An Efficient Parallel Algorithm for Accelerating Computational Protein Design

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Duke University

Jul, 2014

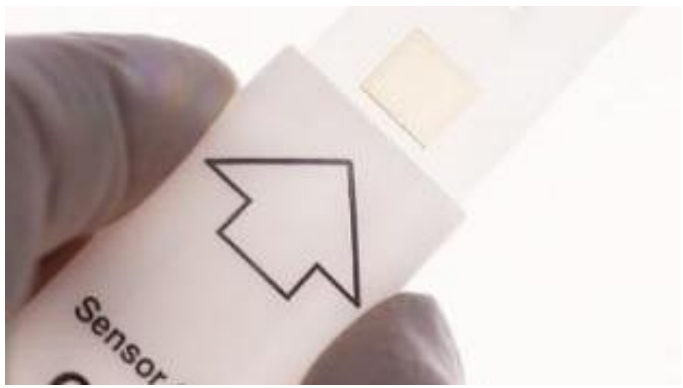
Why We Need Protein Design?

Applications

New Drug Discovery

Drug Resistance Prediction

Enzyme Optimization

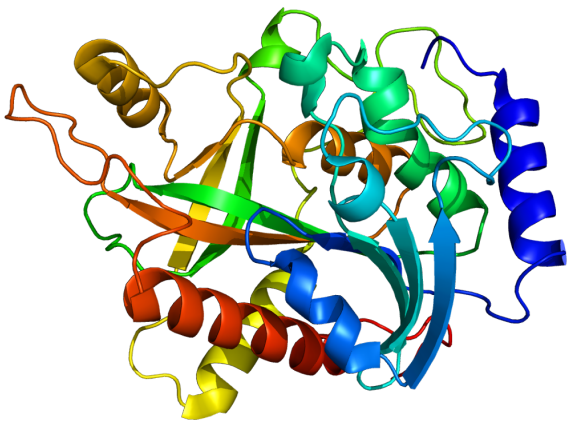


New Biosensor Design

What is Structure-Based Protein Design?

Toolbox

- Energy Functions
- Rotamer Library
- Backbone Template



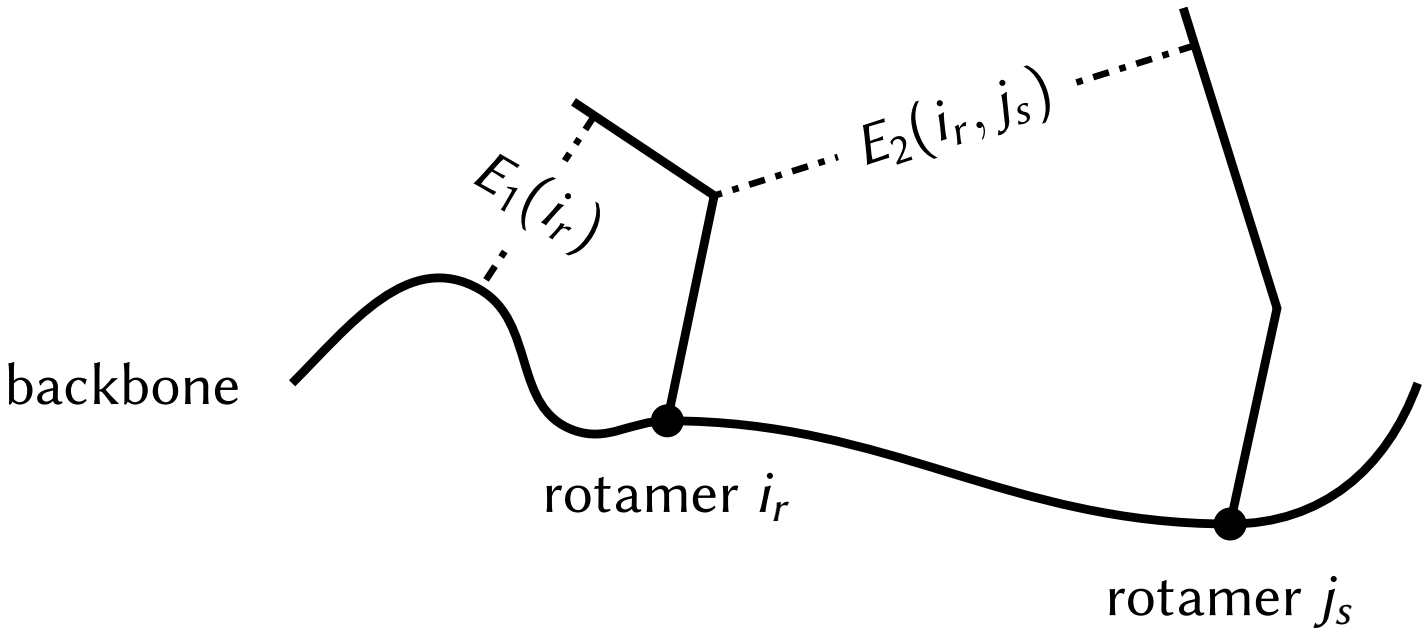
Wild-type protein's structure

Design Algorithm

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

1D amino acid sequence

Protein Design as an Optimization Problem



Energy Function (Optimization Target)

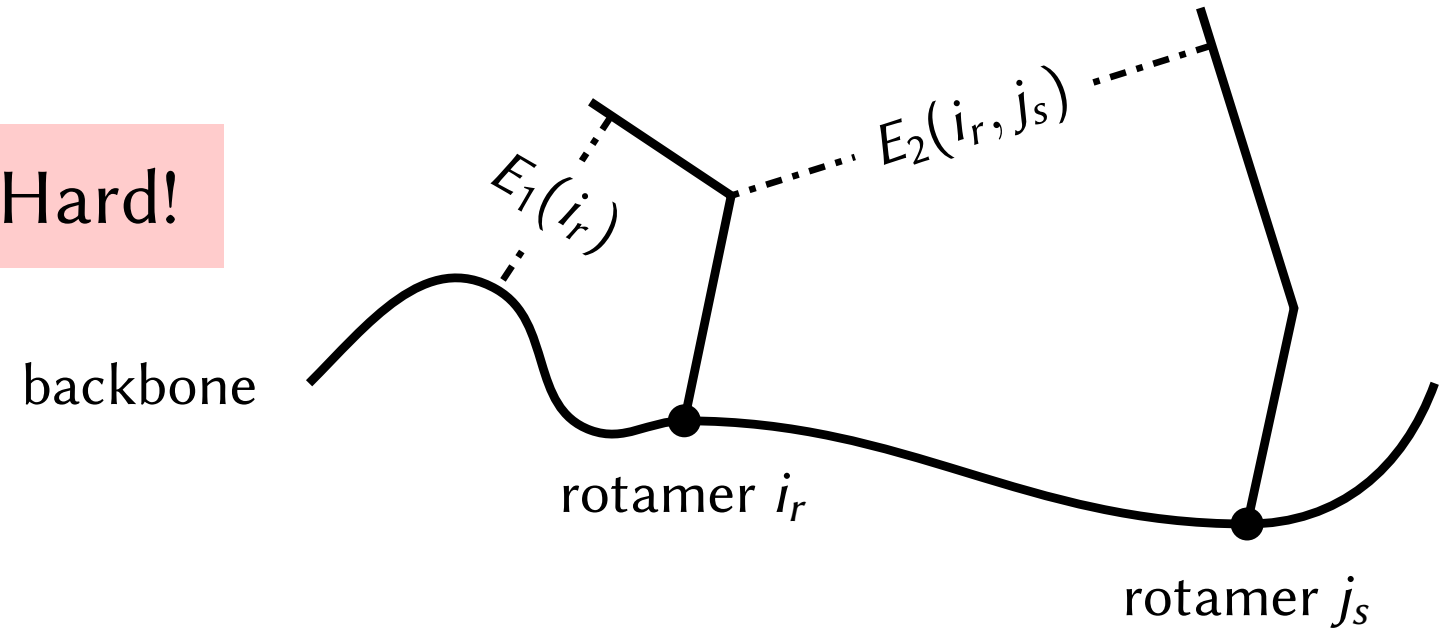
$$E_T = \sum_{i_r} E_1(i_r) + \sum_{i_r} \sum_{j_s, i<j} E_2(i_r, j_s)$$

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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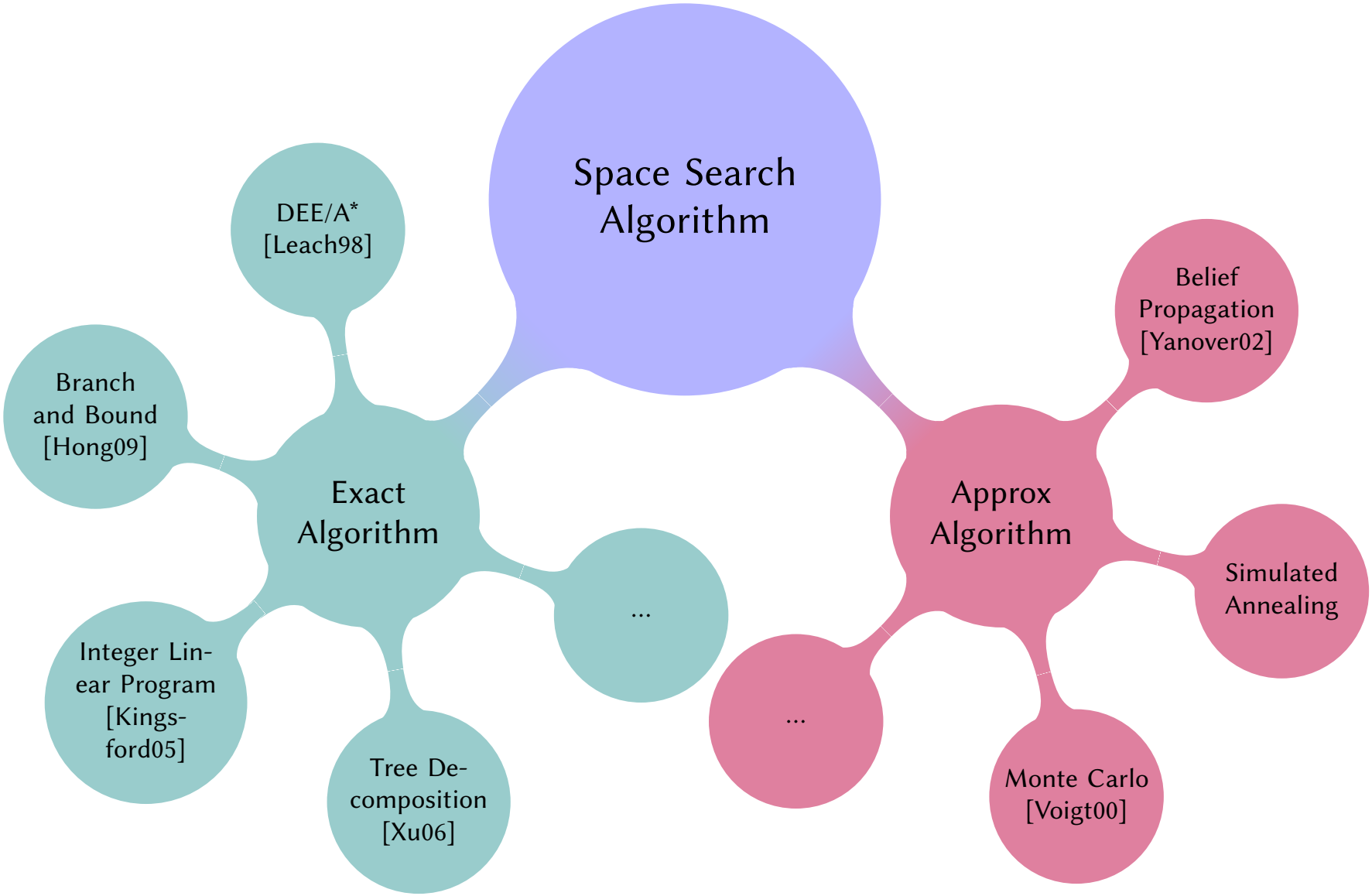
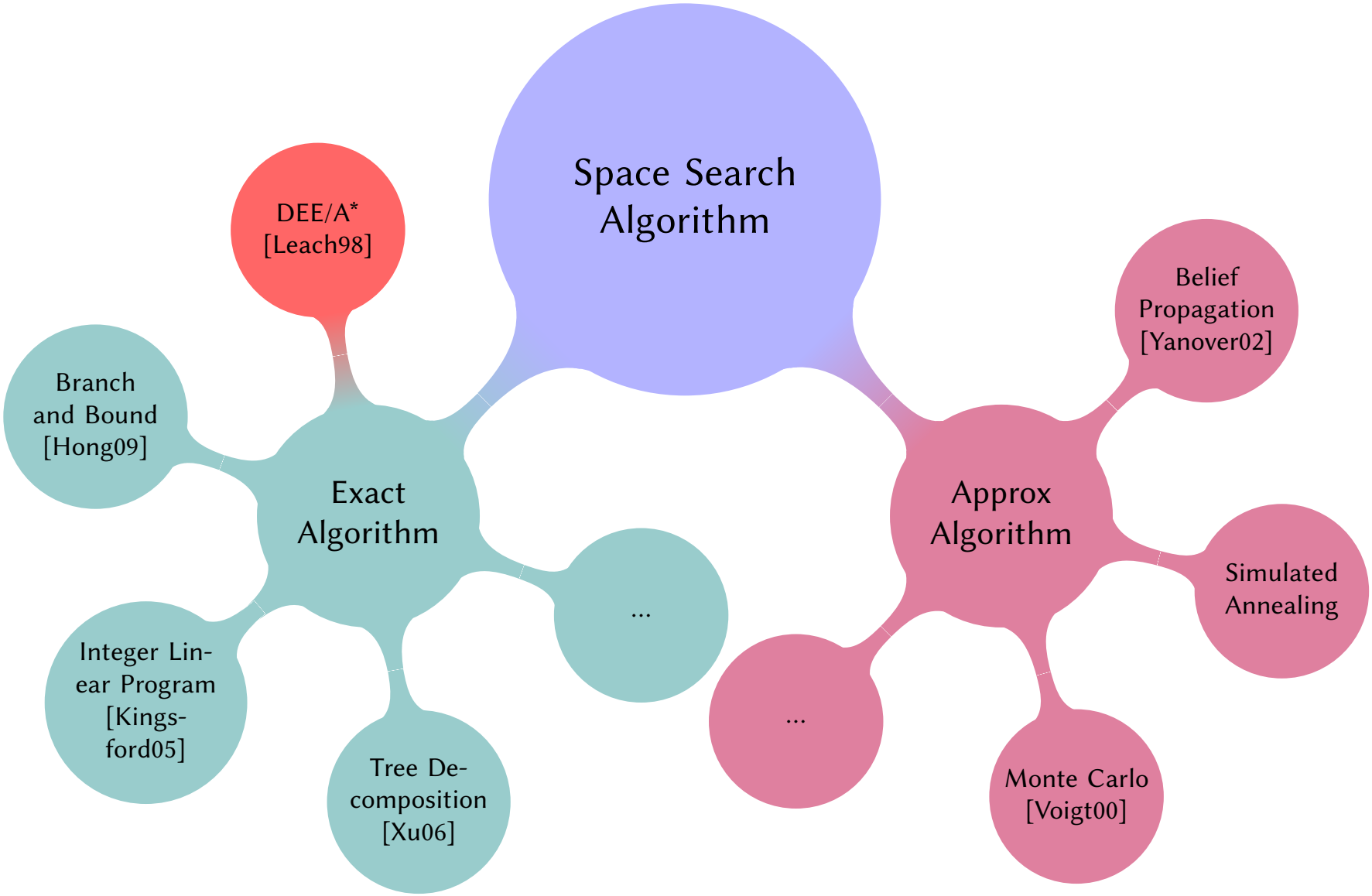
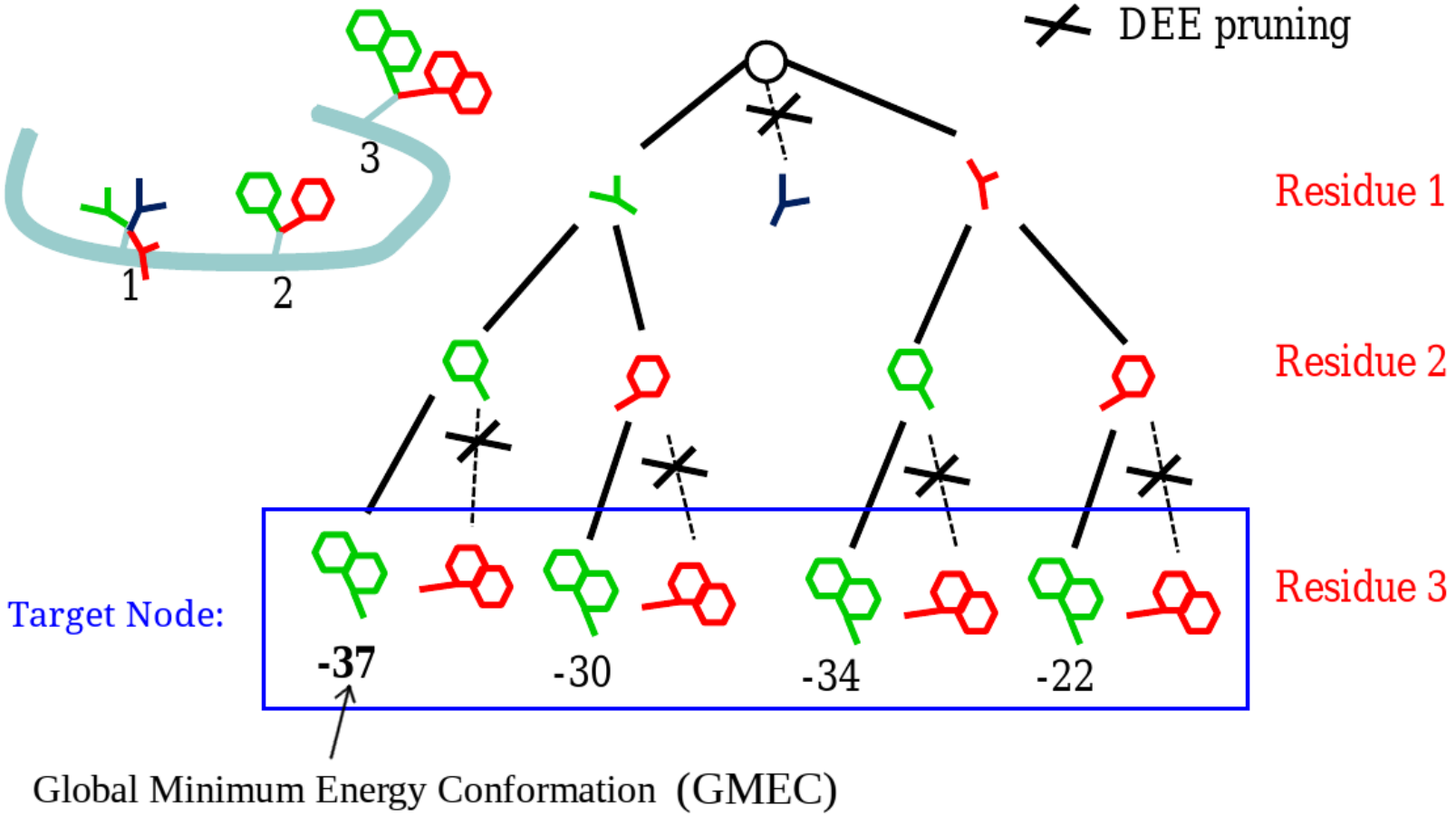
Search Algorithm



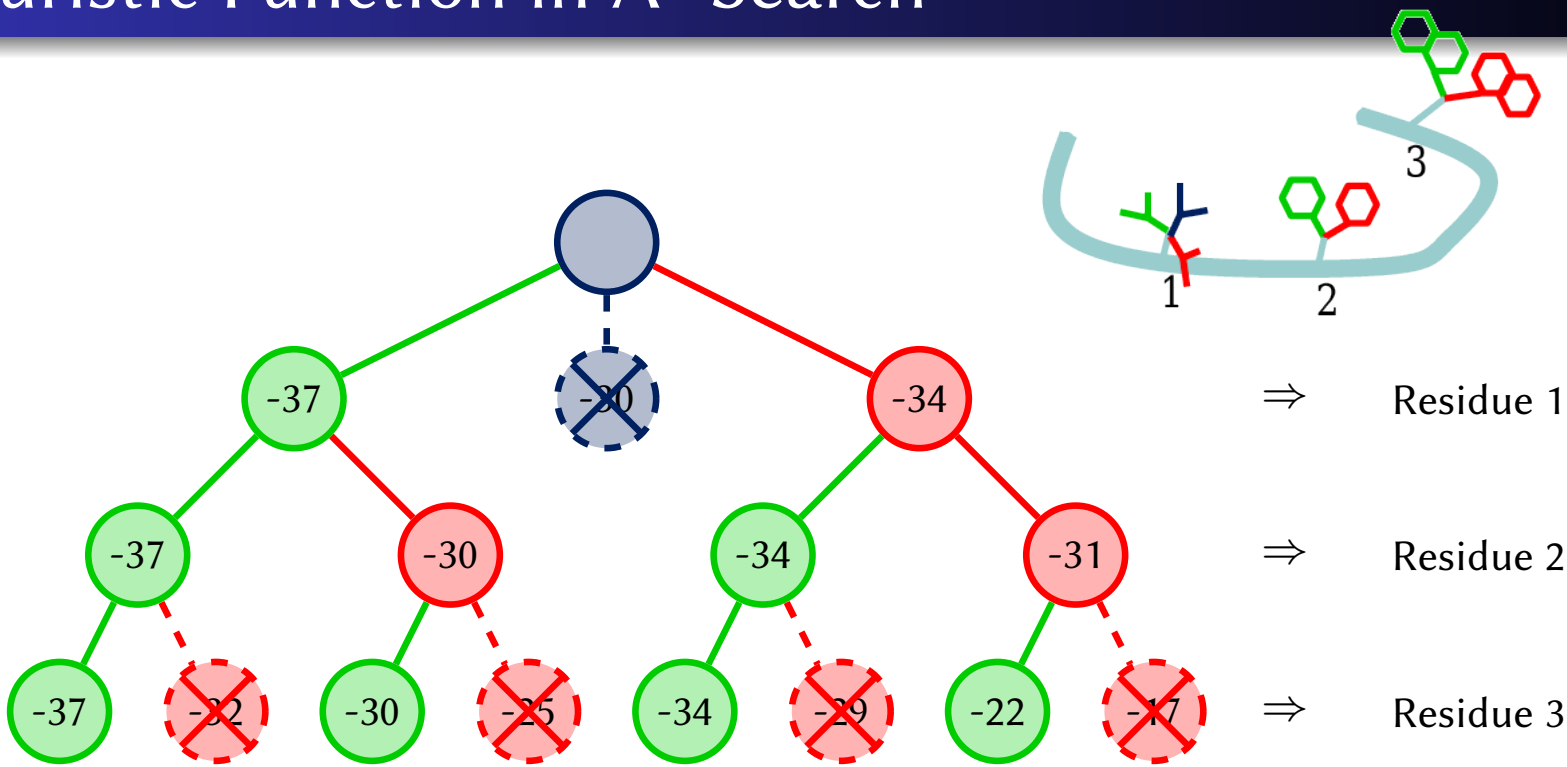
Search Algorithm



Dead End Elimination/A* Algorithm



Heuristic Function in A* Search

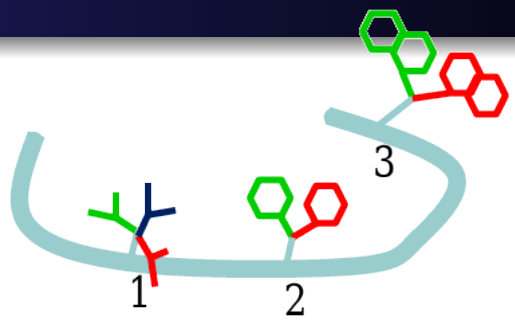


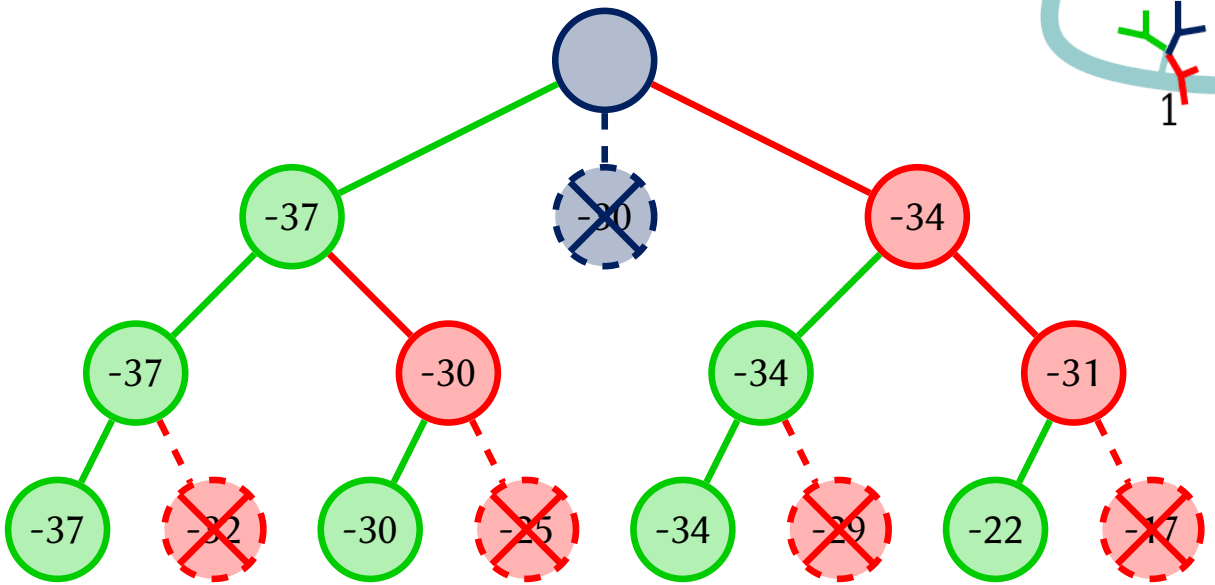
$$f(x) = g(x) + h(x)$$

$$g(x) = \sum_{i_r \in D(x)} E_1(i_r) + \sum_{i_r \in D(x)} \sum_{\substack{j_s \in D(x), \\ i<j}} E_2(i_r, j_s)$$

$$h(x) = \sum_{i \in U(x)} \min_r \left(E_1(i_r) + \sum_{j_s \in D(x)} E_2(i_r, j_s) + \sum_{k \in U(x)} \min_u E_2(i_r, k_u) \right)$$

Heuristic Function in A* Search





⇒ Residue 1

⇒ Residue 2

⇒ Residue 3

$$f(x) = g(x) + h(x) \qquad \Longrightarrow$$

Admissible

$$g(x) = \sum_{i_r \in D(x)} E_1(i_r) + \sum_{i_r \in D(x)} \sum_{\substack{j_s \in D(x), \\ i<j}} E_2(i_r, j_s)$$

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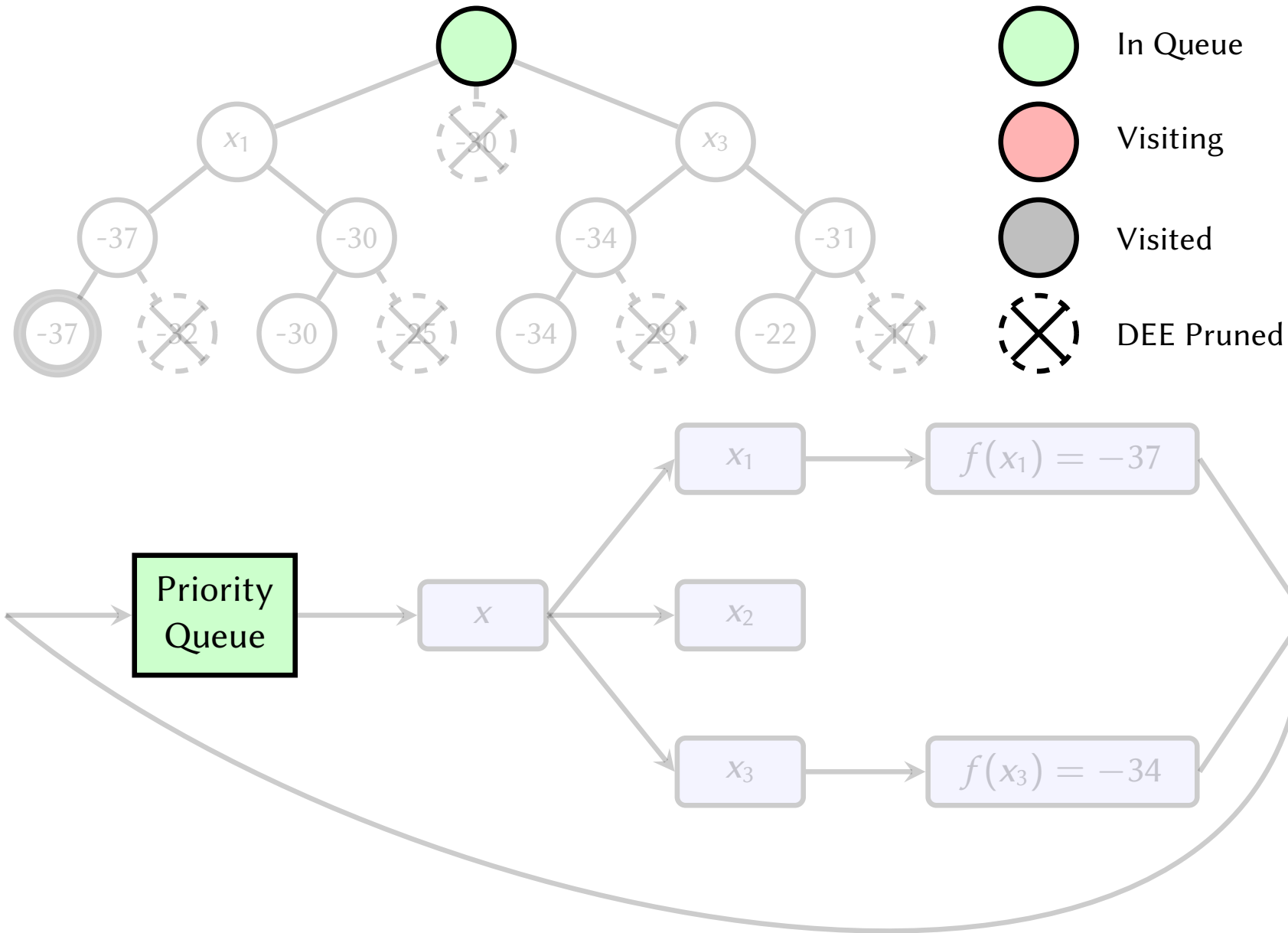
A* Search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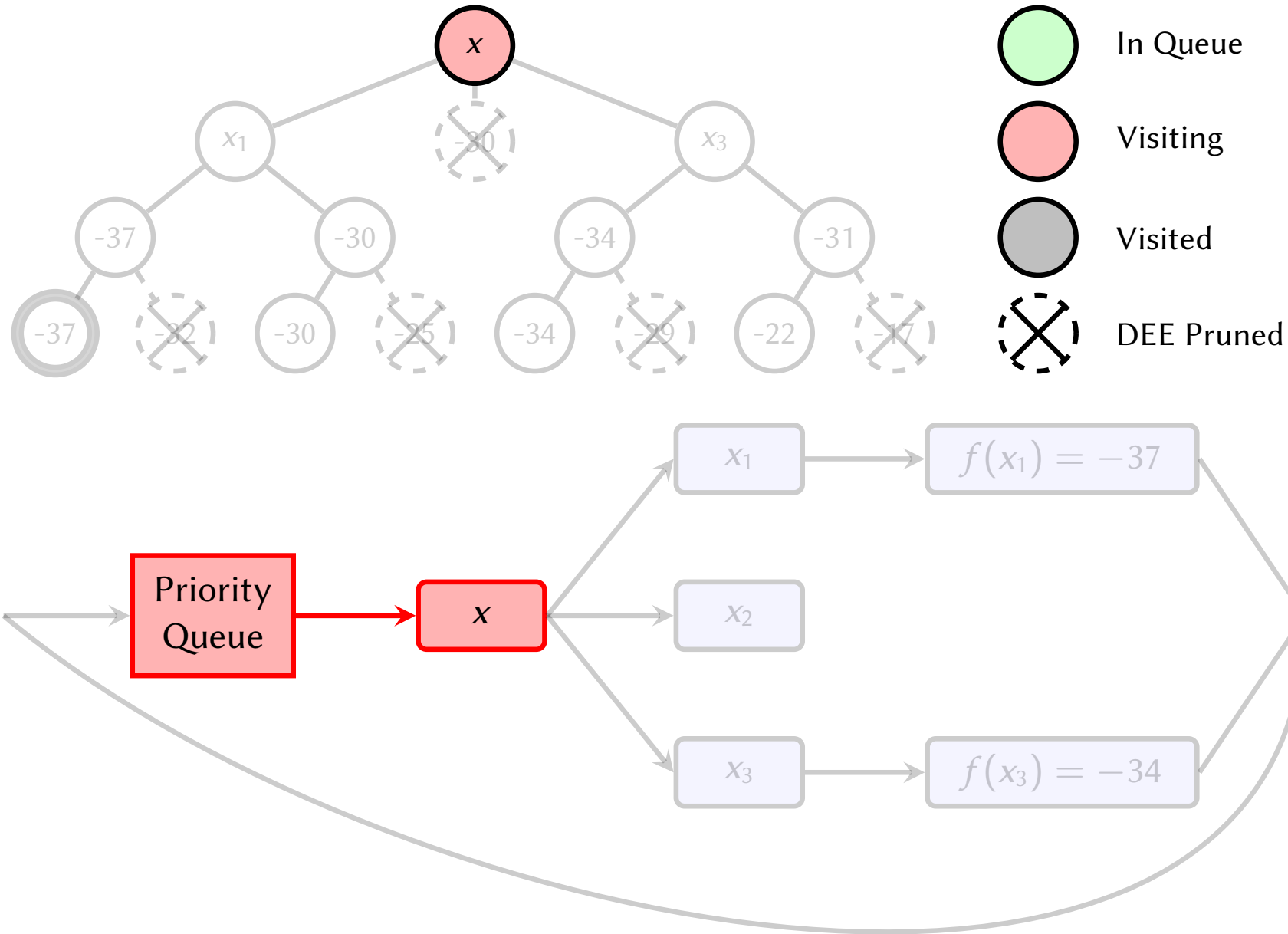
$f(x_1) = -37$
$f(x_3) = -34$

A* Search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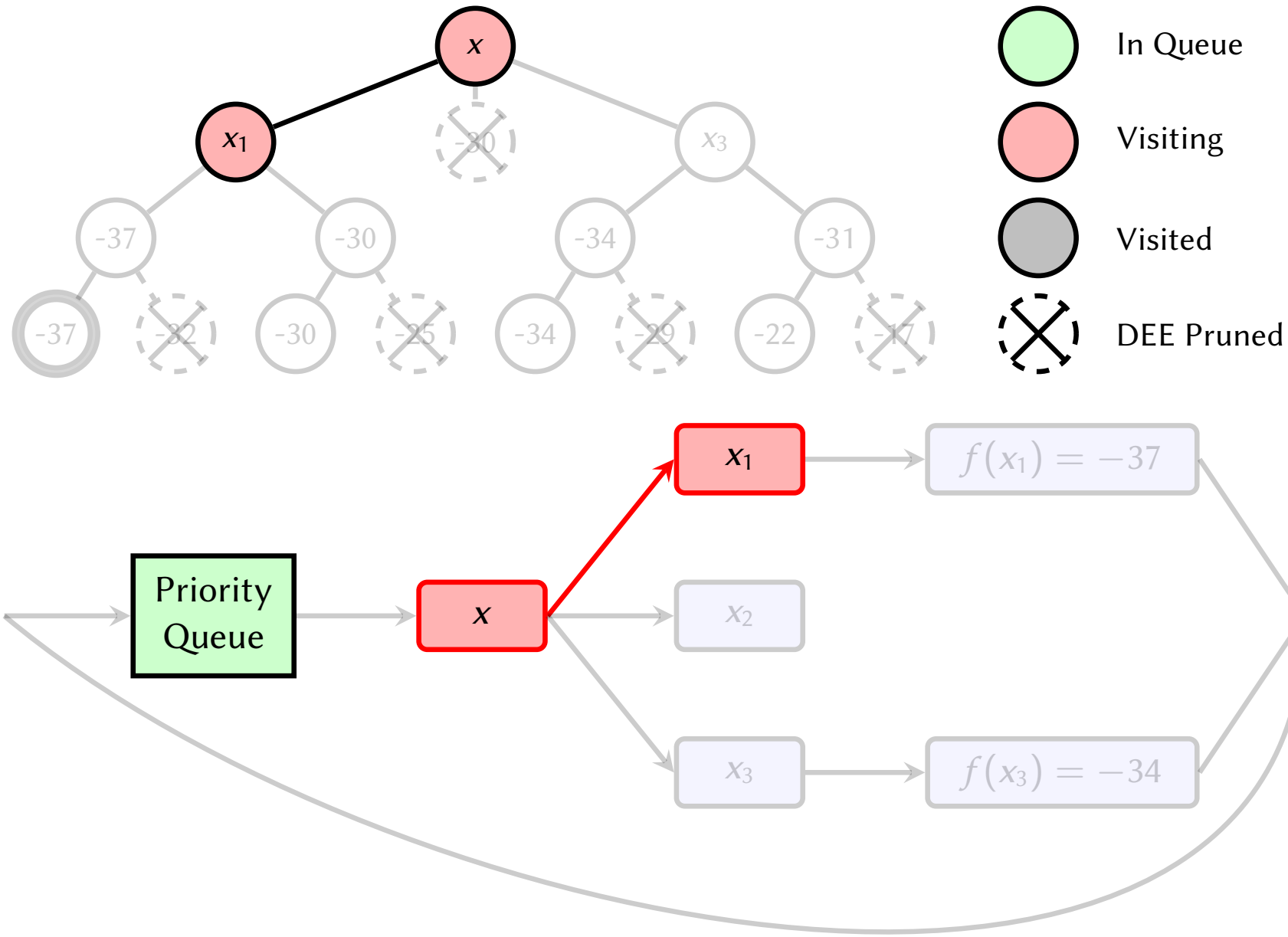
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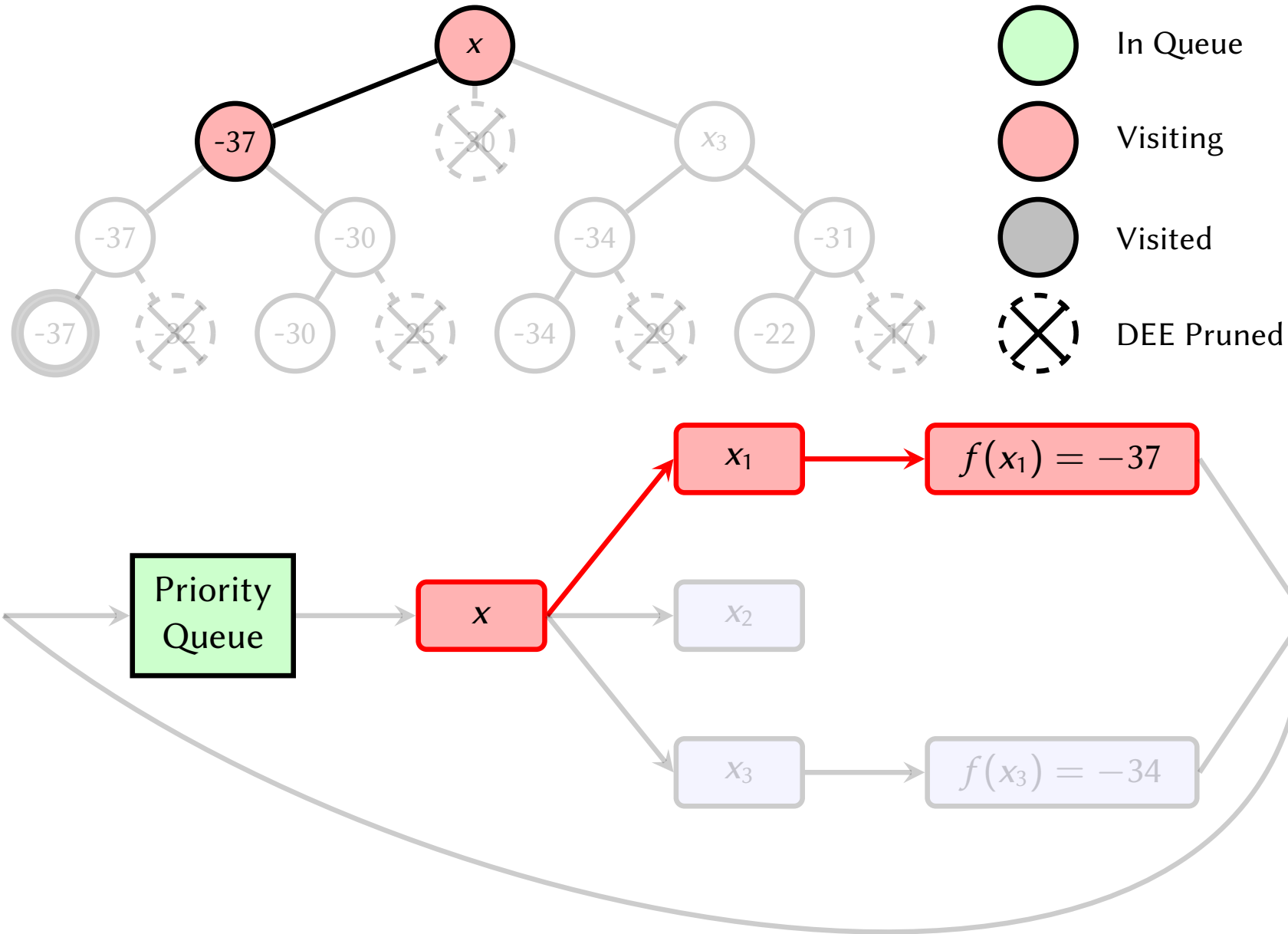
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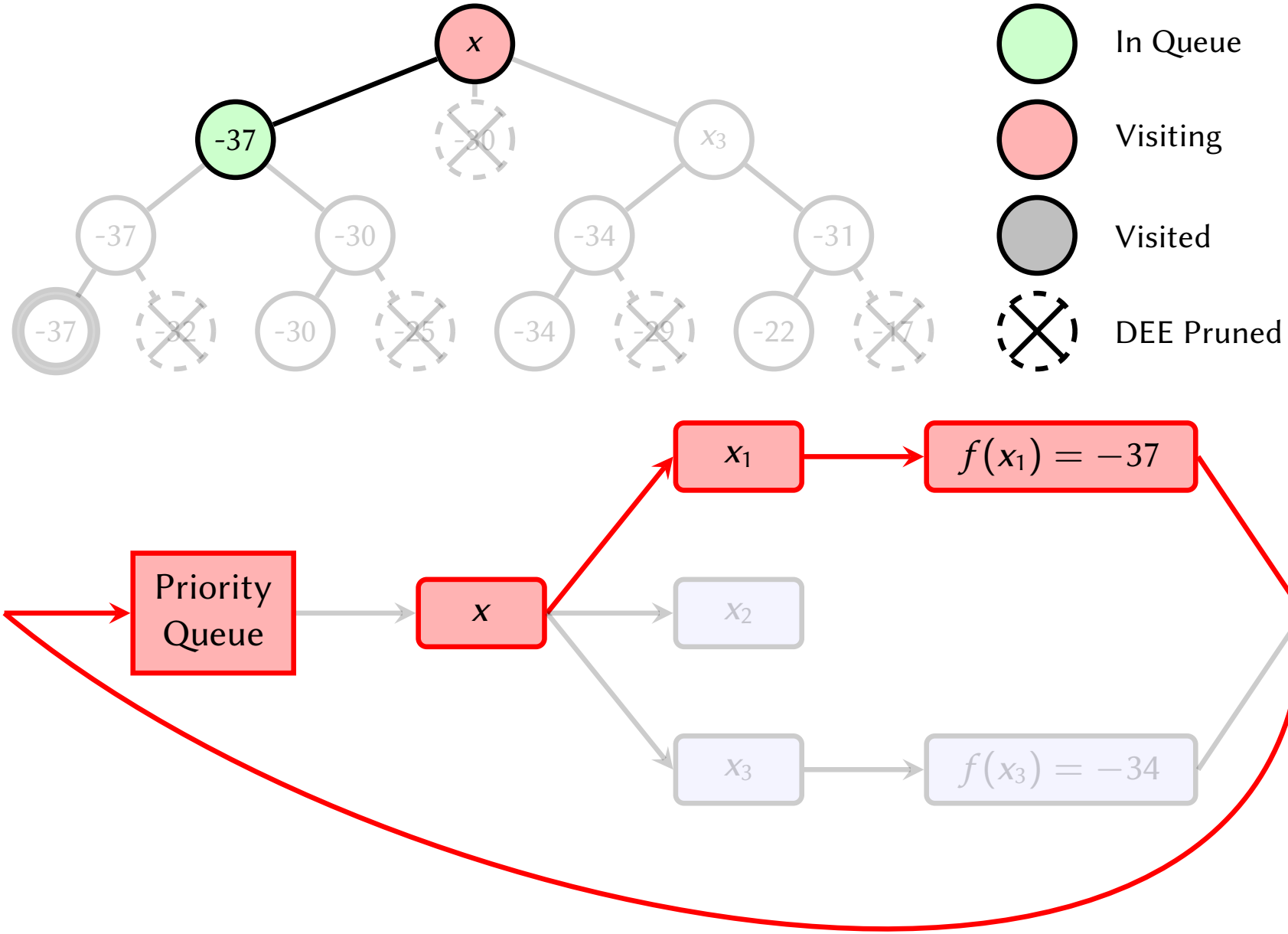
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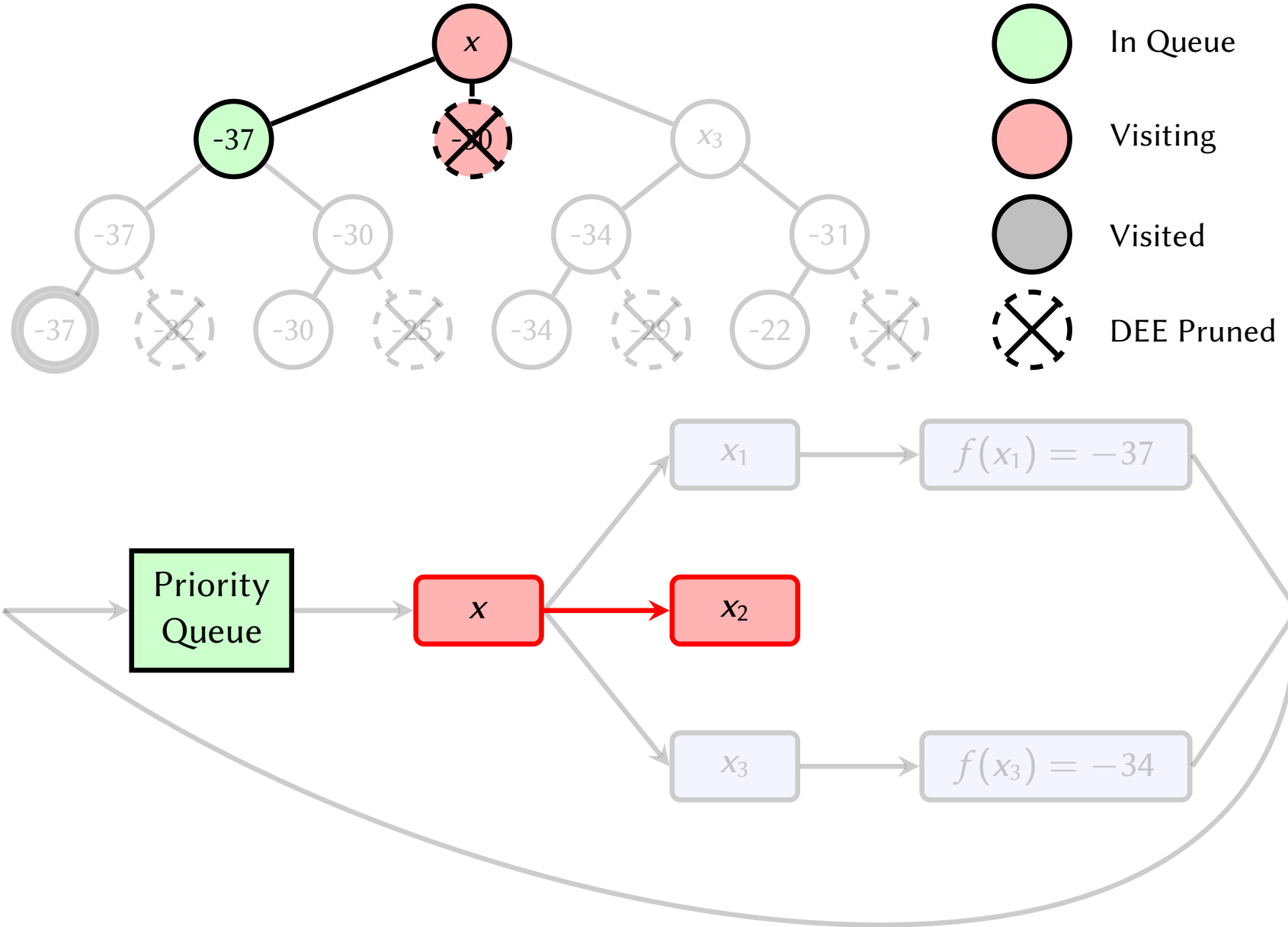
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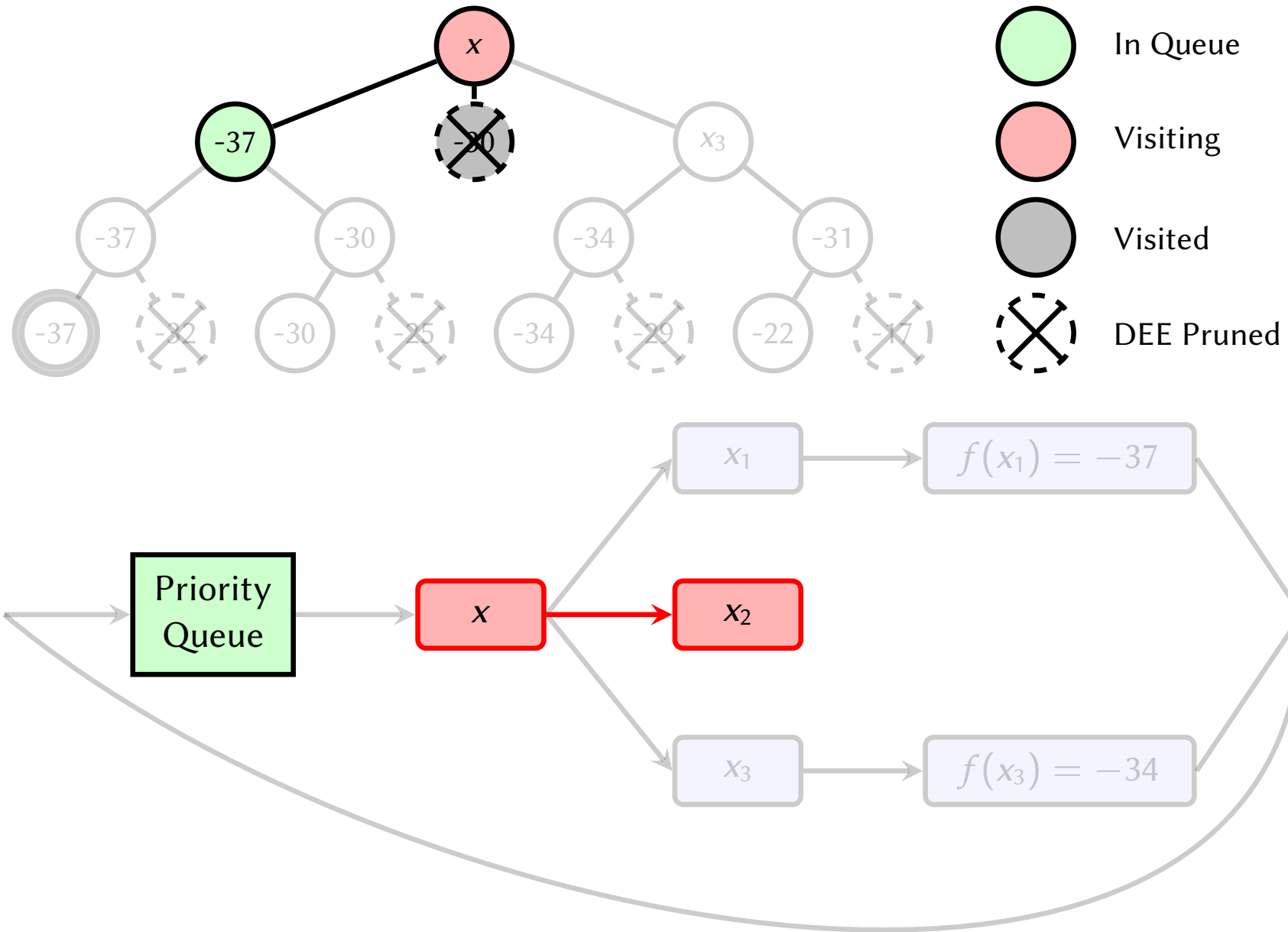
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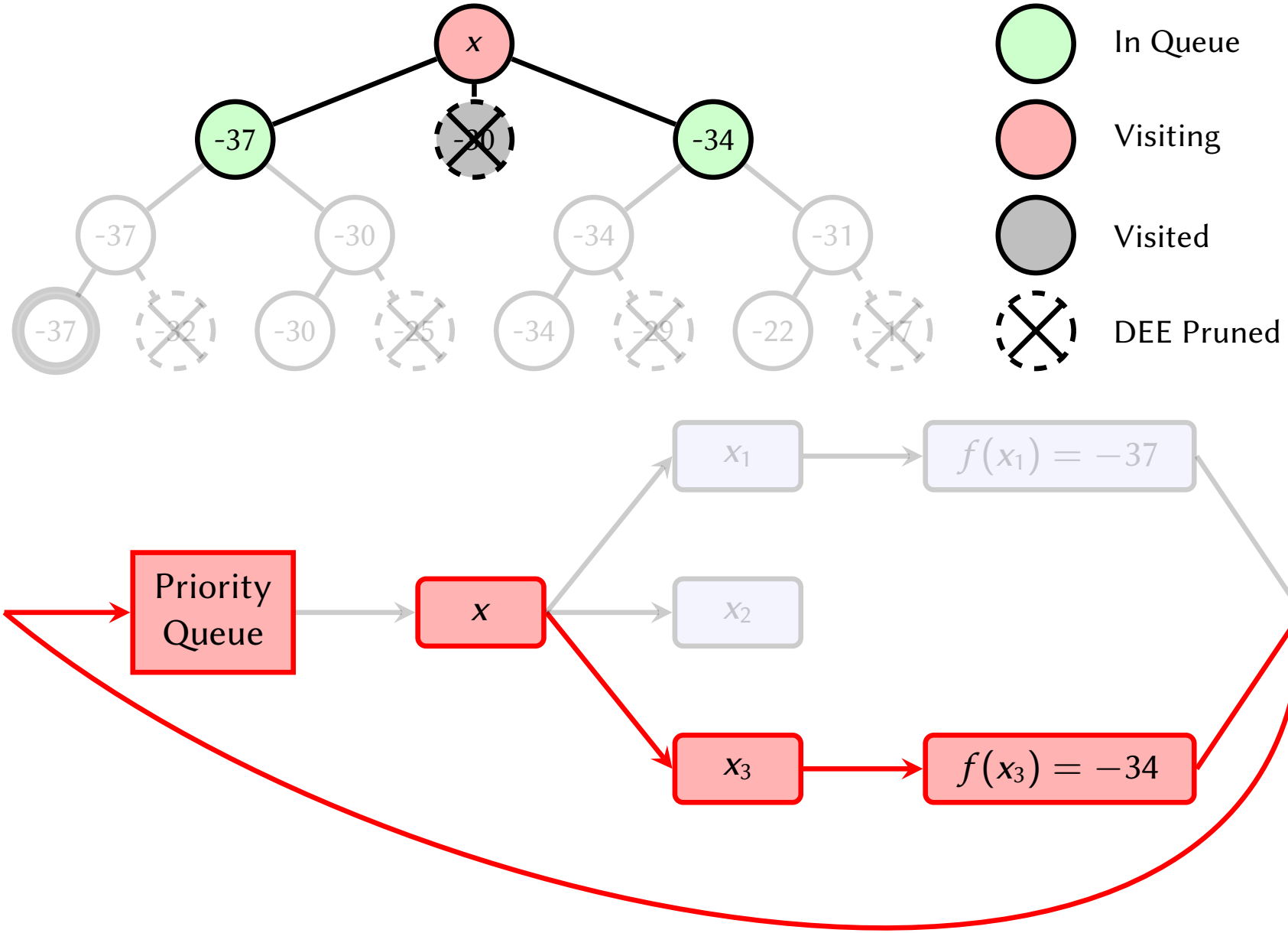
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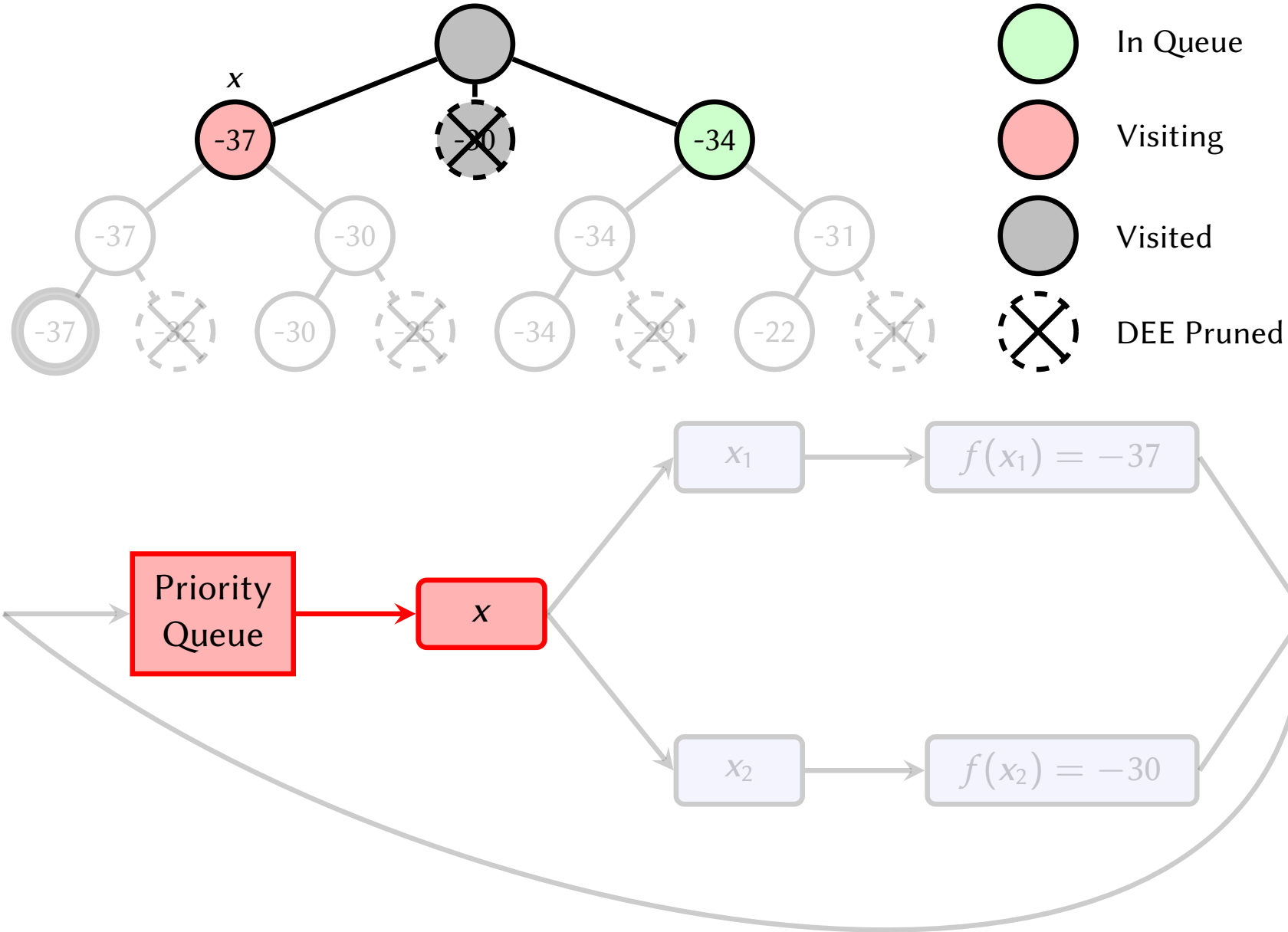
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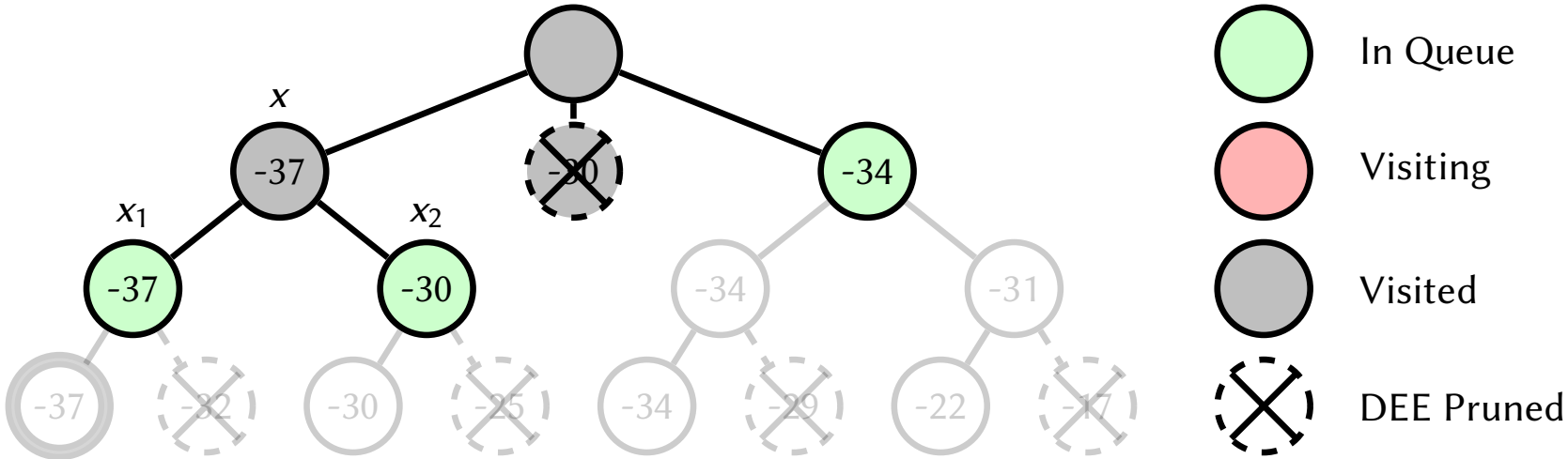
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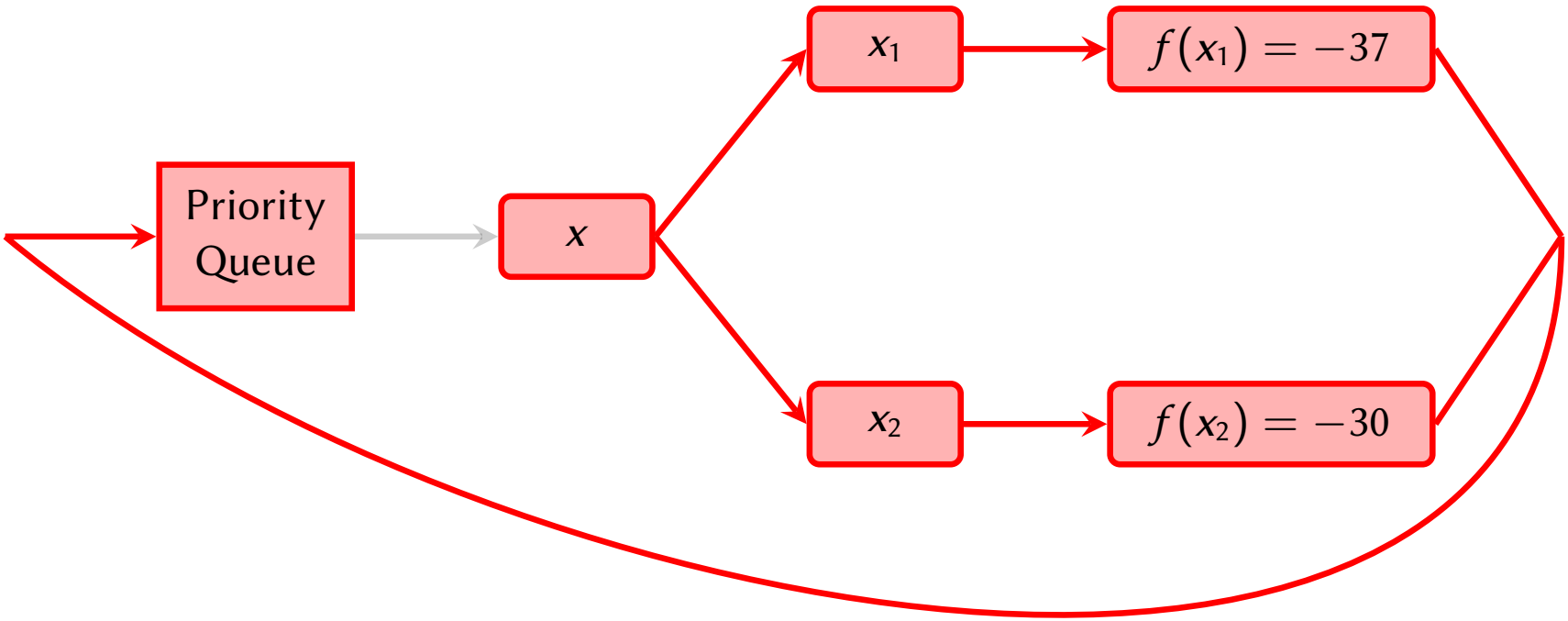
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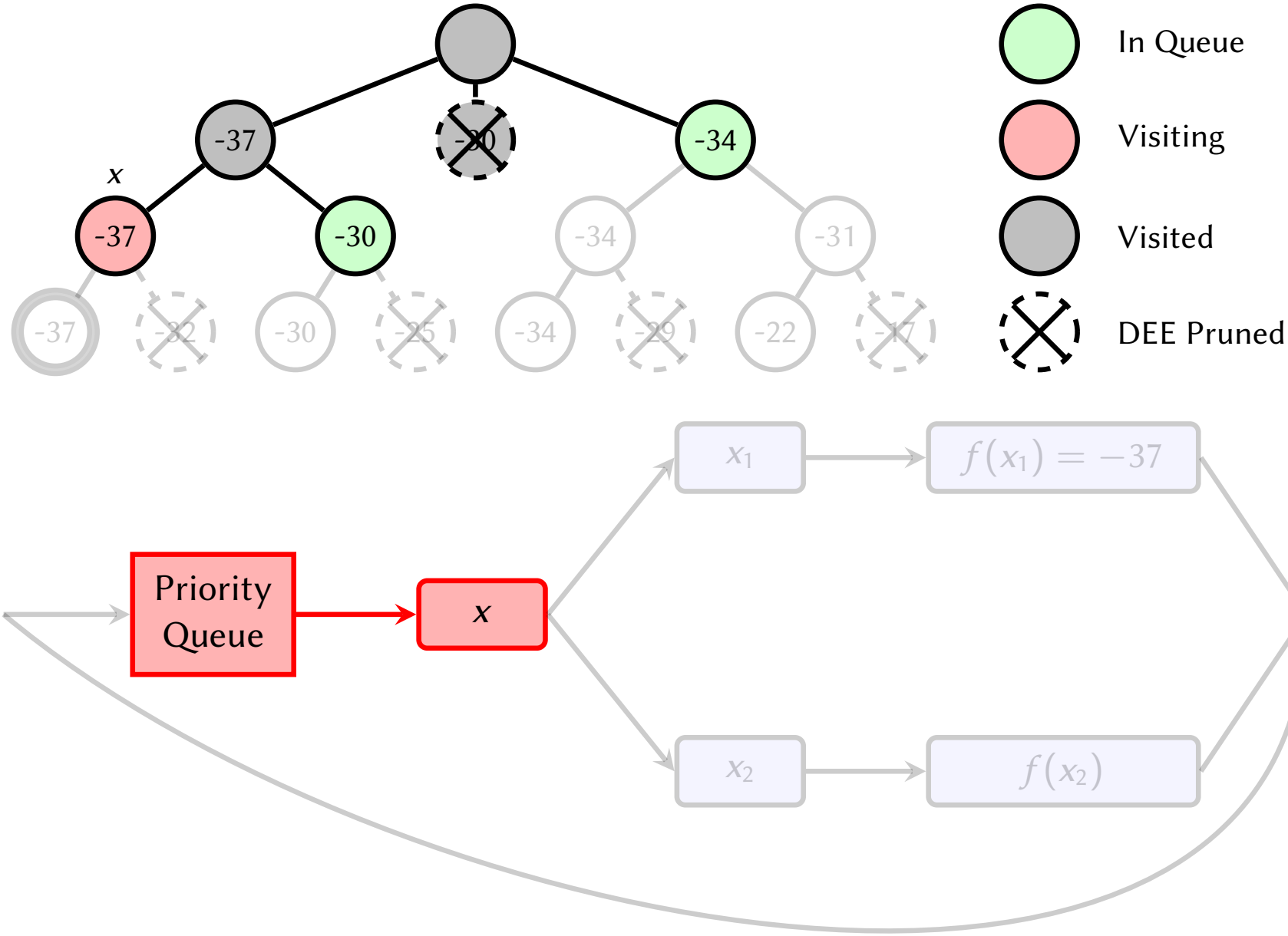
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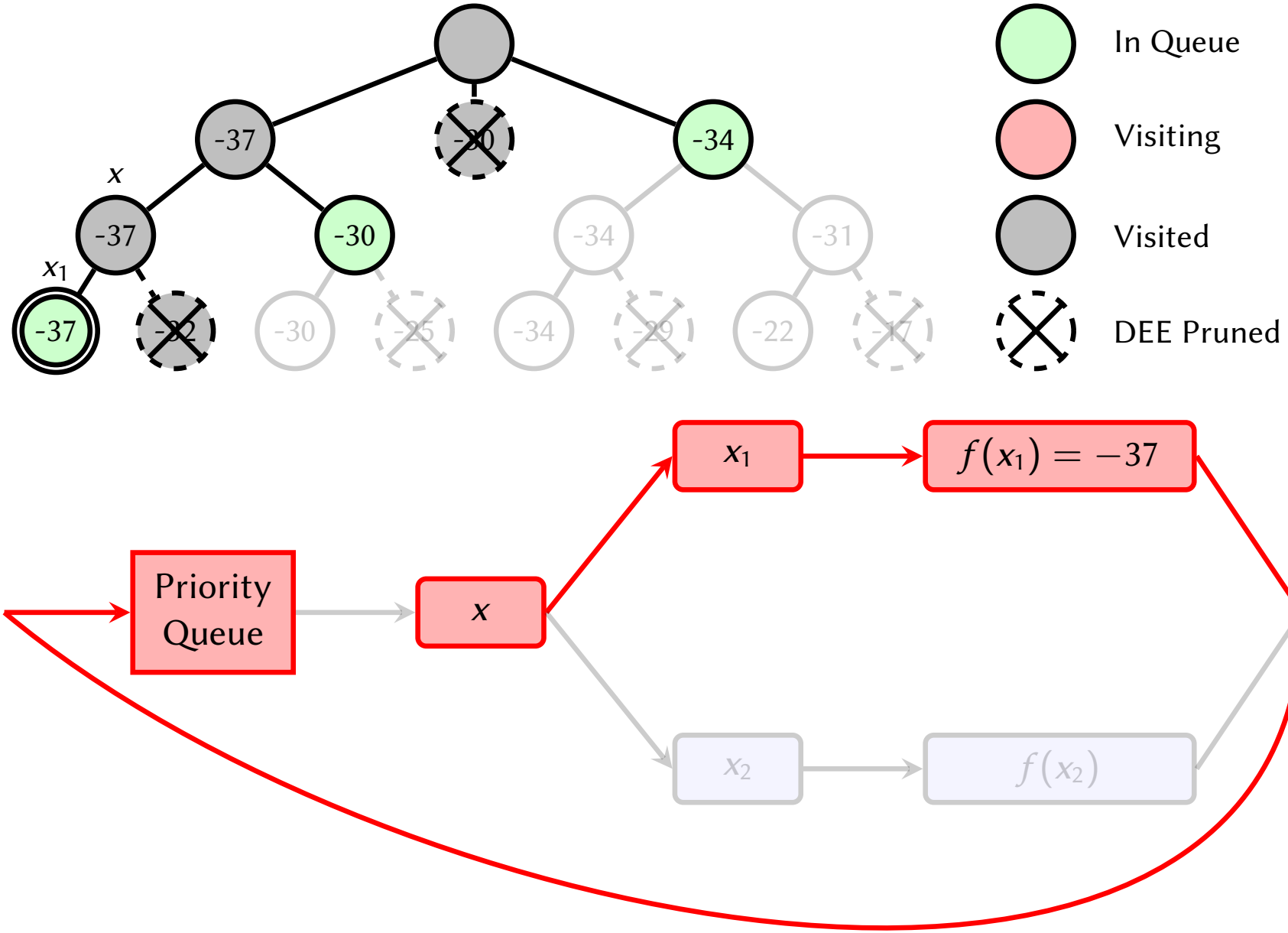
A* Search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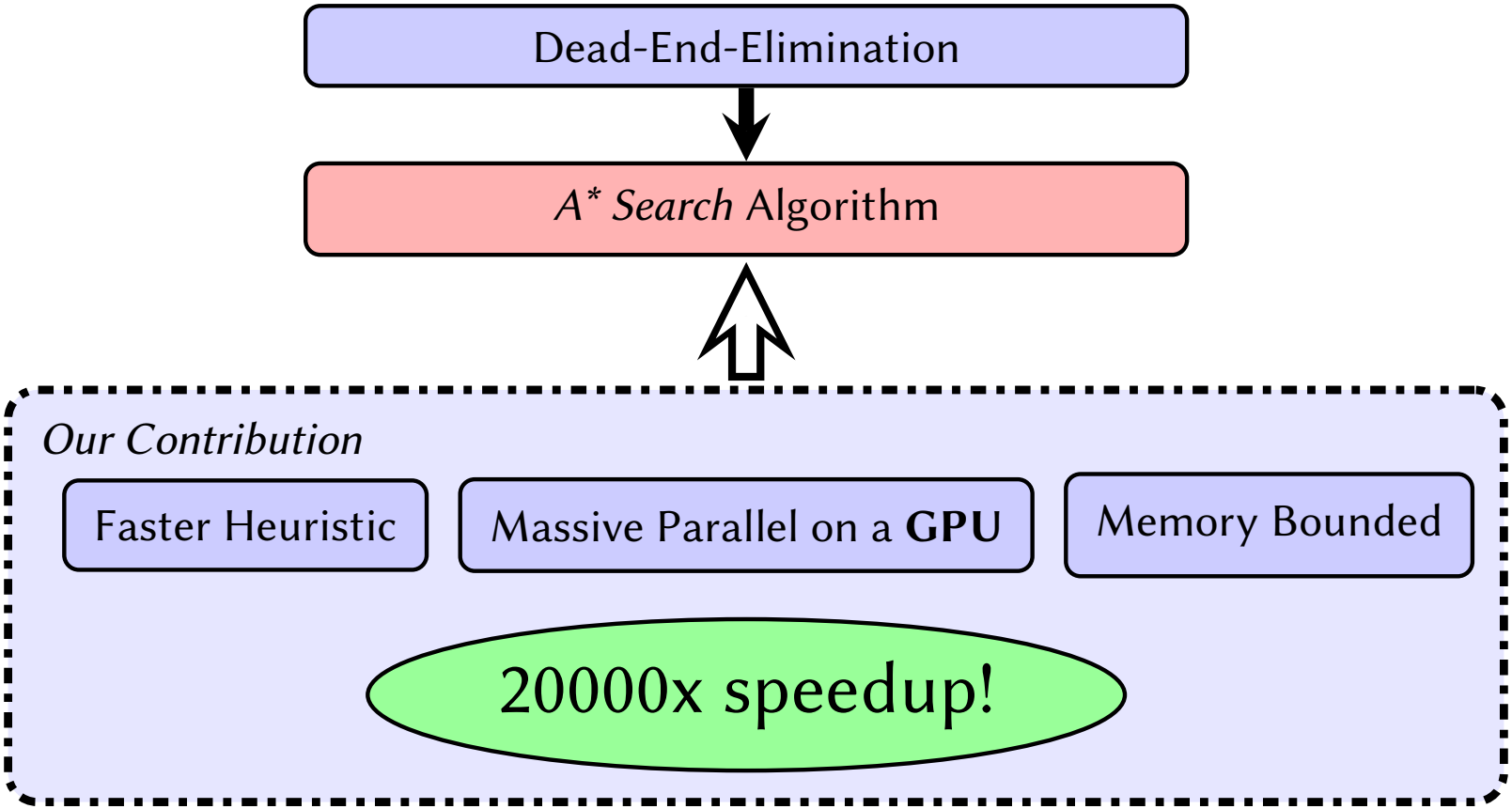
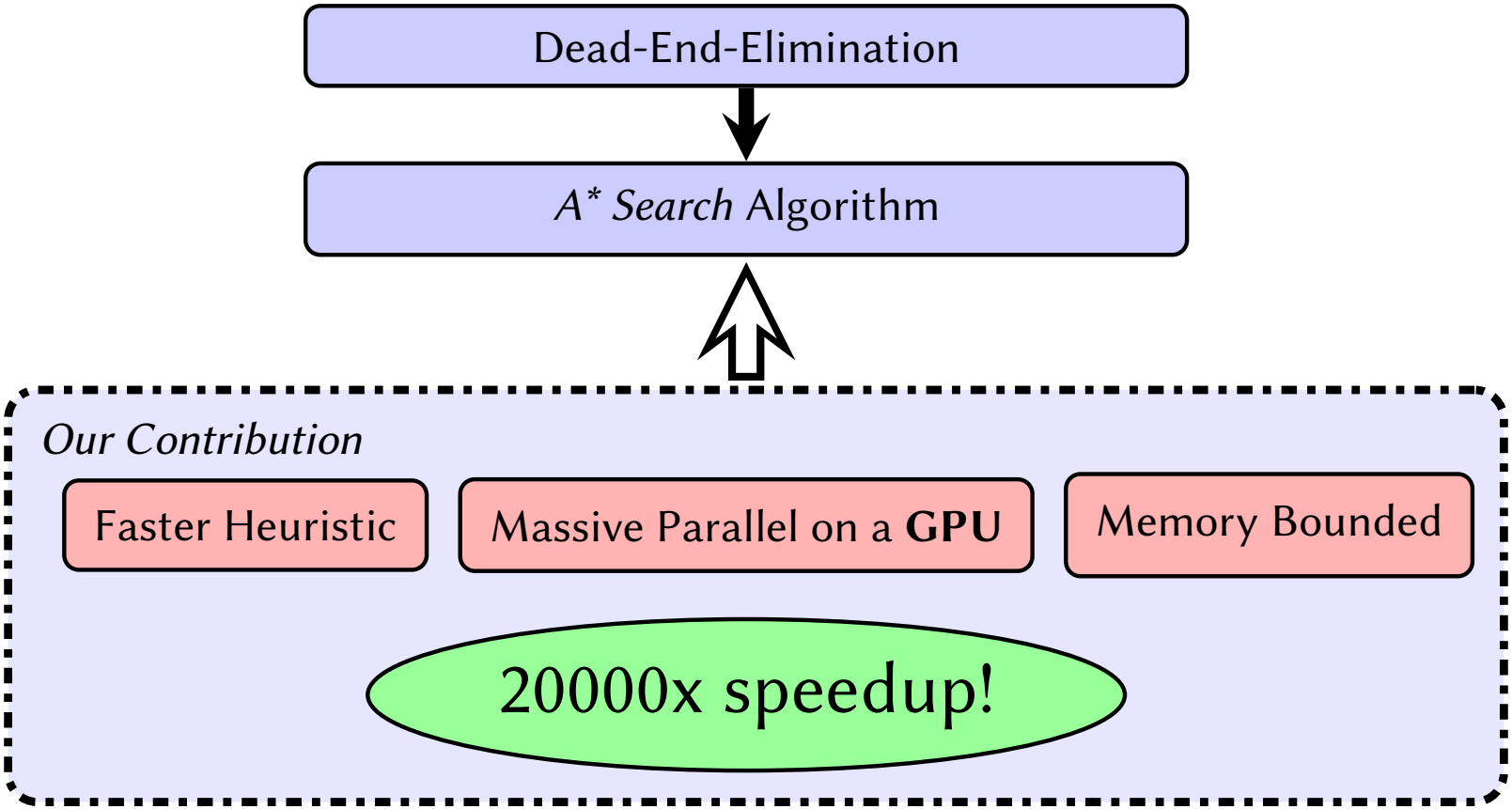
Our Contribution

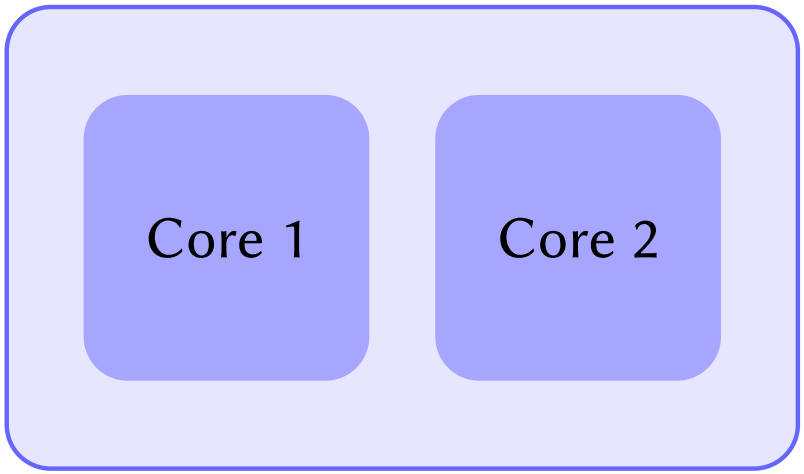


Our Contribution



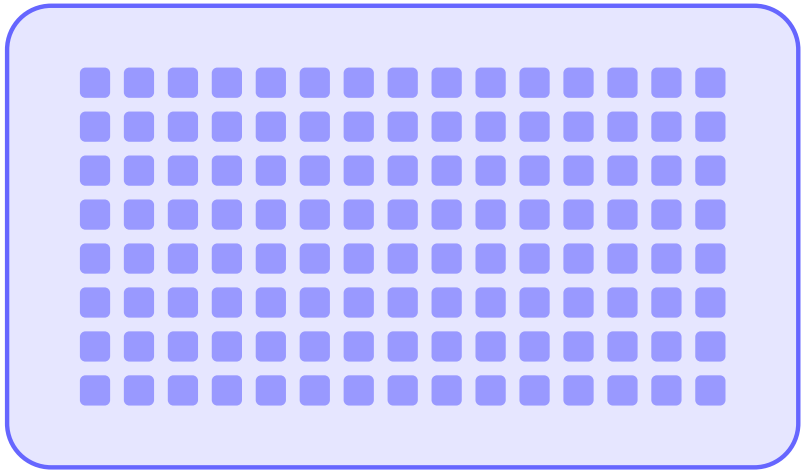
A Brief Concept to GPU

CPU (several cores)



- ☺ Decent single thread performance
- ☹ Limited in parallelism

GPU (thousands of cores)

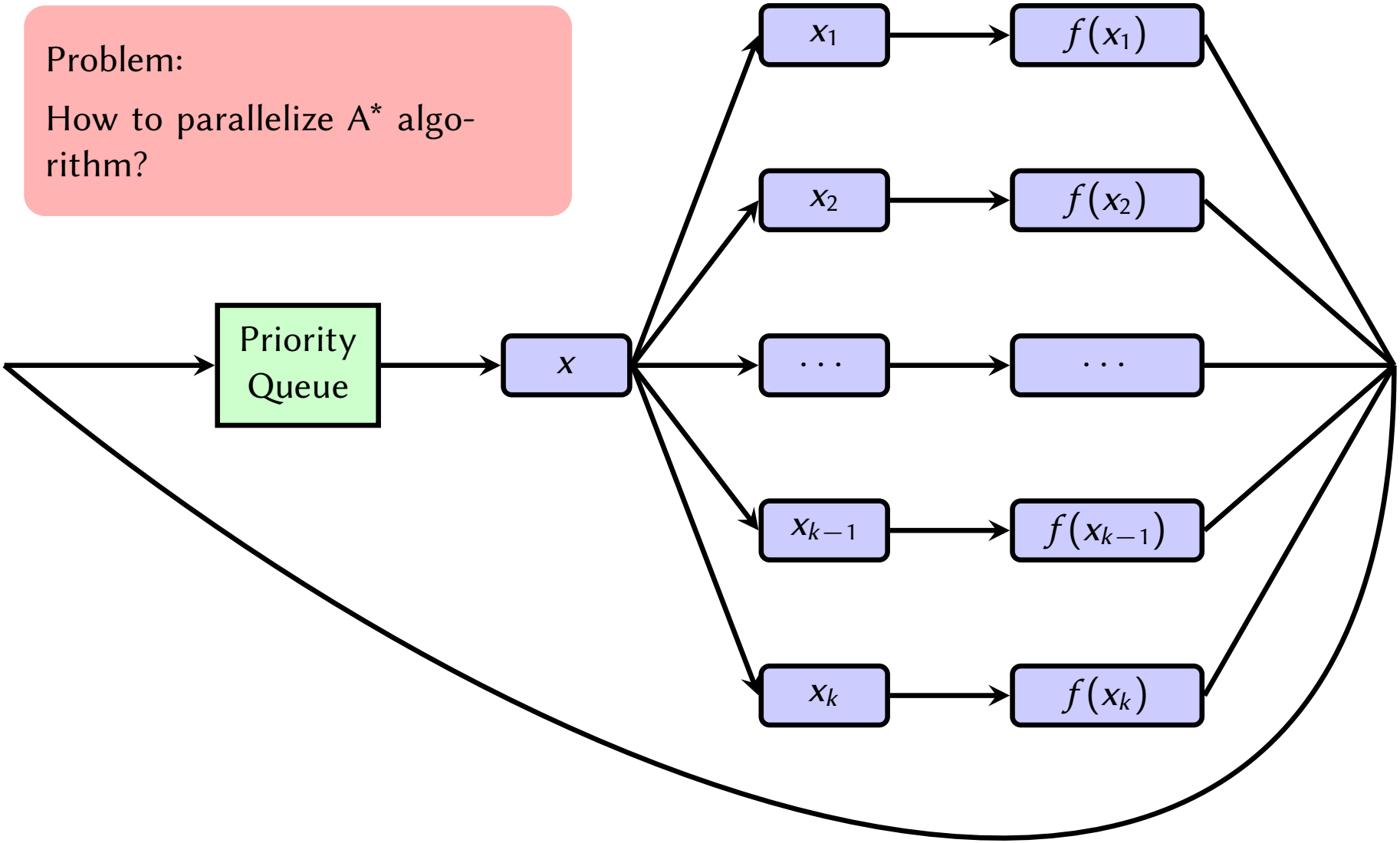


- ☺ More computational units
- ☺ Energy efficient
- ☹ Need massive parallelism

First Level of Parallelism

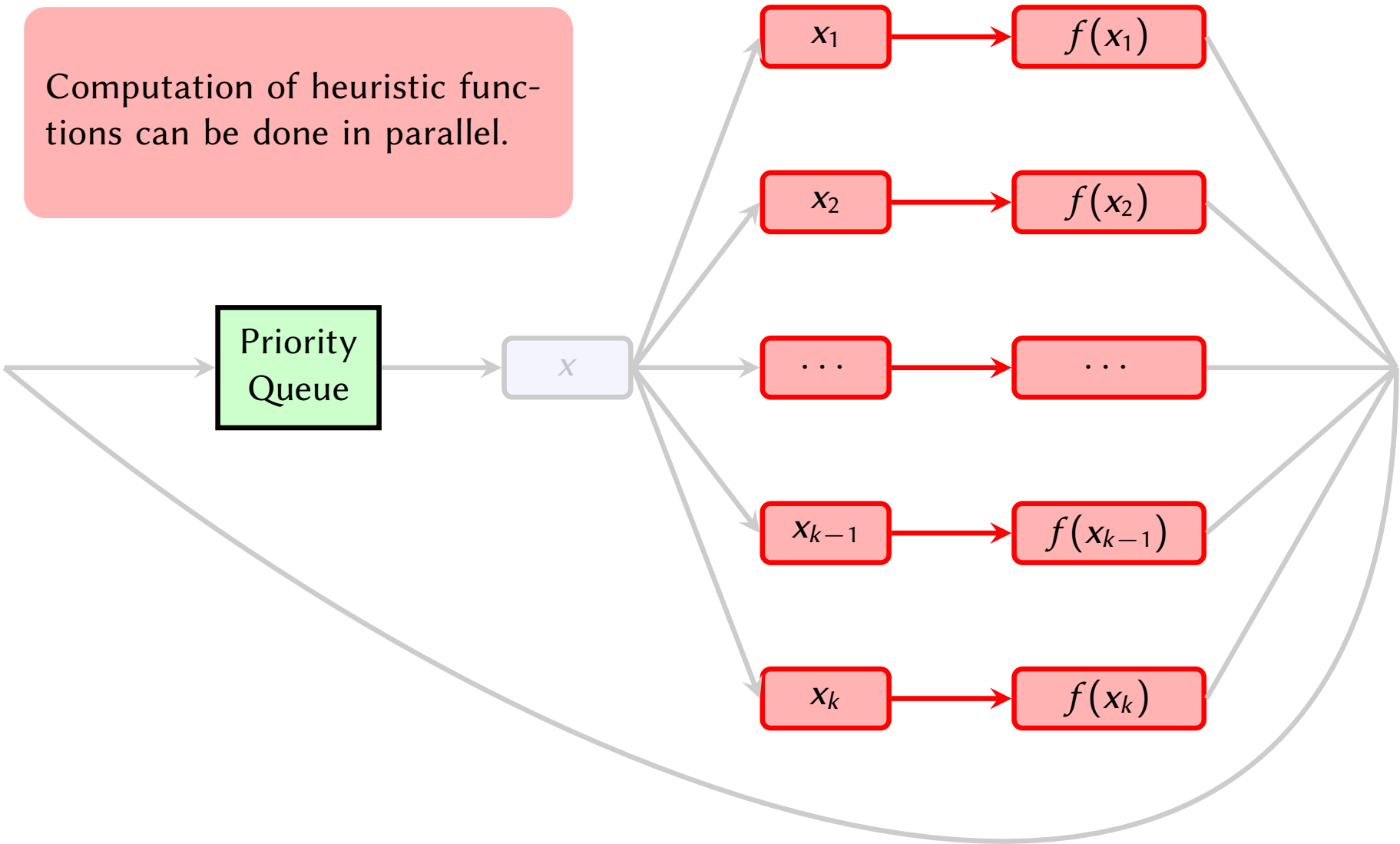
Problem:

How to parallelize A* algorithm?



First Level of Parallelism

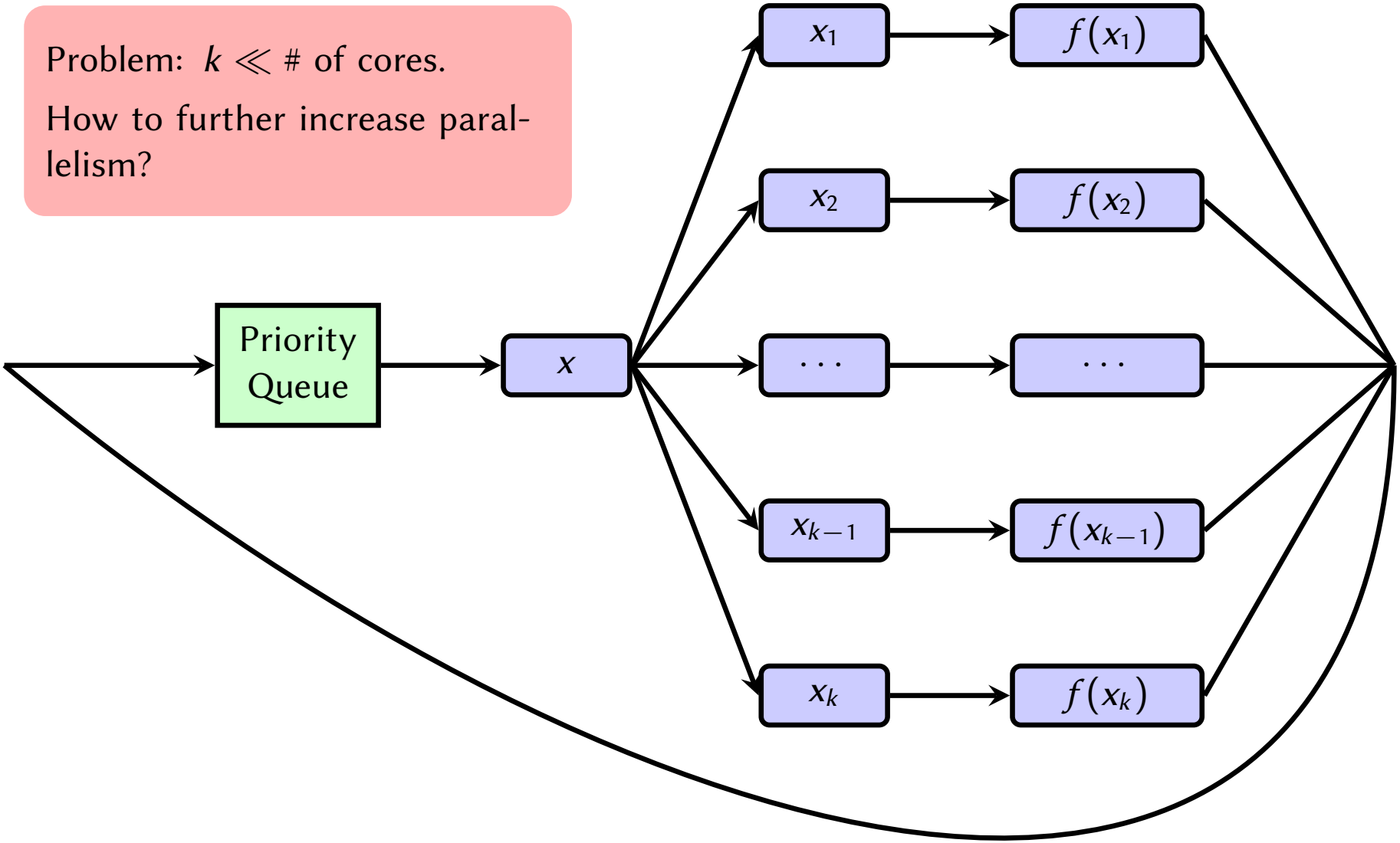
Computation of heuristic functions can be done in parallel.



First Level of Parallelism

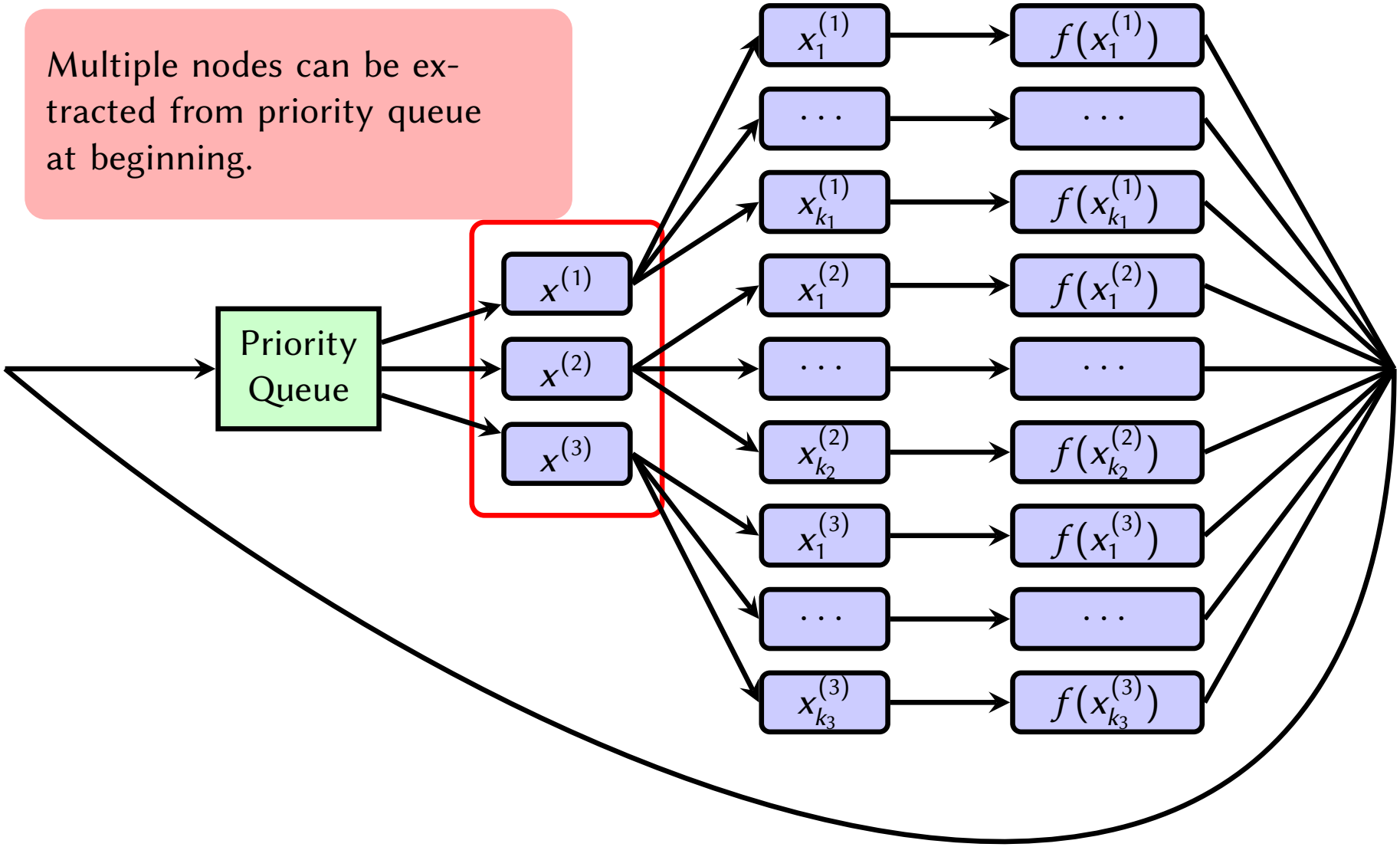
Problem: $k \ll$ # of cores.

How to further increase parallelism?

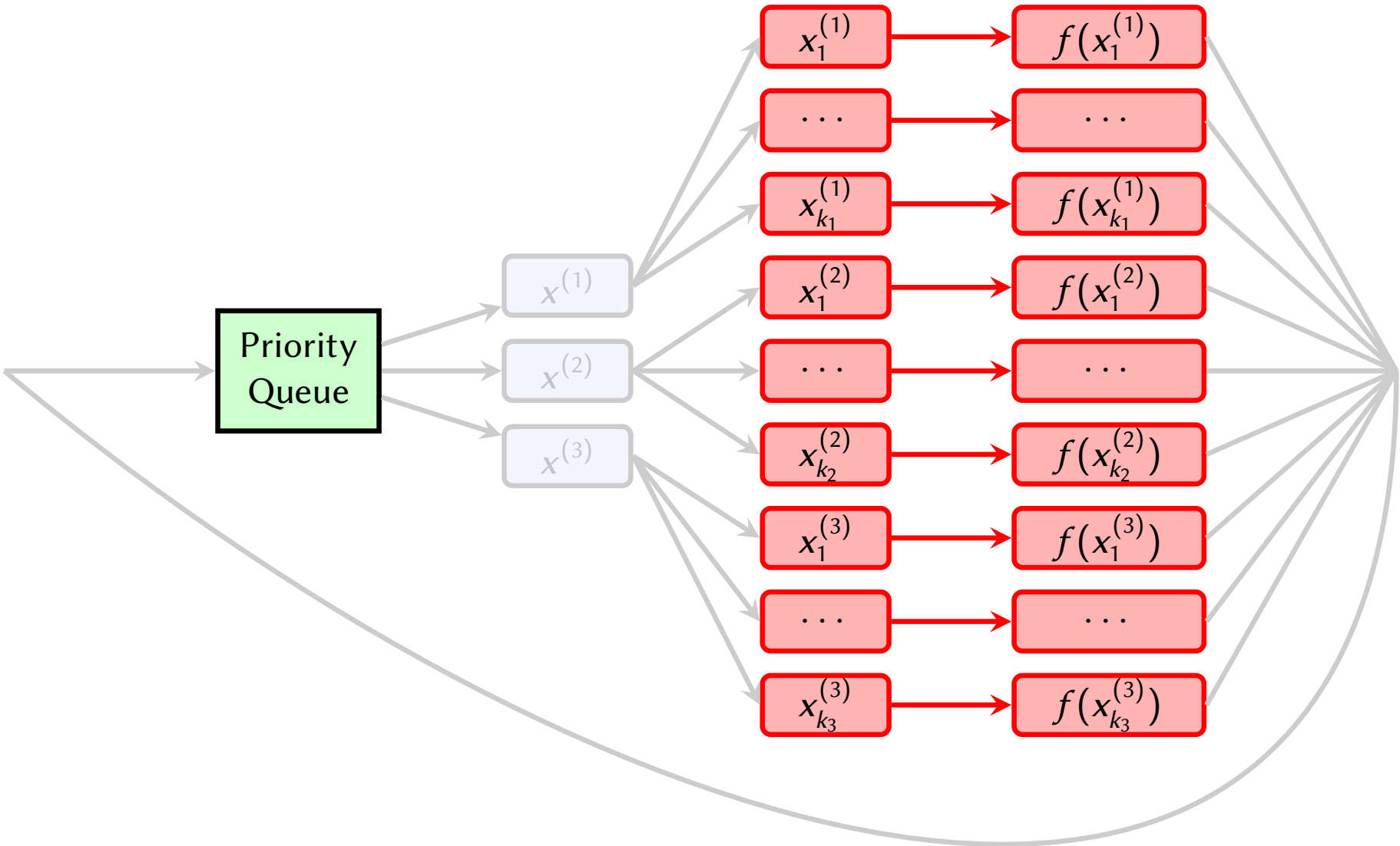


One Possible Solution

Multiple nodes can be extracted from priority queue at beginning.



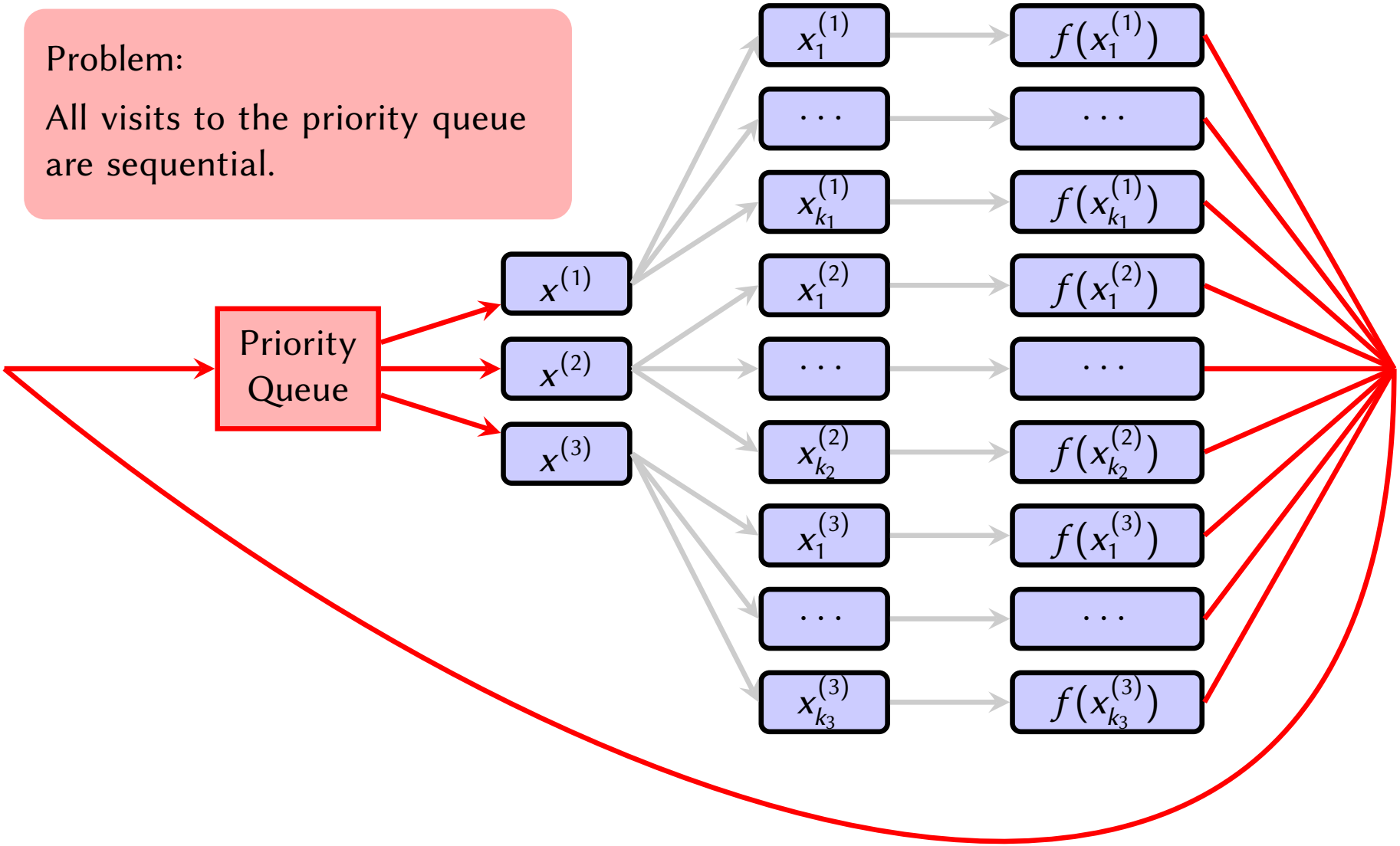
One Possible Solution



One Possible Solution

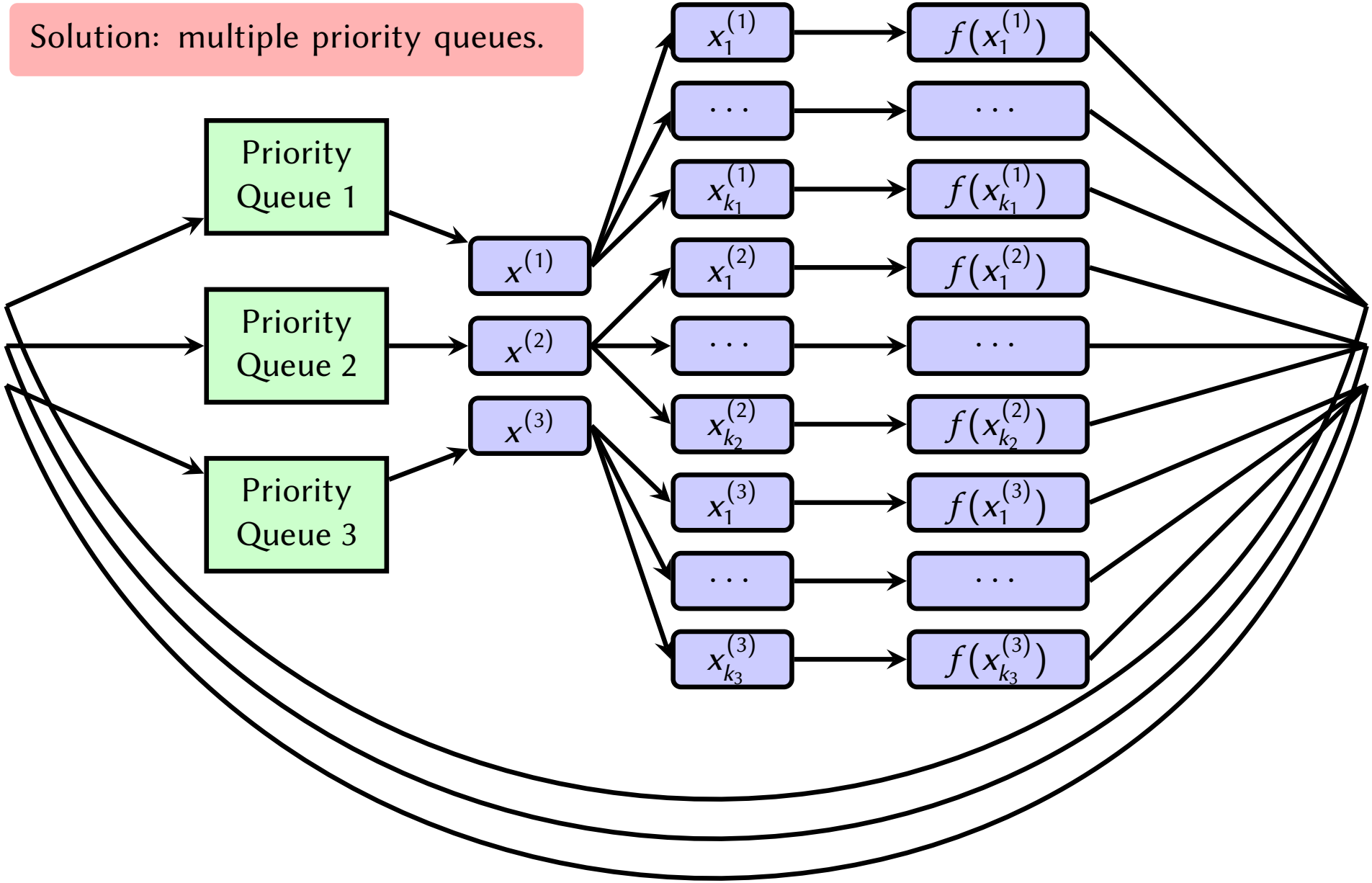
Problem:

All visits to the priority queue are sequential.



Full Parallelization of A* Search Algorithm

Solution: multiple priority queues.



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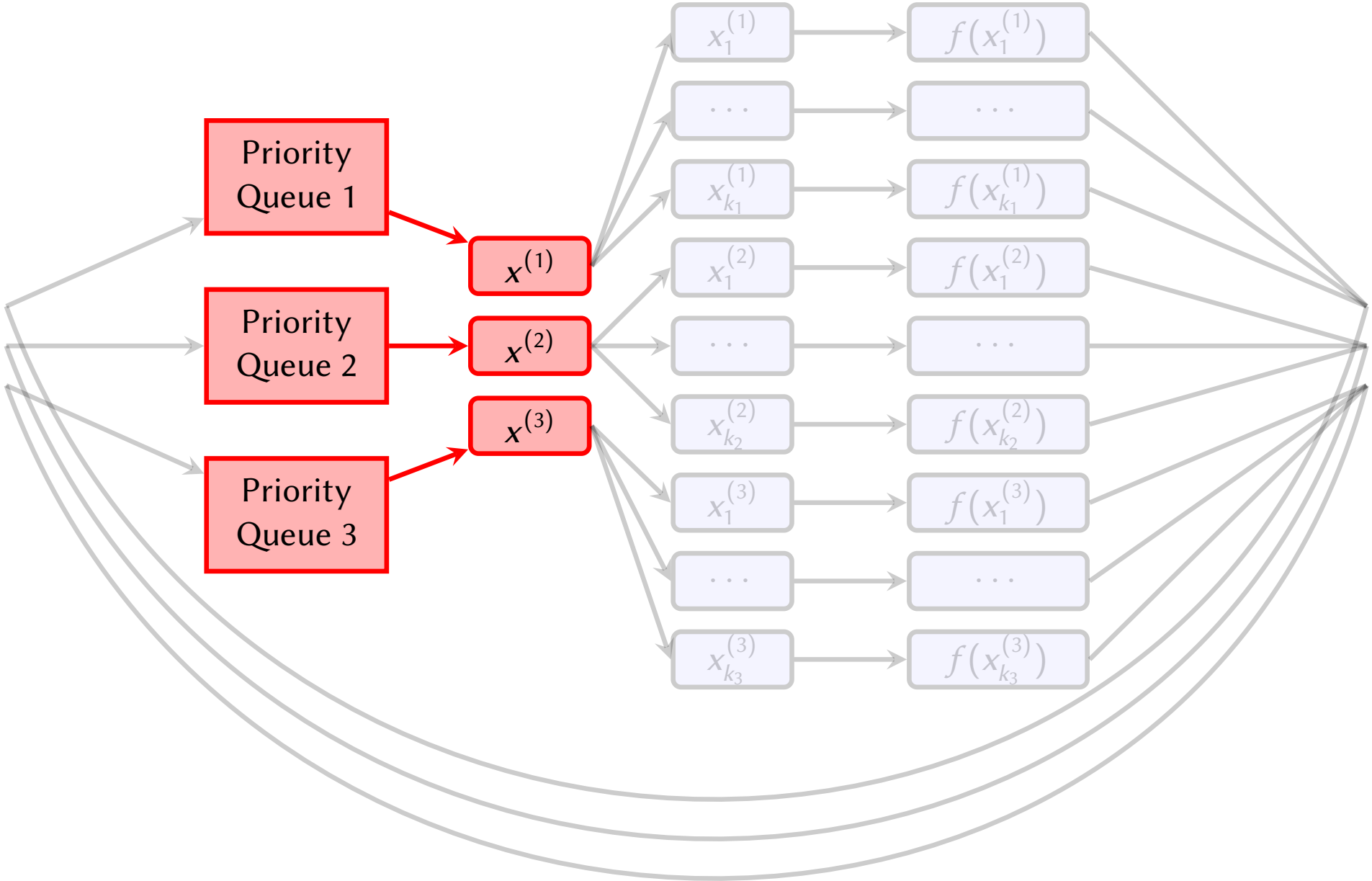

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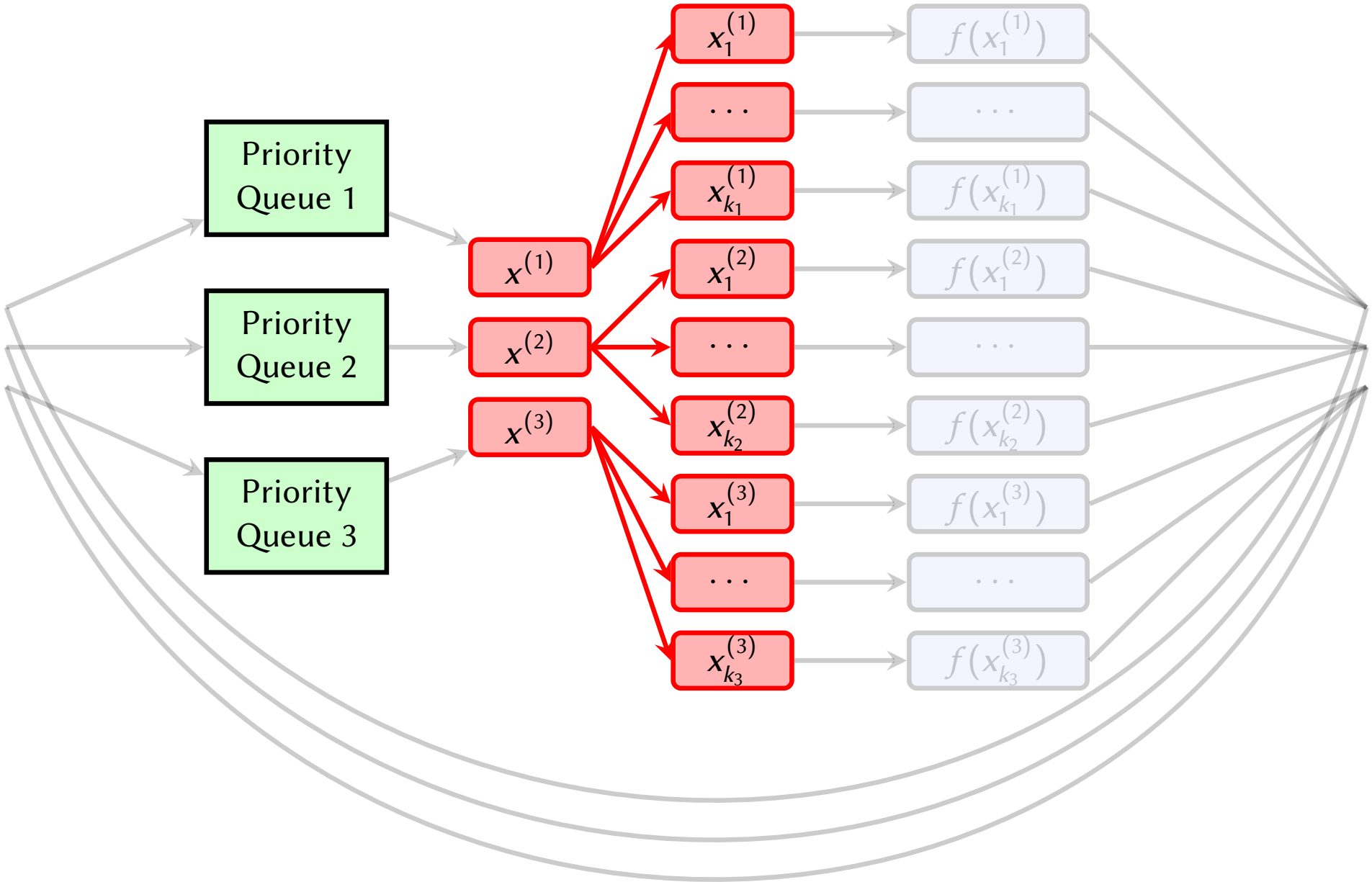

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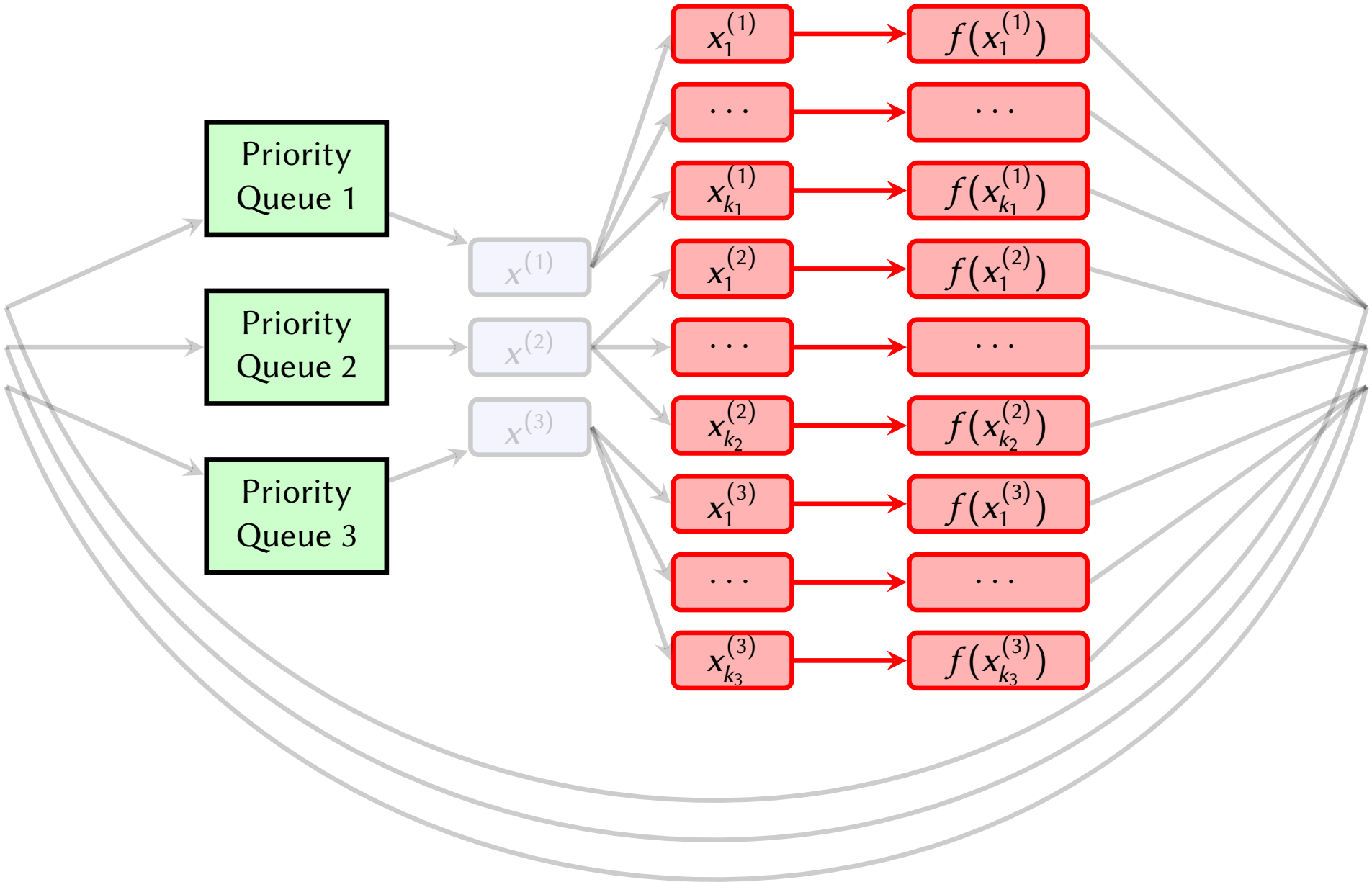

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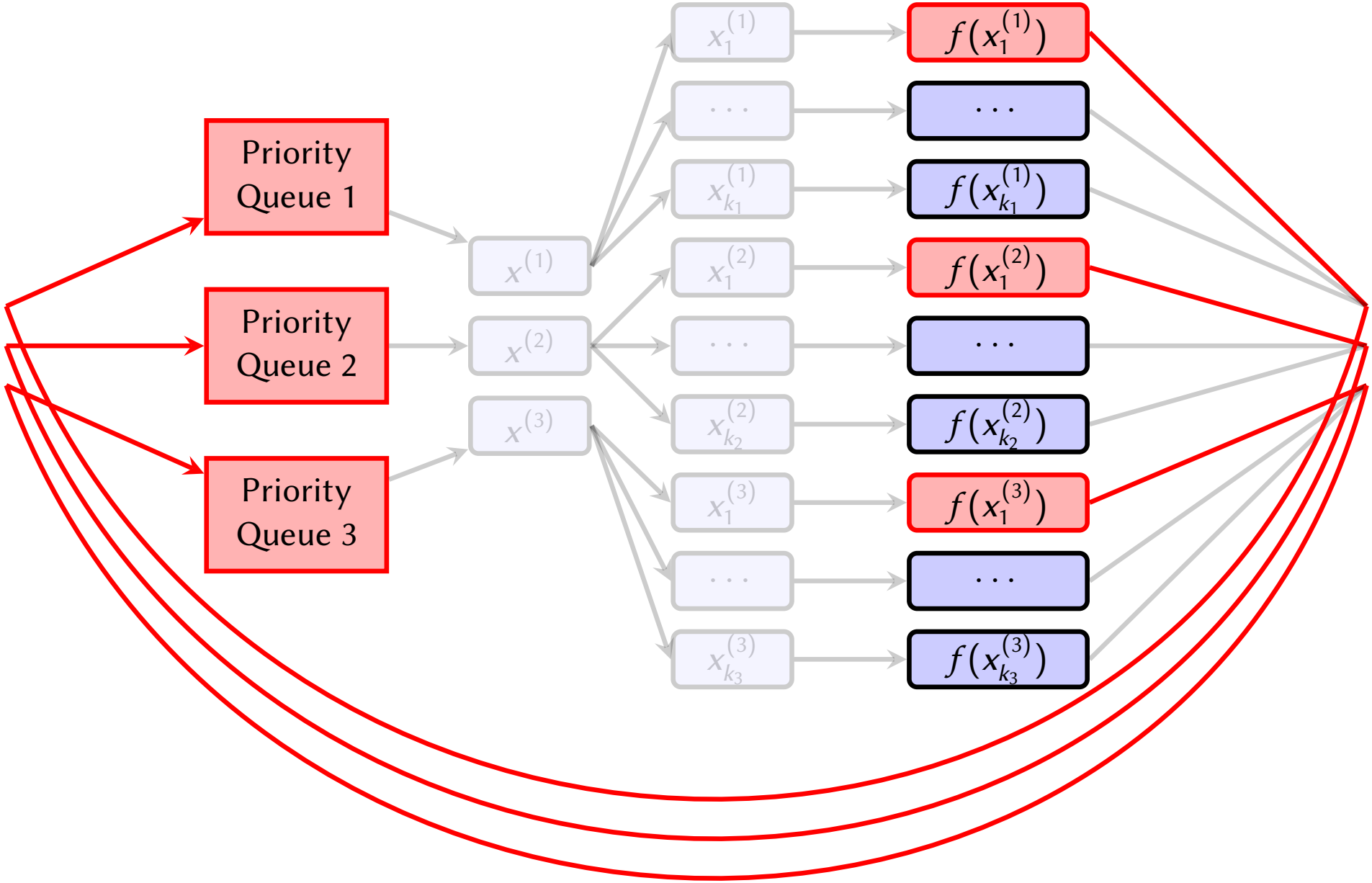

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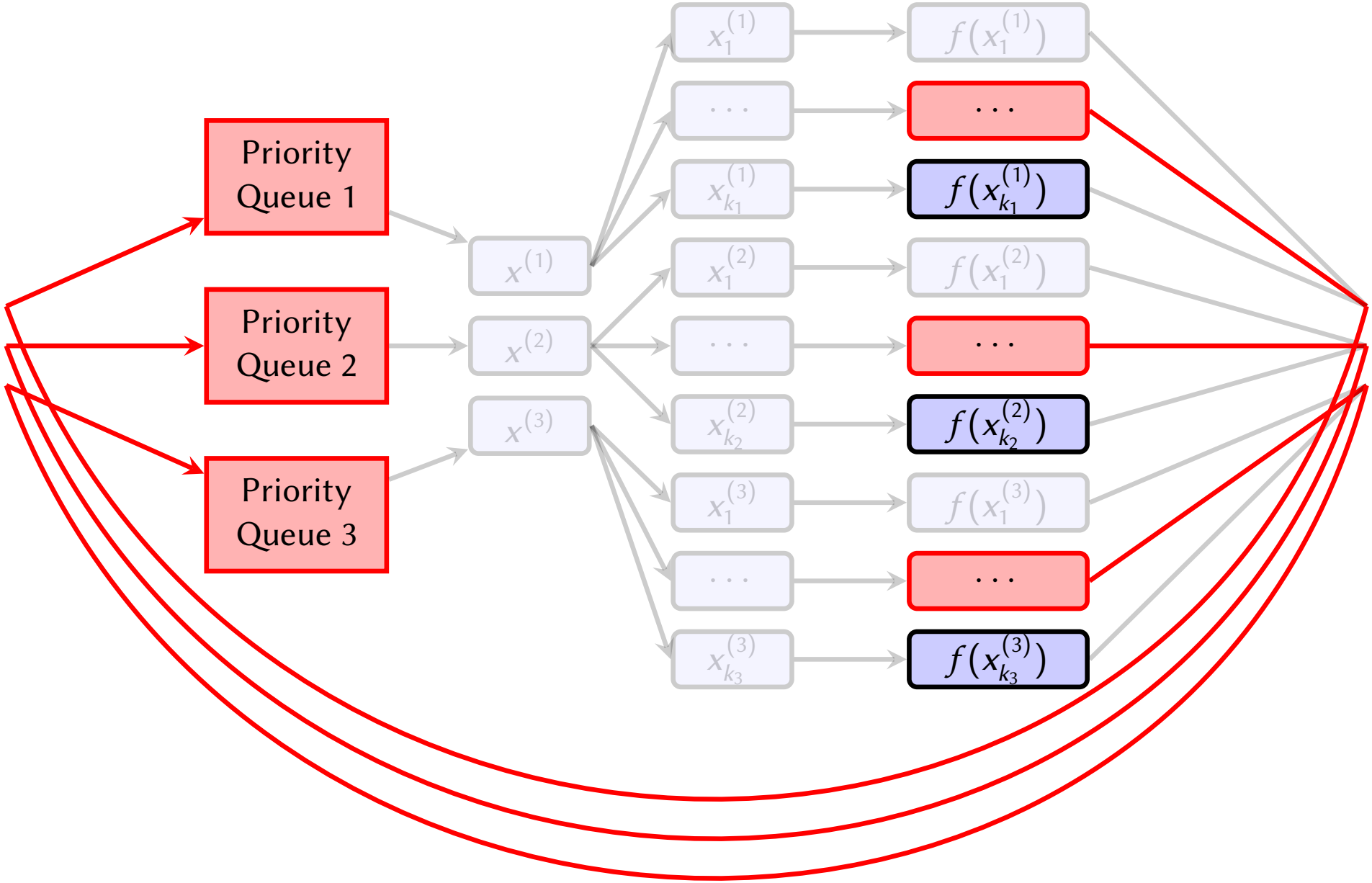

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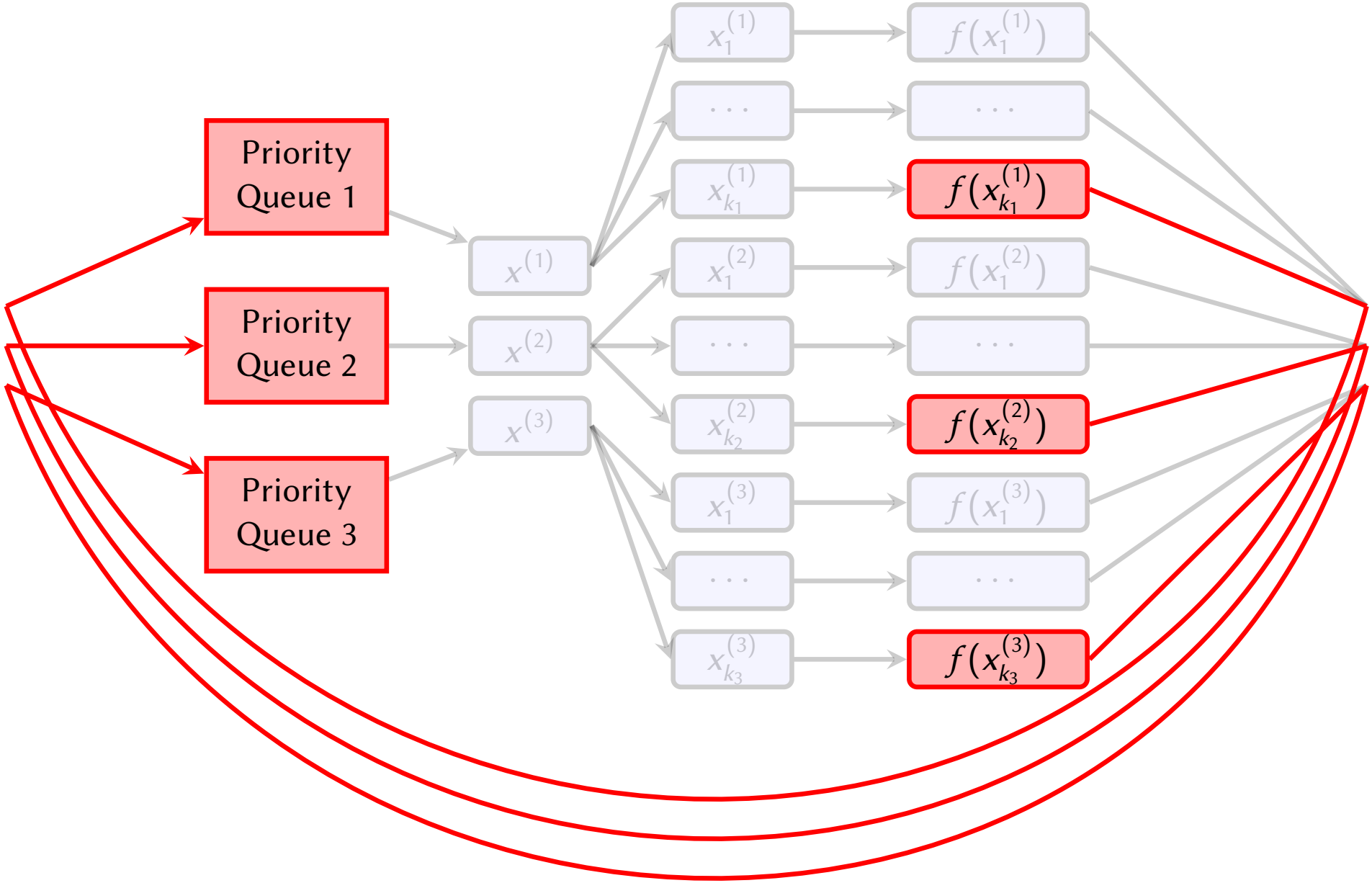

Parallel Memory Bounded A* Algorithm

Memory Exausted Problem

- Memory Resources prevents us from solving larger problem!
- Basic idea: throws aways unpromising nodes
  - Do a global sort according to nodes' heuristic values
  - Only keep nodes whose ranks exceed threshold

Pros and cons

- ☺ Continue to execute after running out of memory
- ☹ Cannot fully guarantee of GMEC
- 😐 Compared to traditional heuristic algorithm:
  - ☺ Guarantee GMEC solution when memory is large enough
  - ☺ Possible to know whether we get GMEC solution

Parallel Memory Bounded A* Algorithm

Memory Exausted Problem

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- 😐 Compared to traditional heuristic algorithm:
  - ☺ Guarantee GMEC solution when memory is large enough
  - ☺ Possible to know whether we get GMEC solution

Environment

Experiment

- On OSPREY platform from *Donald Lab* (Duke University)
- Native sequence recovery (core redesign)
- iMinDEE to consider *side-chain flexibility*
- To measure:
  - speed and memory consumption of GPU-Based A*
  - *correctness* of parallel A* under bounded memory
- Availability: `http://github.com/zhou13/gOSPREY`

Environment Information

CPU: Intel Xeon™ E5-1620 3.6GHz

GPU: NVIDIA Tesla K20C (2496 logic cores)

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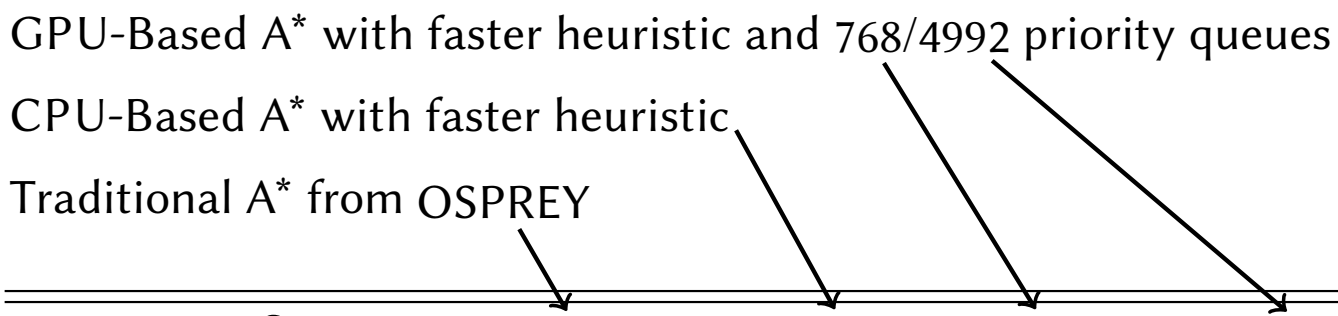
Performance of GPU-Based A*



PDB	Space	OSPREY	A*1	GA*768	GA*4992
2QCP	$2 \cdot 10^{17}$	21551916	51091	3075	1146
1XMK	$2 \cdot 10^{14}$	247585	2990	296	121
1X6I	$7 \cdot 10^{13}$	96990	1406	138	73
1UCS	$6 \cdot 10^{12}$	88135	1771	182	79
1CC8	$3 \cdot 10^{14}$	77614	1078	99	53
2CS7	$8 \cdot 10^{12}$	64187	1154	149	57
...	...	...	...	...	...

Time is measured in millisecond.

Performance of GPU-Based A*

GPU-Based A* with faster heuristic and 768/4992 priority queues

CPU-Based A* with faster heuristic

Traditional A* from OSPREY

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20 000x speedup

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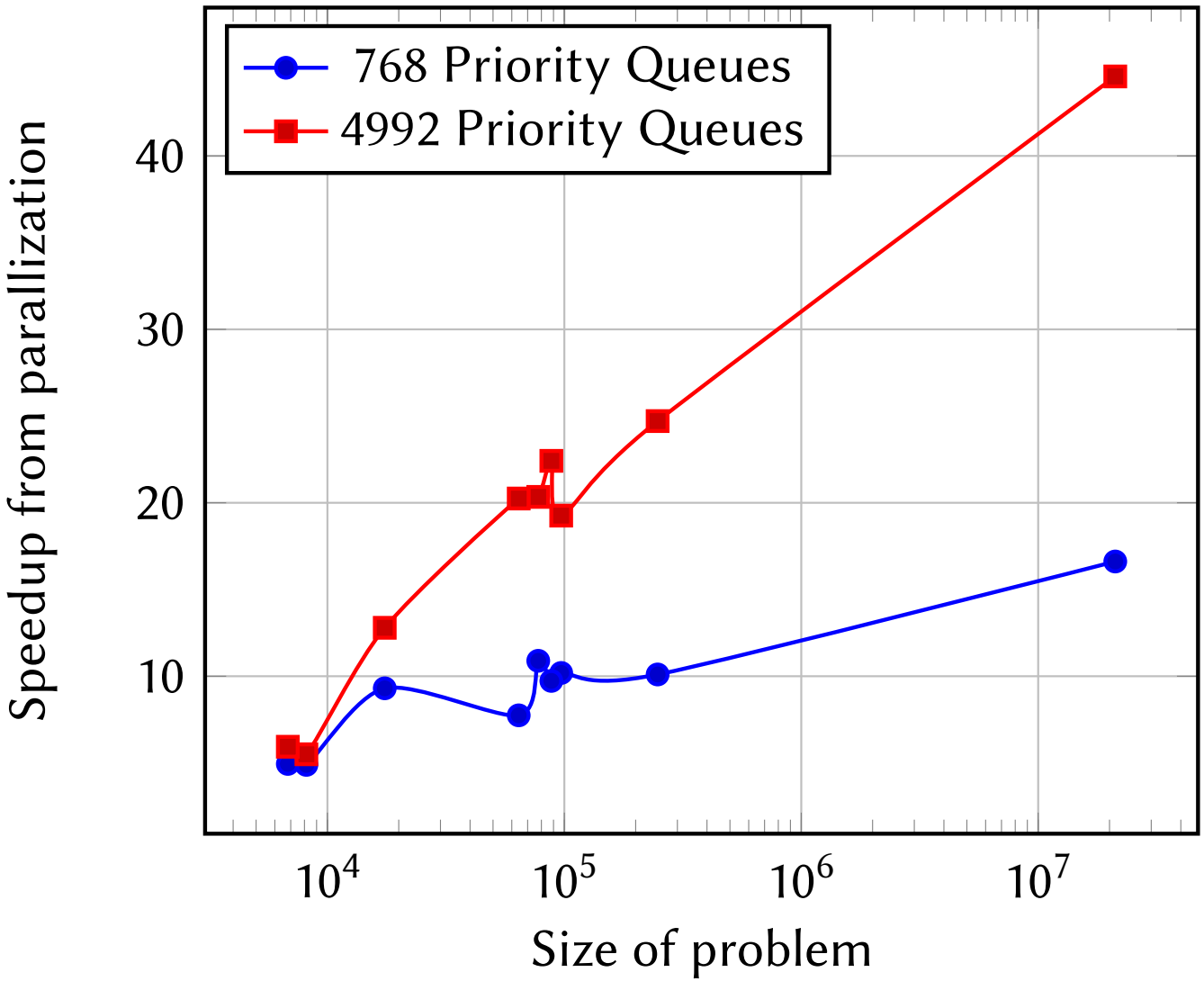
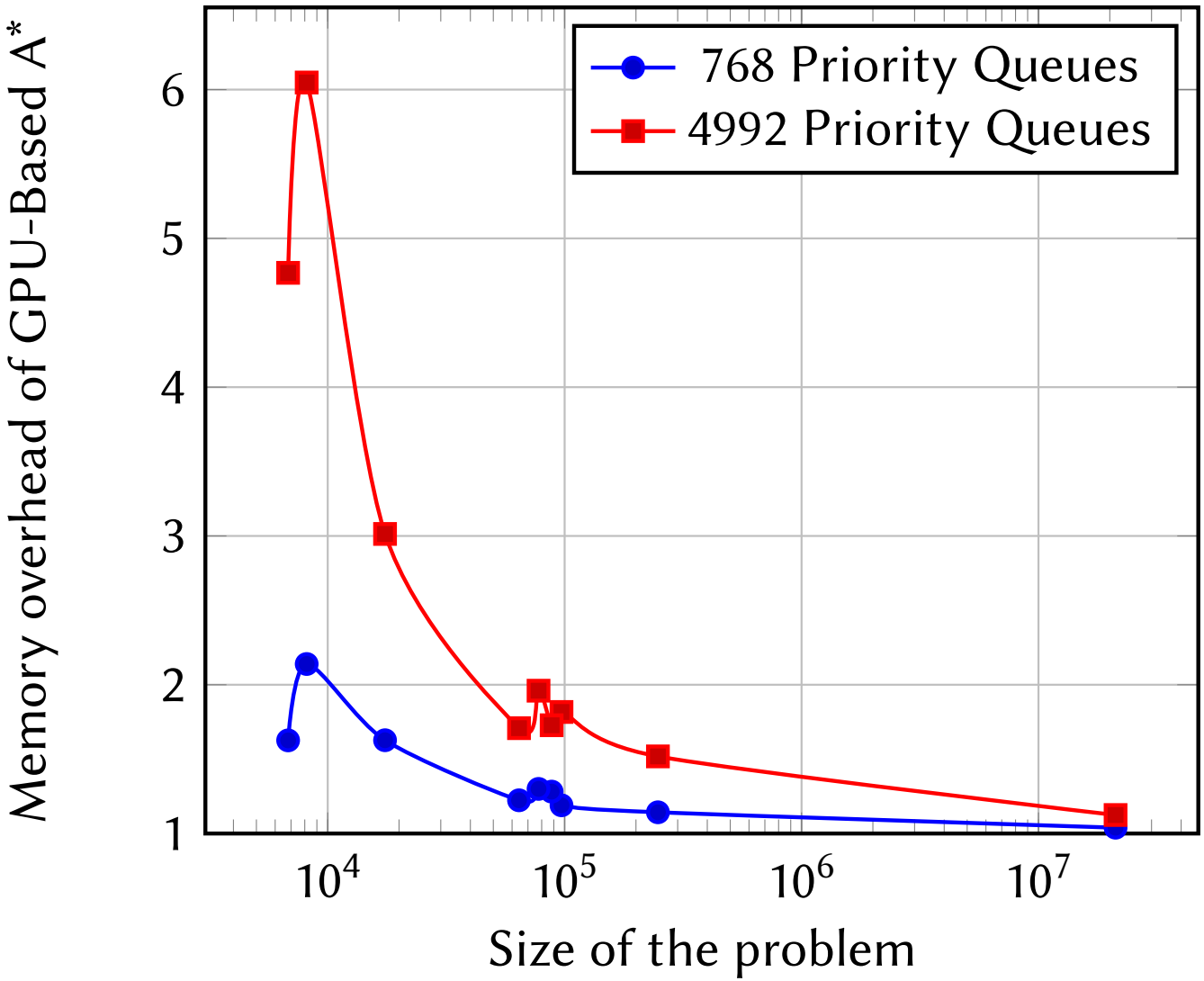
Speedup from Parallelization



Memory Overhead



Native sequence recovery experiment

PDB		1OAI	1U2H	1ZZK	2CS7	2DSX	3D3B
# of Mutable Residues		16	18	14	15	15	15
Conformation Space		$2 \cdot 10^{22}$	$2 \cdot 10^{20}$	$2 \cdot 10^{15}$	$2 \cdot 10^{23}$	$3 \cdot 10^{20}$	$6 \cdot 18^{18}$
A* Search Space		$4 \cdot 10^{7}$	$8 \cdot 10^{6}$	$8 \cdot 10^{6}$	$4 \cdot 10^{7}$	$4 \cdot 10^{7}$	$3 \cdot 10^{7}$
3×10^{6} node limit	GMEC Gotten	YES	YES	YES	YES	YES	YES
	GMEC Assured	YES	YES	YES	YES	YES	YES
	Recover Ratio	74%	75%	87%	46%	48%	53%
3×10^{5} node limit	GMEC Gotten	YES	YES	YES	YES	YES	YES
	GMEC Assured	NO	YES	YES	NO	NO	NO
	Recover Ratio	74%	75%	87%	46%	48%	54%
3×10^{4} node limit	GMEC Gotten	NO	YES	YES	NO	YES	NO
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Conclusion and Future Work

Our Contribution

- Optimized computation of heuristic function
- Massively parallel GPU-Based A*
- Memory bounded search algorithm

Results

- a 20000x speedup in *native sequence recovery*
- 1/10 memory while guaranteeing GMEC

Future Work

- Testing on more affordable GPUs
- Porting to large CPUs/GPUs cluster
- Parallelizing other parts of the framework

Acknowledgement

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  - Mr. Kyle Roberts
  - Mr. Mark Hallen
  - Mr. Pablo Gainza
- Tsinghua University
  - Mr. Pufan He
  - Mr. Qiwei Feng

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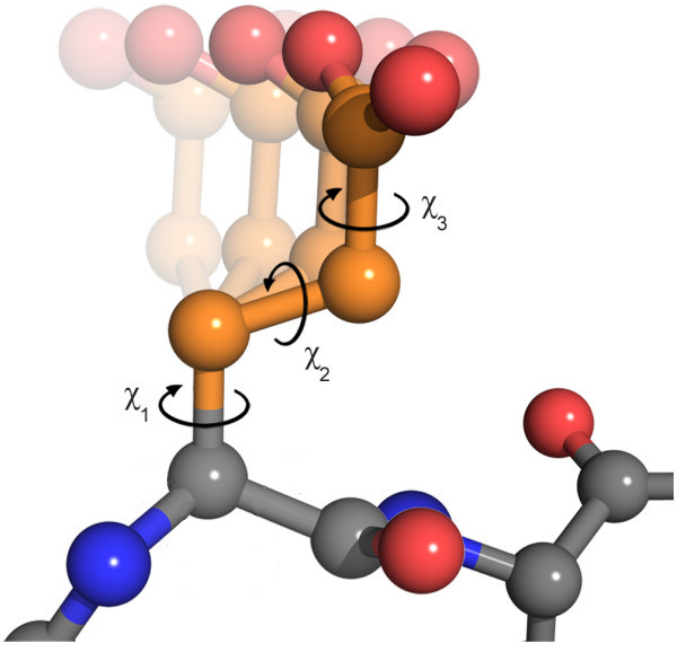
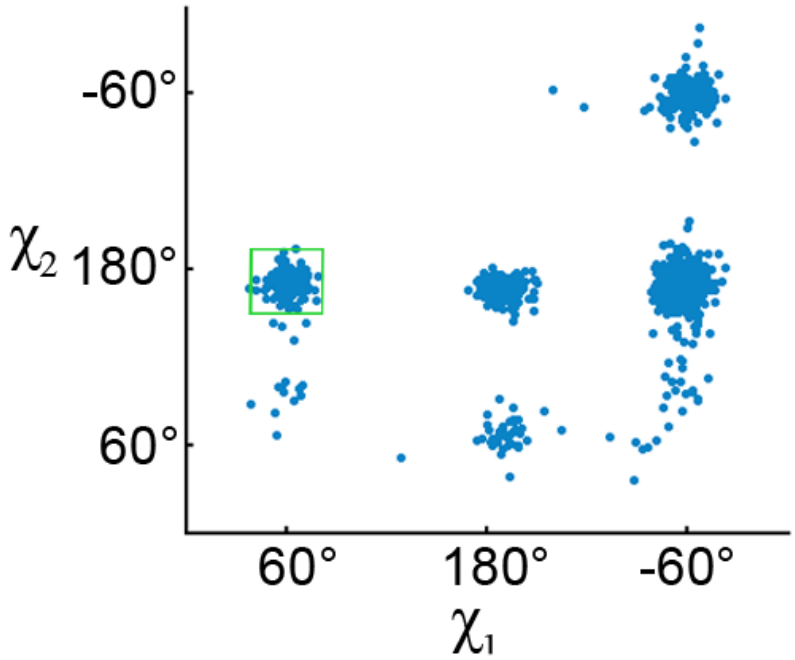
- National Basic Research Program of China
- National Natural Science Foundation of China
- National Institutes of Health from B.R.D

Question and Answer

Thank you!

Rotamer Library



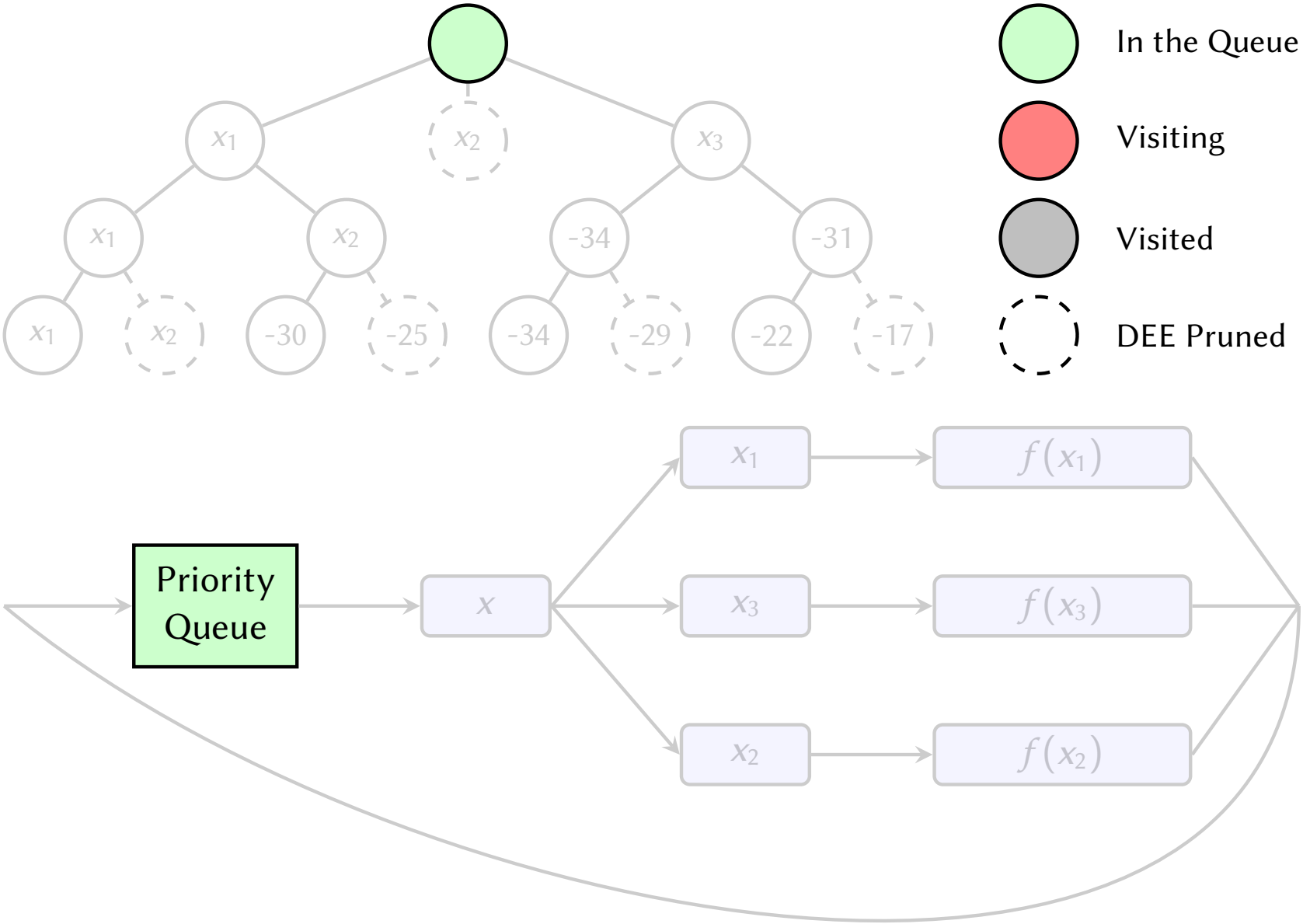


Harder, Tim, et al. (2010) and Gainza, P., Roberts, K. E., & Donald, B. R. (2012).

Price Table (2014)

Model	Price	Release Year	SP GFLOPS
Intel Xeon E5-1620	300$	2012	488
NVIDIA Tesla K20C	3000$	2012	3520
NVIDIA GeForce GTX 680	300$	2012	3090
NVIDIA GeForce GTX 770	400$	2013	3213
NVIDIA GeForce GTX 780	600$	2013	3977

Full A* Search



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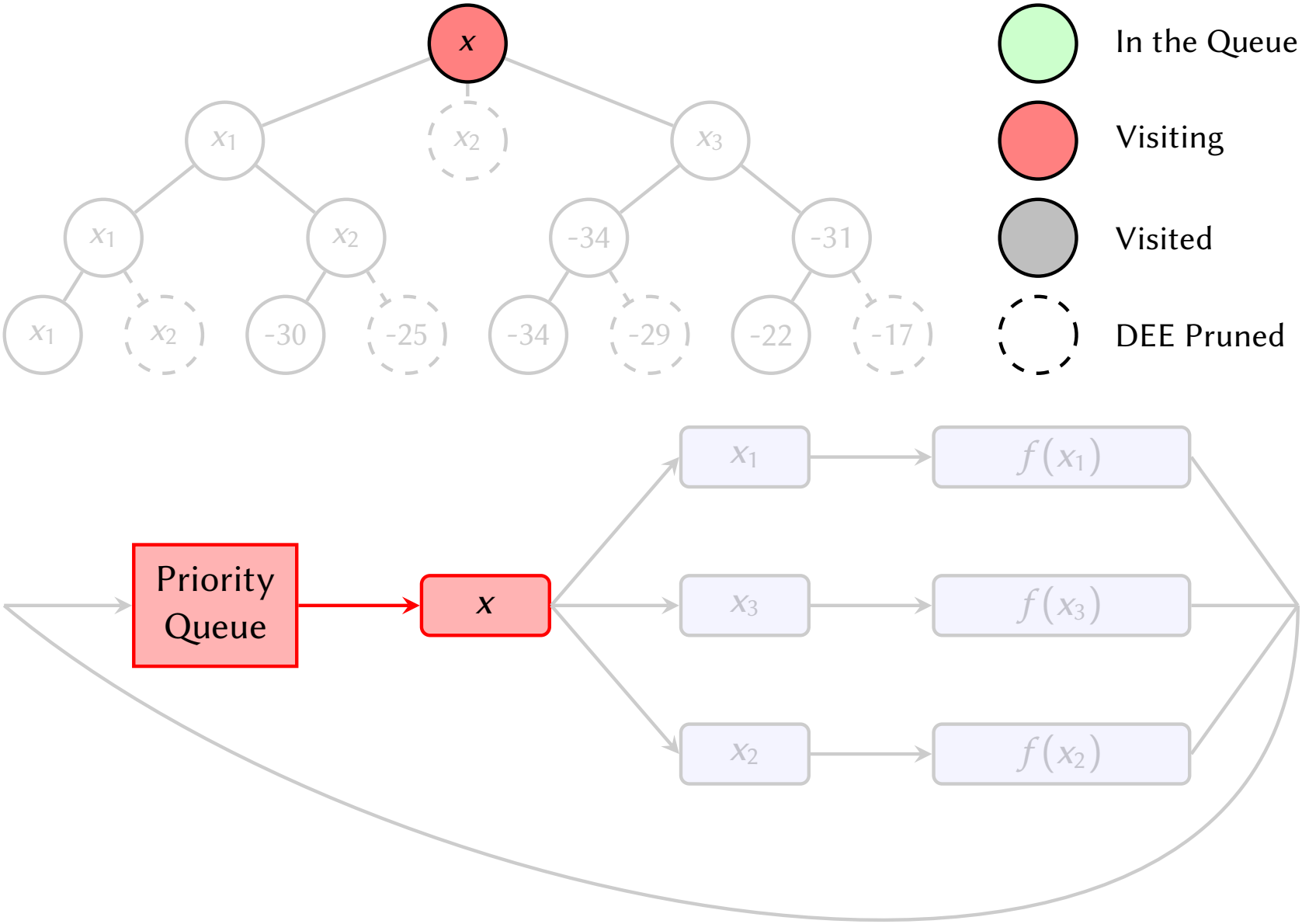

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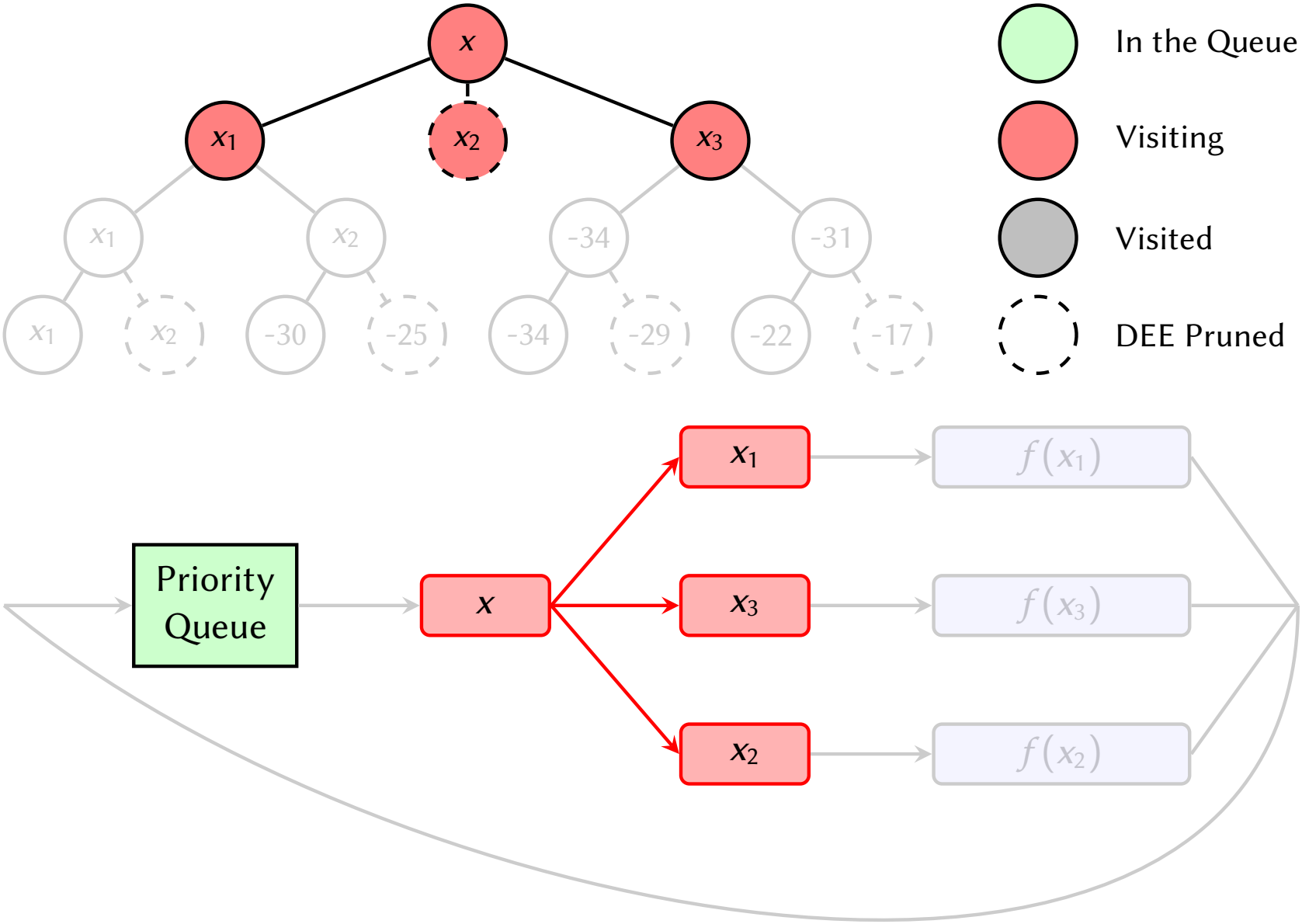

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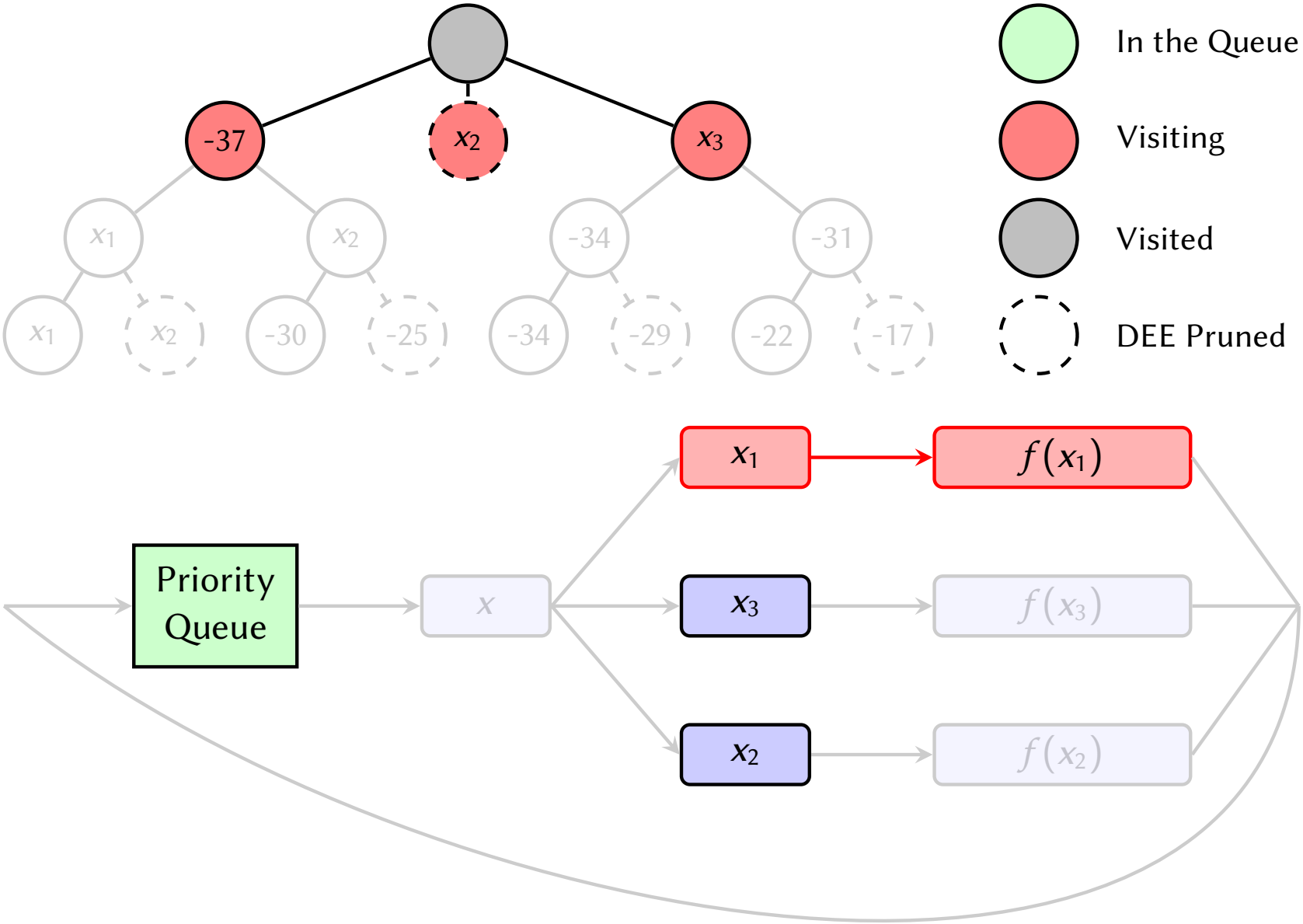

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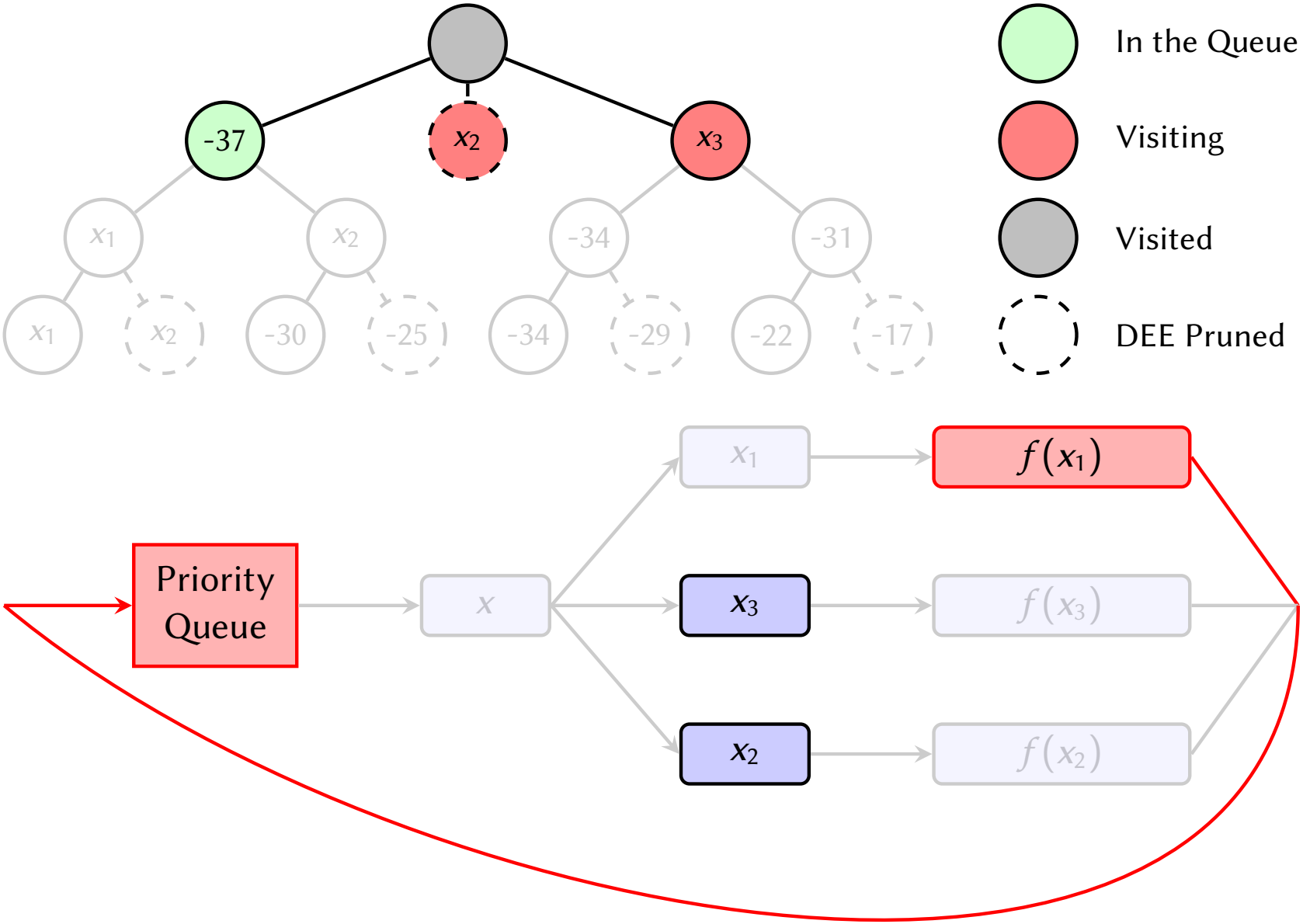

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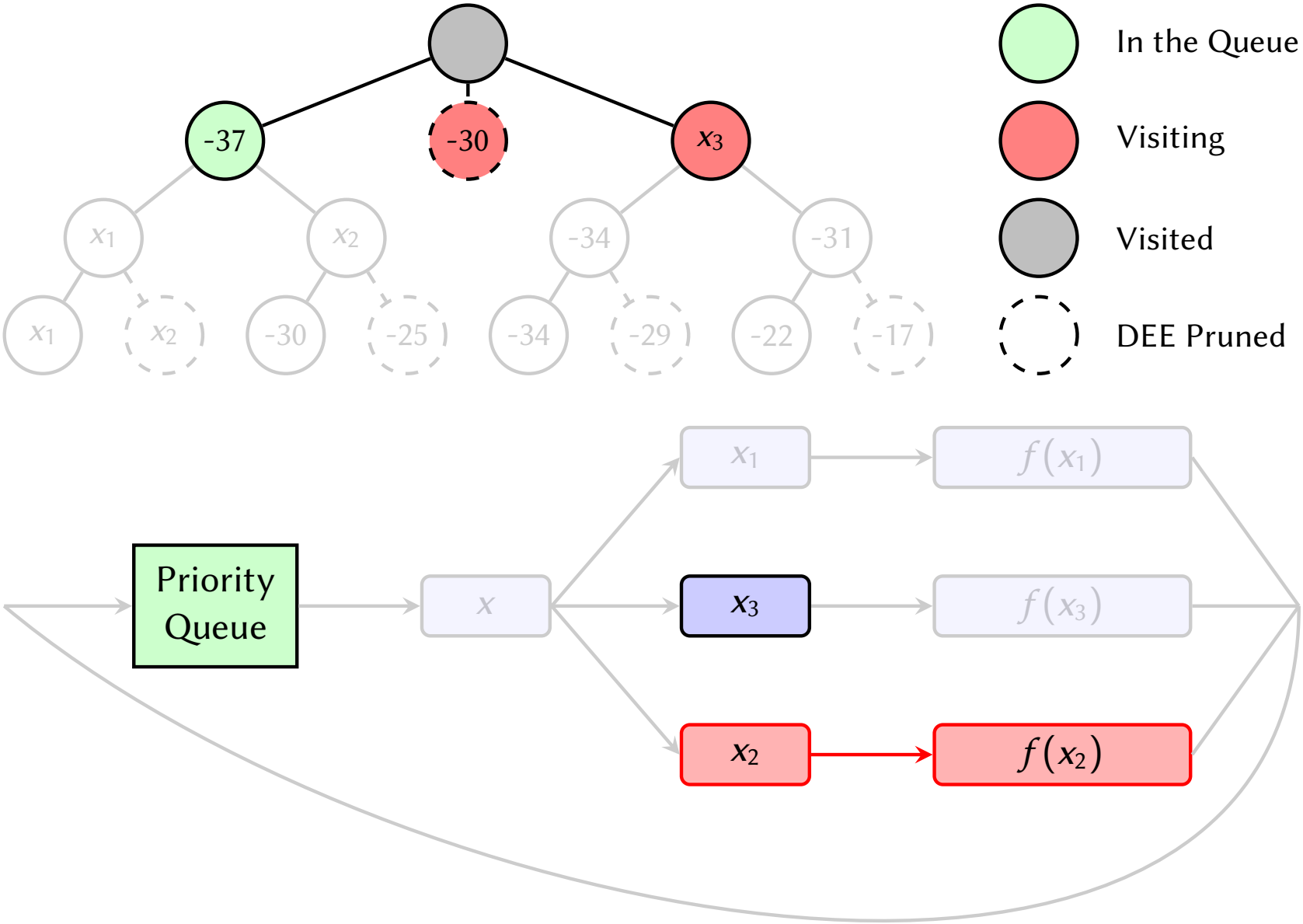

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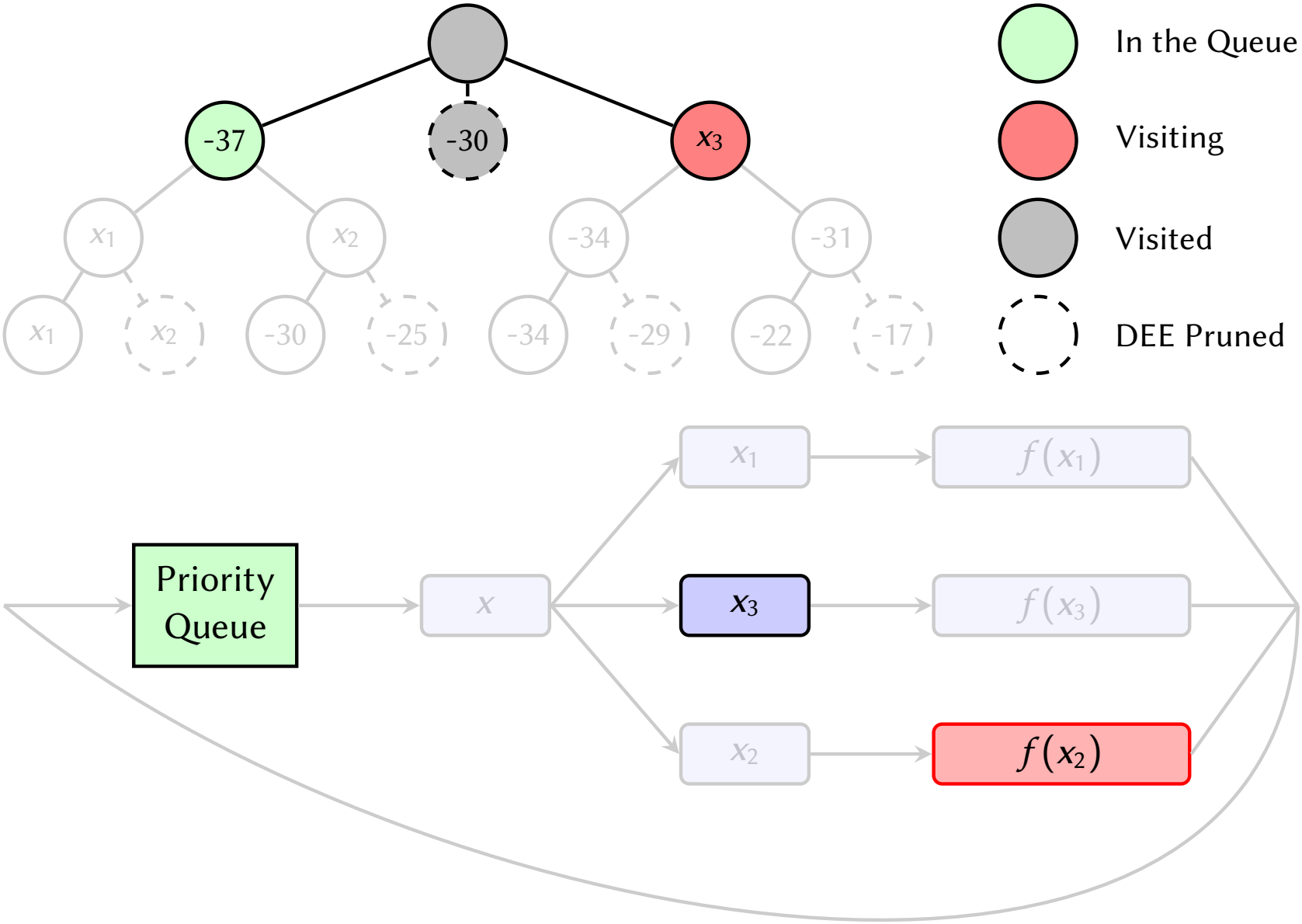

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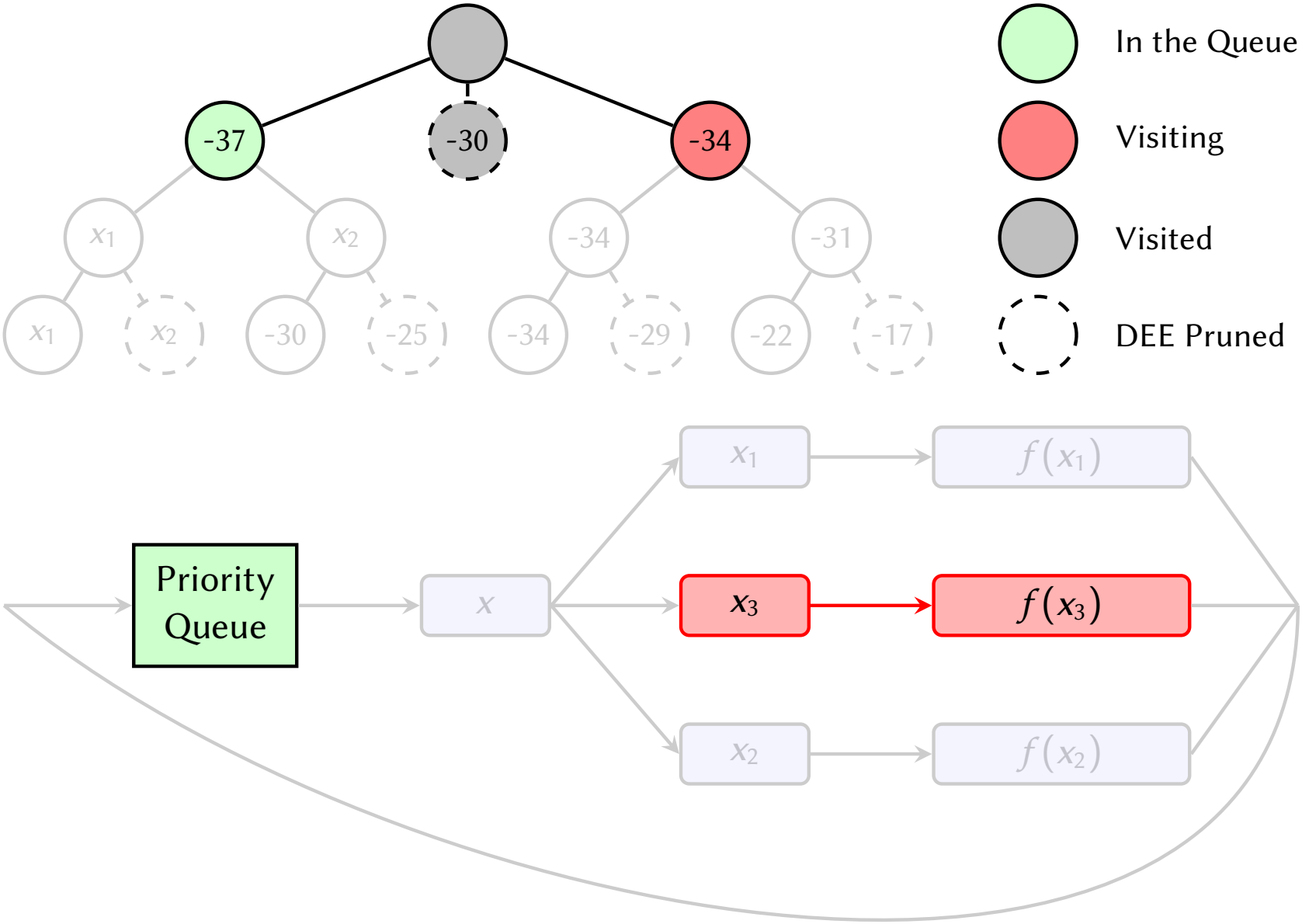

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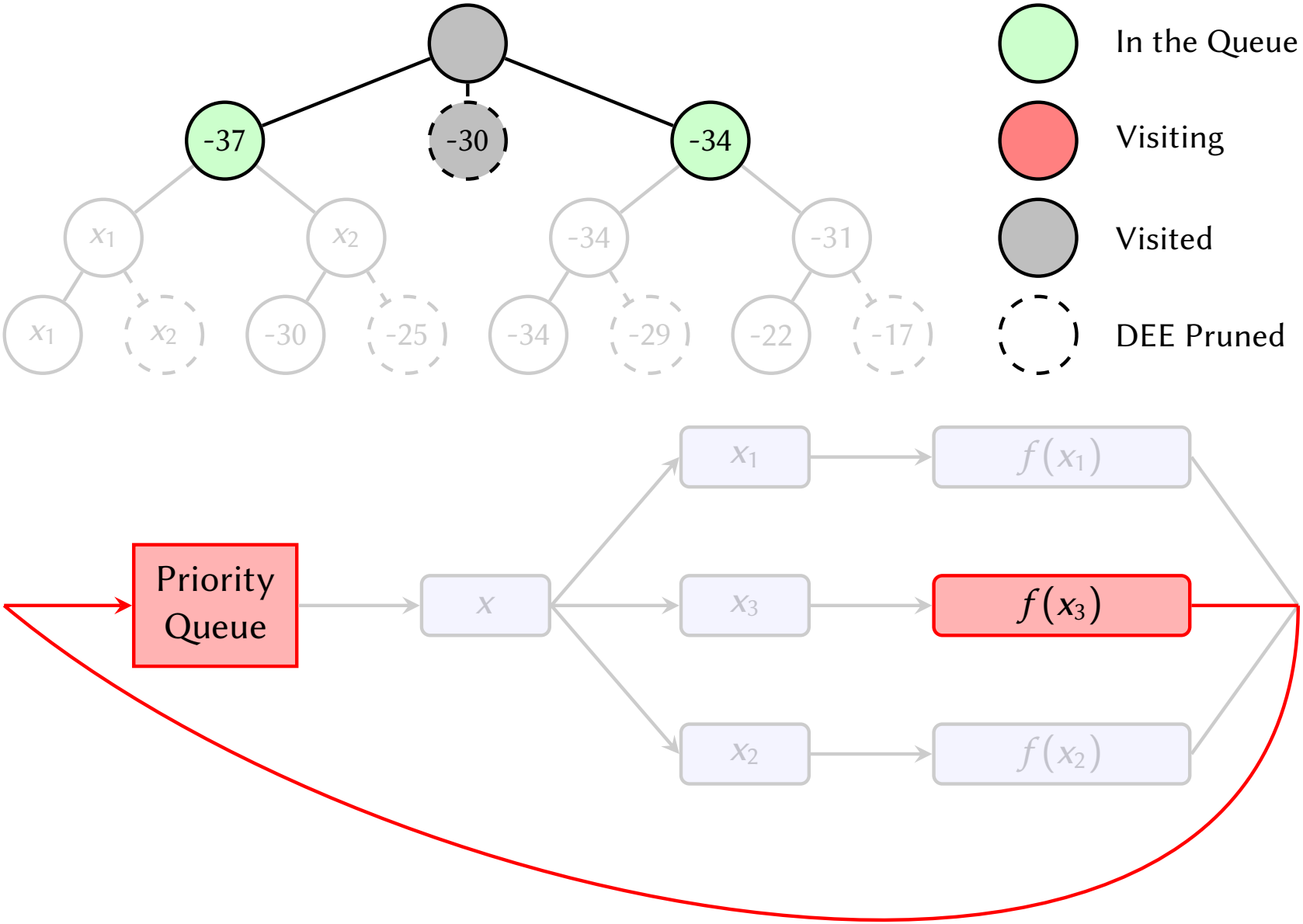

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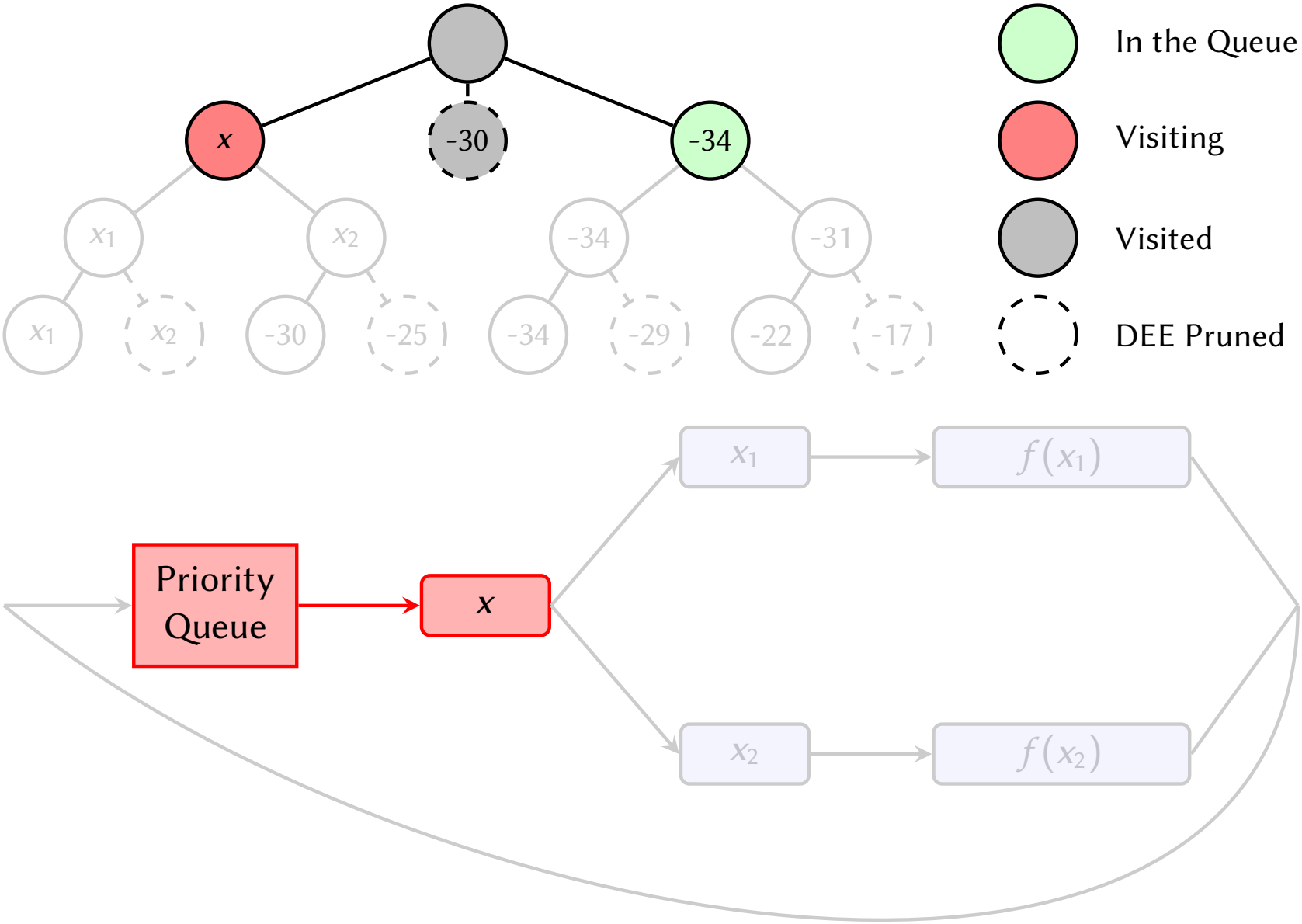

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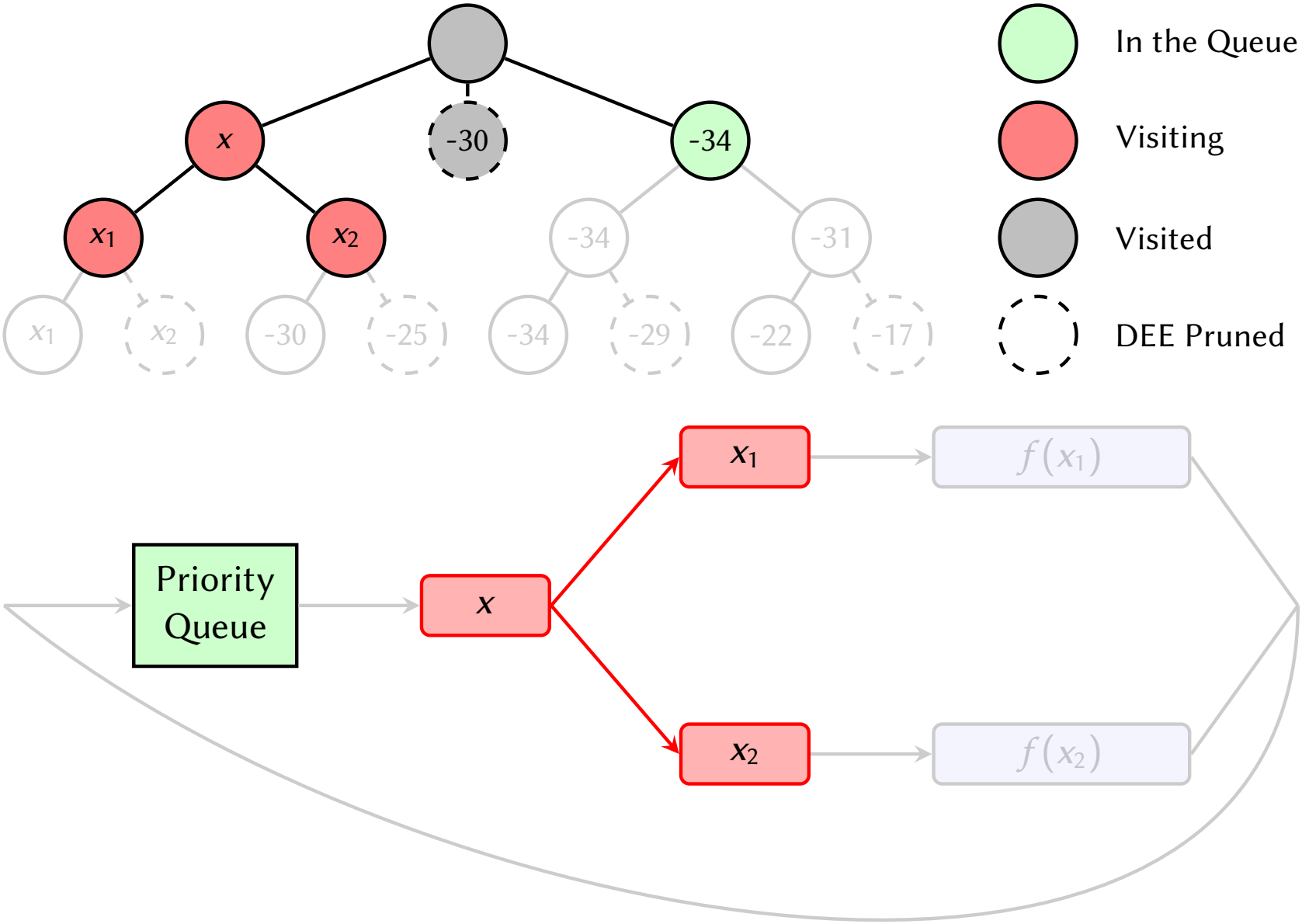

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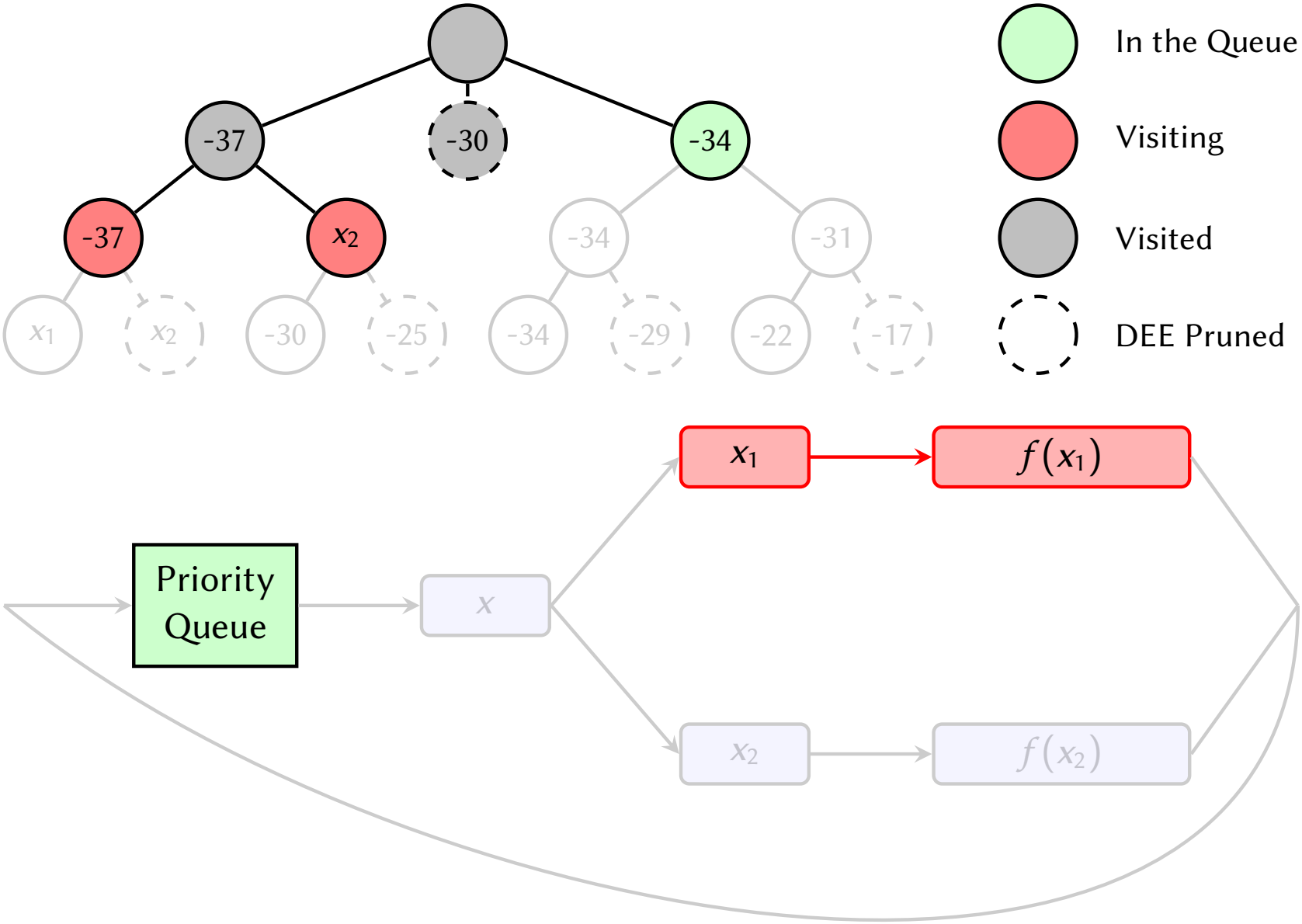

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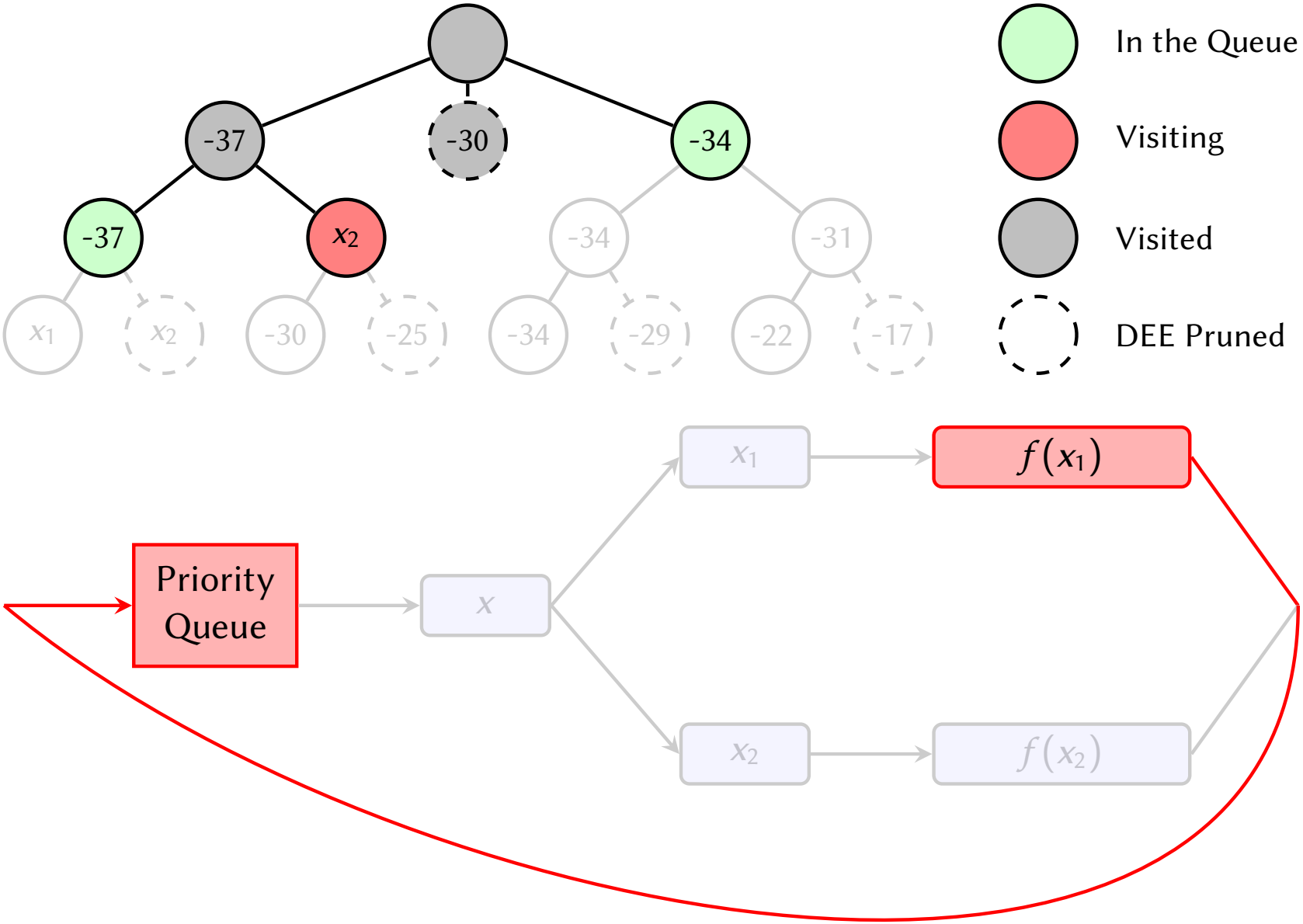

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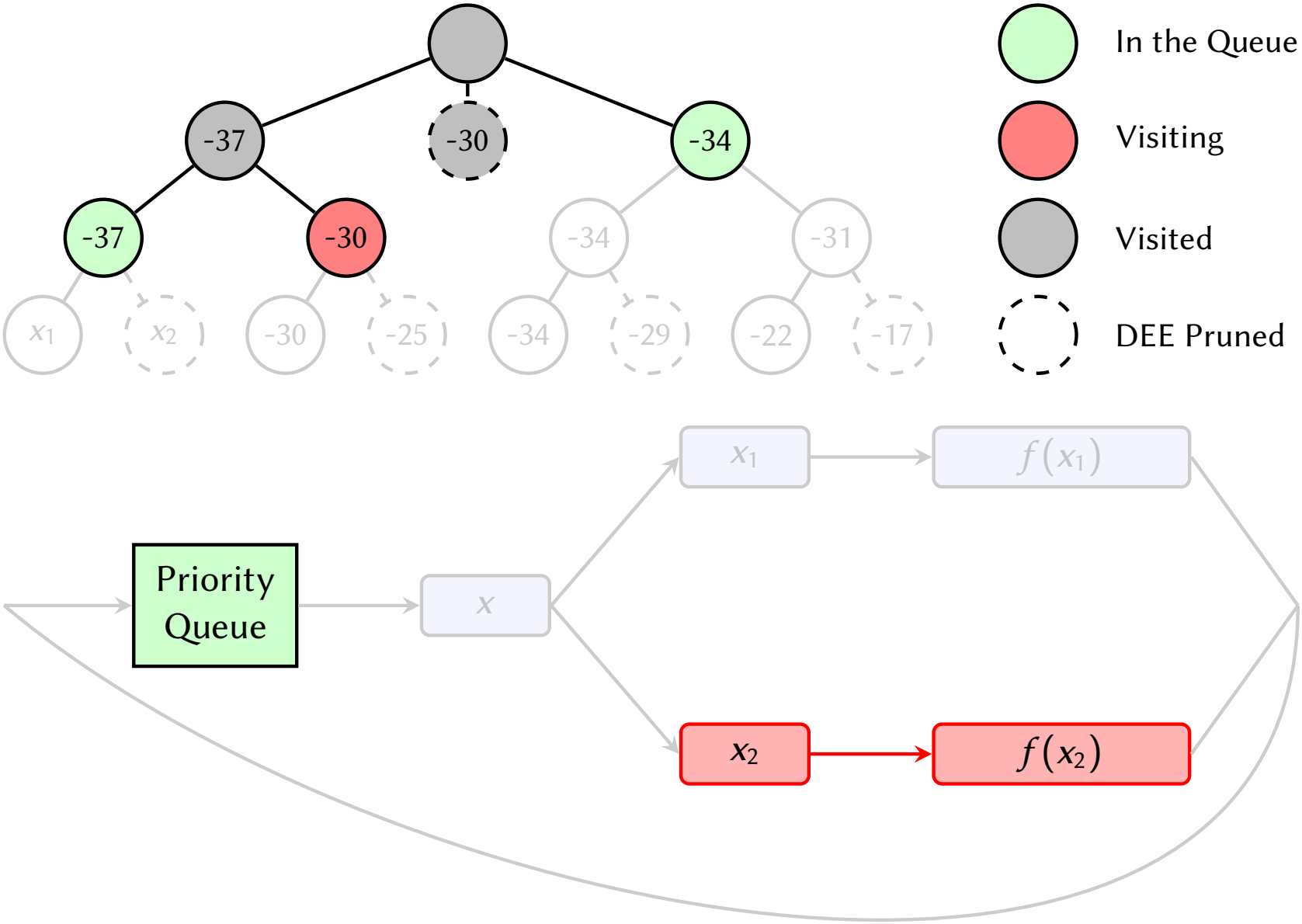

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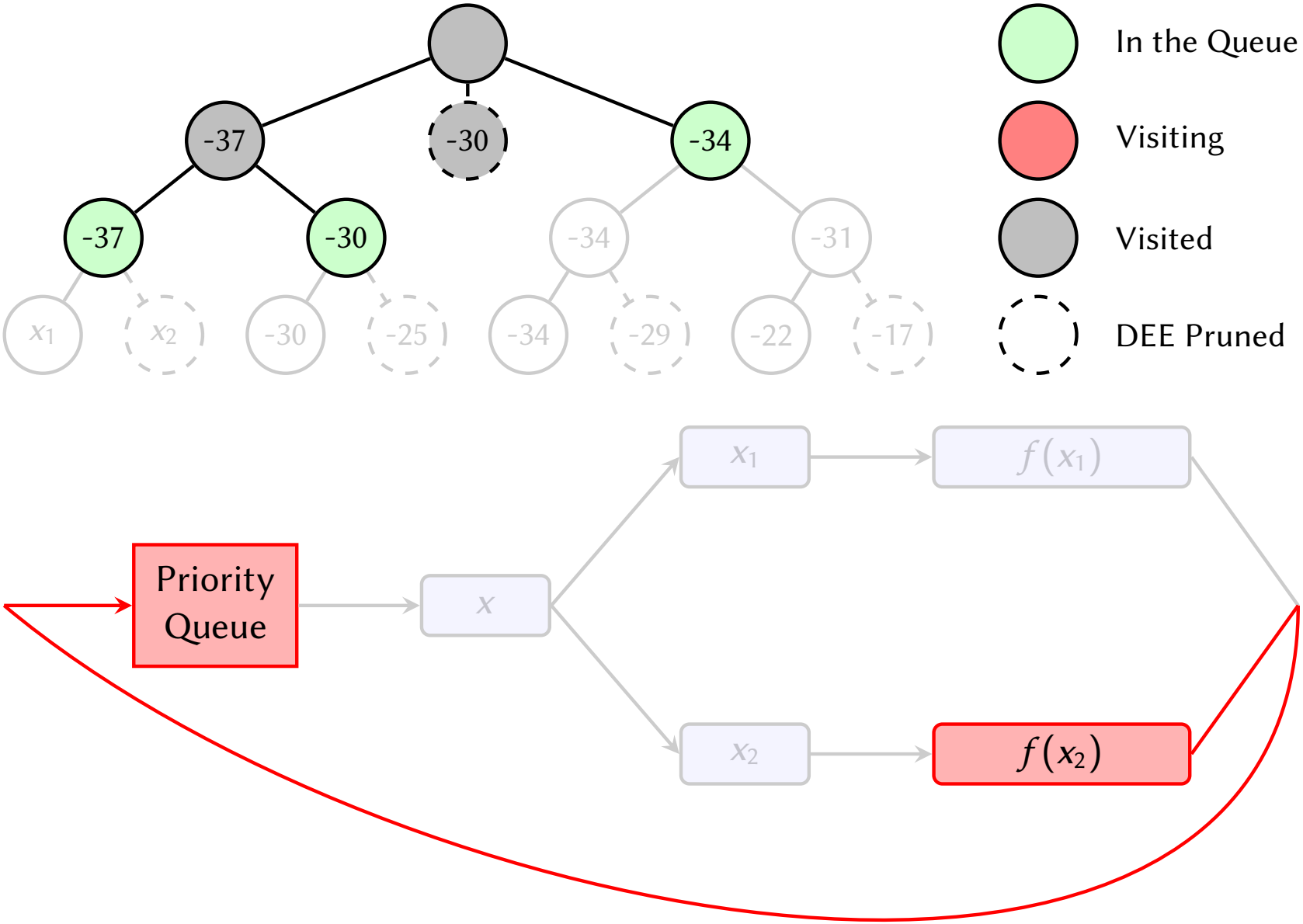

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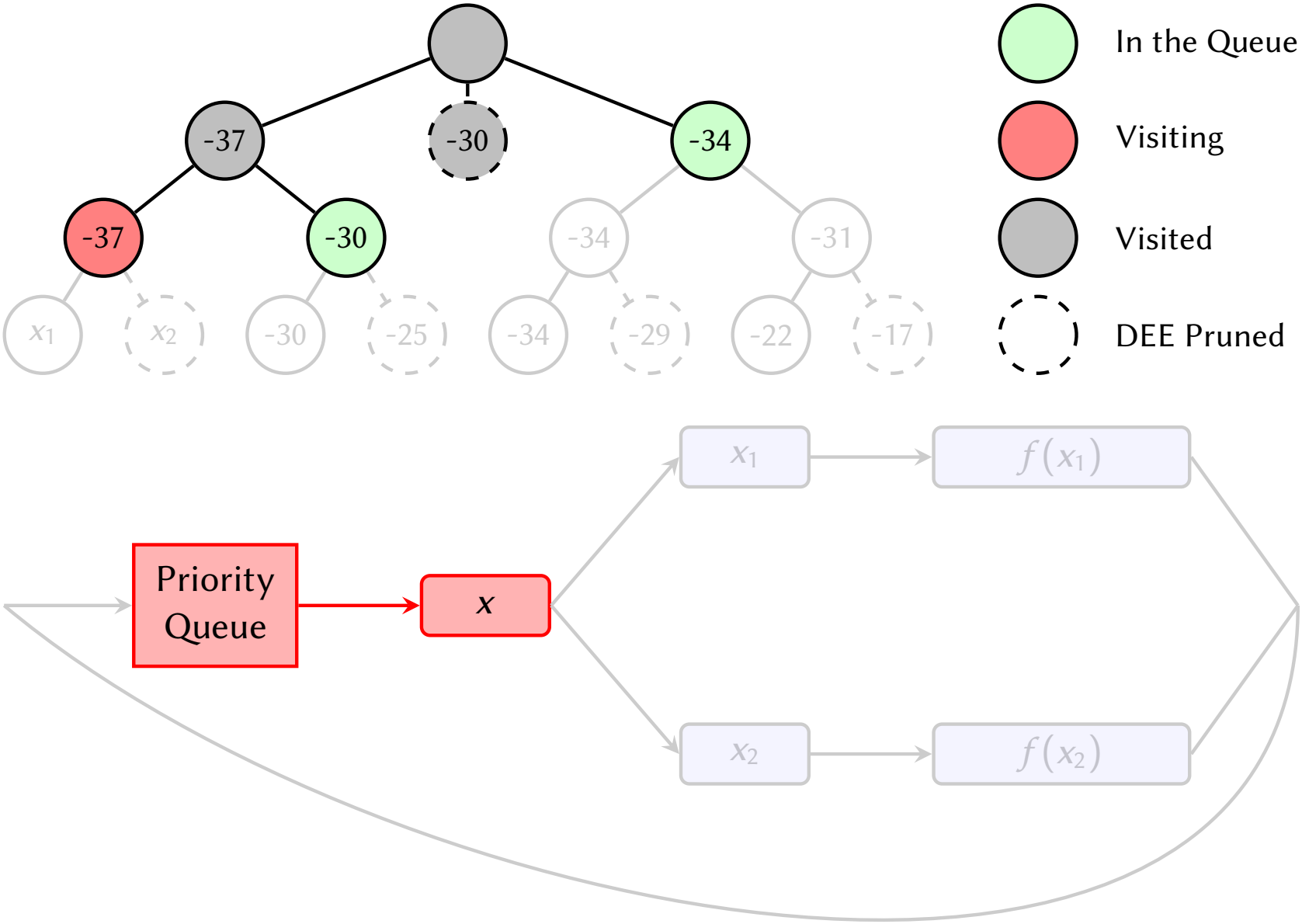

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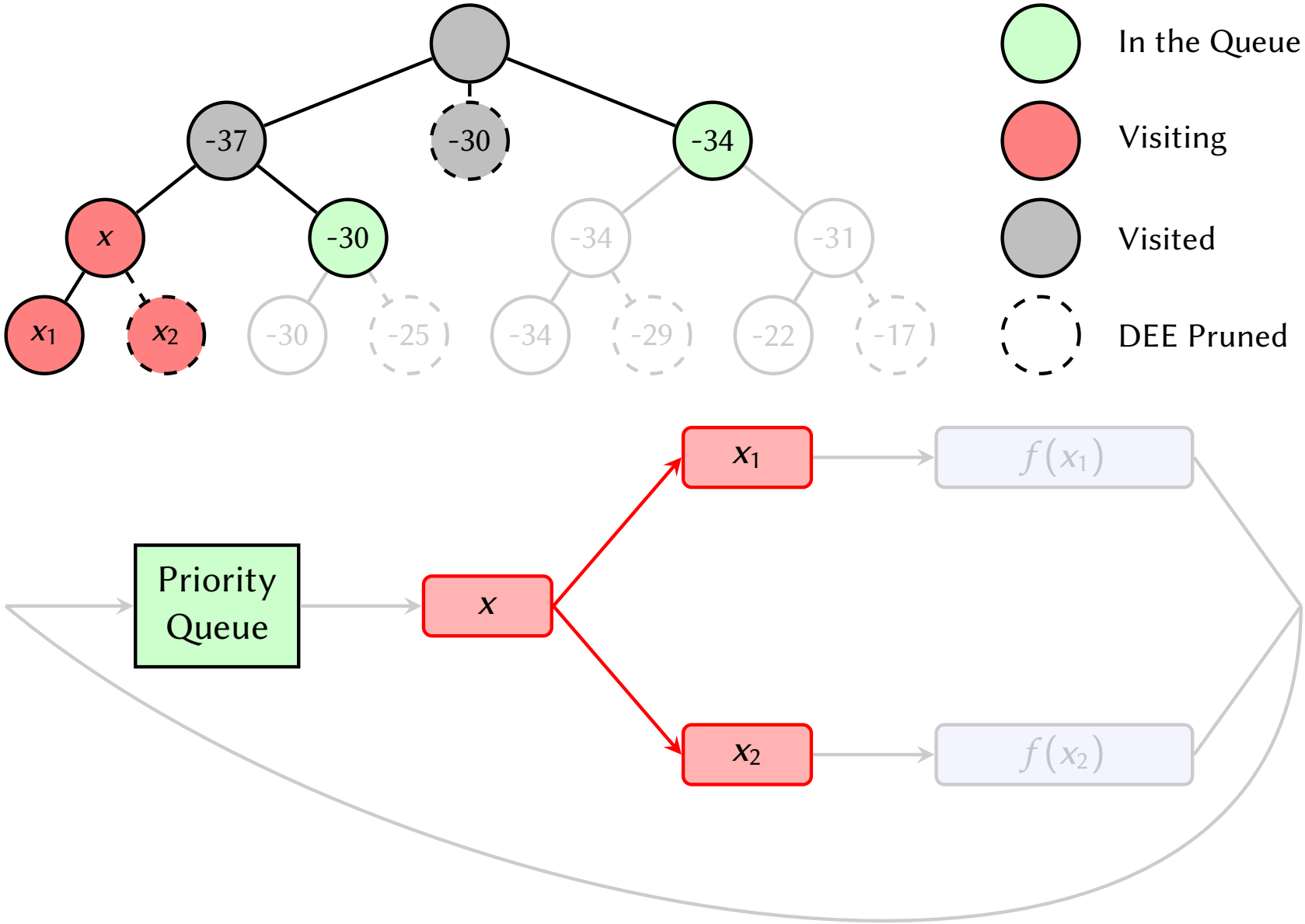

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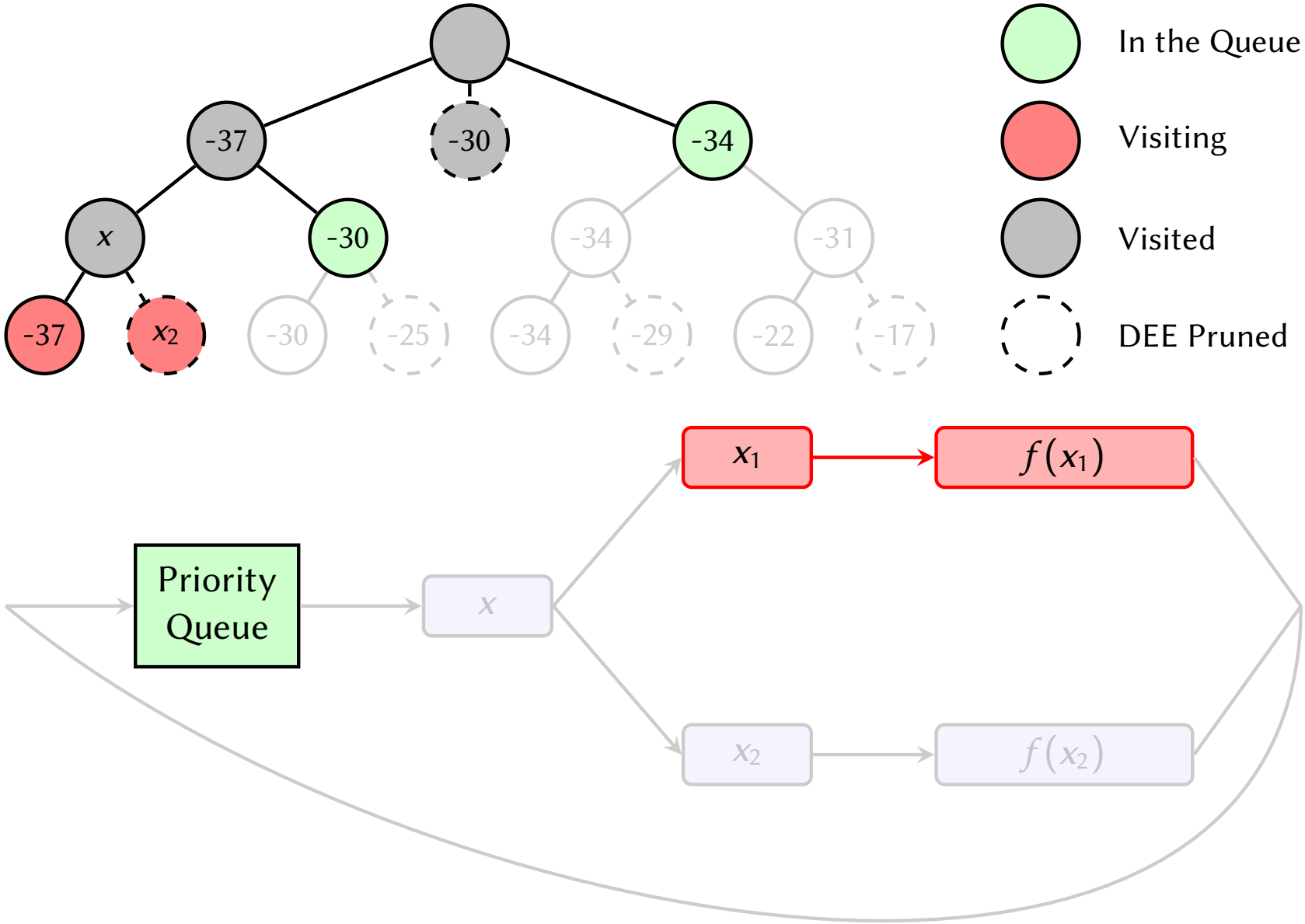

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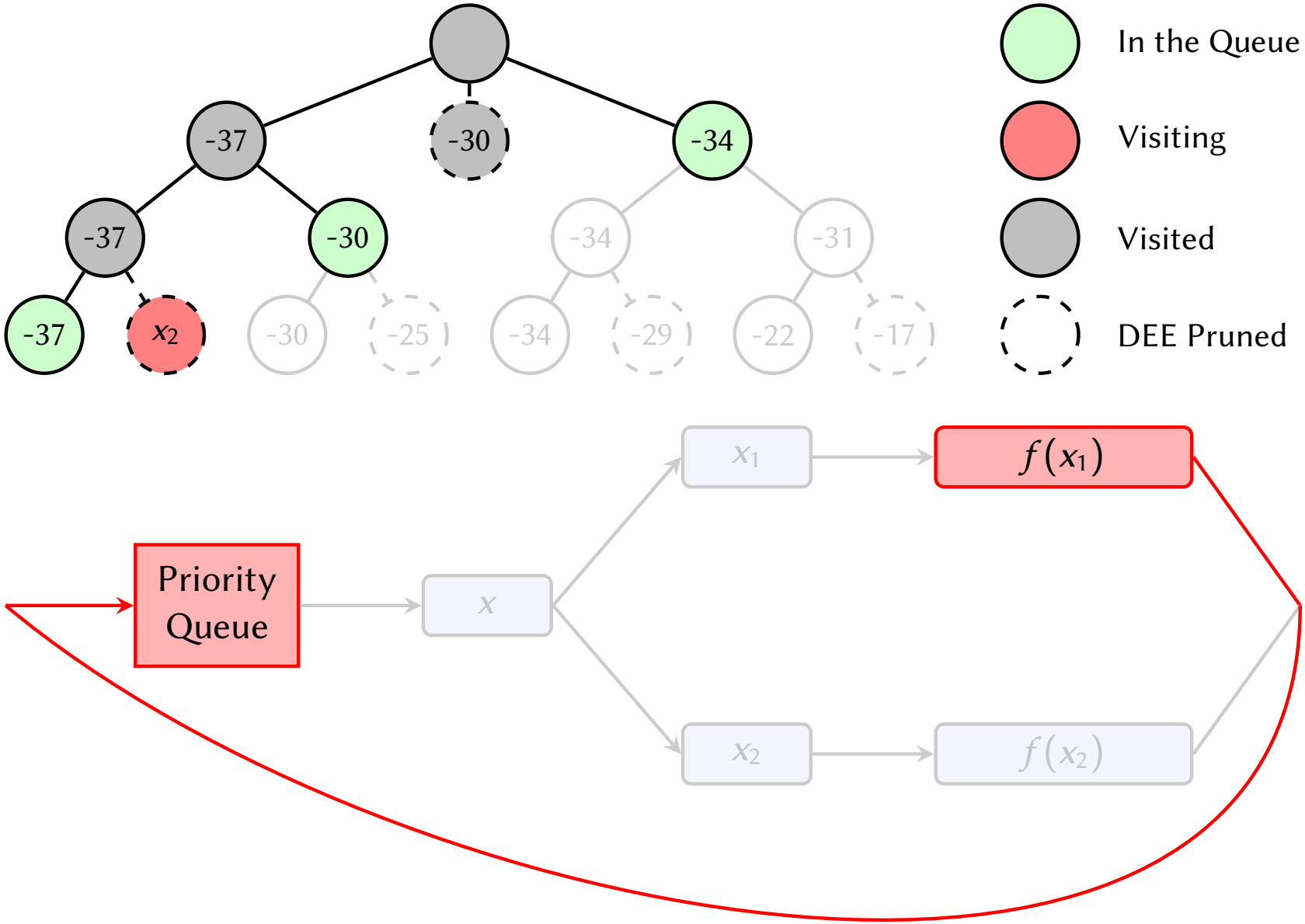

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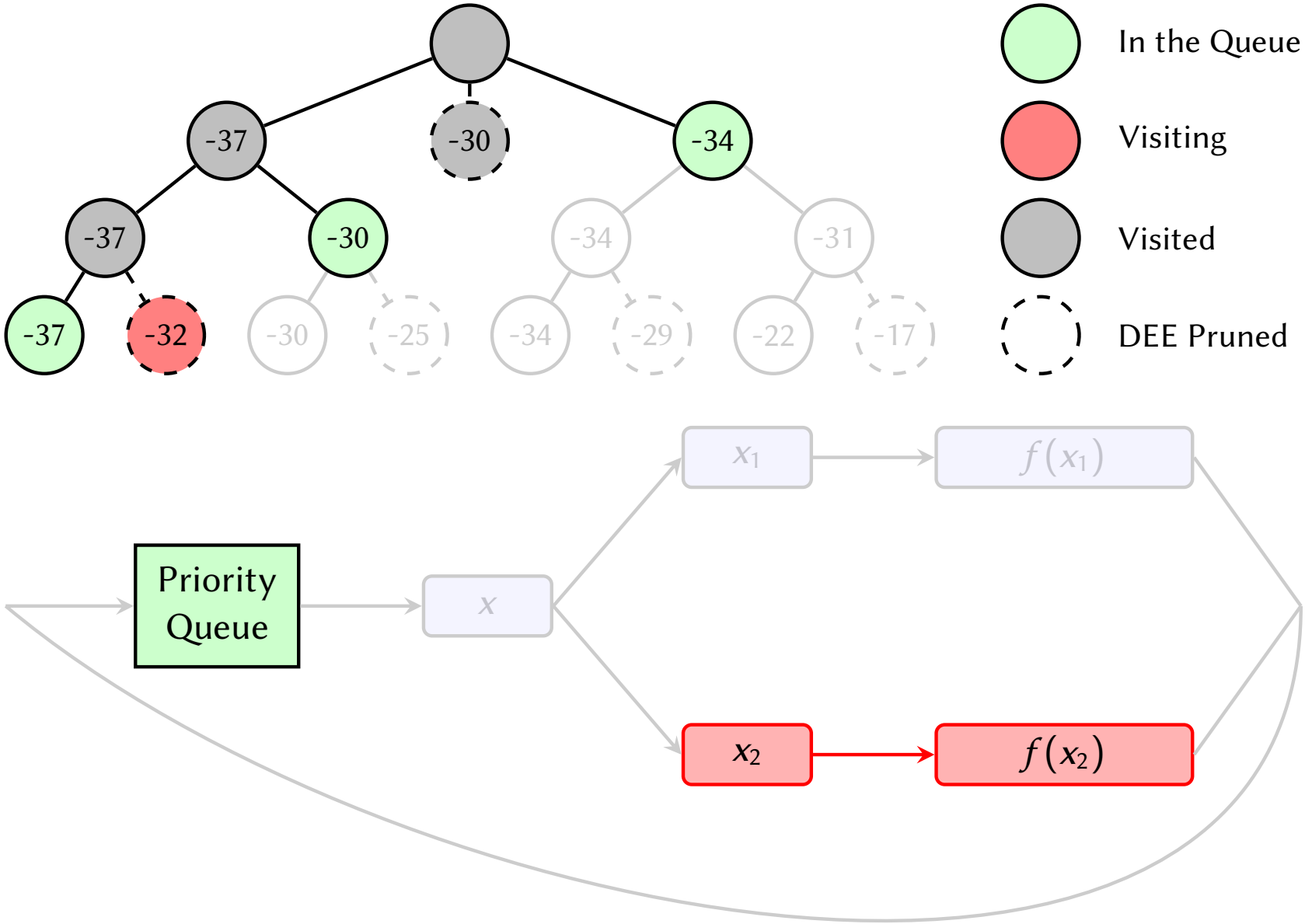

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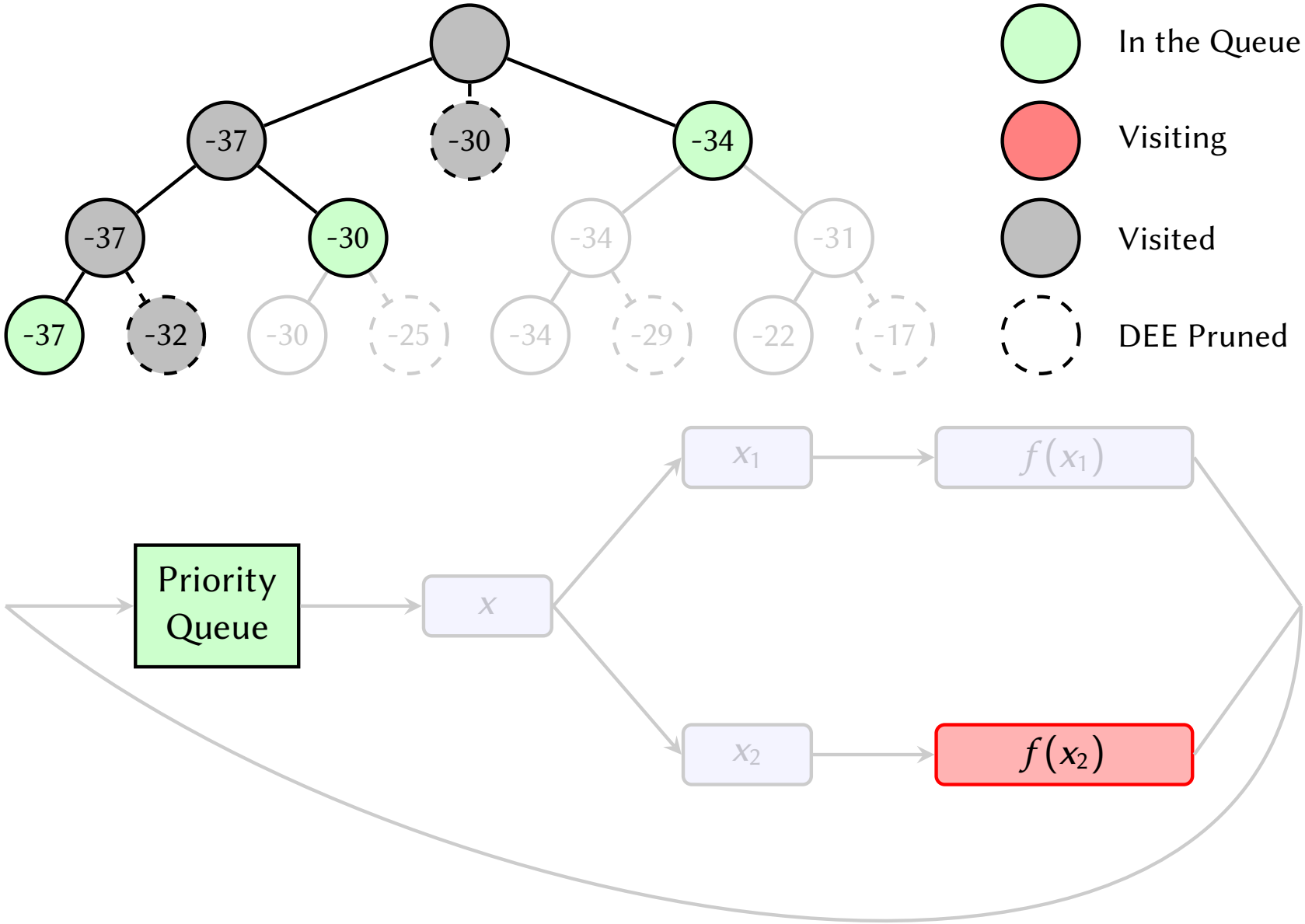

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