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3D Protein Modeling of L-segment of Heartland virus

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ABSTRACT
3D Protein Modeling of the L-segment of the Heartland virus represents one of the most important problems in computational biology. The present study is designed to build a 3D Structure of heartland virus. It pioneered the field of automated modeling which is used for the 3D Protein Modeling of the L-segment of Heartland virus by the SWISS-MODEL and the quality of the resulting models was inspected based on the output of protein model assessment tools (Ramachandran Plot assessment, SWISS-MODEL quality assessment). From the data evaluated, it has been observed that all the information is valid. Another server, I-TASSAR, has generated a protein structure by which webuildthemostacceptable3DProteinModelingofthe L-segment of the Heartland virus.
Here, all the computational models I made can be useful for receptor-based drug design and may be useful tools for biological predictions that can be tested experimentally.
Keywords: SWISS-MODEL,I-TASSAR, CDC, RT-PCR, Crystallography

I. INTRODUCTION

The Heartland virus (HRTV) is a tick-borne phlebo virus of the Bhanja sero complex discovered in 2009.Heartland virus is likely spread by the lone star tick. As of September 2018, more than 40 cases of Heartland virus disease have been reported. Most people diagnosed with the disease became sick from May through September. Heartland virus is not currently a notifiable disease, but the CDC asks states to report possible cases of heartland virus voluntarily.

Heartland virus	
Virus classification	
Group:	Group V((−)ssRNA)
Order:	Bunyavirales
Family:	Phenuiviridae

L segment of Heartland virus:
Sequence:
>tr|J3TRD1|J3TRD1_9VIRUPolymeraseOS=Heartland virus PE=4SV=1
MNLEALCSRVLSERGLSTGEPGVYDQIFERPGLP
NLEVTVDSTGVVVDVGAIPDSASQLG

SSINAGVLTIPLSEAYKINHDFTFSGLTKTTDRKL
SEVFPLVHDGSDSMTPDVIHTRLDG
TVVVIEFTTTRSTNMGGLEAAYRSKLEKYRDPL
NRRTDIMPDASIYFGIIVVSASGVLTN
MPLTQDEAEELMFRFCVANEIYSQARAMDAEV
ELQKSEEEYEAISRARAFFTLFDYDDGK
LSEAFPNSDIEMLRRFLSQPVDTSFVTTTLKEKE
QEAYKRMCEEHYLKSGMSTKERLEAN
RSDAIDKTRALMERLHNMSSKELHSNKSTVKLP
PWVVKPSDRTLDVKTDTGSGELLNHGP
YGELWSRCFLEIVLGNVEGVISSPEKELEIAISDD
PEADTPKAAKIKYHRFRPELSLESK
HEFSLQGIEGKRWKHSARNVLKDEMSHKTMSP
FVDVSNIEEFLIMNNLLNDTSFNREGLQ
ETINLLLEKATEMHQNGLSTALNDSFKRNFN
TNVVQWSMWVSCLAQELA

Model Made
SALKQHCKPGE
FIIKKLMHWPIFVIIKPTKSSSHIFYSLAIKKANIK
RRLIGDVFTDTIDAGEWEFSEFKS
LKTCKLTNLINLPCTMLNSIAFWREKMGVAPWI

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VEGCPVRLMPSSFRIKELQNPDEVFLRVRGDILN
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AASYLWMNRTDFSFGKKEPSCSWMCLKTLDS
WAWNQAARVLERNIKTPGIDNTAMGNIFK
DCLESSLRKQGLLRSRIAEMVERHVIPLTSQELV
DILEEDVDFSEMMQSDIMEGDLDIDI
LMEGSPMLWAAEVEEMGEAMVILSQSGKYYH
LKLMDQAATTLSTILGKDGCRLLLGRPTG
RSNLREQVKPYLTLLQIREGDVNWVSEYKDD
TRGLDEDSAEMWG
MNLEALCSRVLSERGLSTGEPGVYDQIFERPGLP
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VLTIPLSEAYKINHDFTFSGLTKTTDRKLSEVF
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FLSQPVDTSFVTTTLKEKEQEAYKRMCEEHY
LKSGMSTKERLEANRSDAIDKTRALMERLHN
MSSKELHSNKSTVKLPPWVVKPSDRTLDVKTD
TGSGELLNHGPYGELWSRCFLEIVLGNVEGVI
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NLPCTMLNSIAFWREKMGVAPWISRKACSELRE
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SPPLLPKPQKMVEKLEVPLRTKLQVFLFRRHL
DAIVRVAASPFPIVARDGRVEWTGTFNAITGRST
GLENMVNNWYIGYYKNKEESTELNALGEMY
KKIVEIEAEKPTSSEYLGWGDTSSPKRHEFSRS
FLKSACISLEKEIEMRHGKSWKQSLEERVLKEL
GSKNLLDLATMKATSNFSKEWEAFSEVRTKEY
HRSKLLEKMAELIEHGLMWYVDAAGHAWK
AVLDDKCMRICLFKKNQHGGLREIYVTNANAR
LVQFGVETMARCVCELSPHETIANPRLKSSIIEN
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HGNVEVPWMTQGATYLQTETGMMQGILHFT
SSLLHSCVQSFYKAYFLSRLKEGIAGRTIKAAID
VLEGSDDSAIMISLKPASDNEEAMARFLTANLL
YSVRVINPLFGIYSSEKSTVNTLFCVEYNSEFH
FHKHLVRPTIRWVAASHQISESEALASRQEDY
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AGGAGFRFNLWRSCKFTNLGKKYAFFFNEIQG
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KYQHLLDRMGLPKDWVERIDENPSILYRRPEN
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LTLLDEVTALTGKFVVRERNIVKSRVELFQEP
VDLRCKAENLIAEMWFGLKRTKLGPRLLKEEW
DKLRASFSWLSTDHKETLDVGPFLSHVQFRNFI
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LNGPYTDEQKKAMVLETFQYFALPHAAEVVK
RSRSLTLCLMKNFIEQRGGSILDQIEKAQSGT
VGGFSKPQKPYRKQSGGIGYKGKGVWSGIMEN
TNVQILIDGDGSSNWIEEIRLSSESRLFDVIESVR
RLCDDINVNNRVTSSFRGHCMVRLSNFKVKP
ASRVEGCPVRLMPSSFRIKELQNPDEVFLRVRG
DILNLSILLQEDRVMNLLSYRARDTDISESAASY

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LWMNRTDFSFGKKEPSCSWMCLKTLDSWA
WNQAARVLERNIKTPGIDNTAMGNIFKDCLESS
LRKQGLLRSRIAEMVERHVIPLTSQELVDILEED
VDFSEMMQSDIMEGDLDIDILMEGSPMLWA
AEVEEMGEAM

VILSQSGKYYHLKLMDQAATTLSTILGKDGCRL
LLGRPTGRSNLREQVKPYLTLLQIREGDVNWV
SEYKDDTRGLDEDSAEMWG

Table T1: Primary amino acid sequence for which templates were searched and models were built.

MNLEALCSRVLSERGLSTGEPGVYDQIFERPGLP
NLEVTVDSTGVVVDVGAIPDSASQLGSSINAG
VLTIPLSEAYKINHDFTFSGLTKTTDRKLSEVF
PLVHDGSDSMTPDVIHTRLDGTVVVIEFTTTRST
NMGGLEAAYRSKLEKYRDPLNRRTDIMPDASI
YFGIIVVSASGVLTNMPLTQDEAEELMFRFCV
ANEIYSQARAMDAEVELQKSEEEYEAISRARAF
FTLFDYDDGKLSEAFPNSDIEMLRR
FLSQPVDTSFVTTTLKEKEQEAYKRMCEEHY
LKSGMSTKERLEANRSDAIDKTRALMERLHN
MSSKELHSNKSTVKLPPWVVKPSDRTLDVKTD
TGSGELLNHGPYGELWSRCFLEIVLGNVEGVI
SSPEKELEIAISDDPEADTPKAAKIKYHRFRPEL
SLESKHEFSLQGIEGKRWKHSARNVLKDEMSH
KTMSPFVDVSNIEEFLIMNNLLNDTSFNREGL
QETINLLLEKATEMHQNGLSTALNDSFKRNFN
TNVVQWSMWVSCLAQELASALKQHCKPGEFII
KKLMHWPIFVIIKPTKSSSHIFYSLAIKKANIKR
RLIGDVFTDTIDAGEWEFSEFKSLKTCKLTNLI
NLPCTMLNSIAFWREKMGVAPWISRKACSELRE
QVAITFLMSLEDKSTTEELVTLTRYSQMEGFV
SPPLLPKPQKMVEKLEVPLRTKLQVFLFRRHL
DAIVRVAASPFPIVARDGRVEWTGTFNAITGRST
GLENMVNNWYIGYYKNKEESTELNALGEMY
KKIVEIEAEKPTSSEYLGWGDTSSPKRHEFSRS
FLKSACISLEKEIEMRHGKSWKQSLEERVLKEL
GSKNLLDLATMKATSNFSKEWEAFSEVRTKEY
HRSKLLEKMAELIEHGLMWYVDAAGHAWK
AVLDDKCMRICLFKKNQHGGLREIYVTNANAR
LVQFGVETMARCVCELSPHETIANPRLKSSIIEN
HGLKSARQLGQGTINVNSSNDAKKWSQGHY
TTKLAMVLCWFMPAKFHRFIWAGISMFRCKK
MMMDLRFLEKLSTKANQKTDDDFRKDLAGAF
HGNVEVPWMTQGATYLQTETGMMQGILHFT
SSLLHSCVQSFYKAYFLSRLKEGIAGRTIKAAID
VLEGSDDSAIMISLKPASDNEEAMARFLTANLL
YSVRVINPLFGIYSSEKSTVNTLFCVEYNSEFH
FHKHLVRPTIRWVAASHQISESEALASRQEDY
ANLLTQCLEGGSSFSLTYLIQCAQLVHHYMLLG
LCLHPLFGTFVGMLIEDPDPALGFFIMDNPAF
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KTKGDADYRALDATTGGTLSHSVMTYWGDRR
KYQHLLDRMGLPKDWVERIDENPSILYRRPEN
KQELILRLAEKVHSPGVTSSFSKGHVVPRVVA
AGVYLLSRHCFRYTASIHGRGASQKASLIKLLV
MSSTSAERNQGRLNPNQERMLFPQVQEYERV
LTLLDEVTALTGKFVVRERNIVKSRVELFQEP
VDLRCKAENLIAEMWFGLKRTKLGPRLLKEEW
DKLRASFSWLSTDHKETLDVGPFLSHVQFRNFI
AHVDAKSRSVRLLGAPVKKSGGVTTVSQVV
KSNFFPGFILDSSESLDDQERVEGVSILKHILFMT
LNGPYTDEQKKAMVLETFQYFALPHAAEVVK
RSRSLTLCLMKNFIEQRGGSILDQIEKAQSGT
VGGFSKPQKPYRKQSGGIGYKGKGVWSGIMEN
TNVQILIDGDGSSNWIEEIRLSSESRLFDVIESVR
RLCDDINVNNRVTSSFRGHCMVRLSNFKVKP
ASRVEGCPVRLMPSSFRIKELQNPDEVFLRVRG
DILNLSILLQEDRVMNLLSYRARDTDISESAASY
LWMNRTDFSFGKKEPSCSWMCLKTLDSWA
WNQAARVLERNIKTPGIDNTAMGNIFKDCLESS
LRKQGLLRSRIAEMVERHVIPLTSQELVDILEED
VDFSEMMQSDIMEGDLDIDILMEGSPMLWA
AEVEEMGE

VILSQSGKYYHLKLMDQAATTLSTILGKDGCRL
LLGRPTGRSNLREQVKPYLTLLQIREGDVNWV
SEYKDDTRGLDEDSAEMWG

Table T 2:

Template	Seq Identity	Oligo-state	Found by	Method	Resolution	Seq Similarity	Coverage	Description
5amr.1.A	18.32	monomer	HH blits	X-ray	2.57Å	0.29	0.39	RNAPOLYMERASEL
5amq.1.A	18.32	monomer	HH blits	X-ray	3.00Å	0.29	0.39	RNAPOLYMERASEL
5amq.1.A	27.64	monomer	BLAST	X-ray	3.00Å	0.34	0.15	RNAPOLYMERASEL
5amr.1.A	27.64	monomer	BLAST	X-ray	2.57Å	0.34	0.15	RNAPOLYMERASEL

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4wsb.1.B	18.51	hetero-oligomer	HH blits	X-ray	2.65Å	0.30	0.13	RNA-directed RNA polymerase catalytic sub unit
5epi.2.B	18.44	hetero-oligomer	HH blits	X-ray	4.10Å	0.29	0.14	RNA-directed RNA polymerase catalytic subunit
4wsa.1.D	18.44	hetero-oligomer	HH blits	X-ray	3.40Å	0.29	0.14	RNA-directed RNA polymerase catalytic sub unit
4wrt.1.D	18.44	hetero-oligomer	HH blits	X-ray	2.70Å	0.29	0.14	RNA-directed RNA polymerase catalytic sub unit
5d98.1.B	17.02	hetero-oligomer	HH blits	X-ray	3.90Å	0.28	0.14	RNA-directed RNA polymerase catalytic sub unit
1qys.1.A	15.79	monomer	HH blits	X-ray	2.50Å	0.28	0.05	TOP7
2pjp.1.B	5.71	monomer	HH blits	X-ray	2.30Å	0.24	0.03	Sele nocysteine-specific elongation factor
4kyz.1.A	21.43	monomer	HHblits	X-ray	2.49Å	0.31	0.03	Designed proteinOR327
Template	**Seq Identity**	**Oligo-state**	**Found by**	**Method**	**Resolution**	**Seq Similarity**	**Coverage**	**Description**
4ky3.2.A	21.43	monomer	HH blits	X-ray	2.96Å	0.31	0.03	Designed protein OR327
4ky3.3.A	21.43	monomer	HH blits	X-ray	2.96Å	0.31	0.03	Designed protein OR327
4ky3.1.A	21.43	monomer	HH blits	X-ray	2.96Å	0.31	0.03	Designed protein OR327
4qbn.1.A	13.16	homo-dimer	HH blits	X-ray	1.85Å	0.28	0.02	Nuclease
2lb2.1.A	36.00	hetero-oligomer	HH blits	NMR	NA	0.37	0.01	E3 ubiquit in-protein ligase NEDD4-like

Methodologies for protein structure determination

X-ray Crystallography:

Most of the structures included in the PDB archive were determined using X-ray crystallography. The first solved protein crystal structure was of Sperm Whal emyoglobin determined by Max Perutz and Sir John Cowdery Kendrew in 1958. They were

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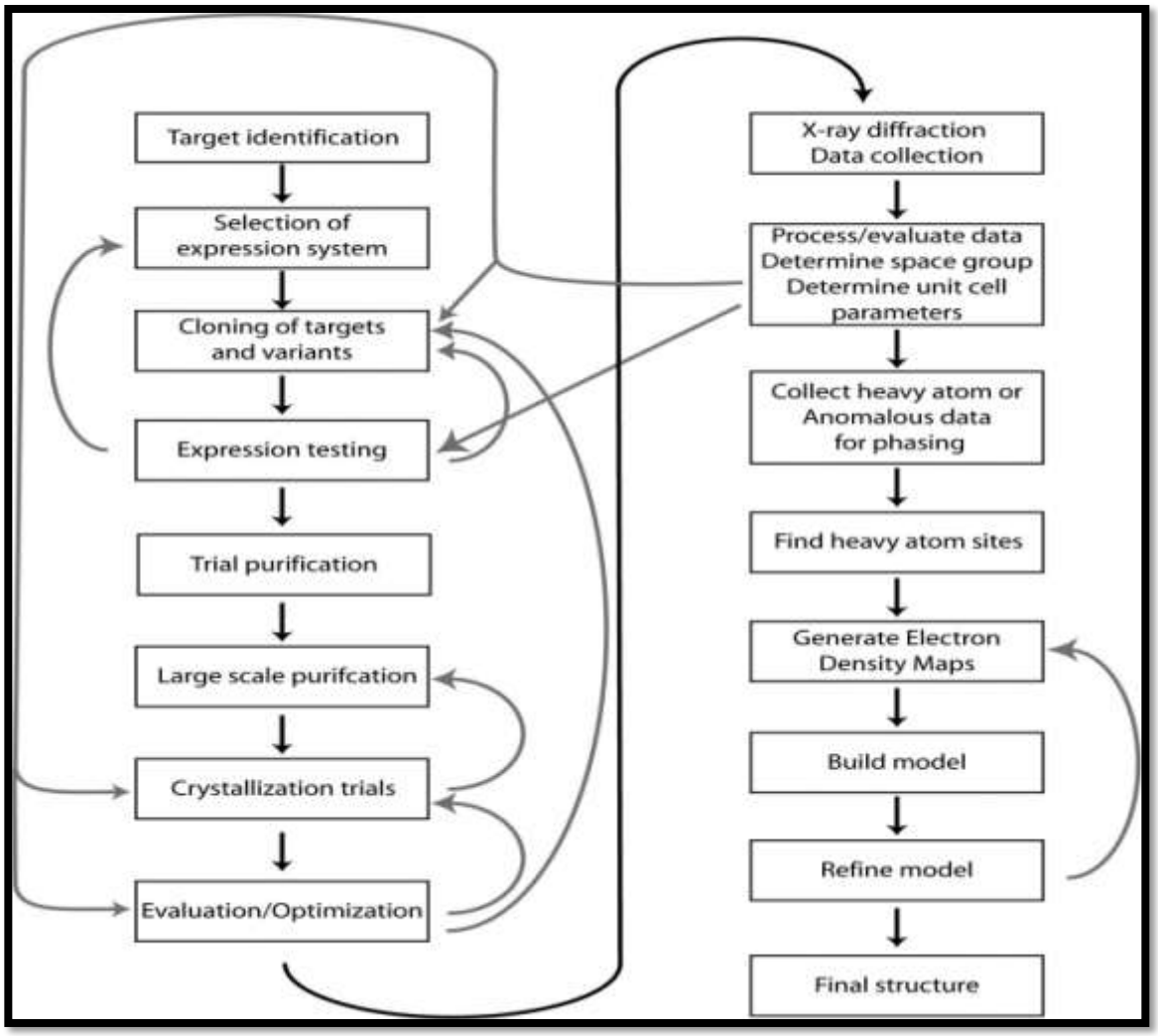
awarded the NobelPrizein Chemistry in 1962.

The whole process of X-ray Crystallography is shown in the flow–chart.



NMR Spectroscopy:

Nuclear magnetic resonance spectroscopy, most commonly known as NMR spectroscopy, is a research technique that exploits the magnetic properties of certain atomic nuclei. It determines the physical and chemical properties of atoms or the molecules they contain.

Electron Microscopy:

Electron microscopy is used to obtain 3D images. If the proteins can be coaxed into forming small crystals or if they pack symmetrically in a membrane, electron diffraction can generate a 3D density map, using methods similar to X-ray diffraction. If the molecule is symmetrical, such as in virus capsids, many separate images may be taken, providing several different views. These views are then aligned and averaged to extract 3D information. Electron tomography, on the other hand, obtains many views by rotating a single specimen and taking several electron micrographs. These views are then processed to give the 3D information.

Electron diffraction produces atomic-level data for a few well-behaved systems, but typically, electron micrographic experiments do not allow the researcher to see each atom. Electron micro graphic studies often combine information from X-ray crystallography or NMR spectroscopy to sort-out the atomic details. Atomic structures are docked

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into the electron density map to yield a model of the complex.

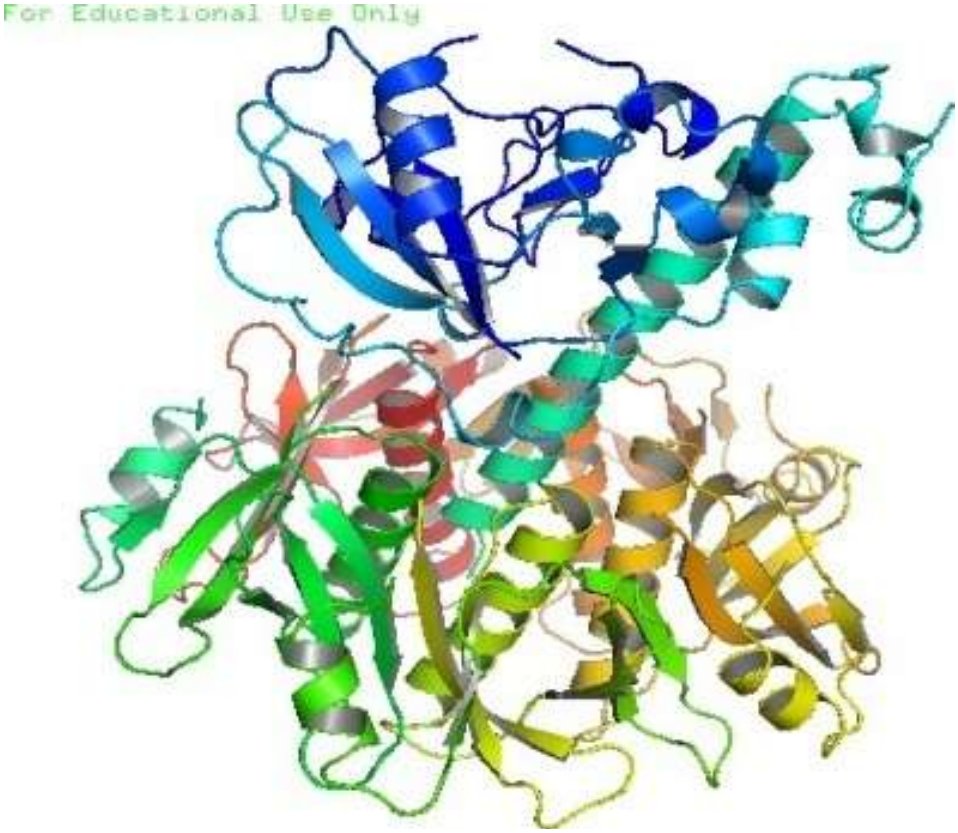
Materials: Availability and requirements
Project name: SWISS-MODEL SERVER (For Homology modeling),
I-TASSER server (For Ab initio modeling)
Project homepage: http://www.uniprot.org/uniprot/
http://Swissmodel.expasy.org/interactive
Software: Chimera, Python Molecular Viewer, PDB Viewer.

MODELING PROCEDURE
All homology-modeling methods consist of the following foursteps:
1. template search
2. target selection
3. model building
4. energy minimization and validation of the model

Template Search: With the help of BLAST & HHBlits, the template was searched against the Swiss model template library. With the help of BLAST, the target sequence was searched against the primary amino acid sequences. A total of 2 templates were found from the BLAST profile and HHBlits 15.

Template Selection:
The templates with the highest quality have been selected for model building.
Model Building; Using a fragment library, insertions and deletions were remodeled, and side chains were rebuilt. If ProMod3 failed, an alternative model was built with PROMOD2.

Model1 obtained from UCSF Chimera



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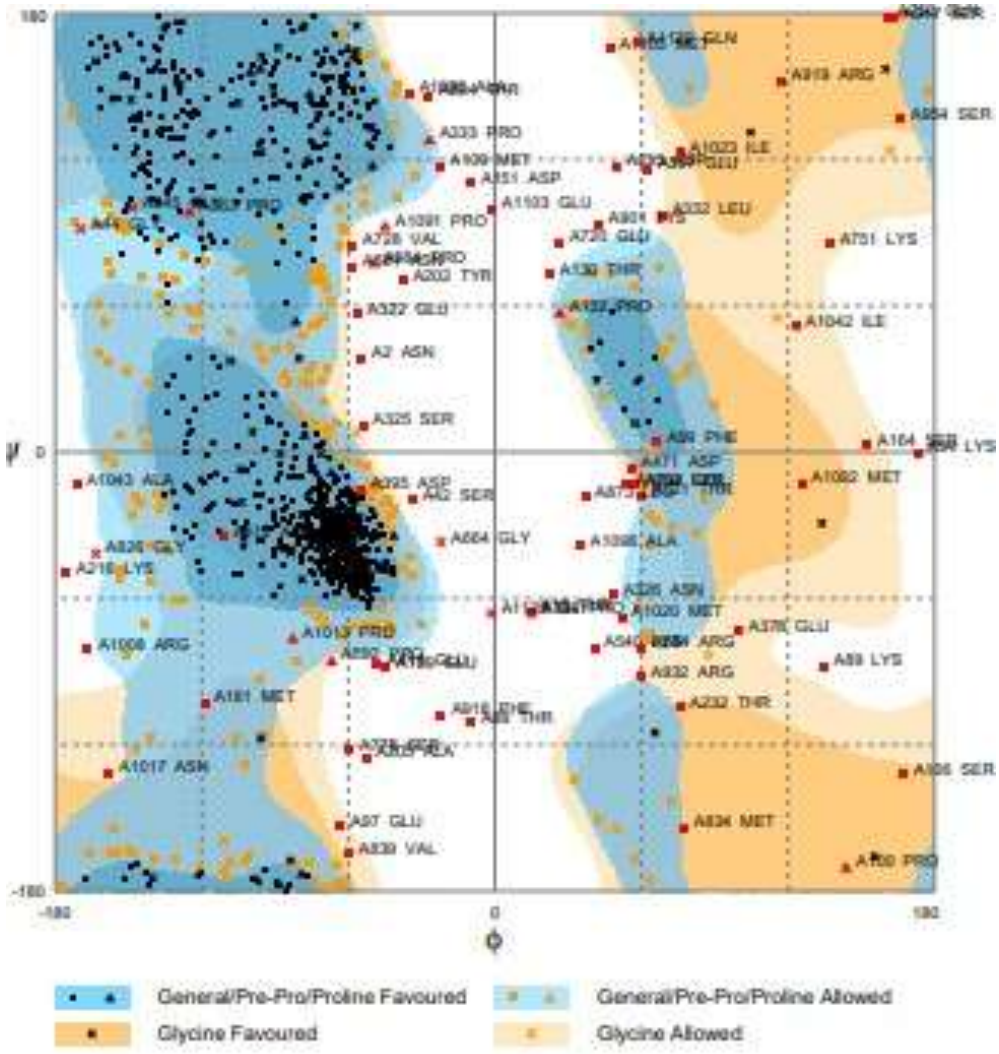
Rampage Ramachandran Plot of Model1



Number of residues in favoured region (~98.0% expected)	: 895 (75.4%)
Number of residues in allowed region (~2.0% expected)	: 215 (18.1%)
Number of residues in outlier region	: 77 (6.5%)

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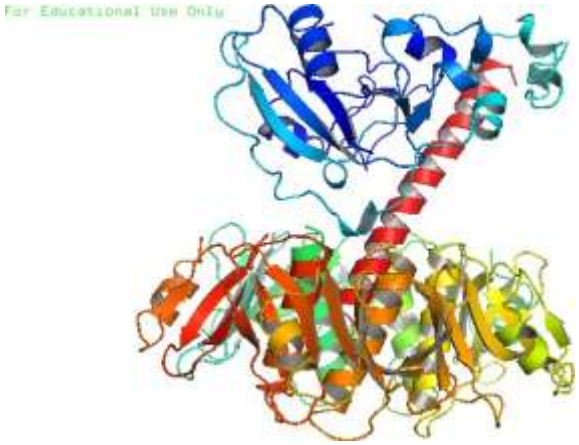
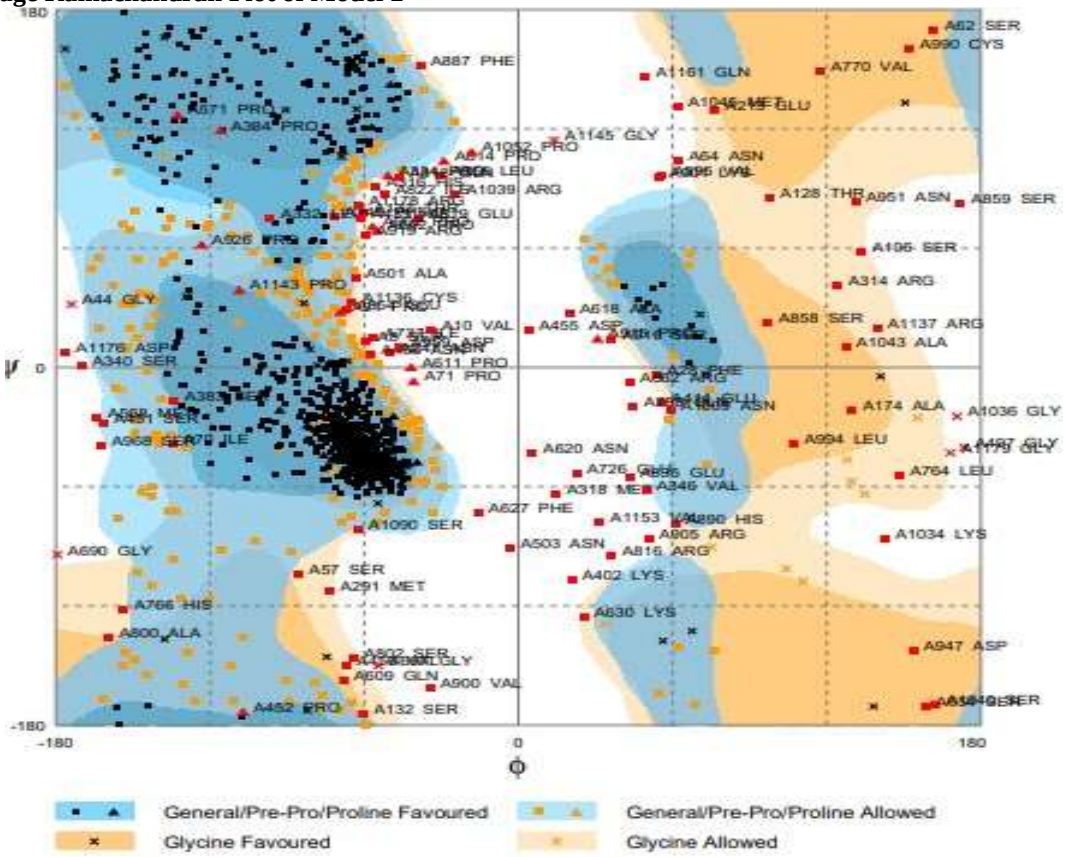
Model 2 obtained from UCSF Chimera



Rampage Ramachandran Plot of Model 2



Number of residues in favoured region (~98.0% expected)	: 864 (72.8%)
Number of residues in allowed region (~2.0% expected)	: 218 (18.4%)
Number of residues in outlier region	: 105 (8.8%)

RAMPAGE by Paul de Bakker and Simon Lovell available at http://www-cryst.bioc.cam.ac.uk/rampage/
Please cite: S.C. Lovell, I.W. Davis, W.B. Arendall III, P.I.W. de Bakker, J.M. Word, M.G. Prisant, J.S. Richardson & D.C. Richardson (2002)
Structure validation by Cα geometry: ϕ,ψ and Cβ deviation. *Proteins: Structure, Function & Genetics* **50**: 437-450

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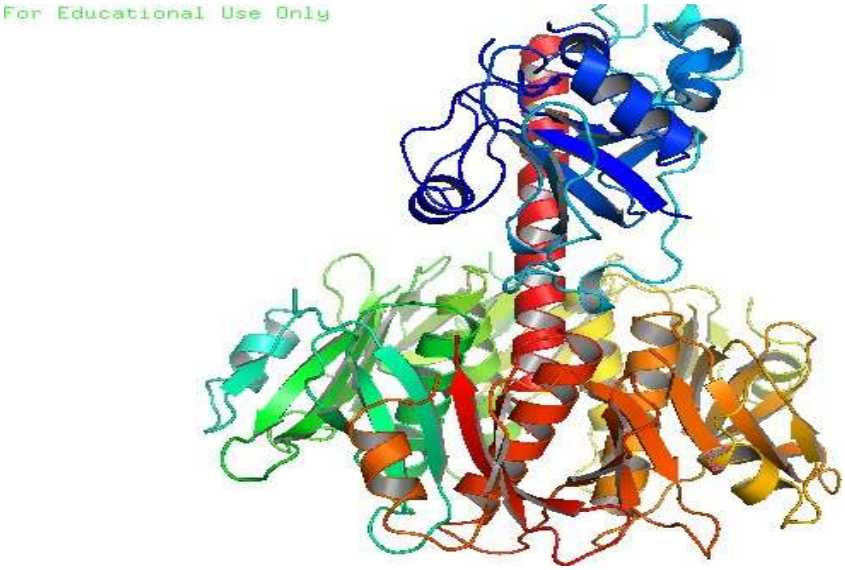
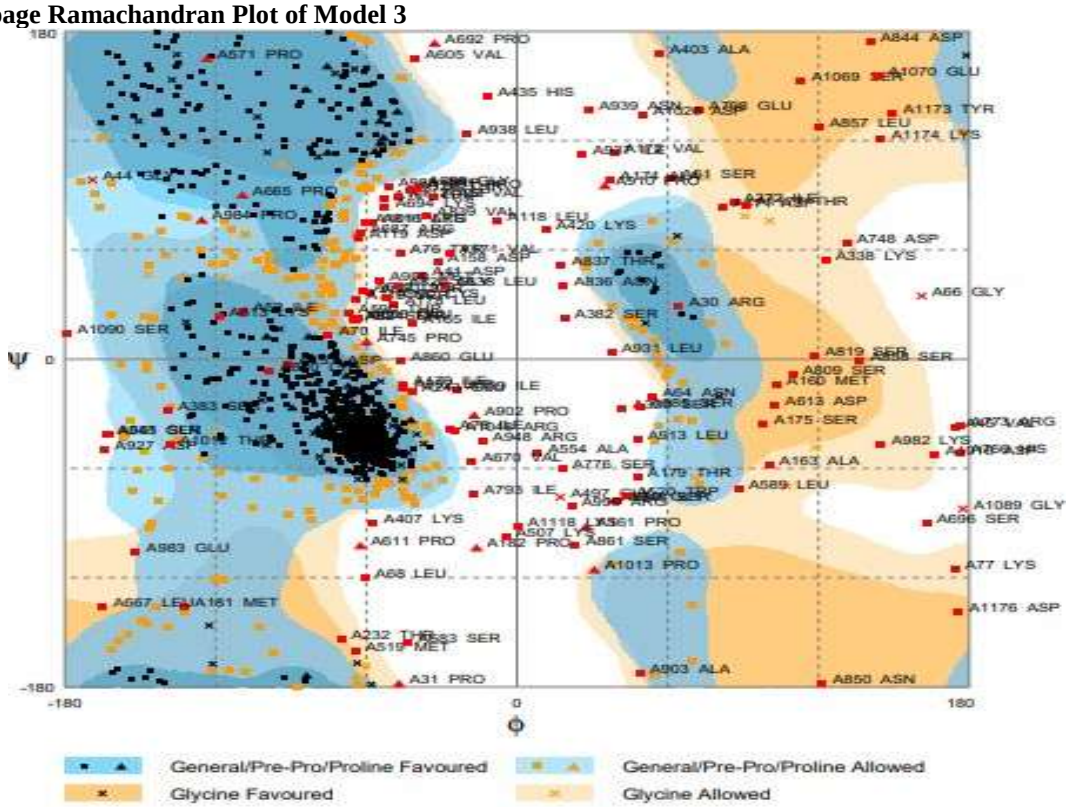
Model 3 obtained from UCSF Chimera



Rampage Ramachandran Plot of Model 3



Number of residues in favoured region (~98.0% expected) : 836 (70.4%)
Number of residues in allowed region (~2.0% expected) : 215 (18.1%)
Number of residues in outlier region : 136 (11.5%)

RAMPAGE by Paul de Bakker and Simon Lovell available at http://www-cryst.bioc.cam.ac.uk/rampage/
Please cite: S.C. Lovell, I.W. Davis, W.B. Arendall III, P.I.W. de Bakker, J.M. Word, M.G. Prisant, J.S. Richardson & D.C. Richardson (2002) Structure validation by Cα geometry: ϕ,ψ and Cβ deviation. *Proteins: Structure, Function & Genetics* **50**: 437-450

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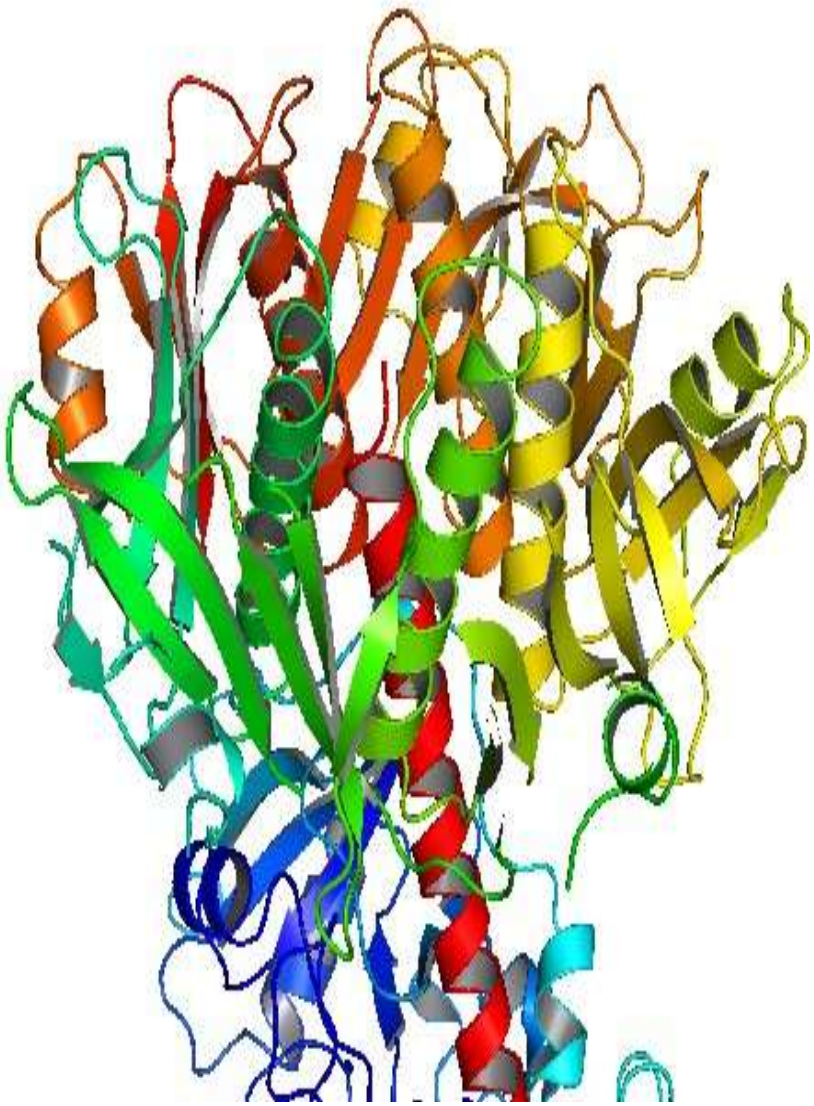
Model 4 obtained from UCSF Chimera



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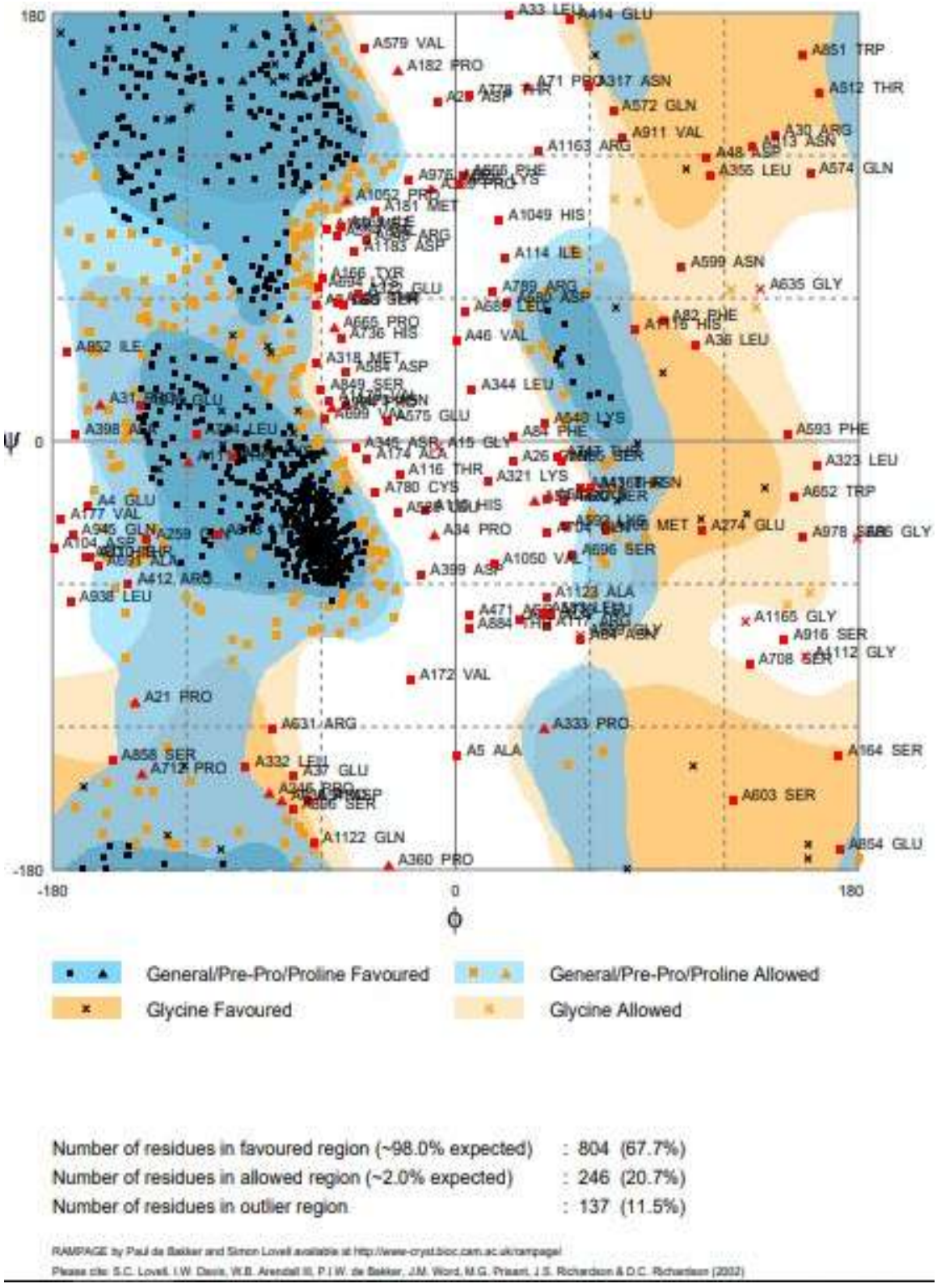
Rampage Ramachandran Plot of Model4



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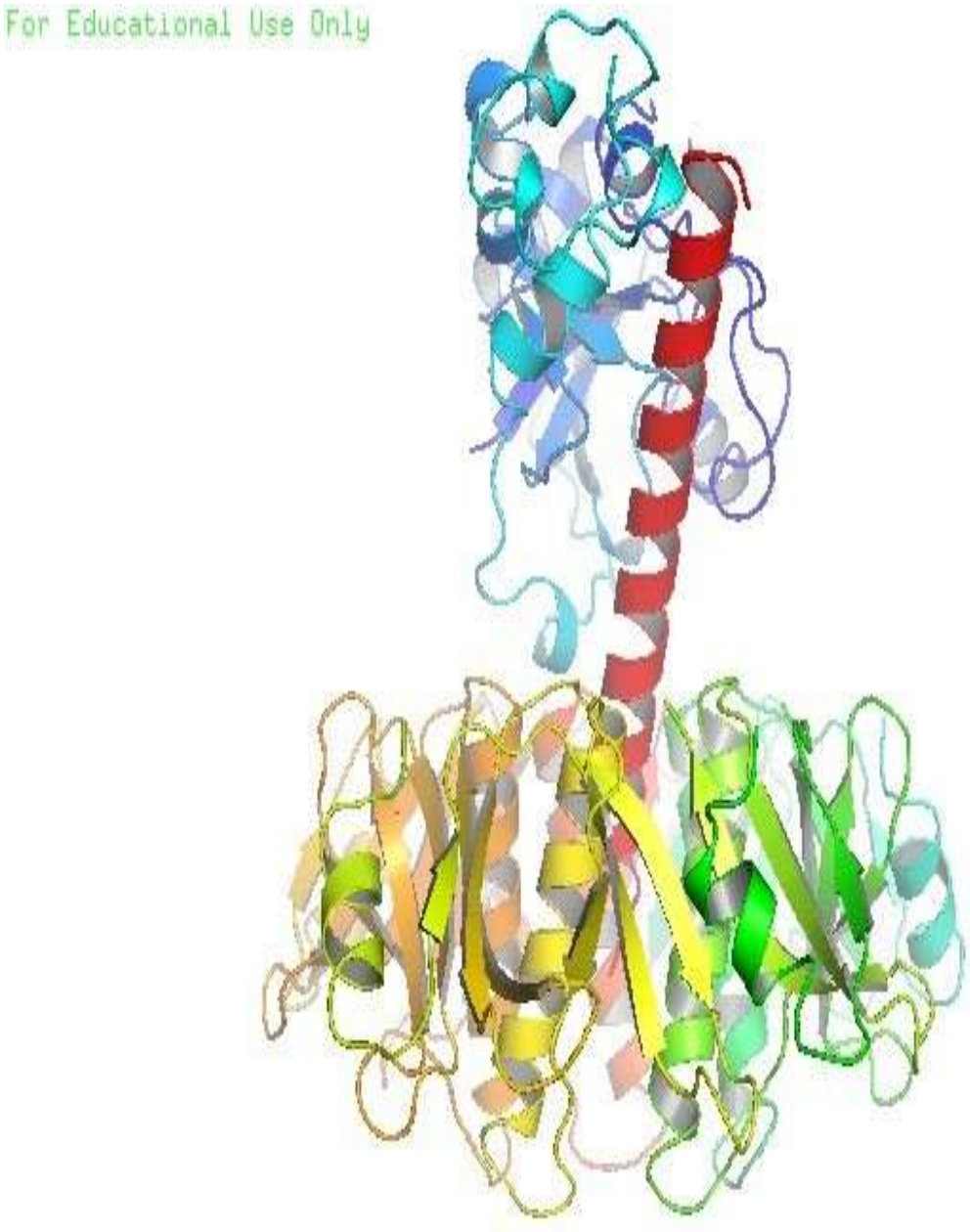
Model 5 obtained from UCSF Chimera



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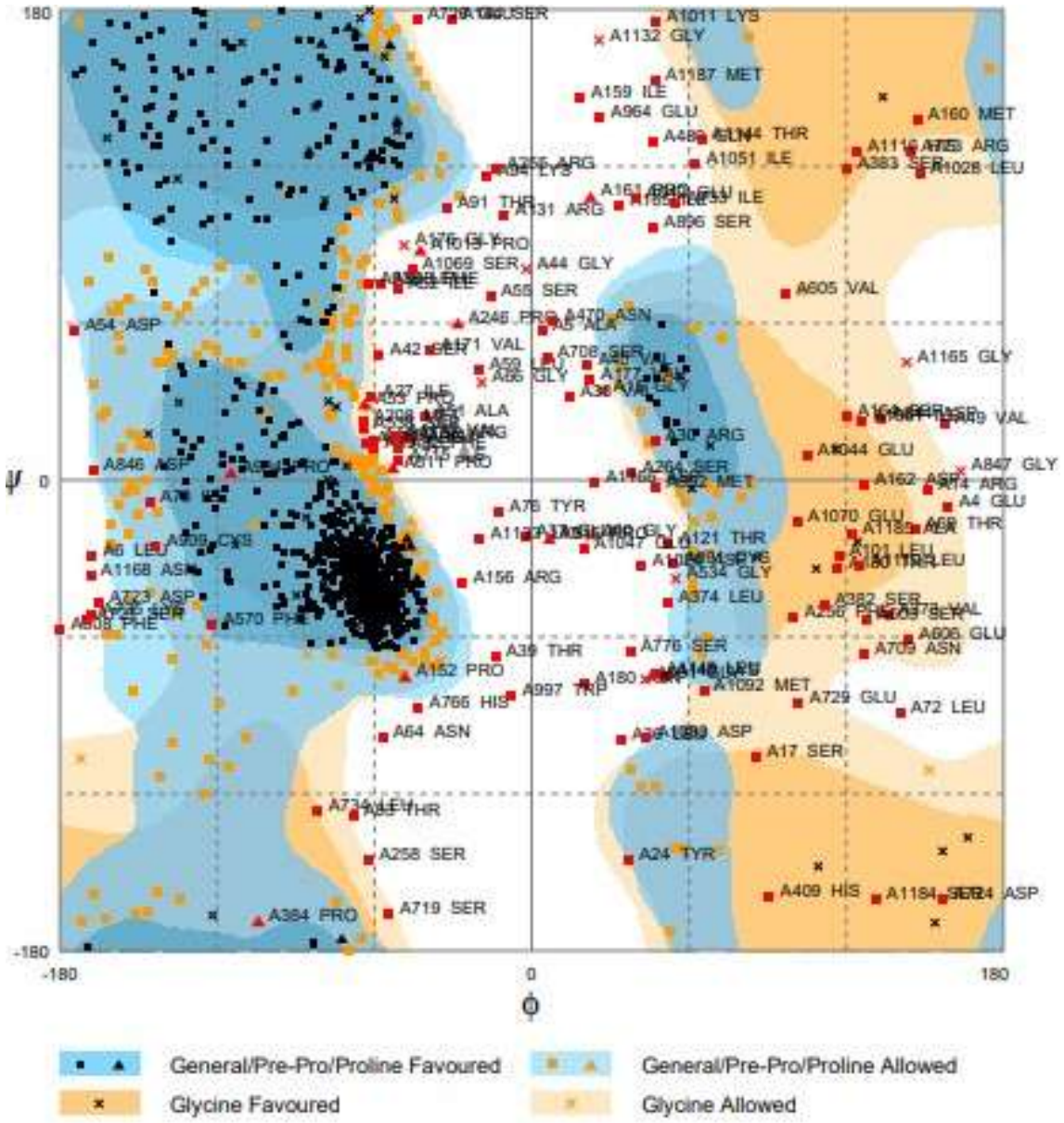
Rampage Ramachandran Plot of Model 5



Number of residues in favoured region (~98.0% expected)	: 825	(69.5%)
Number of residues in allowed region (~2.0% expected)	: 229	(19.3%)
Number of residues in outlier region	: 133	(11.2%)

RAMPAGE by Paul de Bakker and Simon Lovell available at http://www-cryst.bioc.cam.ac.uk/rampage/

Please cite: S.C. Lovell, I.W. Davis, W.B. Arendall III, P.I.W. de Bakker, J.M. Word, M.G. Prisant, J.S. Richardson & D.C. Richardson (2002) Structure validation by Cα geometry: ϕ,ψ and Cβ deviation. *Proteins: Structure, Function & Genetics* **50**: 437-450

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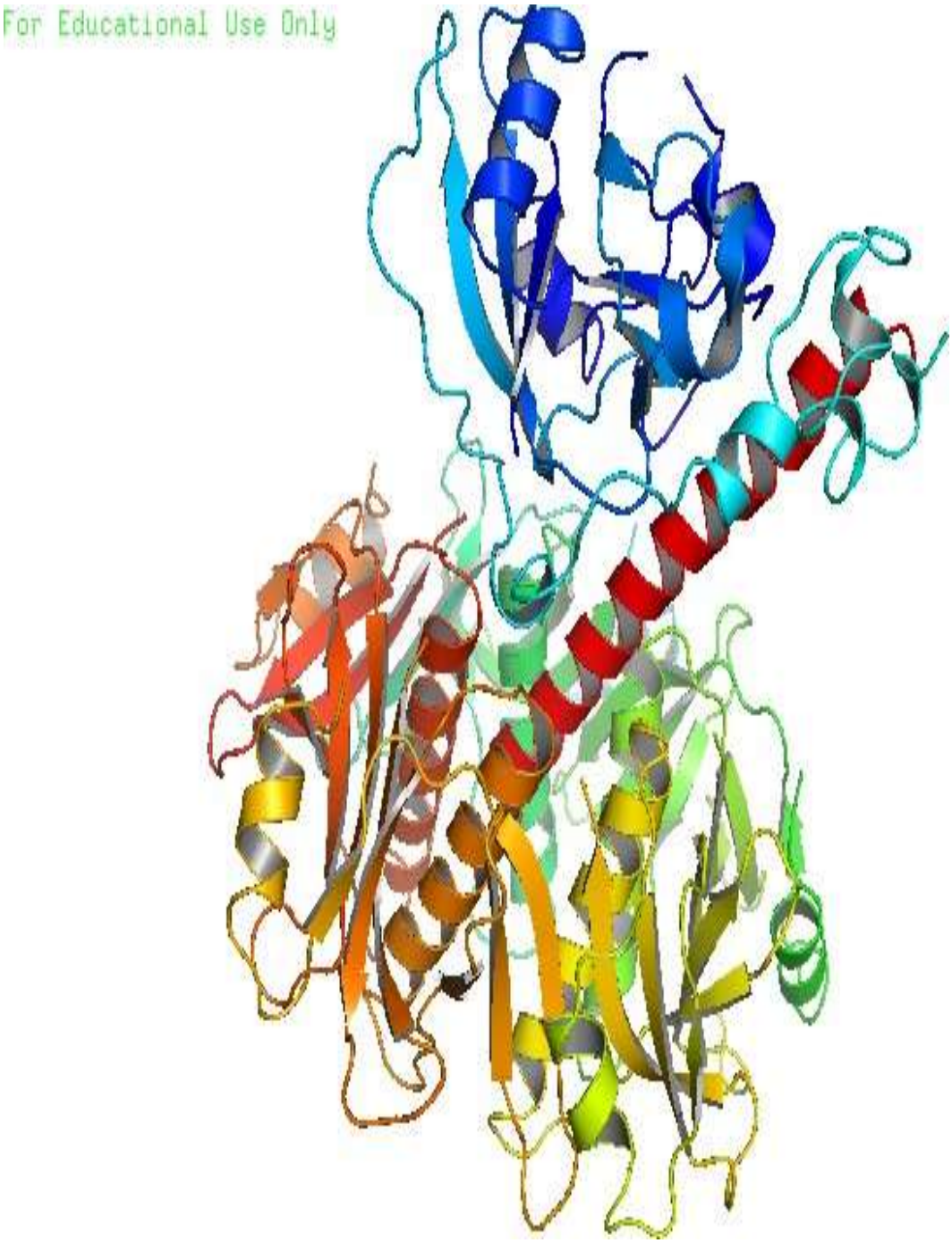
Homology modeling of Part 1+Part 2 +Part 3 of heartland virus



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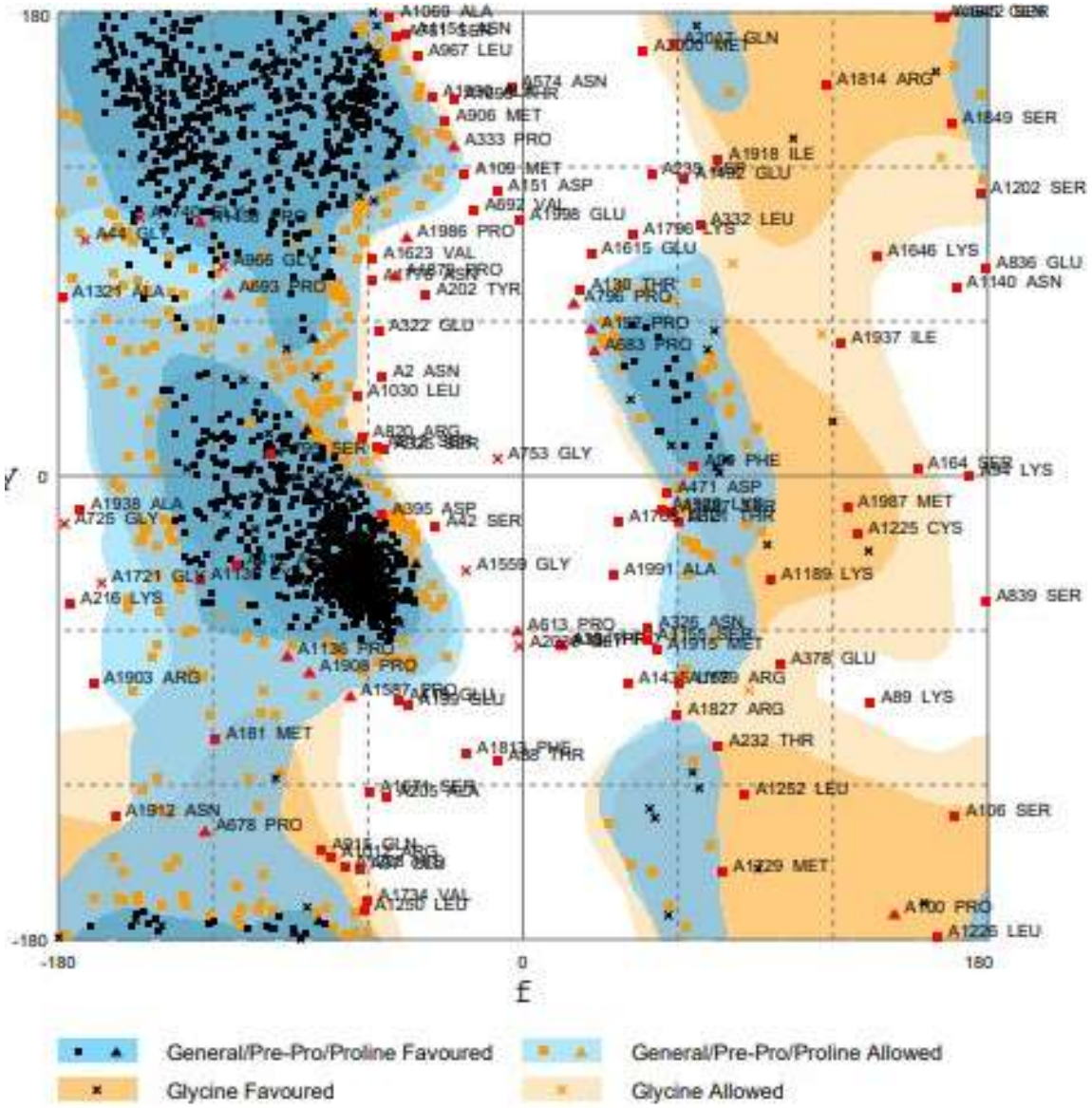

Number of residues in favoured region (~98.0% expected)	: 1661 (79.9%)
Number of residues in allowed region (~2.0% expected)	: 305 (14.7%)
Number of residues in outlier region	: 112 (5.4%)

RAMPAGE by Paul de Bakker and Simon Lovell available at http://www-cryst.bioc.cam.ac.uk/rampage/
Please cite: S.C. Lovell, I.W. Davis, W.B. Arendall III, P.I.W. de Bakker, J.M. Word, M.G. Prisant, J.S. Richardson & D.C. Richardson (2002) Structure validation by Cα geometry: ϕ/ψ and Cβ deviation. Proteins: Structure, Function & Genetics, 50: 437-455

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Rampage Ramachandran Plot of Homology full-length model of Heartland virus

Validate the Model

Ramachandran plot Assessment

The Ramachandran plot is a way to visualize backbone dihedral angles ψ against φ of amino acid residues in protein structure and identify sterically allow edregions for these angles. From the result of the Ramachandran plot, if the favored and Allow edregion is > 90% the model will be validated, which specifies that the model is appropriate for docking.

First, I will take the functional domains amino acid sequence and save those in a text file. Then we are going to do SWISS-MODELLING by uploading eachdomain sequence. After selecting the suitable template, we will choose the whole amino acid sequence of the protein and submit it to the I-TASSER server. I-TASSER will give the top 5 predicted models. Ramachandran plot analysis is done for all the models. We will select the model with the highest Favored + Allowed region. The chosen model is submitted to the Gromacs energy minimization server. Then, we write PDB files from the minimized model for selecting the sequences.

Validation Table:

		Ramachandran plot				Validation from SWISS-MODEL		
Sl.#	Name of the protein	Favored(F)	Allowed(A)	Non-Allowed	F+A (good when >>90%)	Z-score	LQE	QMEAN4
1	Part-2	86.0	10.1	3.9	96.1			
2	model-1	75.4	18.1	6.5	93.5			
3	model-2	72.8	18.4	8.8	91.2			
4	model-3	70.4	18.1	11.5	88.5			
5	model-4	67.7	20.7	11.5	88.4			
6	model-5	69.5	19.3	11.2	88.8			
7	P1+P2+P3	79.9	14.7	5.4	94.6	>-4	>1	-6.89

*P=Part
LQE=Local quality estimate

II. CONCLUSION & FUTURE WORK

Conclusion:

The L-Segment of the protein structure of the Heartland virus is a great achievement. As it has never been done before, I feel lucky to have done this work. Also, I know that the X-ray crystallography process to find the structure is so time-consuming and the labꝺ of X-ray crystallography is not sufficient. So predicting the structure by homology modeling is a good alternative way. This allows me to work on several promisingsides of Protein Molecule and Bioinformatics.

Future Direction:

With this structure, it is possible to do the molecular docking of the potential small molecules. This structure may shed light on the signaling path ways which involve other proteins in the cascade. This protein structure can be the template that makes it possible to build models for other segments of the heartland virus for further research and development.

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