Post-translational modification bias between organism complexity: Trends observed across diverse lifeforms

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A Tailored Customization:
A Short Intro to Post Translational Modifications

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PTMs in the Central Dogma of Biology

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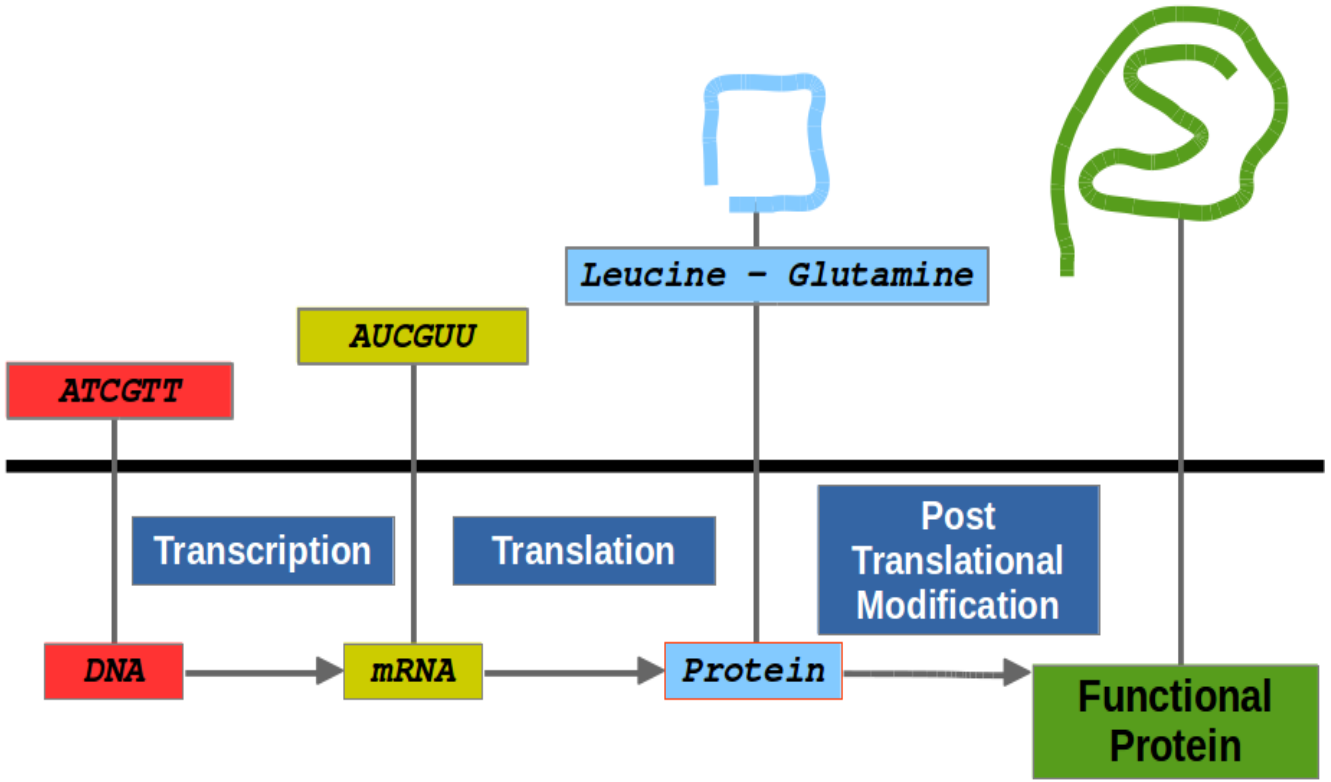
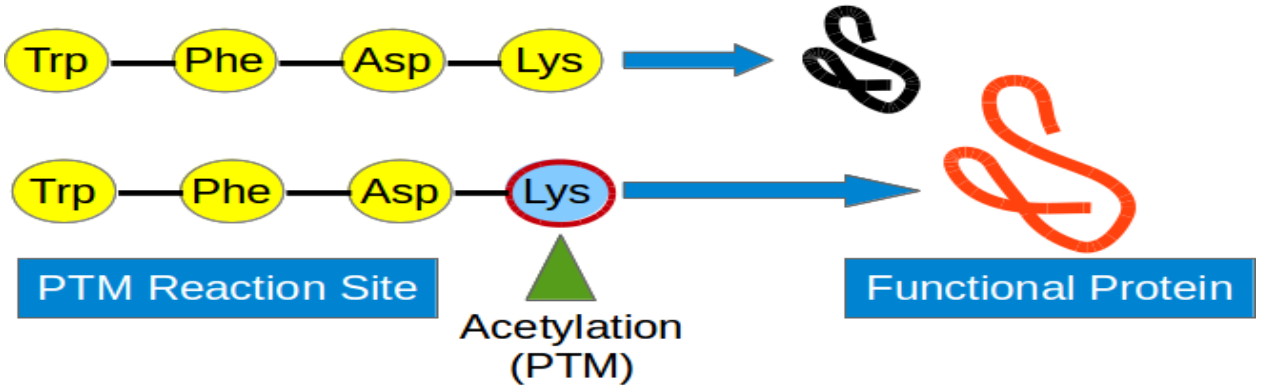


PTMs: a Step in Protein Biosynthesis



- Protein regulators
- Able to quickly change protein behaviors and functions

Gene expression	acetylation	glycosylation
Protein regulation	phosphorylation	sumoylation

PTMs Are Not Used Consistently Across Organisms

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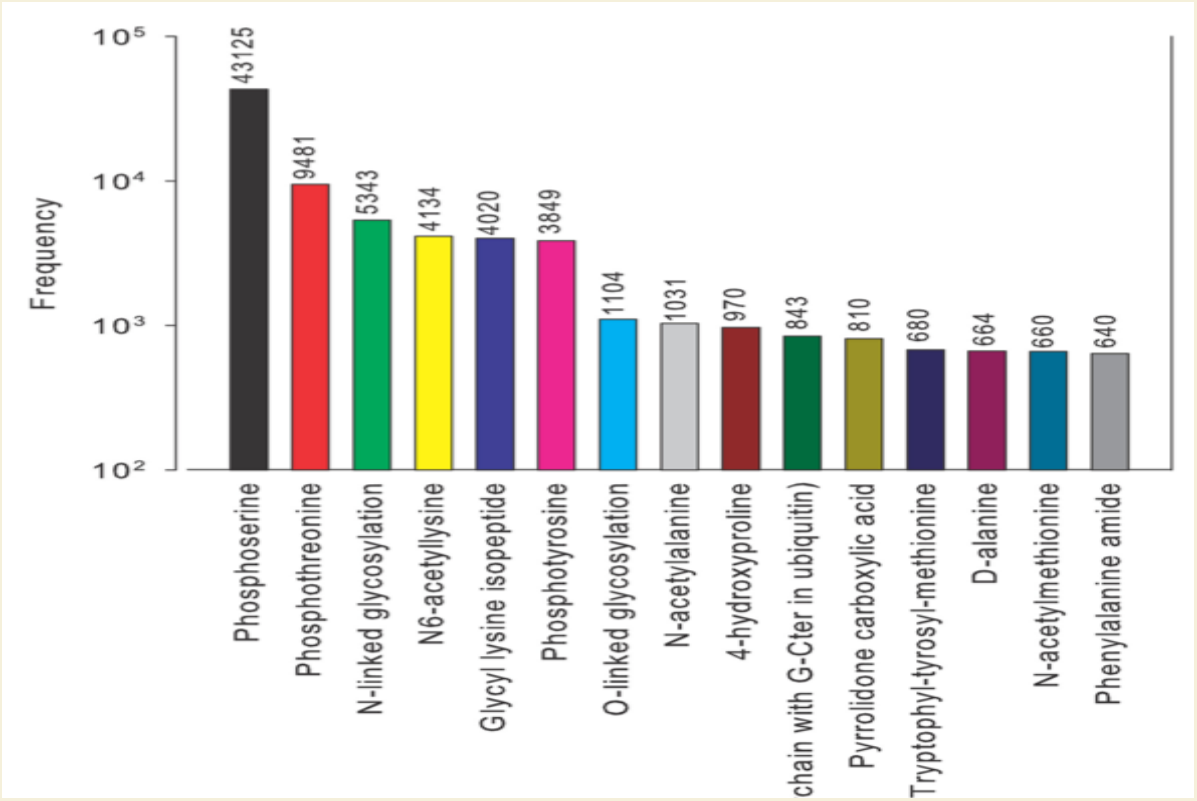
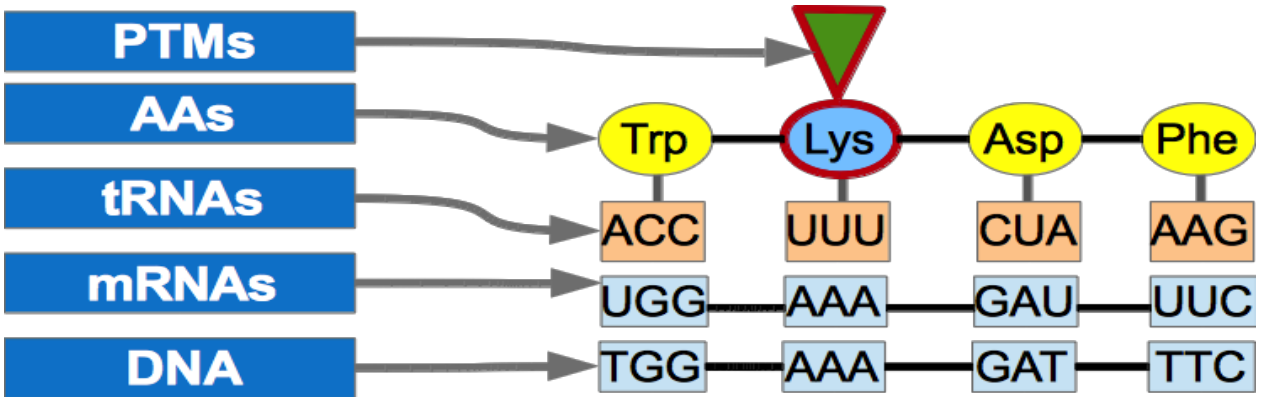


- What could alter the way that PTMs are used across organisms?

Khoury *et al.* Proteome-wide post-translational modification statistics. `http://selene.princeton.edu/PTMCuration/`

PTMs Interact With Protein at Reactive Sites



- Reactive Site: a point of reaction between proteins and PTMs (lysine for acetylation).
- Lysine is a specific amino acid that targets PTM interaction
- Could reactive site placement interfere with PTM bias?

Could tRNA Bias Influence PTM Bias?

tRNA Biases Interfere With Amino Acid Biases!

Evidence of a Pathway of Reduction in Bacteria: Reduced Quantities of Restriction Sites Impact tRNA Activity in a Trial Set

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- Bonham-Carter, Oliver, Lotfollah Najjar, and Dhundy Bastola. "**Evidence of a pathway of reduction in bacteria: Reduced quantities of restriction sites impact trna activity in a trial set.**" Proceedings of the International Conference on Bioinformatics, Computational Biology and Biomedical Informatics. ACM, 2013.

A Connection Between Variables
tRNAs, AAs and PTM Reaction Sites → PTMs

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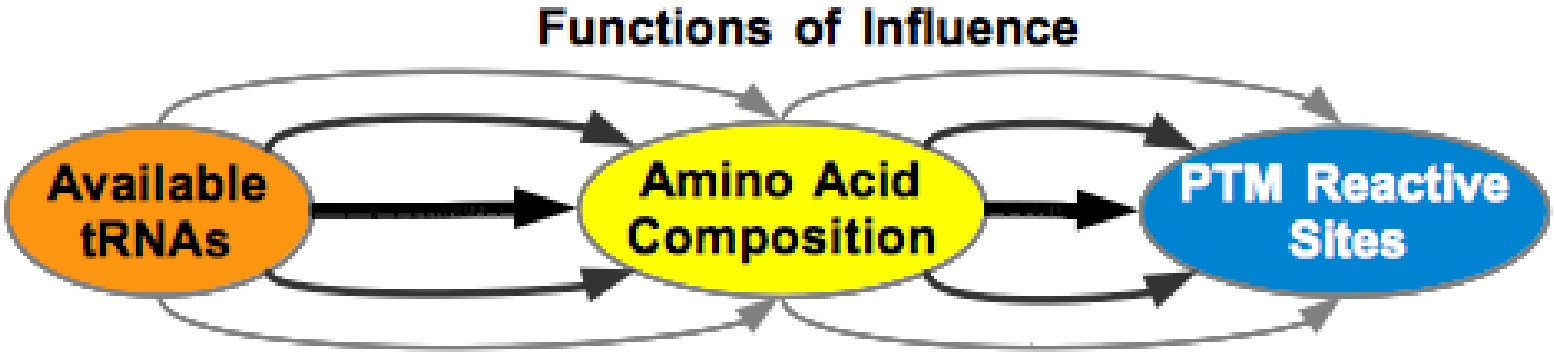

- AAs form the specific reactive sites where PTMs interact with protein

Stresses Influence PTMs

Nor rain, wind, thunder, fire are my daughters. -Shakespeare (King Lear)

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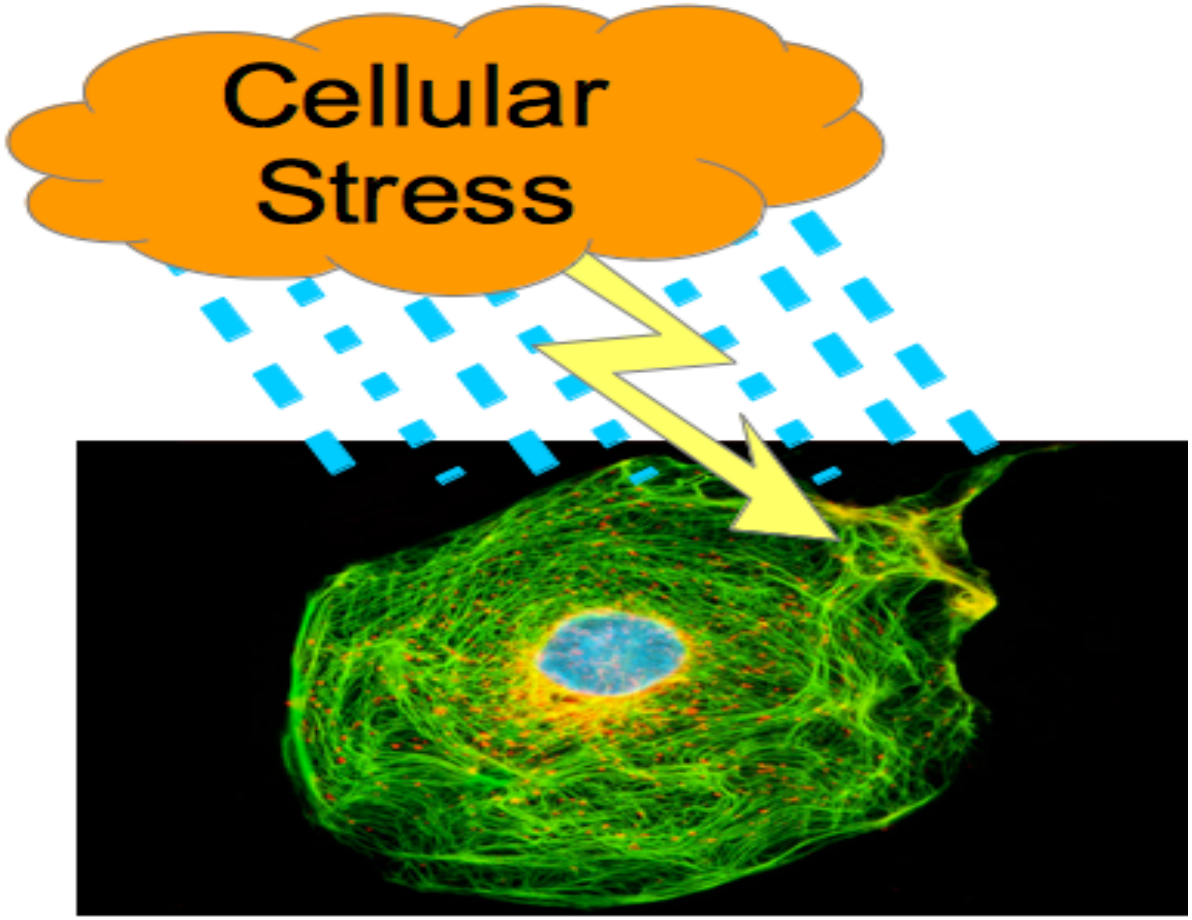

- Cellular Stresses: Carbonylation, Free Radicals, Heat Shock, Microgravity, Saline, and others.

PTMs: Quick Adaptations to Env. Stresses

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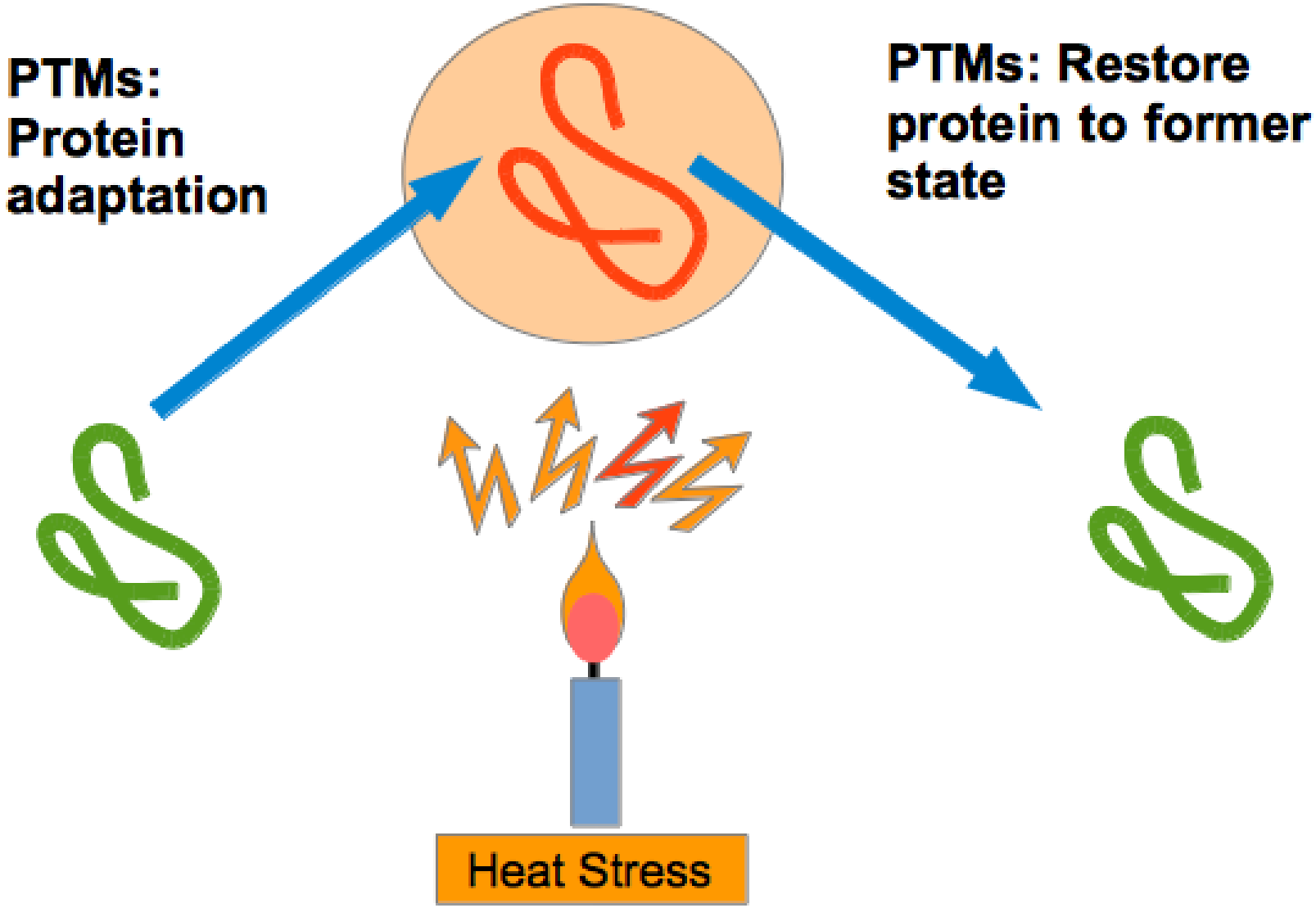

Could a Bias Come From Stresses

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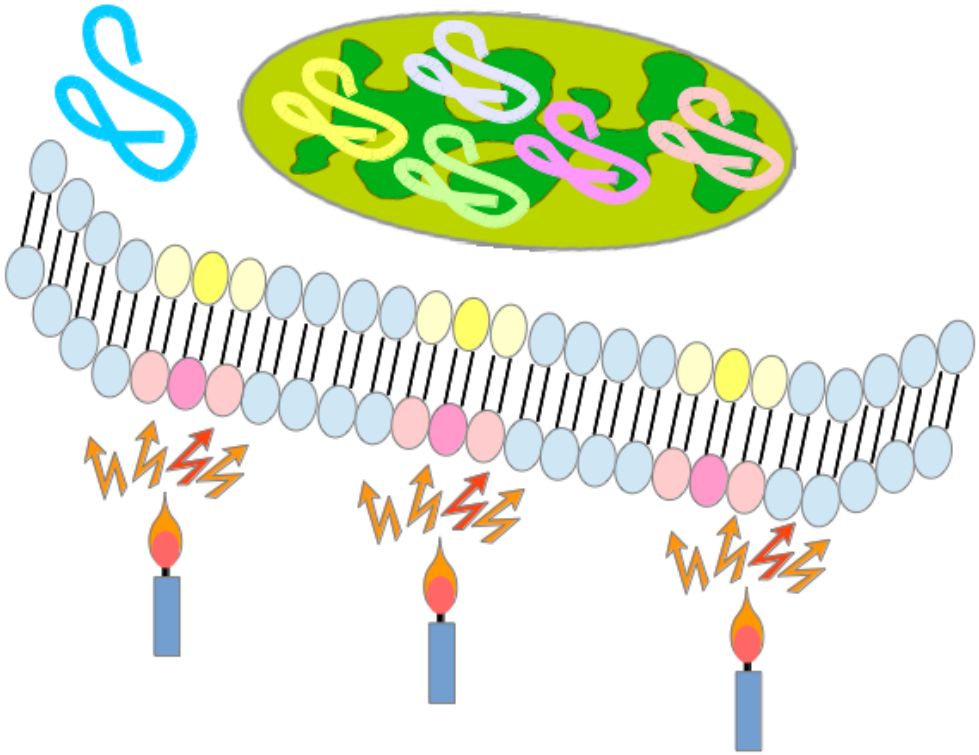

- Mitochondria (Mt): Cellular Energy Producers
- Mt proteins: Likely evolved with different stress types to influence tRNA distributions
- Is there bias observed in Mt PTM composition?

Research Interests

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One of Our Paper's Hypotheses...

- Mt proteins are likely protected from main stream cellular stresses.
- Are there fewer PTMs available to Mt for stress response?
- Can biases be observed from across organisms (in both Mt and non-Mt)?

Data: Organisms

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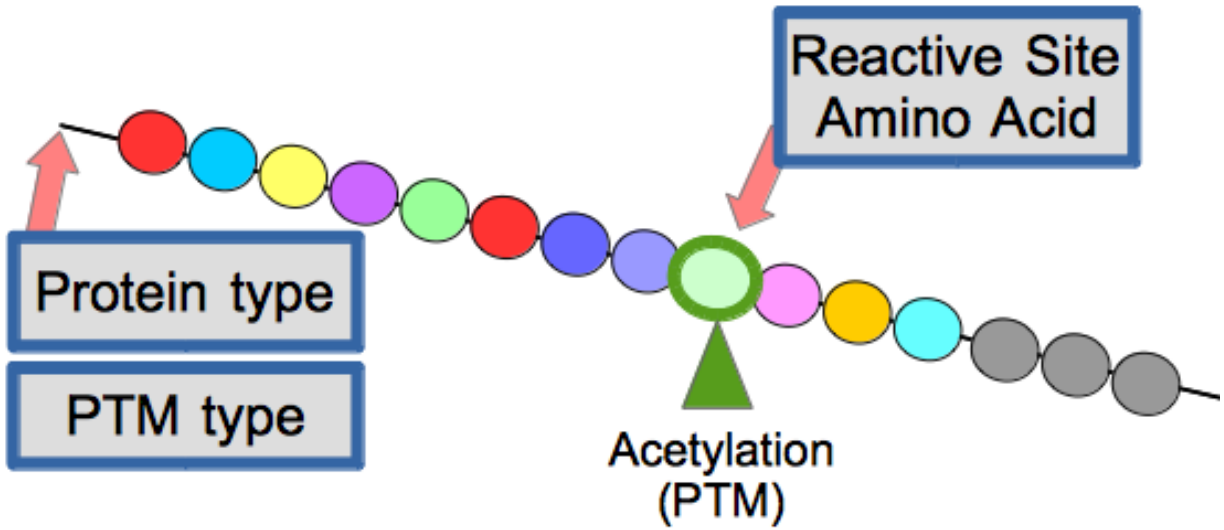
Table : The proteomes came from these organisms for our study.

No.	Organism	Commonly	Top PTM
1	Arabidopsis thaliana	Plant	Glycos
2	Caenorhabditis elegans	Worm	Glycos
3	Canis familiaris	Dog	Glycos
4	Danio rerio	Fish	Glycos
5	Homo sapiens	Human	Phospho
6	Mus musculus	Mouse	PhosPho
7	Oryctolagus cuniculus	Rabbit	Glycos
8	Rattus norvegicus	Rat	Glycos
9	Saccharomyces cerevisiae	Yeast	Phospho

Data: Frequencies of Elements

DataBase: Uniprot

```
for each protein by organism:
 obtain type and count of:
   PTMs,
   Reaction Locations (Active Sites),
   Amino Acids (composition)
```



- Collected over Mt and nonMt proteins

Three Frequency Equations for Three Questions

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- Composition of **PTM** content in Mt versus nonMt protein?
  - $freq(PTM_{(i,j)}) = \frac{count(PTM_{(i,j)})}{\sum_{i=1}^{N_{(PTMs)}} count(PTM_{(i,j)})}$
- Composition of **AA** content in Mt versus nonMt protein?
  - $freq(aminoAcid_{(i,j)}) = \frac{count(aminoAcid_{(i,j)})}{\sum_{i=1}^{N_{(reactiveSites)}} count(reactiveSite_{(i,j)})}$
- Composition of PTM **reactive sites** in Mt versus nonMt protein?
  - $freq(ReactiveSite_{(i,j)}) = \frac{count(aminoAcid_{(i,j)})}{|\sum_{i=1}^{N_{Proteins}} Seq_{(i,j)}|}$

- For $(i, j) = (element[i], organism[j])$
- $N =$ size of set
- $count()$ function returns number of an element in set of size N

A Network Comparison

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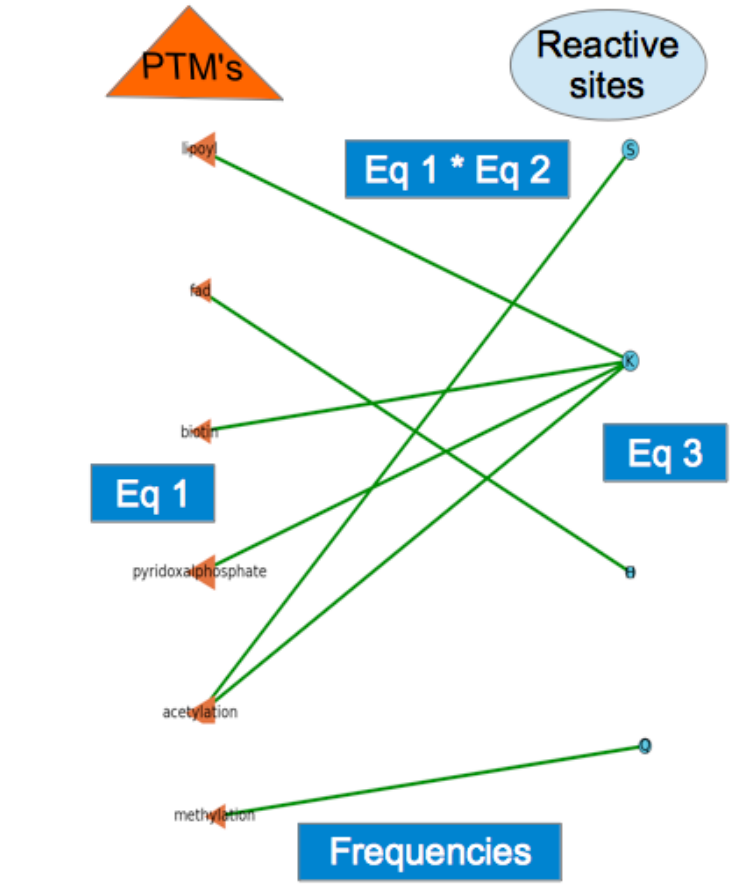
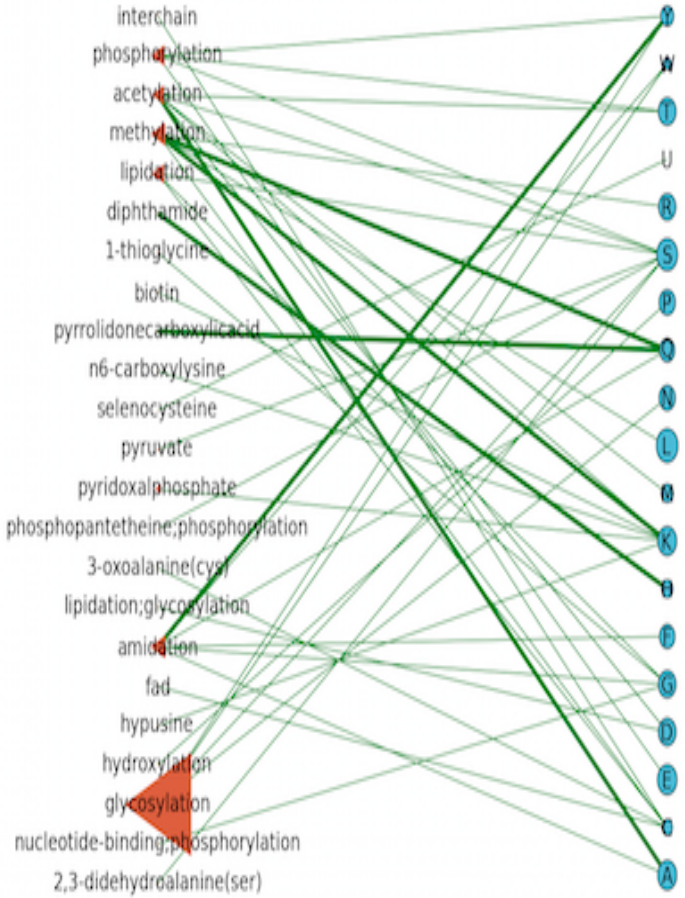
- How are the PTM distributions different between the Mt and non-Mt proteomes?

Mt and non-Mt Networks

Caenorhabditis elegans (Worm)



Mt

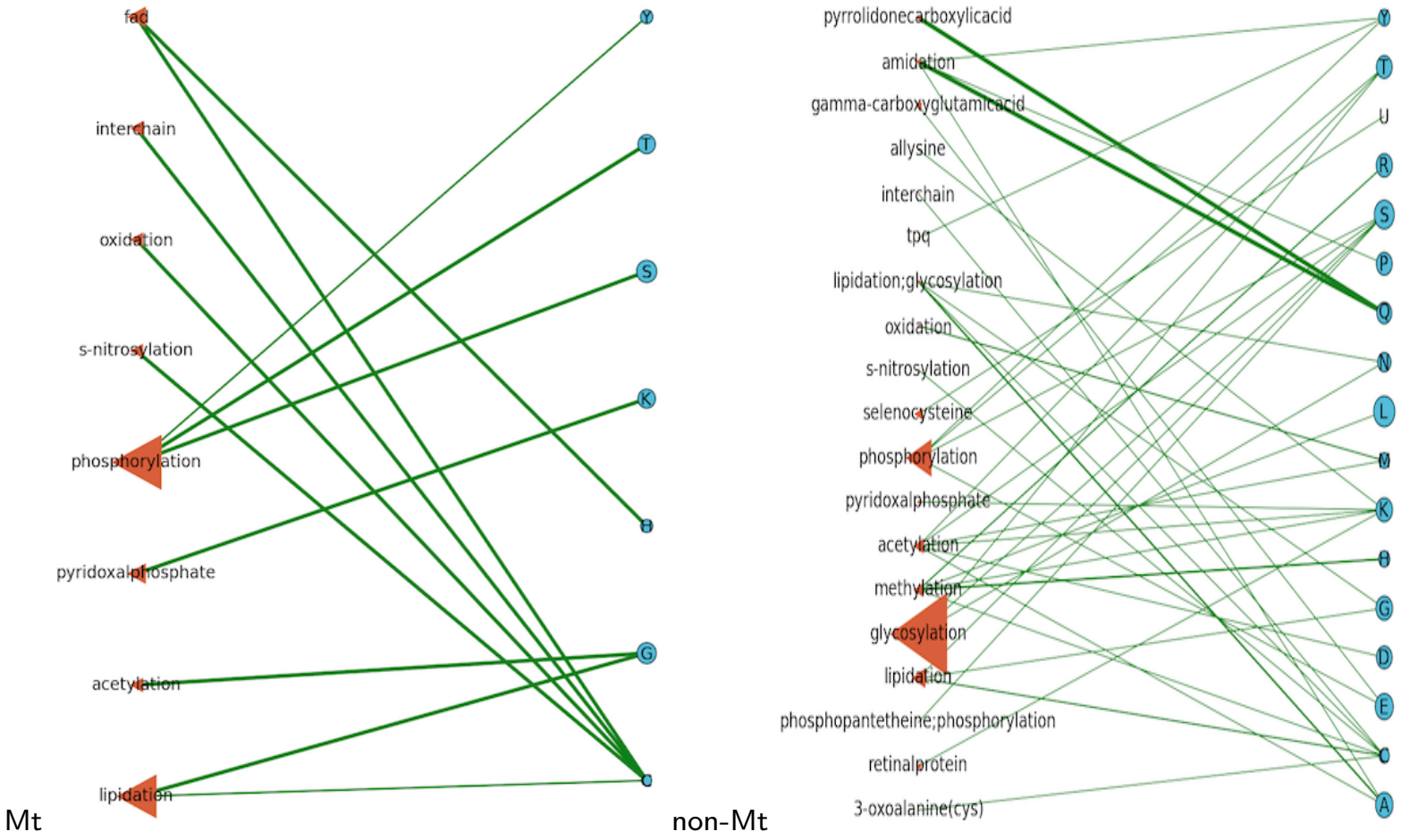


non-Mt

- Nodes: **PTMs** (left) node size is freq magnitude, **reactive site** (right)
- Edges: reactive site freq, thickness magnitude of reactive site interactions

Mt and non-Mt Networks

Danio rerio (Zebra fish)



- Nodes: **PTMs** (left) node size is freq magnitude, **reactive site** (right)
- Edges: reactive site freq, thickness magnitude of reactive site interactions

Mt and non-Mt Networks

Arabidopsis thaliana (plant)

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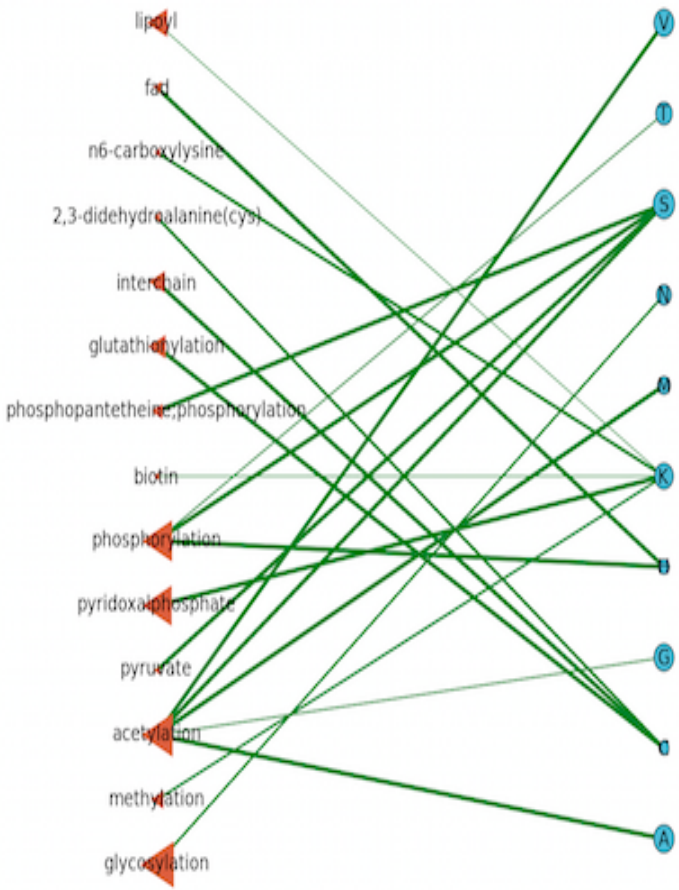

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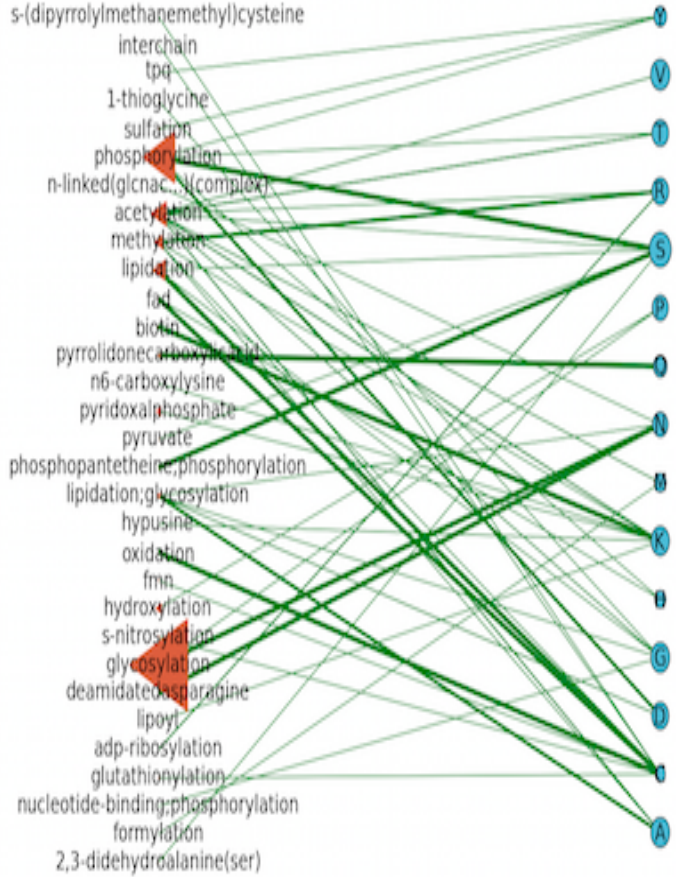
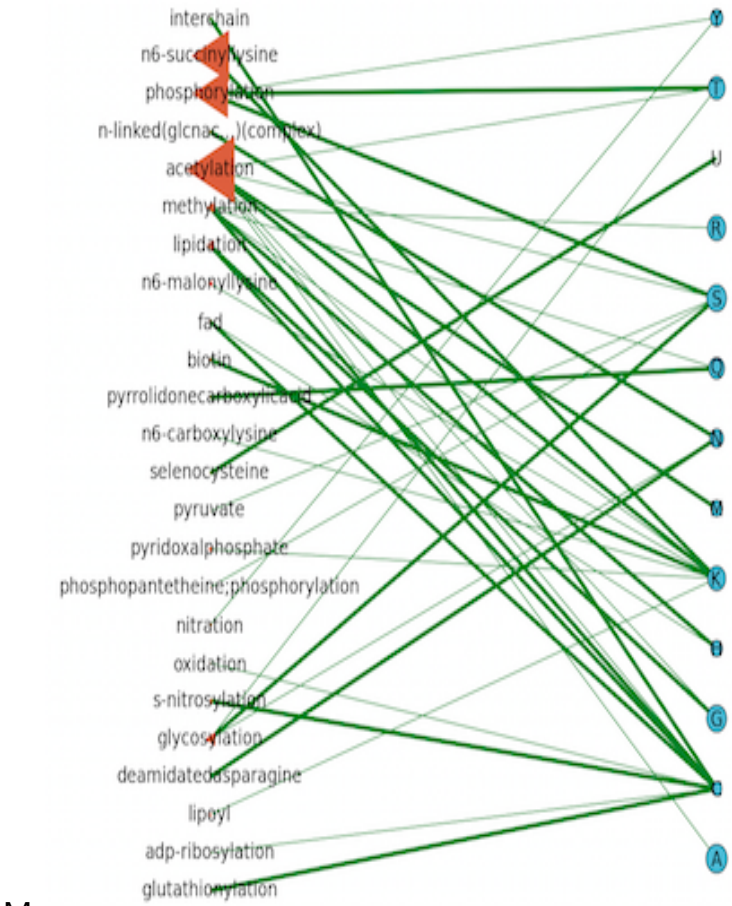


non-Mt

- Nodes: **PTMs** (left) node size is freq magnitude, **reactive site** (right)
- Edges: reactive site freq, thickness magnitude of reactive site interactions

Mt and non-Mt Networks

Homo sapiens (Human)



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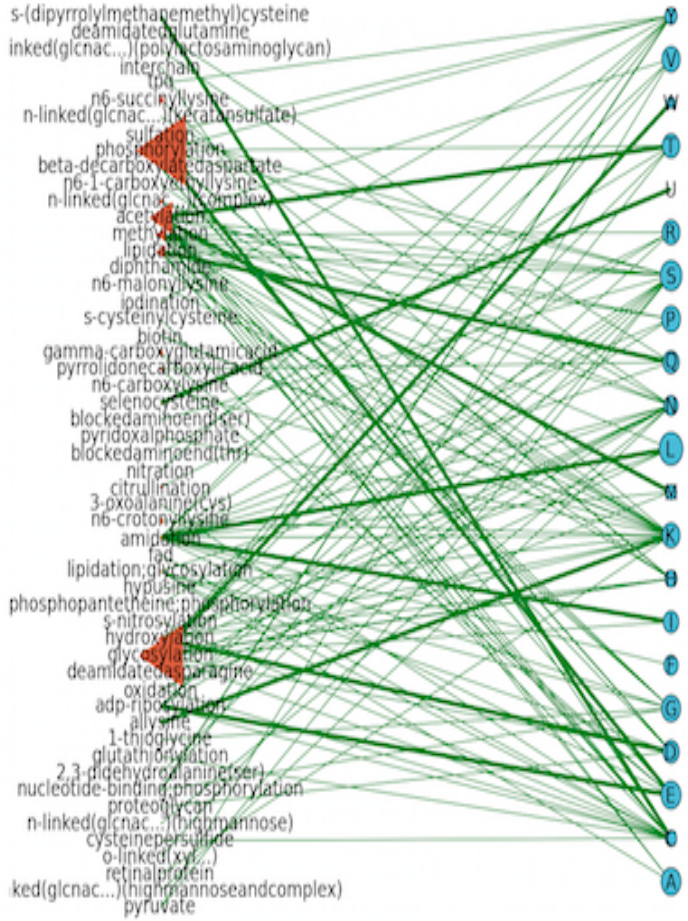

non-Mt

- Nodes: **PTMs** (left) node size is freq magnitude, **reactive site** (right)
- Edges: reactive site freq, thickness magnitude of reactive site interactions

A Heatmap Comparison

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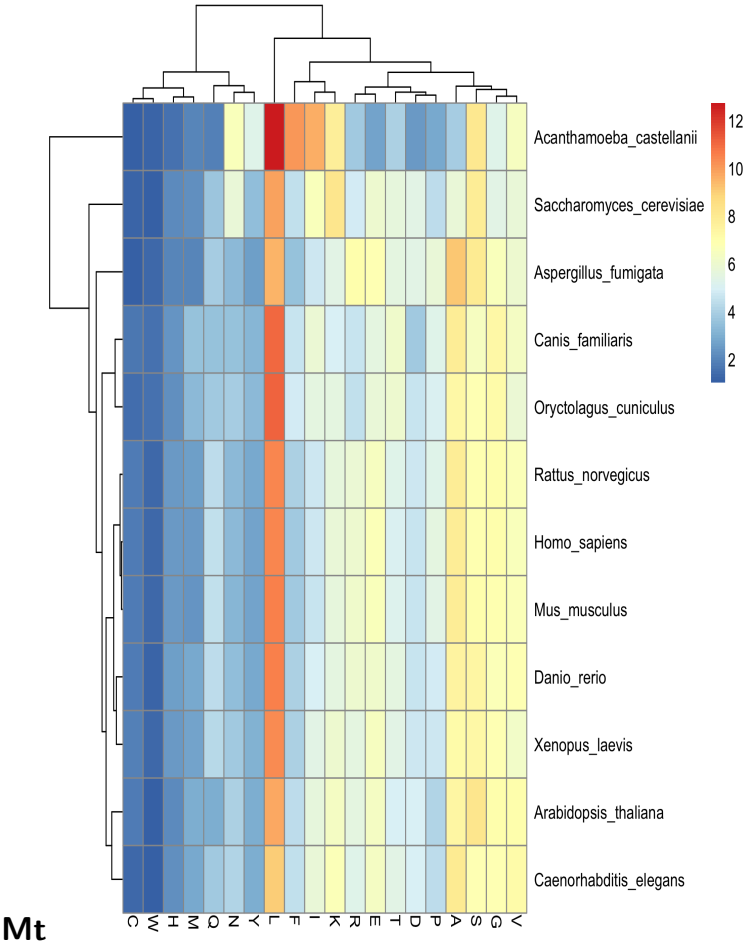
- How are the **amino acid** distributions different between the Mt and non-Mt proteomes?
  - $freq(aminoAcid_{(i,j)}) = \frac{count(aminoAcid_{(i,j)})}{\sum_{i=1}^{N_{(reactiveSites)}} count(reactiveSite_{(i,j)})}$

Composition of All AA's Across Organisms



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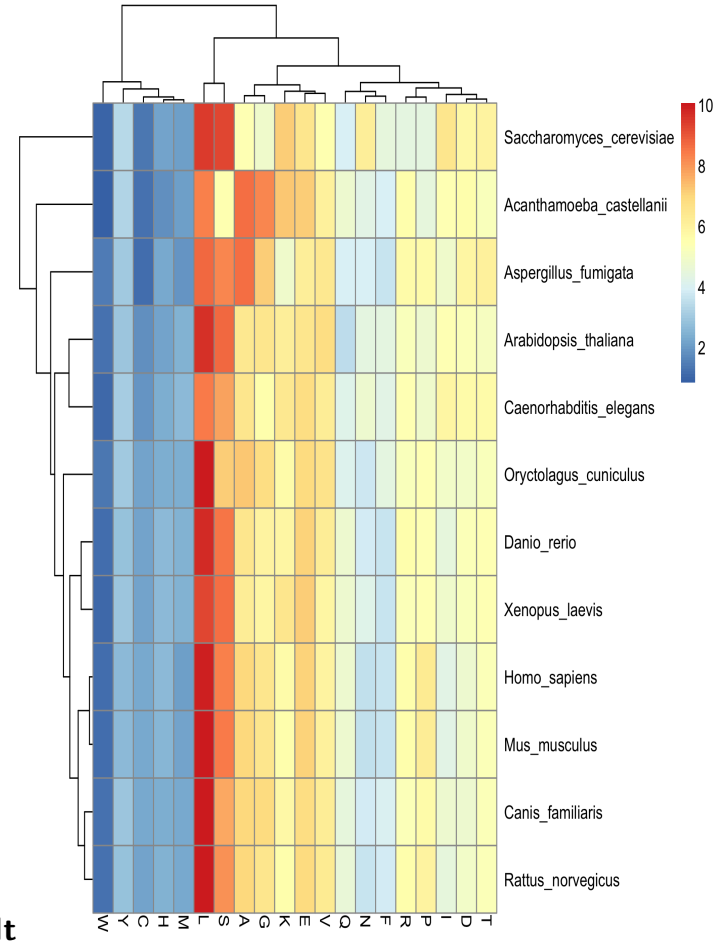

non-Mt

- Amino acids frequencies are similar across related organisms
- Dark blue values are very close to zero

A Heatmap Comparison

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- How are the **PTM Reactive Site** distributions different between the Mt and non-Mt proteomes?
  - $freq(ReactiveSite_{(i,j)}) = \frac{count(aminoAcid_{(i,j)})}{|\sum_{i=1}^{N_{Proteins}} Seq_{(i,j)}|}$

Composition of All PTM RSs Across Organisms

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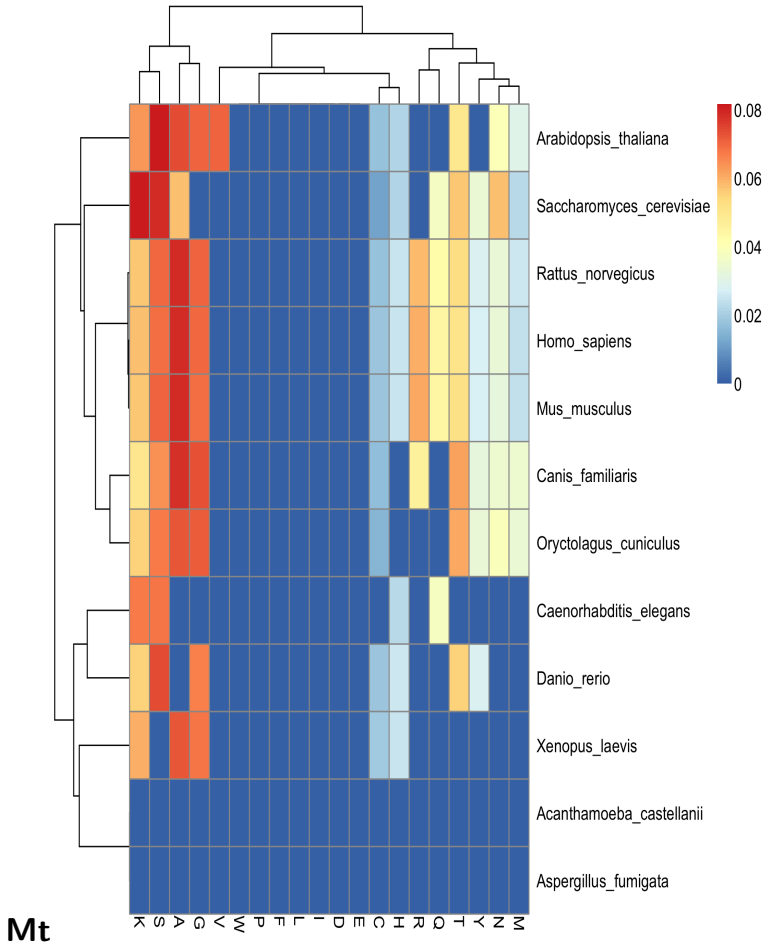
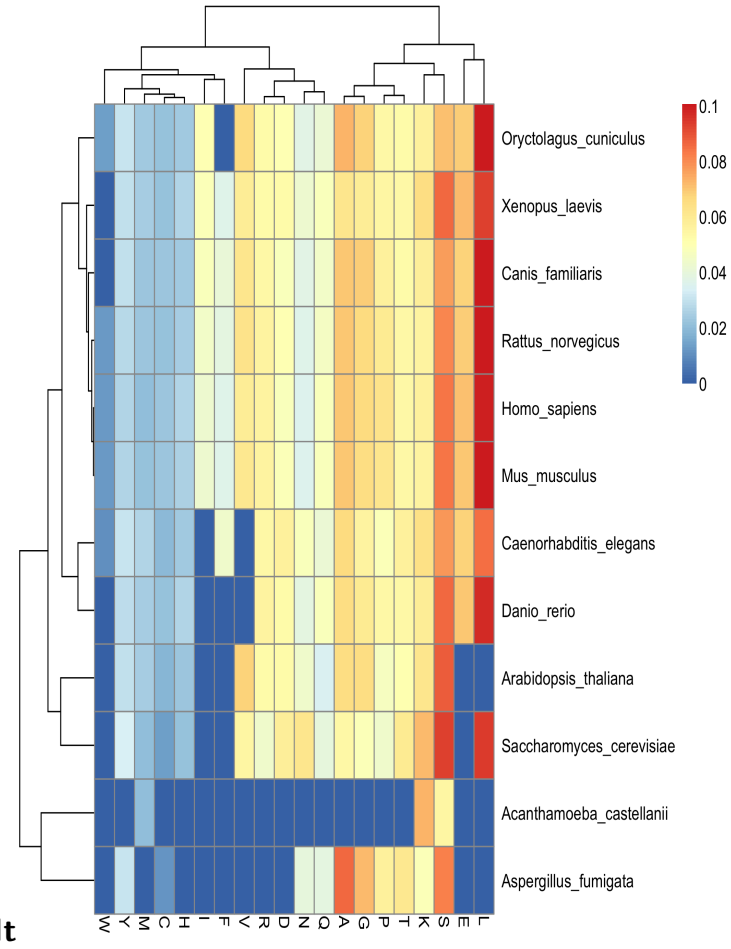


Mt



non-Mt

- Fewer reactive sites in Mt
- Dark blue values are very close to zero

Some of the Conclusions

Network Particulars

Protein Type	PTMs	Reactive Sites per PTM	Networks
Mt	Few	Few	Sparse and organized
Non-Mt	Many	Many	Dense, disorganized and messy

- **From Hypothesis**: Mt proteins have fewer PTMs and associated reactive sites than non-Mt proteins
- Future work: To study first effects of stress on protein reactive sites by observing PTM *first-responders*.

References: Cited in this Presentation

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- Bonham-Carter, Oliver, Ishwor Thapa, and Dhundy Bastola. **"Evidence of post translational modification bias extracted from the tRNA and corresponding amino acid interplay across a set of diverse organisms**." Proceedings of the 5th ACM Conference on Bioinformatics, Computational Biology, and Health Informatics. ACM, 2014.

- Bonham-Carter, Oliver, Lotfollah Najjar, and Dhundy Bastola. "**Evidence of a pathway of reduction in bacteria: Reduced quantities of restriction sites impact trna activity in a trial set.**" Proceedings of the International Conference on Bioinformatics, Computational Biology and Biomedical Informatics. ACM, 2013.

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Thank You! Questions?

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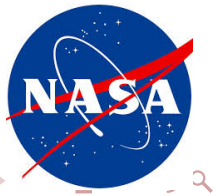
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