

Protein subunit association: a social network

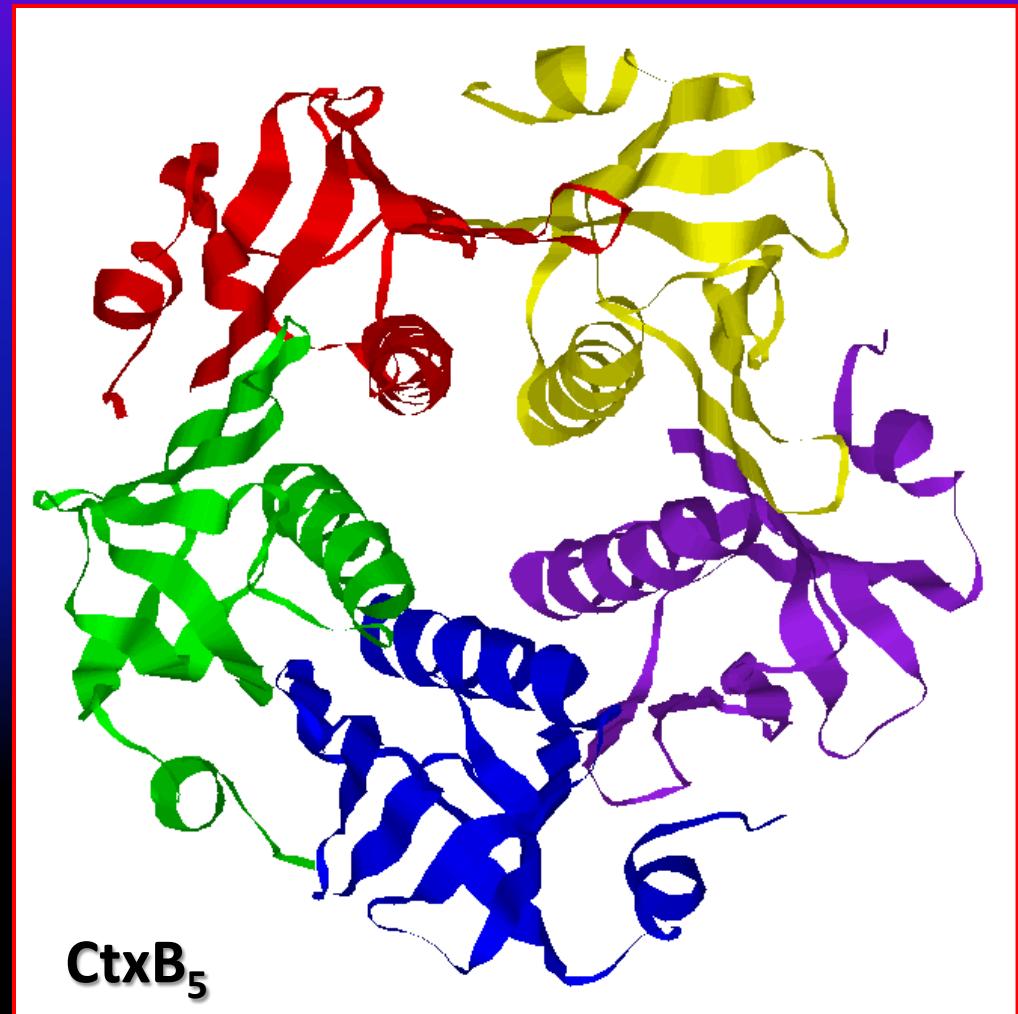
Mounia Achoch, Giovanni Feverati, Laurent Vuillon,
Kave Salamatian and Claire Lesieur



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Case of study: Protein oligomers

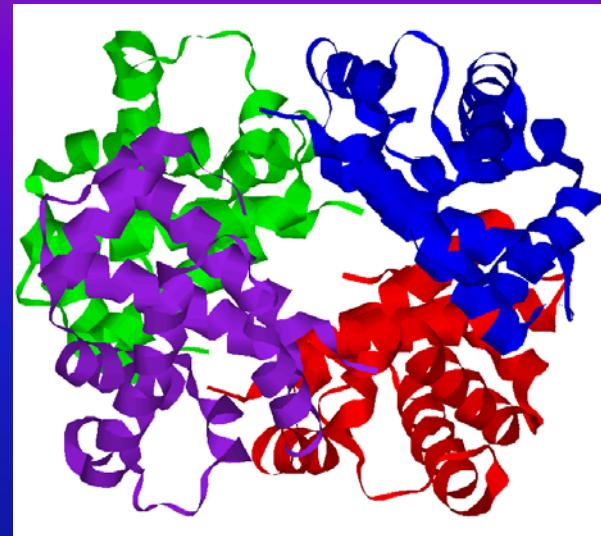
Cholera toxin B subunit pentamer



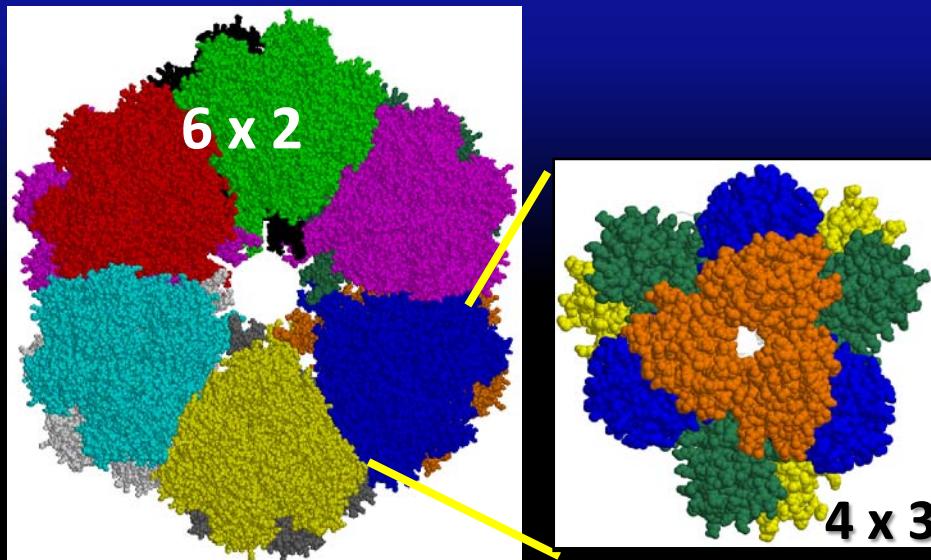
Protein oligomer flavors



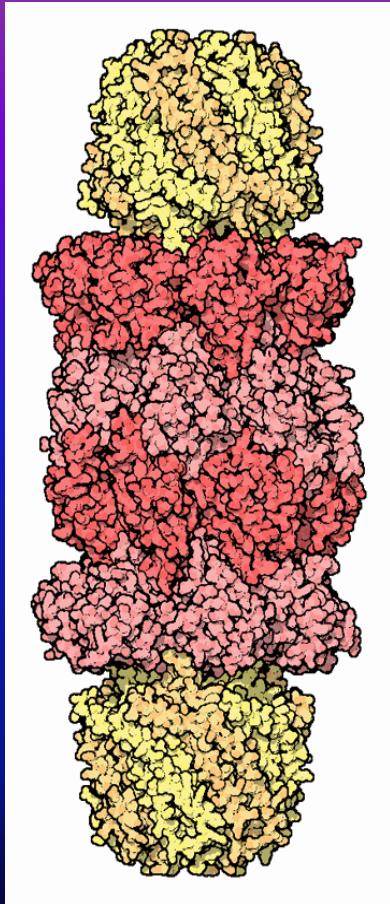
C2: rubisco from
Rhodospirillum rubrum (9rub)



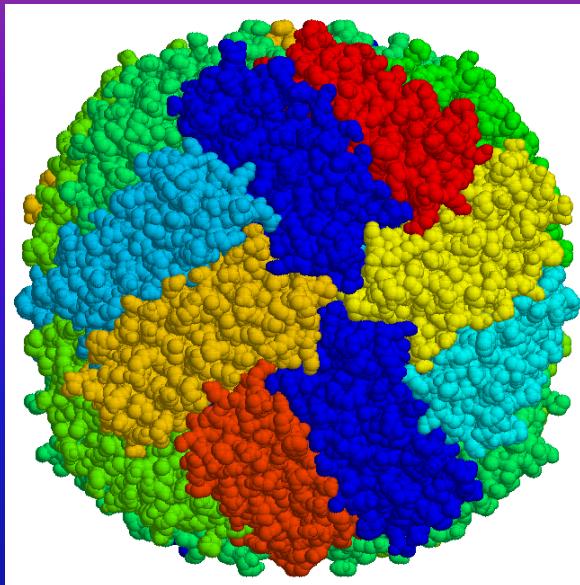
C2: $\alpha_2\beta_2$
hemoglobin
from Homo
sapiens
(2Hhb)



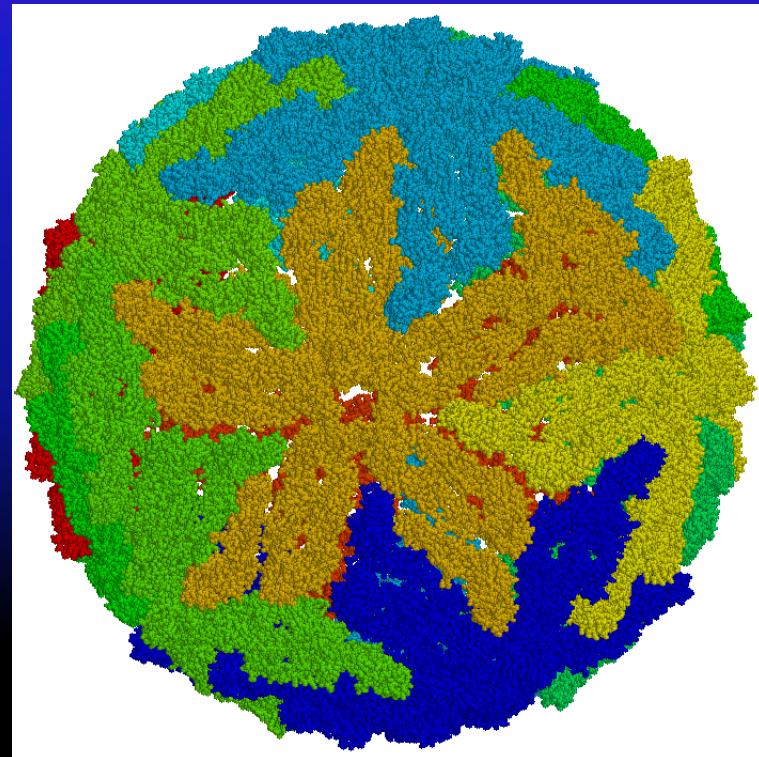
D6: 2GTL, earthworm
hemoglobin
(144 hemoglobin chains:
 $4 \times 3 \times 6 \times 2$)



Proteasome
(1FNT) C2
symmetry for 42-
mer)



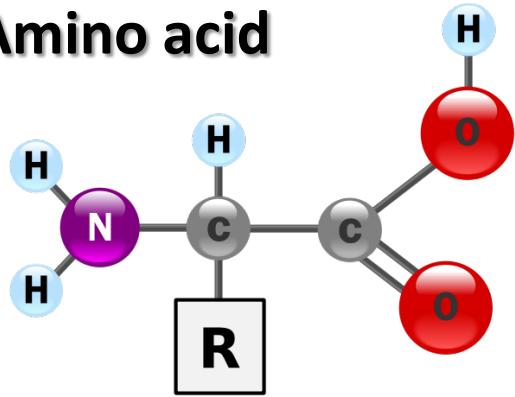
Human ferritin H chain
(2FHA)



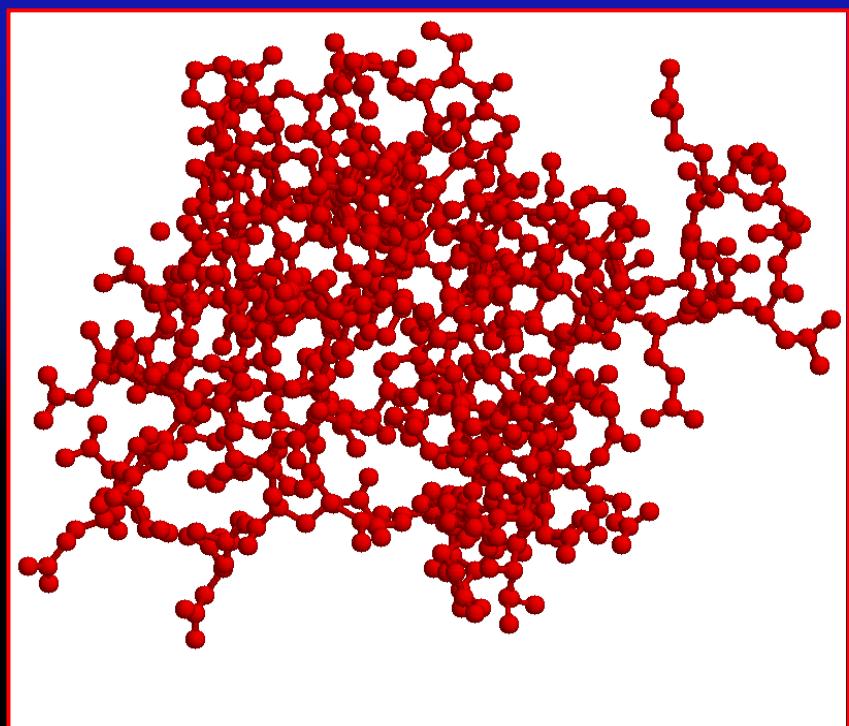
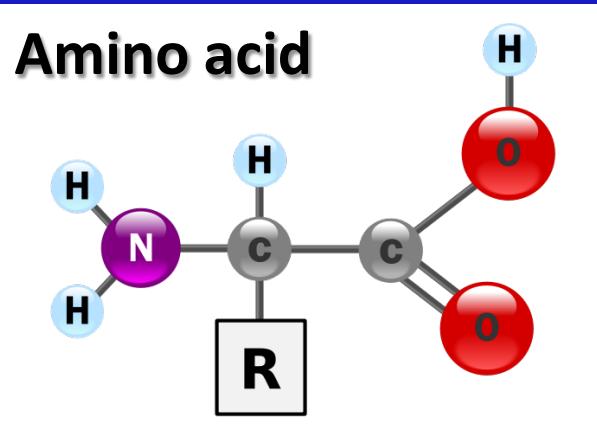
Denge virus

Interest: construction of a protein oligomer

Amino acid



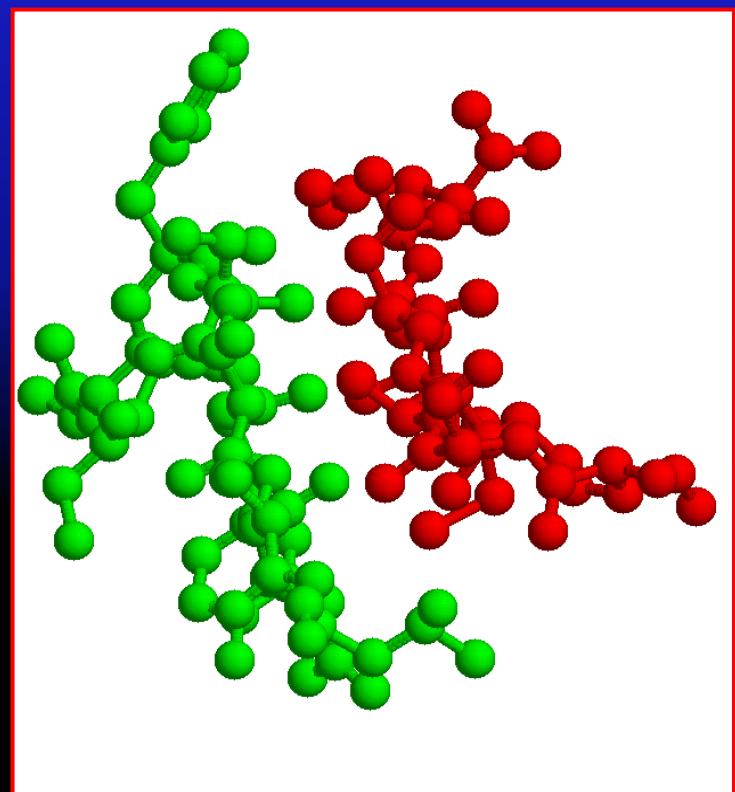
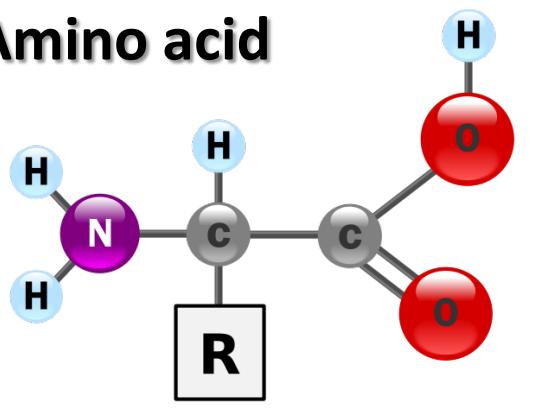
Intramolecular interactions



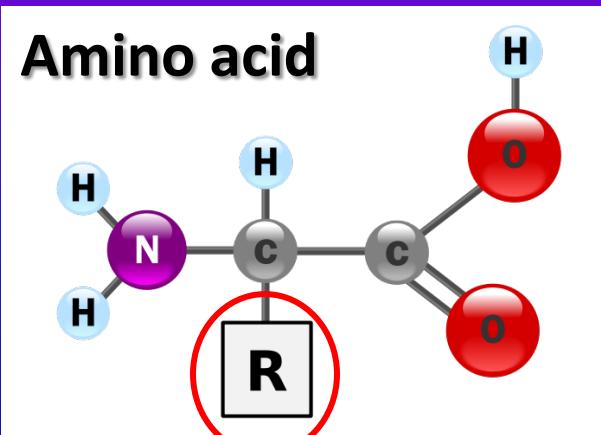
Intermolecular interactions



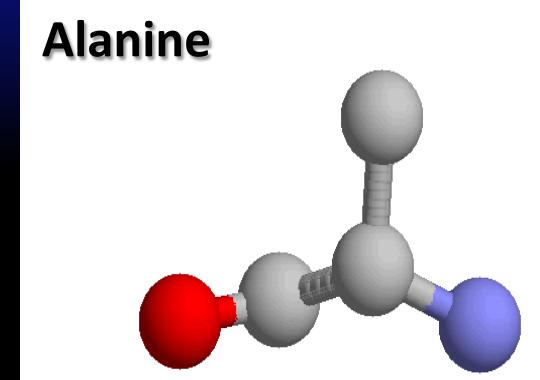
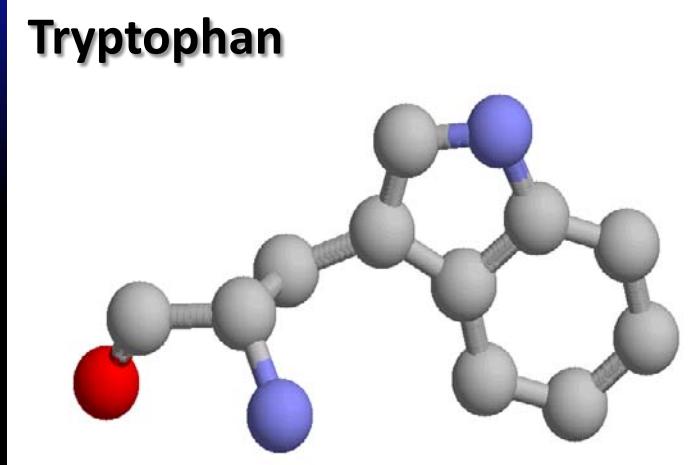
Amino acid



Amino acid flavors

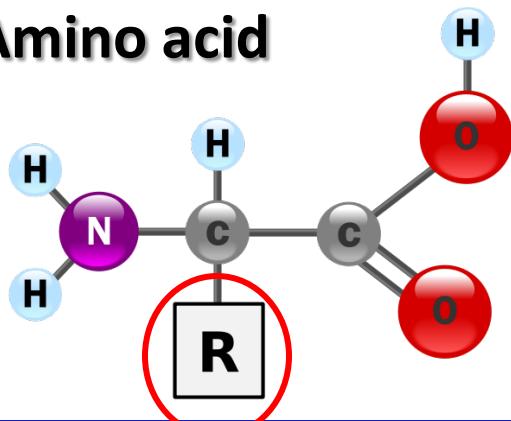


- Size
- Atom number
- Chemistry
- Geometry



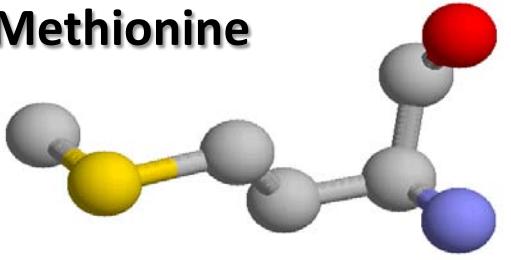
Amino acid flavors

Amino acid

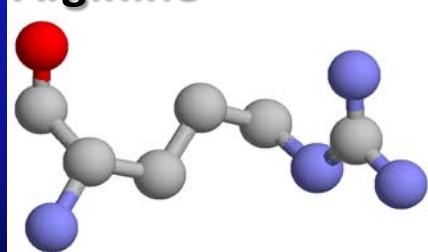


- Size
- Atom number
- Chemistry
- Geometry

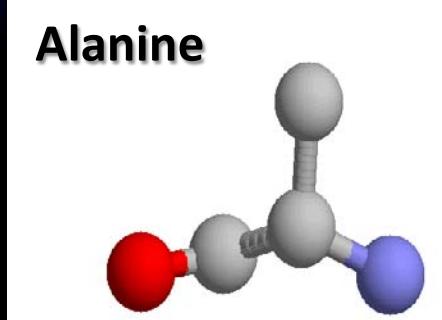
Methionine



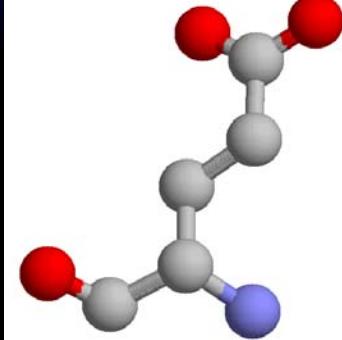
Arginine



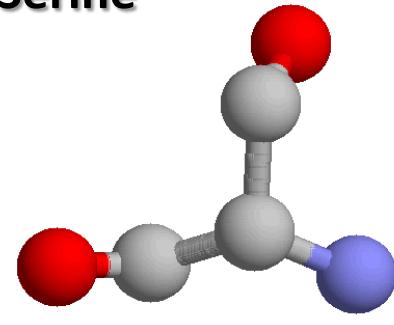
Alanine



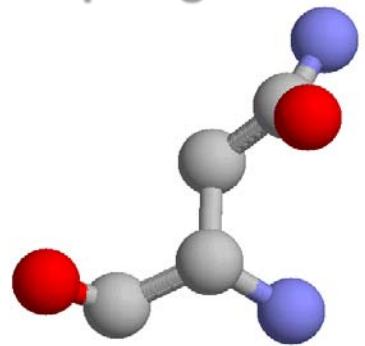
Glutamic acid



Serine

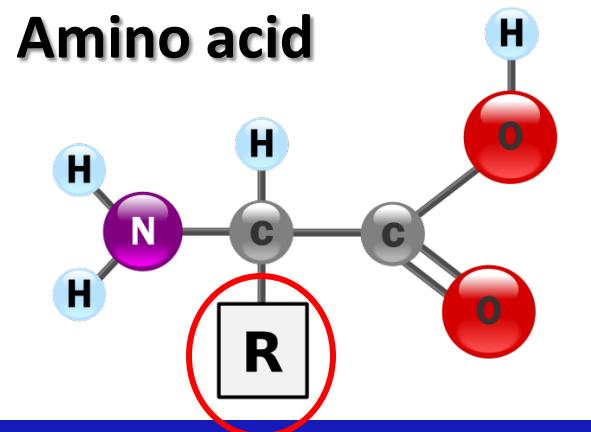


Asparagine



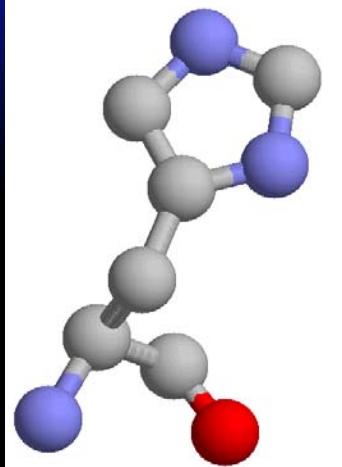
Amino acid flavors

Amino acid

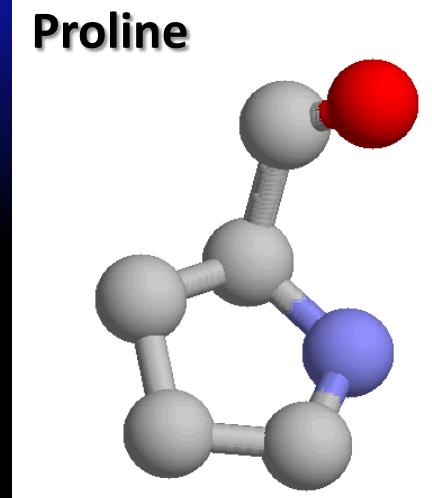


- Size
- Atom number
- Chemistry
- Geometry

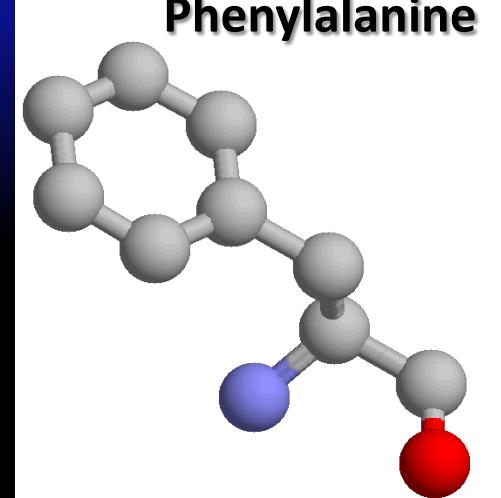
Histidine



Proline

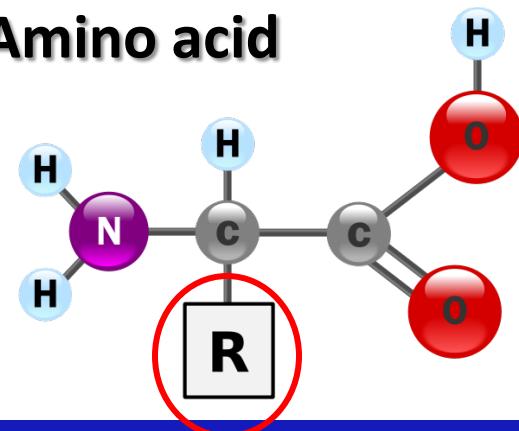


Phenylalanine



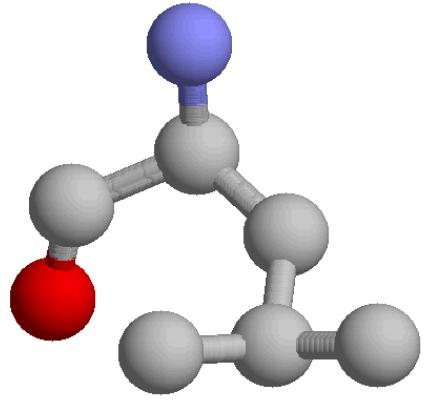
Amino acid flavors

Amino acid

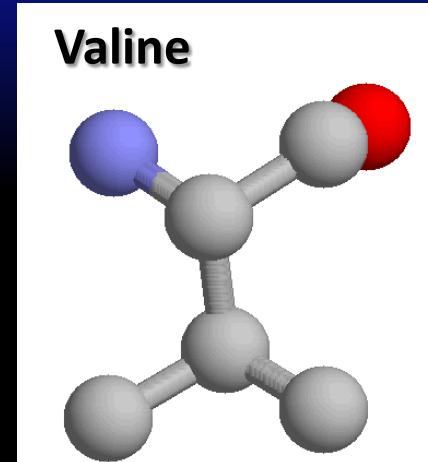


- Size
- Atom number
- Chemistry
- Geometry

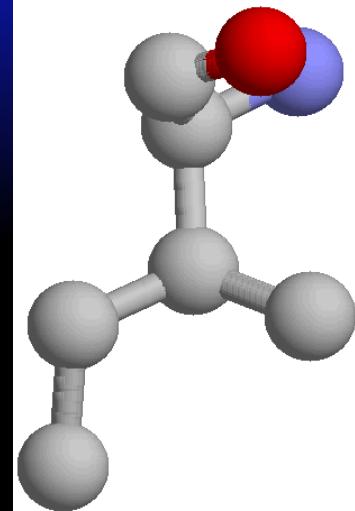
Leucine



Valine



Isoleucine



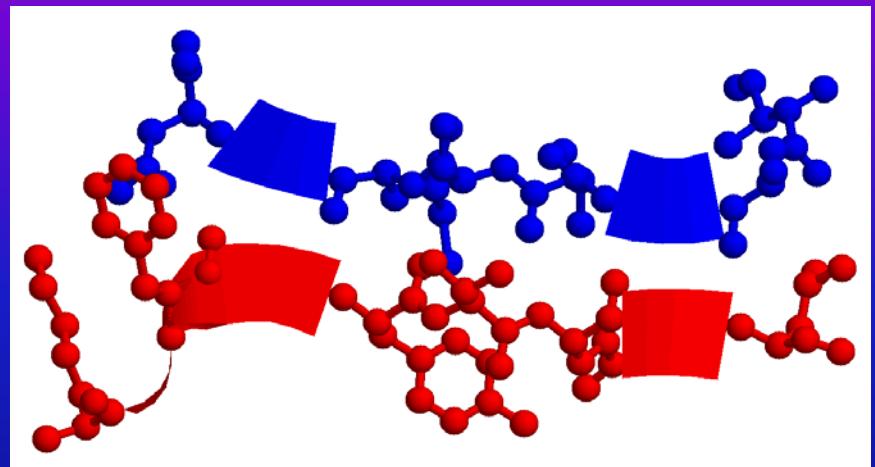
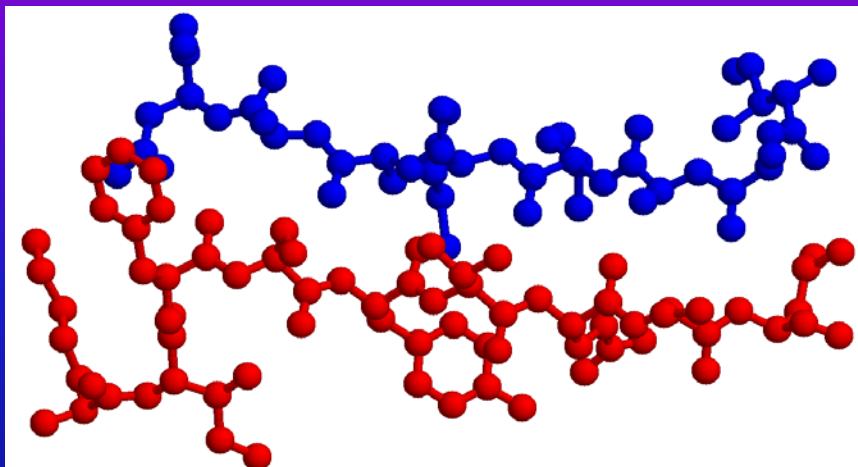
Construction of a protein oligomer

- Association:
- Interface formation



- Mechanism of oligomerization:
 - folding and association steps

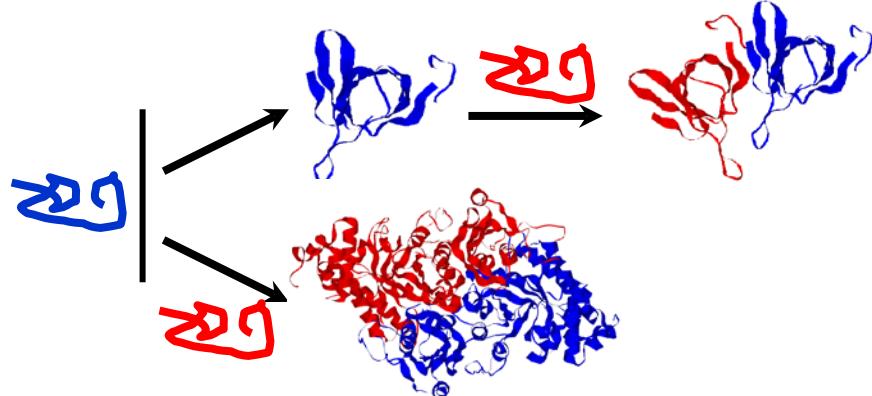
Association: intermolecular interactions



Hot spots

- Talavera, D., Robertson, D. L., and Lovell, S. C. (2011). *PLoS one* 6, e21053
- Guharoy, M., and Chakrabarti, P. (2007) *Bioinformatics* 23, 1909-1918
- Aloy, P., and Russell, R. B. (2003) *Bioinformatics* 19, 161-162
- Ma, B., and Nussinov, R. (2007) *Current topics in medicinal chemistry* 7, 999-1005
- Tuncbag, N., Kar, G., Keskin, O., Gursoy, A., and Nussinov, R. (2009) *Briefings in Bioinformatics* 10, 217
- Feverati, G. and Lesieur, C. (2010) *PLoS one* 5, e9897

Three-state mechanism

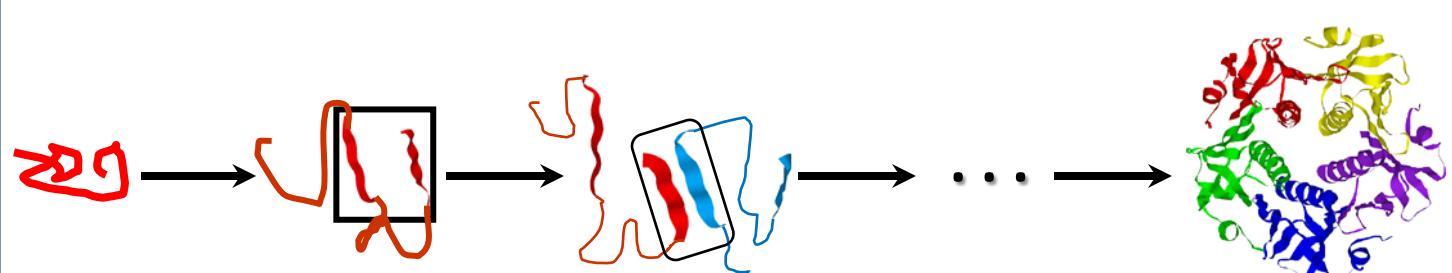
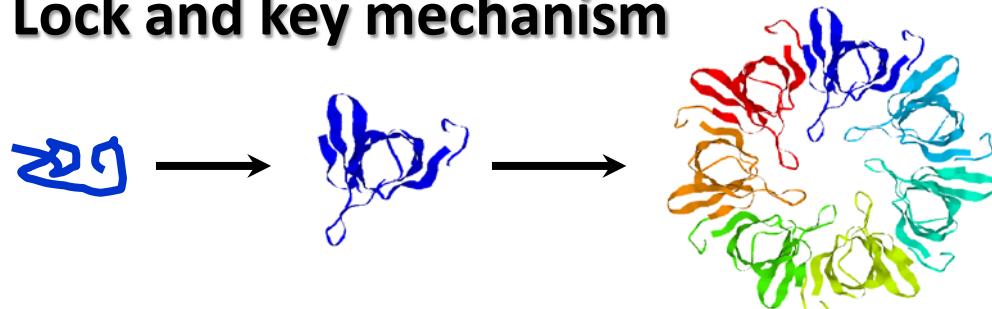


Two-state mechanism

D'Alessio, G. (1999) *Prog Biophys Mol Biol* 72, 271-298

Csermely, P., Palotai, R., and Nussinov, R. (2010) *Trends Biochem Sci* 35, 539-546

Lock and key mechanism



Fly casting mechanism

What rules protein oligomerisation ?

- Global fold of the protein oligomer
- Symmetry of the oligomer
- Evolution
- Interface size
- Intramolecular/intermolecular interactions

Prediction from the atomic structures

- of assembly intermediates¹
- of mechanism of oligomerization²

1. Levy, E. D., Erba, E. B., Robinson, C. V., and Teichmann, S. A. (2008) *Nature* 453, 1262-1265

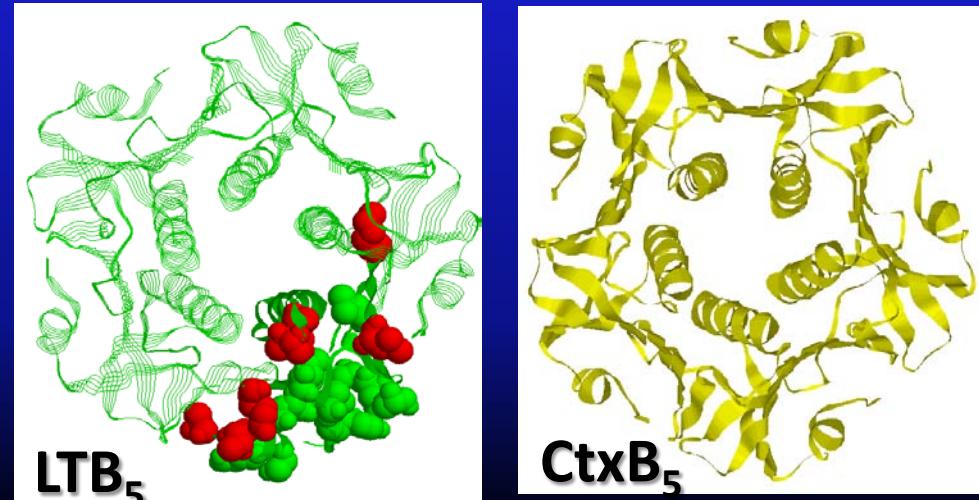
2. Weihua Zheng, c., Nicholas P. Schaferb,c, Aram Davtyan, Garegin A. Papoiand,e, and Peter G. Wolynes. (2012) *Proc Natl Acad Sci U S A* 109, 19244-19249

Exceptions to the rule...

A single amino acid mutation alters the oligomeric state
Alzheimer like pathologies

Few amino acid mutations alter the mechanism of
oligomerization

- AB₅ toxins, cpn10

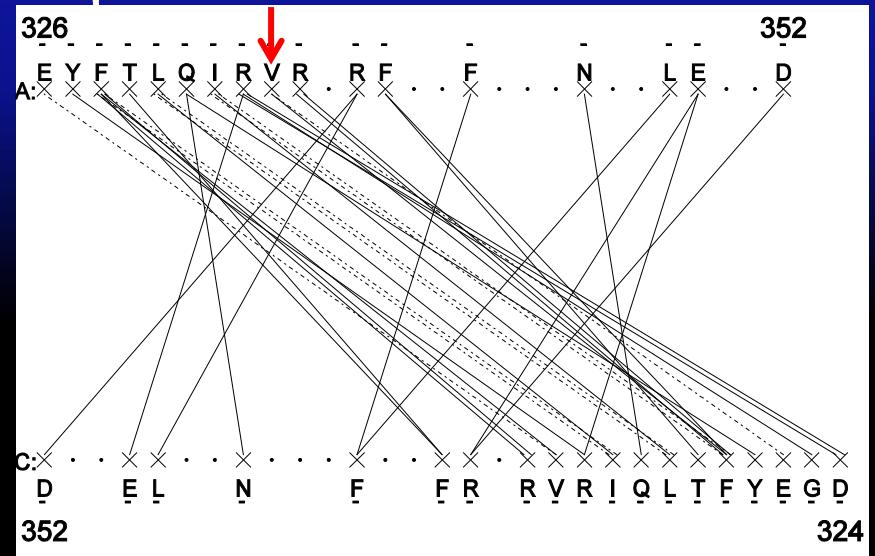
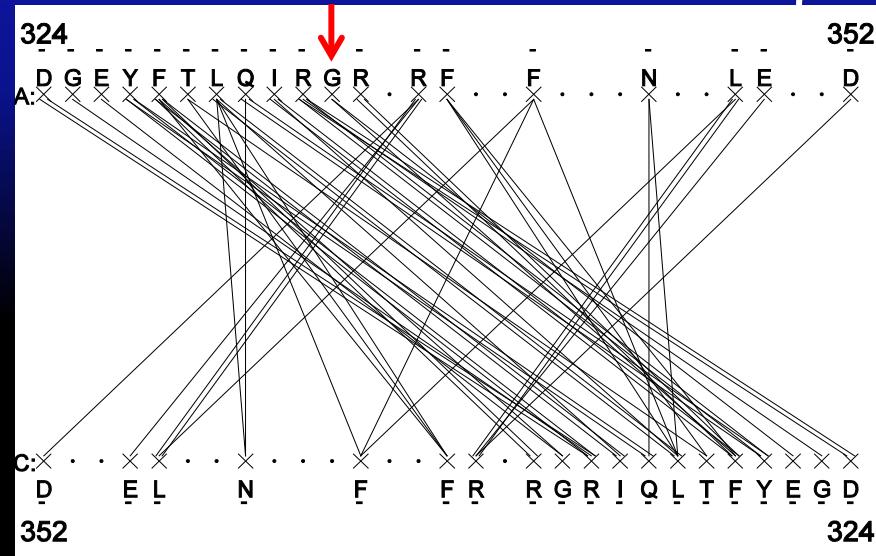


- Weighted interactions: Role in the oligomerization?
- Networks/graph theory approach

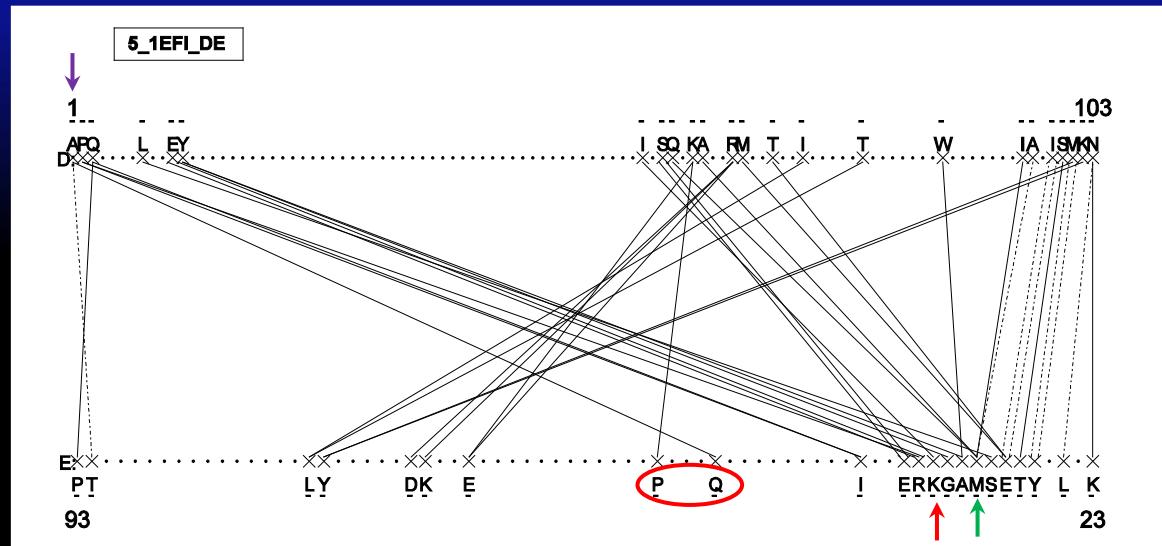
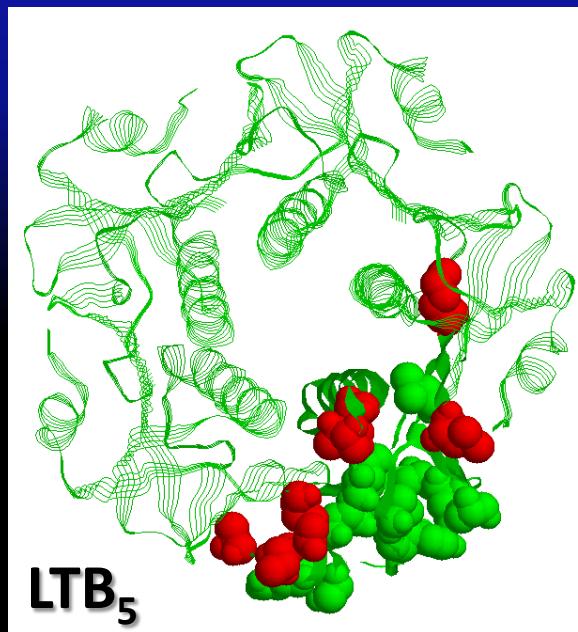
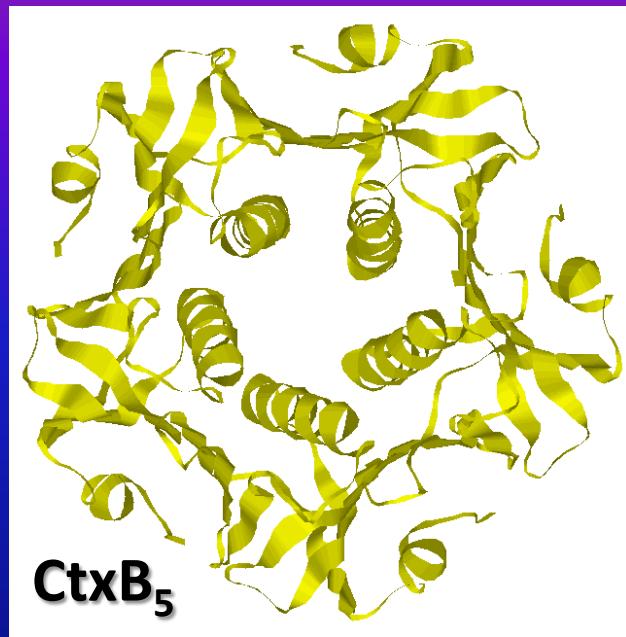
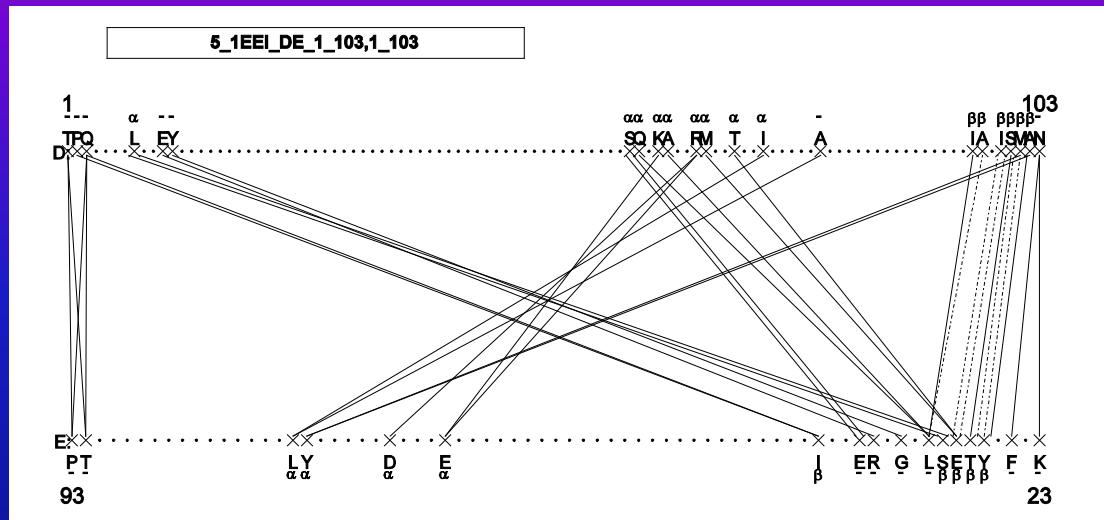
Validation 1: p53 cancer G34V



G34V



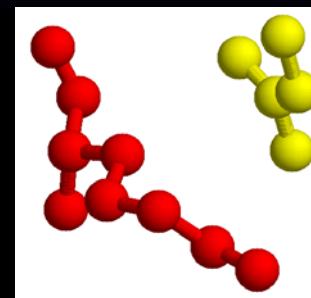
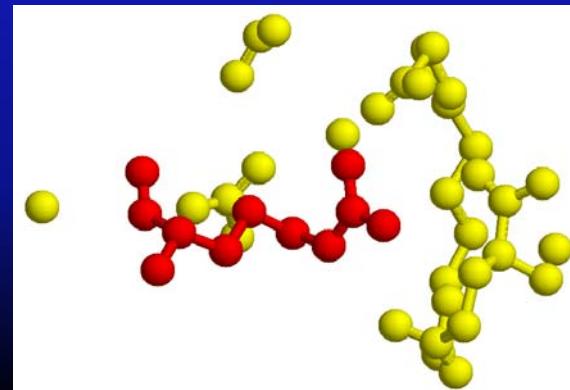
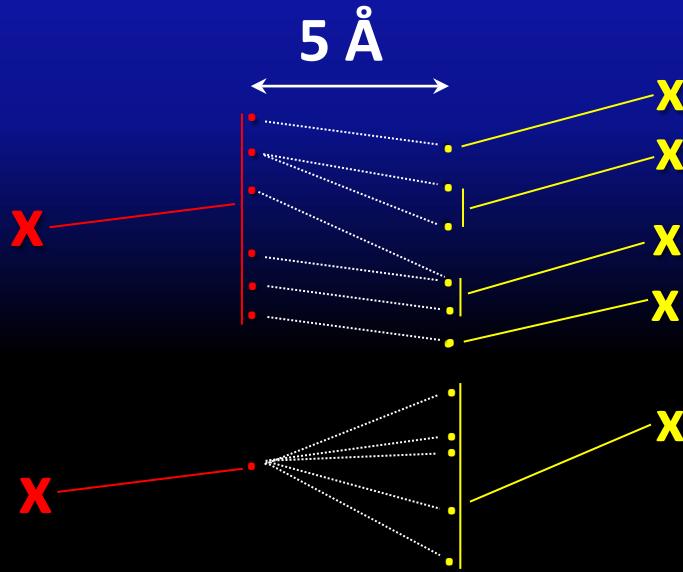
Validation 2: AB₅ toxins



- Identify hierarchy within hot spots
- Relation with protein oligomerization

SpectralPro

- Select all atoms within interatomic distance of 5 Å from one another
- It retains the ten closest contacts to each selected atoms
- Create a residue interaction network with the selected amino acids as a node and their interactions as their links



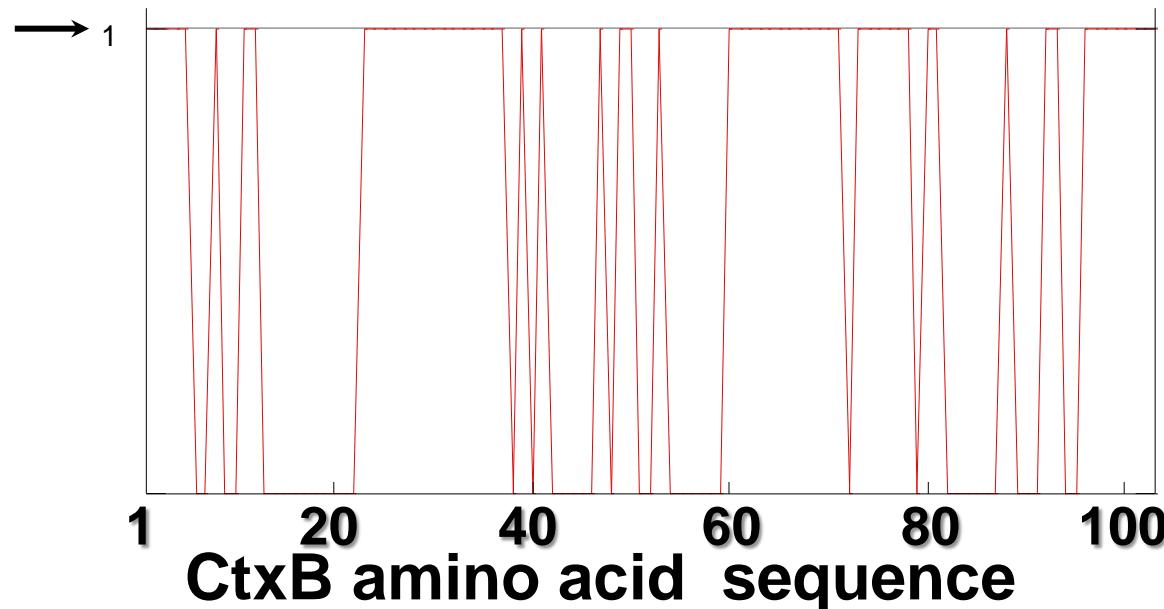
Network properties related to protein assembly: the CtxB₅ case

SpectralPro detects 61 hot spots

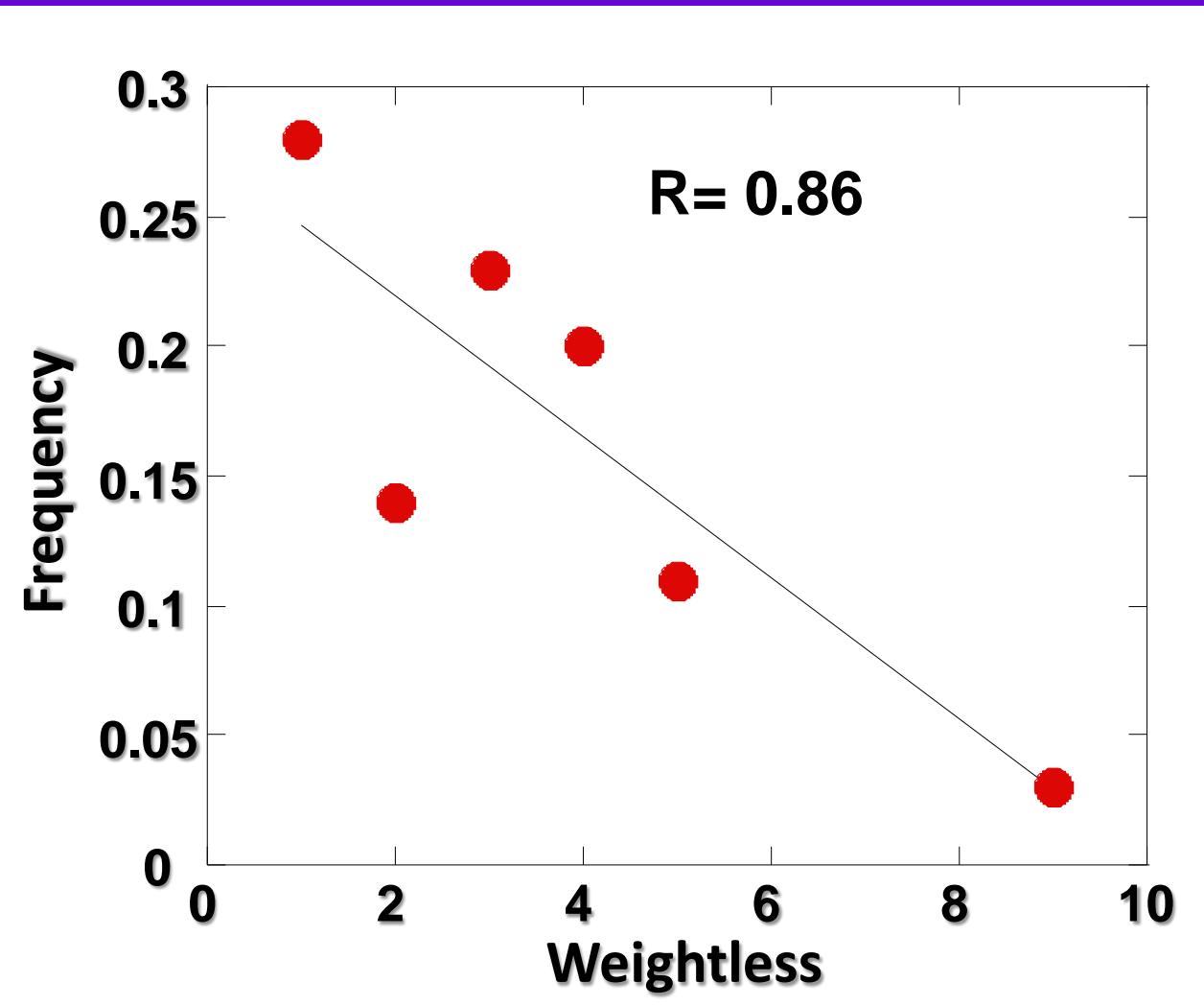
ASA detects 53 hot spots

SCOWLP detects 54 Hot spots

PSIBASE detects 58 hot spots

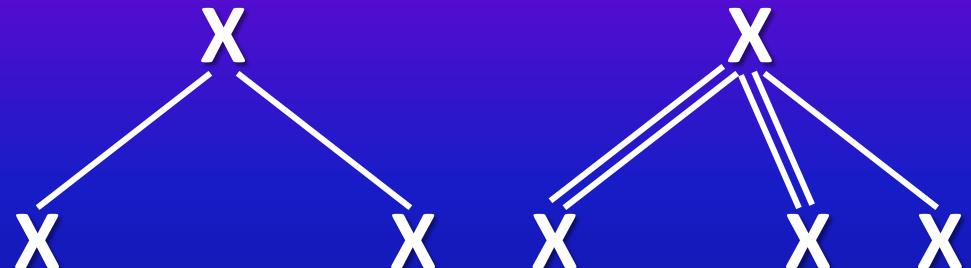
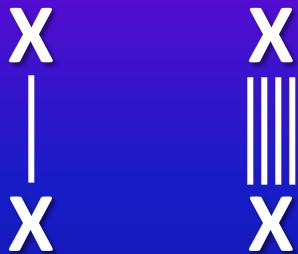


Degree of hot spots



3 ± 2 contacts
 19 ± 16 links

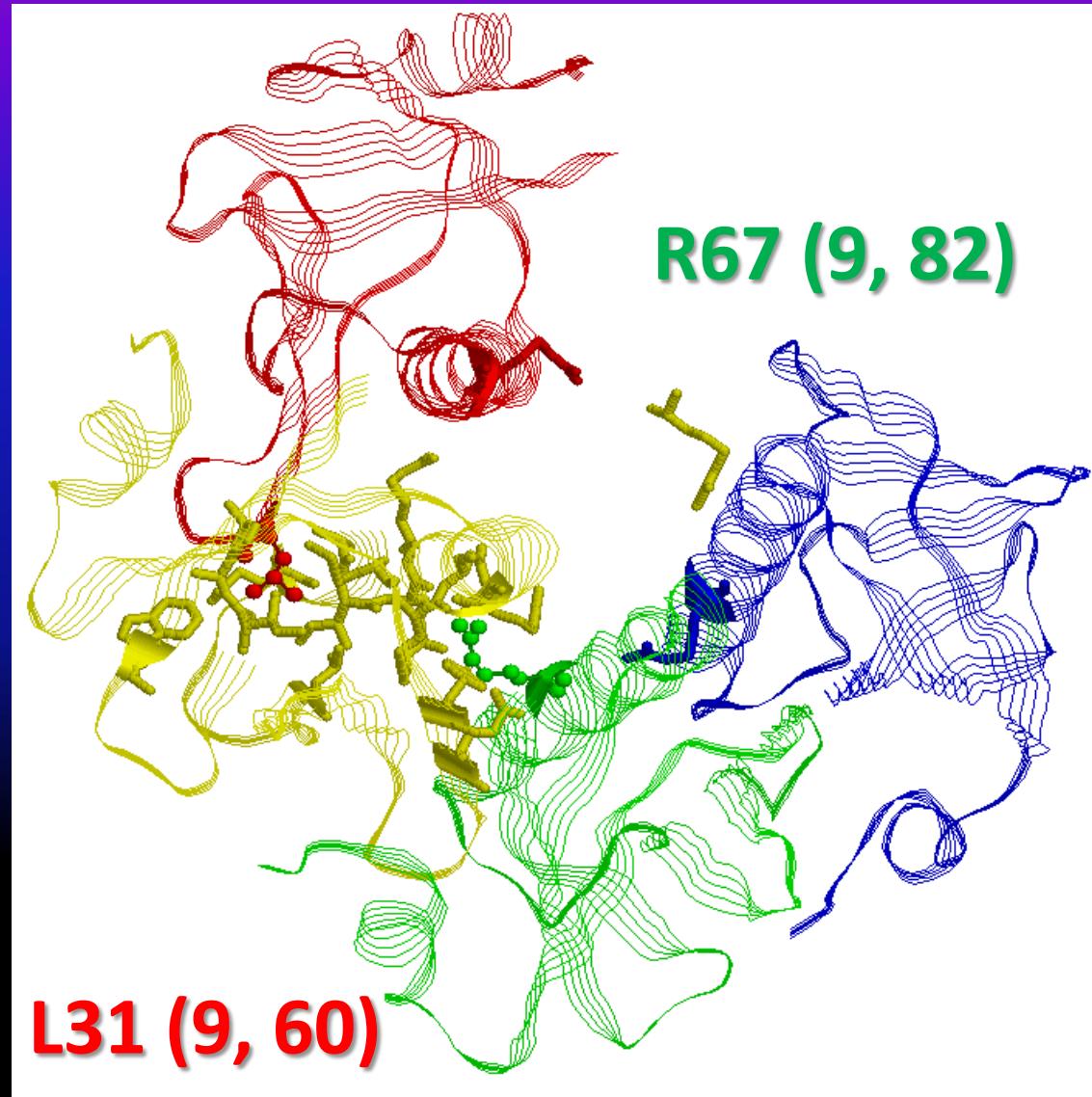
Residue connectivity



- Weightless: number of residue in contact
- Weighted: number of links

Hot spot (weightless, weighted)

Betweenness



Influential versus connected

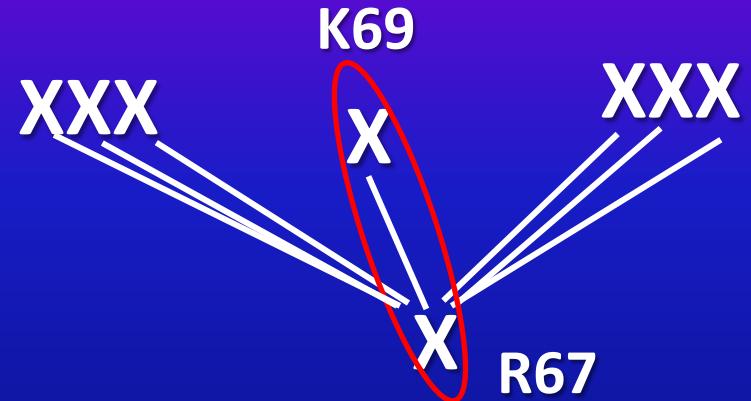
HUB

R67N: 63 % effect

L31N: 38 % effect

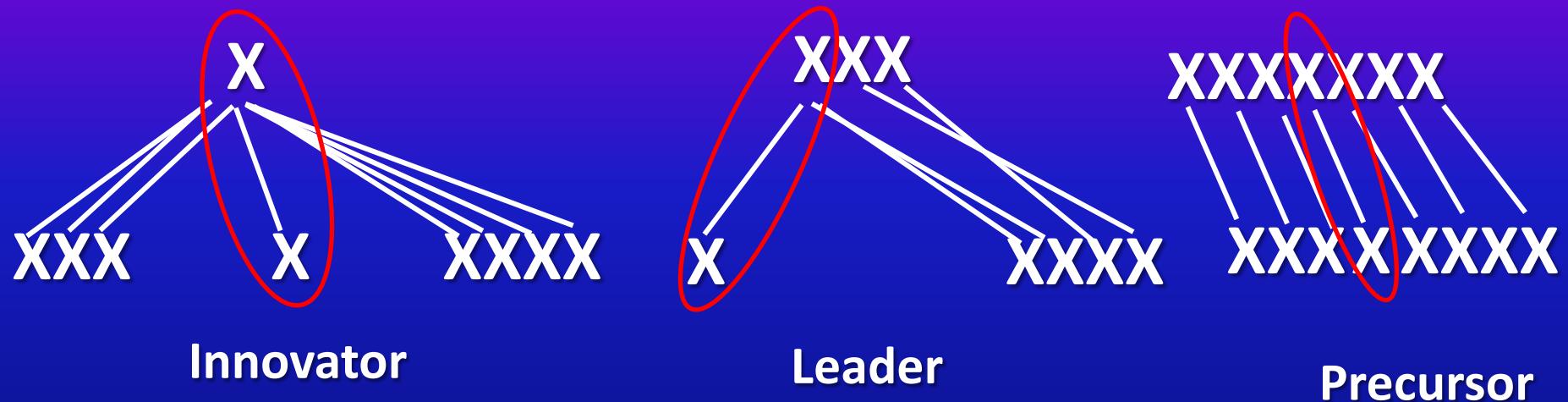
K69 (1, 24) and K69N: 100 % effect

A98 (3, 15) and A98N: 100 % effect



**Highly connected does not imply influential
Many contacts does not make you powerful**

Hypothesis: Innovator, leader, precursor contacts



22 Hot spots out of 61: 19 are influential
25 influential hot spots.

What counts is who you are connected to!!!

Future

- LTB₅ similar study
- Alzheimer like familial mutation:
 - Precursor/innovator/leader hot spots?

Acknowledgment

- Kave Salamatian (LISTIC, University of Savoie)
- Mounia Achoch (LISTIC, University of Savoie)
- Giovanni Feverati (LAPTH, CNRS-University of Savoie)
- Laurent Vuillon (LAMA, CNRS-University of Savoie)
- Research federation Modelization, Simulation, Interactions fundamental: MSIF