Is Sharing Caring?

Elucidating the Effects of the Presence of CRISPR-Cas Systems on Rates of Horizontal Gene Transfer Using Network Analysis

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MolBiol 4C12 Thesis

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Biology Department,
McMaster University

April 4, 2019

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CRISPR-Cas systems

What Are They?

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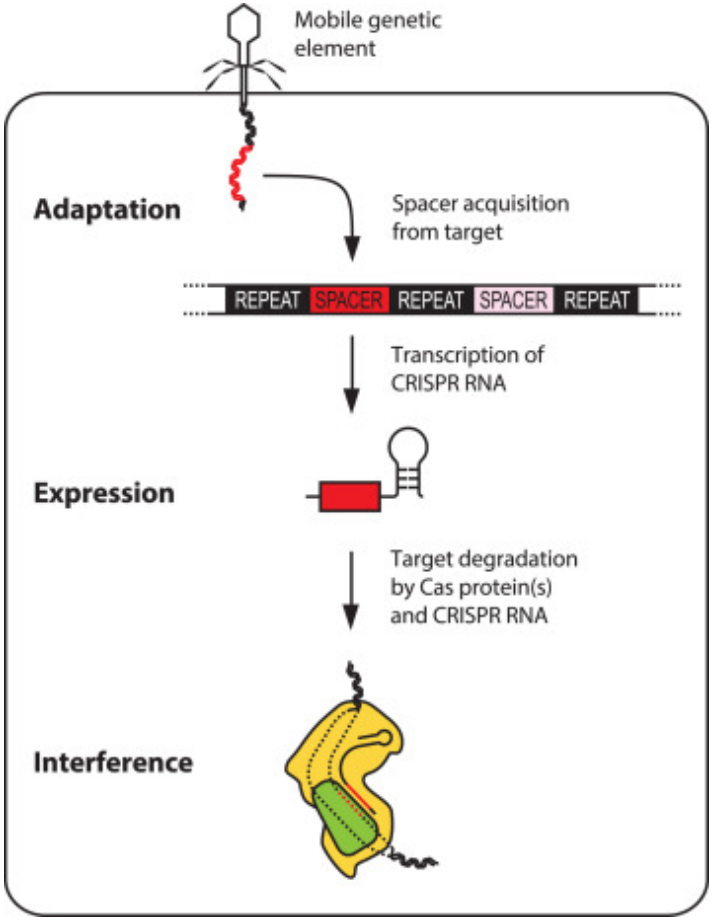
- Adaptive Bacterial Immune System



(Rath et al., 2015)

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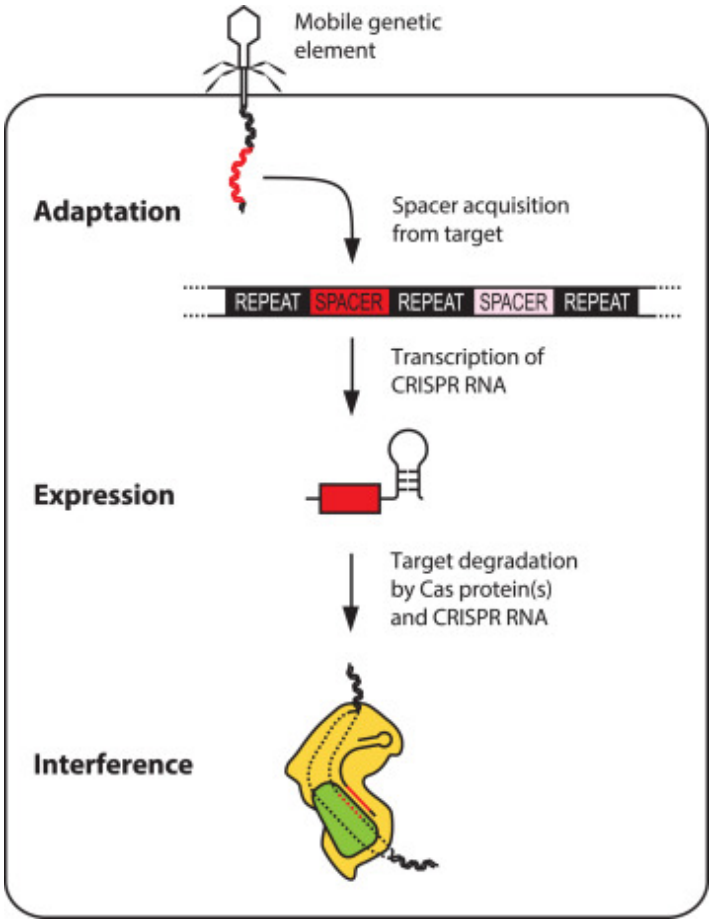

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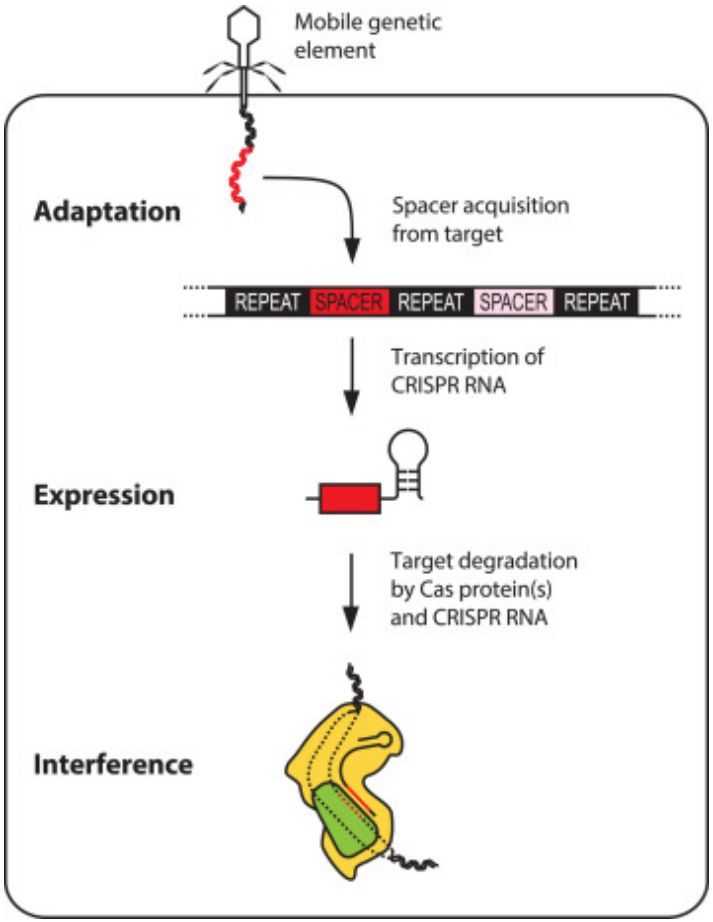

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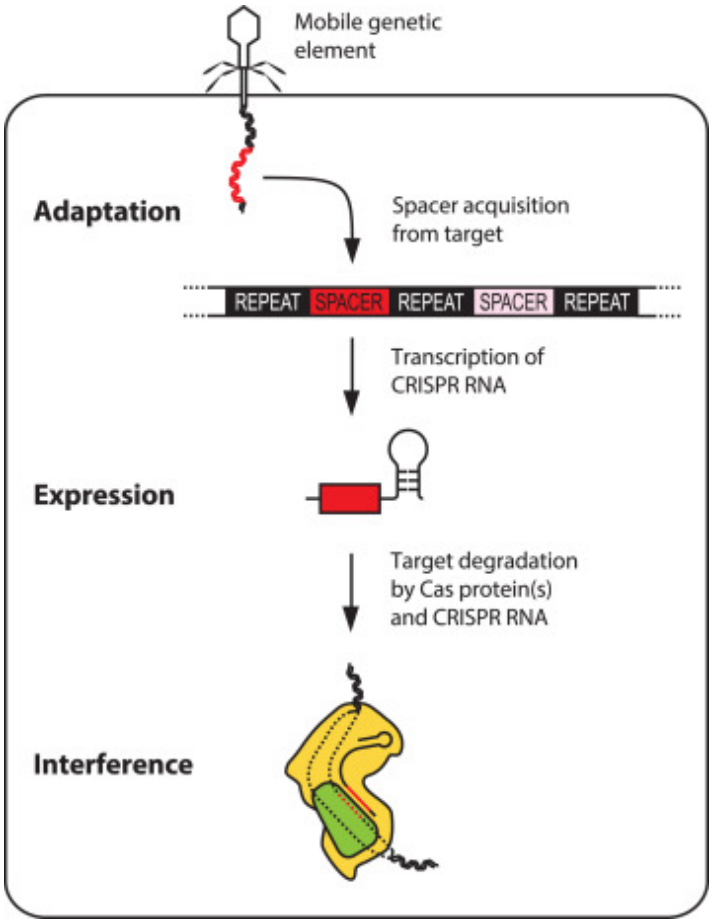

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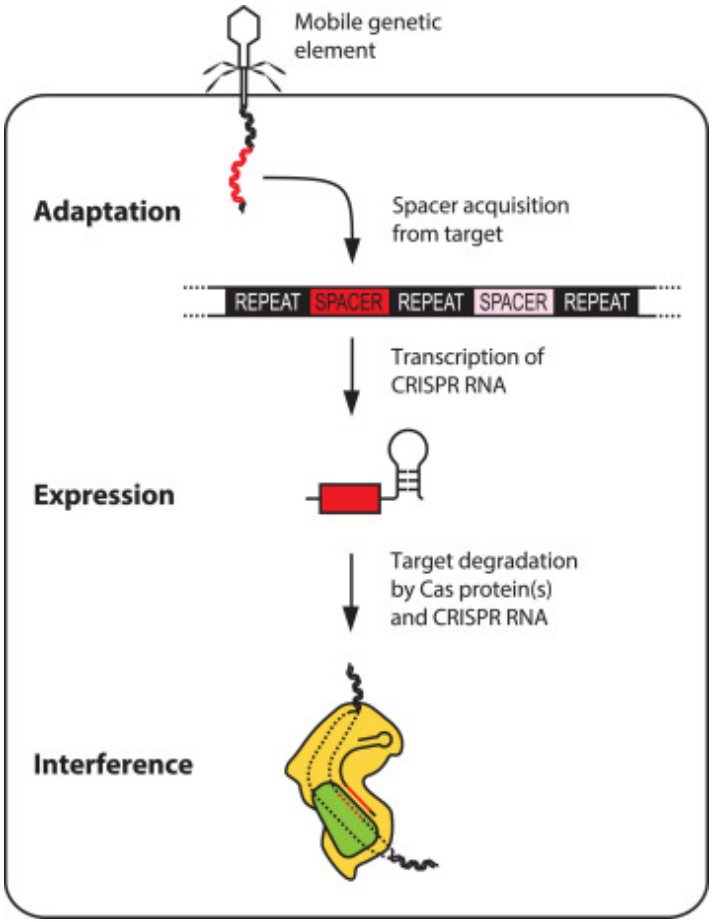
- 45% of bacteria have CRISPR loci ($n = 6782$) (Grissa, I. and Drevet, C. and Couvin, D., 2017)



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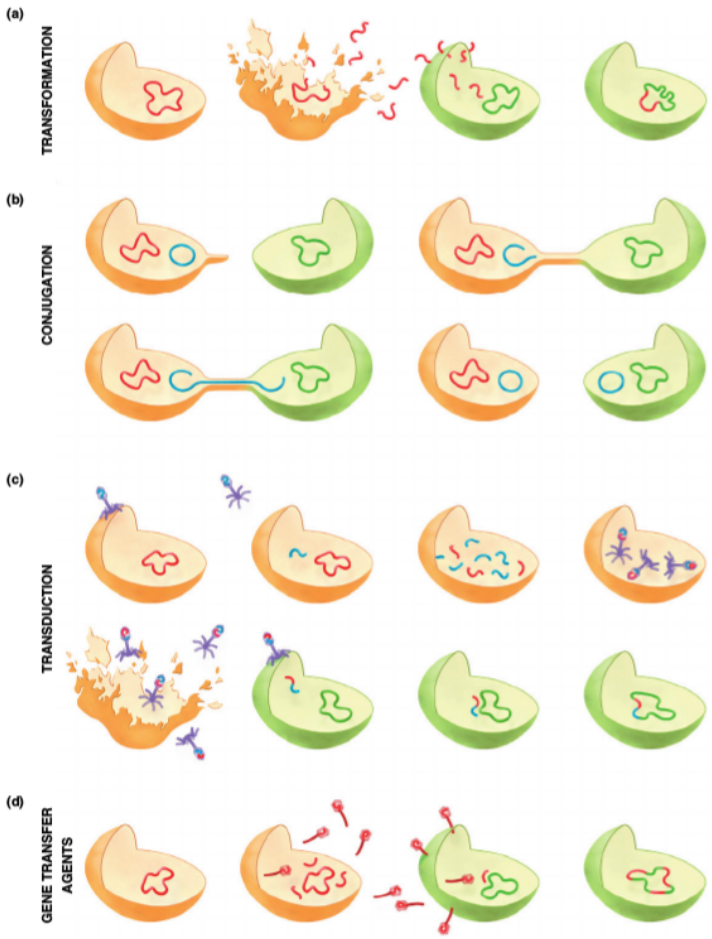
Horizontal Gene Transfer Mechanisms



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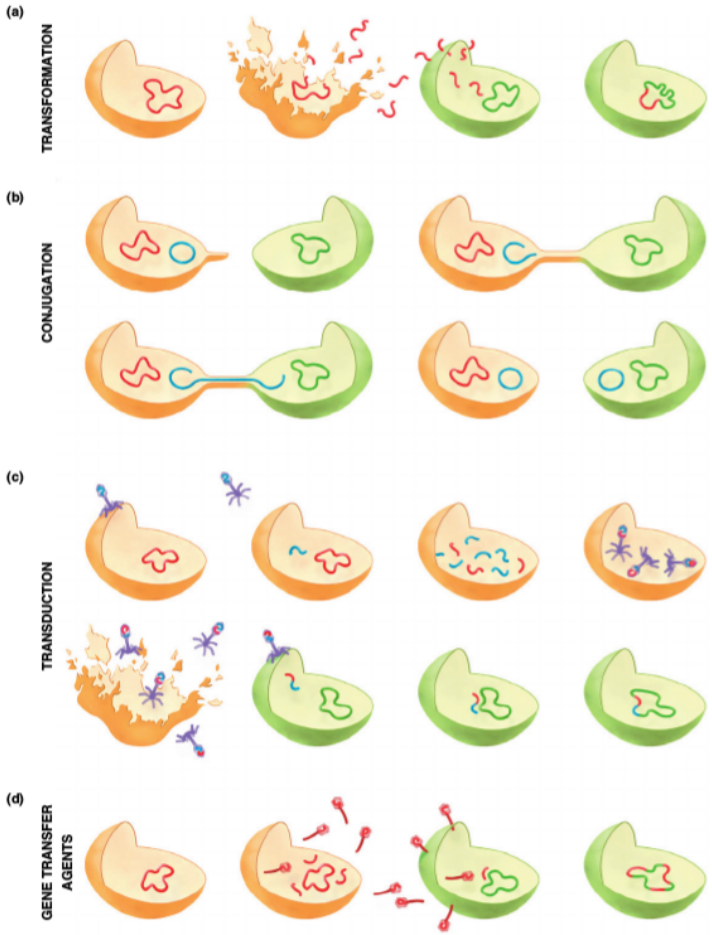

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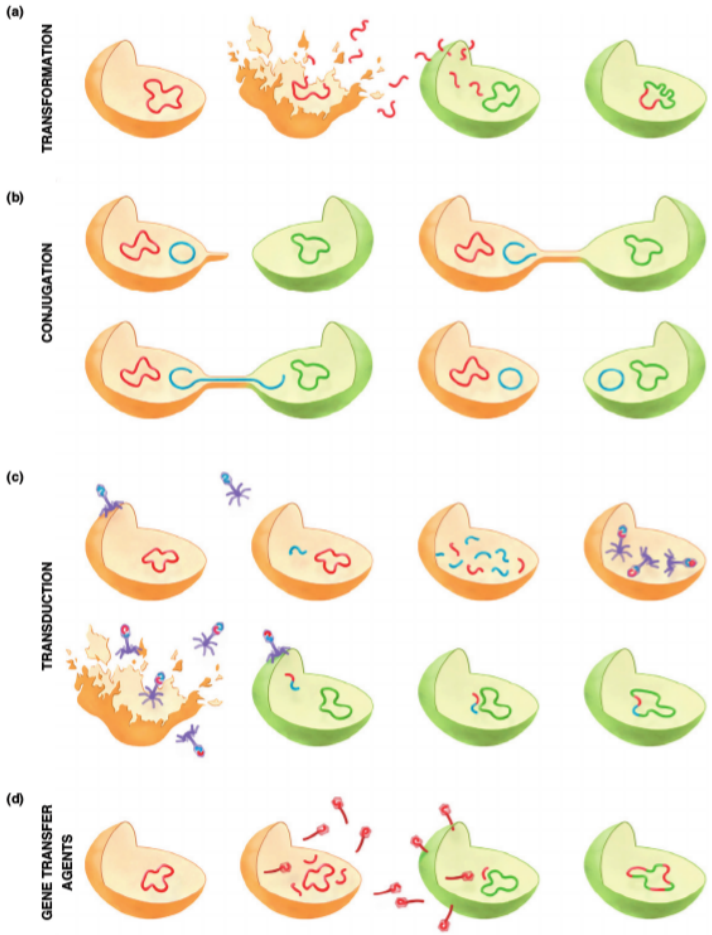

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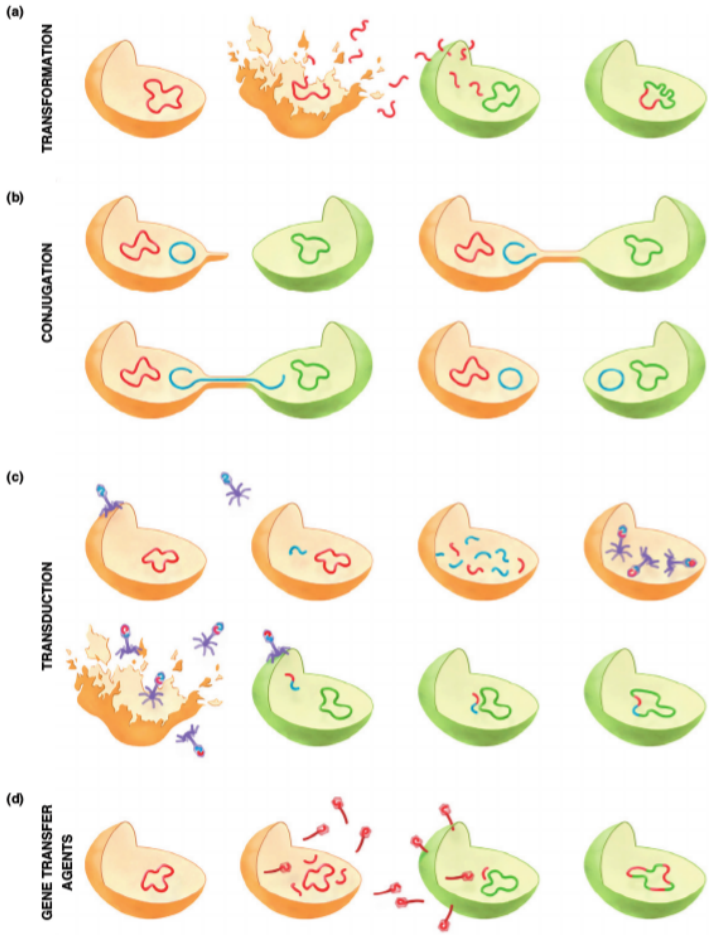

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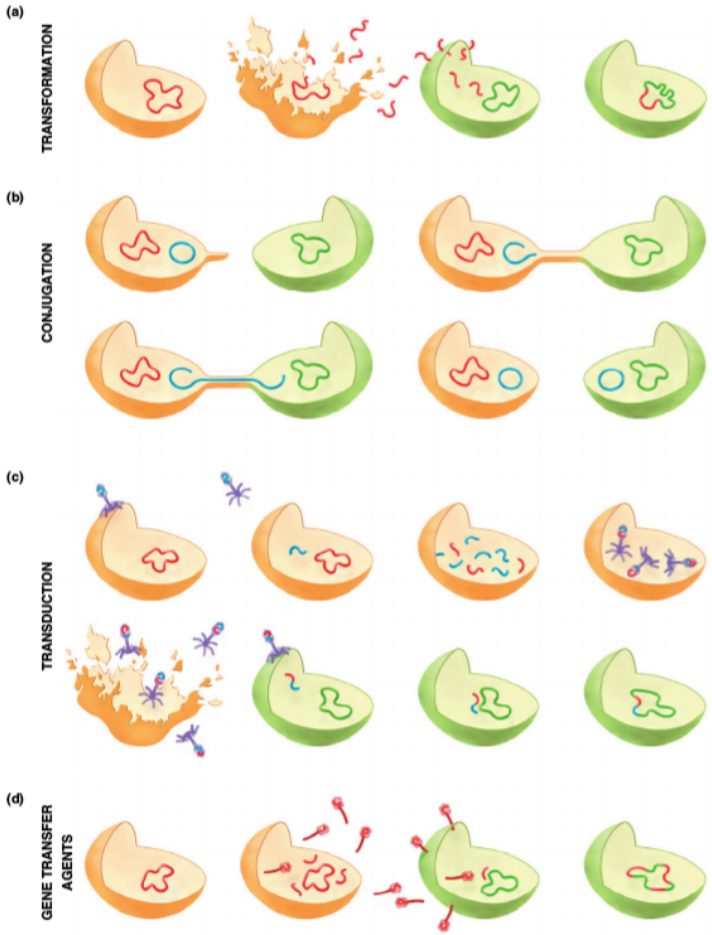

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- **CRISPR-Cas directly affects HGT** (Popa and Dagan, 2011)

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- Amount of exogenous DNA/cell density/phage density

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Phylogenomic Networks

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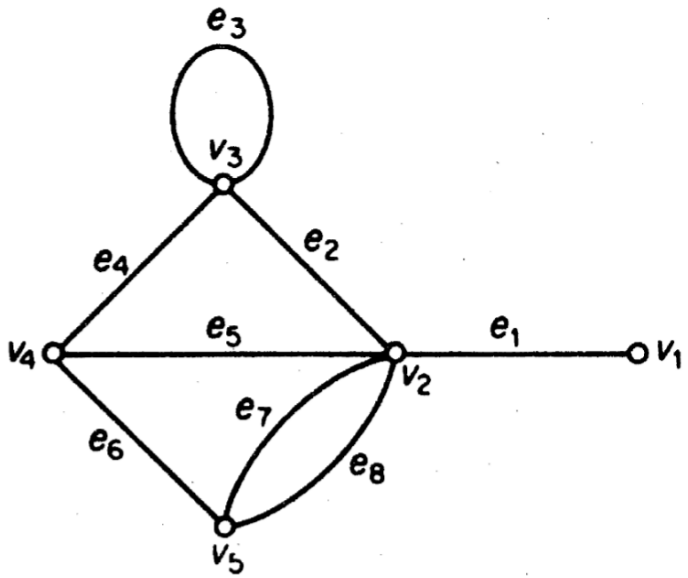

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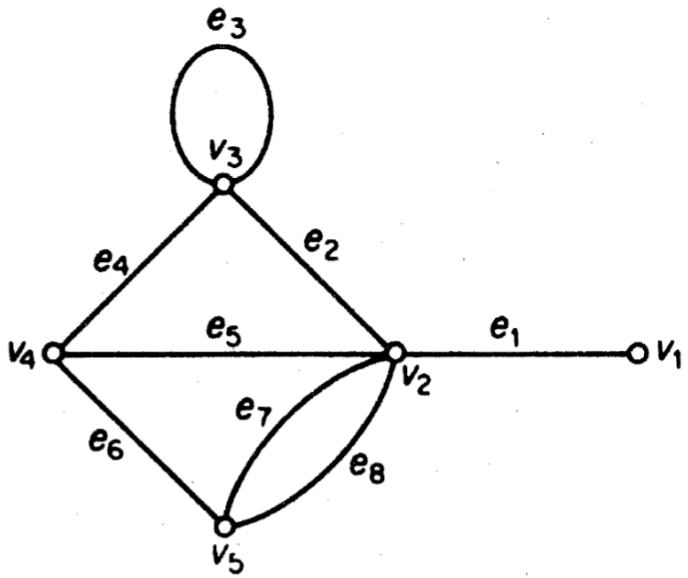

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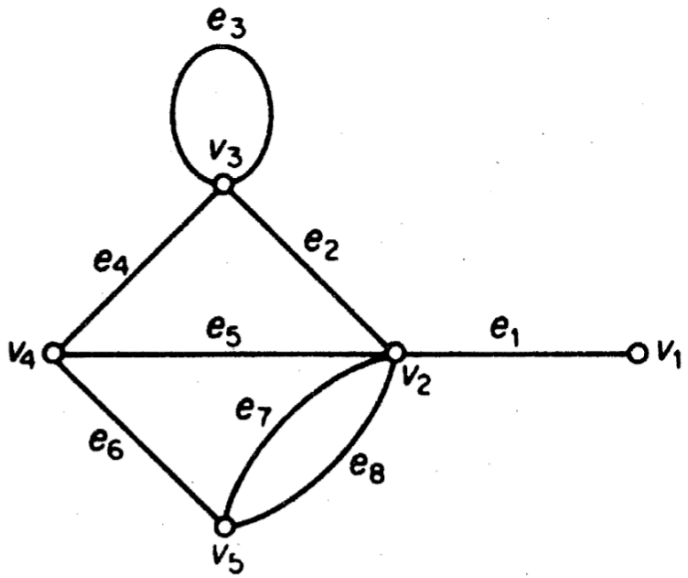

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- Edges can have weights

Do CRISPR Systems Affect Horizontal Gene Transfer?

Yes

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  - CRISPR can enhance transduction-mediated HGT (Watson, Staals, and Fineran, 2018)

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  - Can see inhibitory effects of CRIPSR on HGT over short evolutionary time scales
  - Higher gene indel rates for CRISPR containing OTUs than non-CRISPR containing outgroups

My Project

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Within Network Comparisons

For genera with CRISPR containing OTUs, compare the node statistics of CRIPSR containing OTUs to non-CRISPR containing OTUs.

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Gene Indel Rates vs. Network Statistics

Compare gene Indel rates to node/network statistics for CRISPR containing and non-CRISPR containing OTUs

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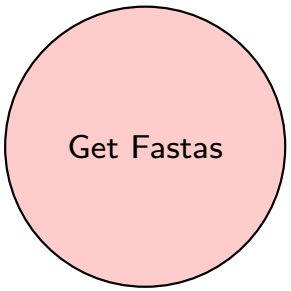

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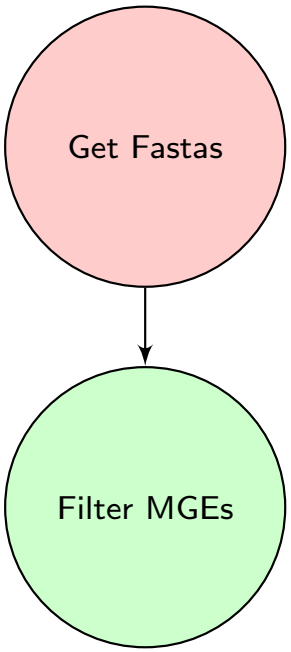

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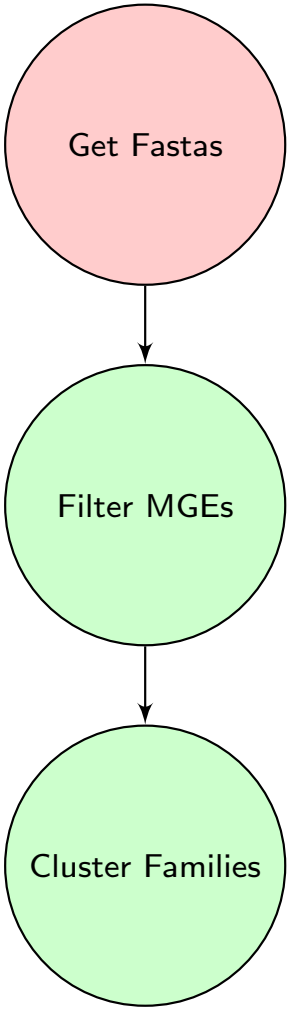

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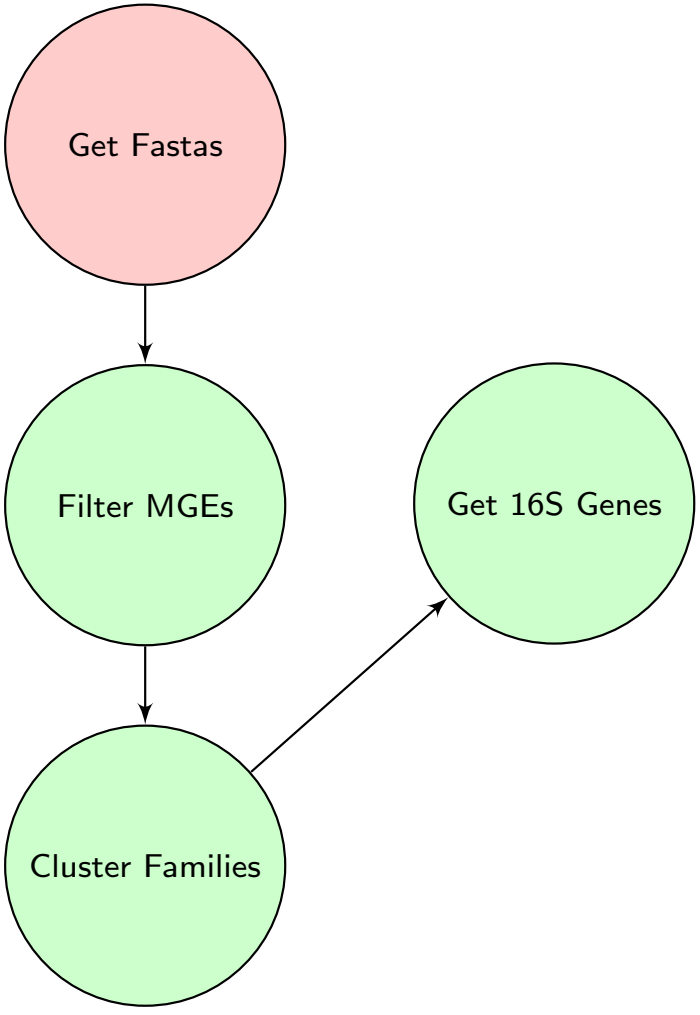

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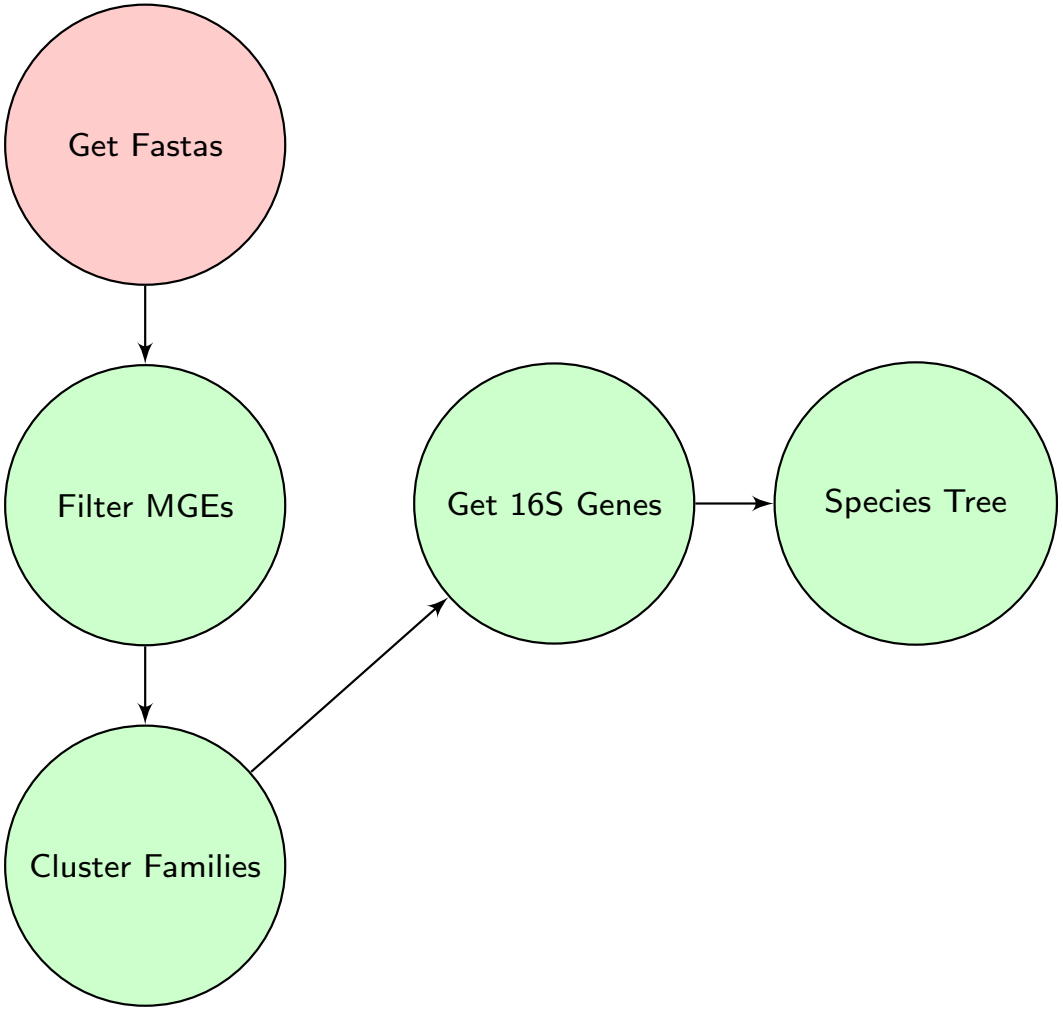

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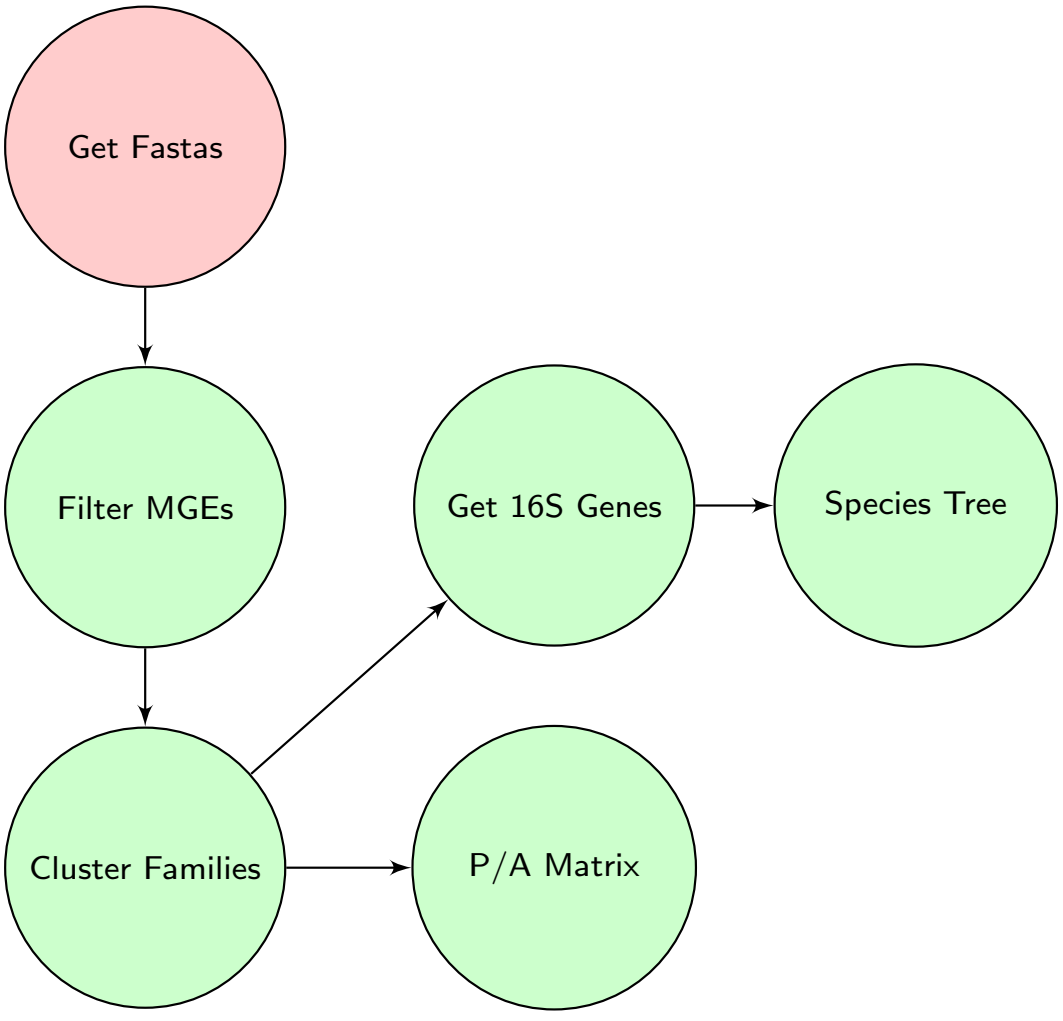

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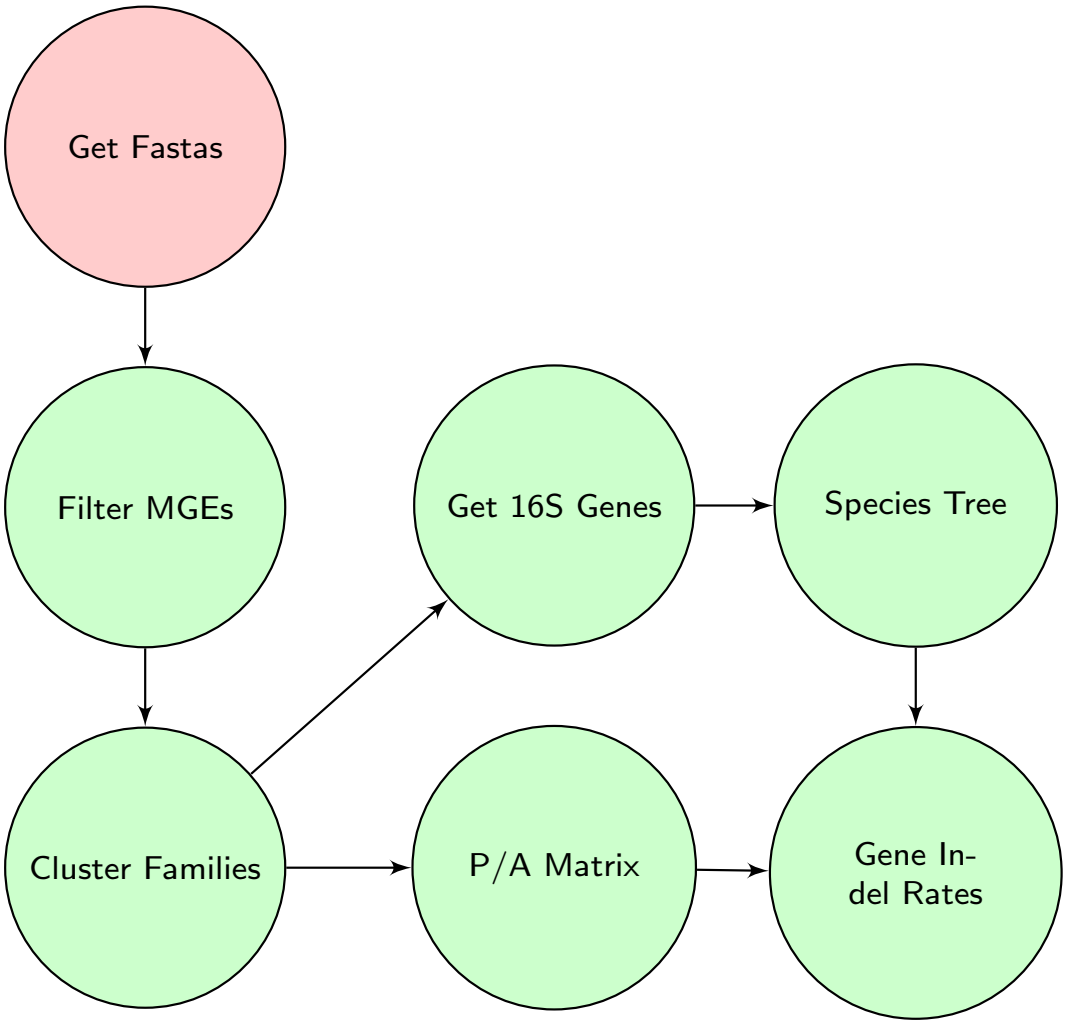

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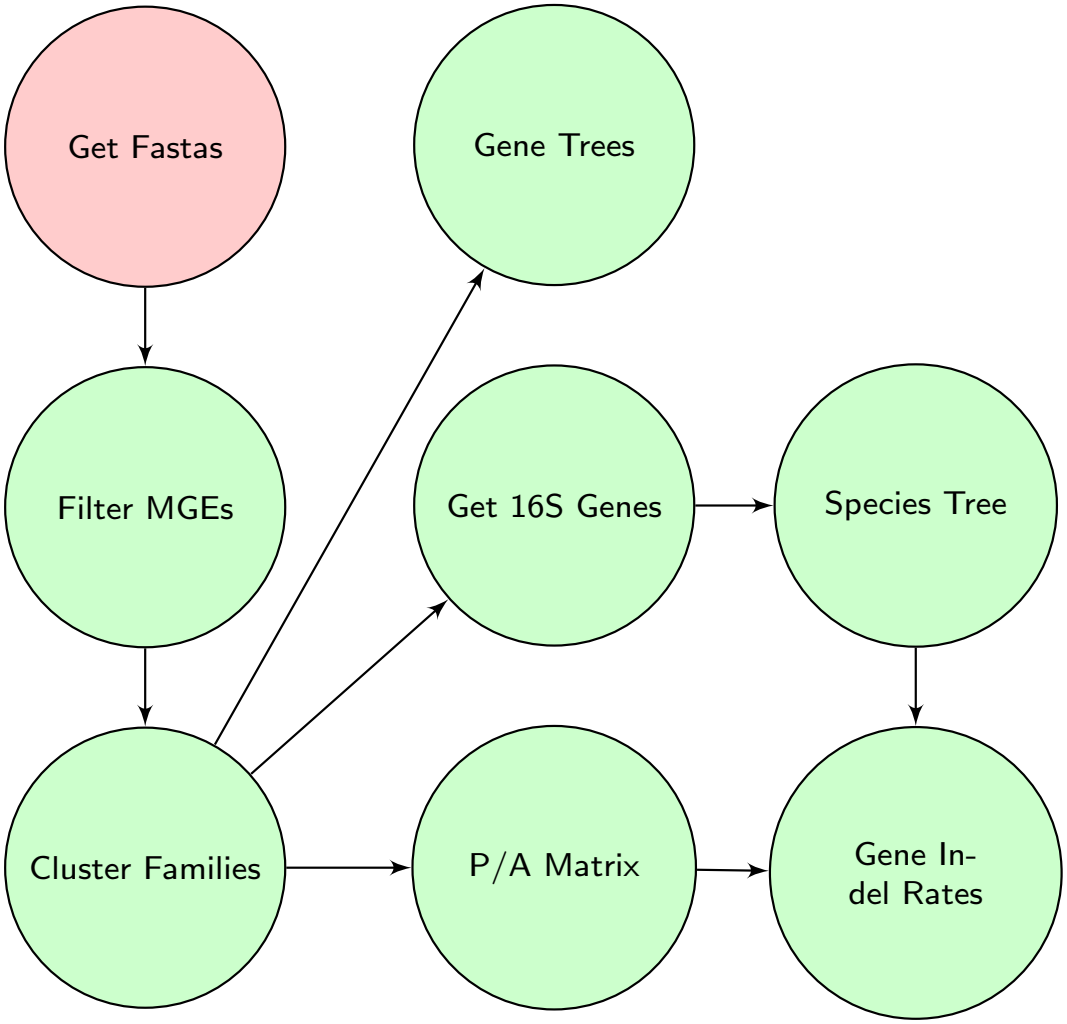

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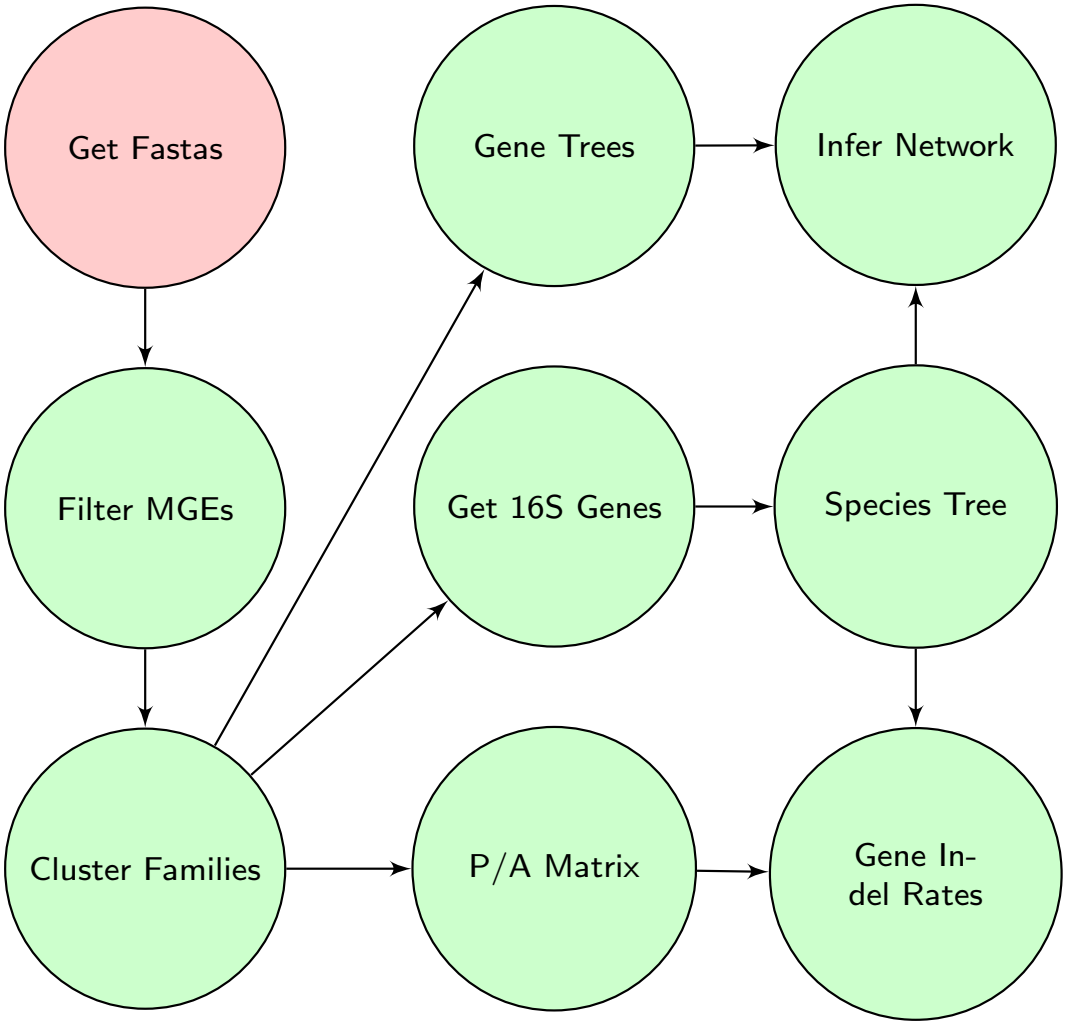

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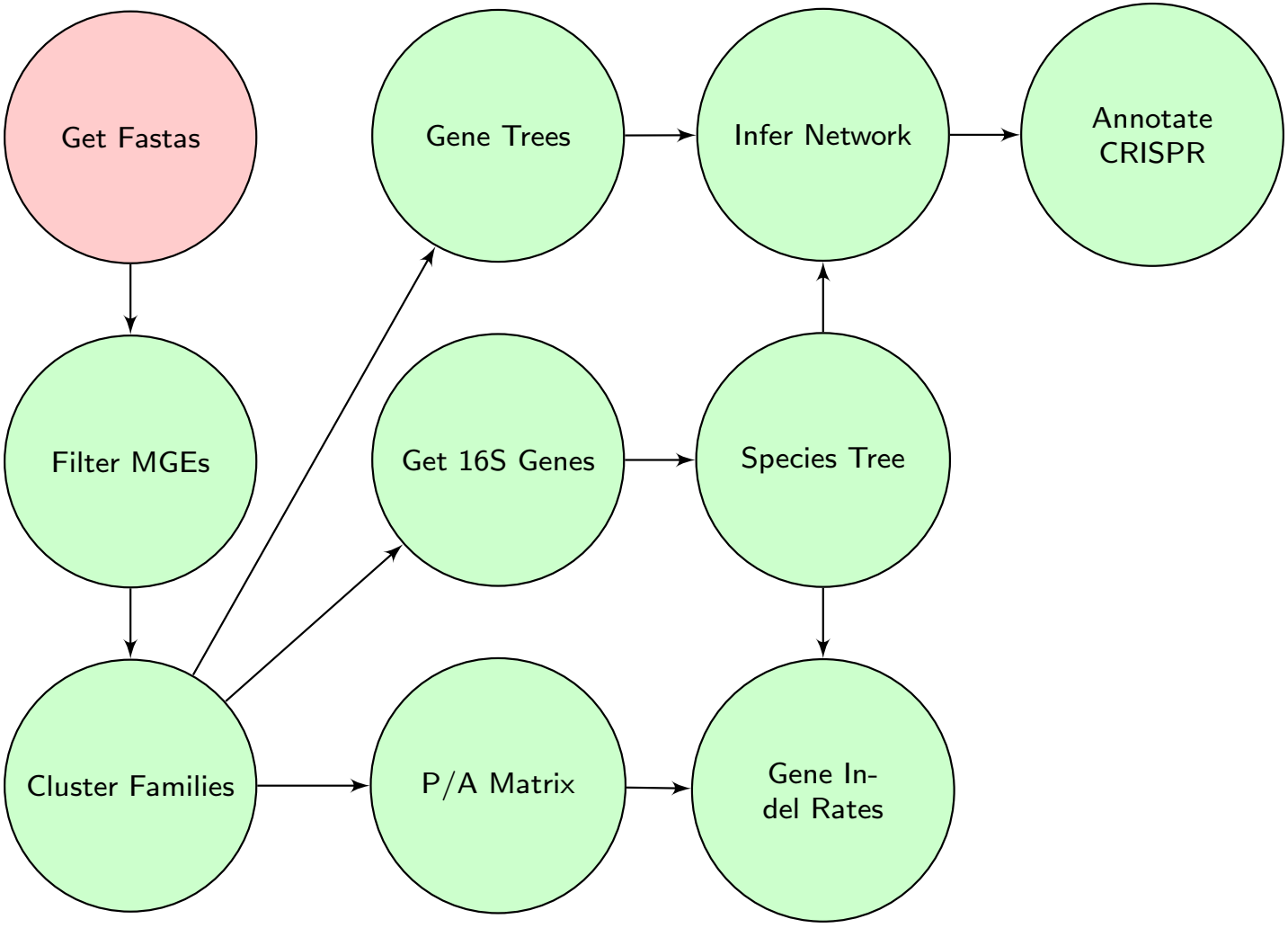

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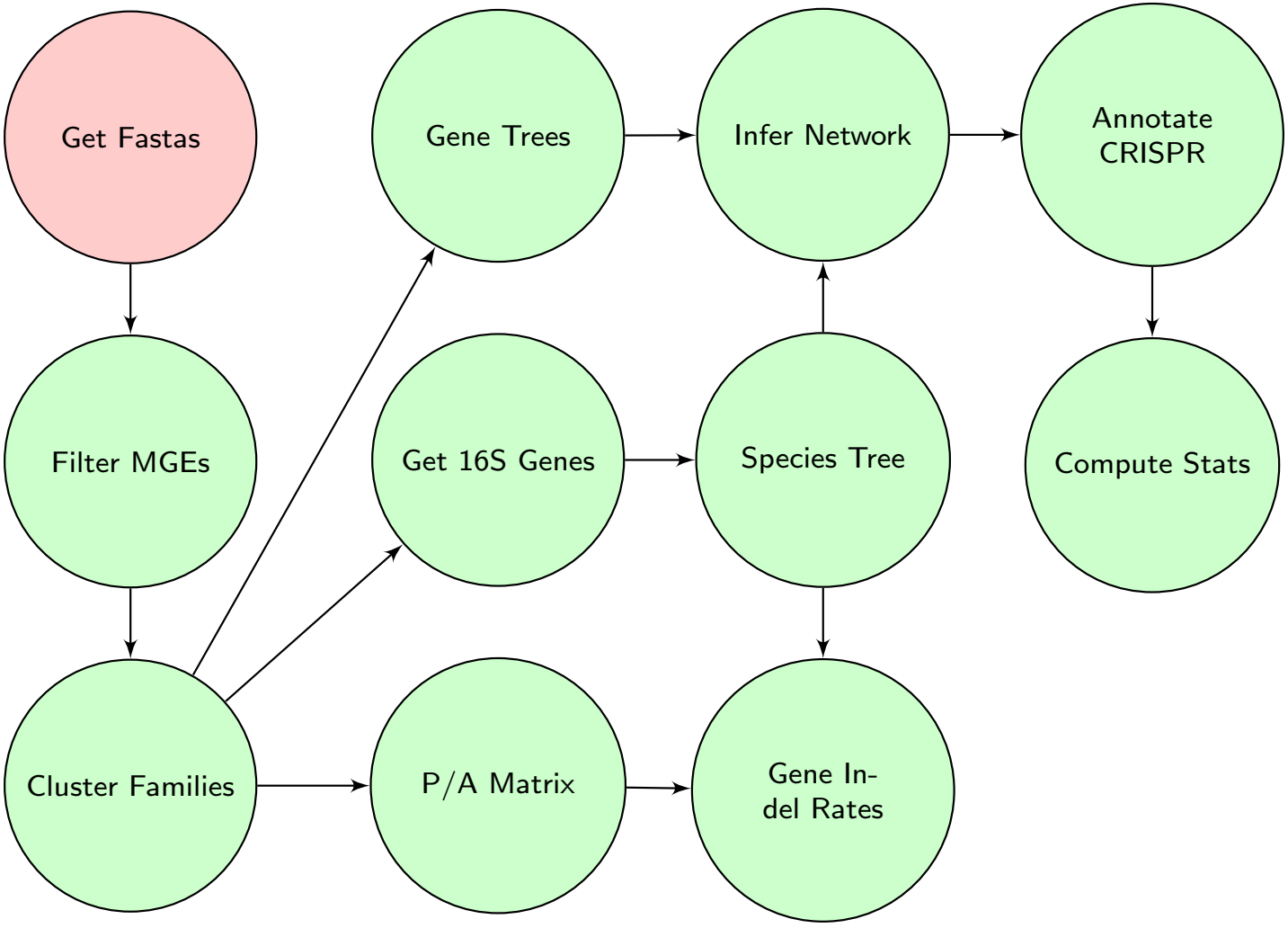

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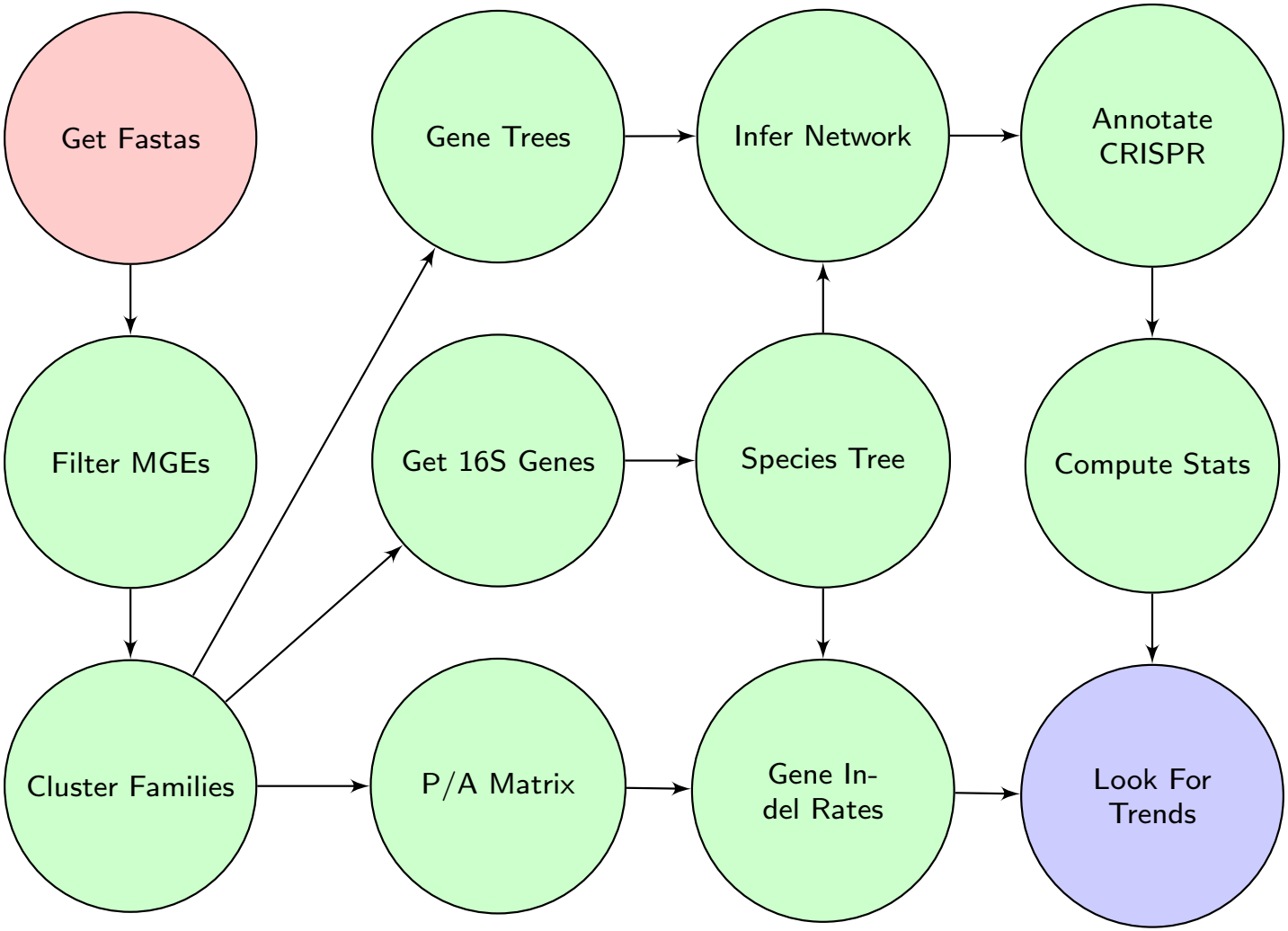
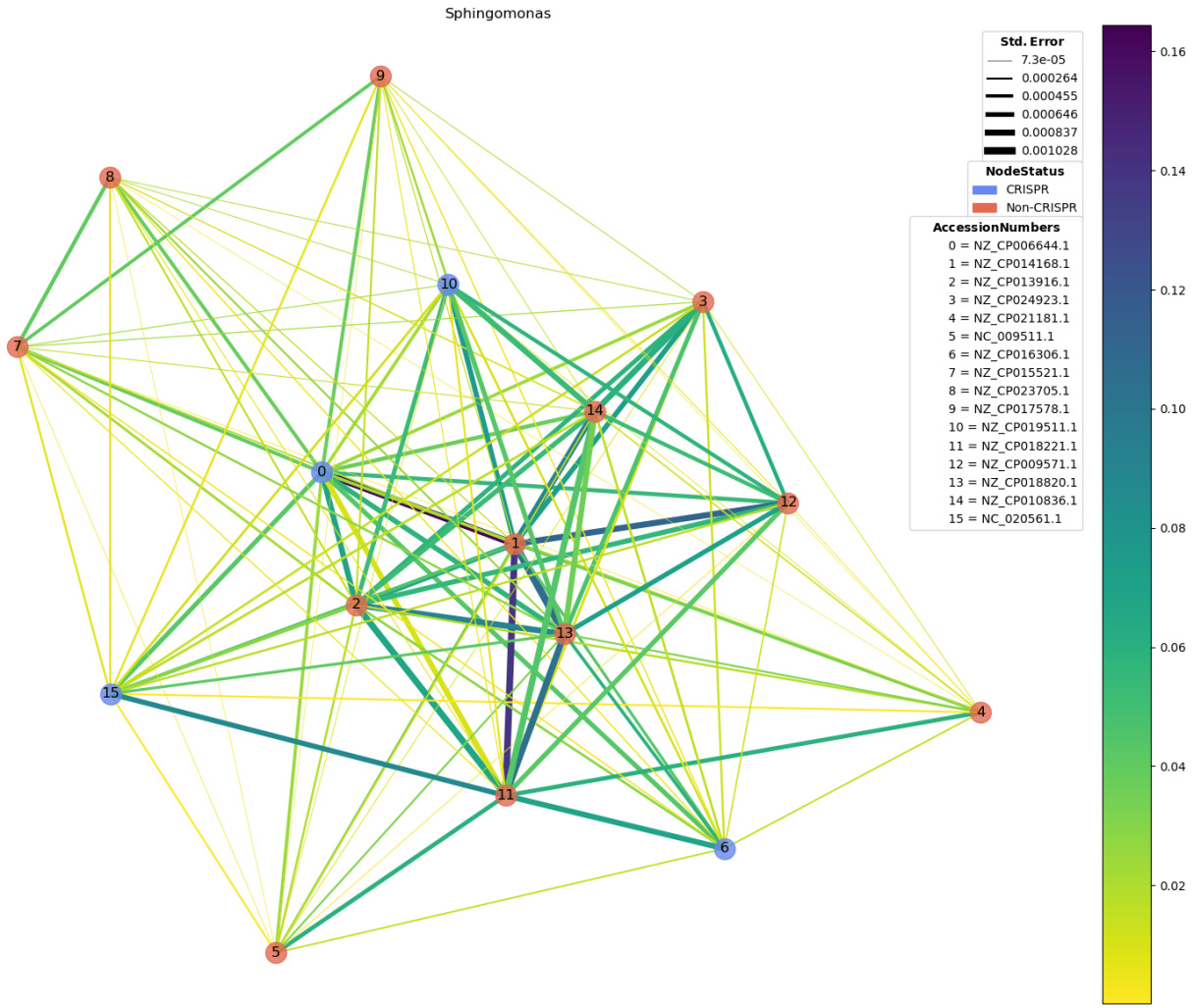
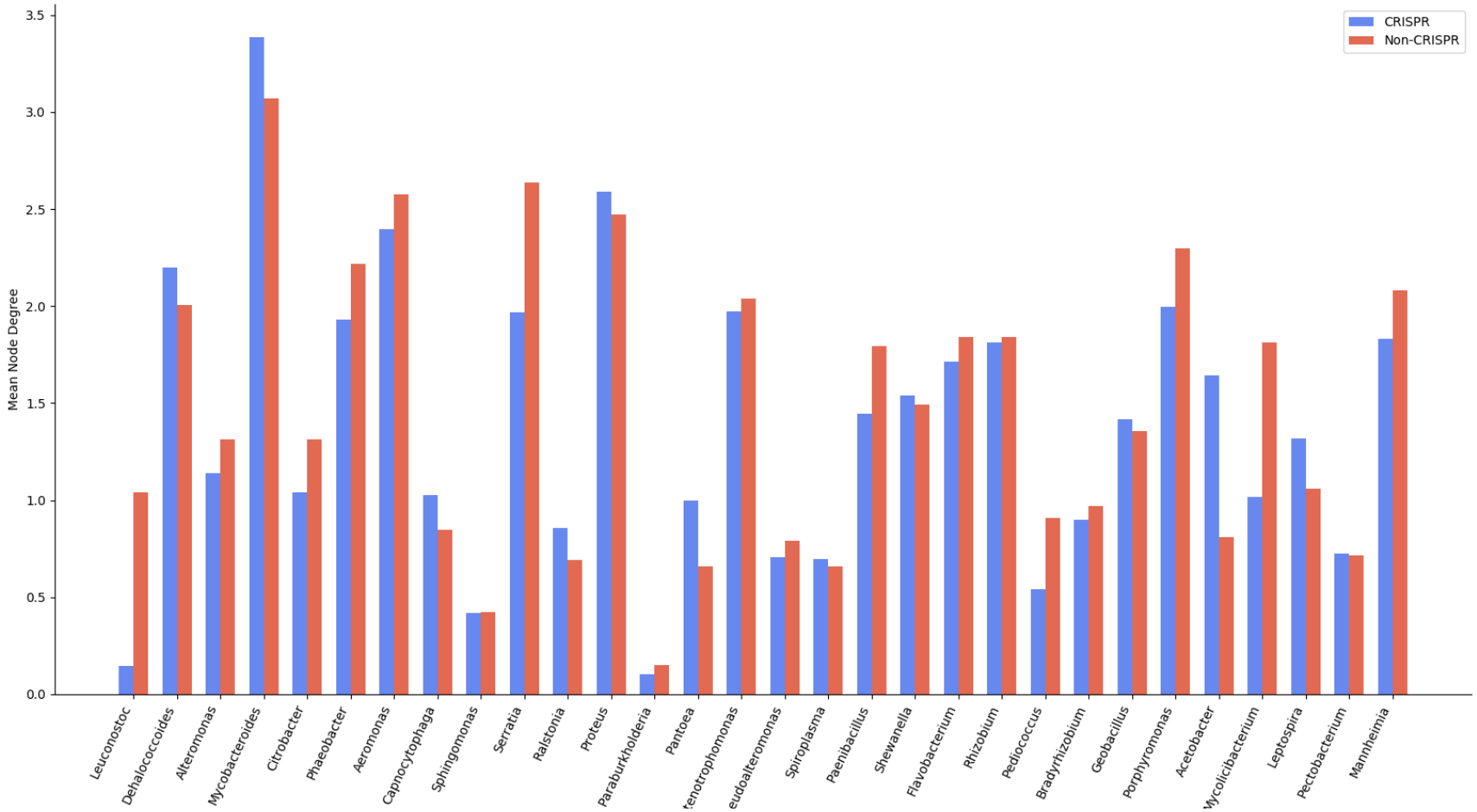


Results

Example "Consensus" Network



Mean Node Degree



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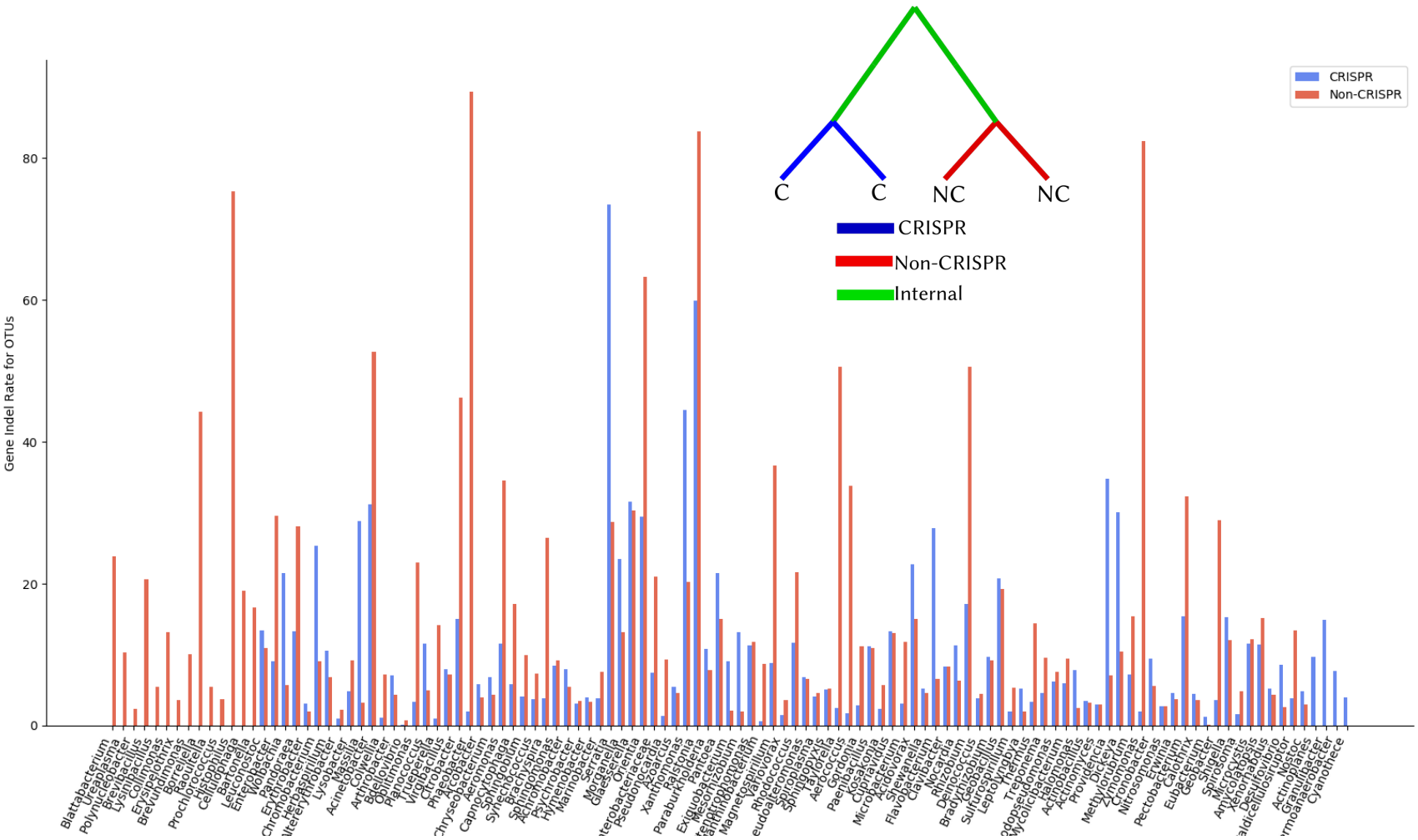

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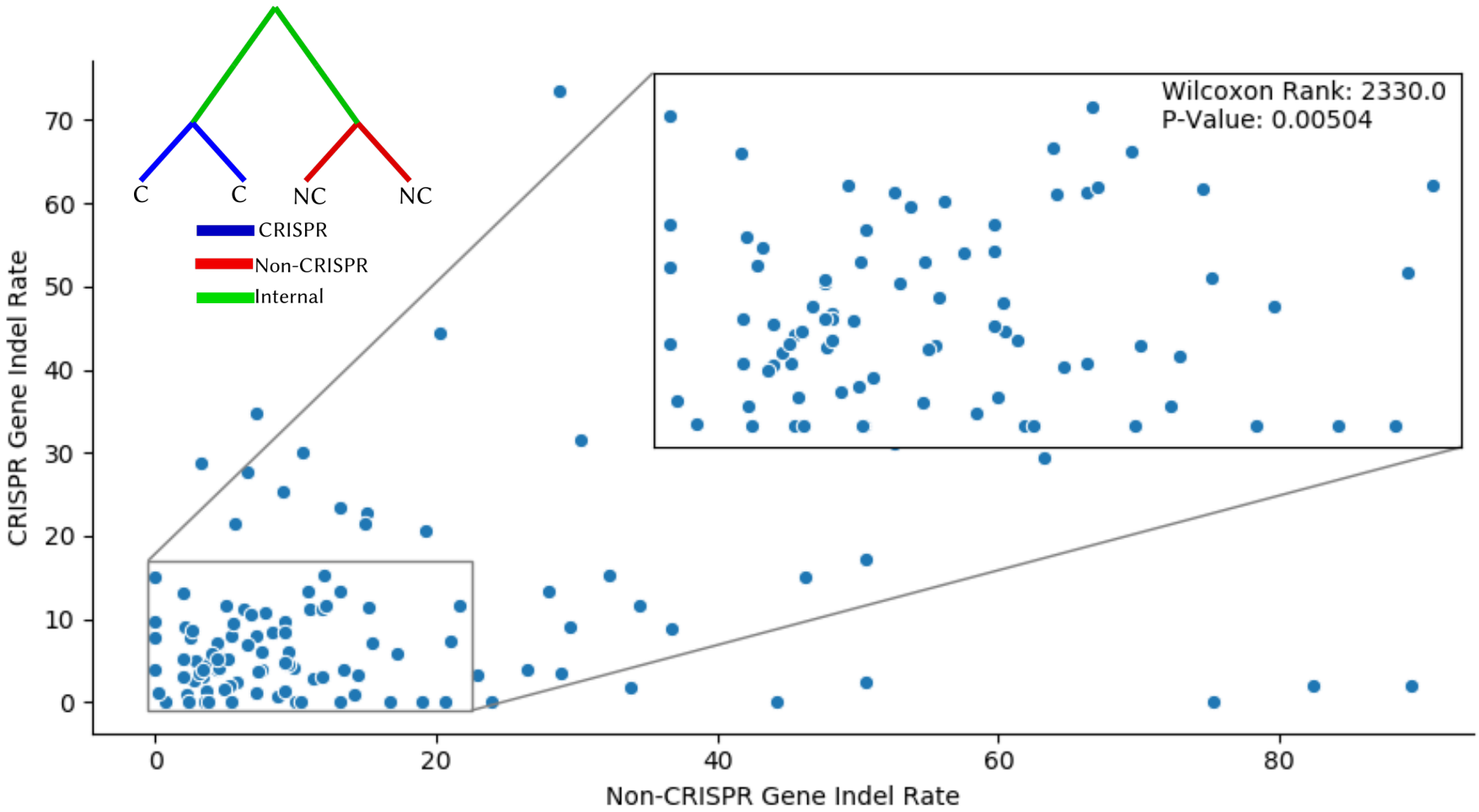
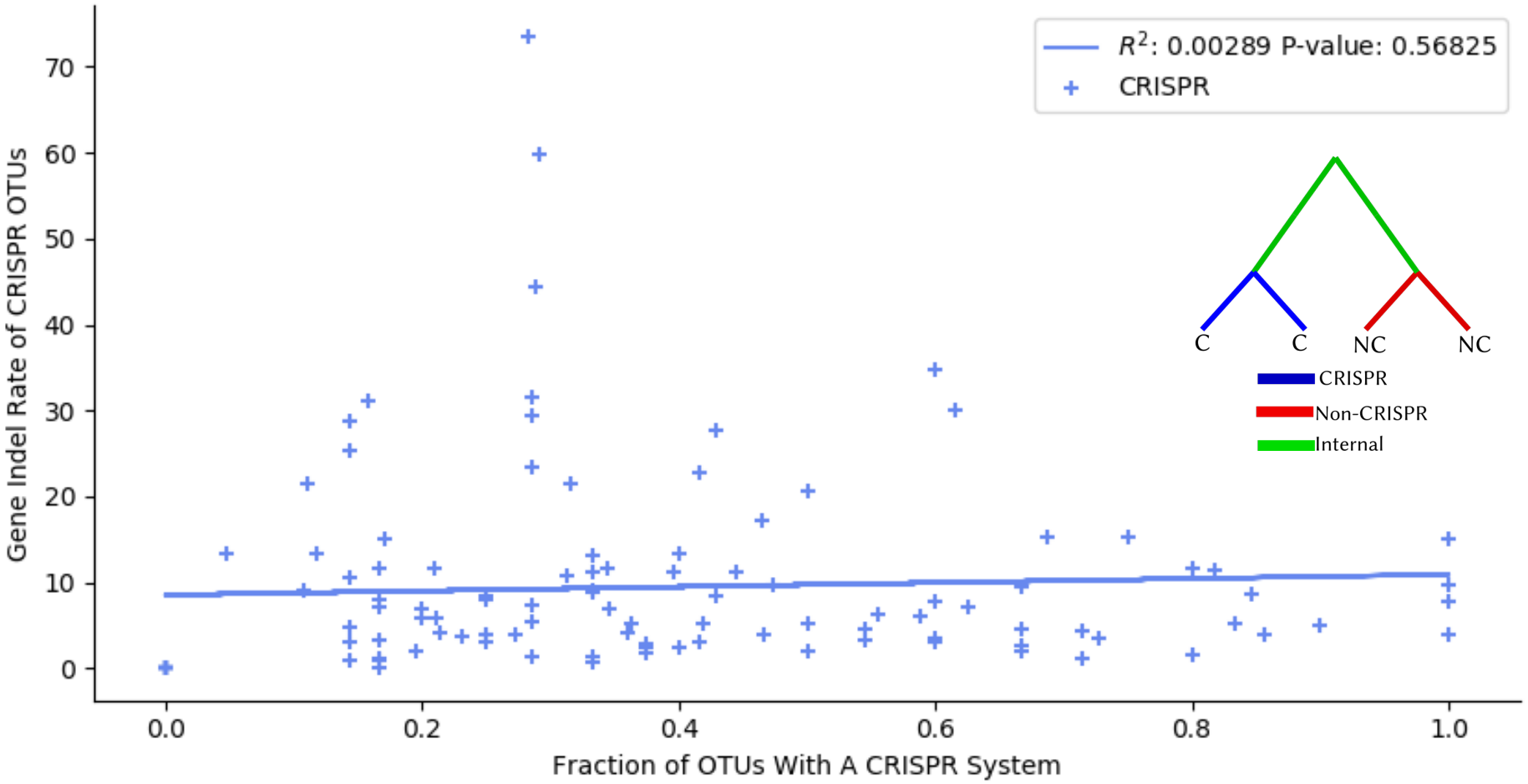


Gene Indel Rate Vs. Fraction of CRISPR OTUs



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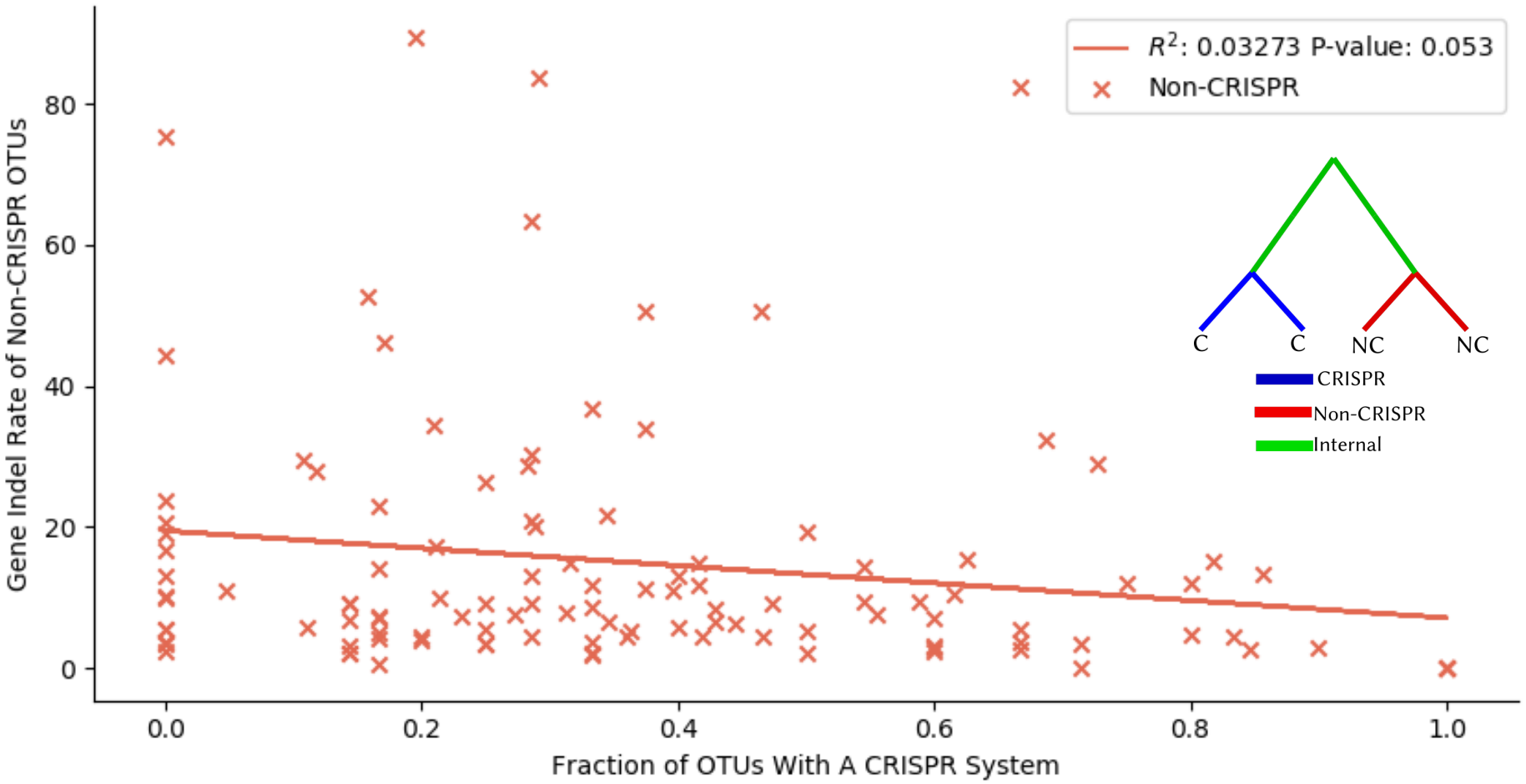
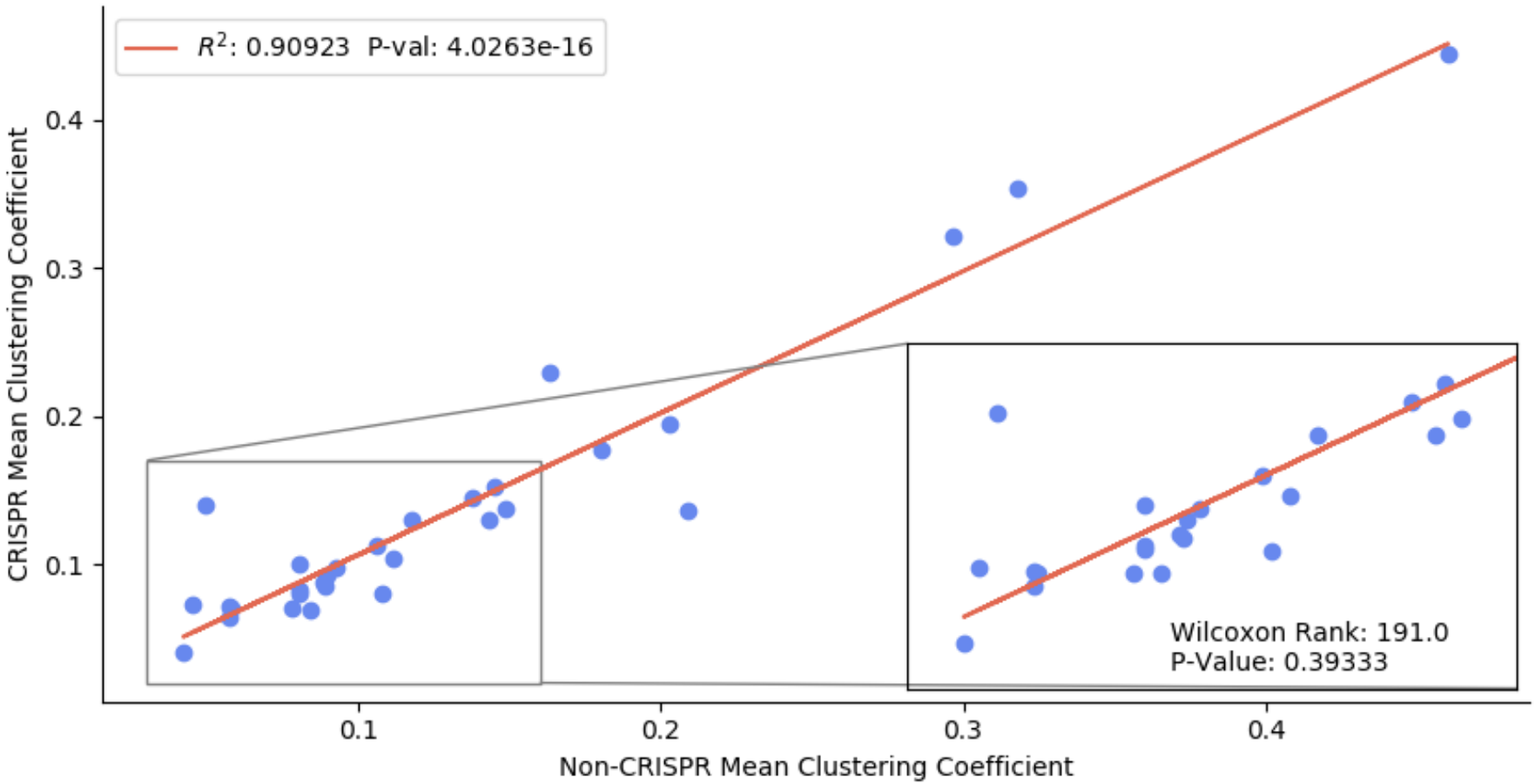
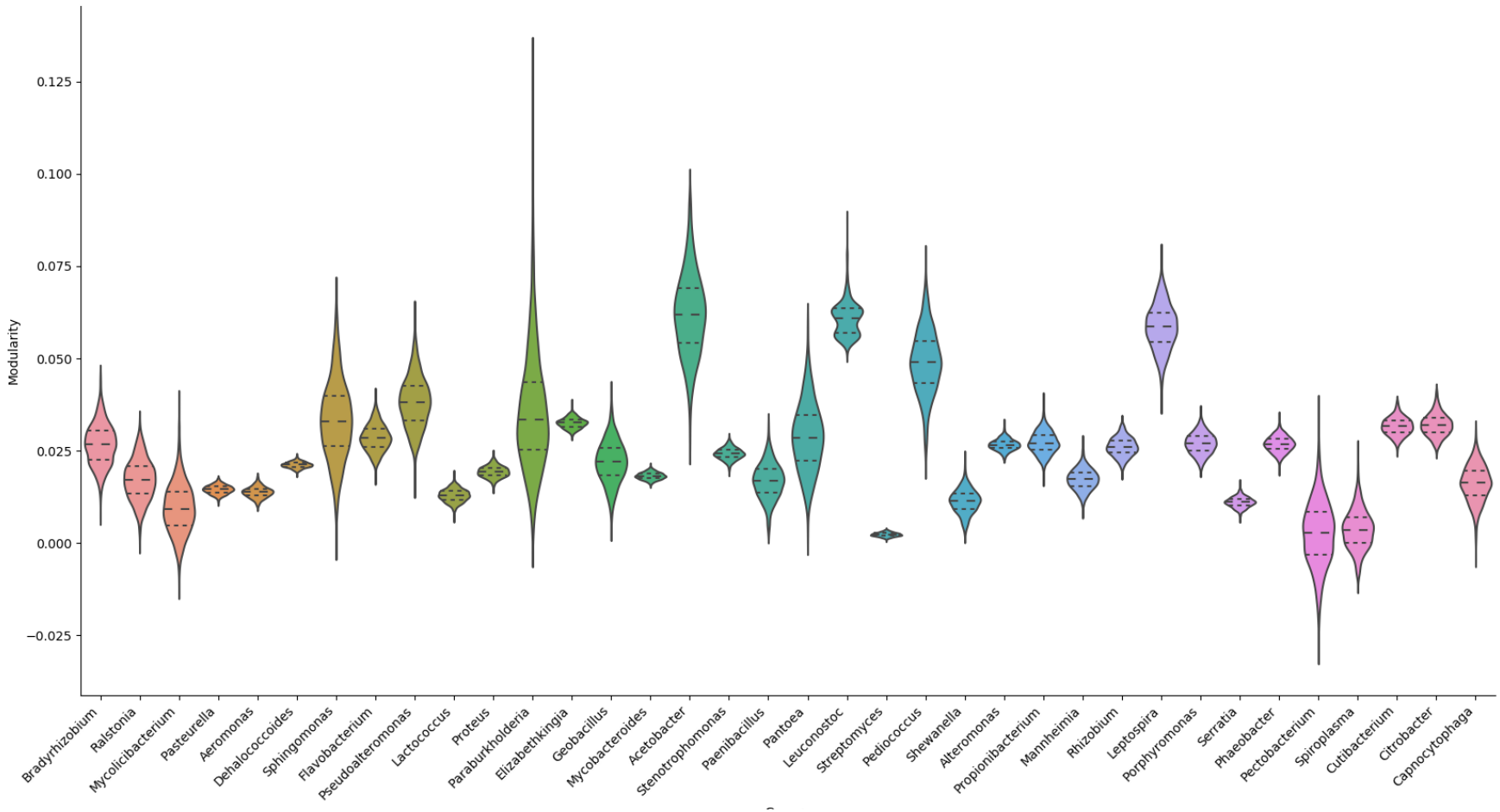


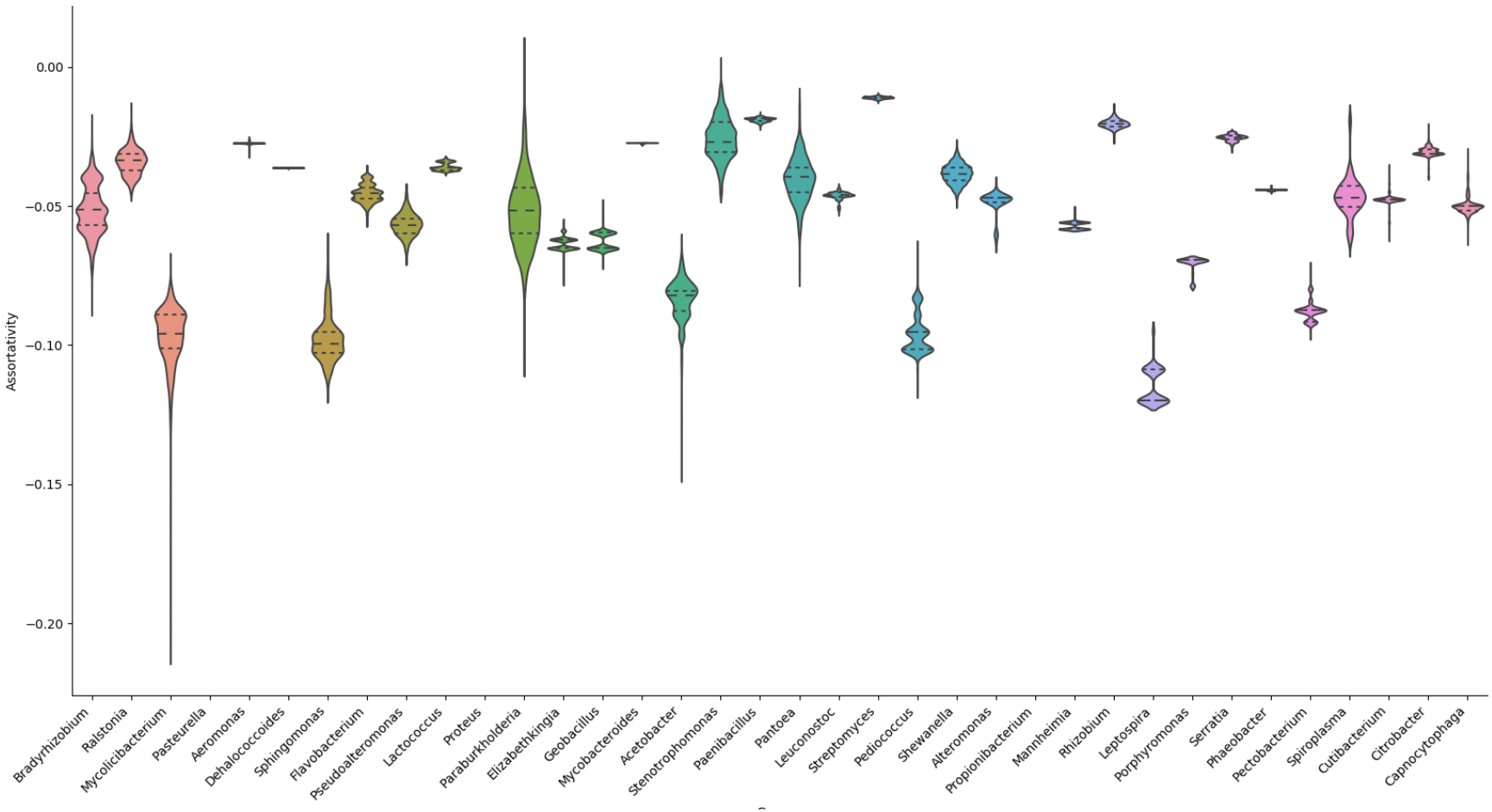
Mean Node Weighted Clustering Coefficient



Modularity Distributions



Assortativity Distributions



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- Interplay of CRISPR-Cas systems and HGT is complex and warrants further study

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- **Intergenic comparisons**: Combine any set of fasta files from OTUs for analyzing transfer dynamics

Possible Future Directions

- **Inferring direction**: Directed networks have a host of available analytic tools Undirected networks do not
- **Continuous CRISPR activity**: Labeling nodes by estimated CRISPR activity (array length, transciptomic data, etc.)
- **Gene function analysis**: Considering the transfer dynamics of different functional classes of genes
- **Studying movement of CRISPR systems**: Studying how frequently CRISPR systems themselves are transferred from arrays, *Cas* genes
- **Intergenic comparisons**: Combine any set of fasta files from OTUs for analyzing transfer dynamics
- **Considering bacterial ecology and environments**: Consider geographically close OTUs or differences between networks due to environmental factors

Is Sharing Caring?

Is Sharing Caring?

Yes, for researchers

Is Sharing Caring?

Yes, for researchers

Jury's still out for bacteria

Thanks

Thank you to

- Dr. G. Brian Golding
- Dr. Ben Evans
- The Golding lab
  - Caitlin Simopoulos
  - Daniella Lato
  - Zachery Dickson
  - Sam Long
  - Geoge Long
  - Lucy Zhang
  - Brianne Laverty
  - Nicole Zhang
- Everyone here for listening

All code used for this project is available at https://github.com/DJSiddharthVader/thesis_SidReed

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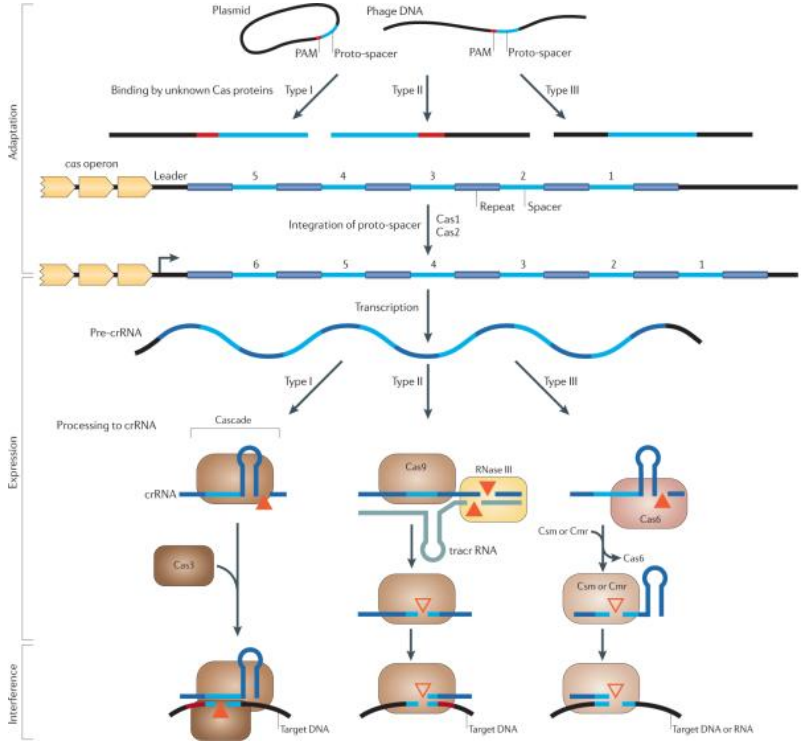
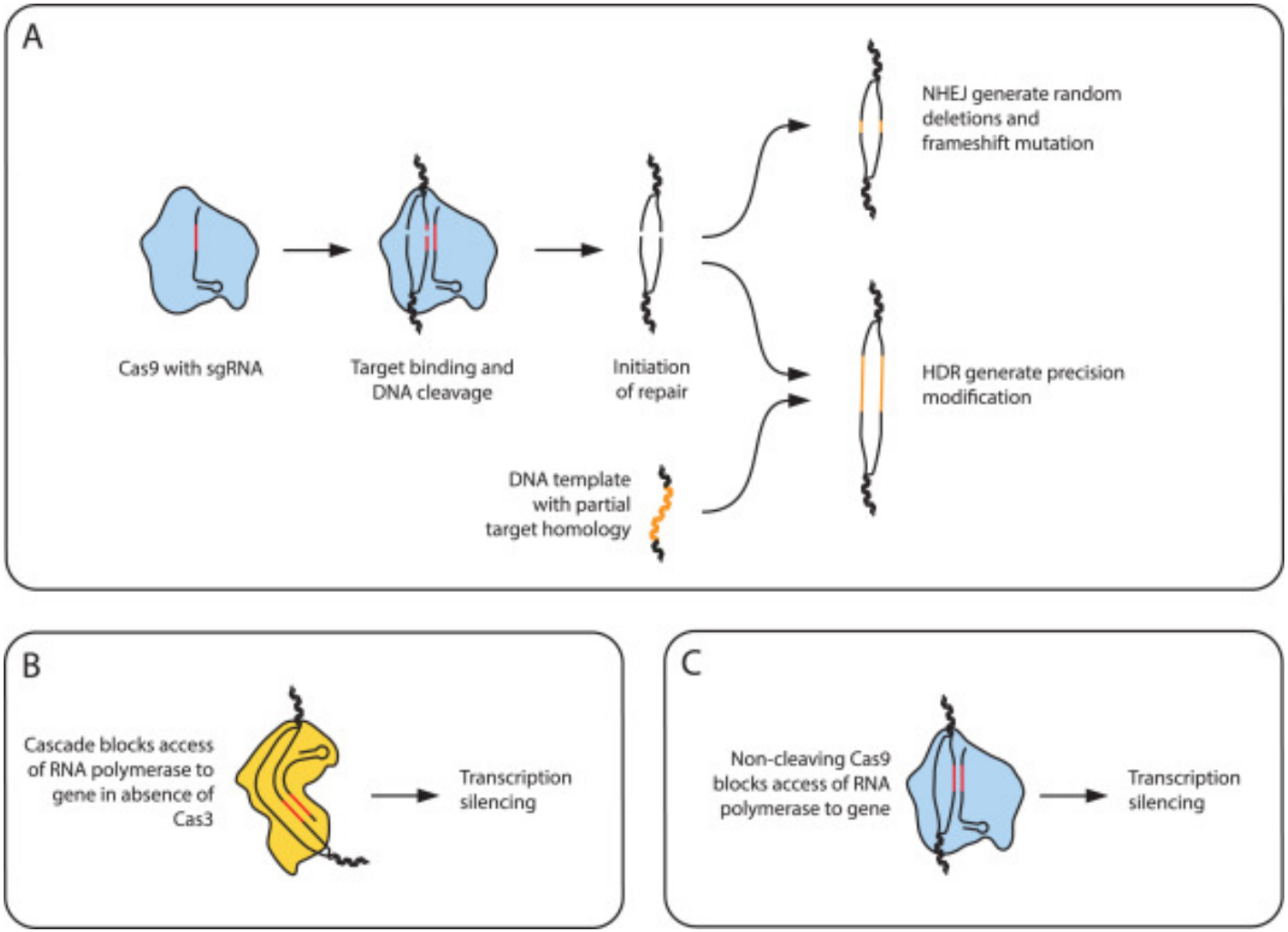
Diversity & Ubiquity

- 45% of bacteria have CRISPR loci ($n = 6782$) (Grissa, I. and Drevet, C. and Couvin, D., 2017)
- 3 Main Types, multiple sub types (Bondy-Denomy and Davidson, 2014)
- CRISPR arrays represent unique life history of an organism
- $11\% - 28\%$ are false or orphaned CRISPR loci (Zhang and Ye, 2017)



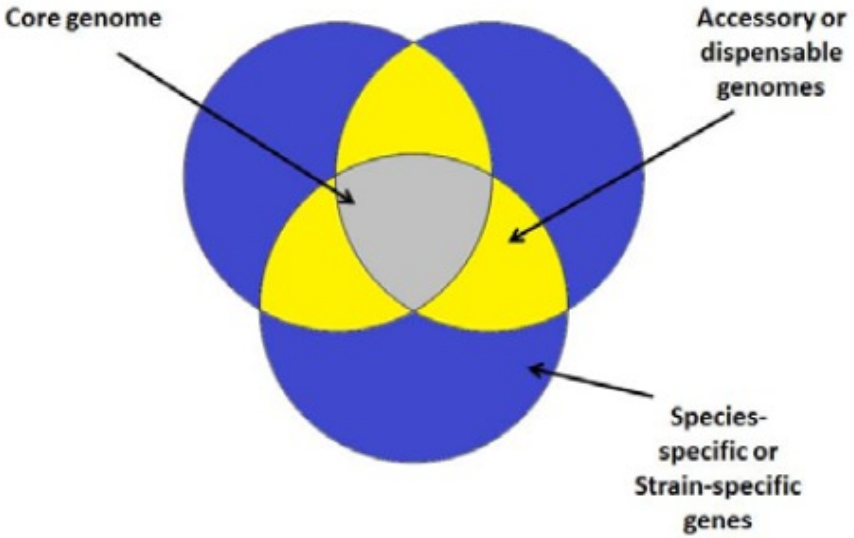
(Makarova et al., 2011)

CRISPR Biotech Application

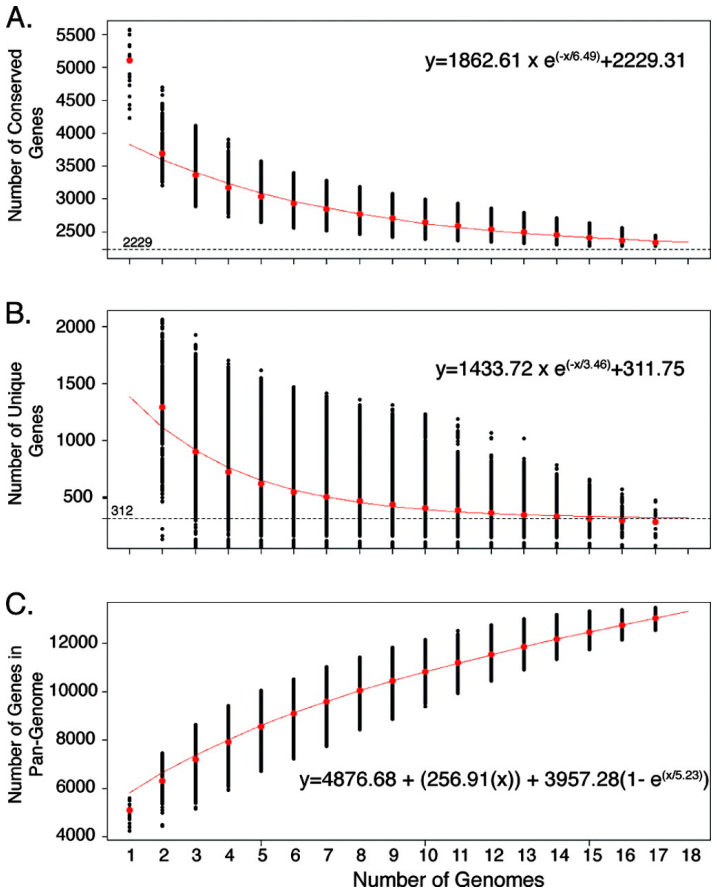


(Rath et al., 2015)

Pan-Genomes

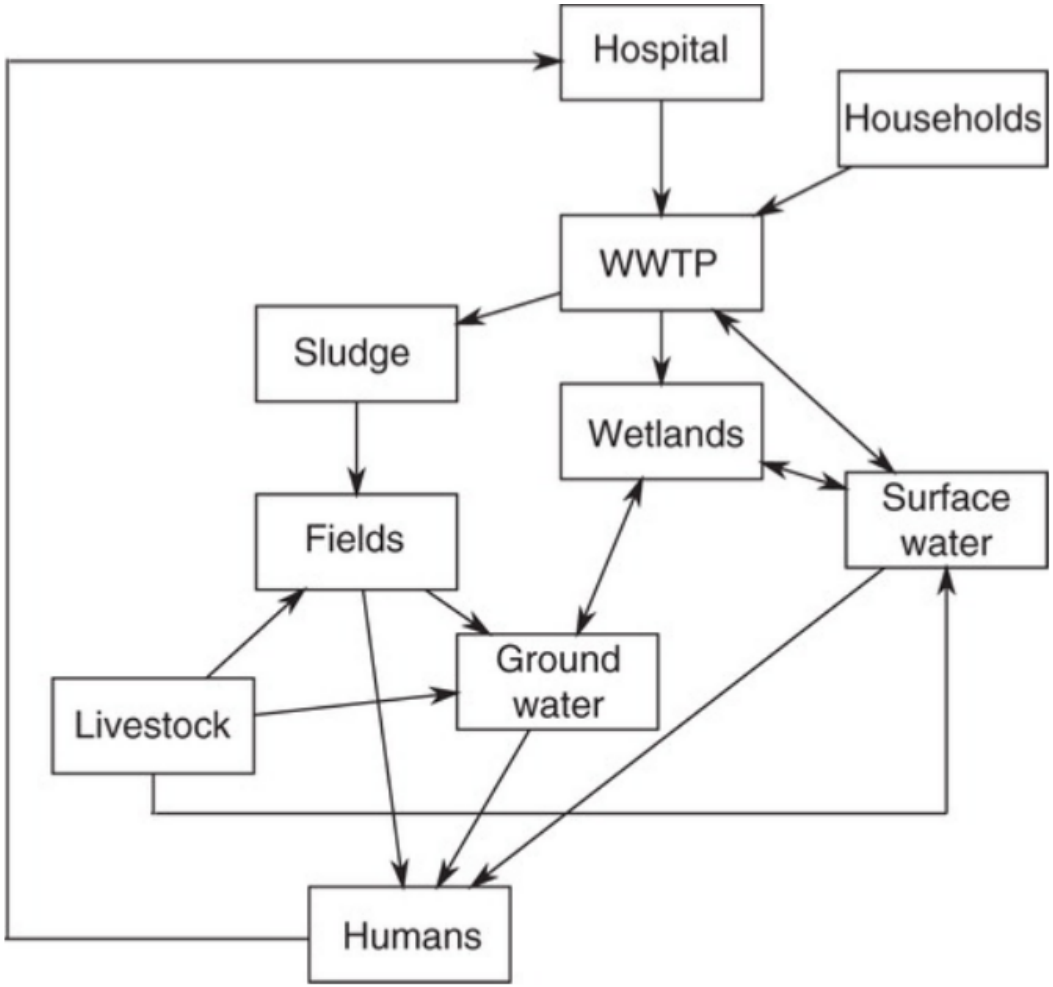


(Guimaraes et al., 2015)



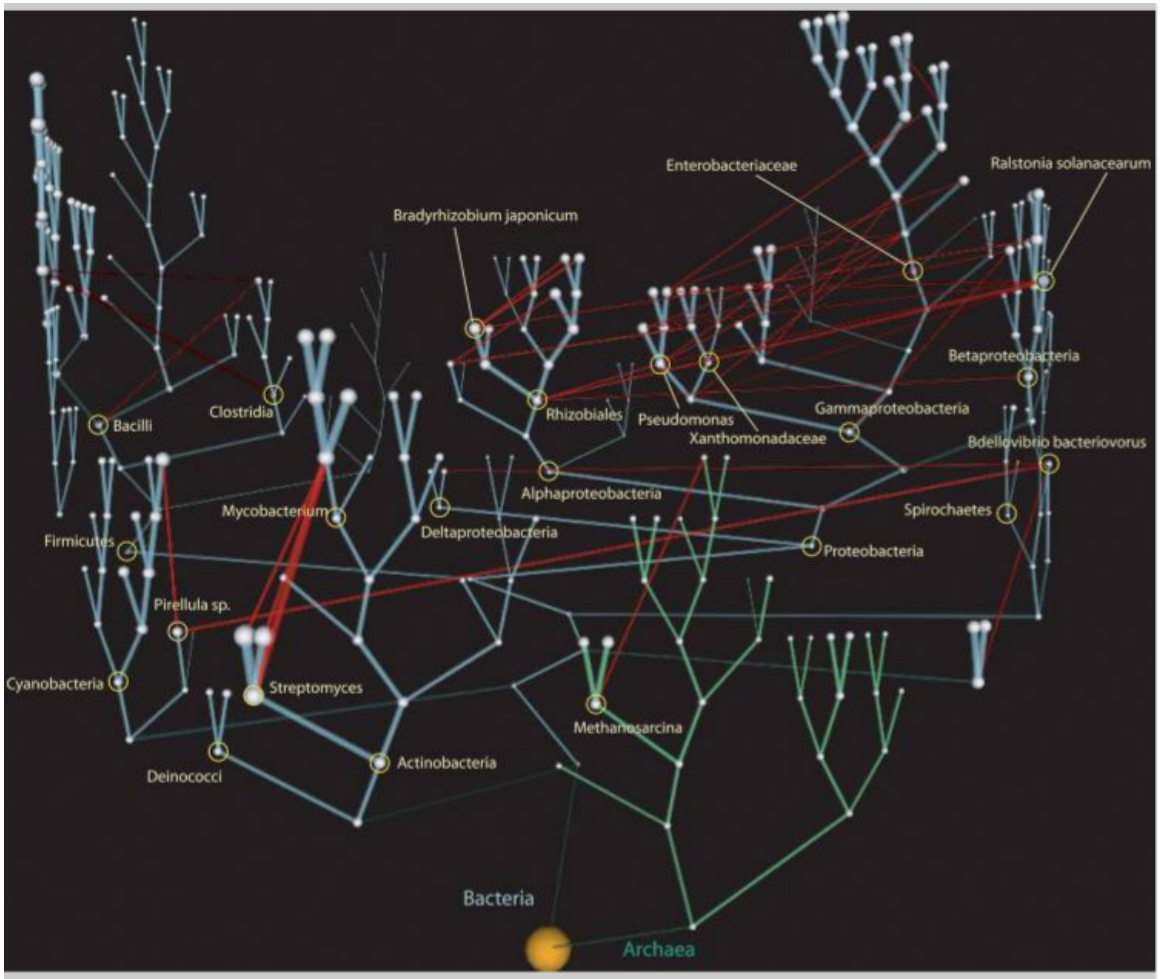
(Rasko et al., 2008)

HGT Applications



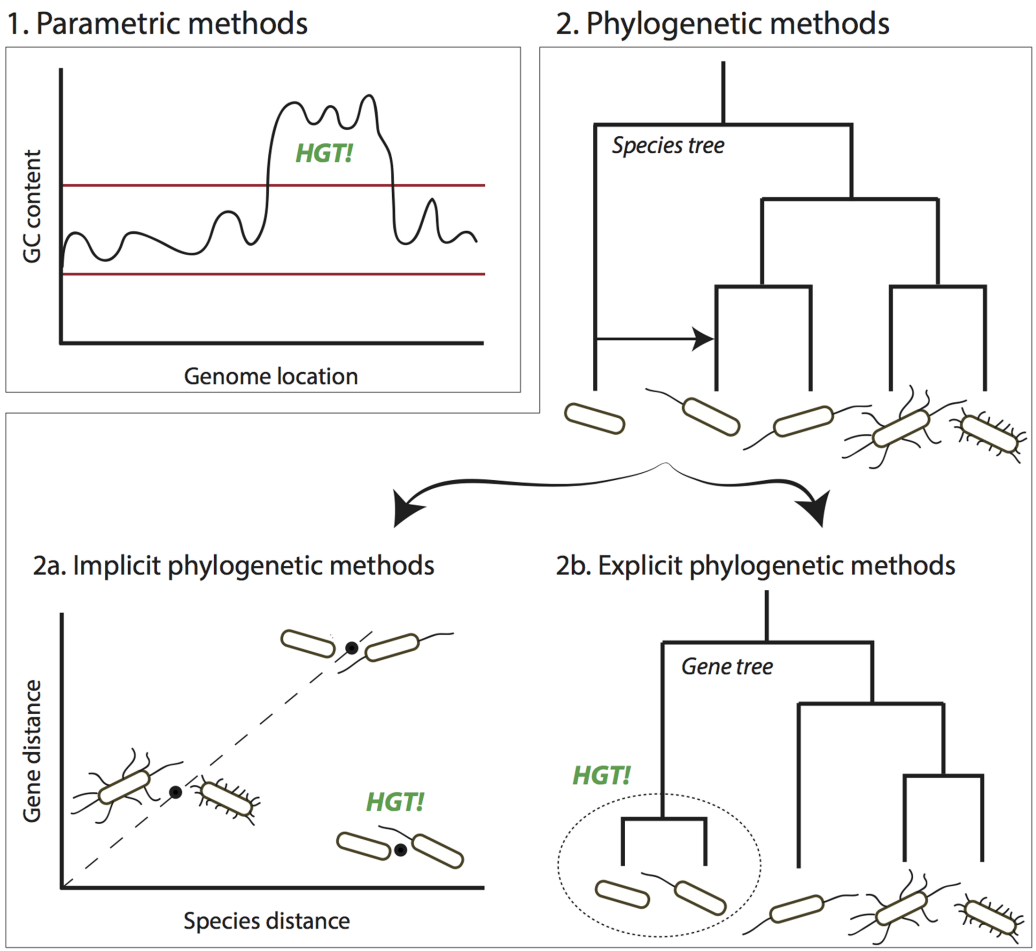
(Berglund, 2015)

Prokaryotic "Net of Life"



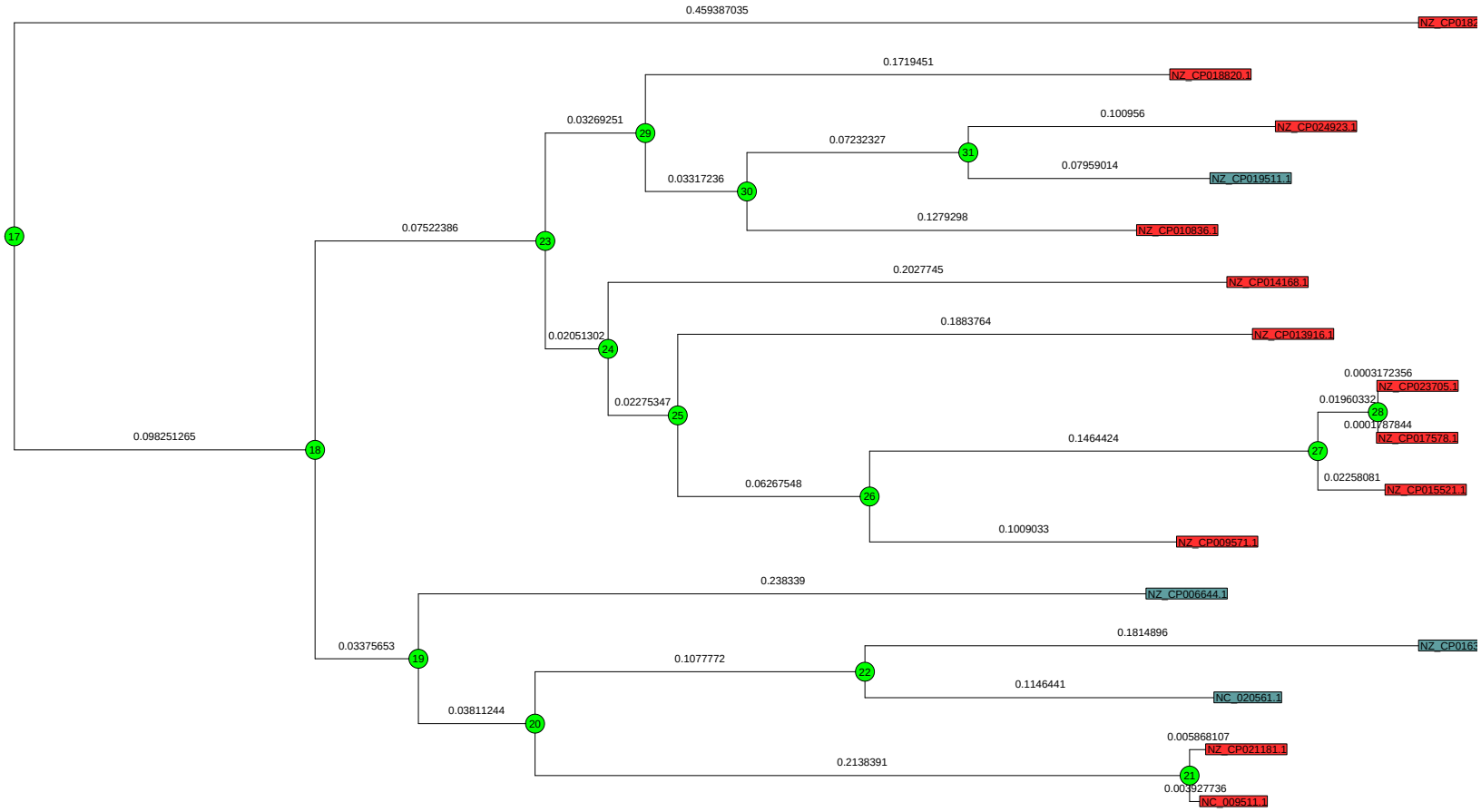
(Kunin et al., 2005)

Phylogenomic Network Construction



(Ravenhall et al., 2015)

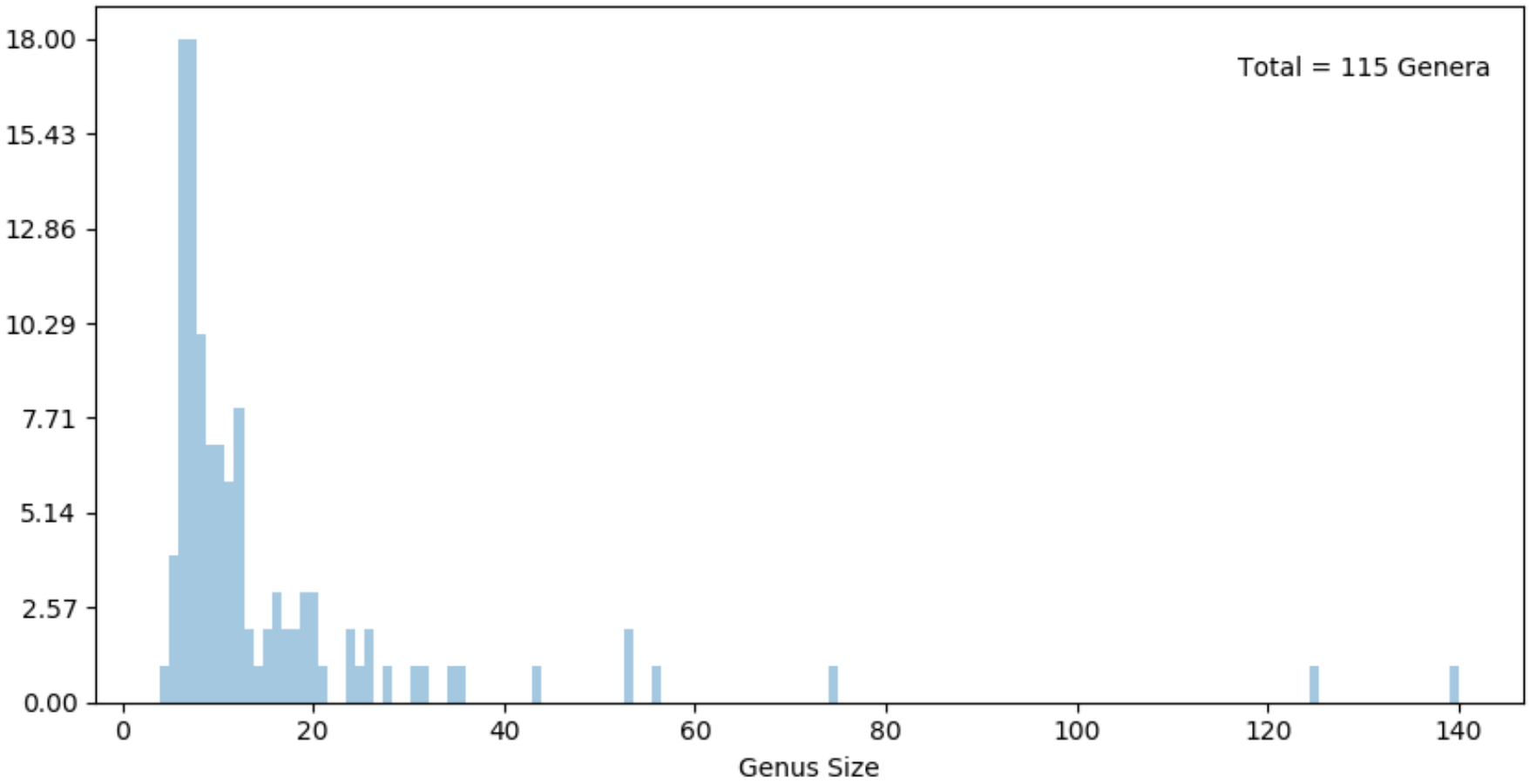
Sphingomonas Species Tree



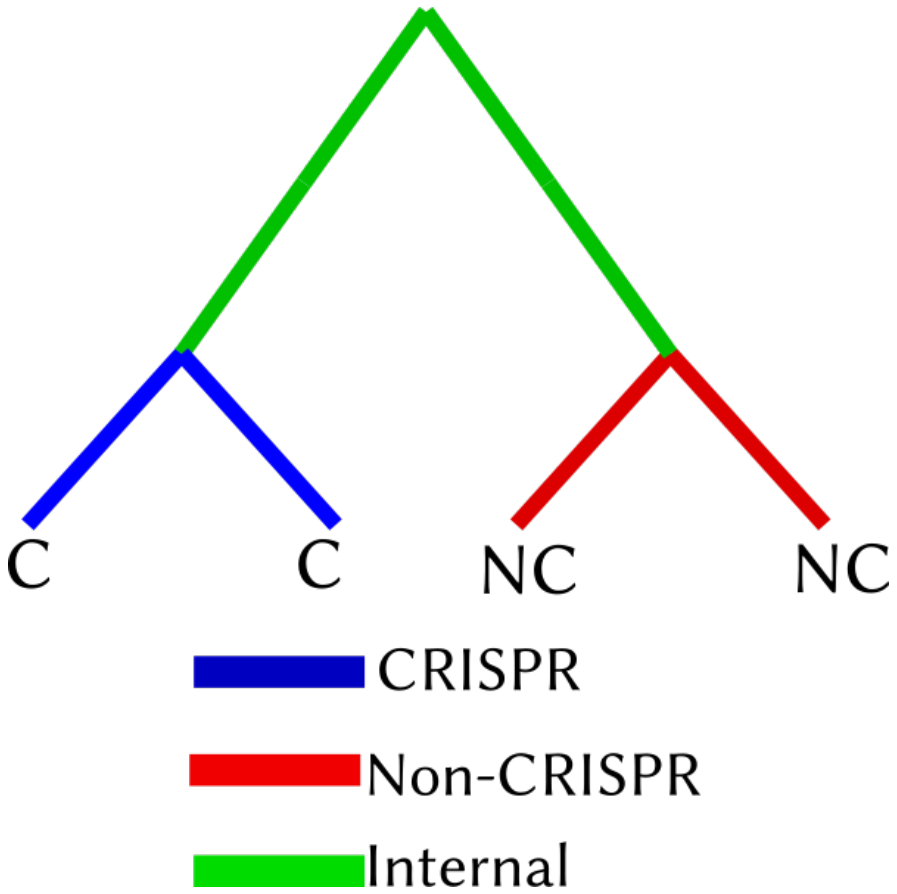
Network Statistics

- **Average Node Degree**: $\frac{1}{|N_u|}\sum_{uv}^{N_u} w_{uv}$ where N_u is the set of nodes incident to u
- **Node Clustering Coefficient**: $\frac{1}{k_u(k_u-1)}\sum_{vw}^{T(u)}(\hat{w}_{uw}\hat{w}_{vw}\hat{w}_{uv})^{\frac{1}{3}}$ where $T(u)$ is the set of triangles containing u (Onnela et al., 2005)
- **Node Assortativity**: $A = \frac{Tr(M)-||M^2||}{1-||M^2||}$ Where M is the mixing matrix of a given attribute and $||M||$ is the sum of all elements of M. $A \in [-1, 1]$. (Newman, 2002)
- **Network Modularity**: $Q = \frac{1}{2m}\sum_{uv}^{W}[W_{uv} - \frac{k_u k_v}{2m}]\delta(u, v)$ where m is the total weight of alledges, k_u is the degree of u and $\delta(u, v)$ is 1 if u and v both have or do not have CRISPR systems and 0 otherwise. $Q \in [-1, 1]$ (Newman, 2004)

Genus Size Distribution



Branch Partition Example



Indel Rate Pair Plot