Utilizing Machine Learning to Accelerate Automated Assignment of Backbone NMR Data

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Overview

Motivations

Nuclear Magnetic Resonance Spectroscopy

- Gain knowledge about protein structure
- Study how mutations lead to diseases

Problems

- Generates large amounts of data
- Data analysis is slow and error prone
- Takes a few days to months to assign manually[1]

Goal

- Automate the assignment process
- Decrease human error
- Increase productivity

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1. Jens P. Linge et al., "ARIA: Automated NOE assignment and NMR structure calculation," *Bioinformatics*:2003.

NMR Experiments

NMR Data Sets

- Produces data corresponding to structure

HNCACB experiment

- Generates C_α and C_β residue i and $i-1$

CBCA(CO) NH experiment[2]

- Generates C_α and C_β for residue i
- Confirms residue data

2. Linge et al., "ARIA: Automated NOE assignment and NMR structure calculation."

Machine Learning

Overview

- Generalize large amounts of data
- Predicts a label based on attributes
- Many different algorithms exist

Supervised vs Unsupervised Learning

- Supervised
  - Given large amounts of labeled data
  - Classifies data based on attributes
- Unsupervised
  - Given large amounts of unlabeled data
  - Looks for patterns

Machine Learning Algorithms

J4.8[3]

- Decision tree model
- Splits by a single attribute

Logistic Model Tree (LMT)[4]

- Decision tree model
- Splits by linear regression of attribute

Decision Table[5]

- Set of labeled data is searched
- Majority match is used

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3. Ross Quinlan, *C4.5: Programs for Machine Learning* (San Mateo, CA: Morgan Kaufmann Publishers, 1993).

4. Niels Landwehr, Mark Hall, and Eibe Frank, "Logistic Model Trees," *Machine Learning* 95, nos. 1-2 (2005): 161–205.

5. Ron Kohavi, "The Power of Decision Tables," in *8th European Conference on Machine Learning* (Springer, 1995), 174–189.

Algorithmic Overview

Model Training

Preprocessing

The Search

Model Training

Biological Magnetic Resonance Bank (BMRB)[6]

- 9,736 datasets containing chemical shifts for the C_α and C_β resonances of 689,977 residues
- Removing outliers leaves 681,363 pairs of C_α and C_α
  - 3 standard deviations from the mean
  - Avoids over-fitting
  - Improves algorithmic performance

6. Eldon L. Ulrich et al., "BioMagResBank.," *Nucleic Acids Research* 36, no. Database-Issue (January 23, 2008): 402–408, http://dblp.uni-trier.de/db/journals/nar/nar36.html#UlrichADHILLMMMNSTWYM08.

Model Training

Training the Model

Performed Once

- Time consuming task
- Trained once, used many times

Models Trained

- DecisionTable, J4.8, LMT

Reading Data

Protein Sequence

- Read in as letters
- Converted to BMRB average values
- Used for comparison in the search

NMR Data Set

- Read in C_α, C_β for Residue i and $i-1$
- Stored in Tile

Tile

Residue $i-1$

C_α, C_β

Residue i

C_α, C_β

Confidence Level Calculation

Machine Learning

- Input
  - C_α, C_β values for residue i
- Output
  - Confidence levels for each of the 20 amino acids
  - $P_1, P_2, \cdots, P_{19}, P_{20}$
  - Confidence levels are on a scale from 0.0-1.0
  - 1.0 being a prefect match

Tile

Residue $i-1$
C_α, C_β
Residue i
C_α, C_β
Confidence Levels
P_1, P_2, $\cdots$, P_{19}, P_{20}

Missing Data

Blank Tile Creation

- Compare length of protein sequence to NMR Data set
- Blank tiles are created to make up the gap

Proline

- Lacks H-N spin system
- Does not produce C_α, C_β values
- Protein sequence is examined
- Special flags are set

Blank Tile

Residue $i-1$

\- , -

Residue i

\- , -

Confidence Levels

$1.0, 1.0, \cdots, 1.0, 1.0$

Proline

yes/no

First Tile

Tiles to assign:	$i-1$	9	11	13	12	–
	i	12	13	9	9.2	–
	P_1	0.935	0.013	0.003	0.000	0.000
	P_2	0.002	0.001	0.04	0.403	0.000
	Proline	No	No	No	No	Yes

Reference Protein Chain		**Nodes**
Chemical Shift	P_n	
13.5	1	
9.5	2	
11.4	1	
-	Proline	
8.8	2	

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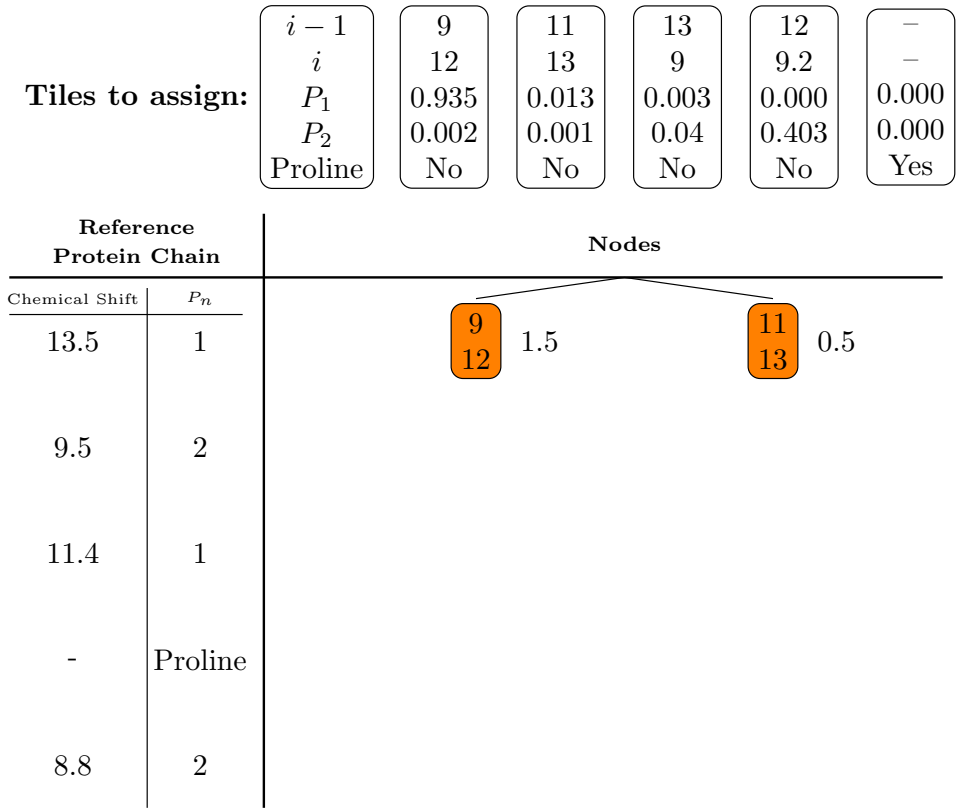
Nodes

Cost Calculation

- Accuracy matching the protein chain residue
- Accuracy matching the tile above current tile
- Cost of placing all previous tiles



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Nodes

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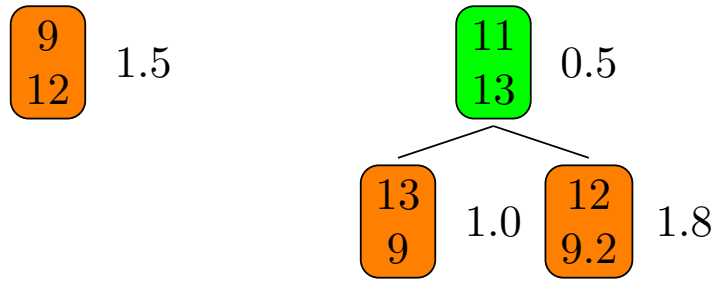

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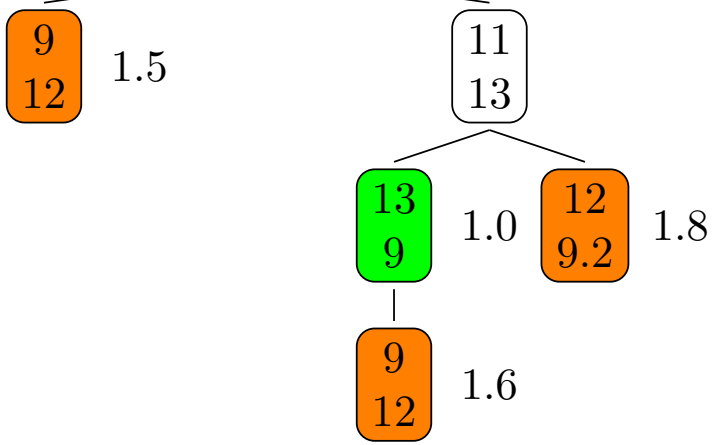

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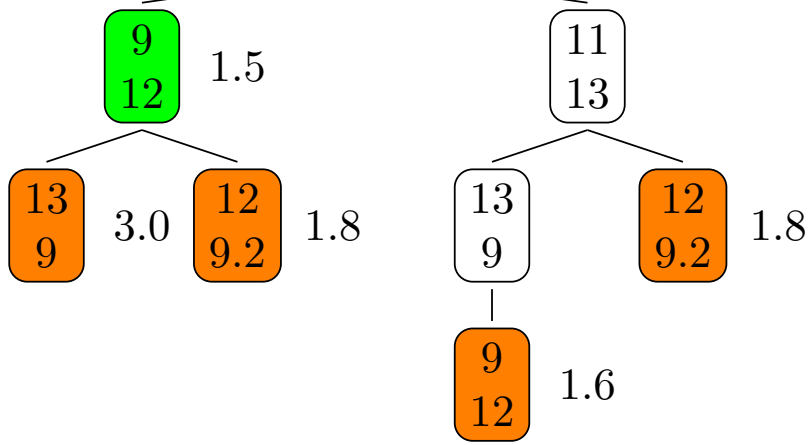

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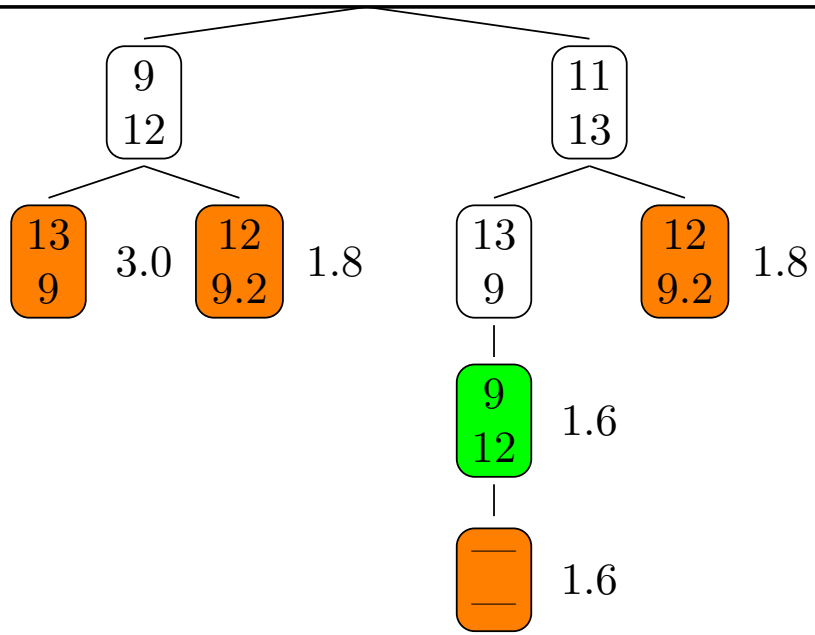

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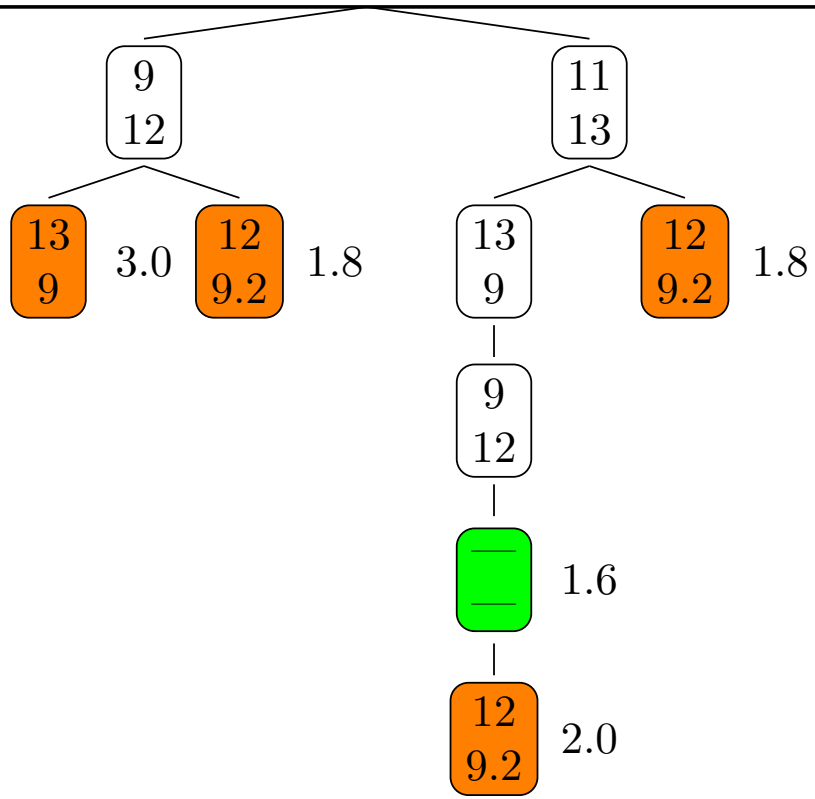

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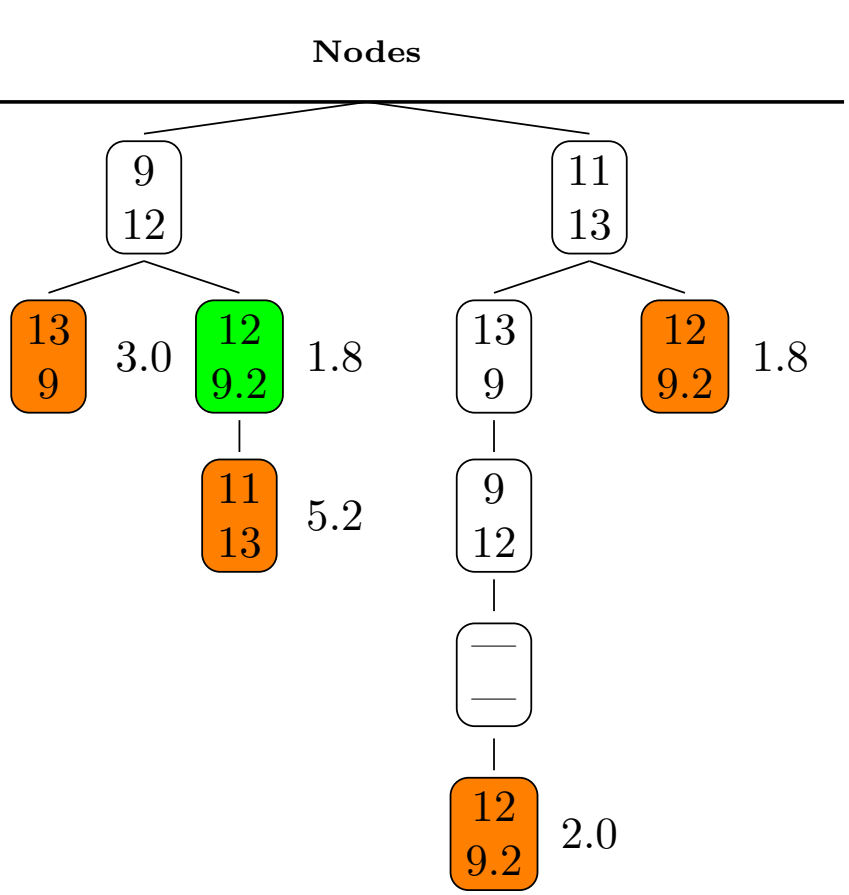

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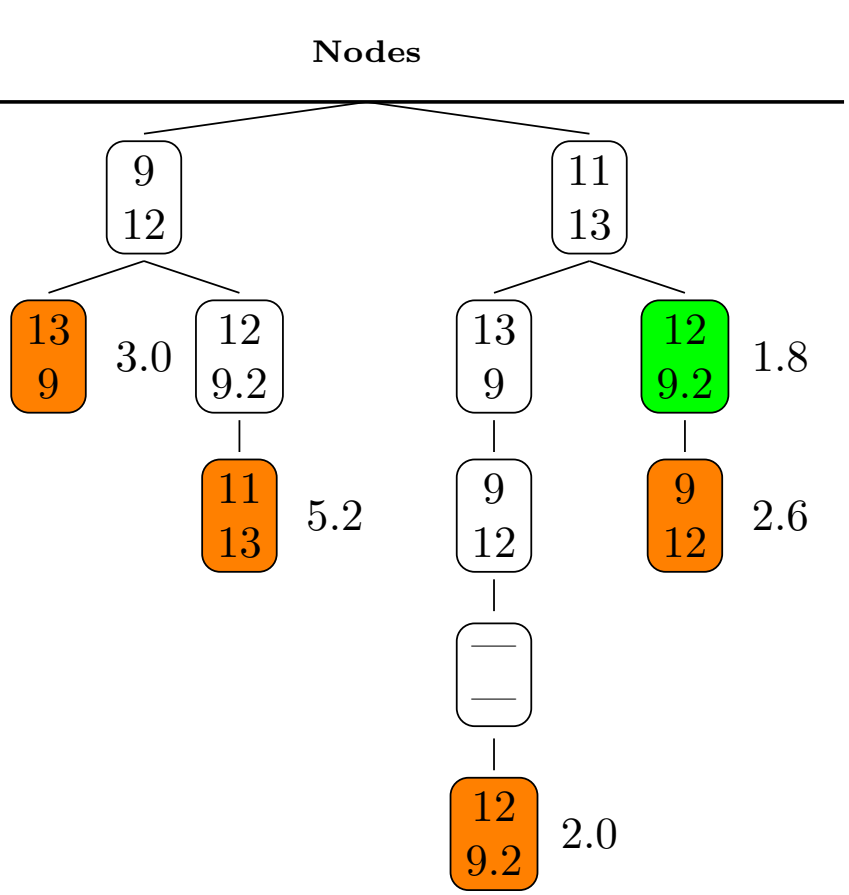

Finished Assignment

Tiles to assign:

$i-1$	9	11	13	12	–
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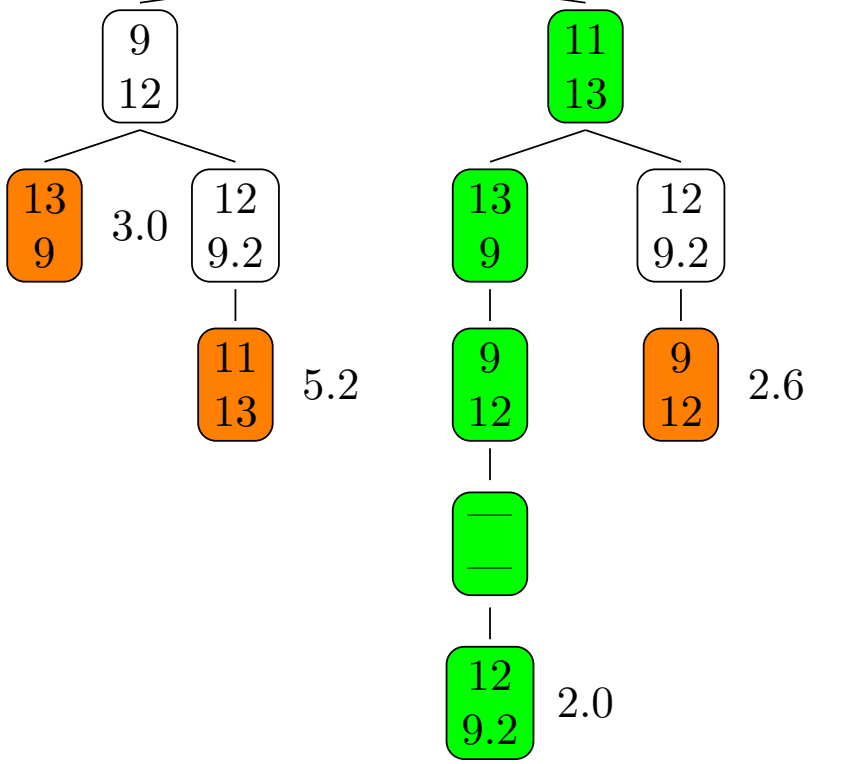

Algorithm Performance

Correct Assignments

- Assigned a protein sequence of length 62 in approximately 40 minutes
- Major progress in time of assignment

Protein used

- C-terminal domain of the Tfg1 subunit of the yeast transcription factor TFIIF[7]

7. Adina M. Kilpatrick et al., "Structural and binding studies of the C-terminal domains of yeast TFIIF subunits Tfg1 and Tfg2," *Proteins: Structure, Function, and Bioinformatics* 80, no. 2 (2012): 519–529, doi:10.1002/prot.23217, http://dx.doi.org/10.1002/prot.23217.

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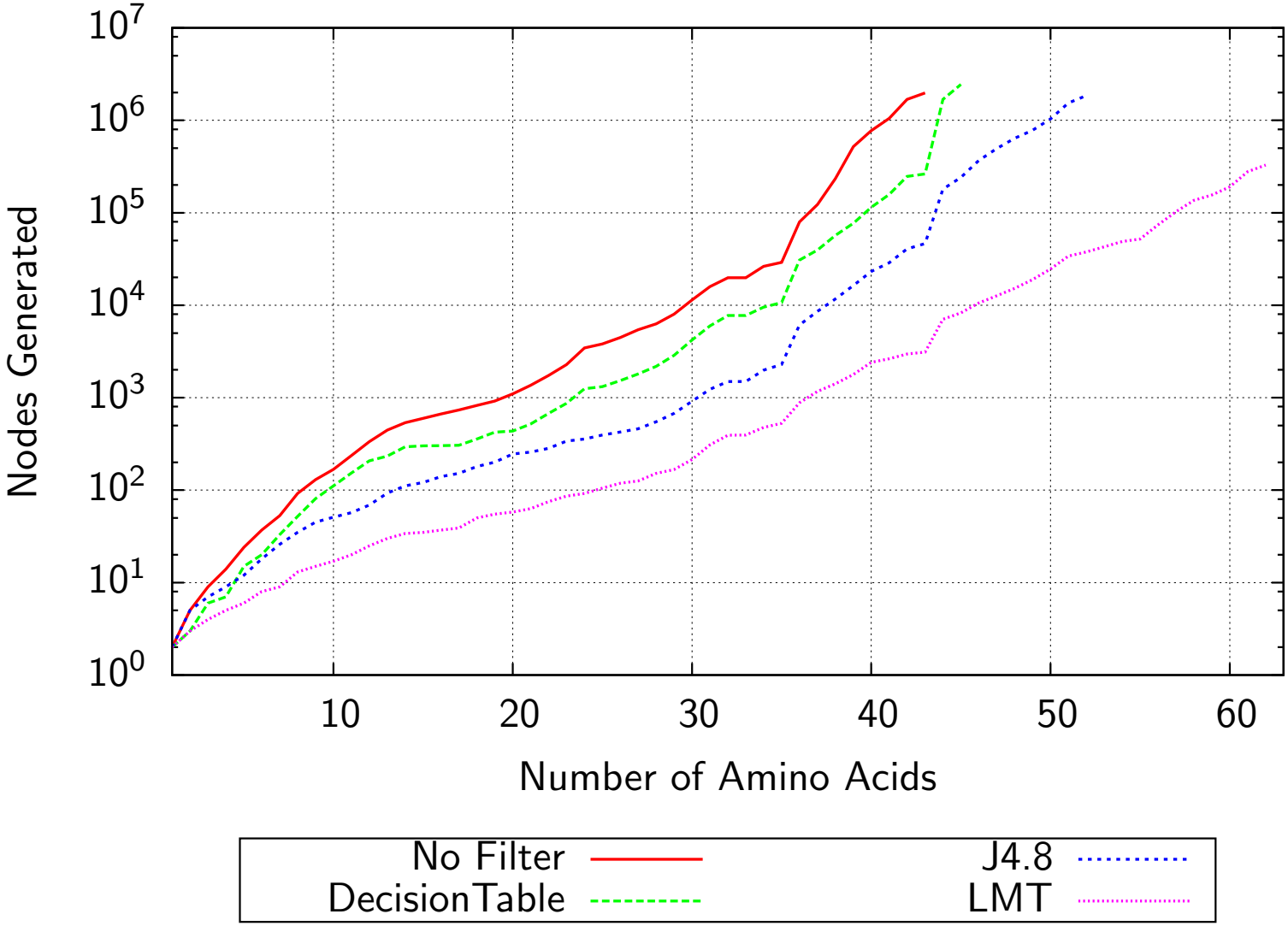
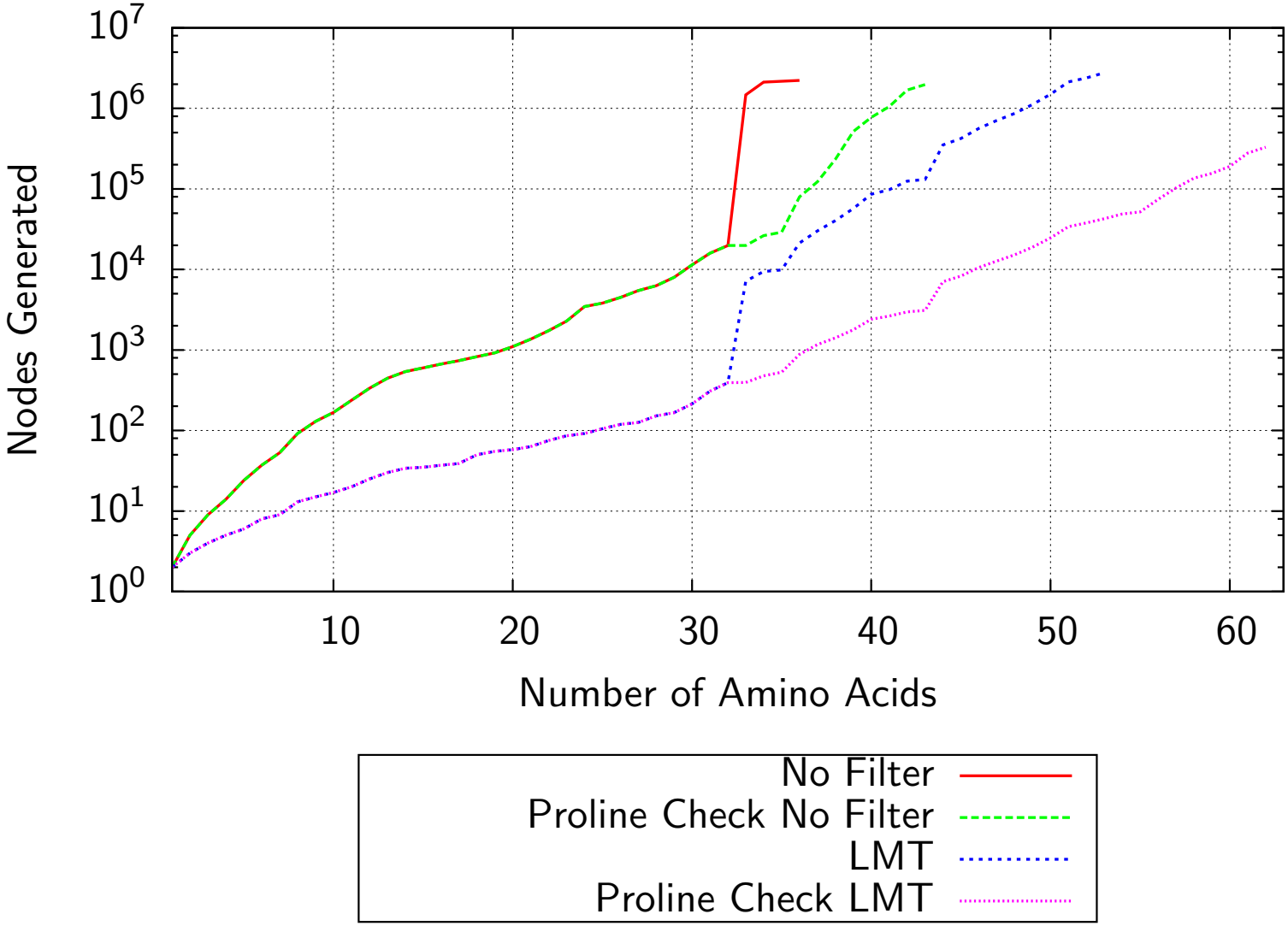
A. Kilpatrick

Machine Learning Algorithms



Proline Checking



Future Research

Extend the Proline checking to other amino acids

Include a heuristic for assignment cost prediction

Assign subsets and combine to generate full assignments

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- Adina Kilpatrick
- Timothy Urness

Research team

- David Mascharka
- Paxten Johnson
- Rachel Davis
- Katherine Roth
- Leah Robison

Drake University

DUCURS

References I

Kilpatrick, Adina M., Leonardus M.I. Koharudin, Guillermo A. Calero, and Angela M. Gronenborn. "Structural and binding studies of the C-terminal domains of yeast TFIIF subunits Tfg1 and Tfg2." *Proteins: Structure, Function, and Bioinformatics* 80, no. 2 (2012): 519–529. doi:10.1002/prot.23217. http://dx.doi.org/10.1002/prot.23217.

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Thank You

Questions?