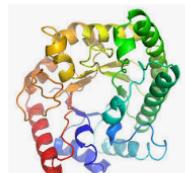


Protein dynamics adaptation during evolution

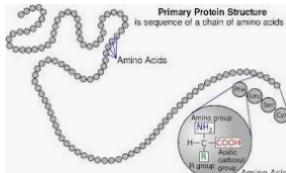
Protein

Google protein biology

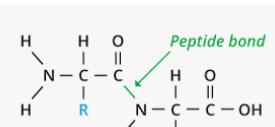
Tous Images Vidéos Shopping Actualités Plus Paramètres Outils



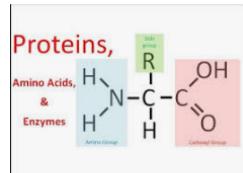
bioinformatics - By just look...
biology.stackexchange.com



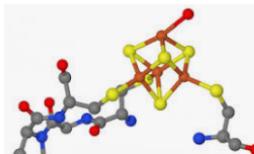
Biology for Kids: Proteins and Amino Acids
ducksters.com



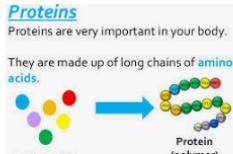
Biological Proteins | Biology | Visionlearning
visionlearning.com



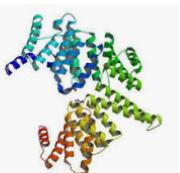
Proteins & Enzymes (regular biology)...
youtube.com



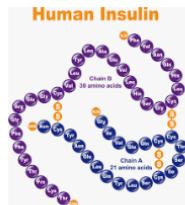
Researchers describe protein previously u...
phys.org



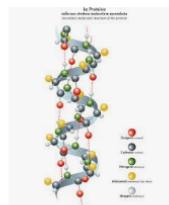
Protein Denaturation-An Important C...
pinterest.com



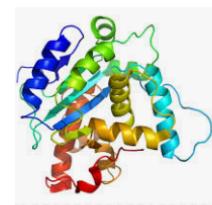
Proteins
biology-questions-and-answers....



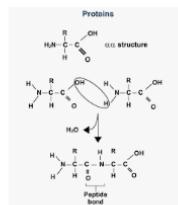
The Basics of Protein Struct...
interactive-biology.com



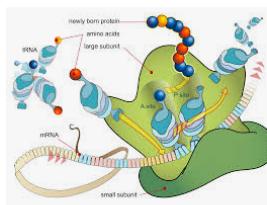
Protein Structure - Biology...
biologyreference.com



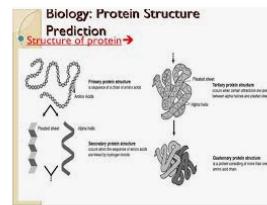
Protein structure Amino acid Bi...
kis.spg.com



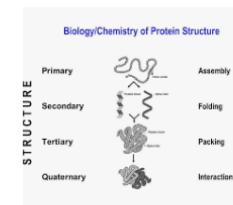
Proteins | S-cool, the revisi...
s-cool.co.uk



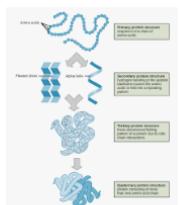
Translation (biology) - Wikipedia
en.wikipedia.org



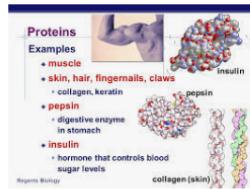
Biology: Protein Structure
Prediction
Structure of protein →
slideplayer.net



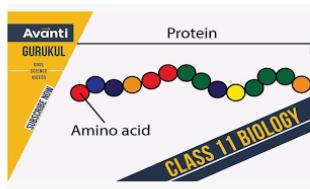
Protein Structure. - ppt video online d...
slideplayer.com



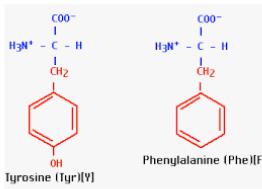
Introduction to proteins an...
khanacademy.org



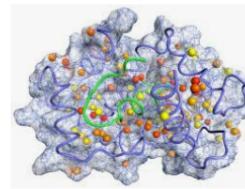
Regents Biology Proteins. Regents Biol...
slideplayer.com



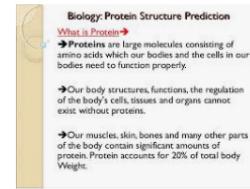
Proteins | Amino acids | Class 11 Biology - YouTube
youtube.com



Proteins
biology-pages.info



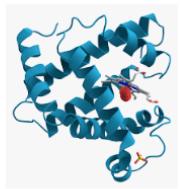
TSRI Scientists Develop New Toolkit for...
labroots.com



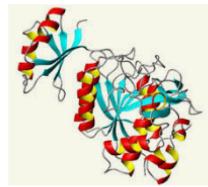
Biology protein structure
slideplayer.net



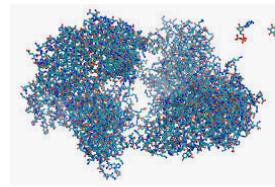
Using computational biology for ...
phys.org



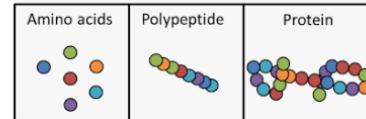
Protein - Wikipedia
en.wikipedia.org



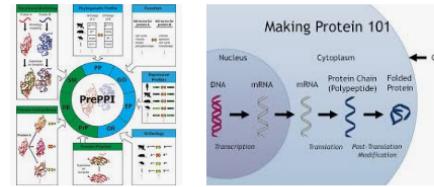
Protein Folding, Misfolding and ...
ocw.mit.edu



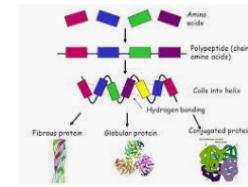
Proteins - Biology
sites.google.com



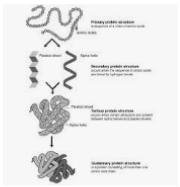
6 Difficult HSC Biology Concepts You Need to Know | Matrix...
matrix.edu.au



Making Protein 101
PrePTI
2014-2015 » High School » Biology pr...
systemsbiology.columbia.edu



Ch5 – Proteins + Enzymes | Mrs Smith' ...
mrs.smith.biology.wordpress.com



MLA CE Course Manual: M...
ncb.nlm.nih.gov

Protein

Google protein biology

Tous Images Vidéos Shopping Actualités Plus Paramètres Outils

The search results are organized into several circular clusters:

- Top Left Cluster (Blue Circles):**
 - Primary Protein Structure: Amino Acids sequence.
 - Peptide bond diagram: R-NH-C(=O)-CH2-C(=O)-NH-R'.
 - Proteins, Amino Acids, & Enzymes: Amino group (NH_2) and Carboxyl group (COOH).
 - Researchers describe protein previously u...: A 3D ribbon model of a protein.
 - Protein Denaturation-An Important C...: A 3D ribbon model of a protein.
 - Proteins: Proteins are very important in your body.
- Middle Left Cluster (Blue Circles):**
 - Human Insulin: Structure of insulin chains A and B.
 - Protein Structure - Biology: A 3D ribbon model of a protein.
 - Protein structure Amino acid Bi...: A 3D ribbon model of a protein.
 - Proteins | S-cool, the revisi...: A detailed diagram of protein structure levels (Primary, Secondary, Tertiary, Quaternary) and assembly.
 - Translation (biology) - Wikipedia: A diagram of protein synthesis on a ribosome.
 - Biology: Protein Structure Prediction: A diagram of protein structure prediction steps.
 - Protein Structure. - ppt video online d...: A slide presentation on protein structure.
 - Introduction to proteins an...: An introduction to protein structure.
- Middle Center Cluster (Pink Circles):**
 - Proteins Examples: Examples like muscle, skin, hair, insulin, pepsin, collagen, keratin.
 - Avant! GURUKUL Protein: A diagram of an amino acid chain.
 - Proteins | Amino acids | Class 11 Biology - YouTube: A 3D ribbon model of a protein.
 - Proteins: Amino acid structures (Tyrosine, Phenylalanine).
 - TSRI Scientists Develop New Toolkit for...: A 3D ribbon model of a protein.
 - Biology protein in structure: A diagram of protein structure levels.
 - Using computational biology for...: A diagram of protein structure prediction.
 - Protein - Wikipedia: A 3D ribbon model of a protein.
- Bottom Center Cluster (Pink Circles):**
 - Protein Folding, Misfolding and ...: A diagram of protein folding.
 - Proteins - Biology: A 3D ribbon model of a protein.
 - Amino acids, Polypeptide, Protein: A diagram showing the relationship between amino acids, polypeptides, and proteins.
 - 6 Difficult HSC Biology Concepts You Need to Know | Matrix...: A diagram of protein structure levels.
 - Database of Protein-Protei...: A diagram of protein structure prediction.
 - Making Protein 101: A diagram of protein synthesis (Transcription, Translation, Post-Translation modification).
 - Ch5 - Proteins + Enzymes | Mrs. Smith' ...: A diagram of protein structure levels.
 - MLA CE Course Manual: H...: A diagram of protein structure levels.

1) structure 2) primary to quaternay structure 3) protein translation

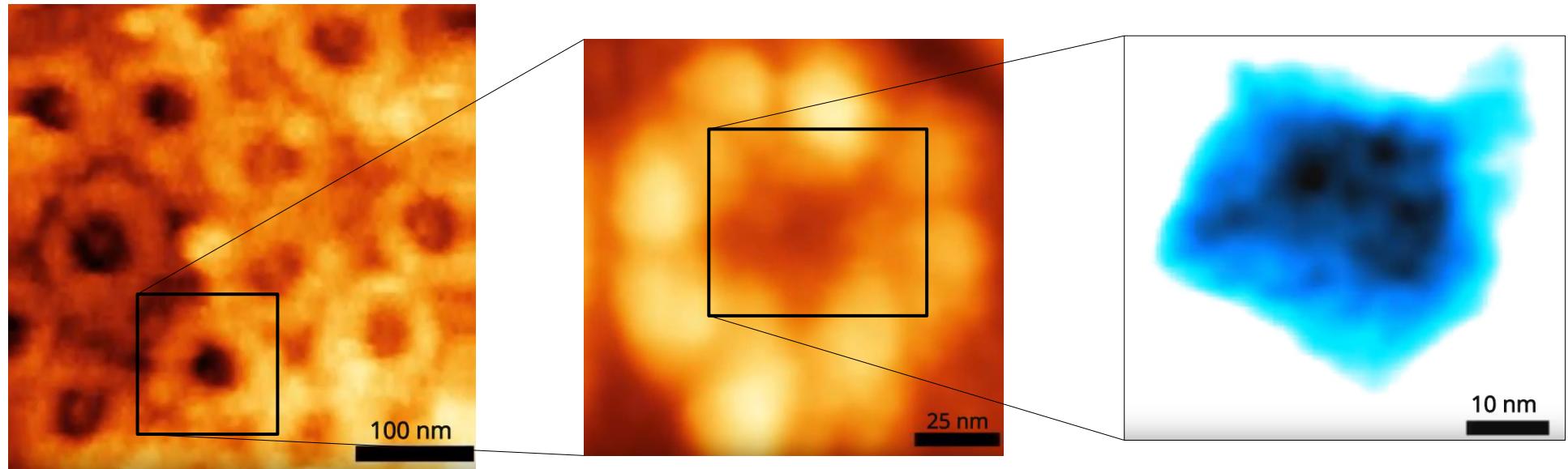
Protein dynamics

Experimental approaches

- NMR spectroscopy
- Cryo-EM conformations
- AFM (soon)



Science et al. Using Backbone-Only Data NMR Structure Determination for Larger Proteins – Sciences (2010)

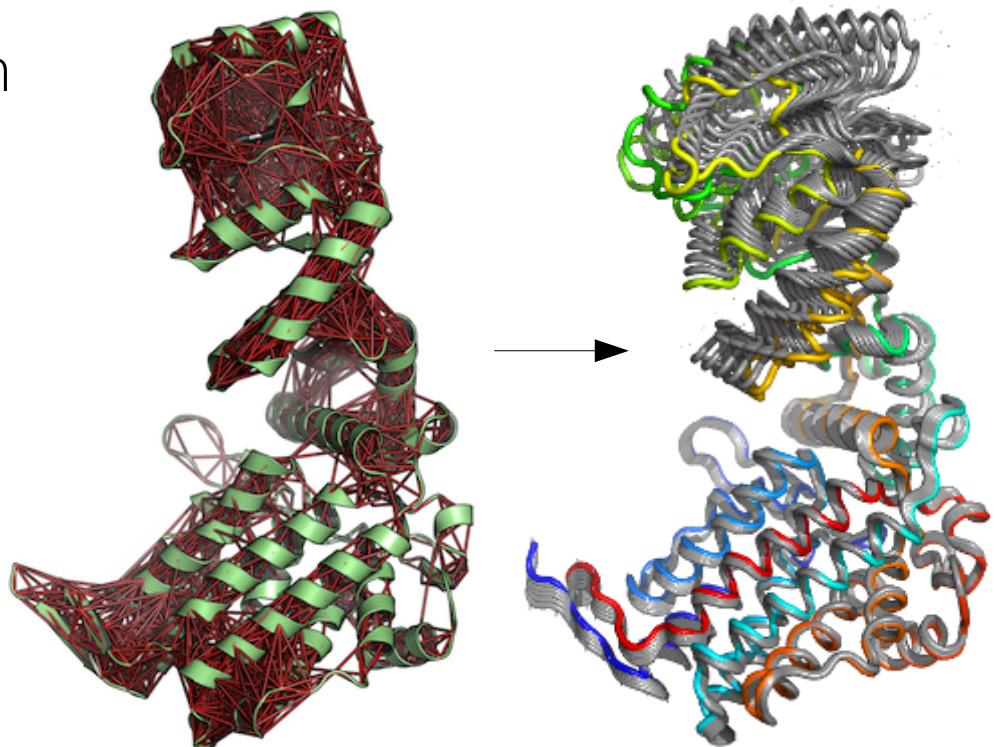
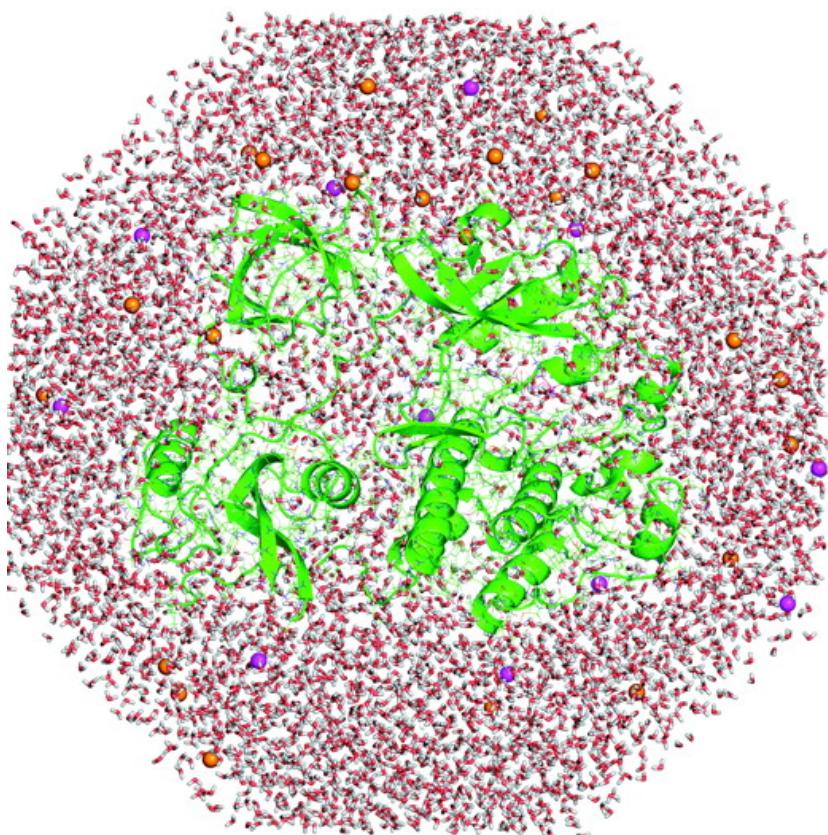


Sakiyama, Mazur, Kapinos, Roderick. Spatiotemporal dynamics of the nuclear pore complex transport barrier resolved by high-speed atomic force microscopy - Nature Nanotechnology (2016)

Protein dynamics

Computational approaches

- Molecular Dynamics simulation
- Conformational sampling
- Normal mode analysis



Bio3D – Grant lab

Karplus, Kuriyan. Molecular dynamics and protein function - PNAS (2005)

Protein dynamics and evolution

Structural constraints vs Functional constraints:

- dynamical changes between homologous protein sequences with different functions
- importance of flexibility for protein function
- relation between substitution rate and flexibility/density

OPEN  ACCESS Freely available online

PLOS COMPUTATIONAL BIOLOGY

Collective Dynamics Differentiates Functional Divergence in Protein Evolution

Tyler J. Glembi¹, Daniel W. Farrell², Z. Nevin Gerek¹, M. F. Thorpe¹, S. B.

Evolution of Conformational Dynamics Determines the Conversion of a Promiscuous Generalist into a Specialist Enzyme

Taisong Zou,¹ Valeria A. Rissi,² Jose A. Gavira,³ Jose M. Sanchez-Ruiz,^{*2} and S. Banu Ozkan^{*1}

¹Center for Biological Physics, Department of Physics, Arizona State University

²Consejo Superior de Investigaciones

Universidad de Granada, Granada, Spain

³Instituto de Ciencias de la Tierra (Consejo Superior de Investigaciones

3/molbev/msu281 Advance Access publication October 13, 2014

Sequence Evolution Correlates with Structural Dynamics

Ying Liu¹ and Ivet Bahar^{*1}

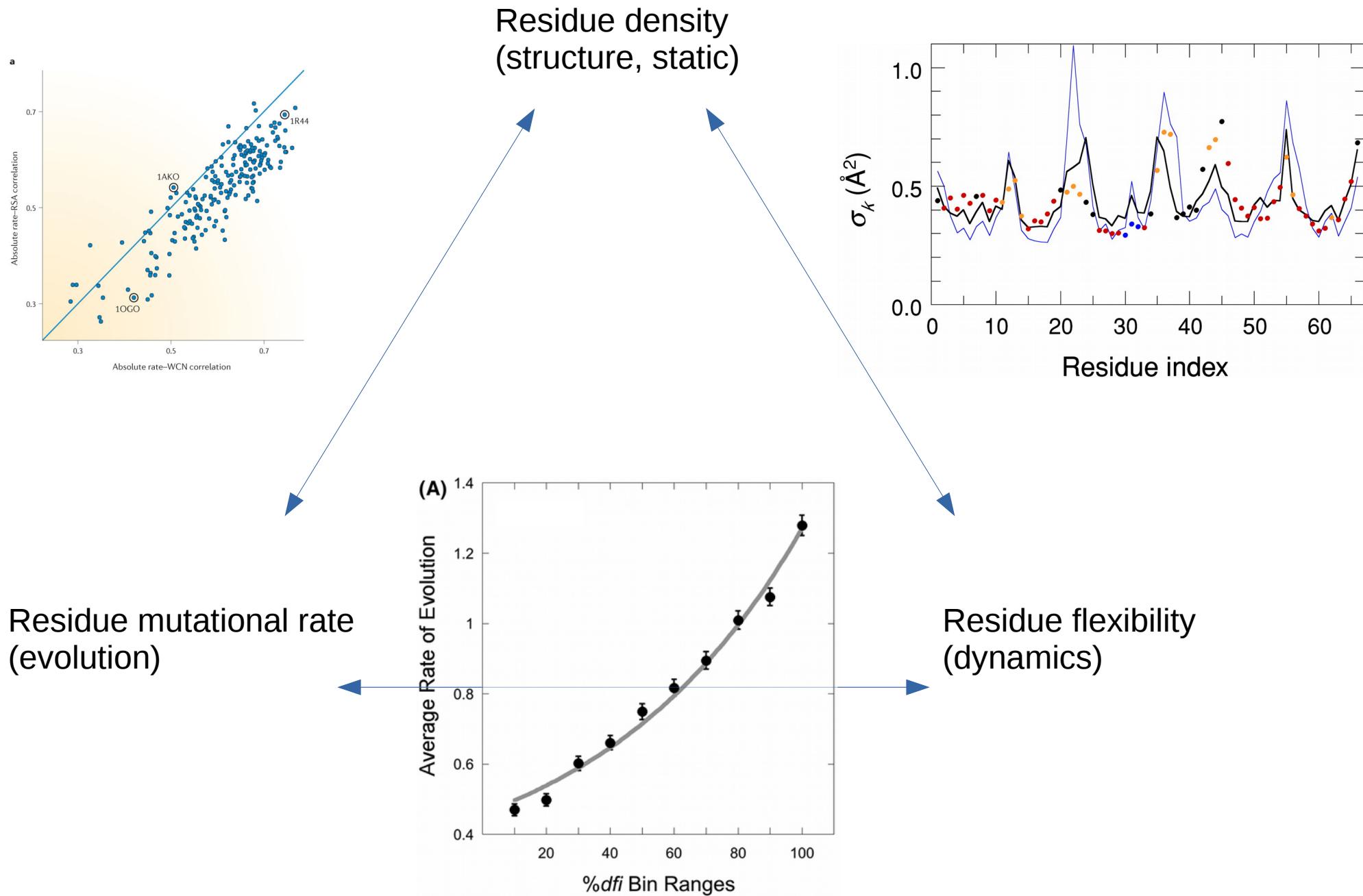
¹Department of Computational and Systems Biology, School of Medicine, University of Pittsburgh

Mol. Biol. Evol. 29(9):2253–2263. 2012 doi:10.1093/molbev/mss097 Advance Access publication March 16, 2012

Causes of evolutionary rate variation among protein sites

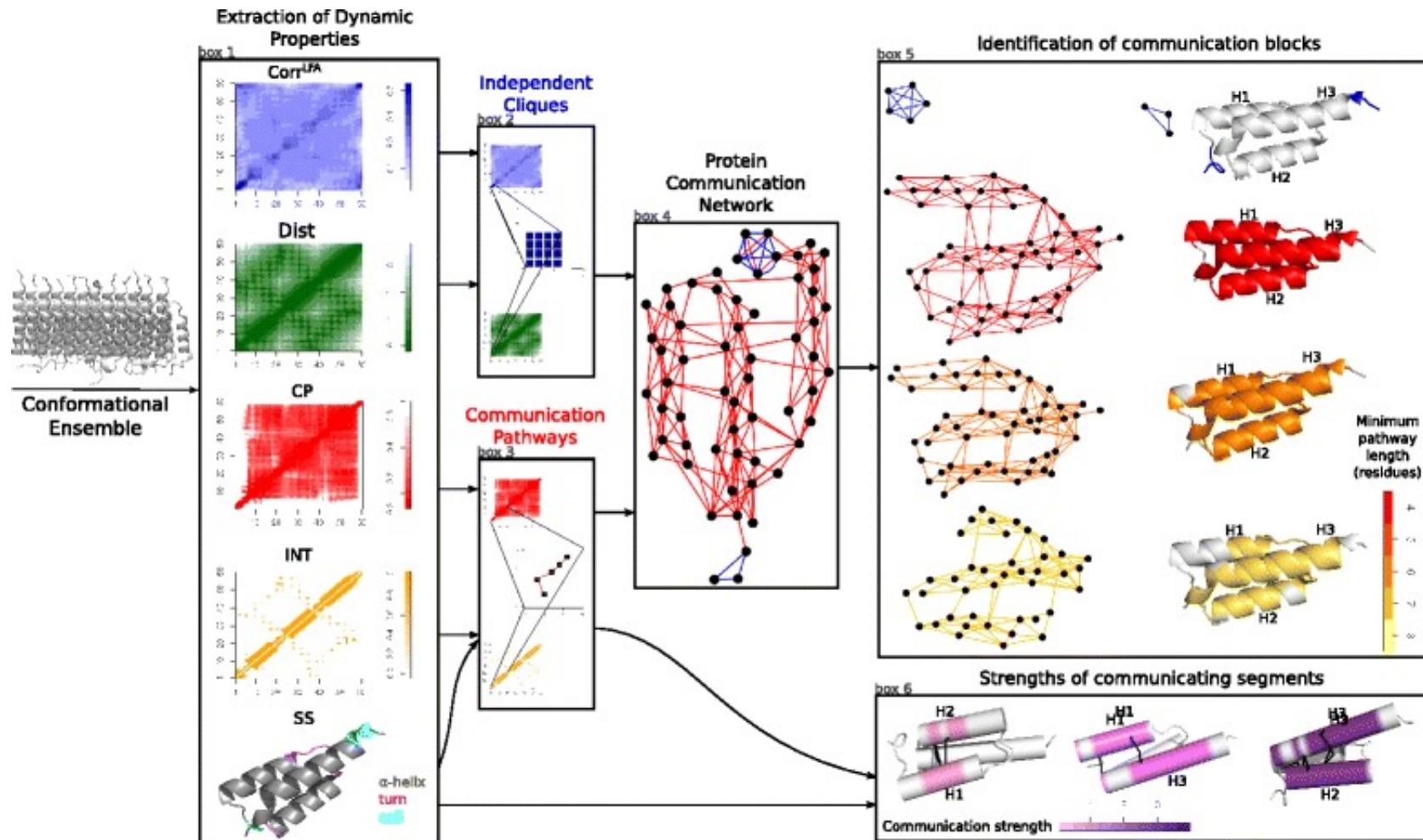
Julian Echave¹, Stephanie J. Spielman² and Claus O. Wilke²

Protein dynamics and evolution



When dynamics/flexibility is relevant ?
How to access this information ?

COMunication MApping

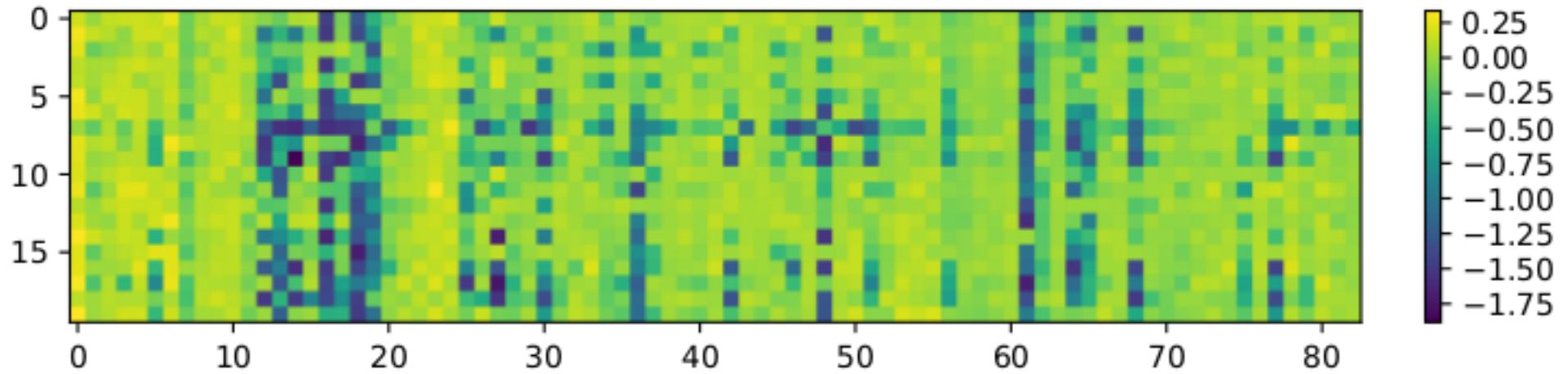


Identification of local averaged properties
Blocks (clusters) of residues and pathways between residues

Karami, Laine, Carbone. Dissecting protein architecture with communication blocks and communicating segment pairs - BMC bioinformatics 2016

COMunication MApping 2

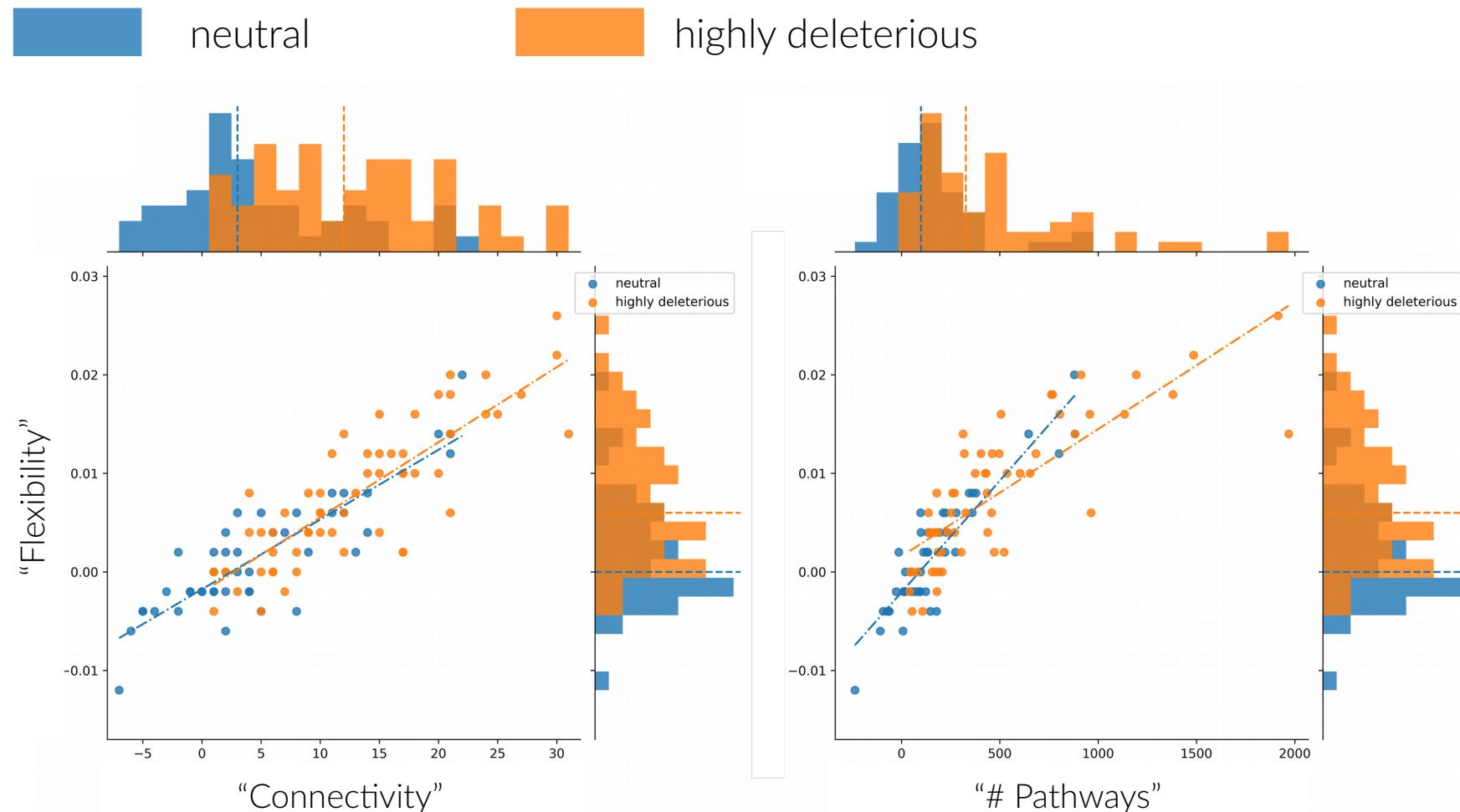
PDZ deep mutational scanning → 19 substitutions for each position



Protein fitness ~ protein activity to bind cognate ligand

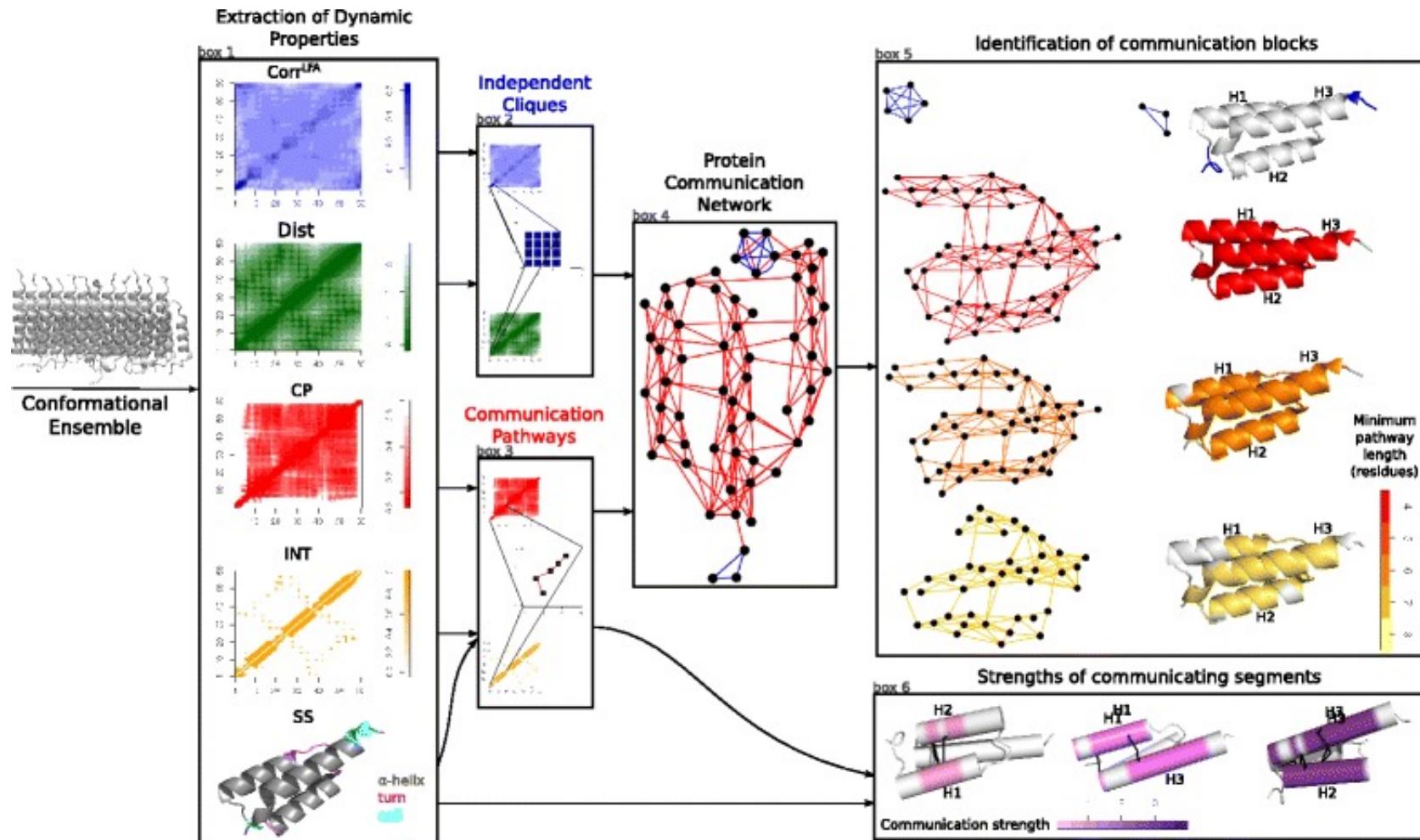
COMunication MApping 2

PDZ deep mutational scanning → structural modeling (175 mutants) → dynamical properties



Karami, Bitard-Feildel, Laine, Carbone. "Infostery" analysis of short molecular dynamics simulations identifies highly sensitive residues and predicts deleterious mutations – Scientific Reports 2018

COMunication MApping



Identification of local averaged properties
Blocks (clusters) of residues and pathways between residues

Karami, Laine, Carbone. Dissecting protein architecture with communication blocks and communicating segment pairs - BMC bioinformatics 2016

Exploratory analysis

Single mutation to epistasis effects

Beta-lactamases

- Enzyme, catalyzing degradation of beta-lactams antibiotics
- TEM family probably the most known/studied
- Large diversity of families (TEM, SHV, OXA)
- Major health issues: Extended-spectrum beta-lactamase (ESBL), previously made of TEM and SHV and now joined by CTX-M

Preserved activity against:

- Penicillins
- Cephalosporin

Extended to :

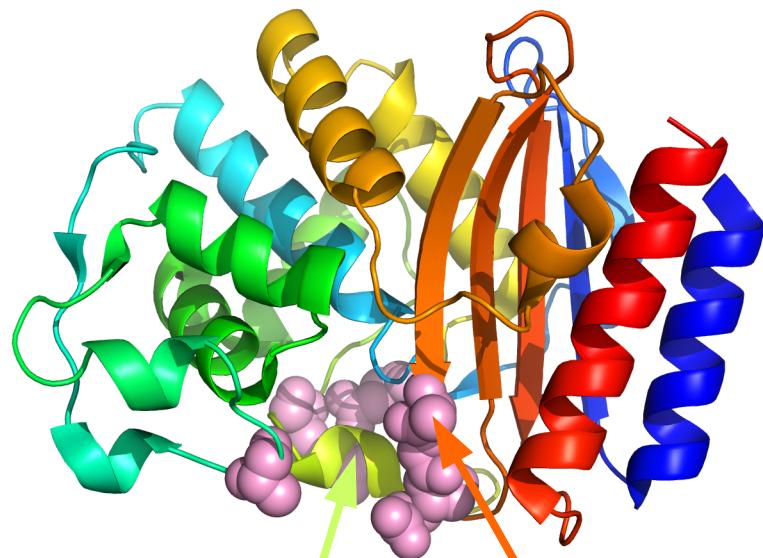
- Cefotaxime
- Ceftazidime
- Aztreonam

...

Beta-lactamases

TEM (SHV)

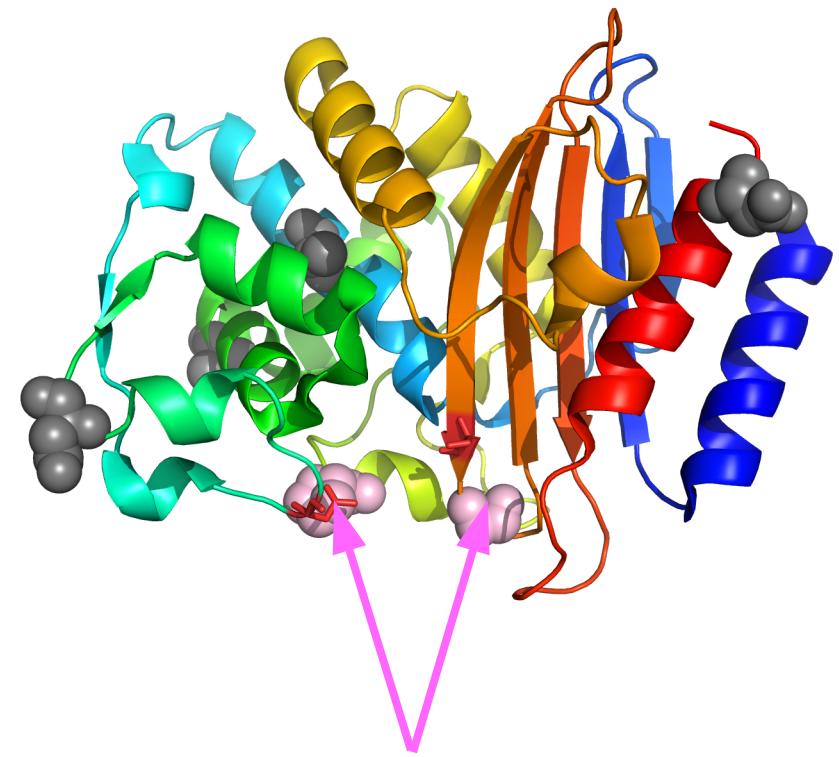
ESBL gain through mutations



Most mutations in the oxyanion pocket
Substitutions in the **B3 β-strand** or **Ω-loop** critical for ESBL

CTX-M

Intrinsic ESBL activity



Two mutations close to pocket
Narrow active site compared to TEM-1
Roles of other variant <UNK>

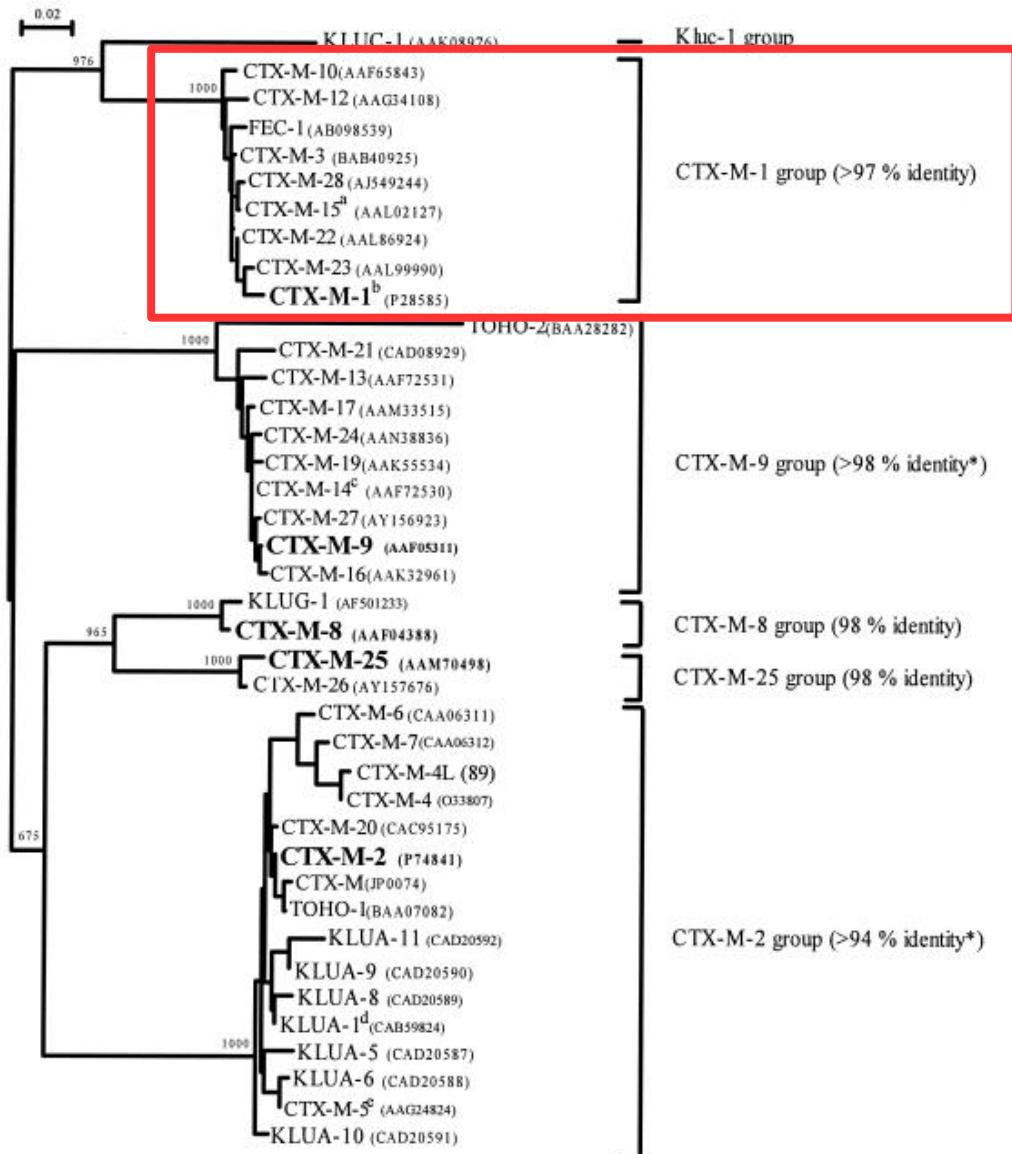
CTX-M Beta-lactamases

~ 80 known members

5 major groups characterized by:

- very similar sequences
- very similar structures
- different activities

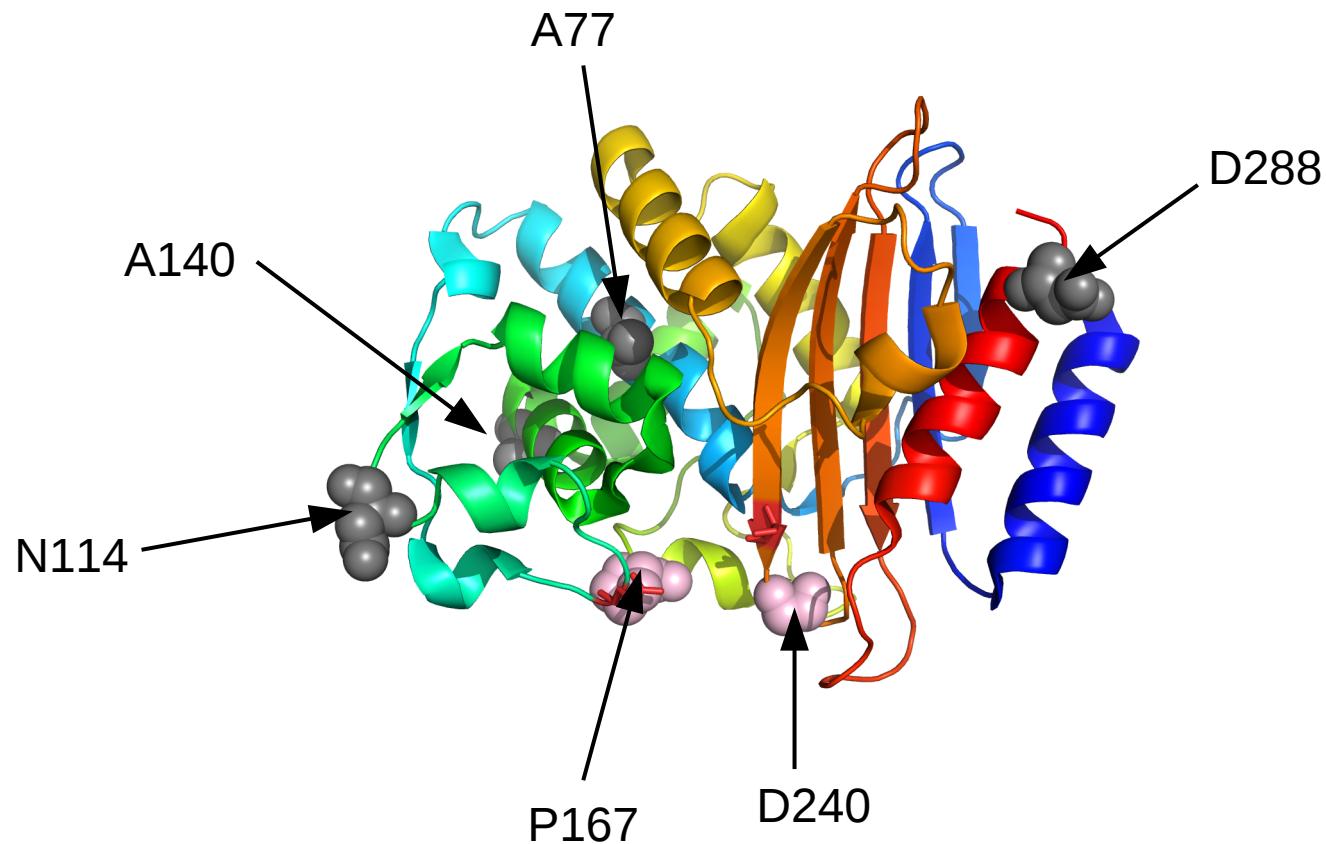
Focus on CTX-M-1 group



CTX-M-1 group

Mutually exclusive: **P167T/S D240G**

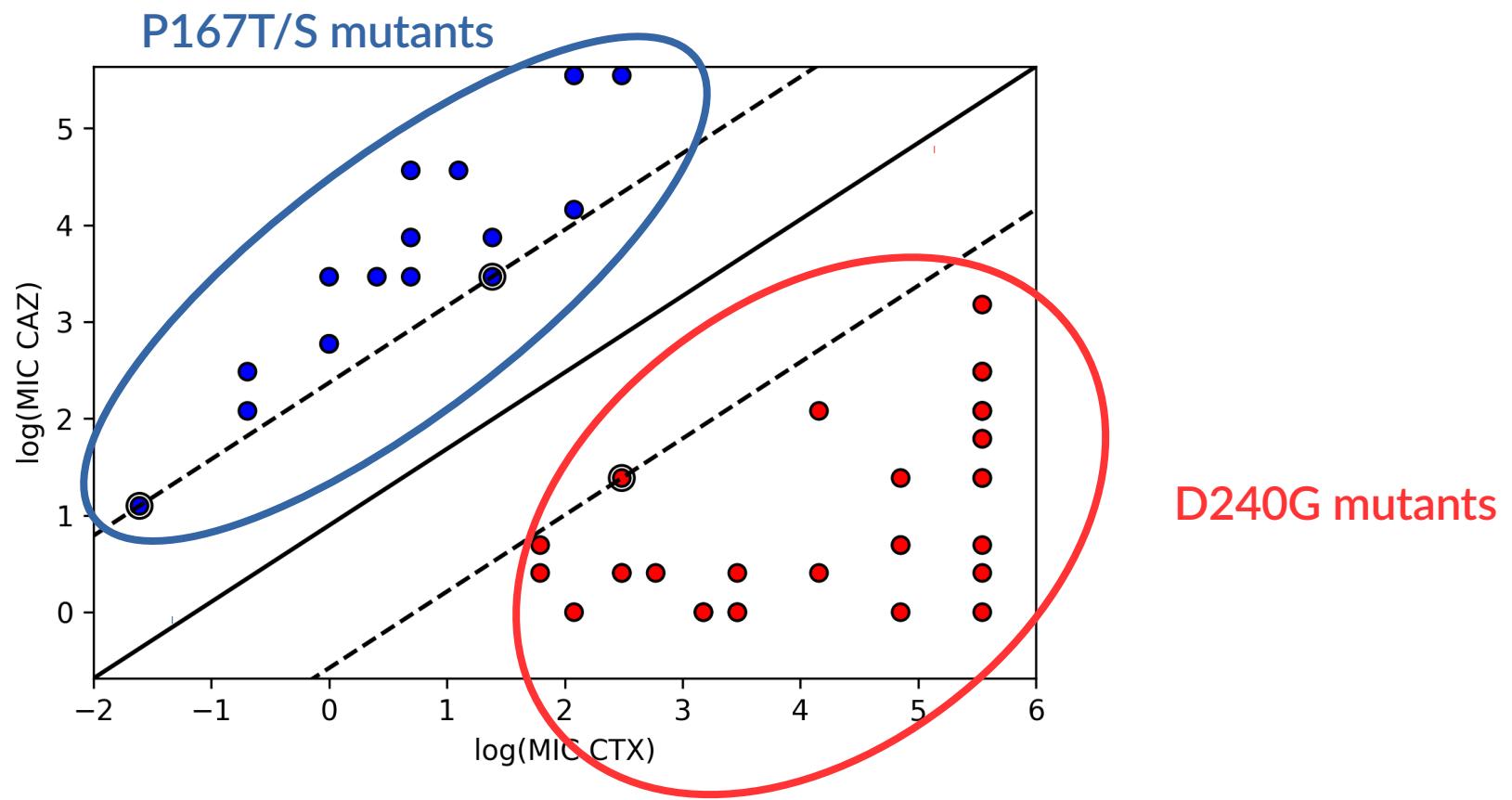
Other observed mutations: **A77V, N114D, A140S, N288D**



CTX-M-1 group

Mutually exclusive: **P167T/S D240G**

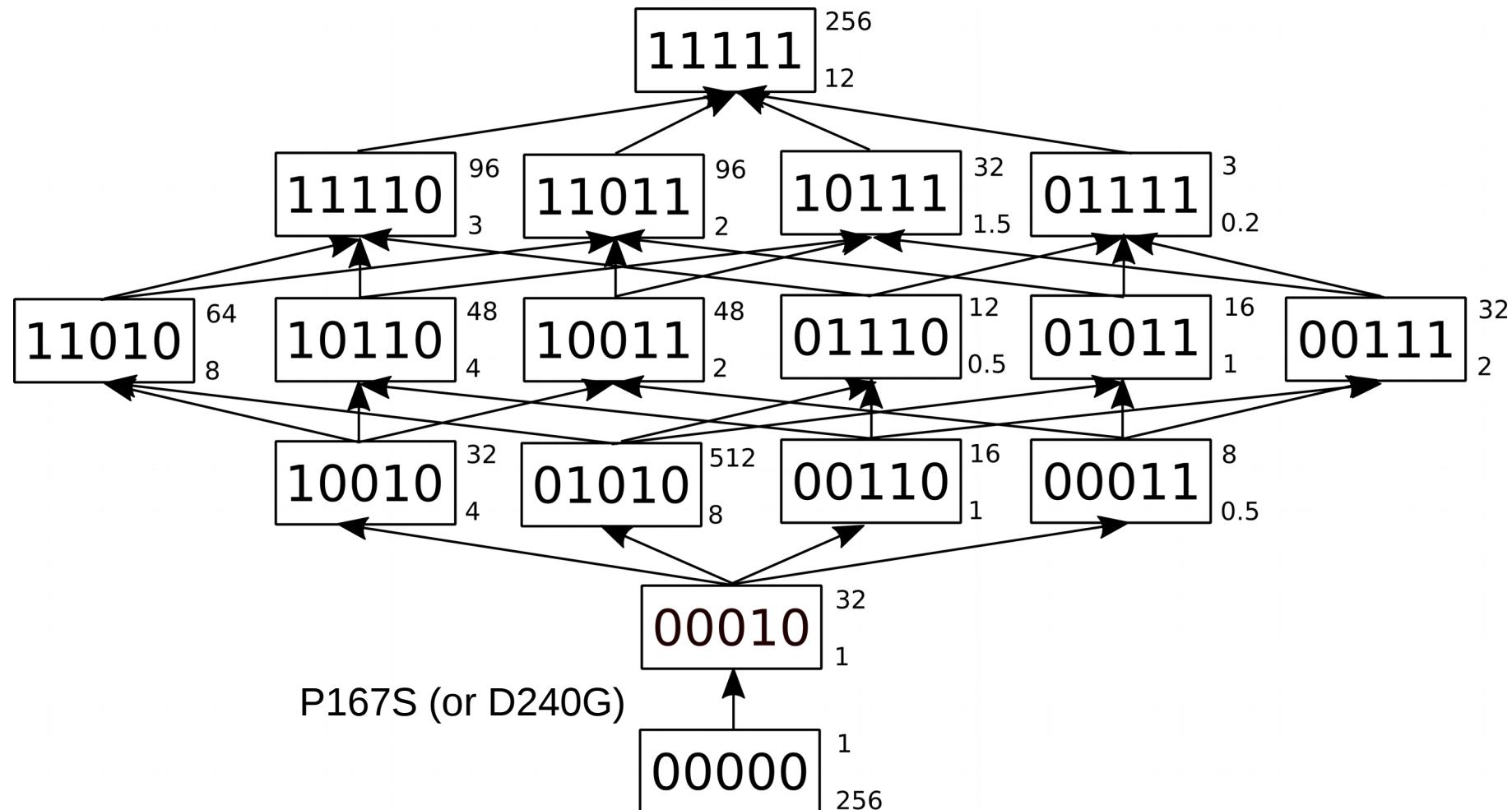
Other observed mutations: **A77V, N114D, A140S, N288D**



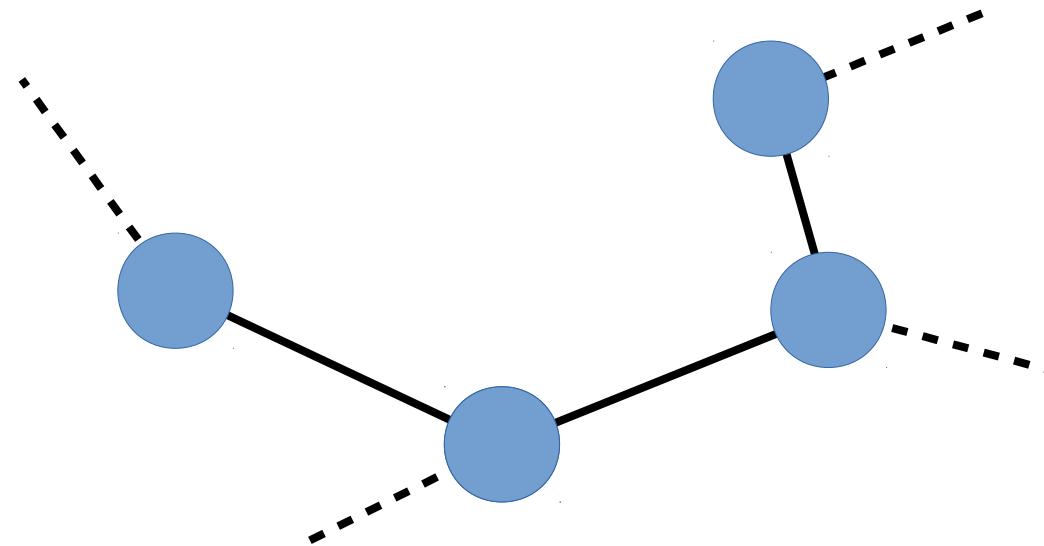
CTX-M-1 group

96 mutational paths possible
with CTX and CAZ experimental values (fitness)

Genotype CAZ MIC
CTX MIC

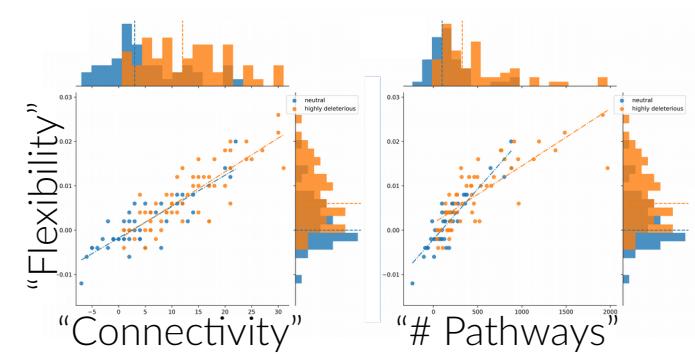


CTX-M-1, dynamical properties



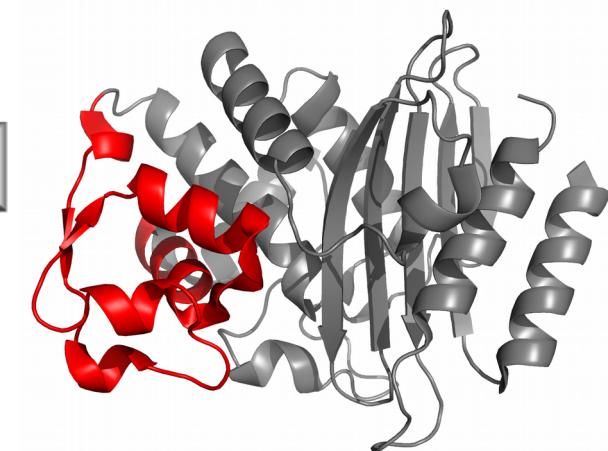
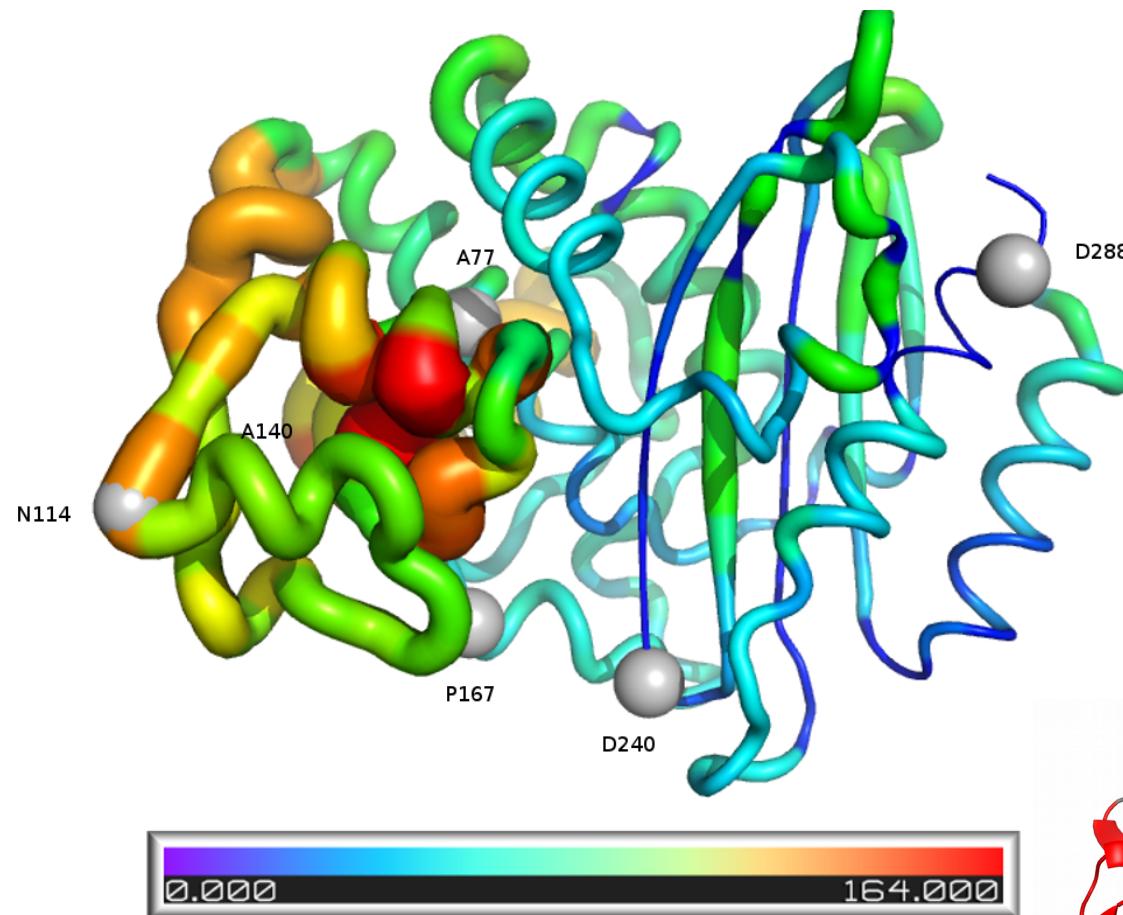
Step wise analysis of COMMA's dynamical pathways :

- pathways lengths
- number of pathways
- **shortest paths**
- **residue connectivity**
- ...



CTX-M-1, dynamical properties

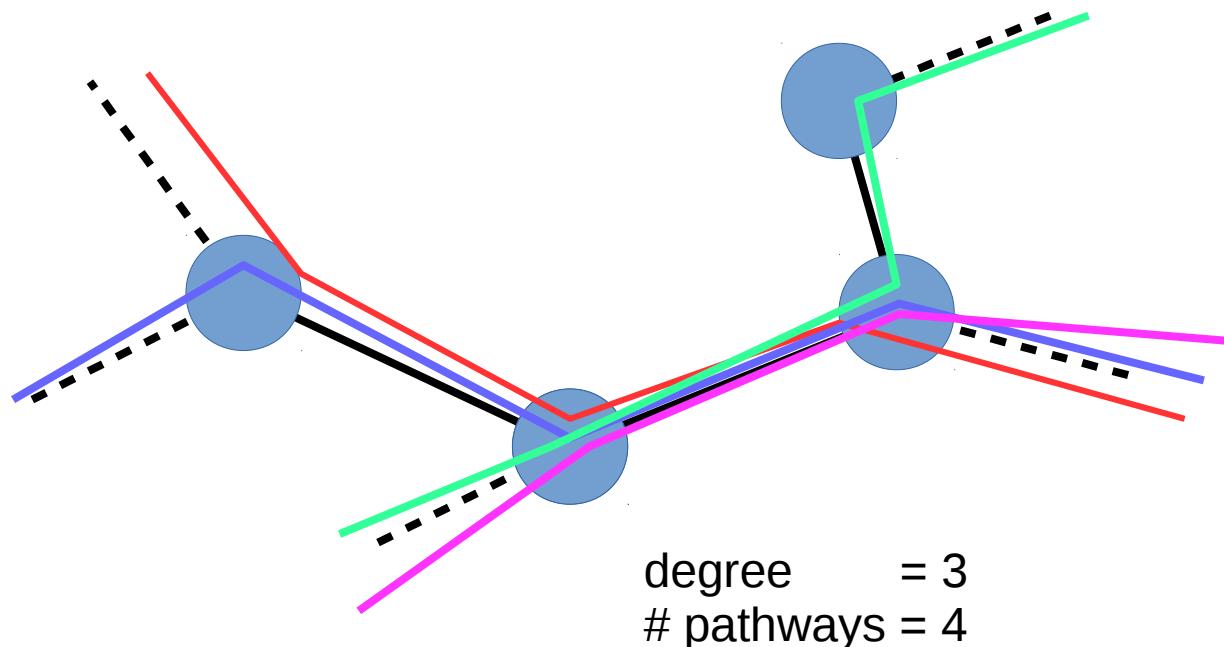
Measure the distance from P167/D240 to each of the other residues



CTX-M-1, dynamical properties

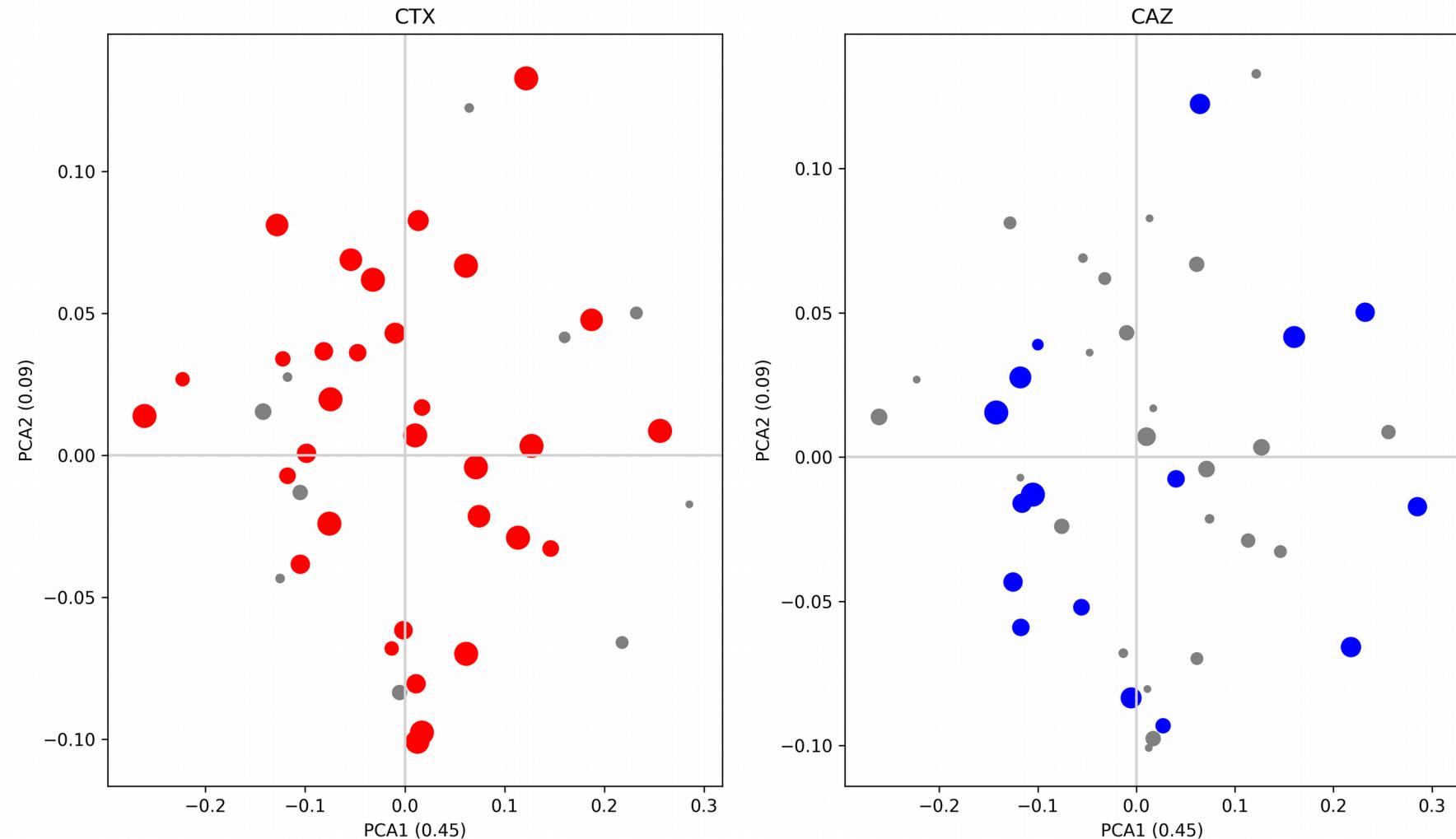
Residue connectivity:

number of pathways passing through a residue
(not degree centrality)



CTX-M-1 dynamical properties

Connectivity matrix (# members x # residues) → PCA

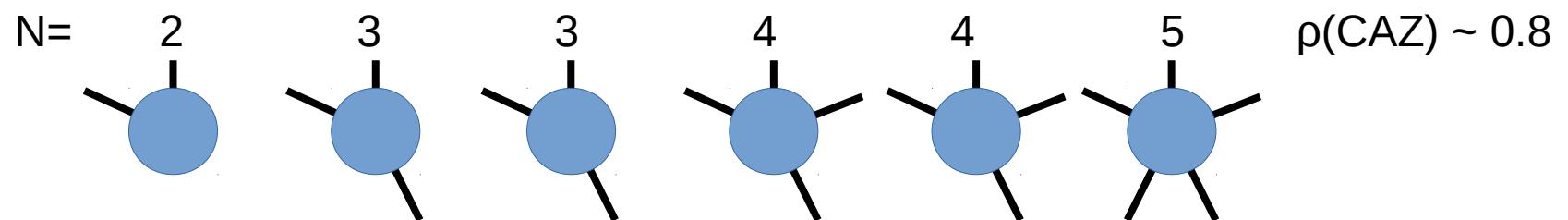
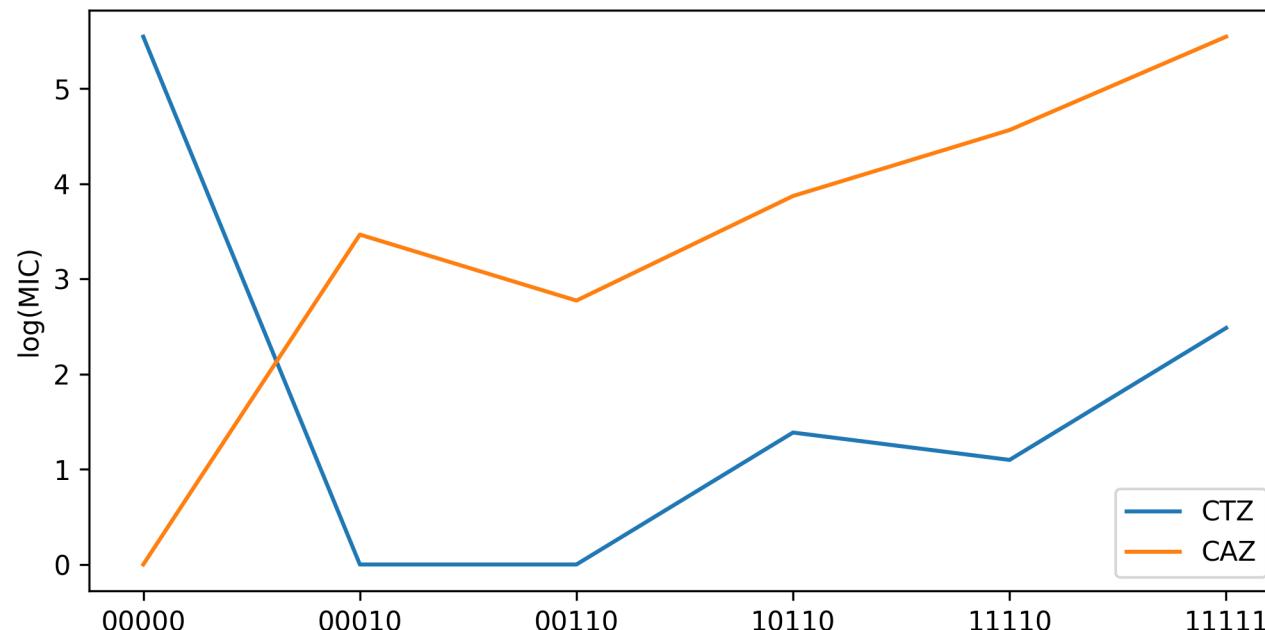


45% of variance explained by first axis but does not correspond to CTX/CAZ resistance
→ Reducing the noise

CTX-M-1, dynamical properties

Step wise analysis of mutational pathways:

- "WT" → +P167S → +A140S → +A77V → +N114D → +D288N
(00000, 00010, 10010, 10011, 11011, 11111)



For each mutational path: count the number of time a residue dynamical property is observed correlated (above a threshold) with CAZ/CTX resistance

CTX-M-1, dynamical properties

28 → ?

222, 232 → ? (link between alpha and beta domain)

41 → close to position G42
(TEM) inhibitor

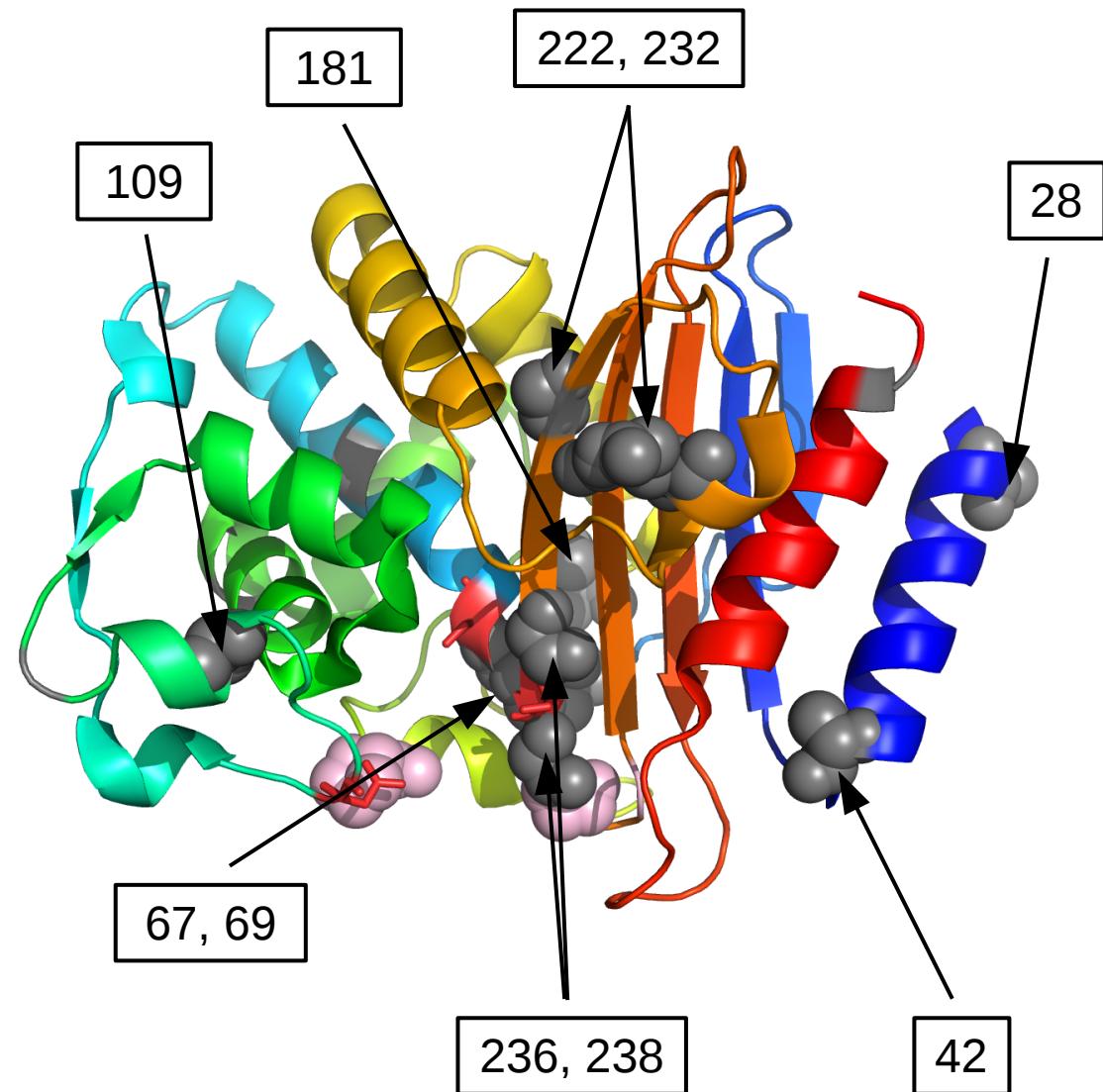
181 ~ M182 in TEM stability

67 → Q-loop stabilization

69 → proximity to S70
(catalytic site)

109 → proximity to N104
(catalytic site) (?)

236, 238 → proximity to S237
(catalytic size)



**None of these positions belong to the list of mutants
(A77V, N114D, A140S, N288D)**

Summary

- COMMA's properties effectively summarize protein dynamics
- Change of local dynamical properties can capture functionally important positions
- Difficult to analysis (non additive effect, pleiotropy ...)

Thanks for your attention

IBPS - Laboratoire de Biologie Computationnelle et Quantitative

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Elodie Laine

Elin Teppa

IMPMC

Jacques Chomillier



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