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Biochemistry & Pharmacology: Open Access

ISSN: 2167-0501

Jiapu Zhang

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Molecular Dynamics (MD), Quantum Mechanics / Molecular Mechanics (QMMM), and Molecular Modeling (MM) Studies of Prion Proteins and Prions

Biochemistry & Pharmacology: Open Access
ISSN: 2167-0501

Introduction to Prions (PrPSc) and Prion Proteins (PrPC)

1. MD

2. MM

3. QM/MM

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0. Introduction to Prions and Prion Proteins

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Introduction to prion diseases (**Prions**)

Unlike conventional infectious diseases which require that a microorganism bring DNA, RNA or both into the body, prion diseases can be caused by the body's own proteins.

Prions differ from conventional infectious agents in being highly resistant to treatments that destroy the nucleic acids found in bacteria and viruses.

A prion is neither a virus, a bacteria nor any microorganism so the disease cannot be caused by the vigilance of the organism immune system and it can freely spread from one species to another species.

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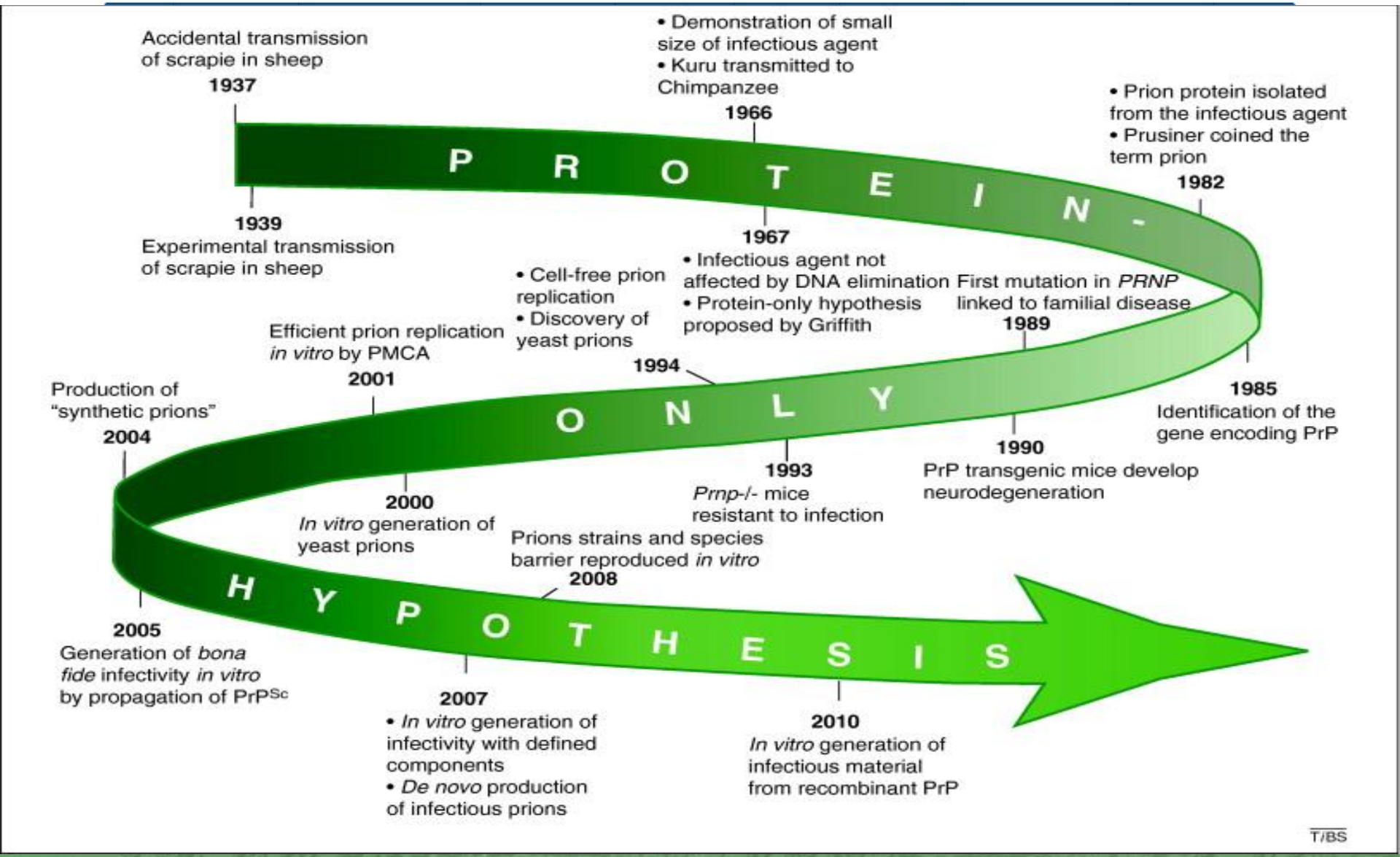

T/BS

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Cow is mad:

Deer chronic wasting disease (CWD):

Sheep goat scrapie:

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"Mad":

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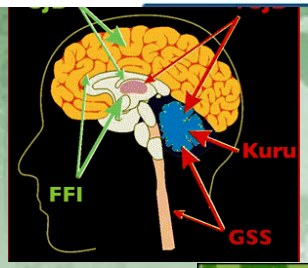
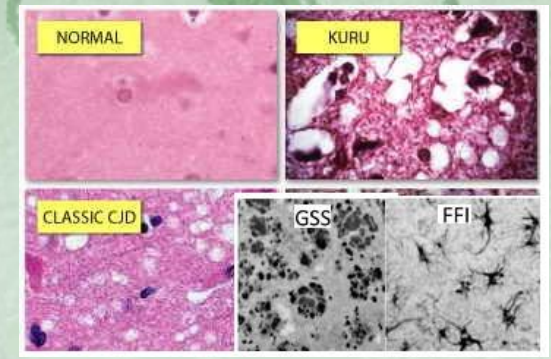
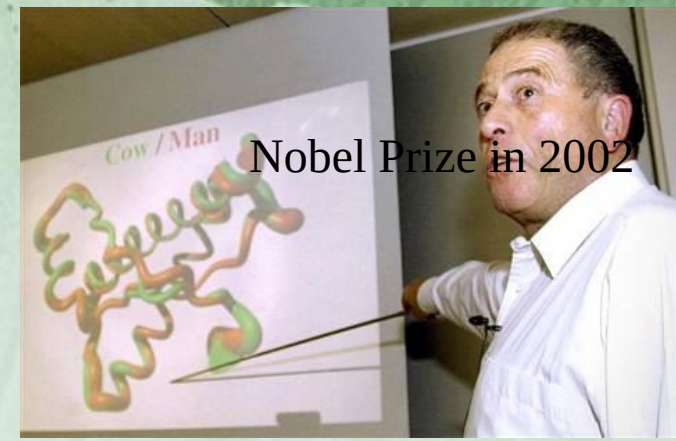


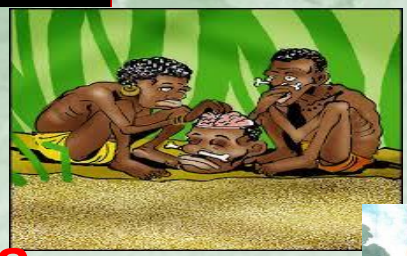
Humans:

CJD



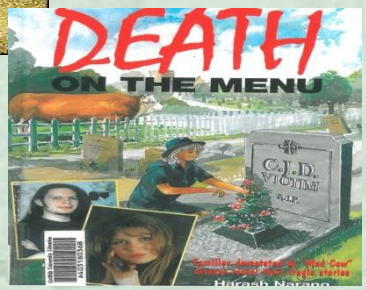


Nobel Prize in 2002

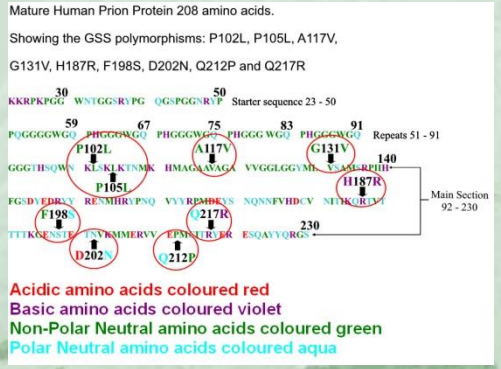


Kuru disease

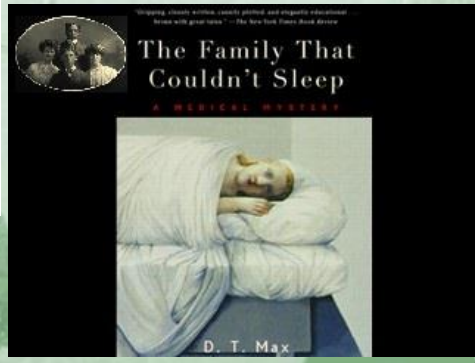
Nobel Prize in 1976

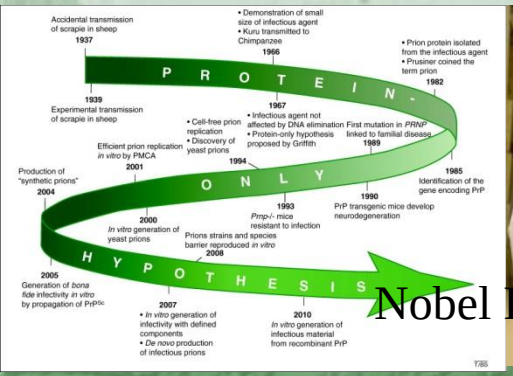


GSS



FFI





Nobel Prize in 1997

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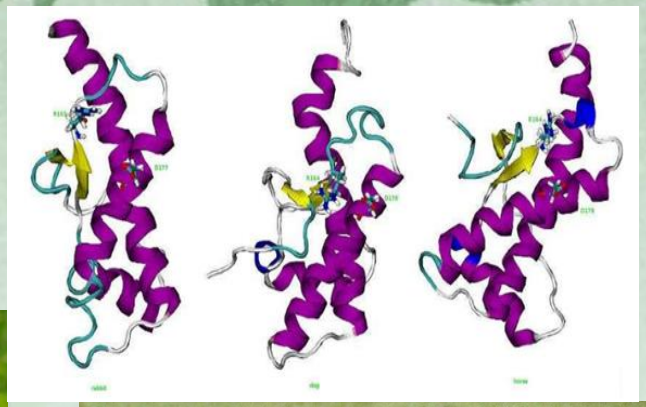
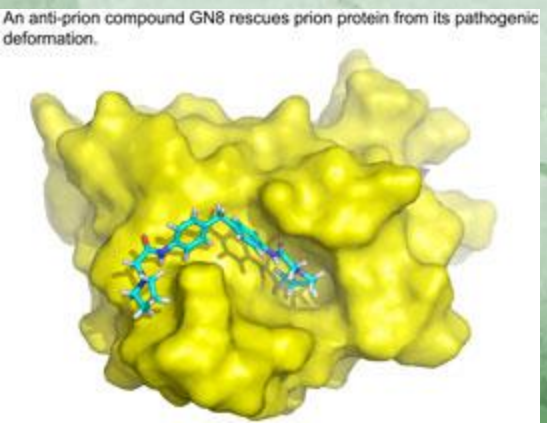
Rabbits, Dogs, and Horses are not easily "mad":





Jiapu Zhang (2011) Molecular Dynamics - Practical Application: Mechanism underlying the resistance to prion diseases in rabbits. ISBN 978-3-8465-4843-1.

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[1] Mad cows and cannibals: a guide to the transmissible spongiform encephalopathies / Charlotte A.Spencer, Pearson Prentice Hall,2004 - 38 pages
[2] Mad cow disease: the history of BSE in Britain - "Dead-end host?"/ Richard W.Lacey, Cypsela,1994 - 200 pages

[3] Deadly feasts : tracking the secrets of a terrifying new plague / Richard Rhodes, Simon & Schuster,1997 - 259 pages

[4] Deadly feasts: the "prion" controversy and the public's health / Richard Rhodes, Touchstone Books,1998 - 278 pages
[5] Death on the menu: CJD victims - diagnosis and cure : families devastated by "mad cow" disease reve / Narang, Harash, Newcastle upon Tyne: H.H.,1997 - 266 pages
[6] The trembling mountain : a personal account of kuru, cannibals, and mad cow disease / Robert Klitzma, Plenum Trade,1998 - 333 pages (free download at website: **ishare.iask.sina.com.cn/f/36888814.html**)
[7] Mad Cow U.S.A. - Could the Nightmare Happen Here? / Sheldon Rampton & John Stauber, Common Courage Press, 1997 (free download at website: **http://healthcoalition.ca/archive/mcusa.pdf**)

[8] Brian Trust: The Hidden Connections Between Mad Cow and Misdiagosed Alzheimer's Disease / Colm A. Kelleher, 2004 - 312 pages

[9] How the Cow Turned Mad: Unlocking the Mysteries of Mad Cow Disease / Maxime Schwartz, University of California Press, 2004 - 238 pages
[10] The Pathological Protein: Mad Cow, Chronic Wasting, and Other Deadly Prion Diseases / Philip Yam, Copernicus Books, 2003 - 284 pages (free download at website: **http://ishare.iask.sina.com.cn/f/33613529.html**)

[11] The Social Construction of Disease: From Scrapie to Prion / Kiheung Kim, Routledge Taylor & Francis Group, 2007 - 253 pages
[12] Fatal Flaws - How a Misfolded Protein Baffled Scientists and Changed the Way We Look at the Brain, Jay Ingram, Harper Collins Publishers Ltd, 2012 - 260 pages

[13] Mad Cow Disease - The Risks for Humans, Jean-Philippe Deslys & André Picot, Flammarion, 2001 - 125 pages free download at website: **www.neuroprion.org/resources/pdf_docs/documentation/madcow_deslys.pdf**

[14] Infectious Process, Knowledge, Discourse and the Politics of Prions, Eve Seguin (ed), Palgrave macmillan, 2004 - 191 pages

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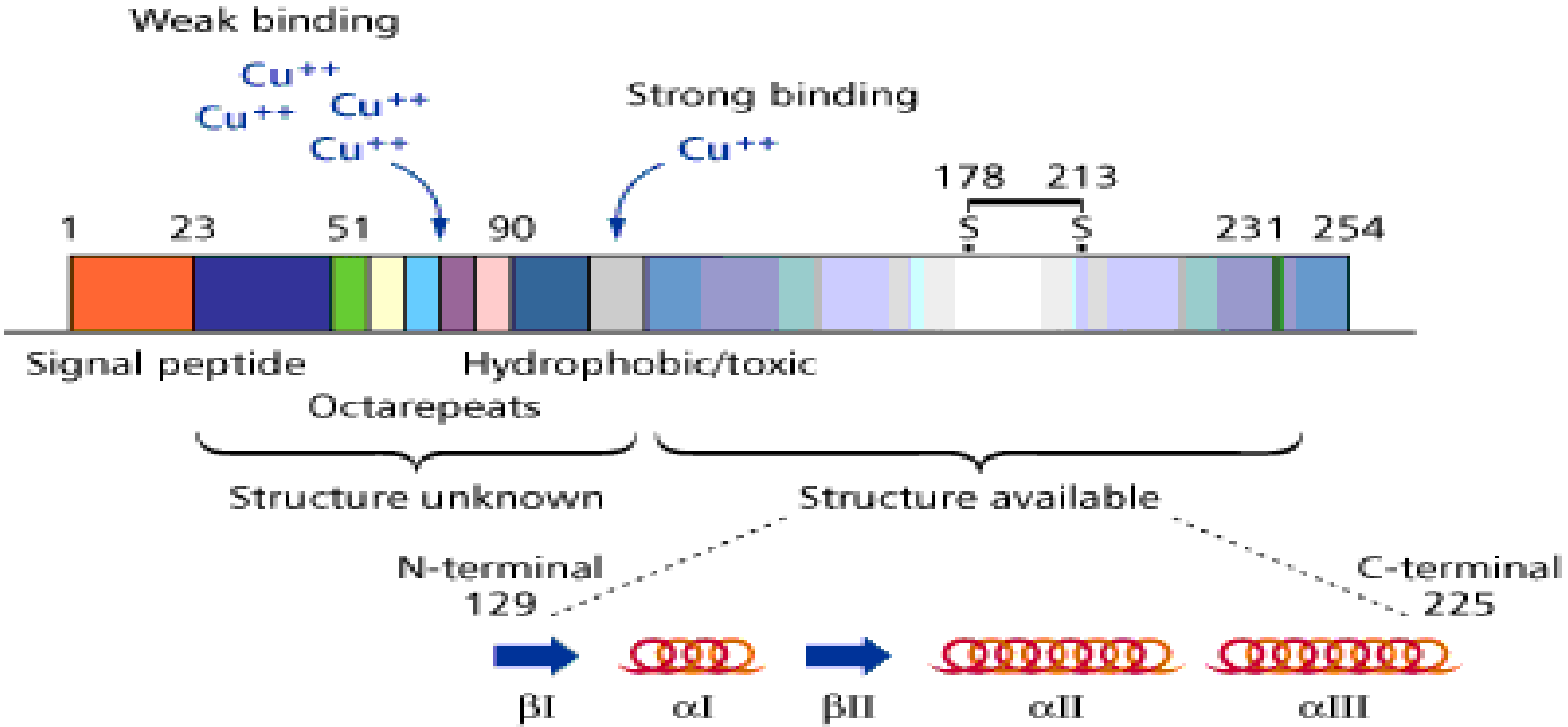

Structured region we use MD, unstructured region we use MM, and the cooper bindings we use QM/MM.

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1. MD (Molecular Dynamics)

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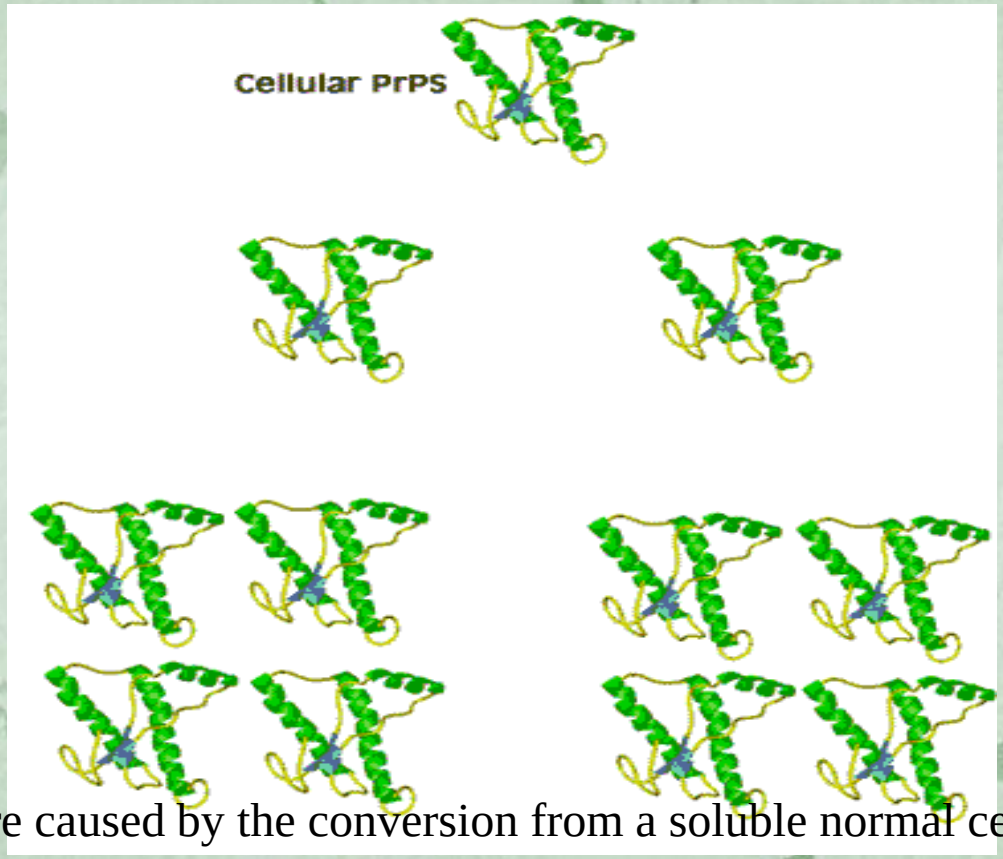
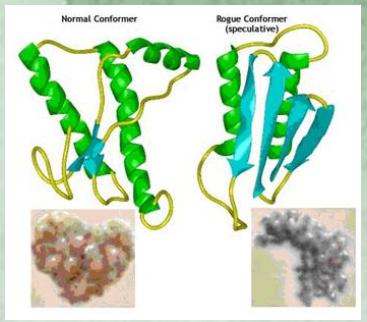
Prion:





Prion diseases are caused by the conversion from a soluble normal cellular prion protein (PrPC) into insoluble abnormally folded infectious prions (PrPSc) and the conversion of PrPC→PrPSc is believed to involve conformational change from a predominantly α-helical protein to one rich in β-sheet structure.

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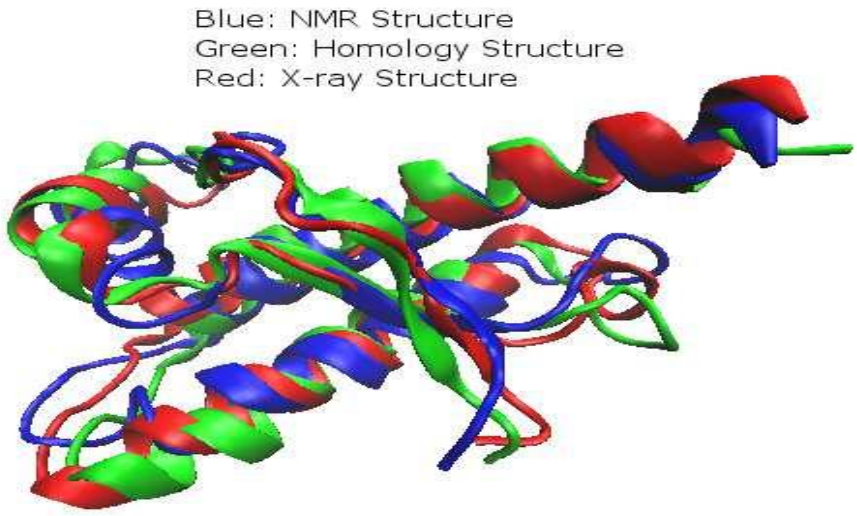
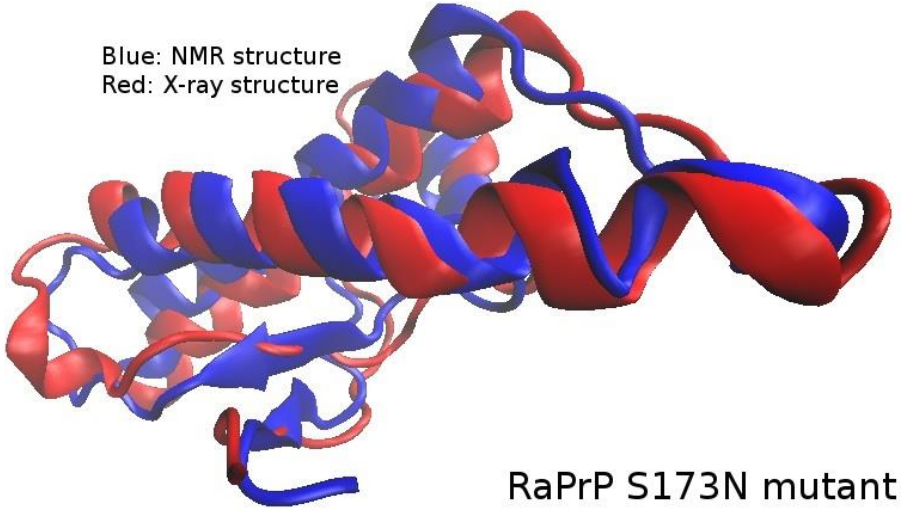
Molecular structures of RaPrP:



Rabbit PrP



RaPrP S173N mutant

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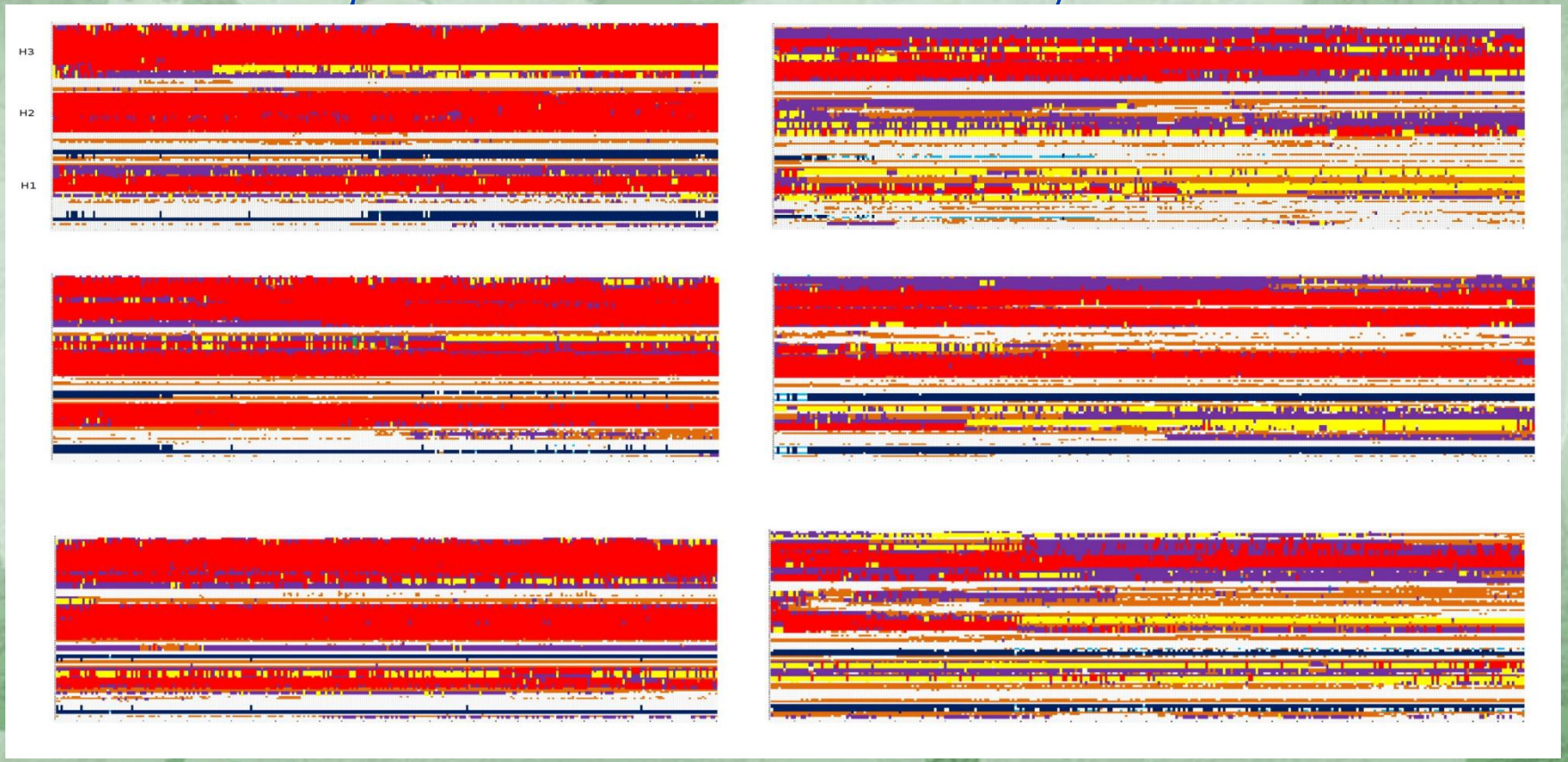
The Dynamics of molecular structures of RaPrP (at 300 K):

predominant in α-helices → rich in β-sheet



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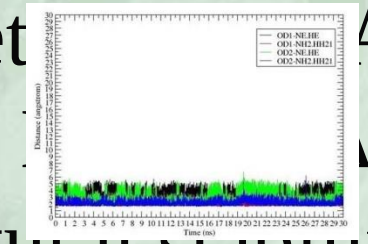
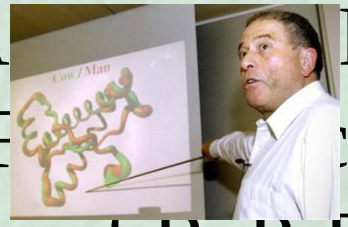
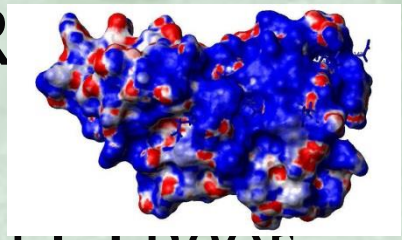
My proposed reasons for the "structural conformational" changes of PrPC→PrPSc:

• The salt bridge net A R ASP177–ARG163, AR) greatly to the structural stability of RaPrP [J Theor Biol 342(1) 70-82].







• Surface electrostatic charge distributions contribute greatly to the structural stability of RaPrP [Bioinformatics Research: New Developments,

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Amber computer codes (http://ambermd.org/tutorials/advanced/tutorial8):

Minimization with Cartesian restraints for the solute

```
 &cntrl
 imin=1, maxcyc=200,
 ntpr=5,
 ntr=1,
 &end
Group input for restrained atoms
100.0
RES 1 155
END
END
```

Minimization of the entire molecular system

```
 &cntrl
 imin=1, maxcyc=200,
 ntpr=5,
 &end
```


Before we start a MD simulation, we need to remove bad contacts. The reason is that if we start the molecular dynamics with

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Heating up the system equilibration stage 1

&cntrl

nstlim=5000, dt=0.002, ntx=1, irest=0, ntpr=500, ntwr=5000, ntwx=5000,

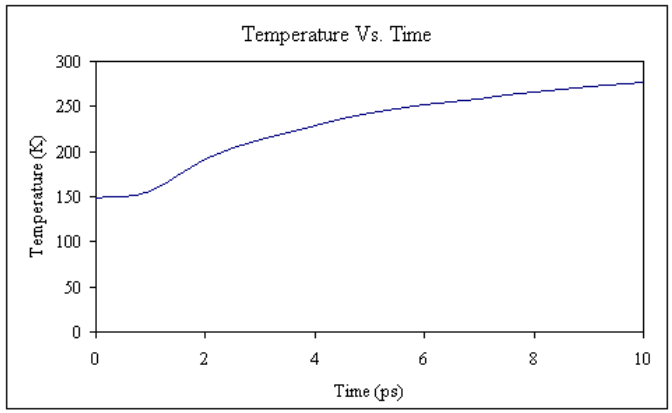
tempi =100.0, temp0=300.0, ntt=1, tautp=2.0, ig=209858,

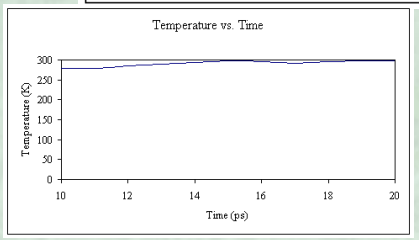
ntb=1, ntp=0, //constant volume

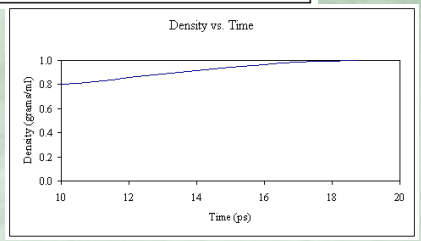
ntc=2, ntf=2,

nrespa=2,

&end







Constant pressure constant temperature equilibration stage 2 & 3 & 4 & 5

&cntrl

nstlim=5000, dt=0.002, ntx=5, irest=1, ntpr=500, ntwr=5000, ntwx=5000,

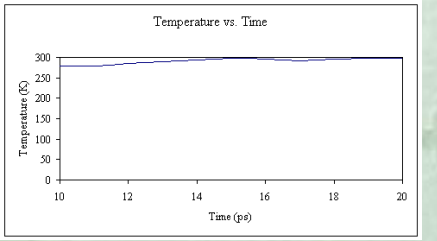
temp0=300.0

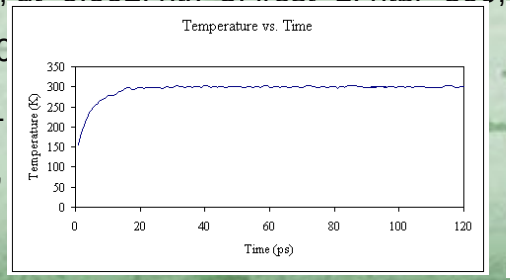
ntb=2, ntp=1

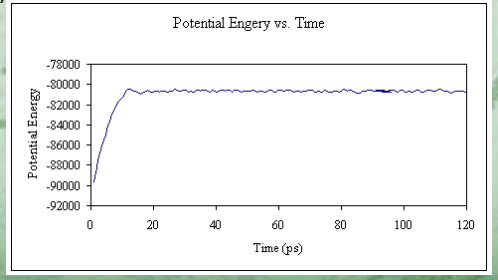
ntc=2, ntf=2,

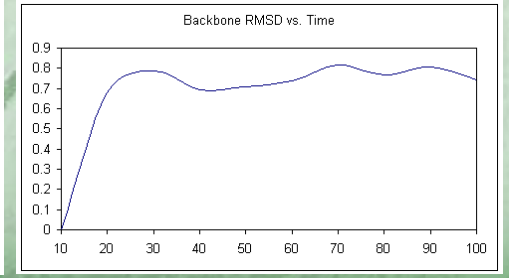
nrespa=1,

&end









Go to Production phase.

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2. MM (Molecular Modeling)

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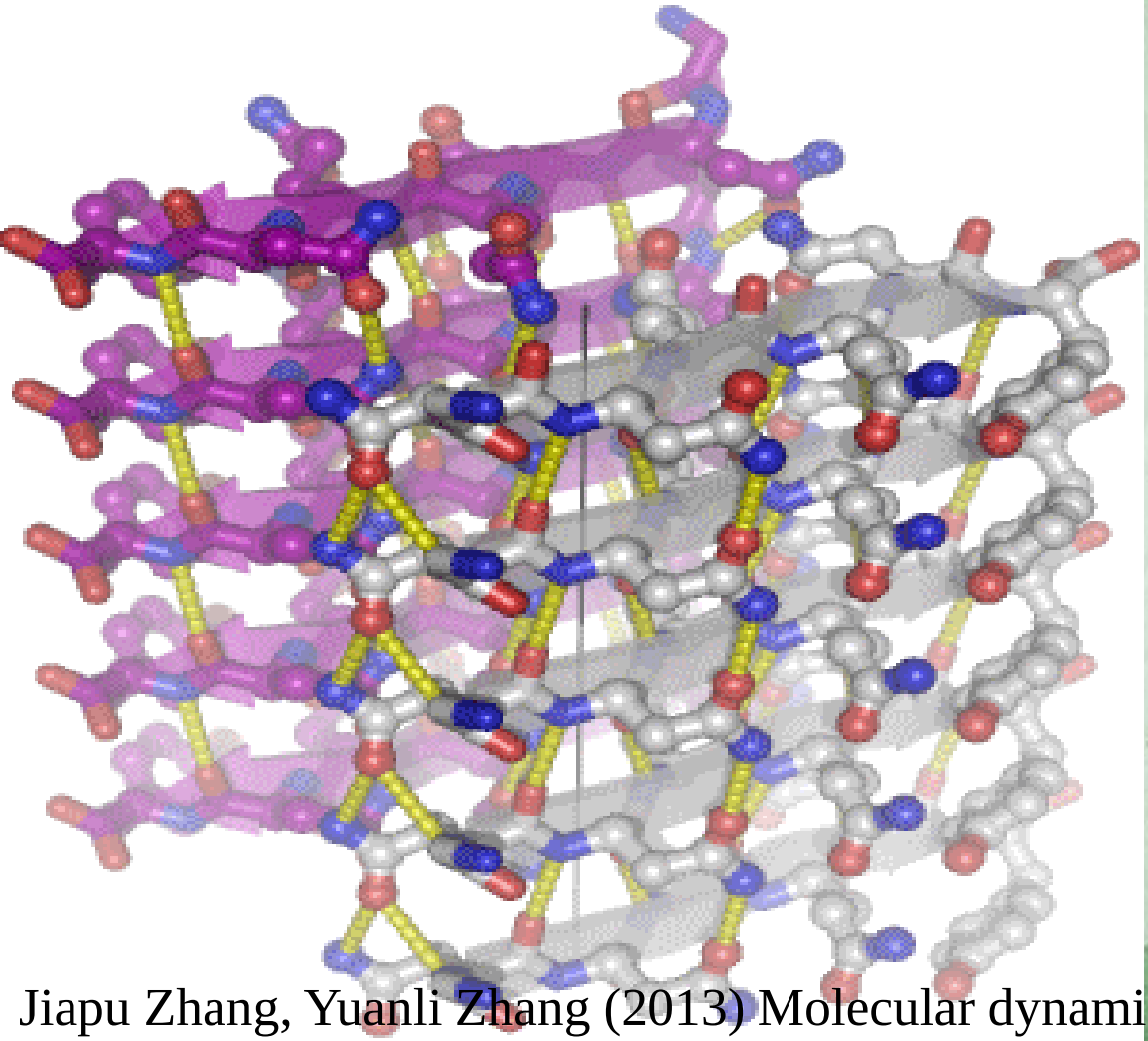

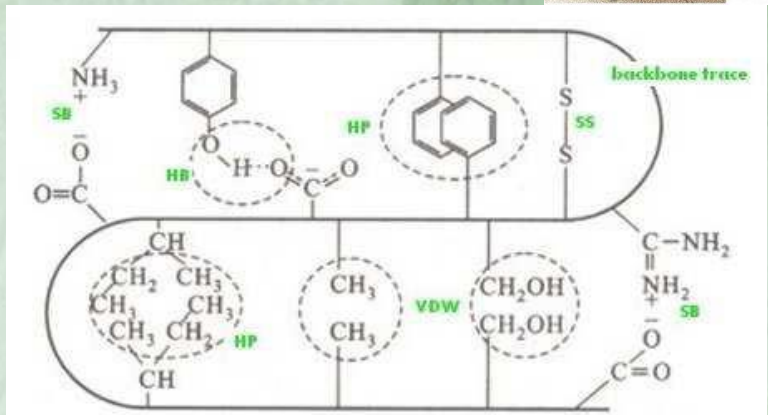

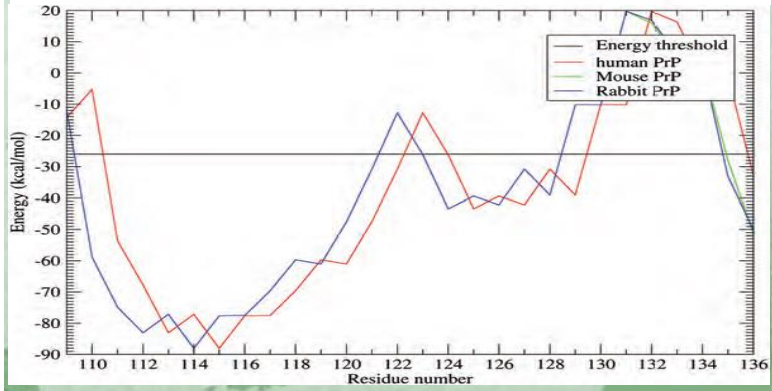

Jiapu Zhang, Yuanli Zhang (2013) Molecular dynamics studies on 3D structures of the hydrophobic region PrP(109-136). Acta Biochim Biophys Sin 45(6) 509–519.

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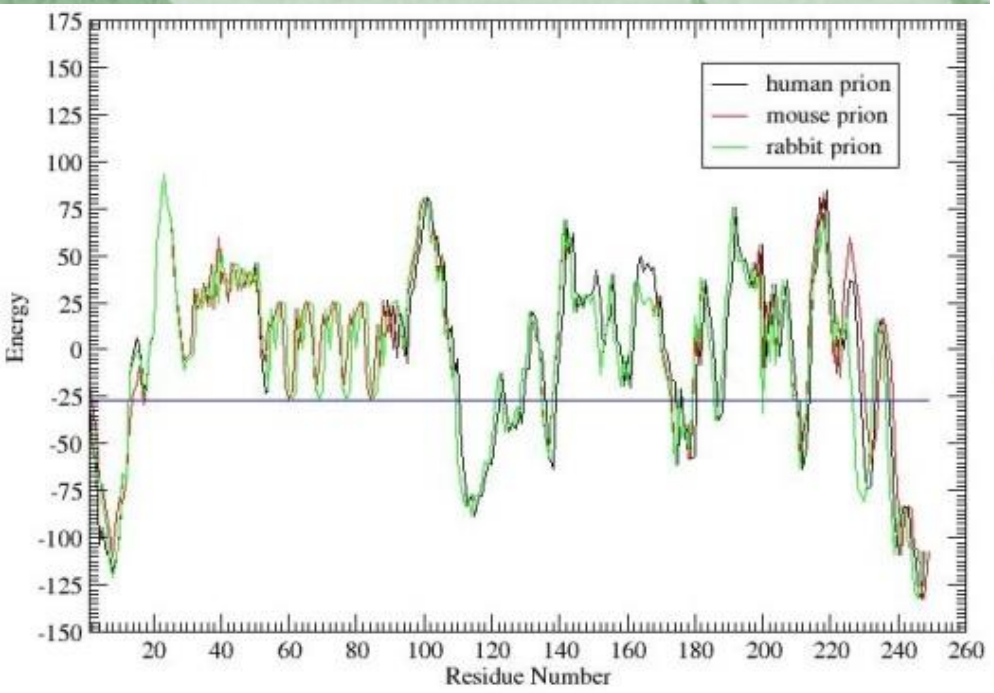

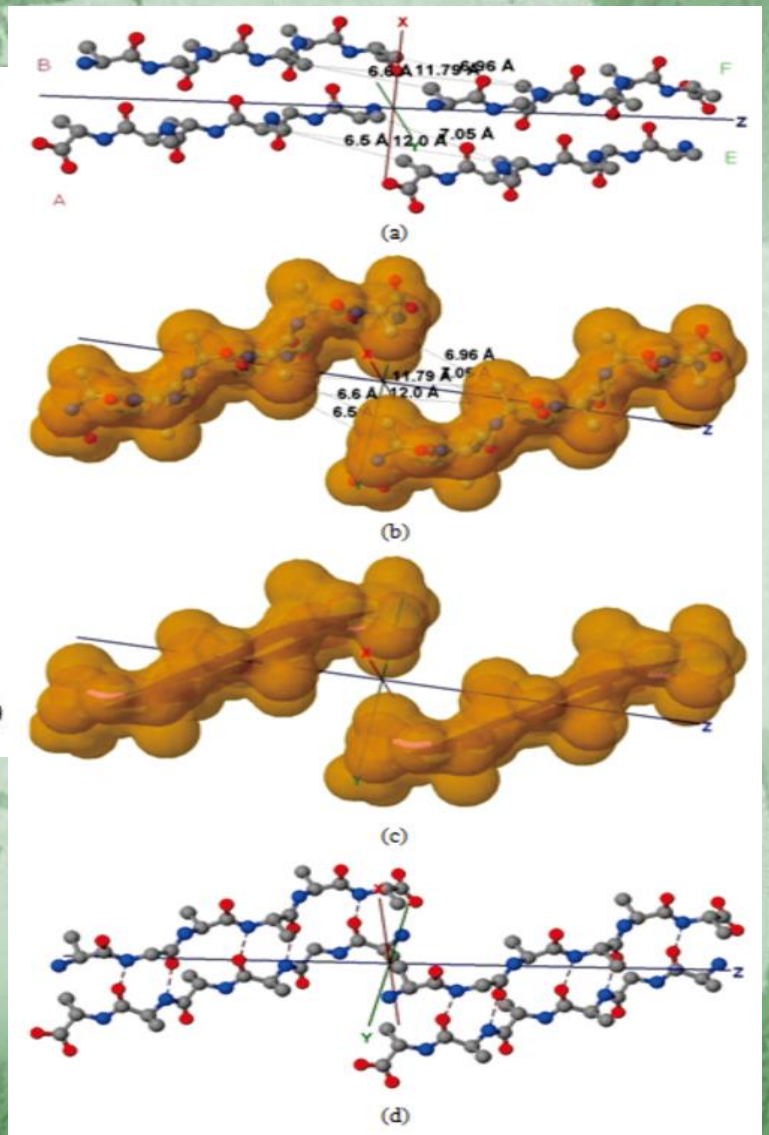

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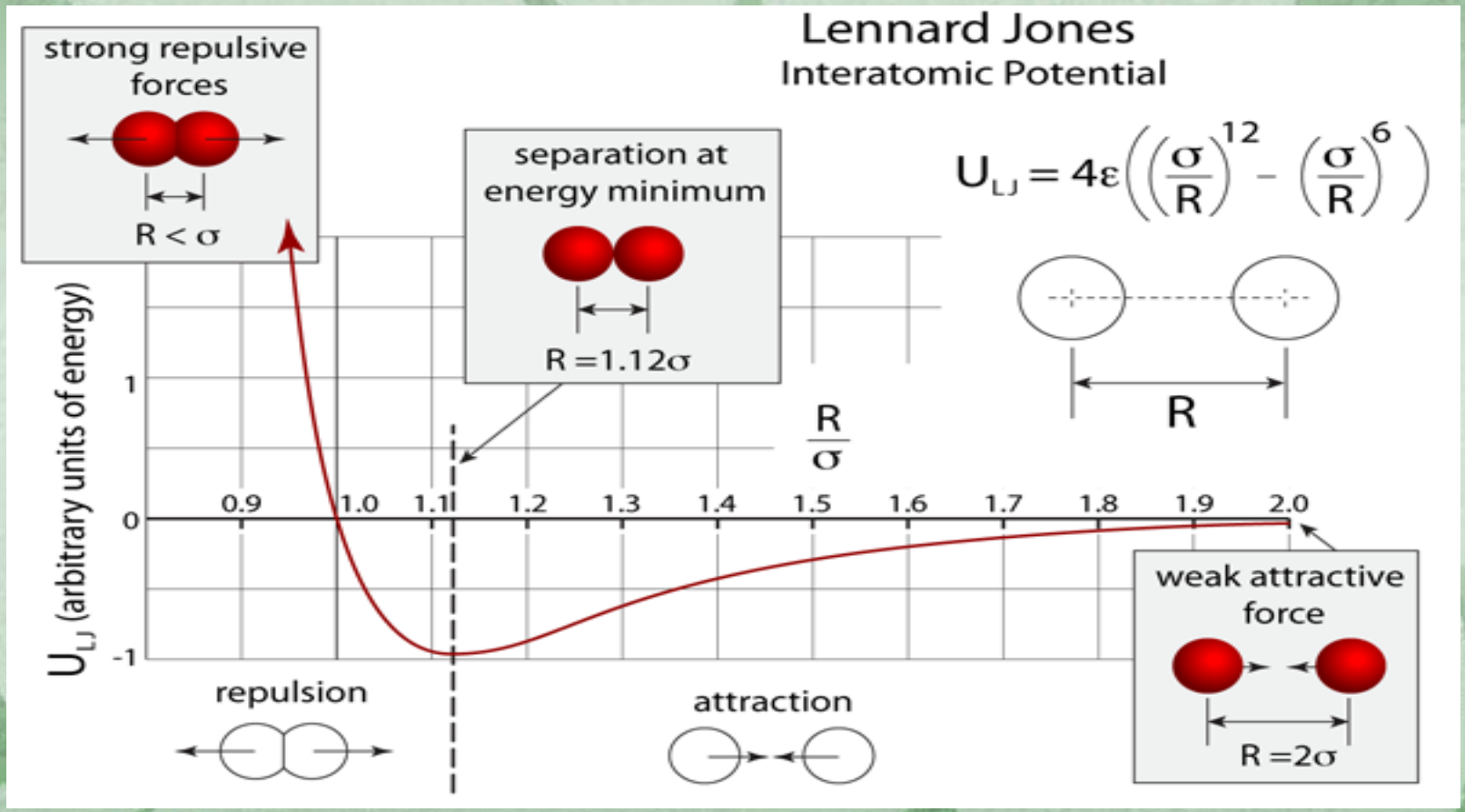
Lennard-Jones function



Jiapu Zhang, Jie Sun, Changzhi Wu (2011) Optimal atomic-resolution structures of prion AGAAAAGA amyloid fibrils. J Theor Biol 279(1) 17–28.

Jiapu Zhang, Yating Hou, Yiju Wang, Changyu Wang and Xiangsun Zhang (2012) The LBFGS quasi-Newtonian method for molecular modeling prion AGAAAAGA amyloid fibril, Natural Science 4(12A) (Issue: Bioinformatics, Proteomics, Systems Biology and Their Impacts to Biomedicine) 1097-1108.

Jiapu Zhang, David Y Gao, John Yearwood (2011) A novel canonical dual computational approach for prion AGAAAAGA amyloid fibril molecular modelling. J Theor Biol 284 (1) 149-157.

Jiapu Zhang (2011) Optimal molecular structures of prion AGAAAAGA palindrome amyloid fibrils formatted by simulated annealing. J Mol Model 17 (1) 173-179.

Jiapu Zhang (2011) Practical global optimization computing methods in molecular modeling – for atomic-resolution structures of amyloid fibrils. ISBN 978-3-8465-2139-7.

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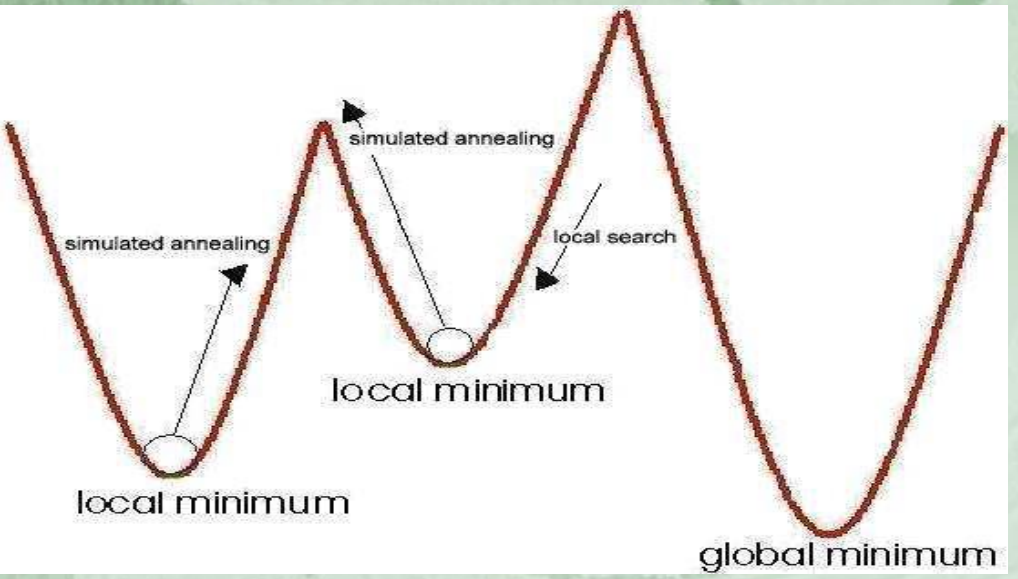

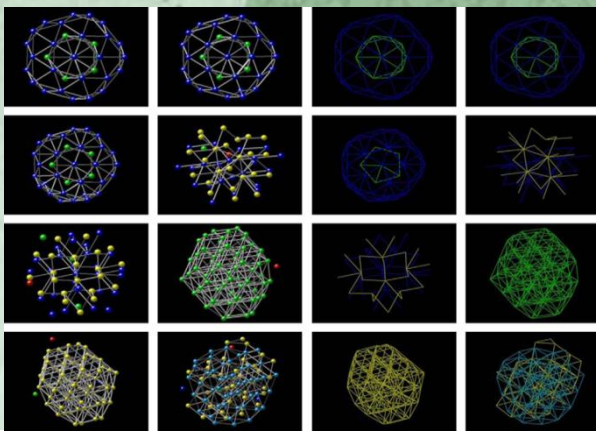

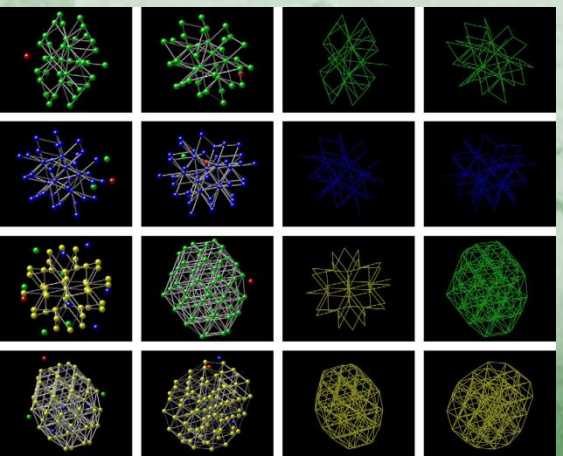

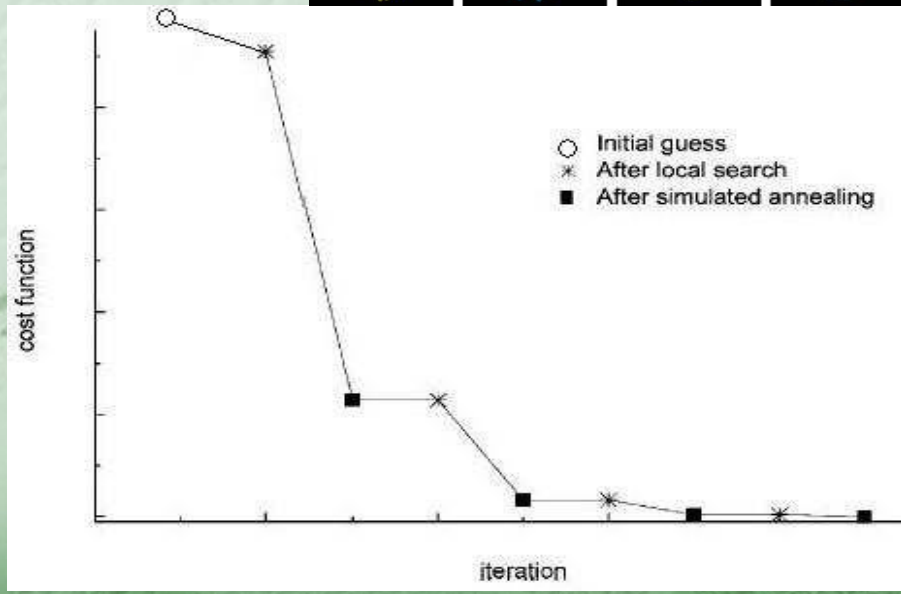

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"In a (macro) molecular system, if it is very far from equilibrium, then the forces may be excessively large, a robust energy minimization (EM) is required; another reason to perform an EM is the removal of all kinetic energy from the system: EM reduces the thermal noise in the structures and potential energies [20]. EM, with the images at the endpoints fixed in space, of the total system energy provides a minimum energy path. EM can be done using steepest descent (SD), conjugate gradient (CG), and Limited-memory Broyden Fletcher Goldfarb Shanno (LBFGS) methods."

"SD local search method converges fast [21]. SD is robust and easy to implement but it is not most efficient especially when closer to minimum; at this moment, we may use the efficient CG. CG is slower than SD in the early stages but more efficient when closer to minimum. The hybrid of SD-CG will make SD or CG more efficient than SD or CG alone. However, CG cannot be used to find the EM path, for example, when "forces are truncated according to the tangent direction, making it impossible to define a Lagrangian" [22,23]. In this case, the powerful and faster quasi-Newtonian method (e.g. the LBFGS quasi-Newtonian minimiser) can be used [22,24-28]. The relaxation is done in the use of local search LBFGS Quasi-Newton method (lbfgs_memory_depth = 3) within AMBER 11 [23]."

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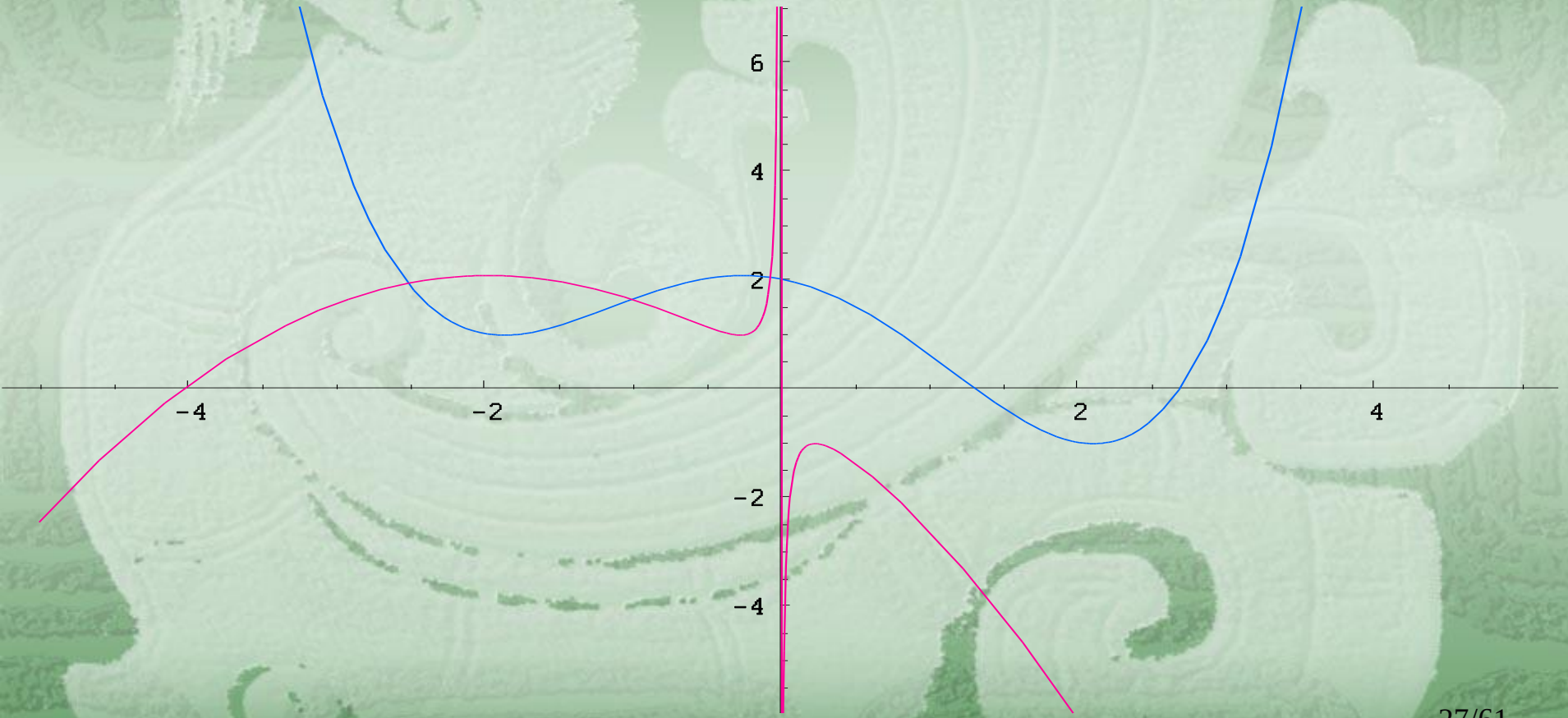

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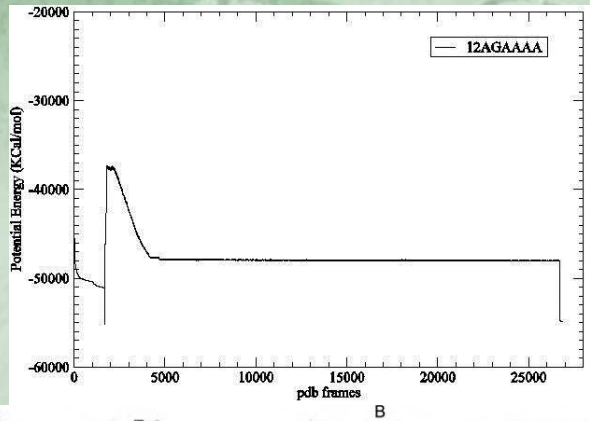
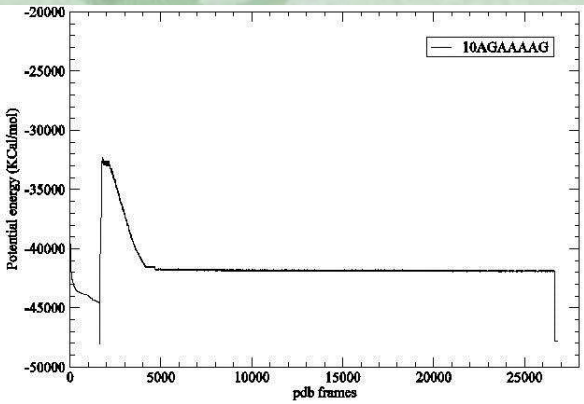
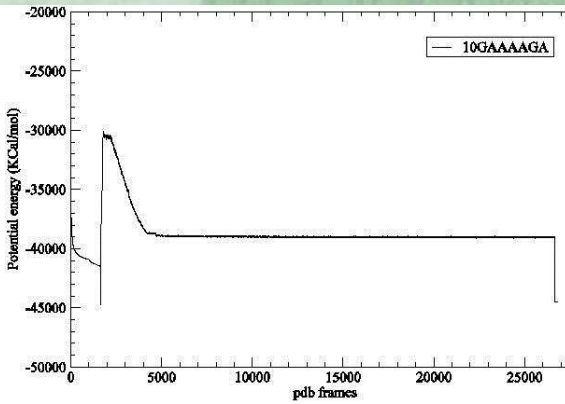
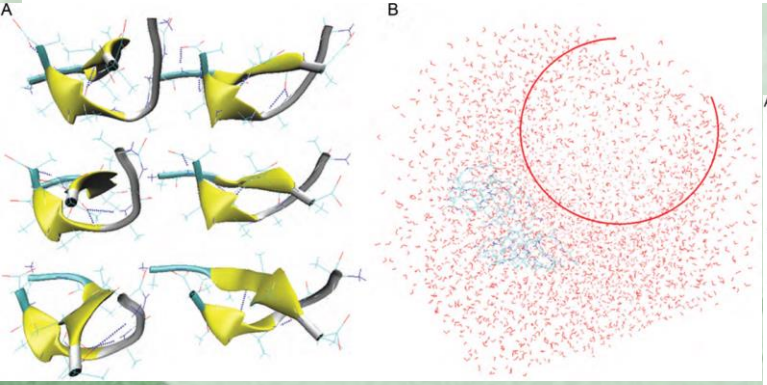
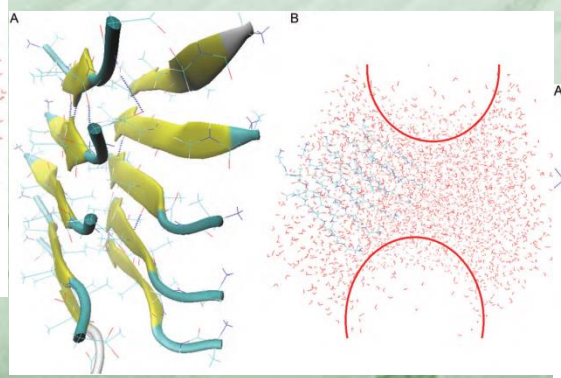
Jiapu Zhang (2011) Optimal molecular structures of prion AGAAAAGA palindrome amyloid fibrils formatted by simulated annealing. J Mol Model 17 (1) 173-179.

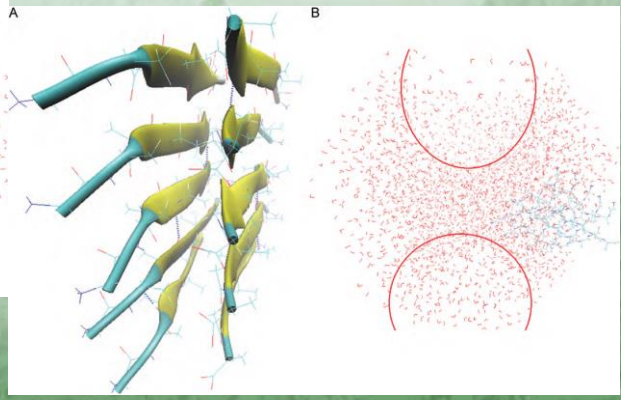












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3. QM/MM (Quantum Mechanics / Molecular Mechanics)

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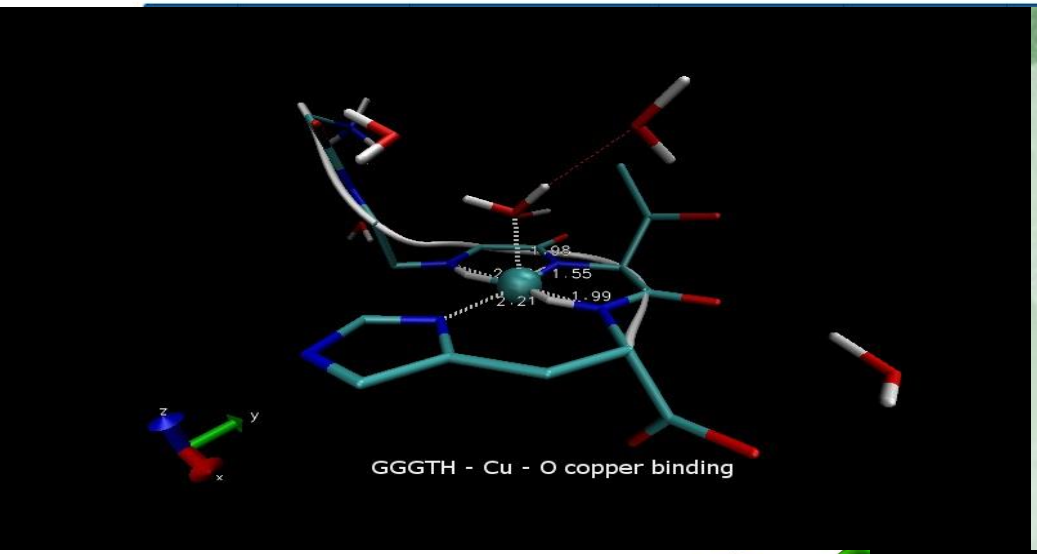

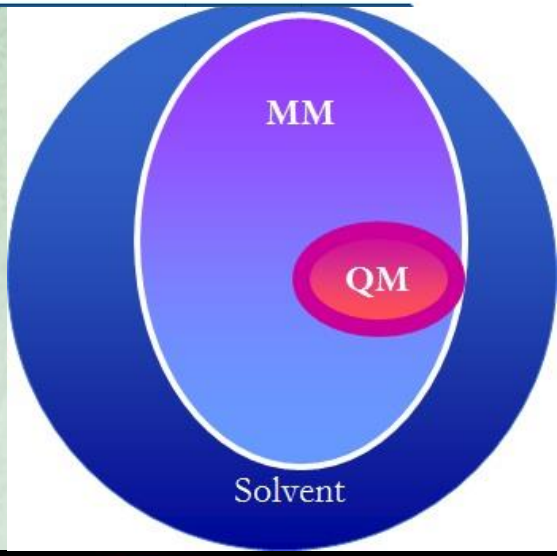

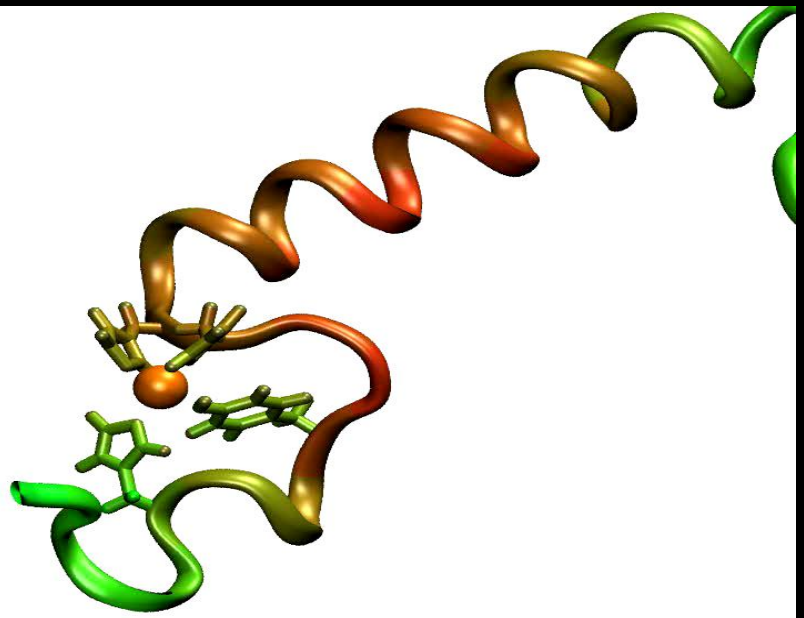

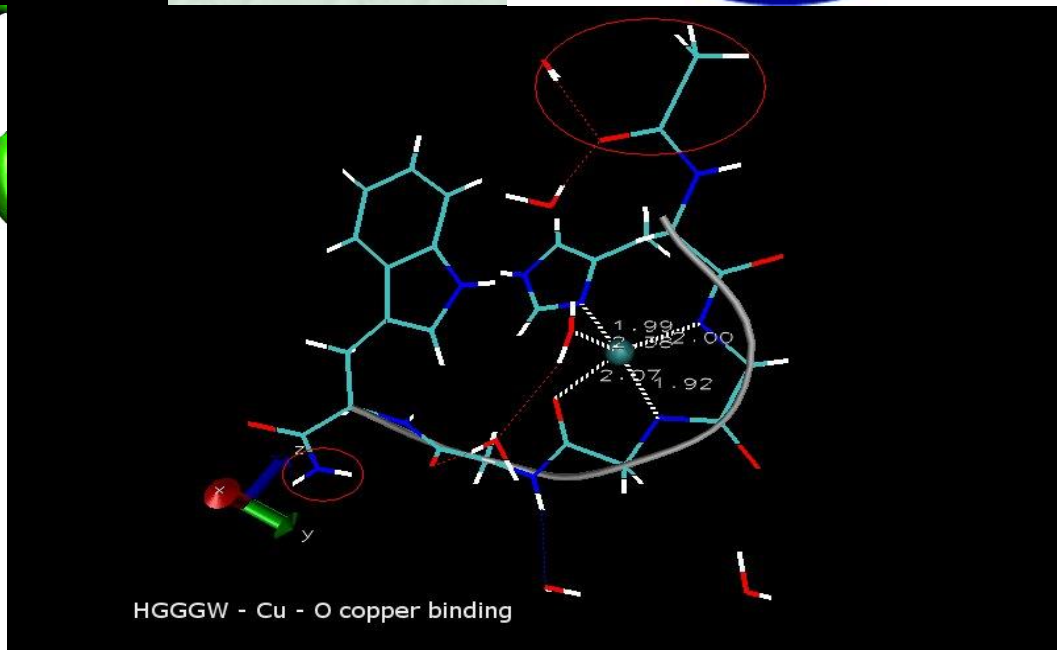

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Amber computer codes (http://ambermd.org/tutorials/advanced/tutorial1_adv):

plc.frcmod:

```
#  modifications to force field for poplar plastocyanin
MASS
SM 32.06
CU 65.36

BOND
NB-CU  70.000   2.05000 #kludge by JRS
CU-S    70.000   2.10000 #kludge by JRS
CU-SM 70.000   2.90000 #for pcy
CT-SM 222.000 1.81000 #met(aa)

ANGLE
CU-NB-CV   50.000     126.700  #JRS estimate
CU-NB-CR   50.000     126.700  #JRS estimate
CU-NB-CP   50.000     126.700  #JRS estimate
CU-NB-CC   50.000     126.700  #JRS estimate
CU-SM-CT   50.000     120.000  #JRS estimate
CU-S -CT     50.000     120.000  #JRS estimate
CU-S -C2     50.000     120.000  #JRS estimate
CU-S -C3     50.000     120.000  #JRS estimate
```

NB-CU-NB 10.000 110.000 #dac estimate

NB-CU-SM 10.000 110.000 #dac estimate

NB-CU-S 10.000 110.000 #dac estimate

SM-CU-S 10.000 110.000 #dac estimate

CU-SM-CT 50.000 120.000 #JRS estimate

CT-CT-SM 50.000 114.700 #met(aa)

HC-CT-SM 35.000 109.500

H1-CT-SM 35.000 109.500

CT-SM-CT 62.000 98.900 #MET(OL)

DIHE

X -NB-CU-X 1 0.000 180.000 3.000

X -CU-SM-X 1 0.000 180.000 3.000

X -CU-S -X 1 0.000 180.000 3.000

X -CT-SM-X 3 1.000 0.000 3.000

NONBON

CU 2.20 0.200

SM 2.00 0.200

$AMBERHOME/exe/xleap -s -f $AMBERHOME/dat/leap/cmd/leaprc.ff99

> loadamberparams plc.frcmod

> loadoff 1PLC.lib

> saveamberparm 1PLC 1PLC.prmtop 1PLC.inpcrd

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Amber computer codes (http://ambermd.org/tutorials/advanced/tutorial2/section3.htm):

Initial min of our structure QMMM

```
 &cntrl
  imin=1, maxcyc=500, ncyc=200,
  cut=8.0, ntb=1, ntc=2, ntf=2,

  ifqnt=1 //This is the flag that tells sander that we want a QMMM run. It will then look for a &qmmm namelist.
 /
 &qmmm
  qmmask=':1-2', //This specifies what (residues) to treat quantum mechanically using standard AMBER mask notation.
  qmcharge=0, //The integer charge of the QM region (default = 0)
  qmtheory=1, //Use the PM3 Hamiltonian (default = 1)
  qmshake=1, //Shake QM hydrogen atoms (default = 1 if ntc=2)
  qm_ewald=1, //Use an Ewald type treatment for long range electrostatics (default = 1 if ntb>0)
  qm_pme=1 //Use an Particle Mesh Ewald method as Ewald type (default = 1 if qm_ewald=1 and use_pme=1)
 /
```

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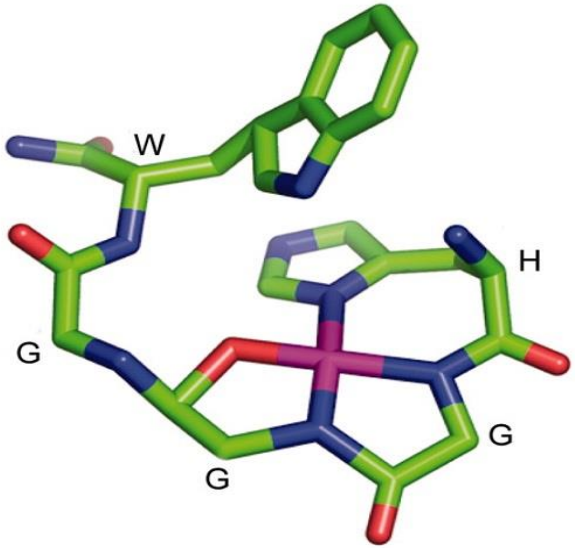
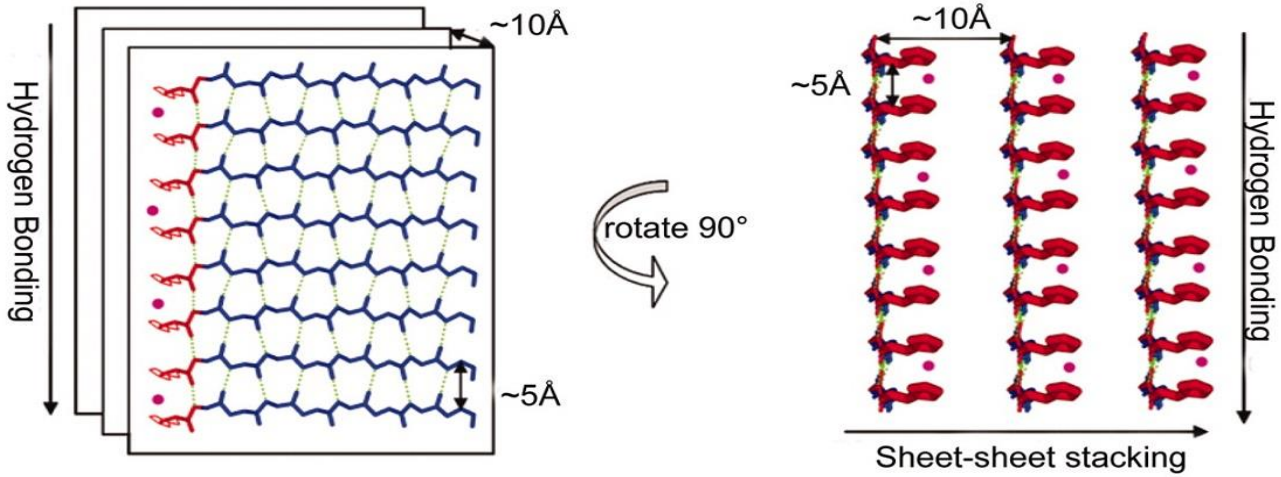
300K constant temp QMMM MD

```
&cntrl
 imin=0, ntb=1
 cut=8.0, ntc=2, ntf=2,
 tempi=300.0, temp0=300.0,
 ntt=3, gamma_ln=1.0,
 nstlim=1000, dt=0.002,
 ntpr=1, ntwx=1,ifqnt=1
/
&qmmm
 qmmask=':1-2',
 qmcharge=0,
 qmtheory=1,
 qmshake=1,
 qm_ewald=1, qm_pme=1
/
```





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All the pictures of this presentation were gotten from Google internet search.

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