Optimally Solving Hard Combinatorial Problems in Computational Biology

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Multiple Sequence Alignment

T_1 A_2 C_3 G_4 T_5 A_6

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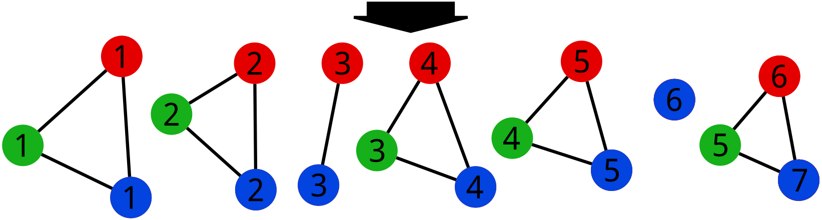

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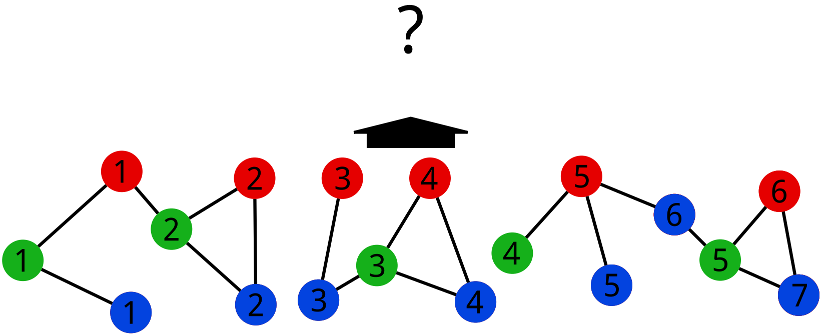

Idea

Use alignment graph constructed by local alignment to reconstruct global alignment.

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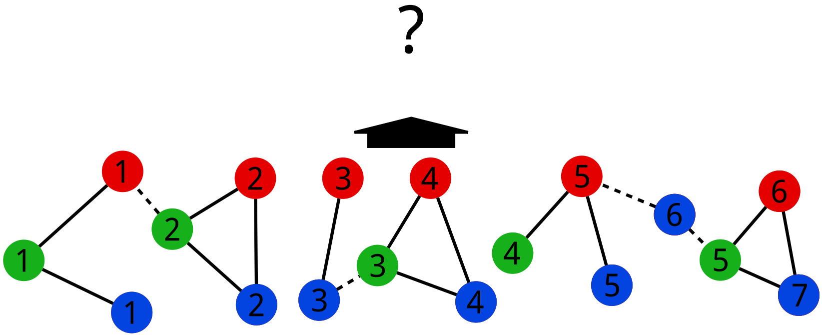

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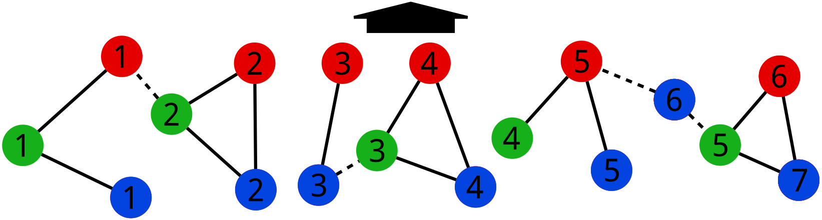

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Colorful Components

Part of a Multiple Sequence Alignment pipeline suggested by Corel, Pitschi & Morgenstern (Bioinformatics 2010).

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Colorful Components

Instance: An undirected graph $G = (V, E)$ and a coloring of the vertices $\chi : V \to \{1, \ldots, c\}$.
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Other application: Orthologs in multiple genomes: From the set of all pairwise homologies, find disjoint orthology sets of genes.
[Zheng, Swenson, Lyons & Sankoff, WABI ’11]

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- Colorful Components can be approximated by a factor of $4\ln(c+1)$.

Exact solutions

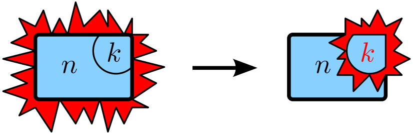
Want to solve COLORFUL COMPONENTS exactly:

- Can interpret solutions within the model;
- Can differentiate between weaknesses of model and weaknesses of algorithm;
- Can judge quality of heuristics;
- Time-limited exact algorithms often give good heuristics.

Fixed-parameter algorithms

Idea

Find an algorithm that gives optimal solutions and thus has exponential running time, but restrict the combinatorial explosion to a *parameter*.



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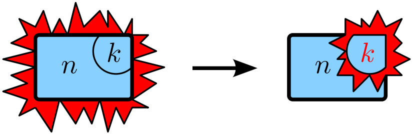

Definition

A problem is called fixed-parameter tractable with respect to a parameter k if an instance of size n can be solved in $f(k) \cdot n^{O(1)}$ time for an arbitrary function f.

Fixed-parameter algorithm

Observation

COLORFUL COMPONENTS can be seen as the problem of destroying by edge deletions all bad paths, that is, simple paths between equally colored vertices.

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Theorem

COLORFUL COMPONENTS can be solved in $O(c^k \cdot m)$ time, where k is the number of edge deletions.

Improved fixed-parameter algorithm

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Colorful Components can be solved in $O((c-1)^k \cdot m)$ time, where k is the number of edge deletions.

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Proof.

If there is a degree-3 or higher vertex v, find a bad path with at most $(c-1)$ edges by BFS from v. Otherwise, the instance is easy. □

Limits of fixed-parameter algorithms

Question

How much further can we improve this algorithm?

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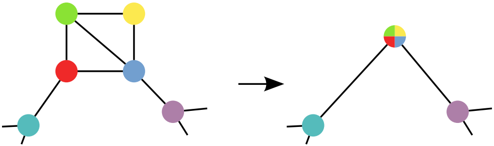
Theorem

Colorful Components with three colors cannot be solved in $2^{o(k)} \cdot n^{O(1)}$ unless the Exponential Time Hypothesis is false.

Data reduction

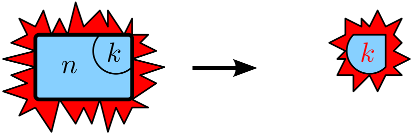
Data reduction

Let $V' \subseteq V$ be a colorful subgraph. If the cut between V' and $V \setminus V'$ is at least as large as the connectivity of V', then merge V' into a single vertex.



Kernelizations

- In classical (one-dimensional) complexity analysis, nothing can be proven about the power of data reduction.
- In parameterized complexity, we have the concept of a *problem kernel*: a data reduction rule that creates an instance whose size depends only on the parameter k, and not on the original input size n anymore.



Data

- We generated one Colorful Components instance for each multiple alignment instance from the BAliBASE 3.0 benchmark.
- We restricted the experiments to the 135 of instances that have at most 10 colors.

Data reduction: Largest connected component

	original			after data red.		
	n	m	c	n	m	c
average	504	921	6.2	354	607	5.3
median	149	232	6	42	58	5

Branching algorithms: running time

	< 1 s	1 s to 10 min	> 10 min
branching branching	70	9	56

Sequence alignment quality

DIALIGN with several methods for solving the COLORFUL COMPONENTS subproblem:

	TC score
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DIALIGN with the min-cut heuristic is about 10 percentage points worse than current state-of-the-art multiple alignment methods. Hence, an improvement of 3 percentage points is a sizable step towards closing the gap between DIALIGN and these methods.

Integer Linear Programming

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Commercial solvers like CPLEX and Gurobi profit from decades of engineering and can often solve real-world instances surprisingly fast.

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maximize $\sum_{\{u,v\}\in E} w_{uv} e_{uv}$ where

$$w_{uv} = \begin{cases} -\infty & \text{if } \chi(u) = \chi(v), \\ 1 & \text{if } \{u, v\} \in E, \\ 0 & \text{otherwise.} \end{cases}$$

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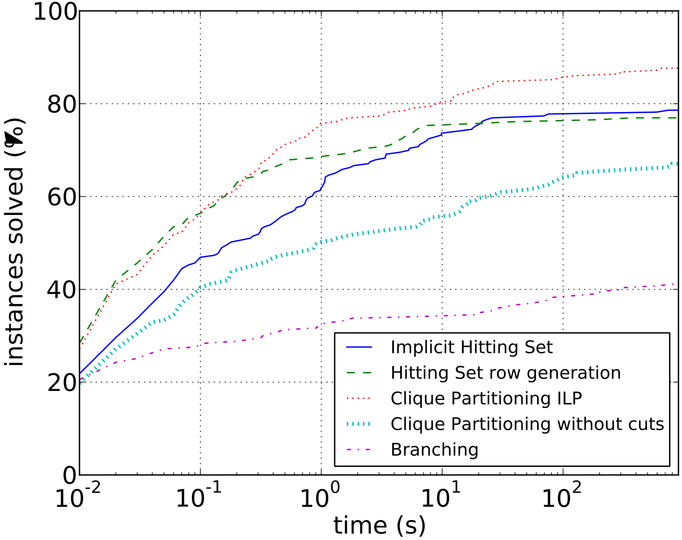
subject to

$$e_{uv} + e_{vw} - e_{uw} \leqslant 1$$

Wikipedia interlanguage links

- 30 most popular languages
- 11,977,500 vertices, 46,695,719 edges
- 2,698,241 connected components, of which 2,472,481 are already colorful
- largest connected component has 1,828 vertices and 14,403 edges
- solved optimally by data reduction + ILP in about 80 minutes
- 618,660 edges deleted, 434,849 inserted.

Random graph model



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- Current technologies like two-hybrid screening can find protein interactions, but cannot decide their direction.
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Graph Orientation

Instance: An undirected graph $G = (V, E)$ and a set $P \subseteq V \times V$ of source–target pairs.
Task: Find an orientation of each edge in E such that for a maximum number of $(s, t) \in P$ there is a directed path from s to t.

Graph orientation

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Join the vertices of a cycle into a single vertex.

Observation

We can assume w. l. o. g. that the input is a tree.

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Theorem (Medvedovsky, Bafna, Zwick & Sharan, WABI ’08)

TREE ORIENTATION is NP-hard, even if the tree has diameter two or maximum degree three.

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Theorem

Tree Orientation can be reduced to Vertex Cover on the conflict graph.

Parameters

p: number of pairs: $2^p \cdot n^{O(1)}$
k: number of unsatisfied pairs: $1.38^k \cdot n^{O(1)}$
m_v: max. number of paths over a tree vertex: $2^{m_v} \cdot n^{O(1)}$
q_v: max. number of cross paths over a tree vertex: $2^{q_v} \cdot n^{O(1)}$
m_e: max. number of paths over an edge: NP-hard for $m_e \geqslant 3$

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n	p	k	m_v	q_v	m_e
799	2014	17	2014	3	59
796	2443	46	2443	35	275
638	2311	68	2310	151	208
441	787	75	785	88	45
299	477	110	411	75	165
192	167	32	161	24	86
114	27	2	26	2	21

Experiments

Data reduction for Vertex Cover

Take the neighbor of a degree-1 vertex into the cover.

Running time:

Branching	0.13s
ILP	0.02s

Conclusions

- Fixed-parameter algorithms can often solve hard problems optimally and have useful worst-case bounds;
- Data reduction can substantially speed up algorithms for hard problems and should always be used, whether using exact or heuristic approaches;
- Integer Linear Programming often yields a simple way to solve hard problems fast.