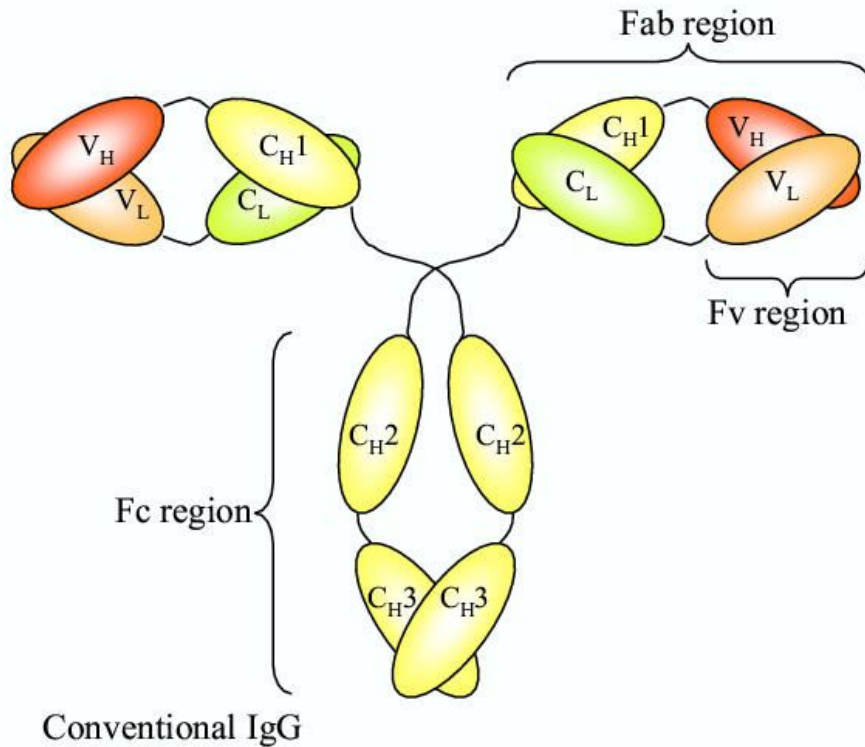


Rosetta Antibody Modeling

Nina Bozhanova

April 30, 2019

Antibody structure

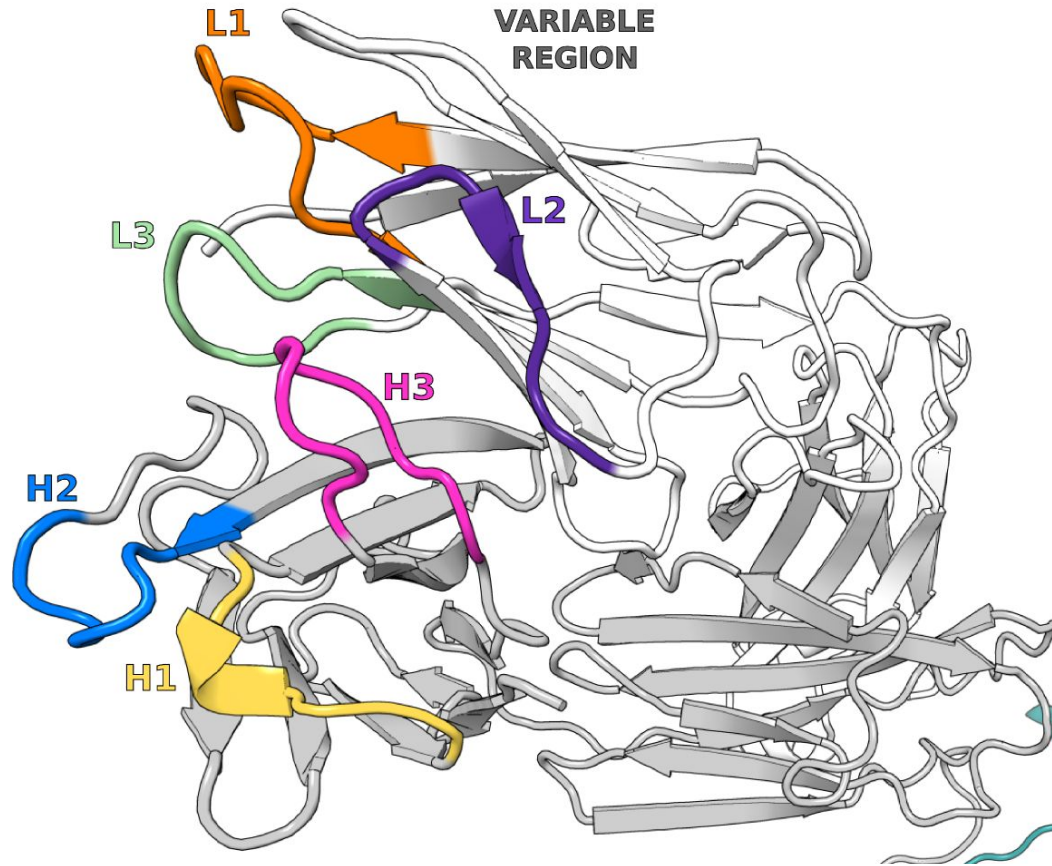


Fc - the crystallizable fragment

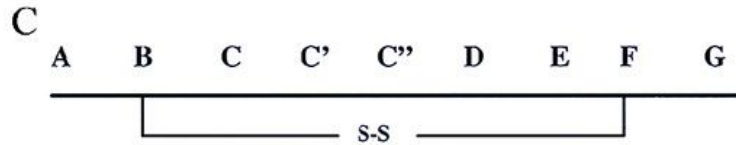
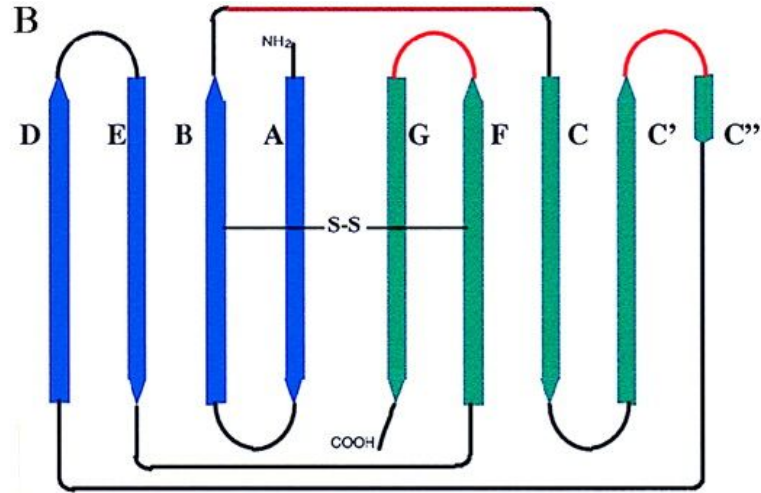
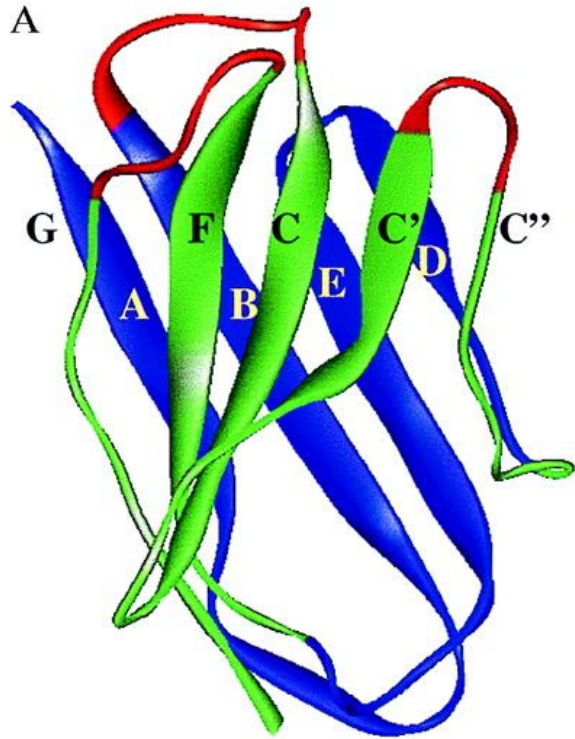
Fab - the antigen-binding fragment

Fv - the variable fragment (domain)

F_v structure

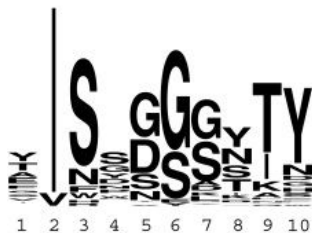
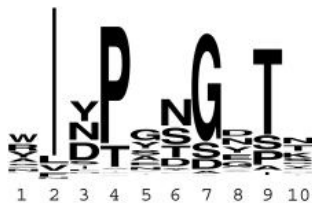


Ig fold

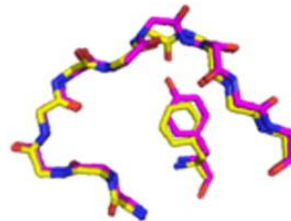


Canonical loop conformations

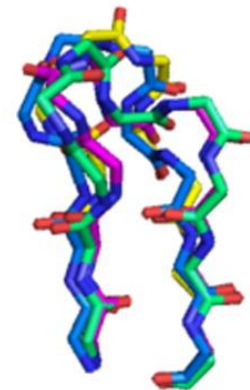
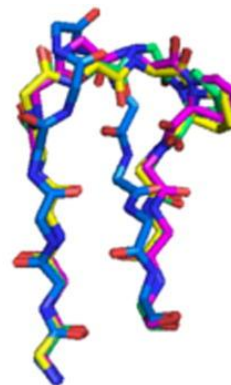
Loop sequence



Structure

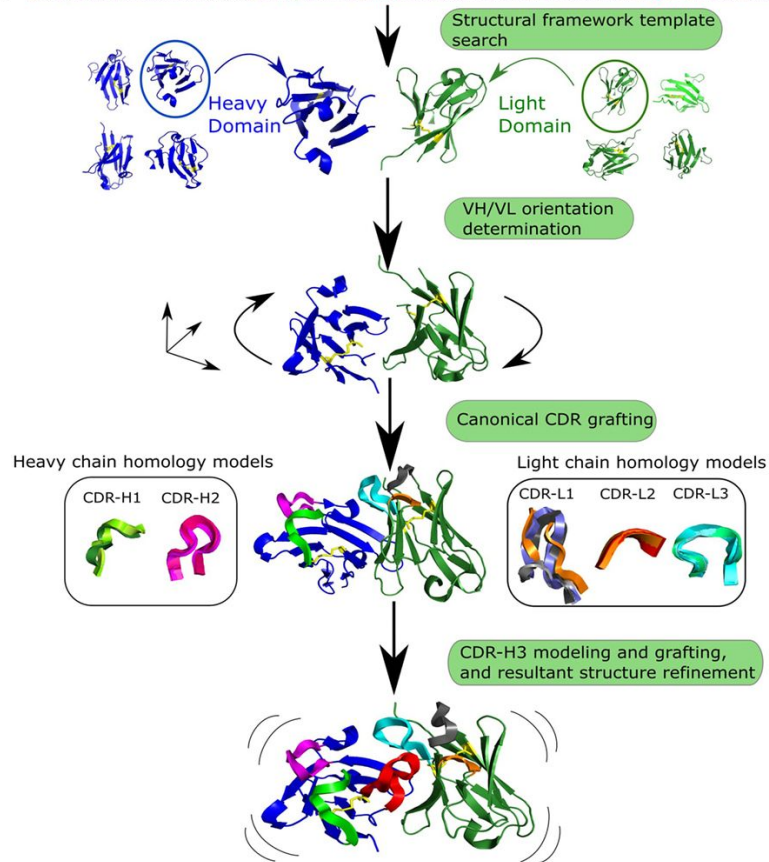


Left: CDR L1 length 11
Middle: CDR L3 length 9
Right: CDR H2 length 10



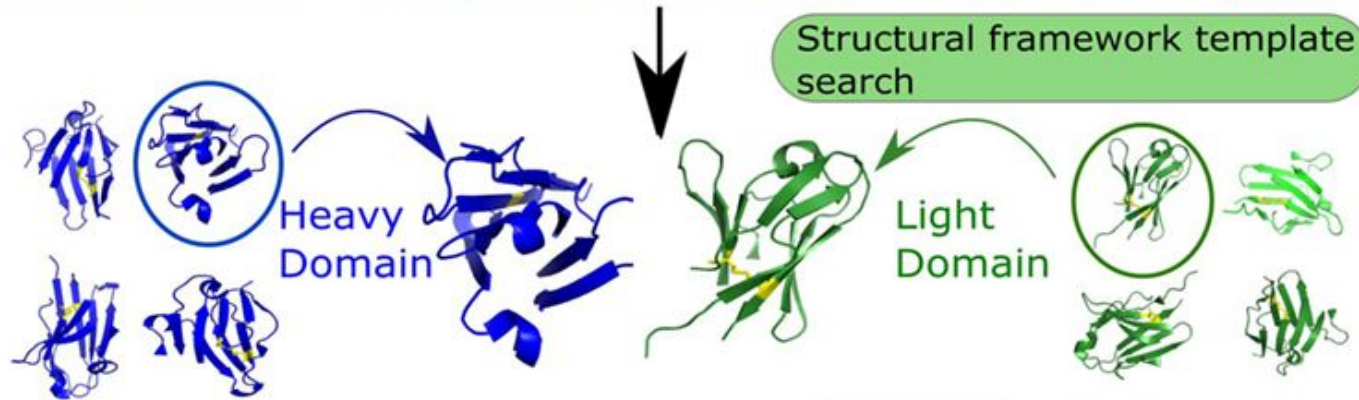
Generalized workflow of antibody modeling

VH QVQLQQSGPELVRPGASVKVCSKASGYFTFTYYWLSRIGRISFRGIGYFDPIYGGTNTNQNFKDKATLTVDKSSSAAYMHLDSLTSEDSAVYFCARSGLDWGQGTLLVYSA
VL DIQLTQSPSSLASLGERVSTITCRASQDIGSNLNLWLQKPKDGTIKRLIYATSSLDGVPKRFSGSRSGSDYSLTISSELEDFVDIYCLQYASSPPTFGGGTKLEIK



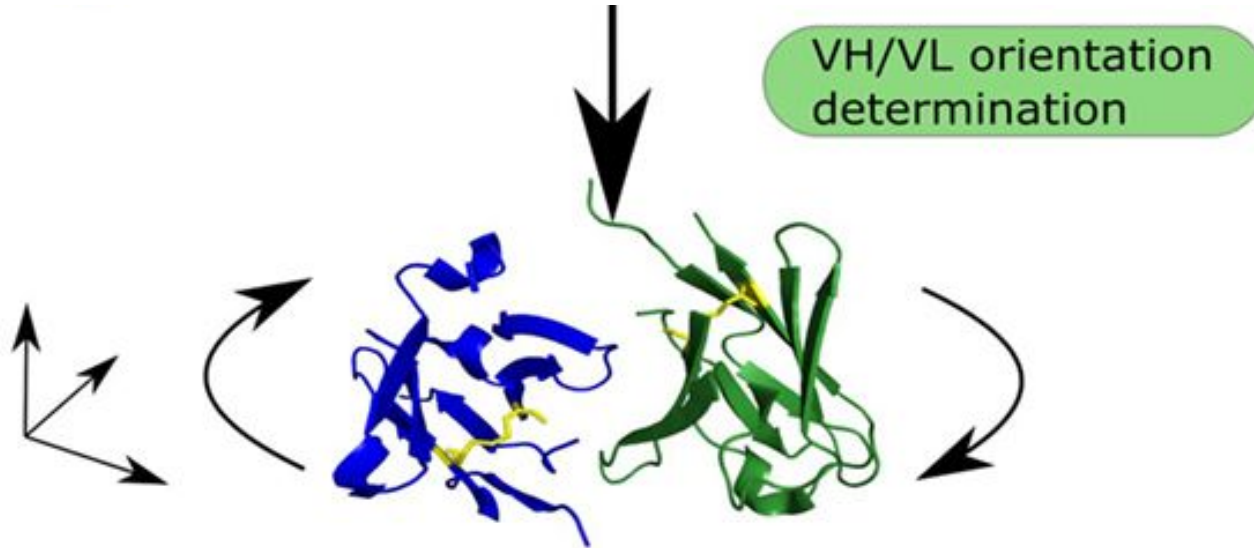
Generalized workflow of antibody modeling

VH QVQLQQSGPELVRPGASVKVSKASGYAFTTYNIYWLSRGIGRSFRGIGYDPYIGGTNTNQNFKDKATLTVDKSSSAAYMHLDLSLTSEDSAVYFCARSGLADWGQGLTVTSA
VL DIQLTQSPSSLSASLGERVSITCRASQDIGSNLNWLQKQPDGTIKRLIYATSSLDSGVPKRFGSGRSRSGSDYSLTISSLESEDFVDYYCLQYASSPPTFGGGTKLEIK



Generalized workflow of antibody modeling

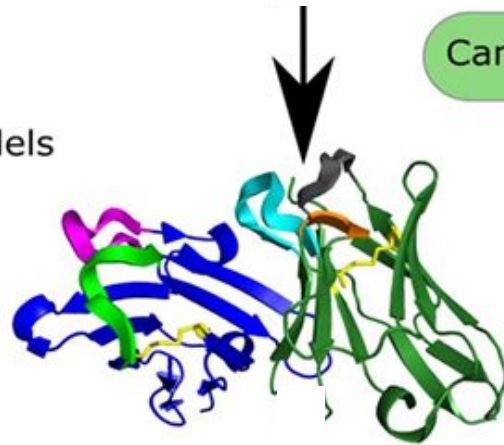
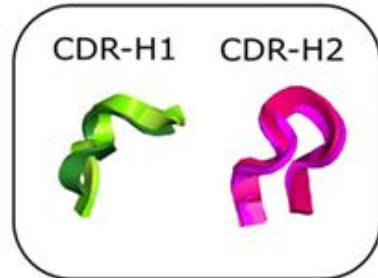
VH QVQLQQSGPELVRPGASVKVSCKASGYAFTTYNIYWLSRGIGRSFRGIGYFDPIYIGGTNTNQFKDKATLTVDKSSSAAYMHLDSLTSSEDSAVYFCARSGLADWGQGLTVTVA
VL DIQLTQSPSSLSASLGERVSITCRASQDIGSNLNLWLQKQKPDGTIKRLIYATSSLDSGVPKRFSGRSRSGSDYSLTSSLESEDFVDYYCLQYASSPPTFGGGTKLEIK



Generalized workflow of antibody modeling

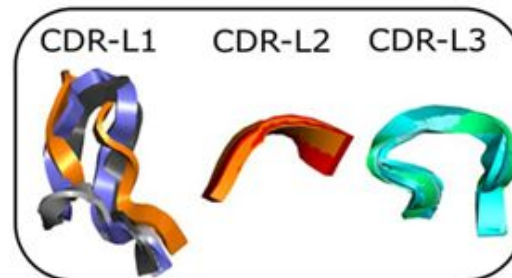
VH QVQLQQSGPELVRPGASVKVCKASGYAFTTYNIYWLSRGIGRSFRGIGYFDPIYIGGTNTNQNFKDKATLTVDKSSSAAYMHLDLSLTSEDSAVYFCARSGLADWGQGLTVTSA
VL DIQLTQSPSSLSASLGERVSITCRASQDIGSNLNWLQKPGDTIKRLIYATSSLDGSGVPKRFSGSRSGSDYSLTISSLESEDFVDYYCLQYASSPPTFGGGTKLEIK

Heavy chain homology models

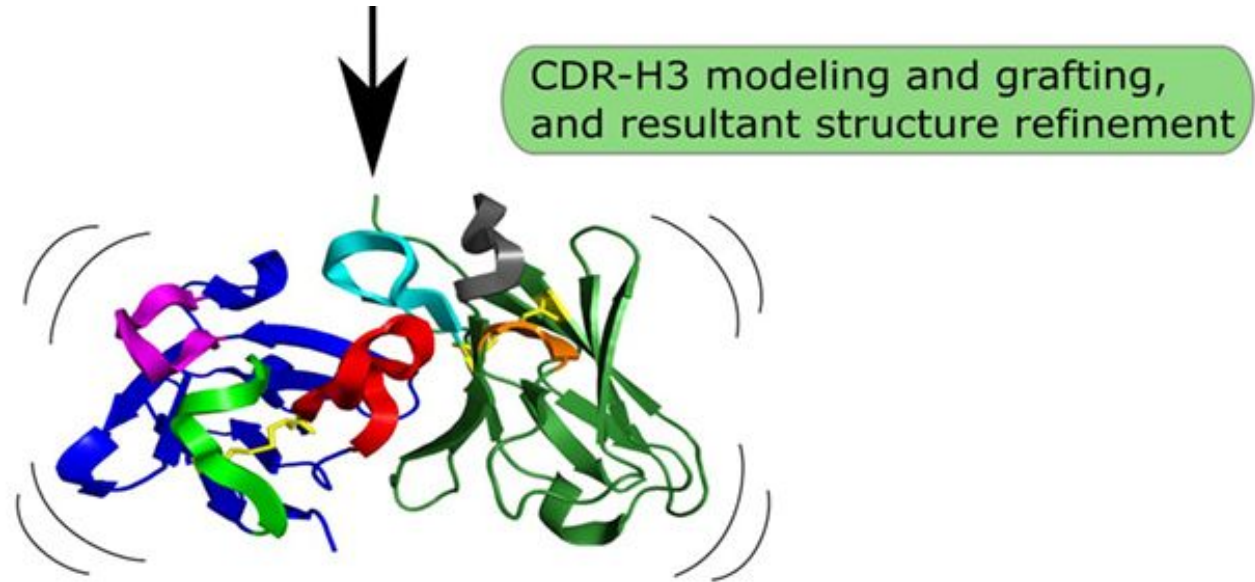


Canonical CDR grafting

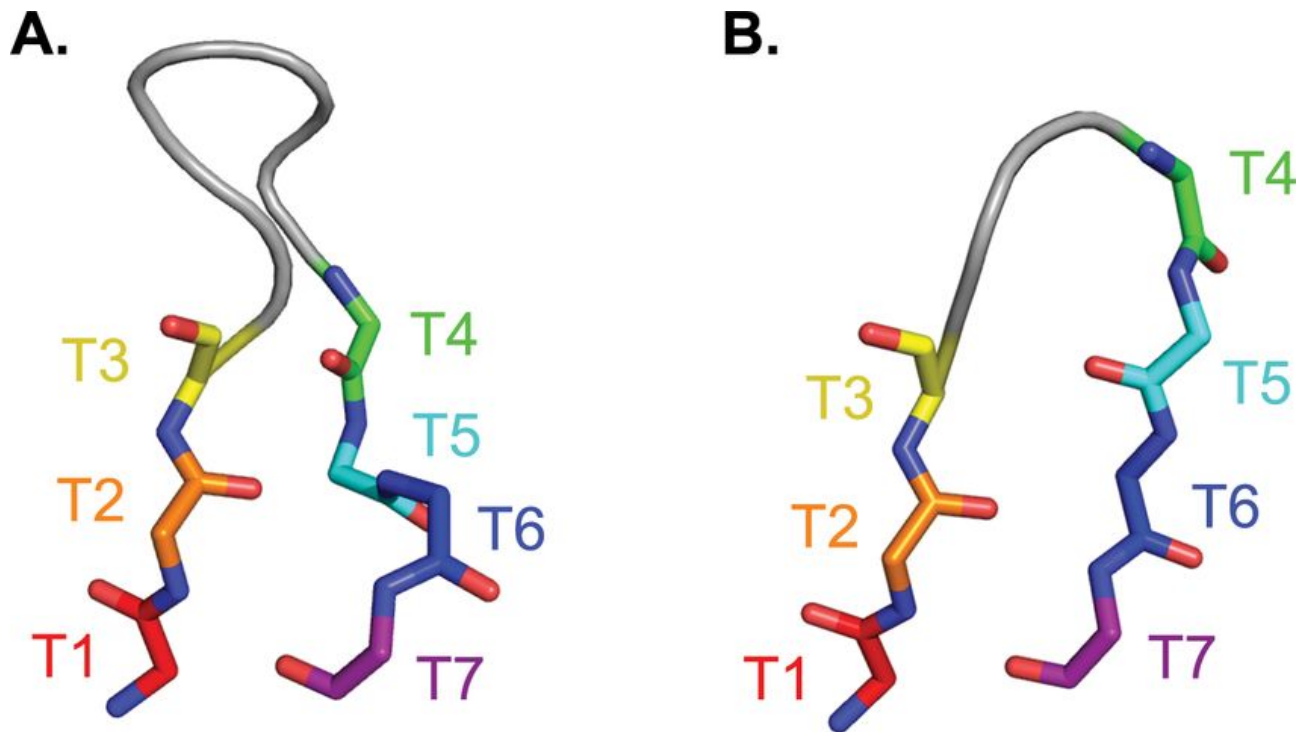
Light chain homology models



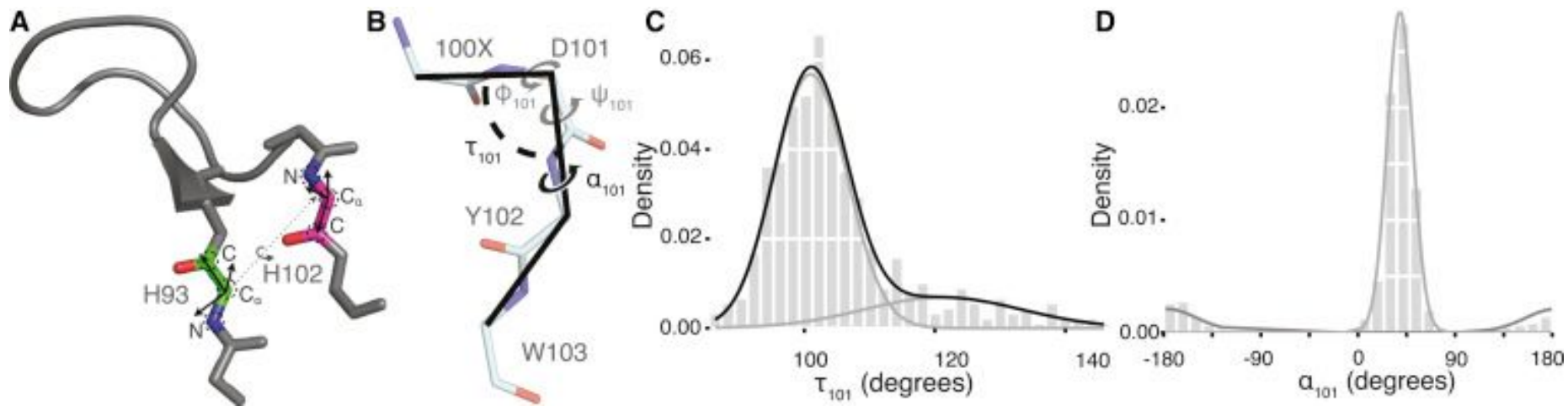
Generalized workflow of antibody modeling



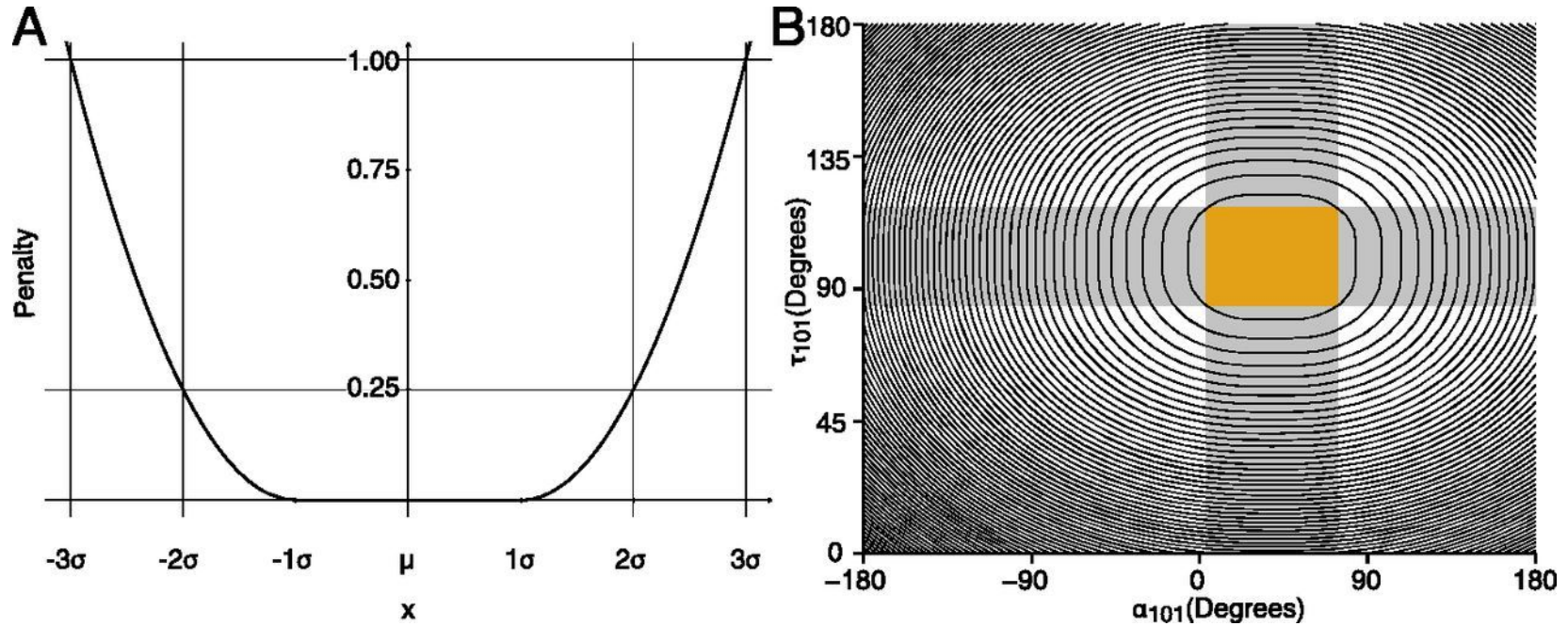
HCDR3 torso



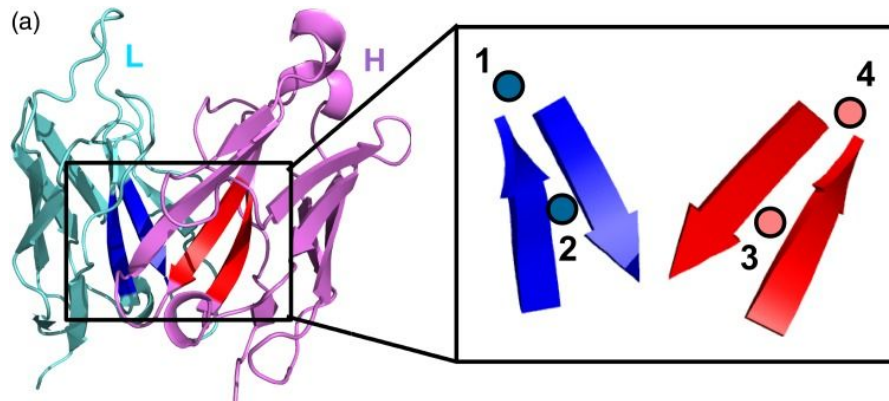
Kink constraints



Kink constraints



VL–VH orientation metrics

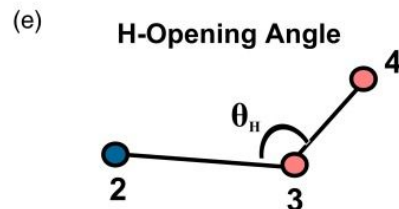
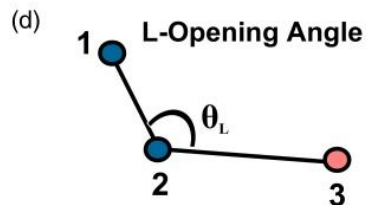
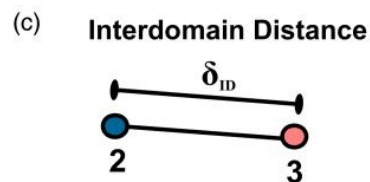
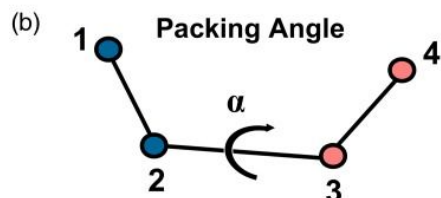


Point 1: located nearer the CDRs than Point 2, along the first principal component line of the coordinate set used to calculate point 2

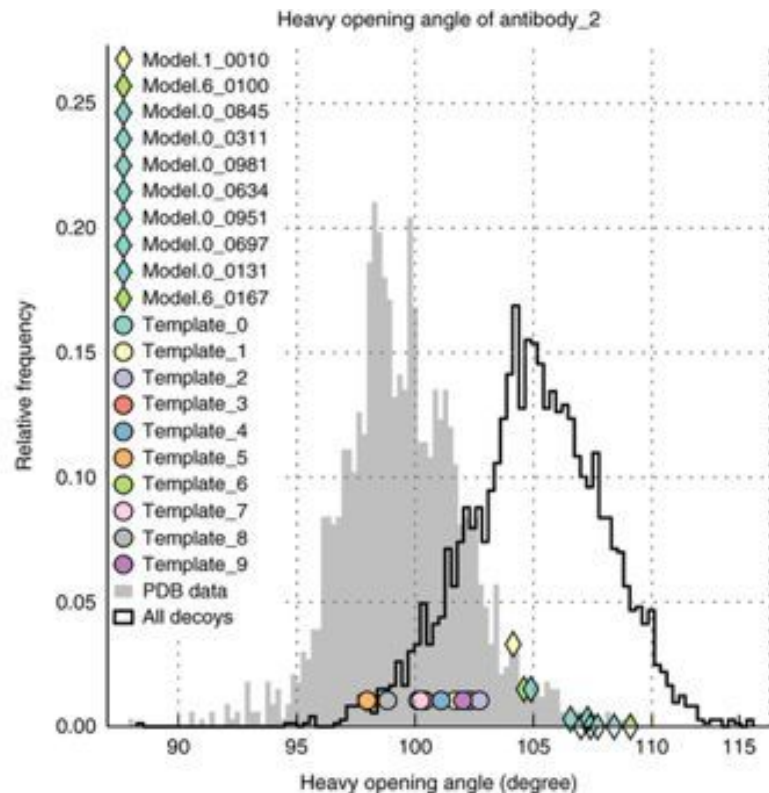
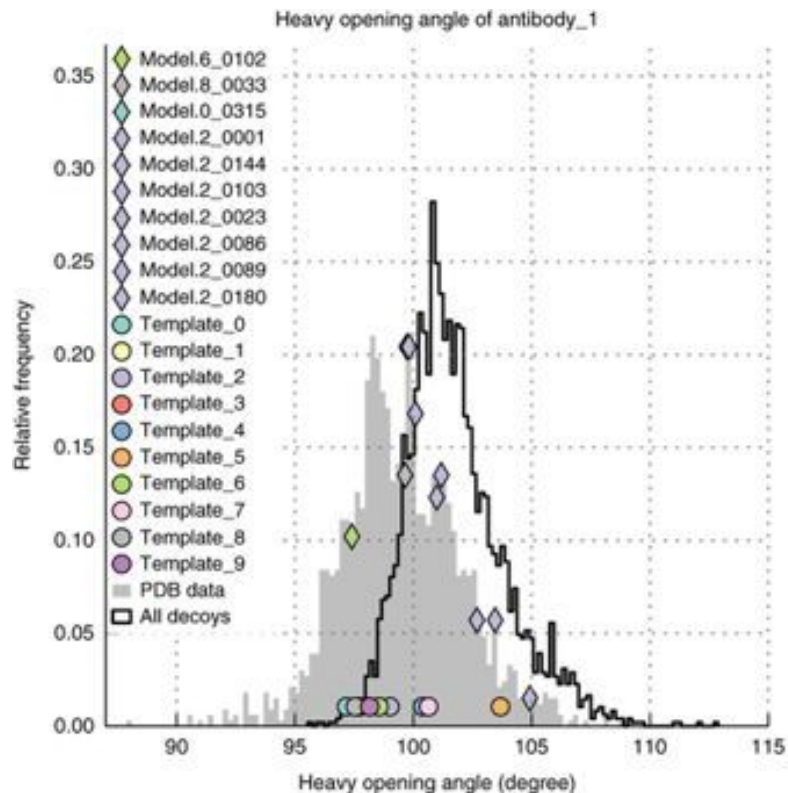
Point 2: centroid of the C α coordinates of residues L35–L38 and L85–L88 (Chothia numbering)

Point 3: the centroid of the C α coordinates of residues H36–H39 and H89–H92 (Chothia numbering)

Point 4: located nearer the CDRs than Point 3, along the first principal component line of the coordinate set used to calculate point 3.



Analysis



ROSIE web server - entirely automated modeling

1. Enter Job name and Ab sequences

2. Wait

3. Analyze output files

Welcome to ROSIE
Rosetta Online Server that Includes Everyone

Welcome Queue About Documentation Support Logout [Workshop2016]

Submit a new Antibody job

Job short description (visible in queue):

Sequence of Fy Light Chain (VL)
or upload the file: No file chosen

Sequence of Heavy Chain (VH)
or upload the file: No file chosen

Model H3 loop

Job Description (for your own records):

Submit

Keep my job-data public (Note that Public Jobs have higher priority and longer life time!)

ROSIE is web front-end for Rosetta software suite. Developed by Sergey Lyskov, GrayLab at JHU. Copyright © 2013 Rosetta Commons Member Institutions.



Welcome to ROSIE
Rosetta Online Server that Includes Everyone

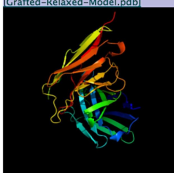
Welcome Queue About Documentation Support Logout [Workshop2016]

Antibody Job Rosetta-Workshop-2016_3O2W_CDR3 「№21247」 Detail

| Inputs | Status |
|--|--|
| [Light Chain] ELVNTQPTPLSLPUSLGDQASISCRSSQELVHNSONTILHW YLQKPGQSPKFLYKVSIRFRSGVDPDRFSQSGSGTDFILKI SRVFAEDLGVVFCQSQTFFPFPGGQZLEIKRTVAAPSV FIFFPSGQGLISGQASVCLLRFYPRKRNQYVQRRMQ SONSQSEVTEQDSKDSYSLGSELTLSKADYEKHKVYACE YTBQGLSPVTKSFNRGE | Job ID 21247 Job Name Rosetta-Workshop-2016_3O2W_CDR3 Visibility PUBLIC (you can share this job) Protocol antibody CPU hours used 1218.2926408 user Workshop2016 Status Finished |
| [Heavy Chain] QVQLVQSGPELKKPQGETVKISCKASGTFNFIQGMHVKQA PQELLRNQHWIIFPTQESTADDFKRFAPFLERSTTAY LQIHLKNEEDTATFCARGTIVRAFDIMGQSTVTVSSA RFGDPRVFFLAPSSGTALGCLVDFPPEPQVVERNSGAL TRQVTEFPALQSGQLSLGSEVTVPSRELQGTTCINW HKPNTKVDKRVSE | Description Model H3 loop True Multiple-Template Crafting False Submitted time 2016-03-08 11:22 Start time 2016-03-08 12:25 End time 2016-03-09 18:05 Daemon TACC.Stampede-4 |

Results:

[Grafted-Relaxed-Model.pdb]



FASTA sequence of Fy Light Chain (VL) with CDR L1, CDR L2, CDR L3 regions:
ELVNTQPTPLSLPUSLGDQASISCRSSQELVHNSONTILHWLQKPGQSPKFLYKVSIRFRS
GVDPDRFSQSGSGTDFILKISRIVEADLVYFCQSQTFFPFPGGQZLEIKRTVAAPSV

FASTA sequence of Heavy Chain (VH) with CDR H1, CDR H2, CDR H3 regions:
QVQLVQSGPELKKPQGETVKISCKASGTFNFIQGMHVKQAPQELLRNQHWIIFPTQESTADDFKRFAPFLERSTTAYLQIHLKNEEDTATFCARGTIVRAFDIMGQSTVTVSSA

<https://rosie.graylab.jhu.edu/antibody>

Literature:

1. Weitzner BD, Jeliaskov JR, Lyskov S, Marze N, Kuroda D, Frick R, Adolf-Bryfogle J, Biswas N, Dunbrack RL Jr, Gray JJ. Modeling and docking of antibody structures with Rosetta. **Nat Protoc.** 2017 Feb;12(2):401-416. Doi: 10.1038/nprot.2016.180. Epub 2017 Jan 26. PubMed PMID: 28125104; PubMed Central PMCID: PMC5739521
2. Weitzner BD, Gray JJ. Accurate Structure Prediction of CDR H3 Loops Enabled by a Novel Structure-Based C-Terminal Constraint. **J Immunol.** 2017 Jan 1;198(1):505-515. Epub 2016 Nov 21. PubMed PMID: 27872211; PubMed Central PMCID: PMC5173470.
3. Finn JA, Koehler Leman J, Willis JR, Cisneros A 3rd, Crowe JE Jr, Meiler J. Improving Loop Modeling of the Antibody Complementarity-Determining Region 3 Using Knowledge-Based Restraints. **PLoS One.** 2016 May 16;11(5):e0154811. Doi: 10.1371/journal.pone.0154811. eCollection 2016. PubMed PMID: 27182833; PubMed Central PMCID: PMC4868311.
4. North B, Lehmann A, Dunbrack RL Jr. A new clustering of antibody CDR loop conformations. **J Mol Biol.** 2011 Feb 18;406(2):228-56. Doi: 10.1016/j.jmb.2010.10.030. Epub 2010 Oct 28. PubMed PMID: 21035459; PubMed Central PMCID: PMC3065967.
5. Lyskov S, Chou FC, Conchúir SÓ, Der BS, Drew K, Kuroda D, Xu J, Weitzner BD, Renfrew PD, Sripakdeevong P, Borgo B, Havranek JJ, Kuhlman B, Kortemme T, Bonneau R, Gray JJ, Das R. Serverification of molecular modeling applications: the Rosetta Online Server that Includes Everyone (ROSIE). **PLoS One.** 2013 May 22;8(5):e63906. doi: 10.1371/journal.pone.0063906. Print 2013. PubMed PMID: 23717507; PubMed Central PMCID: PMC3661552.