Patterns and Signals of Biology: An Emphasis On The Role of Post-Translational Modifications in Proteomes for Function and Evolutionary Progression

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All Mechanisms Send Signals

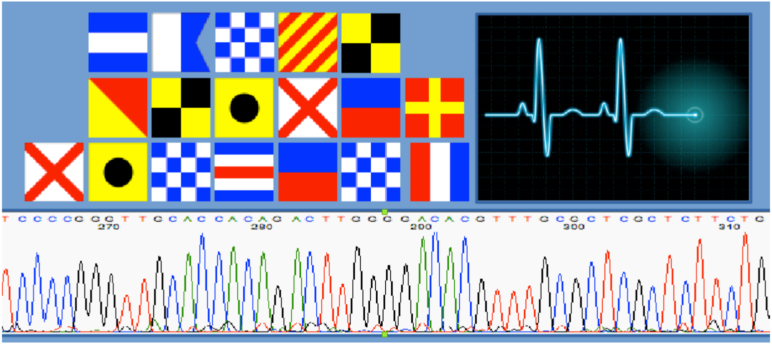
Stressed water

- Ripples in water announce a disturbance.

Signals Surrounding Us

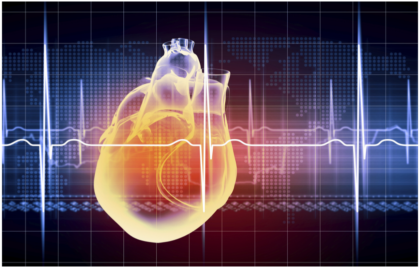
Each signal has a meaning - but which?

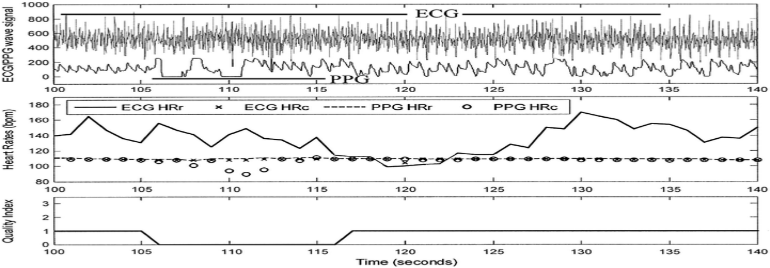
Signals Have Meaning



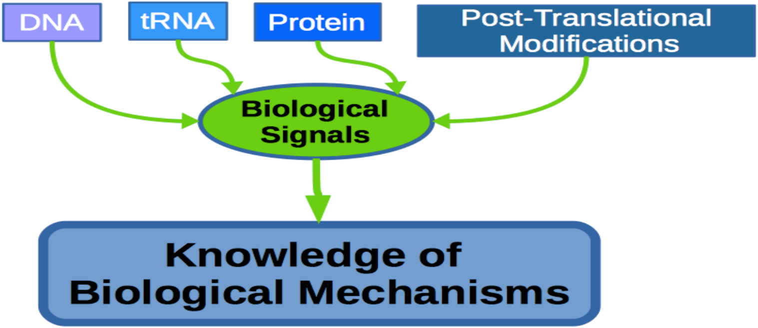
- Signals have meaning and arise from a reality, result or event
- A mechanism's existence is detected by its signals
- Studying signals can be used to determine mechanism details

Biological Signals Have Meaning





Biological Signals Have Meaning



DNA

tRNA

Protein

Post-Translational Modifications

Biological Signals

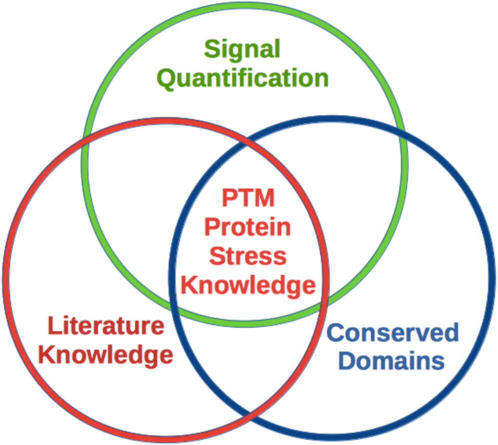
Knowledge of Biological Mechanisms

In this thesis...

- We study and quantify signals from biological processes to determine knowledge of their existence, to understand parts of their meanings.
- In particular, we analyze signals from protein stress response mechanisms involving post-translational modifications (PTMs) to gain understanding of some of their meanings.

Learning Mechanisms From Biological Signals

Three approaches to understanding mechanisms from signals



Signal Quantification

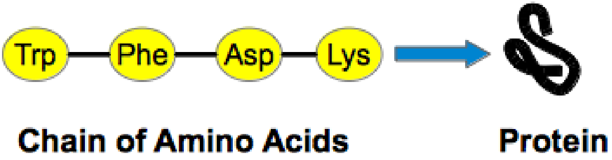
PTM
Protein
Stress
Knowledge

Literature Knowledge

Conserved Domains

- Our analysis of signals by three approaches.
- From the intersection of these approaches, we gain general mechanism knowledge.

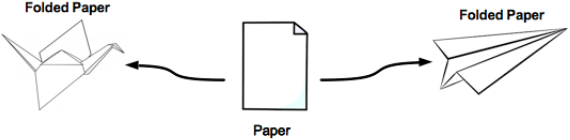
Background: The Mechanism of Protein



Proteins

- Amino Acids (basic building blocks) $\in$ Proteins $\in$ Organisms
- Protein structure implies its function
- Proper structure (i.e., function) is crucial for sustaining organism health

Protein Folding



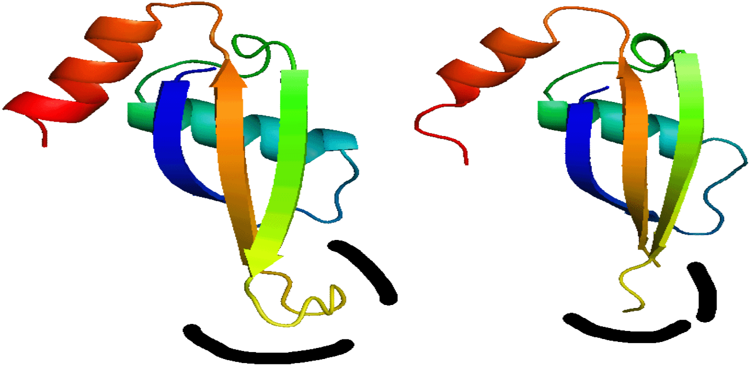
One of the above paper structures will fly...

- Folding: protein chain conformation implies protein function
    - Folding and unfolding are crucial ways of regulating biological activity and targeting proteins to different cellular locations.

Dobson, Christopher M. "Protein folding and misfolding." Nature 426.6968 (2003): 884-890.

Homologous Proteins of Different Function

VP0956 proteins: The same but different



- Two “identical” proteins for oxidation-reduction (stress-response)
- Alternative red and yellow structures, hence, different behaviour
- One has been adapted for specific functionality
- What inspired a conformational (structural) change?

Love is a spirit all compact of fire...

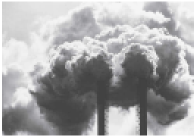
Venus and Adonis, Shakespeare

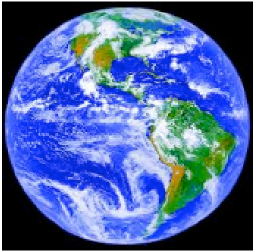
Loss of Protein Structure → Functional Loss

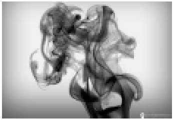
- Oxidation: a chemical stress that *rusts* protein and changes structure.
- Stresses: Protein oxidizers and “burners” destroy protein conformations (structures, hence, functions)
  - *Free Radicals (FR)* and *Reactive Oxygen Species (ROS)*

Environmental Stresses

Environmental stress: *a good source of daily oxidation*







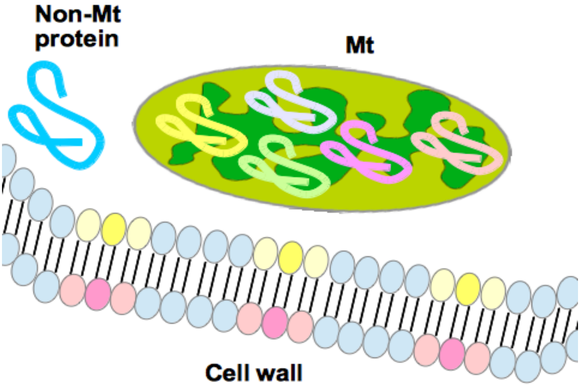
Pollution!

Protein Stress

Two Sources of Protein Stress

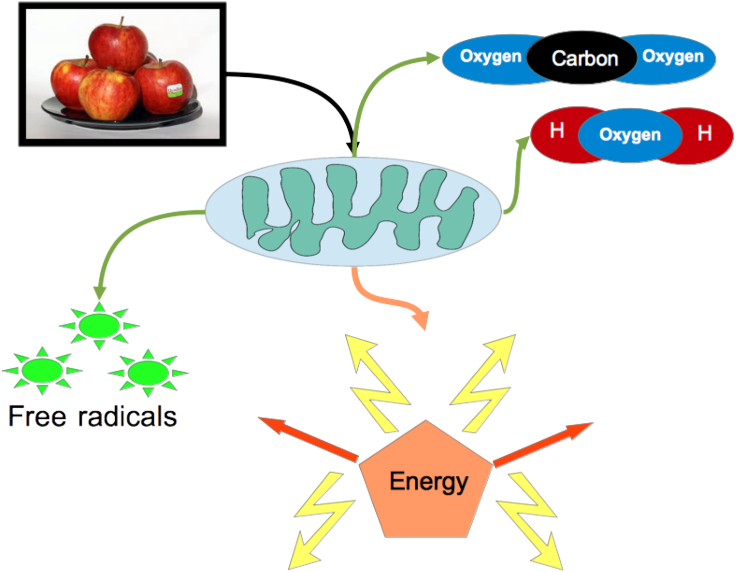
- External Stress originates far from protein's location
- **Internal Stress** occurs from internal processes

The Internal Stress: Mitochondria (Mt)



- Mt are important for cellular survival: involved in cellular regulation, apoptosis (cell death), general development, and other tasks
- Contain own proteins of specific structures and functions
- Play energy-providing role: cellular "batteries"

Simultaneous Production of Energy and *Stress*



Stress From Free Radical By-products

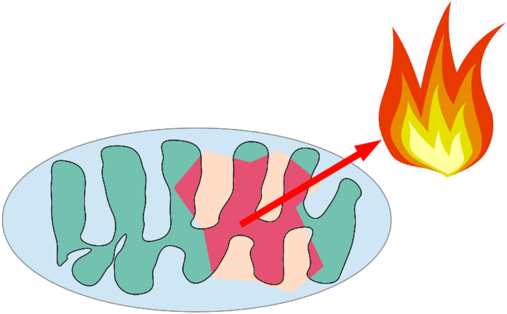
Potential for protein damage

- Free radicals are protein stresses
- Create stress conditions: encourage irreversible, protein damage (*oxidative carbonylation*)
- Protein dysfunction may result from alterations to protein structures

Maisonneuve, Etienne, et al. "Rules governing selective protein carbonylation." PloS one 4.10 (2009): e7269.

Oxidative Carbonylation

Potential for protein damage



- Internal oxidative stress is caustic to own proteins
- Damaged material cannot function
- Loss of function results in aliments and disorders

Literature

Oxidative Carbonylation Causes Protein Damage

Oxidative damage encourages:

- **Parkinson's disease** (1)
- **Alzheimer's disease** (2,3)
- **Aging and protein dysfunction** (4)
- **Increased tissue injury** (5,6)
- **Protein dysfunction in plants roots** (7)

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[1] Beal, M. Flint. "Mitochondria, oxidative damage, and inflammation in Parkinson's disease." Annals of the New York Academy of Sciences 991.1 (2003): 120-131.

[2] Smith, Mark A., *et al.* "Oxidative stress in Alzheimers disease." Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease 1502.1 (2000): 139-144.

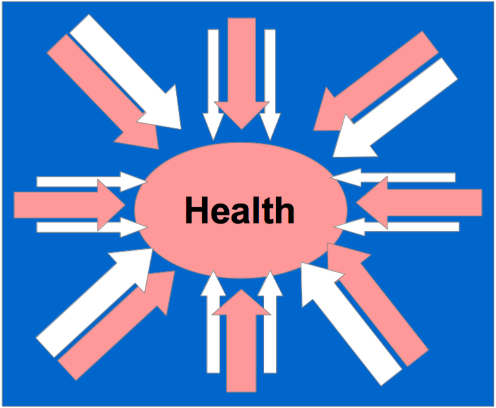
[3] Good, Paul F., *et al.* "Evidence of neuronal oxidative damage in Alzheimer's disease." The American journal of pathology 149.1 (1996): 21. [4] Kolesar, Jill E., *et al.* "Defects in mitochondrial DNA replication and oxidative damage in muscle of mtDNA mutator mice." Free Radical Biology and Medicine 75 (2014): 241-251.

[5] Zhao, W., *et al.* "Oxidative damage pathways in relation to normal tissue injury." (2014).

[6] Lin, Michael T.,*et al.* "Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases." Nature 443.7113 (2006): 787-795. [1] : 8 Hebelstrup, Kim H., *et al.* "Mitochondrial Signaling in Plants Under Hypoxia: Use of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS)." Reactive Oxygen and Nitrogen Species Signaling and Communication in Plants. Springer International Publishing, 2015. 63-77.

Resistance to Environmental Stresses

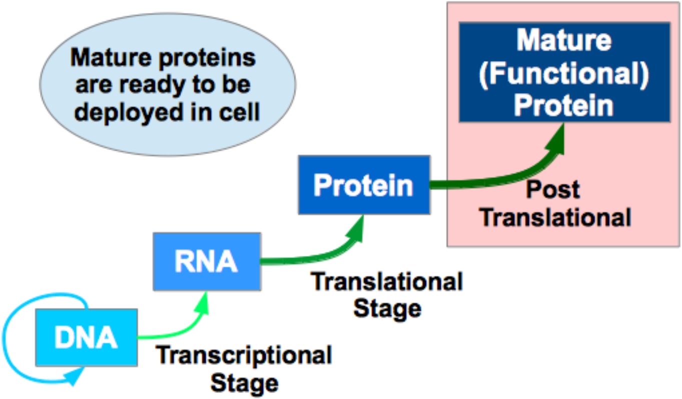
In spite of this oxidative danger, how are we able to stay healthy?



How do proteins commonly resist or cope with stress?

Post-Translational Modifications (PTMs)

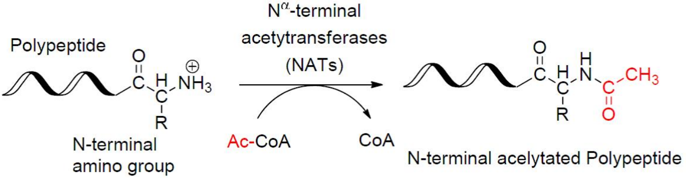
Biology's Central Dogma



- Proteins are folded into special conformations for a unique function

What are PTMs?

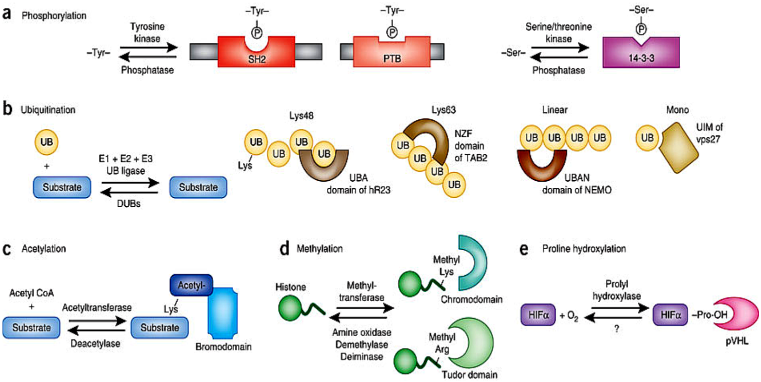
Changing the structural and functional *rules*



- Post-translational modifications refer to the covalent and generally enzymatic modification of proteins during or after protein biosynthesis.
- Proteins are synthesized by ribosomes translating mRNA into polypeptide chains
- Proteins undergo a PTM to form the mature protein product fit for some specific function.

Some Common Types of PTMs

The quick-addition of a group for conformational change and function.

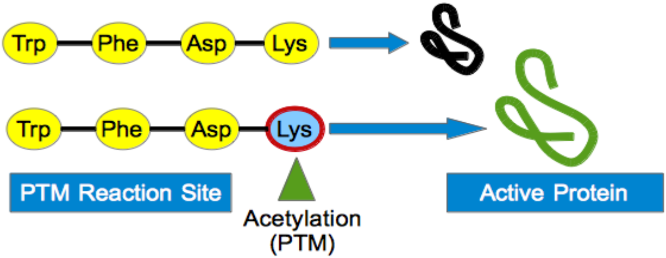


- We are mainly interested in acetylation, phosphorylation, glycosylation since much data exists for their study.

Deribe, *et al* “Post-translational modifications in signal integration.” *Nature structural & molecular biology* 17.6 (2010): 666-672. `http://www.nature.com/nsmb/journal/v17/n6/fig_tab/nsmb.1842_F1.html`

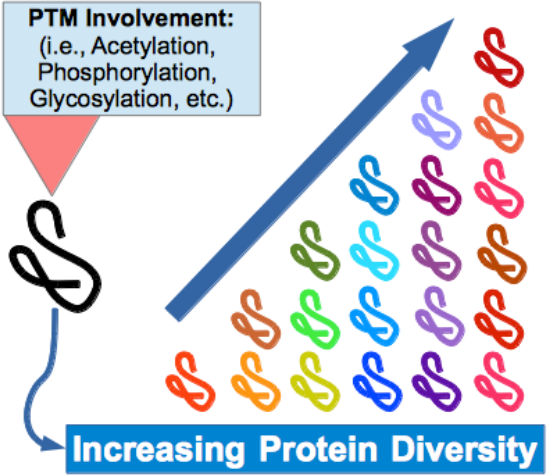
PTMs: A Step In Protein Biosynthesis

A biochemical modification



- PTMs refer to the covalent and generally enzymatic modification of proteins during or after protein biosynthesis.
- Two protein sequences having different functionalities.
- Mature proteins are structurally appropriate for functional tasks.

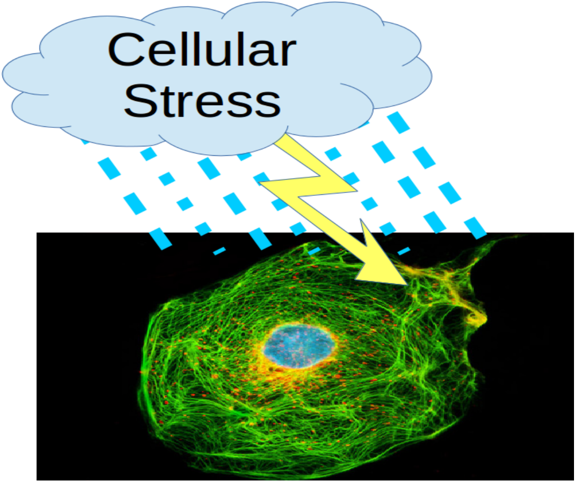
Same Protein, Different Structure



- PTMs biochemically alter proteins to create new functions

Types of Protein Stresses

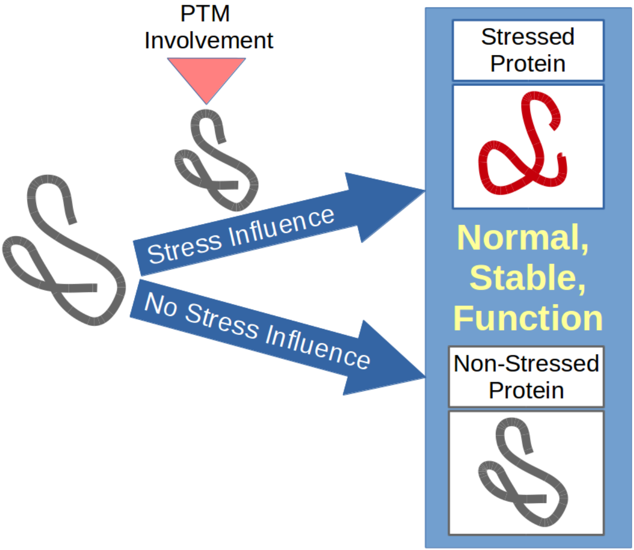
Nor rain, wind, thunder, fire are my daughters. -Shakespeare (King Lear)



- *Stressed Proteins*: Carbonylation, Free Radicals, Heat Shock, Microgravity, Saline, and others.

PTMs Involved In Protein Stress Response

Lightning-fast adaptation



PTM Involvement

Stress Influence

No Stress Influence

Stressed Protein

Normal, Stable, Function

Non-Stressed Protein

Overarching Goal

- **Research question**: How does environmental stress affect protein in terms of PTM activity?
- **Solution**: Build a computational profiling system for the study and prediction of stress responses in protein using PTMs

Specific Contributions

We reduce the model construction to three contributions:

- **Contribution 1**: The determination of a bias of PTMs, modification sites, and amino acids (i.e., amino acid composition) across the proteomes of diverse organisms.
- **Contribution 2**:
- **Contribution 3**:

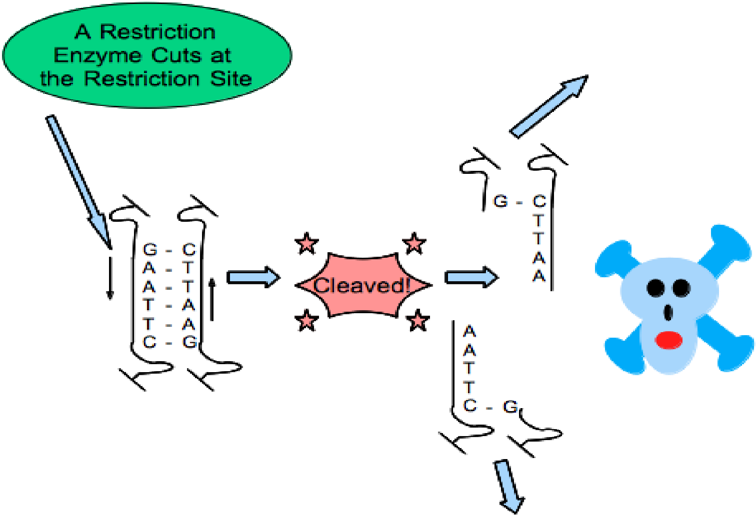
Signals to study

1. Motif (words) frequency of occurrence in DNA, RNA and Protein
2. PTM and modification site locations in proteins
3. Types of PTM involvement with protein.

Research Questions Concerning Bias

- In DNA, what evidence of *bias* is there?
- Solution: We compare palindromic words in DNA coding (*functional*) regions and non-coding (*non-functional*) regions.

Palindromic Restriction Sites

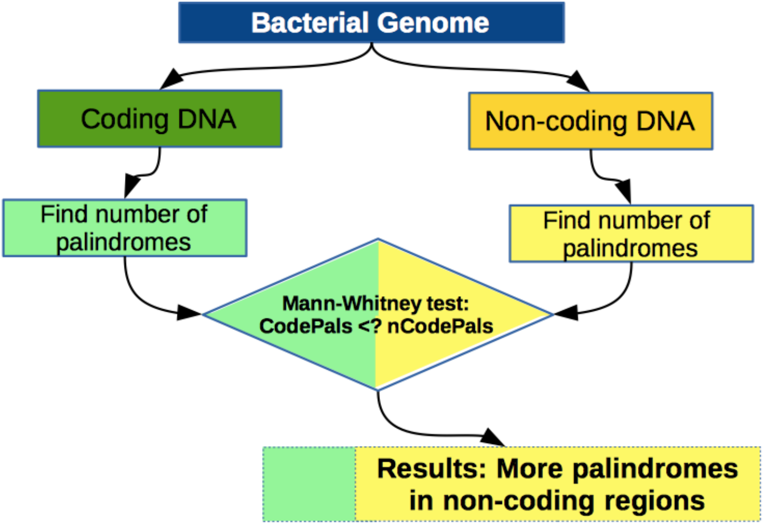


A Restriction Enzyme Cuts at the Restriction Site

Cleaved!

Supporting: Types of Bias in DNA

Contribution: Restriction Sites not randomly placed



Bacterial Genome

Coding DNA

Non-coding DNA

Find number of palindromes

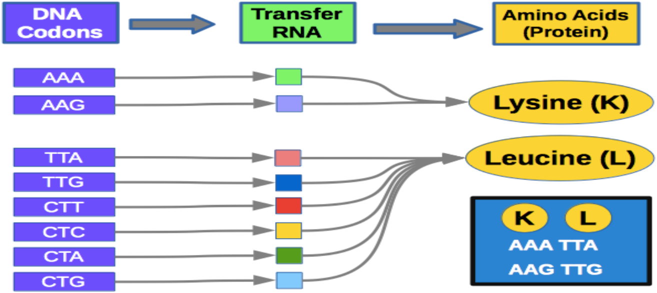
Find number of palindromes

Mann-Whitney test: CodePals <? nCodePals

Results: More palindromes in non-coding regions

Supporting: Types of Bias in tRNA from DNA

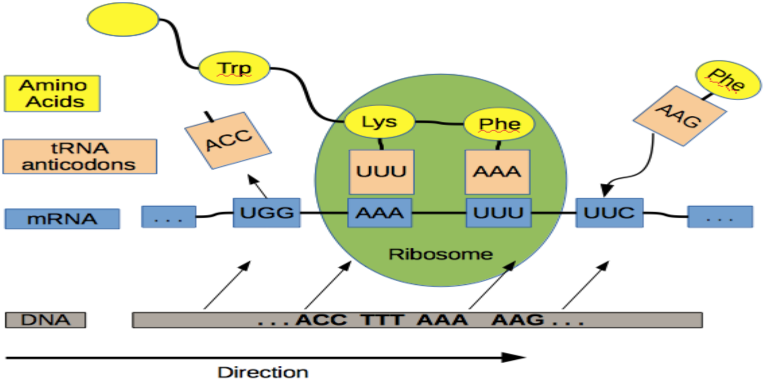
tRNAs are associated to DNA



- Transfer-RNAs (tRNA) are adaptor molecules responsible for delivering amino acids (protein building blocks) into protein chains.
- `AAATTT` (a palindrome) contains codons, `AAA` and `TTT`.
- Absence of `AAATTT` creates an absence of use of the tRNA associated with `AAA` for lysine and `TTT` phenylalanine delivery into protein sequence.

Supporting: Types of Bias in tRNA from DNA

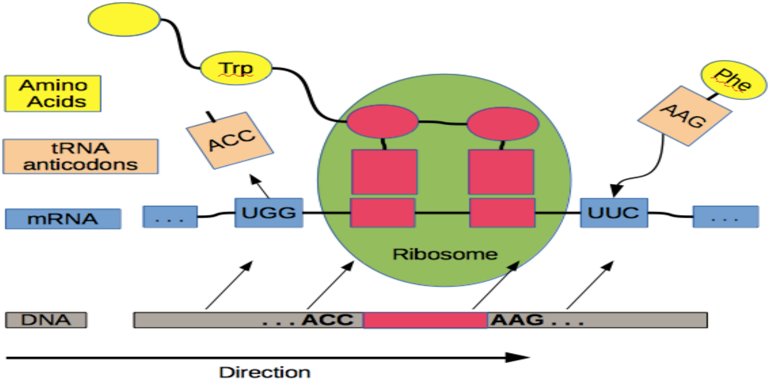
Missing DNA creates a *Pathway of Reduction*



- We note the interconnected nature of DNA and tRNAs

Supporting: Types of Bias in tRNA from DNA

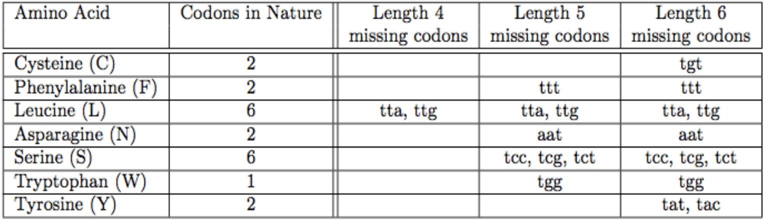
Missing DNA creates a *Pathway of Reduction*



- Missing DNA codons limit use of their tRNAs.

Supporting: Types of Bias in tRNA from DNA

Contribution: Missing tRNAs From missing DNA



Amino Acid	Codons in Nature	Length 4 missing codons	Length 5 missing codons	Length 6 missing codons
Cysteine (C)	2			tgt
Phenylalanine (F)	2		ttt	ttt
Leucine (L)	6	tta, ttg	tta, ttg	tta, ttg
Asparagine (N)	2		aat	aat
Serine (S)	6		tcc, tcg, tct	tcc, tcg, tct
Tryptophan (W)	1		tgg	tgg
Tyrosine (Y)	2			tat, tac

- Missing length-4 palindromic content lead to missing leucine (L)
- Missing length-5 palindromes lead to missing, phenylalanine (F), leucine (L), as- paragine (N), serine (S), and tryptophan (W)
- The biases in DNA created biases in tRNA

Published

Article Details

- **Oliver Bonham-Carter, Lotfollah Najjar, Ishwor Thapa** and **Dhundy Bastola**, "Distributions of palindromic proportional content in bacteria", *The 8th International Symposium on Bioinformatics Research and Applications (ISBRA 2012).*
- **Oliver Bonham-Carter, 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." *The Proceedings of the International Conference on Bioinformatics, Computational Biology and Biomedical Informatics. ACM*, 2013.

Supporting: Types of Bias that Differentiate

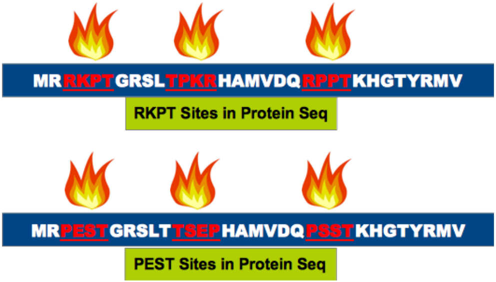
Publications

Article Details

- **Oliver Bonham-Carter, Hesham Ali**, and **Dhundy Bastola**. "A meta-genome sequencing and assembly preprocessing algorithm inspired by restriction site base composition." *Bioinformatics and Biomedicine Workshops (BIBMW)*, 2012 IEEE International Conference on. IEEE, 2012.
- **Oliver Bonham-Carter, Hesham Ali**, and **Dhundy Bastola**. "A base composition analysis of natural patterns for the preprocessing of metagenome sequences." *BMC bioinformatics* 14.11 (2013): 1.

Background: Compositions of Carbonylation Sites

- Literature: oxidation sites may be composed of:
  - "**RKPT** regions", enriched in: arginine (**R**), lysine (**K**), proline (**P**) and threonine (**T**) residues
  - "**PEST** regions", enriched in: proline (**P**), glutamic acid (**E**), serine (**S**), and threonine (**T**) residues
- Oxidation is naturally produced in Mt (is that a problem?)



MRRKPTGRSLTPKRHAMVDQRPPTKHGTYRMV

RKPT Sites in Protein Seq

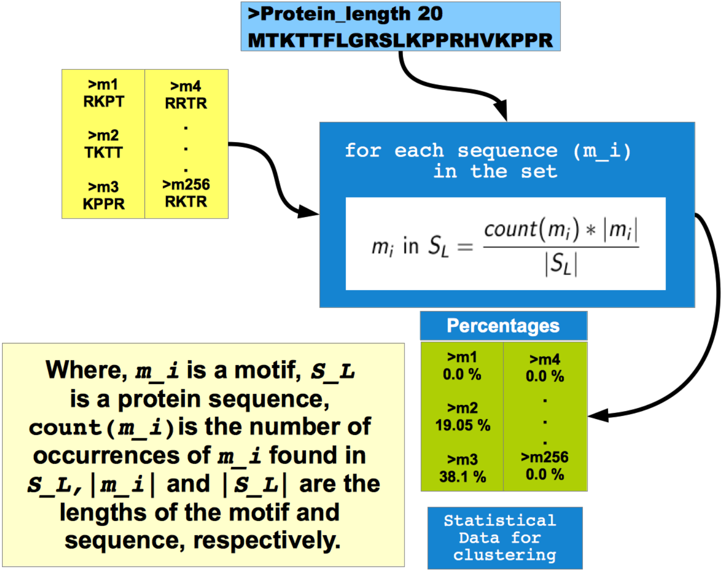
MRPESTGRSLTTSEPHAMVDQPSSTKHGTYRMV

PEST Sites in Protein Seq

Maisonneuve, Etienne, et al. "Rules governing selective protein carbonylation." PloS one 4.10 (2009): e7269.

Proportions: Comparison Between Data Points

The motif coverage in Mt and non-Mt protein



>Protein_length 20
MTKTTFLGRSLKPPRHVKPPR

>m1 RKPT	>m4 RRTR
>m2 TKTT	. . .
>m3 KPPR	>m256 RKTR

for each sequence (m_i) in the set

$$m_i \text{ in } S_L = \frac{count(m_i) * |m_i|}{|S_L|}$$

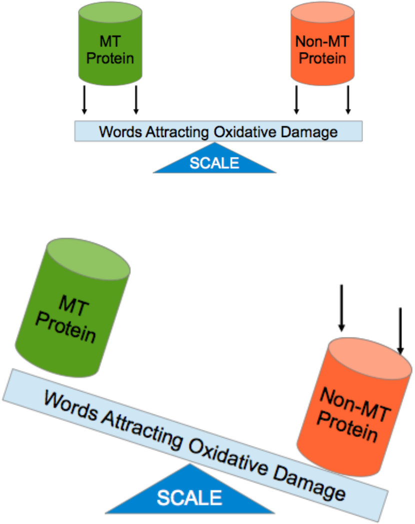
Percentages

>m1 0.0 %	>m4 0.0 %
>m2 19.05 %	. . .
>m3 38.1 %	>m256 0.0 %

Statistical Data for clustering

Where, *m_i* is a motif, *S_L* is a protein sequence, count(*m_i*) is the number of occurrences of *m_i* found in *S_L*, |*m_i*| and |*S_L*| are the lengths of the motif and sequence, respectively.

Results: Missing Carbonylation Sites in Mt



Generally Less Oxidation-Attracting Motif Content in Mt Protein

Published

- **Oliver Bonham-Carter, Jay Pedersen, Lotfollah Najjar** and **Dhundy Bastola**, "Modeling the effects of microgravity on oxidation in mitochondria: A protein damage assessment across a diverse set of life forms." *Data Mining Workshops (ICDMW), 2013 IEEE 13th International Conference on. IEEE*, 2013.
- **Oliver Bonham-Carter, Jay Pedersen**, and **Dhundy Bastola**. "A content and structural assessment of oxidative motifs across a diverse set of life forms." *Computers in biology and medicine*, 53 (2014): 179-189.

Contribution 1: Research Question

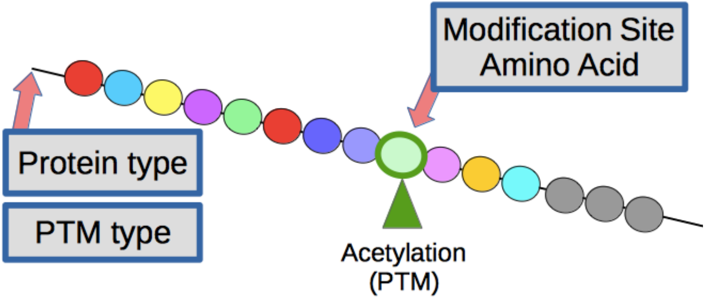
- What are the biases which exist across organisms in terms of PTMs, amino acids and modification sites?

Finding PTMs in Protein

Proposed Method: Frequencies of Elements

DataBase: UniProt

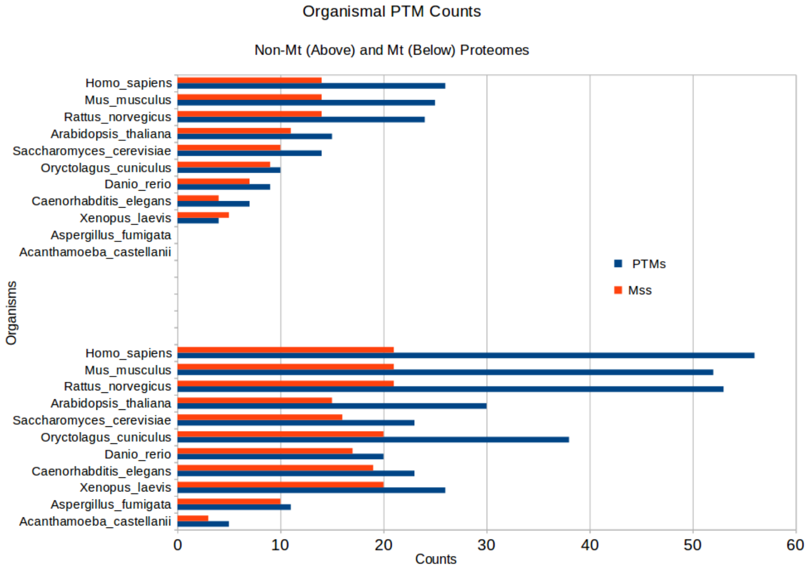
```
for each protein by organism:
 obtain type and count of:
   PTMs,
   Modification Location places (Active Sites),
   Amino Acids (composition)
```



- Data collected from organismal protein records from UniProt (protein database)

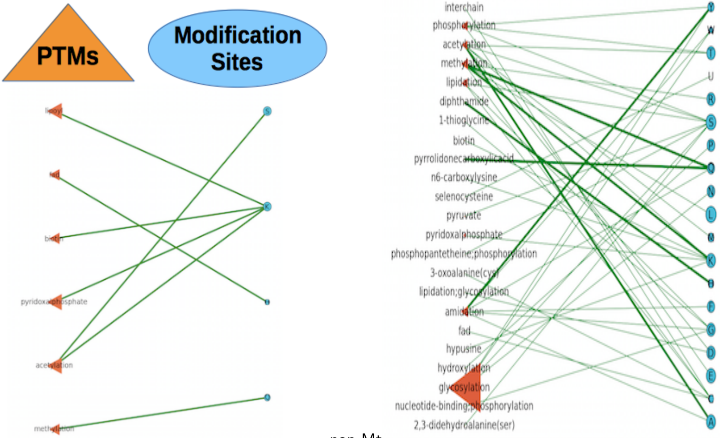
Finding PTMs in Protein

PTMs and MSs counts: unequal numbers across proteomes



Mt and non-Mt Networks

Caenorhabditis elegans (Worm)

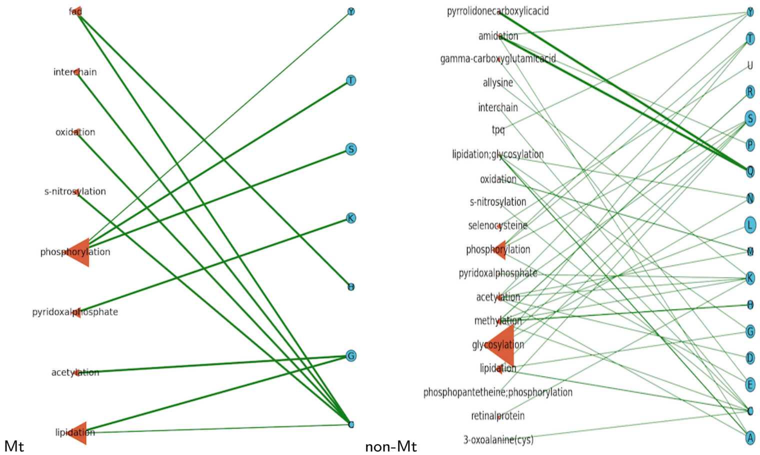


Mt non-Mt

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

Mt and non-Mt Networks

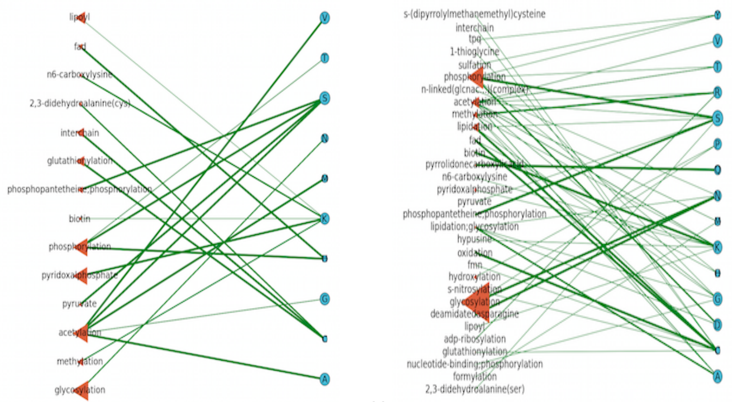
Danio rerio (Zebra fish)



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

Mt and non-Mt Networks

Arabidopsis thaliana (Thale cress plant)

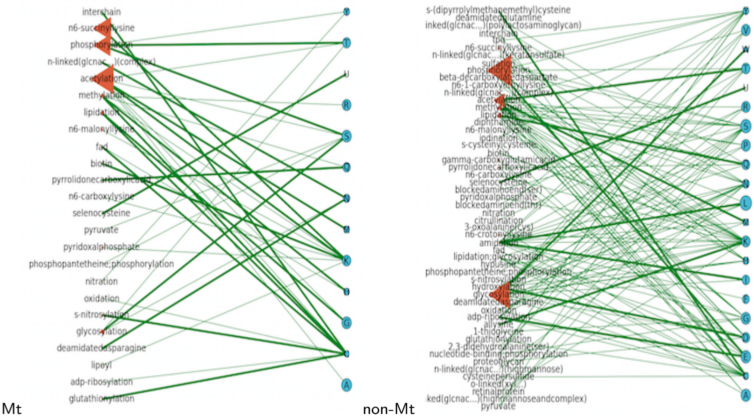


Mt non-Mt

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

Mt and non-Mt Networks

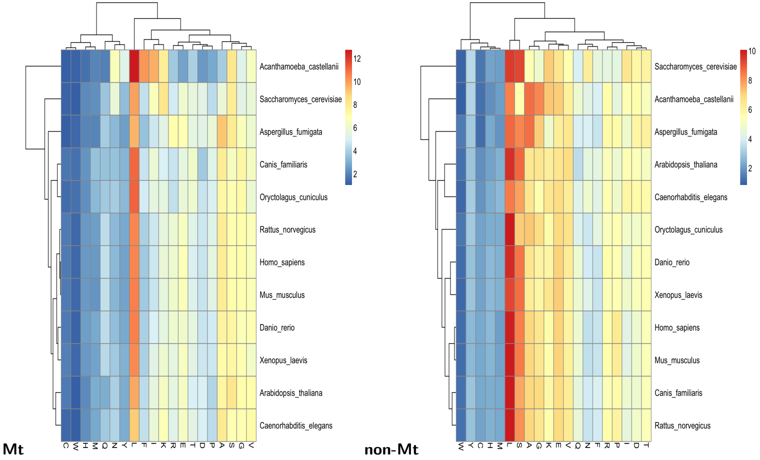
Homo sapiens (A type of monkey)



Mt non-Mt

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

Composition of Amino Acids Across Organisms



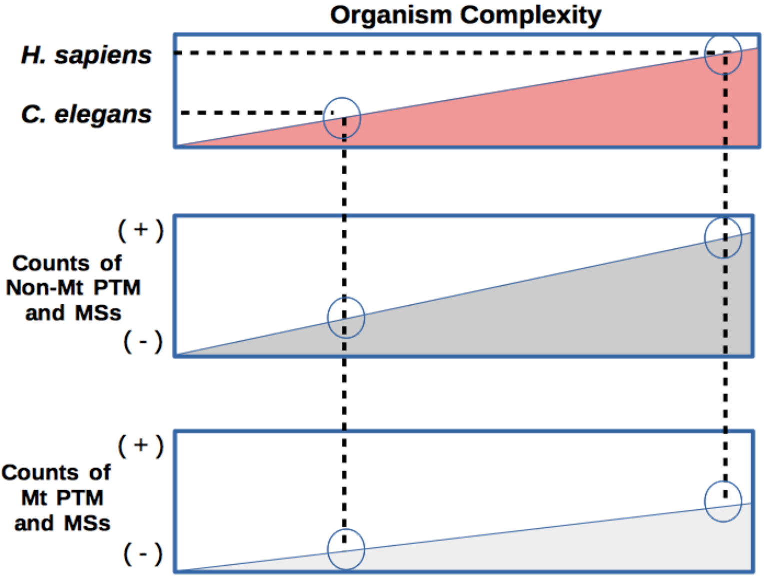
- Amino acids frequencies are similar across related organisms
- PTM bias is not likely a direct consequence of composition
- Dark blue values are very close to zero

Some of the Conclusions

Network Particulars

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

Some of the Conclusions



Contribution 1: Future Work

- A bias is clear: More data is necessary over a diverse group of organisms.
- Data to address the following:
  - Mt have highly conserved genetic material. Is the PTM bias also conserved across large groups of organisms?

Published

- **Oliver Bonham-Carter, 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.
- **Oliver Bonham-Carter, Ishwor Thapa, Steven From** and **Dhundy Bastola**. "A study of bias and increasing organismal complexity from their post-translational modifications and reaction site interplays." *Briefings in bioinformatics*. 2016 Jan 13:bbv111.

Specific Contributions

We reduce the model construction to three contributions:

- **Contribution 1**:
- **Contribution 2**: What are the relationships that exist between stresses, proteins, and types of PTMs (according to the literature)?
- **Contribution 3**:

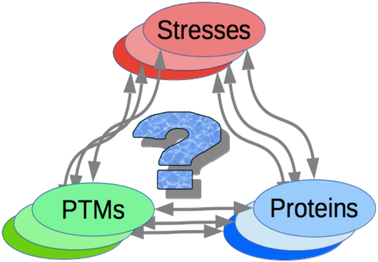
Signals to study

1. In peer-reviewed literature: The usage of keywords pertaining to *proteins*, *stresses* and types of *PTMs*
2. The inter-connectivity of these keywords
3. The number of connections between keywords

Contribution 2: Research Questions

- What relationships can we extract from NCBI, containing many thousands of scientific articles from all sciences?
- What relationships exist between proteins, stresses and PTMs?

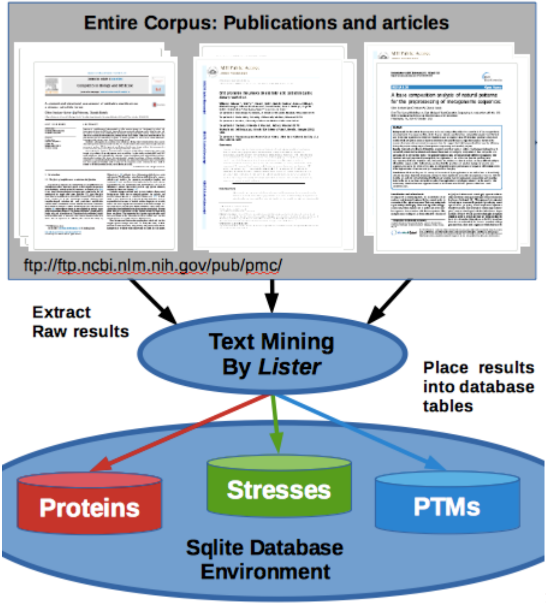
Text Mining



Solution to Obtaining Relationship Details

- *Lister*: Our text mining tool built in Python
- Supervised system: Keyword driven
- Abstracts: mentioned keywords are supported by article

Extract All Relationship Details From Literature



Entire Corpus: Publications and articles

ftp://ftp.ncbi.nlm.nih.gov/pub/pmc/

Extract Raw results

Text Mining By *Lister*

Place results into database tables

Proteins

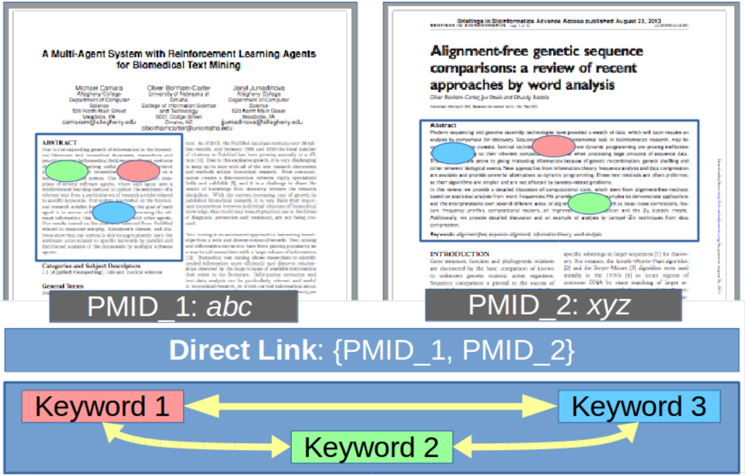
Stresses

PTMs

Sqlite Database Environment

We Determine **Direct** Relationships

Stress, Protein and PTM Relationships From Single Articles



PMID_1: *abc*

PMID_2: *xyz*

Direct Link: {PMID_1, PMID_2}

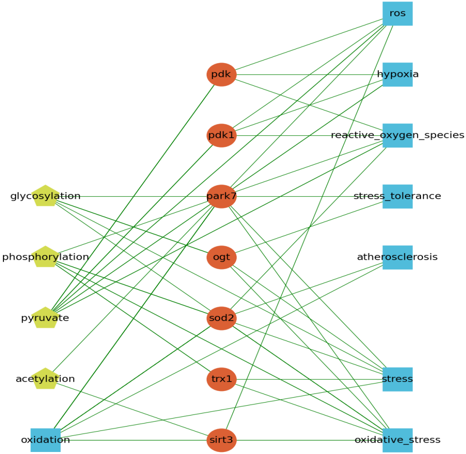
Keyword 1

Keyword 2

Keyword 3

Alzheimer's: Mt, Stressed Proteins and PTMs

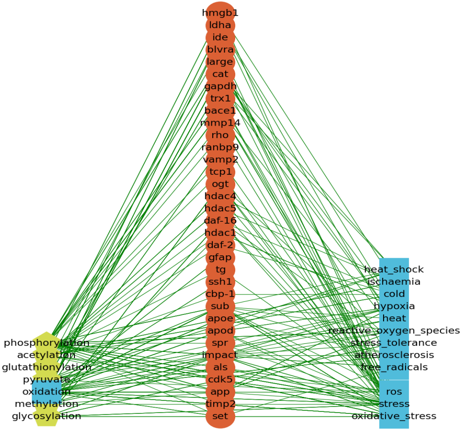
Direct relationships: cliques are created from one article



Nodes: **Yellow**: PTMs, **Red**: Proteins, **Blue**: Alzheimer's disease and **Edges** indicate that a study exists to combine PTM, Protein and Stress (a clique)

Alzheimer's: nMt, Stressed Proteins and PTMs

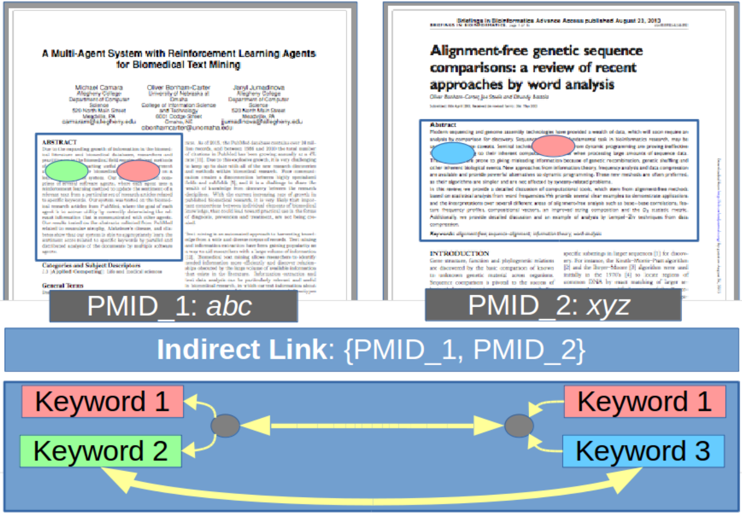
Direct relationships: cliques are created from one article



Nodes: **Yellow**: PTMs, **Red**: Proteins, **Blue**: Alzheimer's disease and **Edges** indicate that a study exists to combine PTM, Protein and Stress (a clique)

We Determine **Indirect** Relationships

Stress, Protein and PTM Relationships From Multiple Articles



A Multi-Agent System with Reinforcement Learning Agents for Biomedical Text Mining

Michael Camara, Allegheny College, Department of Computer Science, 520 North Main Street, Meadville, PA
Oliver Bonham-Carter, University of Nebraska at Omaha, College of Information Science and Technology, 6001 Dodge Street, Omaha, NE, obonhamcarter@unomaha.edu
Janyl Jumadinova, Allegheny College, Department of Computer Science, 520 North Main Street, Meadville, PA

ABSTRACT

Briefings in Bioinformatics Advance Access published August 23, 2013

Alignment-free genetic sequence comparisons: a review of recent approaches by word analysis

Abstract

INTRODUCTION

PMID_1: *abc*

PMID_2: *xyz*

Indirect Link: {PMID_1, PMID_2}

Keyword 1

Keyword 2

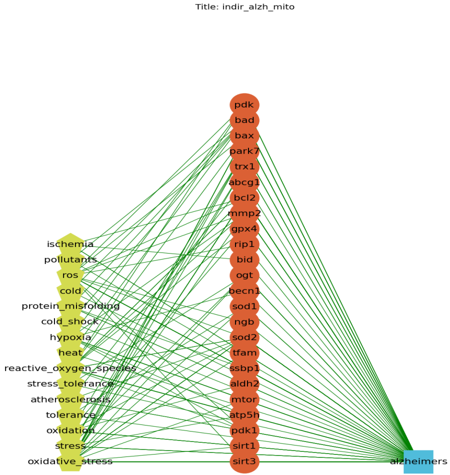
Keyword 1

Keyword 3

- *Guilt by association*

Alzheimer's: Mt, Stressed Proteins and PTMs

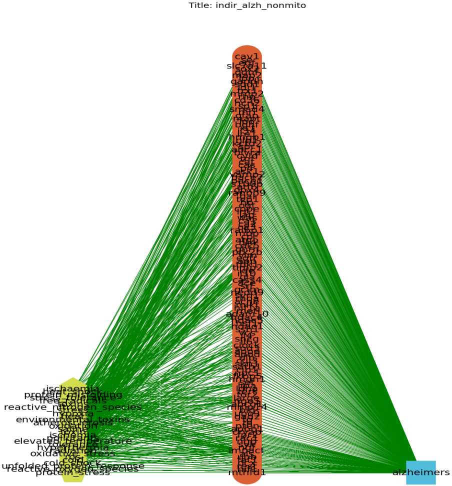
Indirect relationships: cliques are created from several articles



Nodes: **Yellow**: stresses **Red**: Proteins, **Blue**: ailment and **Edges** indicate that a study exists to combine PTM, Protein and Stress (a clique)

Alzheimer's: nMt, Stressed Proteins and PTMs

Indirect relationships: cliques are created from several articles



Nodes: **Yellow**: stresses, **Red**: Proteins, **Blue**: ailment and **Edges** indicate that a study exists to combine PTM, Protein and Stress (a clique)

Some of The Conclusions

- A short listing of proteins (associated with ailments), that are known to be involved with PTMs when stressed in particular ways
- Relationships are supported by literature citations
- This list of actors may describe possible ailment onset conditions

Contribution 2: Future Work

- Text mine NCBI's entire corpus of articles to be able to combine the details of protein, stress and PTMs to get better perspectives.
- Find relationships of other types of disorders (as many as possible)
- Predict relationships of these elements
- Predict the future works by other investigators

Published

- **Oliver Bonham-Carter** and **Dhundy Bastola**, “A text mining application for linking functionally stressed-proteins to their post-translational modifications”, *2015 IEEE International Conference on Bioinformatics and Biomedicine (Semantics and Ontology Track)*, 2015.

Specific Contributions

We reduce the model construction to three contributions:

- **Contribution 1**:
- **Contribution 2**:
- **Contribution 3**: The construction and development of a computational model to ascertain the conserved nature of PTM modification sites (MSs) and the protein domains with which they are likely to interact.

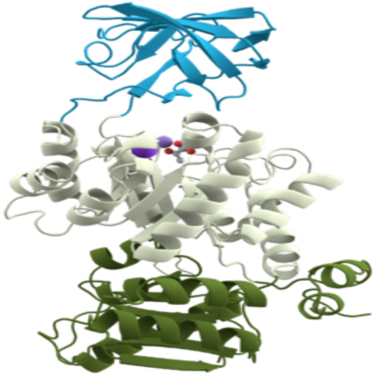
Signals to study

1. PTMs, modification sites and protein domains
2. MS neighbourhoods: selected regions of protein sequences where MSs are grouped
3. Measured distances between protein domain locations and MSs

Research Questions

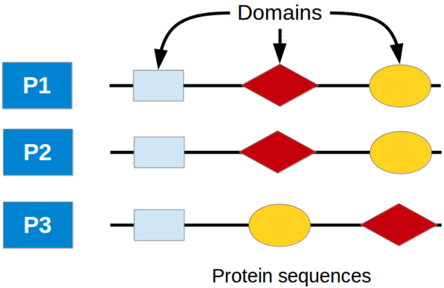
- Domains are initiated by PTMs at specific modification sites: What is conserved in this mechanism?
- What patterns exist?

Protein Domain Architectures



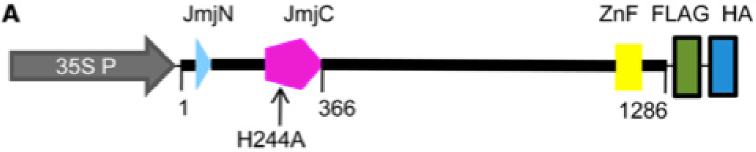
- Conserved parts of a protein sequence and structure, able to evolve, function, and exist independently of the rest of the protein chain
- Pyruvate kinase, a protein with three domains
- *Domain* refers to the location of the region

Domains May Be Found in Diverse Protein



- Domain "copies" may be found in diverse proteins
- Protein domains react directly with PTMs by a mechanism

PTM Interactions With Domain



- JmjN, JmjC and the Znf are domains.
- H244A represents the methylation (PTM) site
- Stress responses initiates **methylation** (PTM) to initiate the domain at this exact site

Li, Tiantian, et al. "Jumonji C domain protein JMJ705-mediated removal of histone H3 lysine 27 trimethylation is involved in defense-related gene activation in rice." The Plant Cell Online 25.11 (2013): 4725-4736.

Two Types of Studies

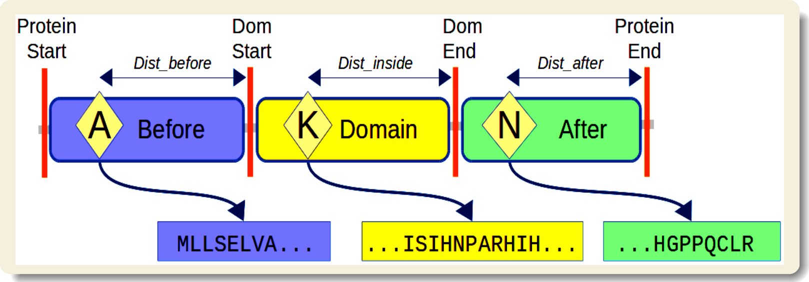
Domains associated with PTMs

- **An Organism-centric study**: All domains associated with a specific type of organism, are selected for study
- **A Domain-centric study**: A particular domain type is selected for study across all the data where is found (in any type of organism)

- We study all domains involved with *acetylation* and its associated modification sites

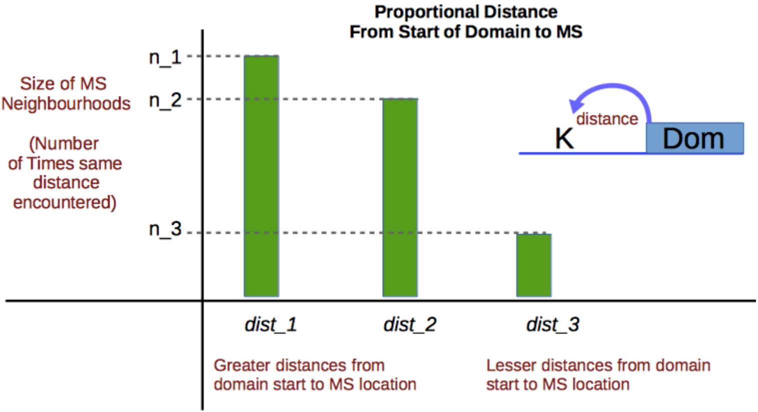
Organism-centric Study: Three Regions To Study

Three Types of Criteria



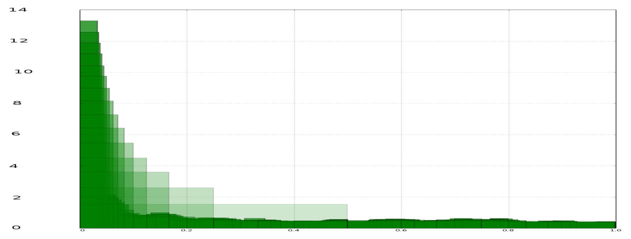
- {A,K,N} are the amino acid modification sites of *acetylation* for the domain (yellow)
- Blue regions: *Before* MSs and upstream of domains
- Yellow regions: *Inside* MSs and within domains
- Green regions: *After* : MSs and downstream of domains

Dist. between domains and MSs: *Before* regions



MSs Upstream of Org-Centric Domains, acetylation

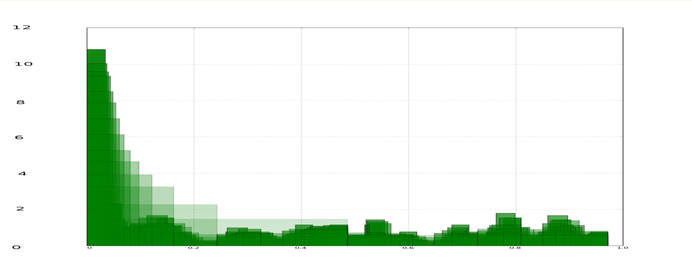
Homo Sapiens (Human)



- The x-axis represents the location of the MS neighbourhoods (green)
- The y-axis describes the number of times that this same location was observed for the element across the samples
- MSs are generally found just outside the domain

MSs Upstream of Org-Centric Domains, acetylation

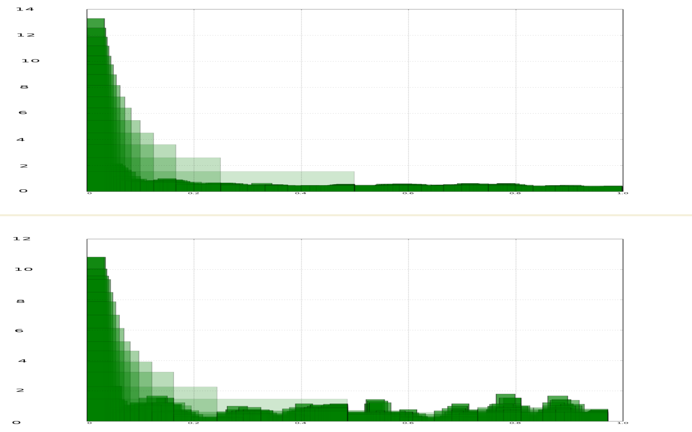
Canis Familiaris (Dog)



- The x-axis represents the location of the MS neighbourhoods (green)
- The y-axis describes the number of times that this same location was observed for the element across the samples
- MSs are generally found just outside the domain but are also in scattered neighbourhoods

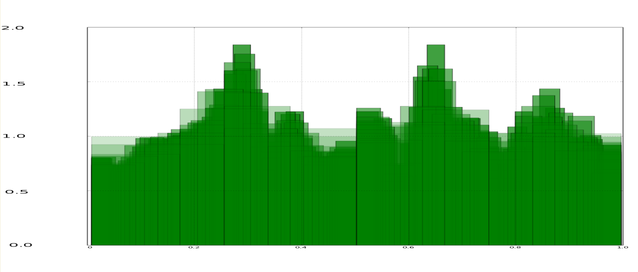
MSs Upstream of Org-Centric Domains, acetylation

Comparison: Human (top) and Dog (bottom)



MSs Within Org-Centric Domains, acetylation

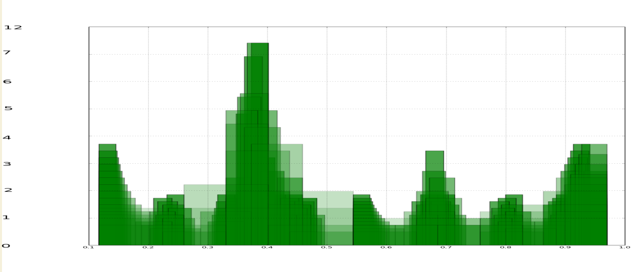
Homo Sapiens (Human)



- The x-axis represents the location of the MS neighbourhoods (green)
- The y-axis describes the number of times that this same location was observed for the element across the samples
- MSs are generally found in *many* scattered neighbourhoods throughout domains

MSs Within Org-Centric Domains, acetylation

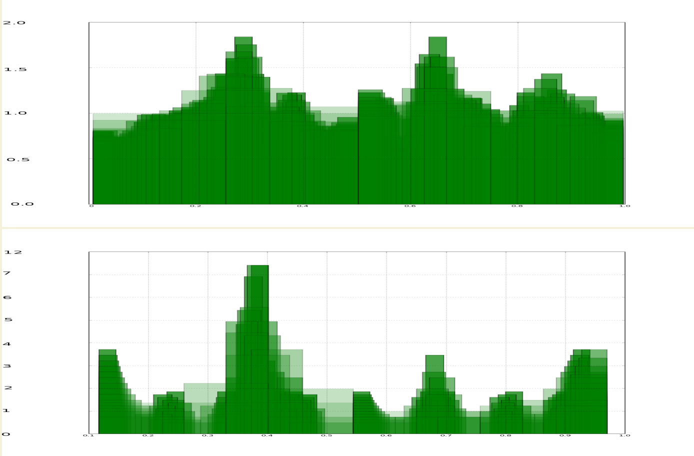
Canis Familiaris (Dog)



- The x-axis represents the location of the MS neighbourhoods (green)
- The y-axis describes the number of times that this same location was observed for the element across the samples
- MSs are generally found in scattered *isolated* neighbourhoods throughout domains

MSs Within Org-Centric Domains, acetylation

Comparison: Human (top) and Dog (bottom)



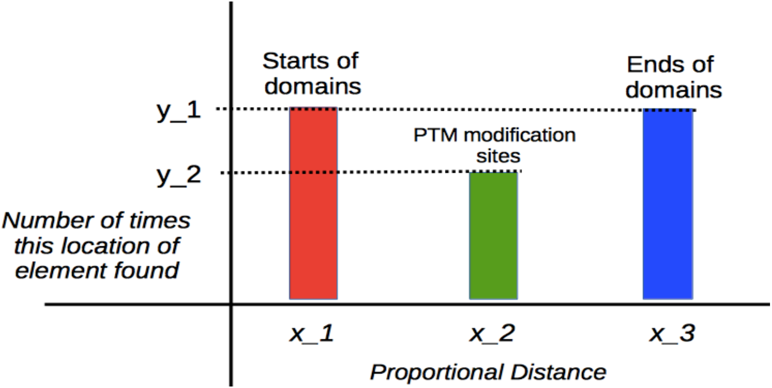
Organism-centric: General Observations

- Many mechanisms appear to be conserved across related organisms
- Striking differences in mechanisms still exist

Domain-Centric Study

- Specific domains are selected for study from any proteins (of all organisms) where they are found

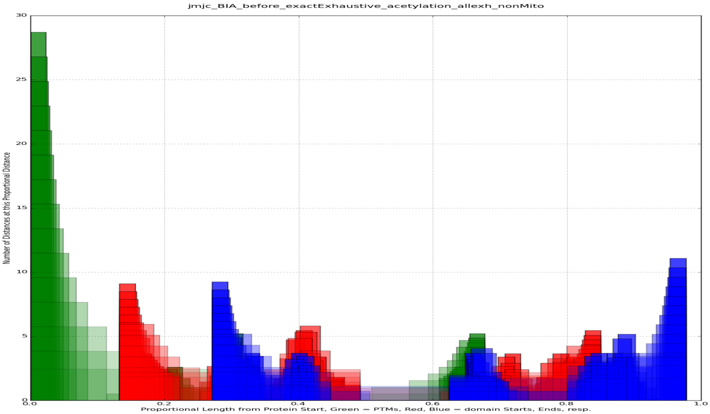
Reading The Plots



- All measurements are proportal distances and can be compared across all protein samples.

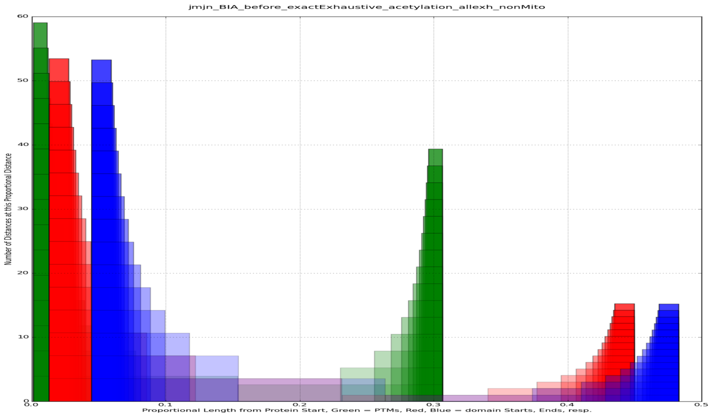
Acetylation, Domain-Centric: jmjc

At least 114 domains found in data

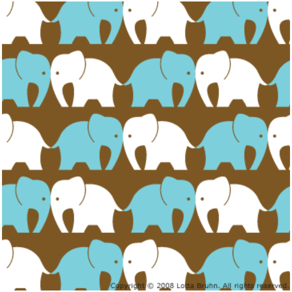


Acetylation, Domain-Centric: jmjn

At least 37 domains found in data



Domain-centric: General Observations



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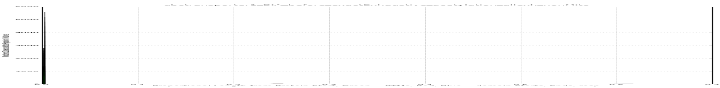
- The domain starts and ends, and their MS neighbourhoods tend to stay in similar relative locations in protein samples
- We can may differentiate different proteins having similar domains.

Acetylation and Domains: abctransporter1

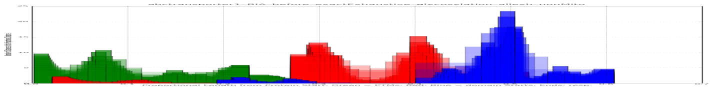
At least 839 domains found in data

Introduction
Signals
–Contrib 1–
–Contrib 2–
–Contrib 3–
Research Question
Method
Conclusions
Future Work
Concluding Thoughts
Thanks To

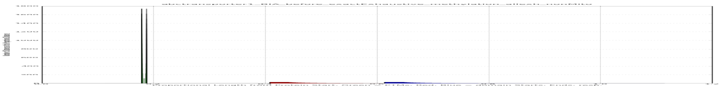
acetylation, 12 samples



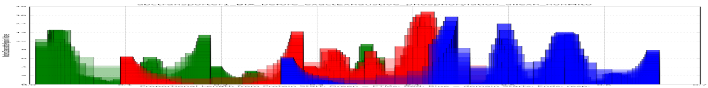
glycosylation, 564 samples



methylation, 6 samples



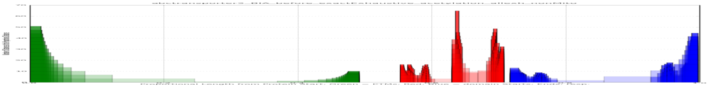
phosphoylation, 257 samples



Acetylation and Domains: abctransporter2

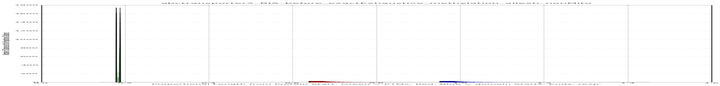
At least 839 domains found in data

acetylation, 6 samples

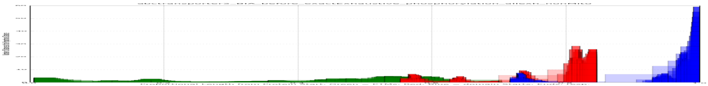


glycosylation, 564 samples

methylation, 6 samples



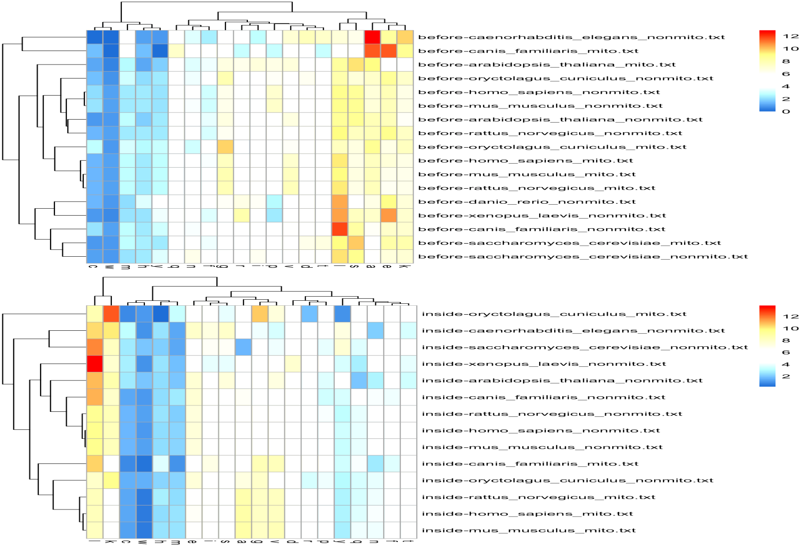
phosphoylation, 257 samples



Domain-Centric Analysis

- The data suggests that the basic distances between the domains and the modification sites are conserved.
- Domain sizes (i.e., beginnings and endings) are also conserved in proteins where they are contained.

Amino Acid Composition To Explain MS Bias?



Conclusions

- MS neighbourhood placements indicate a bias which is not explained by the composition of amino acids
- Our tool, *PTM Tracker*, allows for the detection and visualization of MS - domain patterns
- Similar distances: related organisms have similar clusters of MS *before*, *inside* and *after* their domains
- Similar distances between MSs and domains may imply similar types of stress response mechanisms

Future Work

- Extension: Use this method to compare and contrast domains
- To discover more neighbourhood distributions for more related and non-related domains.

Published

- **Oliver Bonham-Carter** and **Dhundy Bastola**, “PTM Tracker: A system for determining trends of PTM modification sites relative to protein domains”, *2016 IEEE International conference on Electro/ Information Technology*, 2016

Concluding Thoughts

- (Biological) Signals originate from (biological) mechanisms
- Studying the signals enable us to understand parts of these mechanisms
- We may, at least, learn what is not a part of the mechanism
- Further study of different signals will allow to extend the knowledge of the mechanism (what ever it may be).

Thanks to: Dr. Hesham Ali, Dr. Dhundy (Kiran) Bastola, Dr. Lotfollah Najjar, Dr. Steven From, Dr. Sanjukta Bhowmick, Dr. Kate Cooper, Ishwor Thapa, Dr. Jasjit Banwait, Julia Warnke, Sean West, Scott McGrath, Vladimir Ufimtsev, Jay Pedersen, Kritika Karri, Asuda Sharma, Sunandini Sharma, Suyeon Kim, Sahil Sethi
and many others too!

Thank You! Questions?

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