Center for Theoretical Biological Physics, UC San Diego
McCammon Group

Assembly of the smaller ribosomal subunit - reduced model computations

Dr. Kay Hamacher

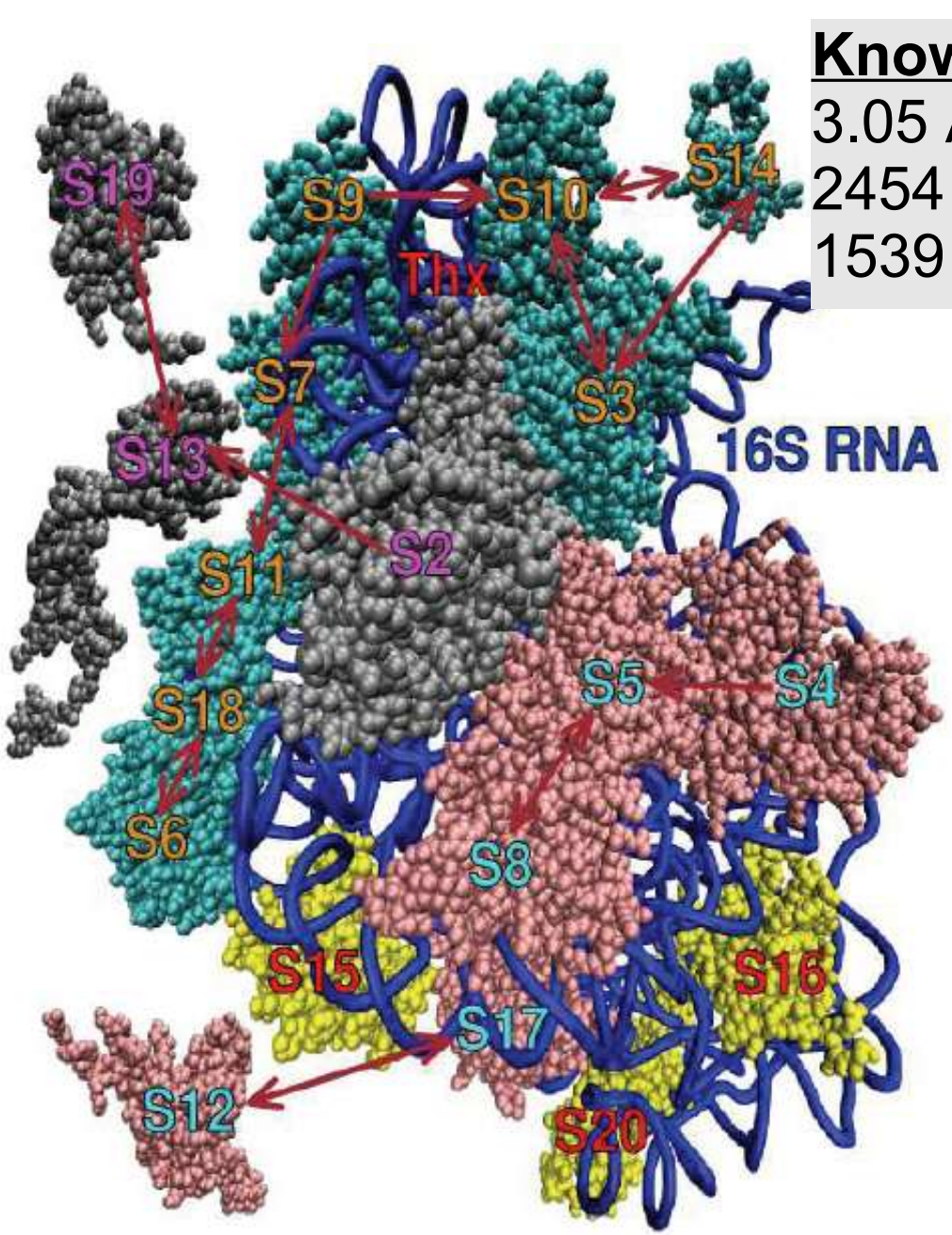
McCammon Group meeting
07.02.2006

Hamacher, Trylska, McCammon, **PLoS Comp. Biol**., 2(2): e10, 2006

Overview

- **Introduction: Ribsome, Structure, Method**
- **Details on computation & Validation**
- **Emerging Picture**
- **Final Remarks**

The Ribosome



Known structure from *T. Thermophilus*:

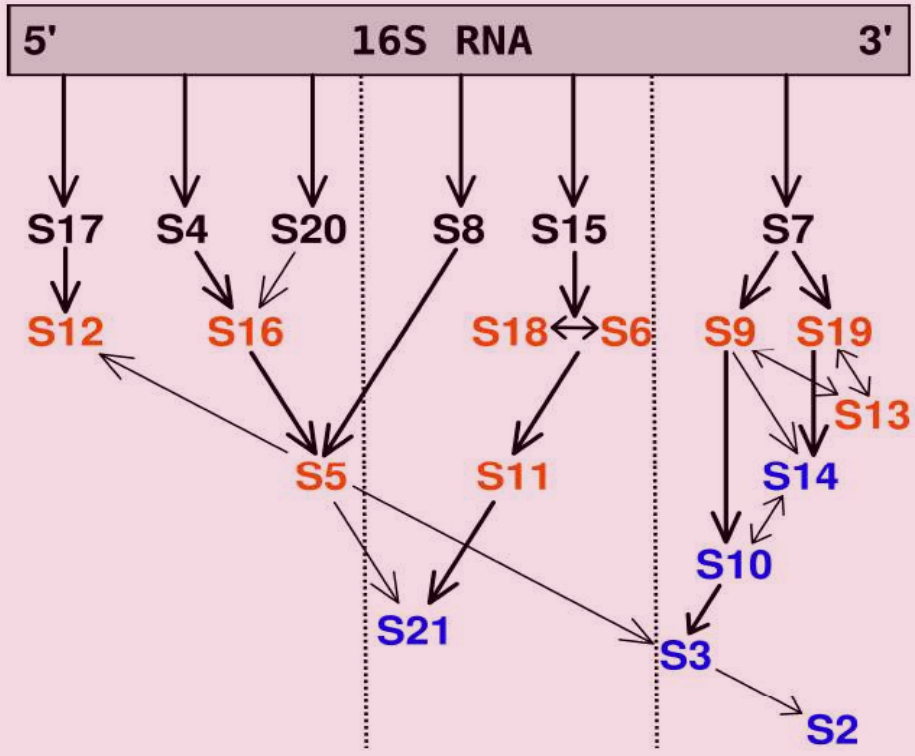
3.05 Å resolution

2454 amino acids

1539 nucleic acids

} ~ 4000 C_α/P beads

Known Assembly Map of *E.coli*



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Self-Consistent-Pair-Contact-Potential (SCPCP) Method

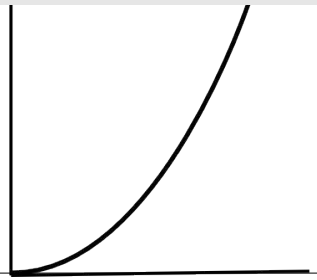
Coarse Grained Hamiltonian (beads on a chain)

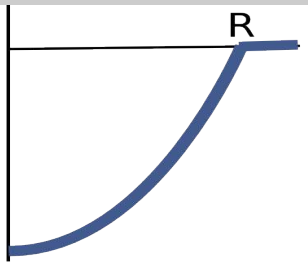
$$H = \frac{TK}{2}\sum_{i=1}^{N-1} \Xi_{i,i+1}\left(\vec{r}_{i,i+1} - \vec{r}^{(0)}_{i,i+1}\right)^2 - \sum_{i,j=1}^{N,N} \frac{\Delta_{i,j}\kappa_{i,j}}{2} X_{i,j}\Theta\left(X_{i,j}\right)$$

Harmonic potential along the chain(s), T: free-energy contribution constant

Attractive contact potential

$\kappa_{i,j}$: specificity of interaction





with

$$X_{i,j} = R^2 - \left(\vec{r}_{i,j} - \vec{r}^{(0)}_{i,j}\right)^2 \quad \text{and} \quad \Xi_{i,i+1} = \begin{cases} 1 : i, i+1 \in same\ chain \\ 0 : i, i+1 \notin same\ chain \end{cases}$$

$$\vec{r}_{i,j} := \vec{r}_i - \vec{r}_j \qquad \vec{r}^{(0)}_{i,j} : \text{native state}$$

Micheletti et al, *Phys. Rev. Lett.* 2001

Self-Consistent-Pair-Contact-Potential (SCPCP) Method

Coarse Grained Hamiltonian (beads on a chain)

C_α

$$H = \frac{TK}{2}\sum_{i=1}^{N-1}\Xi_{i,i+1}\left(\vec{r}_{i,i+1}-\vec{r}^{(0)}_{i,i+1}\right)^2 - \sum_{i,j=1}^{N,N}\frac{\Delta_{i,j}\kappa_{i,j}}{2}X_{i,j}\Theta\left(X_{i,j}\right)$$

Harmonic potential along the chain(s), T: free-energy contribution constant

Attractive contact potential

$\kappa_{i,j}$: specificity of interaction

Computation in a self-consistency-loop:

$$p_{i,j} := \left\langle \Theta\left(X_{i,j}\right)\right\rangle_H$$

with

$$X_{i,j} = R^2 - \left(\vec{r}_{i,j}-\vec{r}^{(0)}_{i,j}\right)^2$$

and

$$\Xi_{i,i+1} = \begin{cases} 1 : i, i+1 \in same\ chain \\ 0 : i, i+1 \notin same\ chain \end{cases}$$

$$\vec{r}_{i,j} := \vec{r}_i - \vec{r}_j$$

$\vec{r}^{(0)}_{i,j}$: native state

Micheletti et al, *Phys. Rev. Lett.* 2001

Validating Approach

Spearman Ranking Coefficient between measured and computed B-factors

RNA	S2	S3	S4	S5	S6
0.556	0.683	0.603	0.458	0.328	0.392
	S7	**S8**	**S9**	**S10**	**S11**
	0.417	0.260	0.611	0.638	0.280
	S12	**S13**	**S14**	**S15**	**S16**
	0.155	0.339	0.479	0.657	0.466
	S17	**S18**	**S19**	**S20**	**THX**
	0.670	0.634	0.448	0.296	0.403

For 95% signifigance we only need to have $r_s > 0.182$

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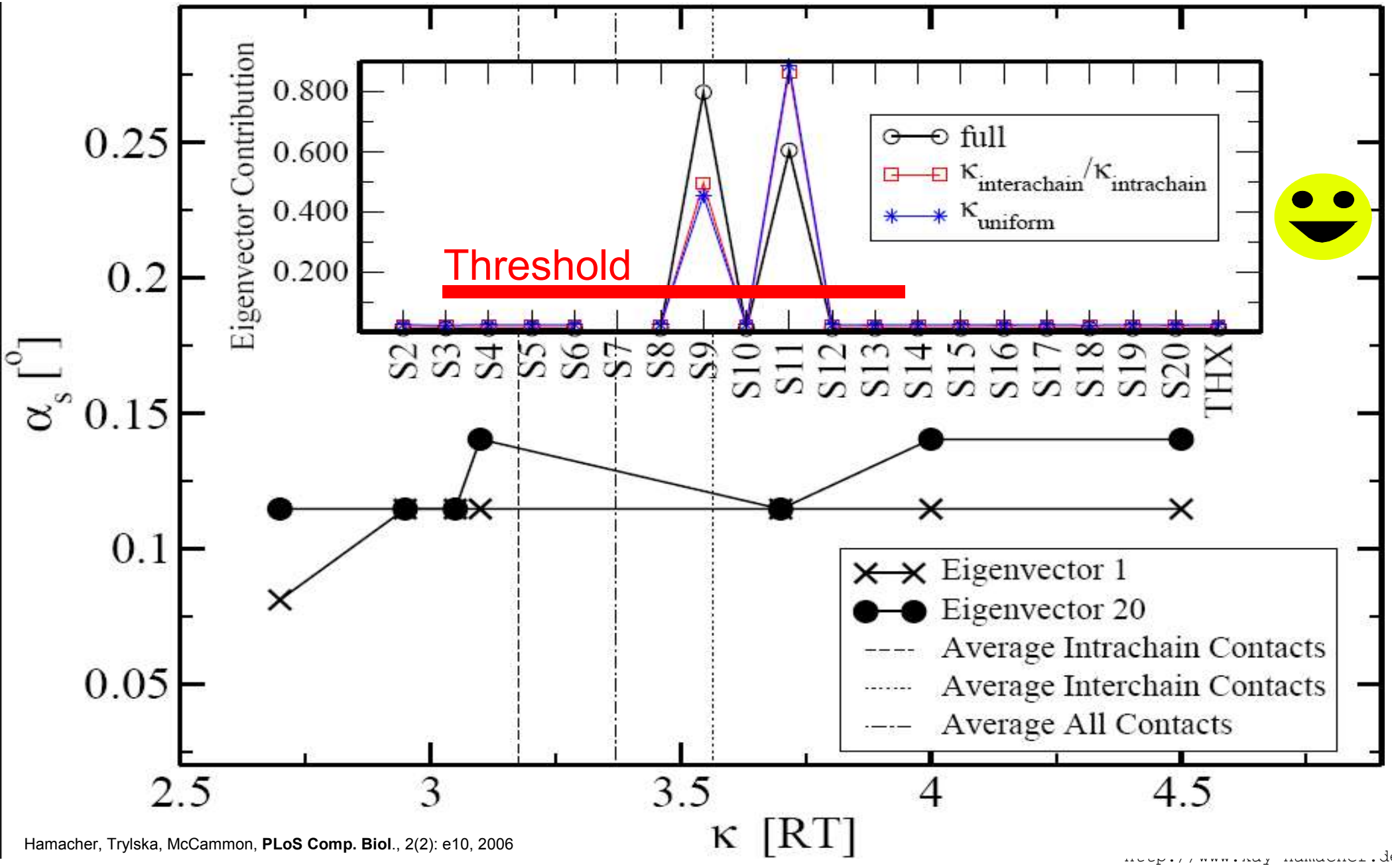
Validating Approach

Sensitivity to parameters



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A *Gedanken*-Experiment

What is the influence of the

presence / absence of

a protein or

a pair of proteins

onto the stability/affinity of a third protein

?

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A *Gedanken*-Experiment

What is the influence of the

All Information constitutes

a Dependency Map

of proteins in the subunit

?

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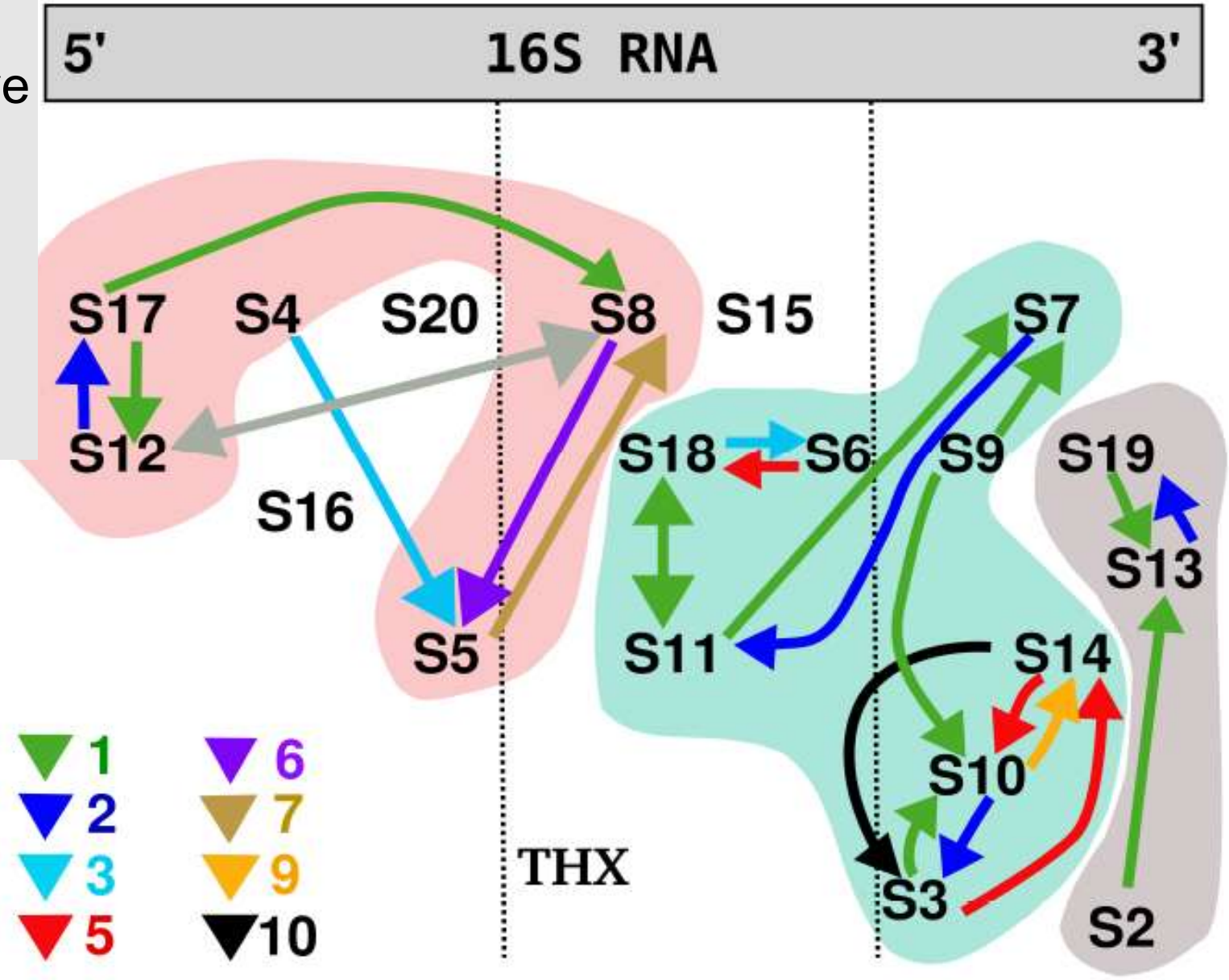
One Protein Removed

Semi-Quantitative Influences

can be

extracted



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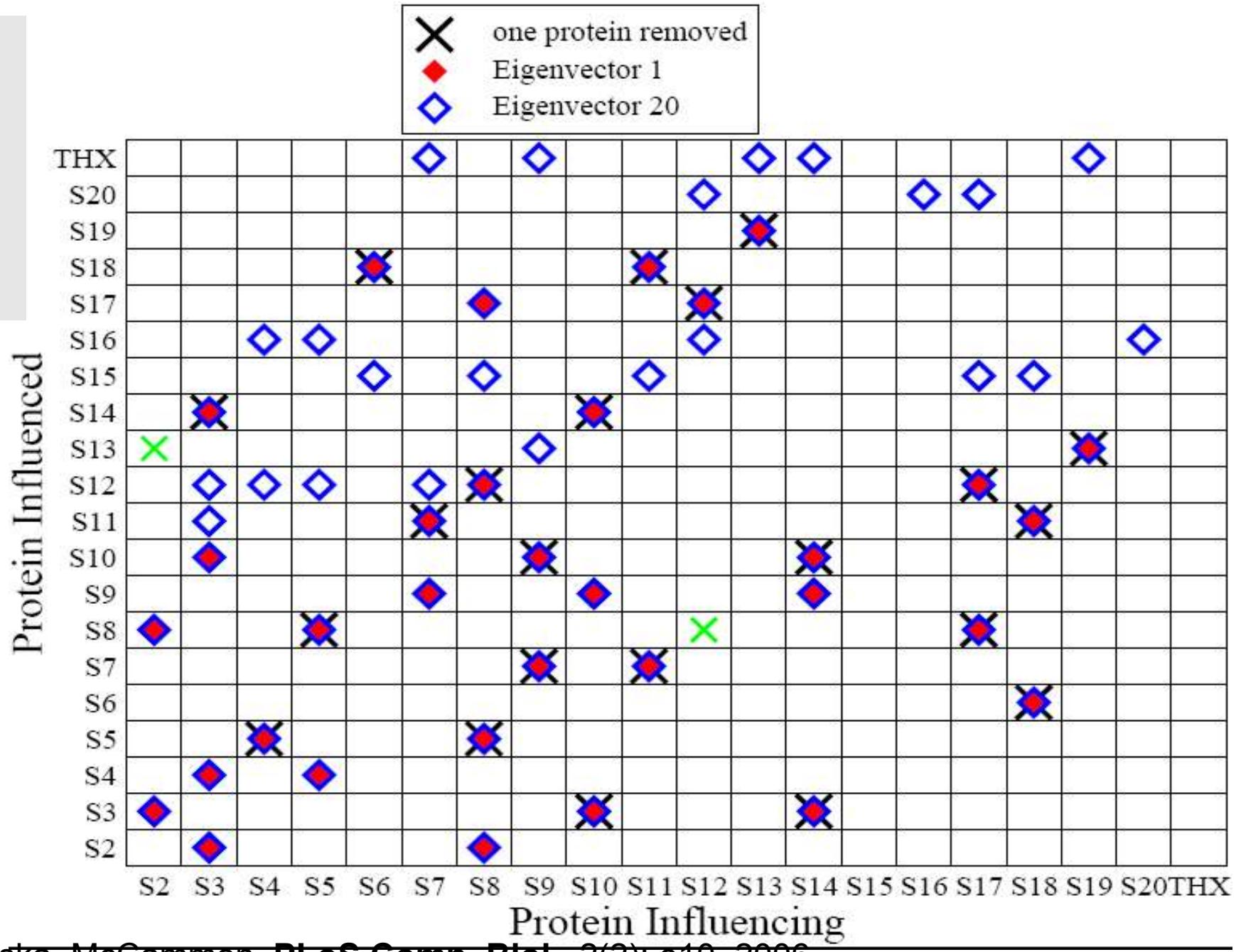
Pairs of Proteins Removed

Consistent with one Protein removal!



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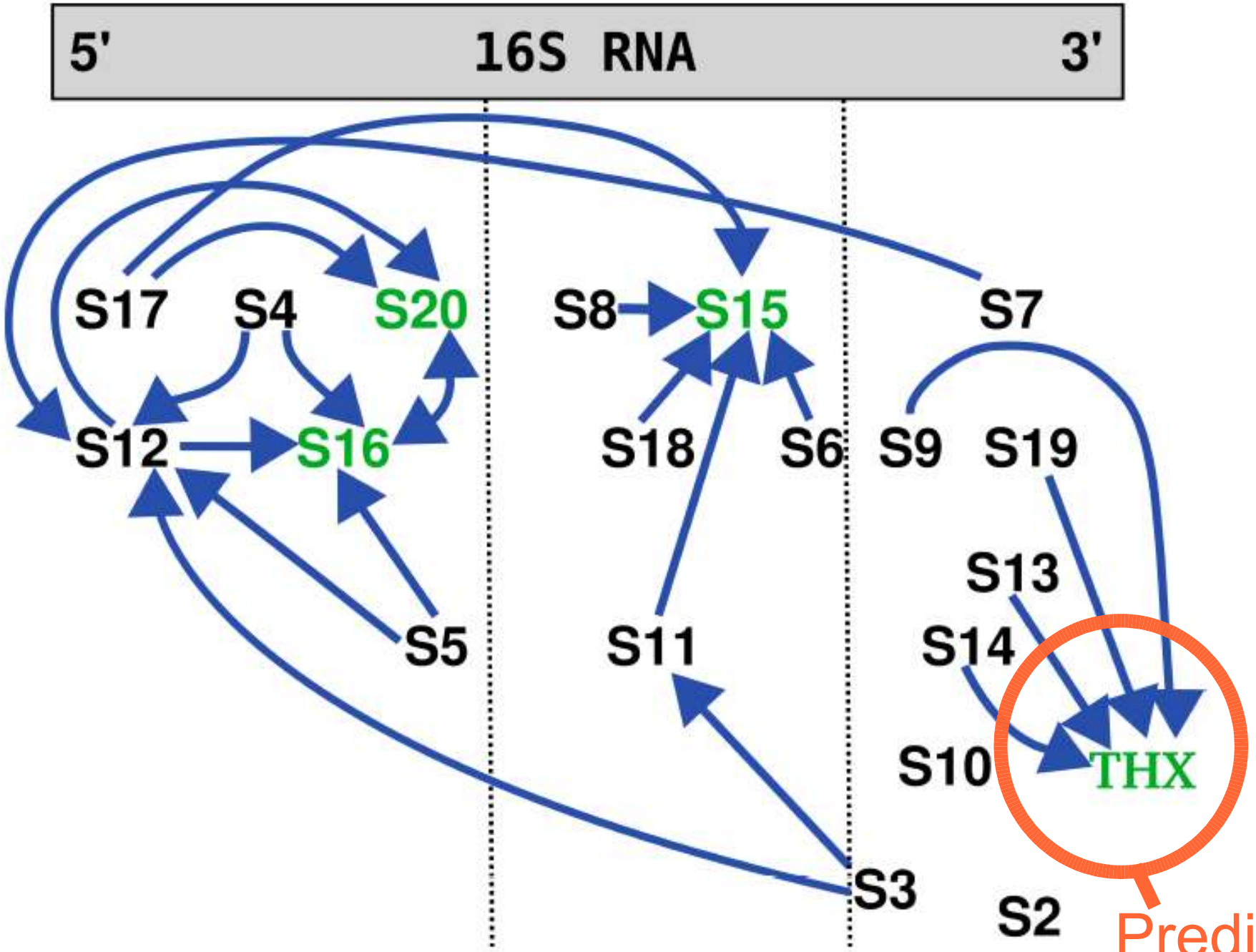
Additional Contributions (no direct contact!)



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Targeting the assembly / the assembled complex

If we want to make the Ribosome dysfunctional

- for therapeutic purposes (antibiotics)

- to validate the results experimentally

the most promising candidates are

S3, S10, S14 or **S6, S18**

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Acknowledgments

Discussions & Support

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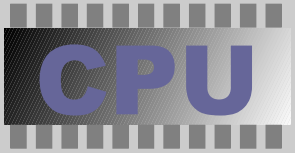

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