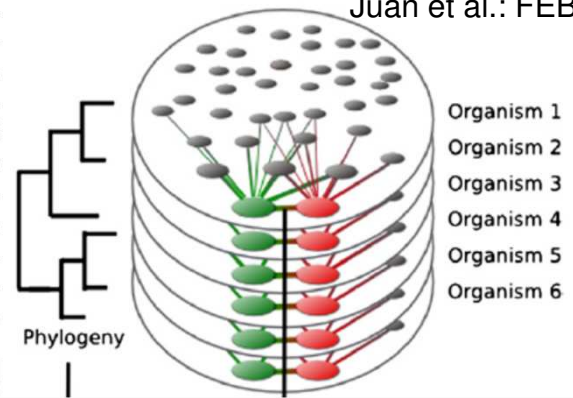
COZOID nástroj: <http://decibel.fi.muni.cz/cozoid/>

```

A1CCH2_ASPCL/14-216   NRAFLQAFM.ARSTMTFAEAKPVLAAIF.SAH.....
A2Q7K6_ASPNC/15-218   NRAFLQAFM.ARSTMTFTQAKPVLAAIF.SIR.....
B8NLA5_ASPFN/14-216   NRAFLQAFM.ARSTMTFAEARPVLAAIF.SVH.....
B6QTR9_TALMQ/14-217   NRAFLQAFM.ARSTMTFDEAKPVLAAIF.SAQ.....
V5FED6_BYSSN/14-236   NRAFLQAFM.ARSTMTFEEAKPVLAAIF.SAHGAQSTIFFDS
S7Z8E9_PENO1/8-209    HRAFLQAFM.ARSTMTFEDAQPVLAAII.SAH.....
B6H9Q9_PENRW/8-210    NRAFLQAFM.ARSCMTFEDAQPILAAIL.TVS.....
H6C926_EXODN/14-207   NRAFLQAFM.ARSVLTLETAKPILAAS.TFQ.....
U1GD89_ENDPU/11-202   NRAFLQAFM.ARGTLTYETSKPLLASIF.TVH.....
C5GY37_AJEDR/11-207   HRAFLQAFM.ARSTMTYEQAKPVLAAIF.SAR.....
C6H5E2_AJECH/11-203   HRALLOAFM.ARSTMTYEOAKPVLAAIF.TAR.....

```

Juan et al.: FEBS Lett, 2008



Browser address bar: http://pfam.xfam.org/family/PF07574#tabview=tab1

EMBL-EBI  **PFAM – databáze proteinových motivů** 

Nse1 motiv


Family: **SMC_Nse1 (PF07574)**


16 architectures | 522 sequences | **2 interactions** | 443 species | 1 structure


- Summary
 - Domain organisation**
 - Clan
 - Alignments
 - HMM logo
 - Trees
 - Curation & model
 - Species
 - Interactions
 - Structures
- Jump to...**
-

Domain organisation

Below is a listing of the unique domain organisations or architectures in which this domain is found. [More...](#)

There are 393 sequences with the following architecture: SMC_Nse1, zf-RING-like
[W9YTD0_9EURO](#) [Capronia epimyces CBS 606.96] Uncharacterized protein {ECO:0000313|EMBL:EXJ92910.1} (323 residues)

[Show](#) all sequences with this architecture.

There are 102 sequences with the following architecture: SMC_Nse1
[R1GGR5_BOTPV](#) [Botryosphaeria parva (strain UCR-NP2) (Grapevine canker fungus) (Neofusicoccum parvum)] Putative dna repair protein {ECO:0000313|EMBL:EOD47456.1} (255 residues)

[Show](#) all sequences with this architecture.

There are 6 sequences with the following architecture: SMC_Nse1 x 2, zf-RING-like
[NSE1_XENTR](#) [Xenopus tropicalis (Western clawed frog) (Silurana tropicalis)] Non-structural maintenance of chromosomes element 1 homolog EC=6.3.2.- (270 residues)

[Show](#) all sequences with this architecture.

There are 2 sequences with the following architecture: DAO, SMC_Nse1, zf-RING-like
[B8MNY1_TALSN](#) [Talaromyces stipitatus (strain ATCC 10500 / CBS 375.48 / QM 6759 / NRRL 1006) (Penicillium stipitatum)] FAD dependent oxidoreductase superfamily {ECO:0000313|EMBL:EEF14330.1} (744 residues)

A1CCH2 ASPCL/14-216	NRAFLQAFM	ARSTMTFAEAKPVLAALIF.SAH.....EG.....QPVSA...DDVTE
A2Q7K6 ASPNC/15-218	NRAFLQAFM	ARSTMTFTQAKPVLAALIF.SIR.....DD.....EQVSP...EDITE
B8NLA5 ASPFN/14-216	NRAFLQAFM	ARSTMTFAEARPVLAALIF.SVH.....EG.....EPVSA...EDVTE
B6QTR9 TALMQ/14-217	NRAFLQAFM	ARSTMTFDEAKPVLAALIF.SAQ.....EN.....REVLA...EDITQ
V5FED6 BYSSN/14-236	NRAFLQAFM	ARSTMTFEEAKPVLAALIF.SAHGAQSTIFFDSSSYVEKEIANLYLATER.....RPVLA...EDITQ
S7Z8E9 PENO1/8-209	HRAFLQAFM	ARSTMTFEDAQPVLAAII.SAH.....EG.....RTVDP...DEVTE
B6H9Q9 PENRW/8-210	NRAFLQAFM	ARSCMTFEDAQPILAAIL.TVS.....EG.....RTVDP...DEVGE
H6C926 EXODN/14-207	NRAFLQAFM	ARSVLTLETAKPILAALIS.TFQ.....DG.....REVQP...QDMTV
U1GD89 ENDP/11-202	NRAFLQAFM	ARSTMTYEQAKPVLAALIF.SAR.....DH.....QDTLP...EDITQ
C5GY37 AJEDR/11-207	HRALLQAFM	ARSTMTYEQAKPVLAALIF.TAR.....DN.....QETLP...EDITQ
C6H5E2 AJECH/11-203	HRAFLQAFM	SRSTMTLEEAKPVLAALIF.TVS.....EG.....REILP...GDITQ
F2PT91 TRIEC/10-199	HRAFLQAFM	ARSTMTLNEAKPILAAIL.SVK.....DG.....REVLP...EDVTQ
E9DEJ9 COCPS/13-202	HRAFLQAFM	ARSVLTFEEAQPILAAIL.TAH.....EG.....RPTLP...ADITT
R7Z157 CONA1/13-202	HRAFLQAFM	ARSSMTGEEELGVTAIH.GVE.....NPEEP...TETTL
U4LU38 PYROM/8-205	HRAFLQAFM	IRPFIDIEEGQELLAALIA.SAE.....SG.....TDVPA...NSITV
S8AAF4 DACHA/9-208	HRAFLQAFM	IRPFIDVQEGRELLAAIK.SAE.....AG.....SDVSI...ESVPP
G1X2Y0 ARTOA/8-207	SKFLLQYVL	RRGVCSEKALAKAKLTL.....ERDG.....EQLEDSETE
C5DCF6 LACTC/23-226	ARYLLQYLL	CRGICHENMLLVLDKL.....QK.....YTQDPTSQVCS.T
C5DQF6 ZYGRC/37-240	RHLLRYIM	SEGICHENMLLLALYAL.....NLDYSGDCQQEVLA.....
I2H1A9 TETBL/24-252	RYLLQYLL	CGICNESFMLLALMRLH.....LTDGSSSDDFYRLNMVELN
G8C139 TETPH/22-276	RIVLQYIL	SRGIVGENILLALMRL.....QGDT..ETND...VQELY
G8ZVJ6 TORDC/16-236	RYLLQYIL	ARGICHENALVVALMRL.....YMDL..GCFDDAWQIDQWL
H2ATC7 KAZAF/7-237	RYLLQYIL	ARGICHENNLILALMKL.....ETDA.....SKWSTEQWT
J5S7B7 SACK1/17-253	RYLLQYIL	ARGICHENALILALMRL.....ETDA..STLNTXSIQQWV
E7NKI9 YEASO/18-258	RYLLQYIL	ARGICHENALILALMRL.....ETDA..LRFDAERSMQQWI
J8PZG2 SACAR/18-258	RYLLQYIL	ARGVCHENALVVALMRL.....KVDS..NTIDPQWTISDWL
G0W7Y8 NAUDC/22-268	RYLLQYIL	ARGVCHENALMLALMRL.....KVDS..HDVNAHWTISDWL
G0V5G7 NAUCC/25-272	RYLLQYIL	ARGVCHENSLLAALMHL.....SLDLDPHSVSTR.SLDEWS
J7S9R2 KAZNA/85-303	RYLLQYIL	CRGICHENALLVLIKL.....DKDSVDEEGSPNRTFEDYL
A7TJ64 VANPO/8-260	RYLLQYIL	CRGICHENALLVLIKL.....DKDSVDEEGSPNRTFEDYL

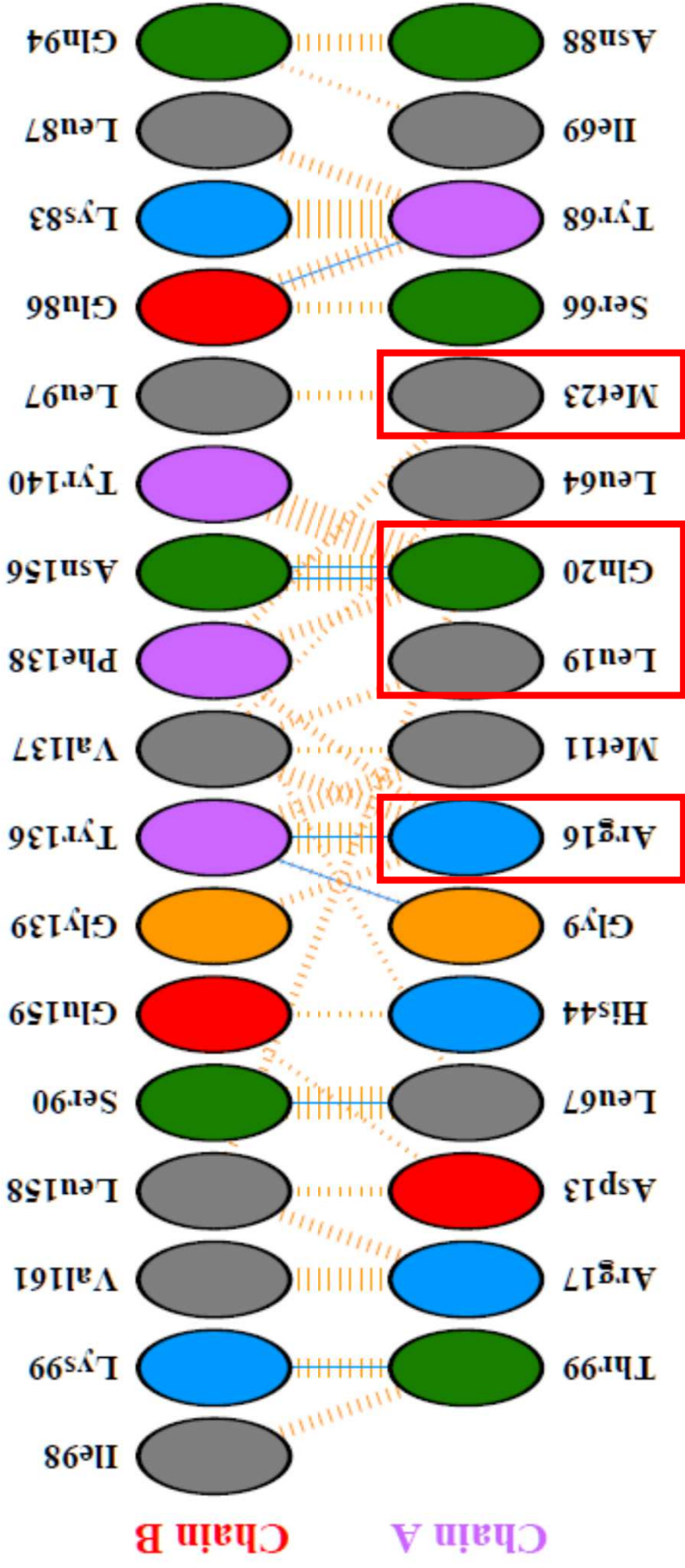
Konzervované AMK svědčí o důležitosti jejich funkce:

- důležité pro proteinovou strukturu
- důležité pro funkci proteinu:
 - enzymy – aktivní centra
 - komplexy – PPI
 - regulační funkce – AMK posttranslačně modifikovaná

A1CCH2_ASPCL/14-216
 A2Q7K6_ASPNC/15-218
 B8NLA5_ASPFN/14-216
 B6QTR9_TALMQ/14-217
 V5FED6_BYSSN/14-236
 S7Z8E9_PENO1/8-209
 B6H9Q9_PENRW/8-210
 H6C926_EXODN/14-207
 U1GD89_ENDPU/11-202
 C5GY37_AJEDR/11-207
 C6H5E2_AJECH/11-203
 F2PT91_TRIEC/10-199
 E9DEJ9_COCPS/13-202
 R7Z157_CONA1/13-202
 U4LU38_PYROM/8-205
 S8AAF4_DACHA/9-208
 G1X2Y0_ARTOA/8-207
 C5DCF6_LACTC/23-226

NRAFLQAFM ARSTMTFAEAKPVLAAIF.SAH.
 NRAFLQAFM ARSTMTFTQAKPVLAAIF.SIR.
 NRAFLQAFM ARSTMTFAEARPVLAAIF.SVH.
 NRAFLQAFM ARSTMTFDEAKPVLAAIF.SAQ.
 NRAFLQAFM ARSTMTFEEAKPVLAAIF.SAHGAQSTIFFDSSYVEKEIANLYLATER.
 NRAFLQAFM ARSTMTFEDAQPVLAAII.SAH.
 NRAFLQAFM ARSCMTFEDAQPILAAIL.TVS.
 NRAFLQAFM ARSVLTLETAKPILAAIS.TFQ.
 NRAFLQAFM ARGTLTYETSKPLLASIF.TVH.
 NRAFLQAFM ARSTMTYEQAKPVLAAIF.SAR.
 NRAFLQAFM ARSTMTYEQAKPVLAAIF.TAR.
 NRAFLQAFM SRSTMTLEEAKPVLAAIF.TVS.
 NRAFLQAFM ARSTMTLNEAKPILAAIL.SVK.
 NRAFLQAFM ARSVLTFEEAQPILAAIL.TAH.
 NRAFLQAFM ARSSMTGEEILGVTVAIH.GVE.
 NRAFLQAFM IRPFIDIEEGQELLAAIA.SAE.
 NRAFLQAFM IRPFIDVQEGRELLAAIK.SAE.
 EKFLLYVVLRRGVCSEKALAKAKITL

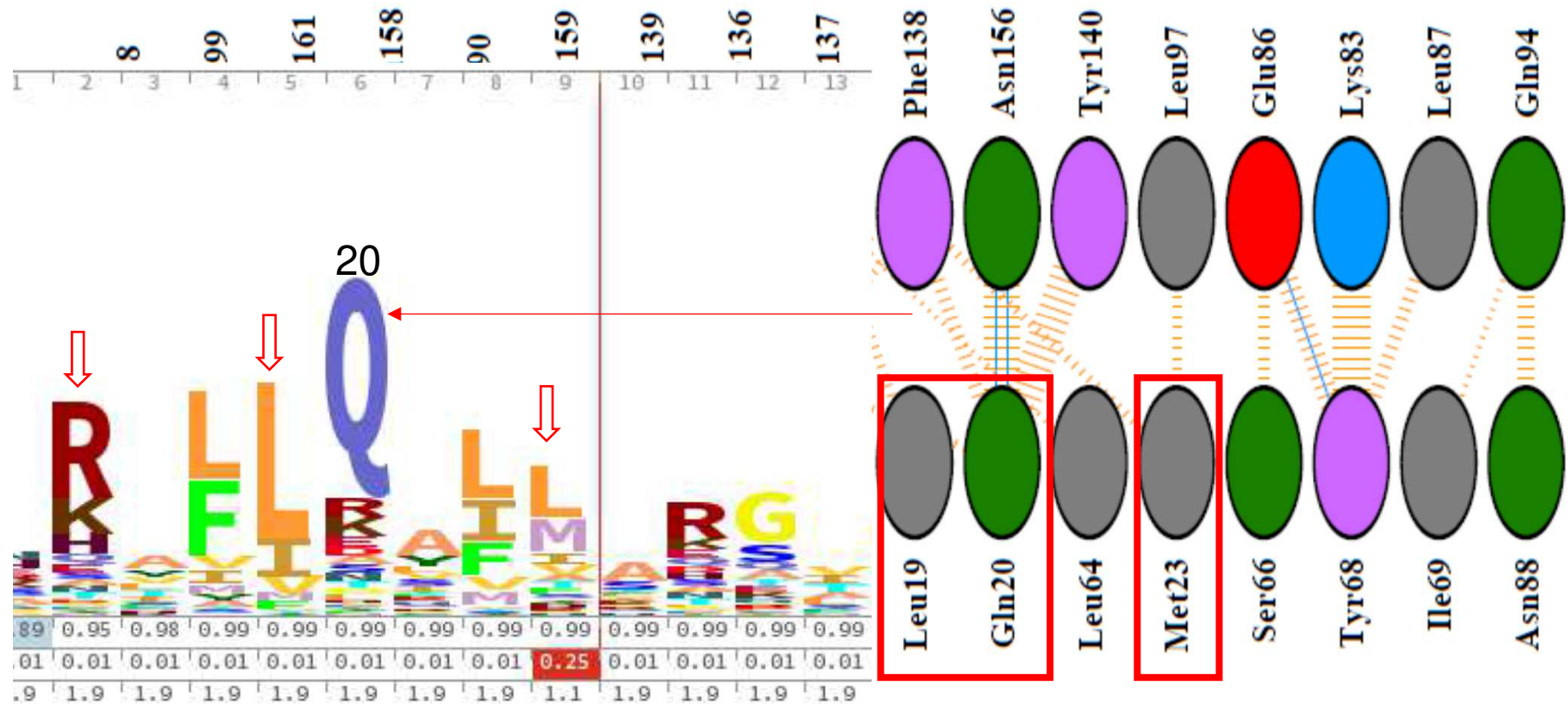
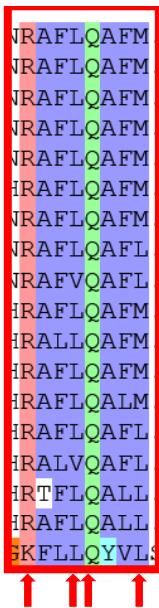
EG...DDVTE
 DD...EDITE
 EG...EDVTE
 EN...EDITQ
 RPVLA...EDITQ
 RTVDF...DEVTQ
 RTVDF...DEVGE
 REVQP...QDMTV
 REILP...NDITE
 QDTLP...EDITQ
 QETLP...EDITQ
 REILP...GDITQ
 REVLP...EDVTQ
 RPTLP...ADITT
 NPEEP...TETTL
 TDVPA...NSITV
 SDVSI...ESVPP
 ERDG...EQLEDESETE




```

A1CCH2_ASPCL/14-216 NRAFLQAFM ARSTMTFAEAKPVLAALF.SAH.....EG.....QPVSA...DDVTE
A2Q7K6_ASPNC/15-218 NRAFLQAFM ARSTMTFTQAKPVLAALF.SIR.....DD.....EQVSP...EDITE
B8NLA5_ASPFN/14-216 NRAFLQAFM ARSTMTFAEARPVLAALF.SVH.....EG.....EPVSA...EDVTE
B6QTR9_TALMQ/14-217 NRAFLQAFM ARSTMTFDEAKPVLAALF.SAQ.....EN.....REVLA...EDITQ
V5FED6_BYSSN/14-236 NRAFLQAFM ARSTMTFEEAKPVLAALF.SAHGAQSTIFFDSSYVEKEIANLYLATER.....RPVLA...EDITQ
S7Z8E9_PENO1/8-209 HRAFLQAFM ARSTMTFEDAQPVLAAII.SAH.....EG.....RTVDP...DEVTE
B6H9Q9_PENRW/8-210 NRAFLQAFM ARSCMTFEDAQPILAAIL.TVS.....EG.....RTVDP...DEVGE
H6C926_EXODN/14-207 NRAFLQAFM ARSVLTLETAKPILAALF.TFQ.....DG.....REVQP...QDMTV
U1GD89_ENDPU/11-202 NRAFLQAFM ARSVLTLETAKPILAALF.TVH.....EG.....REILP...NDITE
C5GY37_AJEDR/11-207 HRAFLQAFM ARSTMTYEQAKPVLAALF.SAR.....DH.....QDTLP...EDITQ
C6H5E2_AJECH/11-203 HRALLQAFM ARSTMTYEQAKPVLAALF.TAR.....DN.....QETLP...EDITQ
F2PT91_TRIEC/10-199 HRAFLQAFM SRSTMTLEEAKPVLAALF.TVS.....EG.....REILP...GDITQ
E9DEJ9_COCPS/13-202 HRAFLQAFM ARSTMTLNEAKPILAAIL.SVK.....DG.....REVLP...EDVTQ
R7Z157_CONA1/13-202 HRAFLQAFM ARSVLTFEEAQPILAAIL.TAH.....EG.....RPTLP...ADITT
U4LU38_PYROM/8-205 HRALVQAFM ARSSMTGEELLGVVTAIH.GVE.....NPEEP...TETTL
S8AAF4_DACHA/9-208 HRTFLQALL IRPFIDIEEGQELLAALF.SAE.....SG.....TDVPA...NSITV
G1X2Y0_ARTOA/8-207 HRAFLQALL IRPFIDVQEGRELLAALF.SAE.....AG.....SDVSI...ESVPP
C5DCF6_LACTC/23-226 SKFLLQYVLRRGVCSEKALAKKTL.....ERDG.....EQLEDSETE

```





Structures Overview
Structure Selections
3D View Controls

Visualization



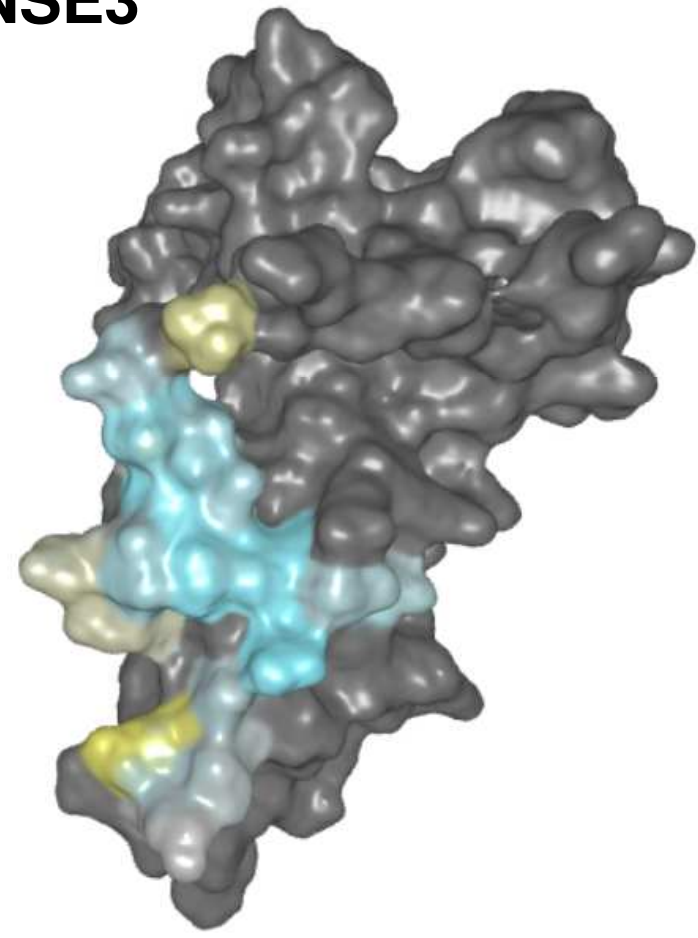
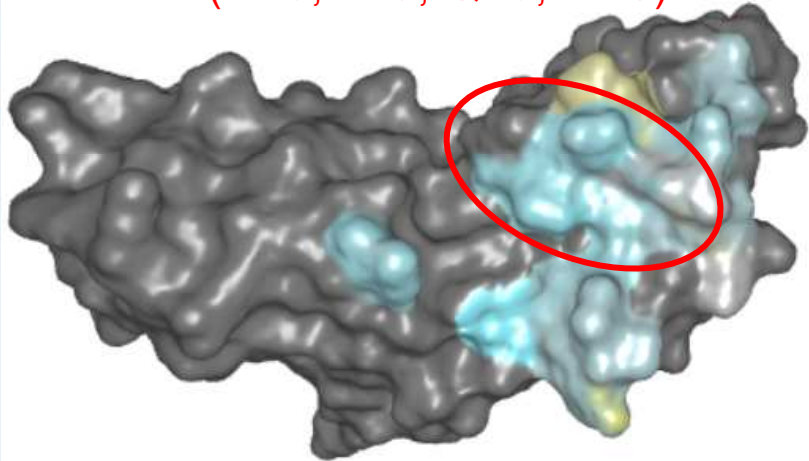
Residue Matrix

Primary Structure: 3

Sort by: Conservati

NSE1 - NSE3

Hot spot
(R16, L19, Q20, M23)



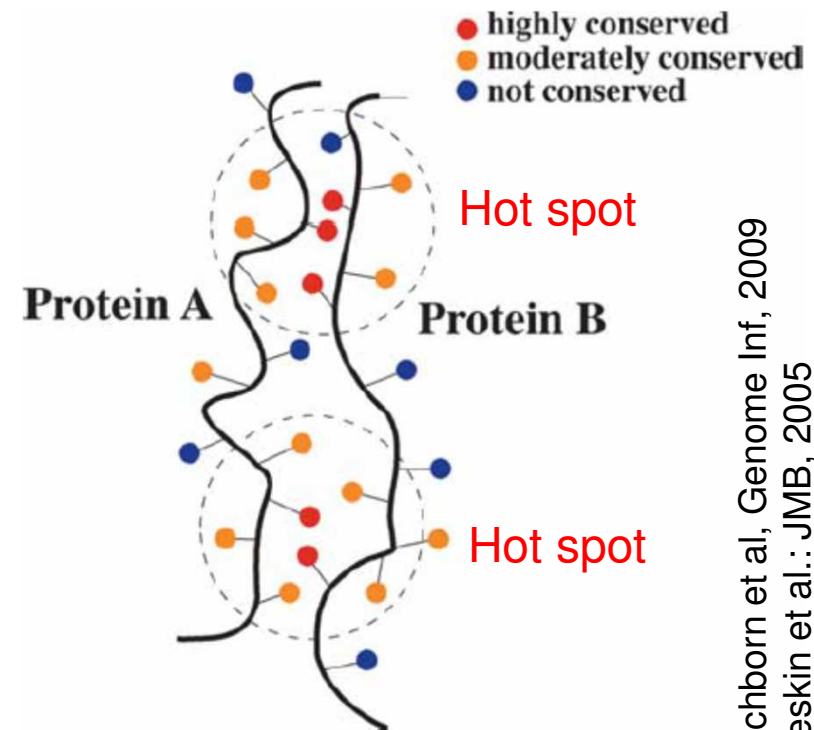
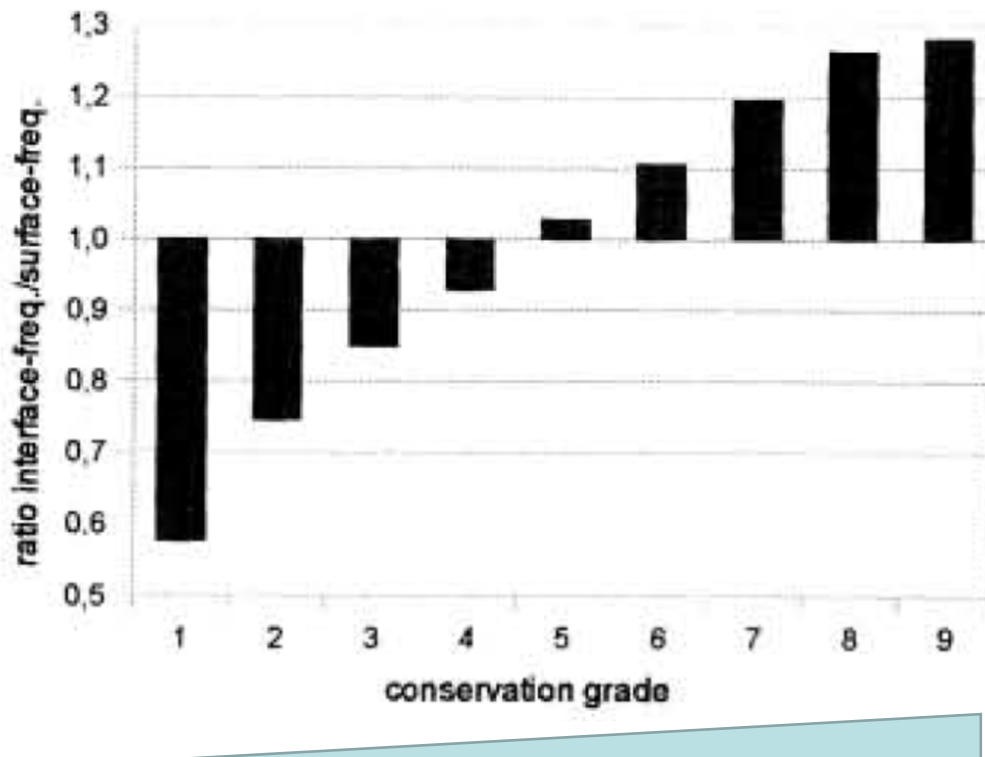
N88
Q20
M23
T99
L64
L19
D13
I69
L67
Y68
H44
S66
M11
R16
G9
R17

Structure Sequence x

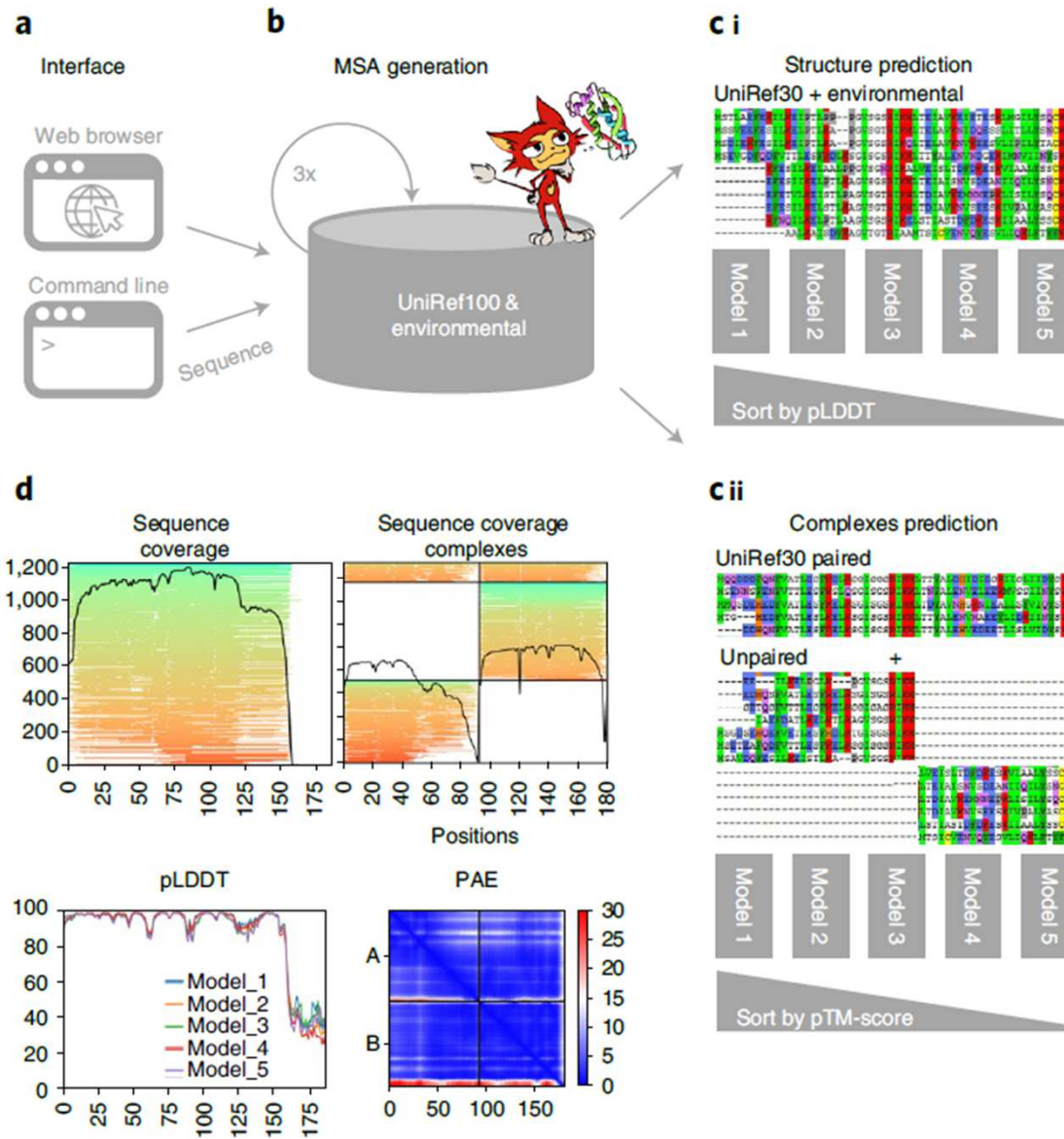
Compact View Selection in All Structures

Silné/důležité interakce (komplexy) jsou evolučně konzervované

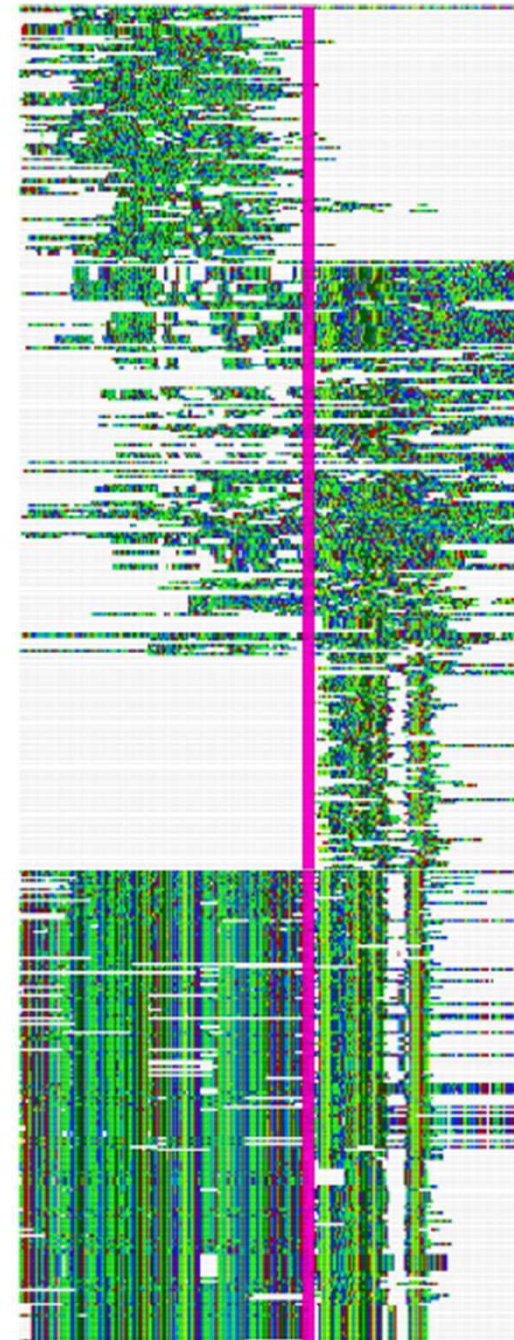
- jako jsou proteiny (jejich funkce) evolučně konzervované, tak i jejich interakce jsou evolučně konzervované (zajišťují funkci)
- graf** – povrchové AMK jsou málo konzervované (grade1), zatímco interakční povrchy jsou hodně konzervované (grade9)



AlphaFold/CoLab



AF2 + Paired MSAs



Bryant et al., Nat Com, 2022; Mirdita et al., Nat Met, 2022

využívá (ko-)evoluční konzervovanosti a struktur v PDB

Kde najít další informace o PPI?

The screenshot shows a Windows Internet Explorer browser window displaying the website <http://proteome.wayne.edu/PIDBL.html>. The page is titled "Links to Protein Interaction Databases" and is part of the "Center for Molecular Medicine and Genetics" website. The page content includes:

- Finley Lab Interactions Databases:
 - Drosophila Interactions Database (DroID)***
 - Campylobacter jejuni Interactions Databases***
- Gene or Protein Interactions Databases in the research community:
 - BioGRID** - A Database of Genetic and Physical Interactions
 - DIP** - Database of Interacting Proteins
 - IntAct** - EMBL-EBI Protein Interaction Database
 - MINT** - A Molecular Interactions Database
 - MIPS** - Comprehensive Yeast Protein-Protein Interactions
 - Yeast Protein Interactions** - Yeast two-hybrid results
 - BRITE** - Biomolecular Relations in Information Transmission
 - The PIM Database** - by Hybrigenics
 - Mouse Protein-Protein Interactions**
 - Human Protein Reference Database**

Na základě PPI v jednom organismu a homologii proteinů v jiných organismech lze odhadnout, zda proteiny interagují i v jiných organismech (lze dovodit i podle genových fúzí)

<http://proteome.wayne.edu/PIDBL.html>

Více Dr. Potěšil



Search Results

Gene / Identifier Search

nse3



GO

All Organisms

Your search for **NSE3** produced the following **4** results:Results matching **official symbol / systematic name** - 2 total proteins:**NSE3 (YDR288W)**

Component of the SMC5-SMC6 complex; this complex plays a key role in the removal of X-shaped DNA structures that arise between sister chromatids during DNA replication and repair; protein abundance increases in response to DNA replication stress

PHO*Saccharomyces cerevisiae* (S288c)

407 unique interactors

497 raw interactions

1 post-translational modification

NSE3 (SPCC645.04)

Smc5-6 complex non-SMC subunit Nse3

Schizosaccharomyces pombe (972h)

10 unique interactors

24 raw interactions

NSE1 | YLR007W

5 2

Component of the SMC5-SMC6 complex; this complex plays a key role in the removal of X-shaped DNA structures that arise between sister chromatids during DNA replication and repair

[\[details\]](#)

Experimental Evidence Code	Role	Dataset	Throughput	Curated By	Notes
Affinity Capture-MS	HIT	Hazbun TR (2003)	High	BioGRID	-
Reconstituted Complex	HIT	Hudson JJ (2011)	Low	BioGRID	-
Two-hybrid	HIT	Hazbun TR (2003)	High	BioGRID	-
	HIT	Hu B (2005)	Low	BioGRID	-
	BAIT/HIT	Duan X (2009)	Low	BioGRID	-
Dosage Rescue	HIT	Magtanong L (2011)	High	BioGRID	
Negative Genetic	BAIT/HIT	Costanzo M (2016)	High	BioGRID	

BioGRID – databáze interakcí (včetně genetických) pro různé organismy pučící kvasinky *S. cerevisiae*, pohlivé kvasinky *S. pombe*, octomilky *D. melanogaster*, člověka *H. sapiens* ...

Experimental Evidence Code	Role	Dataset	Throughput	Curated By	Notes
člověka <i>H. sapiens</i> ... Affinity Capture-MS	HIT	Doyle JM (2010)	Low	BioGRID	-
	BAIT	Taylor EM (2008)	Low	BioGRID	-
	BAIT	Huttlin EL (2015)	High	BioGRID	
	BAIT	Huttlin EL (2017)	High	BioGRID	
Affinity Capture-Western	BAIT	Doyle JM (2010)	Low	BioGRID	-
	BAIT/HIT	Taylor EM (2008)	Low	BioGRID	-
	HIT	Hudson JJ (2011)	Low	BioGRID	-
Co-crystal Structure	HIT	Newman JA (2016)	Low	BioGRID	-
Co-fractionation	BAIT	Taylor EM (2008)	Low	BioGRID	-
	BAIT	Wan C (2015)	High	BioGRID	
Reconstituted Complex	BAIT/HIT	Doyle JM (2010)	Low	BioGRID	-

NSE1 | YLR007W

pučící kvasinky *S. cerevisiae*

5 2

Component of the SMC5-SMC6 complex; this complex plays a key role in the removal of X-shaped DNA structures that arise between sister chromatids during DNA replication and repair

[\[details\]](#)

Experimental Evidence Code	Role	Dataset	Throughput	Curated By	Notes
Affinity Capture-MS	HIT	Hazbun TR (2003)	High	BioGRID	-
Reconstituted Complex	HIT	Hudson JJ (2011)	Low	BioGRID	-
Two-hybrid	HIT	Hazbun TR (2003)	High	BioGRID	-
	HIT	Hu B (2005)	Low	BioGRID	-
	BAIT/HIT	Duan X (2009)	Low	BioGRID	-

NSE1 | SPCC550.05

poltivé kvasinky *S. pombe*

4

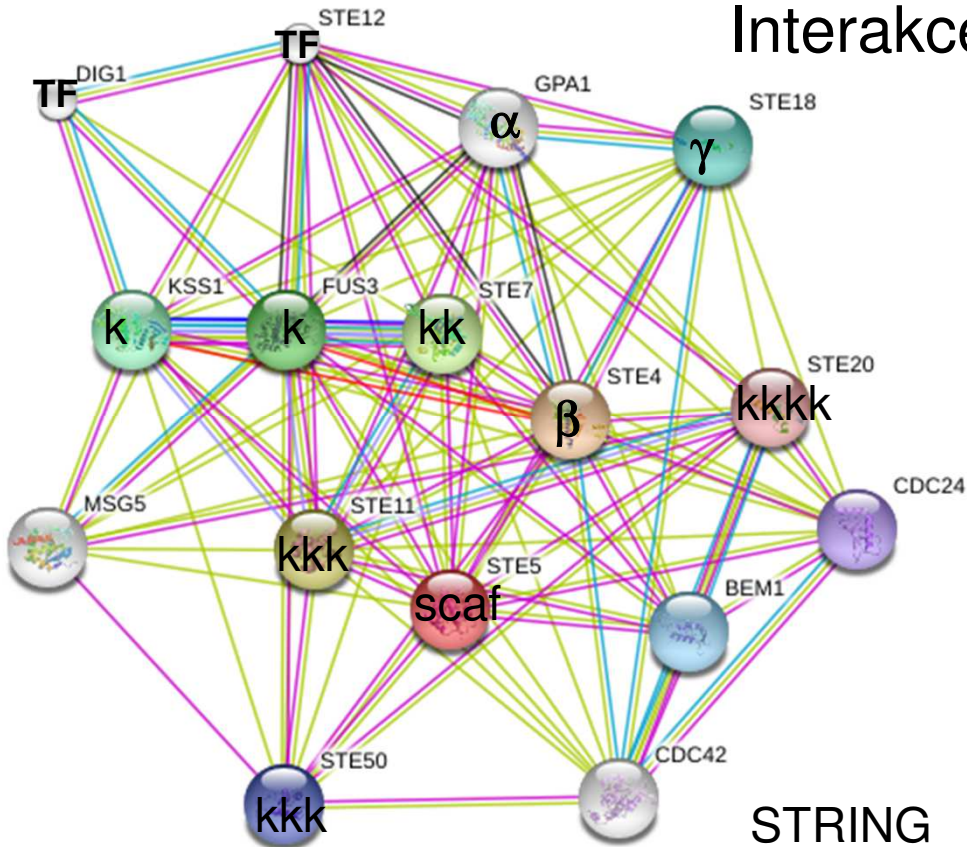
Smc5-6 complex ubiquitin-protein ligase E3 subunit 1

[\[details\]](#)






Experimental Evidence Code	Role	Dataset	Throughput	Curated By	Notes
Affinity Capture-Western	BAIT	Pebernard S (2004)	Low	BioGRID	-
Reconstituted Complex	BAIT	Sergeant J (2005)	Low	BioGRID	-
Two-hybrid	BAIT	Pebernard S (2004)	Low	BioGRID	-
	HIT	Hudson JJ (2011)	Low	BioGRID	-

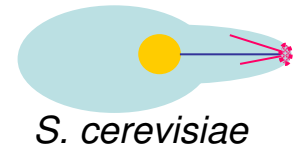
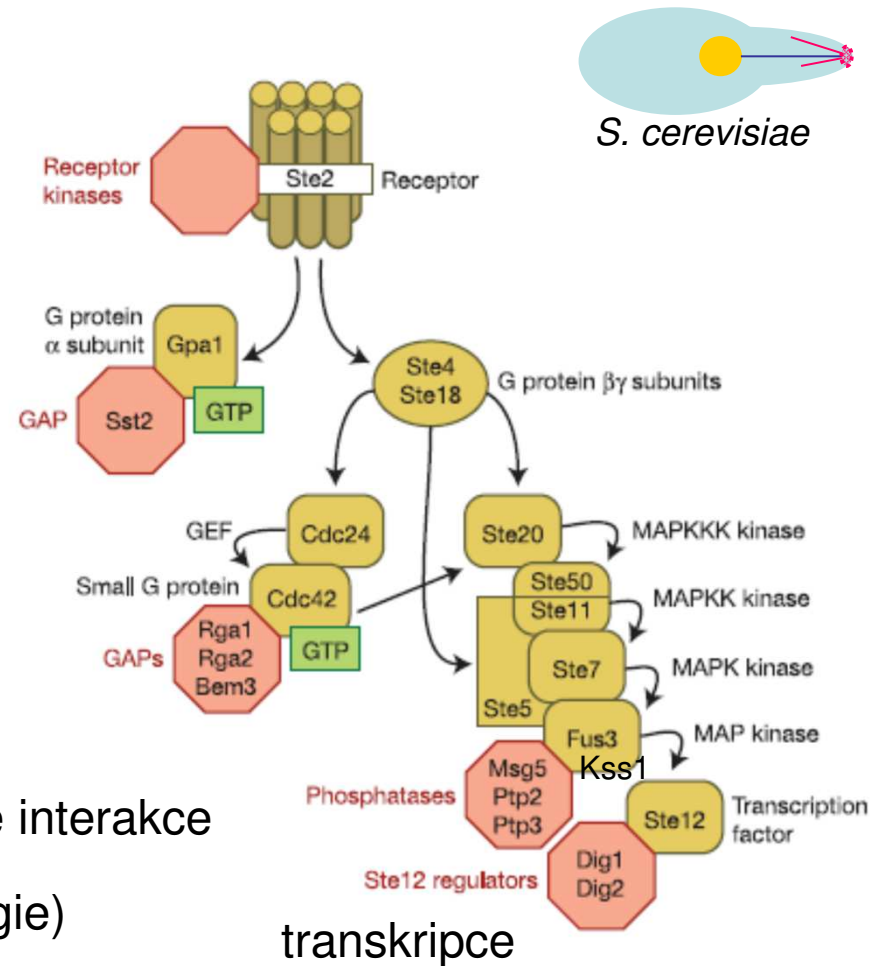
proteinové sítě – chybí info o posloupnosti, síle ... interakcí

Interakce x signální dráha



STRING

-  Experiments Y2H, colP ... genetické interakce
-  Databases Funkční vztahy (ontologie)
-  Textmining
-  Gene Fusion Svědčí o potřebě PPI
-  Coexpression Potřeba výskytu ve stejném okamžiku a společná translace

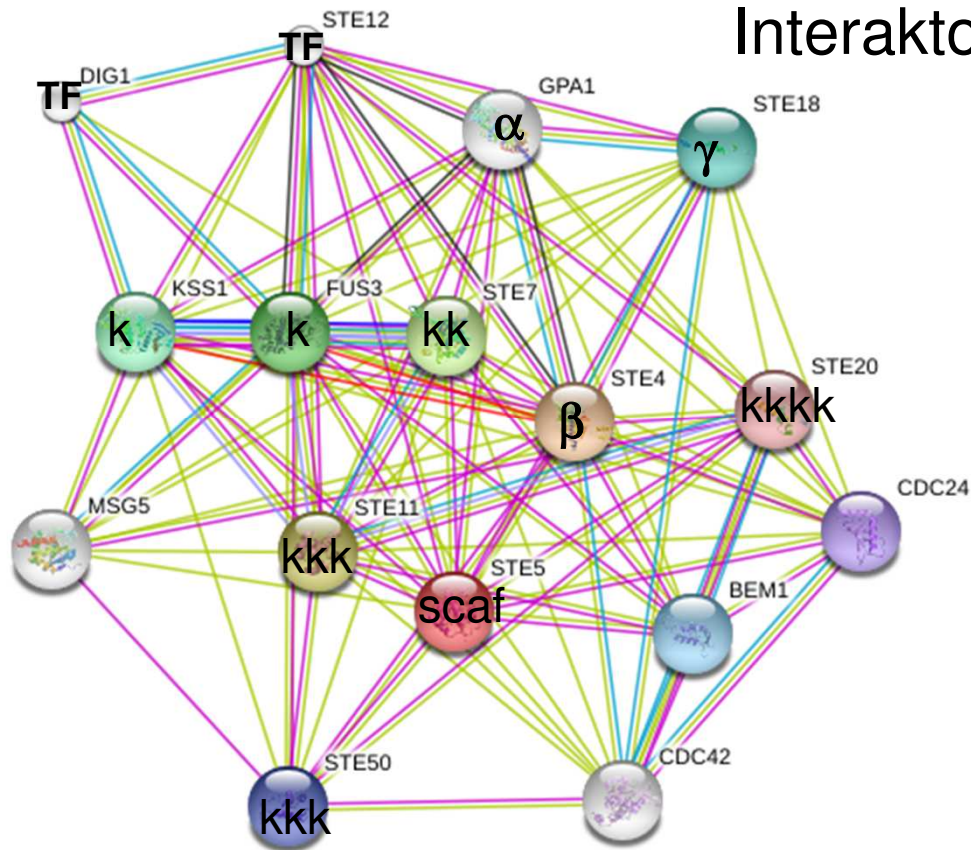


S. cerevisiae

transkripce

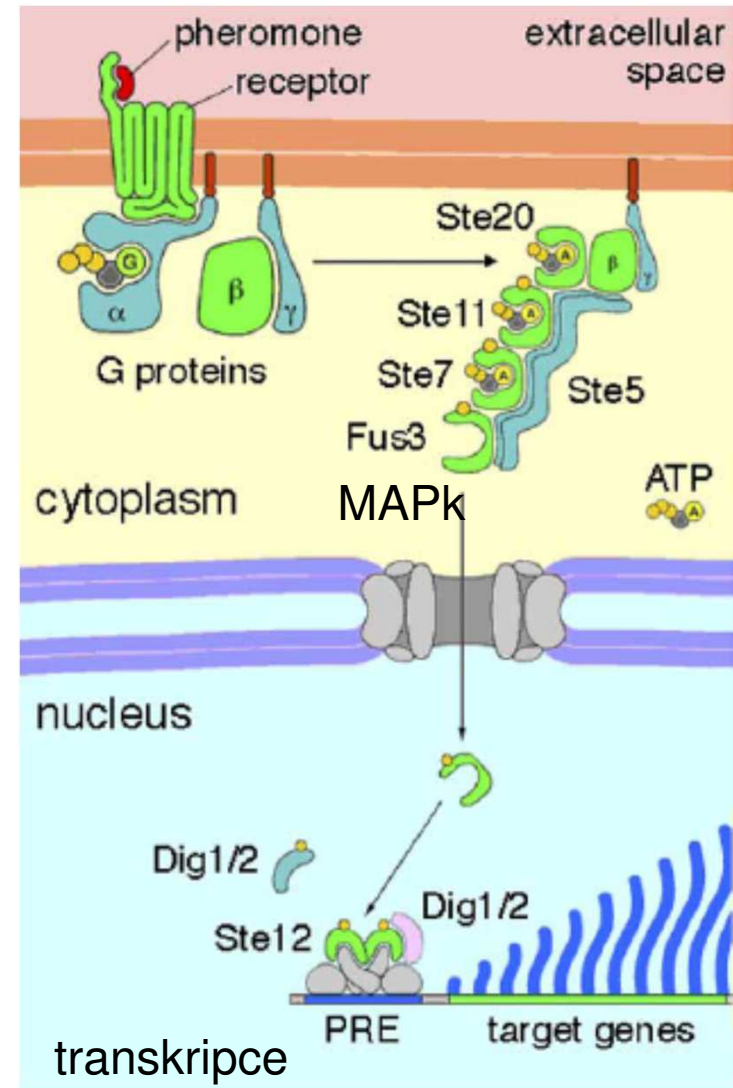
proteinové sítě – chybí info o lokalizaci, komplexech ...

Interaktom x komplexom



- Experiments
- Databases
- Textmining
- Gene Fusion
- Coexpression

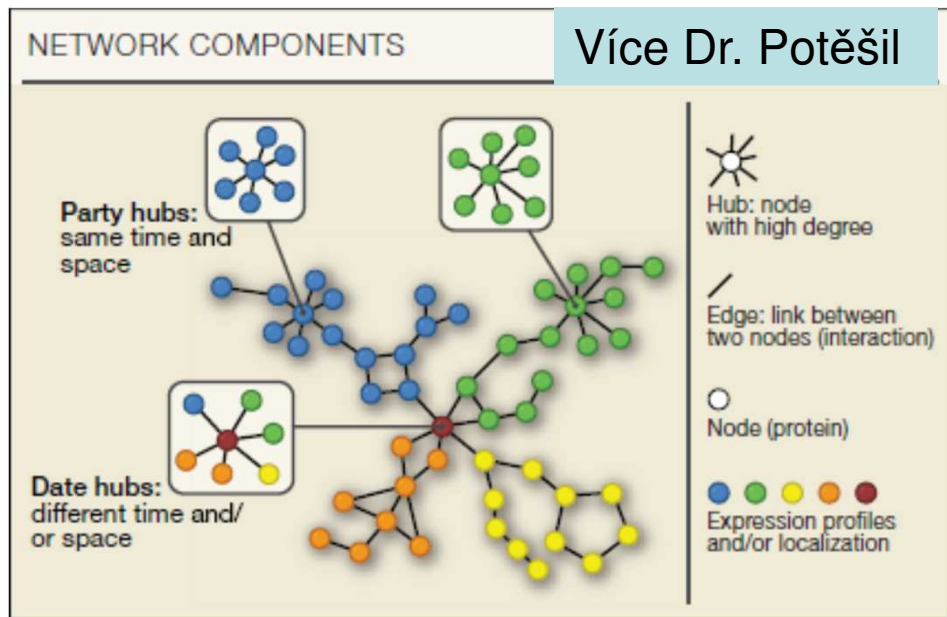
Síť neznamená komplex,
ale vztahy
souhrn proteinových:
interakcí = **interaktom**
komplexů = **komplexom**



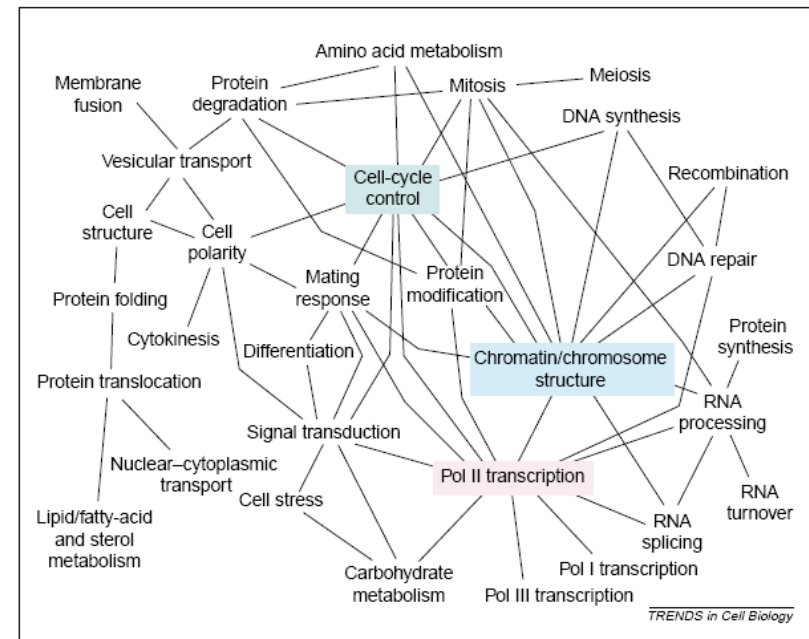
Wang et al., Nature, 2004

Protein-proteinové interakce

- stabilní (velké plochy, většinou součástí komplexů)
 - přechodné/slabe (součást dynamických procesů – předávání signálů, modifikace)
 - posttranslační modifikace mohou změnit vazebné vlastnosti povrchu (fosforylace, metylace, SUMO)
- (modularita díky interakcím domén – různé kombinace domén)



Seebacher & Gavin, Cell (SNAP SHOT), 2011



Network/síť naznačuje funkční vztahy
Tucker et al, TiCB, 2001

Interaktom x komplexom

Figure 3-83 *Molecular Biology of the Cell* (© Garland Science 2008)

Naznačují funkční vztahy (např. buněčný cyklus – struktura chromatinu ... jsou zprostředkovány PPIs)

Modularita – interagují domény (jeden protein více domén – zapojení do více procesů)

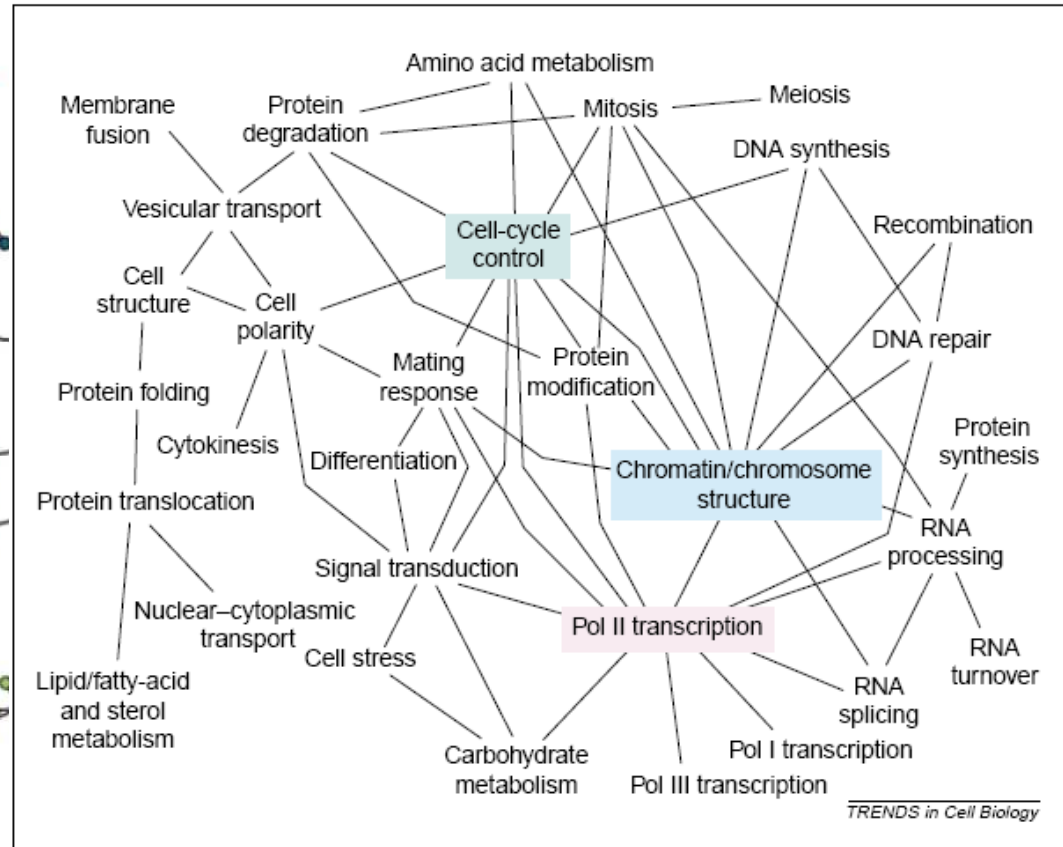
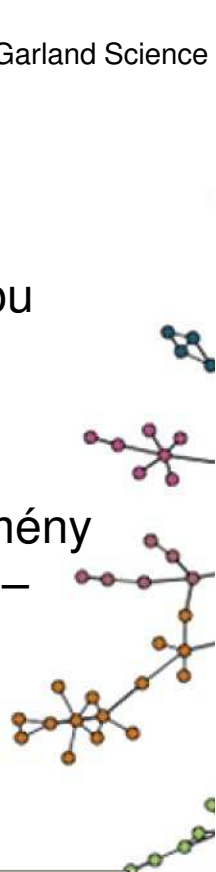
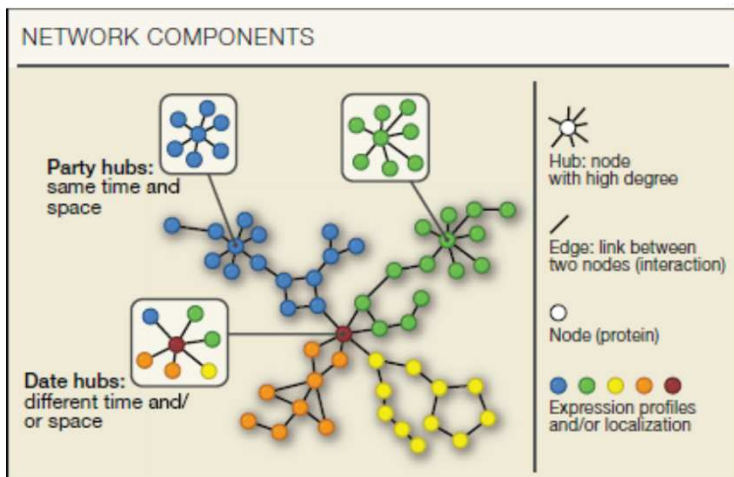
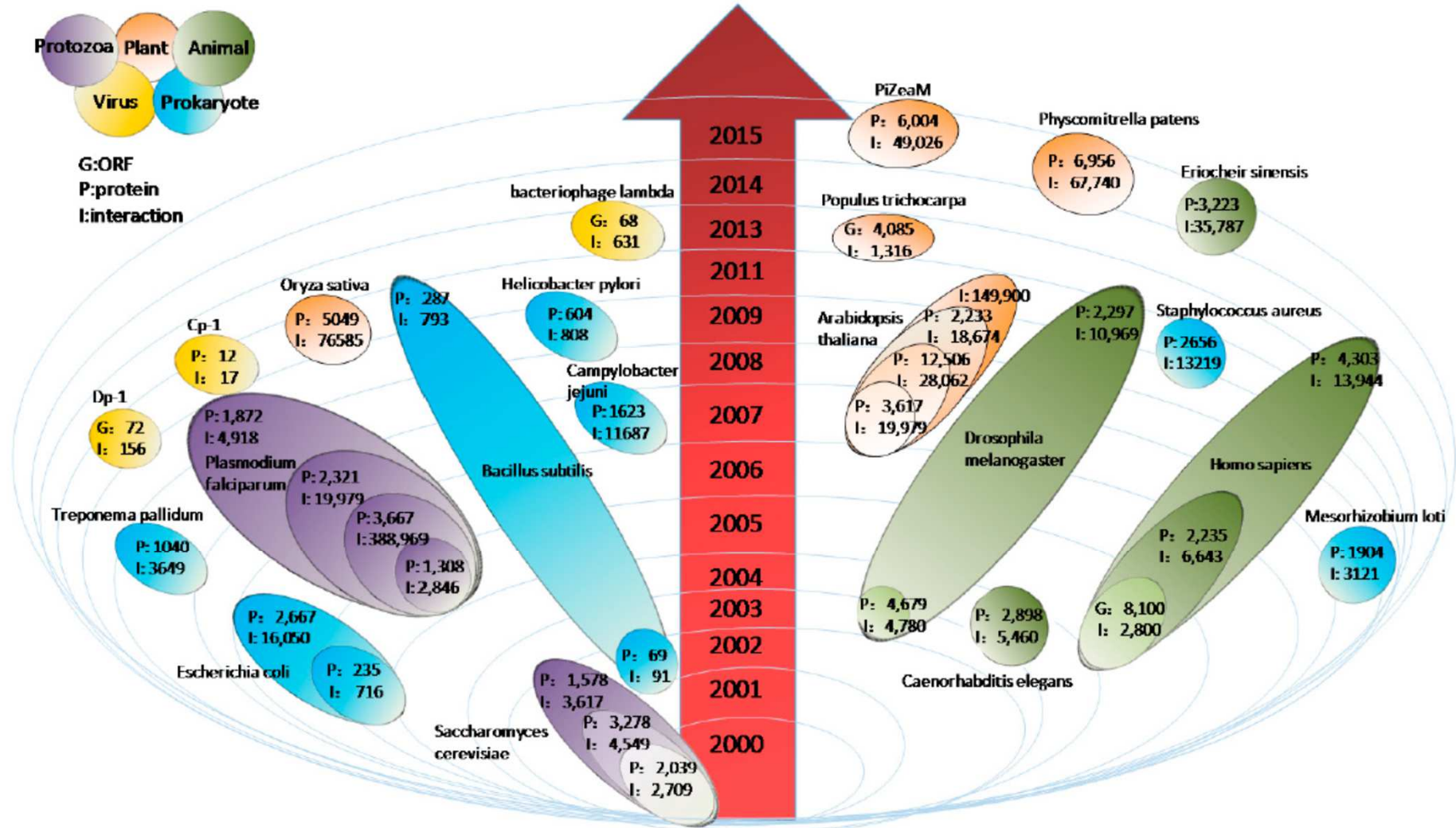


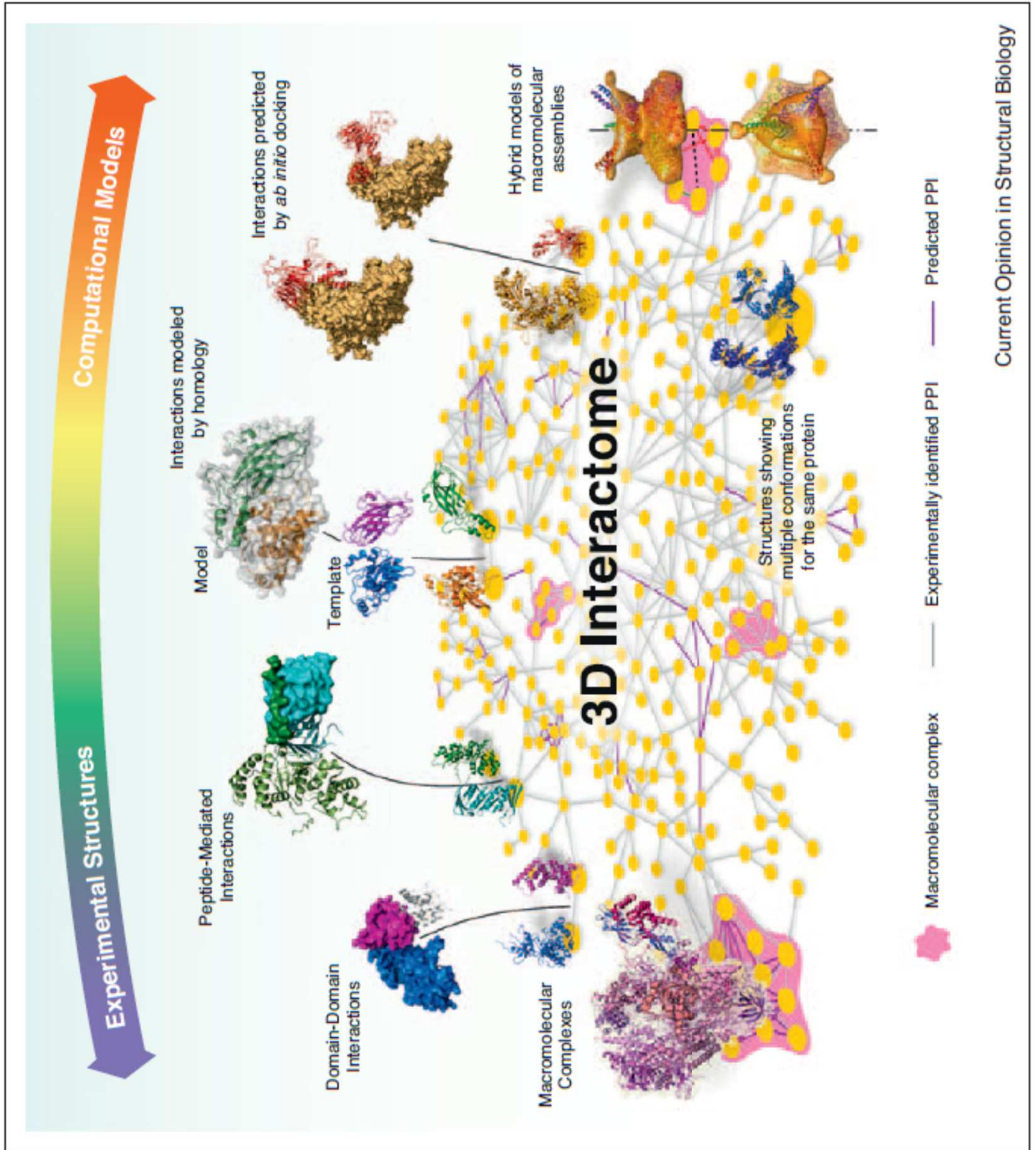
Fig. 2. Functional group interaction map based on Fig. 1 (modified from Ref. 10). Shown are interactions between functional groups of yeast proteins. Each line indicates that there are 15 or more interactions between proteins of the connected groups. Connections with fewer than 15 interactions are not shown because one or a few interactions occur between almost all groups and often tend to be spurious – that is, based on false positives in two-hybrid screens or other assays. Note that only proteins with known function are included and that about one-third of all yeast proteins belong to several classes.



High-throughput screens – interaktomy organismů



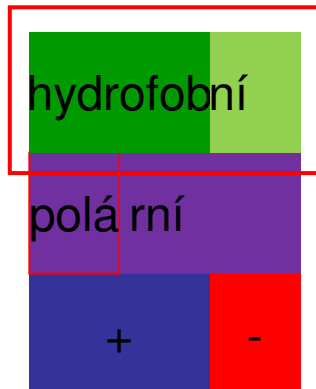
Kvasinkový dvoj-hybridní systém
 TAP-tag s MS analýzou



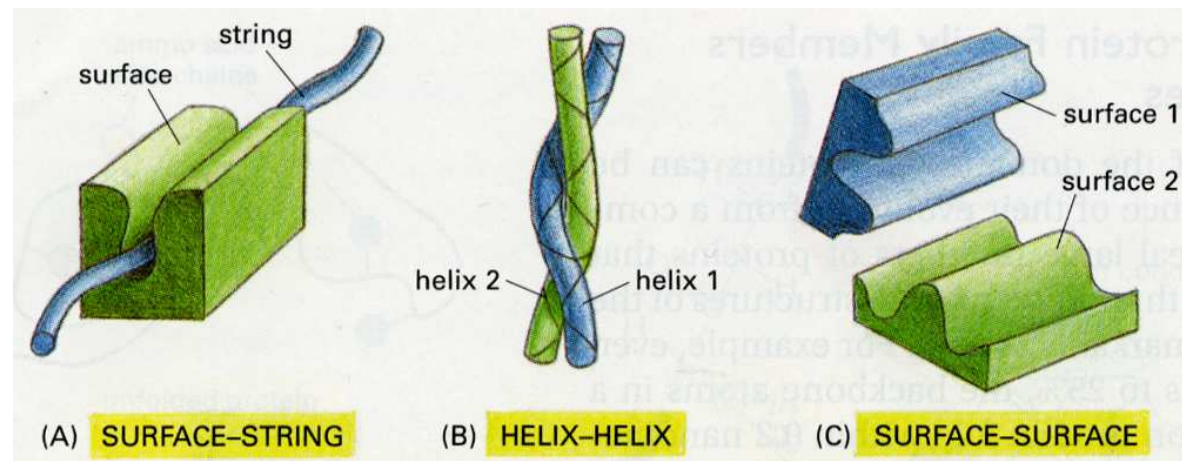
Souhrn - protein-proteinové interakce

- proteiny jsou troj-rozměrné - mají různé tvary a více domén => mají více vazebných míst na povrchu => komplexy a "sítě"
- části proteinů/domény/motivy interagují s partnery
 - domény mají určitou strukturu, která do značné míry determinuje tvar jejího povrchu, ale ...
 - charakter (hydrofobicitu, polaritu, náboj) povrchu určují postraní řetězce aminokyselin směřujících do solventu, takže ...
 - interakce proteinu je determinována povrchem, který musí mít tvar i charakter komplementární s interakčním partnerem (typy interakcí: ...)

primární struktura



sekundární a terciární struktura



Podívejte se u „svých“ proteinů
na jejich interakce v databázích
a v PDB...