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Analysis of allosteric effect of pathologic variants at the light of local protein conformations

Alexandre de Brevern

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Submitted on 3 Aug 2018

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BELBI 2018



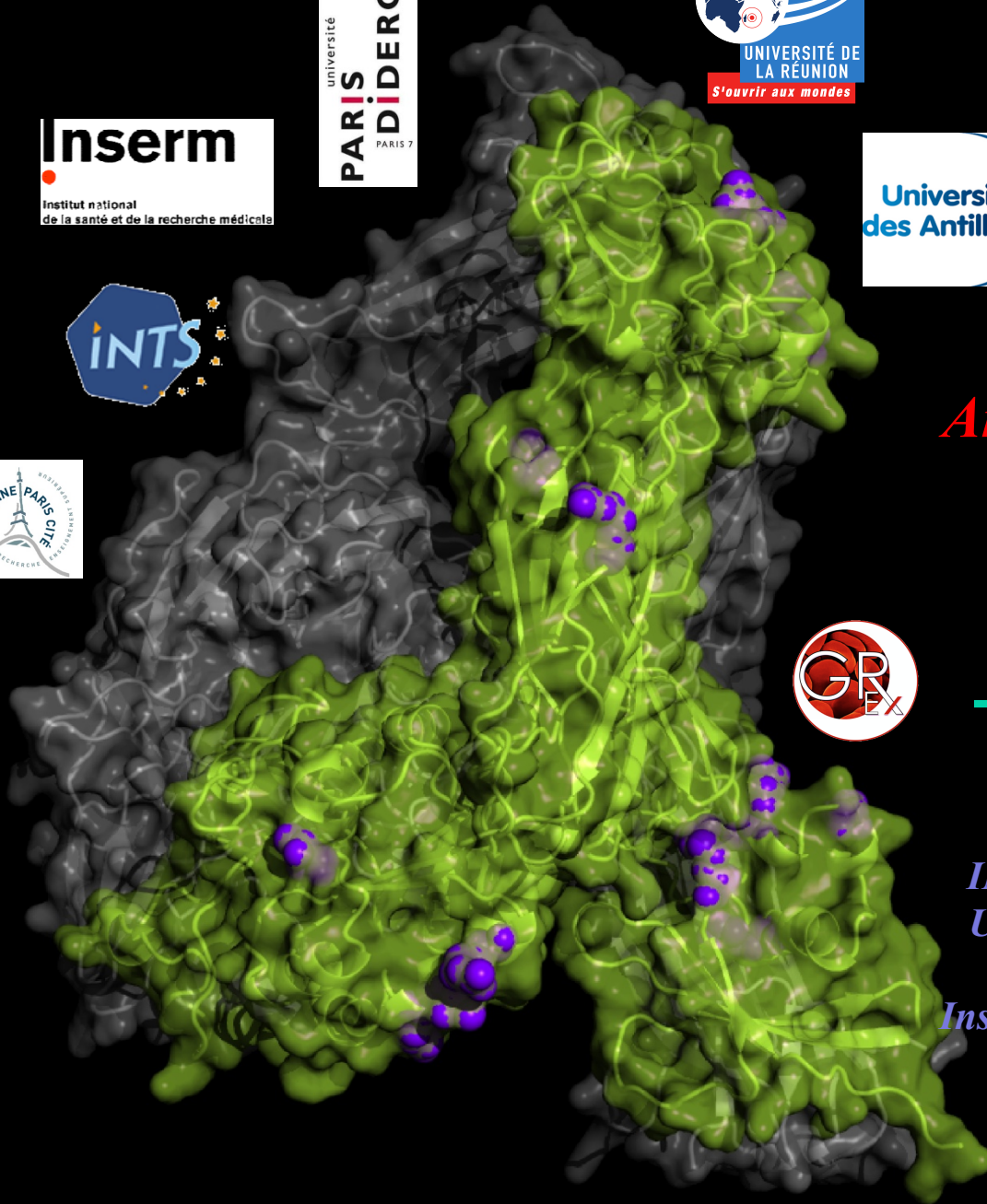


BelBi 2018

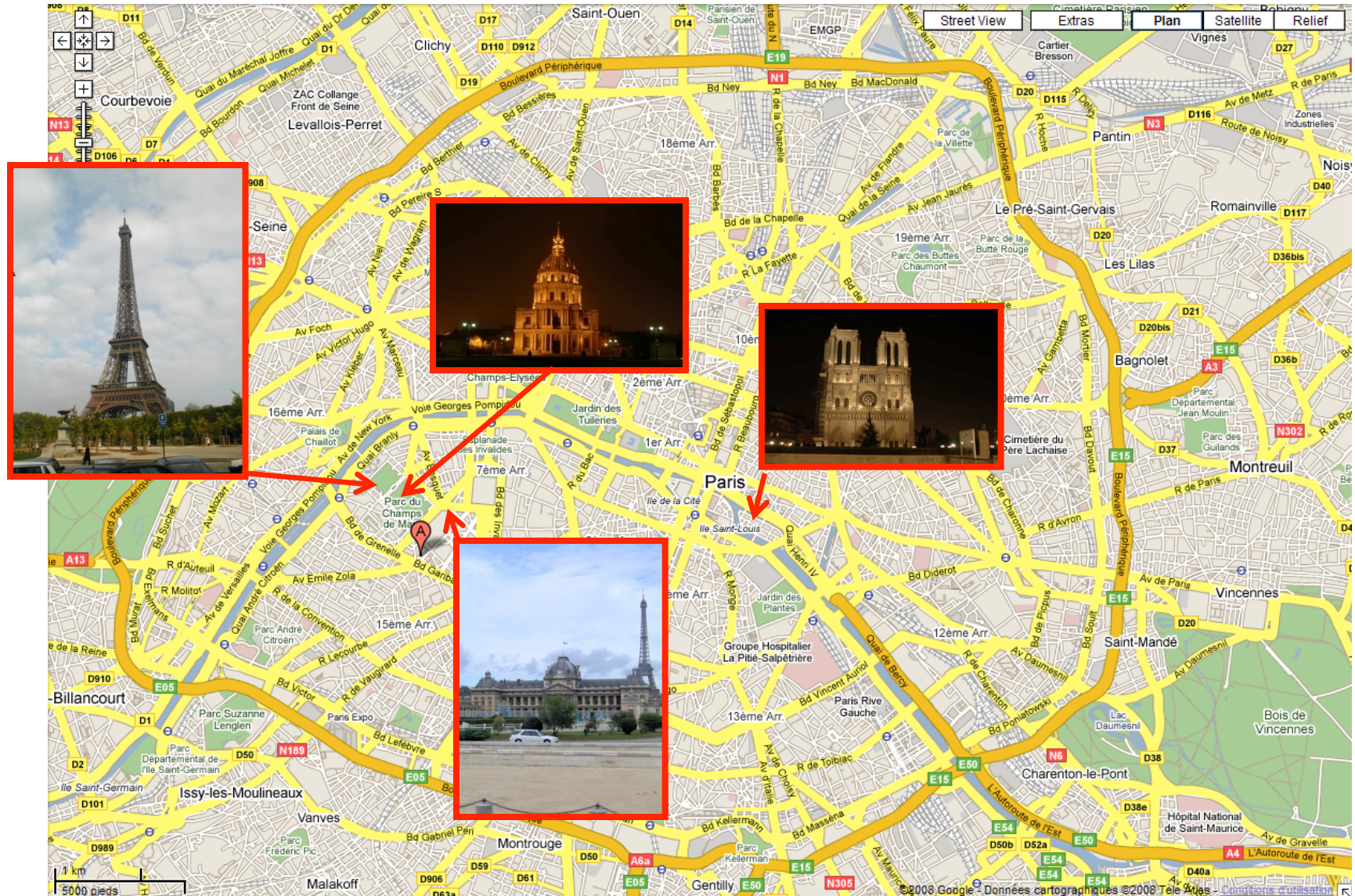
*Analysis of allosteric effect of
pathologic variants at
the light of local protein
conformations*

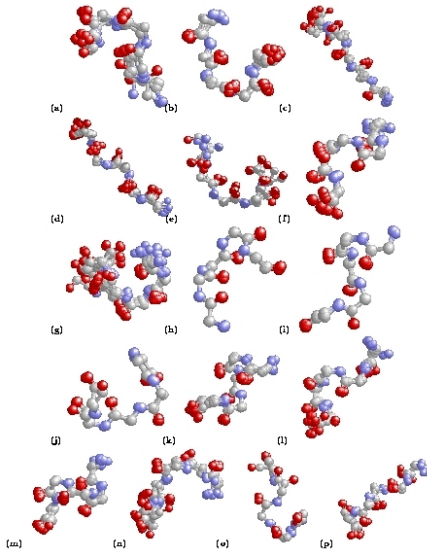
Alexandre G. de Brevern

*INSERM UMR_S 1134, team 2 – DSIMB,
Univ. Paris Diderot, Sorbonne Paris Cité,
Univ de la Réunion, Univ des Antilles,
Institut National de la Transfusion Sanguine
(INTS), GR-Ex*



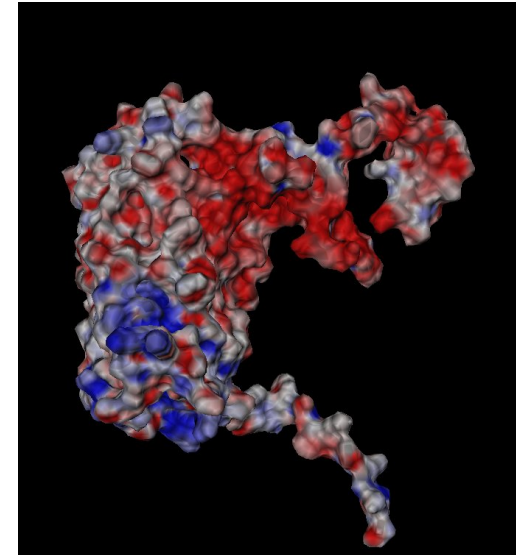
DSIMB: a bioinformatics team

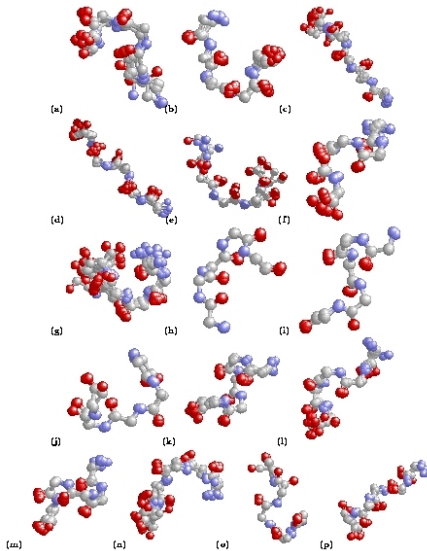




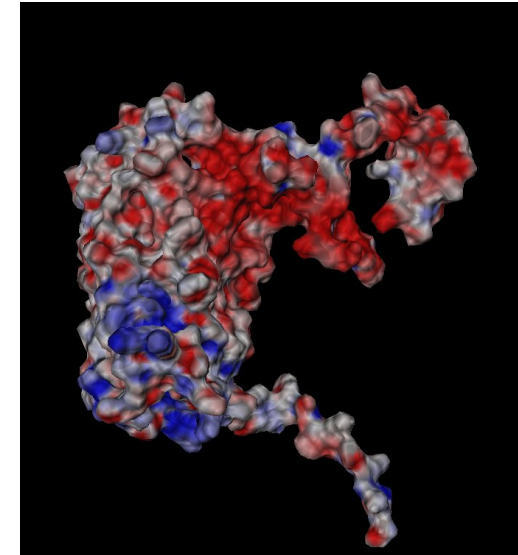
Our main goal:
Sequence - Structure
Function & Dynamics

**Methodological
developments
and applications**

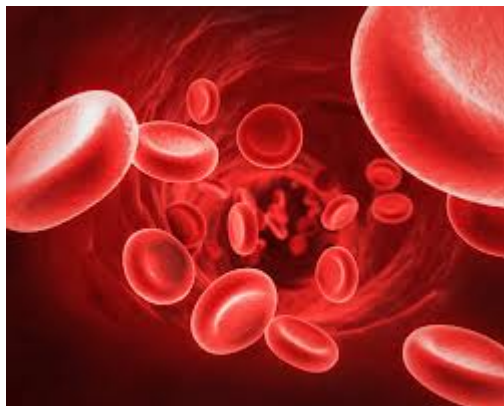




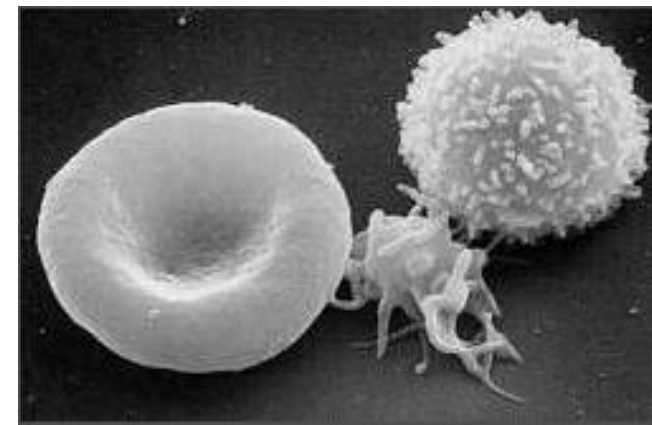
Our main goal:
Sequence - Structure
Function & Dynamics



**Methodological
developments
and applications**



**Red Blood Cells
and Platelets**

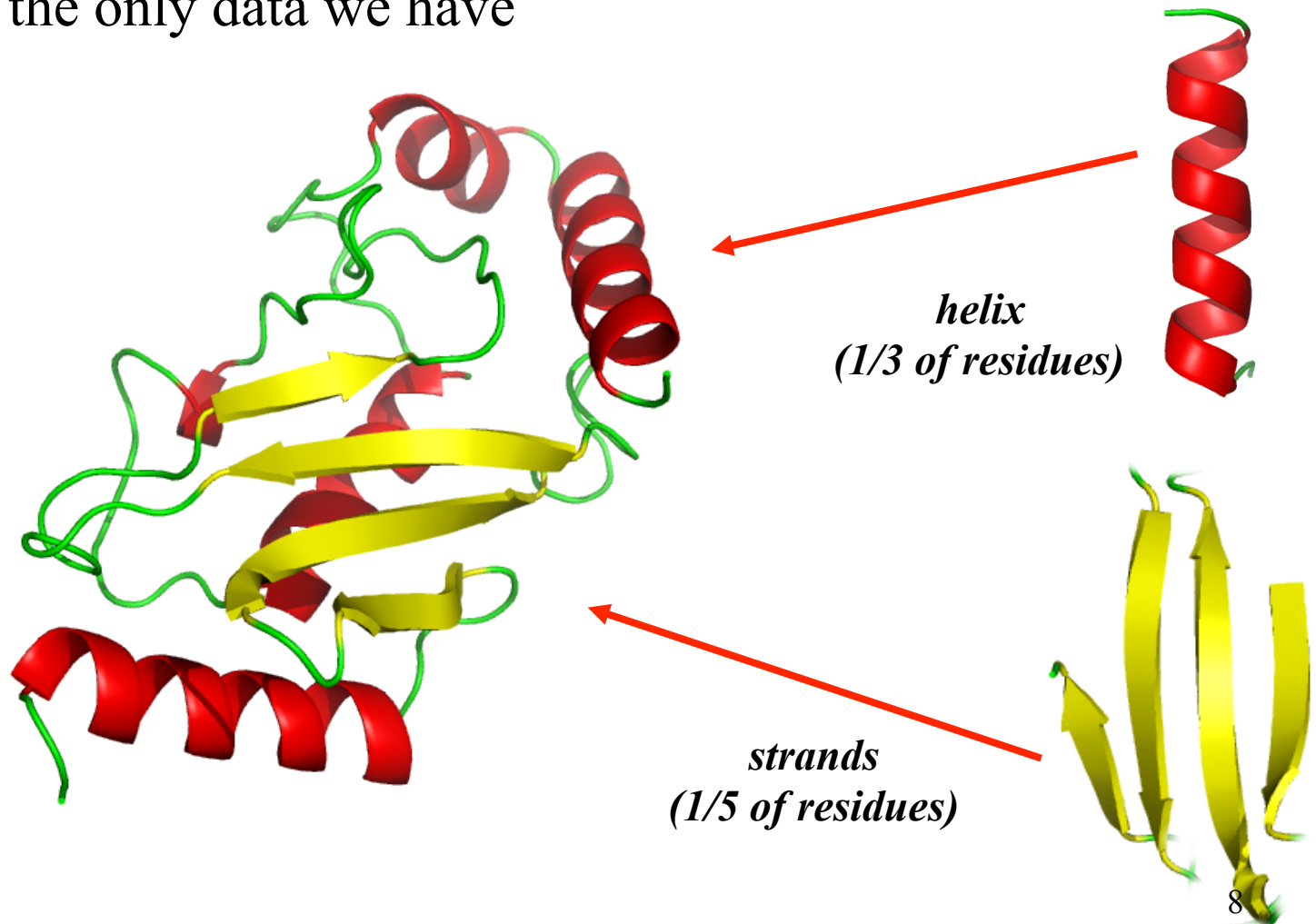


- ❖ Why going beyond classical secondary structure ?
- ❖ How ?
- ❖ How is it useful for analysis of protein dynamics ?
- ❖ Can it be used also for protein disorder ?

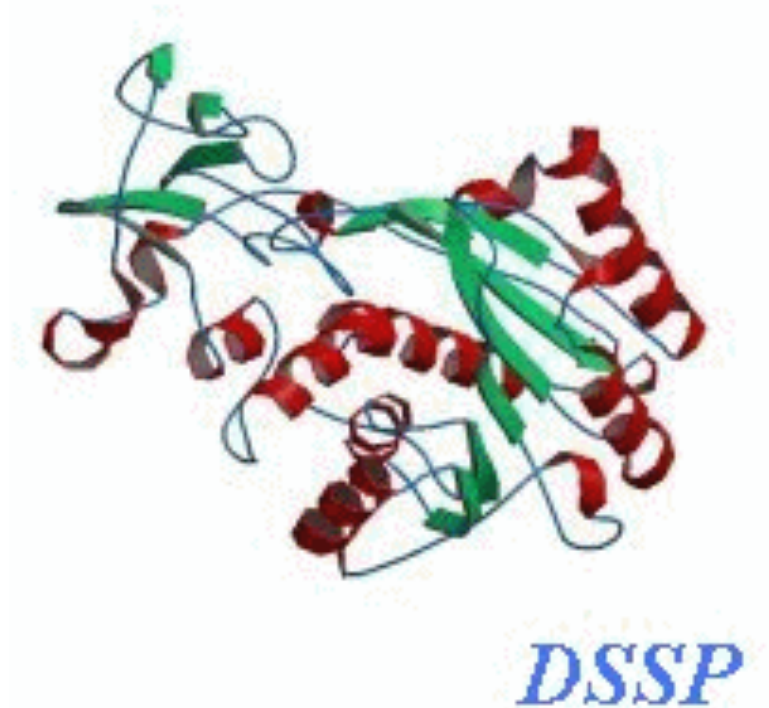
SECONDARY STRUCTURE

The secondary structures

- That's the only data we have



Secondary structures: some questions



No simple consensus between methods

Assignment example for the *Hhai Methyltransferase* protein (PDB code :10MH) by DSSP, STRIDE, PSEA, DEFINE, PCURVE, XTLSSTR and SECSTR.

L. Fourrier, C. Benros & A.G. de Brevern (*BMC Bioinfo*, 2004)

Secondary structures: some questions

DSSP



KAKSI

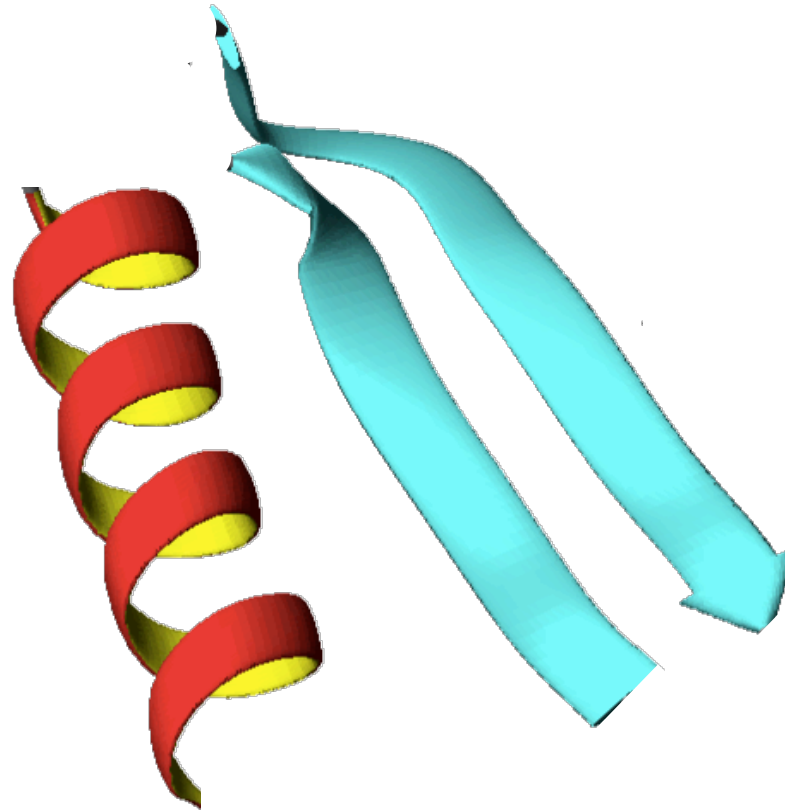


J. Martin, G. Letellier, J.F. Taly, A. Martin, A.G. de Brevern & J.F. Gibrat (*BMC Structural Biology*, 2005)

http://migale.jouy.inra.fr/mig/mig_fr/servlog/kaksi/

Secondary structures: some questions

Moreover .



Secondary structures: some questions

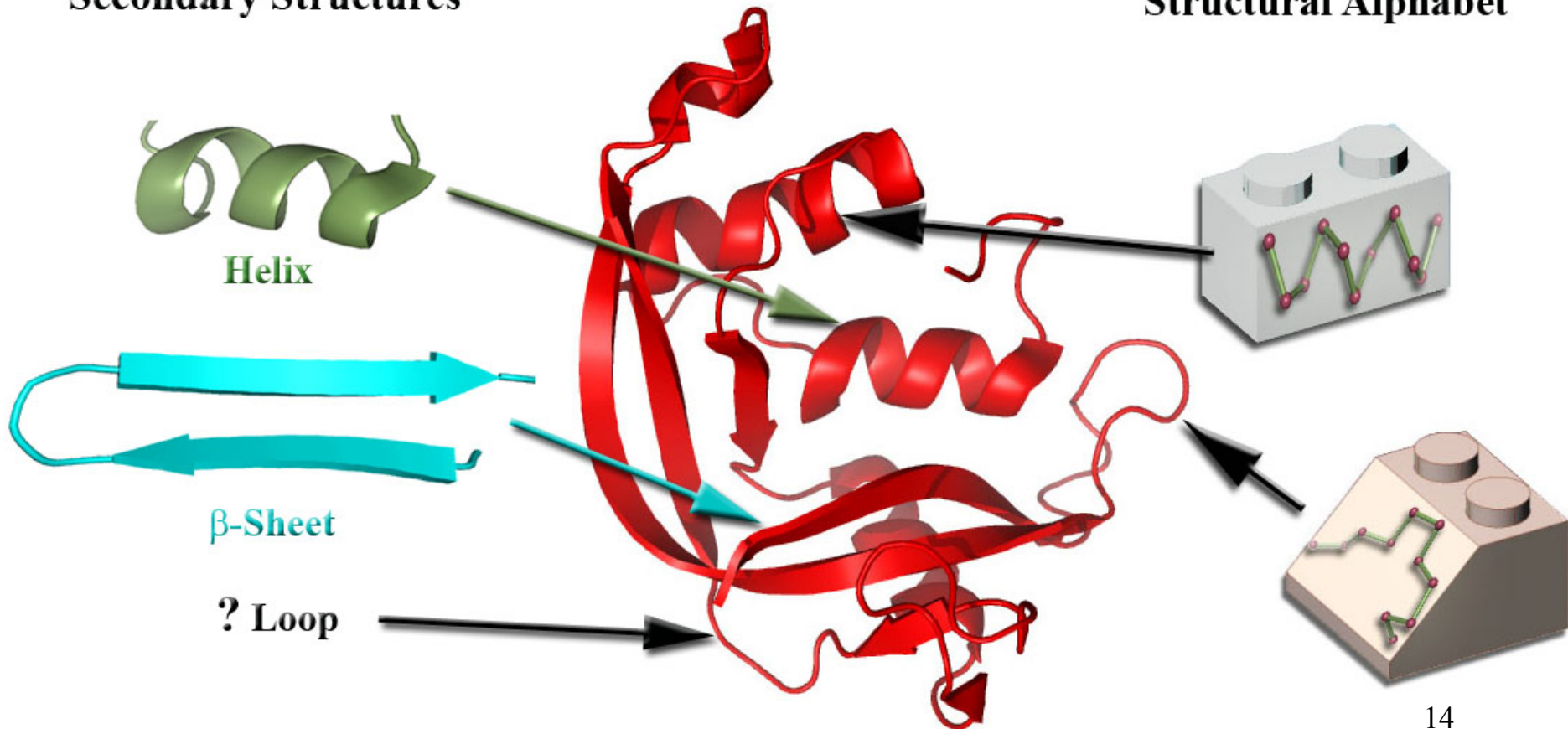
- It is possible to look at protein structures in a different ways
- At a local level.

STRUCTURAL ALPHABET

➤ Another vision

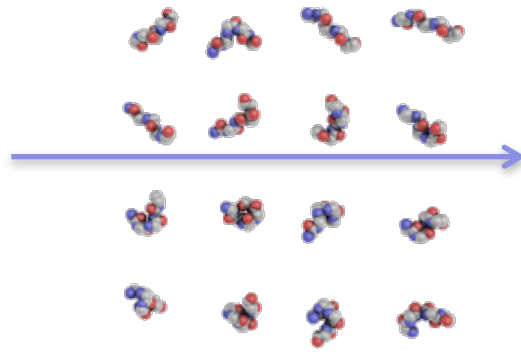
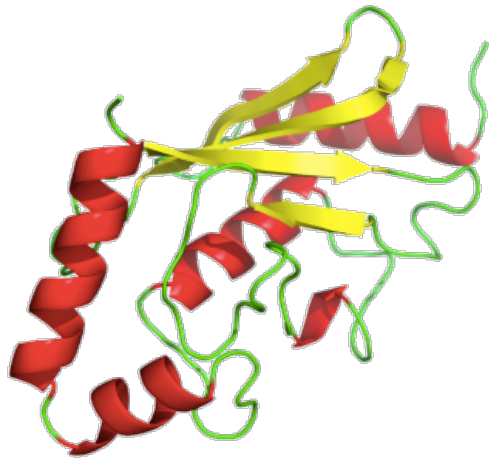
Secondary Structures

Structural Alphabet



➤ Structural Alphabet (SA):

Structure translation (3D -> 1D)



>2aak

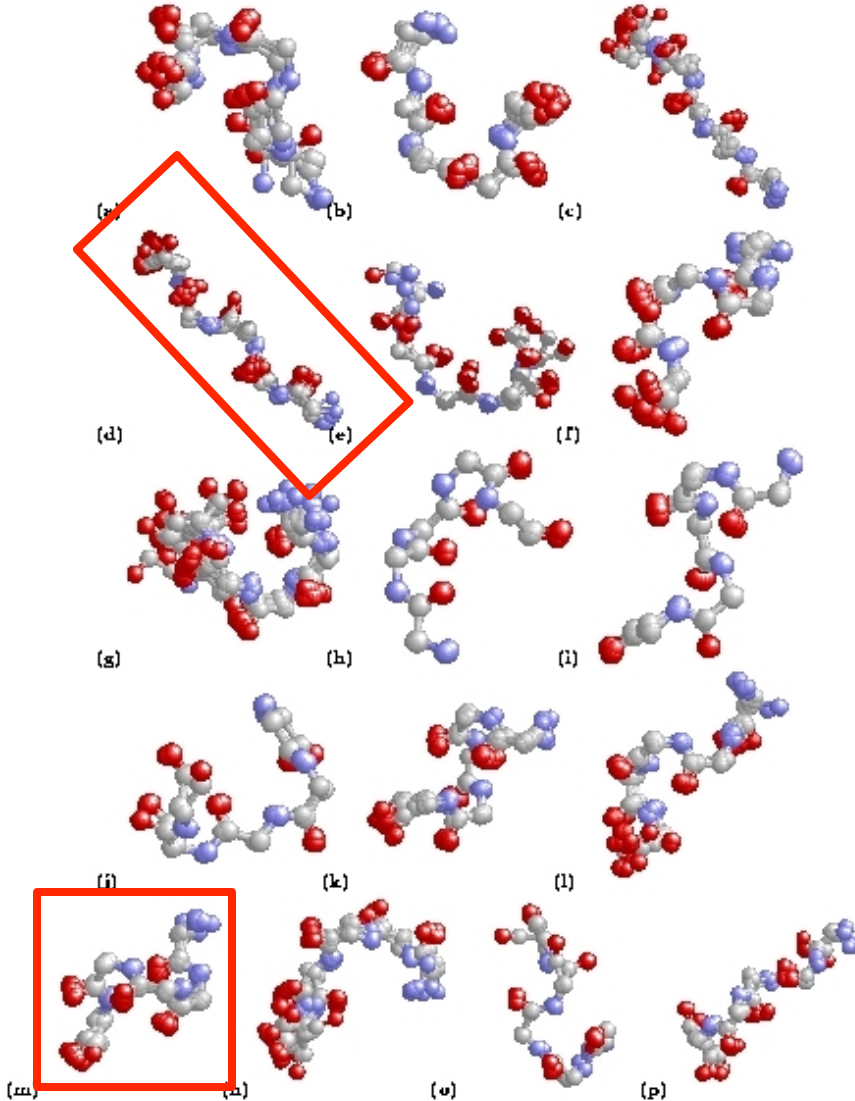
```
ZZfk lmmmmmmmmmmmmmmcccehi
acdddfk bmkbccdddddehia
kgopacdddddddfk bckbccdd
ddfbdcddfk lcfkopacdfklm
mmgcfkbcfk lmmmmmmmmmmmmmc
cfklcfblmlmmmmmmmmmlmmm
mmmmmmmmmmmmZZ
```

3D protein structure

1D Sequence

de Brevern A.G., Etchebest C. & Hazout, S. (*Proteins*, 2000).

Structural alphabet

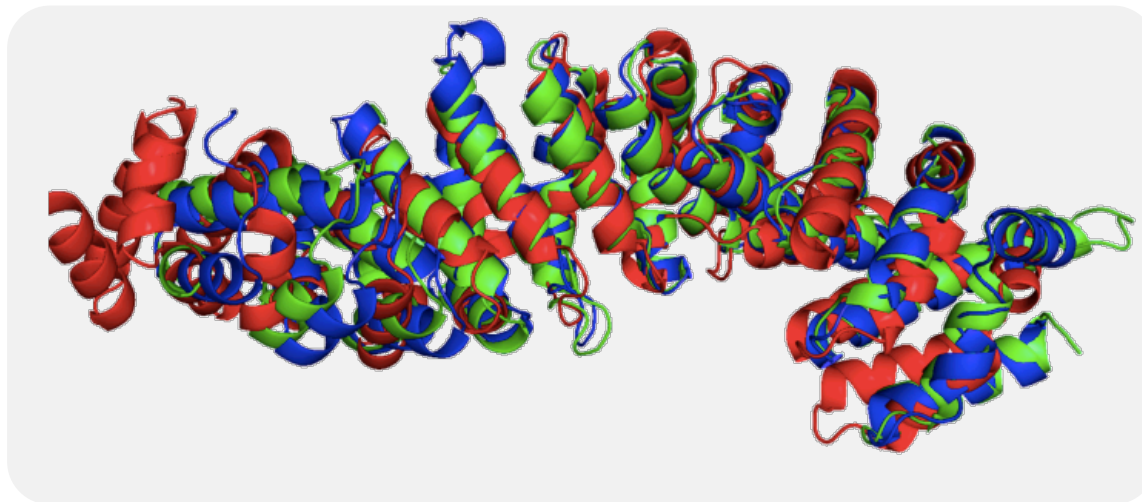


Pr. Serge Hazout

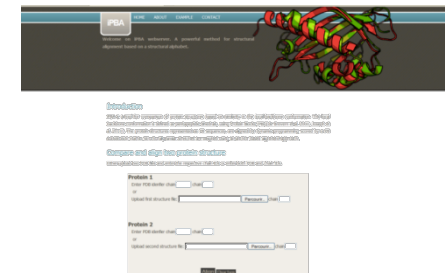
de Brevern A.G., Etchebest C. & Hazout, S. (*Proteins*, 2000).

16 Protein Blocks

➤ Superimposition of 3D protein structures

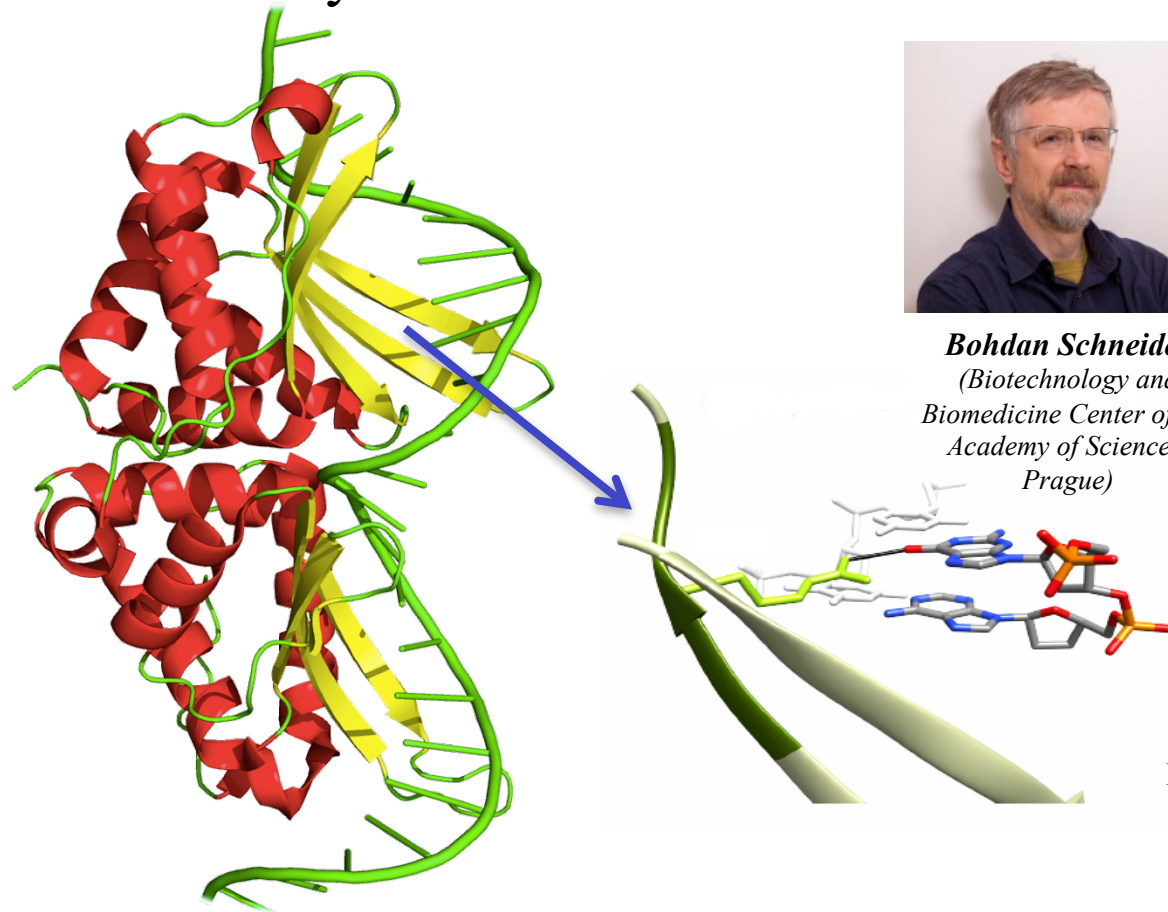


Naraswami Srinivasan
(IISc Bangalore)



- Joseph A.P., Srinivasan N. & de Brevern A.G. (2011) *Biochimie*, **93**(9):1434-45.
Agarwal G., Mahajan S., Srinivasan N. & de Brevern A.G. (2012) *PLoS ONE*, **6**(3):e17826.
Gelly J.-C., Joseph A.P., Srinivasan N. & de Brevern A.G. (2011), *Nucleic Acid Res*, **39**:W18-23.
Joseph A.P., Srinivasan N. & de Brevern A.G. (2012) *Biochimie*, **94**:2025-34.
Léonard S., Joseph A.P., Srinivasan N., Gelly J.-C. & de Brevern A.G. (2014) *J Biol Struct Dyn*, **32**(4):661-8.

➤ Protein interface analyses



PB *d* + Nt 19
PDB code 3eh8

Structural alphabet

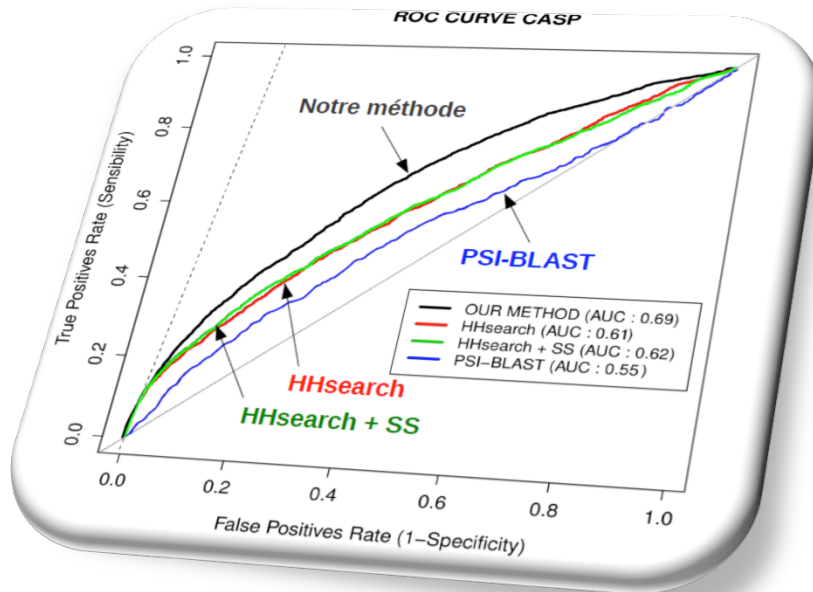
>153L
 TDCYGNVNRIDTTGASCKTAKPEGL
 SYCGVSASKKIAERDLQAMDRYKTI
 IKKVGEKLCVEPAVIAGIISRESHA
 GKVLKNGWDRGNFGMLQVDKRSH
 KPQGTWNGEVHITQGTILINFIKT
 IQKKFPSWTKDQQLKGGISAYNAGA
 GNVRSYARMDIGTTHDDYANDVVAR
 AQYYKQHG Y



*Prediction
of PBs*



>153L
 ZZmnopfklpccebjafklmmnopa
 becjklmmmmmmmmmmmmmmmmmm
 mmmmmnopafklmmmmmmmmnoola
 pgehiafkopagcjkopafklmceh
 jfklmklmmmmmmmmmmmmmmmmmm
 mmbcfklmmmmmmmmmmmmmmmmmm
 klmngoiiahilmmmmmmmmmmmmmm
 oZZ



*Structural
analogy*

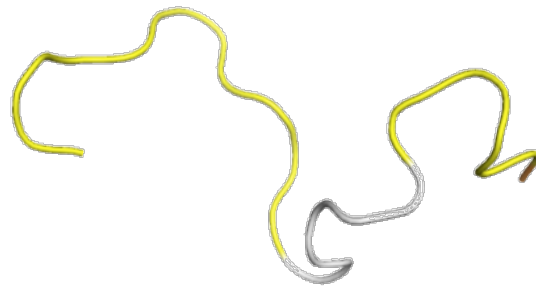


Structural fold

Dr. J.-C. Gelly

(Bioinformatics, 2015; Sci Rep, 2016)

- ❖ The most used structural alphabet at this day (Web Of Sciences: 156 citations, Google scholar: 288)
- ❖ More than 20 teams worldwide
- ❖ Used for local and global analysis, prediction (locale, specific, flexibility), le *protein design*, building of structural models, etc.

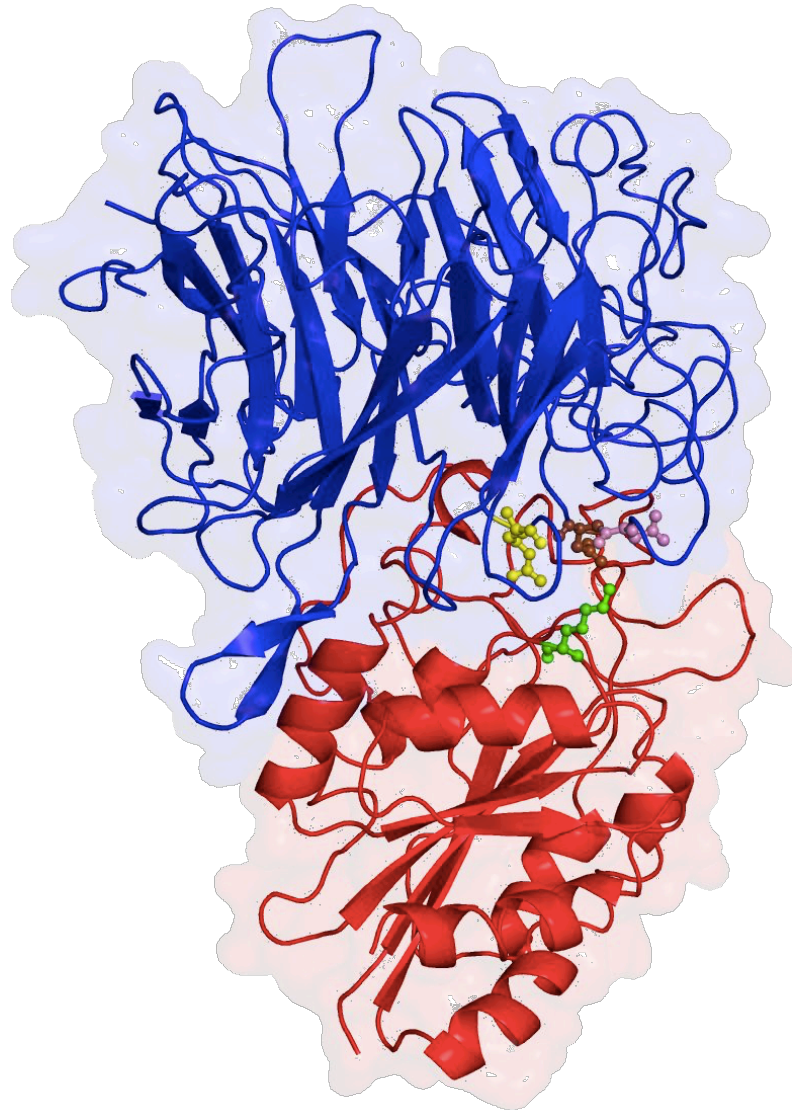


*Analysis of molecular
dynamics of protein and
peptide*

STRUCTURAL ALPHABET & FLEXIBILITY: MD

Integrins

Integrins



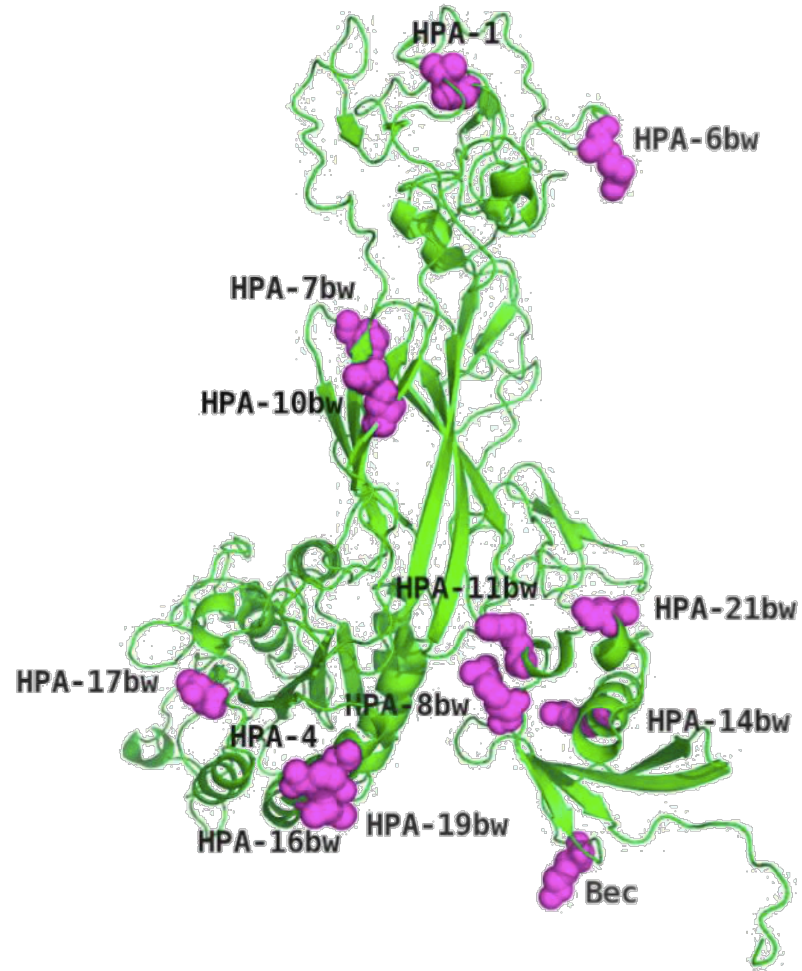
Dr. Vincent Jallu
Platelet departement



One complex (Integrin):

- **Glanzmann's thrombasthenia** is an abnormality of the platelets, an extremely rare **coagulopathy**.
- **Fetal / Neonatal alloimmune thrombocytopenia (FNAIT)**, a severe bleeding syndrome in which fetal / neonatal platelet destruction is mediated by **maternal antibodies** directed to specific antigens (or alloantigens) inherited from the father
Also the **only blood group not on Red Blood Cells**.

Integrins



- This protein is *very* flexible



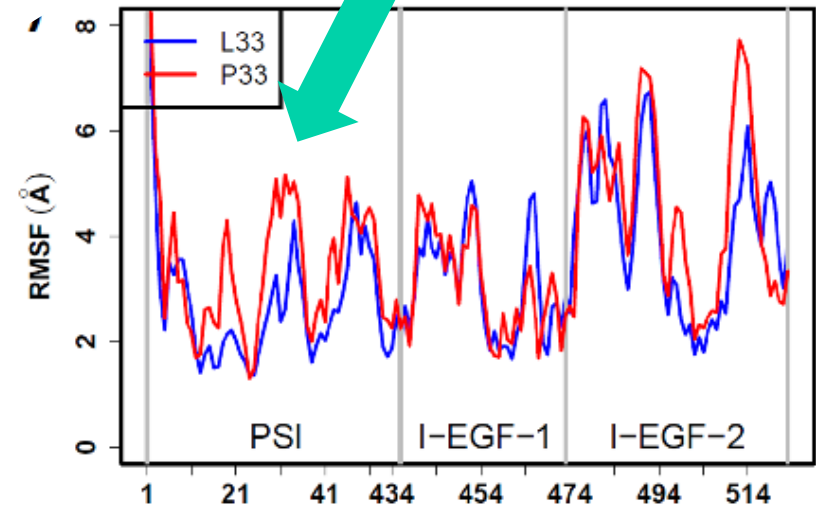
*We compute Root Mean Square
Fluctuation (RMSF)*

$$RMSF_i = \sqrt{\frac{1}{nstep} \sum_{t=1}^{nstep} \|\vec{r}_i(t) - \langle \vec{r}_i \rangle\|^2}$$

- This protein is *very* flexible



Residue 33 is associated to high RMSF

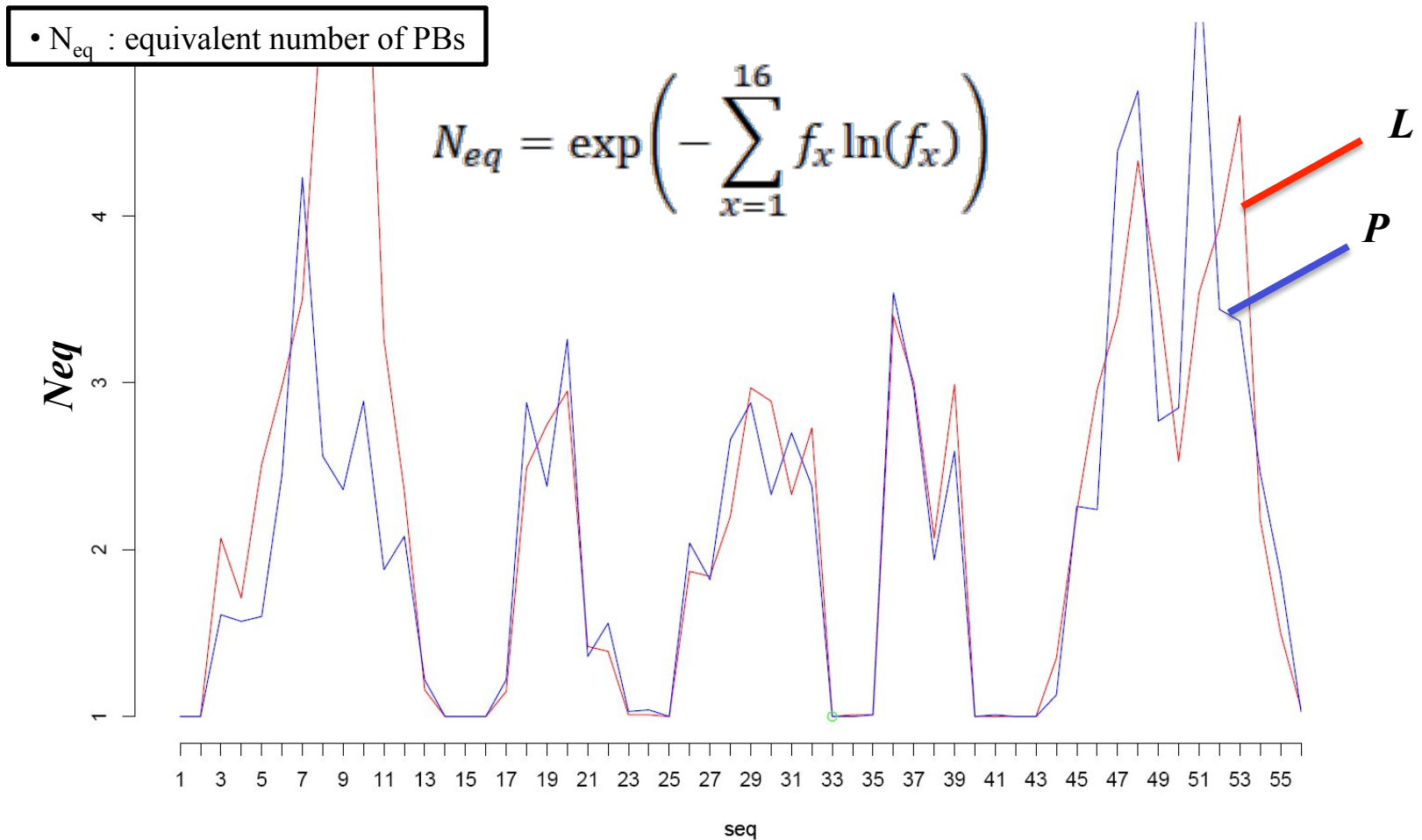


➤ How to use Protein Blocks here ?

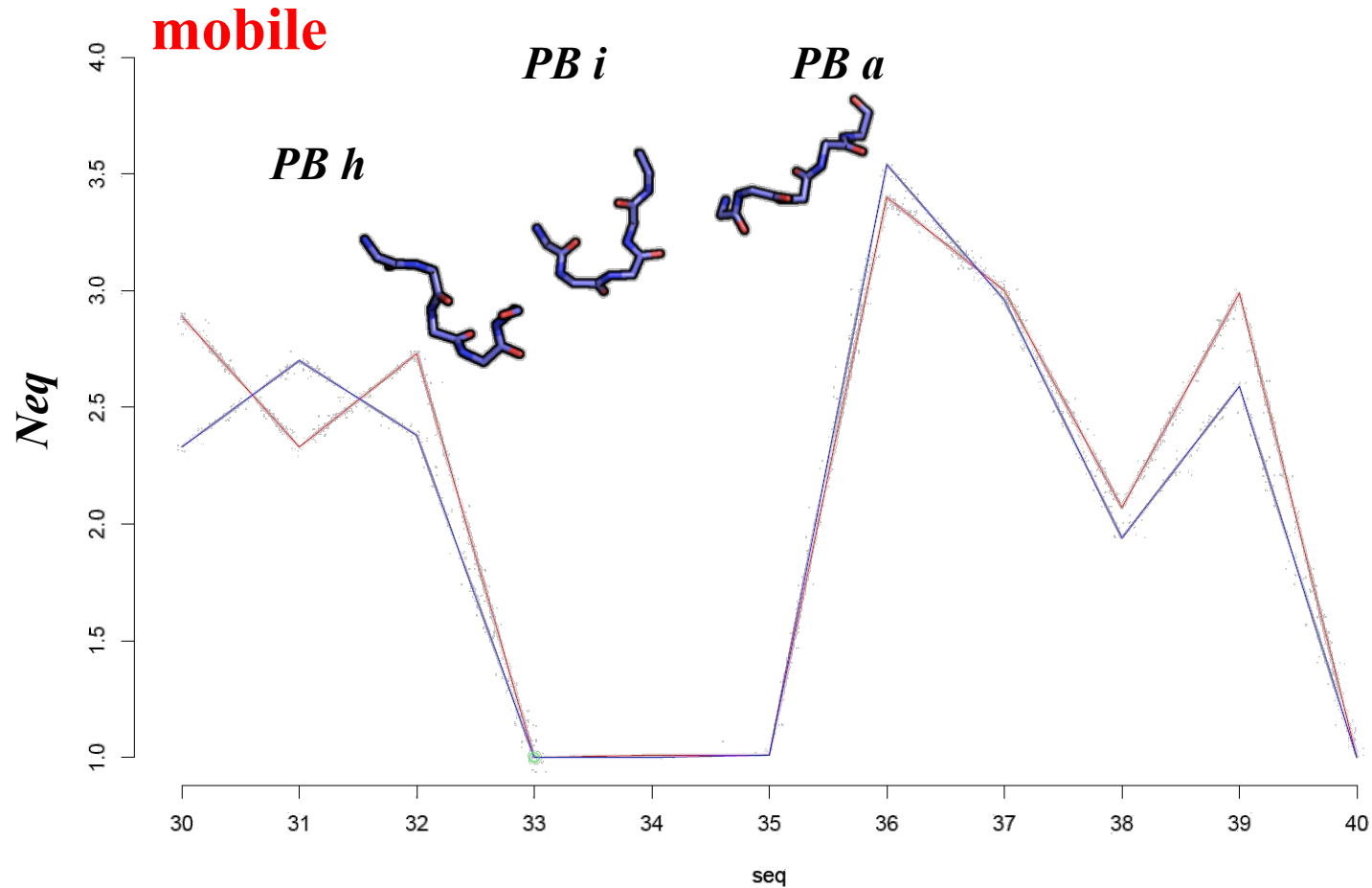


```
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iafklmmnopaflpccddddddfbdcdddfblmb  
ckbccdfbdcfbdcddddehiacddddddddehiac  
dddddddfbfklmmmmmmmmgojlmmmmmmmnpcb  
ccccccccccccdfklpcfbdflmnomclmmbdcdd  
debiadfbdcfbfklmmmmmmmmccdddfblbdcfk  
lmmmmmmommmnopaflkbccdddddfbdcdehkl  
mmnopabccehpacbdfkopafblmpccdfklmmm  
mmmmnopacdddbdfklmmmmmmmmmmghiacddd  
fklmmmmmmmmmmmmmmnccccdddehiafkbccdd  
ddfahjbccehiabdehiaghiacddddddddehjd  
fddddddddehiabdcddddddfbdfklmpcfbg  
cknojhiaccehhiacdehiacjkopafgehjlmng  
jiafbfblkbcehiopaccehhiacdfbdchiaaedj  
kopaccblbccfblpehhlpaccehhiacdehiacj  
kopacfbfklmmgfkopghhlpaccehhiacdfbghi  
edjkopaccbccfklmmmmmmmmnopajklmmmk  
lmmmomcdcdddfbdcdebiacdcdddddfkopacdd  
dddddfkopacdddfbdcdddZZ
```


- Both sets of simulations are quite similar



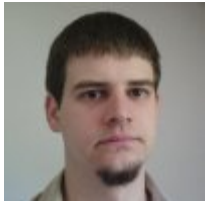
- But position 33 is not 'flexible', it stays highly constraint →



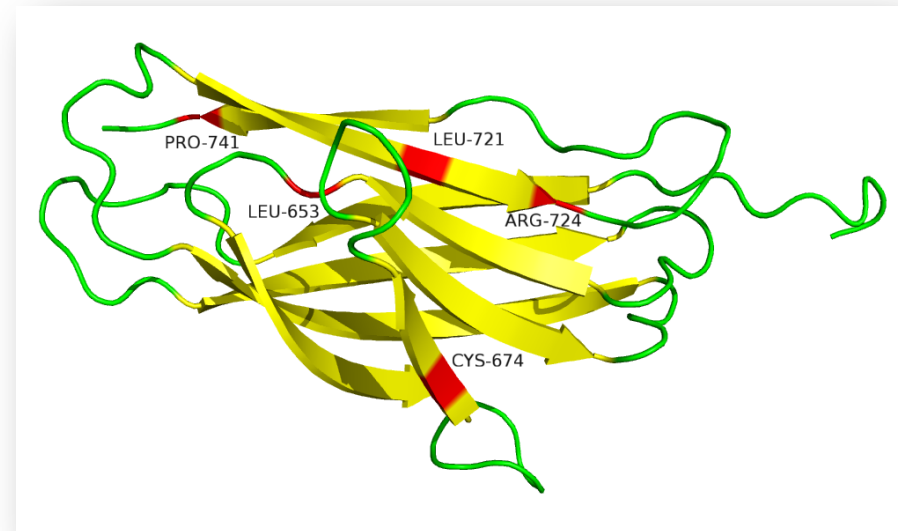
Conclusion

- Not real change of the epitope, always highly accessible
- But not flexible, it is **mobile** within **deformable regions**
- Proof of interest of **Protein Blocks** for the analysis => does not correlate with RMSf

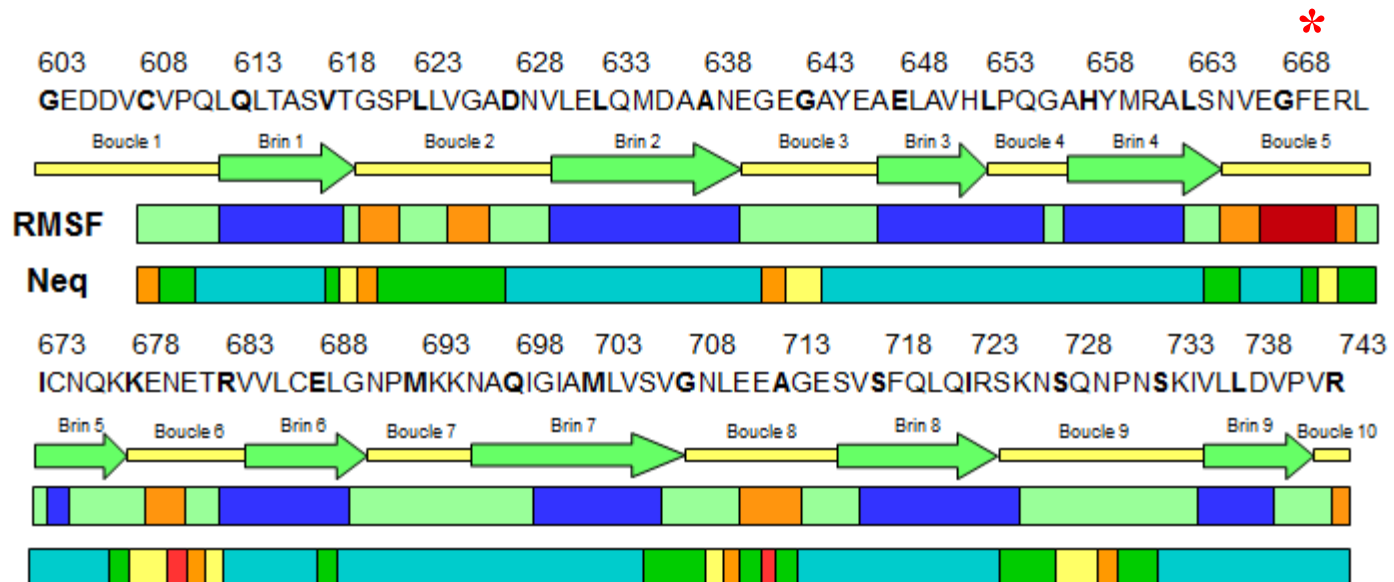
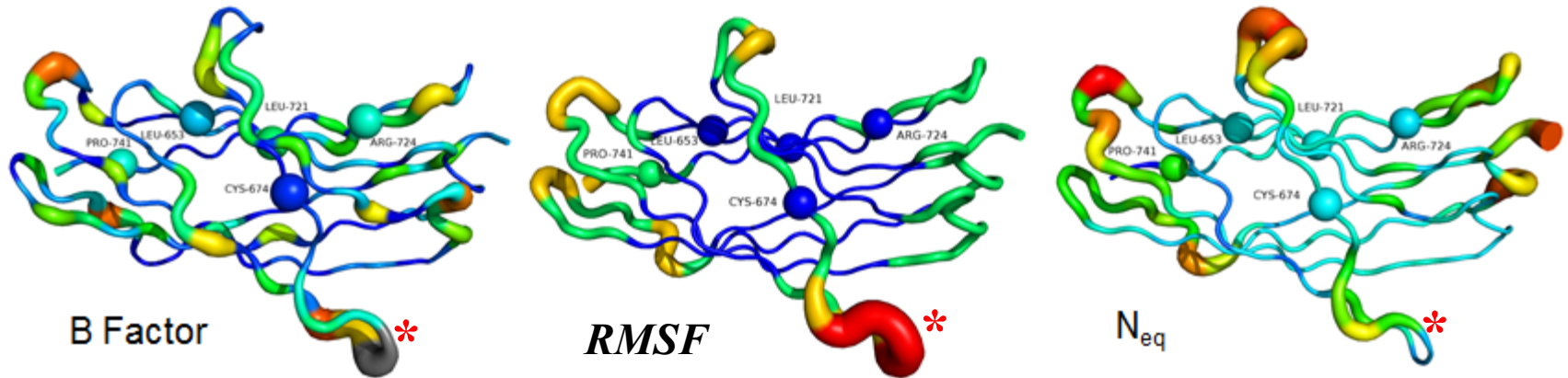
- A more systematic approach: an example of Calf-1 domain
- Calf-1 domain : 141 residus (603-743) from α chain
- 7 mutations involved in GT:



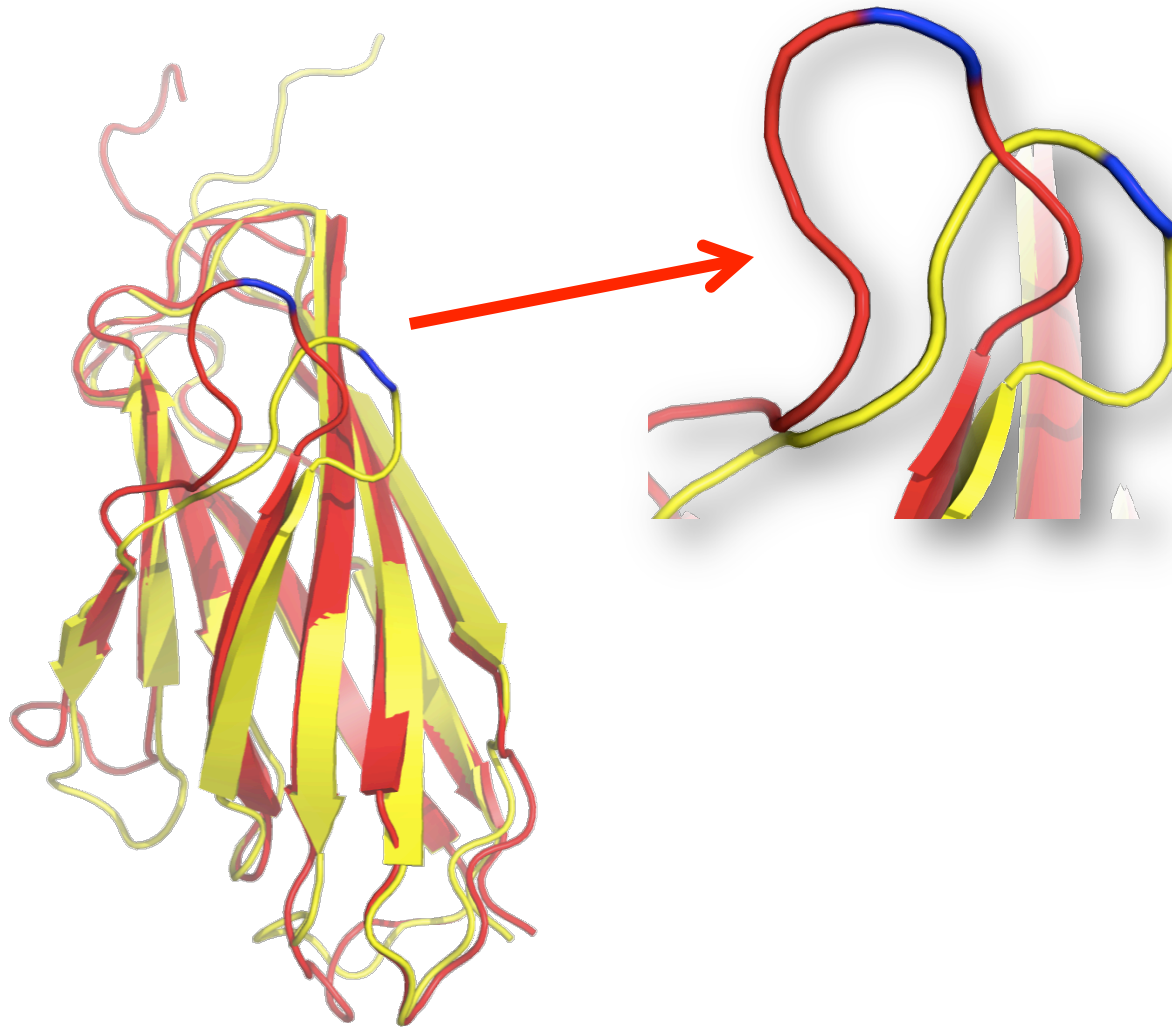
- L653R
- C674R
- L721V / L721R
Matthieu Goguet R724P / R724Q
(master 2 student) P741R



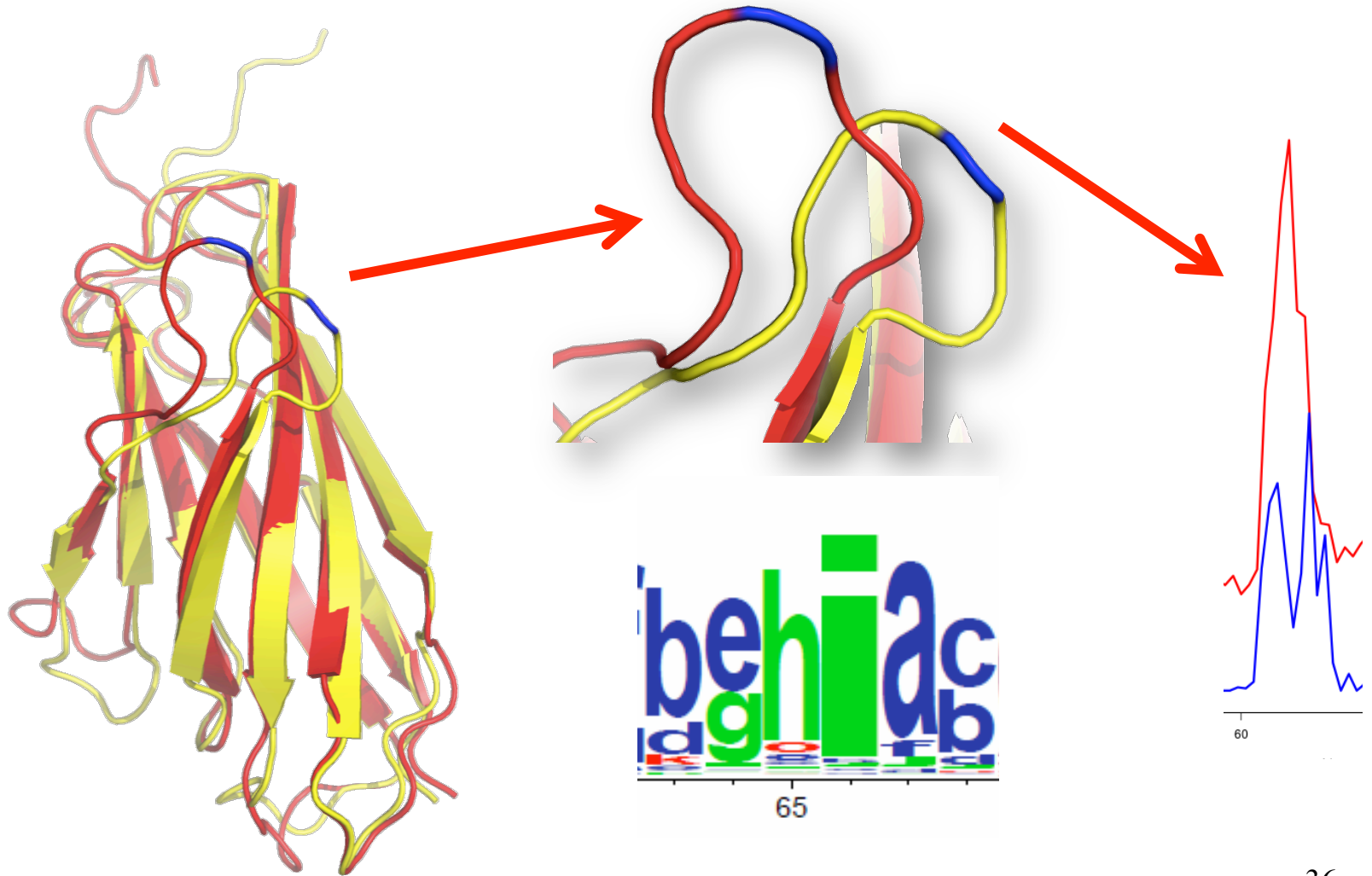
➤ Analysis of WT Calf-1



Allostery



Allostery



➤ More details in

Craveur *et al.*, (*Frontiers in Mol Sci*, 2015)



Protein flexibility in the light of structural alphabets

Pierrick Craveur^{1,2,3,4}, Agnel P. Joseph⁵, Jeremy Esque⁶, Tarun J. Narwani^{1,2,3,4}, Floriane Noël^{1,2,3,4}, Nicolas Shinada^{1,2,3,4}, Matthieu Goguet^{1,2,3,4}, Sylvain Leonard^{1,2,3,4}, Pierre Poulain^{1,2,3,4,7}, Olivier Bertrand^{1,3,4}, Guilhem Faure⁸, Joseph Rebehmed⁹, Amine Ghozlane¹⁰, Lakshmpuram S. Swapna^{11,12}, Ramachandra M. Bhaskara^{11,13}, Jonathan Barnoud^{1,2,3,4,14}, Stéphane Teletchéa^{1,2,3,4,15}, Vincent Jallu¹⁶, Jiri Cerny¹⁷, Bohdan Schneider¹⁷, Catherine Etchebest^{1,2,3,4}, Narayanaswamy Srinivasan¹¹, Jean-Christophe Gelly^{1,2,3,4} and Alexandre G. de Brevem^{1,2,3,4*}

¹ Institut National de la Santé et de la Recherche Médicale U 1134, Paris, France, ² UMR_S 1134, DSIME, Université Paris Diderot, Sorbonne Paris Cité, Paris, France, ³ Institut National de la Transfusion Sanguine, DSIME, Paris, France, ⁴ UMR_S 1134, DSIME, Laboratory of Excellence GR-Ex, Paris, France, ⁵ Rutherford Appleton Laboratory, Science and Technology Facilities Council, Didcot, UK, ⁶ Institut National de la Santé et de la Recherche Médicale U964,7 UMR Centre National de la Recherche Scientifique 7104, IGBMC, Université de Strasbourg, Illkirch, France, ⁷ Ets Poulain, Pointe-Noire, Congo, ⁸ National Library of Medicine, National Center for Biotechnology Information, National Institutes of Health, Bethesda, MD, USA, ⁹ Centre National de la Recherche Scientifique UMR7590, Sorbonne Universités, Université Pierre et Marie Curie – MINA – IRI – IJIC, Paris, France, ¹⁰ Metagenopols, INRA, Jouy-en-Josas, France, ¹¹ Molecular Biophysics Unit, Indian Institute of Science, Bangalore, Bangalore, India, ¹² Hospital for Sick Children, and Departments of Biochemistry and Molecular Genetics, University of Toronto, Toronto, ON, Canada, ¹³ Department of Theoretical Biophysics, Max Planck Institute of Biophysics, Frankfurt, Germany, ¹⁴ Laboratoire de Physique, École Normale Supérieure de Lyon, Université de Lyon, Centre National de la Recherche Scientifique UMR 5672, Lyon, France, ¹⁵ Faculté des Sciences et Techniques, Université de Nantes, Unité Fonctionnelle et Ingénierie des Protéines, Centre National de la Recherche Scientifique UMR 6286, Université Nantes, Nantes, France, ¹⁶ Platelet Unit, Institut National de la Transfusion Sanguine, Paris, France, ¹⁷ Institute of Biotechnology, The Czech Academy of Sciences, Prague, Czech Republic

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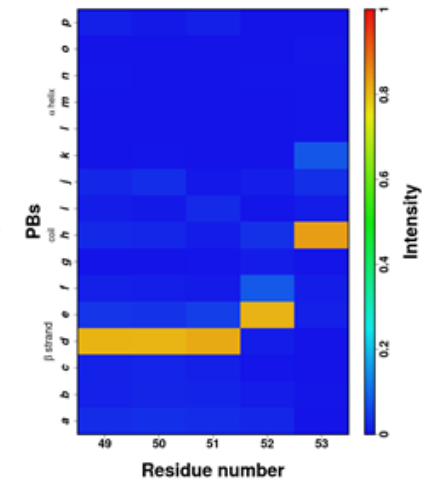
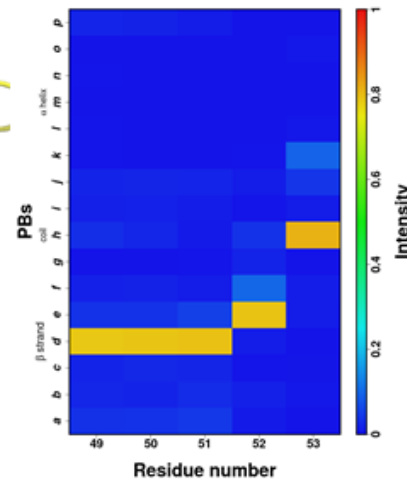
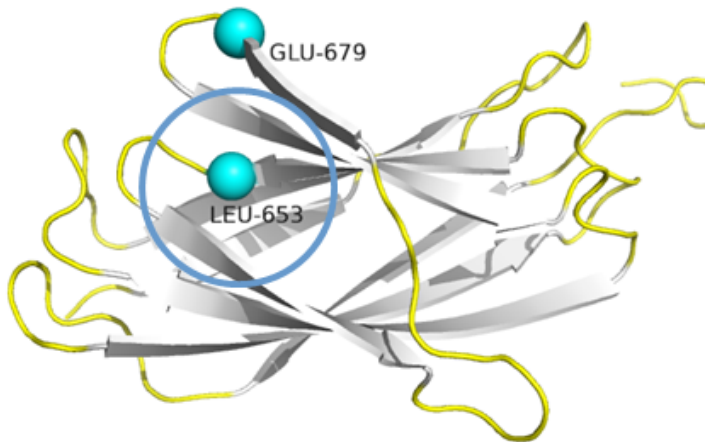
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RM, Barnoud J, Teletchéa S, Jallu V,
Cerny J, Schneider B, Etchebest C,
Srinivasan N, Gelly J-C and de
Brevem AG (2015) Protein flexibility in
the light of structural alphabets.
Front. Mol. Biosci. 2:20.
doi: 10.3389/fmolb.2015.00020

Protein structures are valuable tools to understand protein function. Nonetheless, proteins are often considered as rigid macromolecules while their structures exhibit specific flexibility, which is essential to complete their functions. Analyses of protein structures and dynamics are often performed with a simplified three-state description, i.e., the classical secondary structures. More precise and complete description of protein backbone conformation can be obtained using libraries of small protein fragments that are able to approximate every part of protein structures. These libraries, called structural alphabets (SAs), have been widely used in structure analysis field, from definition of ligand binding sites to superimposition of protein structures. SAs are also well suited to analyze the dynamics of protein structures. Here, we review innovative approaches that investigate protein flexibility based on SAs description. Coupled to various sources of experimental data (e.g., B-factor) and computational methodology (e.g., Molecular Dynamic simulation), SAs turn out to be powerful tools to analyze protein dynamics, e.g., to examine allosteric mechanisms in large set of structures in complexes, to identify order/disorder transition. SAs were also shown to be quite efficient to predict protein flexibility from amino-acid sequence. Finally, in this review, we exemplify the interest of SAs for studying flexibility with different cases of proteins implicated in pathologies and diseases.

Keywords: protein structures, disorder, secondary structure, structural alphabet, protein folding, allostery, protein complexes, protein–DNA interactions

Variant L653R : Mutation site



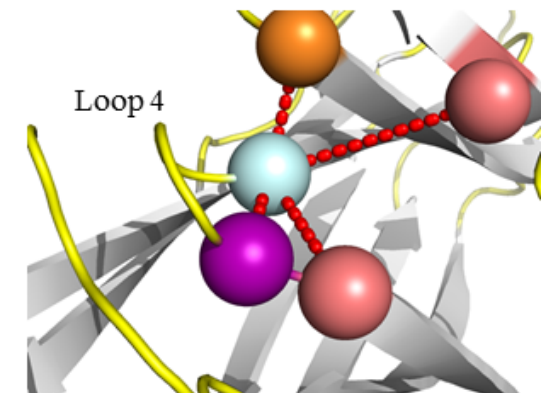
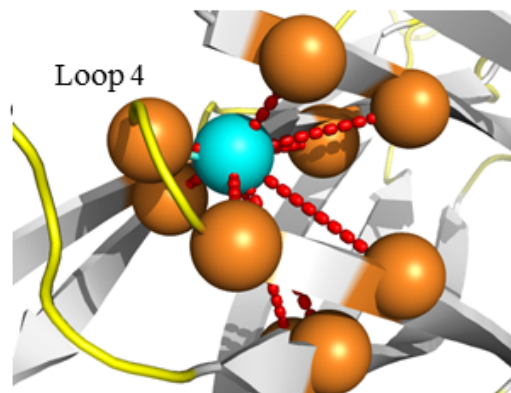
WT

Variant

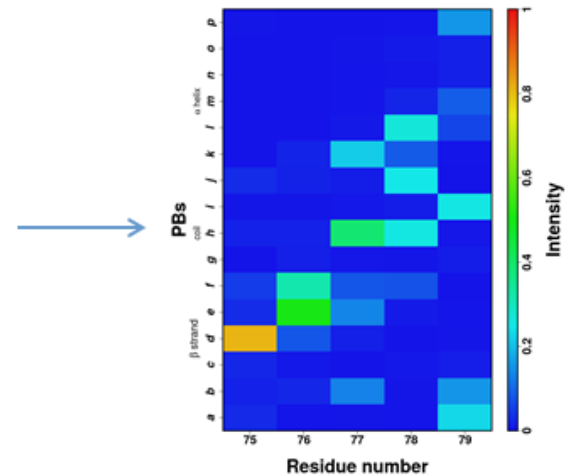
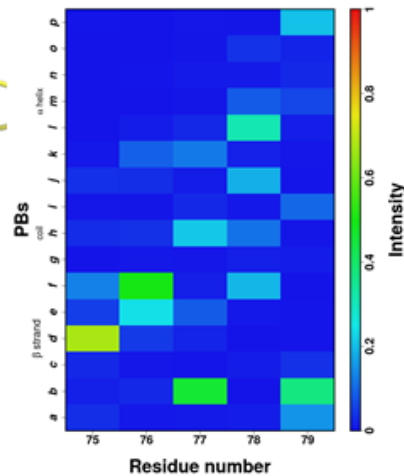
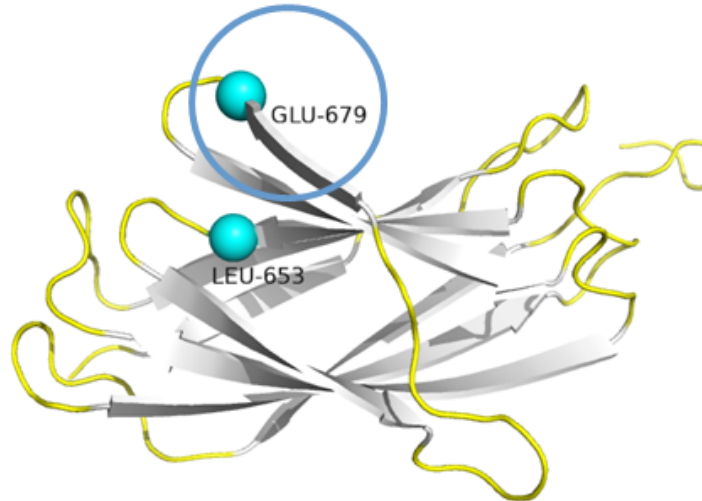
WT : 9 interactions

Variant : only 1 conserved but 3 news to

→ No structural changes



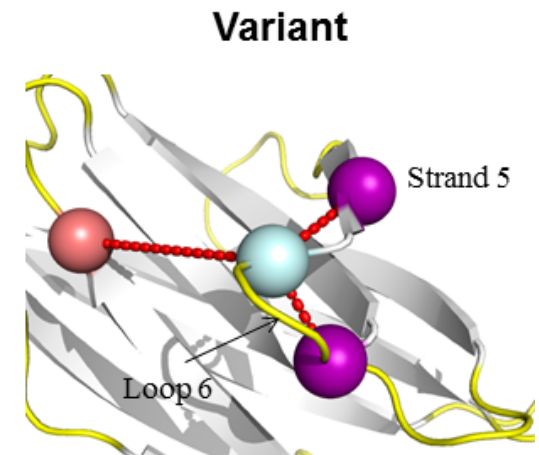
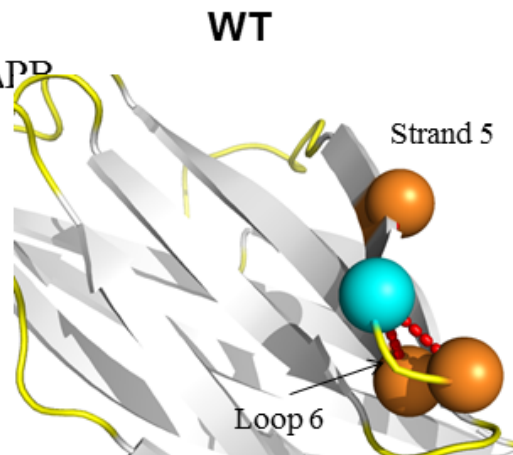
Variant L653R : position E679



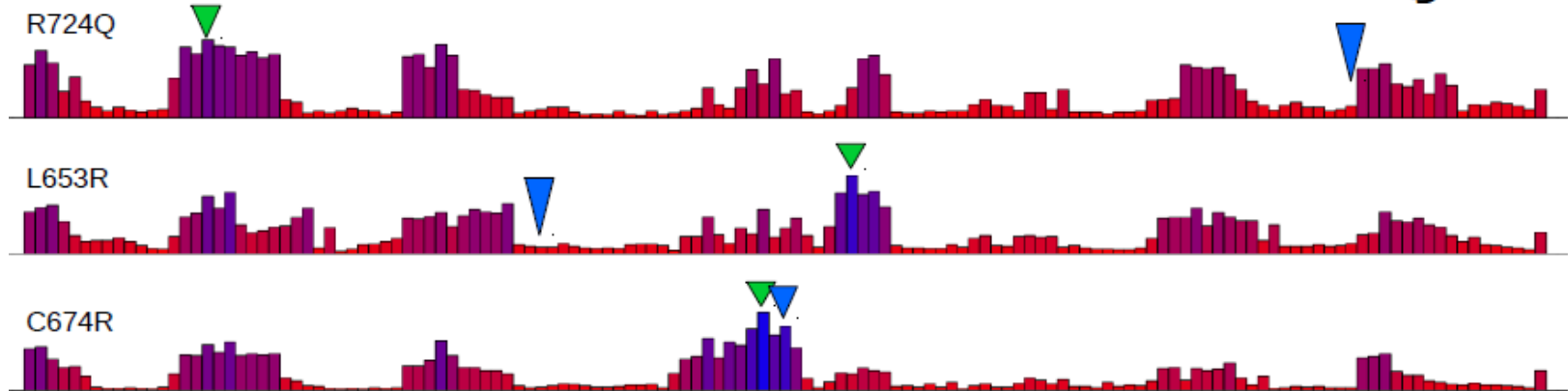
N_{eq} similar in WT and variant but high ΔPP

Interaction reshuffle (no conservation)

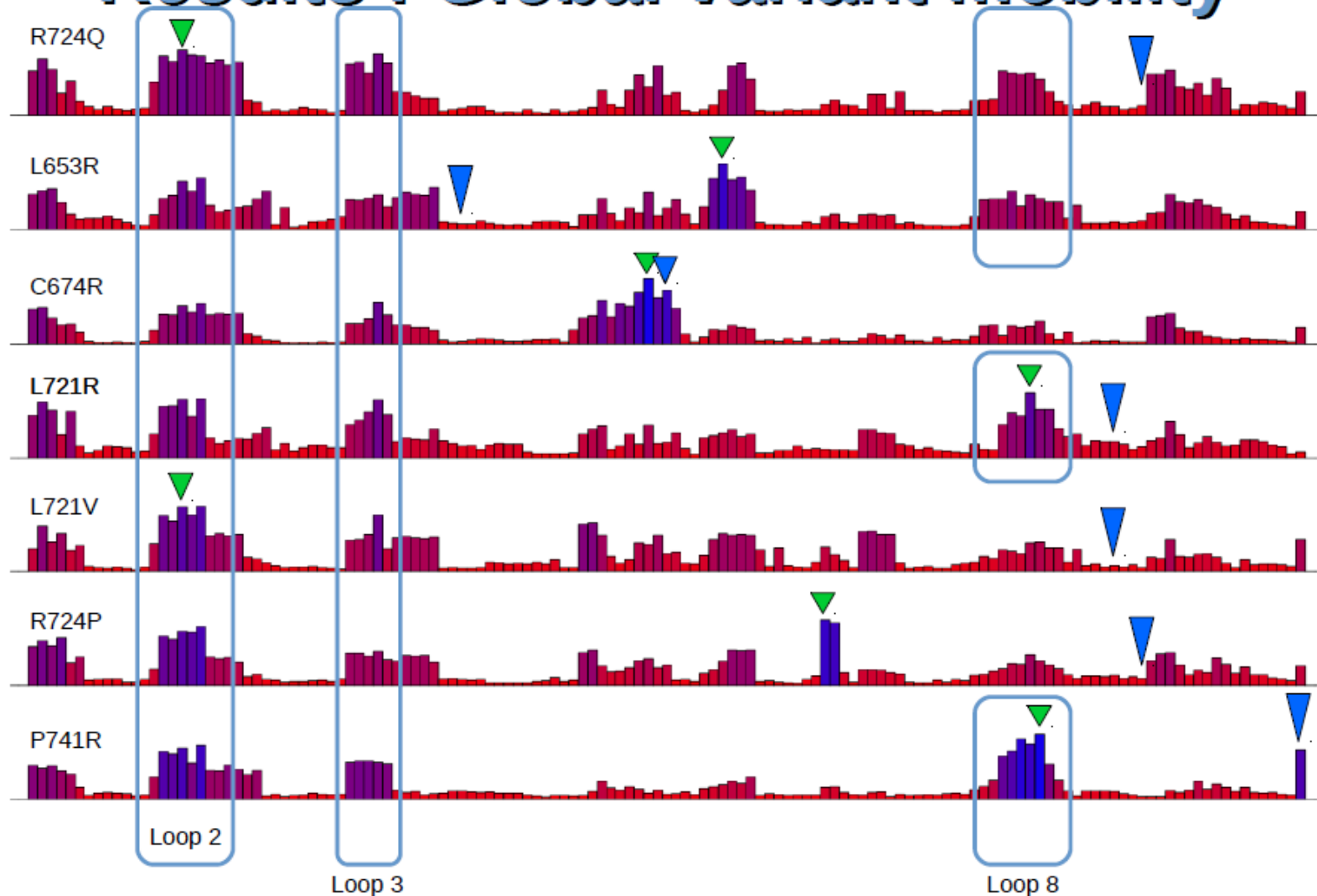
→ Structural desorganization



Results : Global variant mobility



Results : Global variant mobility



Conclusion (1)

-
- Reliable, automated and efficient molecular dynamics protocol with interesting use of Protein Blocks
 - Results on Calf-1 : no changes on mutation spots but structural local impact observed at another place.
 - Does these allosteric effects are common to all of these variants ?
 - Future: Study of this and others integrins

- Last developments: deposit on ArXiv, now published in PeerJ

<https://github.com/pierrepo/PBxplore>

GitHub This repository Search Explore Features Enterprise Blog Sign up Sign in

pierrepo / PBxplore Watch 5 Star 6 Fork 6

A program to explore protein structures with Protein Blocks

312 commits 3 branches 0 releases 3 contributors

Branch: master PBxplore / +

Improved regression tests, demo and doc for PBclust.py

1atest commit b265945a70

demo1 added more test files for PDBx/mmCIF format 7 months ago

demo2 Number of cluster is now a mandatory option in PBclust.py. 3 months ago

demo_paper Added images in demo_paper 5 months ago

doc Improved regression tests, demo and doc for PBclust.py 26 days ago

test_data Uncomment the test for PBcount with negative shift 3 months ago

.coveragerc added .coveragerc for travis 6 months ago

.gitignore Ignore png file only in the root directory 5 months ago

.travis.yml Make travis-CI install R 3 months ago

LICENSE Fixed #12 - added a more permissive license (MIT) 11 months ago

PBassign.py Remove the PB_assign function 2 months ago

PBclust.py -clusters and -compare options are now mutually exclusive 26 days ago

PBcount.py Fixed #47 -first-residue option of PBcount.py can be < 0. 3 months ago

PBlib.py Simplify PBassign command line function 2 months ago

PBs_substitution_matrix.dat New tool to cluster sequences based on PBs similarities 2 years ago

PBstat.py Merge pull request #56 from jbamoud/module_clust 3 months ago

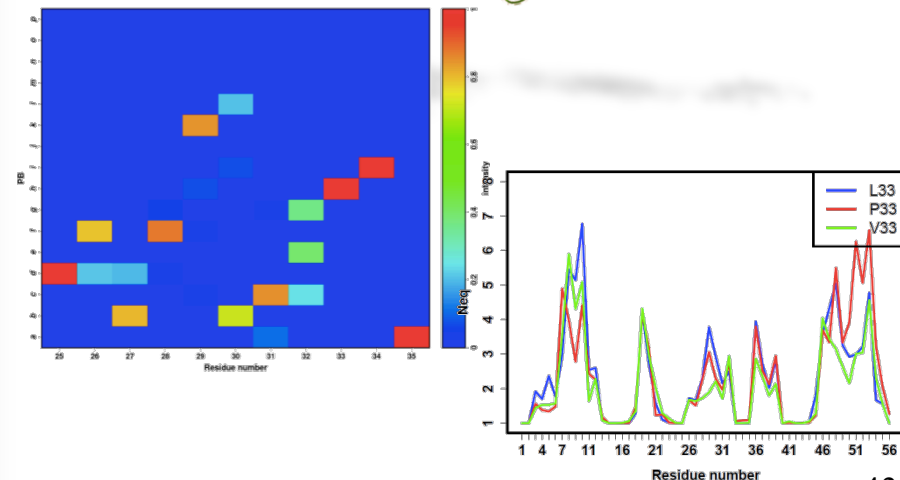
PDBlib.py Improve 'PBassign' modularity 3 months ago

README.md Beginning for issue #30. More to add. 5 months ago

dev_requirements.txt Adapt the tests for when MDAnalysis is missing 5 months ago

Code Issues 11 Pull requests 0 Pulse Graphs

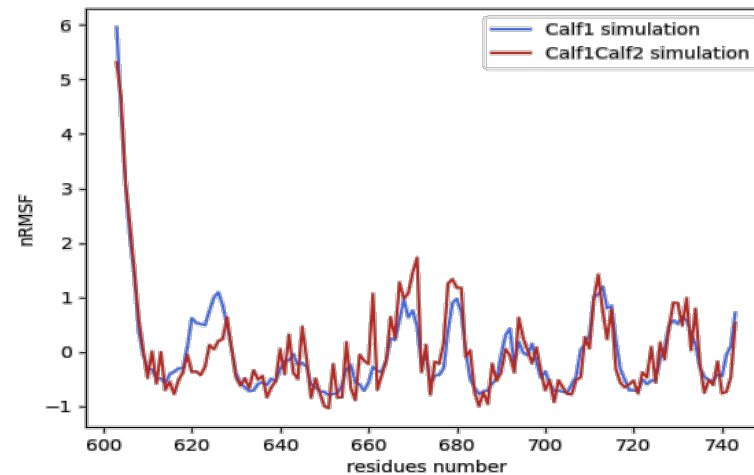
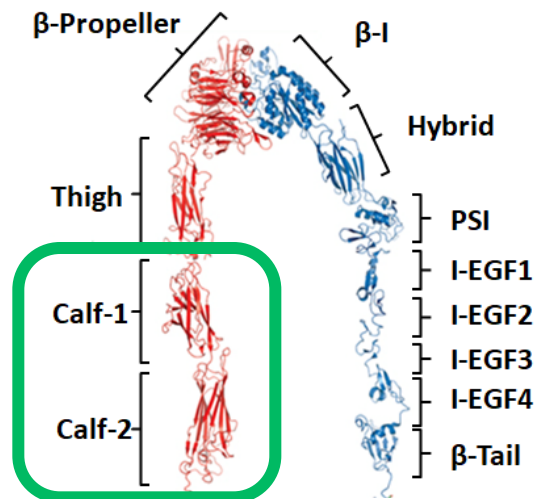
HTTPS clone URL https://github.com/1 Clone in Desktop Download ZIP



Calf-1 + Calf- 2

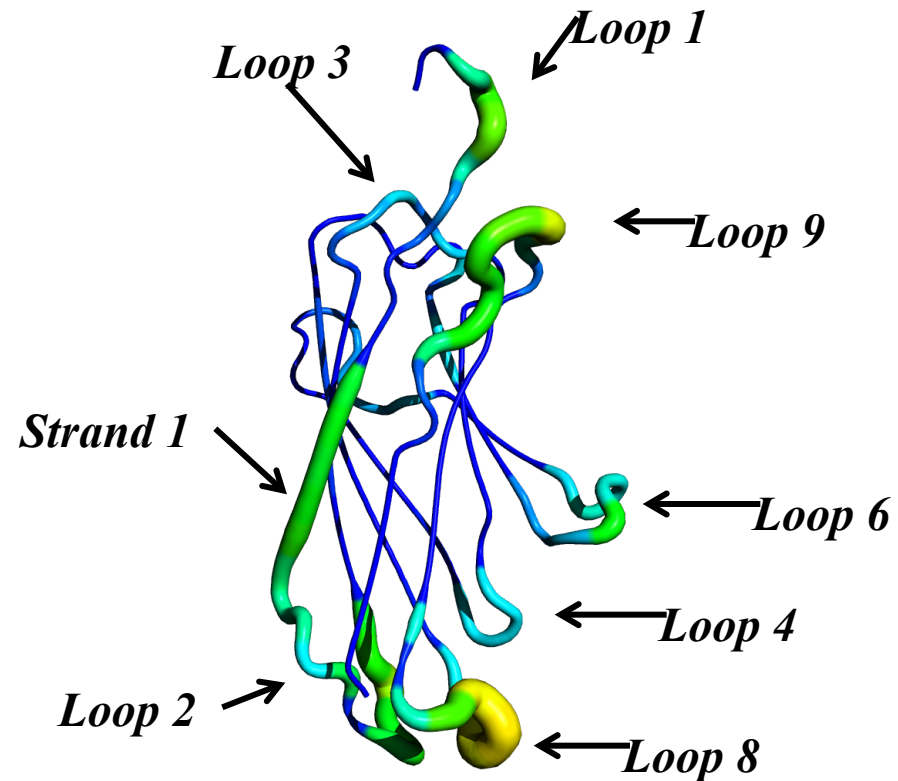
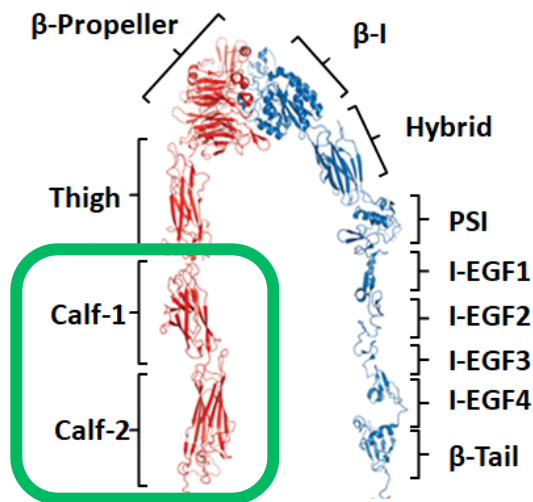
- No impact of the forcefield used
- No impact on the domains cutting

Soubika Bisoo
(master 2 student)



Calf-1 + Calf-2

- BUT allosteric effect of Calf-2 variant on Calf-1 domain !



Calf-1: Δ PB

Conclusions (2)

- Secondary structures are useful tools, but they have their own limitations
- Other complementary approaches are interesting, i.e., a simple structural alphabet as the Protein Blocks
- They can help to analyze molecular dynamics, i.e., you can see what you can see without.

- Thanks to last Belbi 2016, I am now really more interested into this question

The screenshot shows the top navigation bar with links for PED, Home, Browse, Help, and Contact. Below the navigation bar, the main heading reads "PED³: Protein Ensemble Database" with the subtitle "The database of conformational ensembles describing flexible proteins". A search bar is present with the text "Select experimental data type: NMR SAXS BOTH ANY" and a "Search" button.

Welcome to the Protein Ensemble Database!

What is an IDP?

Structural heterogeneity is intimate to the functioning of many proteins and thus describing a protein with a single native structure is often insufficient to elucidate its function. In particular, intrinsically disordered proteins (IDPs) can only be approached by solution techniques and described as structural ensembles. The same is true for multidomain proteins that have disordered linkers. Apparently, the ensemble representations of these proteins carry essential function-related information, yet they have not been available until now.

[Read more about IDPs...](#)

What is an ensemble?

The goal of PED is to serve as an openly accessible database for the deposition of structural information on IDP- and denatured protein ensembles based on Nuclear Magnetic Resonance (NMR) and Small-angle X-ray Scattering (SAXS) data. We are also hosting purely computational models, typically from Molecular Dynamics (MD) simulations. The deposition of structural coordinates as well as primary data can be used for evaluating and re-calculating the ensembles, thus supporting the evolution of new modeling methods leading to much improved skills of connecting "unstructure" Å with function.

[Read more about ensembles...](#)

Latest news

Tweets by @proteinEnsemble



PED
 @proteinEnsemble

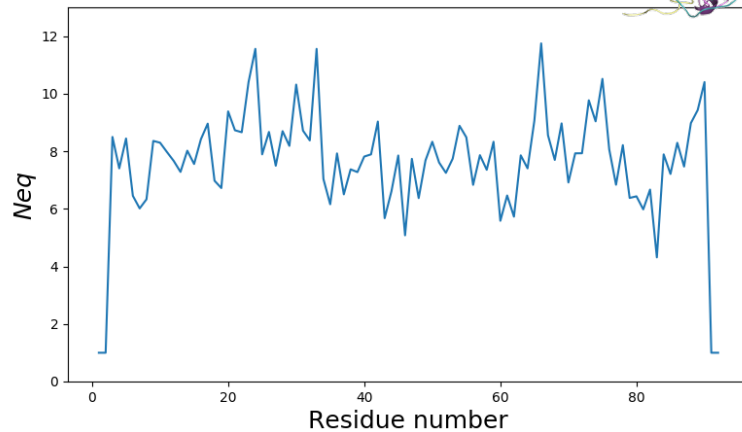
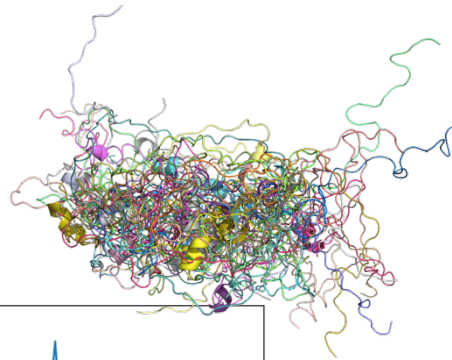
The Protein Ensemble Database (PED) is going under a

Data submission is temporarily suspended until further notice

PED stores 25473 protein structures of 60 ensembles in 24 entries as of 06/17/2018 04:43:16 pm

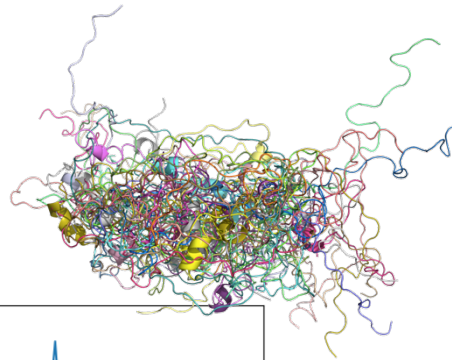
For citing PED, please refer to: Mihaly Varadi, Simone Kosol, Pierre Lebrun, Erica Valentini, Martin Blackledge, A. Keith Dunker, Isabella C. Felli, Julie D. Forman-Kay, Richard W. Kriwacki, Roberta Pierattelli, Joel Sussman, Dmitri I. Svergun, Vladimir N. Uversky, Michele Vendruscolo, David Wishart, Peter E. Wright and Peter Tompa "pE-DB: a database of structural ensembles of intrinsically disordered and of unfolded proteins" *Nucleic Acids Res.* 2014, Jan (Database issue)

- Thanks to last Belbi 2016, I am now really more interested into this question

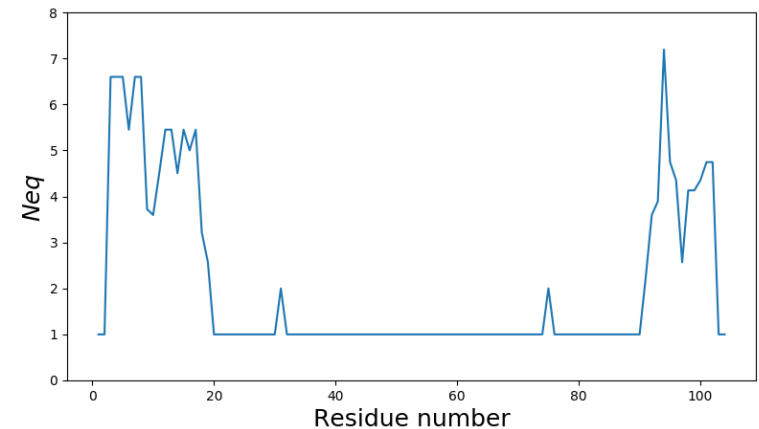
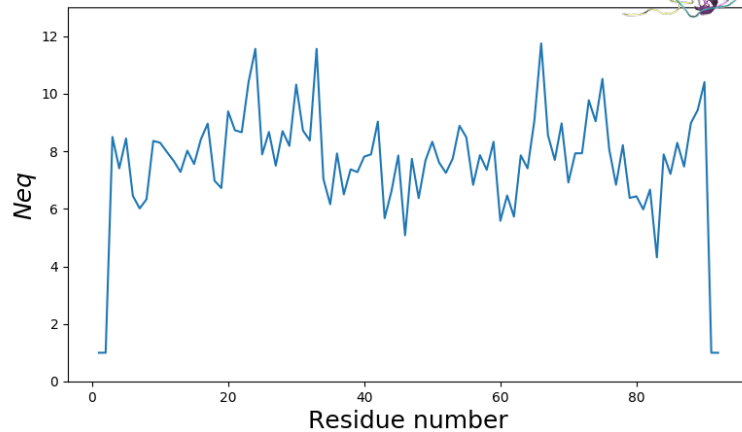


Yes, real disorder everywhere

- Thanks to last Belbi 2016, I am now really more interested into this question



Not really



- PBs can be a good tool for that... needs more works

Rigid → *flexible* → *disorder*

Rigid / mobile → *flexible/deformable* → *disorder*

Acknowledgments

S. Hazout

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N. Mitic



Thank you for your time and attention