Accelerating Biomolecular Nuclear Magnetic Resonance Assignment with A*

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Overview

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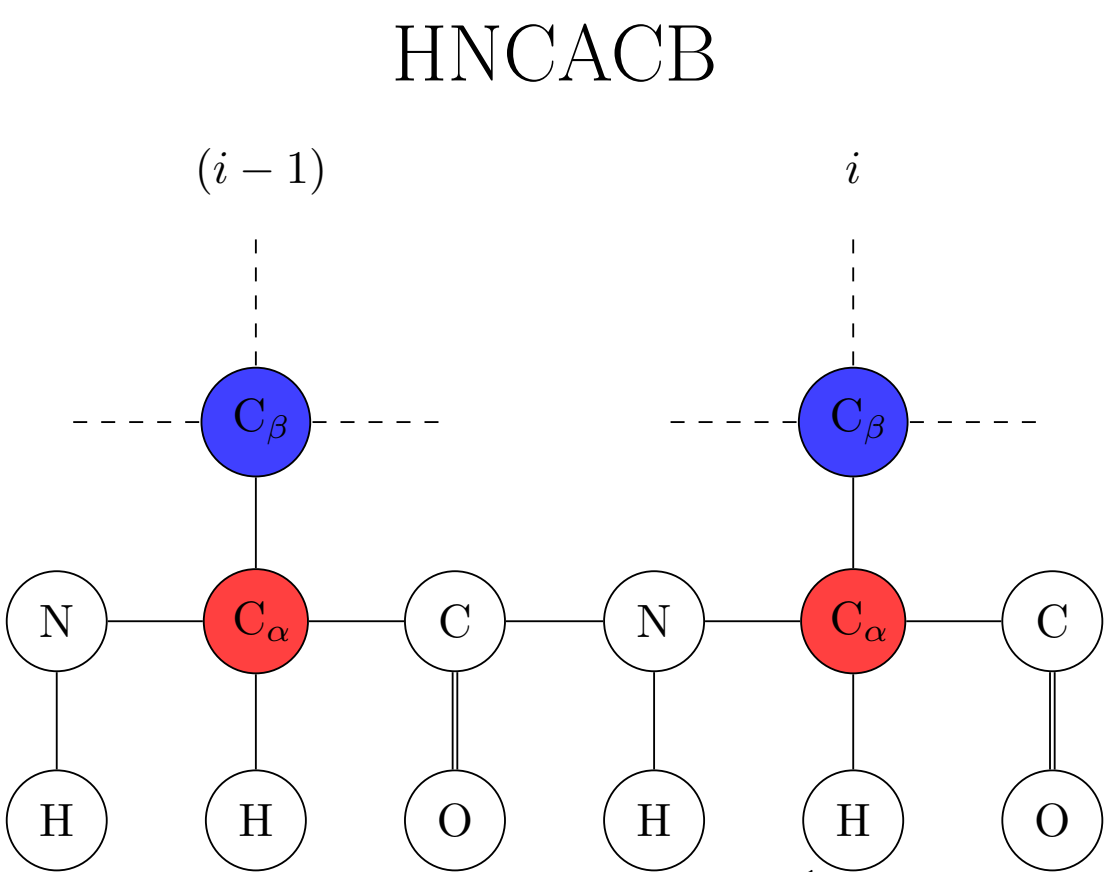
Motivation

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

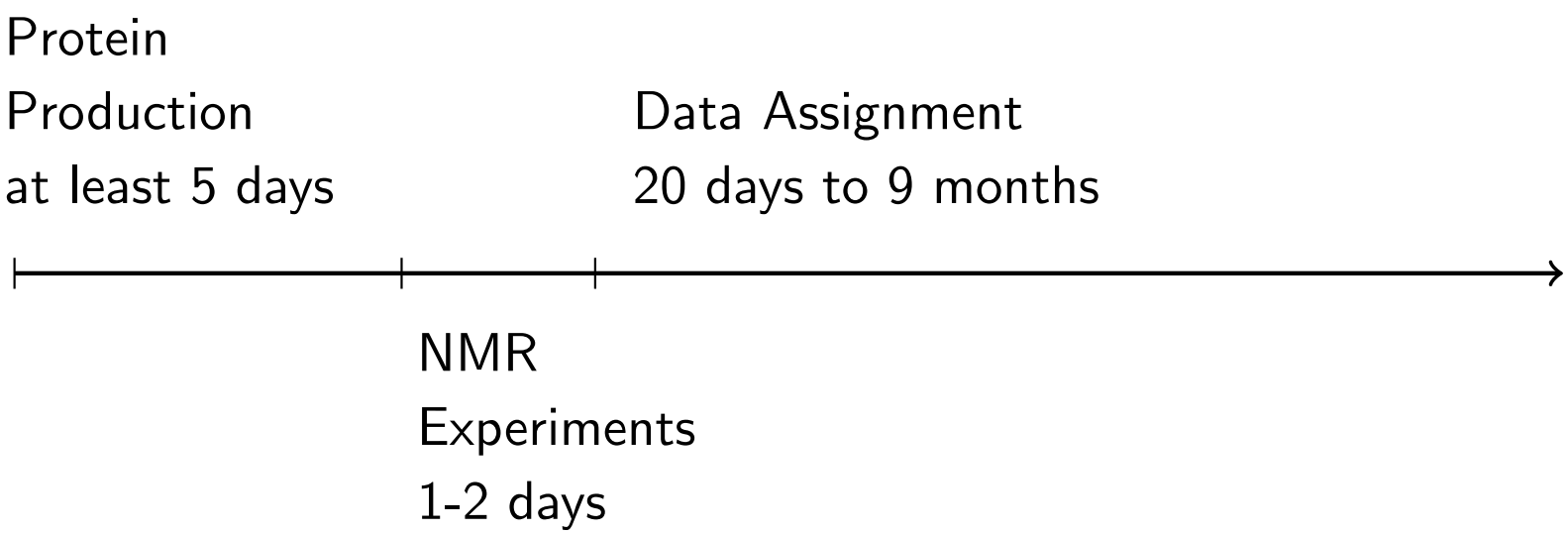
Nuclear Magnetic Resonance (NMR)

- Used to obtain structural information
  - Chemical shift values
- HNCACB experiment
  - Generates C_α and C_β residue i and $i-1$
- CBCA(CO) NH experiment
  - Generates C_α and C_β for residue i
  - Confirms residue data

Chemical Shift Values



Timeline


Protein
Production
at least 5 days
Data Assignment
20 days to 9 months
NMR
Experiments
1-2 days

[1]

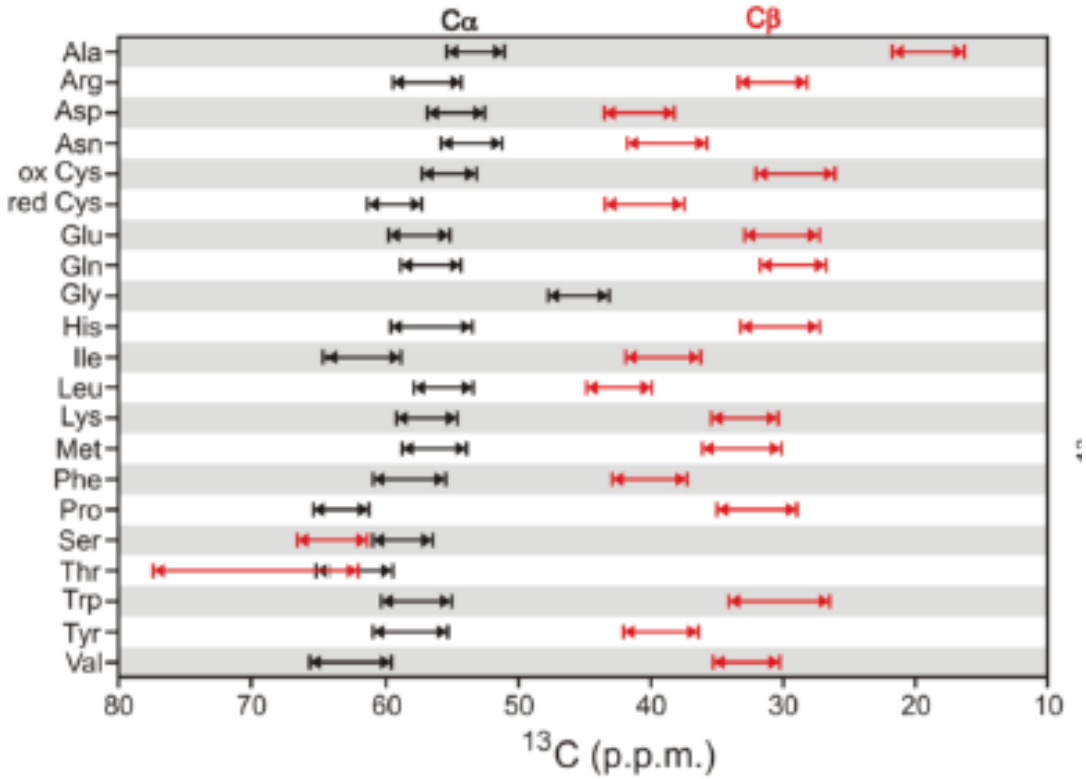
Manual Methods

- Most time consuming part
- Prone to human error
- Missing and ambiguous data forces chunks to be skipped

Initialization

- Input
  - Expected amino acid sequence
    - Covered to expectation chemical shift values
    - Stored as the protein chain
  - NMR chemical shift data
    - C_α and C_β for residue i and $i-1$
    - Stored in a tile
- Missing data
  - Place holder tile generation
- Grouping

Grouping


Cα
Cβ
Ala
Arg
Asp
Asn
ox Cys
red Cys
Glu
Gln
Gly
His
Ile
Leu
Lys
Met
Phe
Pro
Ser
Thr
Trp
Tyr
Val
80
70
60
50
40
30
20
10
13C (p.p.m.)

[2]

Starting the assignment

Tiles to assign: $\begin{matrix}13\\9\end{matrix}$ $\begin{matrix}11\\13\end{matrix}$ $\begin{matrix}9\\12\end{matrix}$

Protein Chain	**Tiles**		
11.5	$\begin{matrix}13\\9\end{matrix}$ 1.5	$\begin{matrix}11\\13\end{matrix}$ 0.5	$\begin{matrix}9\\12\end{matrix}$ 2.5
12.5			
9.6			

Cost Calculation

- Accuracy matching the protein chain residue
- Accuracy matching the tile above current tile
- Cost of all tiles place before current tile

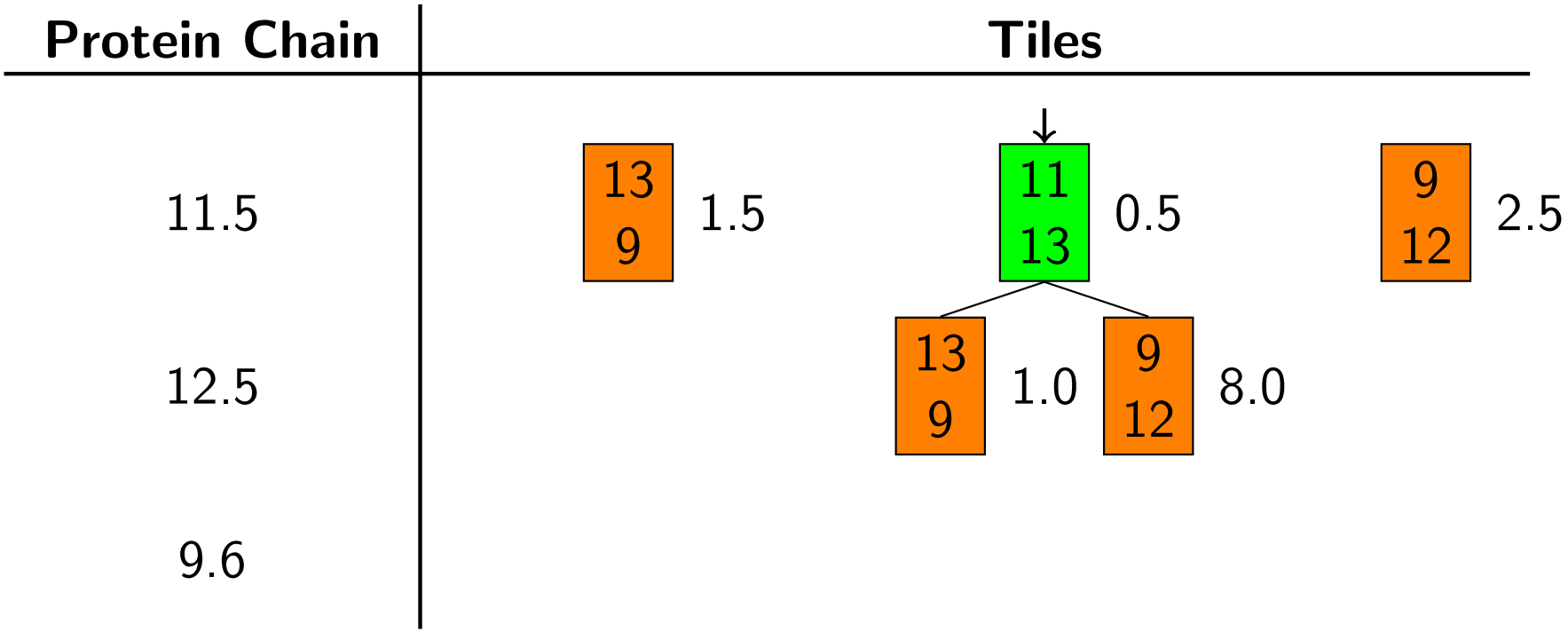
Generating child nodes

Tiles to assign: $\begin{matrix}13\\9\end{matrix}$ $\begin{matrix}11\\13\end{matrix}$ $\begin{matrix}9\\12\end{matrix}$

Protein Chain	**Tiles**					
11.5	$\begin{matrix}13\\9\end{matrix}$	1.5	$\begin{matrix}11\\13\end{matrix}$	0.5	$\begin{matrix}9\\12\end{matrix}$	2.5
12.5						
9.6						

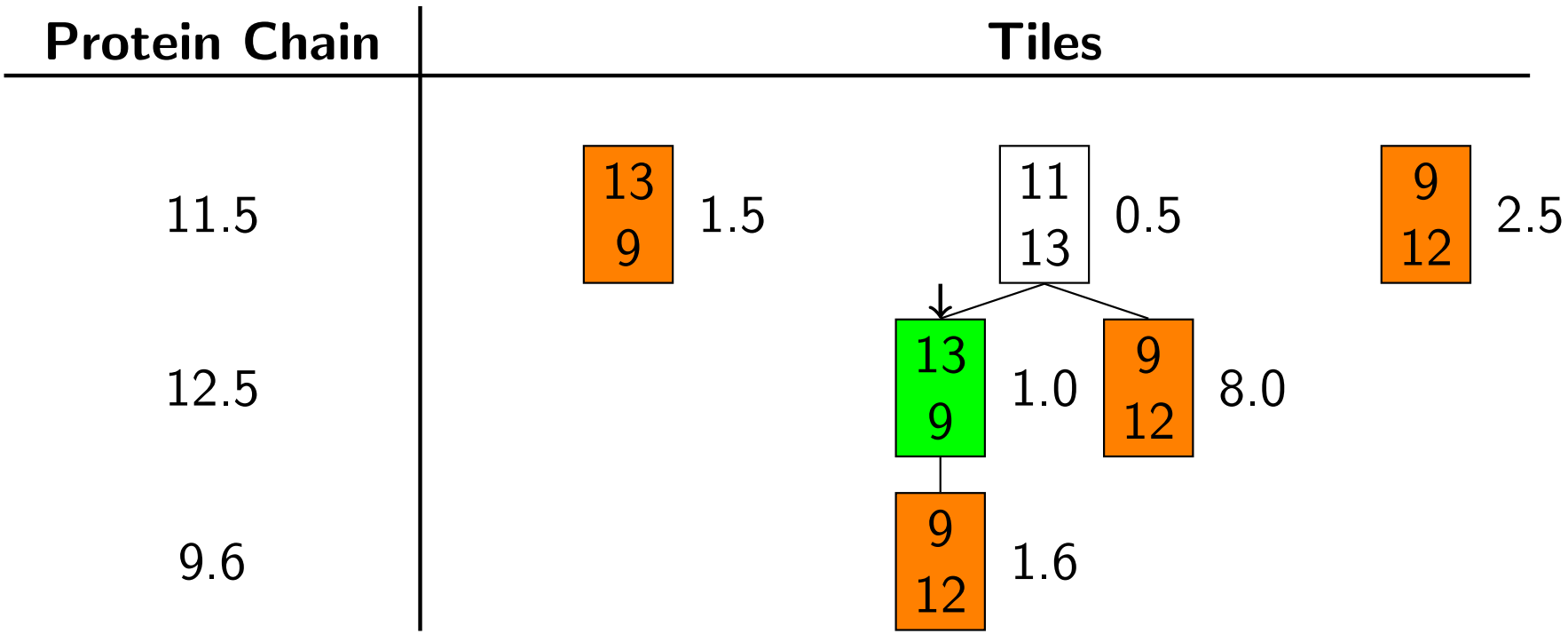
Generating child nodes

Tiles to assign: [13 / 9] [11 / 13] [9 / 12]



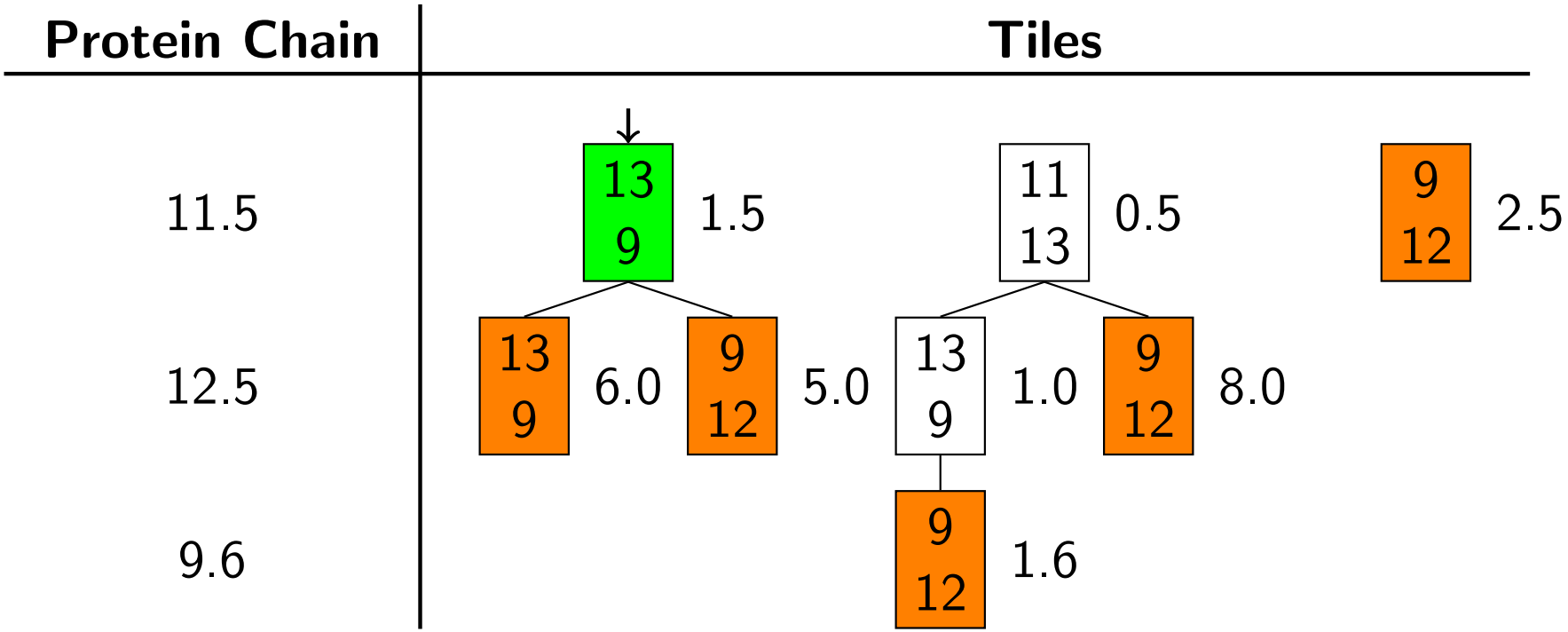
Goal State

Tiles to assign: [13/9] [11/13] [9/12]

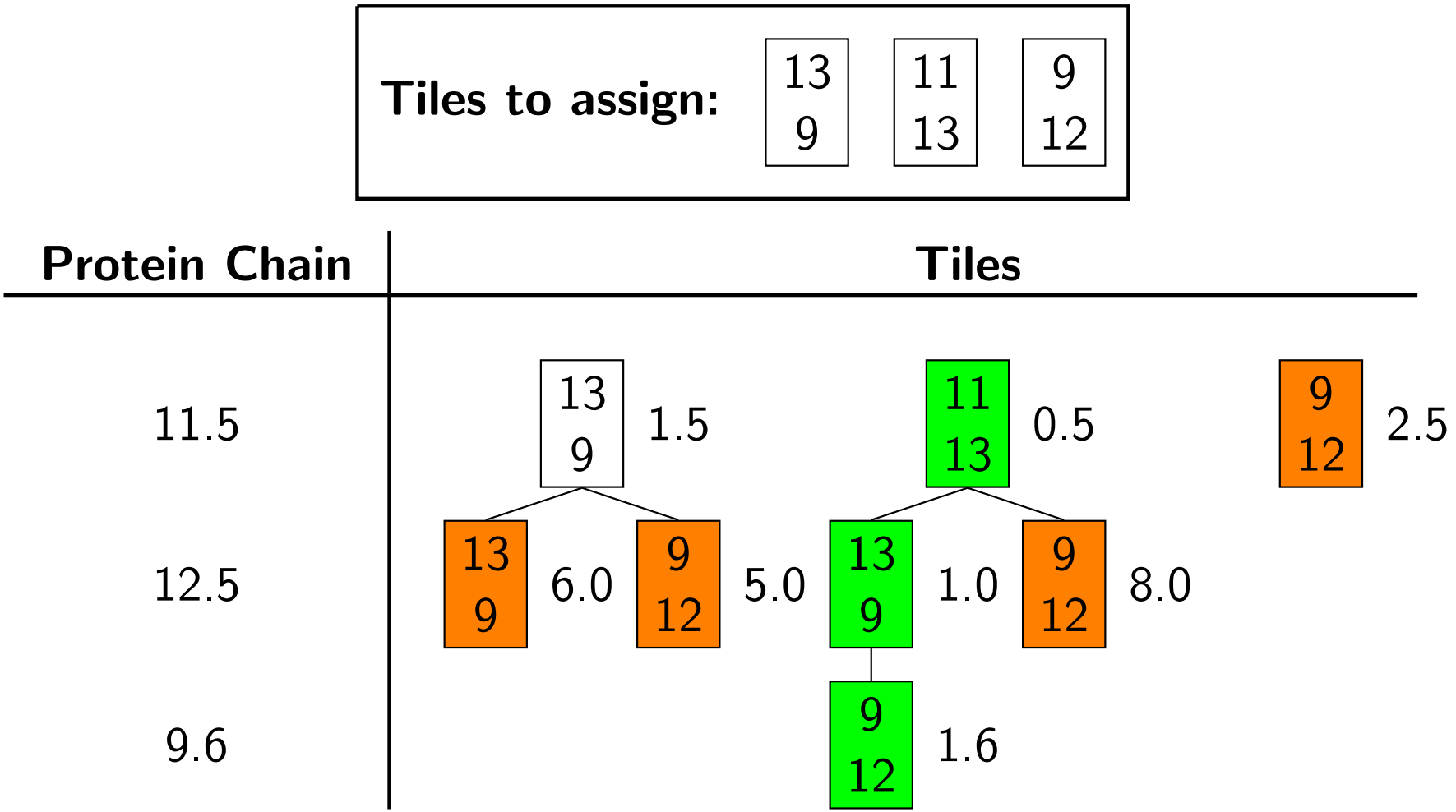


Goal State

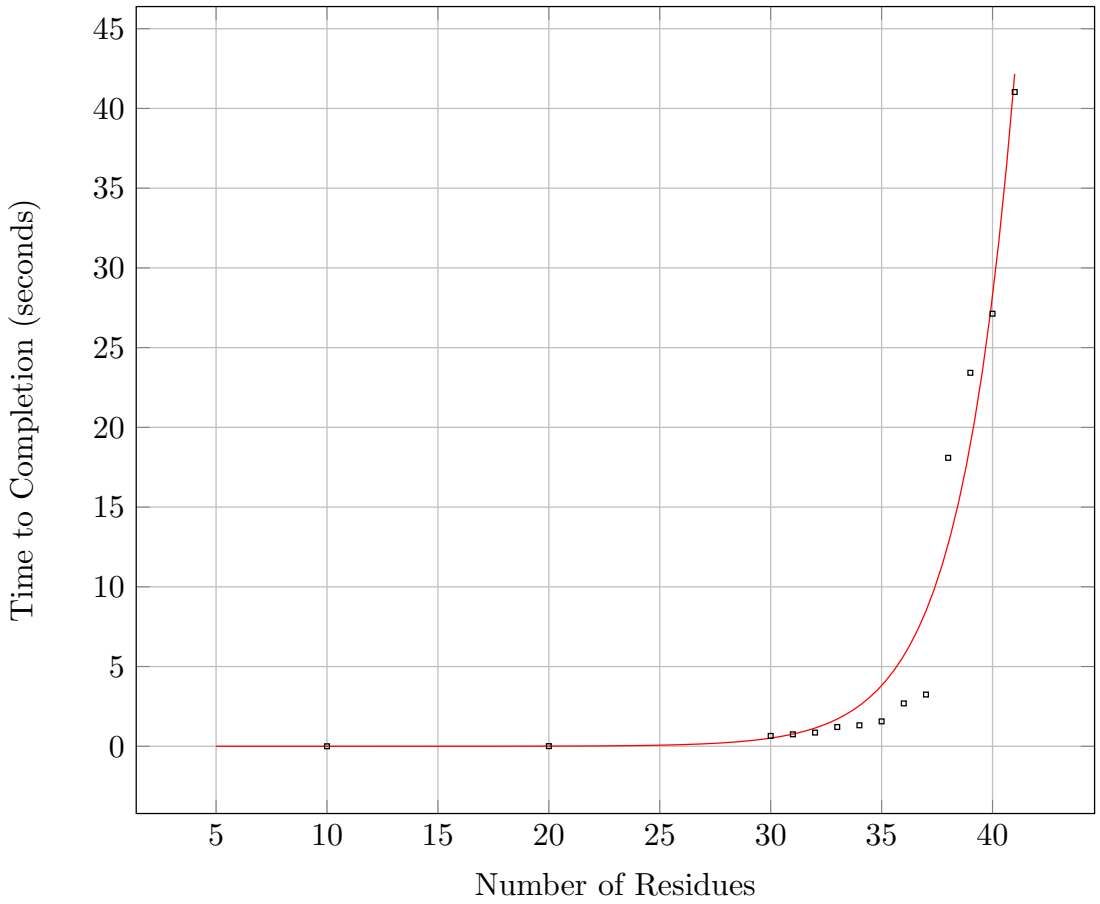
Tiles to assign: [13 / 9] [11 / 13] [9 / 12]



Solution State



Time of Assignment



Future Goals

- Parallelization
  - Decrease assignment time
  - Allow for larger data sets
- Machine learning
  - Increase accuracy of assignment
  - Optimize cost calculation

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- Katherine Roth (research colleague)
- David Mascharka (research colleague)
- Leah Robison (research colleague)

Bibliography

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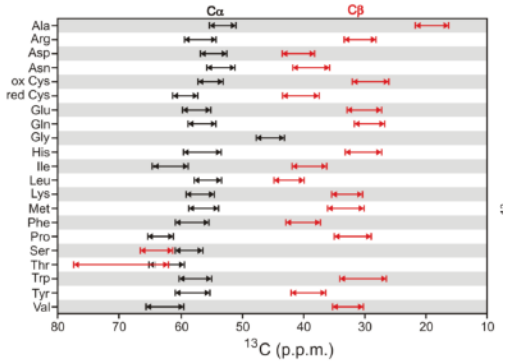
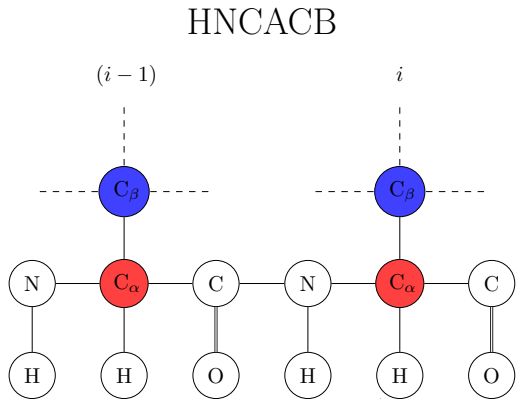
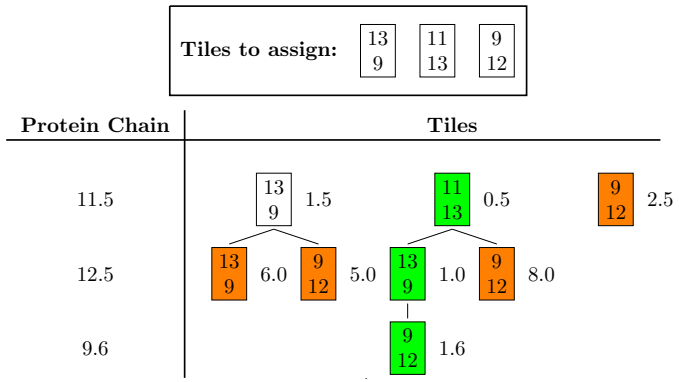
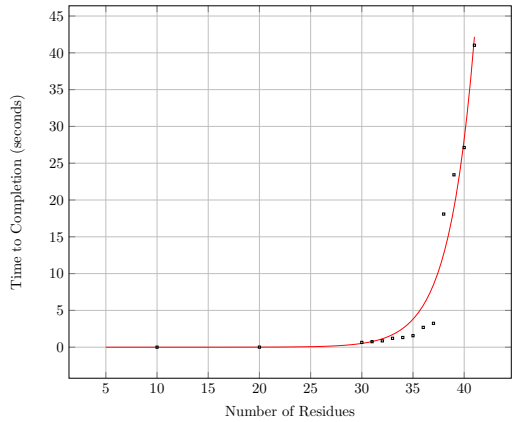
Thank You


Cα
Cβ
Ala
Arg
Asp
Asn
ox Cys
red Cys
Glu
Gln
Gly
His
Ile
Leu
Lys
Met
Phe
Pro
Ser
Thr
Trp
Tyr
Val
80 70 60 50 40 30 20 10
13C (p.p.m.)


HNCACB
(i − 1)
i
Cβ
Cα
N
C
H
O


Tiles to assign:
13 9
11 13
9 12
Protein Chain
Tiles
11.5
12.5
9.6
1.5
0.5
2.5
6.0
5.0
1.0
8.0
1.6


Time to Completion (seconds)
Number of Residues
0 5 10 15 20 25 30 35 40 45
5 10 15 20 25 30 35 40