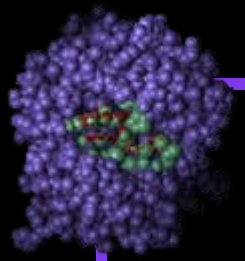
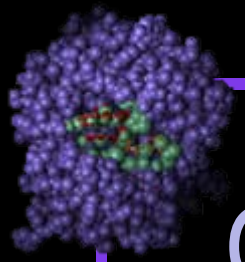


The Molecular Mimicry Hypothesis

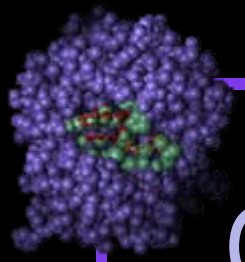
Foundation and limits of rational drug design

Andreas Hoppe and Cornelius Frömmel
Institute of Biochemistry
Charité, Medical faculty of
Humboldt University Berlin



Contents

- What is molecular mimicry?
- Promiscuity types for proteins
- Faces of Mimicry
- Molecular mimicry hypothesis



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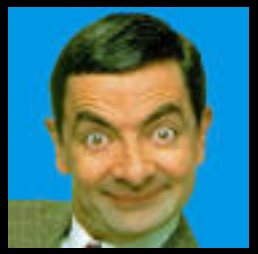
What is mimicry / mimesis?

Actor

Audience



Mimicry!

Mimesis!

What is mimicry / mimesis?

Keys

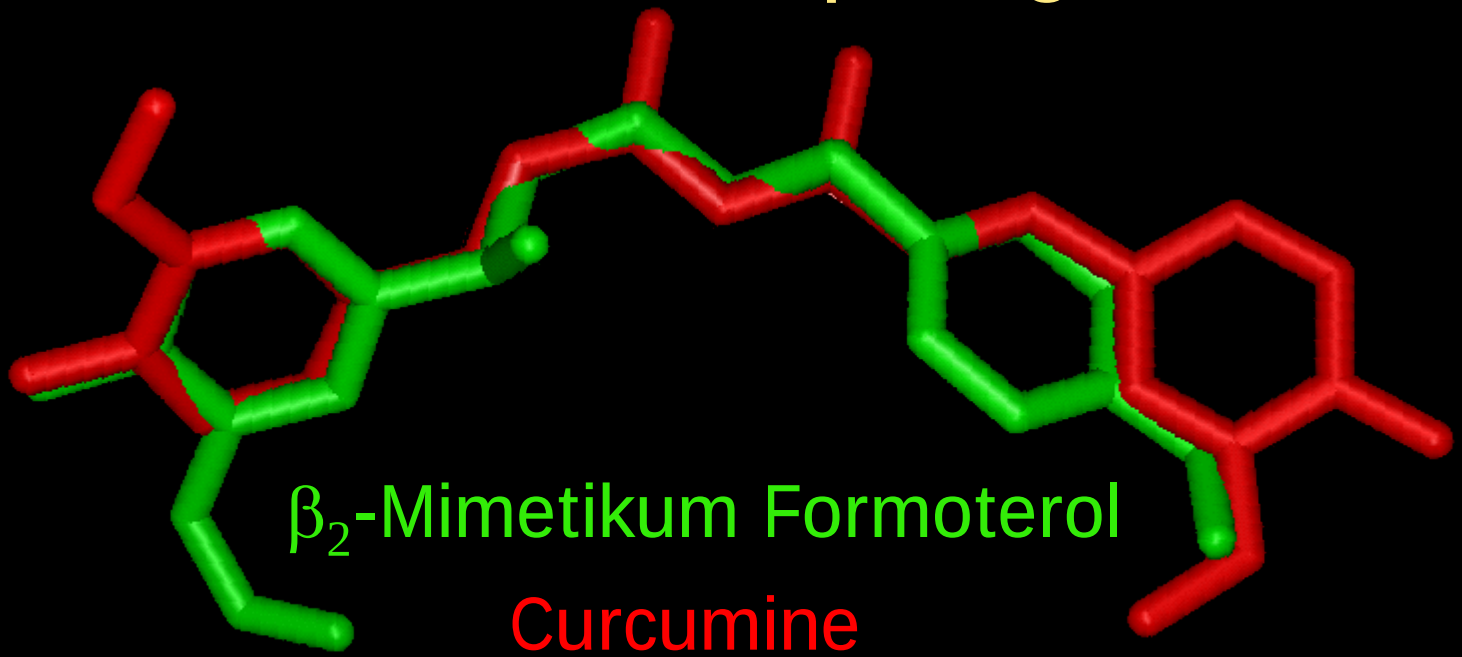
Locks

Mimicry!

Mimesis!

Mimicry for molecules

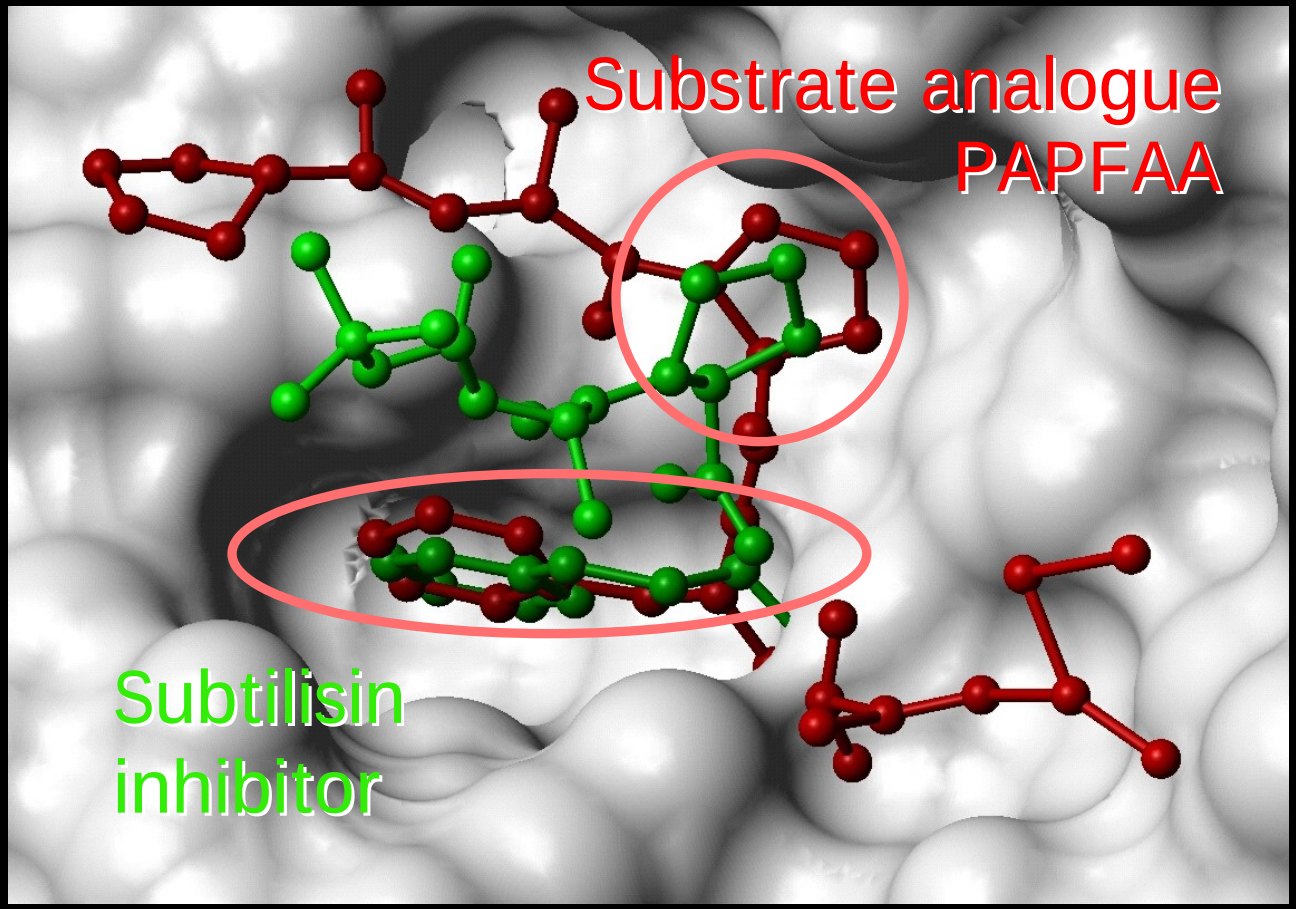
Inhibitors of the cop9 signalosome



Preissner, Dubiel et al. in preparation.

Mimicry for molecules

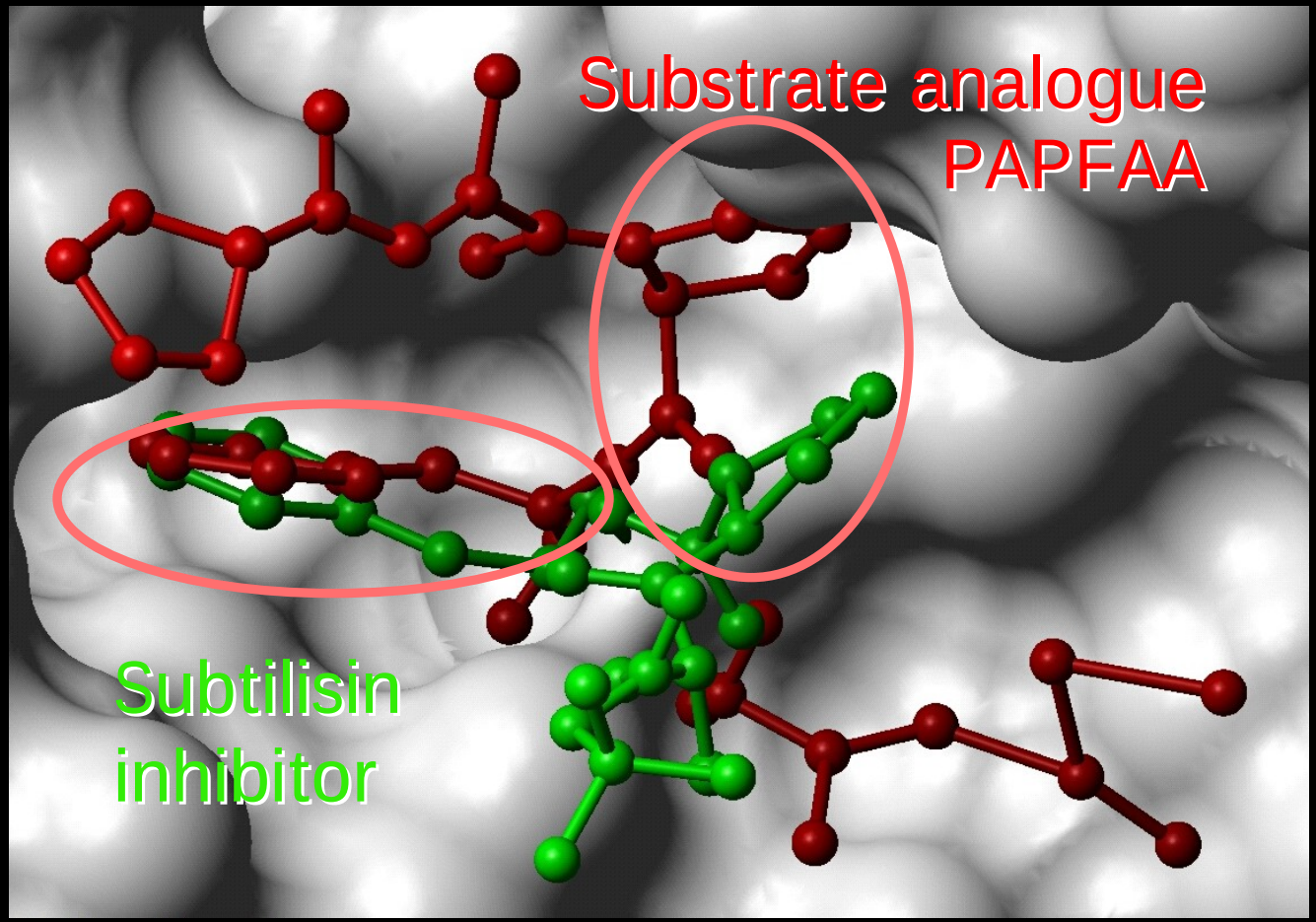
Common features



Proteinase K (1PEK) / Subtilisin Carlsberg (1SCN)

Mimicry for molecules

Common features



Proteinase K (1PEK) / Subtilisin Carlsberg (1SCN)

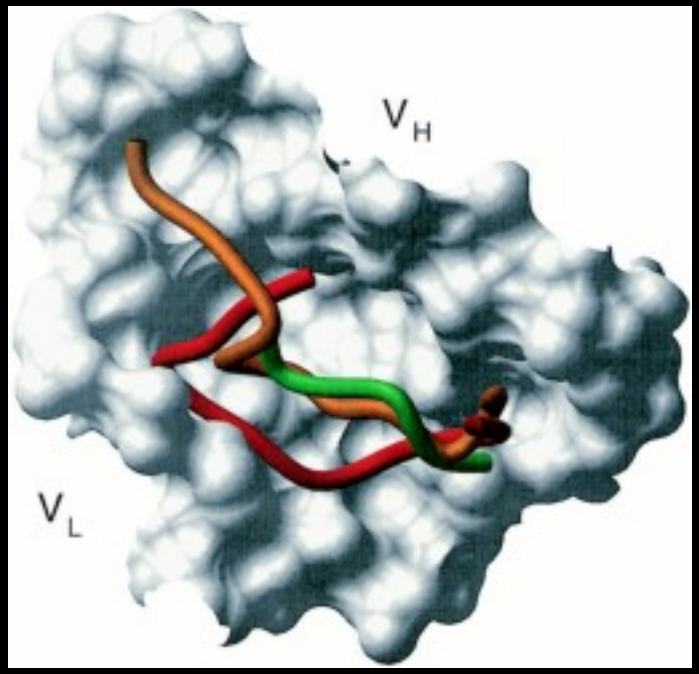
Mimicry / mimesis for proteins

- Different peptides bind to the same region (in CB4-1 antibody against HIV protease p24)

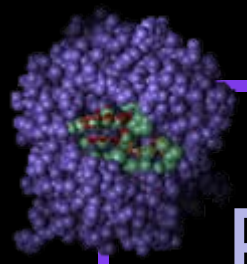
GAEDLQKATPDLNQKL

EWGGARIGLWRIT

kllkGpl



Kramer et al., *Cell*. 1997; **91:**799-809. Keitel et al., *Cell*. 1997; **91:**811-820. PDB codes 1BOG, 1CFS, 1CFT.



Example CB4-1 antibody

- Method:
  - Superposition of those ligand atoms adjacent to the antibody
    - NeedleHaystack program
- Question:
  - Best superposition of ligand — good antibody superposition?

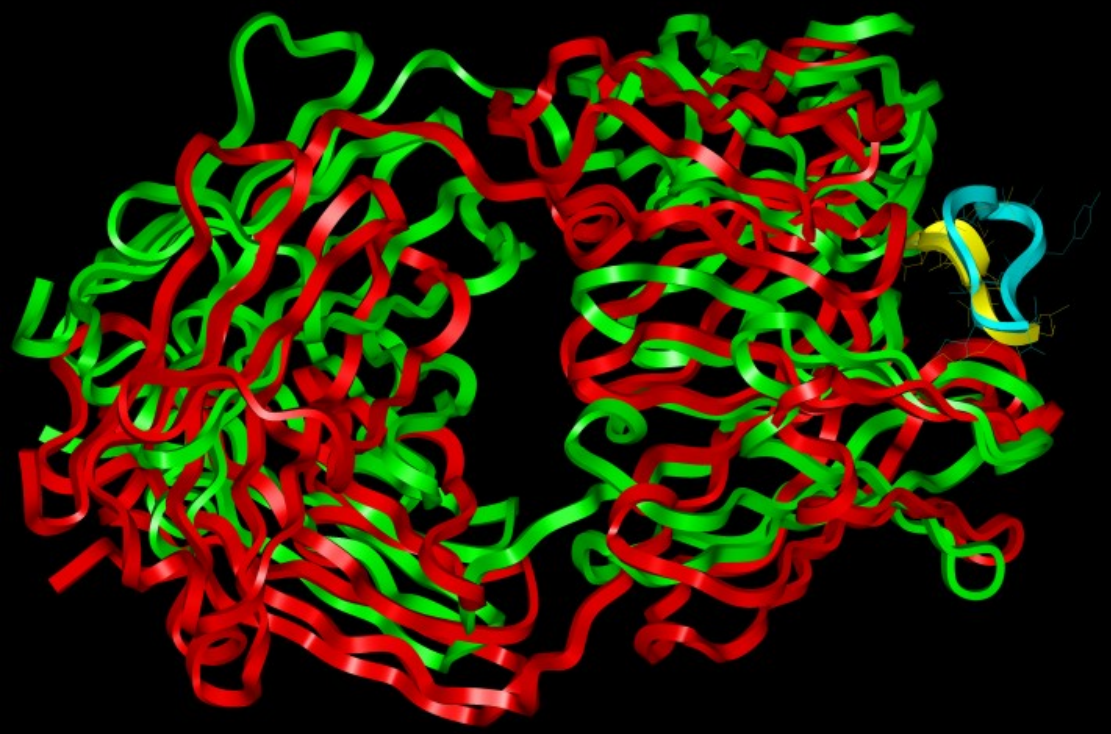
NeedleHaystack ... QSAR2000; see www.charite.de/bioinf/hoppe

CB4-1 ligand superposition, RMSD 1.44Å

GAEDLQKATPDLNQKL EWGGARIGLWRIT

CB4-1 ligand superposition, RMSD 1.44Å

GAEDLQKATPDLNQKL EWGGARIGLWRIT

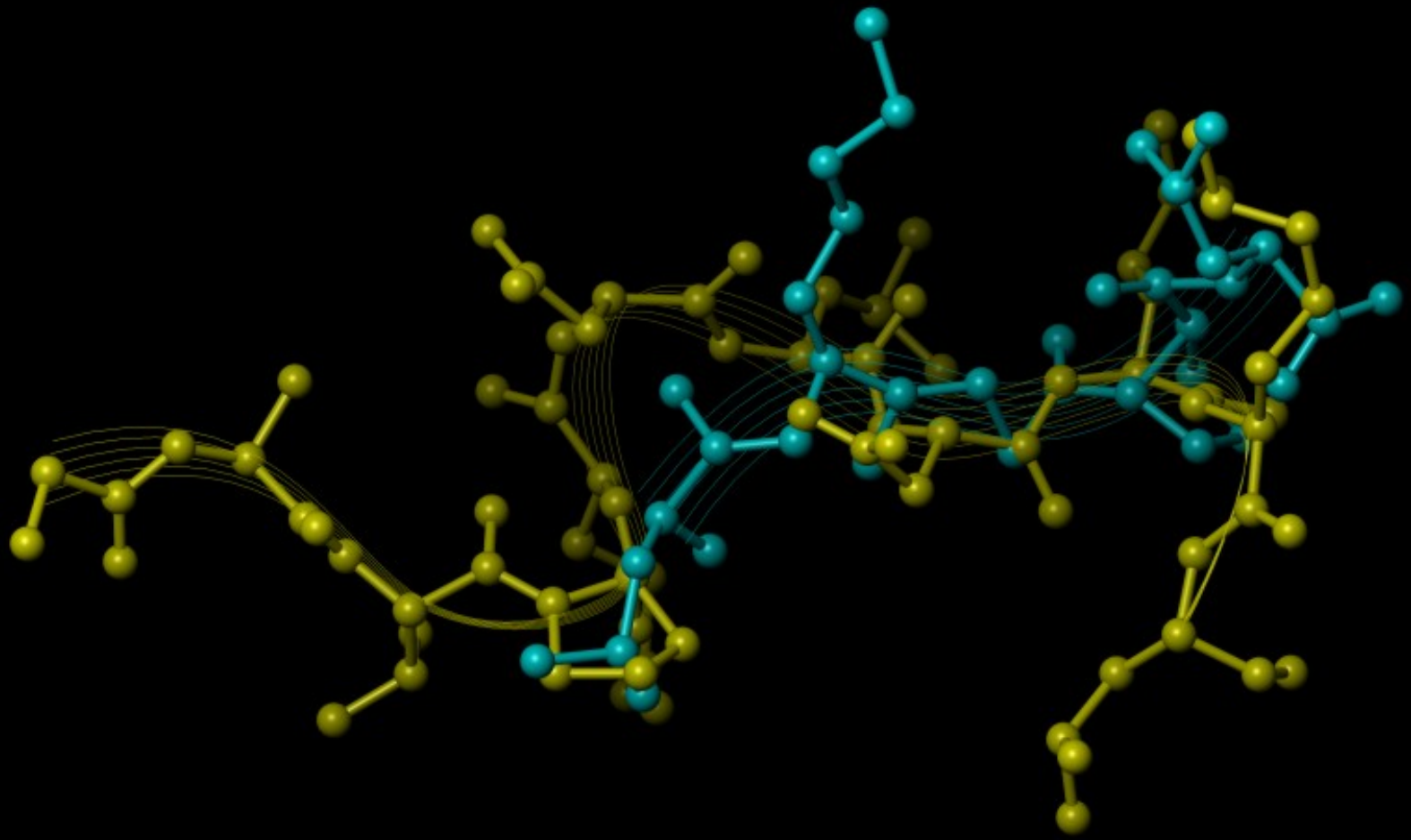


Good superposition of the antibody

Mimicry!

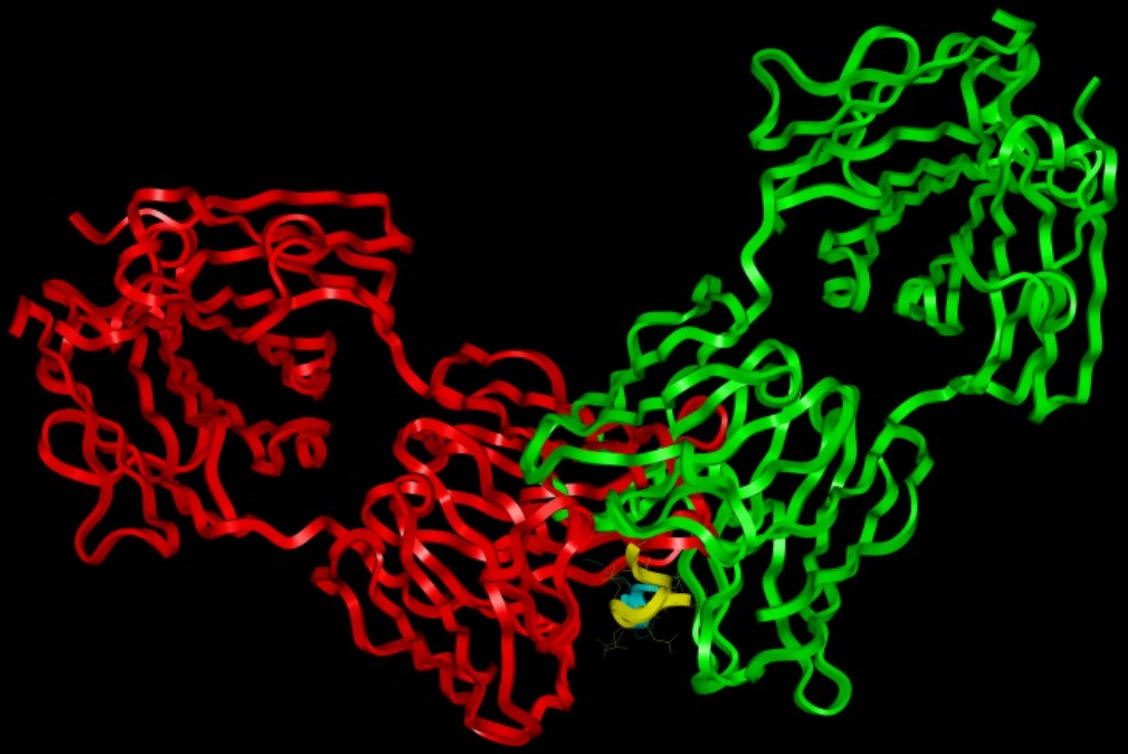
CB4-1 ligand superposition, RMSD 1.29Å

GAEDLQKATPDLNQKL kllkGpl



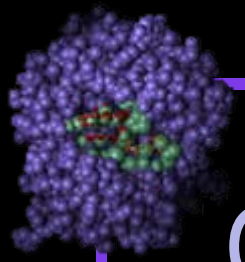
CB4-1 ligand superposition, RMSD 1.29Å

GAEDLQKATPDLNQKL kllkGpl



Bad superposition of the antibody

Mimesis!



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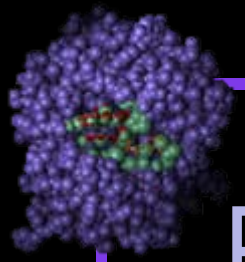
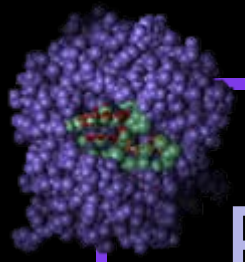


Promiscuity types for proteins

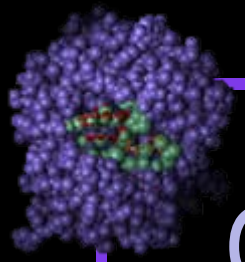
- Homology: evolutionary related
- Local sequence similarity
- Mimicry: structural similarity on atomic level
- Mimesis: structural dissimilarity



Bioinformatical methods

- Homology Sequence comparison programs
- Local sequence similarity Structure alignment programs
- Mimicry 3D similarity methods
- Mimesis indirect similarity methods: DIP; docking, de novo design

DIP ... Preissner et al., *J Mol Biol*. 1998; **280:**535-550



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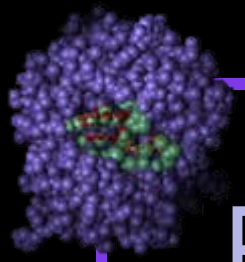
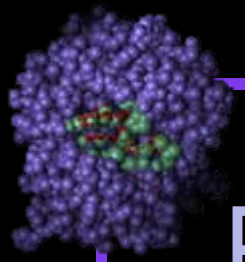


Flavin binding site similarity

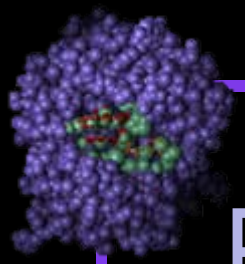
- Data:
  - >500 proteins with bound flavin triple ring (FAD, FMN, Riboflavin etc.)
  - Binding pocket = all protein atoms nearer than 5Å to the flavin rings



Flavin binding site similarity

- Method:
  - Superposition of the triple ring structure
  - Evaluation of the 3D-similarity of the binding pockets
  - Rank these evaluations

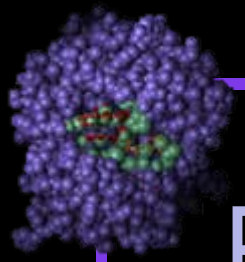
NeedleHaystack ... QSAR2000; see www.charite.de/bioinf/hoppe



Flavin binding site similarity

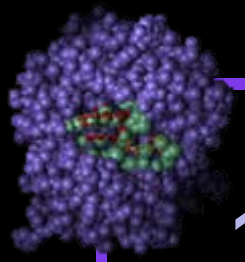
- Method:
  - Sequence similarity scoring (Needleman/Wunsch)
    - Gap penalty
    - Also counting similar residues
  - Rank sequence comparisons
  - Find large discrepancies of structure rank to sequence rank

GCG ... Womble, *Methods Mol Biol* 2000; **132**:3-22



Flavin binding site similarity

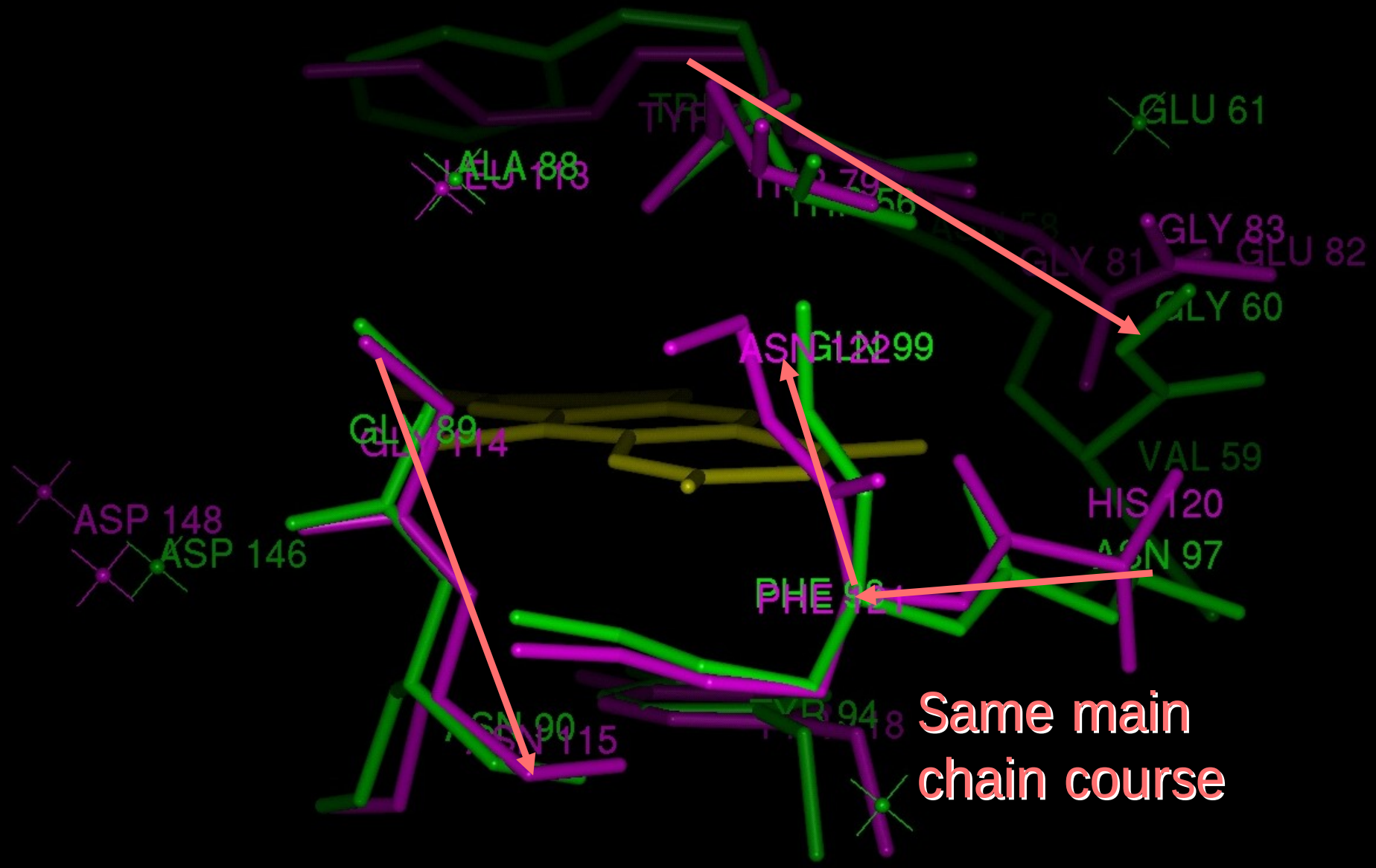
- Results:
  - Proteins with similar sequence have also 3D-similar binding pockets
  - There are 3D-similar binding pockets which show no sequence similarity



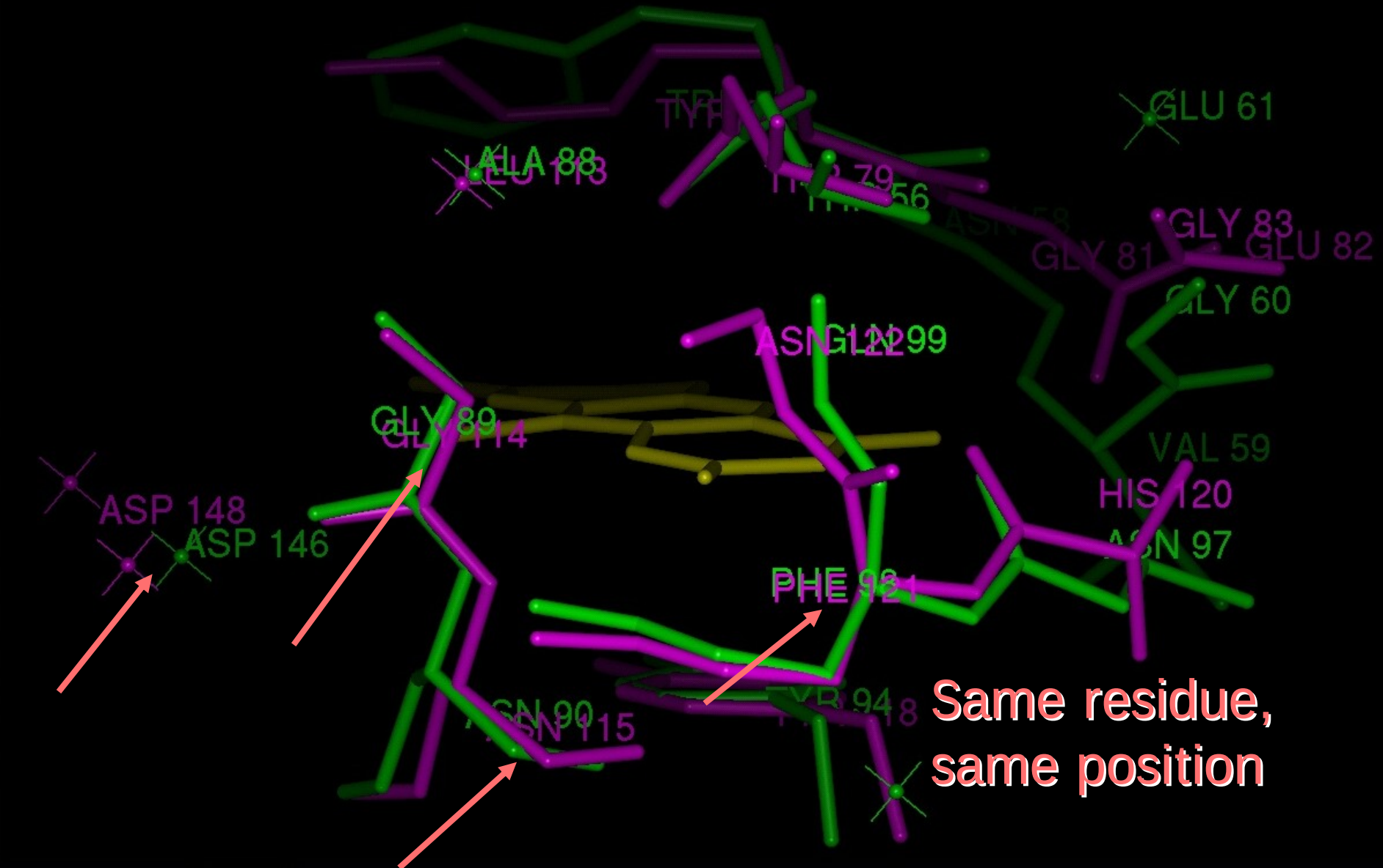
1B1C-1CZR

- 1B1C: Cytochrome p450 reductase/FMN (human)
- 1CZR: Flavodoxin/FMN (*anacystis nidulans*)
- Sequence similarity of protein: 11%
- 3D-similarity of the binding pockets: RMSD 0.75Å

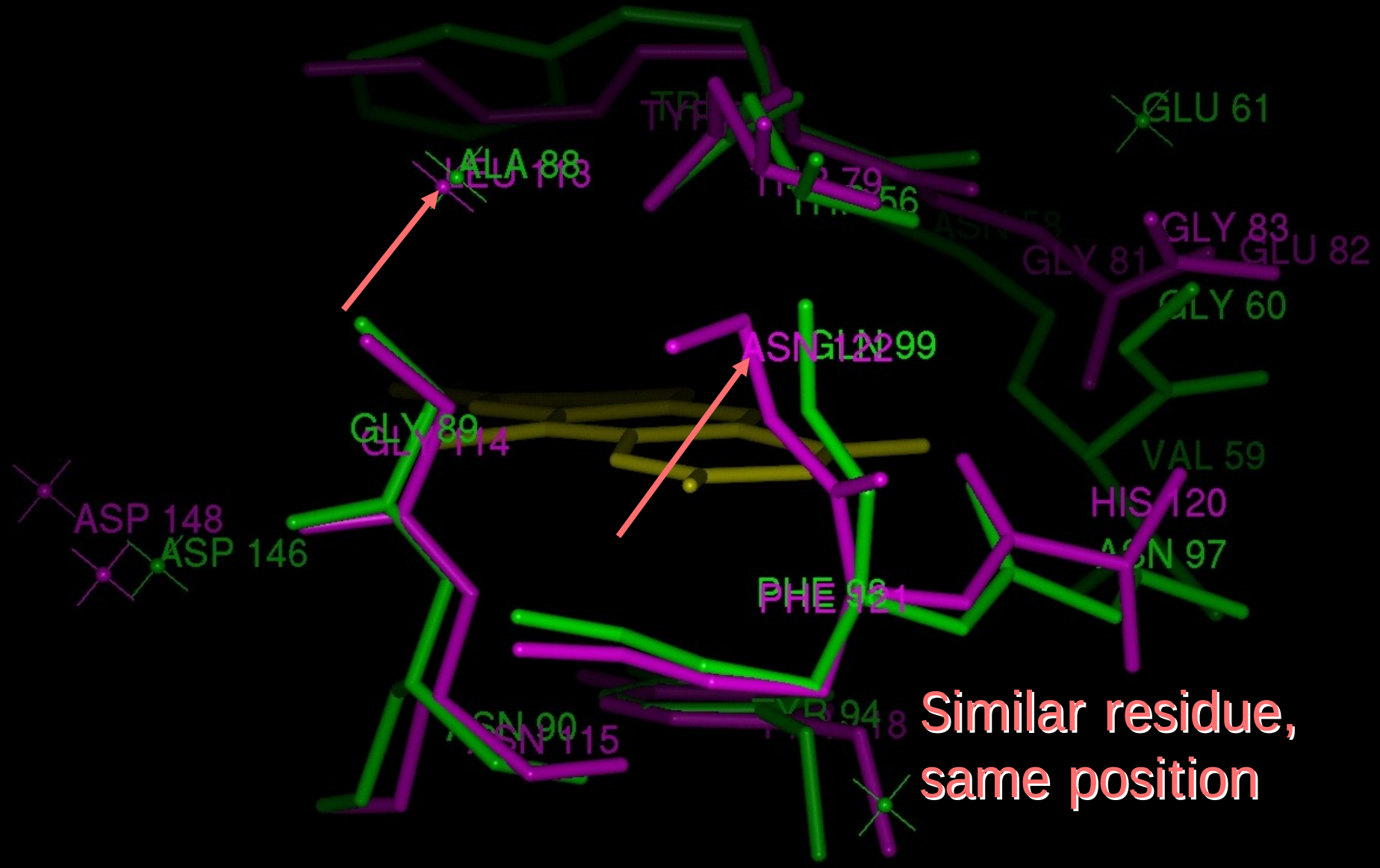
1B1C-1CZR: Seq. sim. 11%, RMSD 0.75Å



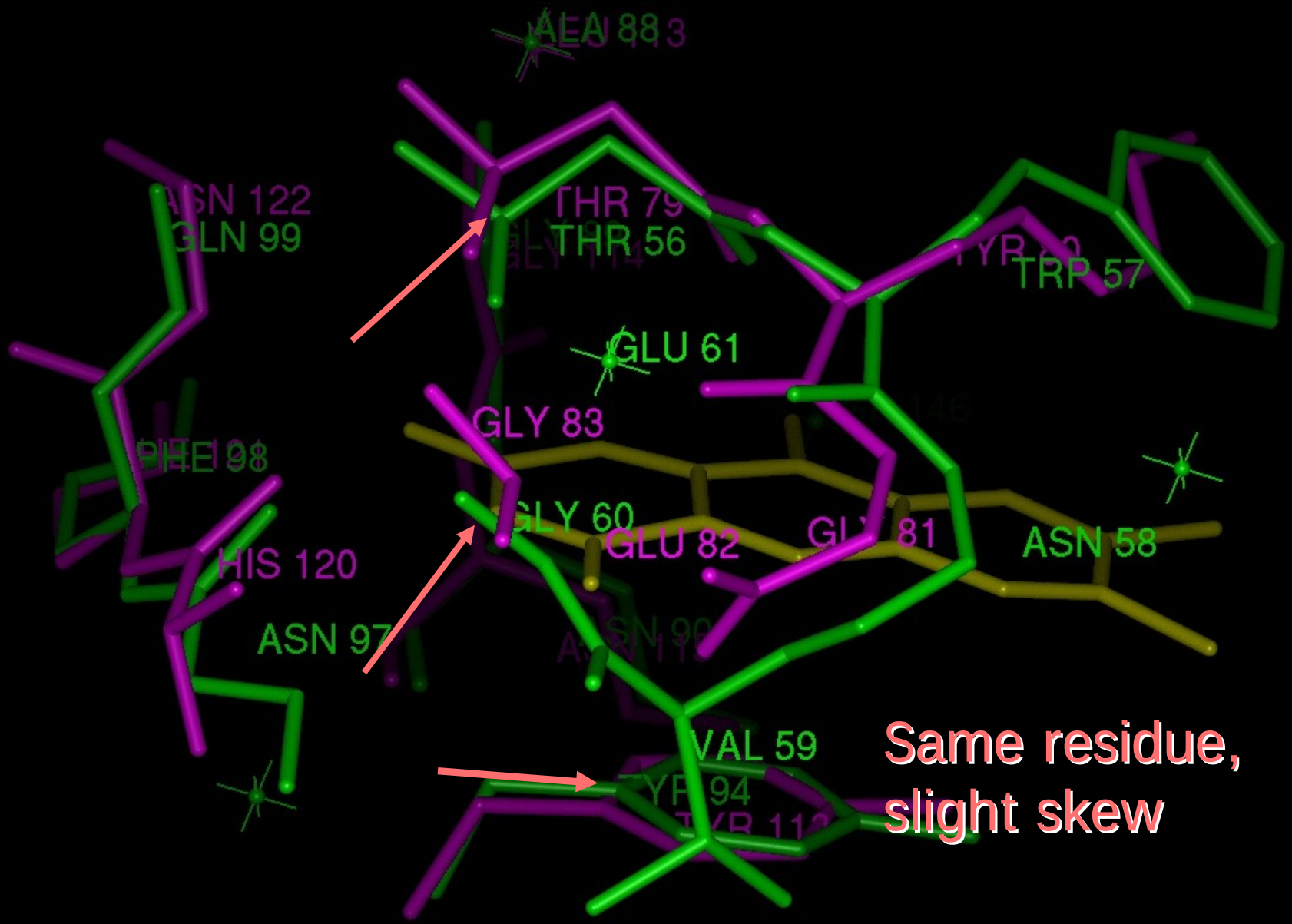
1B1C-1CZR: Seq. sim. 11%, RMSD 0.75Å



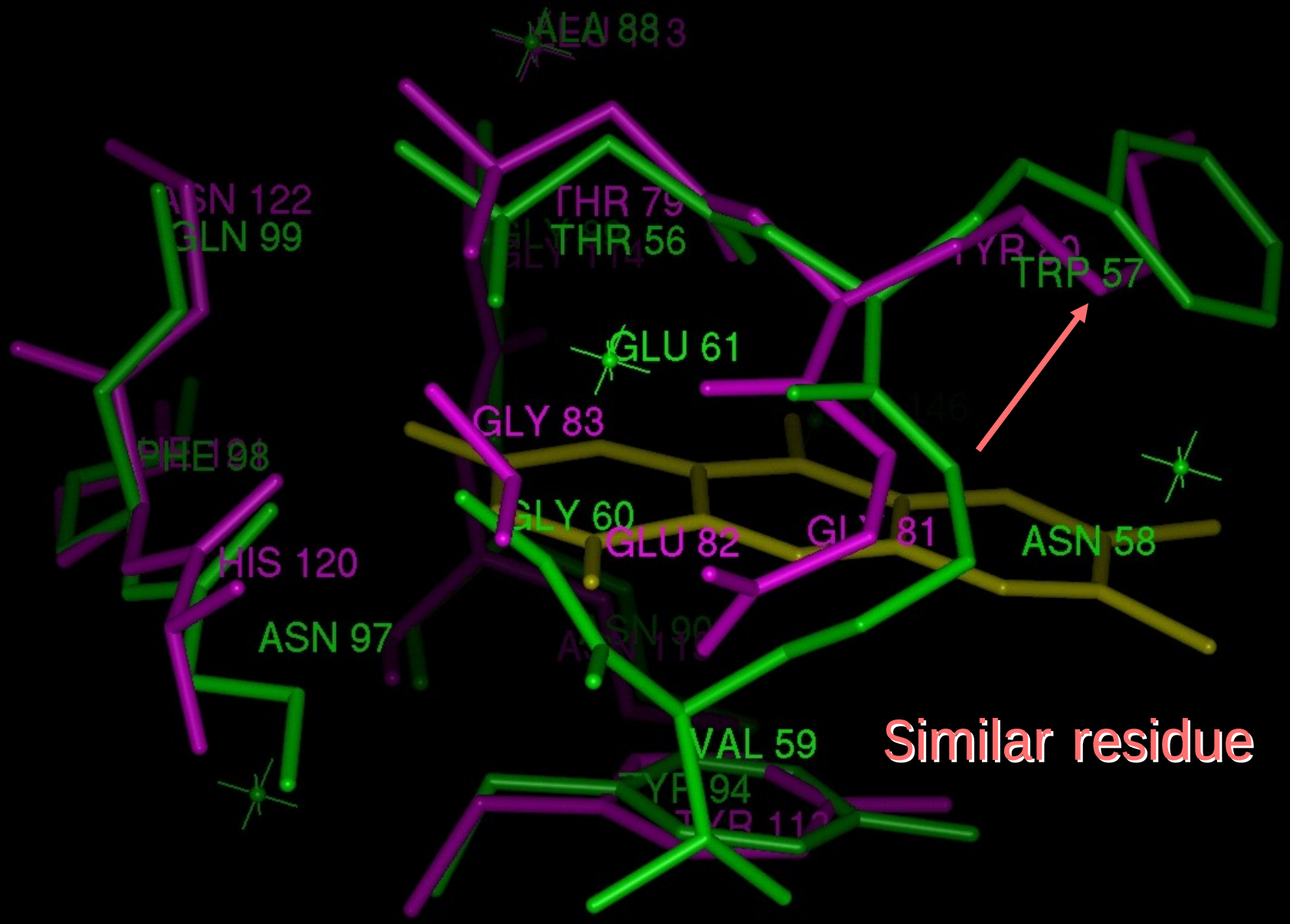
1B1C-1CZR: Seq. sim. 11%, RMSD 0.75Å



1B1C-1CZR: Seq. sim. 11%, RMSD 0.75Å



1B1C-1CZR: Seq. sim. 11%, RMSD 0.75Å



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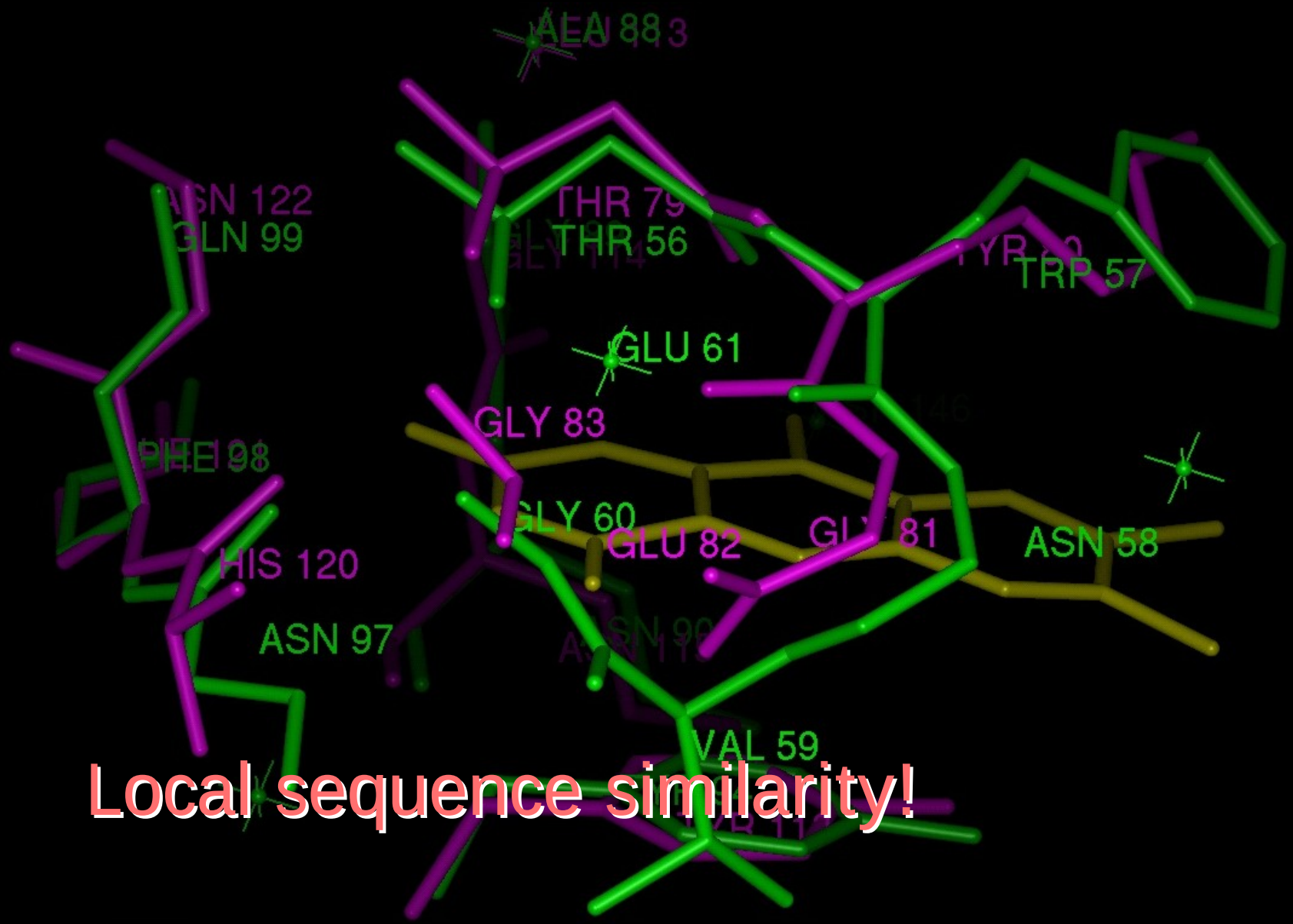
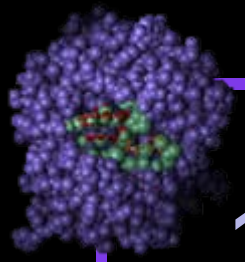


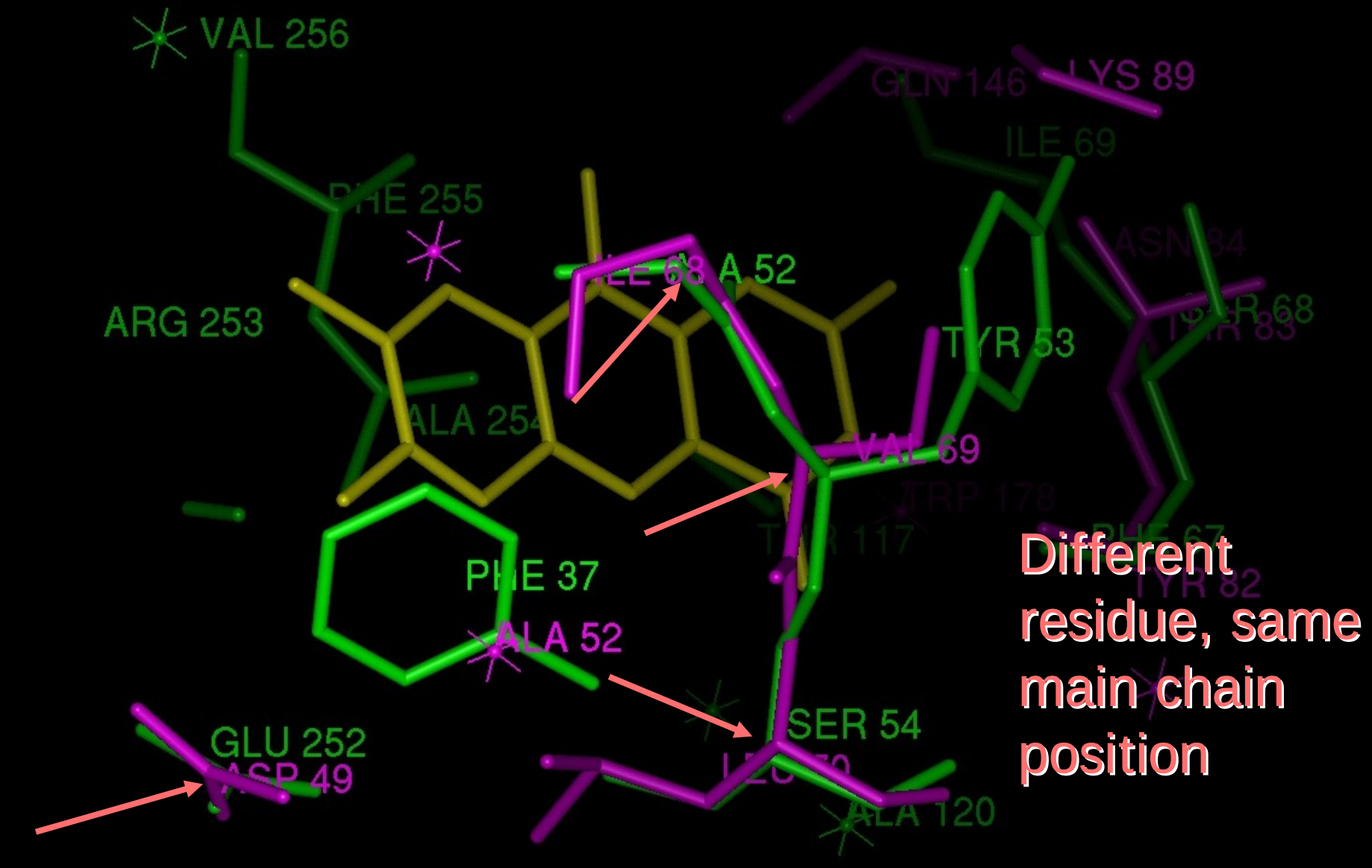
Local sequence similarity!



1A8P-1DNL

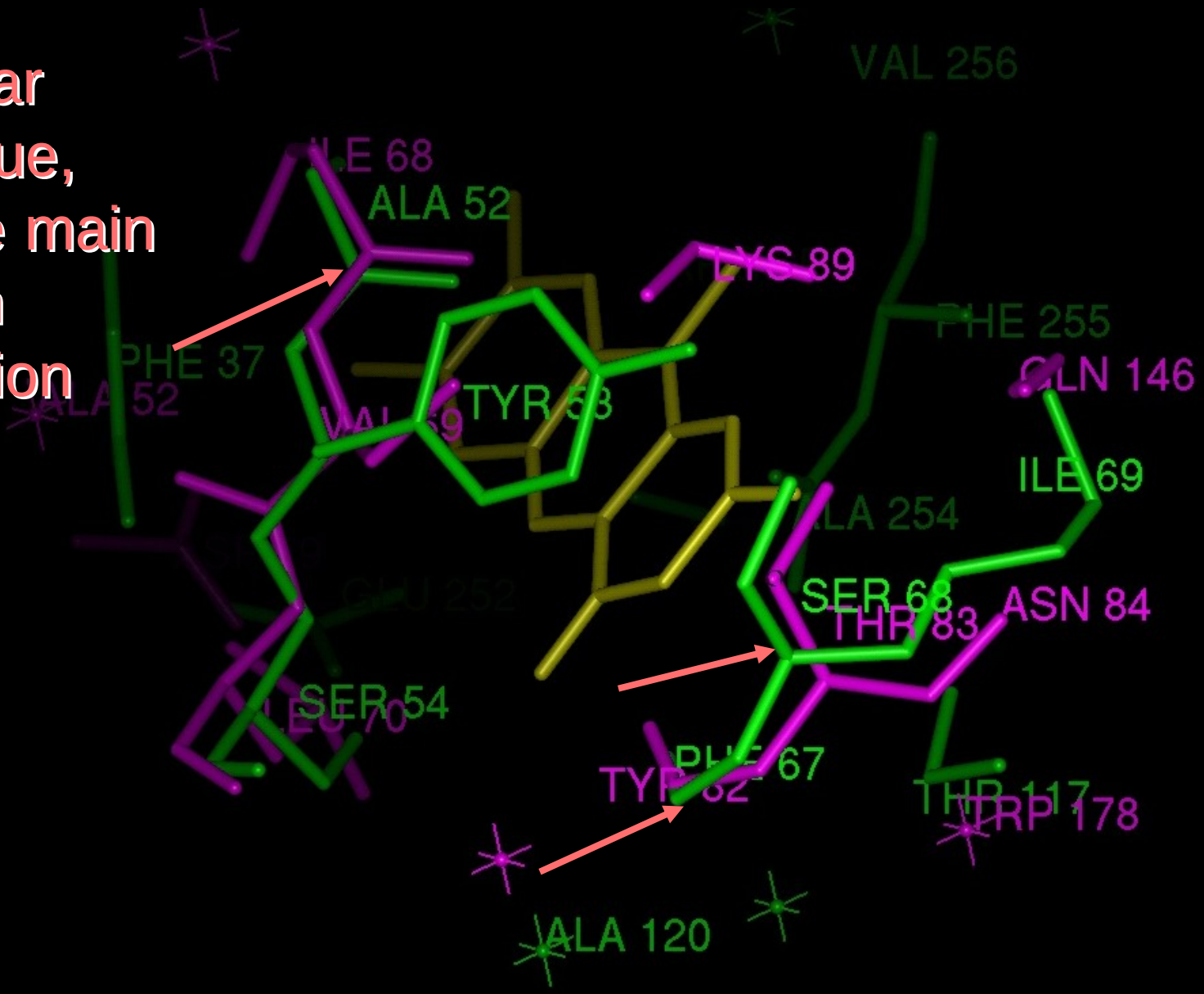
- 1A8P: Ferredoxin reductase/FAD (*azotobacter vinelandii*)
- 1DNL: Pyridoxine 5'-phosphate oxidase/FMN (*e. coli*)
- Sequence similarity 13%
- 3D-similarity of the binding pockets: RMSD 1.05Å

1A8P-1DNL: Seq. sim. 13%, RMSD 1.05Å



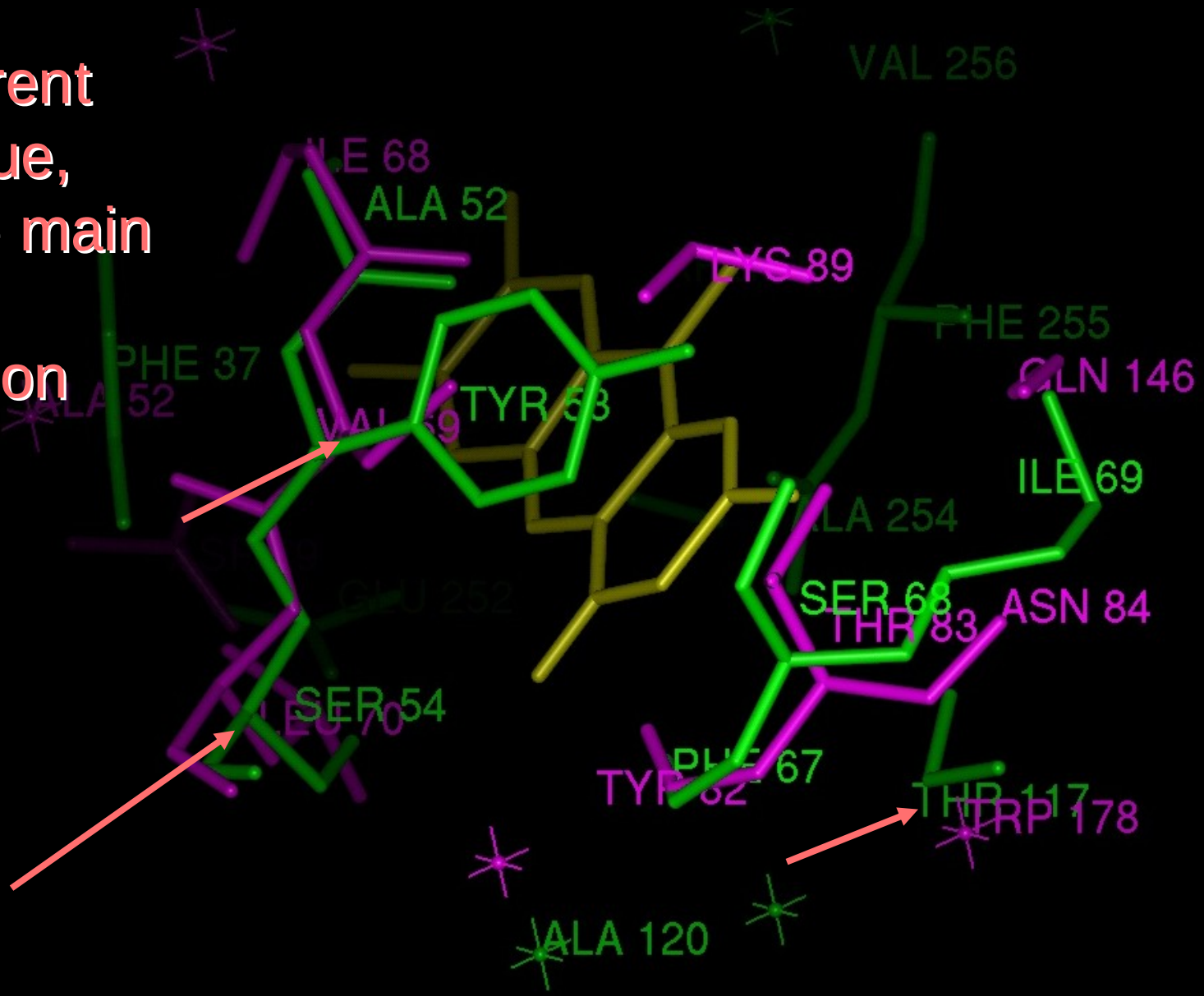
1A8P-1DNL: Seq. sim. 13%, RMSD 1.05Å

Similar residue, same main chain position

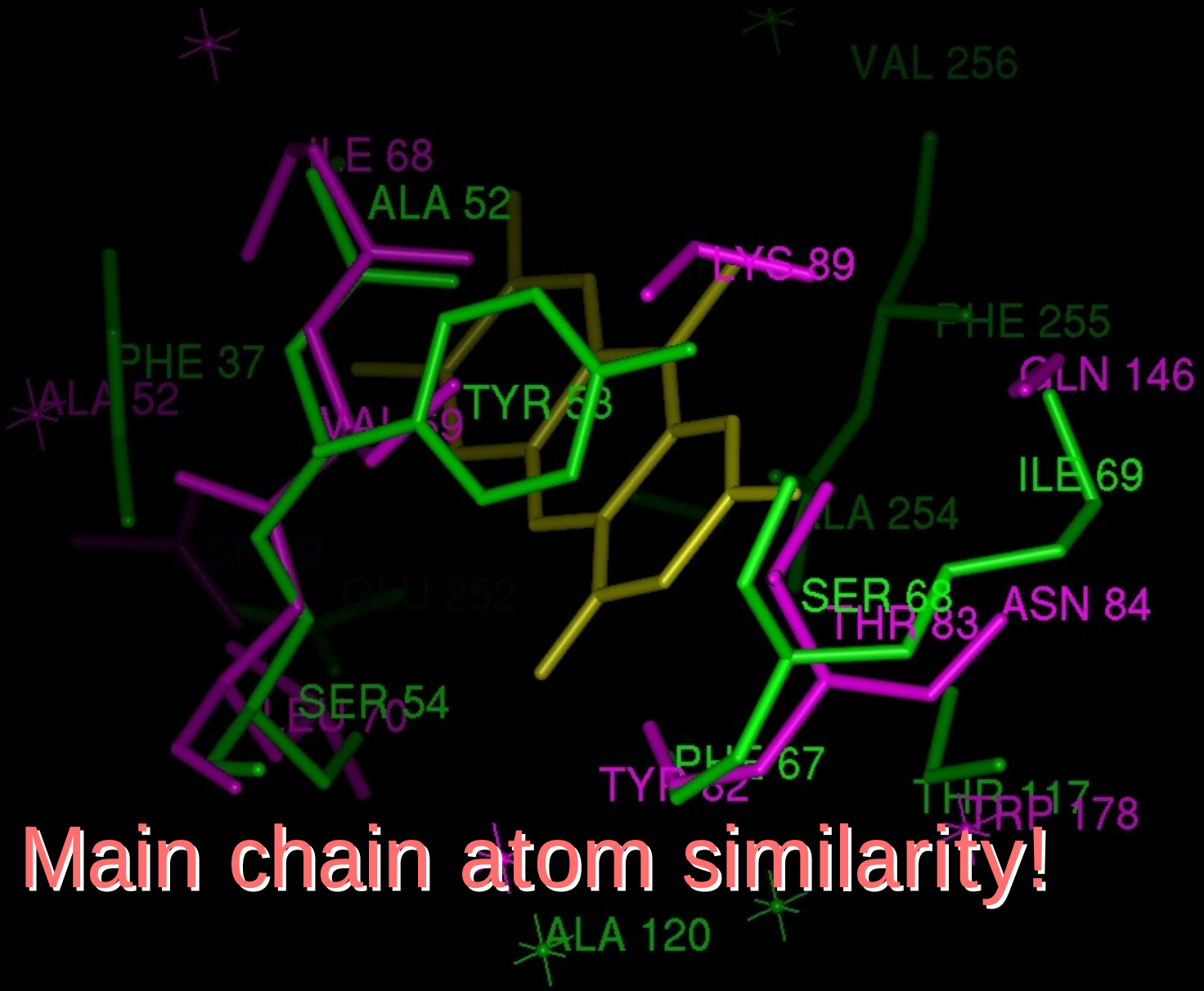


1A8P-1DNL: Seq. sim. 13%, RMSD 1.05Å

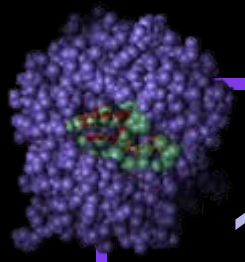
Different residue, same main chain position



1A8P-1DNL: Seq. sim. 13%, RMSD 1.05Å



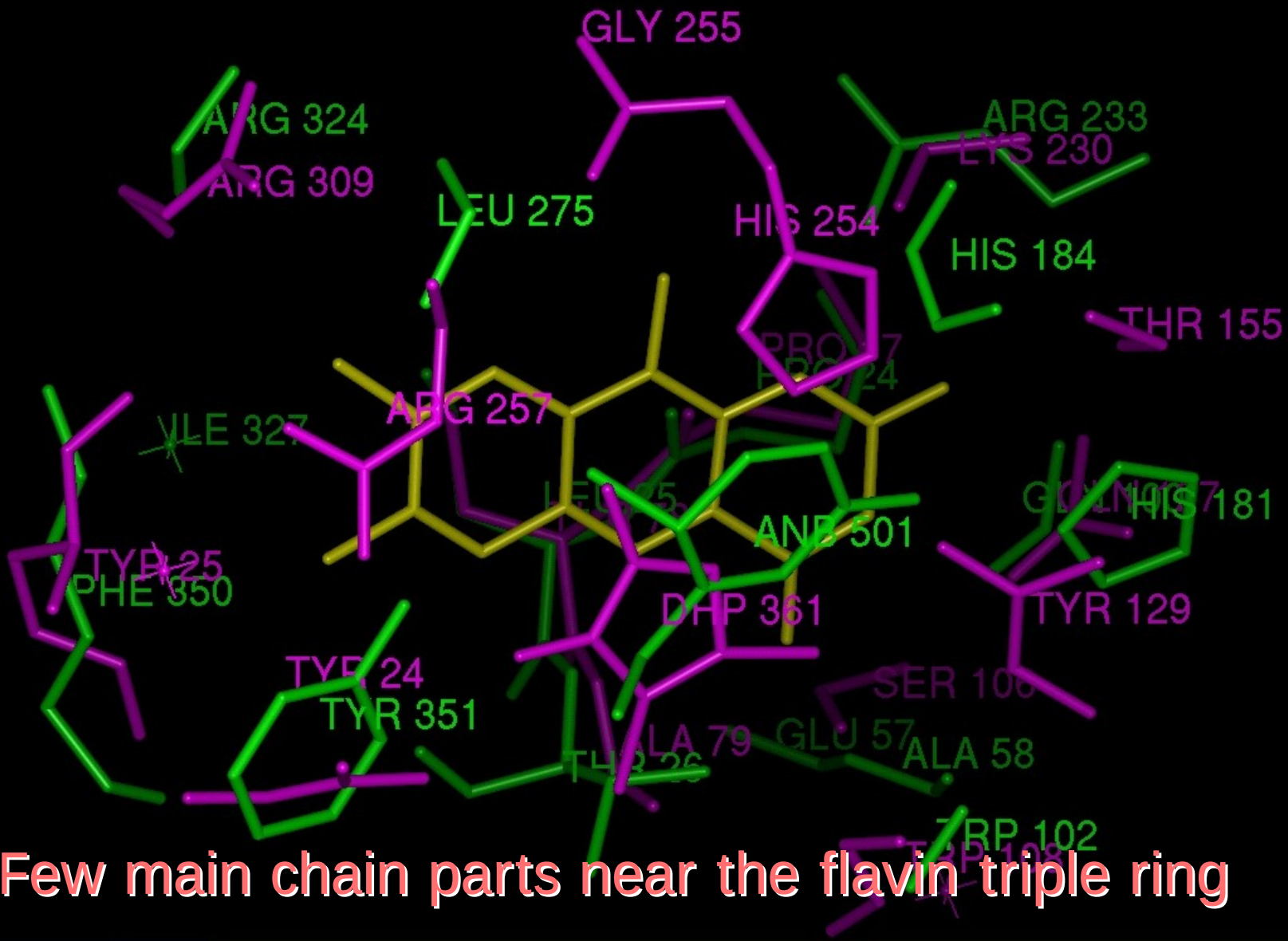
Main chain atom similarity!



1AL8-1H62

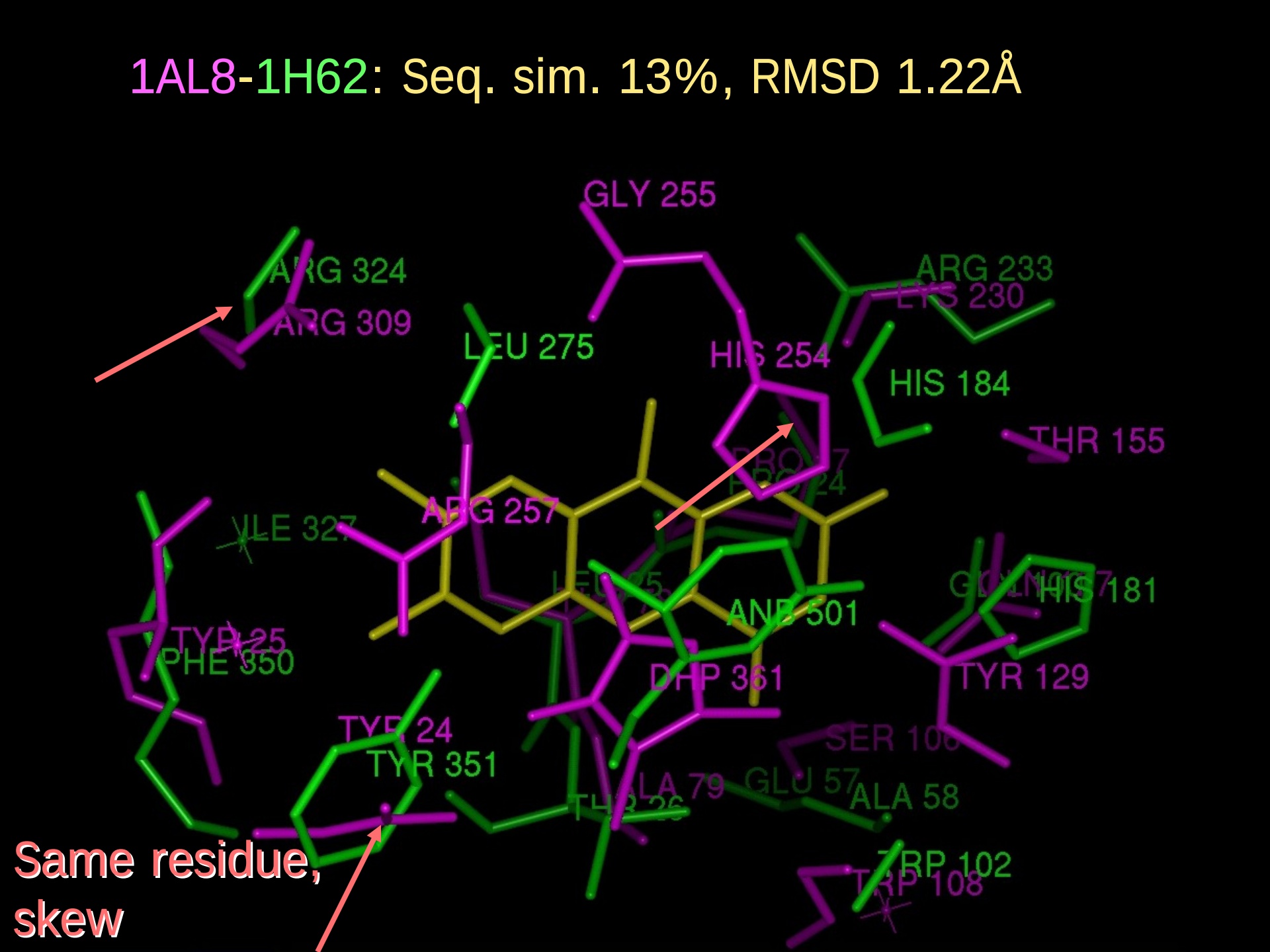
- 1AL8: Glycolate oxidase/FMN (spinach)
- 1H62: Pentaerythritol tetranitrate reductase/FMN (*enterobacter cloacae*)
- Sequence similarity 13%
- 3D-similarity of the binding pockets: RMSD 1.22Å

1AL8-1H62: Seq. sim. 13%, RMSD 1.22Å

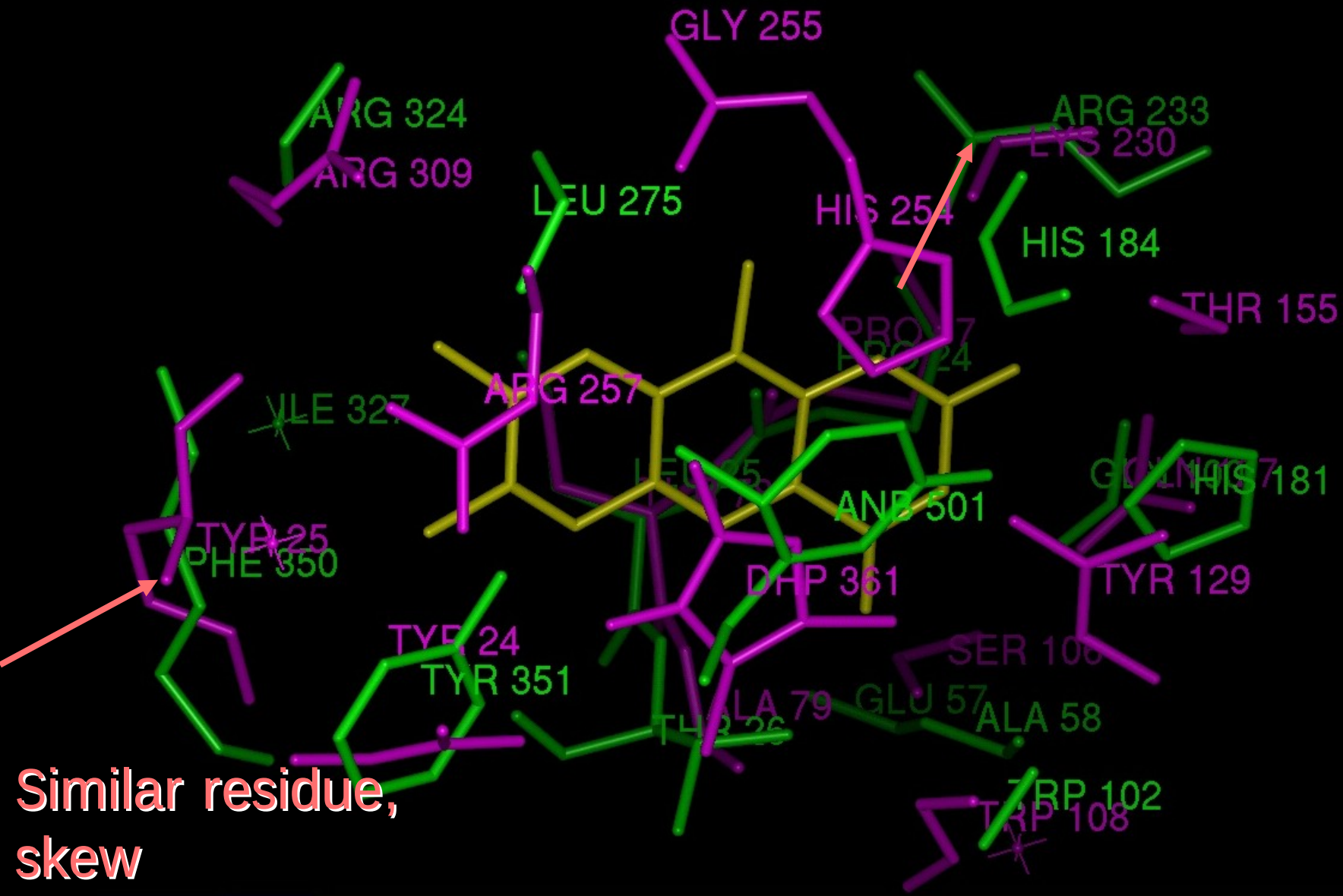


Few main chain parts near the flavin triple ring

1AL8-1H62: Seq. sim. 13%, RMSD 1.22Å



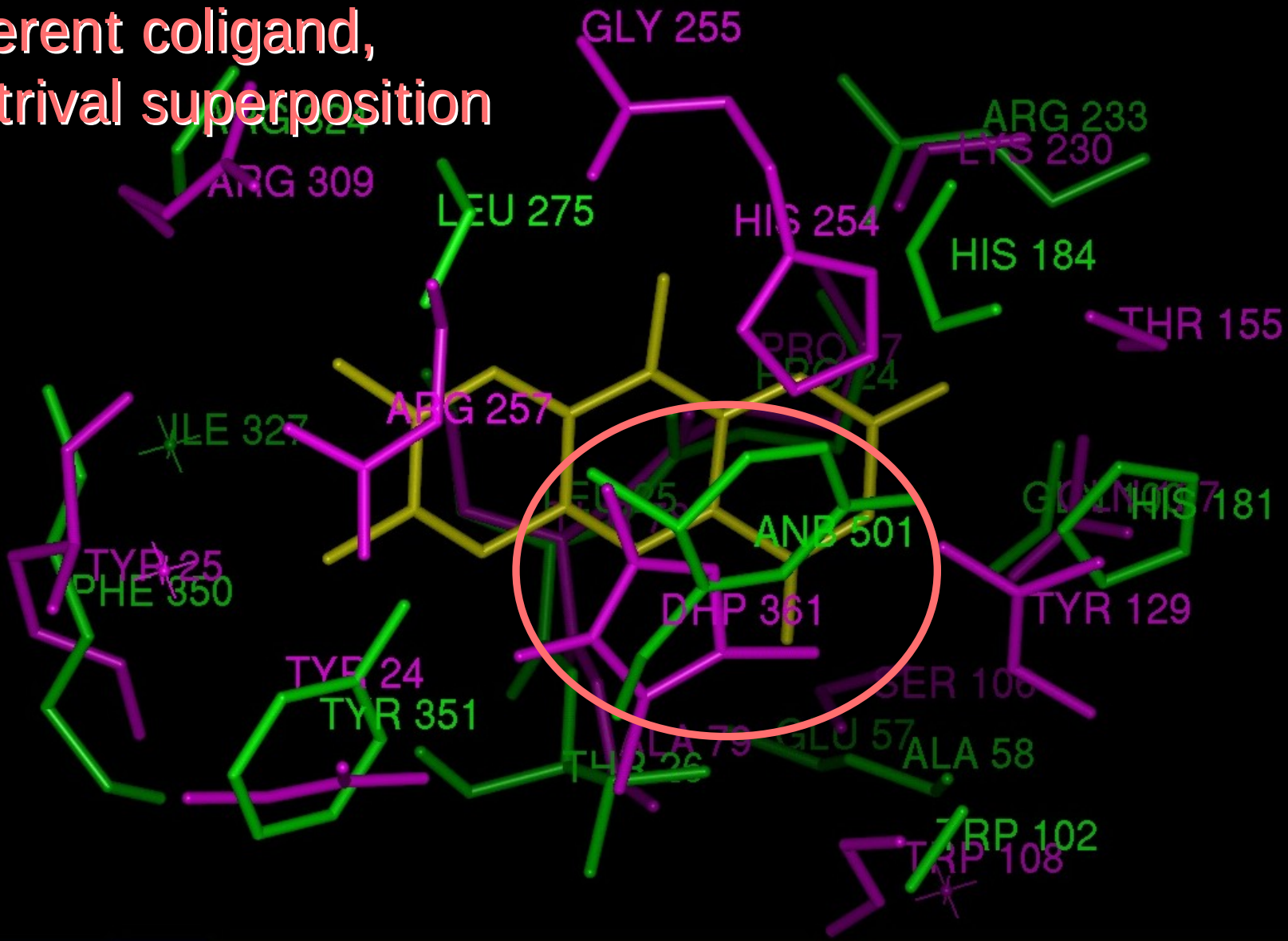
1AL8-1H62: Seq. sim. 13%, RMSD 1.22Å



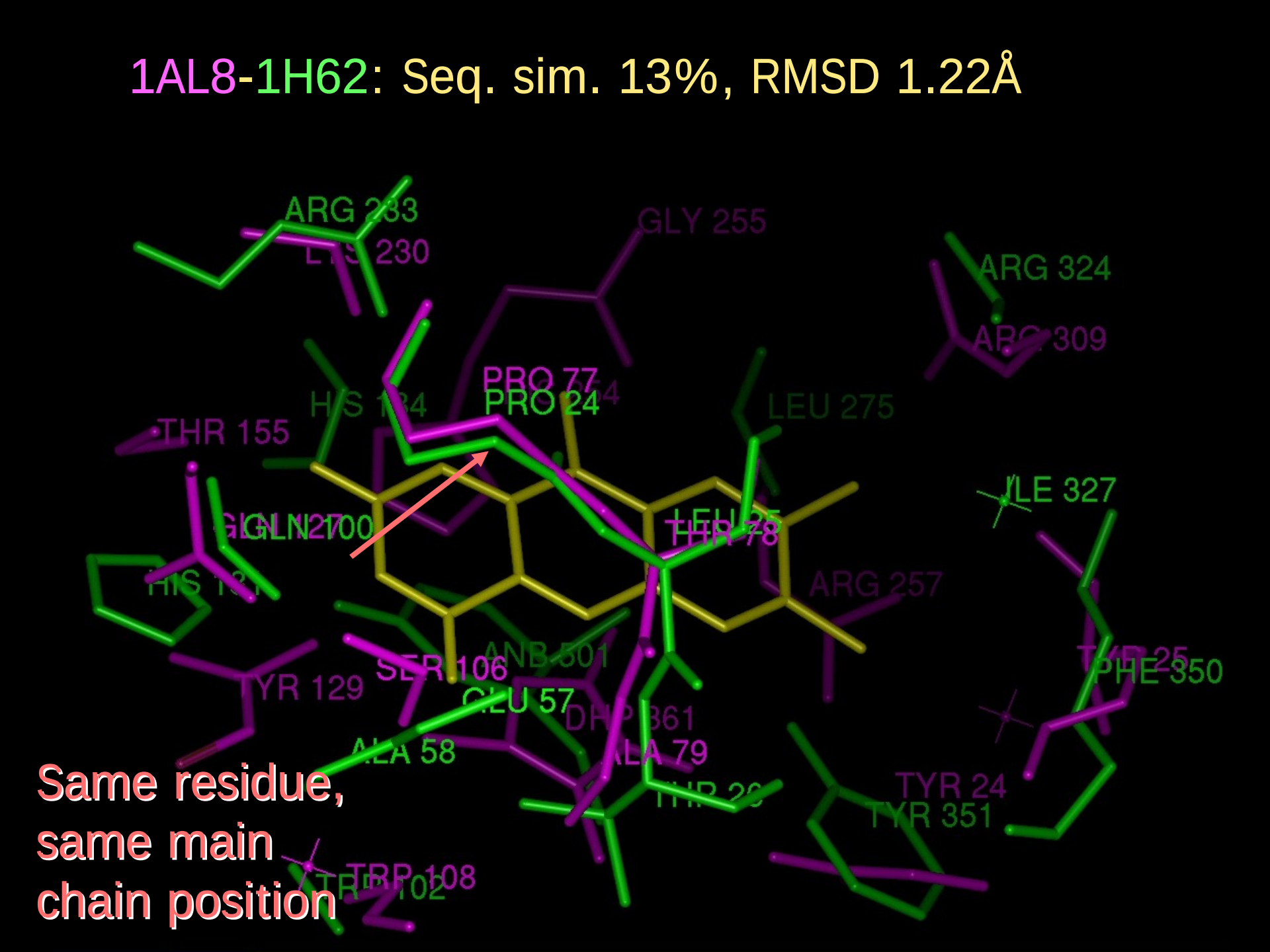
Similar residue, skew

1AL8-1H62: Seq. sim. 13%, RMSD 1.22Å

Different coligand,
nontrival superposition



1AL8-1H62: Seq. sim. 13%, RMSD 1.22Å



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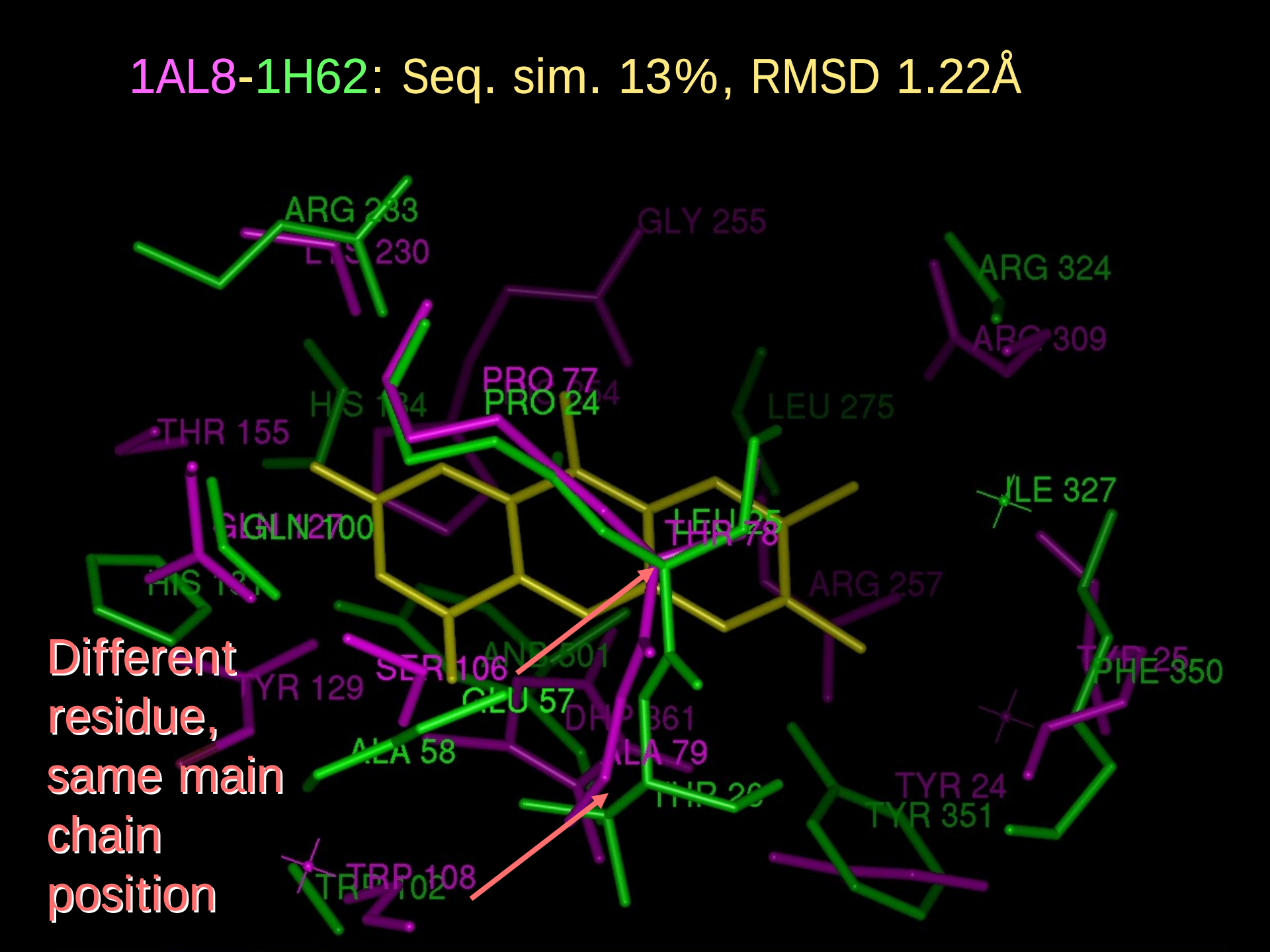

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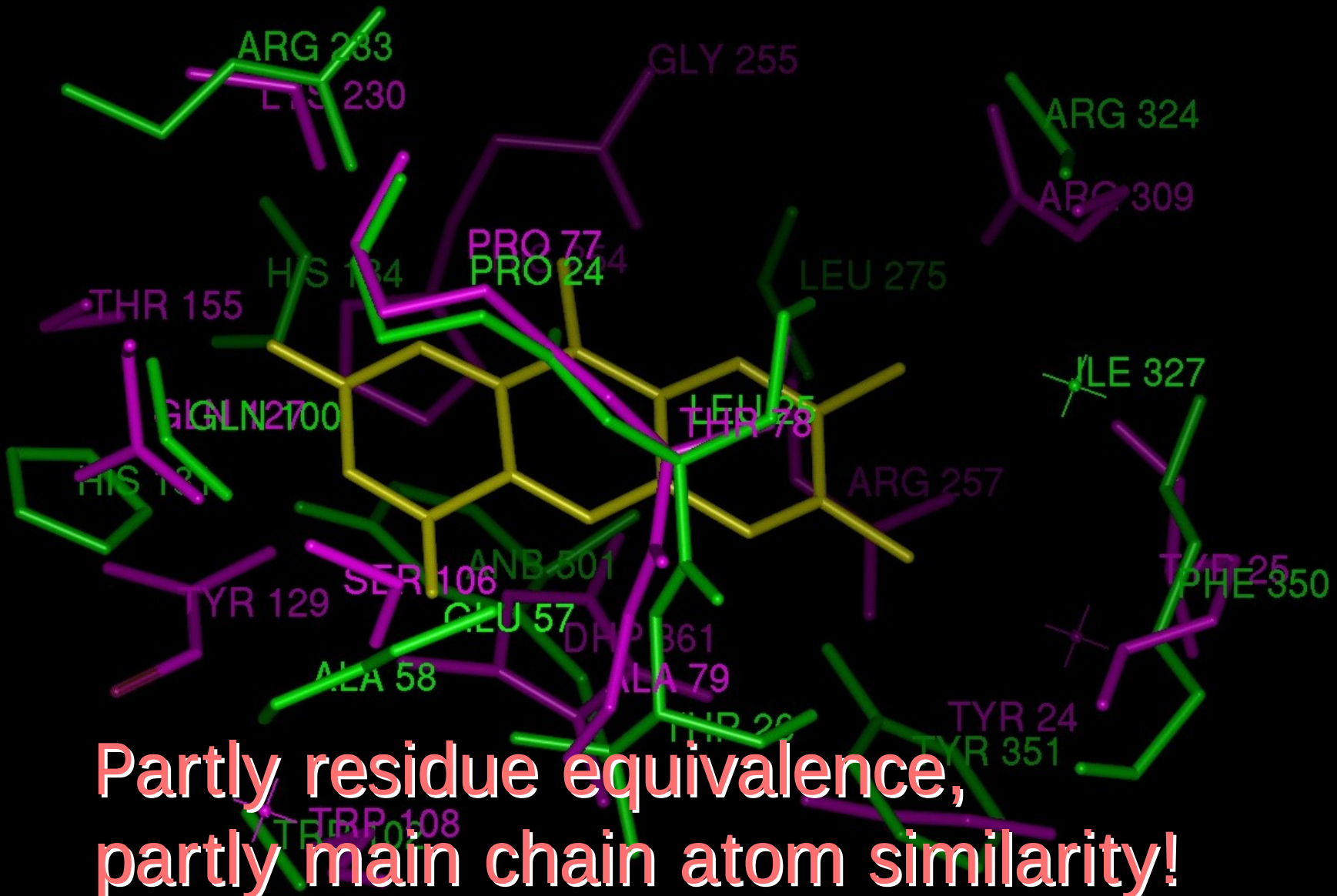
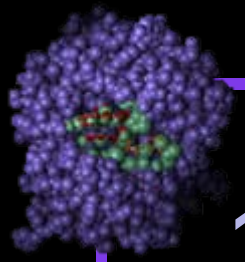


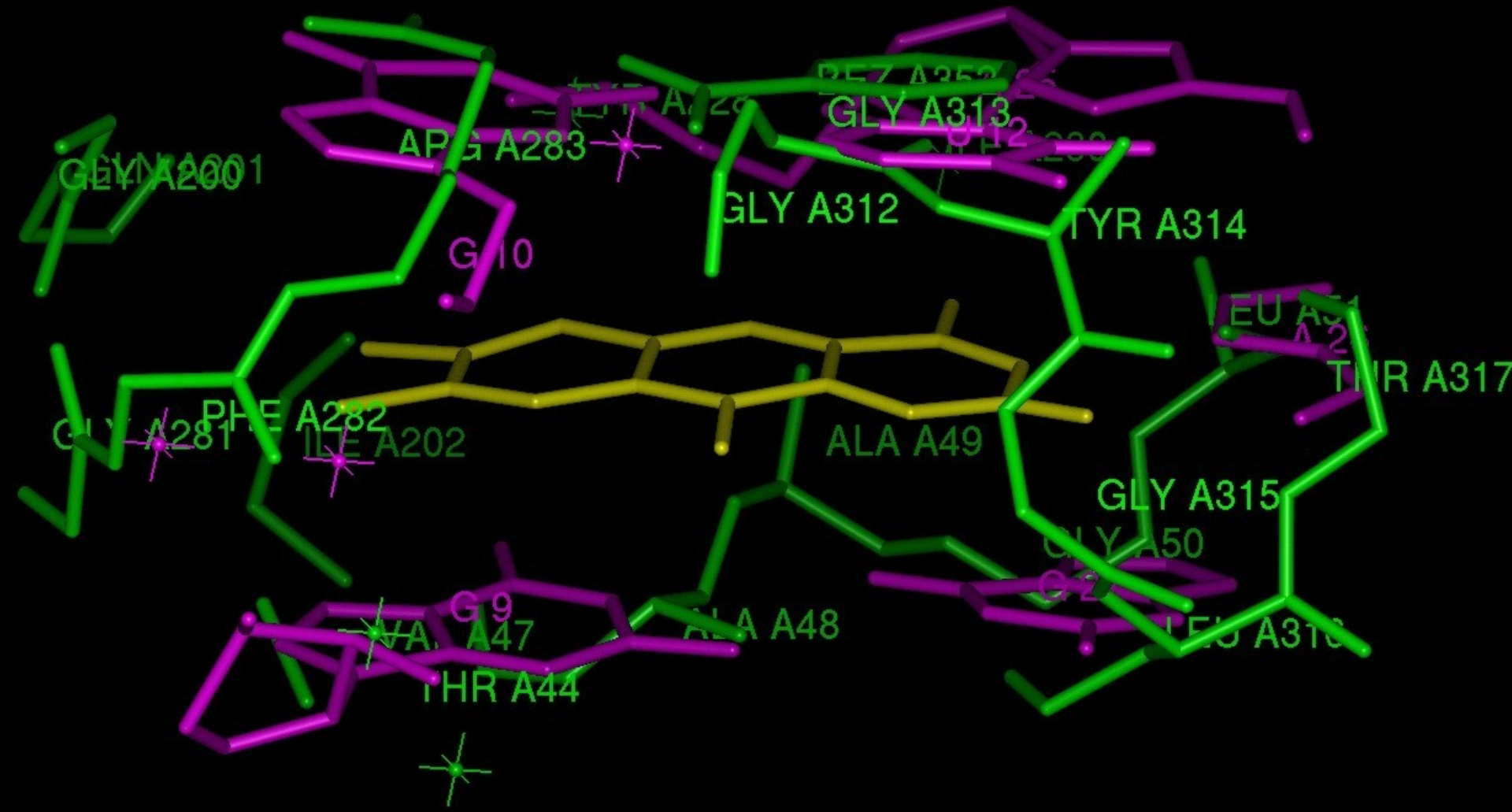
Partly residue equivalence,
partly main chain atom similarity!



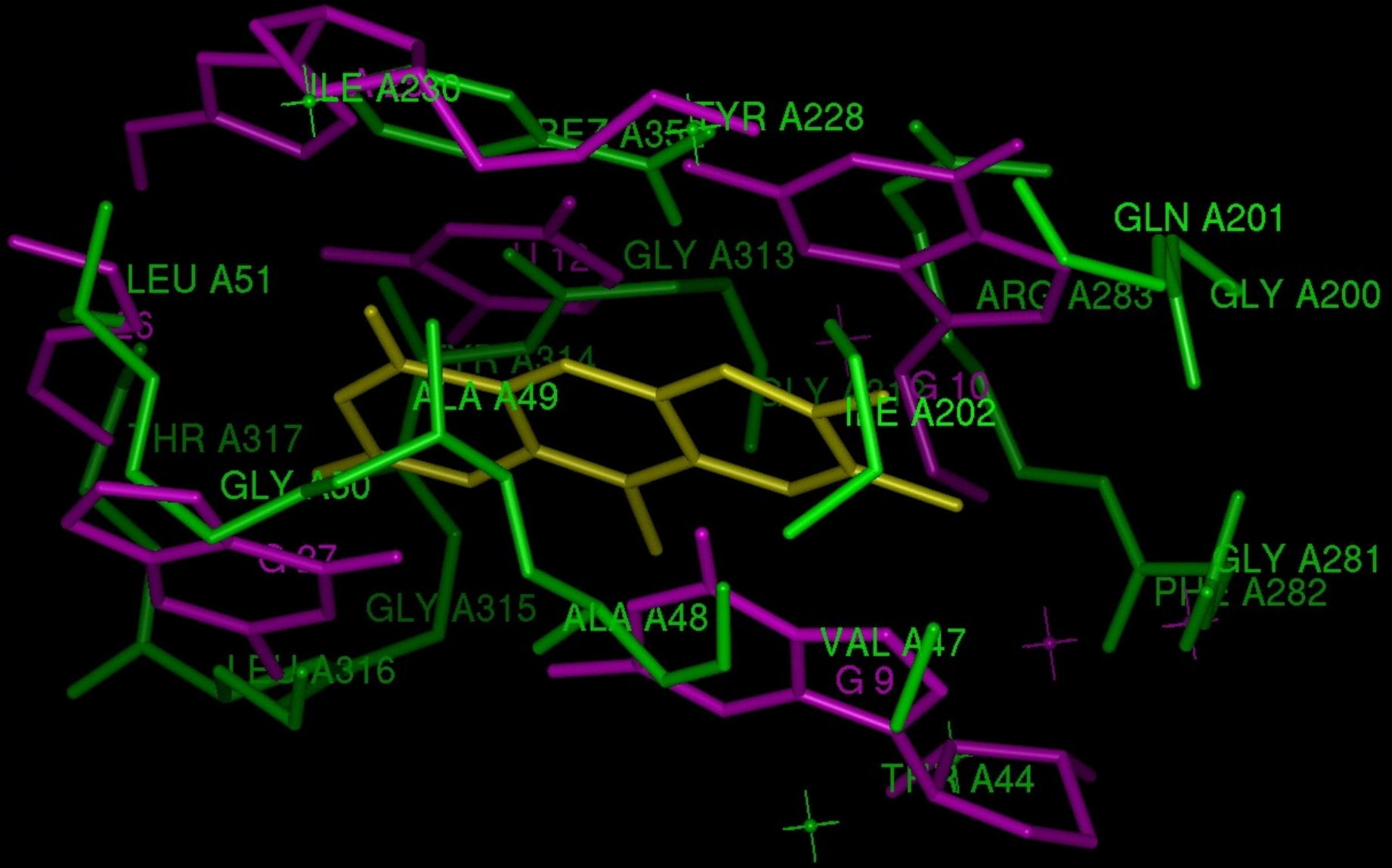
1FMN-1AA8

- 1FMN: FMN-RNA aptamer complex
- 1AA8: D-amino acid oxidase/FAD (pig)
- Obviously no sequence similarity
- 3D-similarity of the binding pockets: RMSD 1.39Å

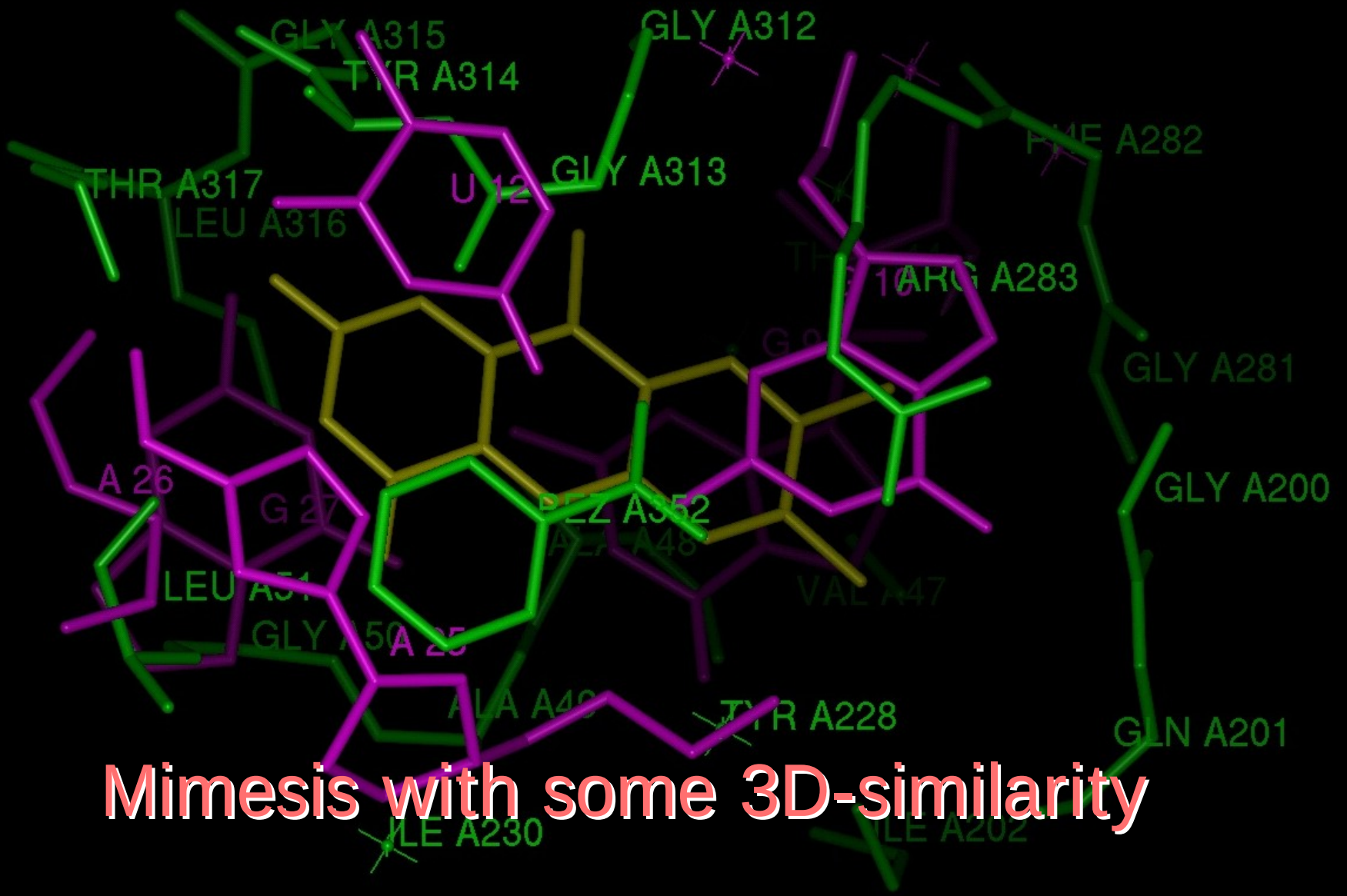
1FMN-1AA8: Nucloetid/protein, RMSD 1.39Å



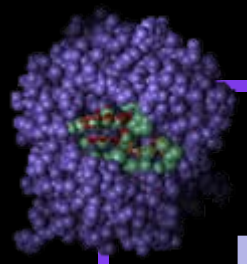
1FMN-1AA8: Nucloetid/protein, RMSD 1.39Å



1FMN-1AA8: Nucloetid/protein, RMSD 1.39Å

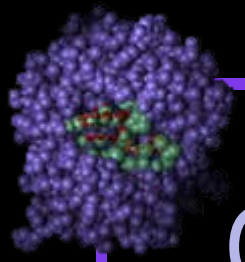


Mimesis with some 3D-similarity



Faces of mimicry

- Same residue – same position
- Same residue – skewed or different orientation
- Similar residue
- Same main chain course
- Superposition of different residues or structures



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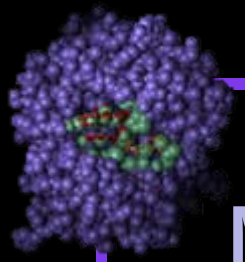
- Faces of Mimicry
- Molecular mimicry hypothesis

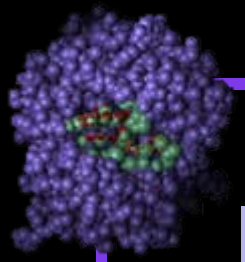


Molecular mimicry hypothesis

- Substantially different binding modes are occurring in reality.

↕ Reflection!

- Different methods of molecular design yield substantially different results.



Implications for drug design

Necessary design decision:

How different should the alternate binding partner be?

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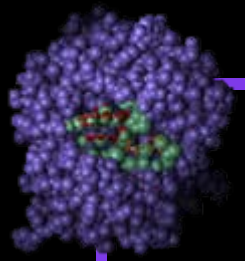

Goodbye!

Thanks for Your attention!

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