Part II - Applications of MultiSeq: Network Analysis of Dynamical Recognition in RNA:Protein Complexes

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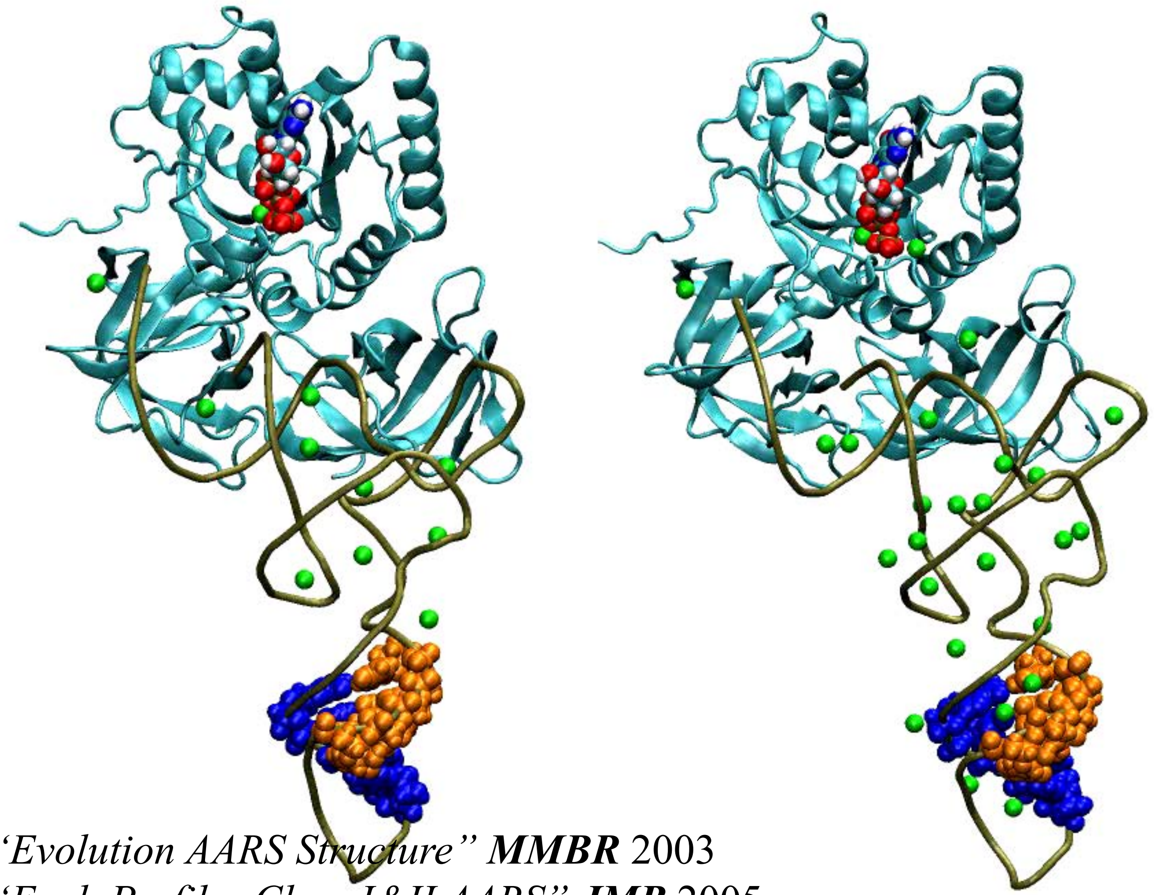
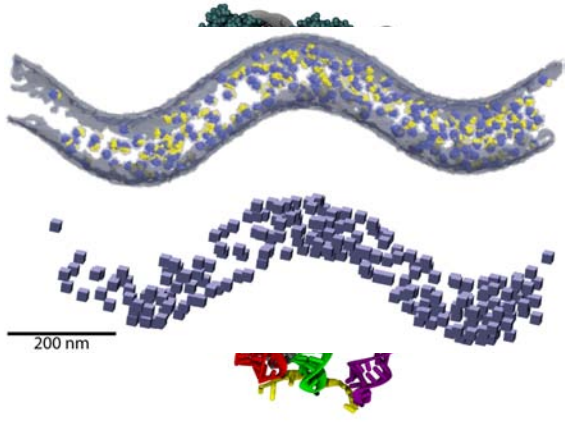
Protein:RNA Complexes in Translation

Evolutionary Analysis & Dynamics





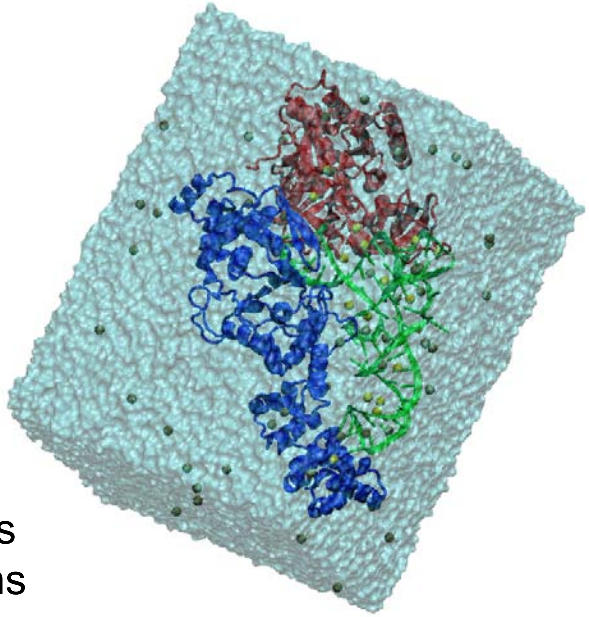
r-Proteins/r-RNA
Ribosome LSU

“Signatures ribosomal evolution”
PNAS 2008, ***BMC*** 2009, ***BJ*** 2010
“Motion L1 Stalk:tRNA” ***JMB*** 2010**,**
“Ribosome Biogenesis” ***JPC*** 2012,3
“Whole cell simulations on GPUs“
IEEE 2009,***Plos CB*** 2011,***PRL***2011,
JCC 2013**,** ***PNAS*** 2013,
PRL 2013**,** ***CSB*** 2013
Nature *2014,* ***BJ*** 2015

“Evolution AARS Structure” ***MMBR*** 2003
“Evol. Profiles Class I&II AARS” ***JMB*** 2005
“Evolution SepRS/CysRS” ***PNAS*** *2005*
“Dynamic Signaling Network” ***PNAS*** 2009
“Exit Strategy Charged tRNA” ***JMB*** 2010
“Mistransl. in Mycoplasma” ***PNAS*** 2011
*“Capture & Selection of ATP”****JACS*** 2013

“ Recognition & tRNA Dynamics”
JMB 2008,***FEBS*** 2010, ***RNA*** 2012
Network Viewer, ***Bioinf., JCTC*** 2012

MD Simulations of RNA:Proteins Complexes[1]



MD performed with NAMD2 (2) - System Setup

Simulation Parameters

Minimization: 290,000 steps
Production run: 108 ns
Forcefields: CHARMM27 (3), AMBER (4)
Time step: 1 fs
VdW frequency: 2 fs
VdW cutoff: 12 Å
Switching distance: 10 Å
Pair list distance: 14 Å
Particle Mesh Ewald
Full electrostatic update: 4 fs
Ensemble: NPT
Langevin temperature: 298.15 K
Langevin pressure: 1 atm
Periodic boundary conditions

Contents of System(5)

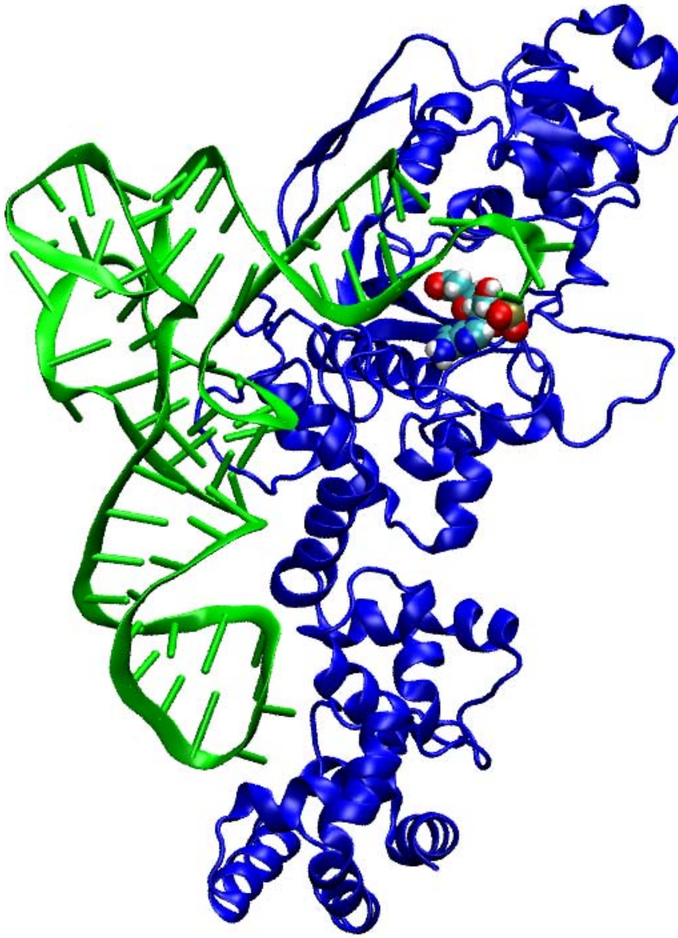
GluRS
Glu-tRNA^{Glu}
EF-Tu
GTP
Ions: Mg^{2+}, K^+
H_2O: ~27,000 molecules
System: ~130,000 atoms

System Perturbations

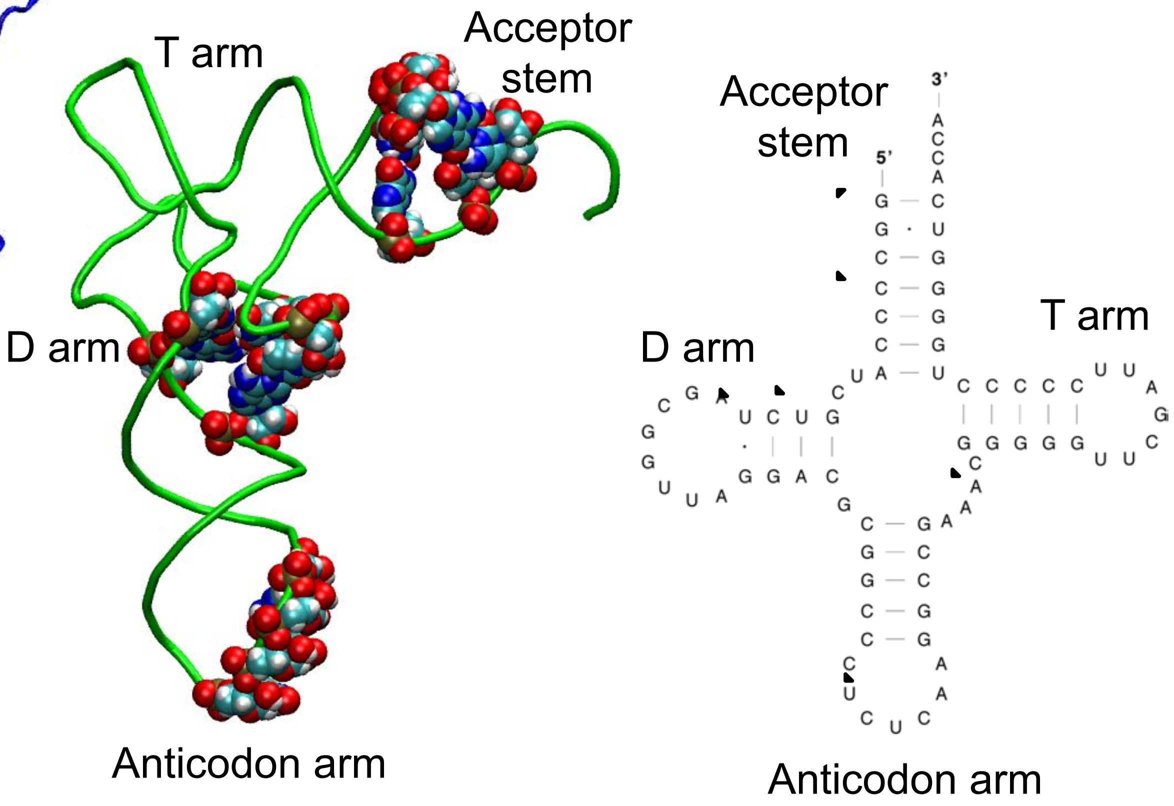
Deprotonation/protonation of reactants (aa,NTs)
Changing rotamer states of residues (6) involved in long-lived salt bridges

(1) Eargle J and ZLS,"Simulating Dynamics of RNA:Protein Complexes" RNA 3D (ed. Westhof, Springer, 2012),
(2) Phillips, J.C. et al. *J. Comput Chem*, (2005);
(3) MacKerell, A. et al. *Biopolymers* (2001); (4) Case, D. et al. *J. Comput. Chem.* (2005);
(5) Eargle, J. et al. JMB 2010, FEBS Let. 2010; (6) Dunbrack Jr. and Cohen. *Protein Sci.* (1997)

Charging tRNA through allosteric signaling



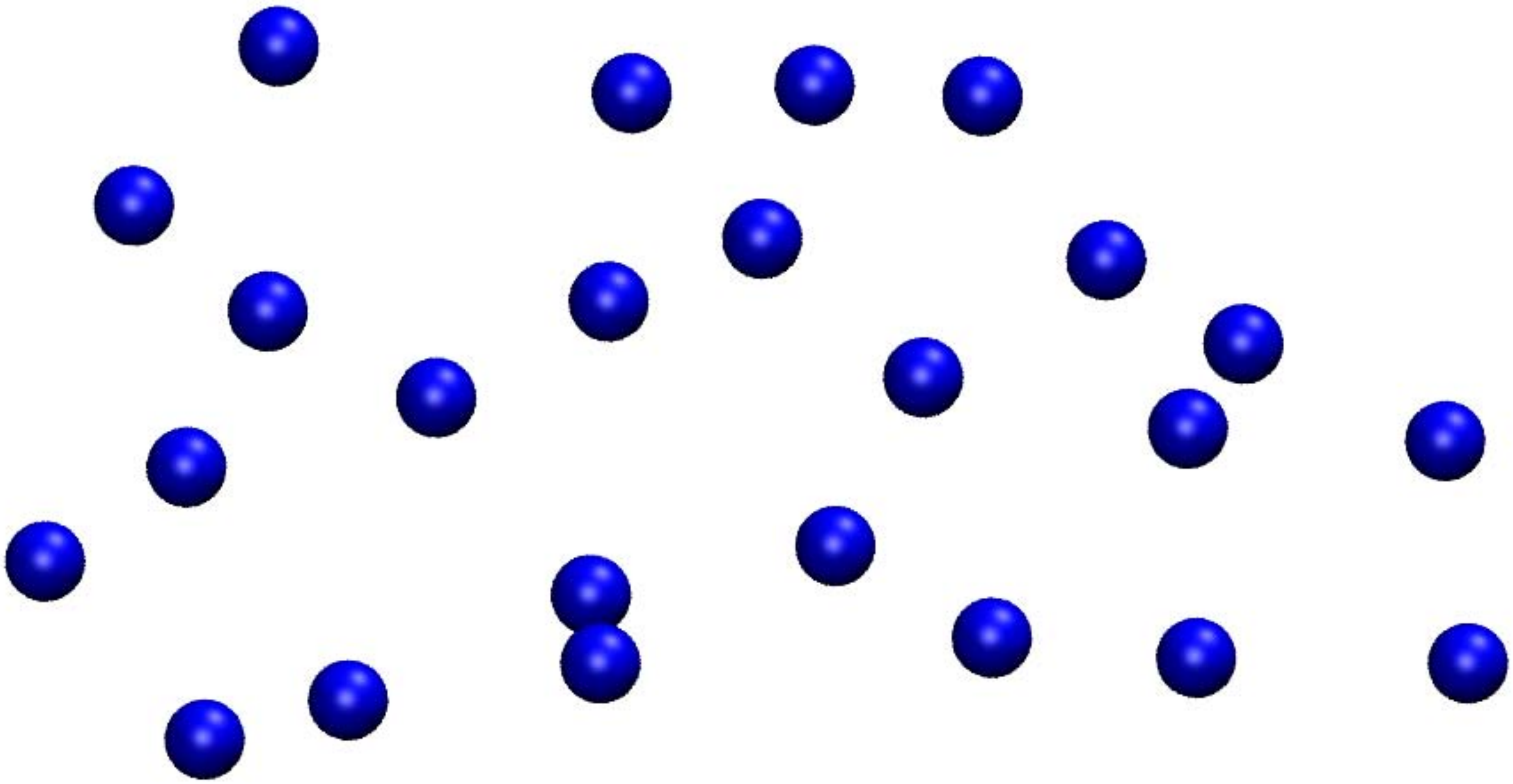
Identity Elements



Overall Charging Reaction

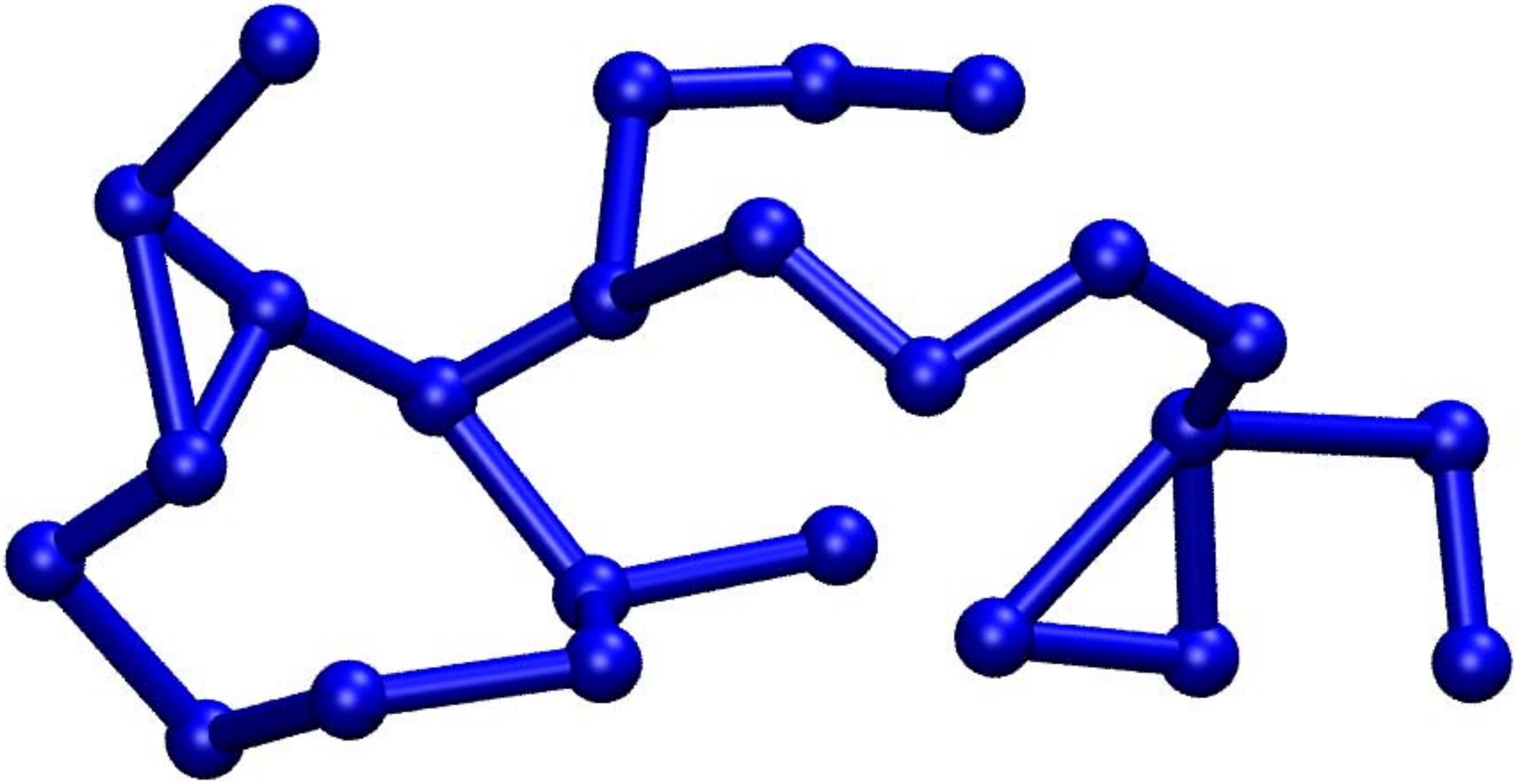
$$\text{ATP} + \text{Glu} + \text{tRNA} \xrightarrow{\text{GluRS}} \text{Glu-tRNA} + \text{AMP} + \text{PP}_i$$

How to Construct a Network?



Nodes - defined at C_a (protein) and P (nucleotide) atoms

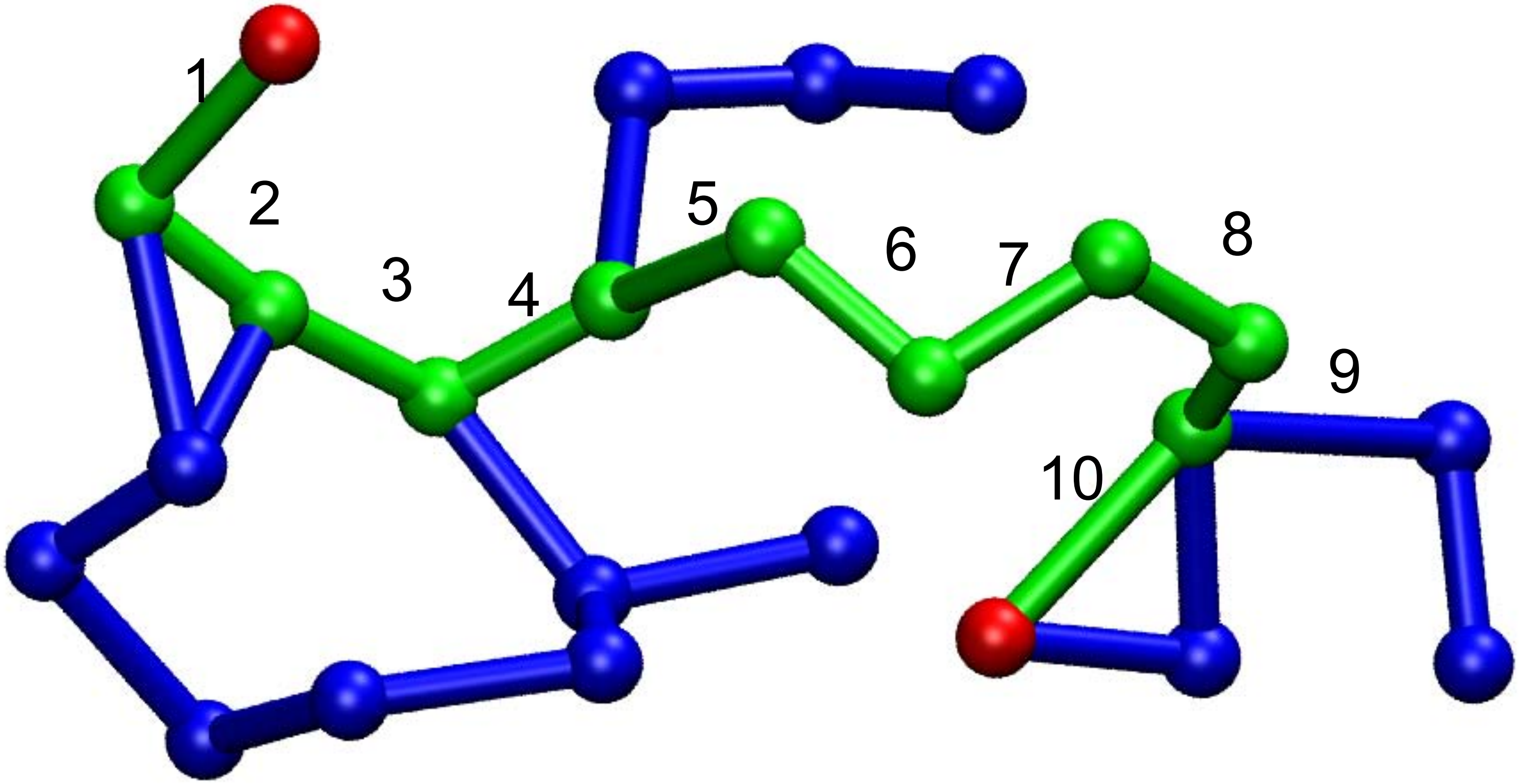
How to Construct a Network?



Edges - connect nodes that are within a contact distance threshold for more than 75% of an MD trajectory

Communication between Identity Elements and Site of Chemistry

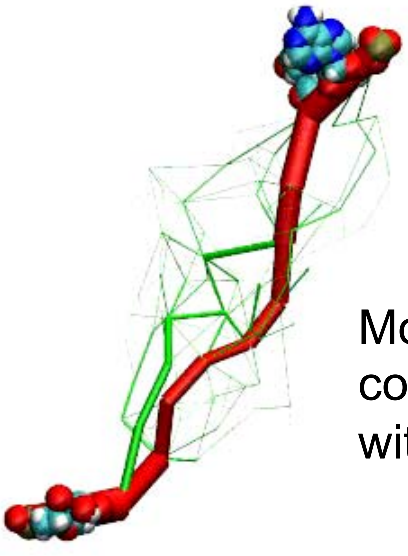
Different Paths can have Different Lengths



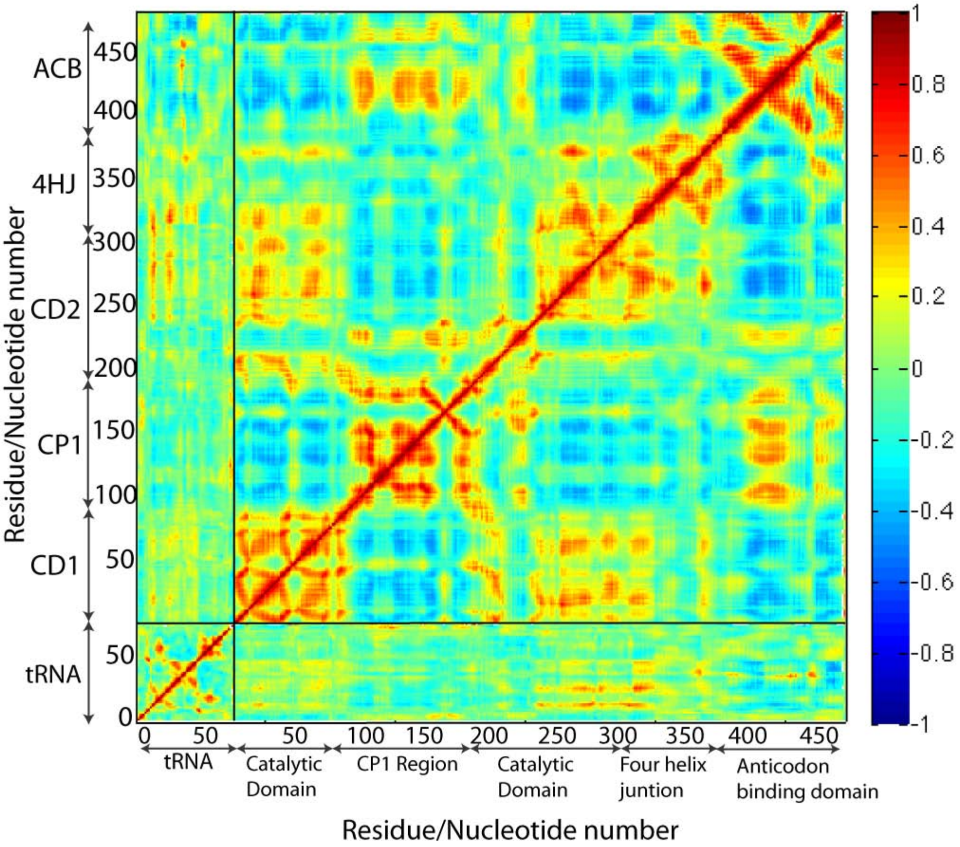
Path length = 10 (*unweighted*)

Information transfer? ***Weight contacts/links by correlations !***

Correlations (C_{ij}) define signaling pathways in GluRS:tRNA

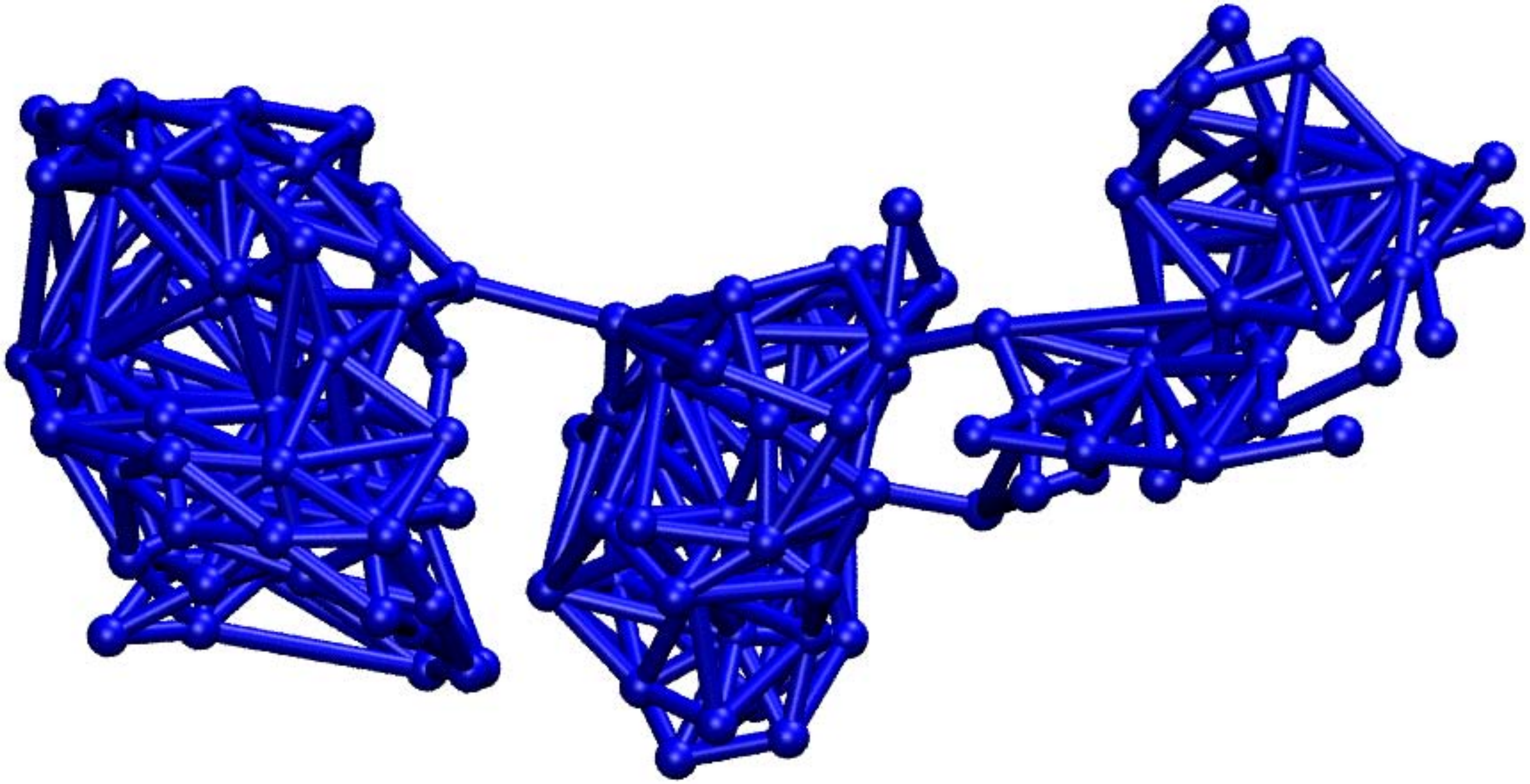


Modular str
communitie
with weight



- MD simulations run with NAMD
- NTP ensemble
- Neutralized with Mg^{2+} and K^{+}
- C_{ij} values calculated over a 16-ns window

Nodes Cluster Together in Modules called Communities



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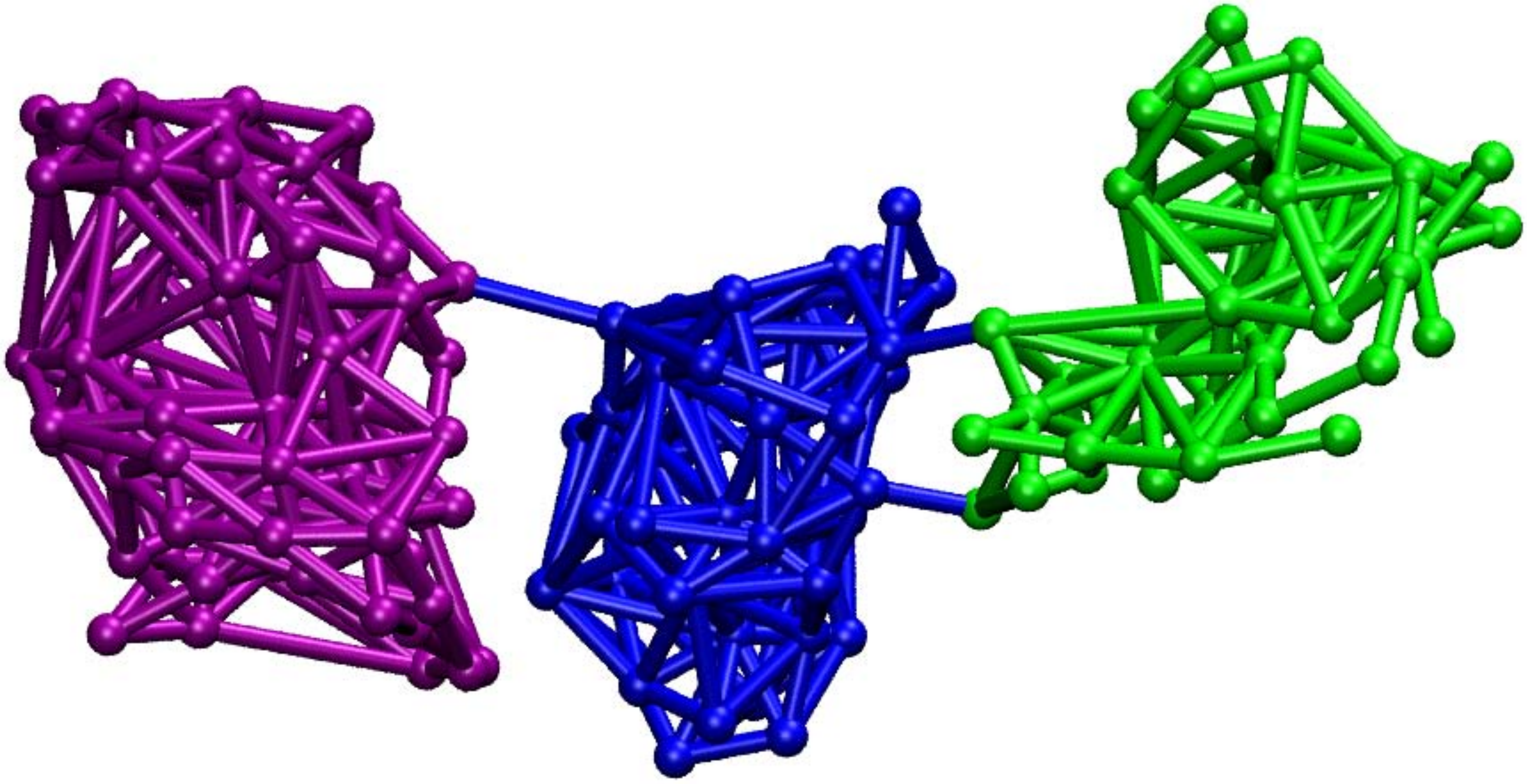
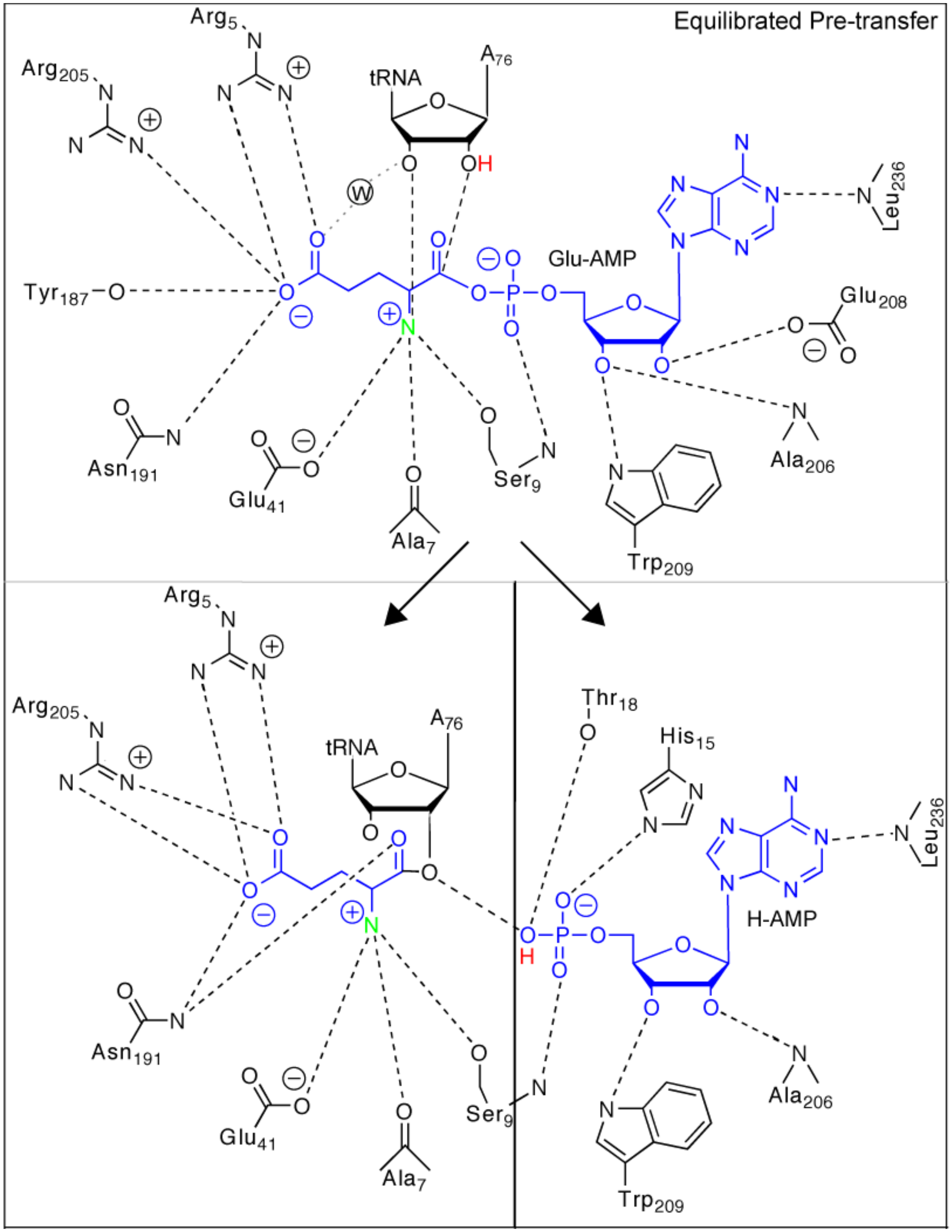


Communities are subnetworks with many intracommunity edges but few intercommunity edges. (Girvan-Newman Algorithm)

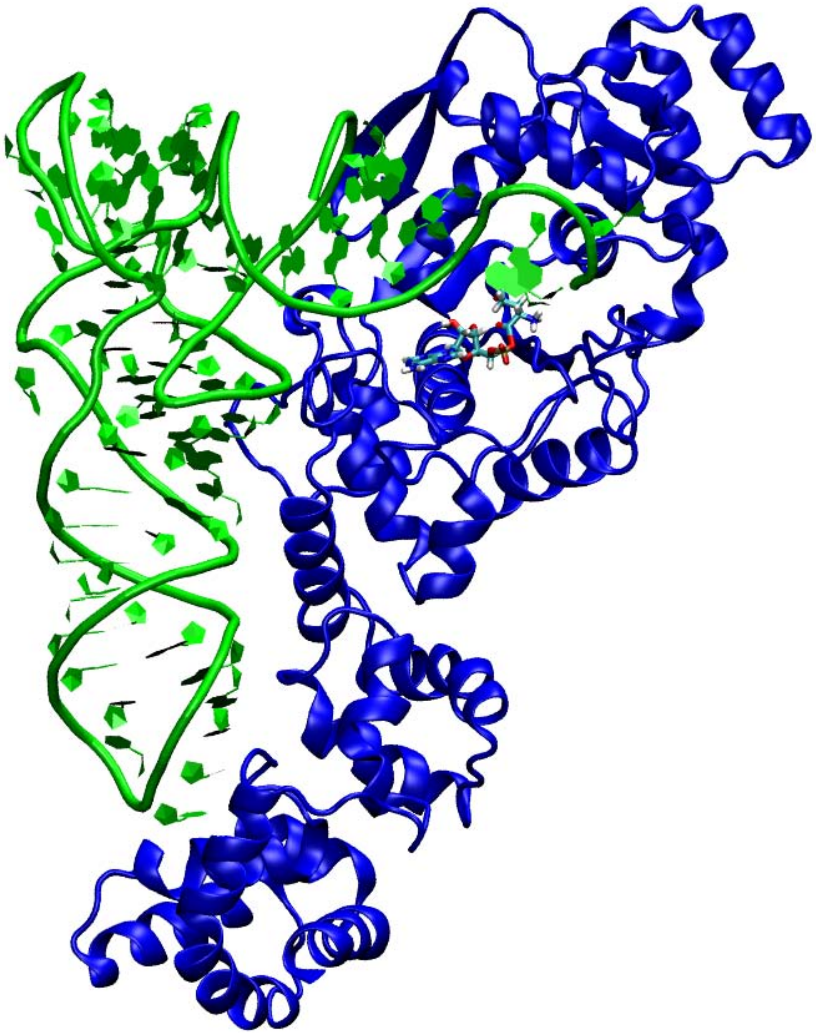


Reaction Mechanism for the Transfer of Glu to tRNA^{Glu}

Perona JJ, Rould MA, Steitz TA
Biochemistry 1993

Black A, Eargle J, Sethi A,
Luthey-Schulten Z. *JMB* 2010
100s ns MD simulations

Community Structure Reveals Function in GluRS



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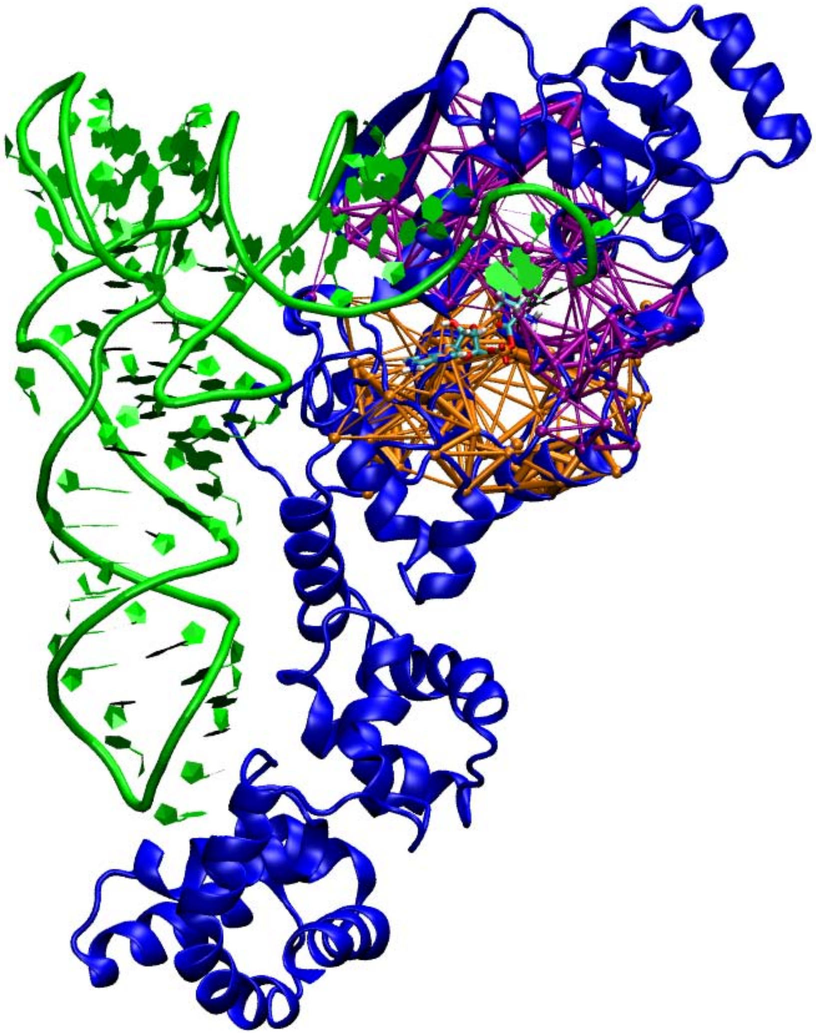

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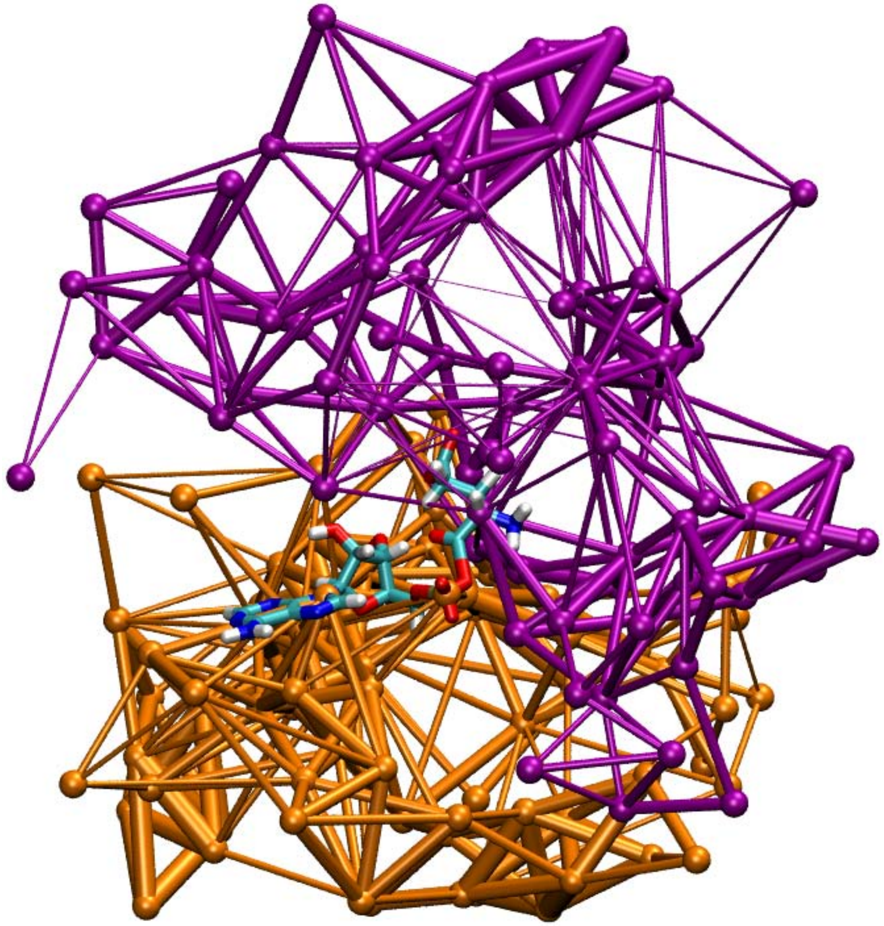

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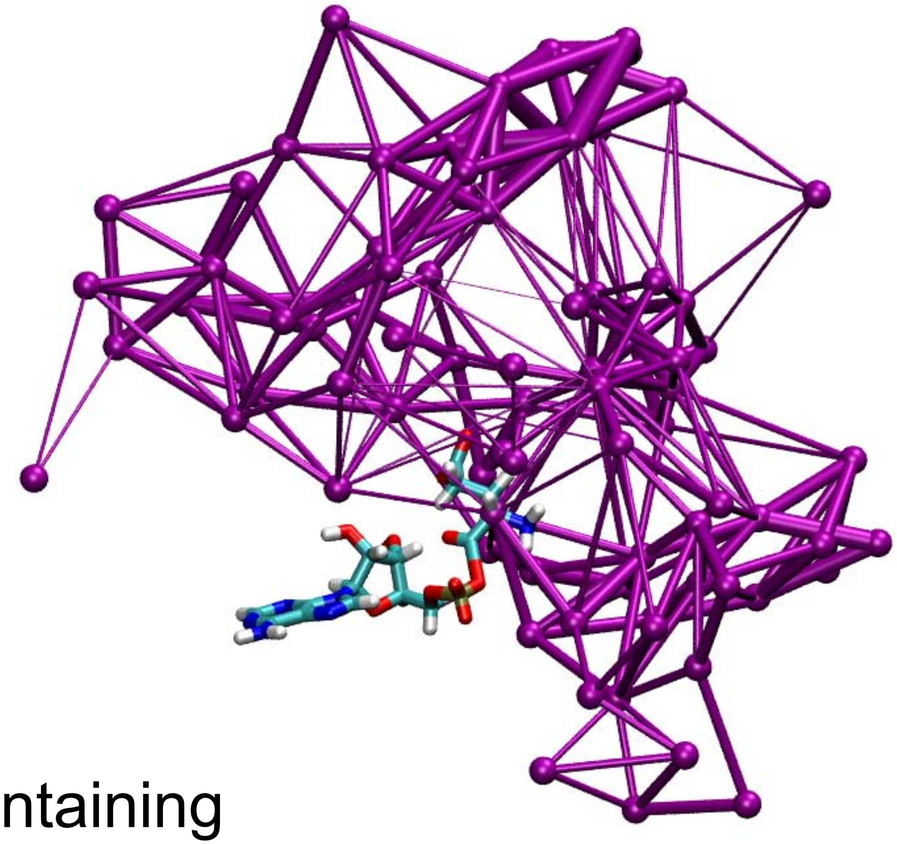
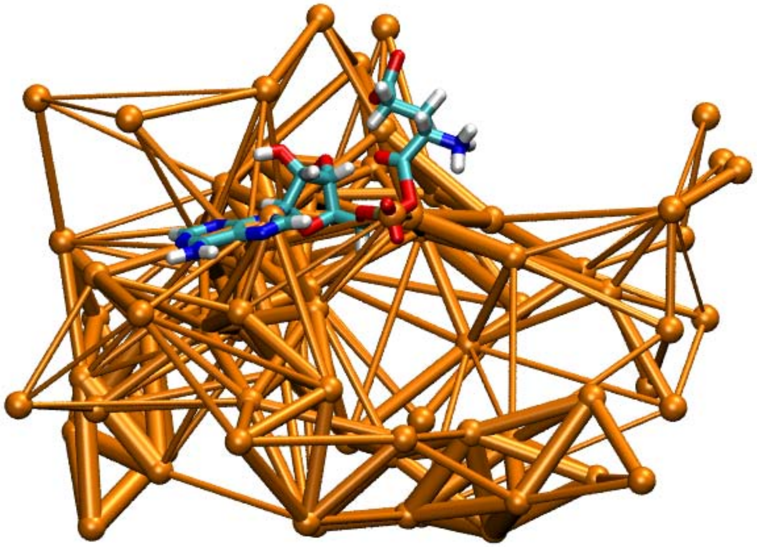


community containing
amino acid moiety

Community Structure Reveals Function in GluRS

community containing
AMP moiety



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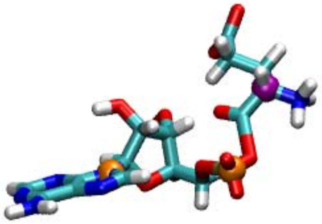

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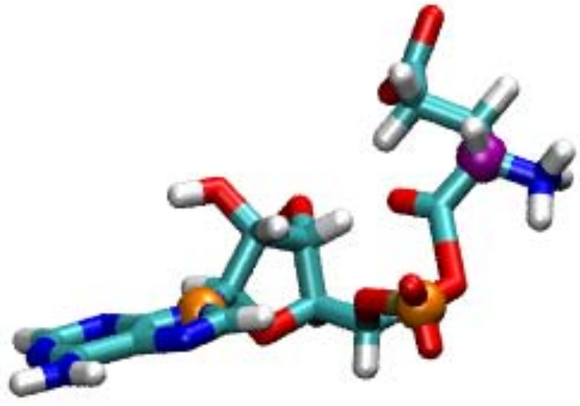
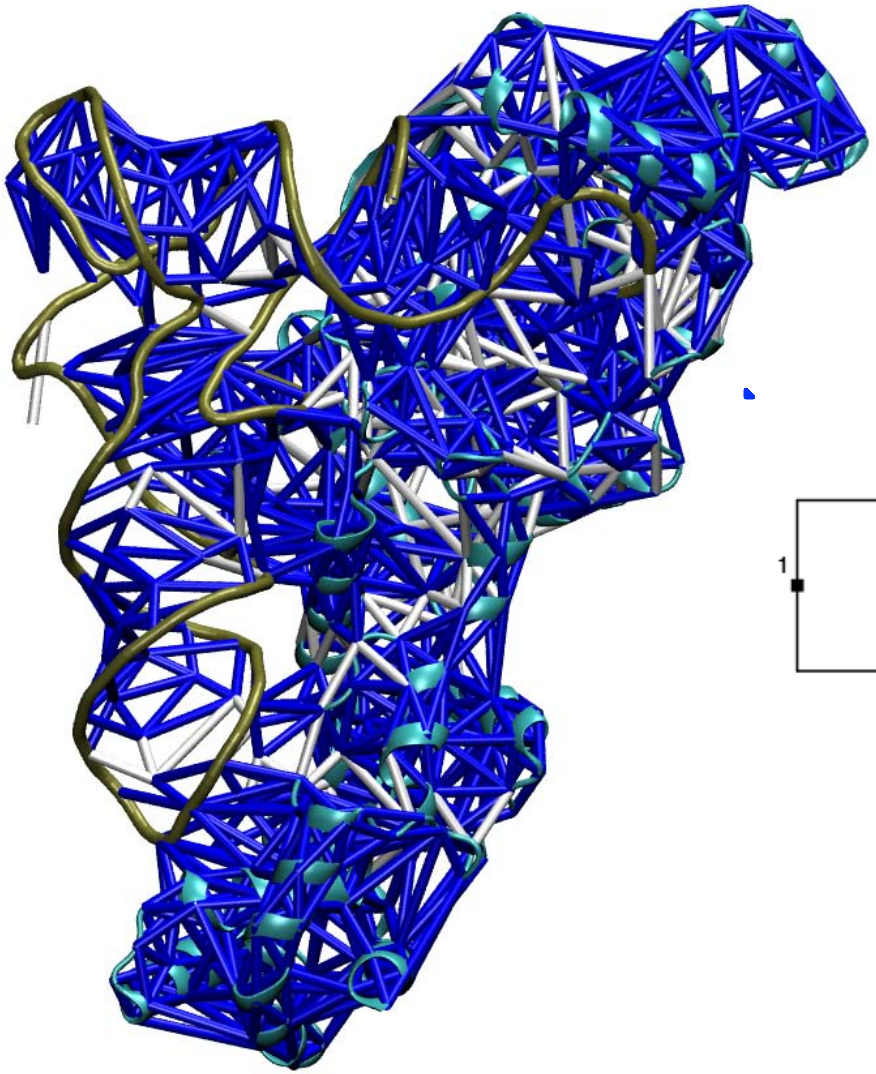
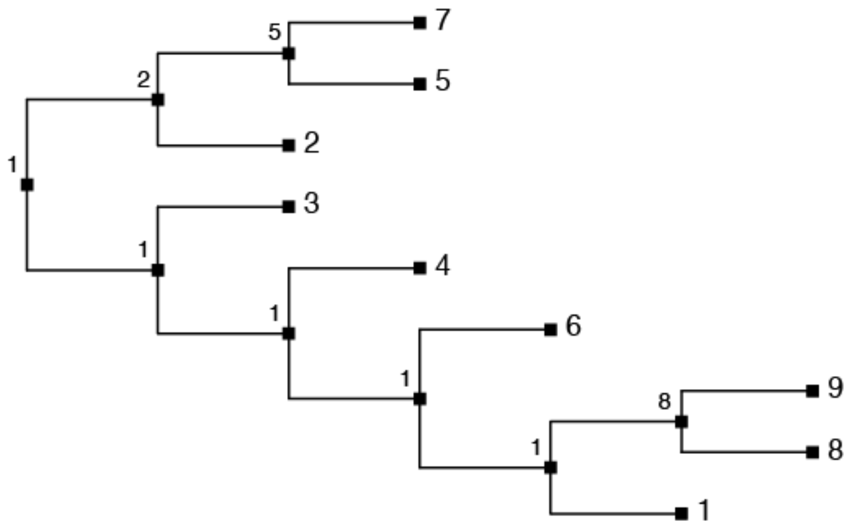


Communities Partition the Interaction Network Hierarchically





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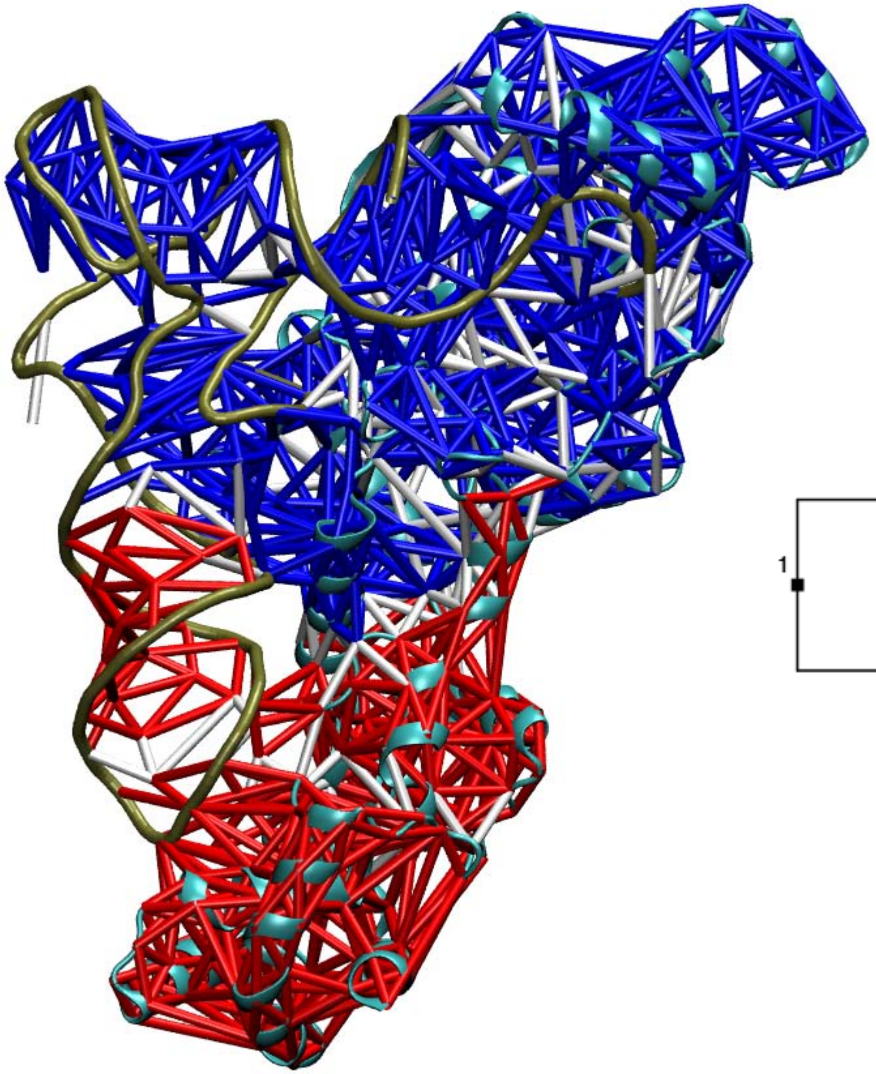
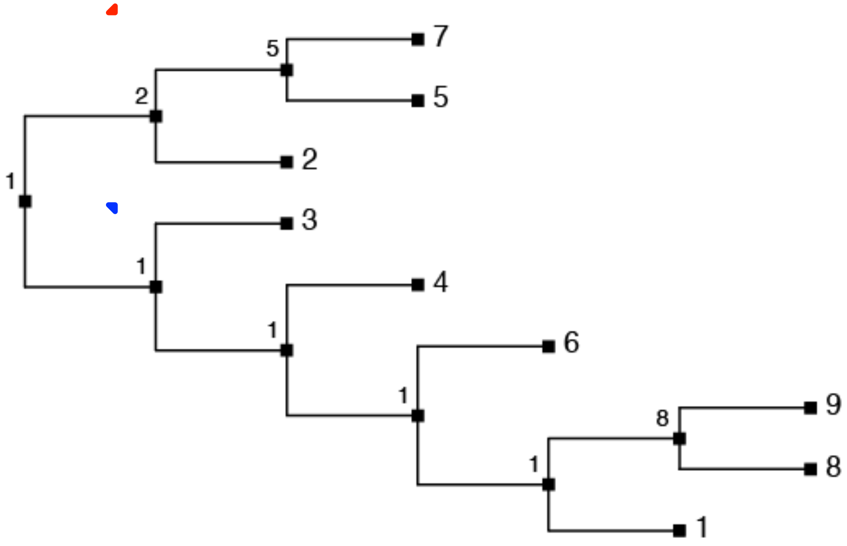
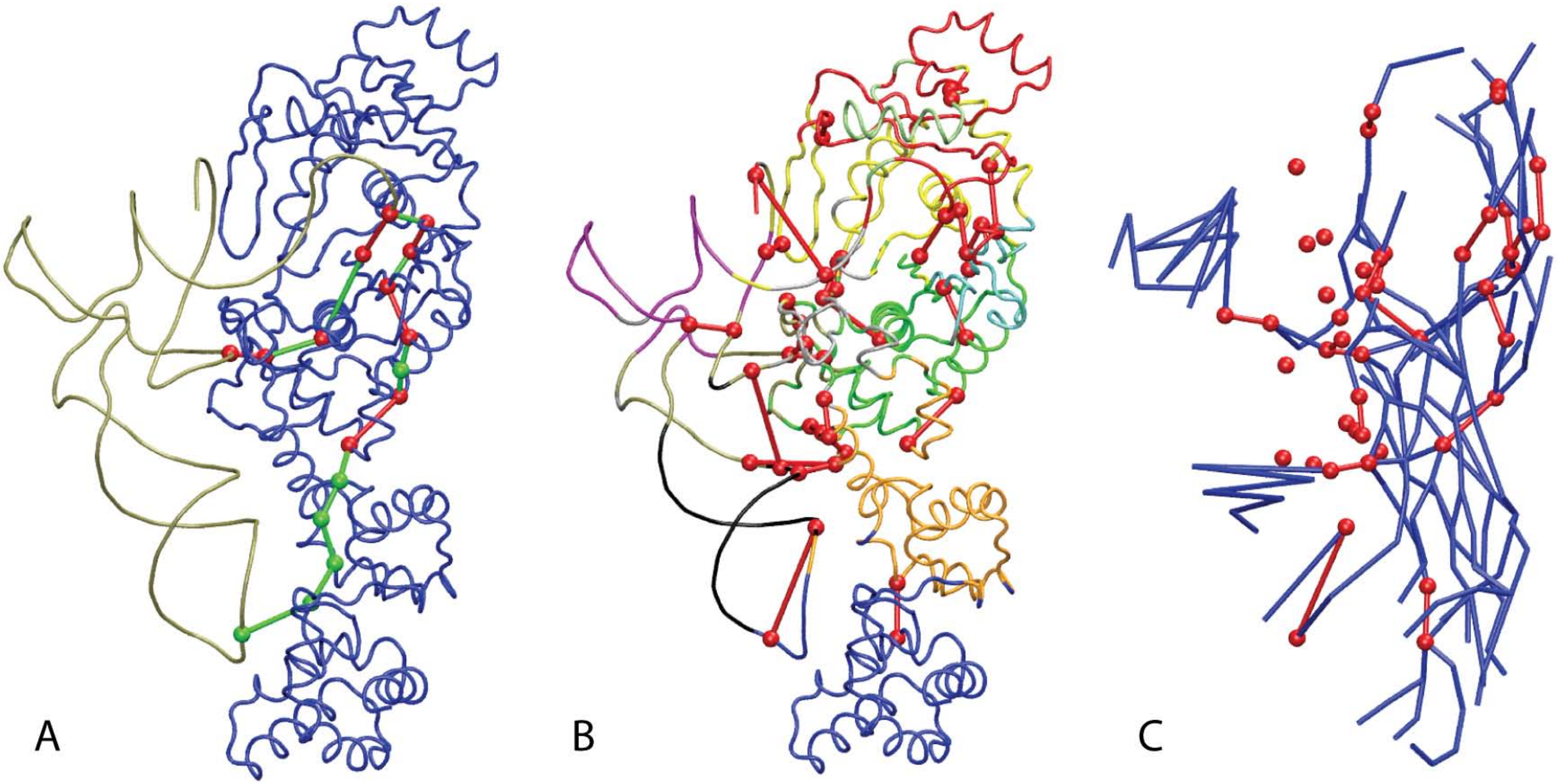




Dynamical Networks, Conservation, and Betweeness



Optimal signal pathways: U13, U35 to A76

Critical(conserved) nodes connecting communities

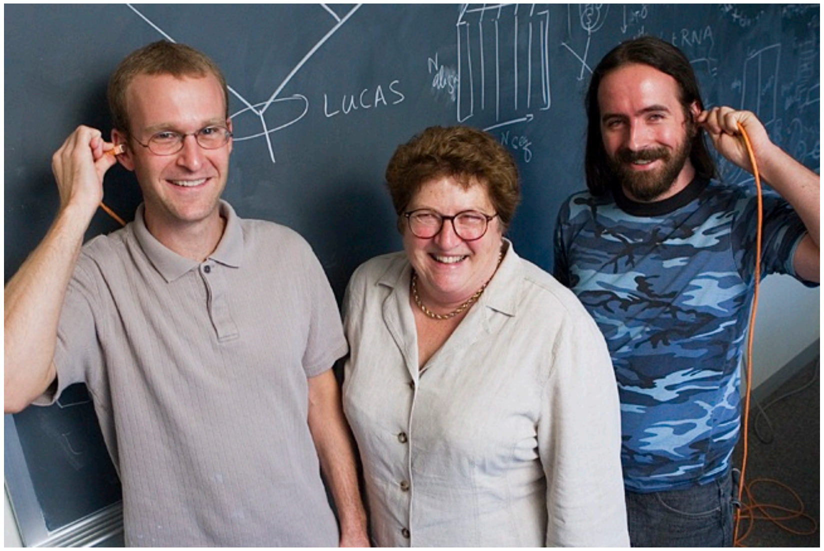
Betweeness routes - highest density pair optimal paths

VMD/MultiSeq Tutorials

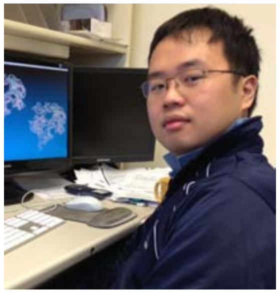
1. Evolution of Translation: AARS:tRNA
2. Evolution of Translation: EF-Tu:tRNA
3. Evolution of Translation: Ribosome
4. Dynamical Network Analysis

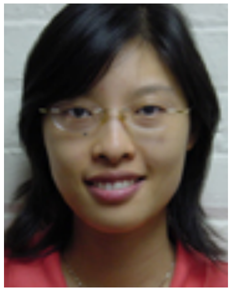
Acknowledgements

- Joe Peterson
- Mike Hallock
- Elijah Roberts
- John Eargle
- Jonathan Lai
- Ke Chen



Kirby Vandivort John Stone





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