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

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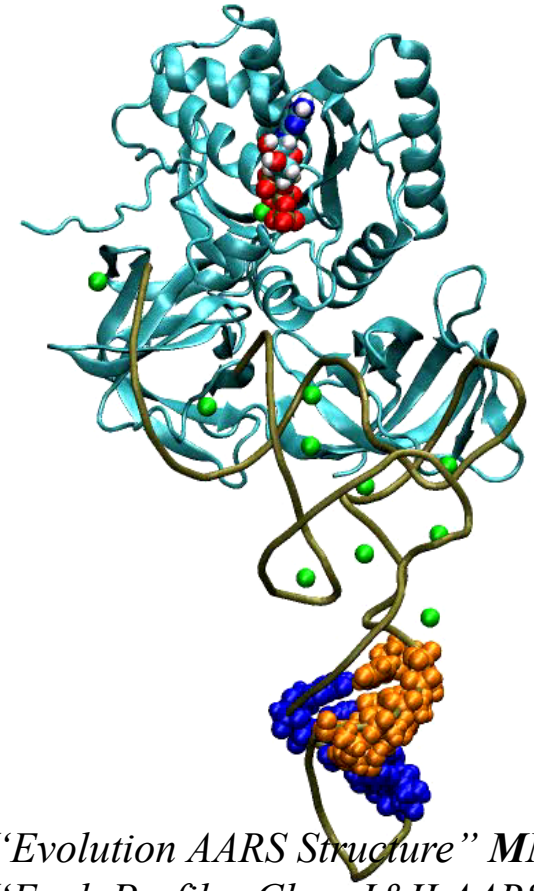
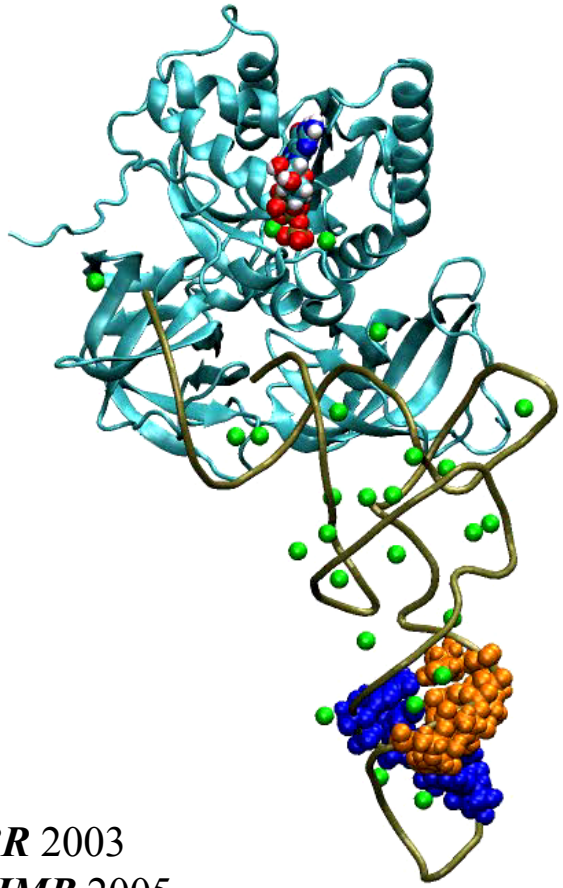
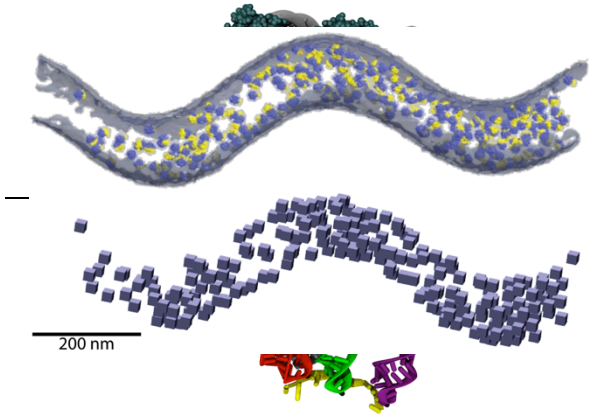
Protein:RNA Complexes in Translation

Evolutionary Analysis & Dynamics







r-Proteins/r-RNA Ribosome LSU

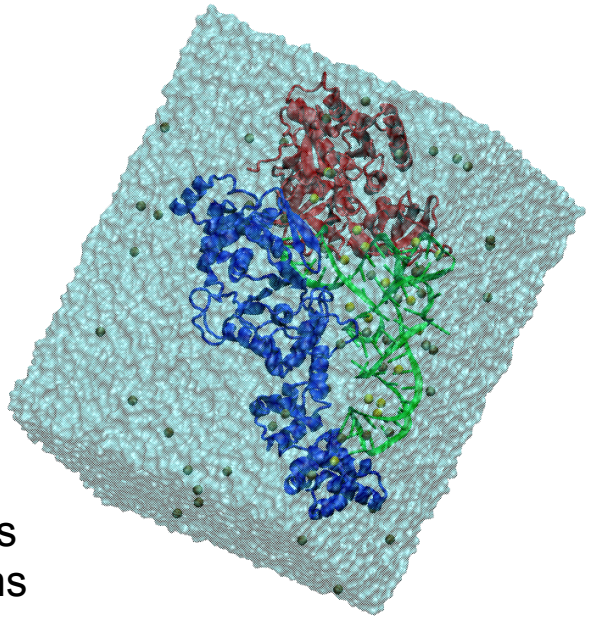
"Signatures ribosomal evolution" ***PNAS*** 2008, ***BMC*** 2009, ***BJ*** 2010
"Motion L1 Stalk:tRNA" ***JMB*** 2010**,**
"*Ribosome Biogenesis"* ***JPC*** 2012,3
"Whole cell simulations on GPUs"
IEEE 2009,***Plos CB*** 2011,***PRL***2011,
JCC 2013**,** ***PNAS*** 2013,
PRL 2013**,** ***CSB*** 2013
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), CHARMM36,22* 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)

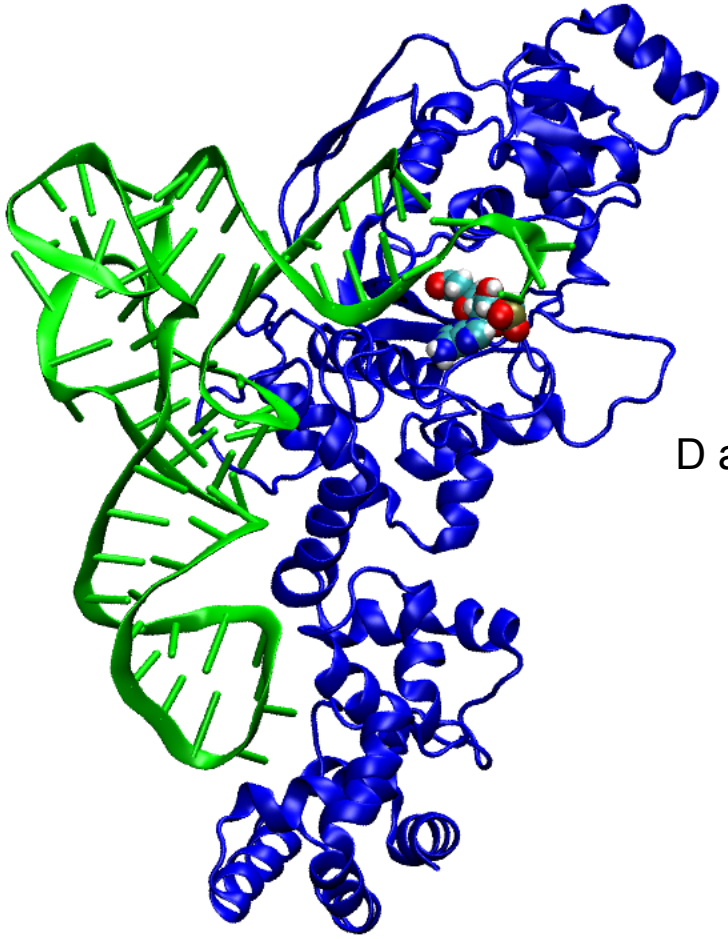
GluRS
Glu-tRNA^{Glu}
EF-Tu
GTP
Ions: Mg^{2+}, K^{+}
H_2O: ~27,000 molecules
System: ~130,000 atoms

System Perturbations

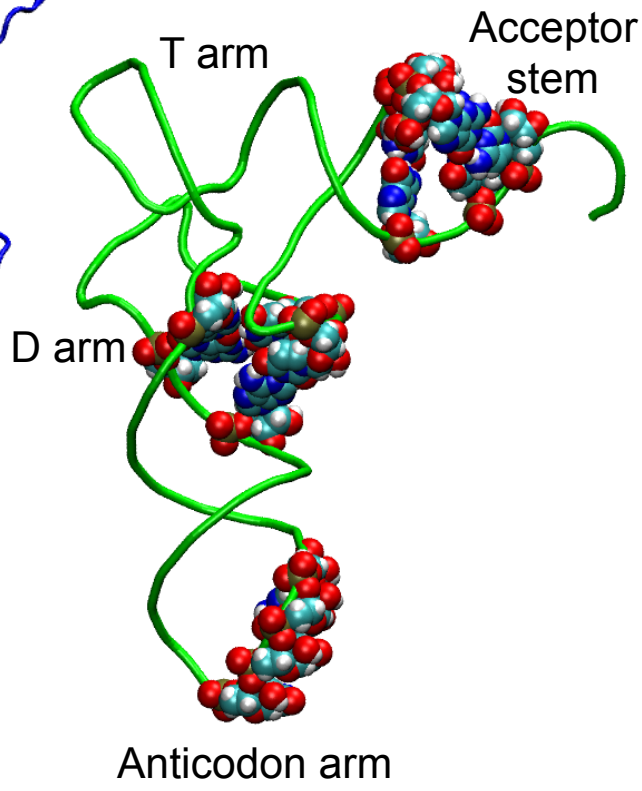
Deprotonation/protonation of reactants (aa,NTs)
Changing rotamer states of residues (6) involved in long-lived salt bridges

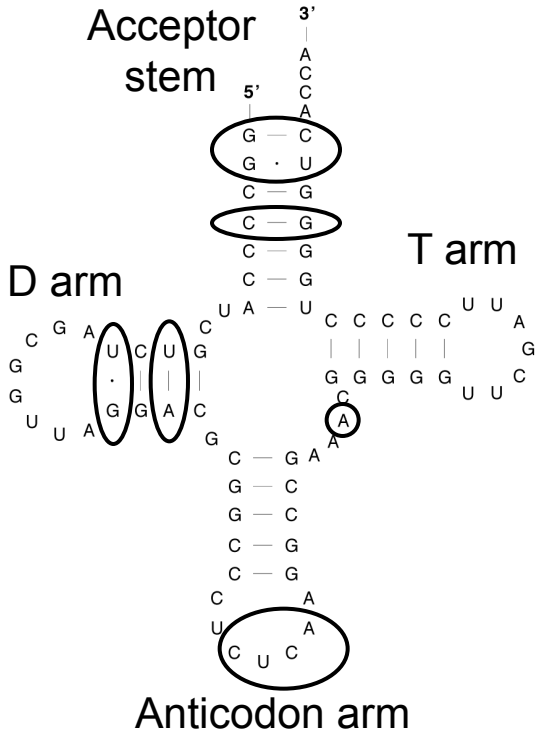
(1) Eargle J and ZLS,"Simulating Dynamics of RNA:Protein Complexes" RNA 3D (ed. Westhof, Springer, 2012),
(2) Phillips, J.C. et al. *J. Comput Chem*, (2005);
(3) MacKerell, A. et al. *Biopolymers* (2001); (4) Case, D. et al. *J. Comput. Chem.* (2005);
(5) Eargle, J. et al. JMB 2010, FEBS Let. 2010; (6)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

Charging tRNA through allosteric signaling



Identity Elements

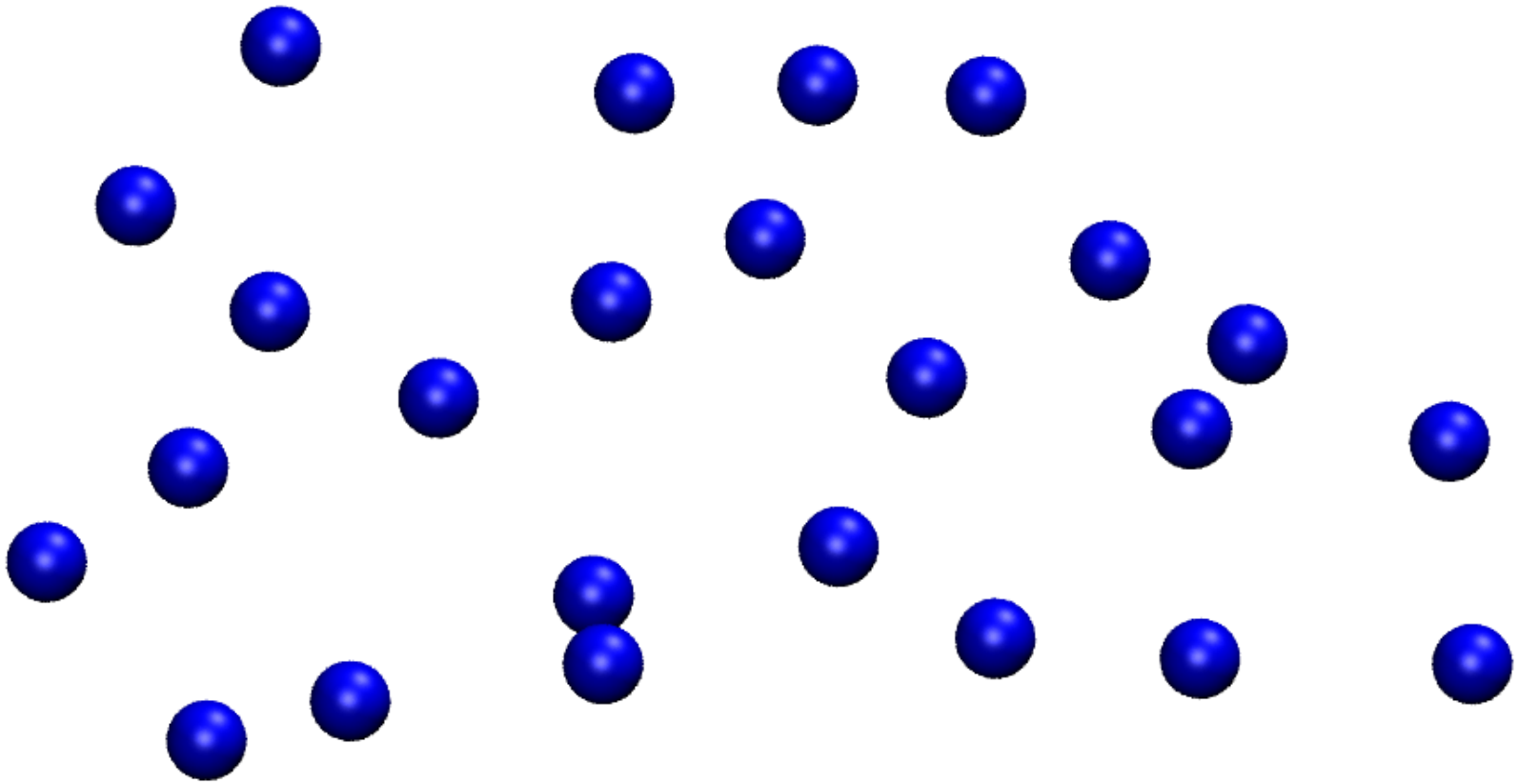




Overall Charging Reaction

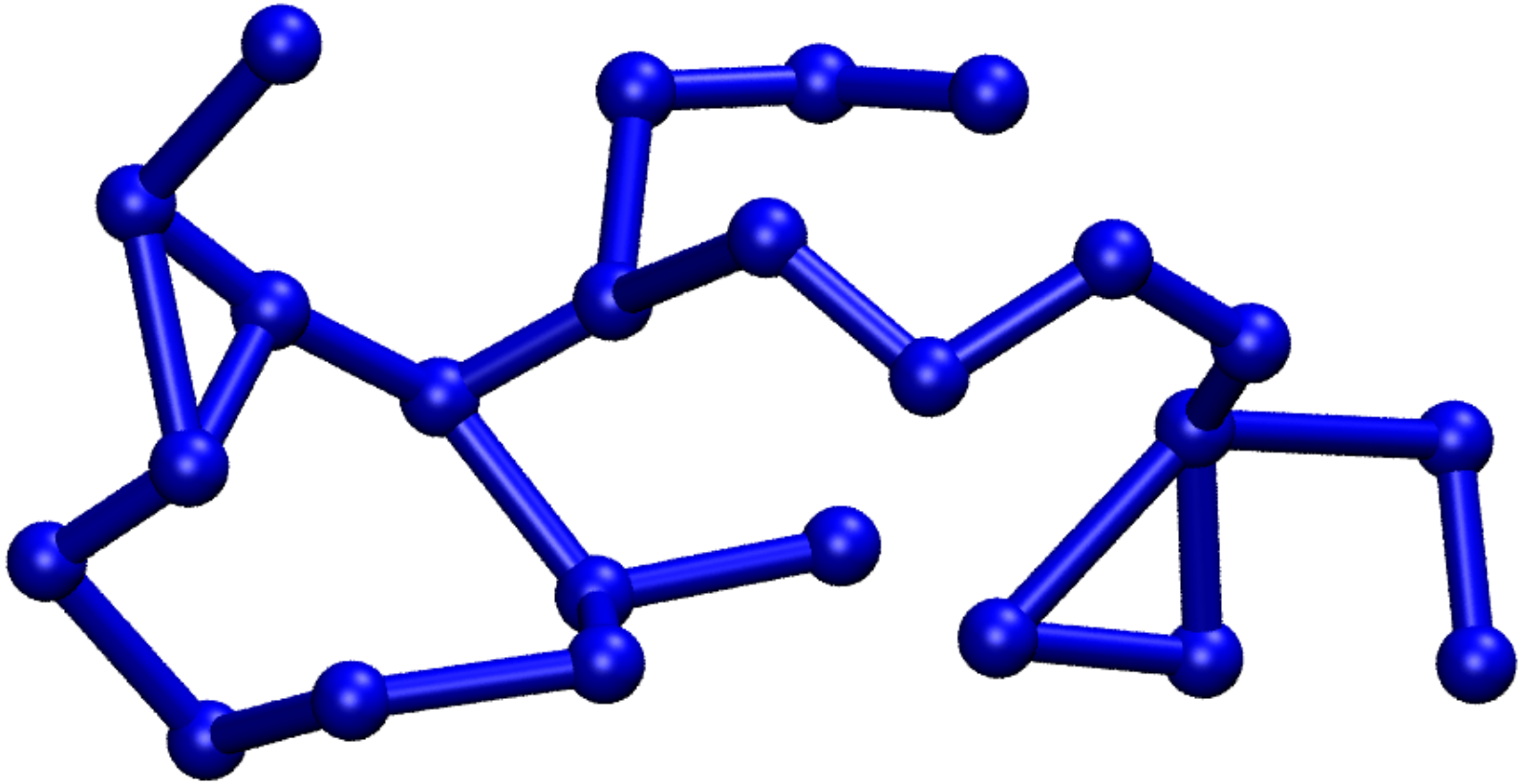
$$\text{ATP + Glu + tRNA} \xrightarrow{\text{GluRS}} \text{Glu-tRNA + AMP + } PP_i$$

How to Construct a Network?



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

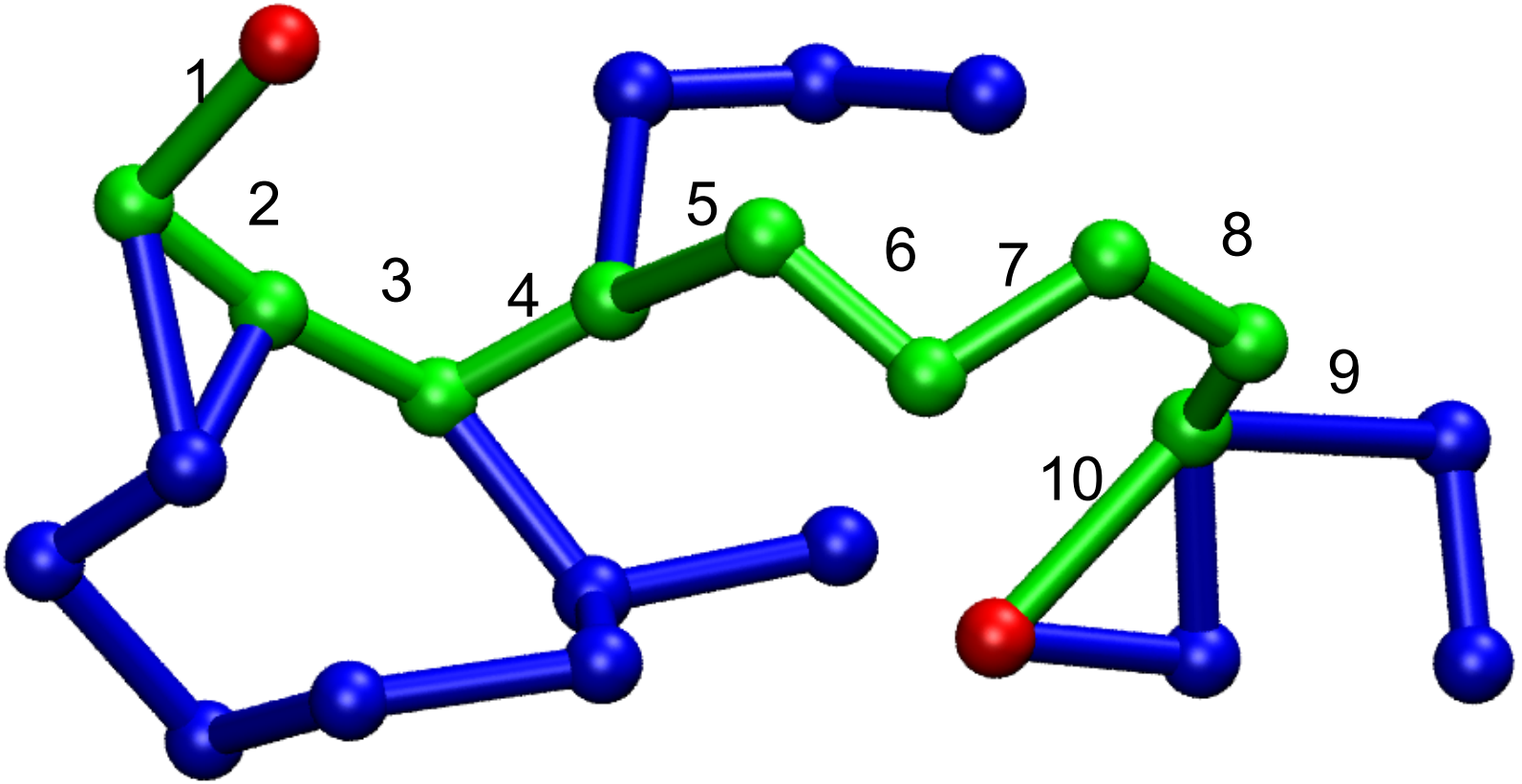
How to Construct a Network?



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

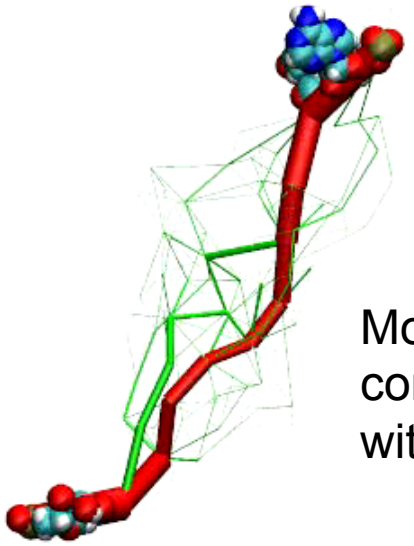
Different Paths can have Different Lengths



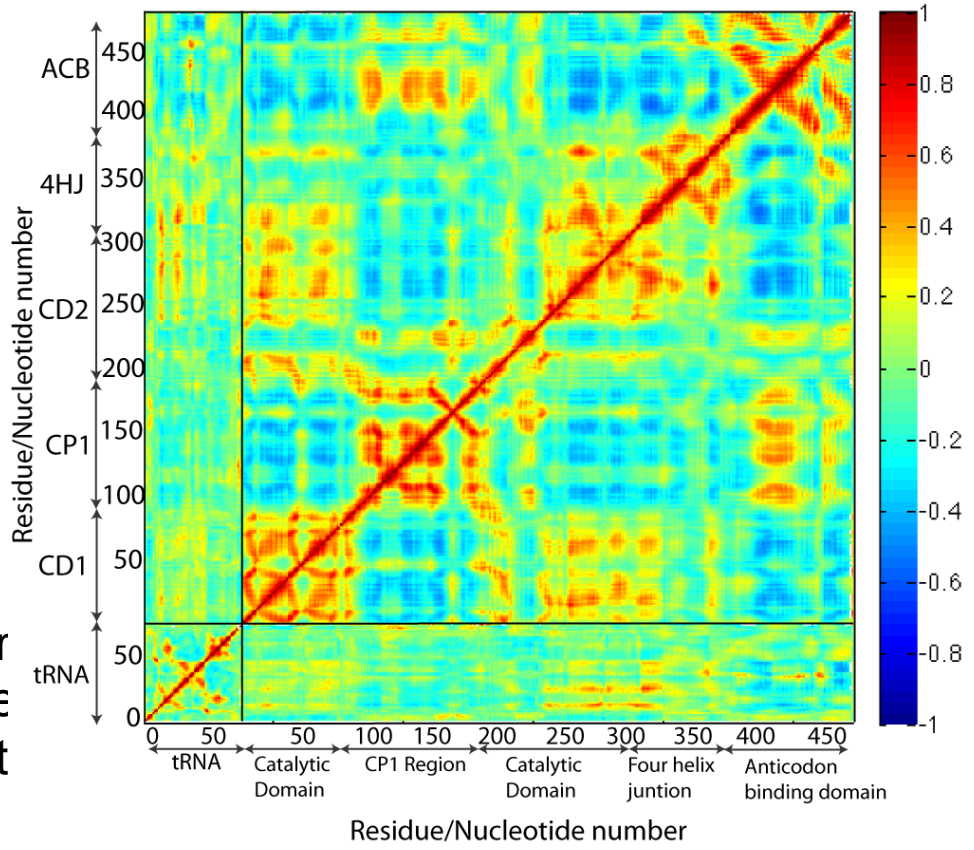
Path length = 10 (*unweighted*)

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

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

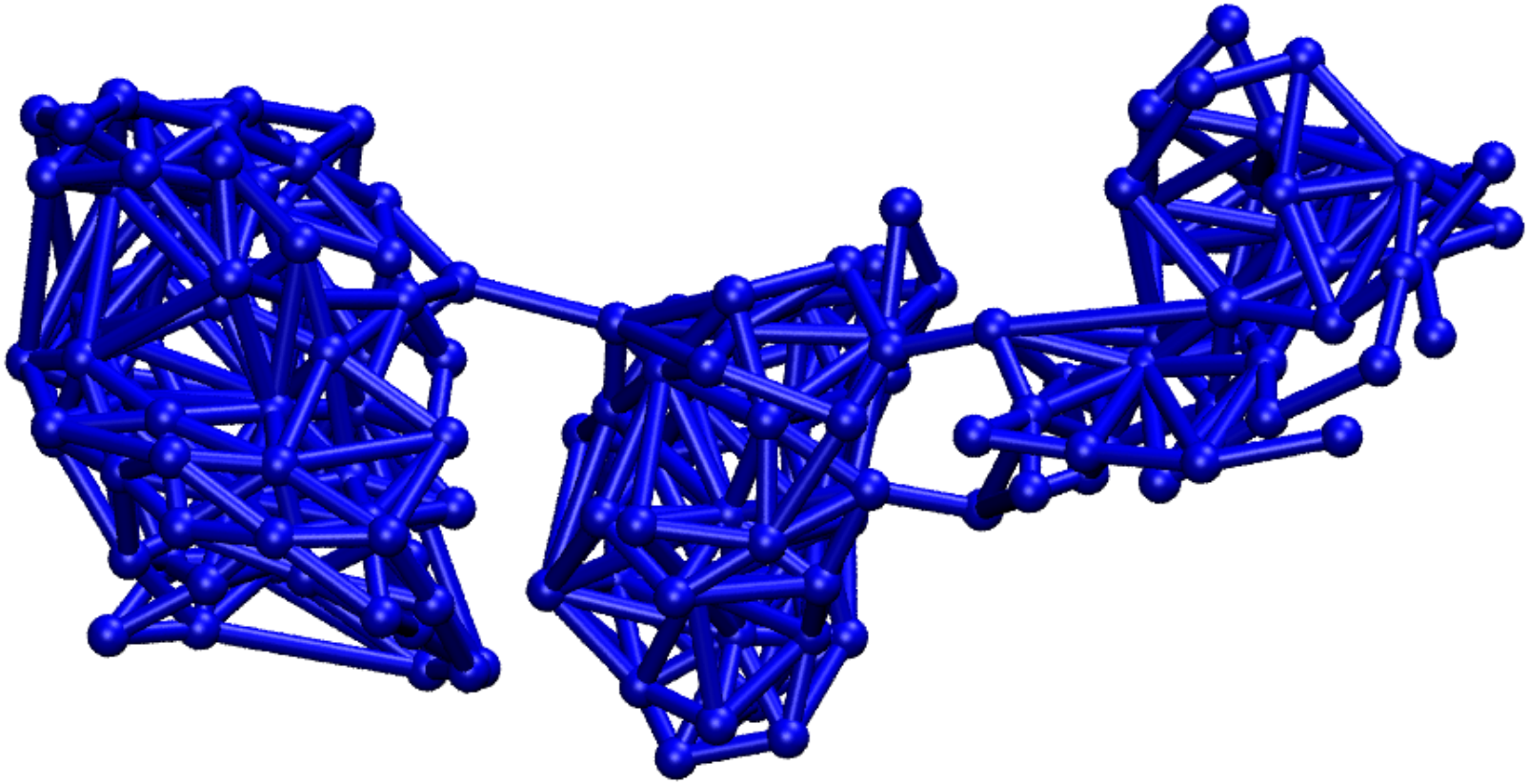


Modular str
communitie
with weight

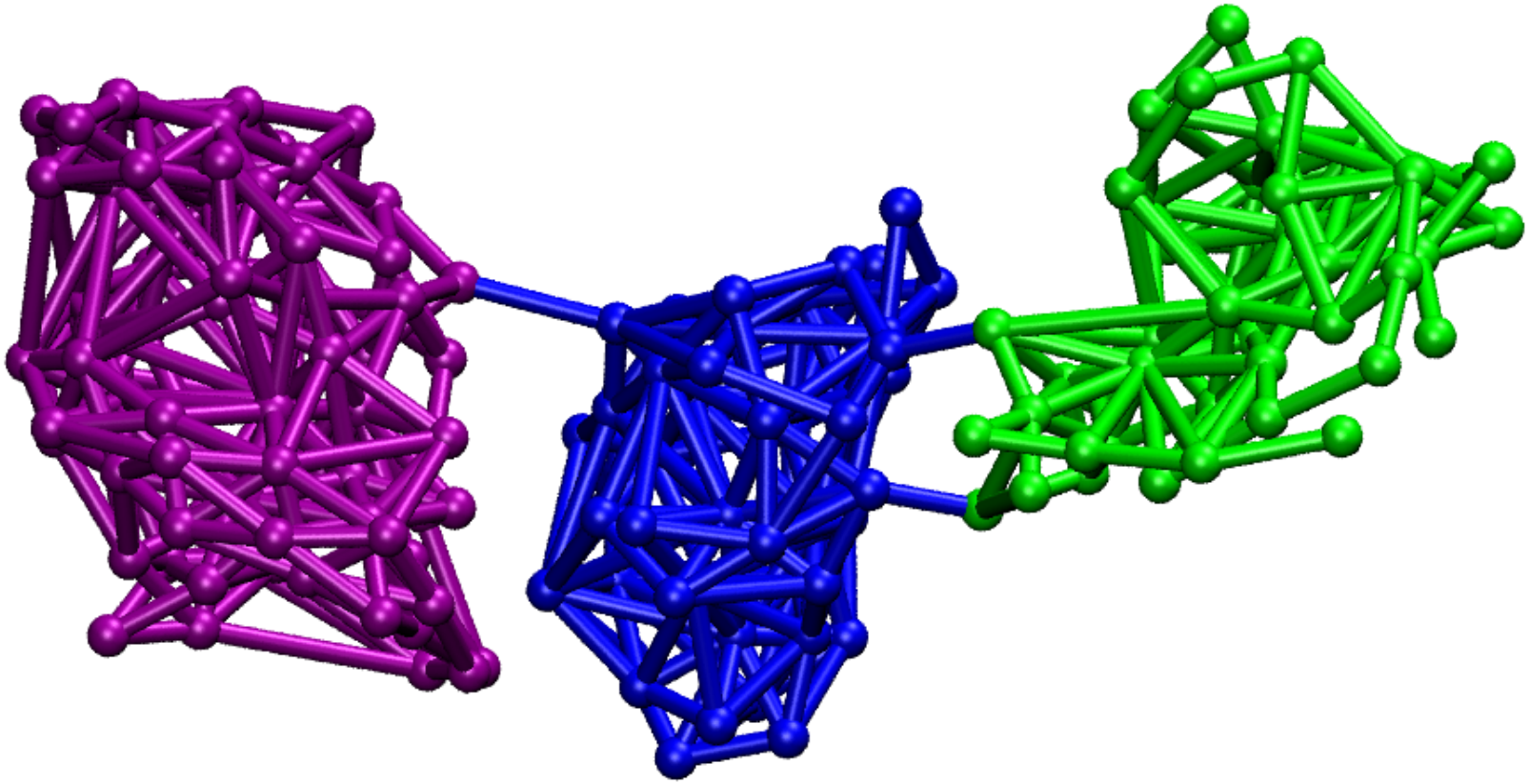


- MD simulations run with NAMD
- NTP ensemble
- Neutralized with Mg^{2+} and K^{+}
- C_{ij} values calculated over a 16-ns window

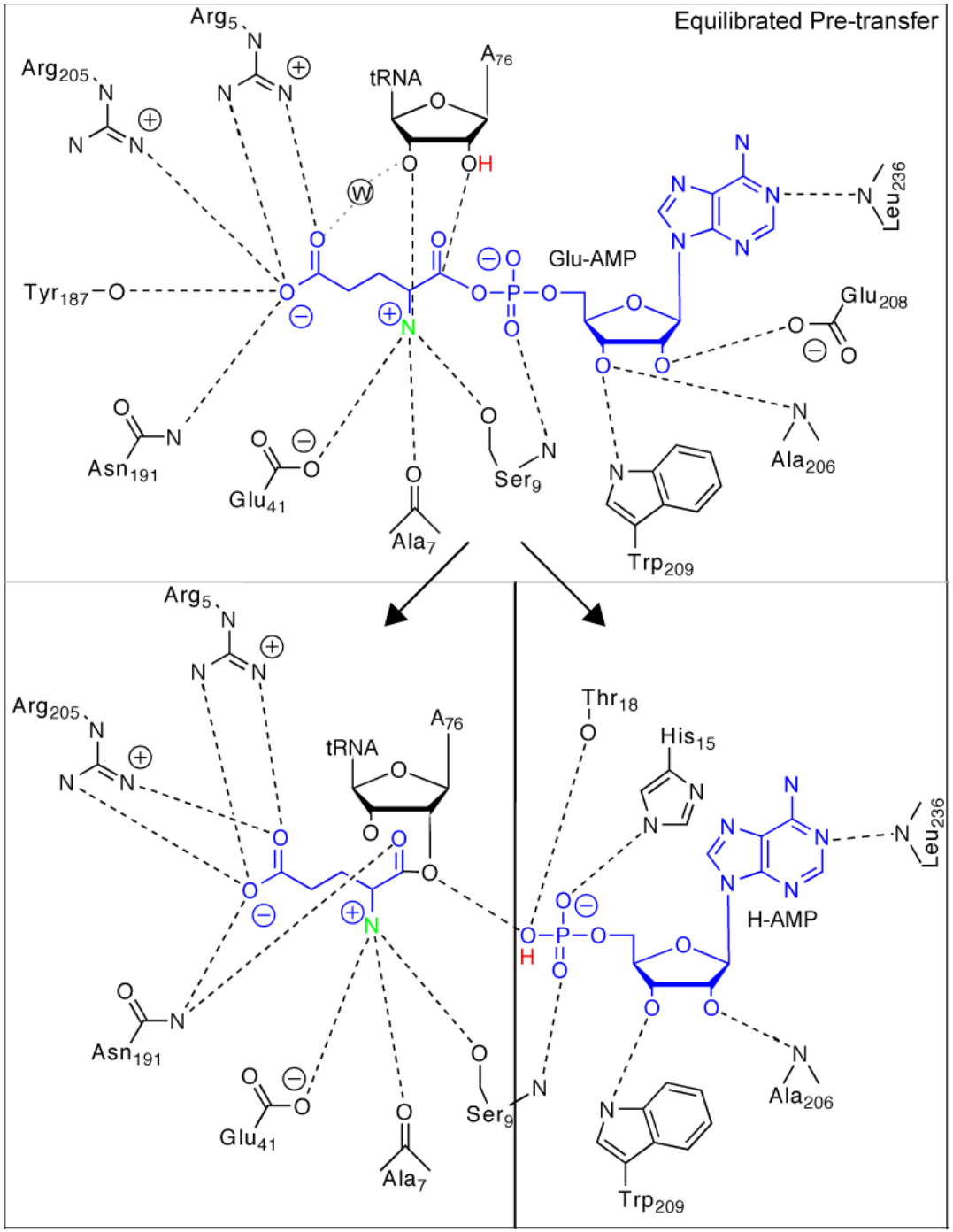
Nodes Cluster Together in Modules called Communities



Nodes Cluster Together in Modules called Communities



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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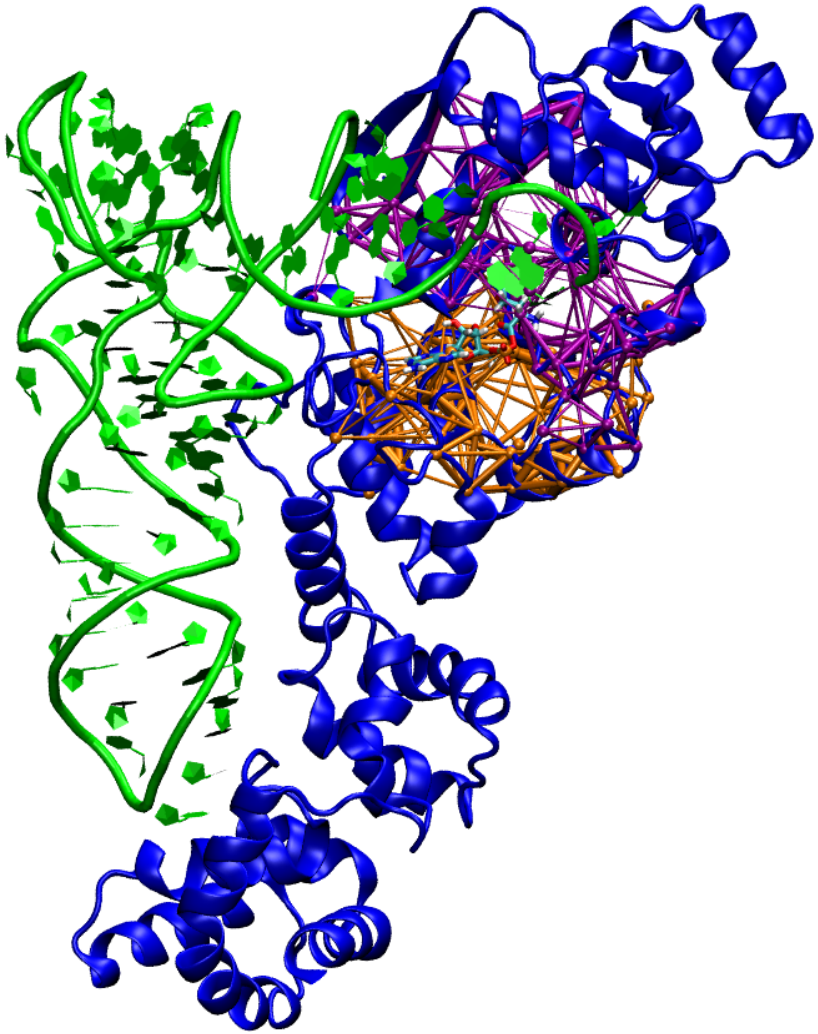
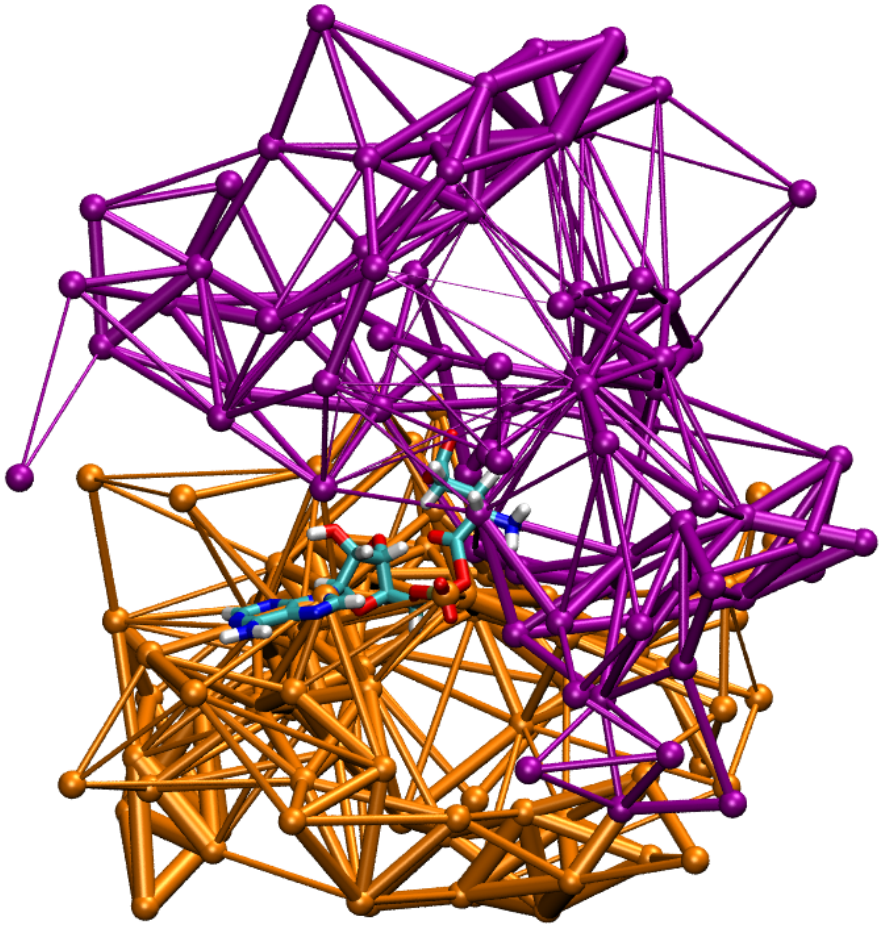
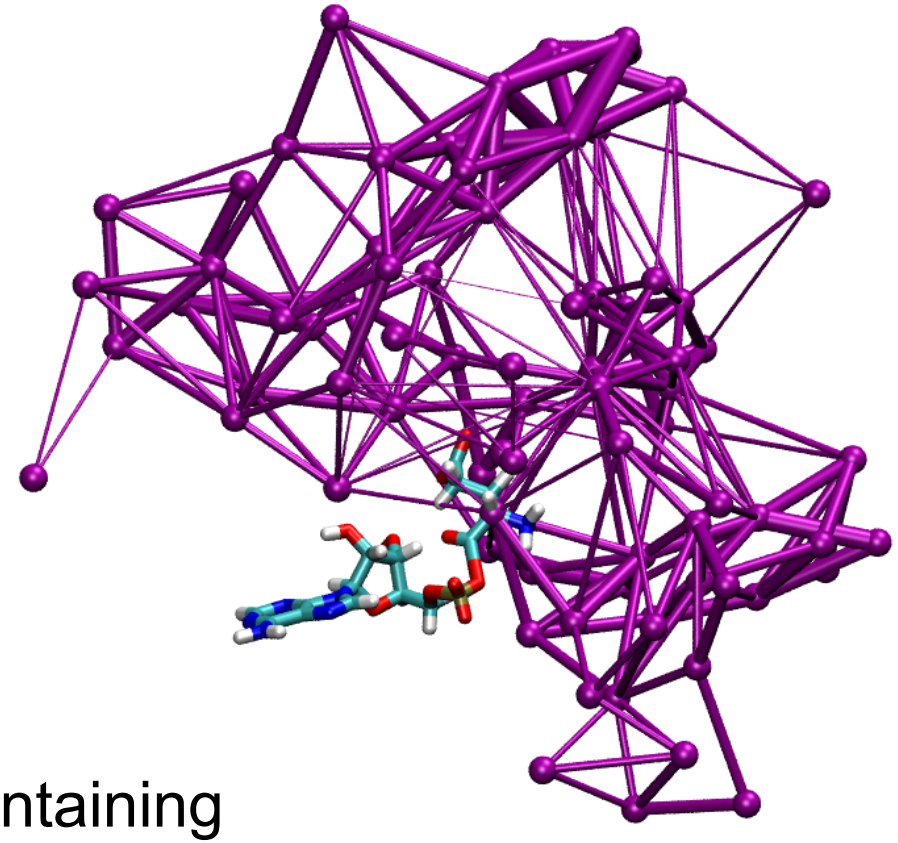


Community Structure Reveals Function in GluRS



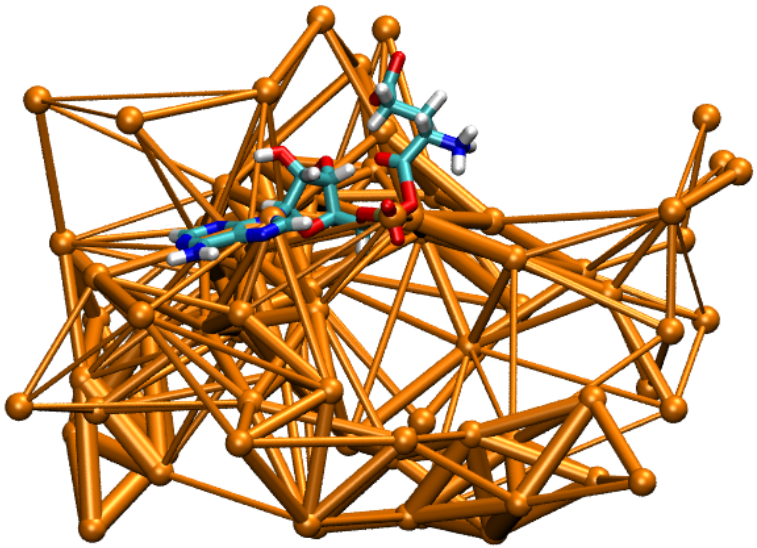
Community Structure Reveals Function in GluRS



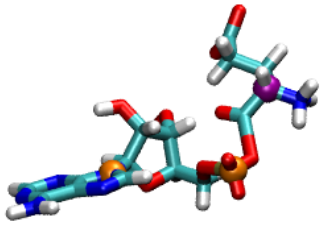
community containing
amino acid moiety

Community Structure Reveals Function in GluRS

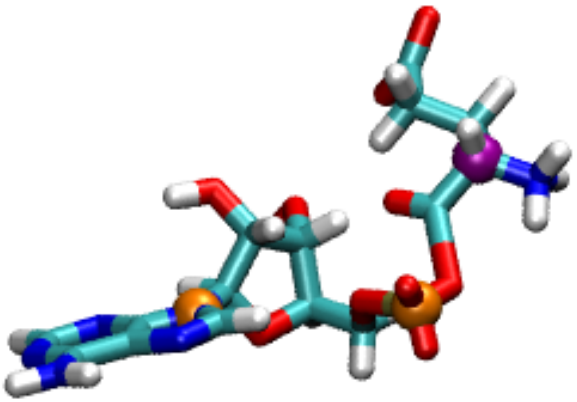
community containing
AMP moiety



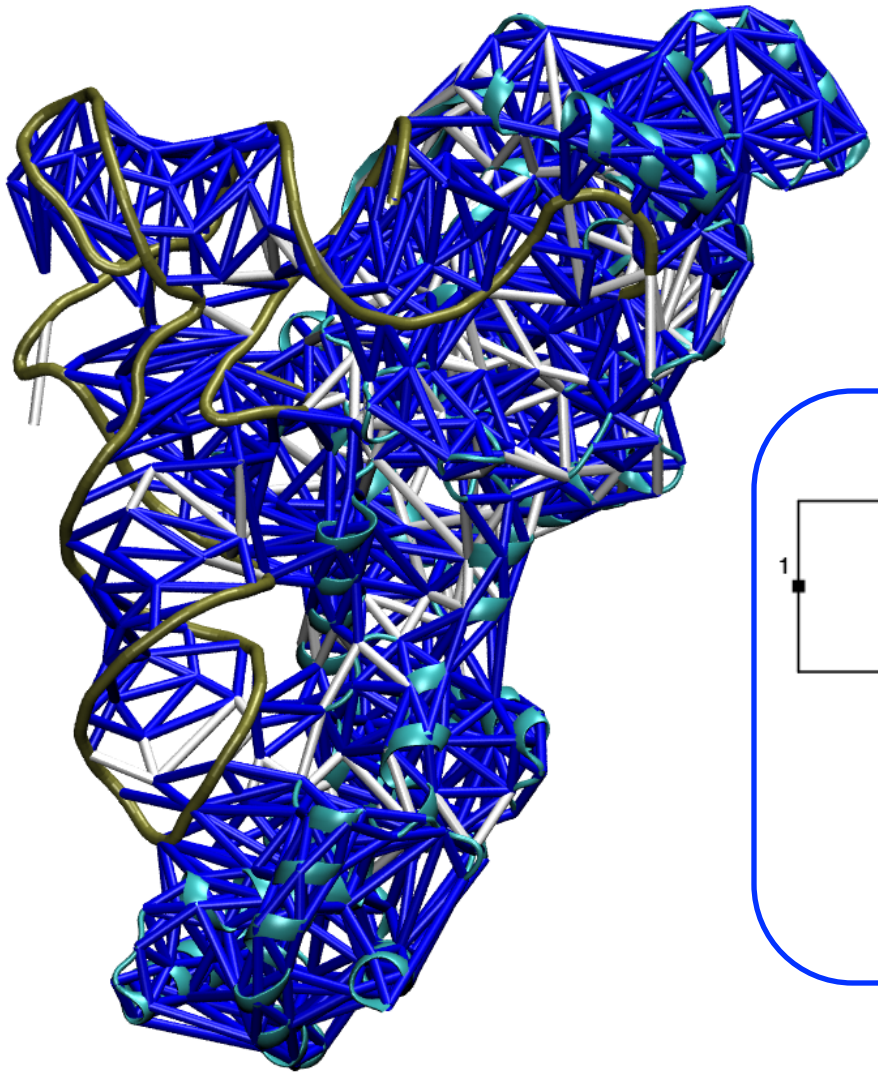
Community Structure Reveals Function in GluRS

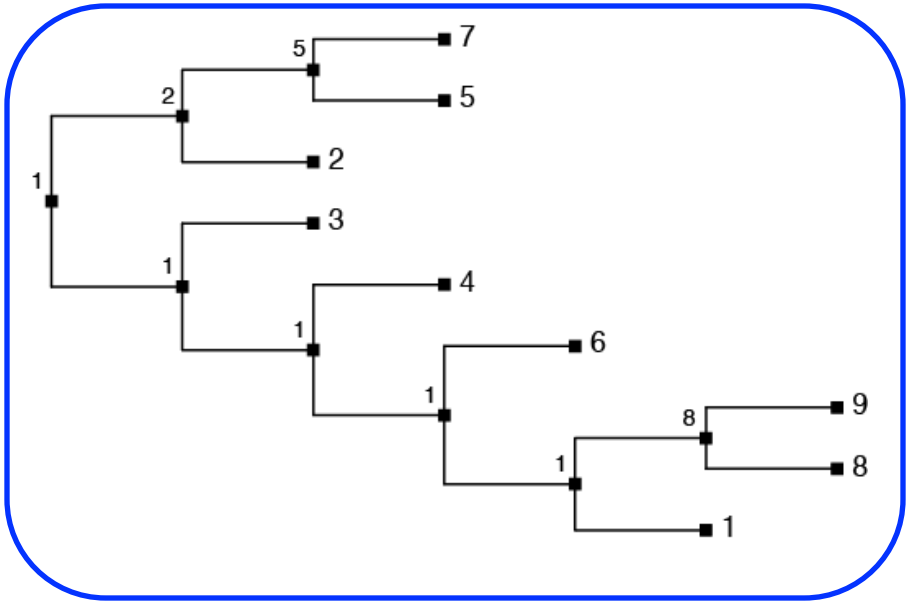


Community Structure Reveals Function in GluRS



Communities Partition the Interaction Network Hierarchically





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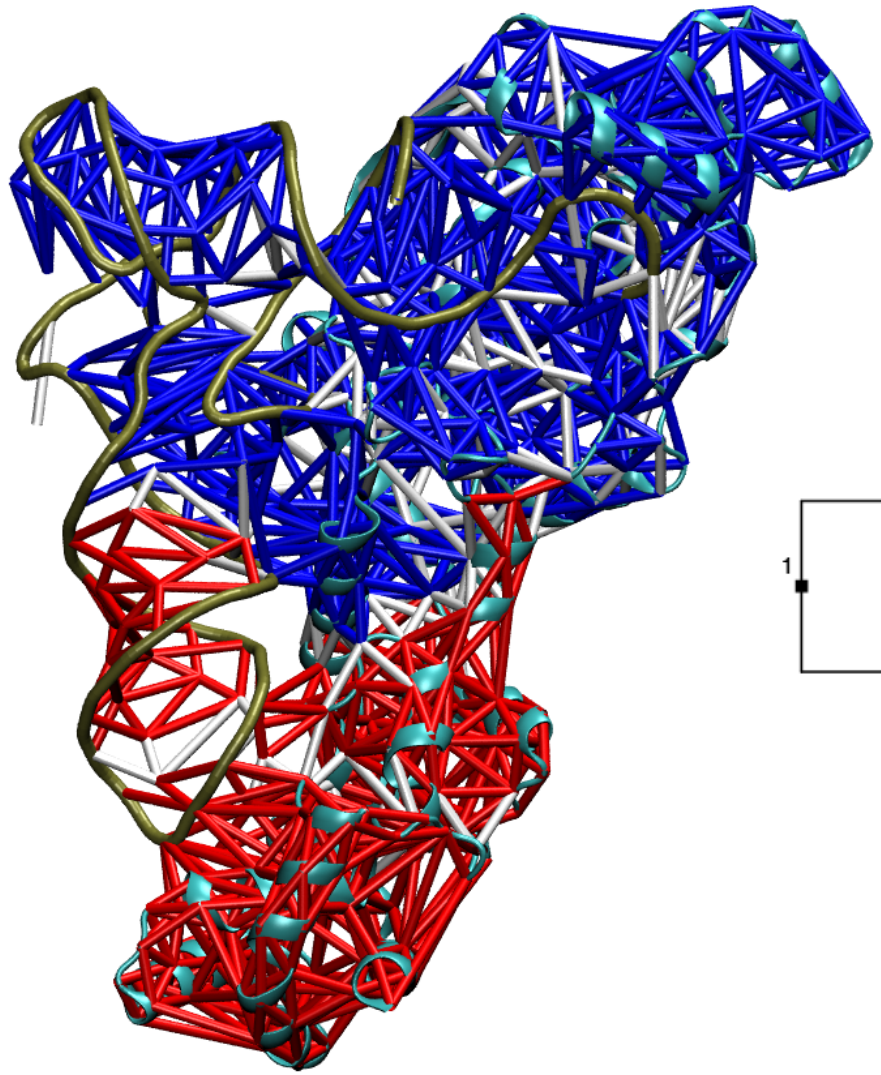
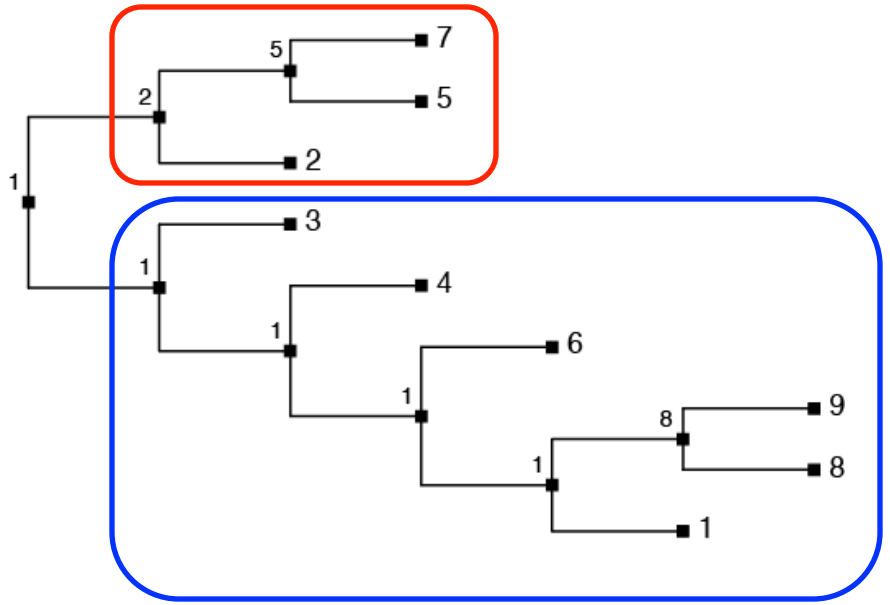
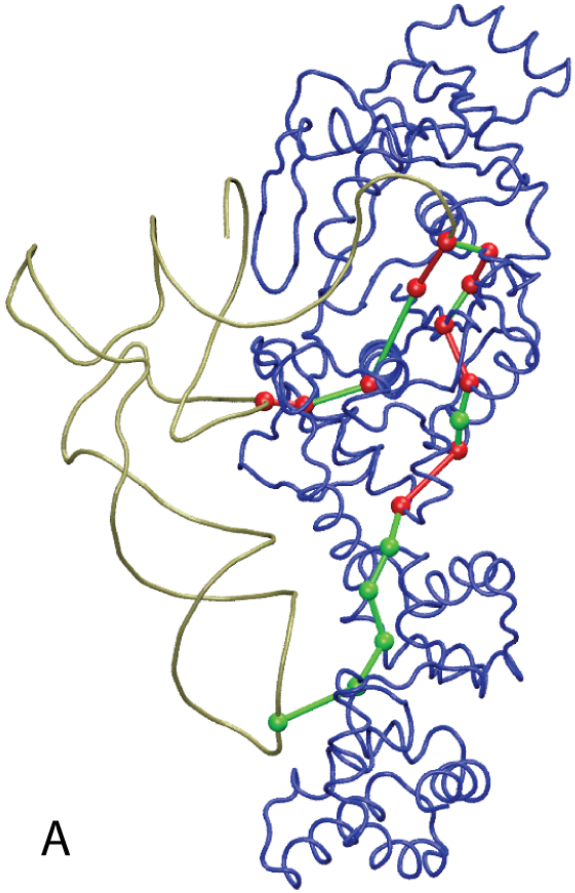




Dynamical Networks, Conservation, and Betweeness

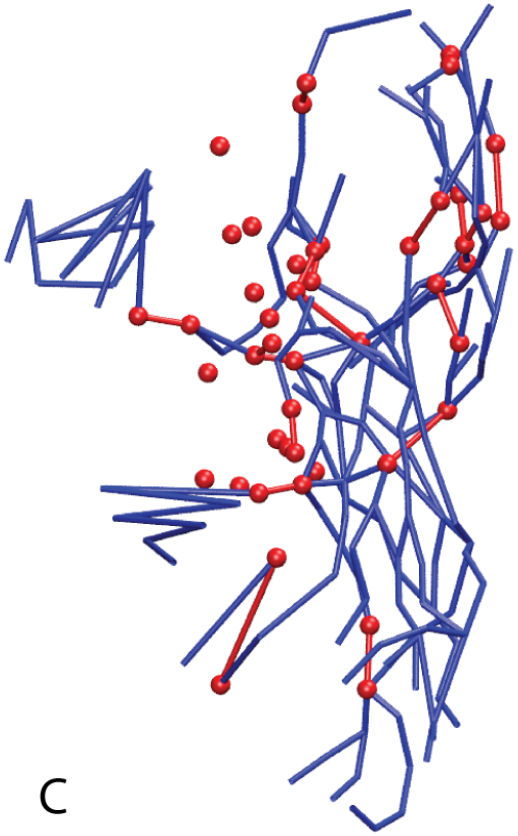


A

Optimal signal pathways:
U13, U35 to A76

B

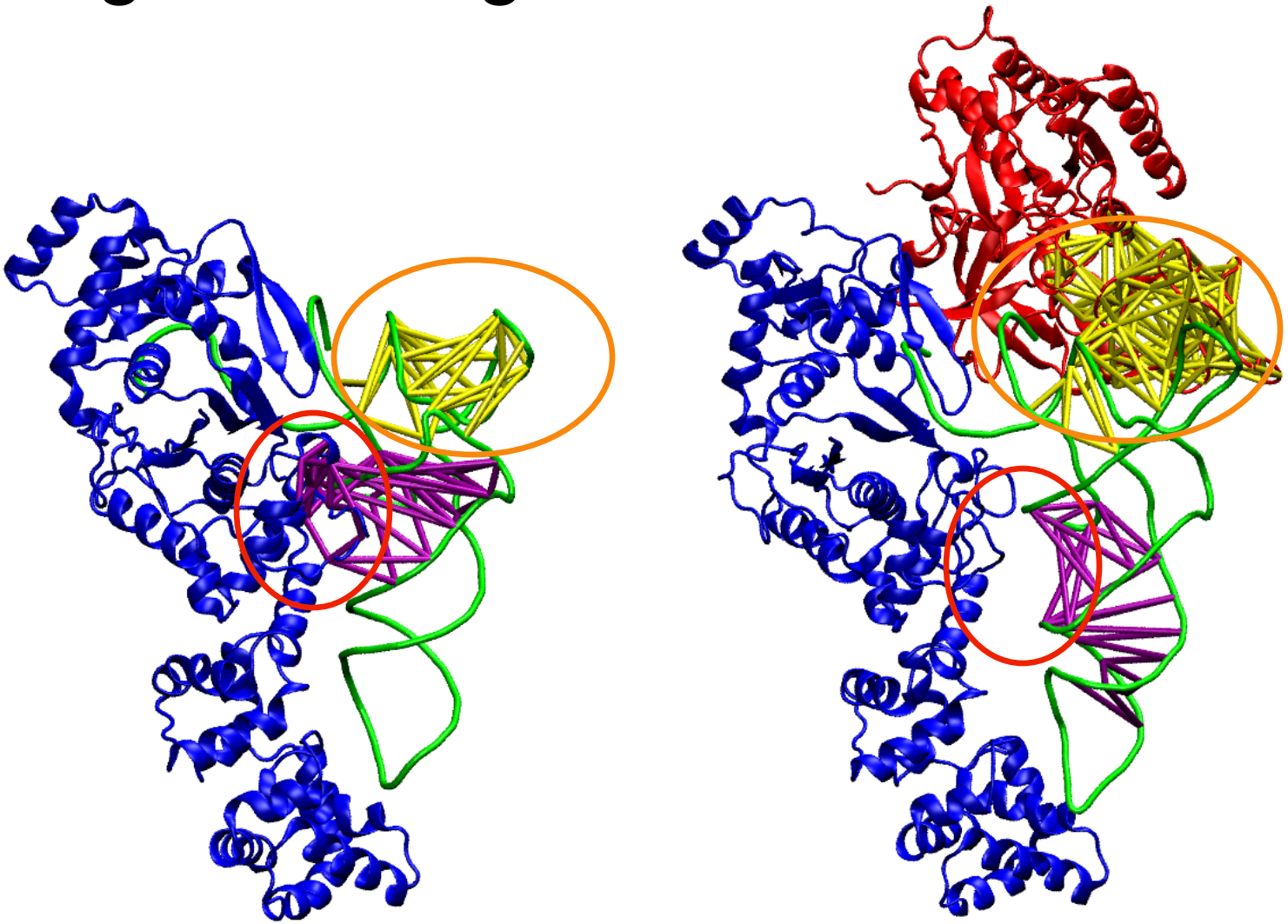
Critical(conserved) nodes
connecting communities



C

Betweeness routes - highest
density pair optimal paths

Change in Protein:RNA Contacts During tRNA Migration: AARS to EF-Tu



FEBS 2010

purple - D arm community

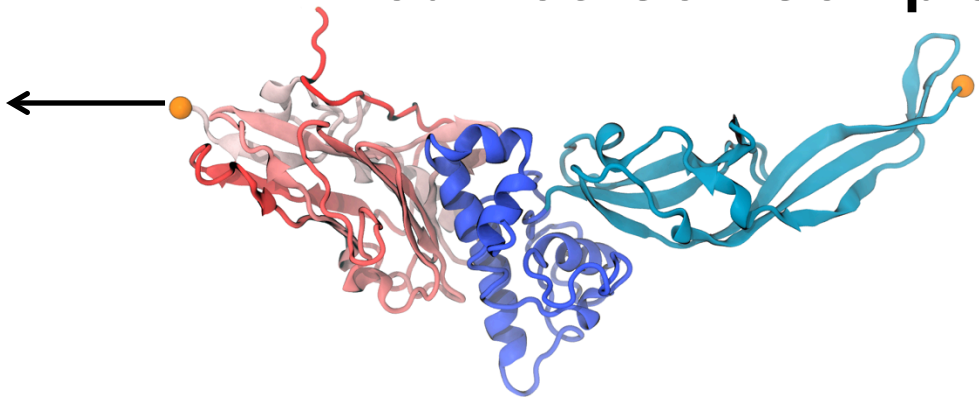
yellow - T arm community

Force Propagation Theory: Network Analysis and AMF Experiments*

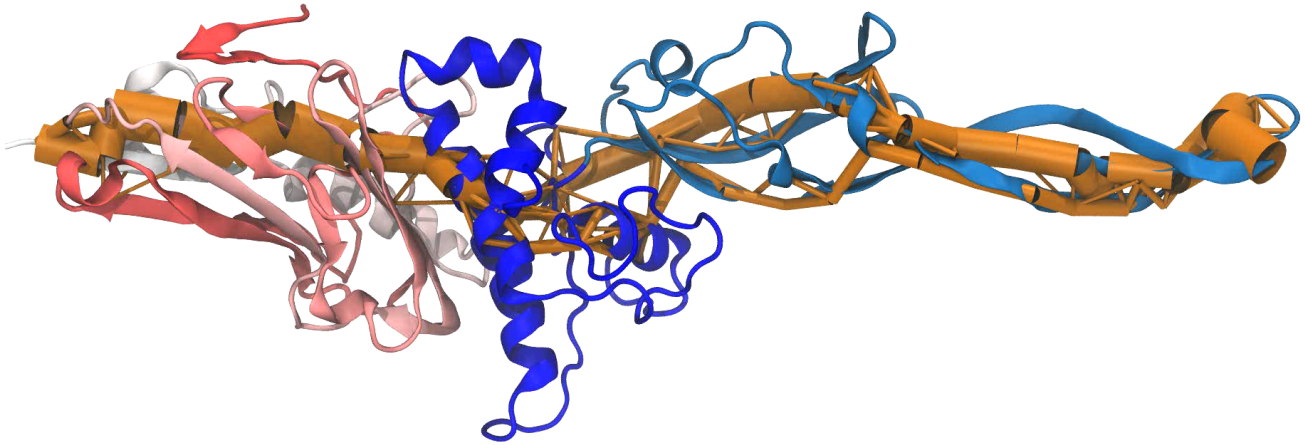
$$\langle \Delta \mathbf{r}_i \Delta \mathbf{r}_j^T \rangle = k_B T \frac{\partial \mathbf{r}_j}{\partial \mathbf{F}_i}$$

Based on Callen (19.14) where $\Delta r_i = r_i(t) - \langle r_i(t) \rangle$ and r_i is the position of atom i.

XMod-Doc:Coh Complex



* Schoeler, Bernardi,…Bayer, Schulten,Nash, Gaub– Dockerin/Cohesin Interactions in Cellulosomes, Nanoletters 2015



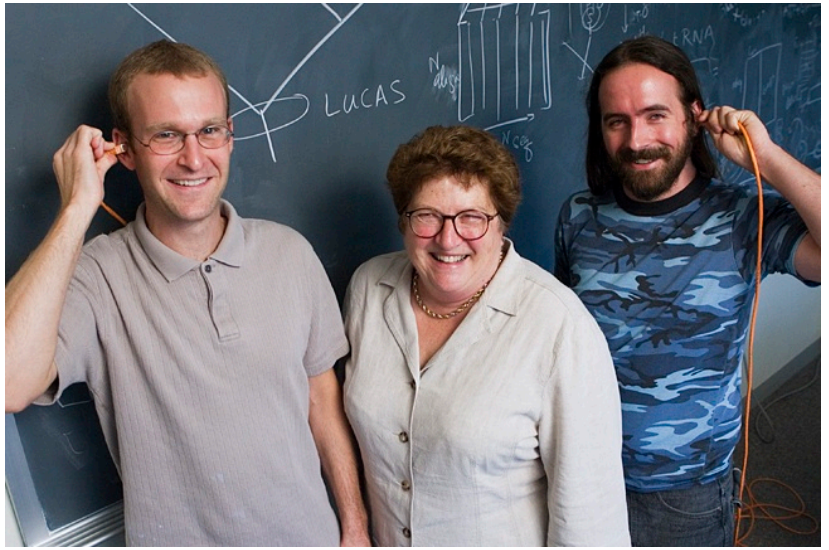
VMD/MultiSeq Tutorials

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

https://uofi.app.box.com/files/0/f/3936123957/BerkeleyWorkshop

Acknowledgements

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



Kirby Vandivort John Stone