



INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

TENTO PROJEKT JE SPOLUFINANCOVÁN EVROPSKÝM SOCIÁLNÍM FONDEM
A STÁTNÍM ROZPOČTEM ČESKÉ REPUBLIKY

anketa

- **Proteinové interakce – 23.10.**

- jak spolu proteiny interagují?
- interaktom

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- **Proteinové komplexy – 30.10.**

- protein-proteinové interakce a komplexy
- komplexom, architektura a funkce komplexů

CG030 – Struktura a funkce proteinových komplexů

CG031 – cvičení z modelování proteinových komplexů

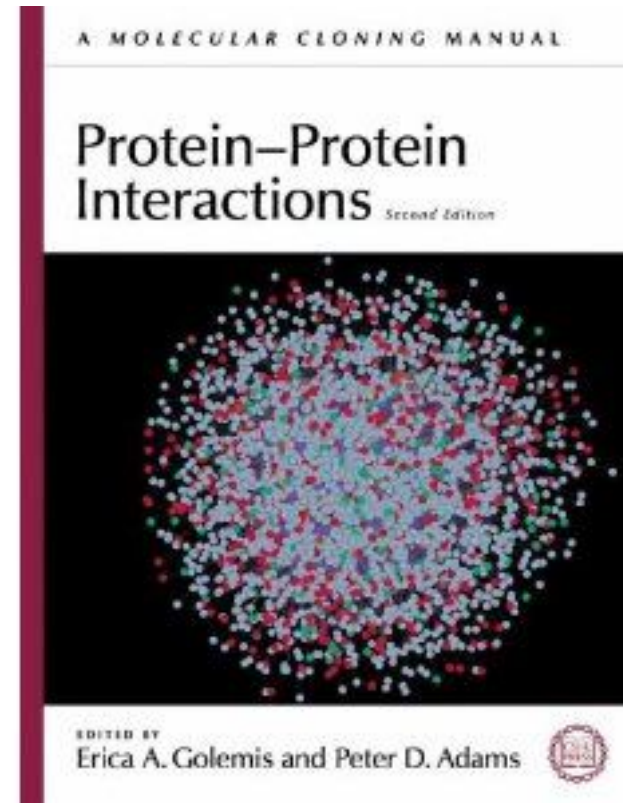
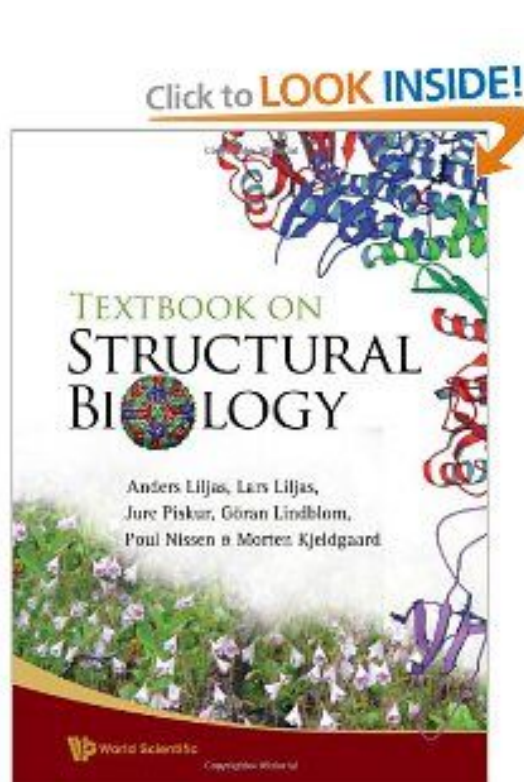
(jarní semestr)

Informační zdroje

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

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

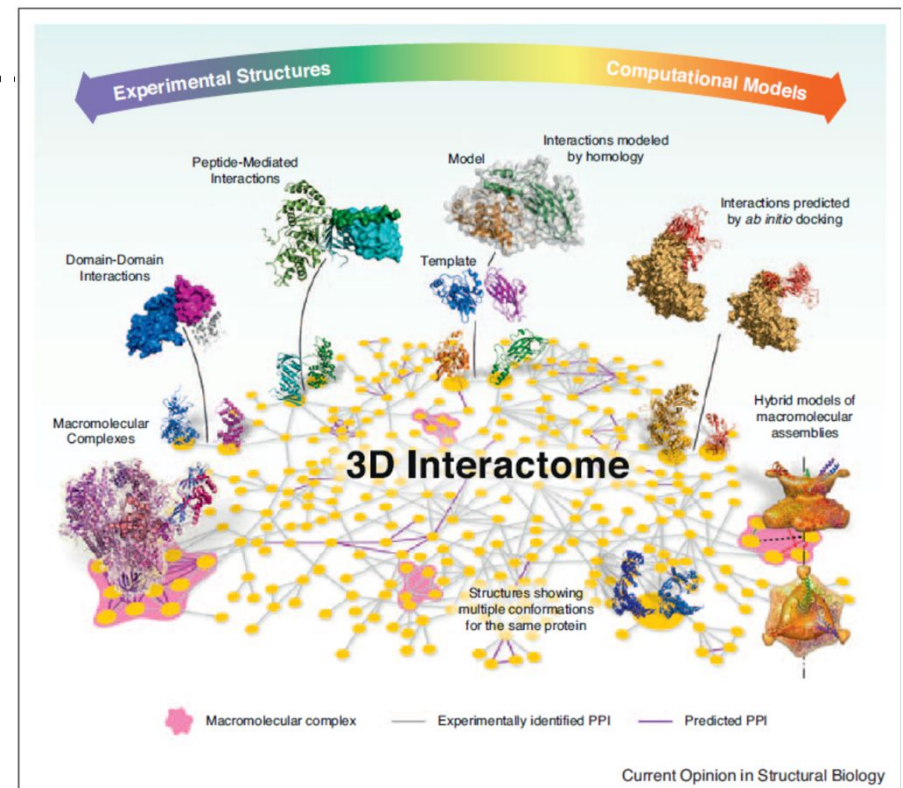
... nejnovější články z časopisů Cell, Nature, Science, PLoS ...

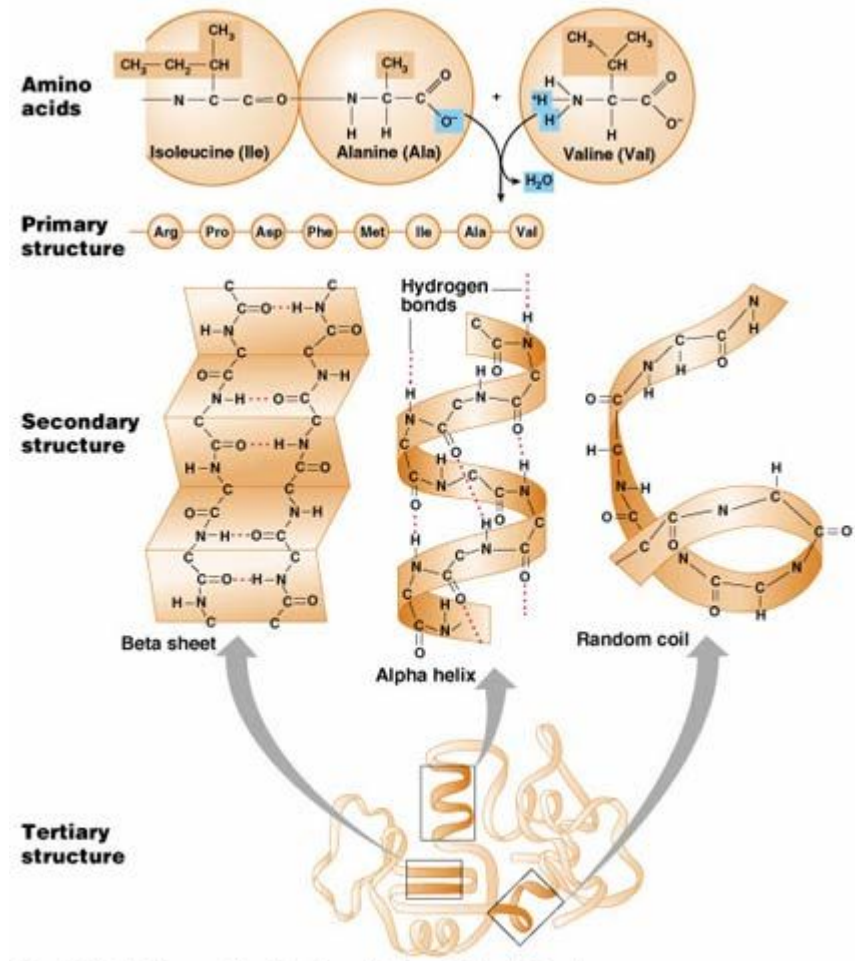
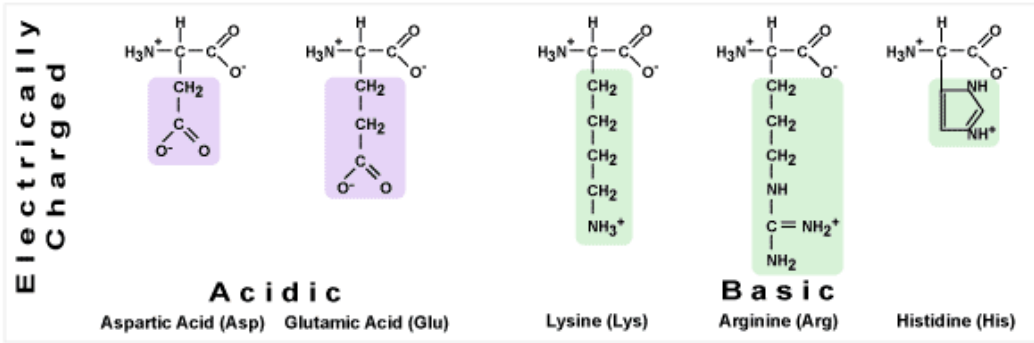
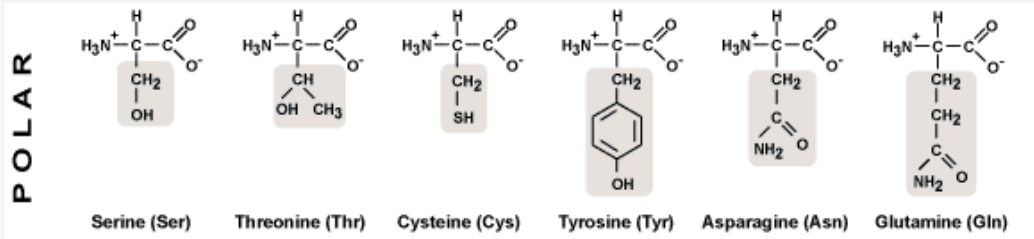
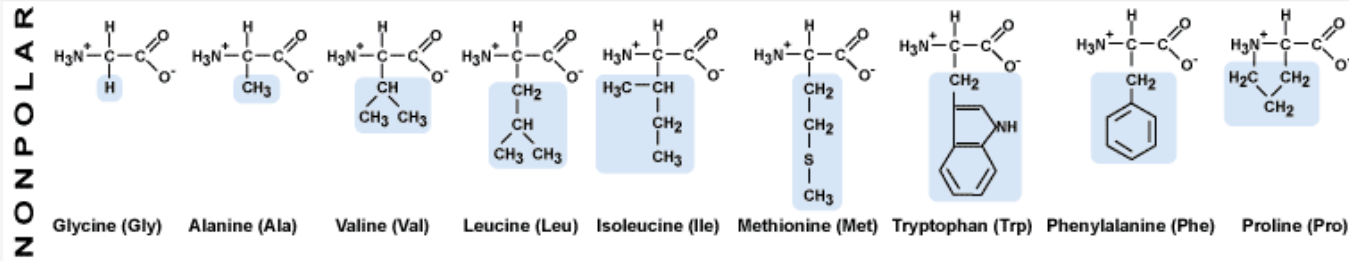


Databáze proteinových struktur: <http://www.rcsb.org/pdb/home/home.do>,
<http://www.ebi.ac.uk/pdbsum/>

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

- Proteinové interakce – 23.10.
 - Interakce: od primární po terciární strukturu
 - Typy vazeb: pohled chemický, geometrický ...
 - Informatika:
 - databáze struktur, interakcí ...
 - docking ...
 - motivy, evoluční aspekty ...
 - nástroje ...
 - interaktom ...



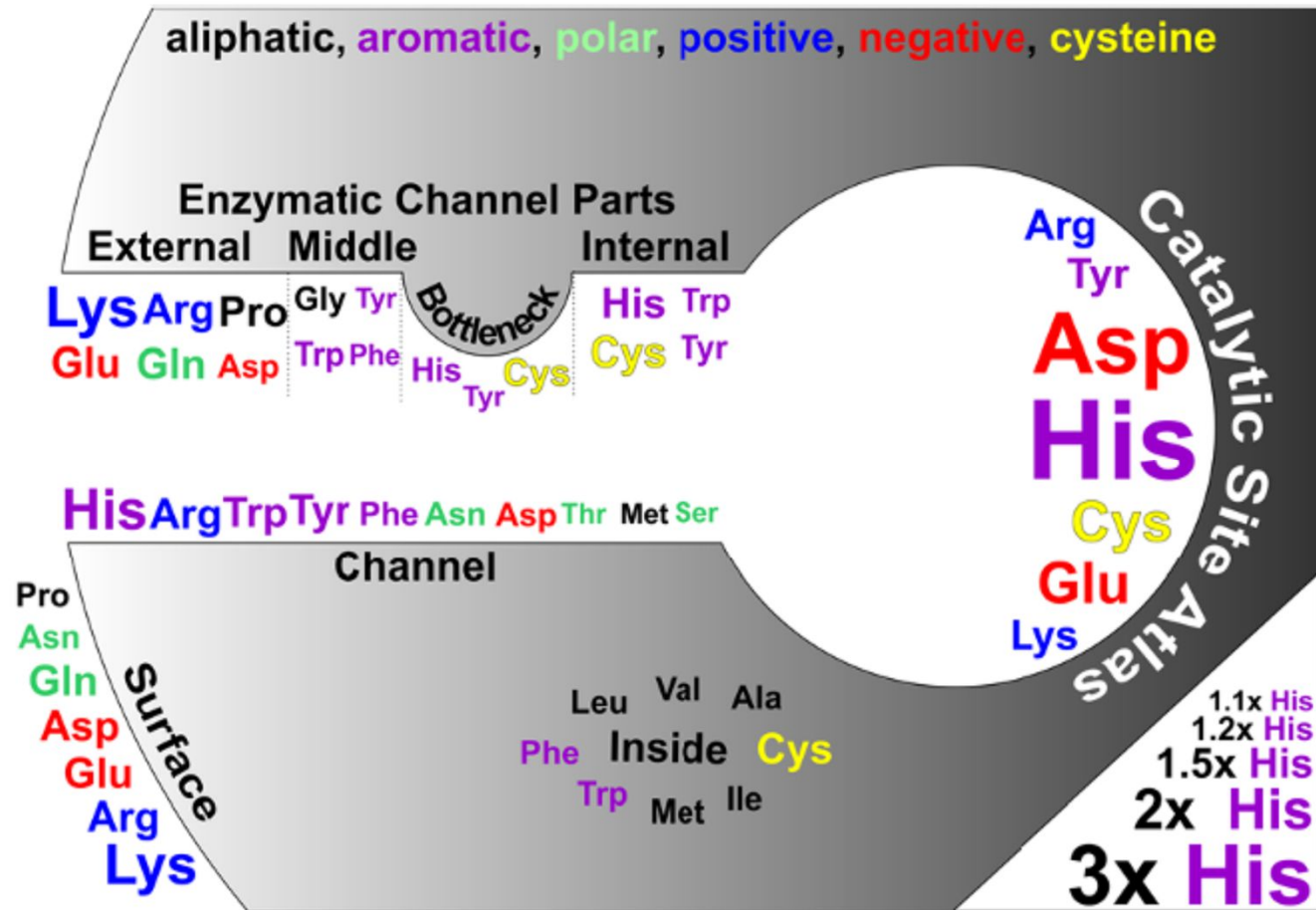


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Základní proteinové charakteristiky

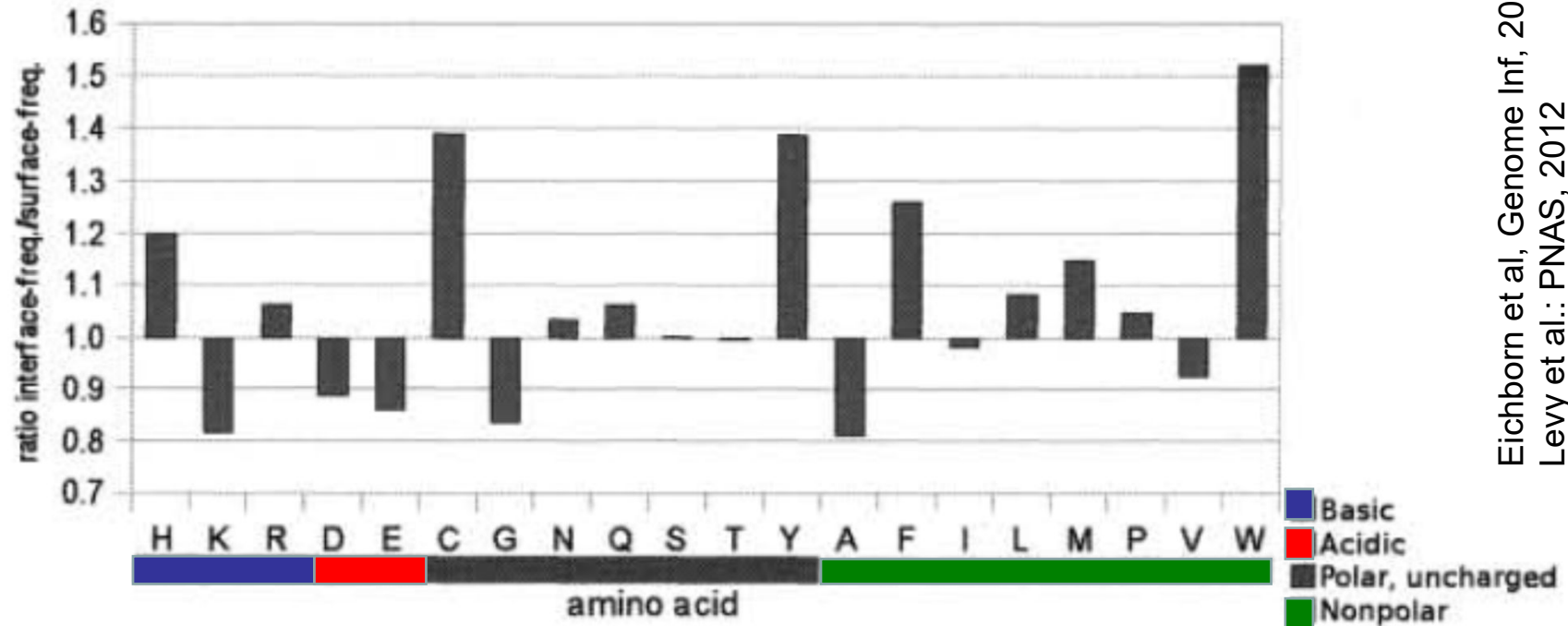
- Primární
- Sekundární
- Terciární
- Kvarterní – dva proteiny a více ...

Podíl AMK (primární struktury) na proteinových interakcích

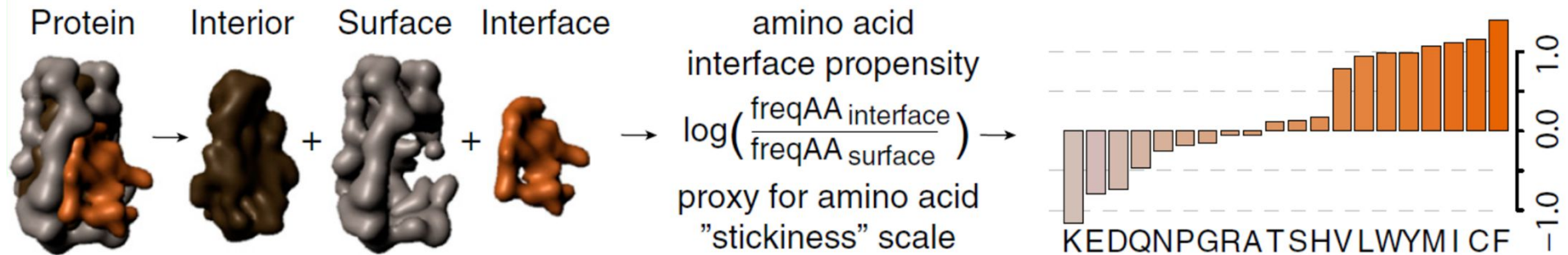


- uvnitř hydrofobní, povrch polární/nabitý (do solventu/vody),
ale katalytická centra (tunely) jsou také polární a nabité
(katalýza biochemické reakce)

PPI od primární struktury ...



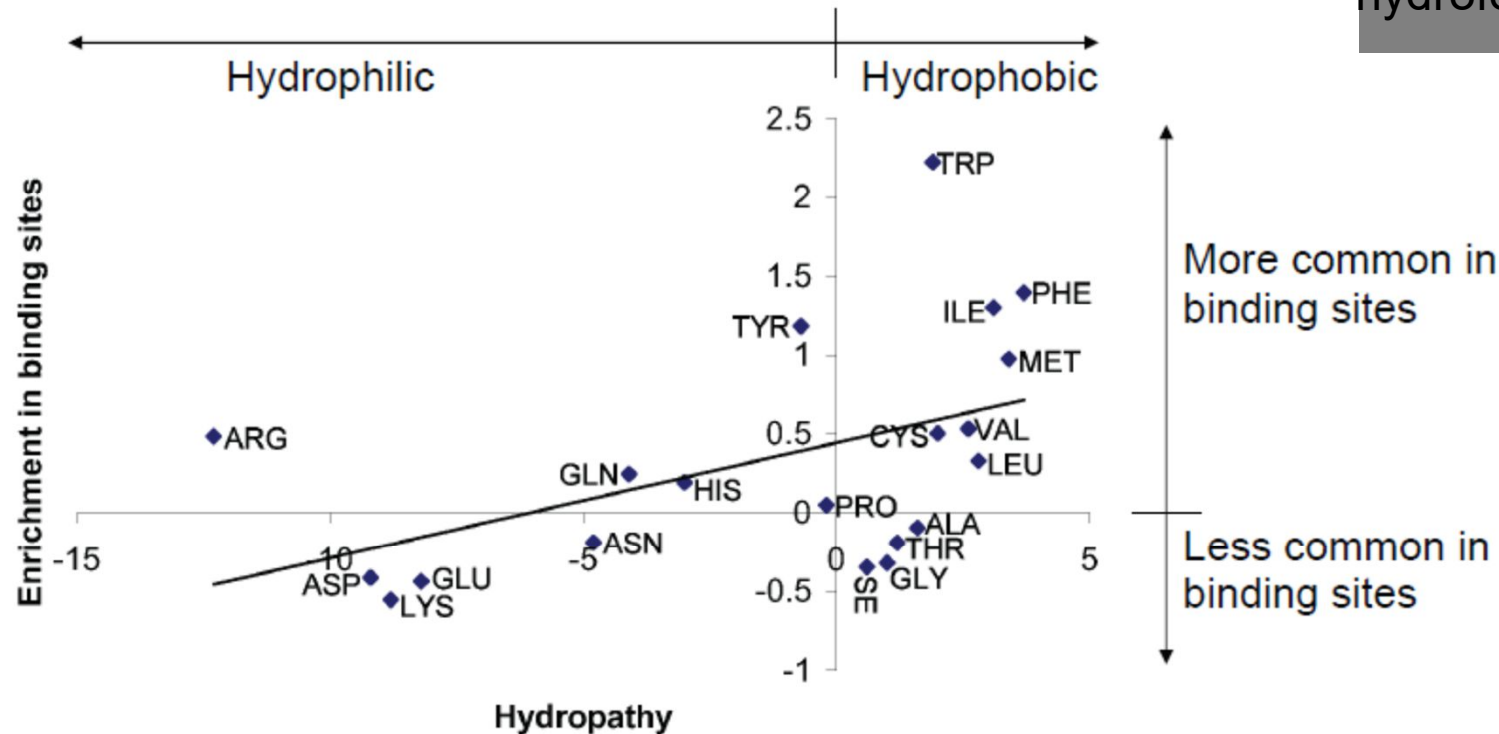
Eichborn et al, Genome Inf, 2009
Levy et al.: PNAS, 2012



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

Protein-proteinové interakce od primární struktury ...

hydrofobní



• **hydrofobní zbytky** jsou tlačeny dovnitř proteinu (ve vodném prostředí se chovají jako „mastnota“ ve vodě) – pro proteiny s hydrofobním povrchem je tedy „výhodnější“ se přes takový povrch navázat na stejně „mastného“ partnera

Typy vazeb v PPI

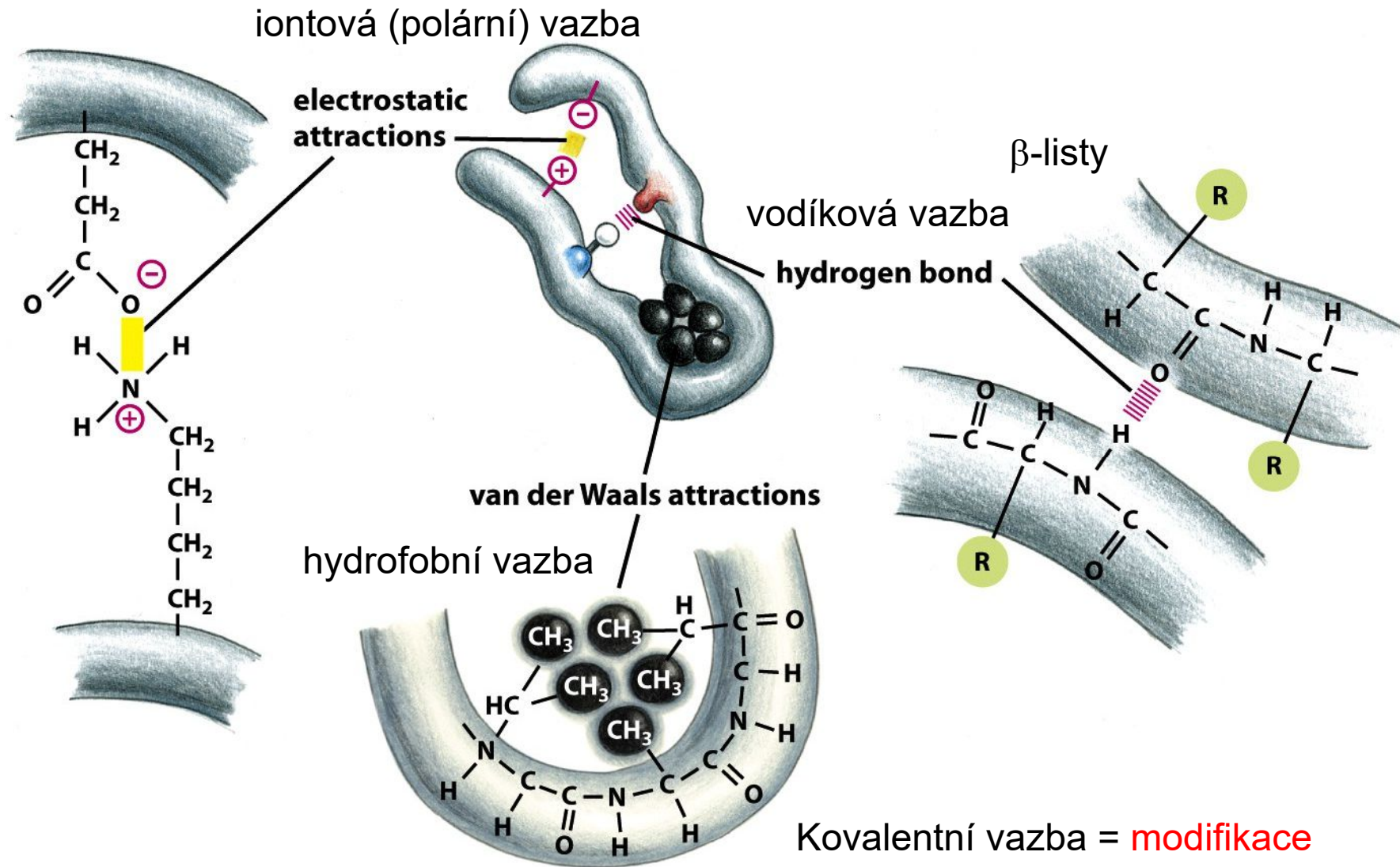
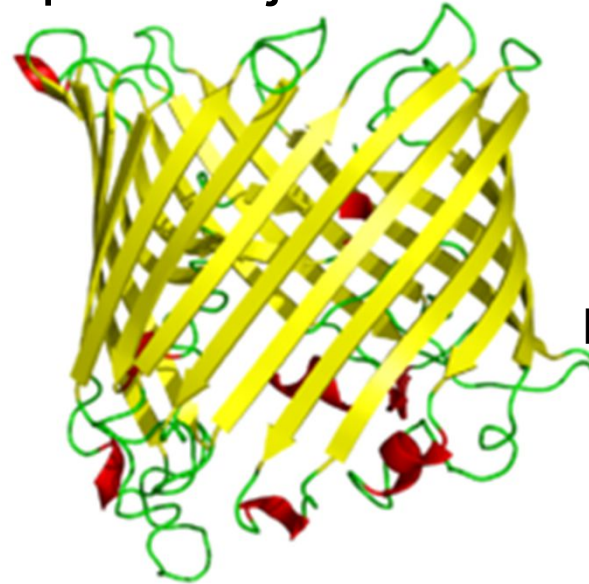
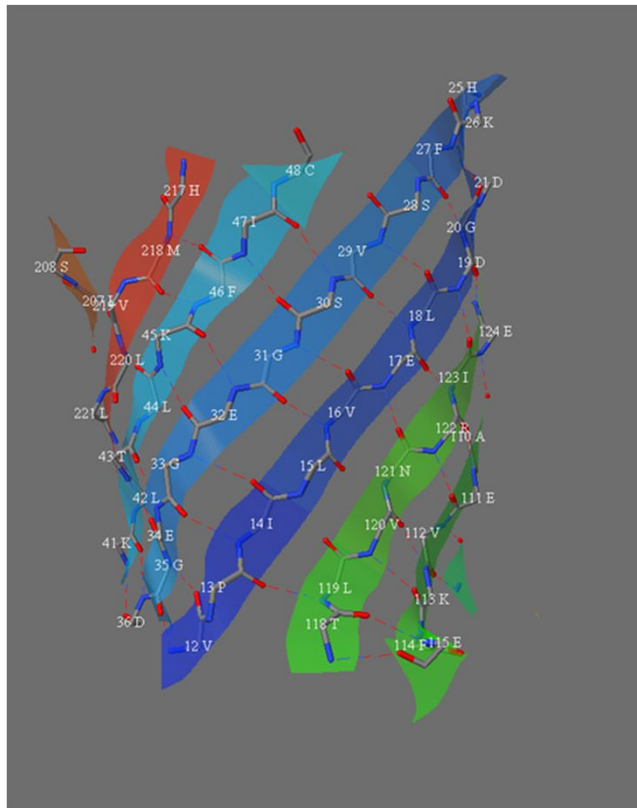


Figure 3-4 *Molecular Biology of the Cell* (© Garland Science 2008)

... sekundární struktury ...

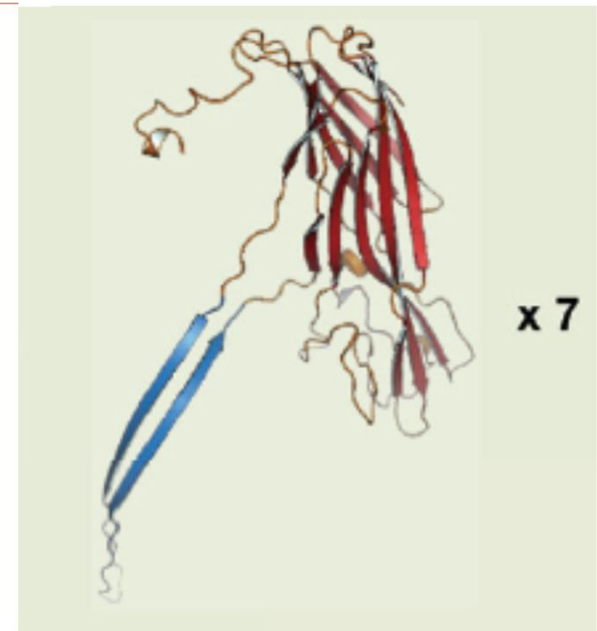
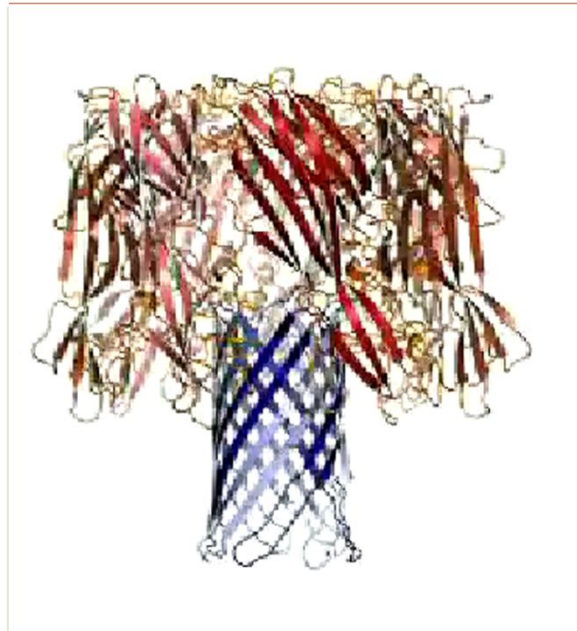
V interakcích beta-listů převažují vodíkové vazby (peptidového řetězce)



Porin
(1 ORF - polypeptid
prostup mitochondriální
membrány)

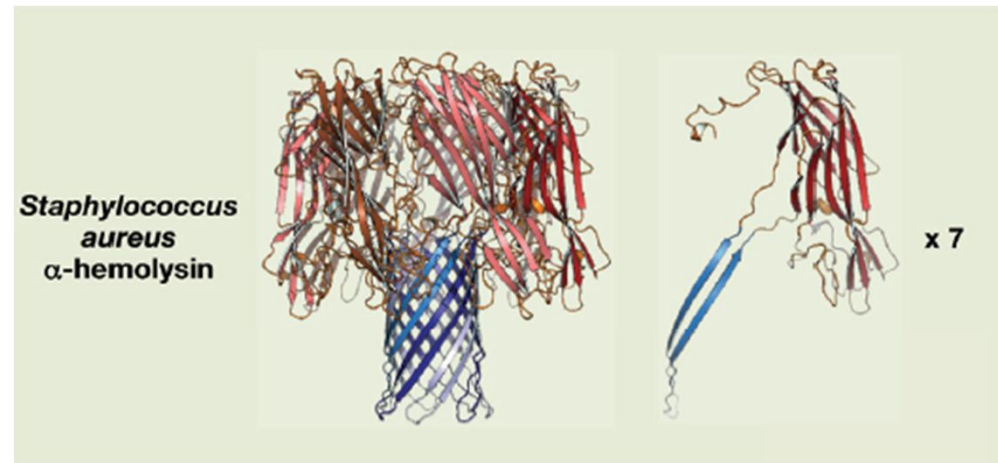
Podobný „pór“ vzniká
interakcí 7 podjednotek

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

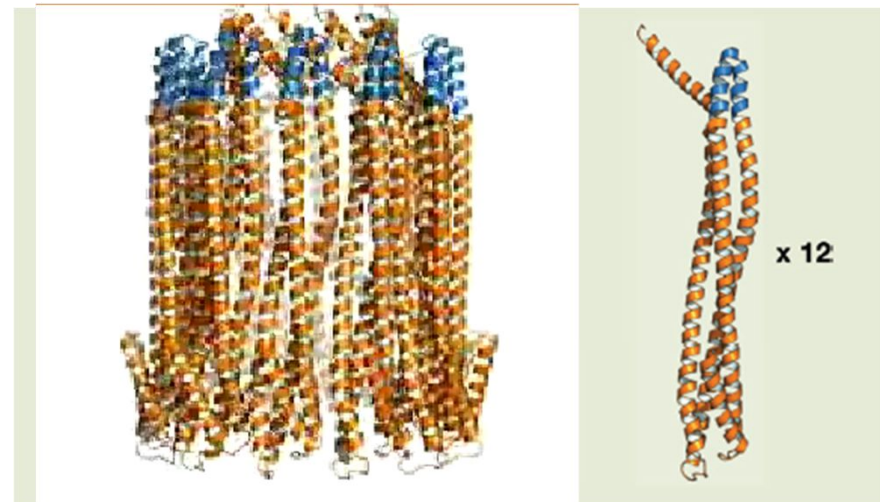
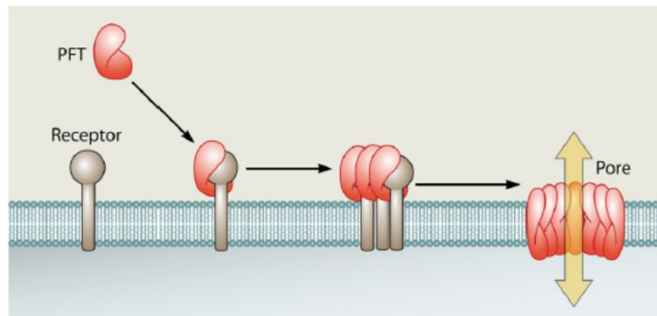


... sekundární struktury ...

- **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



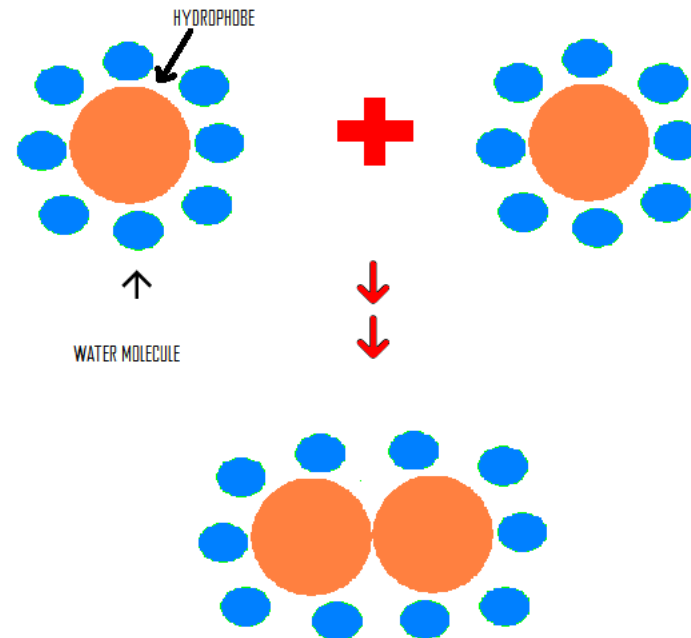
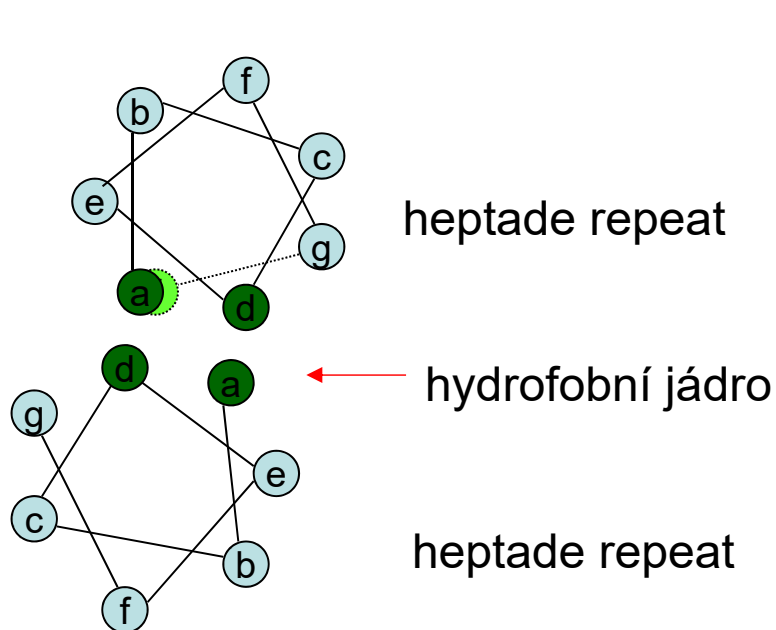
Toxiny – podjednotky se skládají tj. vytváří pór až v místě působení (neublíží původní buňce)

... sekundární struktury ...

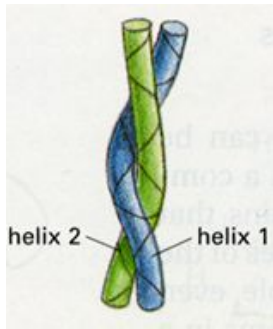
- šroubovice se vůči sobě orientují různým způsobem
- skládání slabých vazeb ovlivňuje sílu a specifitu celkové vazby

coiled-coil struktura

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

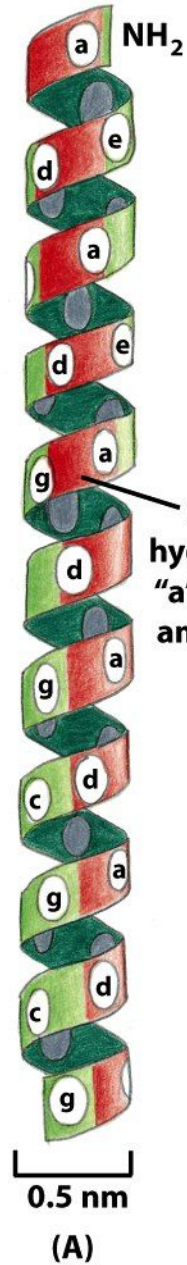


...LKSLHNQLRDLEESLTH...

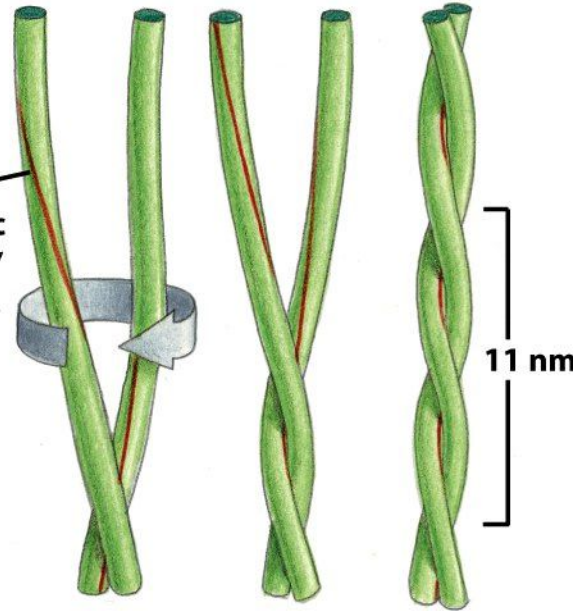


coiled-coil struktura

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



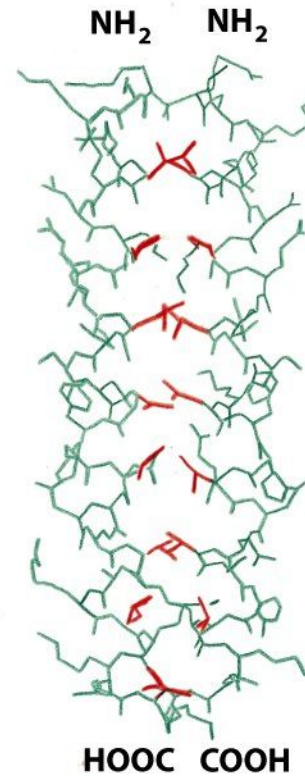
stripe of hydrophobic "a" and "d" amino acids



hydrofobní jádro

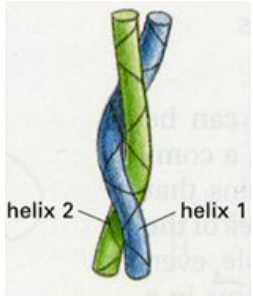
...LKSLHNQLRDL~~EES~~LTH...

(B)



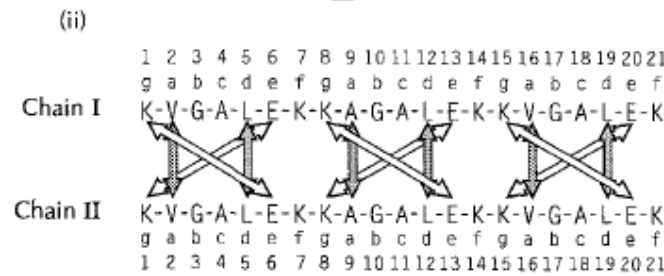
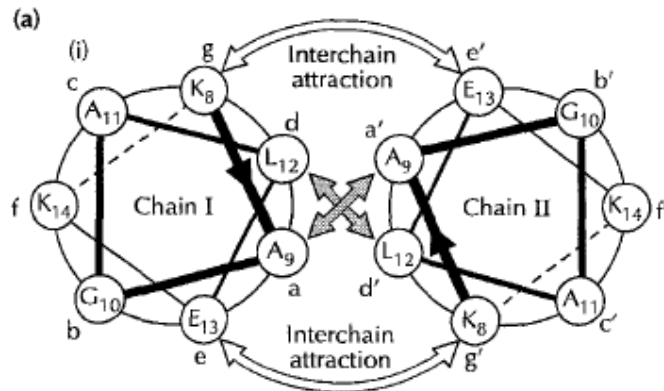
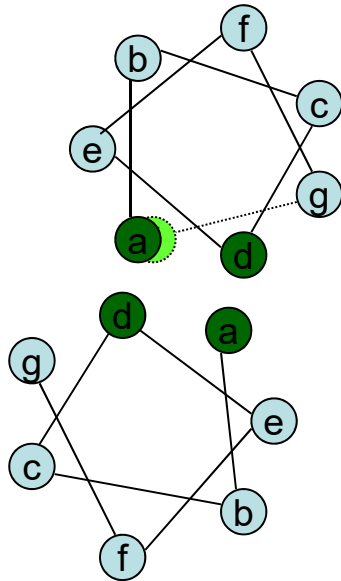
paralelní šroubovice

(C)

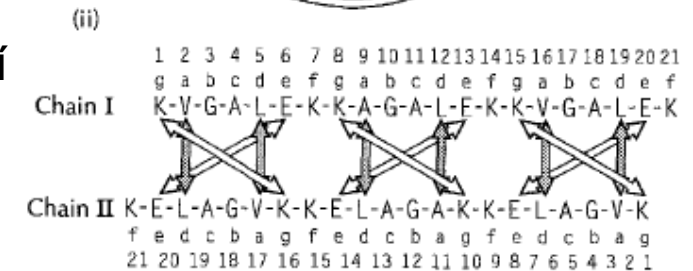
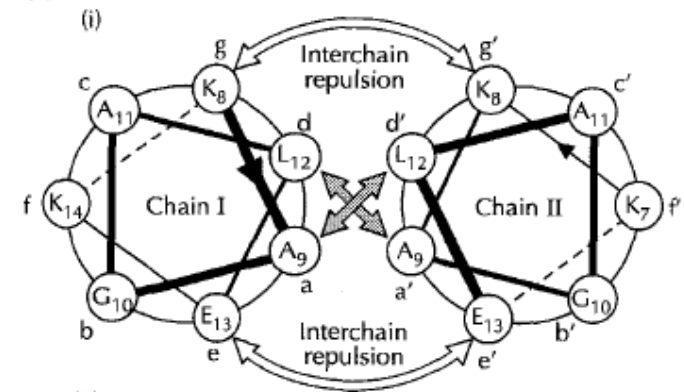


coiled-coil struktura

Síla interakce může být ovlivněna sousedními AMK



Sousední AMK stabilizují interakce šroubovic



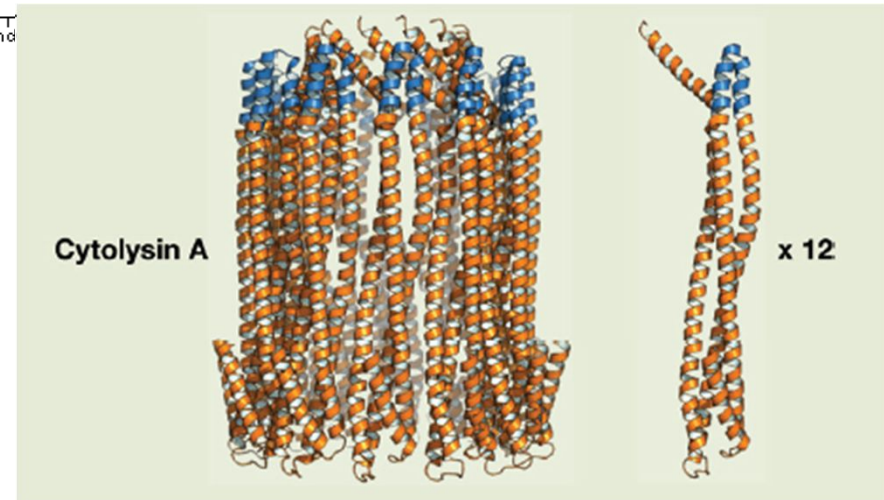
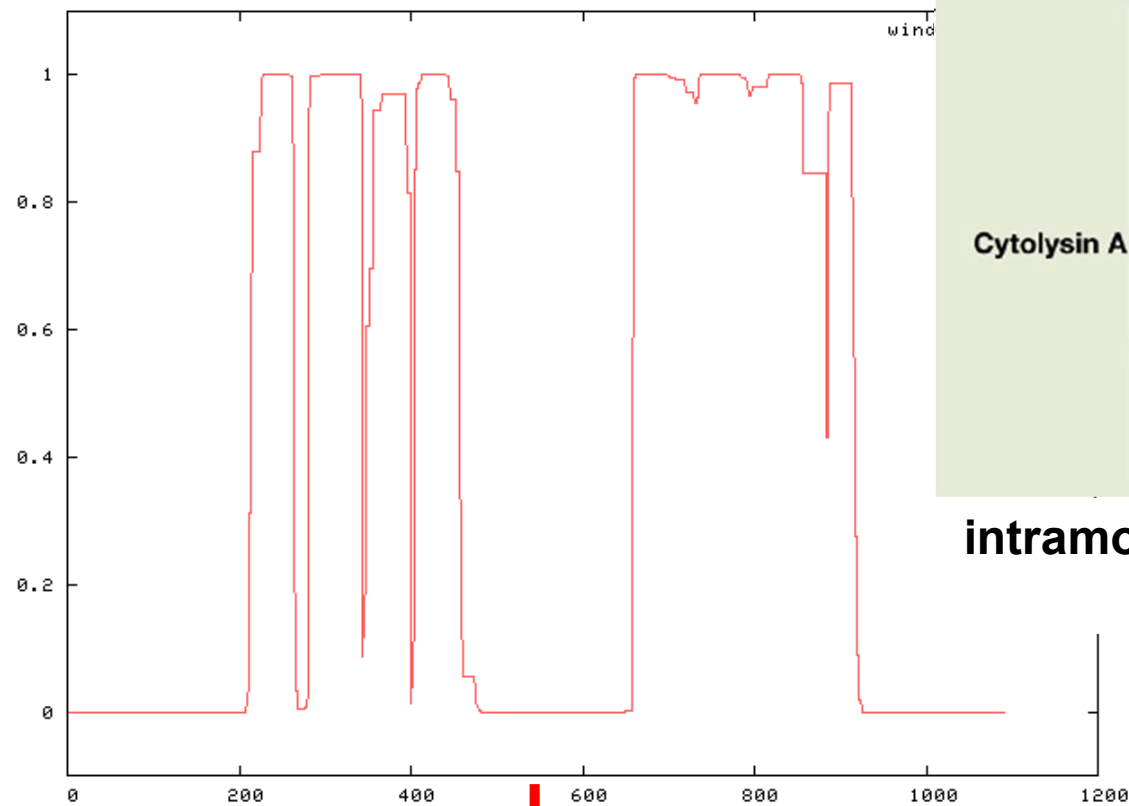
Sousední AMK destabilizují interakce šroubovic

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

coiled-coil struktura

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

profil SMC6



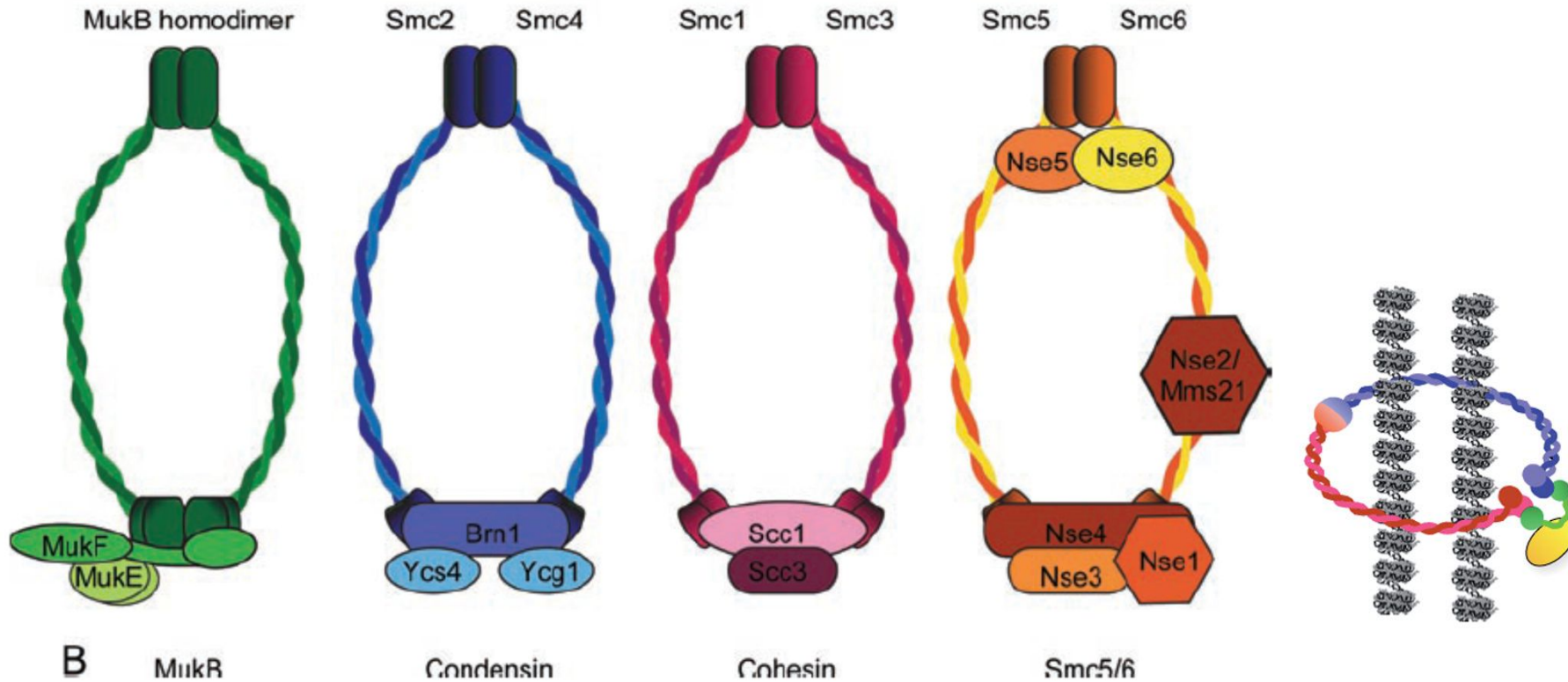
**intramolekulární vs intermolekulární
folding vs PPI**



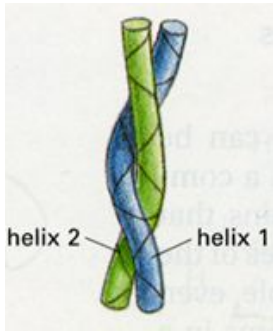
- CC v SMC proteinech jsou intramolekulární
(antiparalelní)

coiled-coil struktura

-dlouhé CC (>100AMK) vytváří vláknité struktury (SMC kruhy obejmou DNA)

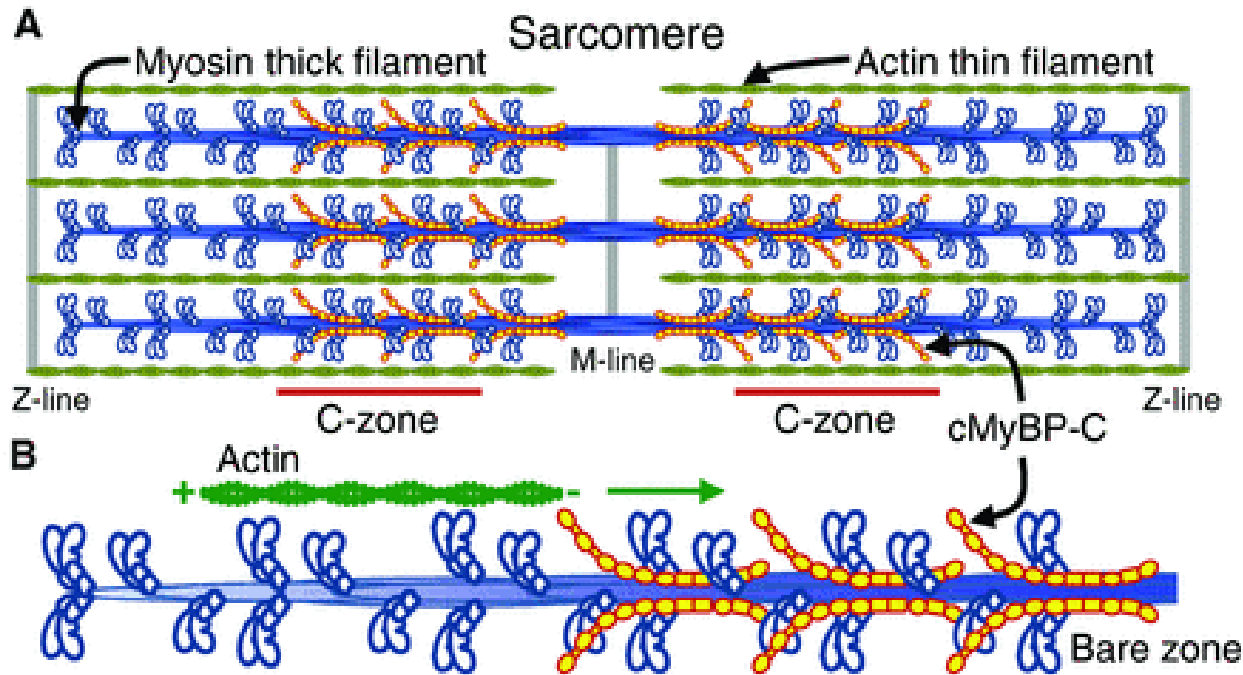


- CC v SMC proteinech jsou intramolekulární (antiparalelní)

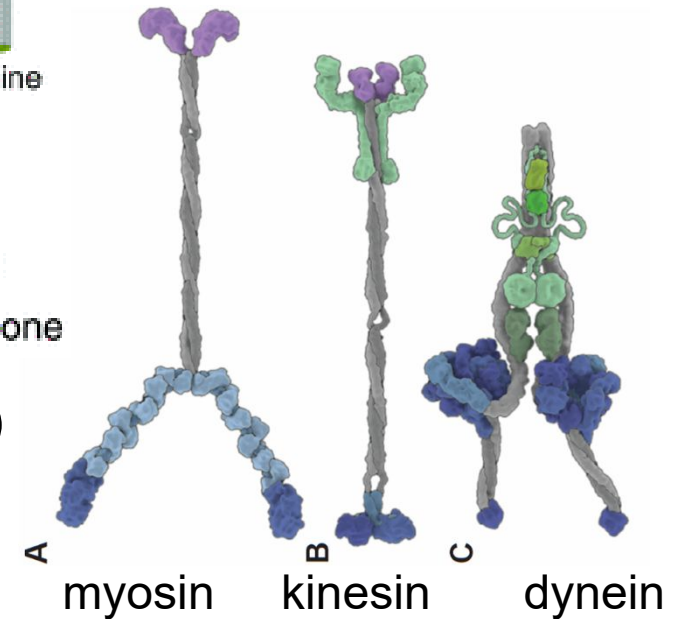


coiled-coil struktura

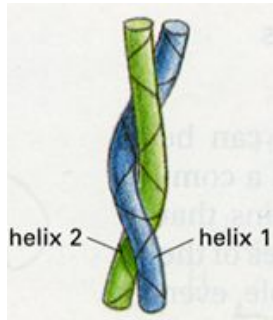
-dlouhé CC (>100AMK) vytváří vláknité struktury (myosin tvoří vlákna - svaly)



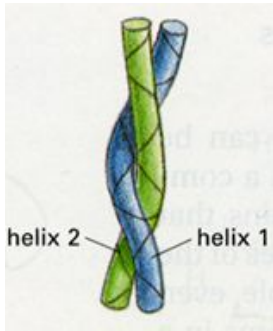
- CC v myosinu je intermolekulární (paralelní)



Kinesiny



members (alias) [orthologues]	Directionality and properties	Structural organization	Length (nm)
Kinesin-6 for example, KIF23 (MKLP1) and KIF20A (MKLP2) [ZEN-4 and Pavarotti]	<ul style="list-style-type: none"> • Plus end • Non-processive • Oligomerizes • Crosslinks 		0 25 50 75 100 125 150 175 200
Kinesin-12 for example, KIF15 (hKLP2) [xklp2]	<ul style="list-style-type: none"> • Plus end • Crosslinks with TPX2 		
Kinesin-7 for example, KIF10 (CENP-E) [CENP-meta and CENP-ana]	<ul style="list-style-type: none"> • Plus end • Processive • $F_{stall} \sim 6$ pN 		
Kinesin-5 KIF11 in humans (EG5) [Cin8, Klp61F and Cut7]	<ul style="list-style-type: none"> • Plus and minus ends • Poor processivity • $F_{stall} \sim 4$ pN • Tetrameric crosslinker 		
Kinesin-14 KIFC1 in mammals (HSET) [Ncd, Kar3, Klp2 and xctk2]	<ul style="list-style-type: none"> • Minus end • Non-processive • Dimeric crosslinker 		
Kinesin-8 for example, KIF18A [Kip3, Klp5, Klp6 and Klp67a]	<ul style="list-style-type: none"> • Plus end • Processive • $F_{stall} \sim 1$ pN • Dampens microtubule dynamics 		
Kinesin-4 for example, KIF4 in mammals [xKlp1 and Klp3a]	<ul style="list-style-type: none"> • Plus end 		



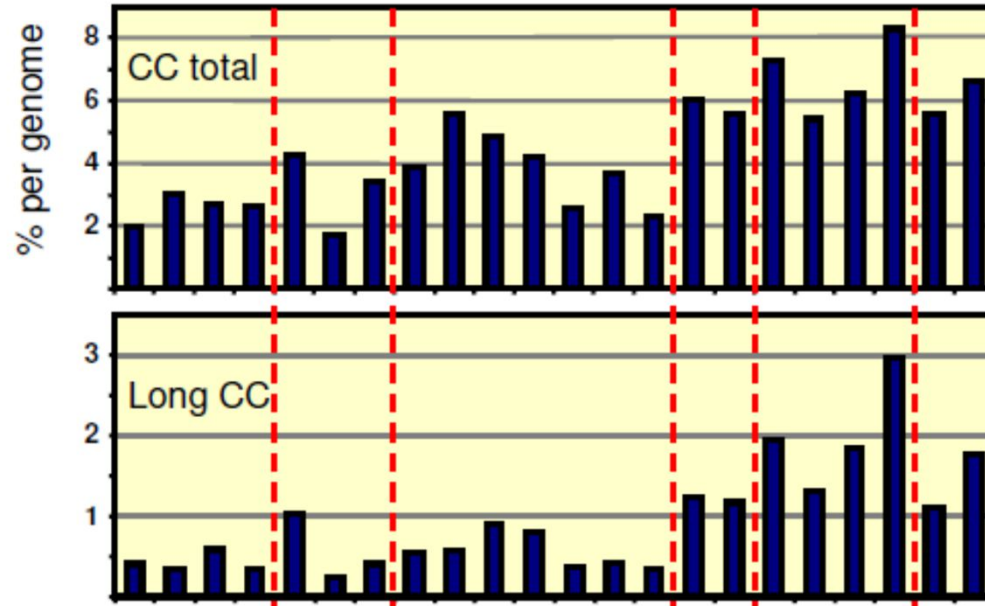
Coiled-coil
doména je
významným
dimerizačním
modulem u mnoha
proteinů (GCN4,
Max ...)

Intermolekulární -
homo- či
heterodimery
(oligomery)

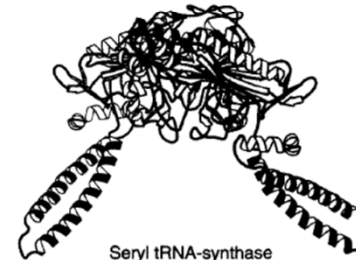


prokaryota

eukaryota



DNA polymerase I



Seryl tRNA-synthase



Transcript cleavage factor GreA



Influenza hemagglutinin HA2 (pH7)



Influenza hemagglutinin HA2 (pH4)

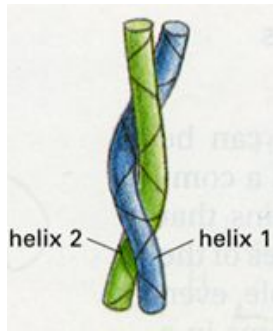


Mannose-binding protein

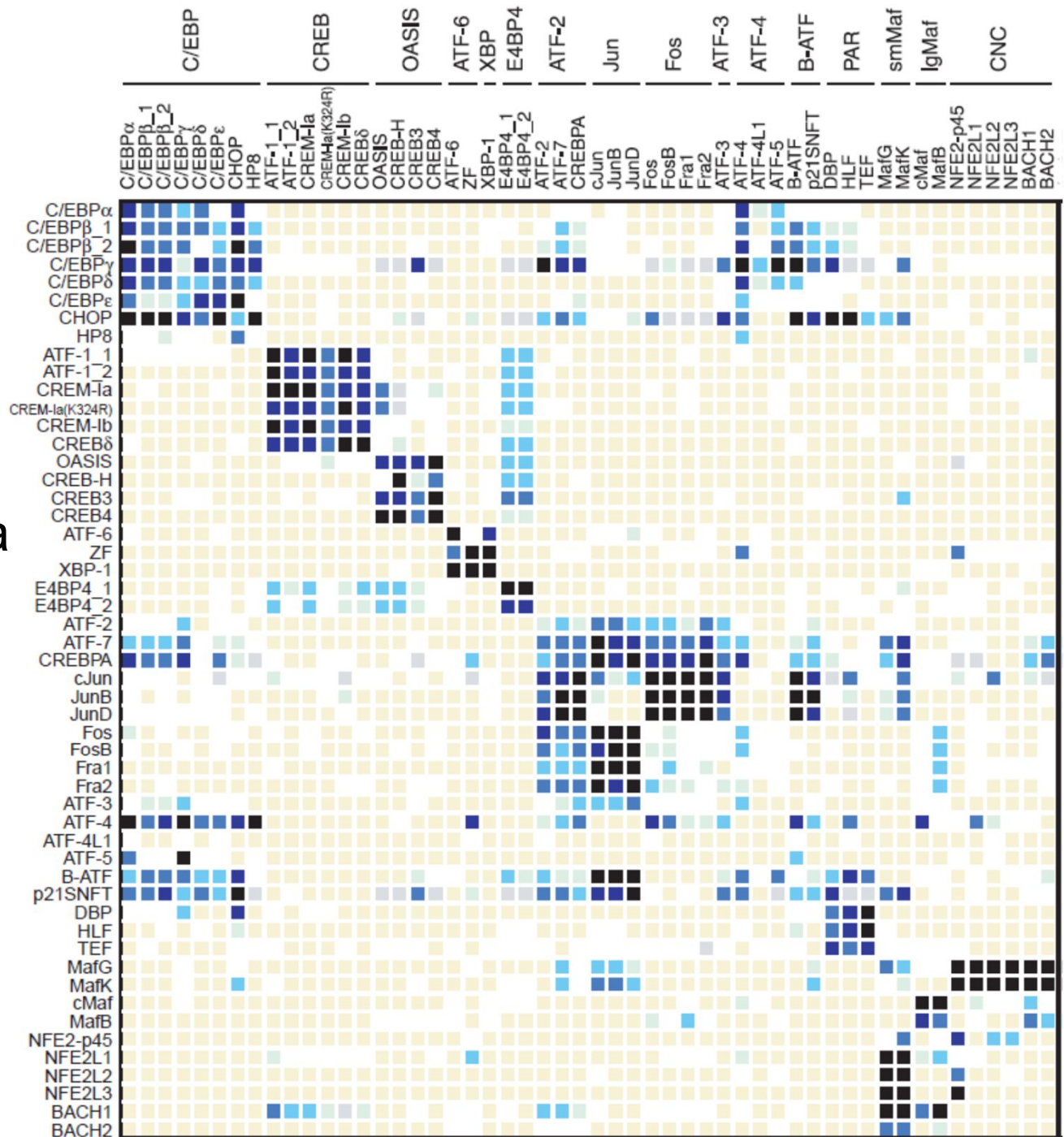


ROP

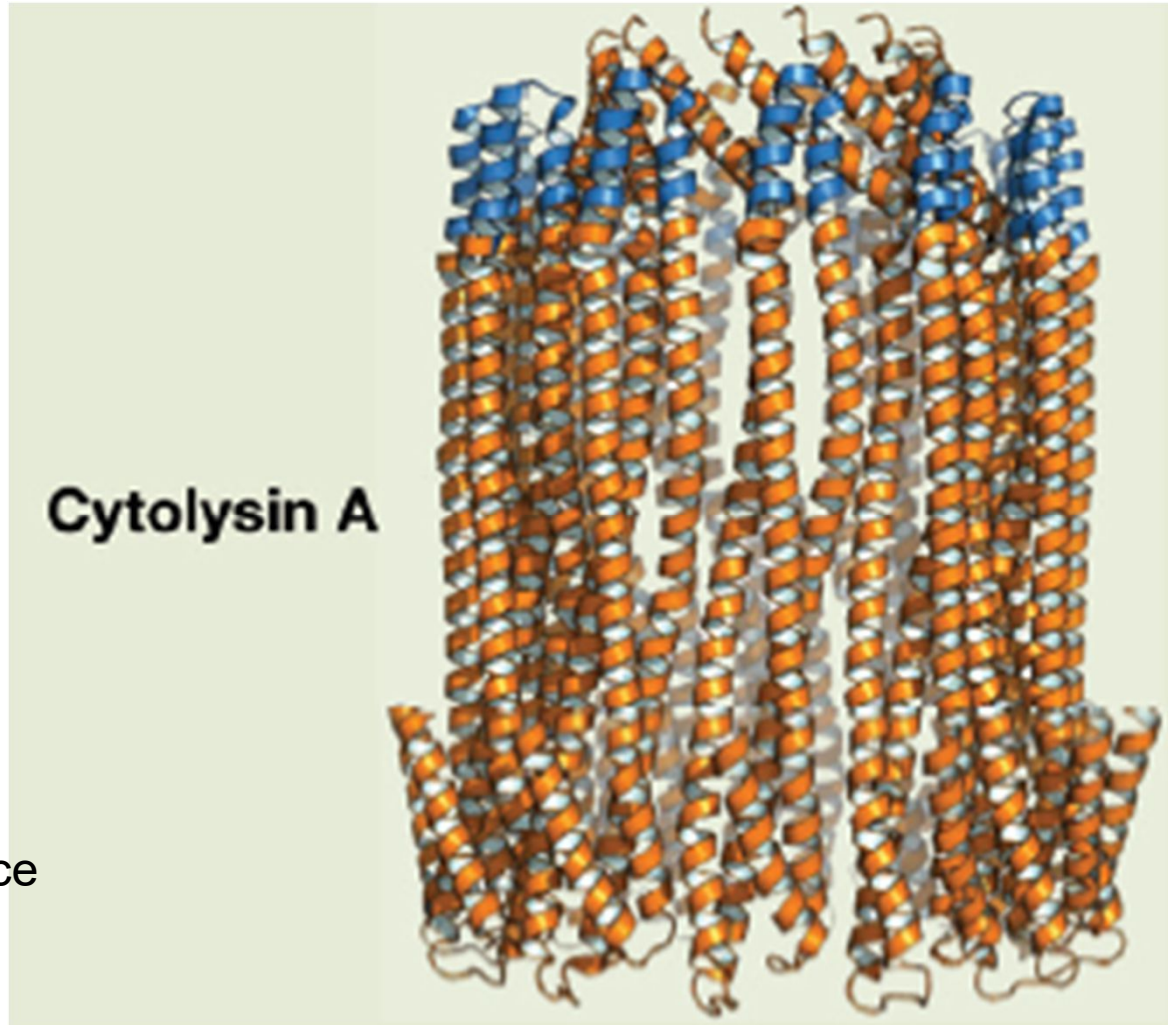
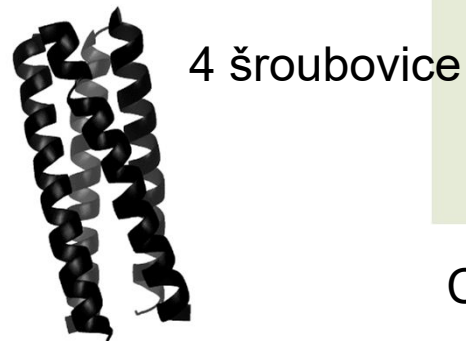
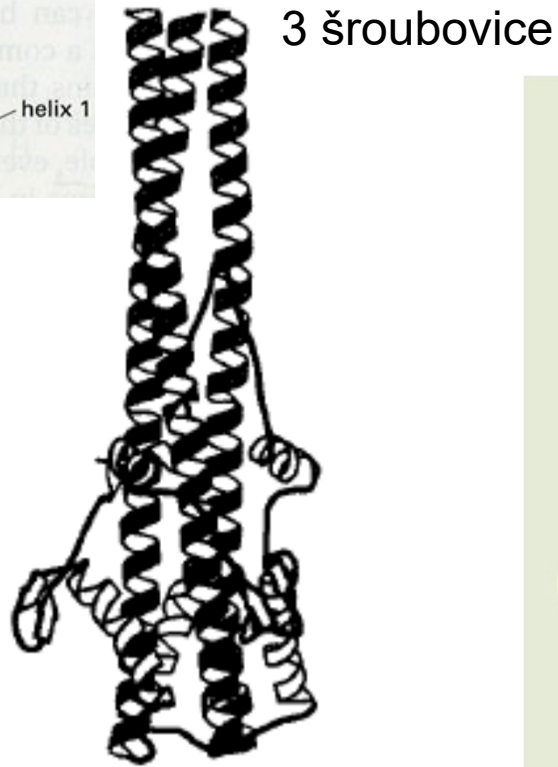
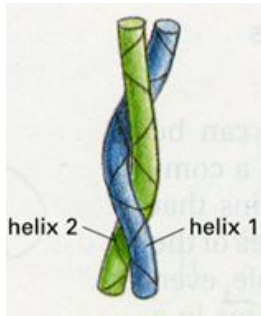
Tropomyosin



Coiled-coil
doména je
významným
dimerizačním
modulem u mnoha
proteinů: bZIP
transkripční
faktory vytváří
homo- i
heterodimery

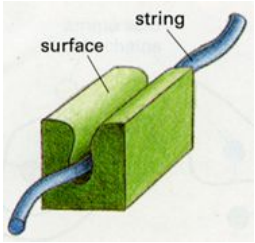


Interakce šroubovic



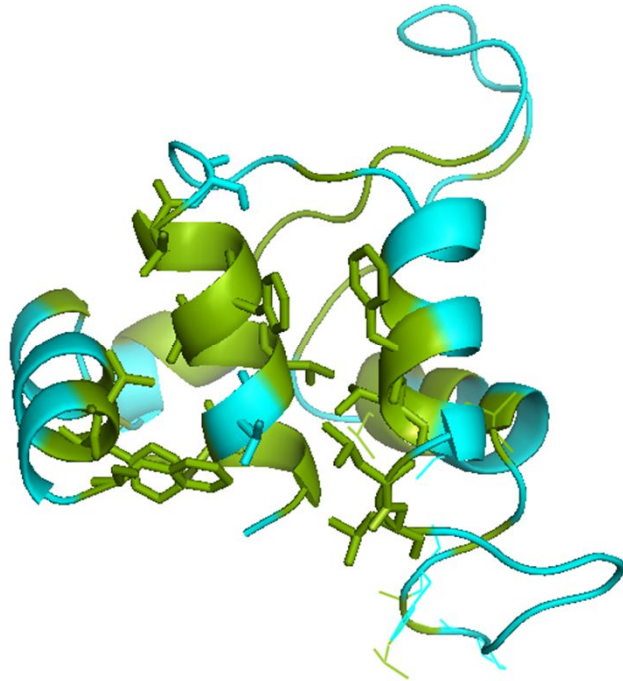
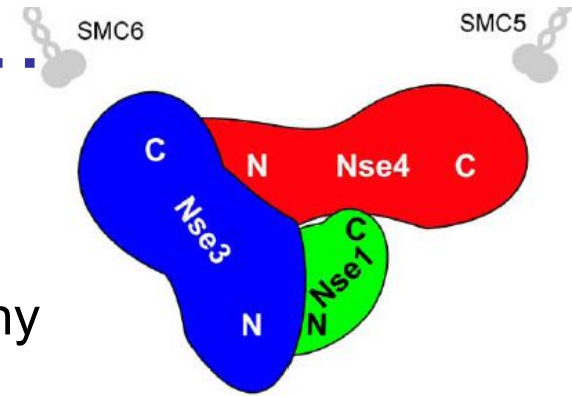
Cytolysin vytváří póry v membránách cizích buněk

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

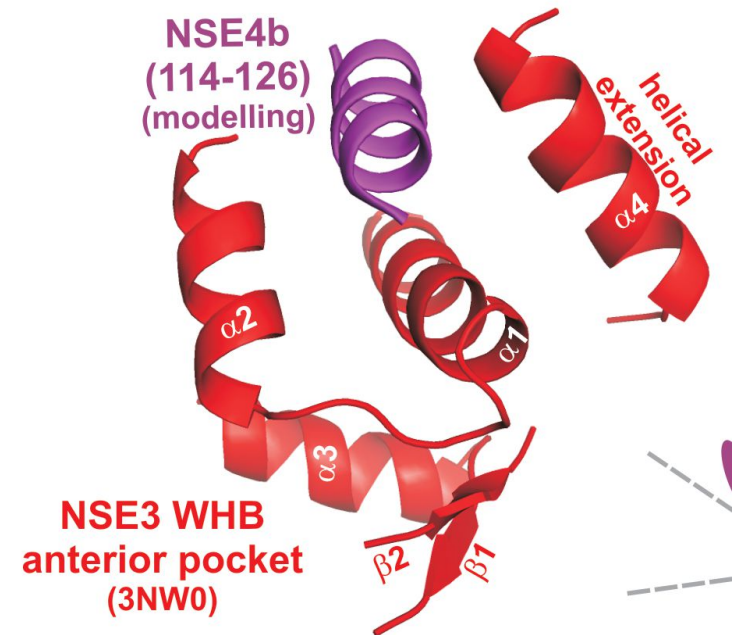


... terciární struktura ... kapsa-peptid

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

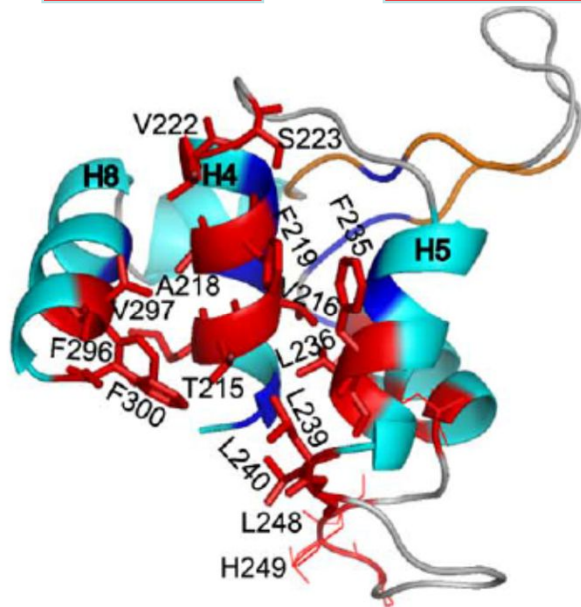
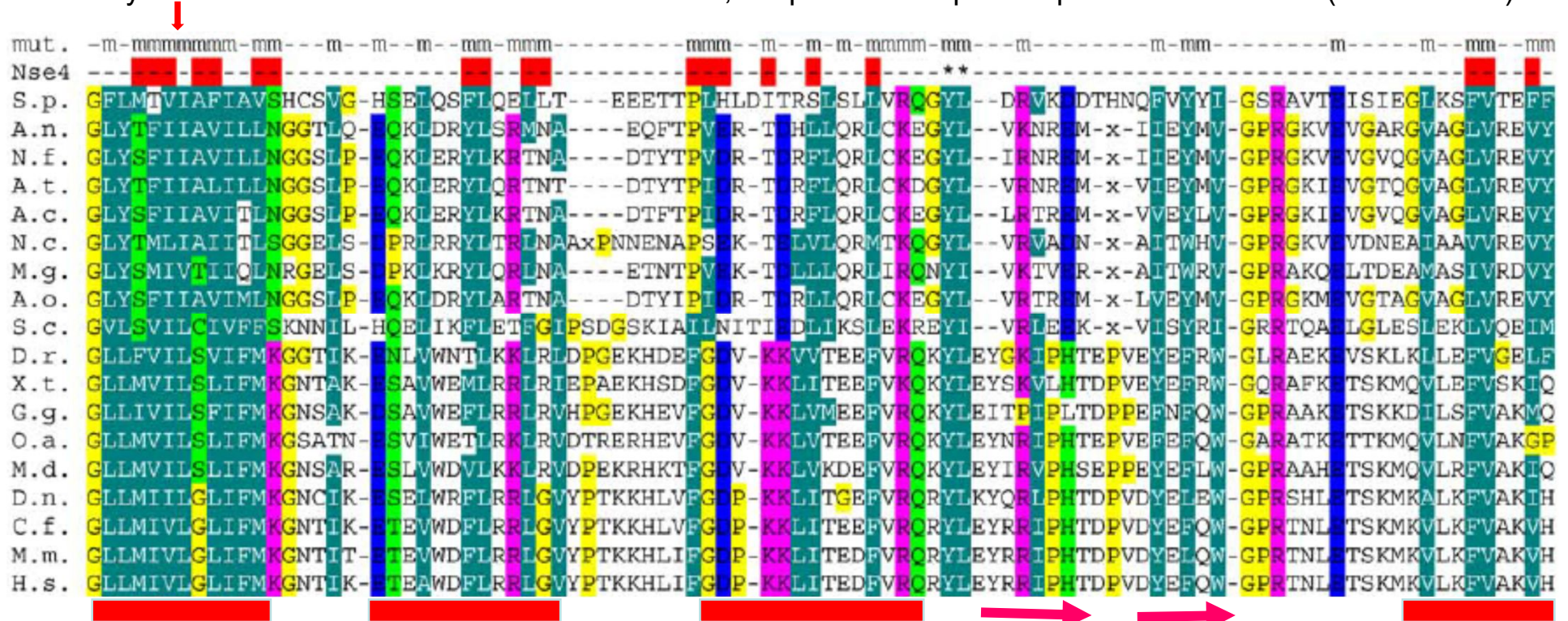


hlubší prohlubně na povrchu
mohou tvořit kapsy pro vazbu
partnera (šroubovice, peptid)

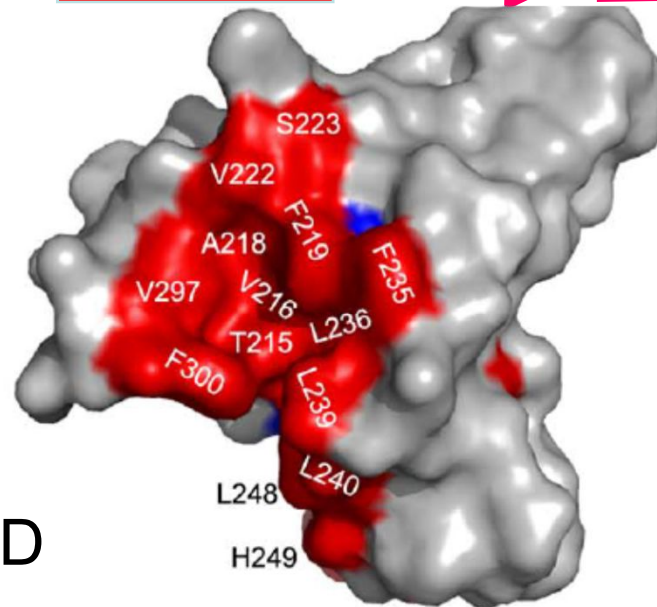


hydrofobní interakce mezi Nse3 a Nse4

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

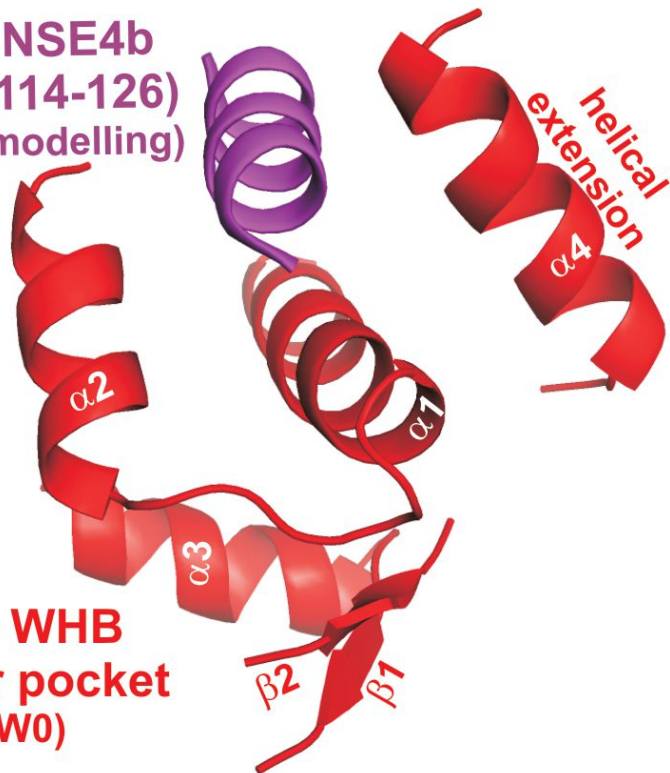
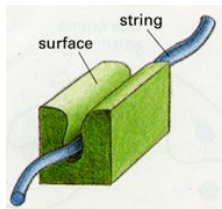


WHD

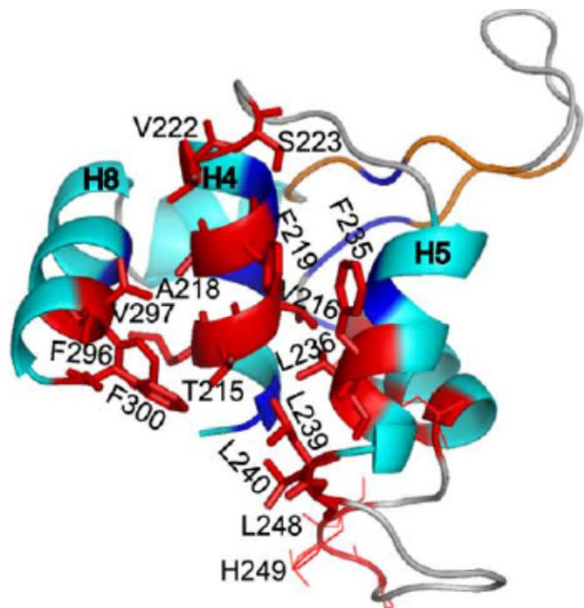


Interakce
mapována
mutagenezí

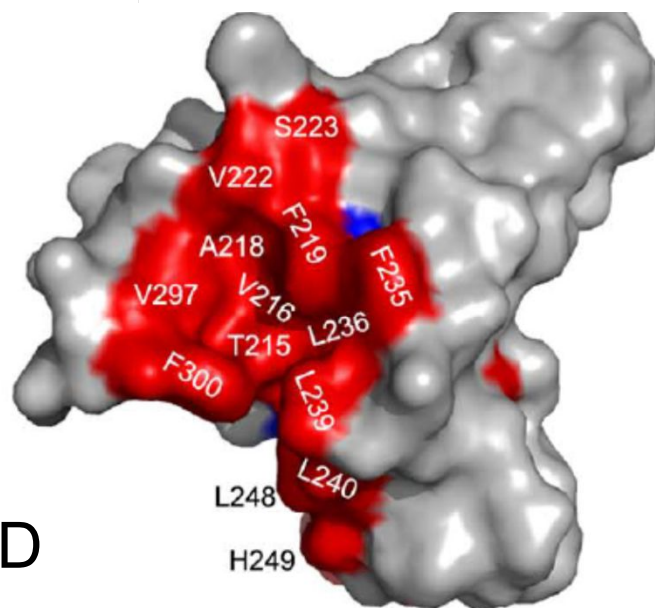
**NSE4b
(114-126)
(modelling)**



**NSE3 WHB
anterior pocket
(3NW0)**



WHD



HADDOCK

Software web portal

Home HADDOCK Whisky CPORT DNA SQUEEZE Publications HADDOCK news Contact

WELCOME TO THE UTRECHT BIOMOLECULAR INTERACTION WEB PORTAL >>

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.

PROFILE >>



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

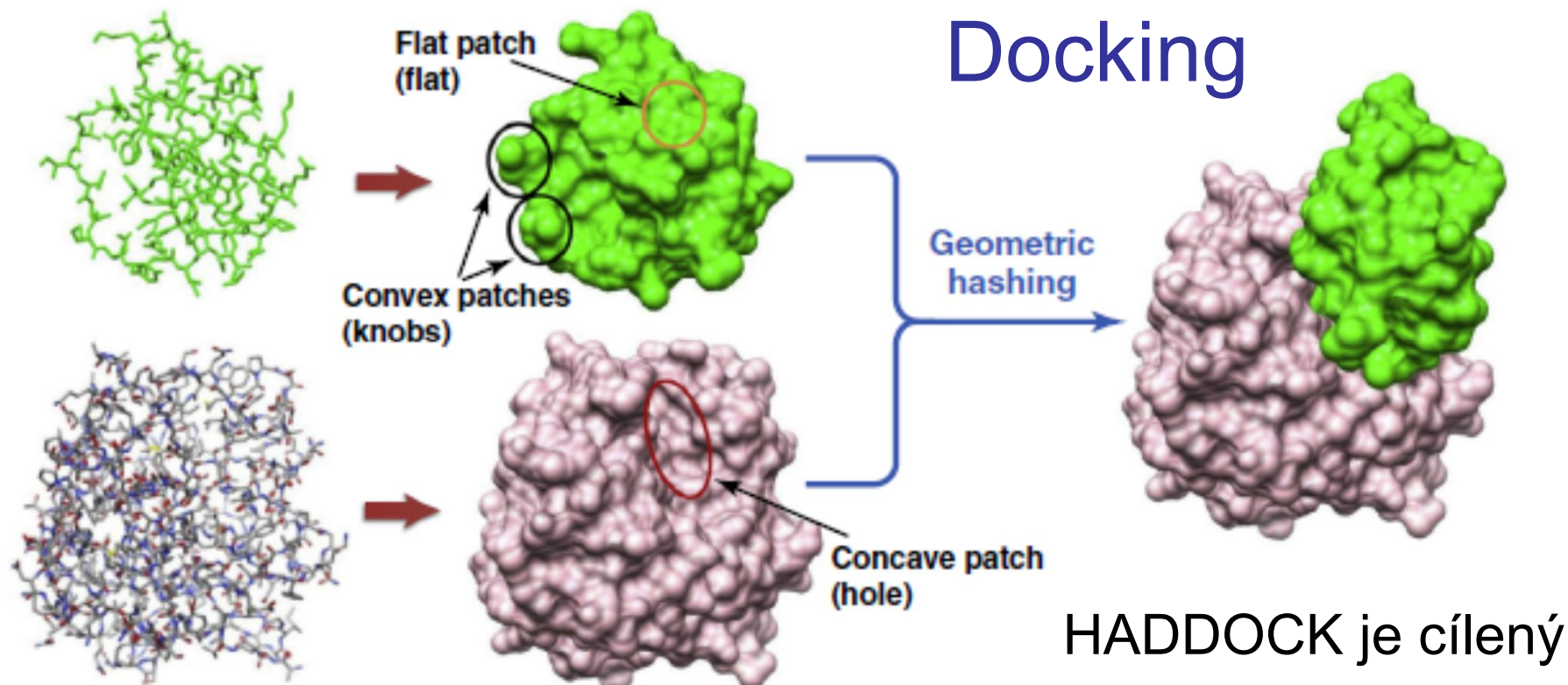
Interakce
mapována
mutagenezí

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

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]



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

MAGEA4

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

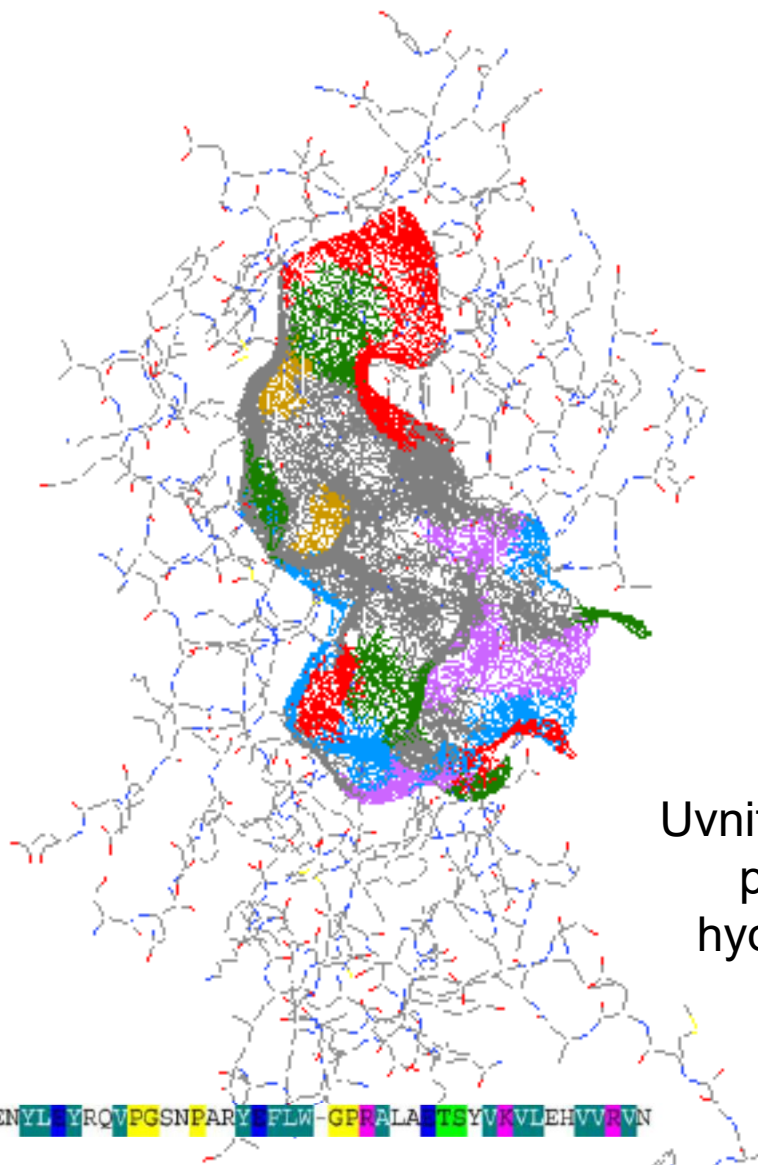
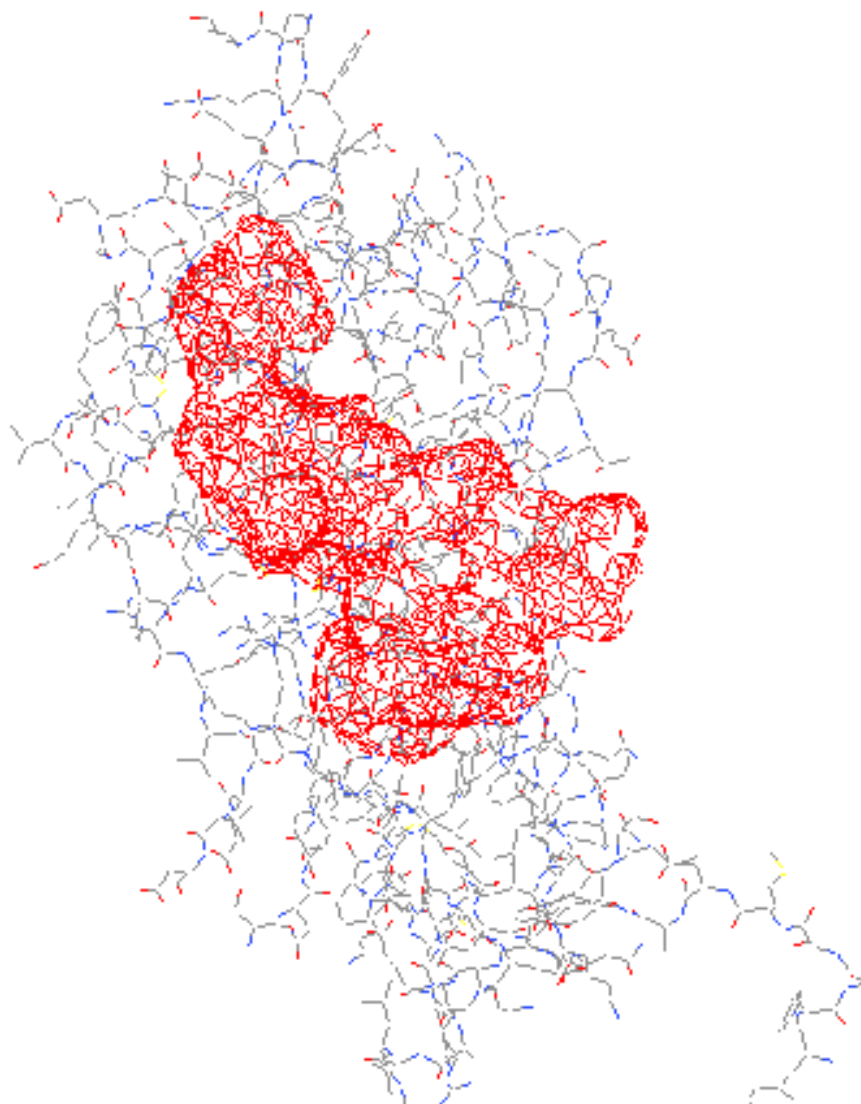
<http://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/pdbsum/>

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

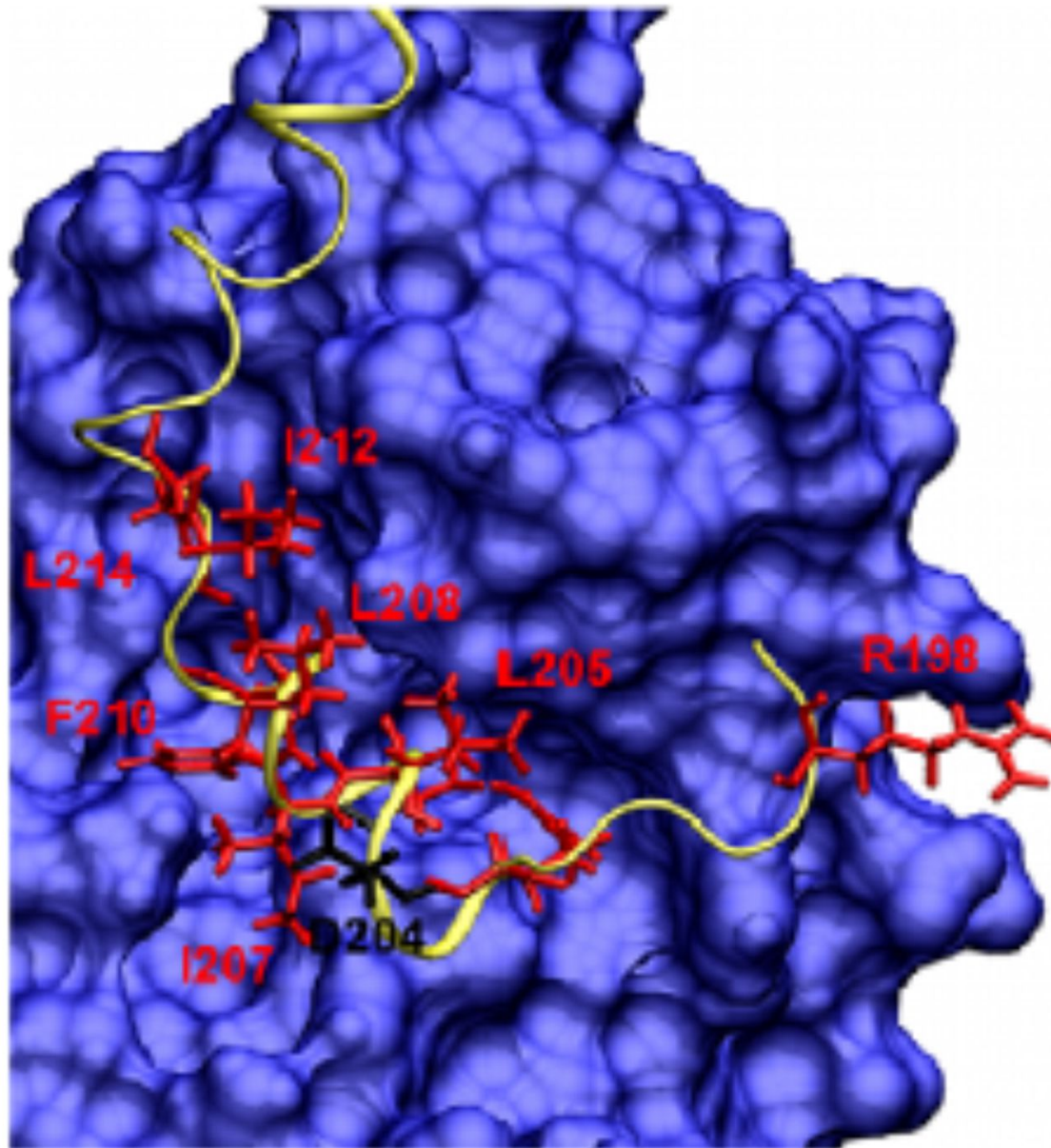
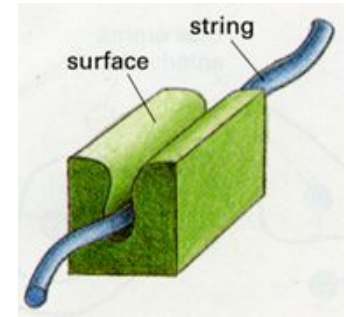
Binding surface



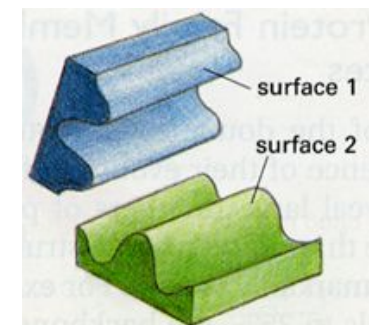
Uvnitř kapsy
převládá
hydrofobní
povrch

A4 GLLIIVLCTIAMEGDSAS-EEIWEELGVWGVYDGREHTVYGF-RKLLTQDWVQENYLNRQVPGSNPARYFLW-GPRALANTSYWVLEHVVRVN

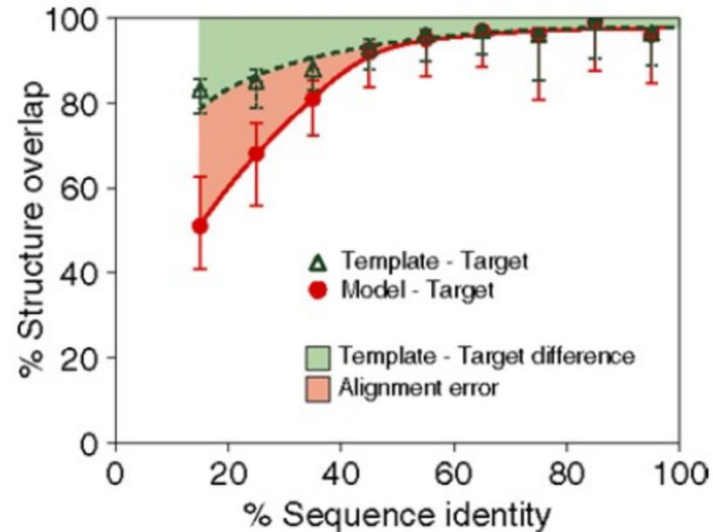
Residue-type colouring						
Positive	Negative	Neutral	Aliphatic	Aromatic	Pro & Gly	Cysteine
H,K,R	D,E	S,T,N,Q	A,V,L,I,M	F,Y,W	P,G	C



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



Modelování proteinů na základě homologií (*de novo* obtížné)



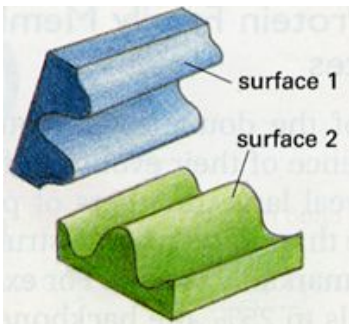
mít struktury všech proteinů (proteom)
nestačí – struktury interagujících
proteinů/komplexů (interaktom/komplexom)
přináší informaci o molekulárních detailech
buněčných procesů

Dr. T. Klumpler

Modelování proteinových komplexů = dockování také na základě podobností (*de novo* ještě obtížnější)

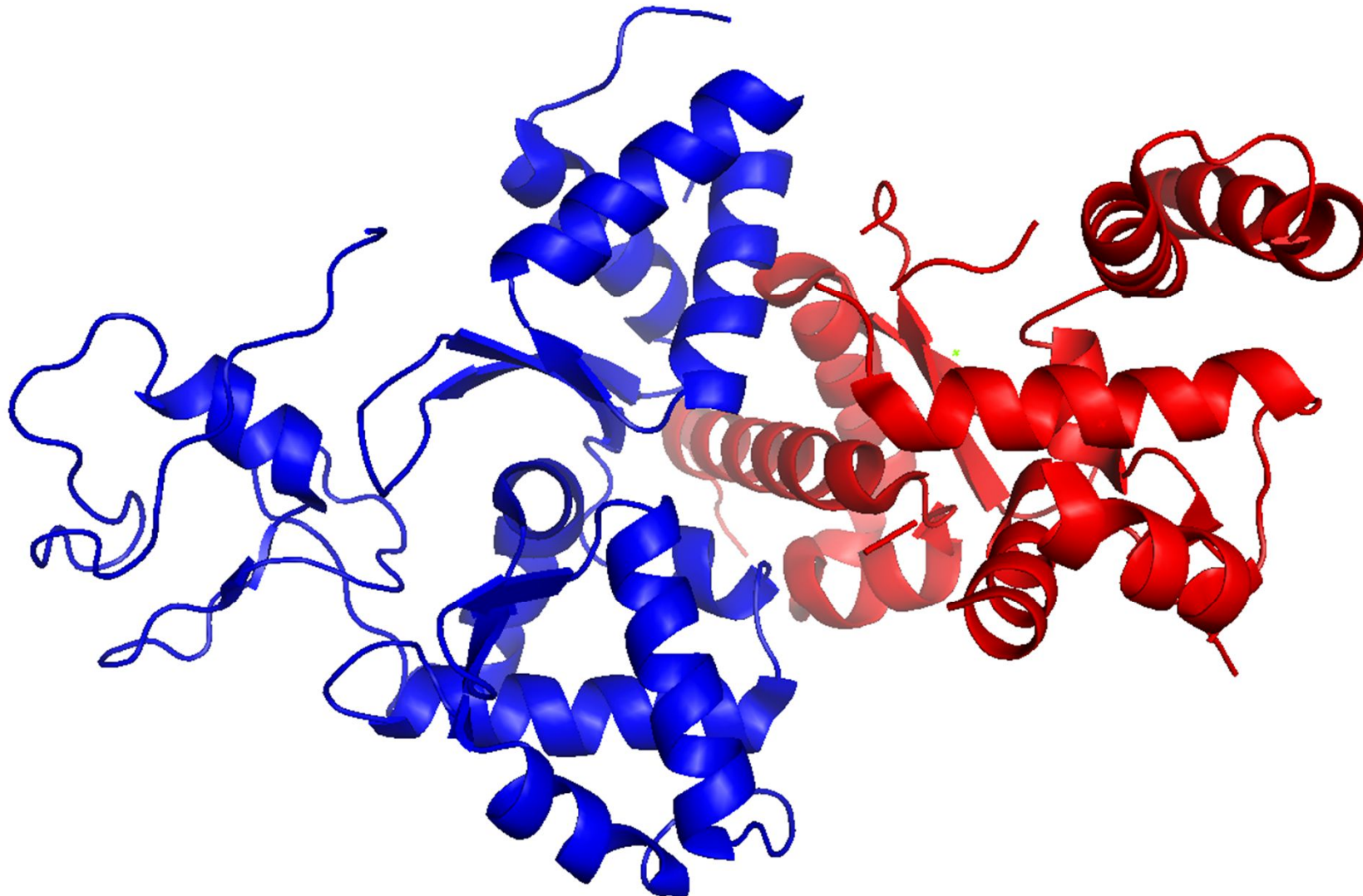
Kde najít další info o interakcích? V kterých organismech spolu dané proteiny interagují?

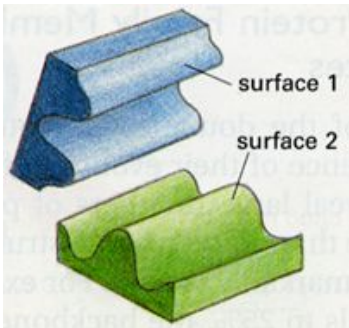
**CG031 – cvičení z modelování proteinových komplexů
(jarní semestr - Doc. Jan Paleček)**



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

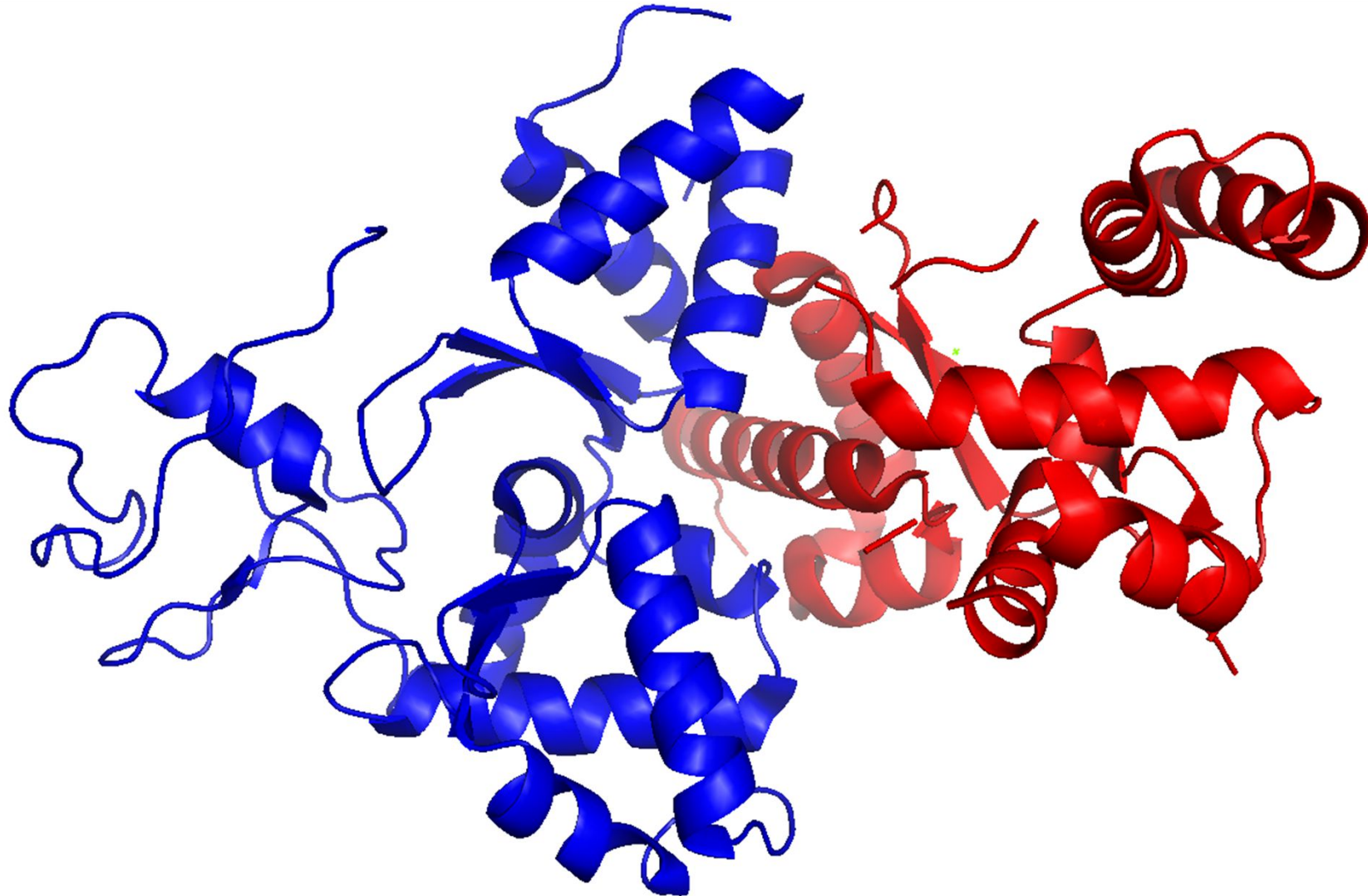
(kokrystal NSE1-NSE3 proteinů)





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

(kokrystal NSE1-NSE3 proteinů)

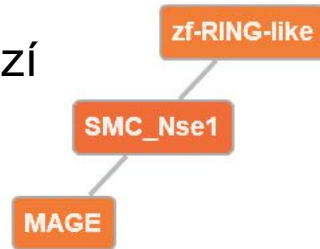


Domain SMC_Nse1 (Pfam: PF07574.11)

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)

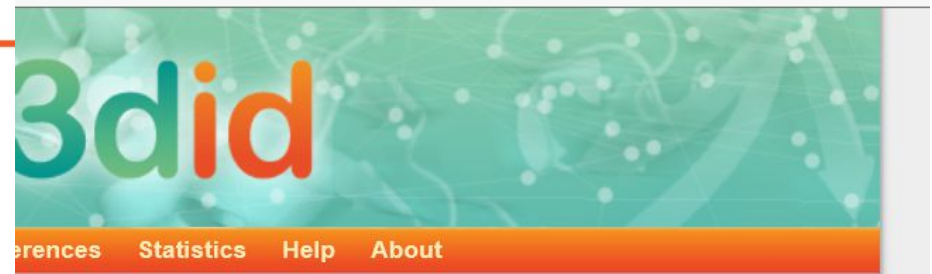
MAGE

zf-RING-like

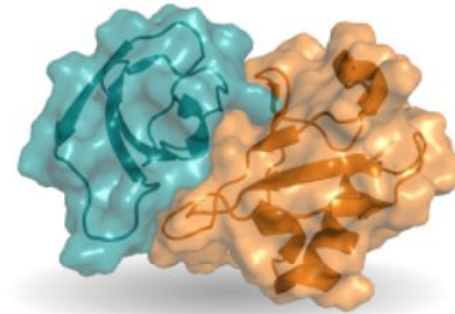
Search motif by name or keyword: ?

Motif name (e.g. SH2_LIG_0)

Search motif



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

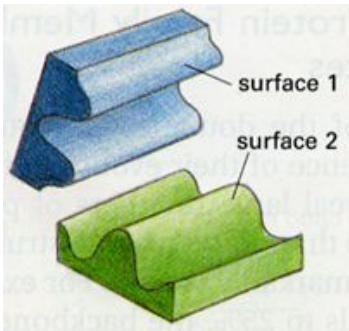


- > **Overview** General information on 3did
- > **Getting Started** Help for new users
- > **Technical Information** Linking to 3did
- > **Download** data files or MySQL tables

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

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

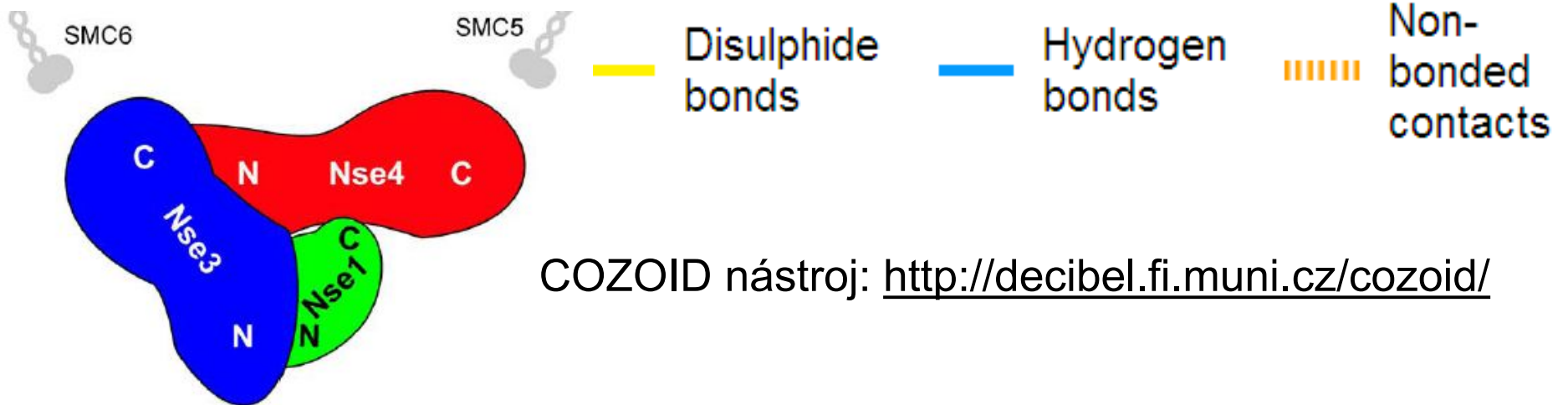
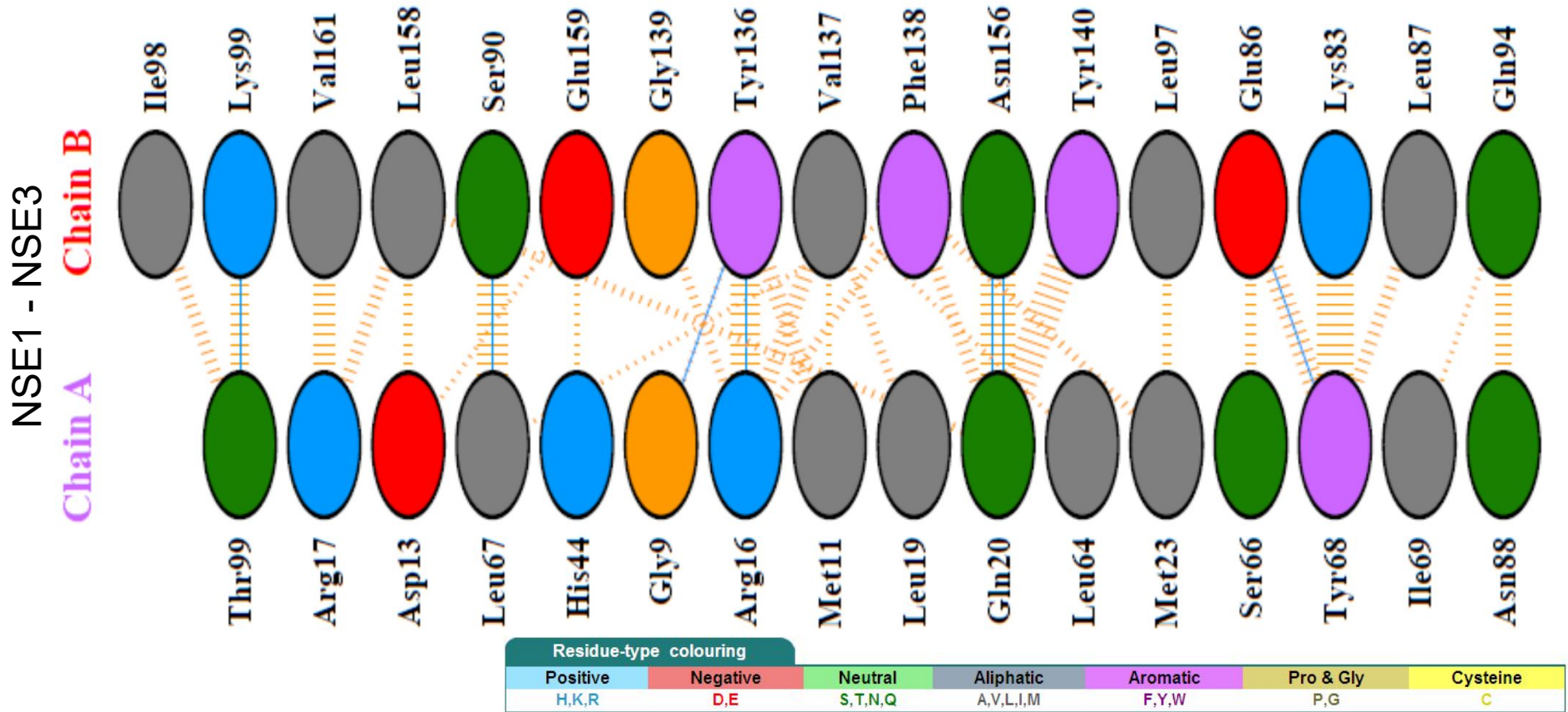
Chains A and B highlighted (click to view)

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	-	-	7	100

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

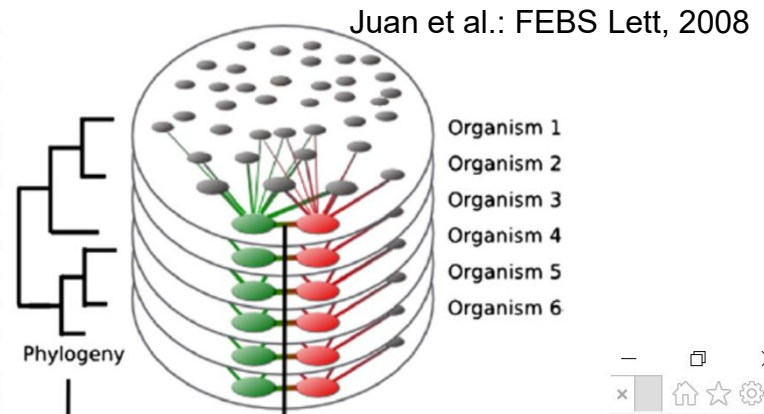


COZOID nástroj: <http://decibel.fi.muni.cz/cozoid/>

```

A1CCH2_ASPCL/14-216   NRAFLQAFM.ARSTMTFAEAKPVLAALIF.SAH.....
A2Q7K6_ASPNC/15-218   NRAFLQAFM.ARSTMTFTQAKPVLAALIF.SIR.....
B8NLA5_ASPFN/14-216   NRAFLQAFM.ARSTMTFAEARPVLAALIF.SVH.....
B6QTR9_TALMQ/14-217   NRAFLQAFM.ARSTMTFDEAKPVLAALIF.SAQ.....
V5FED6_BYSSN/14-236   NRAFLQAFM.ARSTMTFEEAKPVLAALIF.SAHGAQSTIFFDS
S7Z8E9_PENO1/8-209    HRAFLQAFM.ARSTMTFEDAQPVLAAII.SAH.....
B6H9Q9_PENRW/8-210    NRAFLQAFM.ARSCMTFEDAQPILAAIL.TVS.....
H6C926_EXODN/14-207   NRAFLQAFM.ARSVLTLETAKPILAALIS.TFQ.....
U1GD89_ENDPU/11-202   NRAFLQAFM.ARSTMTYEQAKPVLAALIF.SAR.....
C5GY37_AJEDR/11-207   HRAFLQAFM.ARSTMTYEQAKPVLAALIF.SAR.....
C6H5E2_AJECH/11-203   HRALLOAFM.ARSTMTYEQAKPVLAALIF.TAR.....

```



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

Navigation: Najít: plot | Předchozí | Další | Možnosti


Family: SMC_Nse1 (PF07574)

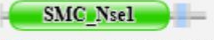
16 architectures | 522 sequences | 2 interactions | 443 species | 1 structure


- 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
[N5E1_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.

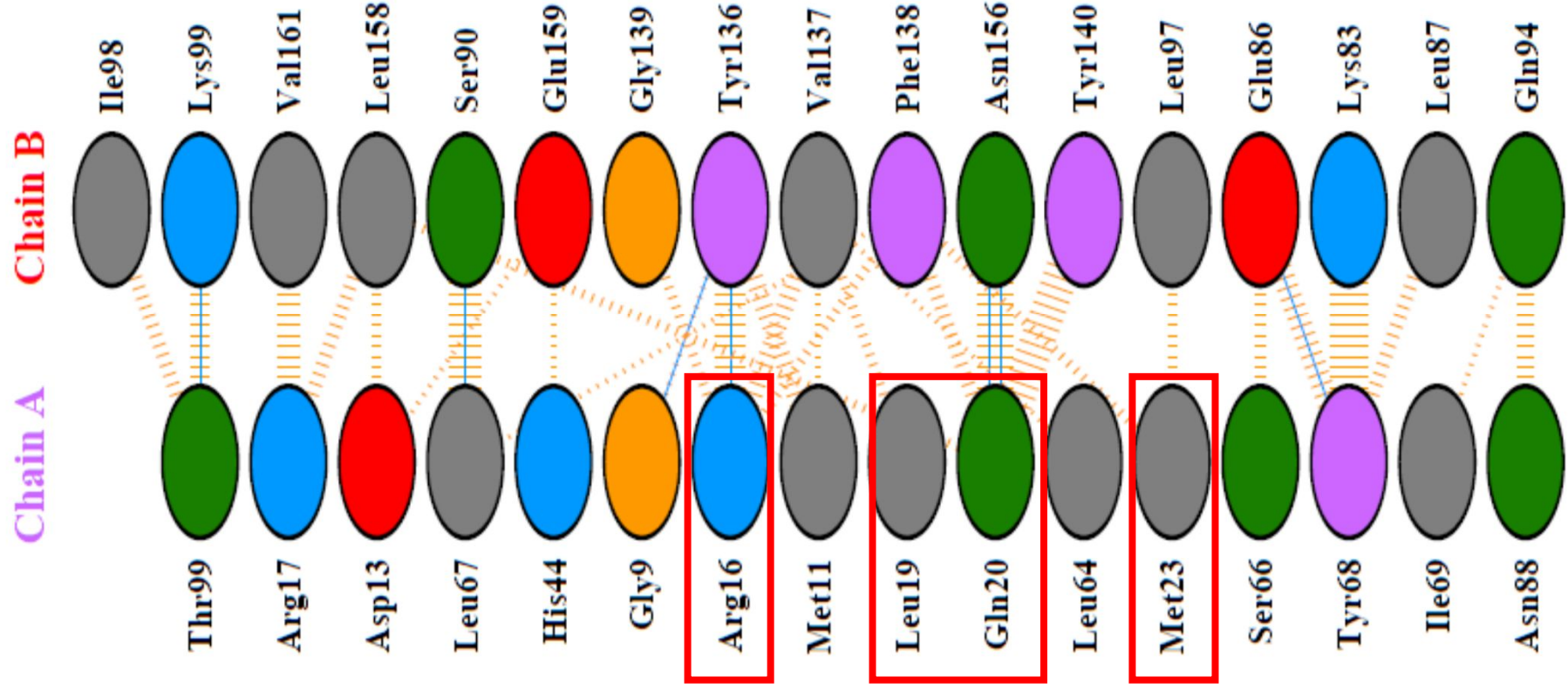
There are 2 sequences with the following architecture: DAO, SMC_Nse1, zf-RING-like
[B8MNY1_TALSN](#) [Talaromyces stipitatus (strain ATCC 10500 / CBS 375.48 / QM 6759 / NRRL 1006) (Penicillium stipitatum)] FAD dependent oxidoreductase superfamily {ECO:0000313|EMBL:EEF14320.1} (744 residues)

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...DEVE
H6C926_EXODN/14-207	NRAFLQAFM	ARSVLTLETAKPILAALIS.TFQ.....DG.....REVQP...QDMTV
U1GD89_ENDPU/11-202	NRAFLQAFM	ARSTMTFEEAKPVLAALIF.SAH.....EG.....REILP...NDITE
C5GY37_AJEDR/11-207	HRAFLQAFM	ARSTMTYEQAKPVLAALIF.SAR.....DH.....QDTLP...EDITQ
C6H5E2_AJECH/11-203	HRALLQAFM	ARSTMTYEQAKPVLAALIF.TAR.....DN.....QETLP...EDITQ
F2PT91_TRIEC/10-199	HRAFLQAFM	SRSTMTLEEAKPVLAALIF.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	ARSSMTGEEELGVTAIH.GVE.....NPEEP...TETTL
S8AAF4_DACHA/9-208	HRTFLQALL	IRPFIDIEEGQELLAALIA.SAE.....SG.....TDVPA...NSITV
G1X2Y0_ARTOA/8-207	HRAFLQALL	IRPFIDVQEGRELLAAIK.SAE.....AG.....SDVSI...ESVPP
C5DCF6_LACTC/23-226	SKFLLQYVL	RRGVCSEKALAKAKKTL.....ERDG.....EQLEDSETE
C5DQF6_ZYGRC/37-240	ARYLLQYLL	CRGICHENMLLVLDKL.....QK.....YTQDPTSQVCS.T
I2H1A9_TETBL/24-252	RHLLRYIM	SEGICHENMLLLALYAL.....NLDYSGDCQQEVLA.....
G8C139_TETPH/22-276	RYLLQYLL	CGICNESFMLLALMRLH.....LTDGSSSDDFYRLNMVELN
G8ZVJ6_TORDC/16-236	RIVLQYIL	SRGIVGENILLALMRL.....QGDT...ETND...VQELY
H2ATC7_KAZAF/7-237	BRYLLQYIL	ARGICHENALVVALMRL.....YMDL...GCFDDAWQIDQWL
J5S7B7_SACK1/17-253	TRYLLQYIL	ARGICHENNLILALMKL.....ETDA.....SKWSTEQWT
E7NKI9_YEASO/18-258	AKYLLQYIL	ARGICHENALILALMRL.....ETDA...STLNTXSIQQWV
J8PZG2_SACAR/18-258	AKYLLQYIL	ARGICHENALILALMRL.....ETDA...LRFDAERSMQQWI
G0W7Y8_NAUDC/22-268	BRYLLQYIL	ARGVCHENALVVALMRL.....KVDS...NTIDPQWTISDWL
G0V5G7_NAUCC/25-272	BRYLLQYIL	ARGVCHENALMLALMRL.....KVDS...HDVNAHWTISDWL
J7S9R2_KAZNA/85-303	RYLLQYIL	ARGVCHENSLLAALMHL.....SLDLDPHSVSTR.SLDEWS
A7TJ64_VANPO/8-260	BRYLLQYLL	CRGICHENALLLVLIKL.....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

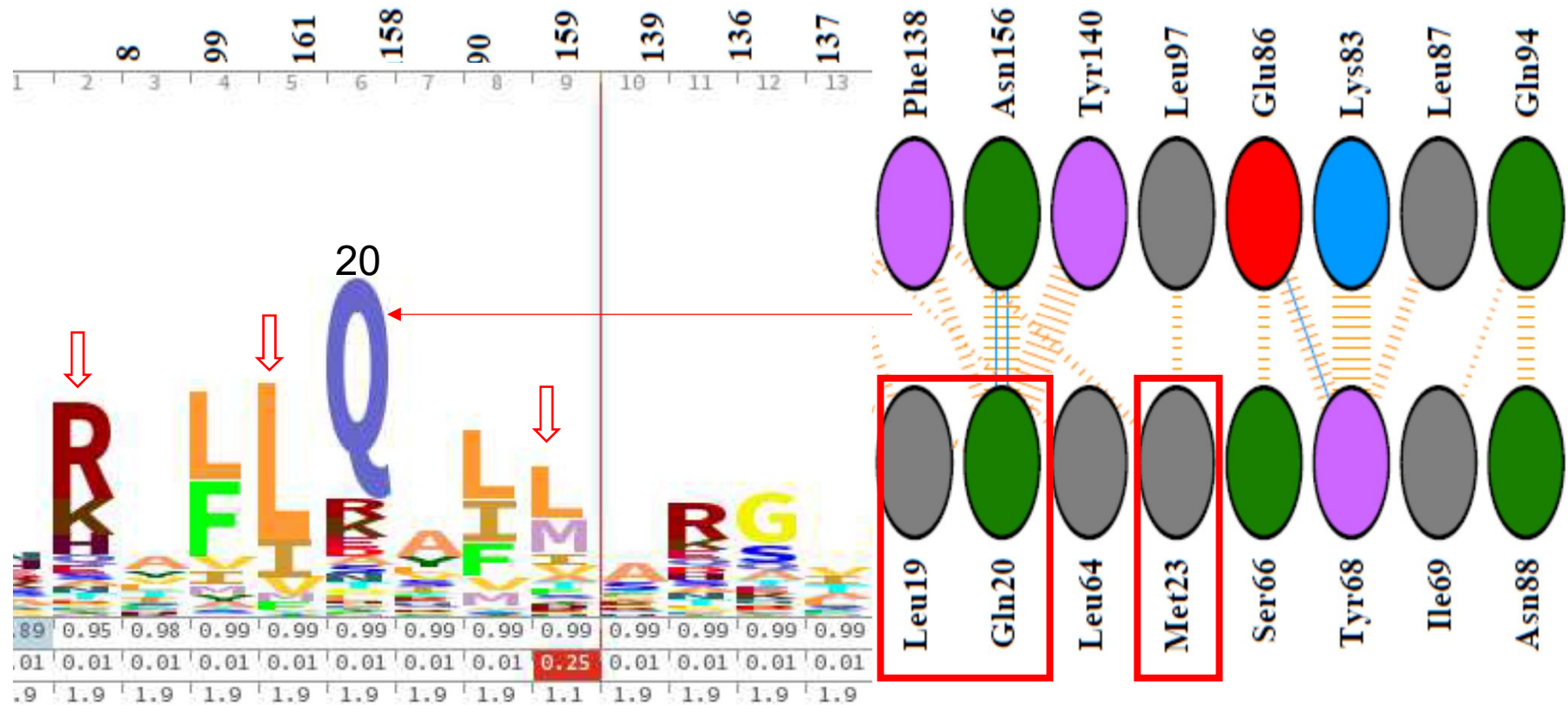
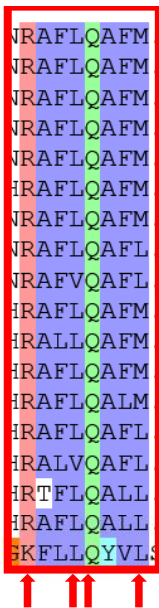
A1CCH2 ASPCL/14-216	NRAFLQAFM	ARSTMTFAEAKPVLA	AIF.SAHEGQPVSA	...DDVTE
A2Q7K6 ASPNC/15-218	NRAFLQAFM	ARSTMTFTQAKPVLA	AIF.SIRDDEQVSP	...EDITE
B8NLA5 ASPFN/14-216	NRAFLQAFM	ARSTMTFAEARPVLA	AIF.SVHEGEPVSA	...EDVTE
B6QTR9 TALMQ/14-217	NRAFLQAFM	ARSTMTFDEAKPVLA	AIF.SAQENREVLA	...EDITQ
V5FED6 BYSSN/14-236	NRAFLQAFM	ARSTMTFEEAKPVLA	AIF.SAHGAQSTIFFDSS	YVEKEIANLYLATERRPVLA	...EDITQ
S7Z8E9 PENO1/8-209	HRAFLQAFM	ARSTMTFEDAQPVLA	AII.SAHEGRTVDP	...DEVTQ
B6H9Q9 PENRW/8-210	NRAFLQAFM	ARSCMTFEDAQPILA	AAIL.TVSEGRTVDP	...DEVGE
H6C926 EXODN/14-207	NRAFLQAFM	ARSVLTLETAKPILA	AIS.TFQDGREVQP	...QDMTV
U1GD89 ENDP/11-202	NRAFLQAFM	ARSTMTYEQAKPVLA	AIF.SARDHQDTLP	...EDITQ
C6H5E2 AJECH/11-203	HRAFLQAFM	ARSTMTYEQAKPVLA	AIF.TARDNQETLP	...EDITQ
F2PT91 TRIEC/10-199	HRAFLQAFM	SRSTMTLEEAKPVLA	AIF.TVSEGREILP	...GDITQ
E9DEJ9 COCPS/13-202	HRAFLQAFM	ARSTMTLNEAKPILA	AAIL.SVKDGREVL	...EDVTQ
R7Z157 CONA1/13-202	HRAFLQAFM	ARSVLTFEEAQPILA	AAIL.TAHEGRPTLP	...ADITT
U4LU38 PYROM/8-205	HRAFLQAFM	ARSSMTGEELLGVV	TAIH.GVENPEEP	...TETTL
S8AAF4 DACHA/9-208	HRTFLQALL	IRPFIDIEEGQELLA	AIA.SAESGTDVPA	...NSITV
G1X2Y0 ARTOA/8-207	HRAFLQALL	IRPFIDVQEGRELLA	AIK.SAEAGSDVSI	...ESVPP
C5DCF6 LACTC/23-226	SKFLLQYVL	RRGVCSEKALAKAL	KTLERDGEQLEDSETE




```

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...DEVTQ
B6H9Q9_PENRW/8-210   NRAFLQAFM ARSCMTFEDAQPILAAIL.TVS.....EG.....RTVDP...DEVGE
H6C926_EXODN/14-207  NRAFLQAFM ARSVLTLETAKPILAALIS.TFQ.....DG.....REVQP...QDMTV
U1GD89_ENDPU/11-202  NRAFVQAFM ARGTLTYETSKPLLASIF.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  HRAFLQALM ARSTMTLNEAKPILAAIL.SVK.....DG.....REVLV...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 IRPFIDIEEGQELLAALIA.SAE.....SG.....TDVPA...NSITV
G1X2Y0_ARTOA/8-207   HRAFLQALL IRPFIDVQEGRELLAAIK.SAE.....AG.....SDVSI...ESVPP
C5DCF6_LACTC/23-226  SKFLLQYVLRRGVCSEKALAKKTL.....ERDG.....EQLEDSETE

```





Structures Overview
Structure Selections
3D View Controls

Visualization



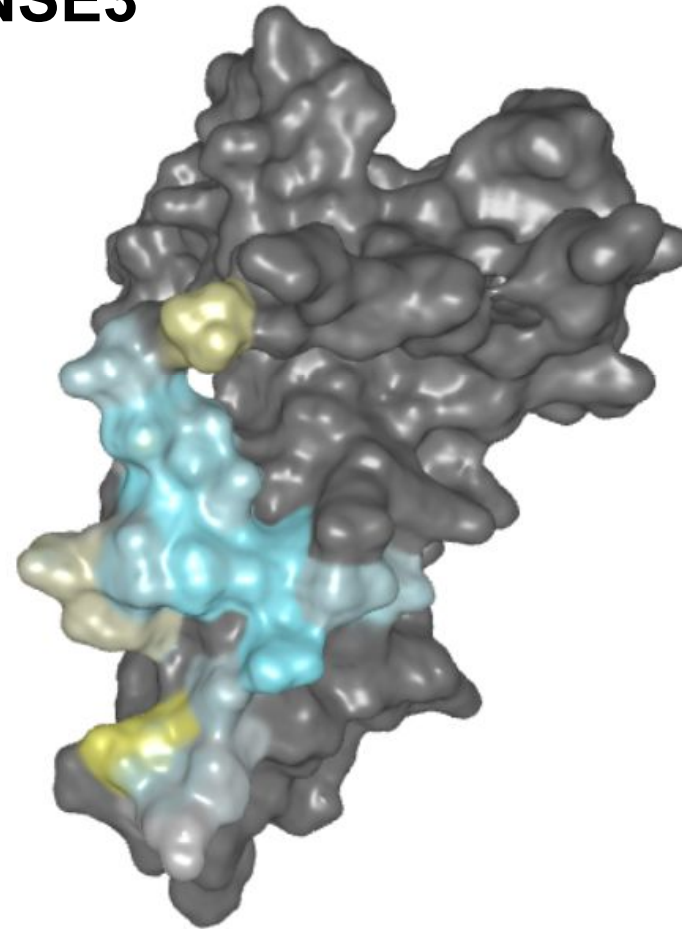
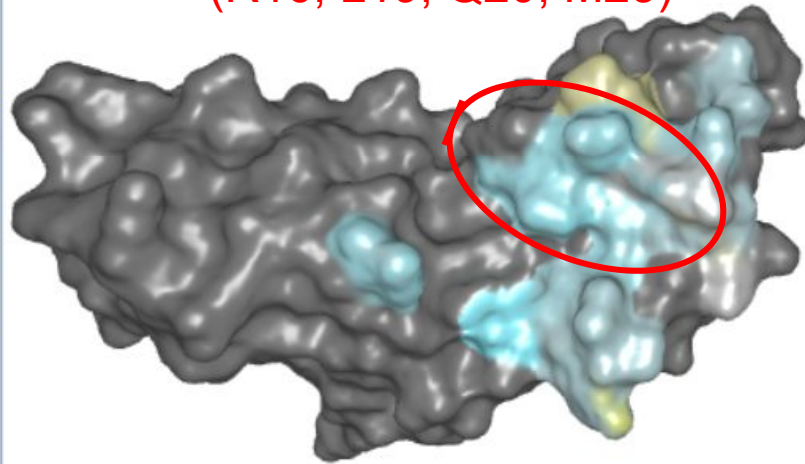
Residue Matrix

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

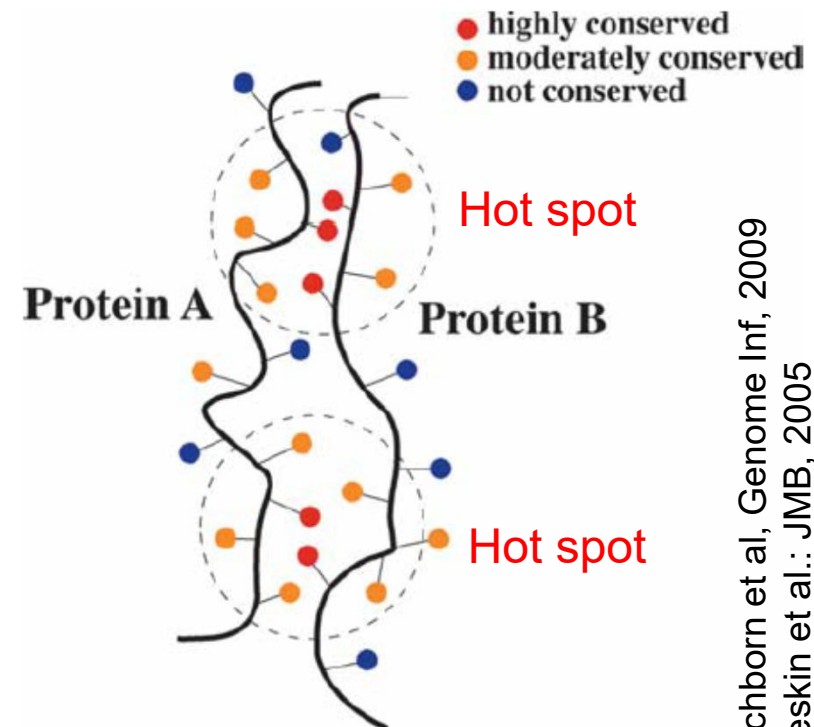
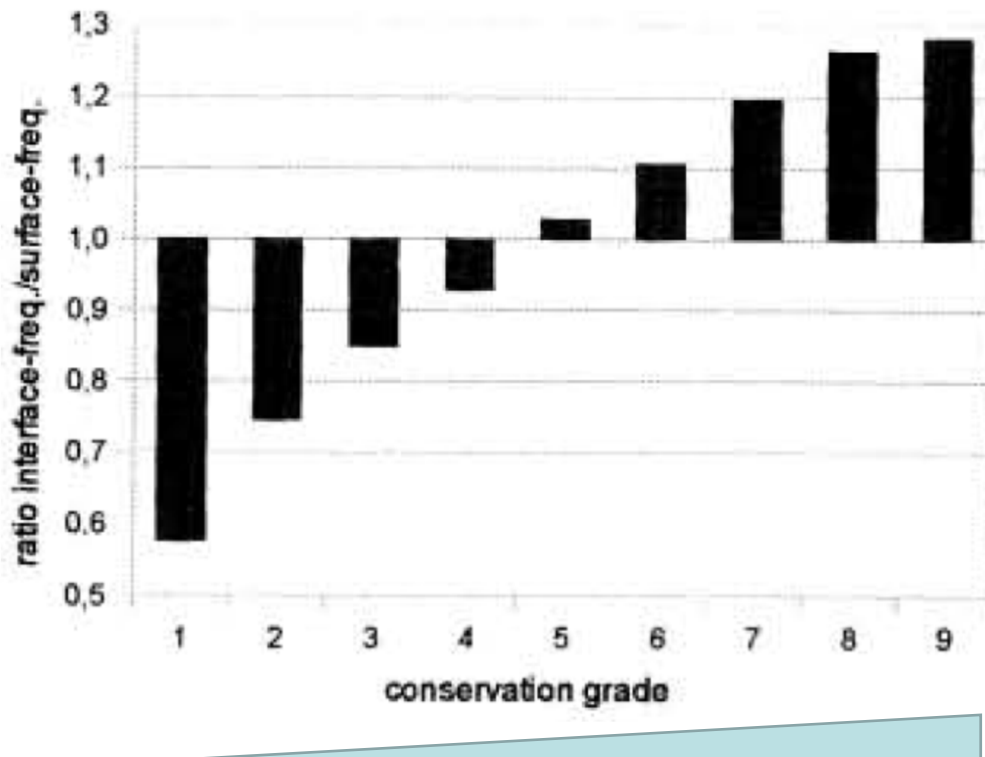


Structure Sequence x

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)





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	-

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 "Finley Lab" website, which is the "Center for Molecular Medicine and Genetics". The page lists "Finley Lab Interactions Databases" including *Drosophila Interactions Database (DroID)* and *Campylobacter jejuni Interactions Databases*. It also lists "Gene or Protein Interactions Databases in the research community" such as **BioGRID**, **DIP**, **IntAct**, **MINT**, **MIPS**, **Yeast Protein Interactions**, **BRITE**, **The PIM Database**, **Mouse Protein-Protein interactions**, and **Human Protein Reference Database**. The browser's taskbar at the bottom shows several open applications, including Microsoft Office, EndNote X1, and a nature journal article.

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 fází)

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

Více Dr. Potěšil

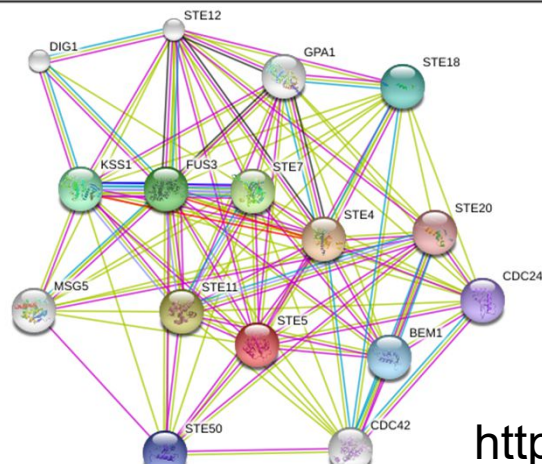
Informační zdroje PPI

Table 2. Databases Available for Searching and/or Downloading Data Related to Protein Interactions

Database	Proteins/Domains	Type	Number of Interactions
DIP ^a , LiveDIP	P	E,S	55,733
BIND ^a	P	E,C,S	83,517
MPact/MIPS ^a	P	E,C,F	15,488 (4,300) ^b
STRING	P ←	E,P,F	730,000 (proteins)
MINT ^a	P	E,C	71,854
IntAct ^a	P ←	E,C	68,165
BioGRID ^a	P ←	E,C	116,000 (30,000) ^b
HPRD	P	E,C	33,710
ProtCom	P,D	S,H	1,770
3did, Interprets	D	S,H	3,304
Pibase, ModBase	D	S,H	2,387
CBM	D	S	2,784
SCOPPI	D	S	3,358
iPfam	D	S	3,019
InterDom	D	P	30,037
DIMA	D	F,S	—
Prolinks	P	F	—

Table 3. URLs and Primary Citations for Protein Interaction-Related Databases

Database	URL/FTP
DIP [102], LiveDIP[103]	http://dip.doe-mbi.ucla.edu
BIND [105]	http://bind.ca
MPact/MIPS [97]	http://mips.gsf.de/services/ppi
STRING [119]	http://string.embl.de
MINT [120]	http://mint.bio.uniroma2.it/mint
IntAct [121]	http://www.ebi.ac.uk/intact
BioGRID [122]	http://www.thebiogrid.org
HPRD [123]	http://www.hprd.org
ProtCom [124]	http://www.ces.clemson.edu/compbio/ProtCom
3did [108], Interprets[125]	http://gatealoy.pcb.ub.es/3did/
Pibase [107], ModBase [126]	http://alto.compbio.ucsf.edu/pibase
CBM [26]	ftp://ftp.ncbi.nlm.nih.gov/pub/cbm
SCOPPI [111]	http://www.scoppi.org/
iPfam [127]	http://www.sanger.ac.uk/Software/Pfam/iPfam
InterDom [128]	http://interdom.lit.org.sg
DIMA [129]	http://mips.gsf.de/genre/proj/dima/index.html
Prolinks [104]	http://prolinks.doe-mbi.ucla.edu/cgi-bin/functionator/pronav/



STRING

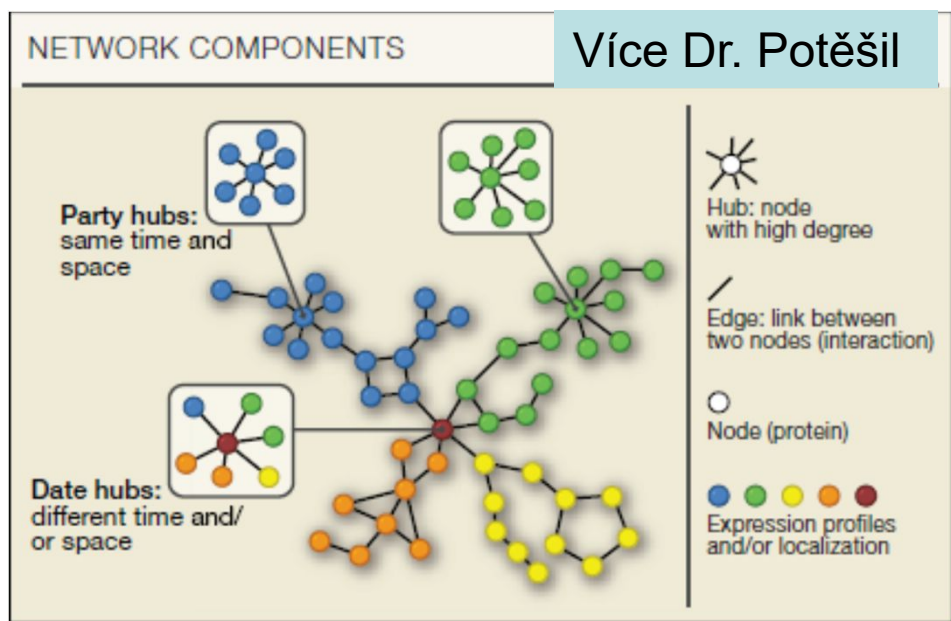
informace o binárních interakcích v databázích – zobrazeny jako síť (různé výsledky = různé čáry)

Shoemaker and Panchenko, PLoS Comp Biol, 2007

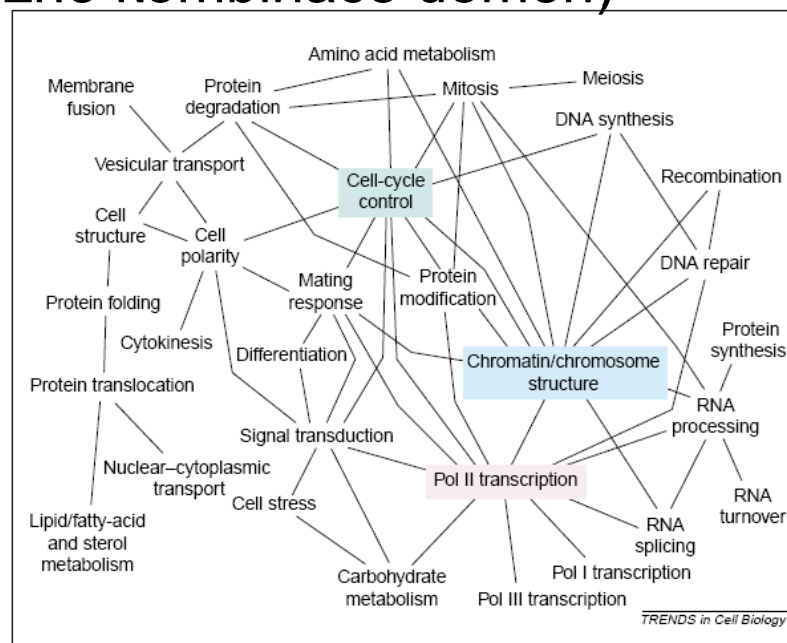
<http://string-db.org> Andreani and Guerois, ABB, 2014

Protein-proteinové interakce

- stabilní (velké plochy, většinou součástí komplexů)
- přechodné/slabé (součást dynamických procesů – předávání signálů, modifikace)
- posttranslační modifikace mohou změnit vazebné vlastnosti povrchu (fosforylace, metylace, SUMO)
- souhrn proteinových interakcí = **interaktom**
(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 ... je zprostředkován PPIs)

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

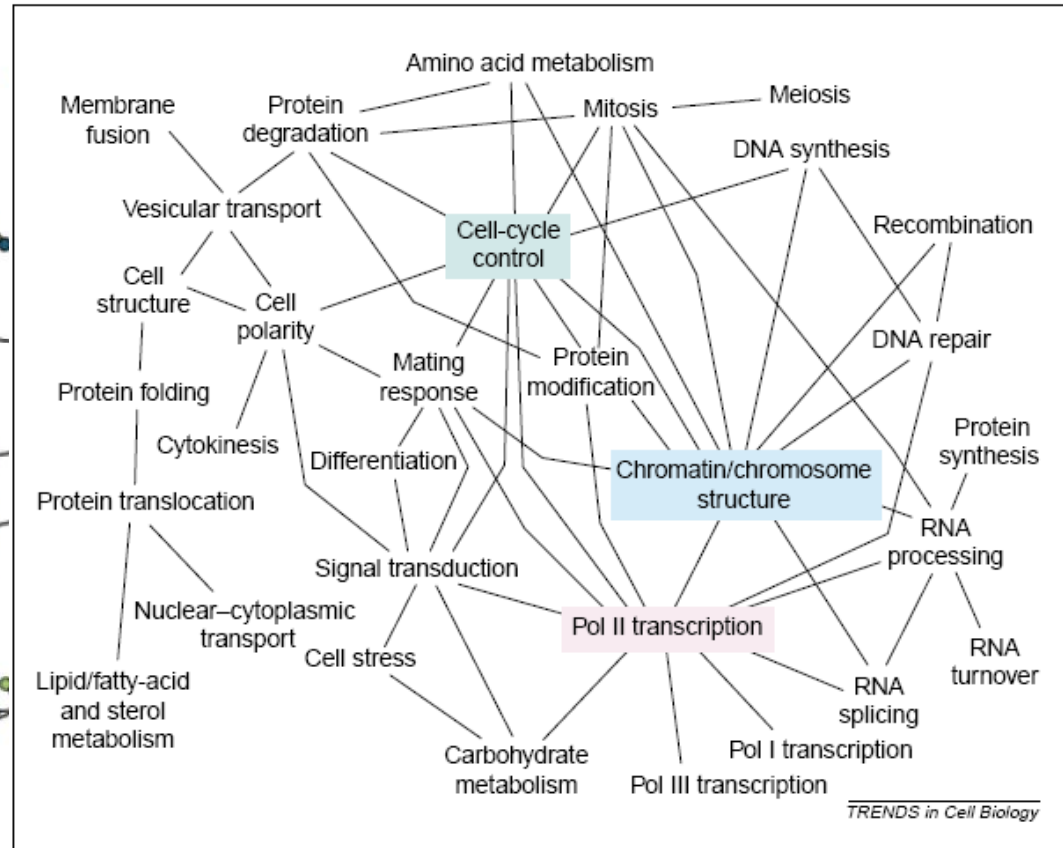
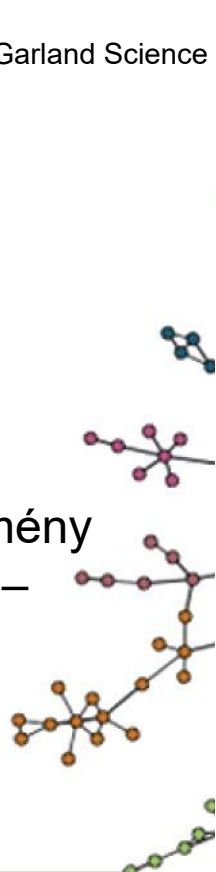
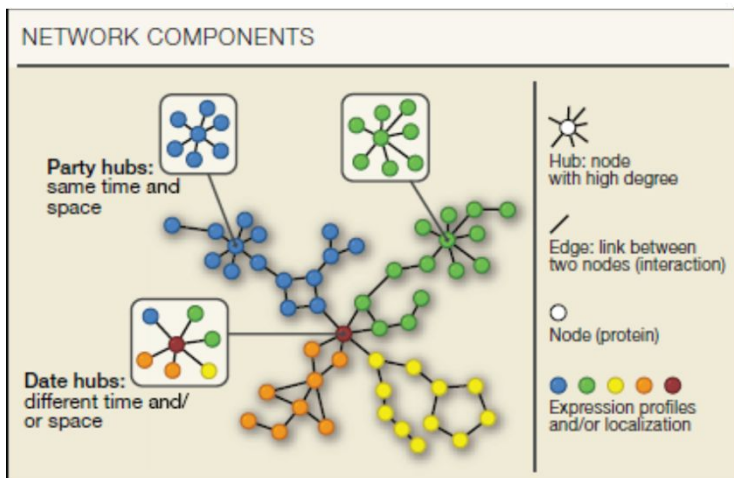
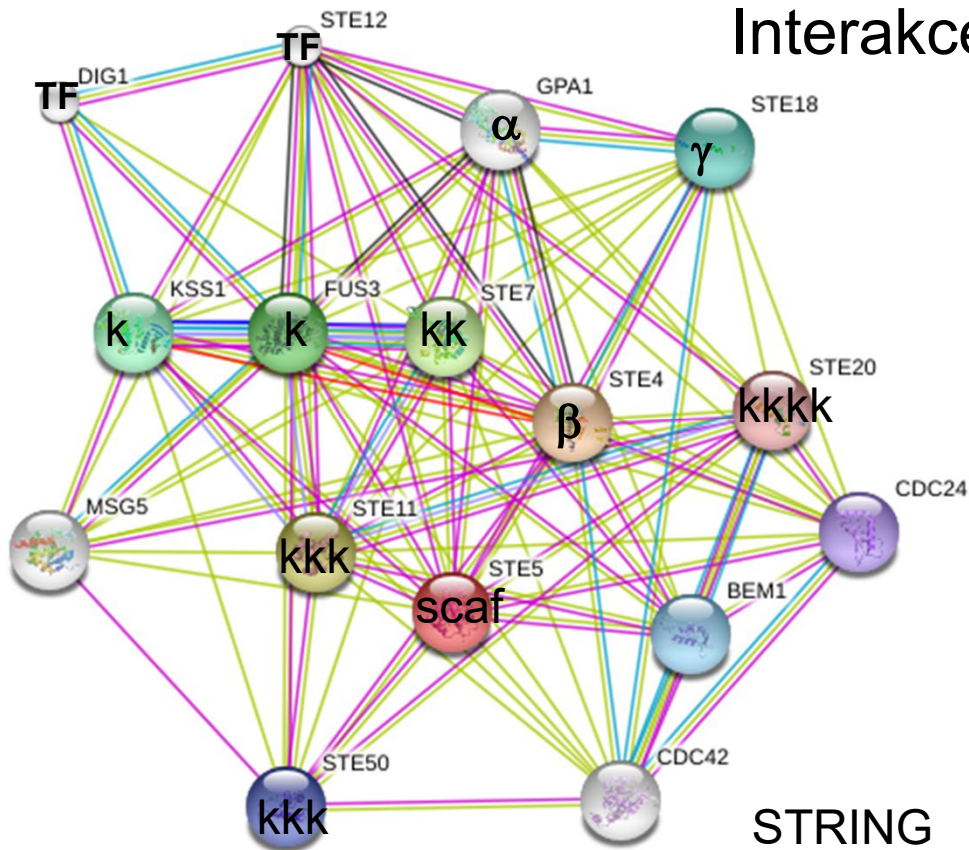


Fig. 2. Functional group interaction map based on Fig. 1 (modified from Ref. 10). Shown are interactions between functional groups of yeast proteins. Each line indicates that there are 15 or more interactions between proteins of the connected groups. Connections with fewer than 15 interactions are not 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.








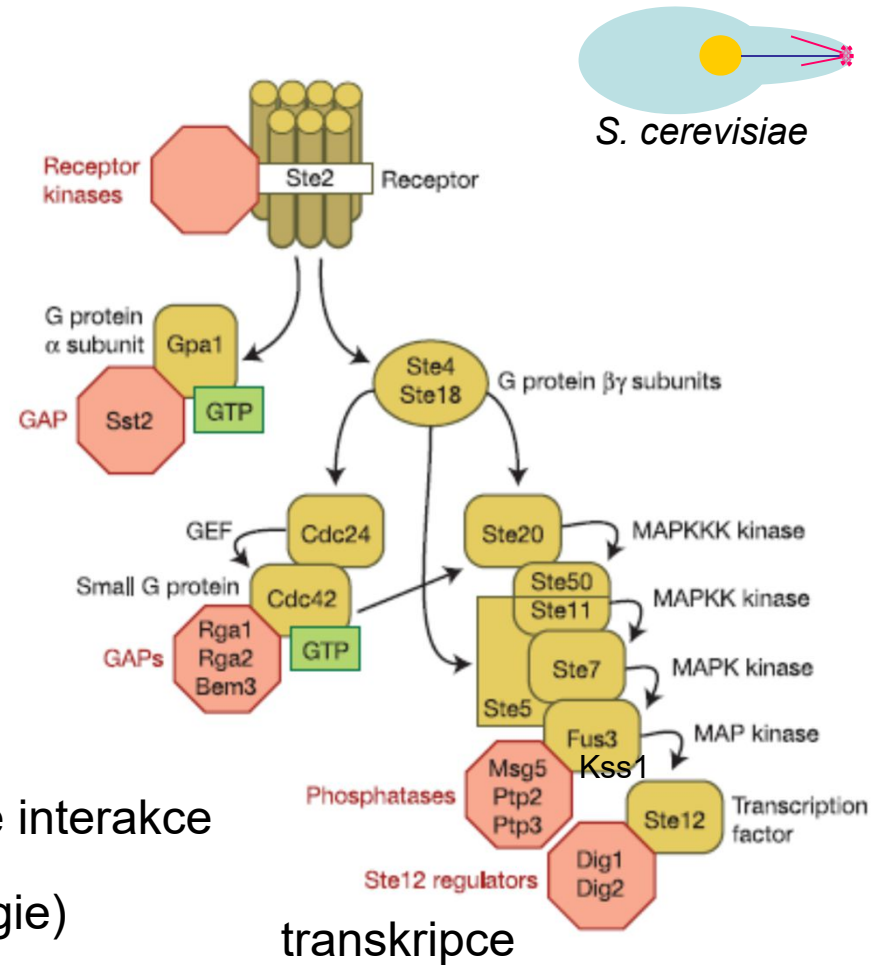
proteinové sítě – chybí info o posloupnosti, síle ... interakcí

Interakce x signální dráha



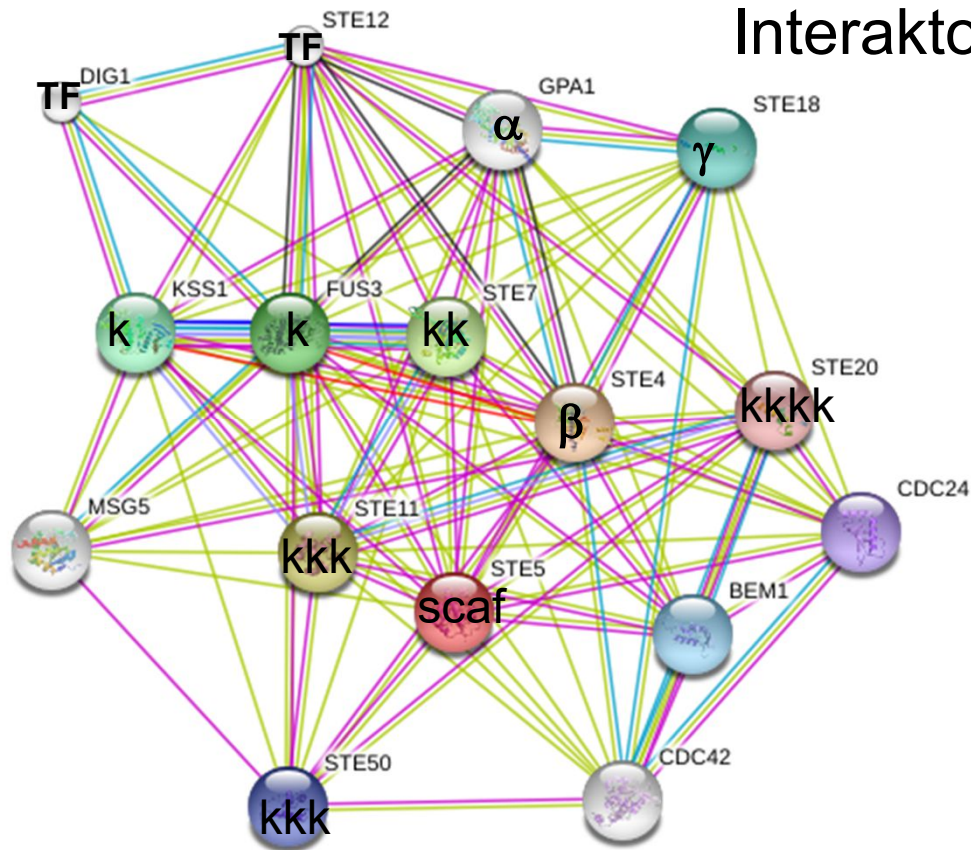
STRING

-  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



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

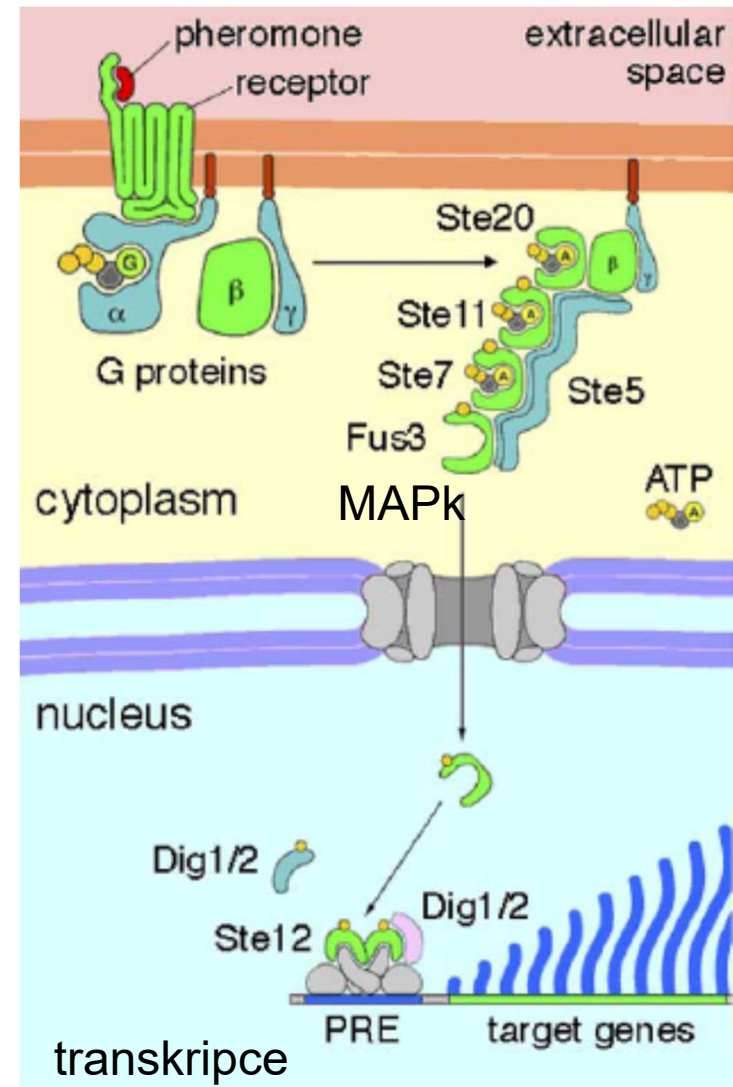
Interaktom x komplexom



-  Experiments
-  Databases
-  Textmining
-  Gene Fusion
-  Coexpression

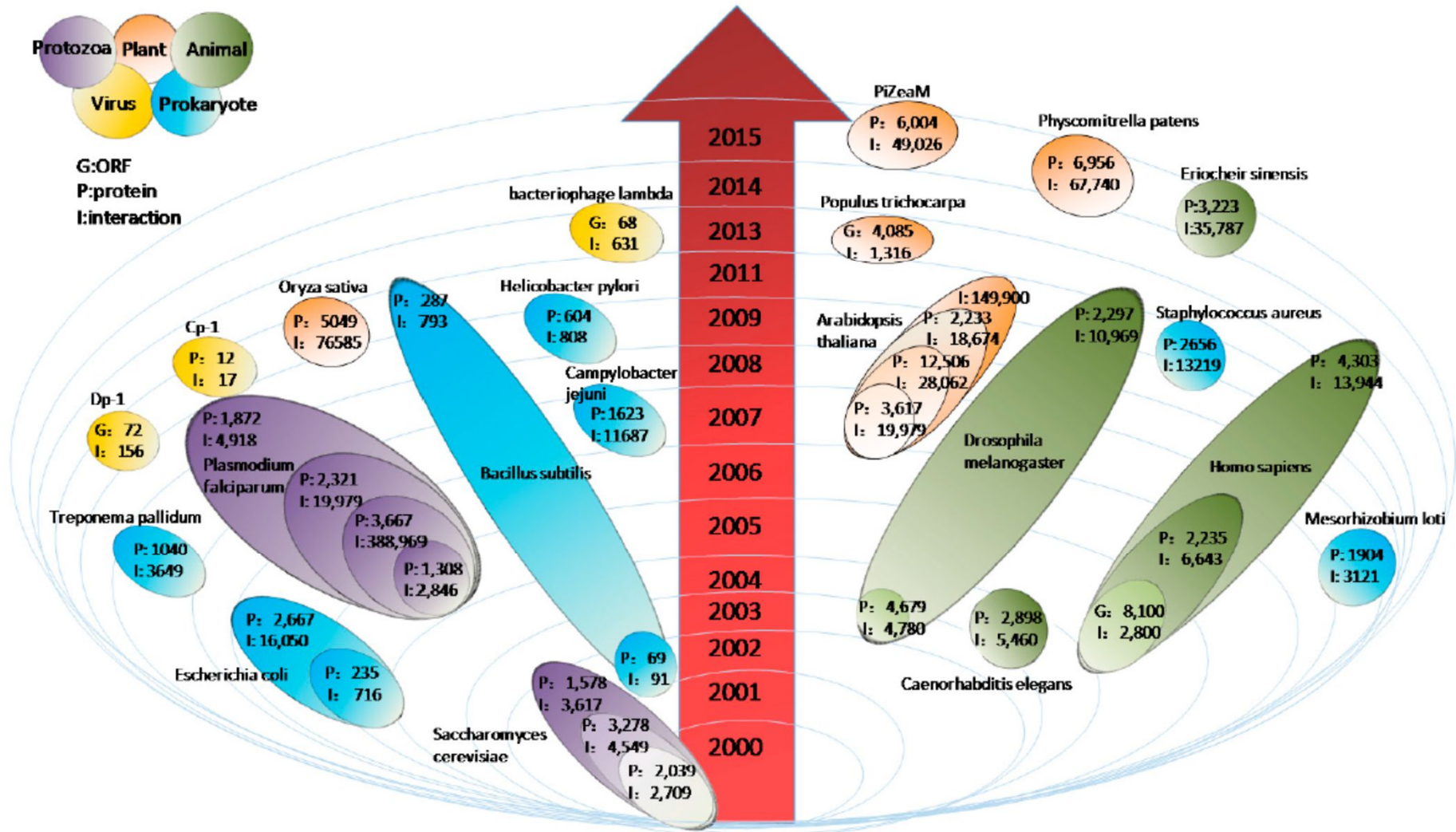
Síť neznamená komplex,
ale vztah

souhrn proteinových
komplexů = **komplexom**



Wang et al., Nature, 2004

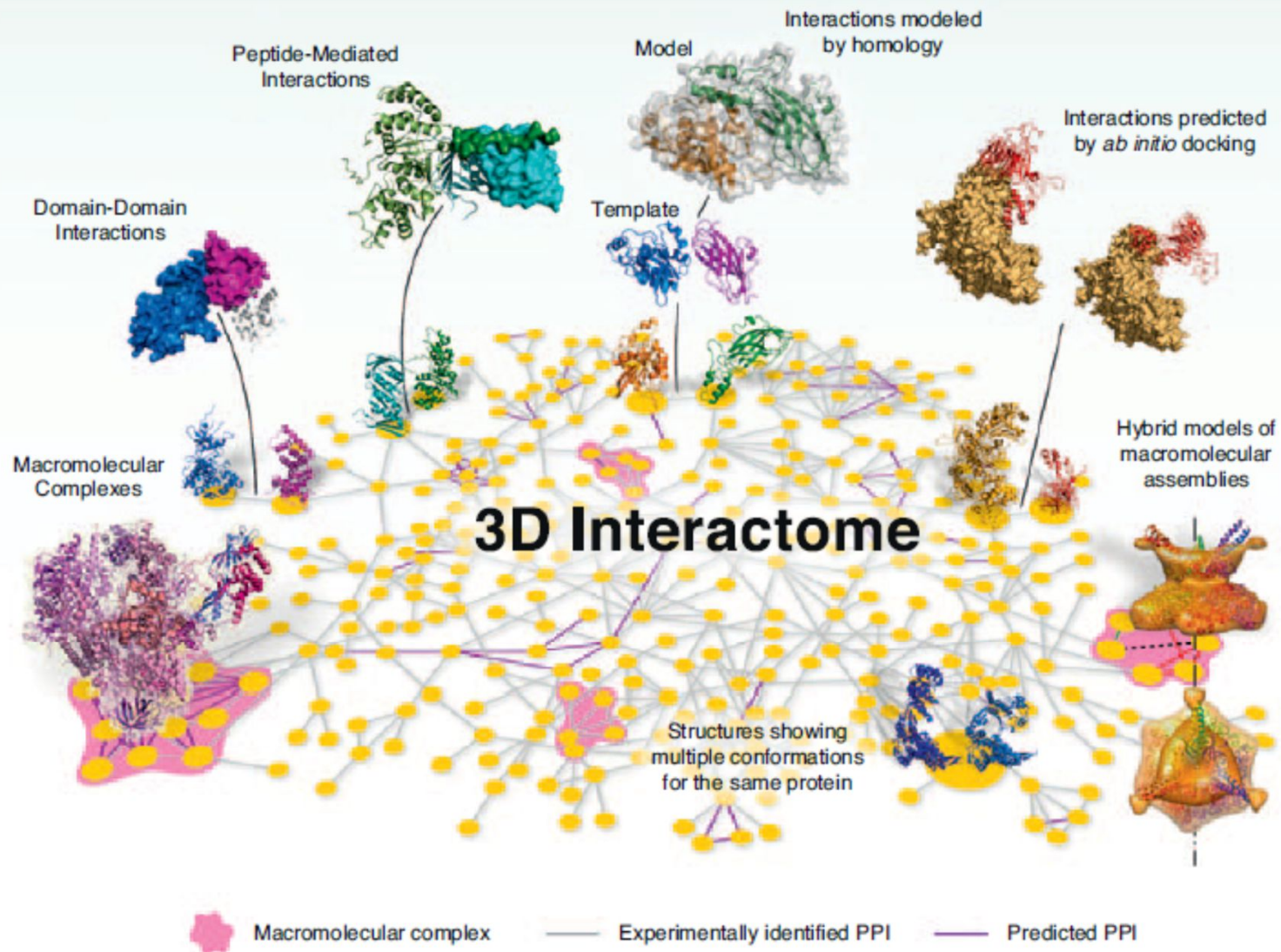
High-throughput screens – interaktomy organismů



Kvasinkový dvoj-hybridní systém
 TAP-tag s MS analýzou

Experimental Structures

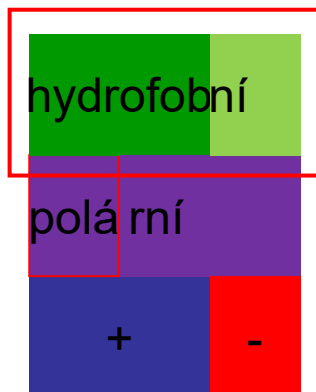
Computational Models



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

