Sabancı Üniversitesi

TÜBİTAK

EURO 4SEE

Residue Networks: Understanding the Time Evolution and Mutations of Proteins from a Graph Theoretical Perspective

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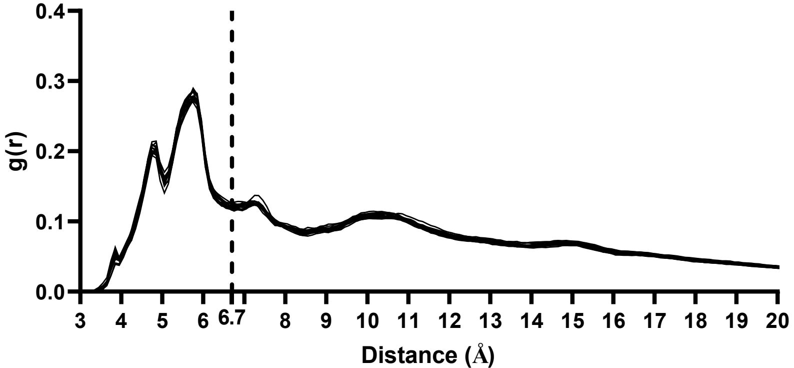
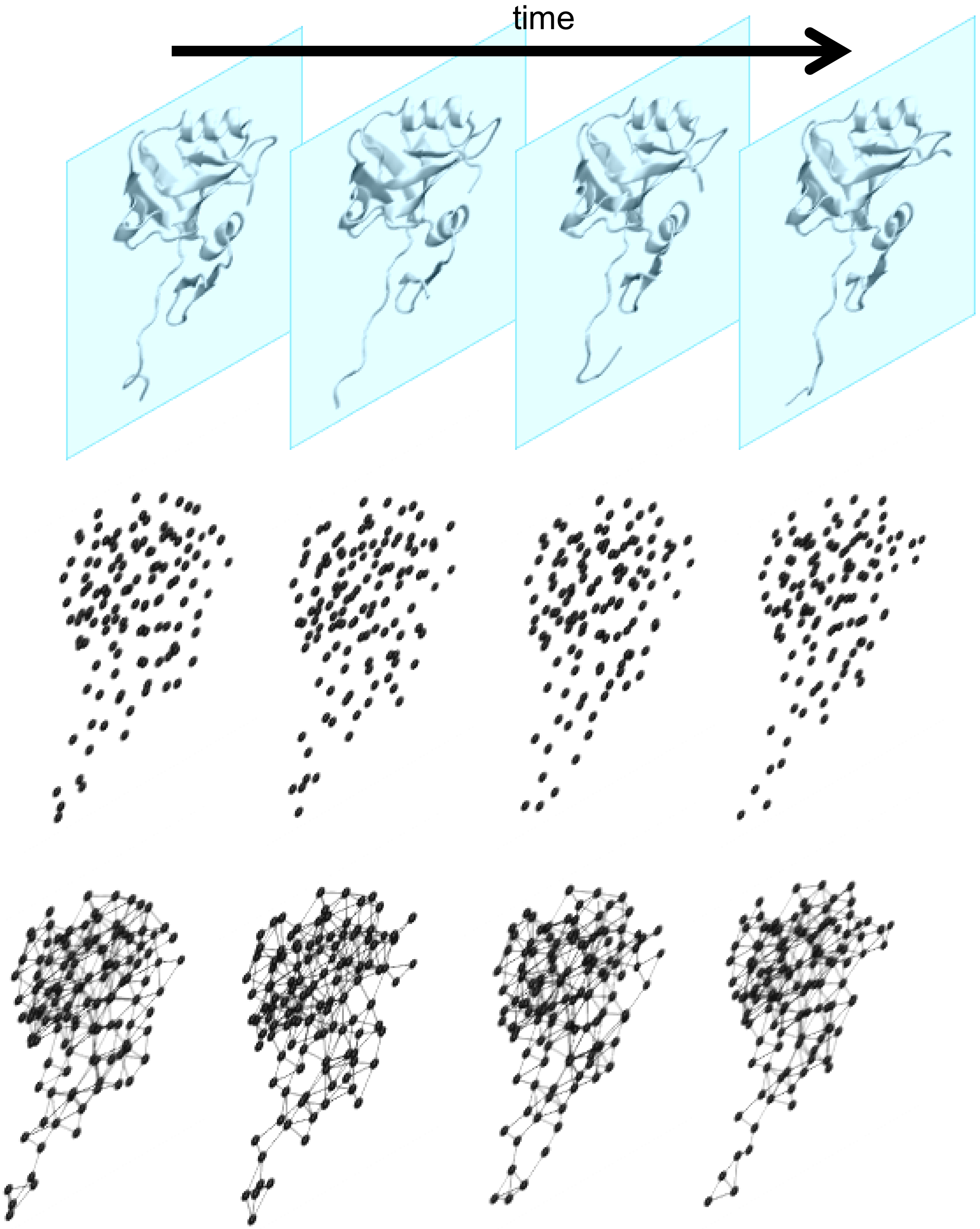
Residue networks (RN)

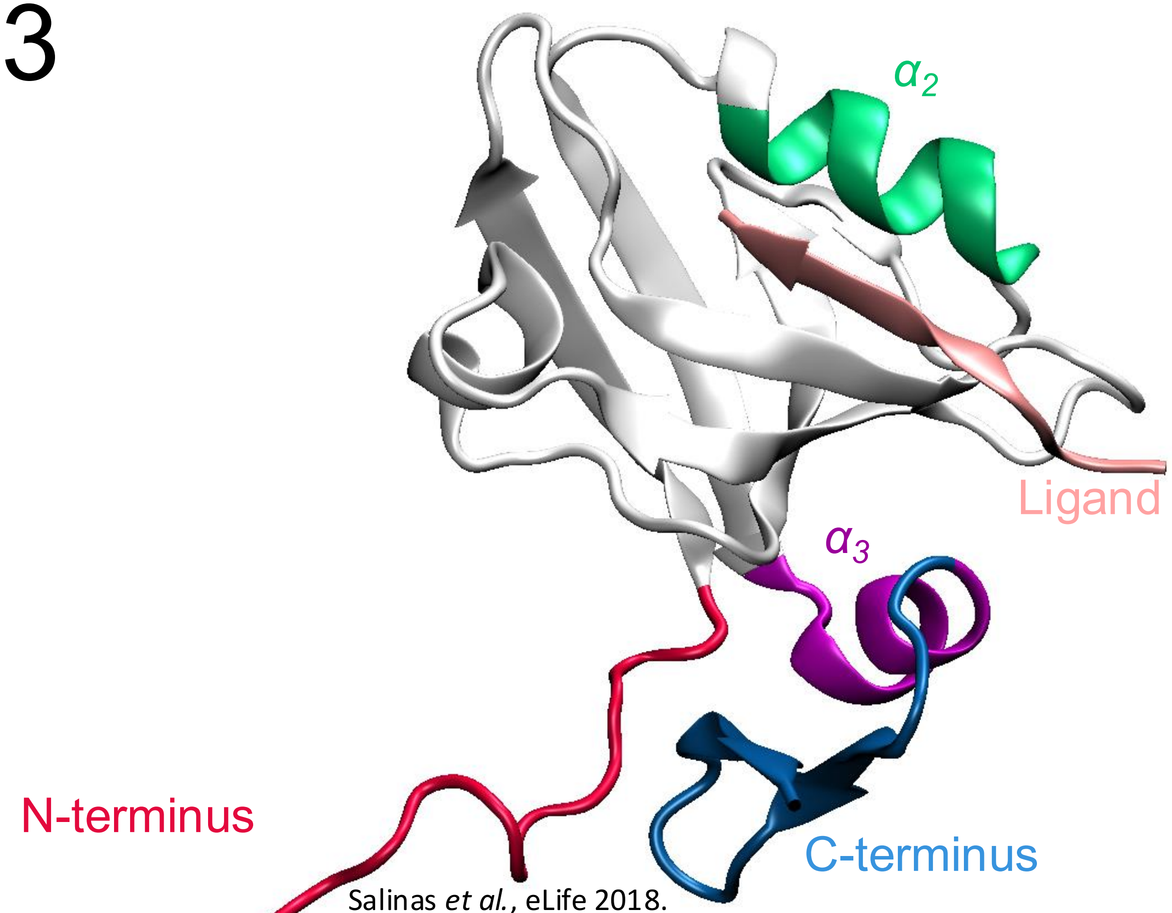
- C_β (C_α for glycine) taken as nodes (vertices)
- Nodes inside of 6.7 Å interpreted as interacting nodes and an edge (link) assigned
- 240 networks (per 1 ns) for each PDZ complex for further centrality analyses





Structural segments of PDZ3

- N-terminus (residues 299-310)
- α_2 (residue 372-380)
- α_3 (residues 393-400)
- C-terminus (residues 401-415)
- Ligand



Salinas *et al.*, eLife 2018.
Camara-Artigas *et al.*, Acta Crystallogr D Struct Biol 2019.
Liu *et al.*, PNAS 2017.
Kumawat *et al.*, PNAS 2017.

WT_{L1} WT_{L2}
$G330T_{L1}$ $G330T_{L2}$
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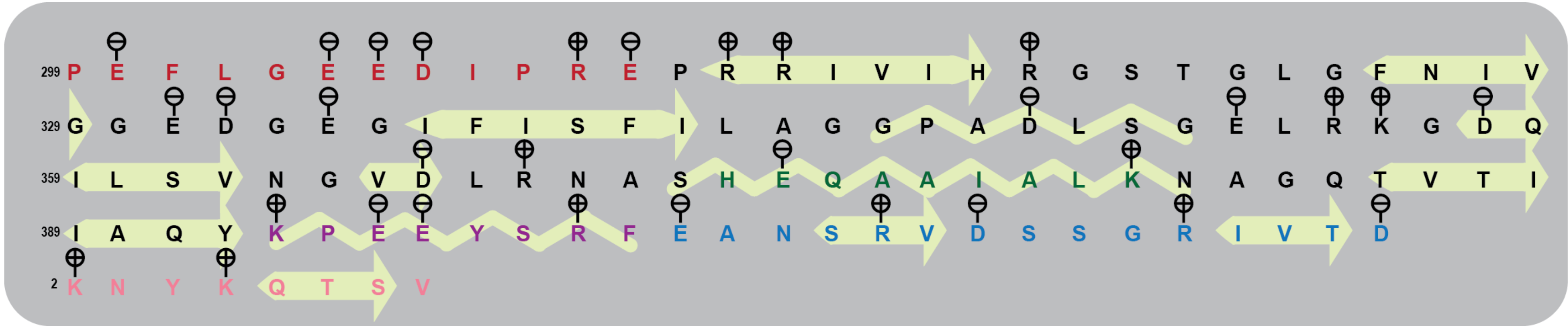
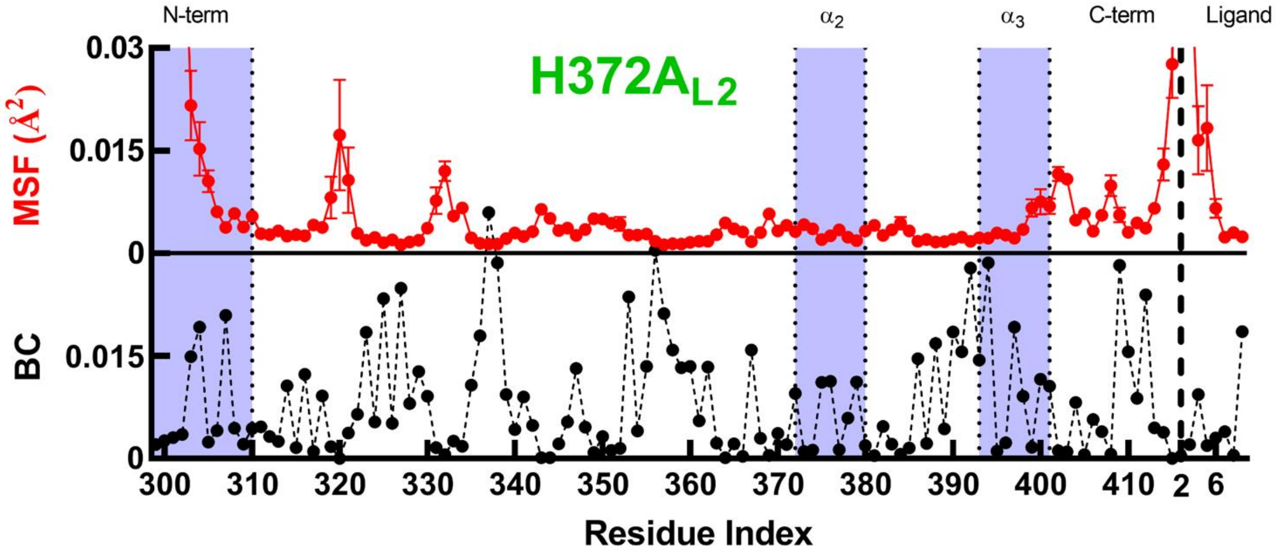
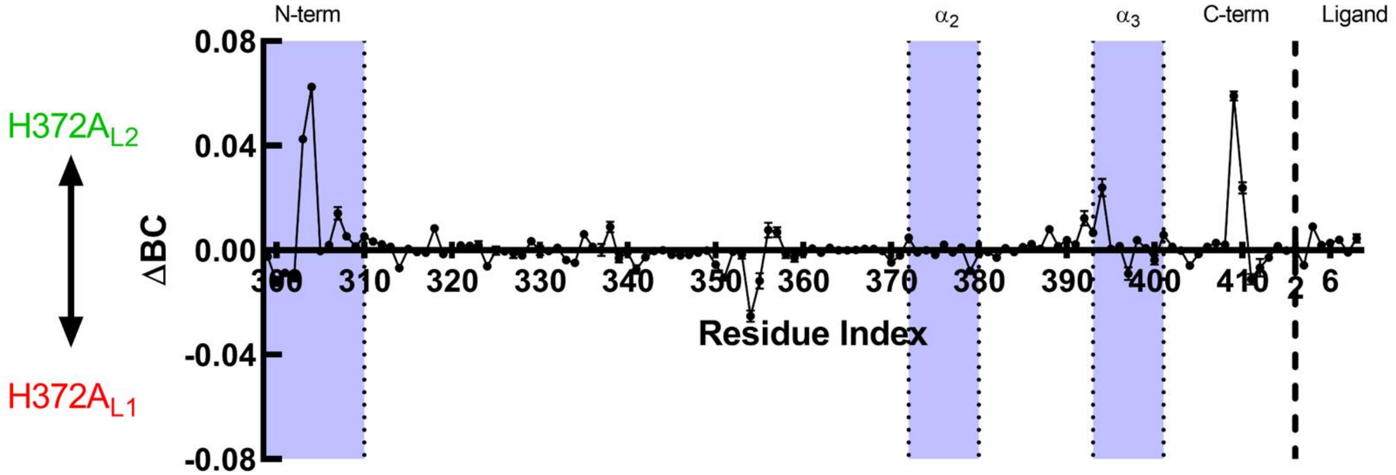
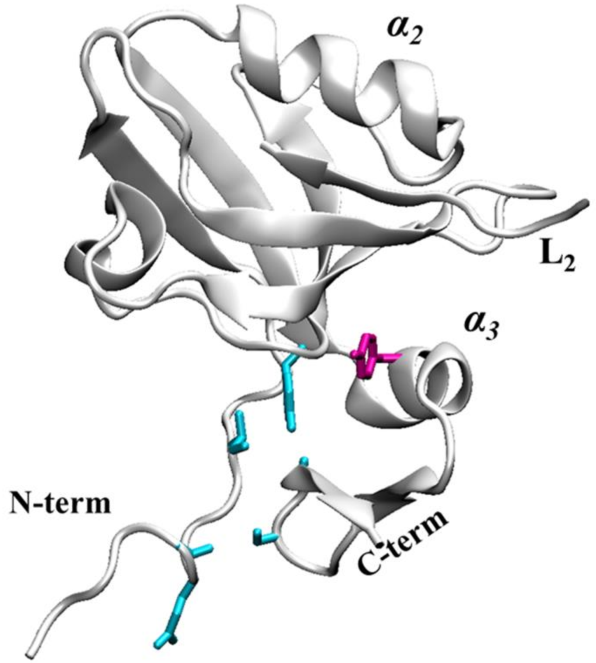
DM_{L1} DM_{L2}

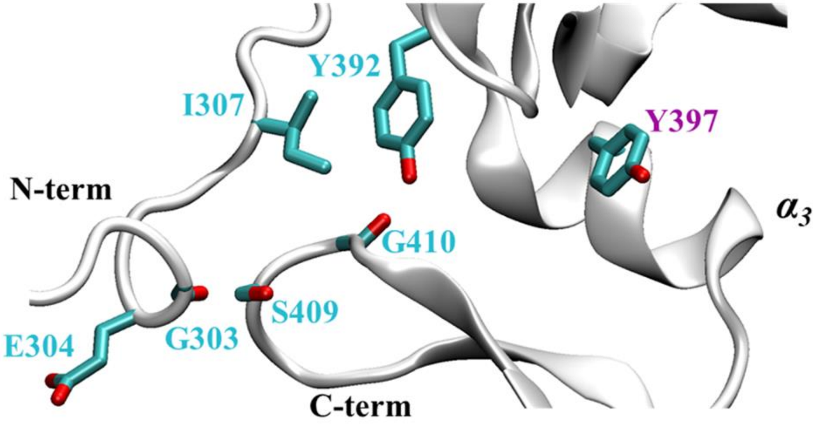


Node BC







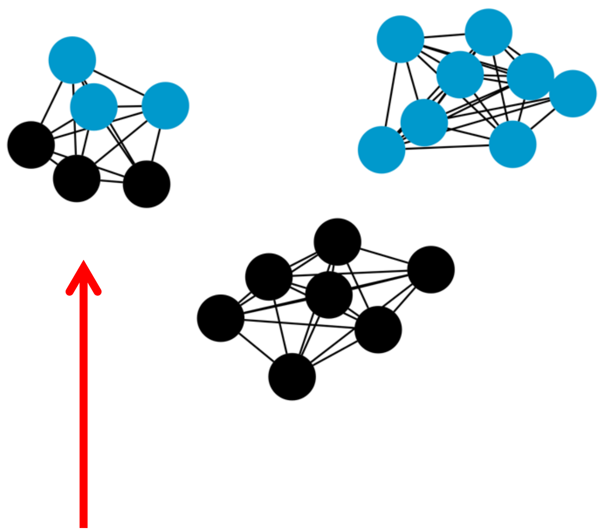


Guclu *et al.*, JPCB 2021.

Community composition

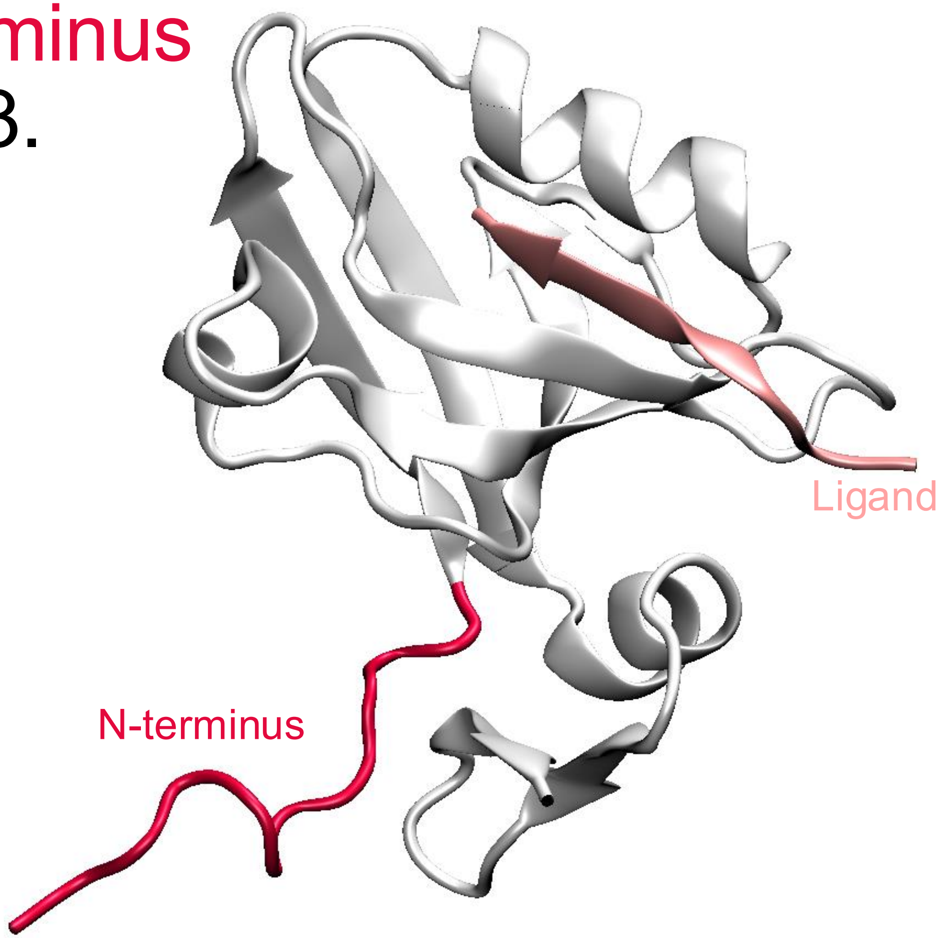
- Assessing the composition of communities and scoring the structural origins of members shed light on communication between the segments

$\Omega = 3$



Blue and Black together in a community in this instance so the score is 1.

Average community co-inhabitance of N-terminus and ligand exhibits ligand specificity in PDZ3.



Community sharing score of N-terminus and ligand for 3-6 community separation.

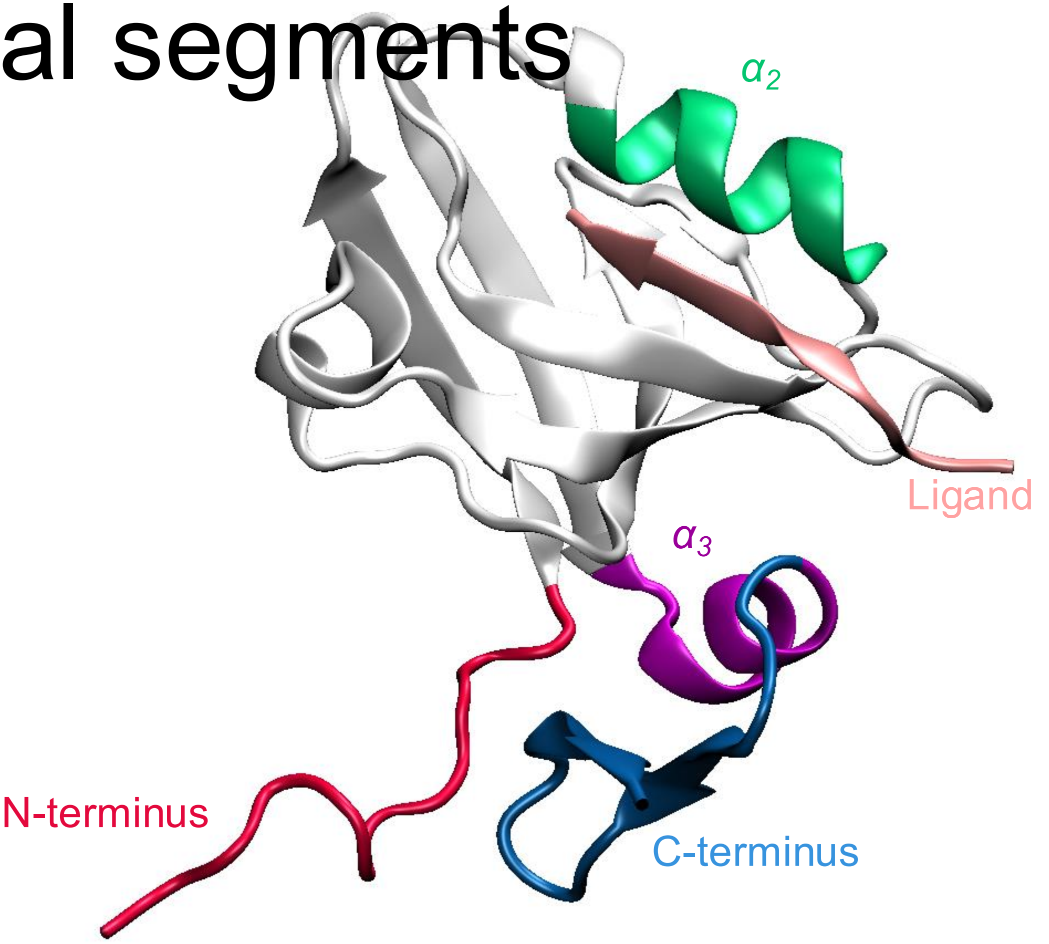
System label	$\Omega = 3$	$\Omega = 4$	$\Omega = 5$	$\Omega = 6$
WT$_{L1}$	**0.93 ± 0.02**	**0.84 ± 0.02**	0.66 ± 0.03	0.56 ± 0.03
WT$_{L2}$	**0.84 ± 0.02**	0.63 ± 0.03	0.32 ± 0.03	0.14 ± 0.02
G330T$_{L1}$	**0.90 ± 0.02**	**0.80 ± 0.03**	0.44 ± 0.03	0.26 ± 0.03
G330T$_{L2}$	**0.93 ± 0.02**	**0.79 ± 0.03**	0.55 ± 0.03	0.48 ± 0.03
H372A$_{L1}$	**0.88 ± 0.02**	0.31 ± 0.03	0.14 ± 0.02	0.09 ± 0.02
H372A$_{L2}$	**0.88 ± 0.02**	**0.70 ± 0.03**	0.35 ± 0.03	0.15 ± 0.02
DM$_{L1}$	**0.97 ± 0.01**	0.56 ± 0.03	0.36 ± 0.03	0.33 ± 0.03
DM$_{L2}$	**0.90 ± 0.02**	0.50 ± 0.03	0.32 ± 0.03	0.21 ± 0.03

*values greater than 0.7 shown in bold; those less than 0.5 are colored blue.

Guclu *et al.*, JPCB 2021.

Community sharing for structural segments

- N and C has > 0.85 co-inhabitance fraction in all forms; essential for binding.
- α_3 acts as a hub in allosteric communication, its fraction is > 0.5 for every other segment and in all PDZ3 forms.
- α_2 , at binding grove, separates with ligand in WT and G330T indicating the drastic underlying changes.



Guclu et al., JPCB 2021.

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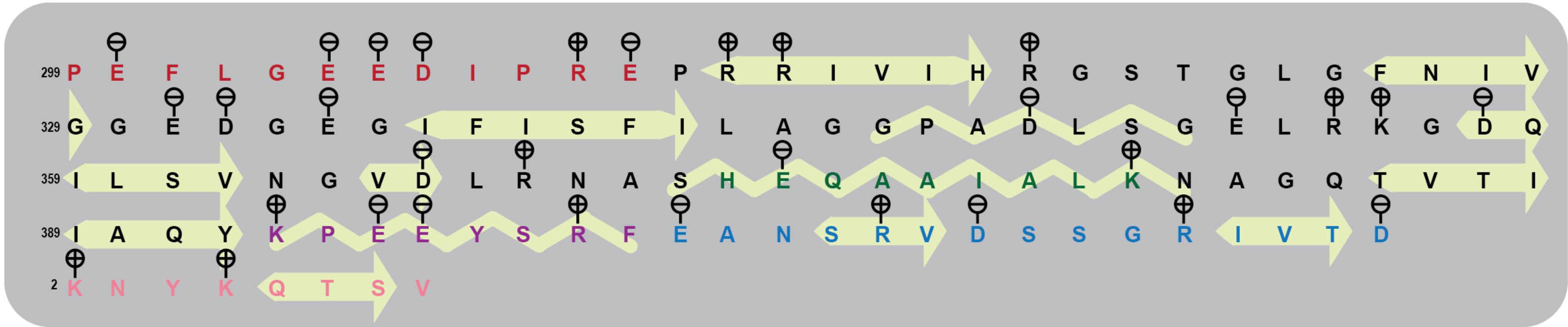

Community composition - RGB coloring based on communities

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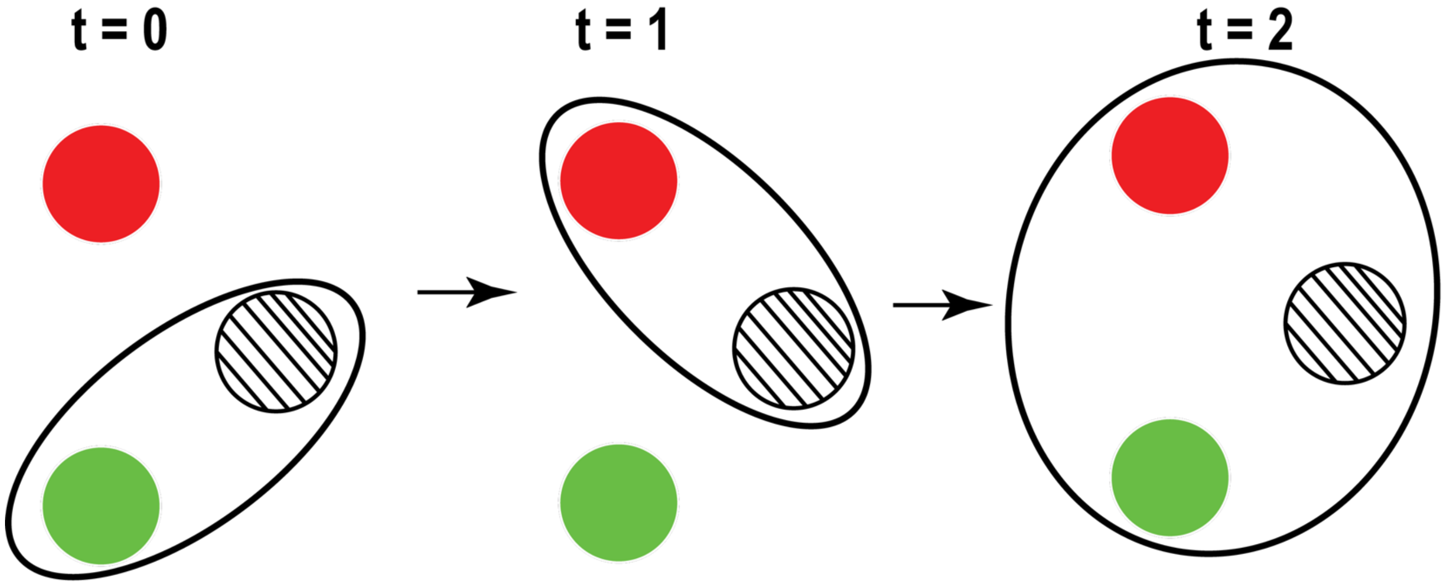

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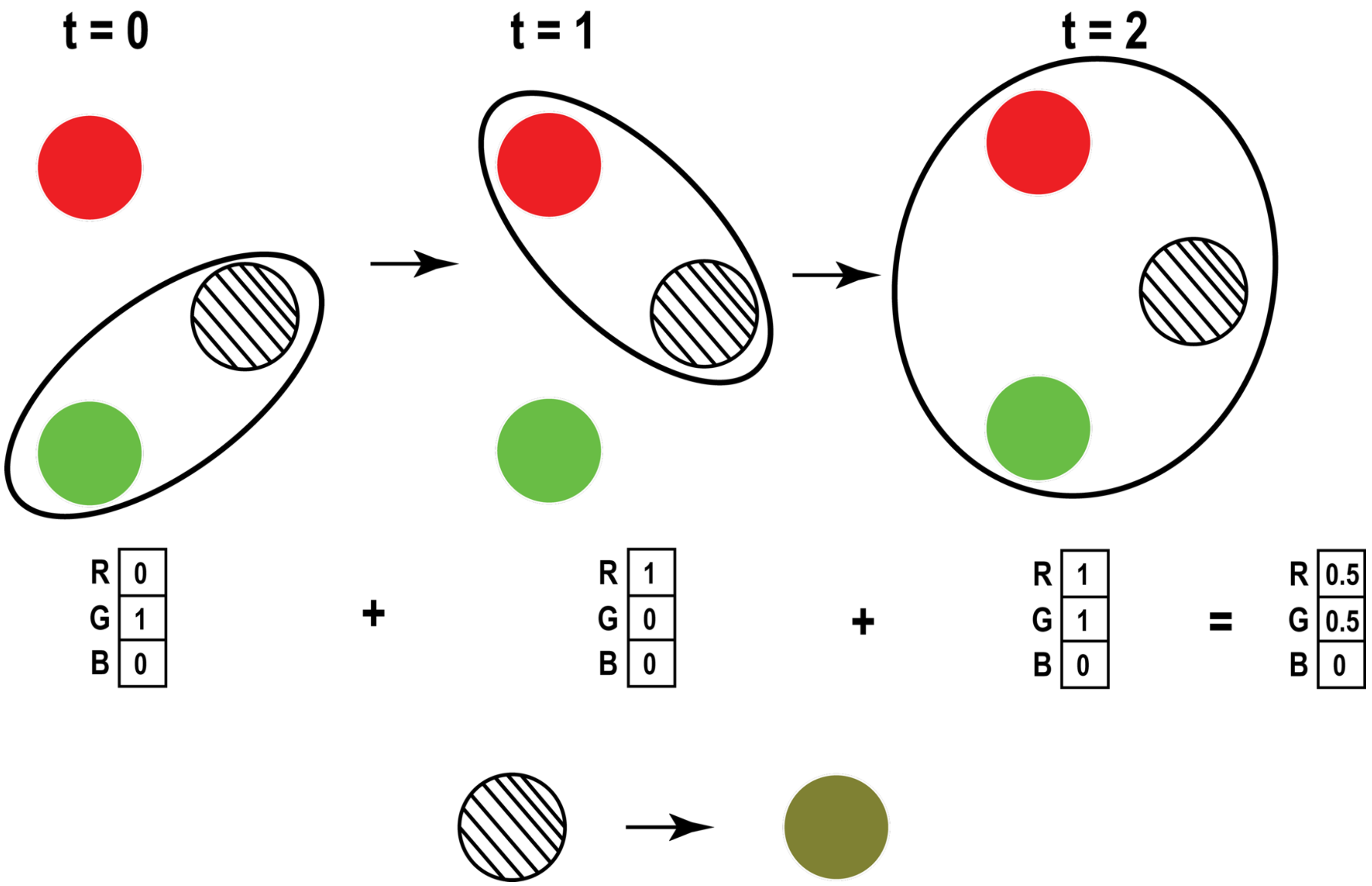

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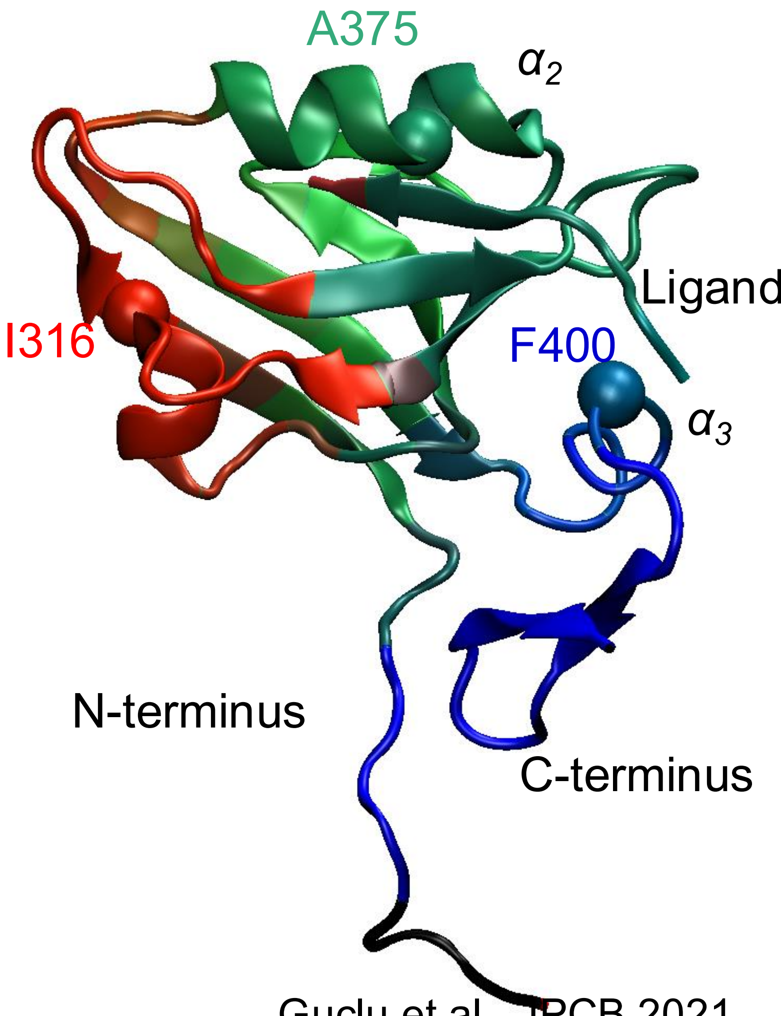

Guclu et al., JPCB 2021.

- By taking I316, A375 and F400 as reference for red, green and blue
- We check if residues share the same community

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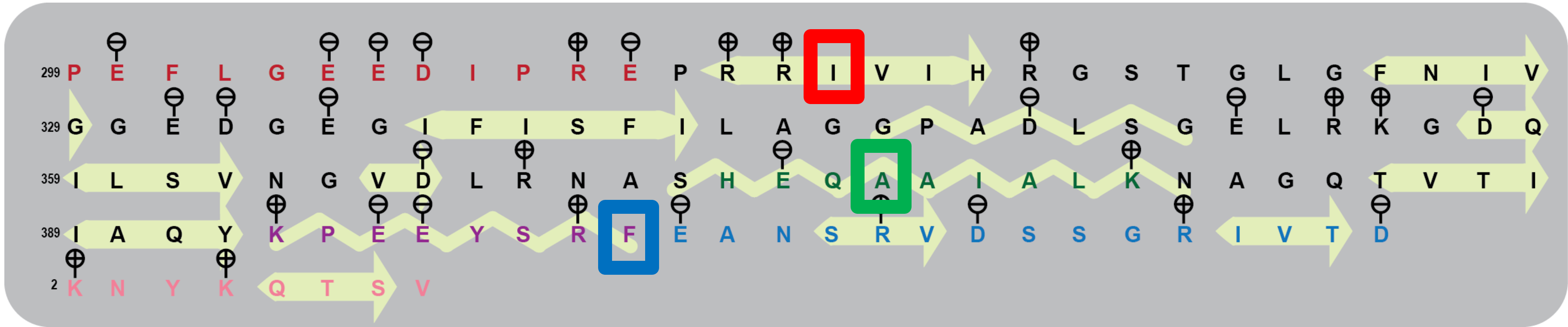
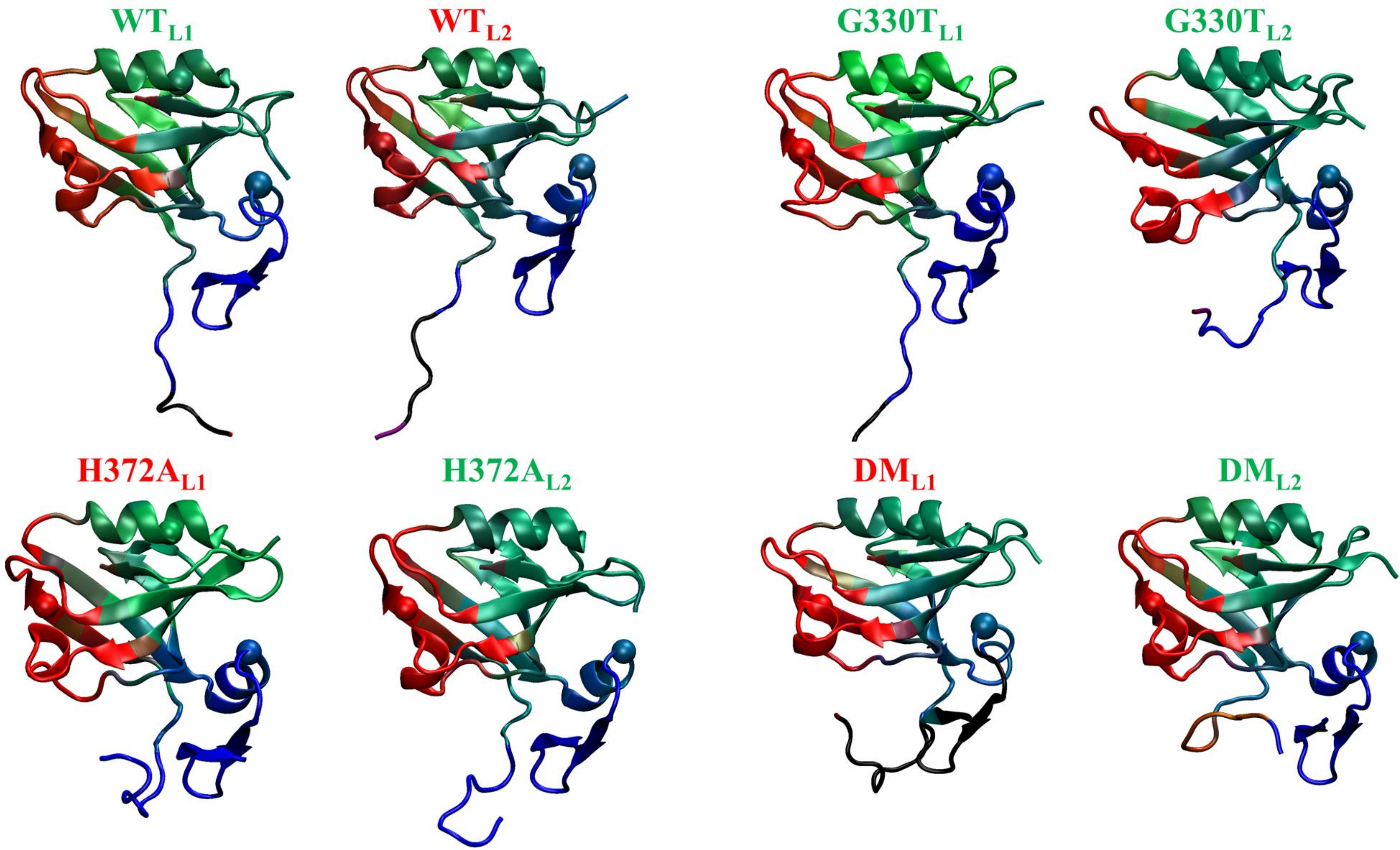


Coloring based on community composition for $\Omega = 4$

For a successful binding:

1. N-terminus must share a community with the C-terminus and α_3 (blue)
2. Ligand must not only be a part of the binding site community (green)



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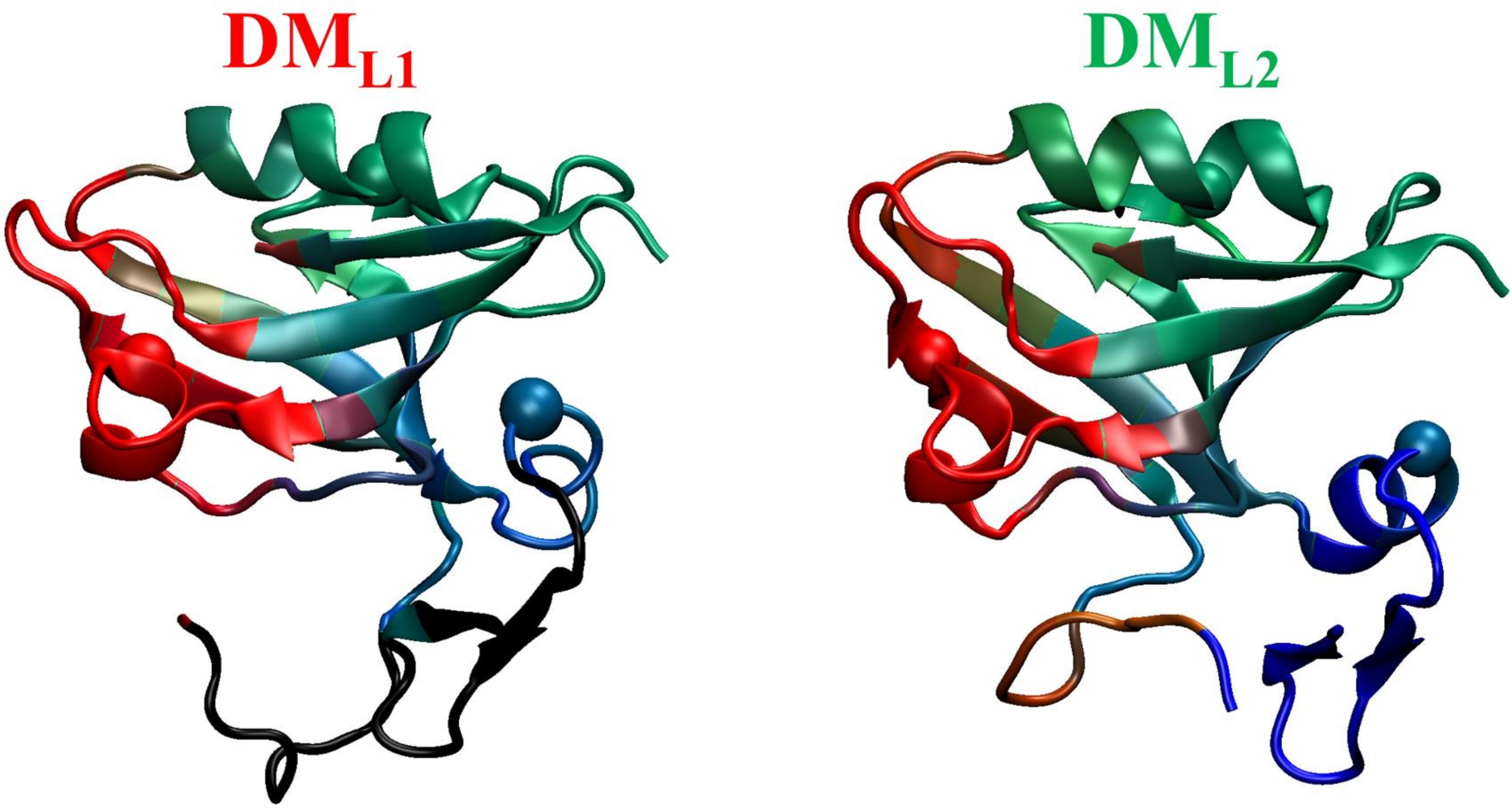

Guclu *et al.*, JPCB 2021.

Thanks!

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