Solving large protein design problems modeled as cost function networks

Guaranteed Discrete Energy Optimization on Large Protein Design Problems.
Journal of chemical theory and computation.

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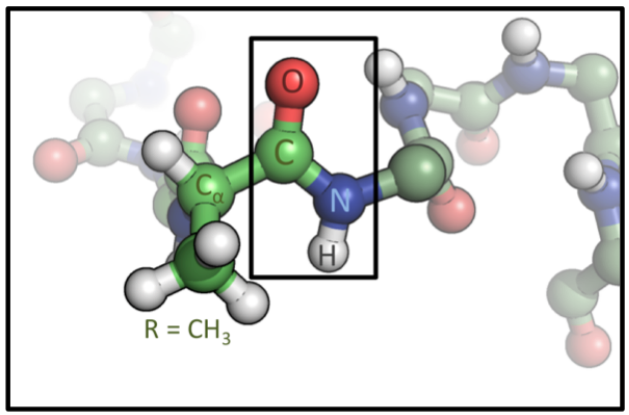
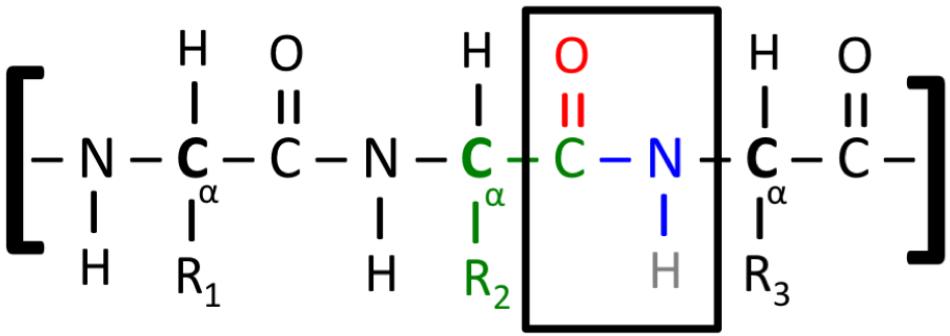
May 2016 - The MIAT seminars

What is a protein ? (Thank you wikipedia)

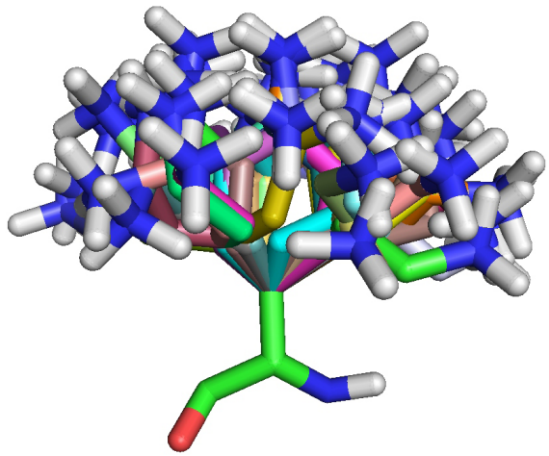
Amino acids, proteins

- Proteins are linear chains of amino-acids (20 natural AAs).
- All AAs share a common "core" and have a variable side-chain.





Side-chains are flexible (ARG)



Protein Design

Why ?

- Proteins have various functions in the cell: catalysis, signaling, recognition, regulation...
- Efficient, biodegrable, 10^6 to 10^{20} speedups
- Nano-technologies (shape more than function).
- Medecine, cosmetics, food, bio-energies...

Protein Design

Protein function linked to its 3D shape through its amino acid composition.

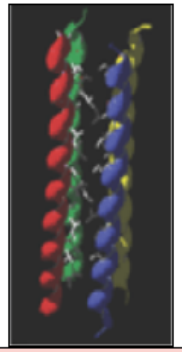
Protein design's aim

Identify sequences that have a suitable function (shape).

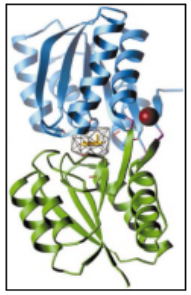
Issue

There are 20^n proteins of length n.
Impossible to synthesize and test all of them.

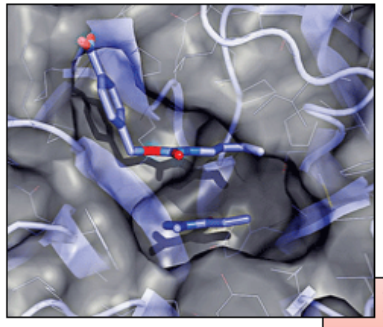
Successes of Protein Design



- Coiled-coils *Harbury et al (Science 1998)*

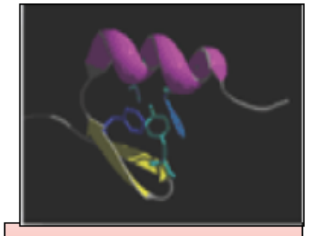


- Sensors & receptors toward non native ligands *Hellinga et al (Nature, 2003)*



2010

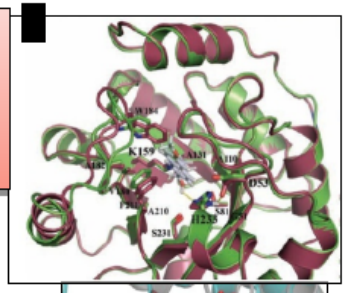
- Design of Biocatalyst for a stereoselective & bimolecular reaction (Diels-alder) *Siegel et al (Science 2010)*



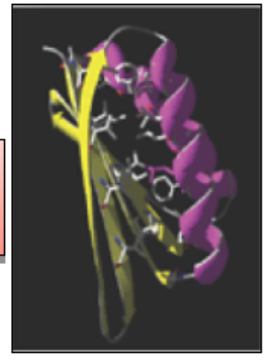
- Zinc-finger *Dahiyat et al (Science 1997)*

2008

- New catalyst for a multi-step-reaction (retro-aldolase) *Jiang et al (Science 2008)*

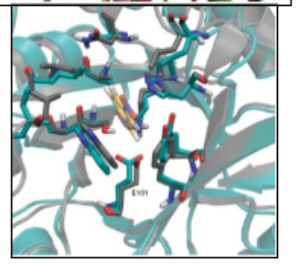


2003



- A novel topology (Top7) *Khulman et al (Science 2003)*

- De novo design of new functional enzyme (Kemp elimination) *Rothlisberger et al (Nature 2008)*

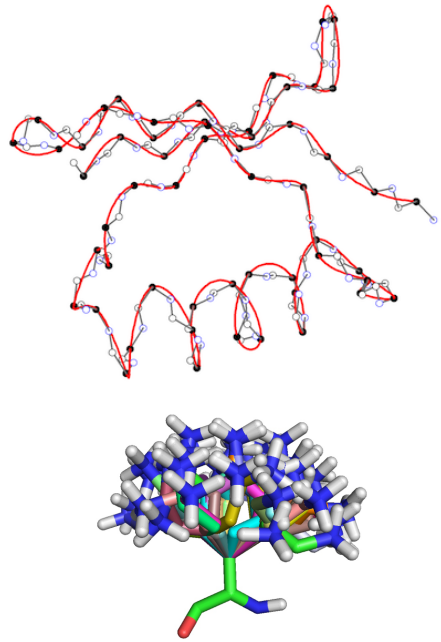


1997

The CPD problem

Rigid backbone variant

1. Assume a rigid protein backbone.
2. Choose 1 AA among possible ones at each mutable position.
3. Side-chain flexibility: discretized in rotamers (Dunbrack).



Search Space

Fully discrete description, defined by a choice of rotamer (AA $\times$ conformation) for each position.

Pairwise decomposable energy function

$$E(c) = E_{\varnothing} + \sum_{i=1}^{n} E(i_r) + \sum_{i<j} E(i_r, j_s)$$

Common approaches to CPD

DEE/A*

Dead End Elimination:

- Removes from the search space rotamers which are dominated.
- Can possibly remove close to optimal solutions.

A algorithm:*

- Best-first search tree-based algorithm.
- A heuristic gives a lower bound on the cost of each path in the tree.

Meta-heuristics

- *Monte-Carlo Simulated Annealing* (Rosetta).
- *Genetic Algorithms* (EGAD).
- ...

What is a Graphical Model ?

Informal

1. A set of discrete variables, each with a domain
2. We want to define a joint function (energy) on all those variables
3. We do this by combining small functions involving few variables

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Why "Graphical" ?

1. a vertex per variable, a (hyper)edge per function
2. Allows to describe knowledge on a lot of variables concisely
3. Usually hard to manipulate (NP-hard queries).

A Cost Function Network is a Graphical Model

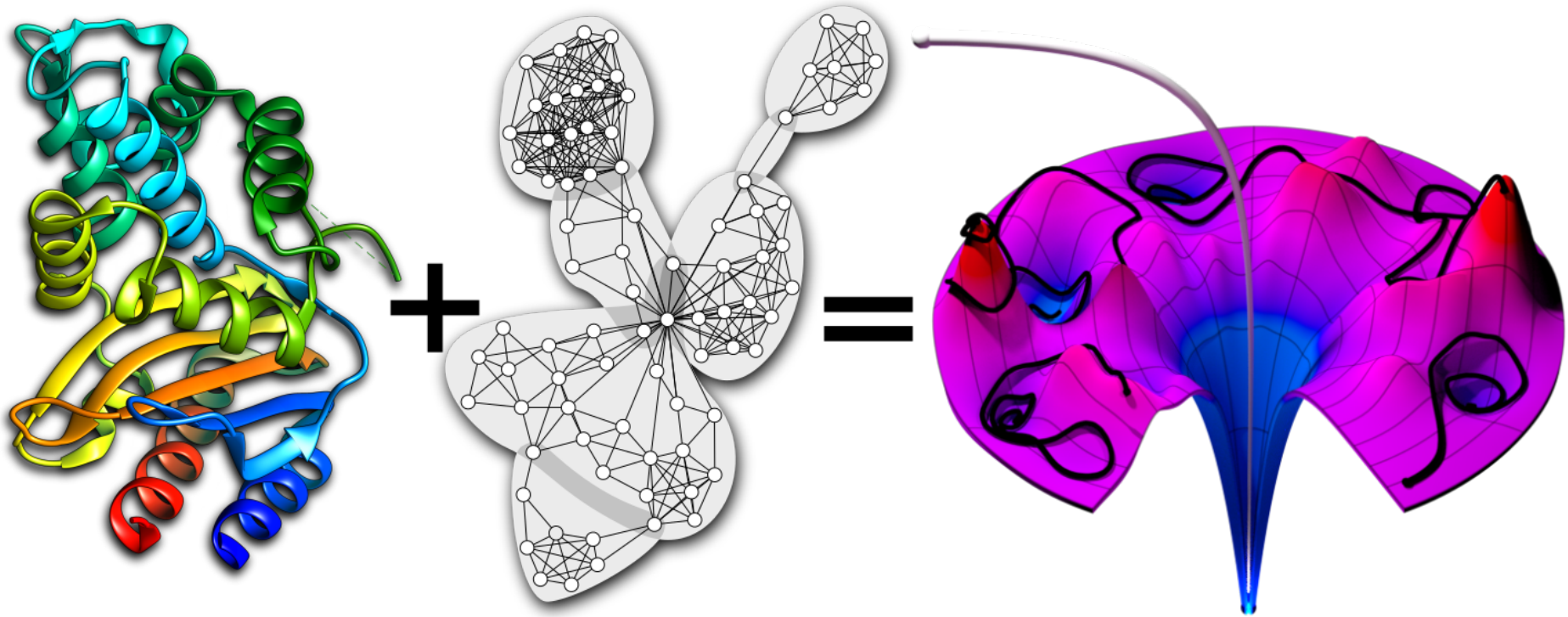
Cost Function Networks

- Variables and domains as usual
- Cost functions $W \ni c_S : D^S \to \{0, \ldots, k\}$ (k finite or not)
- Cost combined by (bounded) addition[3] (other: valued CSP[14]).

$$cost(t) = \sum_{c_S \in C} c_S(t[S]) \qquad c_\varnothing : \text{lower bound}$$

A solution has cost $< k$. Optimal if minimum cost.

Wooo beautiful artwork



Fixed BB discrete rotamers GMEC as a CFN

Straightforward

- Variables: mutable, flexible residues and rotamers
- Domains: available rotamers
- Cost functions:

$$E(c) = E_{\varnothing} + \sum_{i=1}^{n} E(i_r) + \sum_{i<j} E(i_r, j_s)$$

Just shift all energies to make them non negative.

Finding the GMEC is NP-hard[12]

Our secret recipe

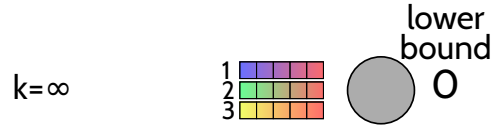
Four main ingredients

1. Depth First Branch and Bound
2. Good initial upperbound
3. Local consistency filtering induced lower bounds instead of DEE
4. Treewidth based problem decomposition

Depth First Branch and bound

Initial upper bound k

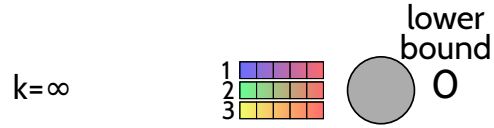
1. Compute a lower bound on the GMEC energy



Depth First Branch and bound

Initial upper bound k

1. Compute a lower bound on the GMEC energy
2. is it $\geq k$?



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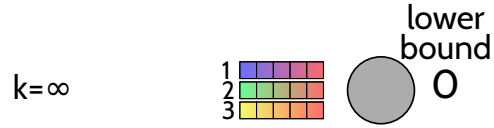

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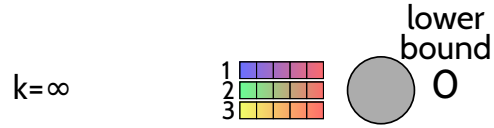

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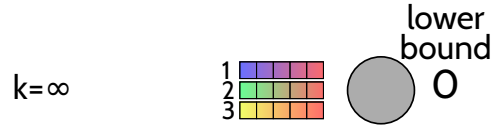

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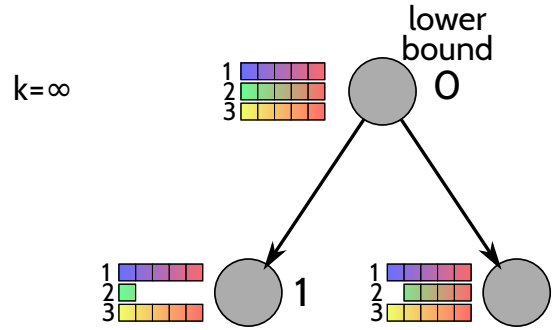
6. For each subset



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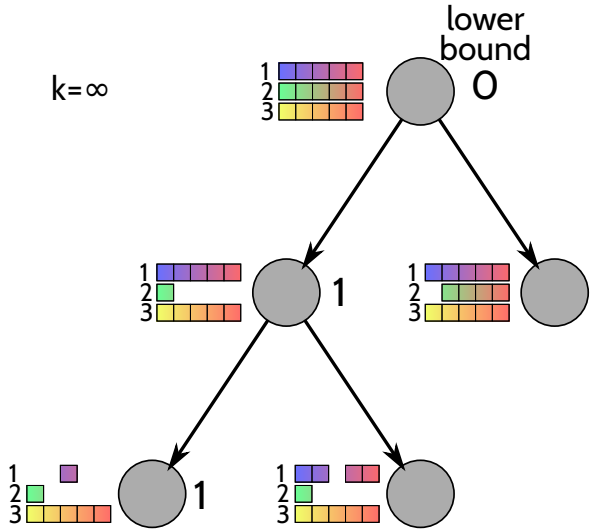

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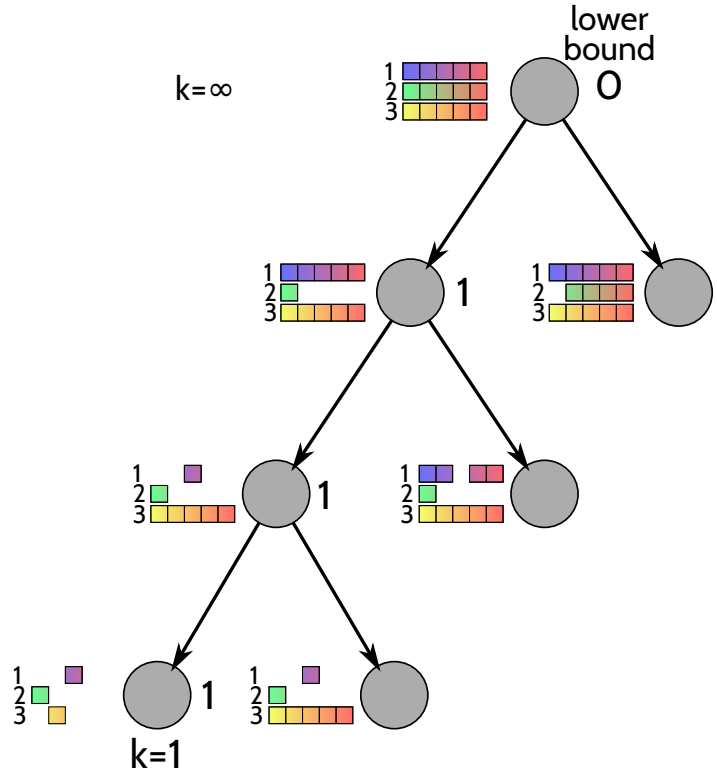

1. When a solution is found, update k to its energy.
2. DFS vs. A^* (BFS): polynomial space vs. exponential space.

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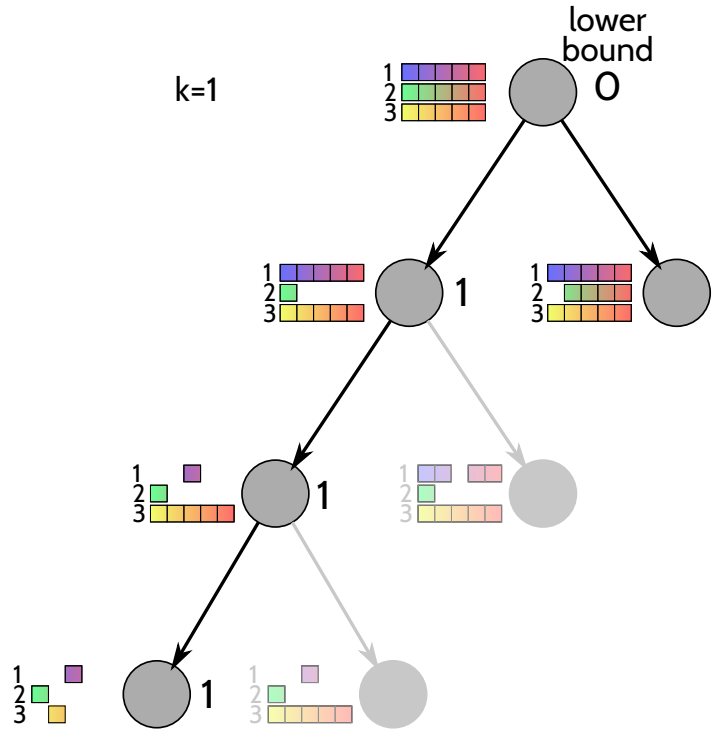

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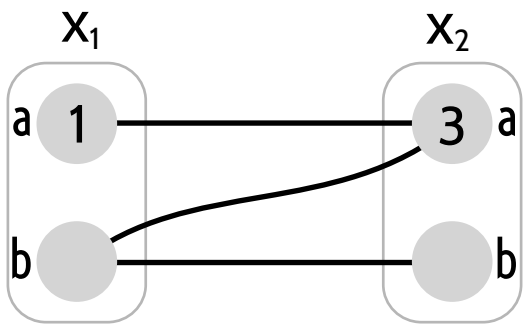
Improving the bound $c_\varnothing$

Assume that initially $c_\varnothing = 0, k = 4$



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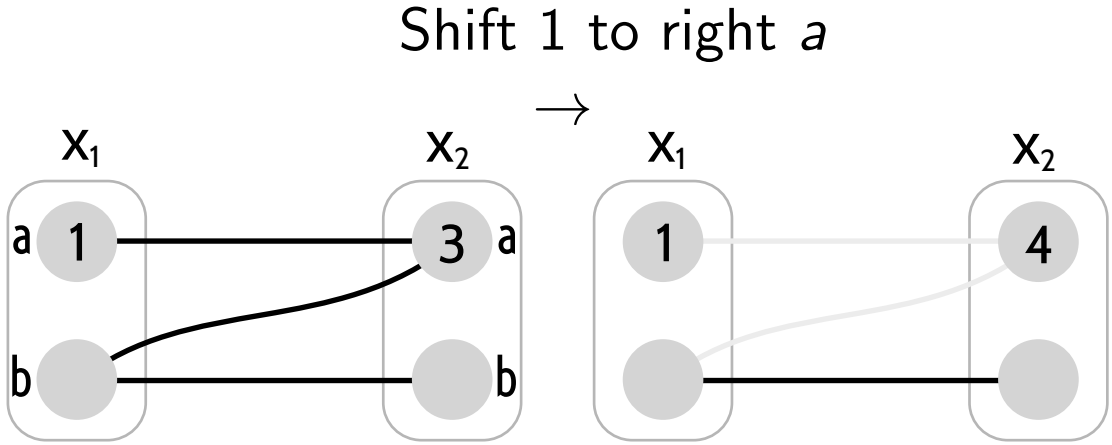

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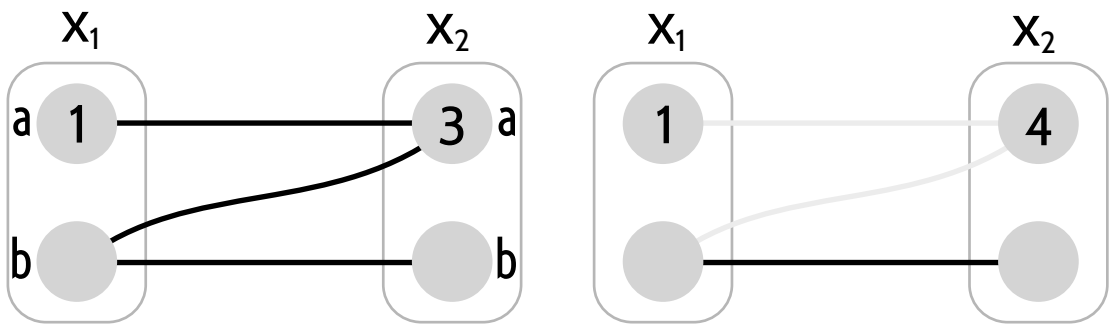


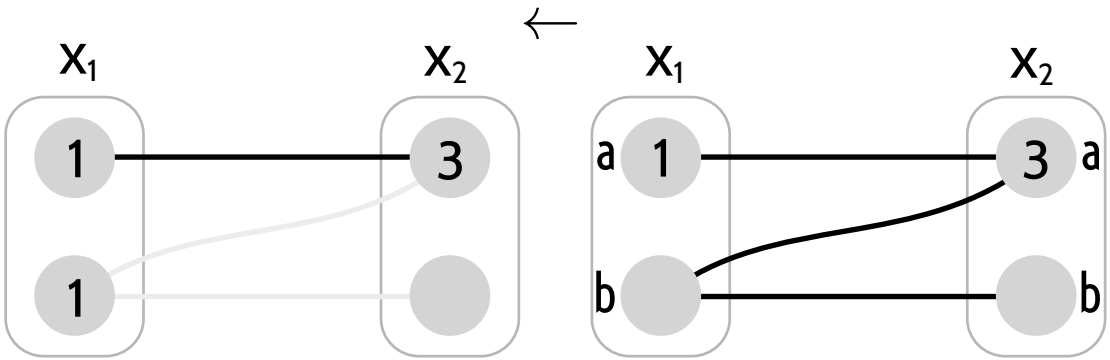
$\leftarrow$

Shift 1 from right a

Improving the bound $c_\varnothing$

Assume that initially $c_\varnothing = 0, k = 4$

Shift 1 to left b



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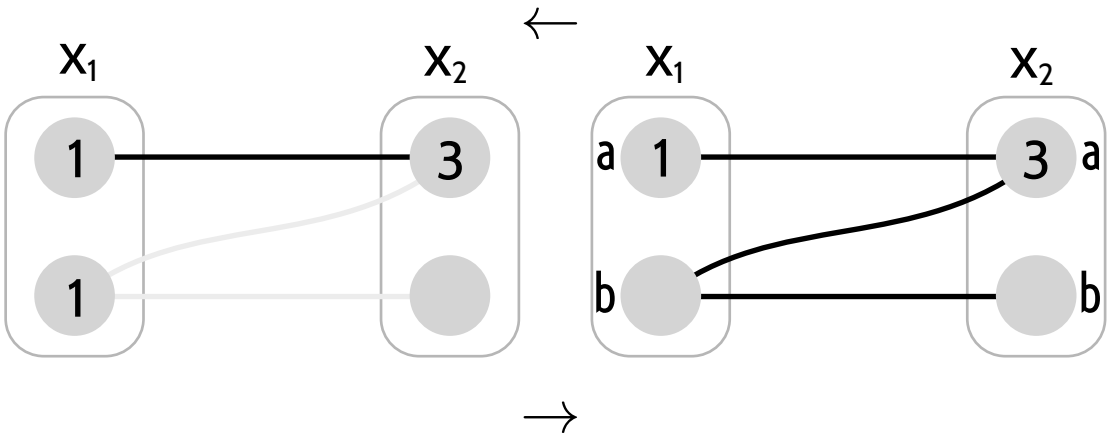

Shift 1 from left b

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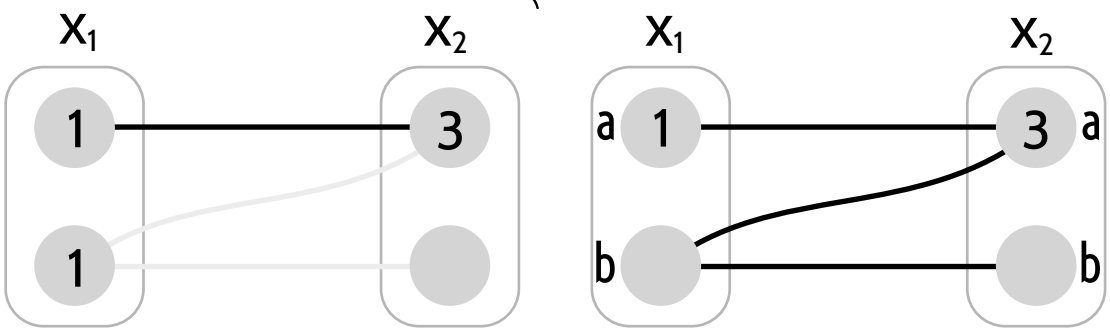
$\leftarrow$

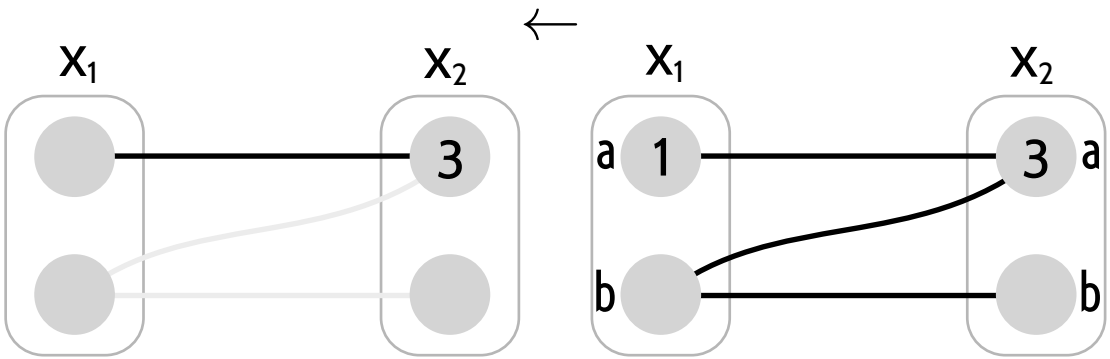


$\Downarrow$ Shift 1 from x_1 to $c_\varnothing$

Improving the bound $c_\varnothing$

Assume that initially $c_\varnothing = 0, k = 4$

Shift 1 to left b



$\Downarrow$ Shift 1 from x_1 to $c_\varnothing$

$c_\varnothing = 1$

Improving the bound $c_\varnothing$

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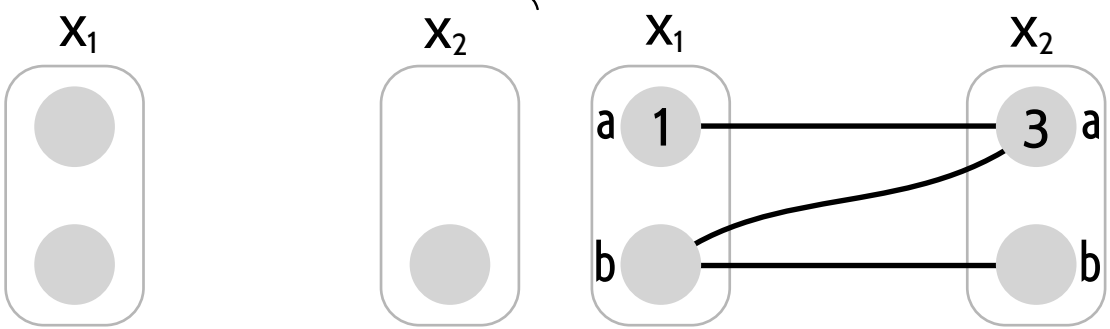
$\leftarrow$



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Preserves global energy below k

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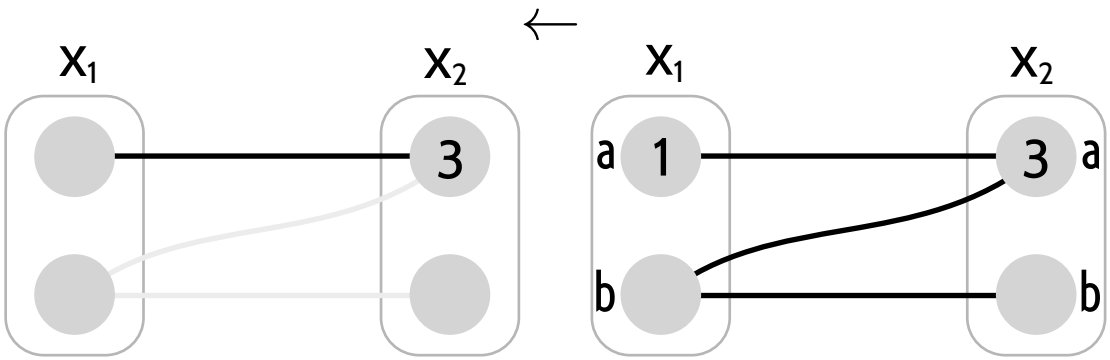


$\Downarrow$ Shift 1 from x_1 to $c_\varnothing$

$c_\varnothing = 1$

Preserves global energy below k

DEE does not

Local consistencies

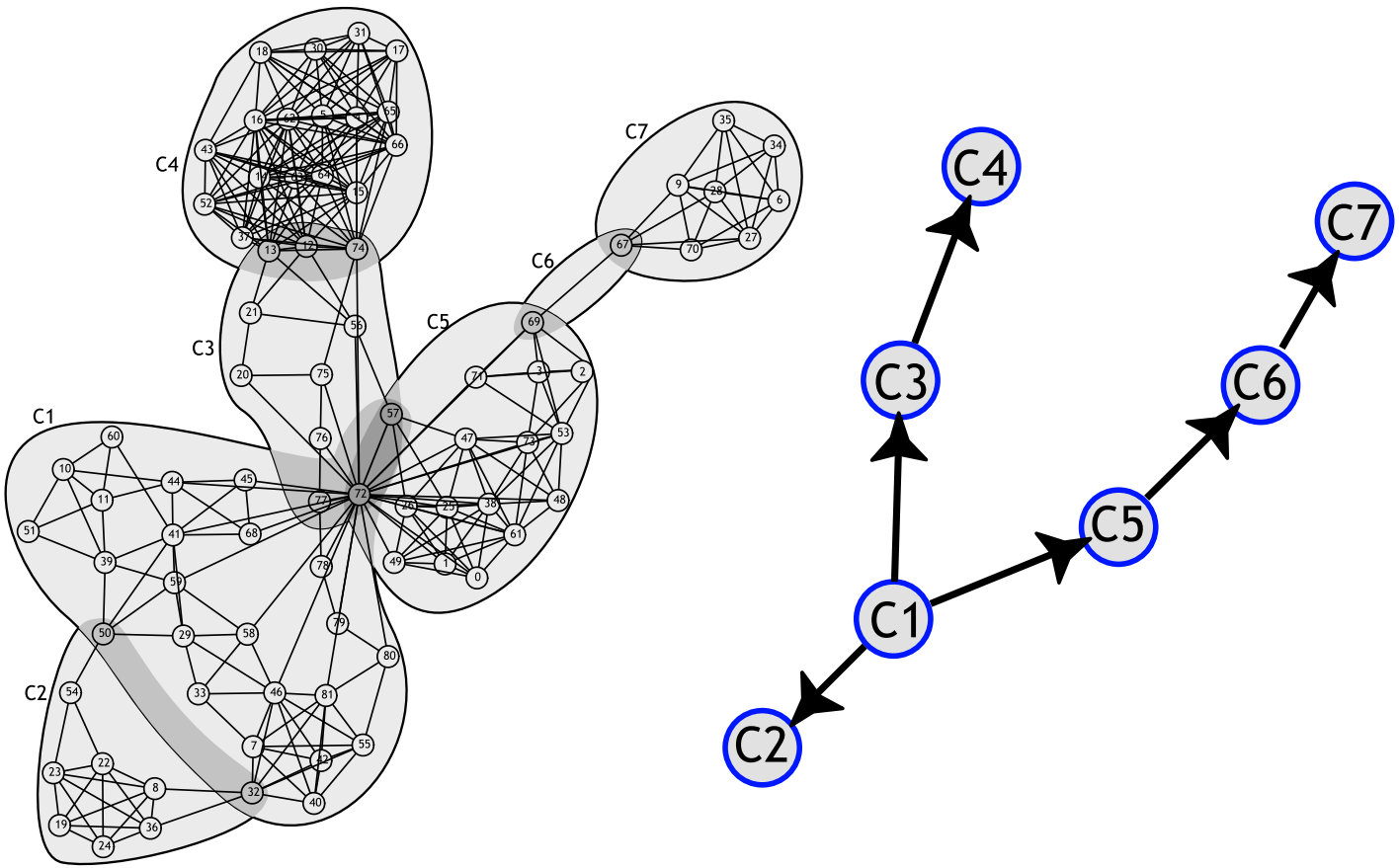
Optimize transformations to maximize lower bound

1. Arc Consistency[13]
2. (Full) Directional Arc Consistency[9]
3. Full Existential Directional Arc Consistency[10]
4. Virtual Arc Consistency[4,5]
5. Optimal Soft Arc Consistency (LP)[2,5]

Tree decomposition

Tree of bags

Decomposition of a problem in a well-formed (RIP) tree of bags of variables.



Full redesign of 107 short proteins

Why full redesigns

1. Challenging
2. Used on $\beta 1$ domain of protein G to tune energy function parameters[1].

The designs

1. Structures extracted from the PDB (September 2014)
2. Length from 50 to 100 AA
3. Resolution better than 2 Å
4. Only representants at 30% identity
5. Talaris14 and Dunbrack's 2010 rotamers
6. PyRosetta: relax + energy matrices

Looking for the Global Minimum Energy Configuration

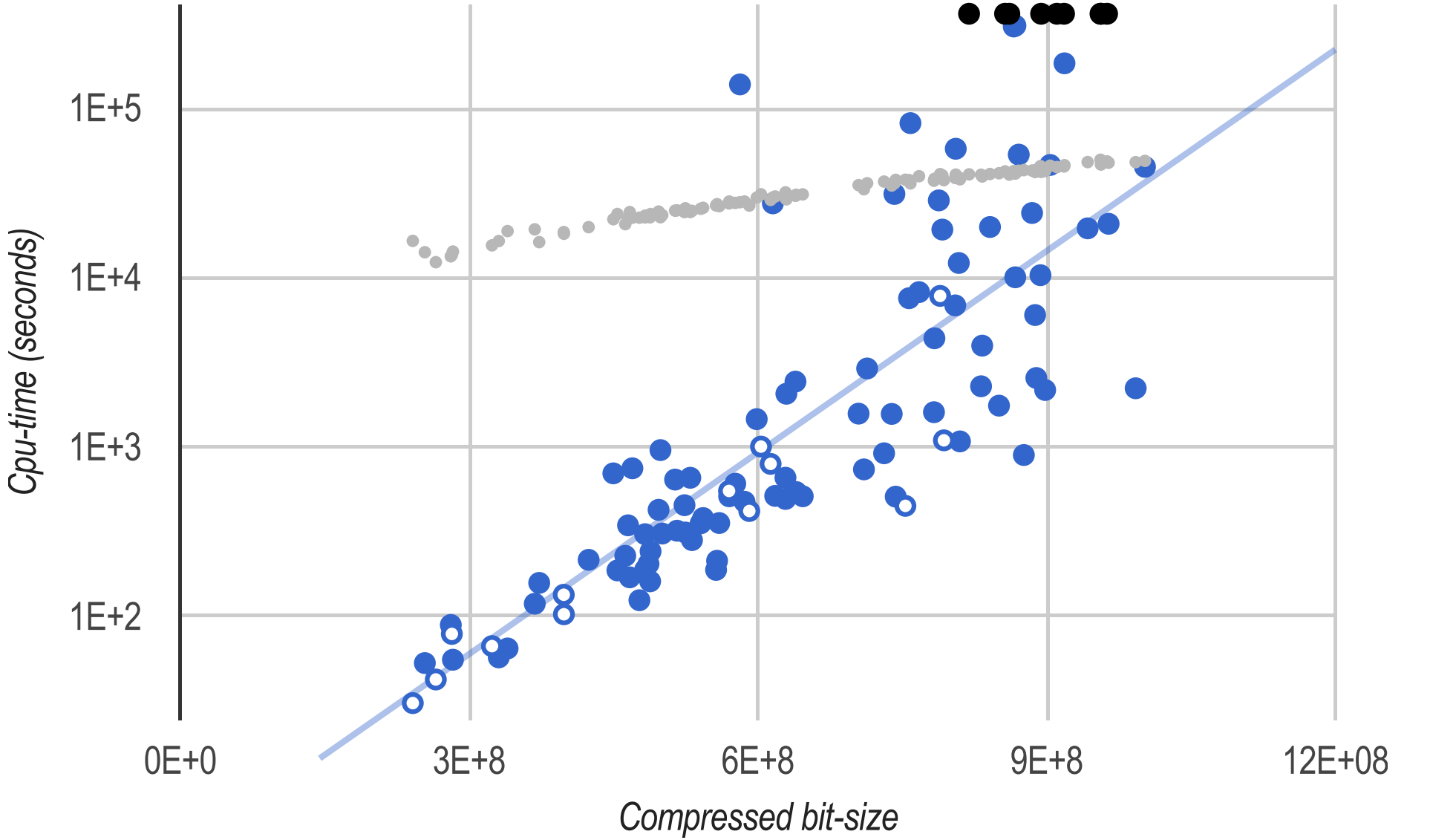
How

1. Intel Xeon E5-2690 2.9GHz (Q1-2012 CPU)
2. Best of 1000 runs of fixbb Rosetta protocol (Simulated Annealing)
3. `toulbar2`: 100 hours limit.

La patate douce

`https://bitbucket.org/satsumaimo/ptcfopd`

Looking for the GMEC



Looking for the GMEC

`toulbar2` (CFN)

1. 98 problems solved to optimality
2. Largest problem solved: 10^{234}, 1.7 GB for energy matrix.
3. Smallest unsolved: 10^{206}.

Looking for the GMEC

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Rosetta/fixbb

1. Rosetta fixbb found the GMEC on 13 of these problems
2. These 13 problems took 90 hours for fixbb.
3. `toulbar2` solved them to optimality in 36 hours.

Exploring Sequence/conformations around of the GMEC

All sequence/conformations in a 0.2 Rosetta unit threshold

1. Same 100h limit

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2. Exhausted sequence/conformation space on 92/98 designs.

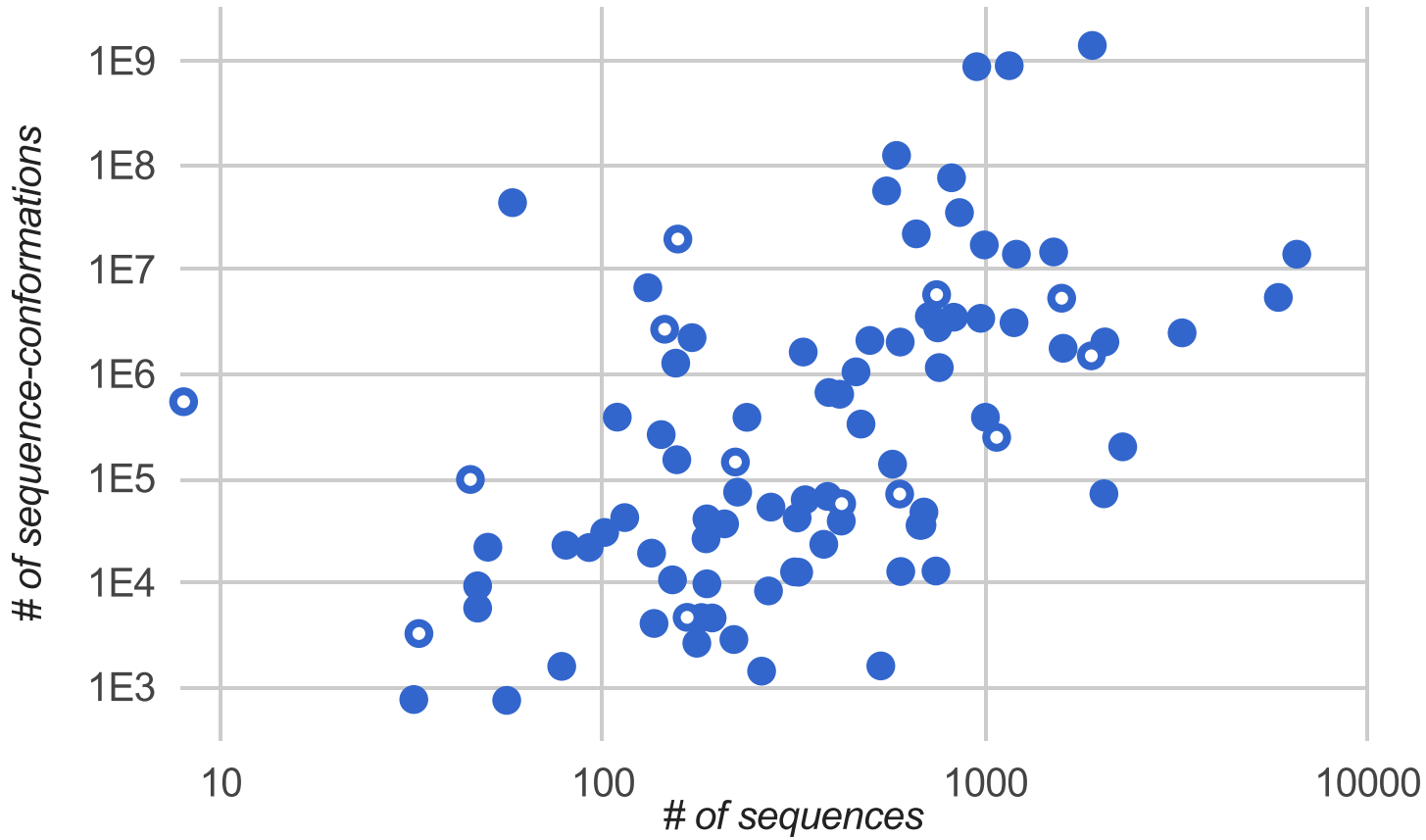
Exploring Sequence/conformations around of the GMEC

All sequence/conformations in a 0.2 Rosetta unit threshold

1. Same 100h limit
2. Exhausted sequence/conformation space on 92/98 designs.
3. Very fast sampling, but huge spaces (up to 1.42 10^9)

Diversity of situations

1. No clear tendancy for simulated annealing success/failure pattern.
2. Not enough successes to see a trend ?



Exploring sequences around the GMEC

Faster exploration of sequences only[15]

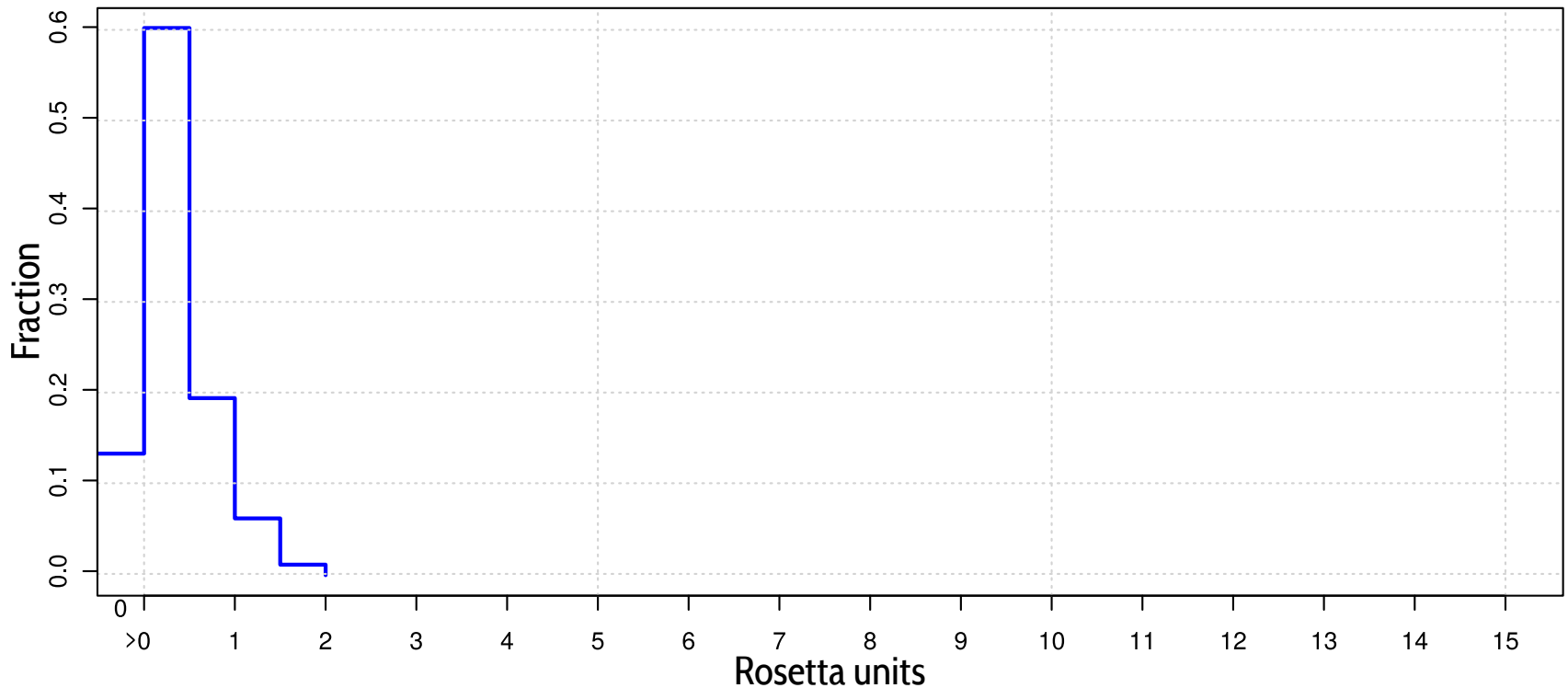
- New "SCP branching" algorithm that explores the sequence space
- Allows to explore far larger energy gaps.
- Gives just one (sub)optimal conformation per sequence.

Faster exploration of sequences only[15]

- A number of CFN algorithms injected directly in OSPREY[6]
- Benefits to continuous/flexible BB design through DEEPer[8], LUTE[7].

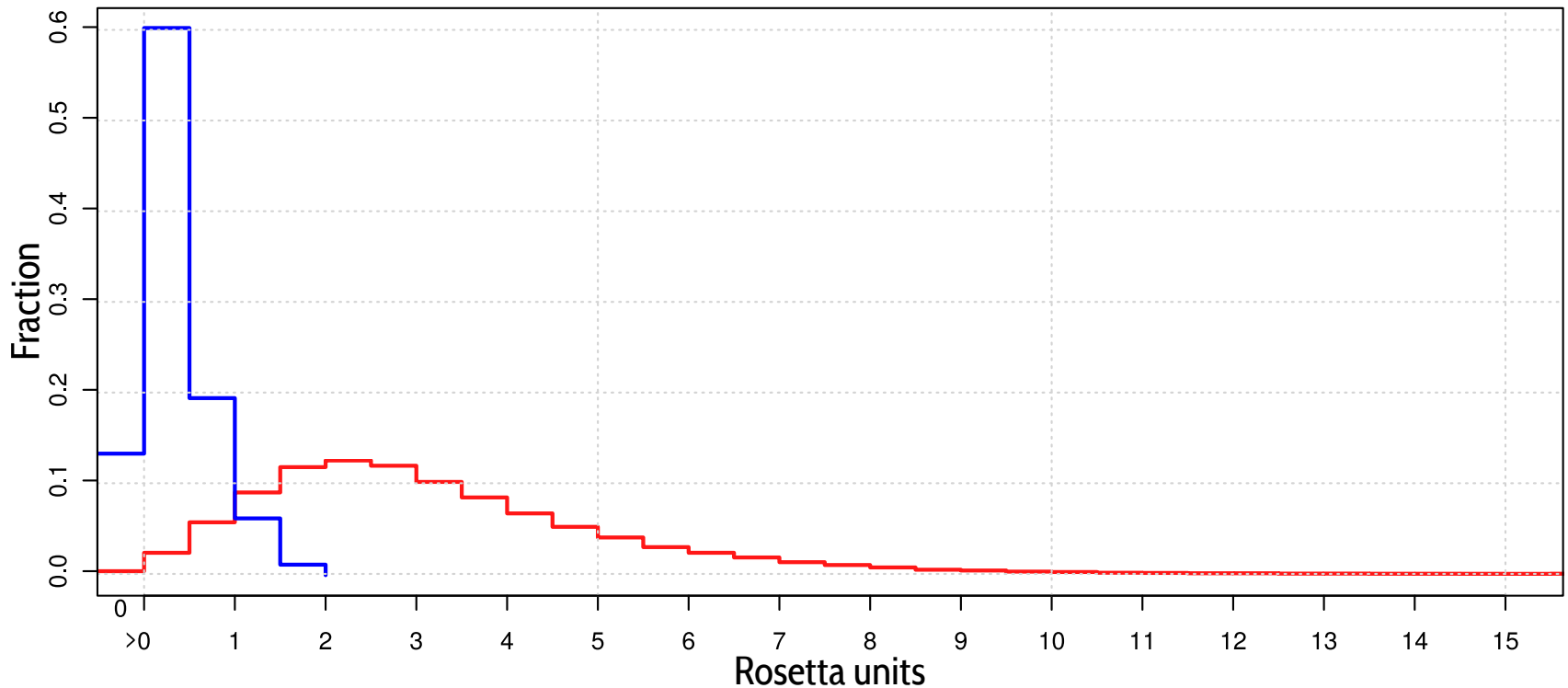
Rosetta fixbb protocol: gap to optimality

- Blue: best over 1 000 runs



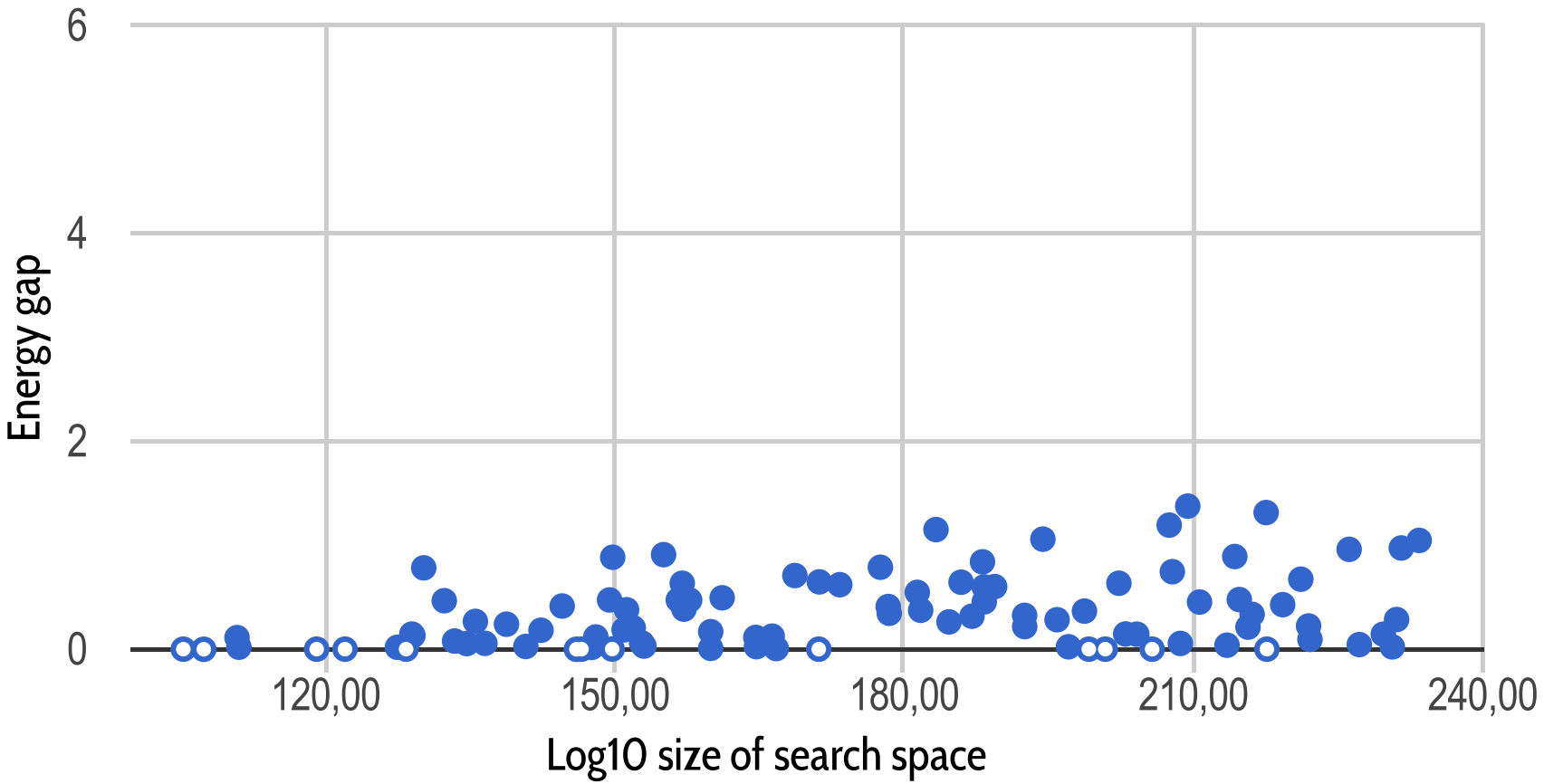
Rosetta fixbb protocol: gap to optimality

- Blue: best over 1 000 runs
- Red: all runs on all designs (worse may be off by 45 RU).



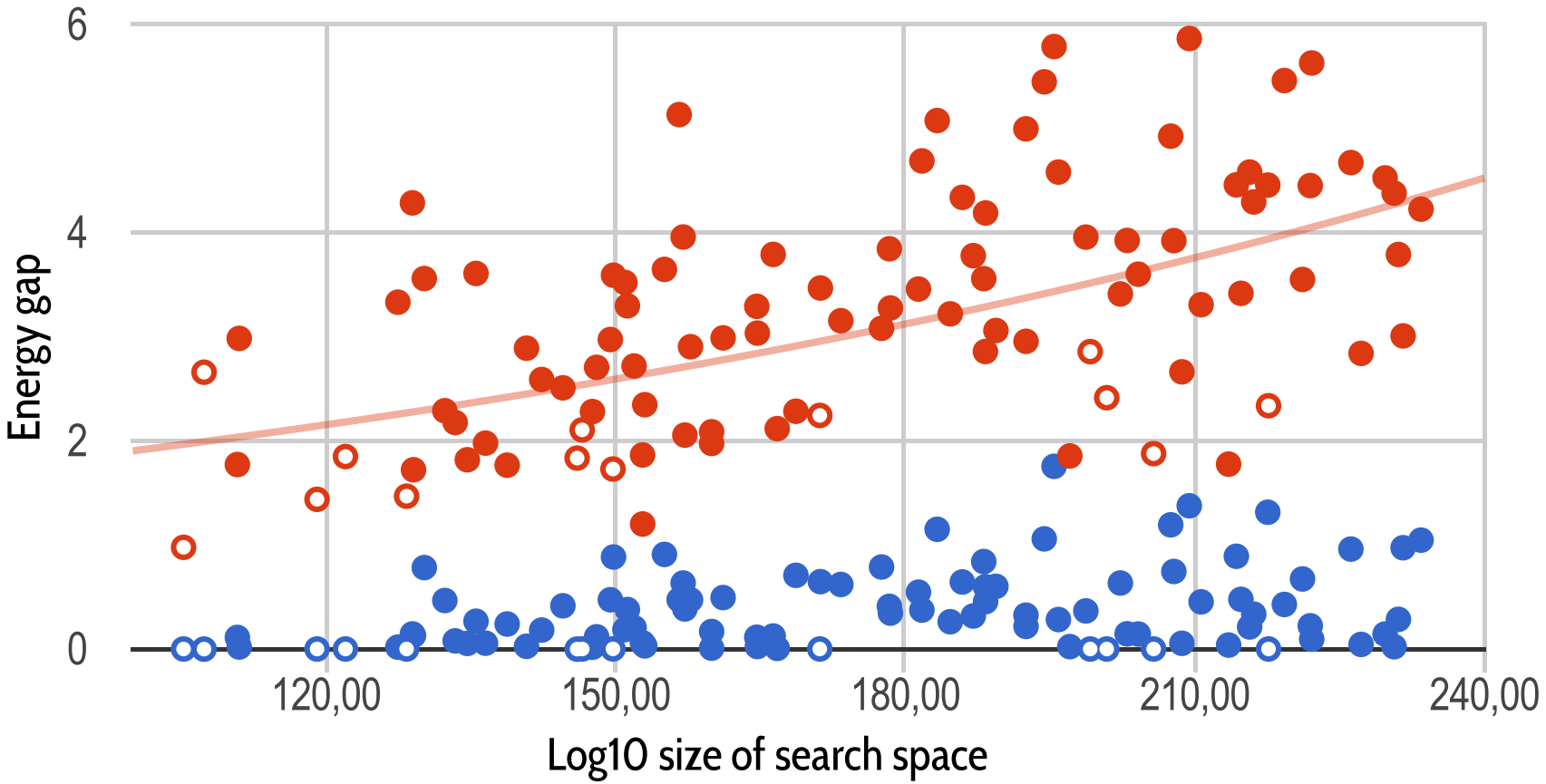
Distance to optimum as a function of space size

- Blue: best over 1 000 runs



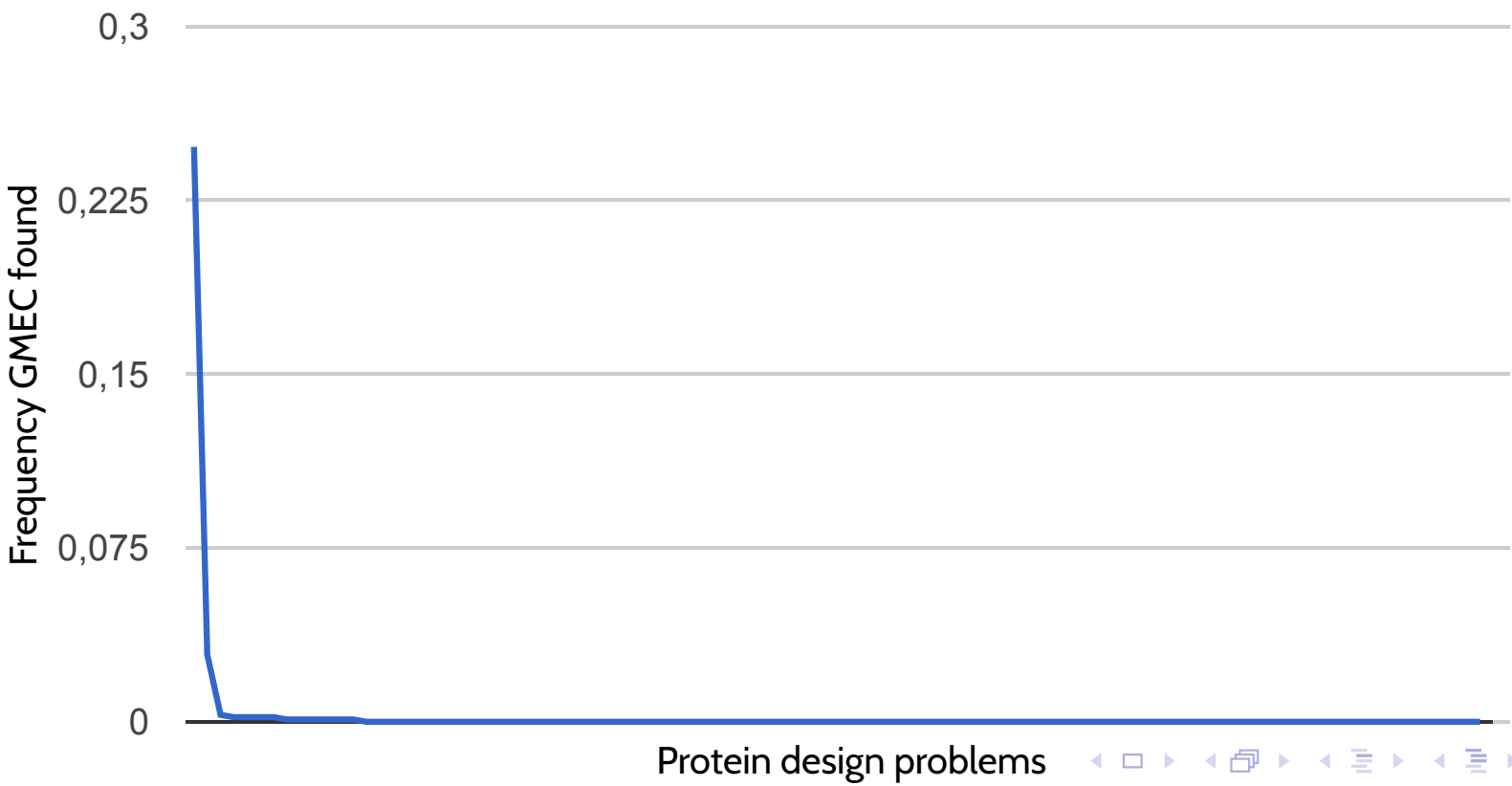
Distance to optimum as a function of space size

- Blue: best over 1 000 runs
- Red: average over 1 000 runs.



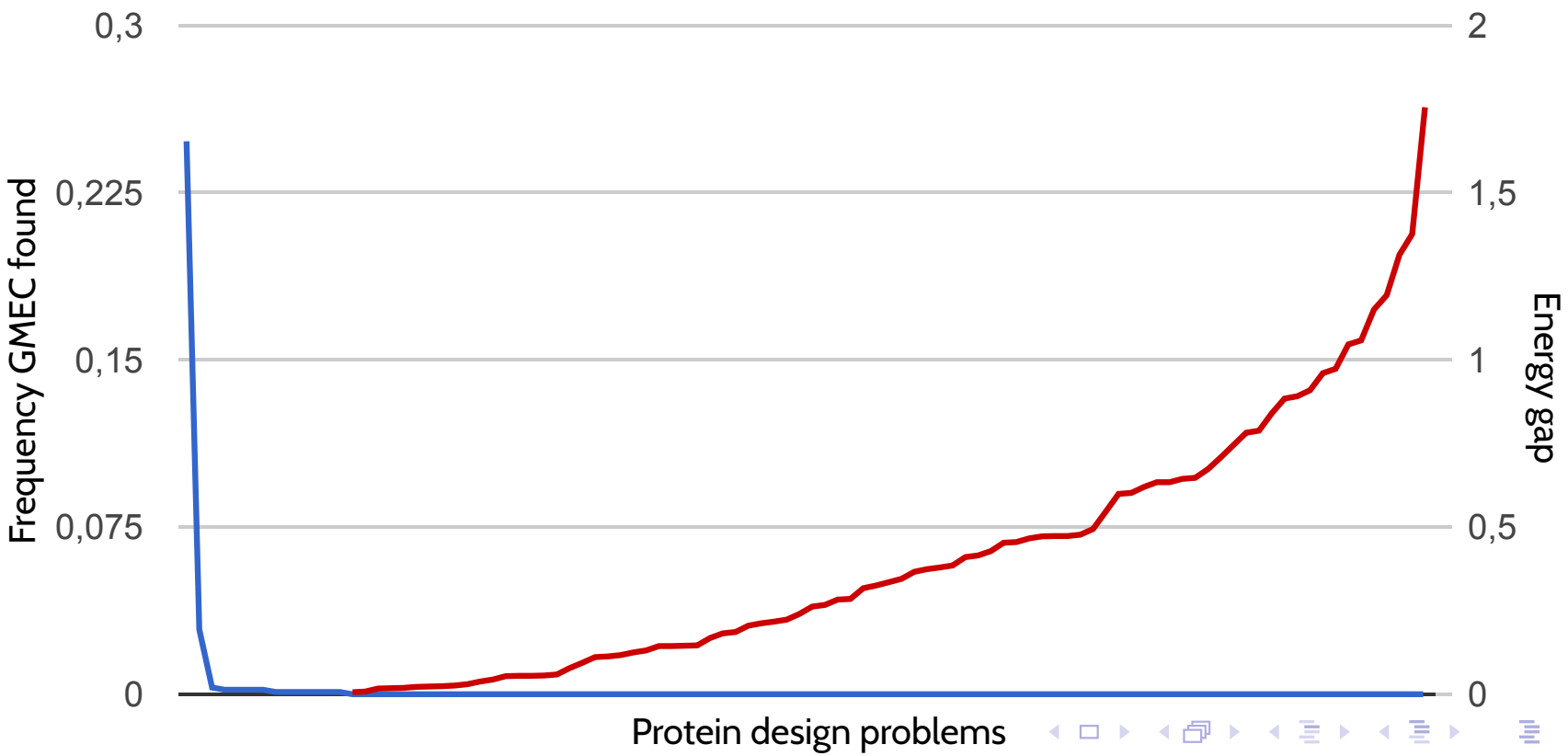
Reliability, distance to optimum and size

- Blue: probability of finding the GMEC (sorted)



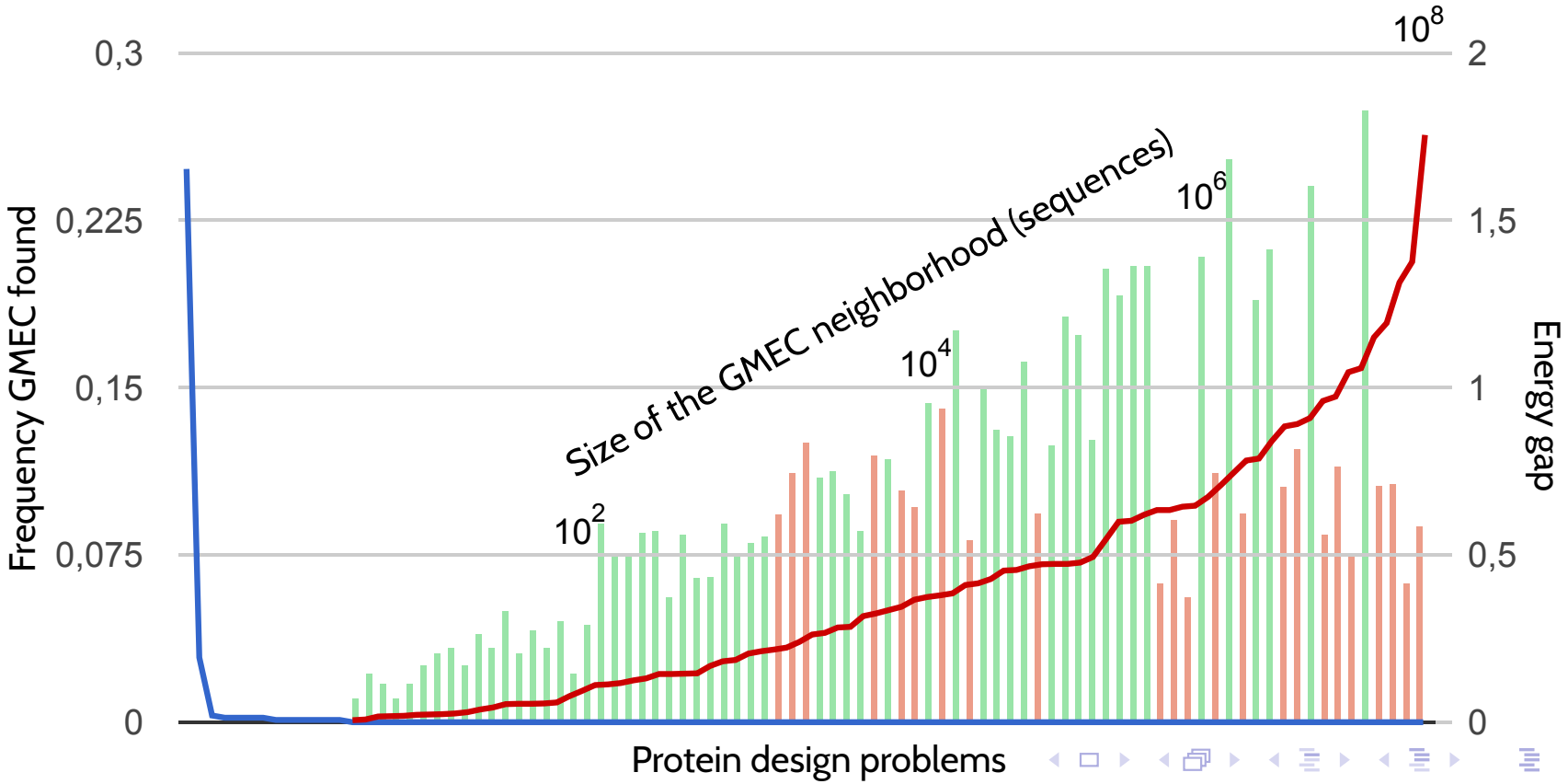
Reliability, distance to optimum and size

- Blue: probability of finding the GMEC (sorted)
- Red: energy gap to GMEC (sorted)



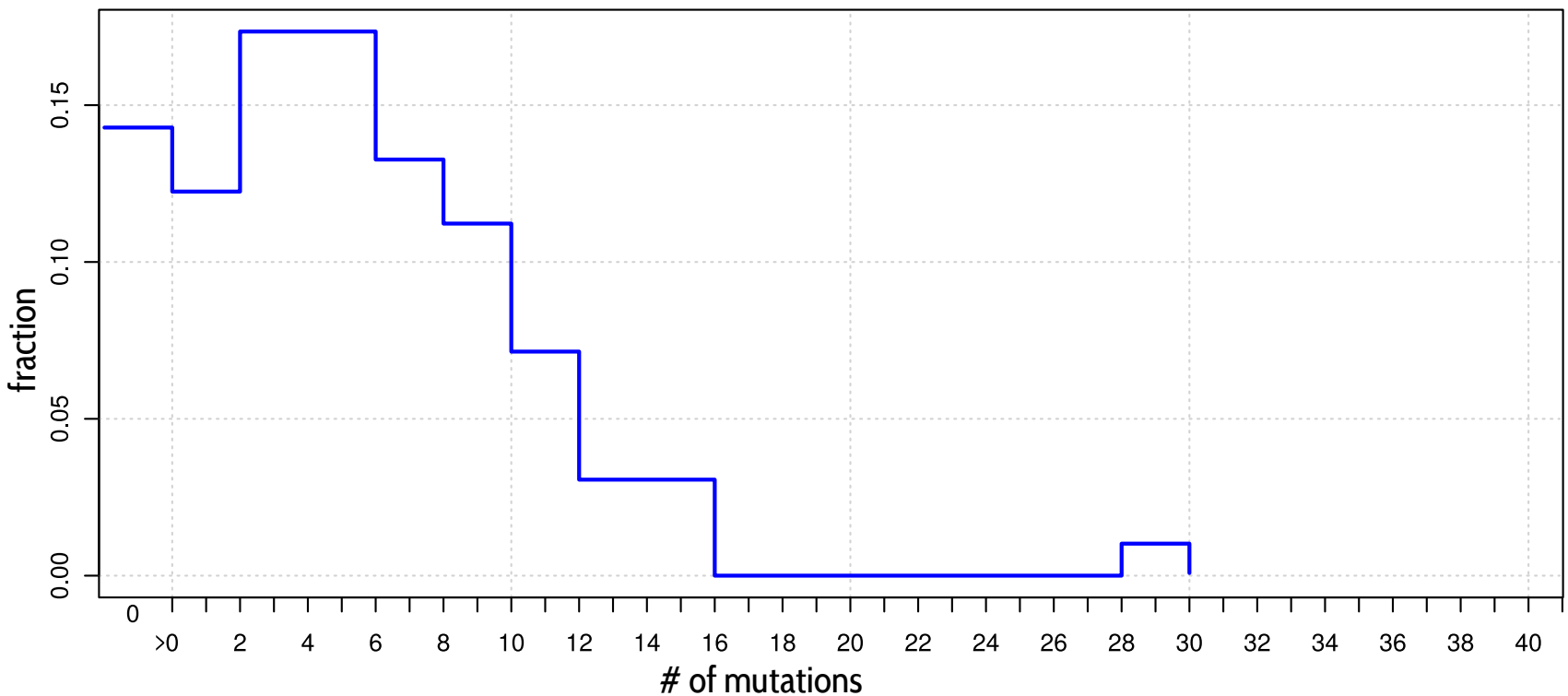
Reliability, distance to optimum and size

- Blue: probability of finding the GMEC (sorted)
- Red: energy gap to GMEC (sorted)
- Histogram: # of unique sequences (x RU gap) (red: lower bound)



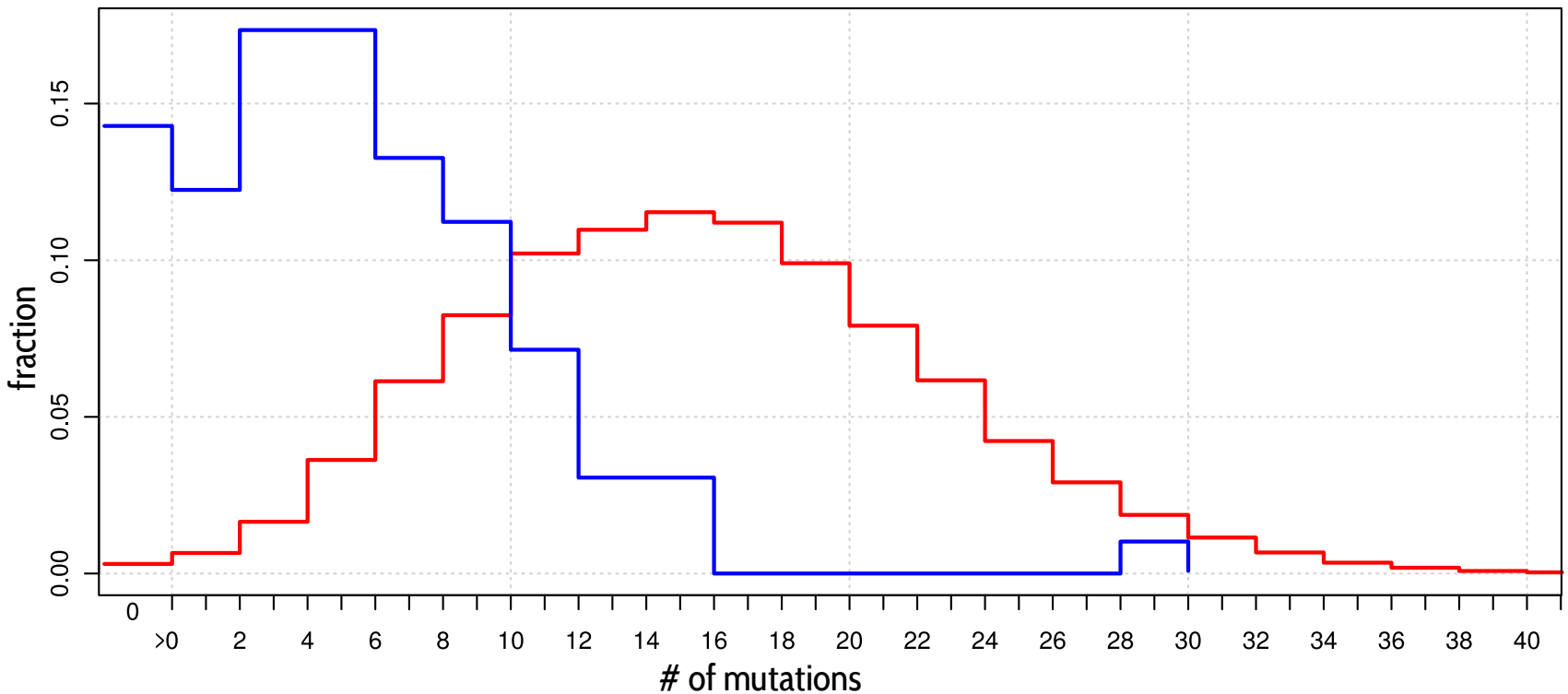
What about sequences: Hamming dist. to GMEC

- Blue: best energy (2.4% core, 7% boundary, 10% surface).



What about sequences: Hamming dist. to GMEC

- Blue: best energy (2.4% core, 7% boundary, 10% surface).
- Red: average over 1 000 runs.



Distance to native as we get closer to the GMEC

Native sequence used to tune energy[1,11].

Distance to native as we get closer to the GMEC

Native sequence used to tune energy[1,11].

Type	native		fixbb best		GMEC
Charged	1,795	↗	1,996	↗	2,097
Aromatic	585	↗	616	↗	622
Polar	1,817	↘	1,730	↘	1,662
Hydrophobic	2,585	↘	2,440	↘	2,401

Cysteines in disulfide bridges: not counted.

Possible lessons

Monte Carlo sampling

- Fixbb SA becomes quickly unable to reach lowest energy regions
- Energy gap increases quickly with the number of mutable residues

Guarantees

- GMEC may be not crucial, but an *upper bound on error* is important
- Guaranteed optimum have different composition
- Talaris favorable for guaranteed optimization (but exponential barrier)
- Exhaustive enumeration can be very fast (but exponential size output)

Continue to contribute to CPD

1. Injected in OSPREY, contributes to “flexible” modeling

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1. Injected in OSPREY, contributes to “flexible” modeling
2. Conformational entropy contribution to affinity
3. Improve the “CPD” model
4. beyond pairwise decomposition[7]
5. multistate (positive/negative)
6. symmetric and fragment design

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