Computational Protein Design Using AND/OR Branch-and-Bound Search

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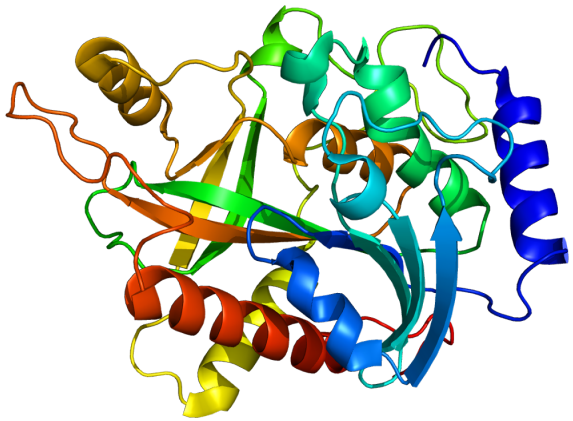
What is Structure-Based Protein Design?

Toolbox

- Energy Functions
- Rotamer Library
- Backbone Template



Protein structure template

Design Algorithm

· · ·	Ile	Ser	Ile
Pro	Ala	Ile	Trp
Val	Gly	Ser	Asp
Gly	Gly	Pro	Glu
Ile	Pro	His	· · ·

1D amino acid sequence

Why We Need Protein Design?

Applications

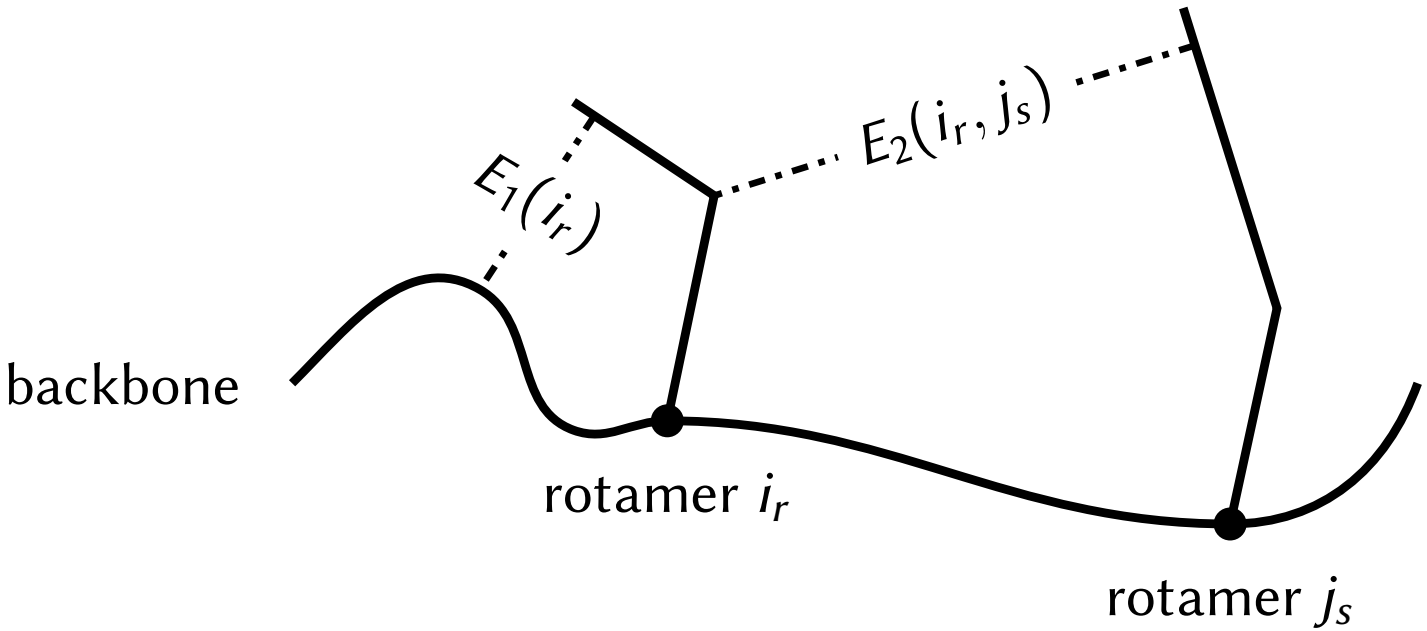
Figure: New Drug Discovery

Figure: Drug Resistance Prediction

Figure: Enzyme Optimization

Figure: New Biosensor Design

Protein Design as an Optimization Problem



Energy Function (Optimization Target)

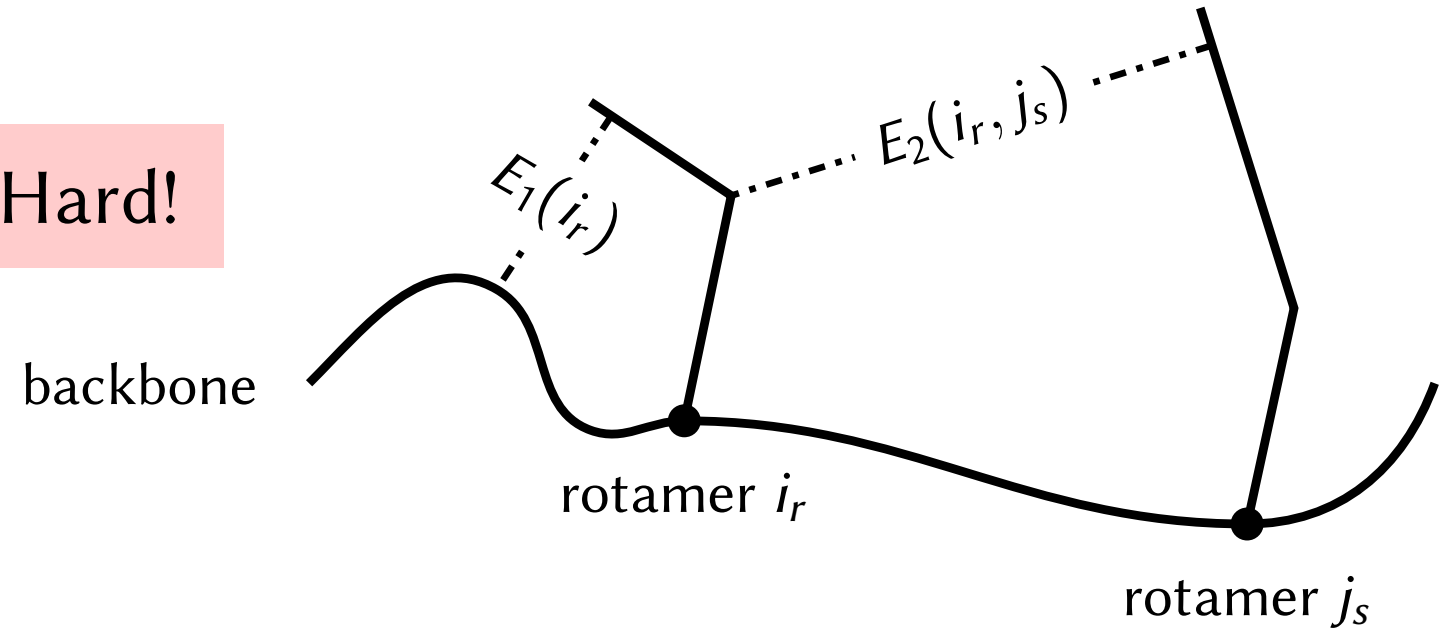
$$E_T = \sum_{i_r} E_1(i_r) + \sum_{i_r} \sum_{j_s, i<j} E_2(i_r, j_s)$$

Self energy of rotamer i_r

Pairwise energy between rotamer i_r and j_s

Protein Design as an Optimization Problem

NP Hard!



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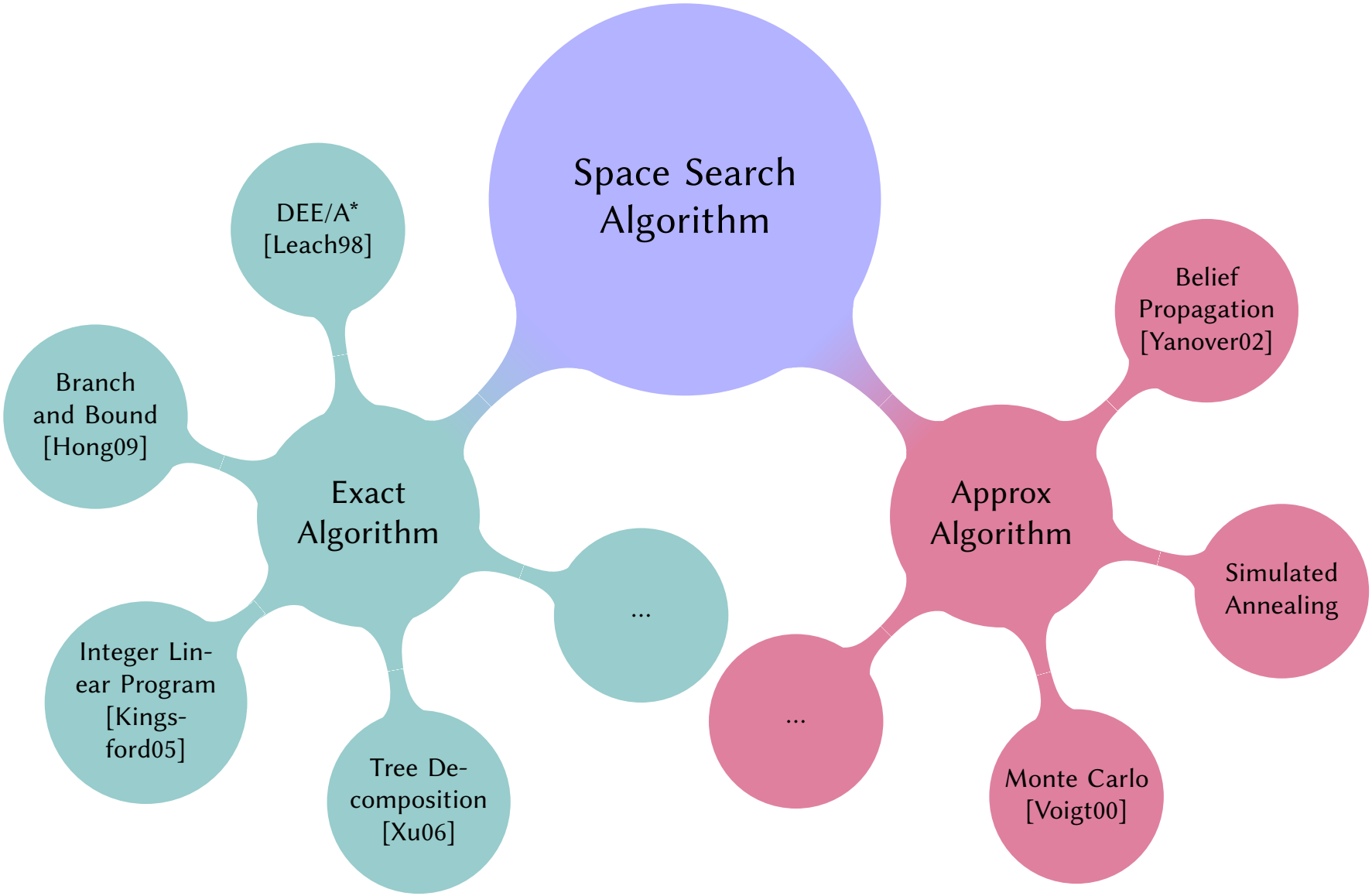
Search Algorithm



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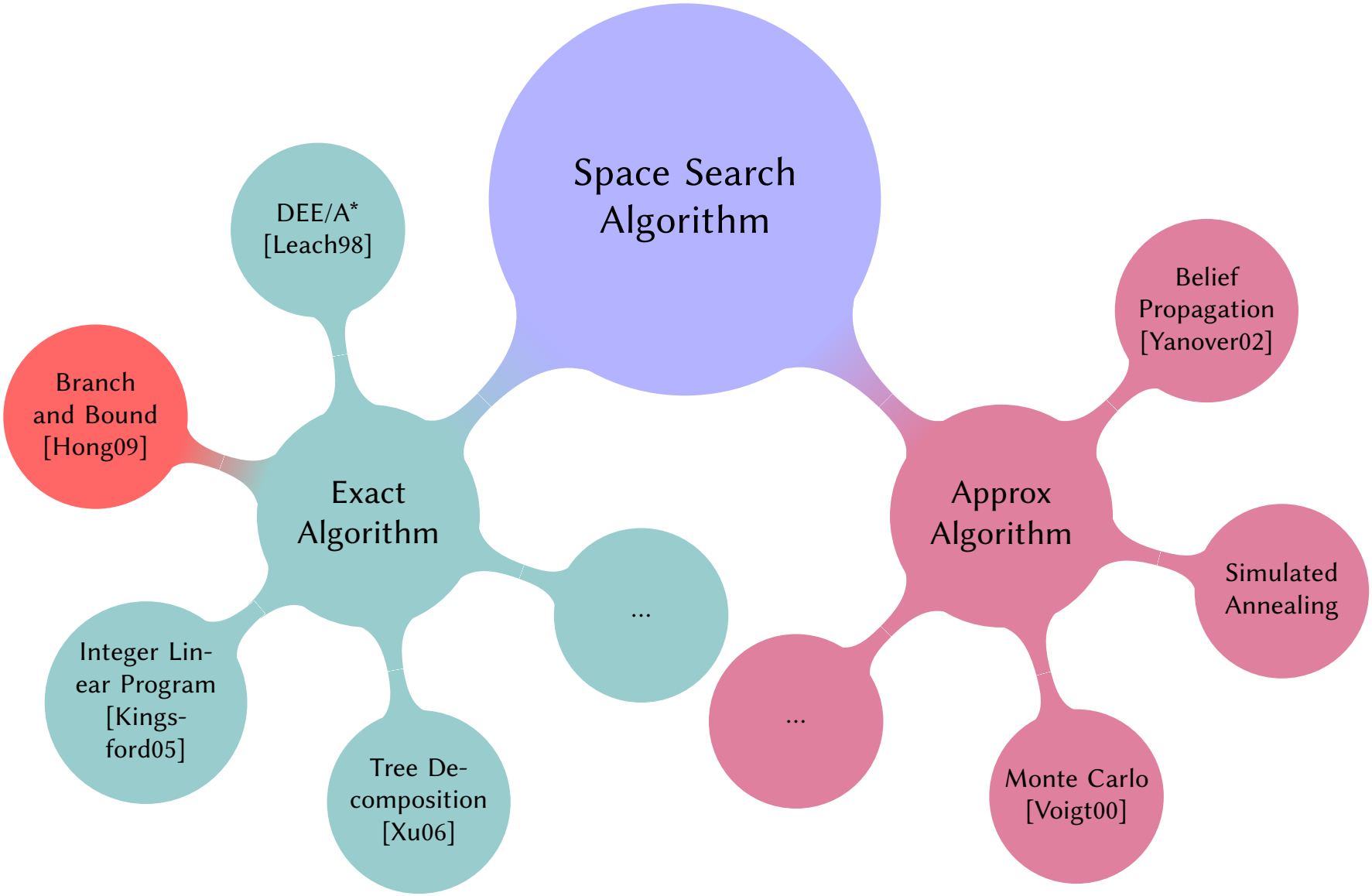
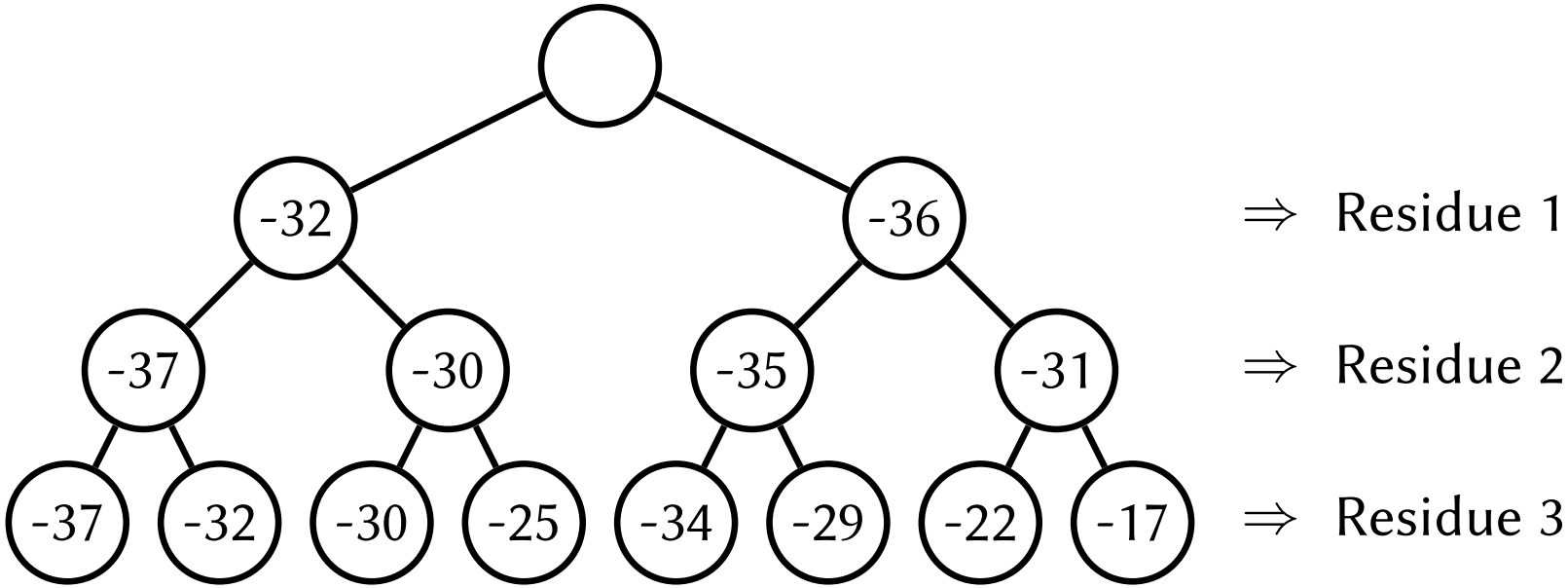


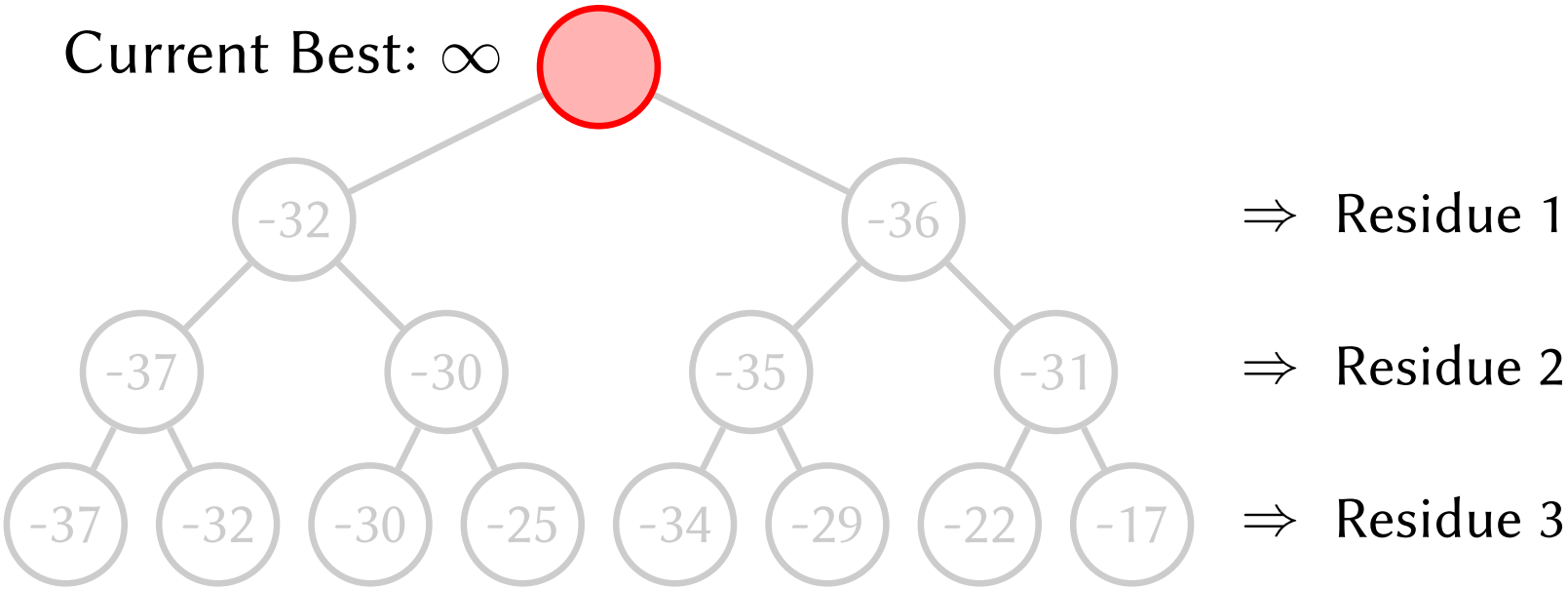
Traditional Branch-and-bound Search Space



Heuristic function

Heuristic function $h(x)$ returns a lower bound of the energy of leaf nodes in the subtree rooted at x.

Traditional Branch-and-bound Search



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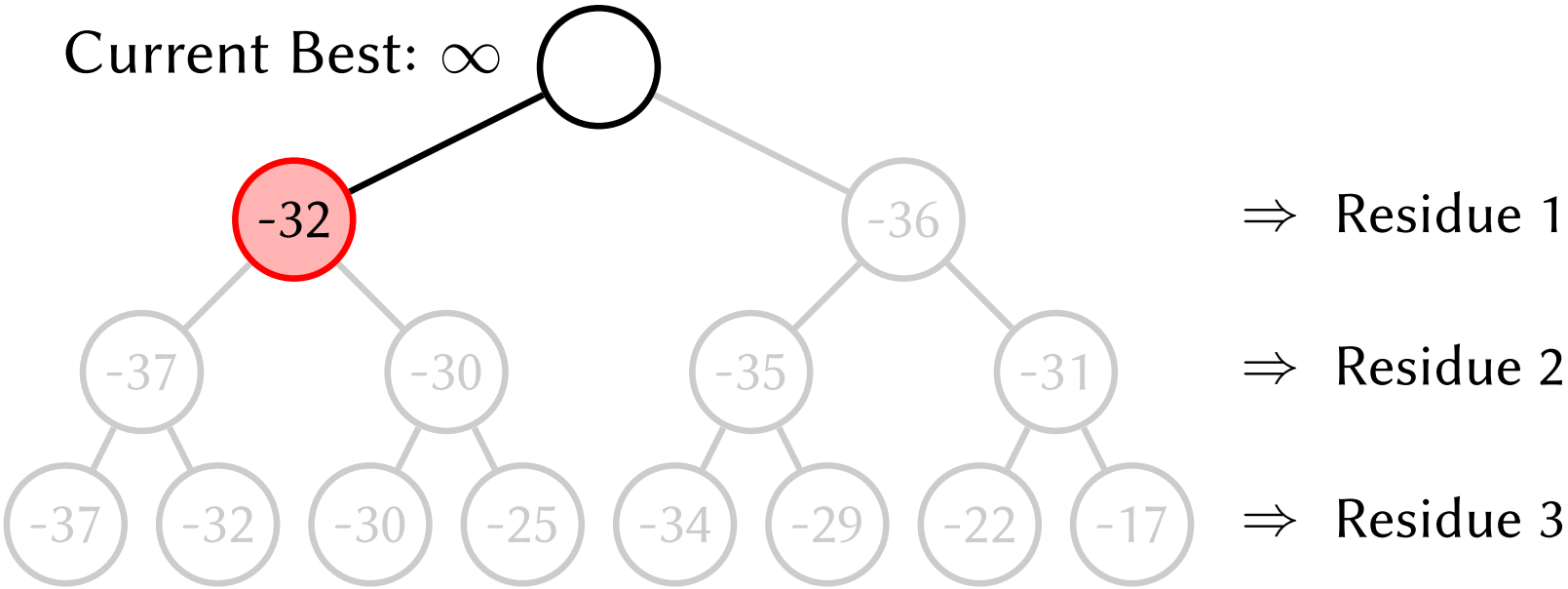

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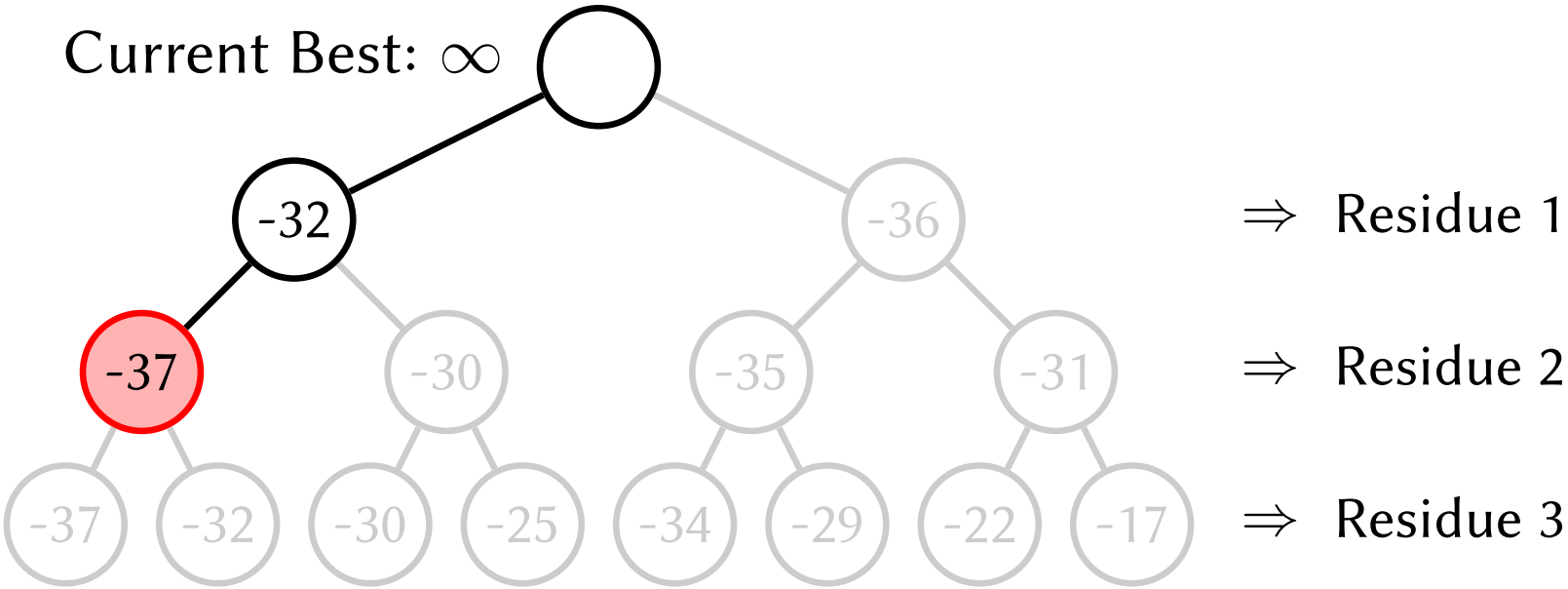

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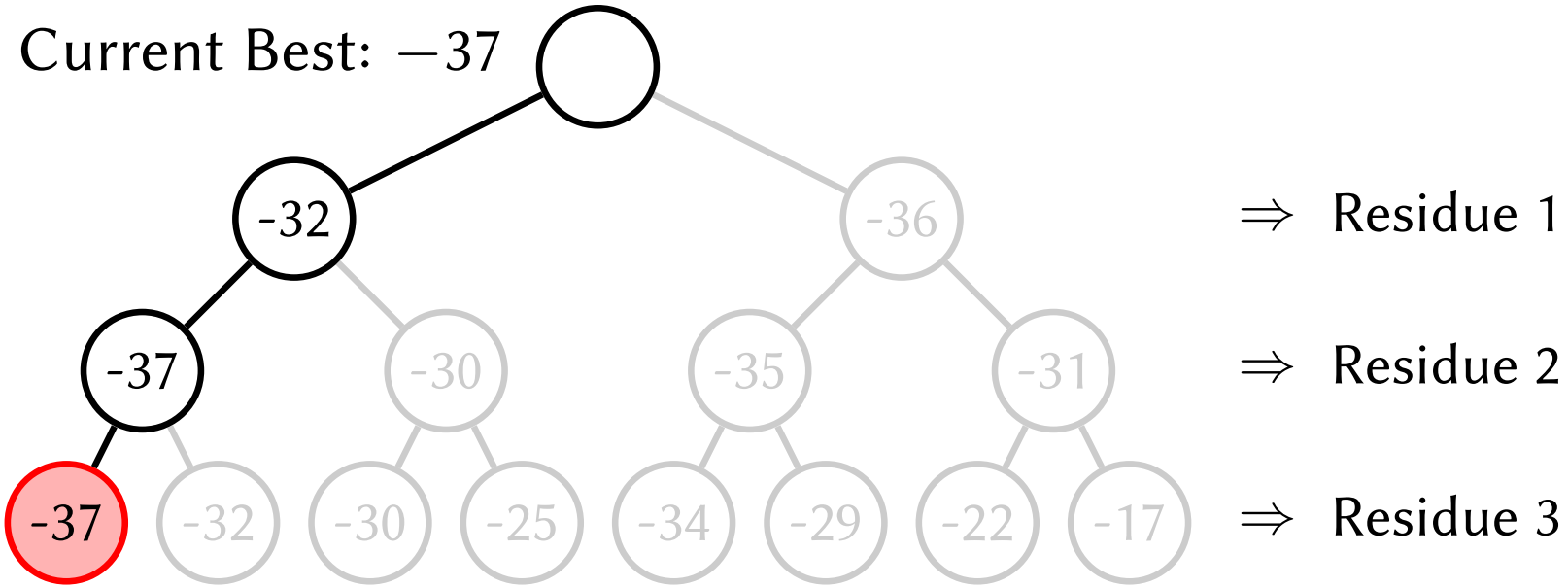

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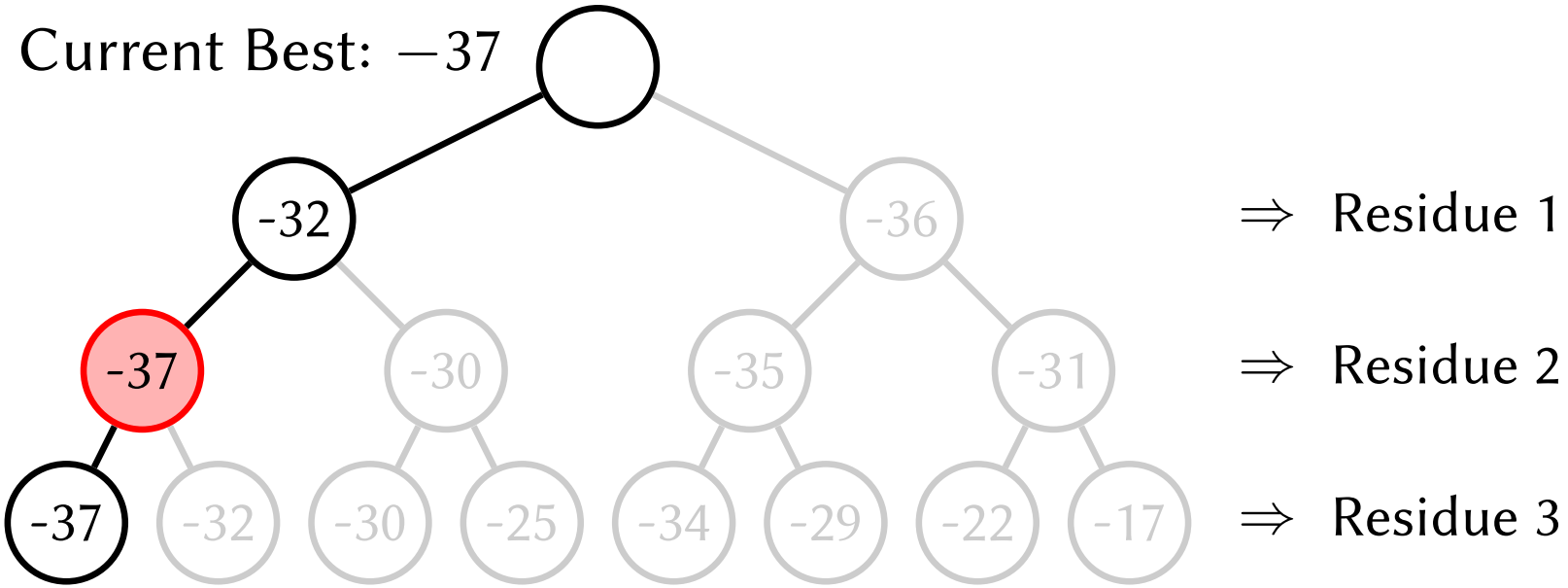

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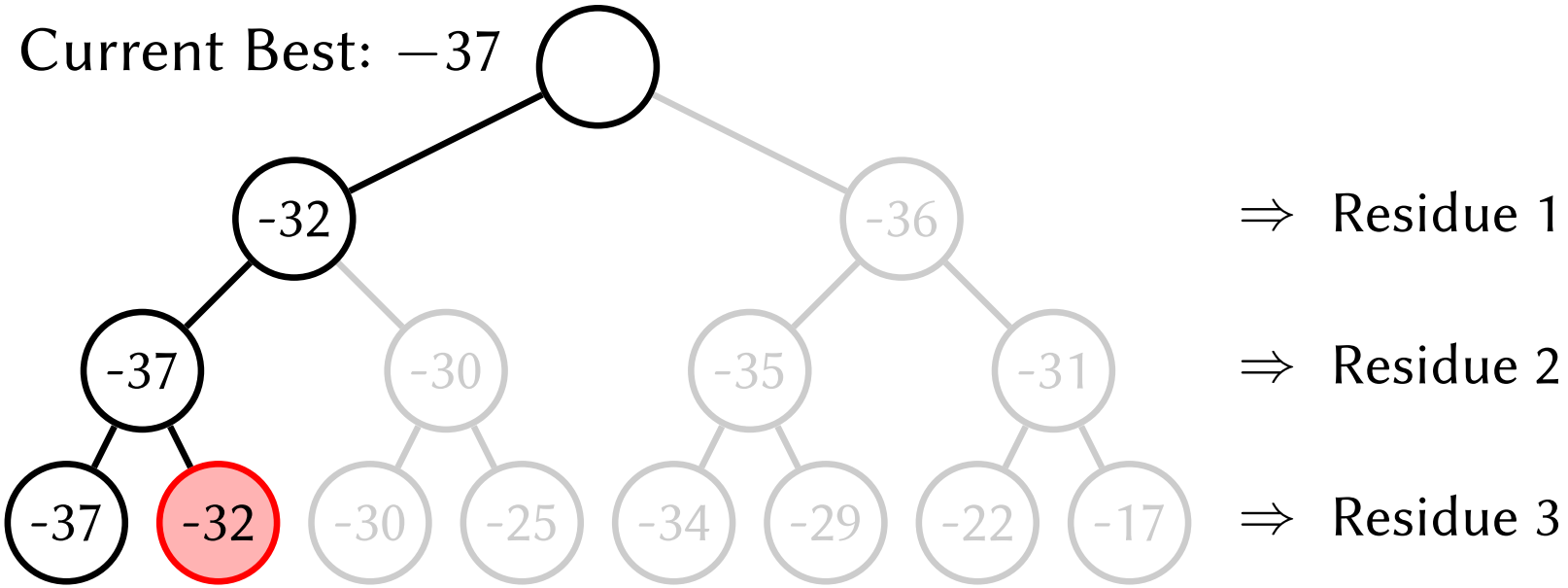

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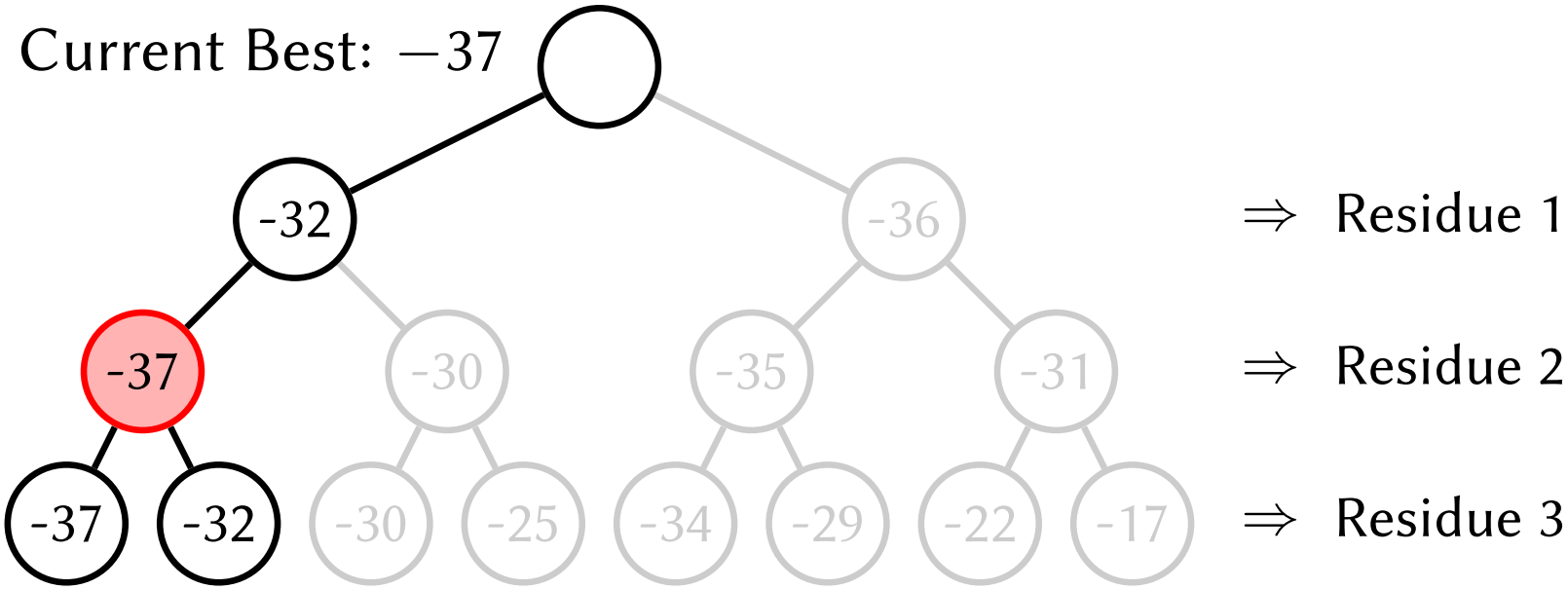

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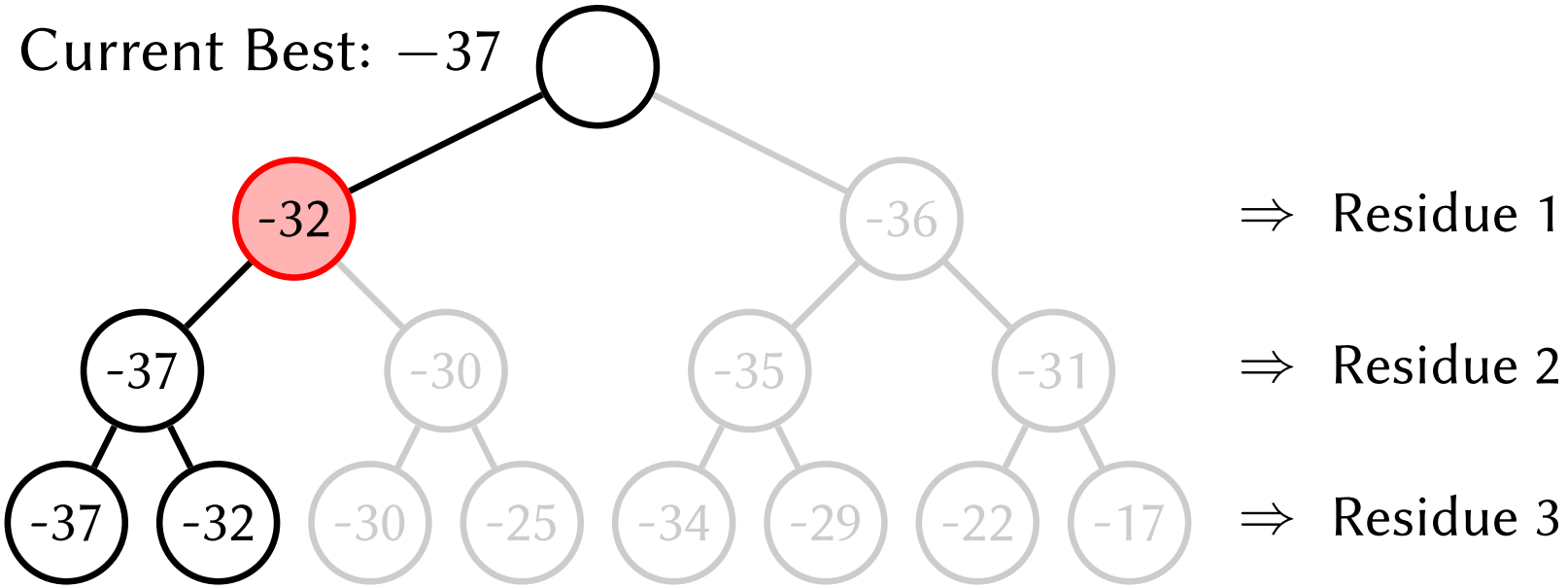

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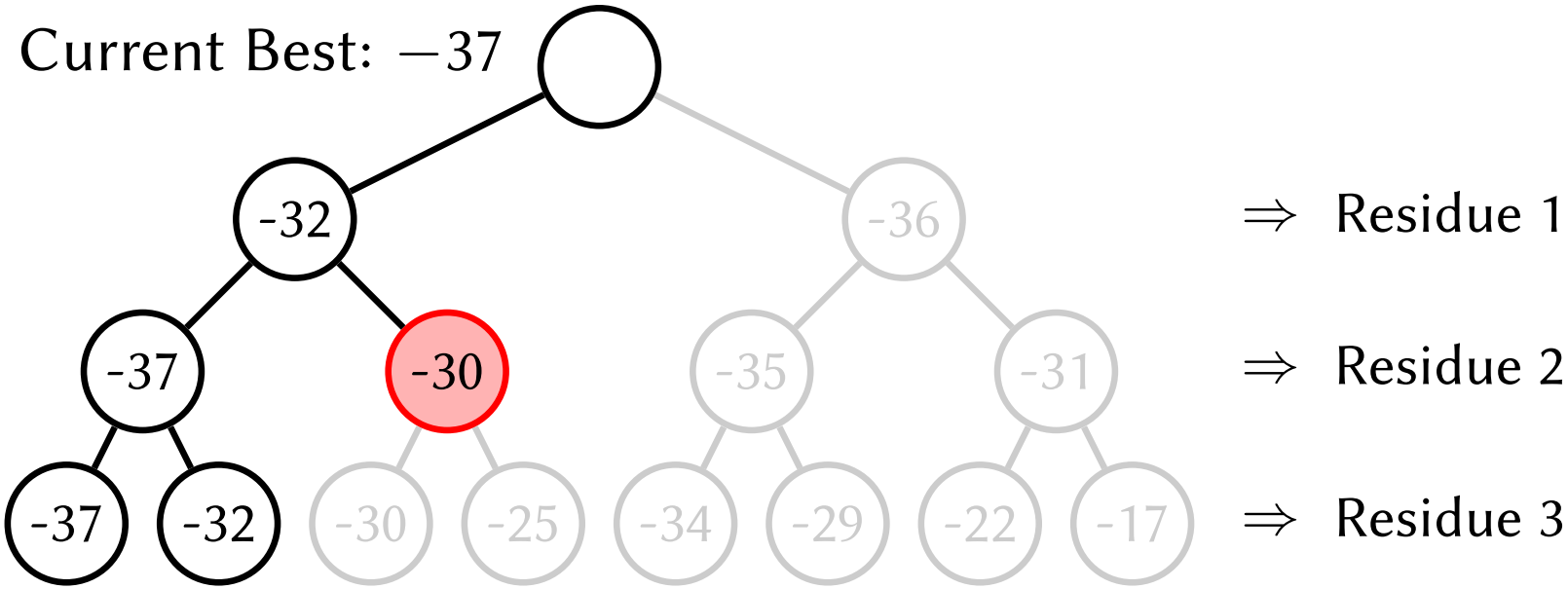

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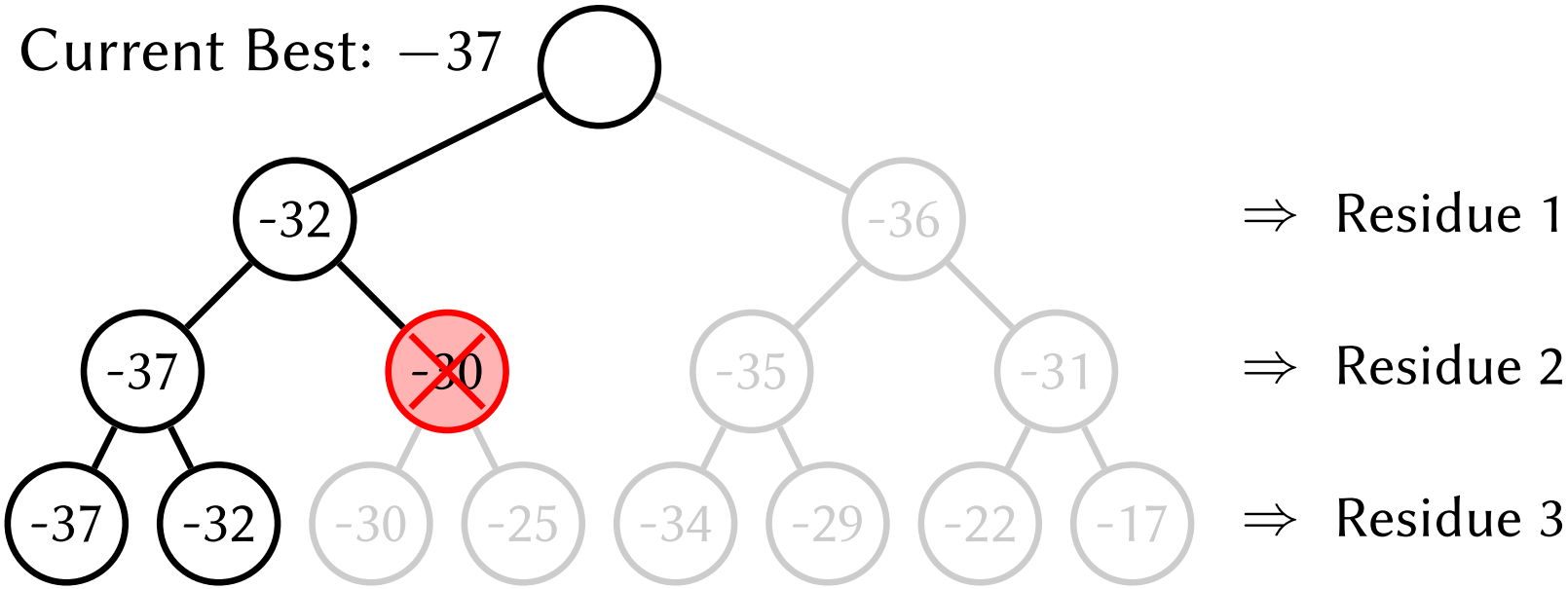

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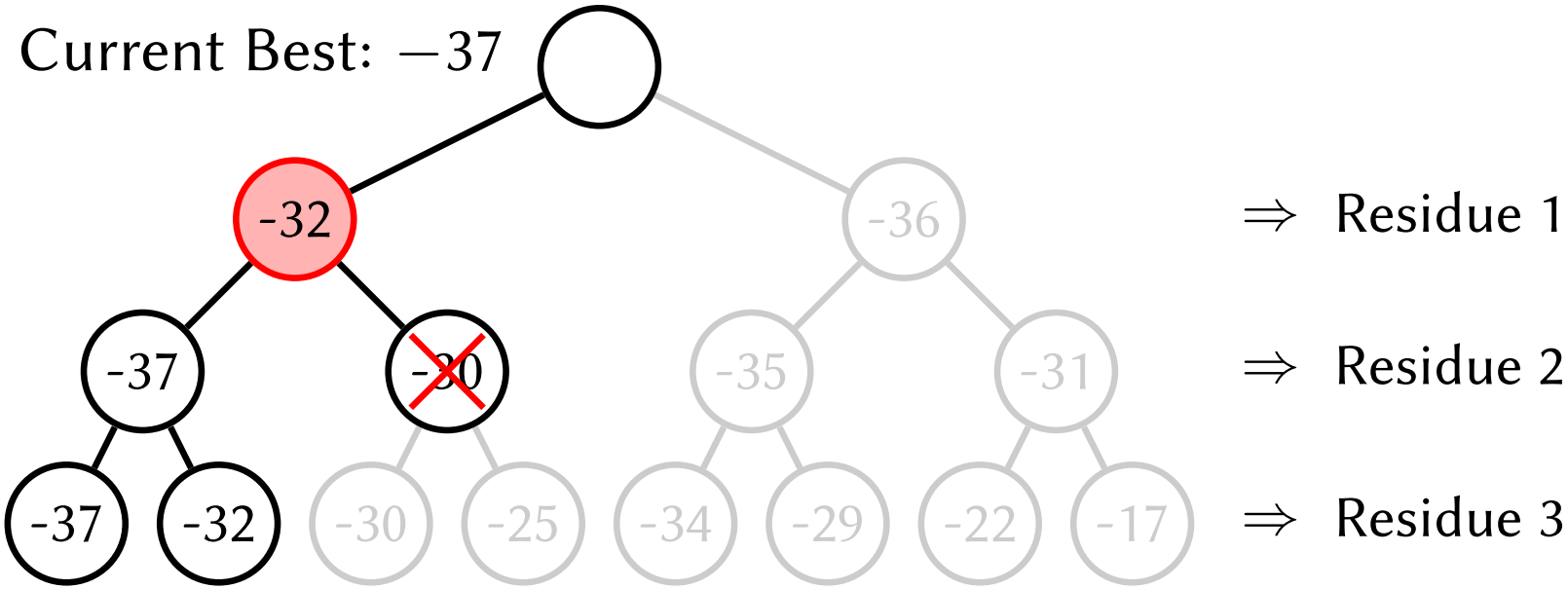

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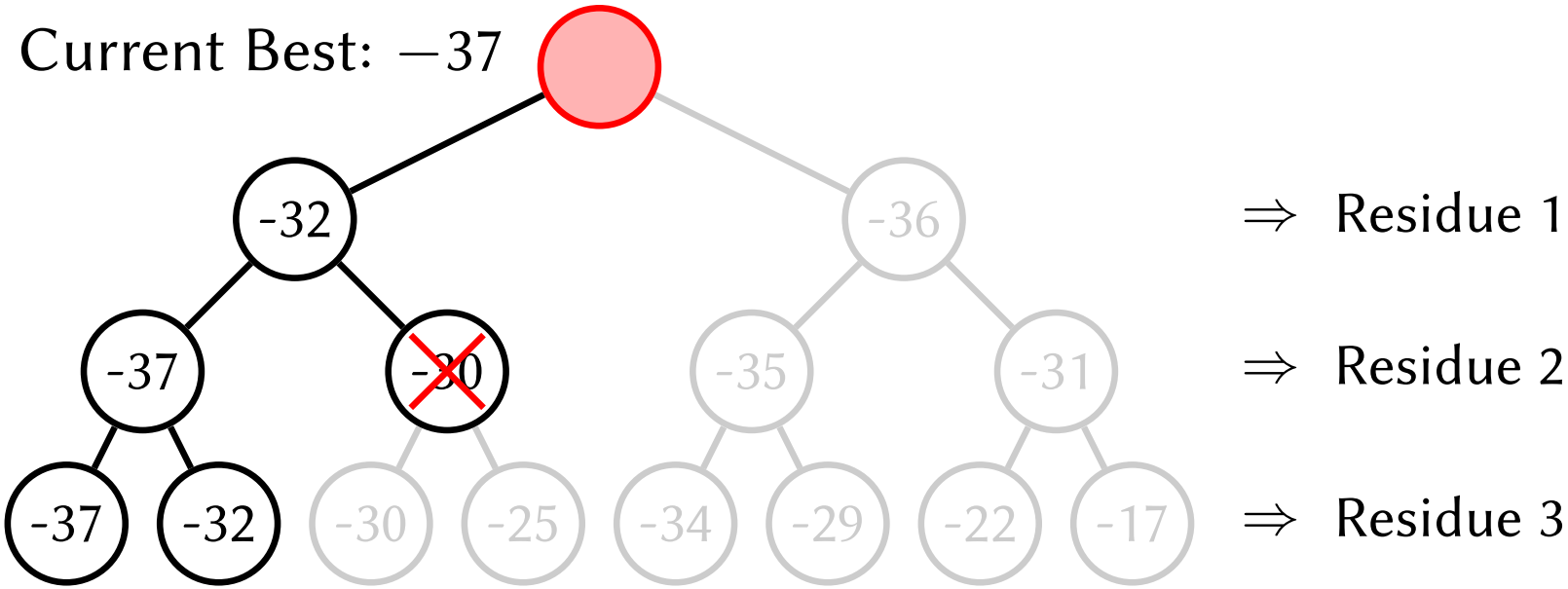

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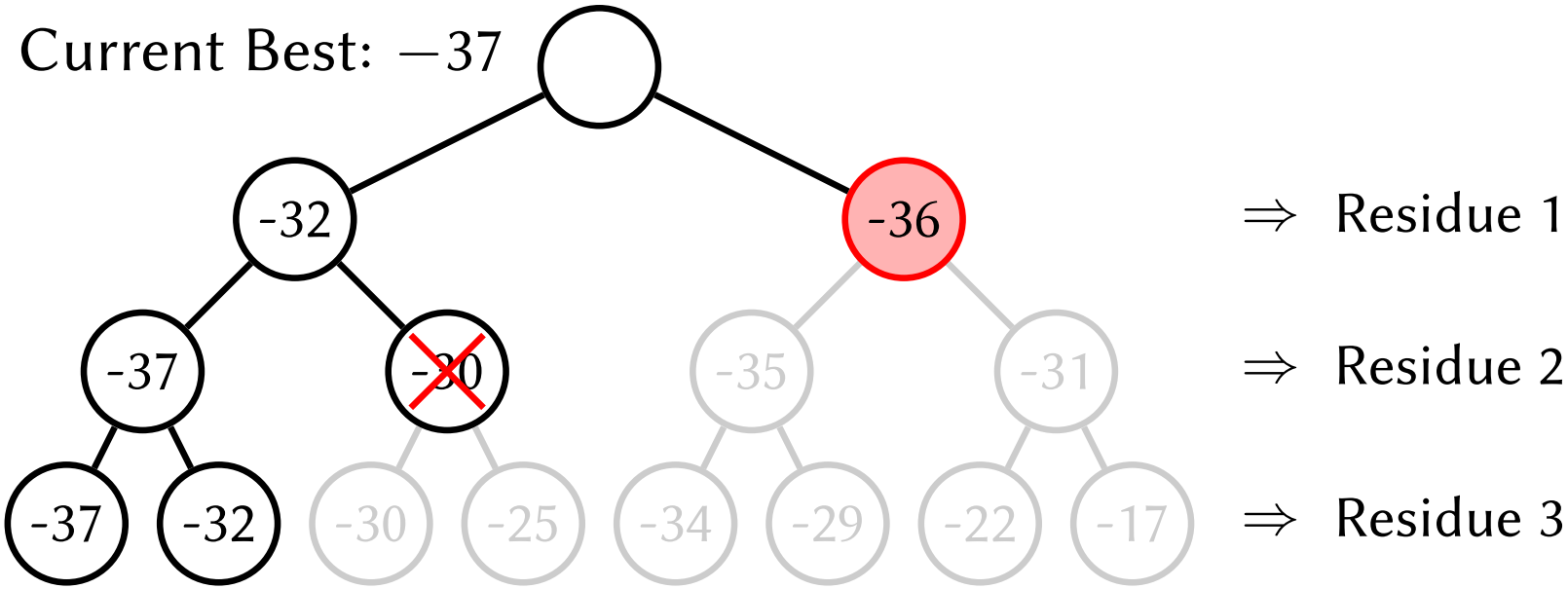

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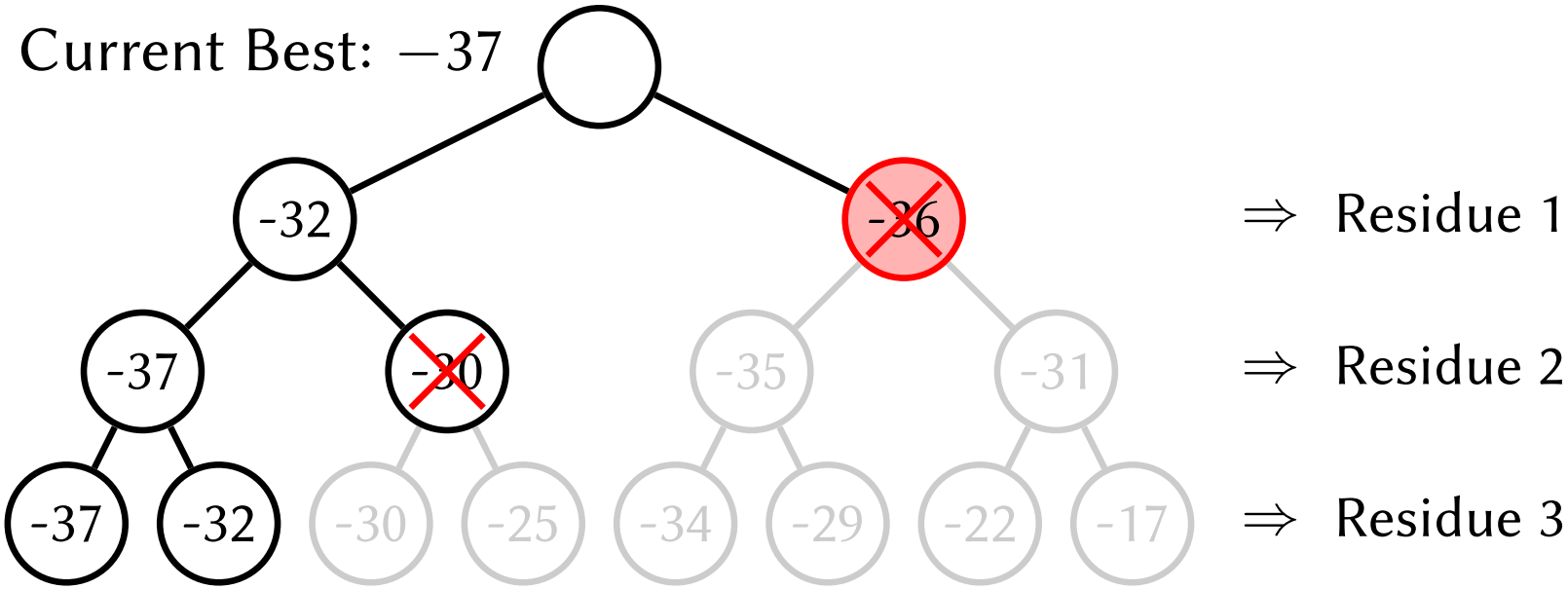

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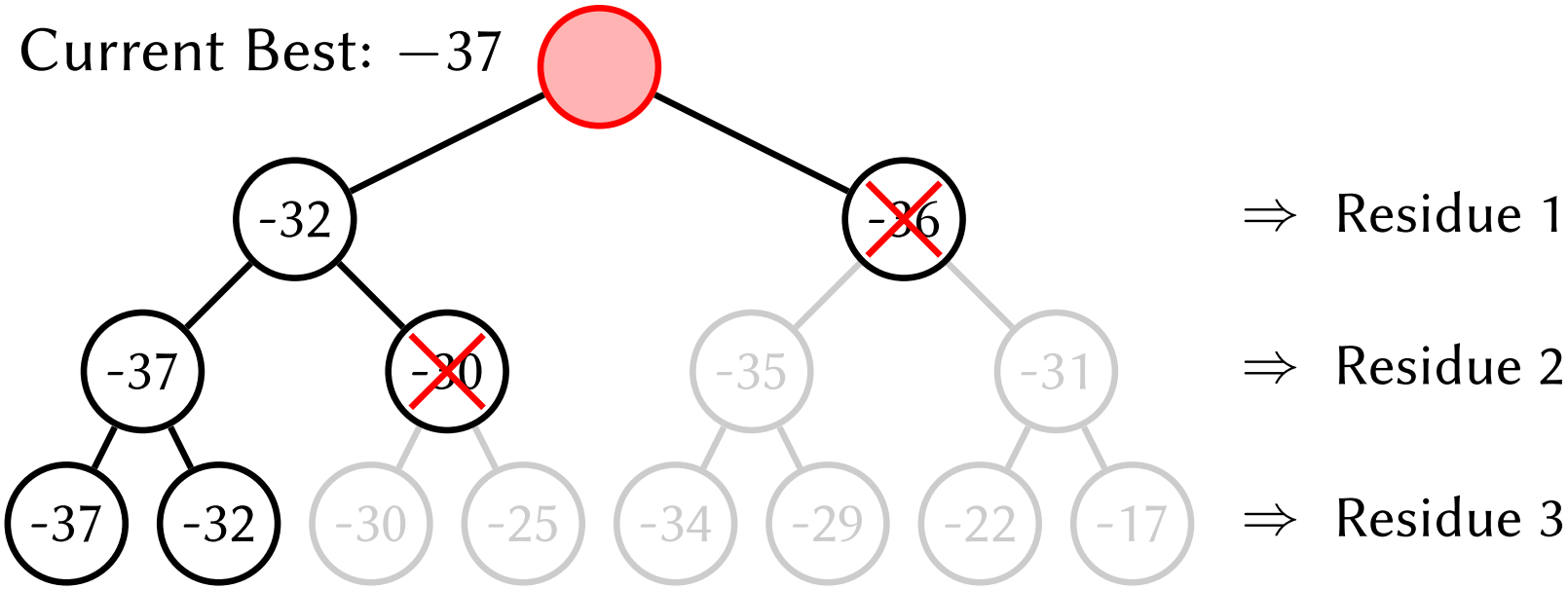

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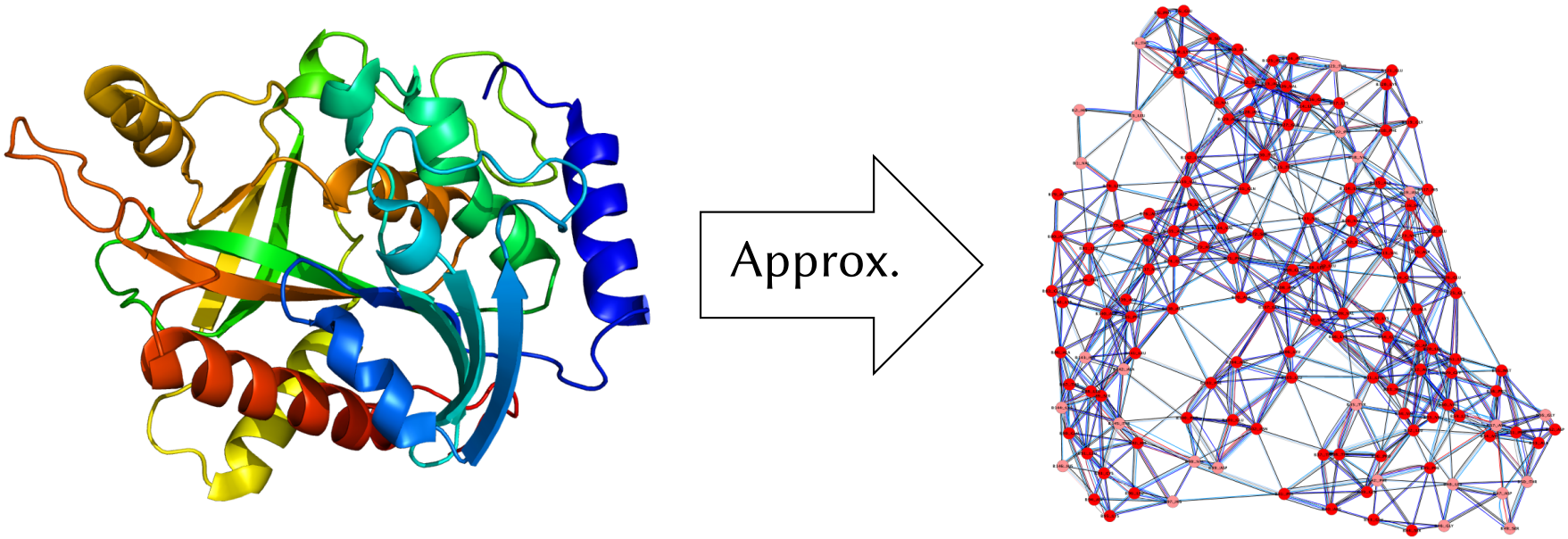
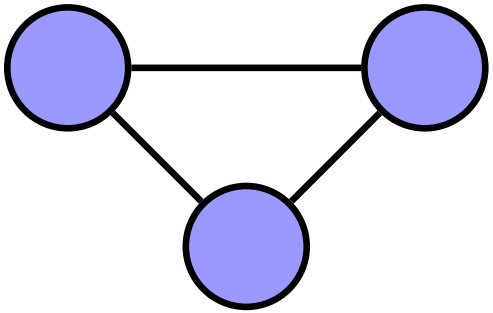
Residue Interaction Network

Approximation

Simplify the energy model by only considering the interaction between residues whose energy term is greater than a threshold.



Problem of Traditional Branch-and-bound



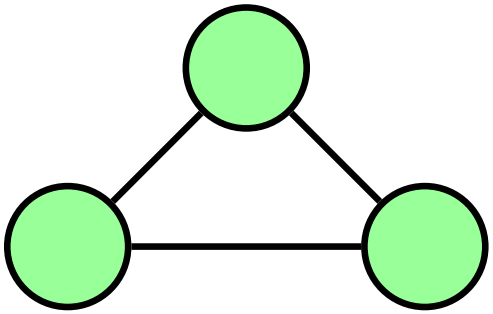
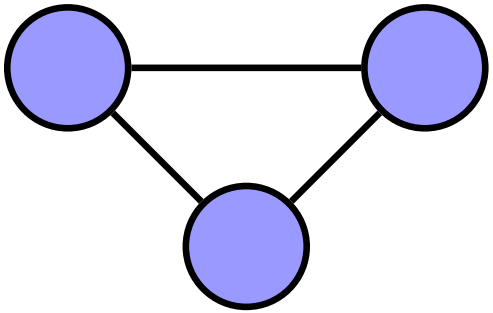
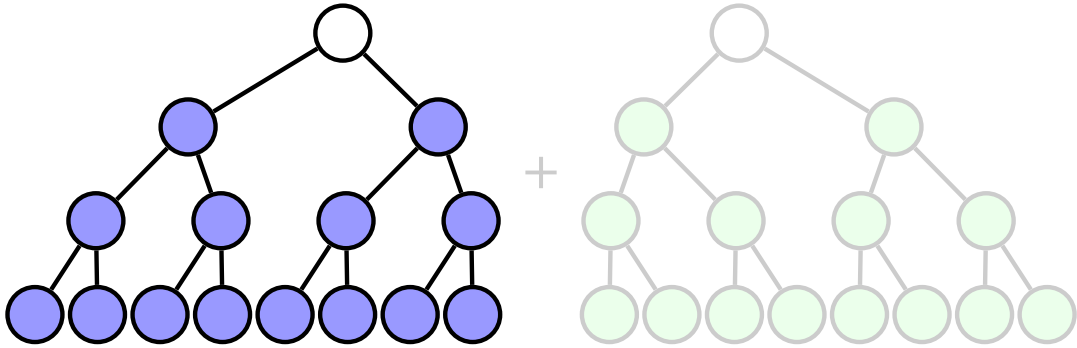


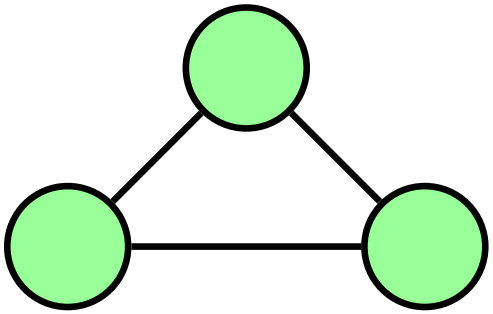
Figure: Residue Interaction Network

VS

Problem of Traditional Branch-and-bound







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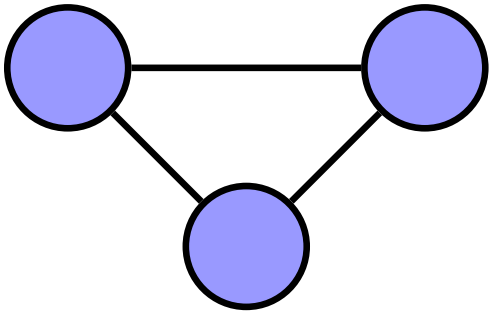

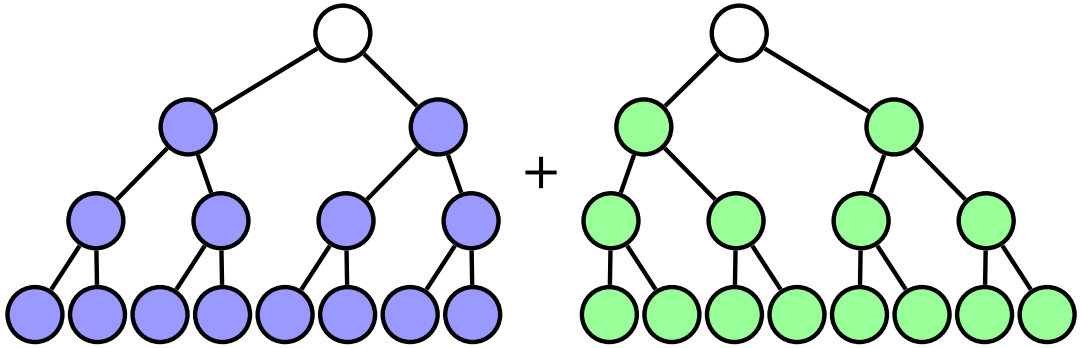

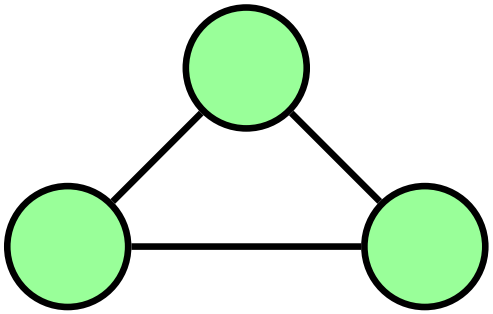

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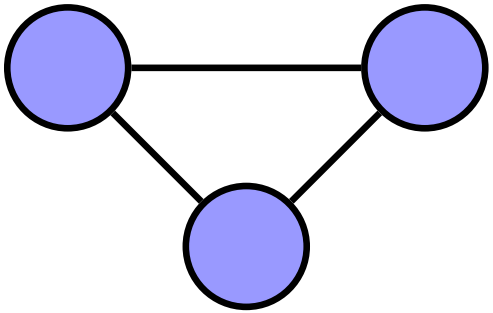

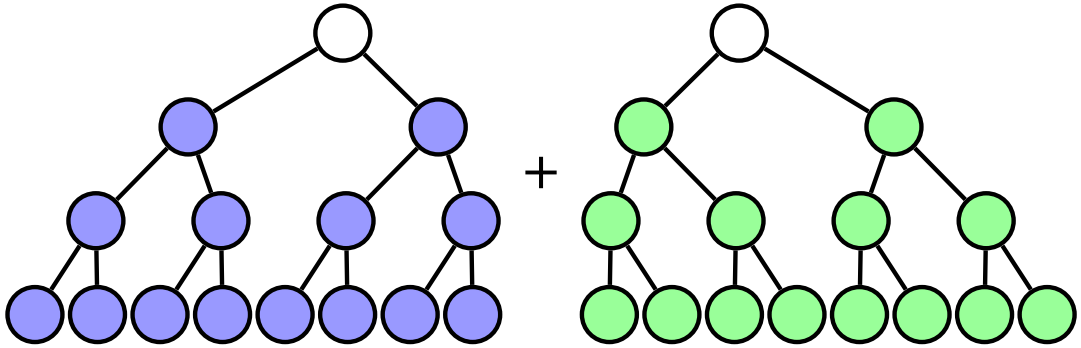

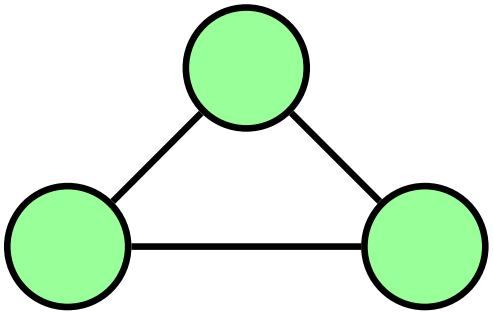

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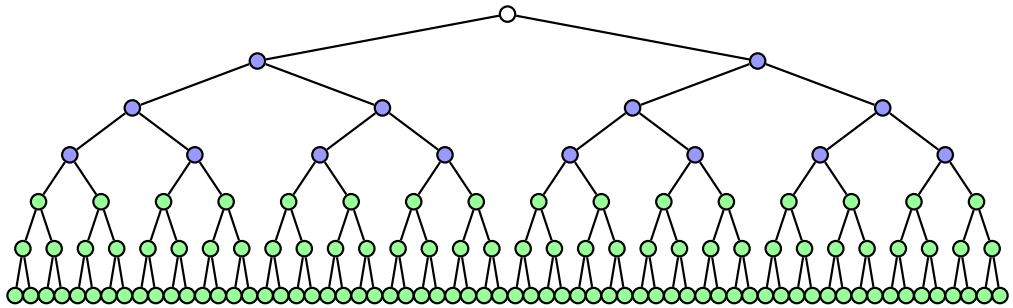

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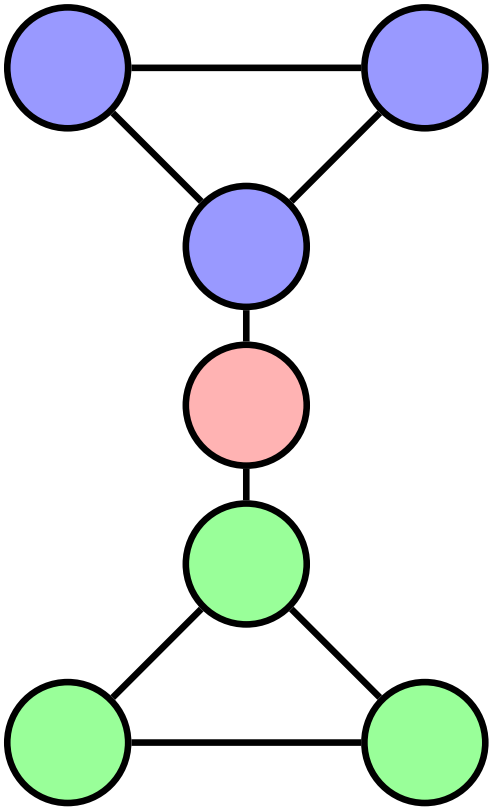

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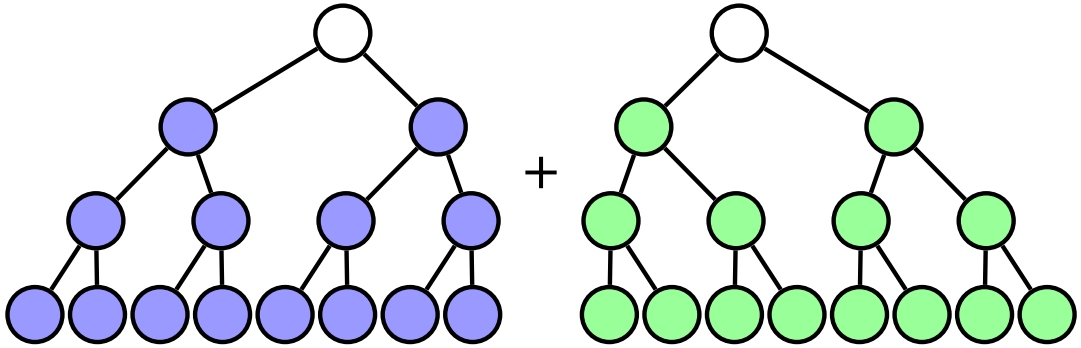

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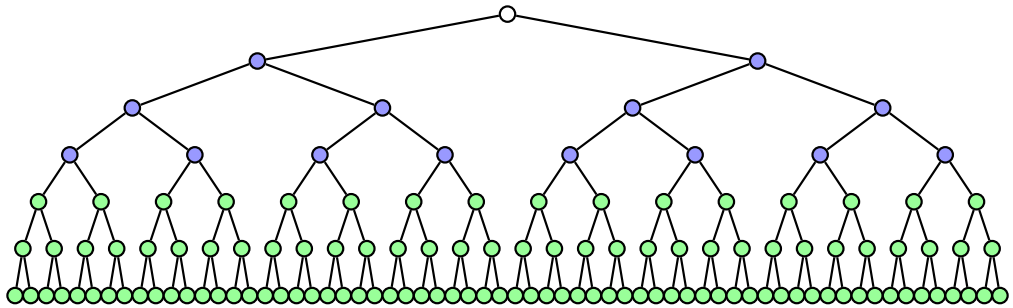
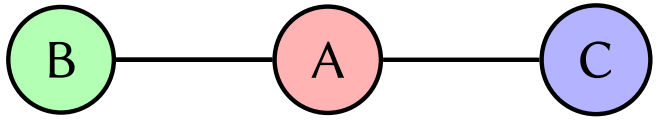
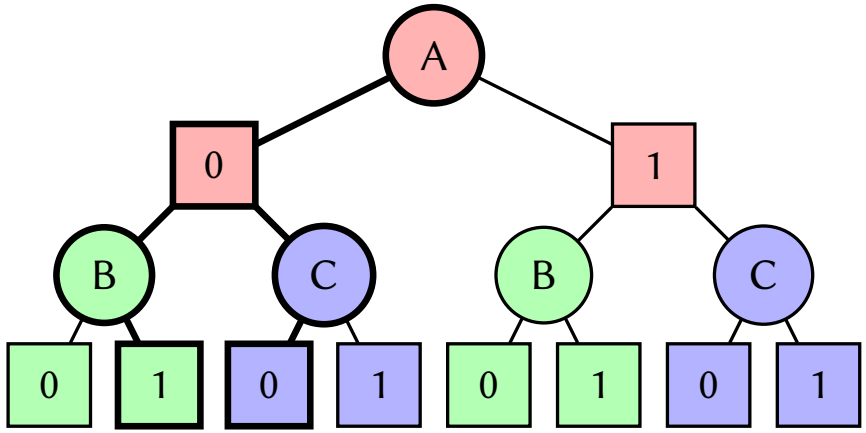


AND/OR Search Space



(a) Residue Interaction Network



(b) AND/OR Search Space

Node value

$$v_x = \begin{cases} \sum_{y \in \text{child}(x)} v_y, & \text{if } x \text{ is an AND node;} \\ \min_{y \in \text{child}(x)} e(y) + v_y, & \text{if } x \text{ is an OR node.} \end{cases}$$

energy terms between y and ancestors of y

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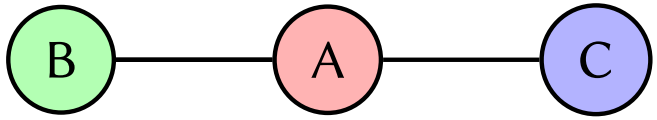

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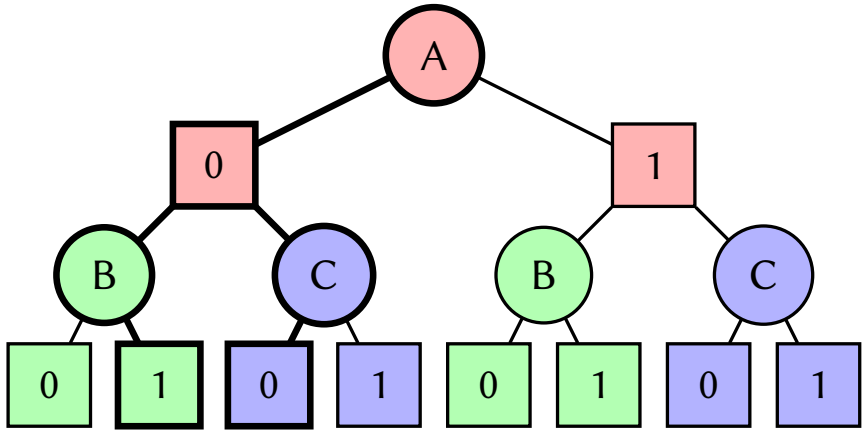

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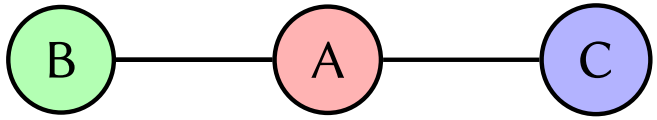

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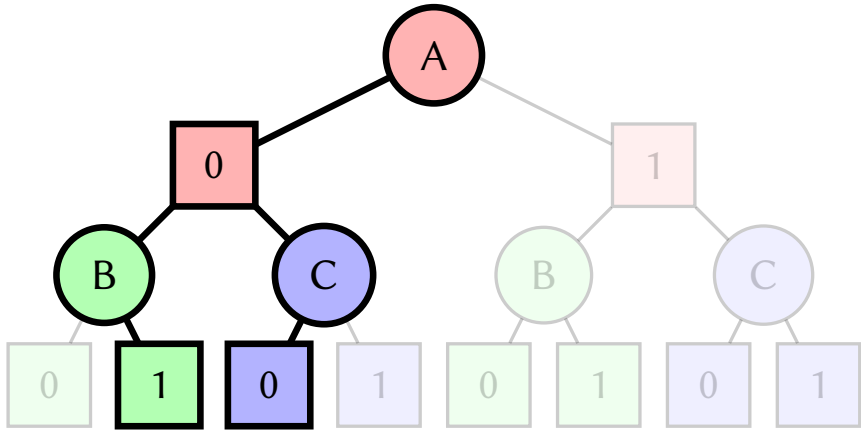

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- AND/OR branch-and-bound search can find GMEC efficiently
- Protein design models are not perfect:
  - errors in energy functions and structure of protein templates
  - assumptions of rigid backbone and discrete side-chain conformations
- The GMEC solution is not sufficient in practice
- Sub-optimal (e.g., *second-best*, ...) conformations are required

Finding the k best solutions

- add a threshold to prevent from pruning sub-optimal solutions
- maintain k node values for each node, i.e., array $v_x[1], v_x[2], \ldots, v_x[k]$

Finding Sub-optimal Solutions

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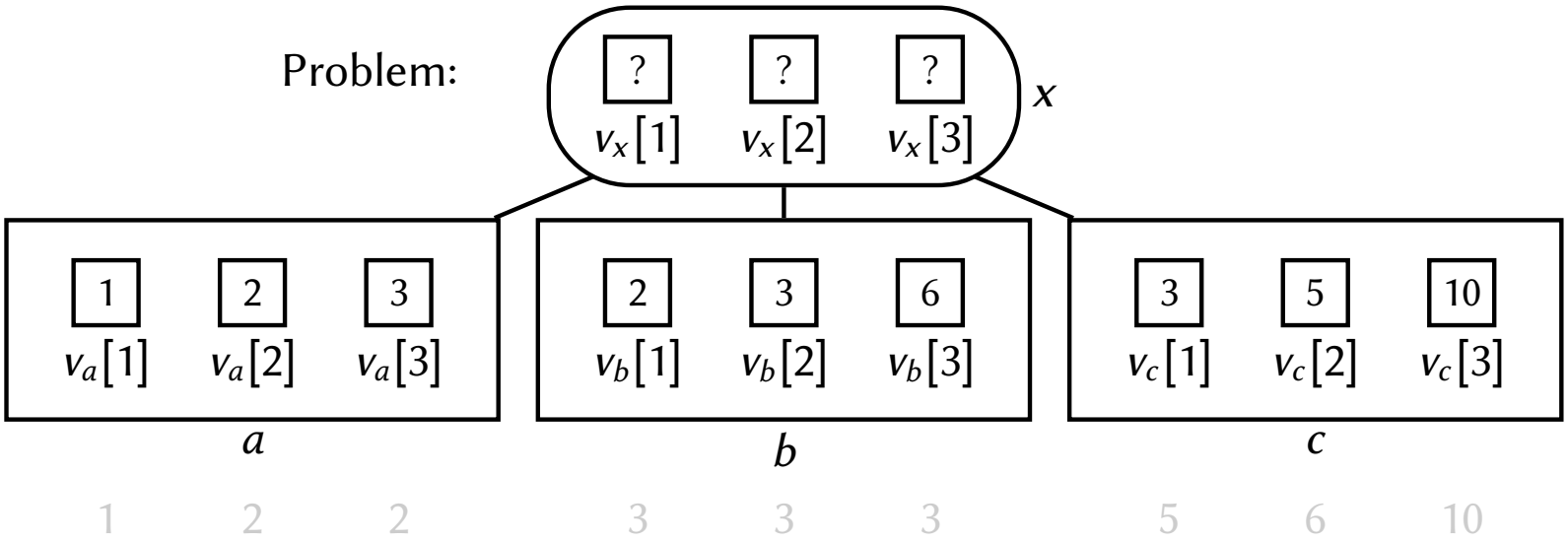
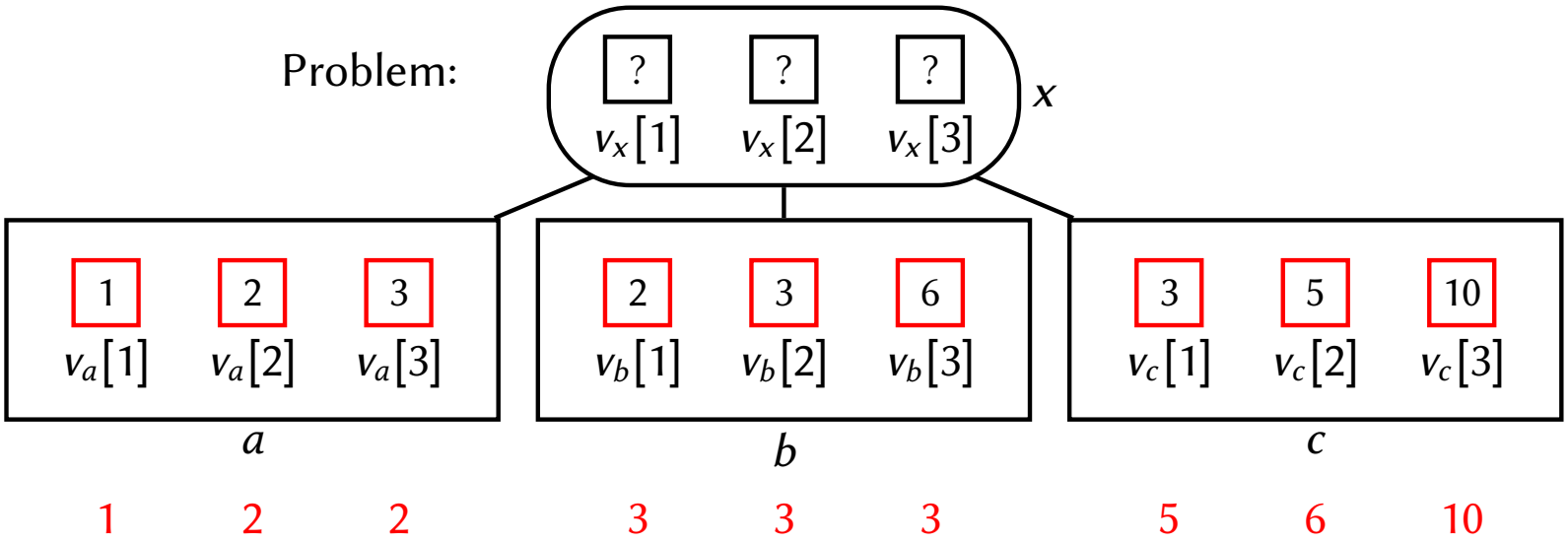
Computing $v[\cdot]$ values for OR nodes



- Find k best rotamer assignments for x;
- Sort all the v values for the child nodes of x;
- Keep k smallest node values

Computing $v[\cdot]$ values for OR nodes



- Find k best rotamer assignments for x;
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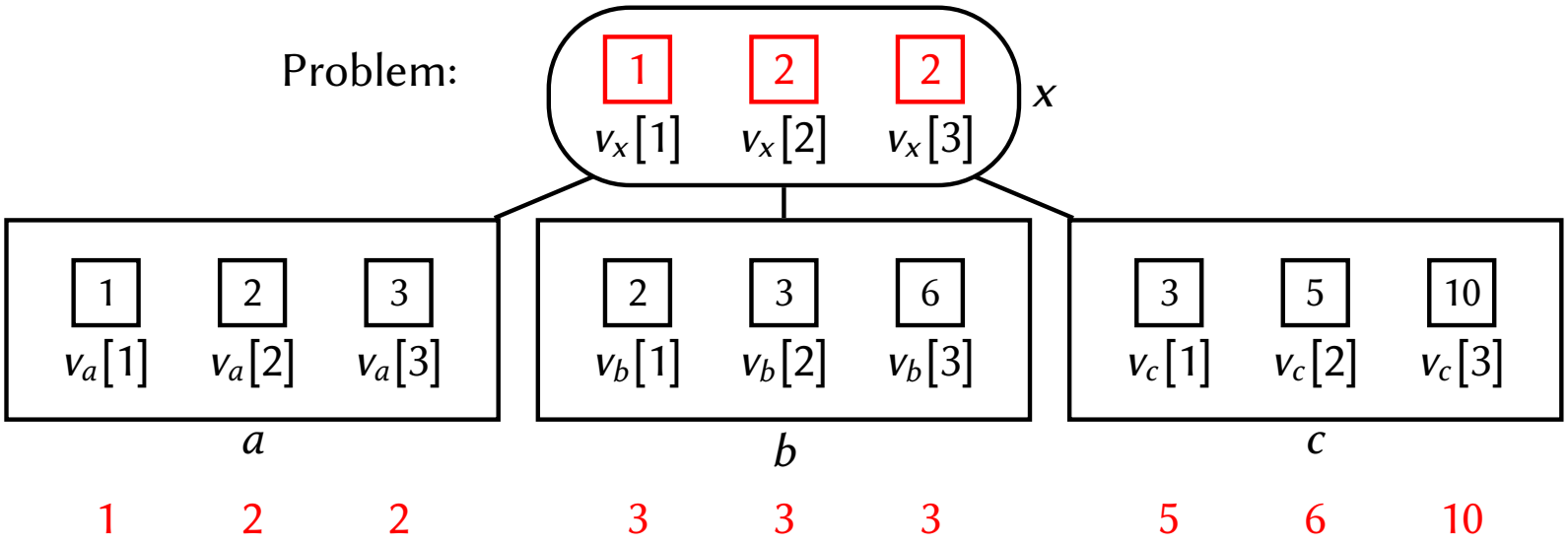

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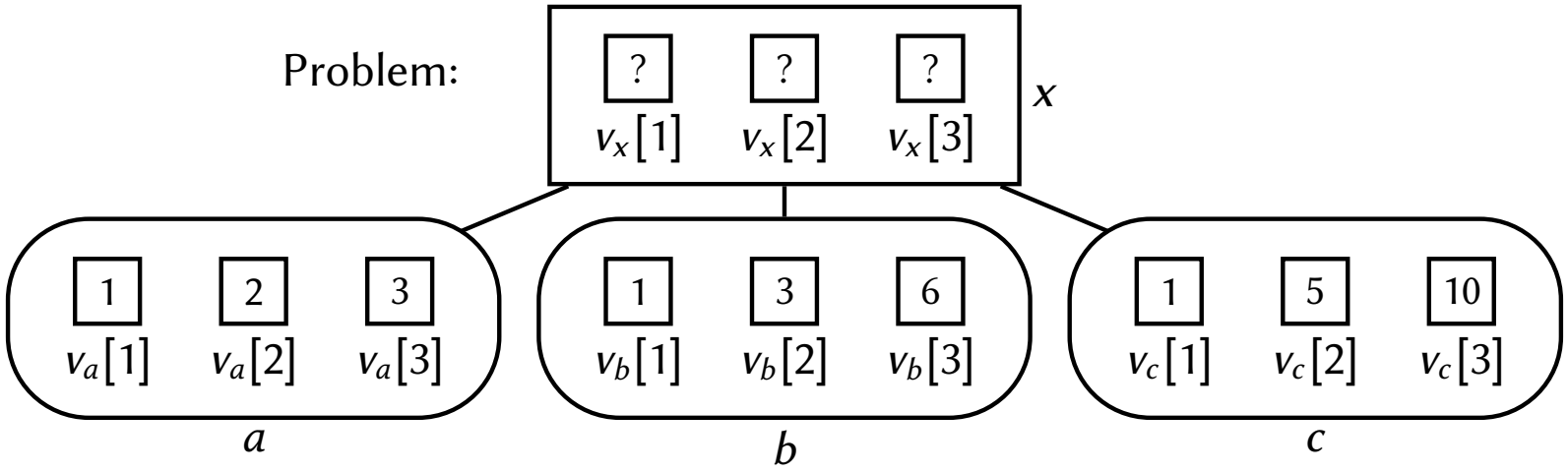

- Want to find k best ways to merge the sub-problems;
- $v_x[i]$ should be the sum of $v_a[i_a] + v_b[i_b] + v_c[i_c]$;
- Obviously $v_x[1] = v_a[1] + v_b[1] + v_c[1]$, hard for $v_x[2]$ and $v_x[3]$;
- Brute force algorithm: $O(k^d)$
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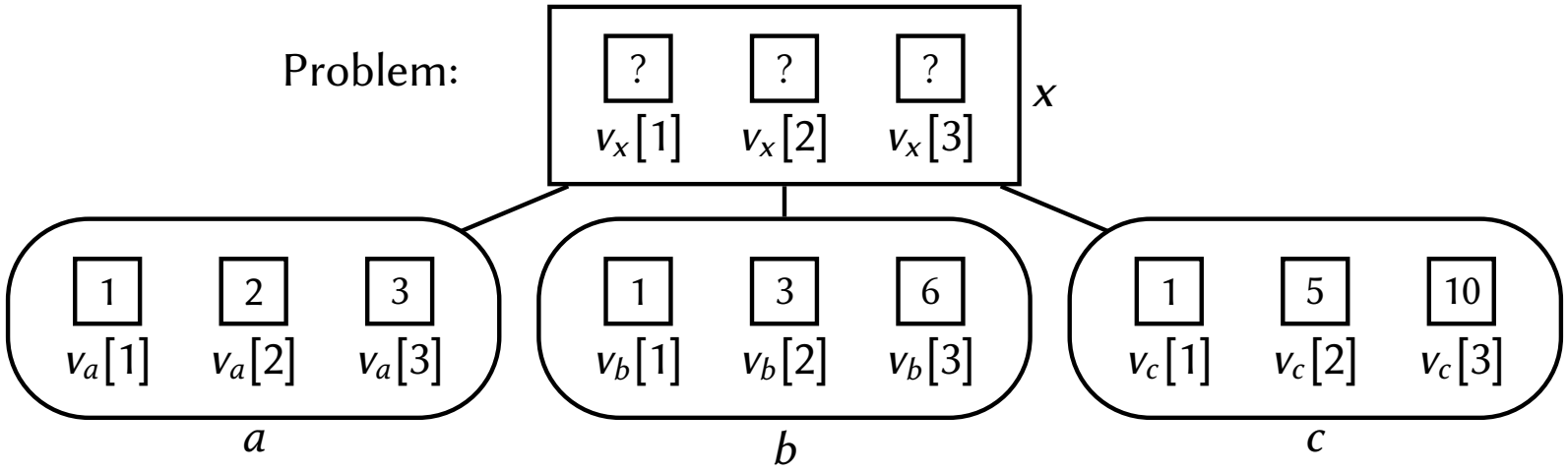

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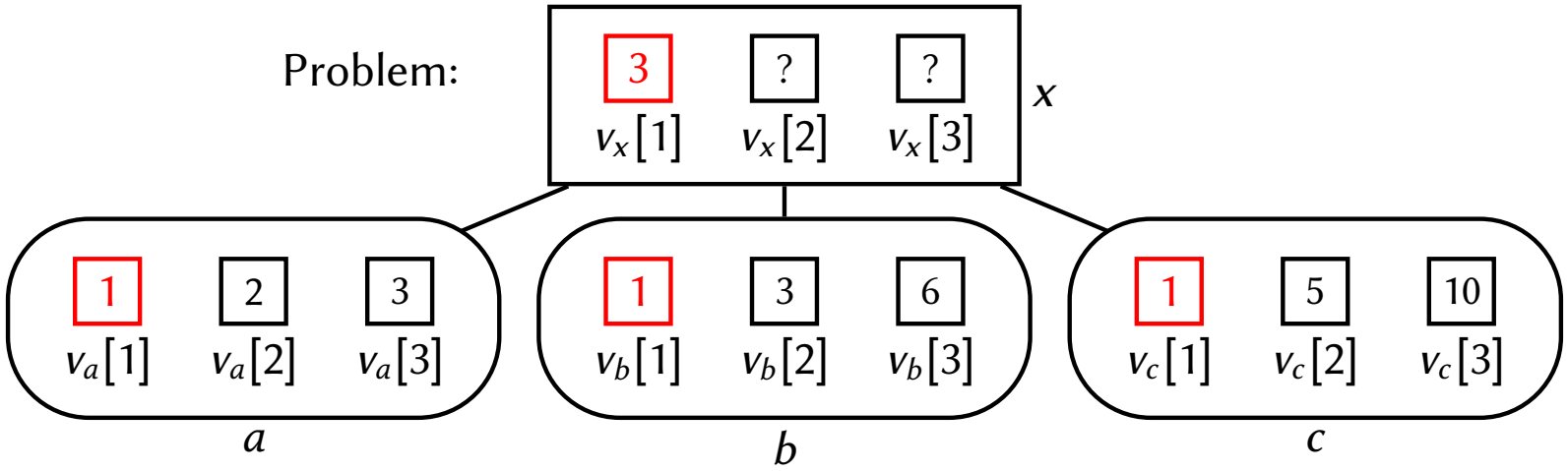

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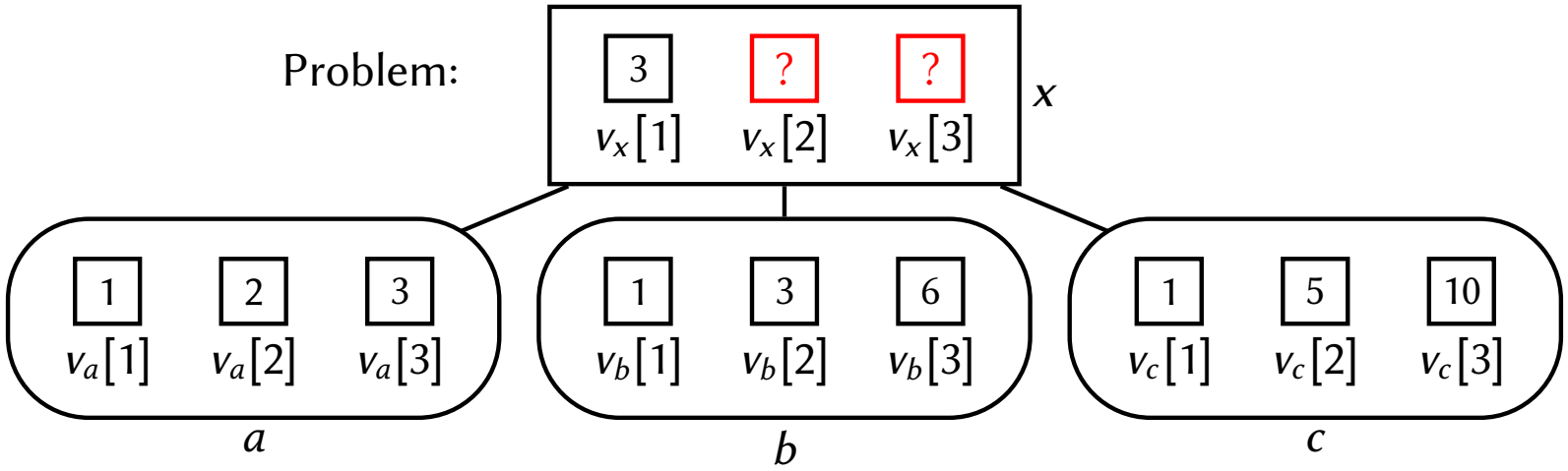

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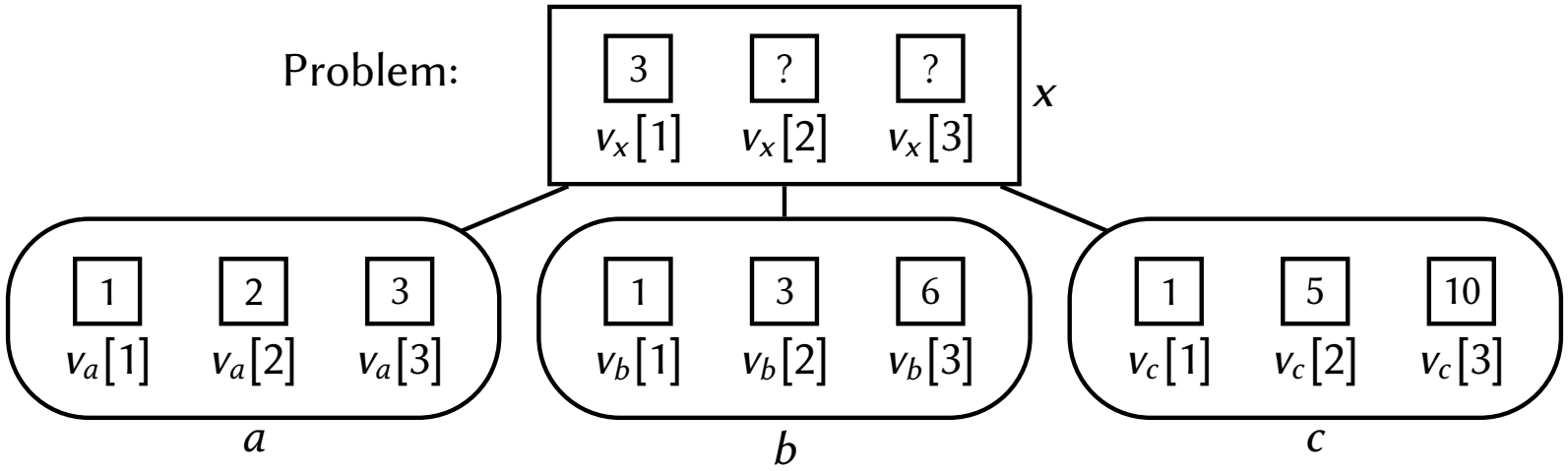

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- OSPREY platform from *Donald Lab* (Duke University)
- daoopt AOBB framework from UC Irvine
- Native sequence recovery (core redesign)
- Large rotamer library for better accuracy
- DEE/A* as the comparison

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CPU: Intel Xeon™ E5-1620 3.6GHz

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- 23 previously unsolvable protein redesign cases
- 5 previously solvable protein redesign cases
- 6 full protein redesign cases

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- solve *21 out of 23 problems* that was previously unsolvable;
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Running time of AND/OR branch-and-bound algorithm

Running time of our optimized OSPREY

Running time of traditional OSPREY

Conformation Space

PDB	Space size	OSPREY	cOSPREY	AOBB
1IQZ	7.11e+17	1,824,235	40,217	117
2COV	1.14e+10	317	21	1
3FGV	6.44e+12	59,589	5,091	< 1
3DNJ	5.11e+12	7,469	570	3
2FHZ	1.83e+18	3,475,716	70,783	13

Time is measured in millisecond.

Conclusion and Future Work

Our Contribution

- Apply AND/OR branch-and-bound search to protein design
- Design an algorithm to find sub-optimal solutions
- Test AOBB search in native sequence recovery experiment

Results

- Memory efficient
- Speedup by several orders of magnitude comparing to A*/DEE

Future Work

- Using AND/OR best-first search for sub-optimal solutions
- Parallelizing AOBB on a super computer

Acknowledgement

Discussion

- Prof. Alexander Ihler
- Dr. Lars Otten

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- National Basic Research Program of China
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Question and Answer

Thank you!