Finding Largest Common Substructures of Molecules in Quadratic Time

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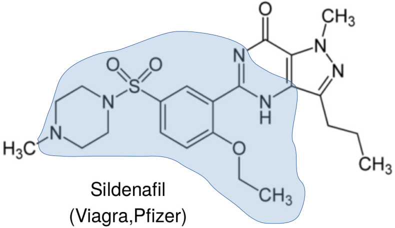
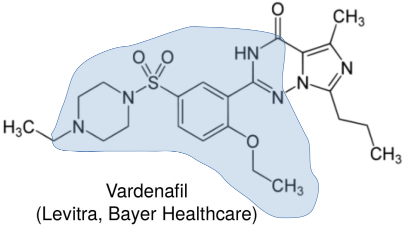
43rd International Conference on Current Trends in Theory and Practice of Computer Science (SOFSEM-FOCS 2017)
January 16 – 20, 2017



Sildenafil
(Viagra,Pfizer)



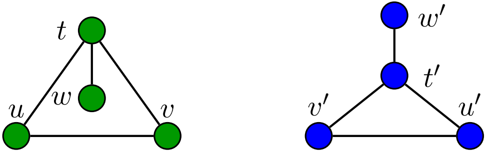
Vardenafil
(Levitra, Bayer Healthcare)

Motivation

- Common Substructure is a natural measurement of similarity
  - Useful for prediction of biological activity and reaction site modeling [Raymond, Willett 2002]

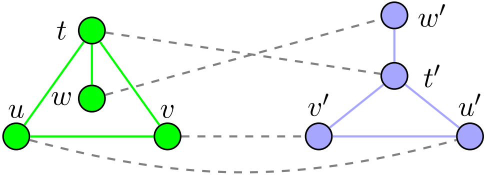
Graph isomorphism

Input: Graphs G and H



Graph isomorphism

Input: Graphs G and H
Output: A Bijection $\varphi : V_G \to V_H$ with
$\forall x, y \in V_G$: $xy \in E_G \Leftrightarrow \varphi(x)\varphi(y) \in E_H$



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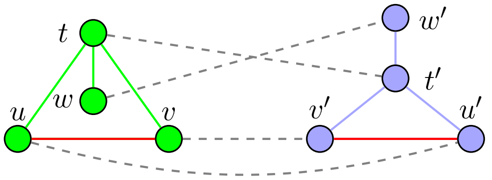
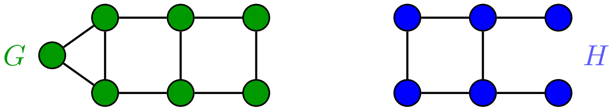


Example: $uv \in E_G$ and $u'v' \in E_H$
$uw \notin E_G$ and $u'w' \notin E_H$

Maximum Common *Edge* Subgraph (MCES)

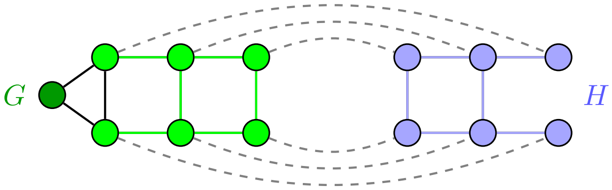
Input: Graphs G and H



Maximum Common *Edge* Subgraph (MCES)

Input: Graphs G and H

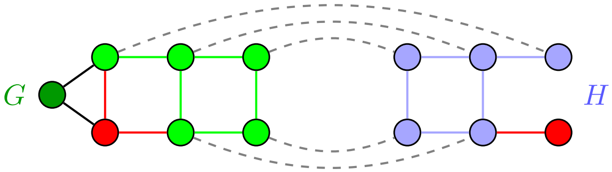
Output: An isomorphism between connected subgraphs of G and H with the maximum possible number of edges



Maximum Common *Induced* Subgraph (MCIS)

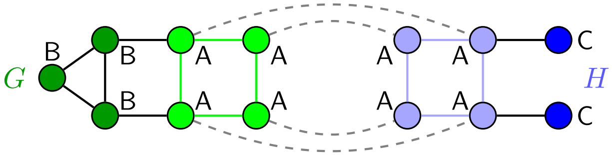
Input: Graphs G and H

Output: An isomorphism between connected *induced* subgraphs of G and H with the maximum possible number of *vertices*

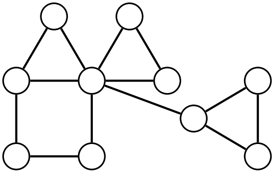


Maximum Common *Induced* Subgraph; labeled

Input: Labeled graphs G and H
Output: A maximum common induced subgraph with respect to the labels



Outerplanar graph: A graph admitting a planar embedding with each vertex on the outer face



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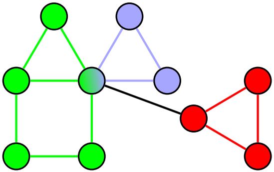

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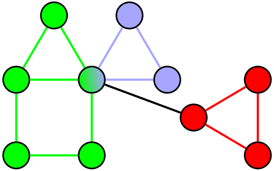
Bridge: Each remaining edge with its incident vertices



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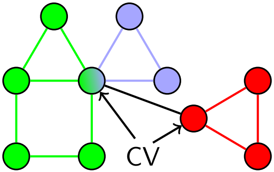

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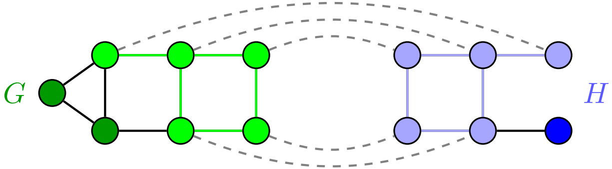

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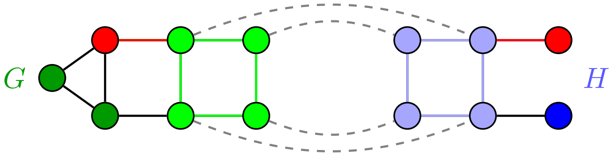

MCIS with Block and Bridge Preserving (BBP)

BBP1: Blocks of common subgraph ↦ blocks of G and H
BBP2: Bridges of common subgraph ↦ bridges of G and H

Complexity of Maximum Common Subgraph

NP-hard on the following graph classes

- General graphs
- Outerplanar graphs [Syslo 1982]
- Trees, if we want to find a common forest [Brandenburg 2000]

Complexity

Polynomial time results on the following graph classes

- Trees: $\mathcal{O}(|G||H|\Delta)$ [D., K., M. 2016]
- Outerplanar graphs, MCS is biconnected
  - MCES: $\mathcal{O}(|G||H|)$ [Schietgat, Ramon, Bruynooghe 2013]
  - MCIS: $\mathcal{O}(|G||H|)$ [Kriege 2015]

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BBP in molecular graphs

- Ring structures are kept intact
- Computation time of few ms

Computing a BBP-MCIS between two outerplanar graphs

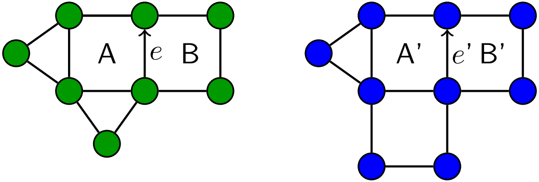
1. Biconnected MCIS between biconnected outerplanar graphs

Computing a BBP-MCIS between two outerplanar graphs

1. Biconnected MCIS between biconnected outerplanar graphs
2. Connect the blocks and bridges → BBP-MCIS

Properties of biconnected outerplanar graphs

- Outerplanar embedding is unique
- Each edge is incident to exactly two uniquely defined faces



Lemma: Given an arc and face mapping, there is exactly one maximal isomorphism fulfilling that mapping.

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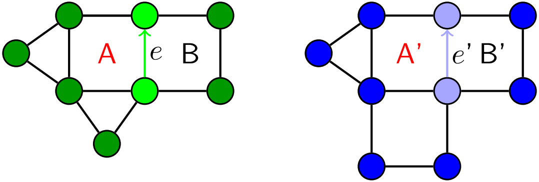

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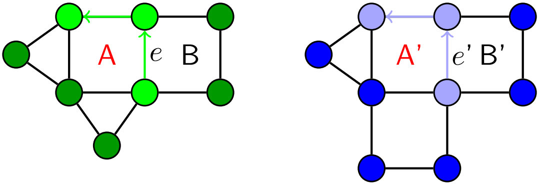

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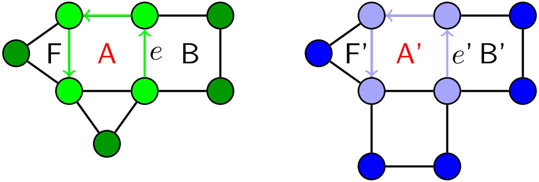

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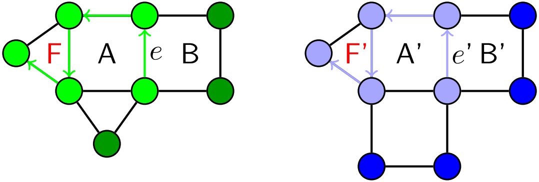

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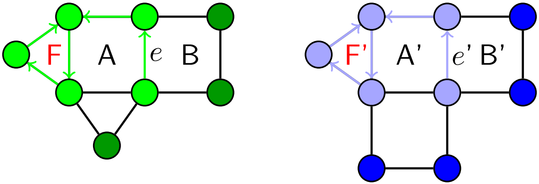

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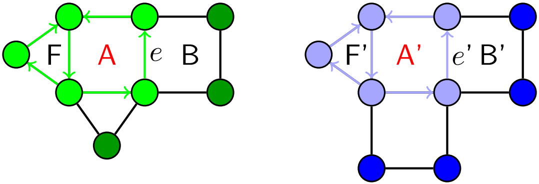

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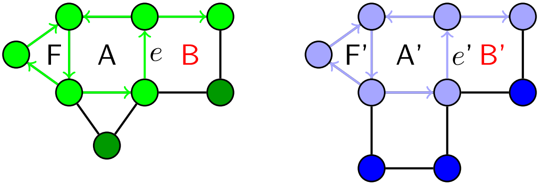

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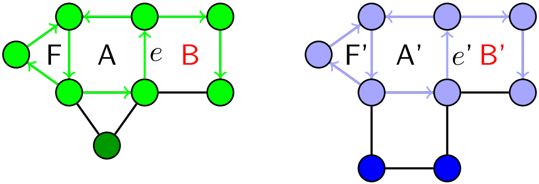

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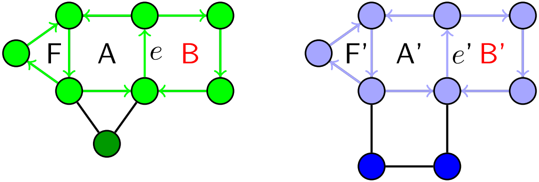

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Algorithm and running time

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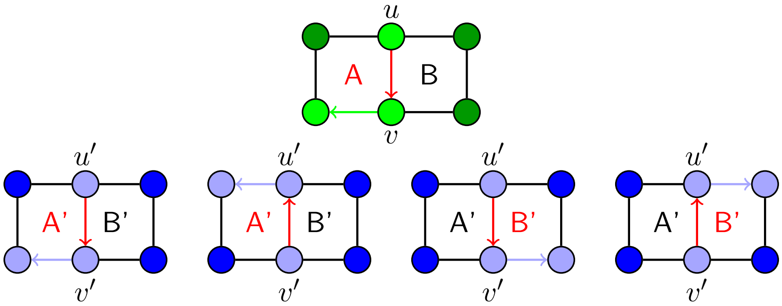
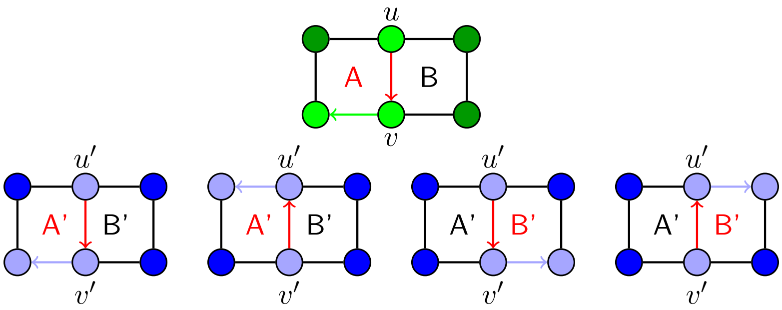


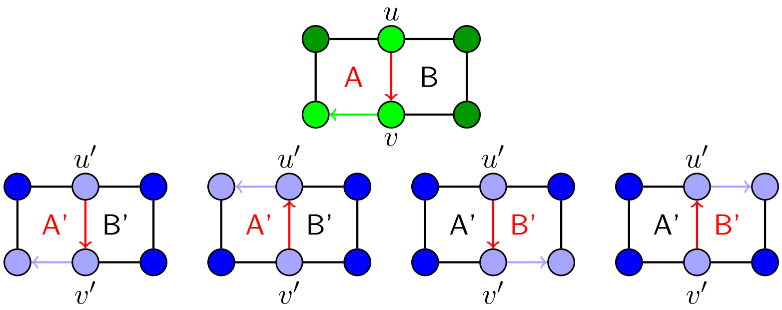
Algorithm and running time

- Compute all maximal solutions to obtain maximum
- 4 possible types of mappings for each edge pair
- Table of size $4|E_G||E_H|$ to store the sizes



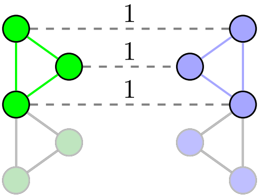
Algorithm and running time

- Compute all maximal solutions to obtain maximum
- 4 possible types of mappings for each edge pair
- Table of size $4|E_G||E_H|$ to store the sizes
- Time per cell $\mathcal{O}(1) \to$ quadratic total time



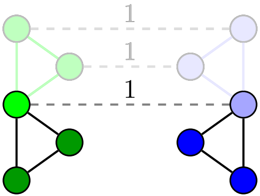
BBP-MCIS between outerplanar graphs – Example 1

1) Compute a maximal isomorphisms between two blocks



BBP-MCIS between outerplanar graphs – Example 1

1) Compute a maximal isomorphisms between two blocks
2) Recursively extend it along cut vertices; consider all possibilities



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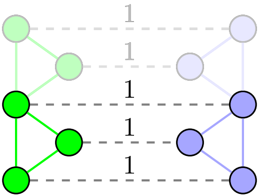

BBP-MCIS between outerplanar graphs – Example 1

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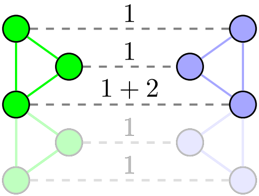
2) Recursively extend it along cut vertices; consider all possibilities
3) Add size of extension to cut vertices → Total size 5.



BBP-MCIS between outerplanar graphs – Example 2

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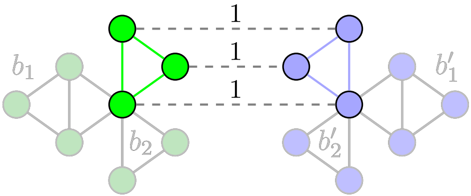

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1) Compute a maximal isomorphisms between two blocks
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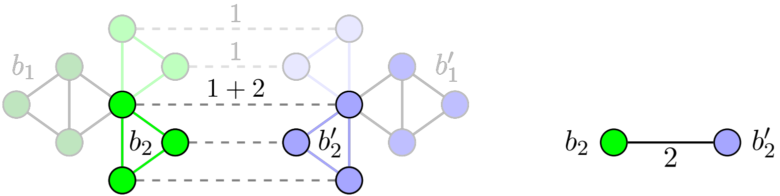

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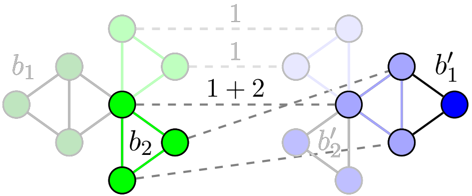

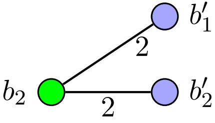

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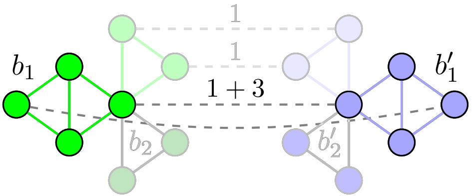

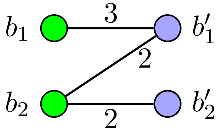

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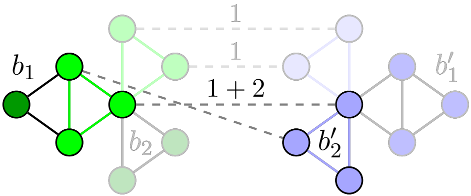
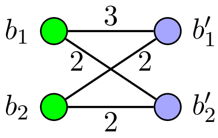
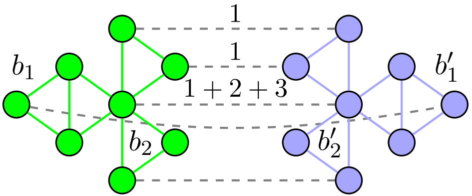
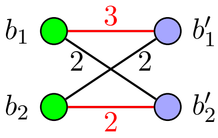




BBP-MCIS between outerplanar graphs – Example 2

1) Compute a maximal isomorphisms between two blocks
2) Try extensions separately for each pair of adjacent blocks
3) Compute maximum weight matching for block to block mapping





Theorem (Main result)

BBP-MCIS between two outerplanar graphs G and H can be solved in time $\mathcal{O}(|G||H|\Delta)$.

$\Delta =$ Maximum degree of all cut vertices (or 1, if none present)

Corollary

The time complexity of BBP-MCIS between outerplanar molecular graphs G and H is $\Theta(|G||H|)$.

Test setup

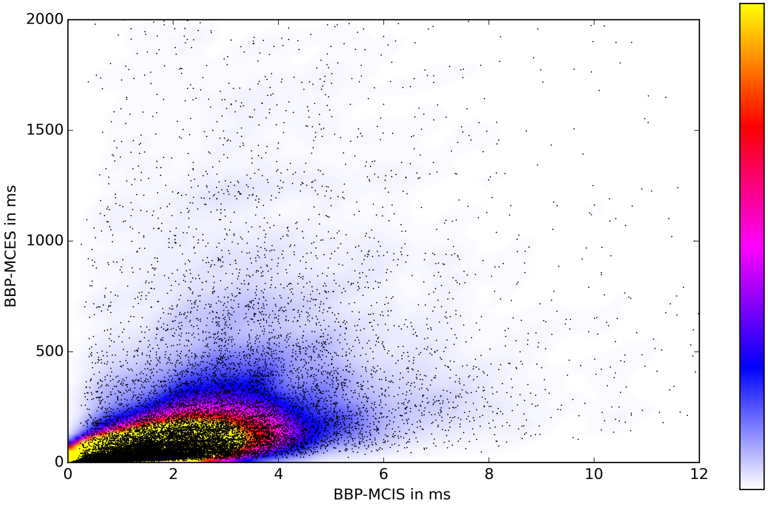
- Molecular graphs from the NCI Open Database GI50
  - 29 000 randomly chosen pairs of outerplanar graphs
  - Up to 104 vertices; average size 22 vertices
- Comparison to BBP-MCES from Schietgat et al.
  - No other BBP-MCIS algorithm available
  - Source kindly provided by Leander Schietgat
  - Goal: Maximize number of edges+vertices
- Both sources compiled with GCC; run on Intel i7-3770 CPU

Results

- BBP-MCES/MCIS differ in only 0.40% of 29 000 randomly chosen pairs of outerplanar molecular graphs.
- (fastest) BBP-MCIS – BBP-MCES – general MCS (slowest)

Table : Running times in ms on randomly chosen molecular graphs

Algorithm	Average	Median	95% less than	Maximum
MCIS	1.97 ms	1.51 ms	5.28 ms	40.35 ms
MCES	207.08 ms	41.43 ms	871.48 ms	26 353.68 ms



(601 of 29 000 BBP-MCS computations did not fit into the borders.)

Conclusion

- First efficient BBP-MCIS computation in theory and practice
  - Supports labels with nonnegative weights attached
- Much faster than BBP-MCES; identical results in 99.6%

Future work

- BBP-MCIS for non outerplanar molecular graphs
- Negative weights; bounded integer weights

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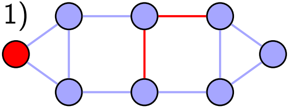
Labeled graphs, post processing

1) Biconnected CIS with different labels; colored red



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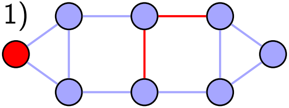

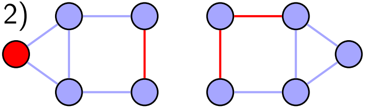

Labeled graphs, post processing

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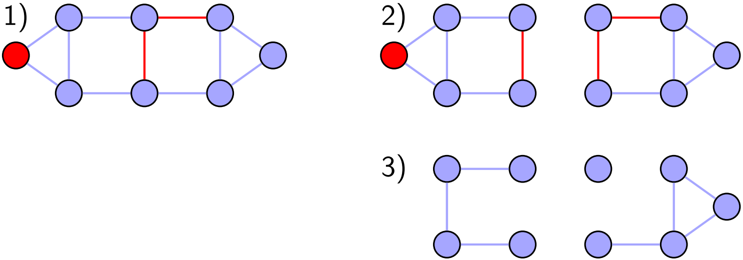
2) Separate graph along inner edges with different labels.
3) Remove edges and vertices with different labels.



Labeled graphs, post processing

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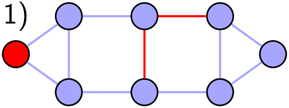
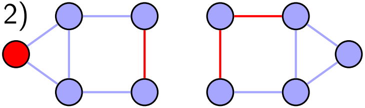
2) Separate graph along inner edges with different labels.
3) Remove edges and vertices with different labels.
4) Strip non-block parts; store size for each component.

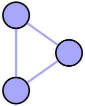
1)



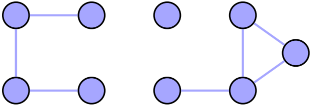
2)



4)



3)



Labeled graphs, post processing

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2) Separate graph along inner edges with different labels.
3) Remove edges and vertices with different labels.
4) Strip non-block parts; store size for each component.
5) Store $-\infty$ for removed edge mappings.