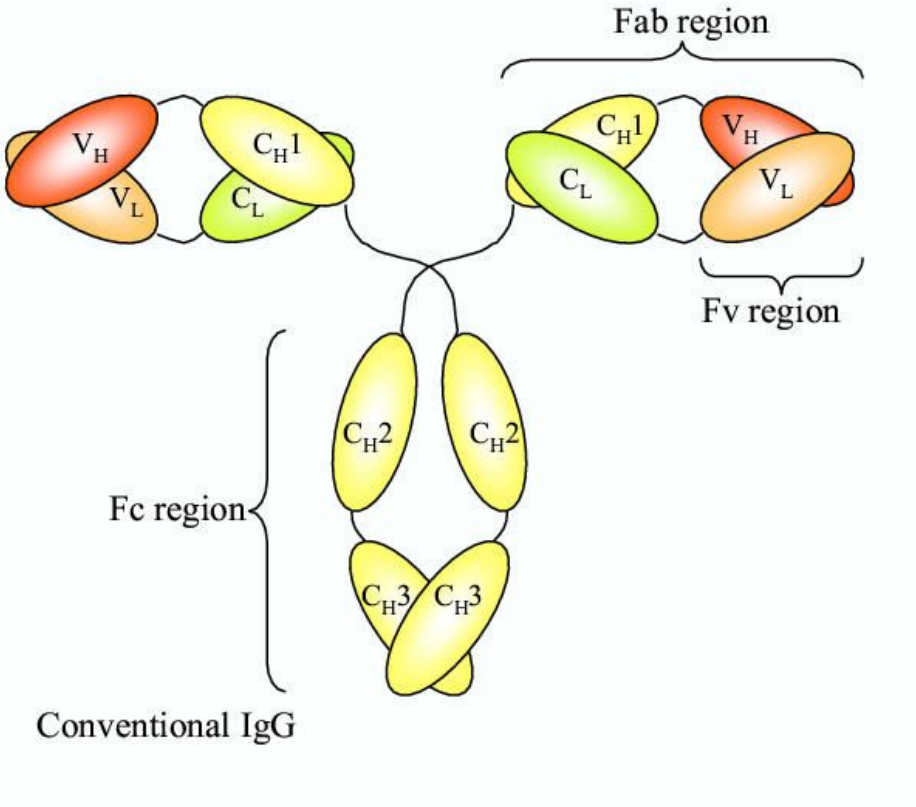
Rosetta Antibody Modeling

Nina Bozhanova
April 30, 2019

Antibody structure

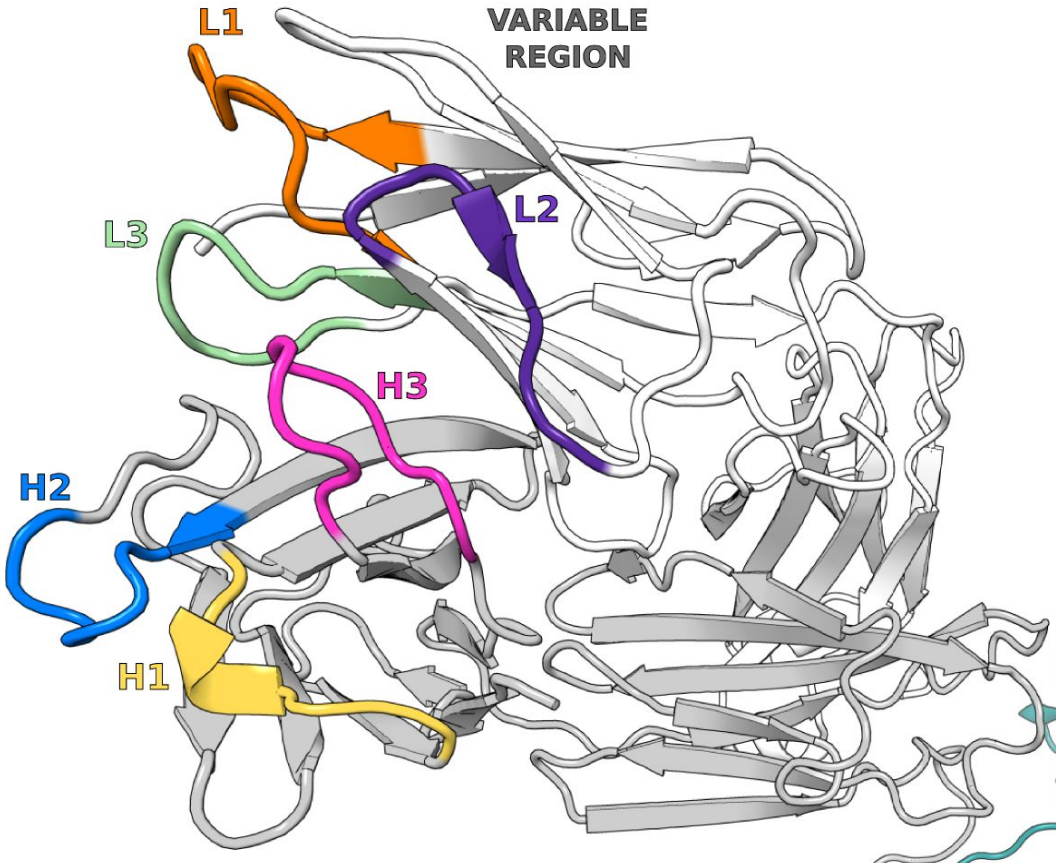


Fc - the crystallizable fragment

Fab - the antigen-binding fragment

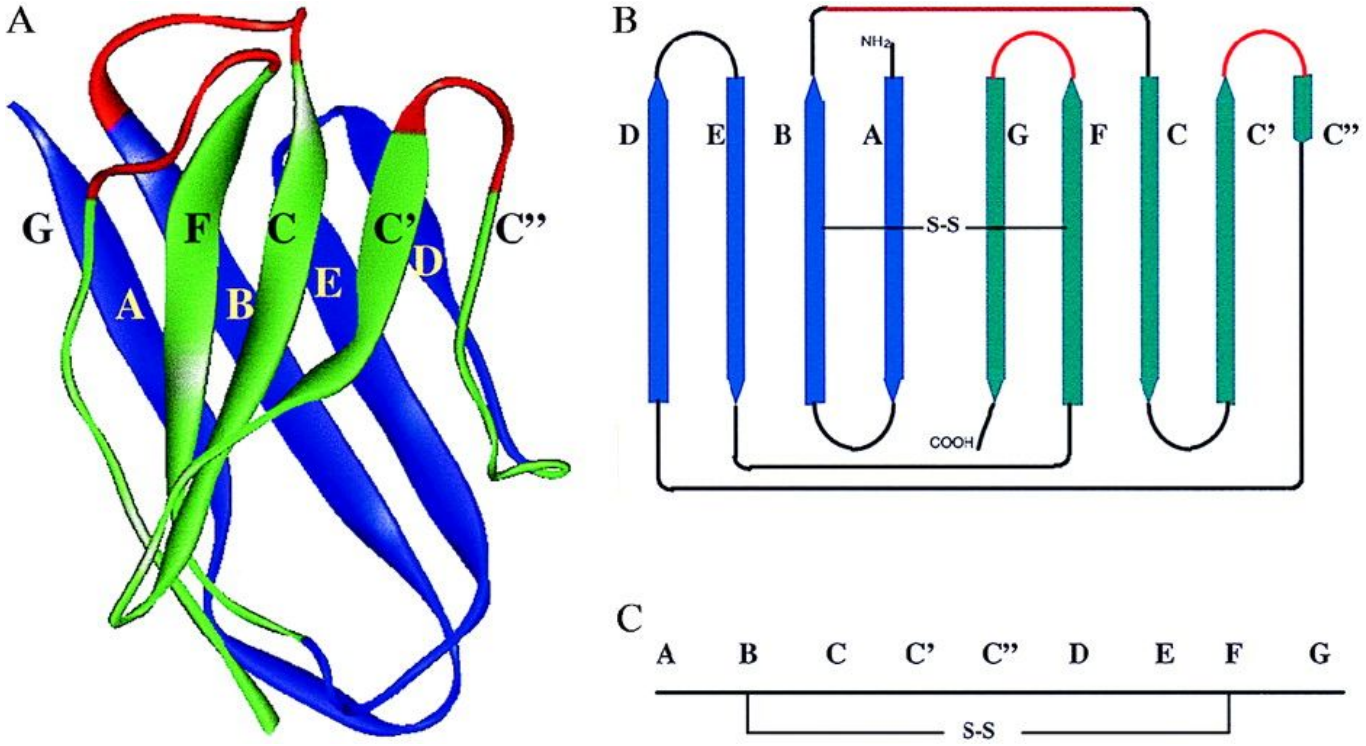
Fv - the variable fragment (domain)

F_V structure



http://2015.igem.org/Team:SDU-Denmark/Tour20

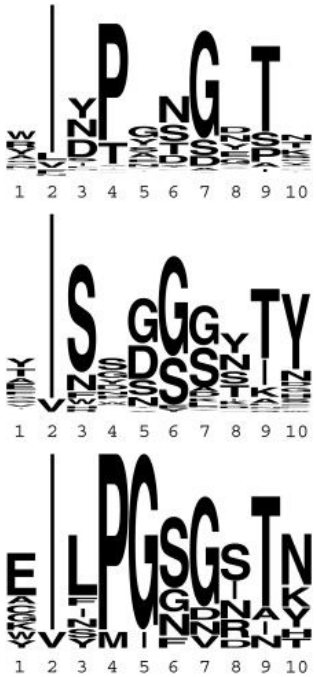
Ig fold



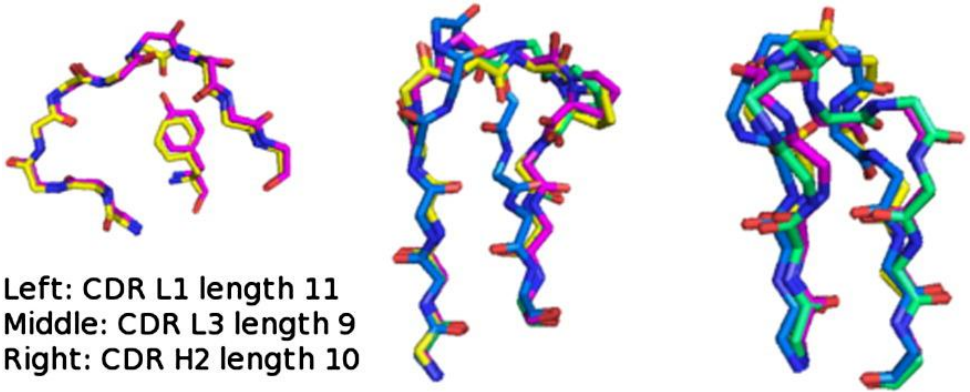
Barclay AN. Proc Natl Acad Sci U S A. 1999 Dec 21;96(26):14672-4
Doi: 10.1073/pnas.96.26.14672

Canonical loop conformations

Loop sequence

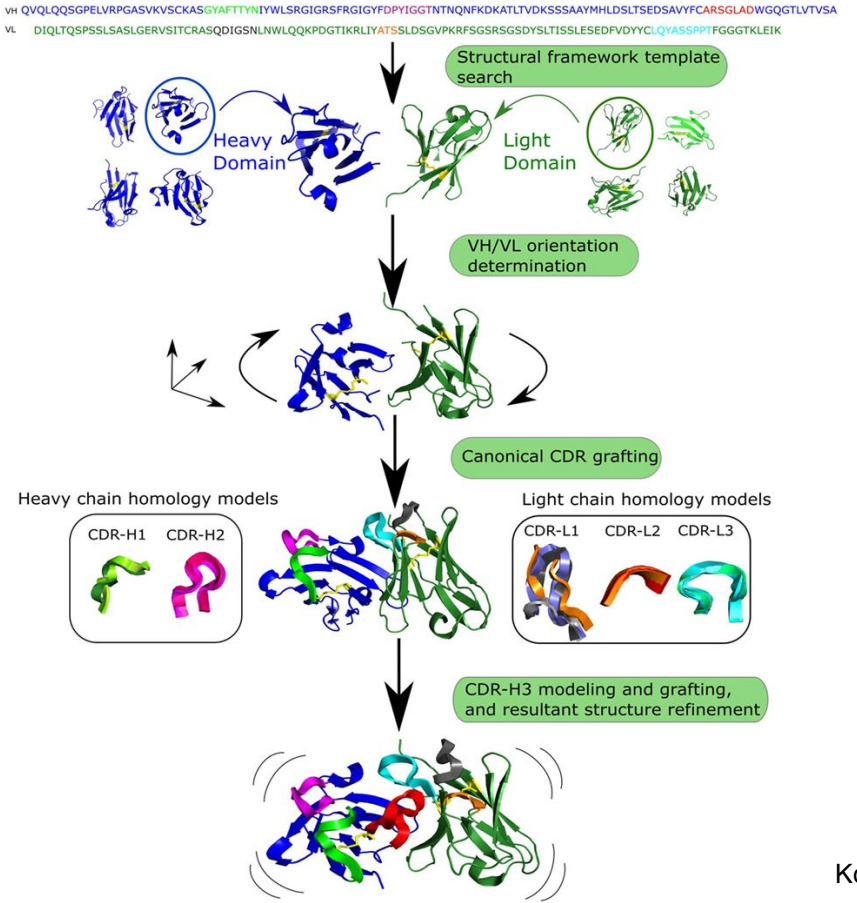


Structure



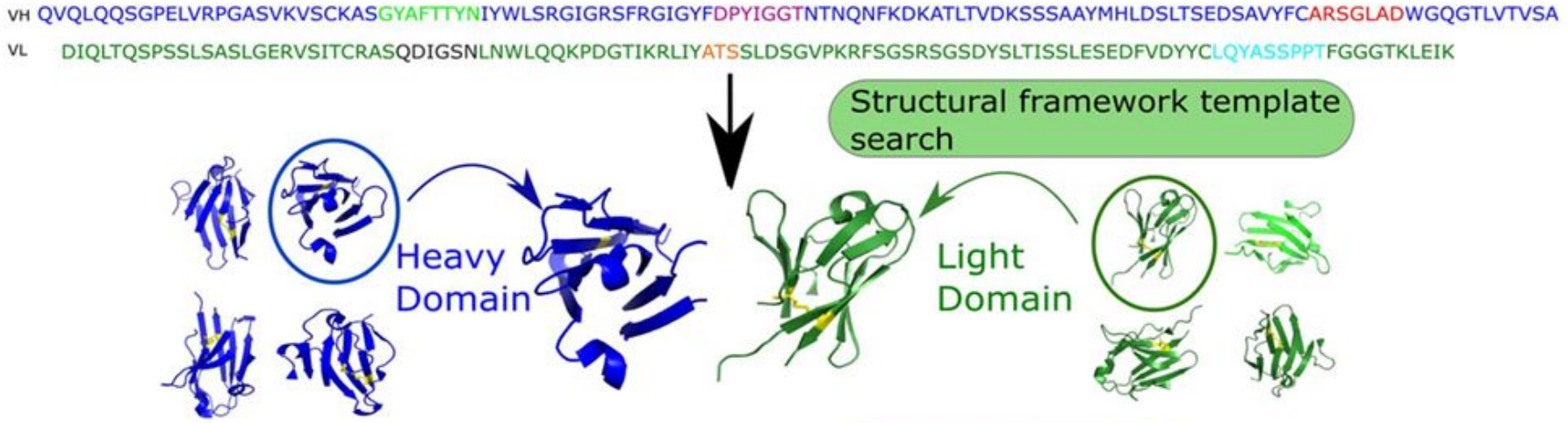
North B et al. J Mol Biol. 2011 Feb 18;406(2):228-56.
doi: 10.1016/j.jmb.2010.10.030

Generalized workflow of antibody modeling



Kovaltsuk A et al. Front Immunol. 2017 Dec 8;8:1753
doi: 10.3389/fimmu.2017.01753

Generalized workflow of antibody modeling

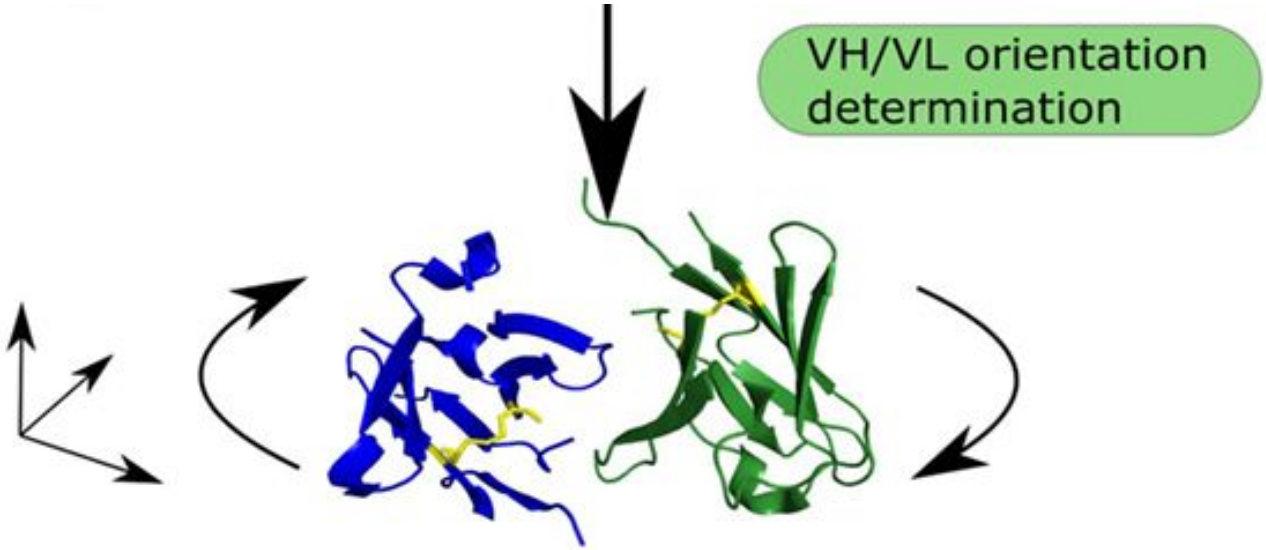


Kovaltsuk A et al. Front Immunol. 2017 Dec 8;8:1753
doi: 10.3389/fimmu.2017.01753

Generalized workflow of antibody modeling

VH QVQLQQSGPELVRPGASVKVSCKASGYAFTTYNIYWLSRGIGRSFRGIGYFDPYIGGTNTNQNFKDKATLTVDKSSSAAYMHLDSLTSEDSAVYFCARSGLADWGQGTLVTVSA

VL DIQLTQSPSSLSASLGERVSITCRASQDIGSNLNWLQQKPDGTIKRLIYATSSLDSGVPKRFSGSRSGSDYSLTISSLESEDFVDYYCLQYASSPPTFGGGTKLEIK

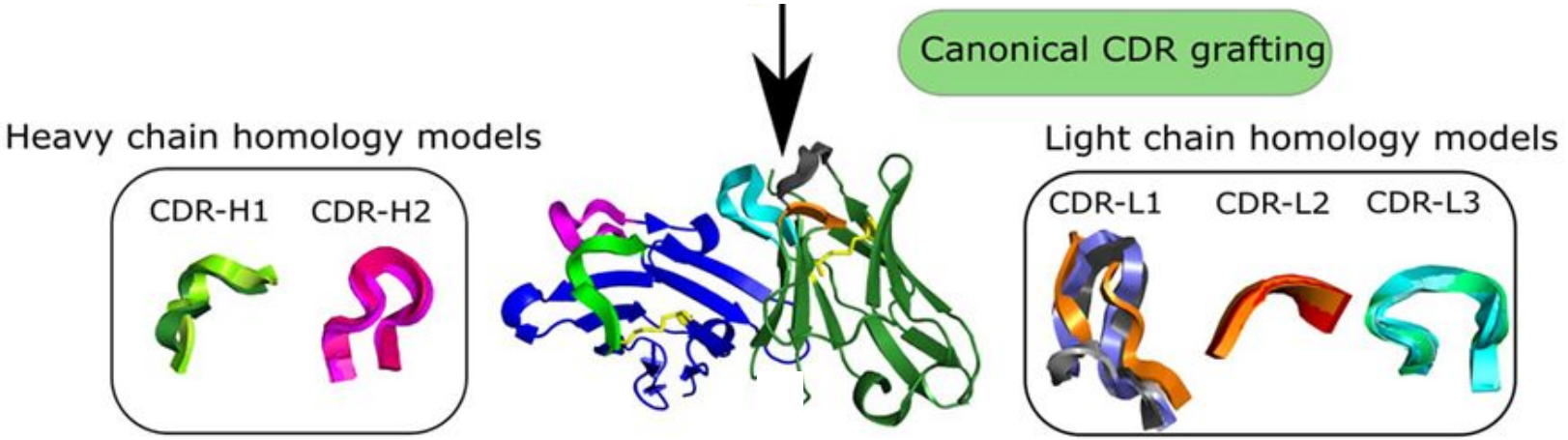


Kovaltsuk A et al. Front Immunol. 2017 Dec 8;8:1753
doi: 10.3389/fimmu.2017.01753

Generalized workflow of antibody modeling

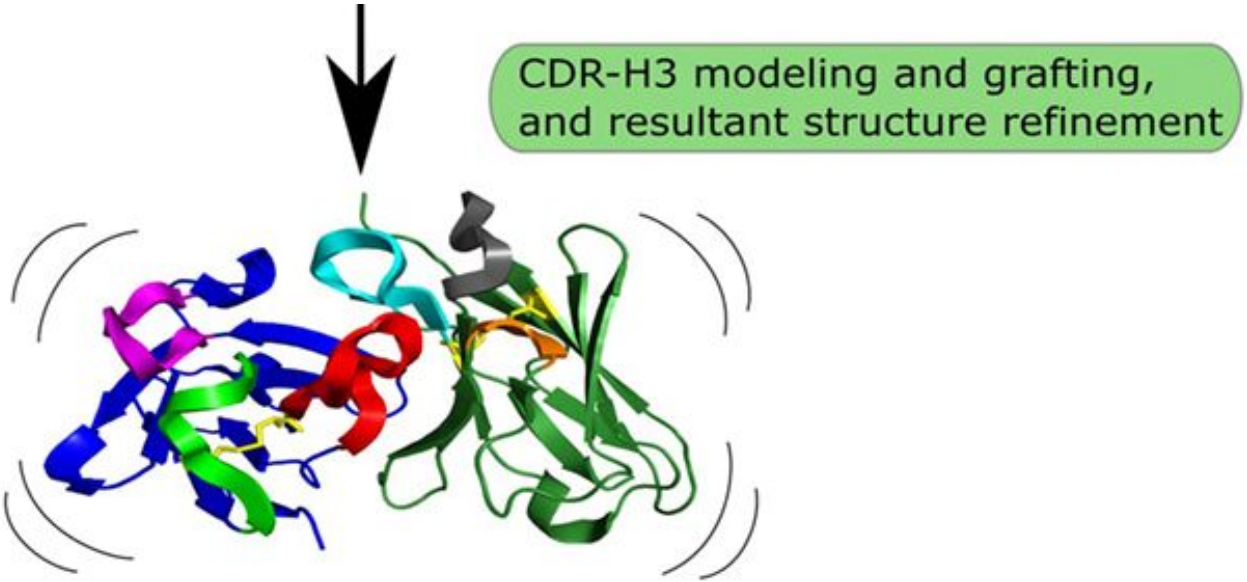
VH QVQLQQSGPELVRPGASVKVSCKASGYAFTTYNIYWLSRGIGRSFRGIGYFDPYIGGTNTNQNFKDKATLTVDKSSSAAYMHLDSLTSEDSAVYFCARSGLADWGQGTLVTVSA

VL DIQLTQSPSSLSASLGERVSITCRASQDIGSNLNWLQQKPDGTIKRLIYATSSLDSGVPKRFSGSRSGSDYSLTISSLESEDFVDYYCLQYASSPPTFGGGTKLEIK



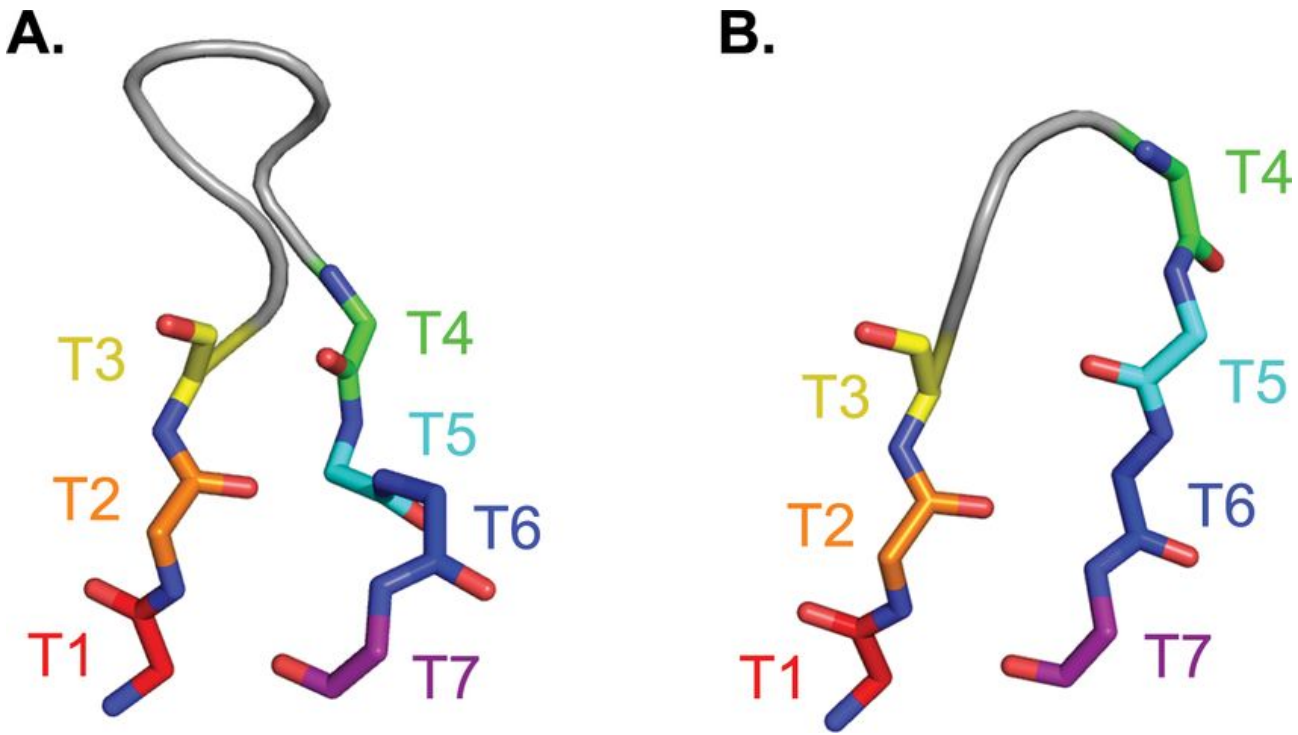
Kovaltsuk A et al. Front Immunol. 2017 Dec 8;8:1753
doi: 10.3389/fimmu.2017.01753

Generalized workflow of antibody modeling



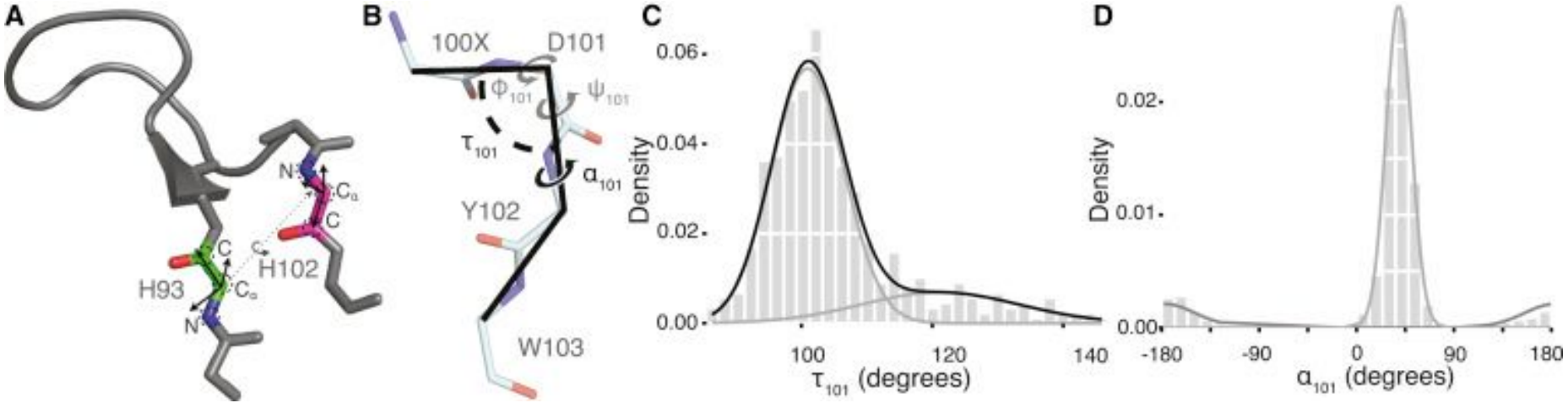
Kovaltsuk A et al. Front Immunol. 2017 Dec 8;8:1753
doi: 10.3389/fimmu.2017.01753

HCDR3 torso



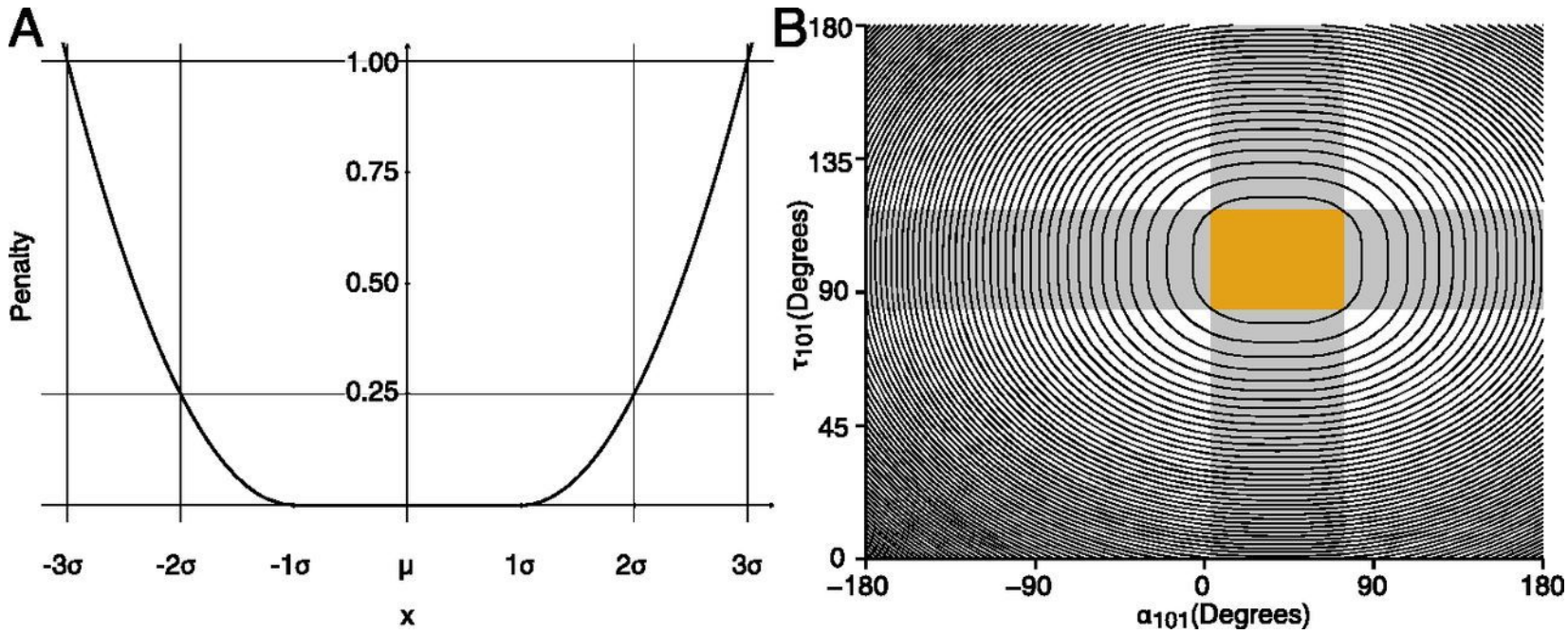
Finn JA et al. PLoS One. 2016 May 16;11(5):e0154811.
doi: 10.1371/journal.pone.0154811

Kink constraints



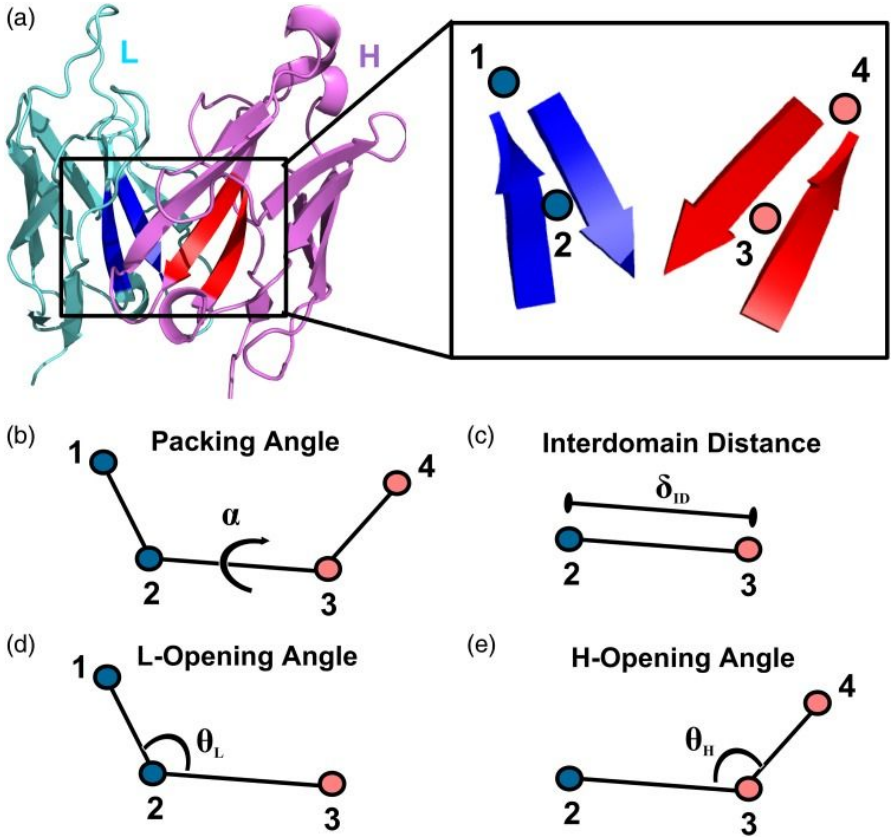
Weitzner BD et al. Structure. 2015 Feb 3;23(2):302-11
doi: 10.1016/j.str.2014.11.010

Kink constraints



Weitzner BD et al. J Immunol. 2017 Jan 1;198(1):505-515
doi: 10.4049/jimmunol.1601137

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

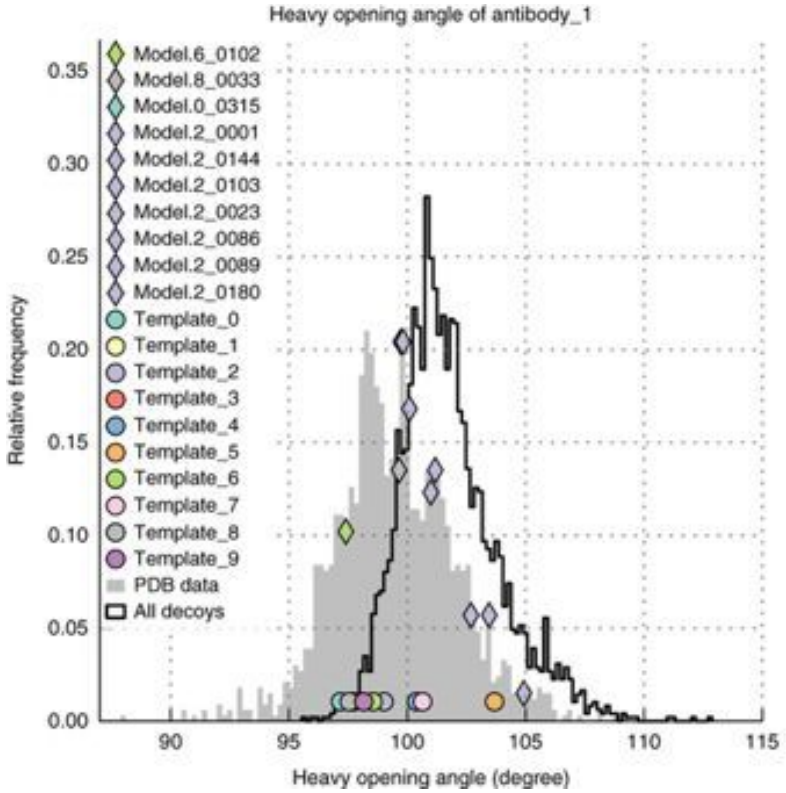
Point 2: centroid of the Cα coordinates of residues L35–L38 and L85–L88 (Chothia numbering)

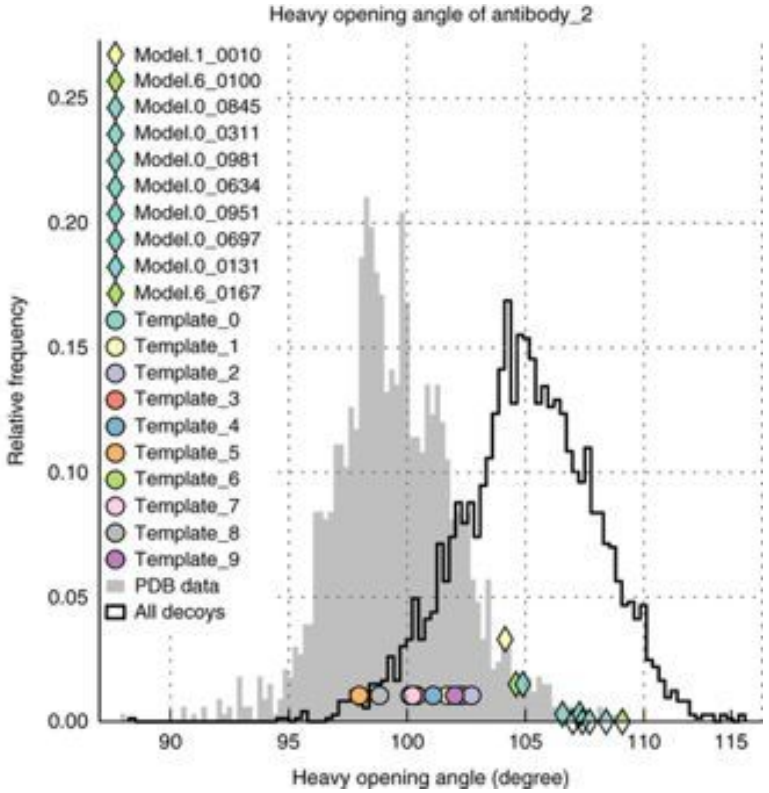
Point 3: the centroid of the Cα coordinates of residues H36–H39 and H89–H92 (Chothia numbering)

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

Marze NA,et al. Protein Eng Des Sel. 2016 Oct;29(10):409-418
doi: 10.1093/protein/gzw013

Analysis





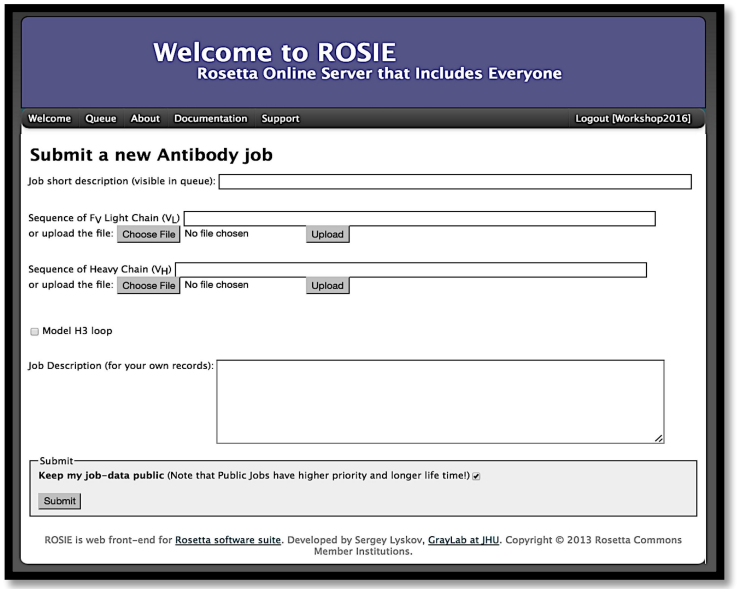
Weitzner BD et al. Nat Protoc. 2017 Feb;12(2):401-416
doi: 10.1038/nprot.2016.180

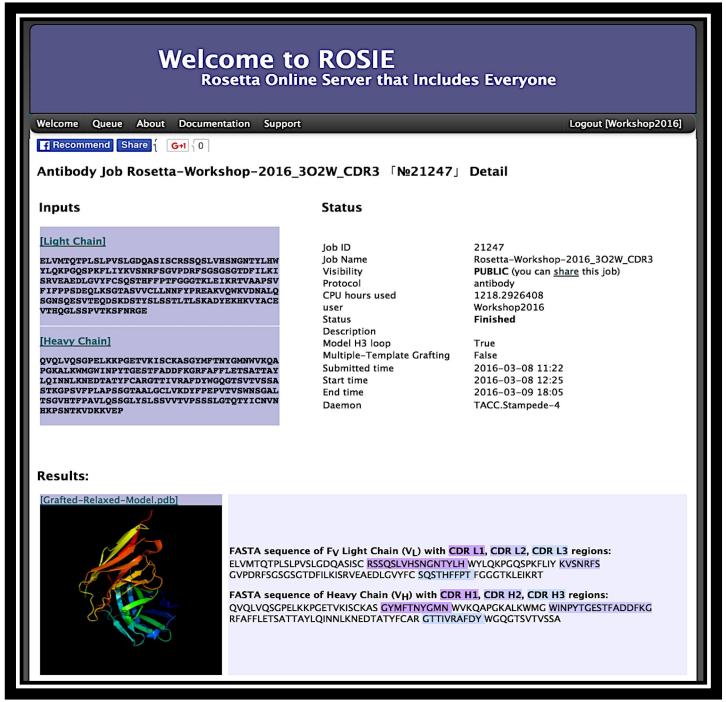
ROSIE web server - entirely automated modeling

1. Enter Job name and Ab sequences

2. Wait

3. Analyze output files





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

Literature:

1. Weitzner BD, Jeliazkov 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.