Independent undergraduate Research Project

Screening of possible antiviral peptides to bind SARS Covid 19 spike protein

Daria Bezbakh

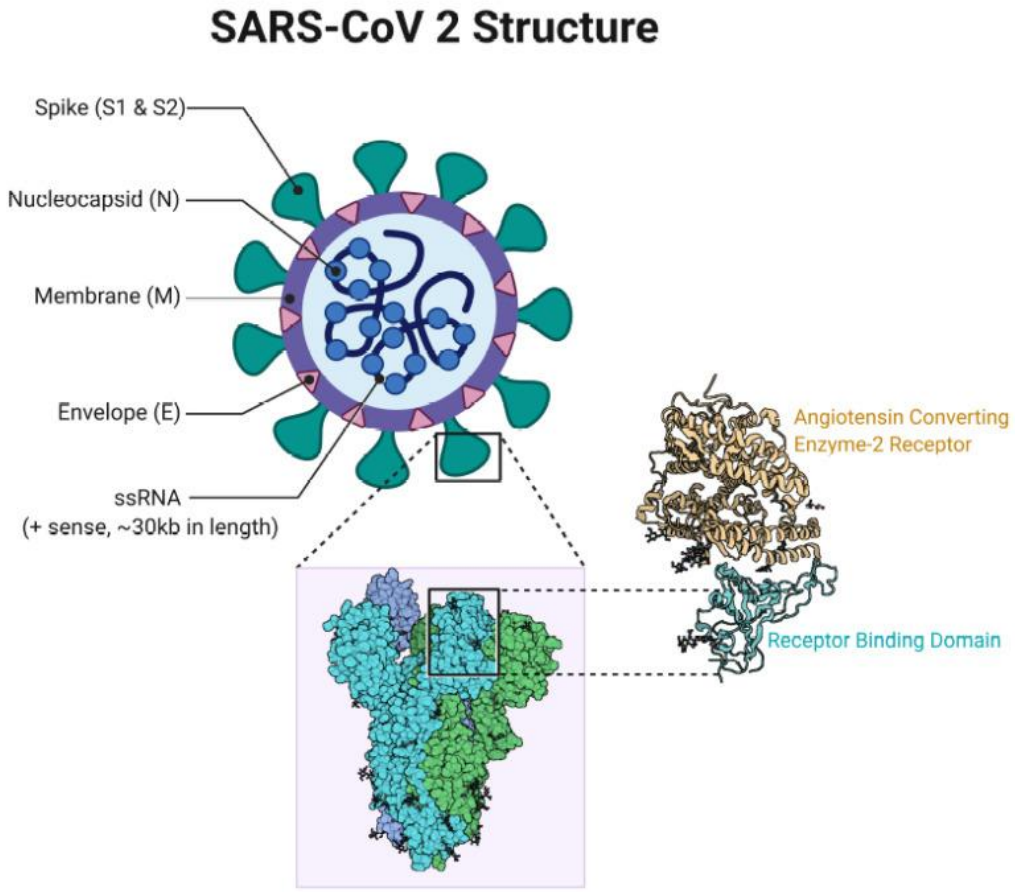
Computational Biochemistry

Group Prof. Sanchez-Garcia

Content

1. Intoduction
2. Sructure of SARS-CoV-2
3. Aim of the study
4. Methods
   - VMD
   - CABS Dock
5. Results

Introduction

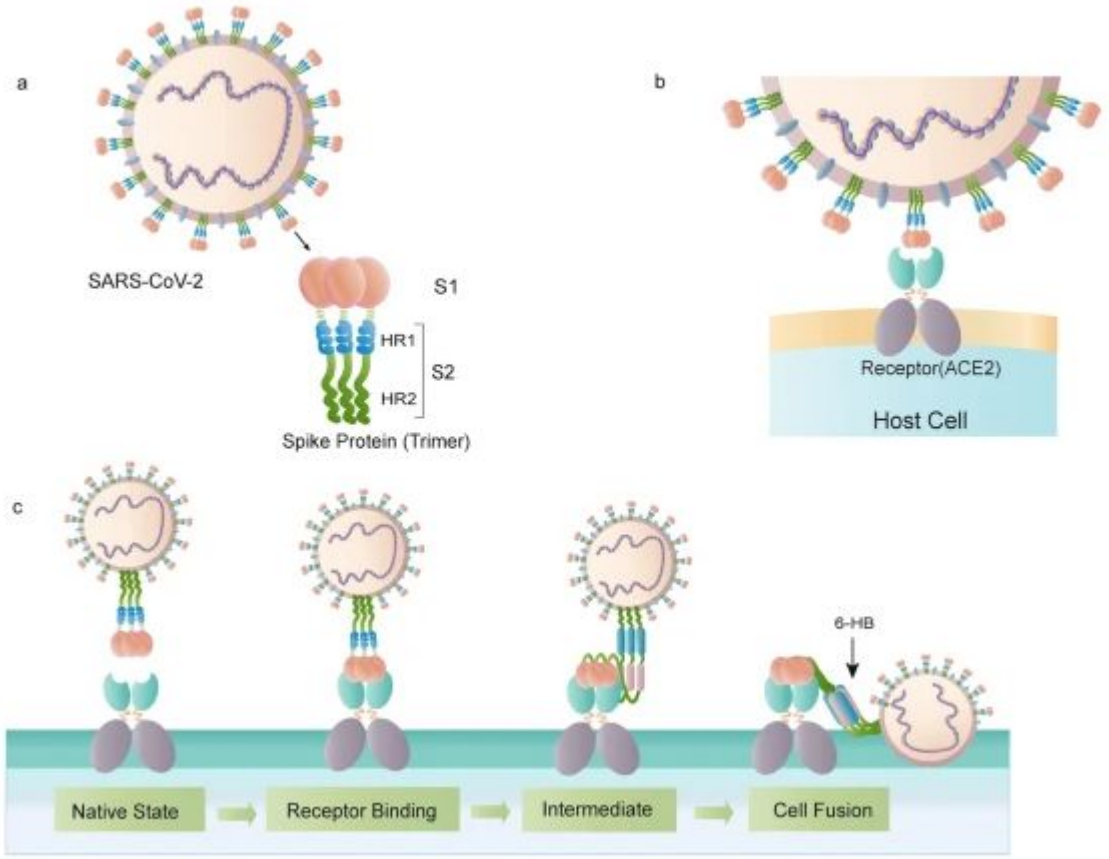


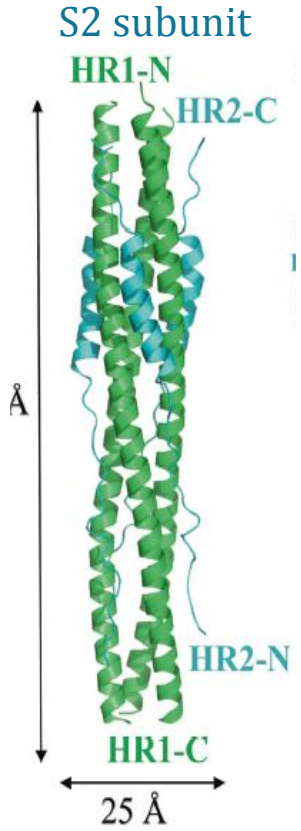
- Single-stranded RNA-enveloped virus
- It bends to the angiotensin converting enzyme 2 (ACE2)
- Basic reproduction number (R0) is around 3,8 [1]
- accumulates two single-letter mutations per month [2]

1 https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Steckbrief.html

2 https://www.nature.com/articles/d41586-020-02544-6

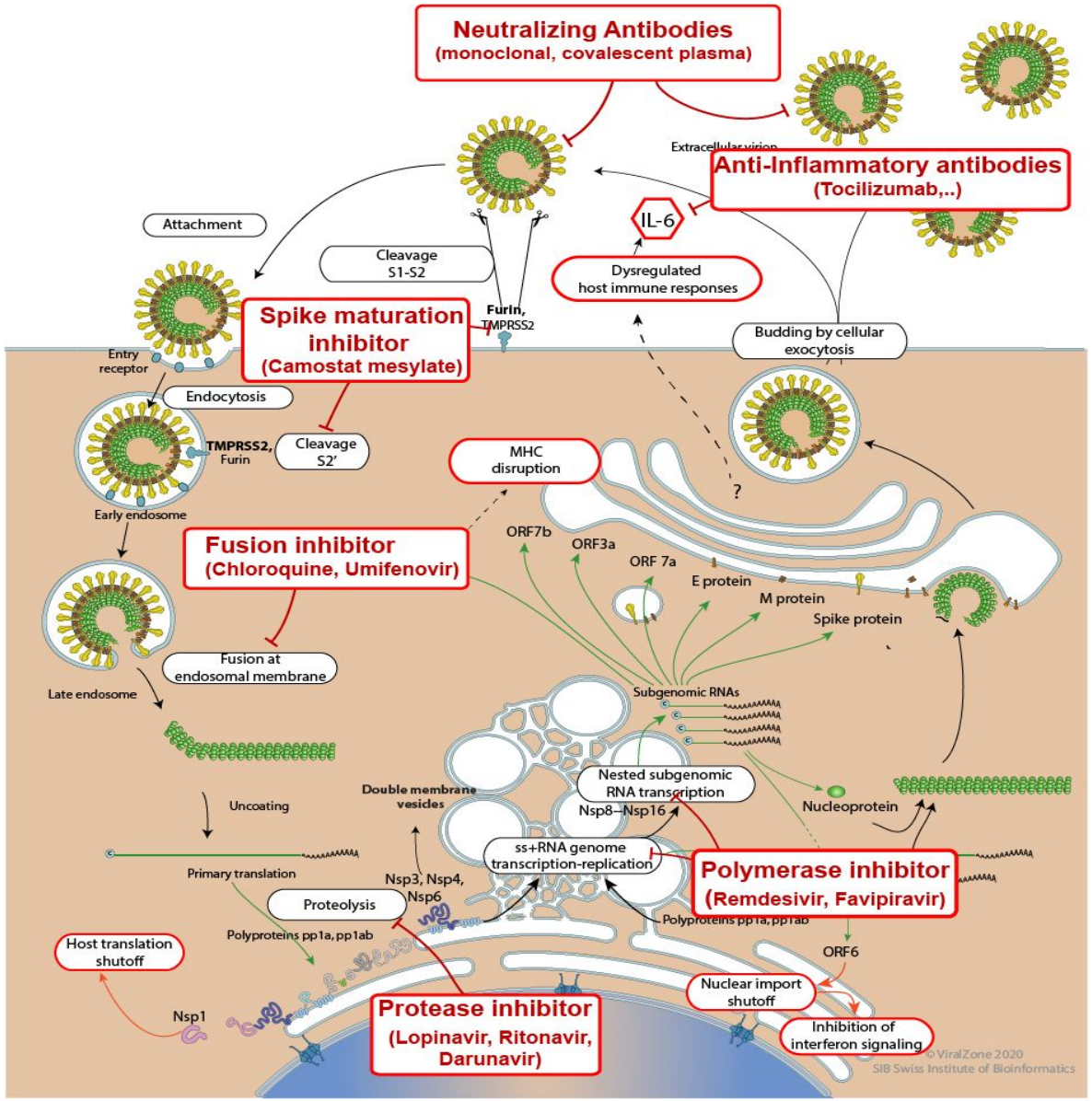
Sructure of SARS-CoV-2 spike protein





- spike protein mediates the membrane fusion process
- Spike protein has 2 subunits – S1 and S2
- S1 catalyzes attachment, S2 -subunit fusion
- S2 forms a six-helical bundle via the two-heptad repeat domain, HR1 and HR2 (“fusion core region”).

Antiviral drugs

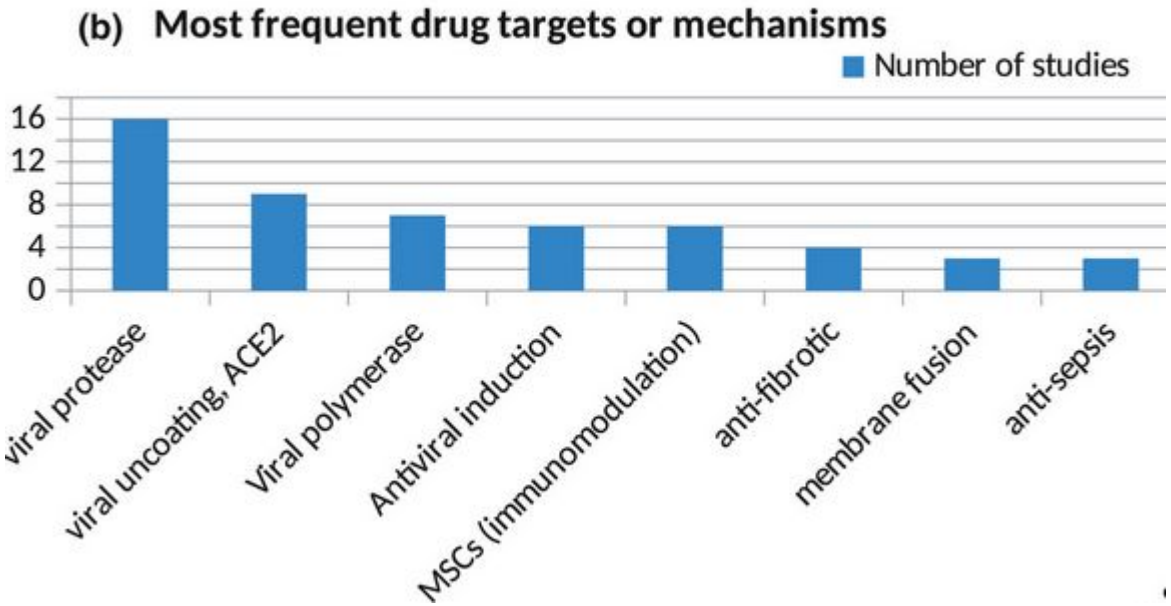


Classes:

- Spike maturation inhibitor
- Protease inhibitor
- Fusion inhibitor
- Polymerase inhibitor

Only Remdesivir was approved by FDA, but was later exluded from the guidline [4]

4. https://apps.who.int/iris/handle/10665/336729

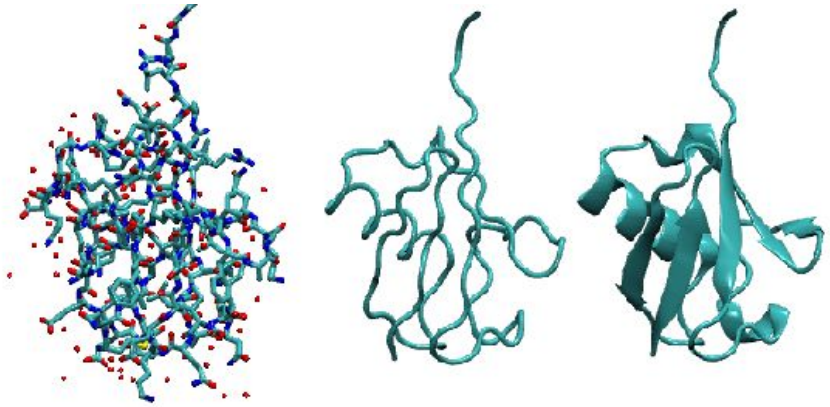

(b) Most frequent drug targets or mechanisms
Number of studies
16
12
8
4
0
viral protease
viral uncoating, ACE2
Viral polymerase
Antiviral induction
MSCs (immunomodulation)
anti-fibrotic
membrane fusion
anti-sepsis

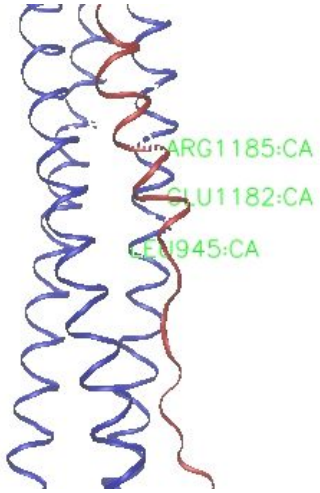
Aim of the study

- to screen a list of peptides which were designed to bind the HR1 domains
- A peptide with the largest number of contacts with the HR1 domains would inhibit the membrane fusion, and therefore infection

Methods

VMD - Visual Molecular Dynamics



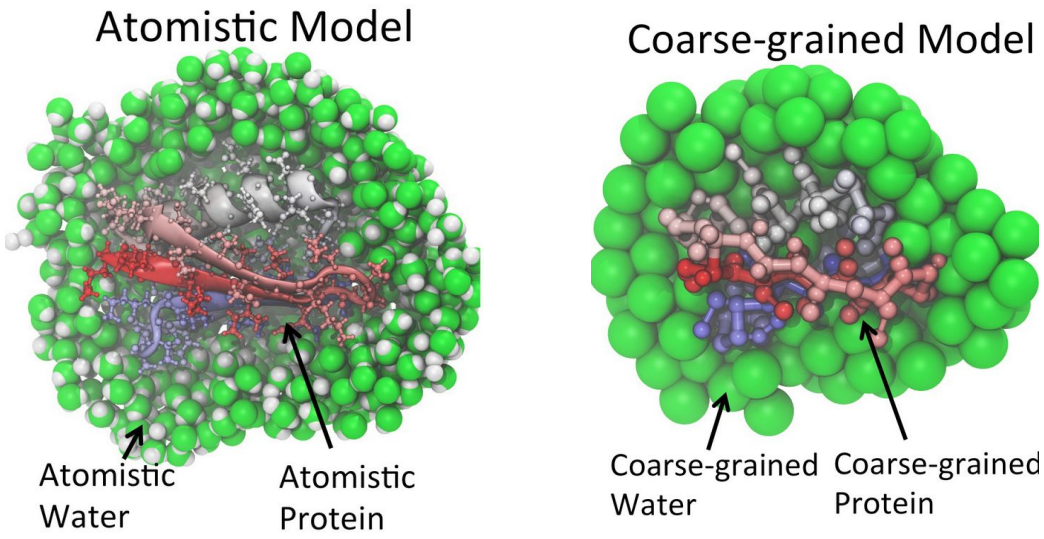


- for structure visualization
- displaying, animating, and analyzing large biomolecular systems using 3-D graphics

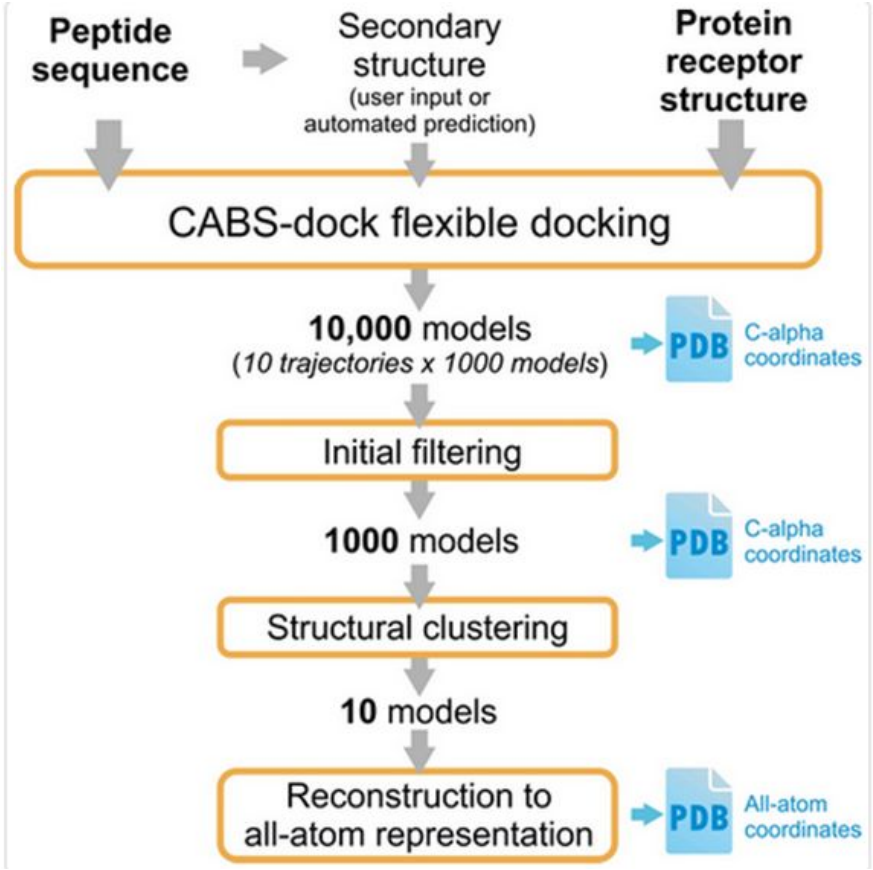
CABS Dock

- for protein-peptide docking
- coarse-grained model (it decreases a time of long simulations)
- advantages:

1. Can be used without knowing the binding site and peptide conformation
2. Peptide conformation is allowed to be fully flexible
3. It is possible to simulate significant conformational changes



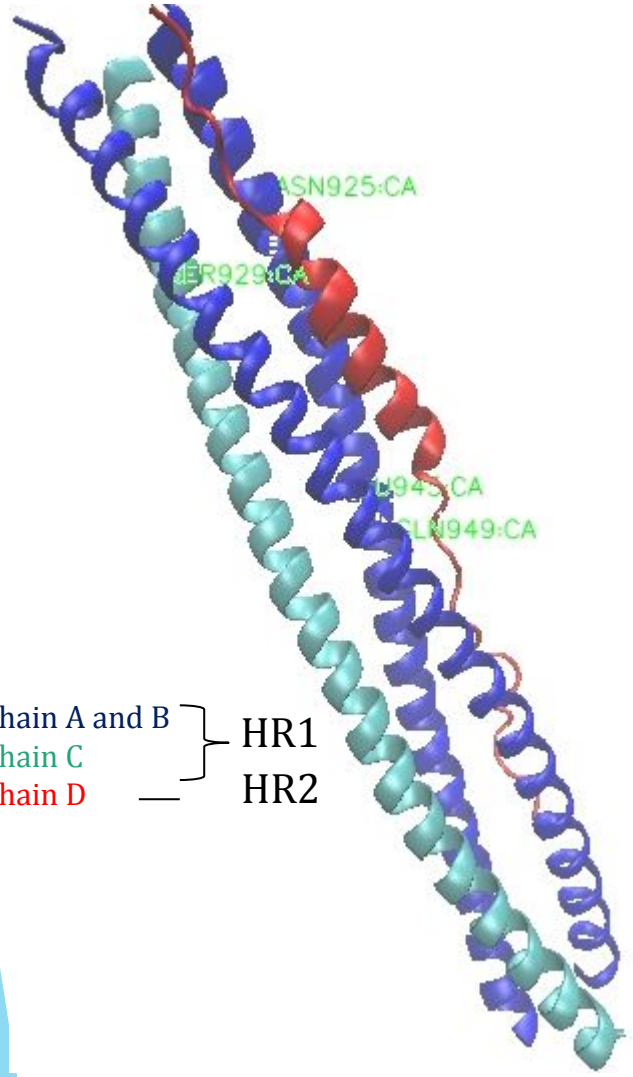
CABS Dock



Steps:

1. Generating random structures
2. Simulation of binding and docking
3. Selection of the final models

Results



- Original structure:
  - Fraction of contacts – 51 % (cutoff – 5Å)
  - number of residues in chain D, that are in contact – 20
  - Chain D of HR2 has 41 amino acids

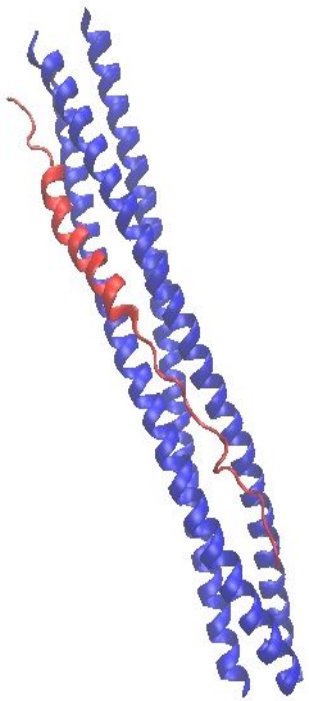
- The docking was run with a shorten version of the peptide HR2 (chain D): VVNIQKEIDRLNEVAKNLNESLID:CCCHHHHHHHHHHHHHHHHHHCCC
  - 24 amino acids, 18 of them form helices,
  - The docking was run 2 times, first time with a number of cycles 100, second time – 200, chain C was excluded.

I. Parameters (100 cycles): model 5 (fraction 62, contacts 15), model 6 (fraction 70, contacts 17).

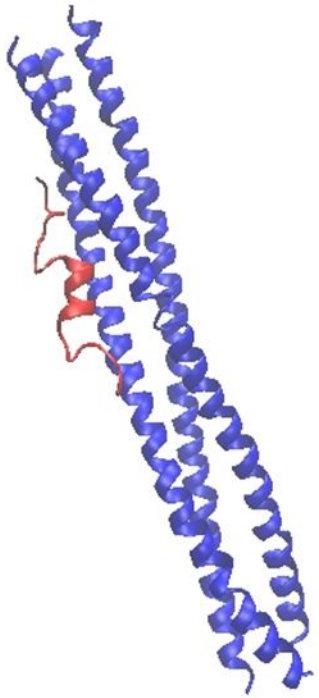
I. Parameters (200 cycles): model 4 (fraction 75, contacts 18), model 6 (fraction 66, contacts 16), model 9 (fraction 54, contacts 13).

I. Parameters (200 cycles+residues beside helix exluded): model 1 (fraction 62, contacts 15), model 4 (fraction 70, contacts 17)

Original



Model 4



Residues of chain A after docking in contact with chain D (within 5):

17 ASN 20 ILE 21 GLY 23 ILE 24 GLN 27 LEU 28 SER 30 THR 31 ALA 34 LEU 35 GLY 38 GLN 39 ASP

Residues of chain B after docking in contact with chain D (within 5):

90 GLN 93 SER 94 ALA 97 LYS 98 ILE 100 ASP 101 SER 104 SER 105 THR 108 ALA 111 LYS

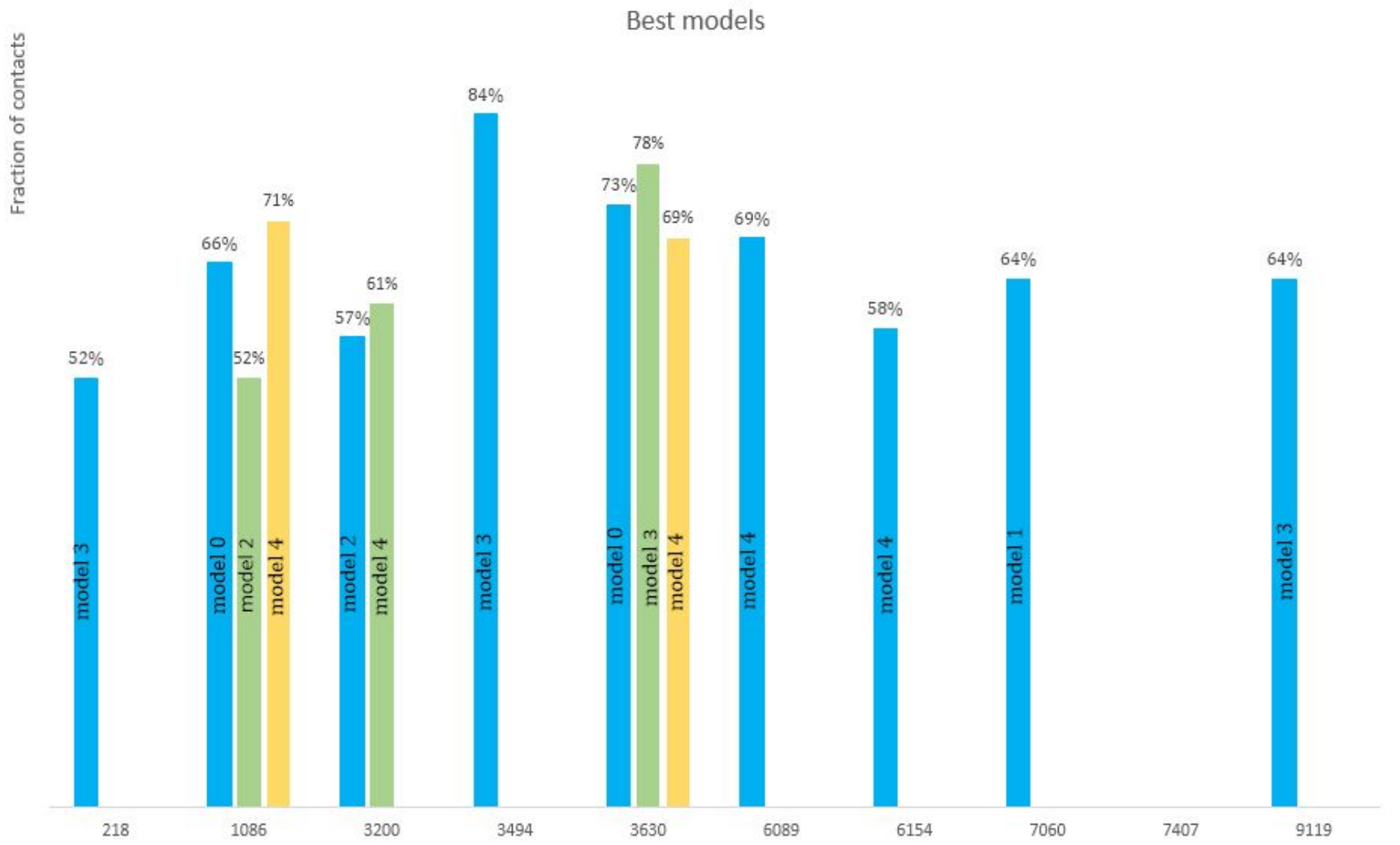
Blue amino acids mean the same contacts as in original structure.

200 cycles were also chosen for docking the derivatives.

- 10 derivatives were tested (additional parameter - all amino acids form helices)
- Best peptide structures need to have higher fraction of contacts than in original peptide (>51)

models	218	1086	3200	3494	3630	6089	6154	7060	7407	9119
model_full-0:	0 0.00 1	14 66.00 1	10 47.00 1	1 3.00 1	17 73.00 1	3 13.00 1	12 50.00 1	1 4.00 1	8 30.00 1	0 0.00 1
model_full-1:	5 20.00 1	0 0.00 1	2 9.00 1	0 0.00 1	1 4.00 1	0 0.00 1	6 25.00 1	16 64.00 1	0 0.00 1	3 12.00 1
model_full-2:	3 12.00 1	11 52.00 1	12 57.00 1	7 26.00 1	0 0.00 1	4 17.00 1	10 41.00 1	6 24.00 1	0 0.00 1	0 0.00 1
model_full-3:	13 52.00 1	0 0.00 1	0 0.00 1	22 84.00 1	18 78.00 1	11 47.00 1	0 0.00 1	1 4.00 1	0 0.00 1	16 64.00 1
model_full-4:	1 4.00 1	15 71.00 1	13 61.00 1	13 50.00 1	16 69.00 1	16 69.00 1	14 58.00 1	10 40.00 1	12 46.00 1	0 0.00 1
model_full-5:	13 52.00 1	0 0.00 1	0 0.00 1	5 19.00 1	0 0.00 1	14 60.00 1	0 0.00 1	0 0.00 1	17 65.00 1	4 16.00 1
model_full-6:	0 0.00 1	0 0.00 1	3 14.00 1	2 7.00 1	0 0.00 1	10 43.00 1	14 58.00 1	8 32.00 1	2 7.00 1	0 0.00 1
model_full-7:	18 72.00 1	10 47.00 1	5 23.00 1	15 57.00 1	1 4.00 1	0 0.00 1	12 50.00 1	18 72.00 1	15 57.00 1	11 44.00 1
model_full-8:	18 72.00 1	0 0.00 1	12 57.00 1	5 19.00 1	7 30.00 1	6 26.00 1	3 12.00 1	0 0.00 1	16 61.00 1	13 52.00 1
model_full-9:	0 0.00 1	8 38.00 1	9 42.00 1	0 0.00 1	8 34.00 1	1 4.00 1	3 12.00 1	6 24.00 1	13 50.00 1	0 0.00 1

First number-number of contacts
Second number-fraction of contacts


Best models
Fraction of contacts
52%
66%
52%
71%
57%
61%
84%
73%
78%
69%
69%
58%
64%
64%
model 3
model 0
model 2
model 4
model 2
model 4
model 3
model 0
model 3
model 4
model 4
model 1
model 3
218
1086
3200
3494
3630
6089
6154
7060
7407
9119

- Ranking according to the predicted number of models, fractions and position of a modal in a rank:
- 1. DERIVATIVE_3630
- 2. DERIVATIVE_1086
- 3. DERIVATIVE_3200
- 4. DERIVATIVE_3494
- 5. DERIVATIVE_6089
- 6. DERIVATIVE_7060
- 7. DERIVATIVE_9119
- 8. DERIVATIVE_6154
- 9. DERIVATIVE_218
- 10. DERIVATIVE_7407

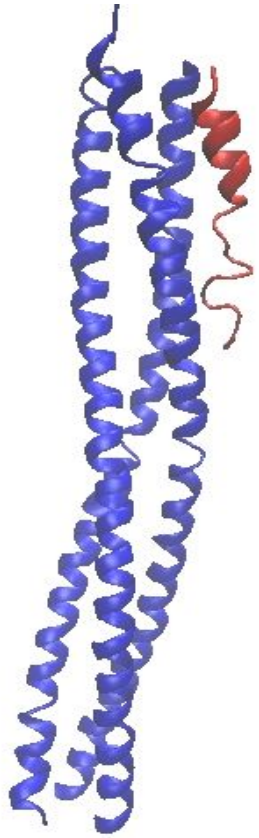
PPI-Affinity

Peptide	Affinity (kcal/mol)
218	Out of AD
1086	-10.1
3200	-9.2
3494	Out of AD
3630	-8.2
6089	-8
6154	-9
7060	Out of AD
7407	Out of AD
9119	Out of AD
original	-8.4

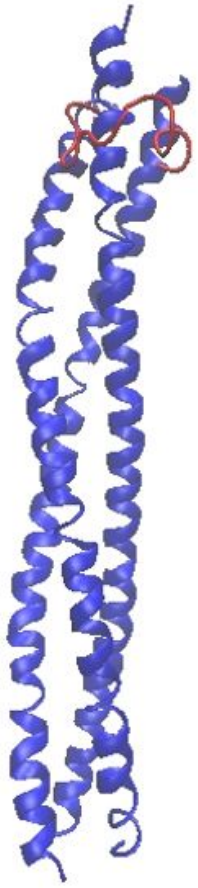
The most promising candidates:

1. DERIVATIVE_1086
2. DERIVATIVE_3200
3. DERIVATIVE_3630

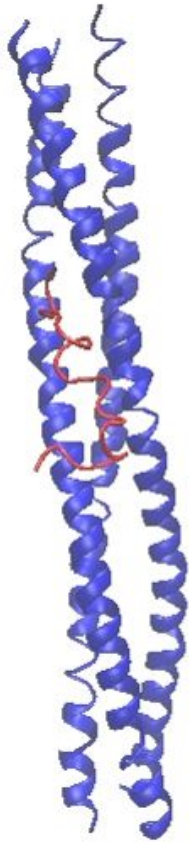
- Vmd images of top 3 candidates



DERIVATIVE_3630,
Model_full 0 (73%, 17 contacts)



DERIVATIVE_1086,
Model_full 0 (66%, 14 contacts)



DERIVATIVE_3200
Model_full 2 (57%, 12 contacts)

Tnanks you for attention!