CSI5180. Machine Learning for Bioinformatics Applications

Learning **Graphs**

by

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Version **December 6, 2019**

Preamble

Preamble

Learning Graphs

A **graph** is a fundamental data structure with a great number of applications, both in computer science and the life sciences. In this lecture, we consider machine learning algorithms where graphs are playing a central role.

General objective :

- **Discuss** the applications of **frequent subgraph mining** in bioinformatics

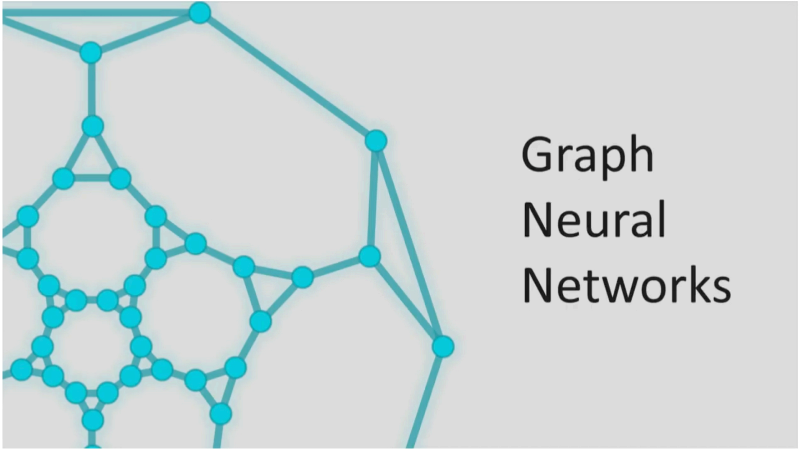
Learning objectives

- **Discuss** the various search strategies from frequent subgraph mining
- **Explain** the two main paradigms, single graph vs multiple graphs

Reading:

- Aida Mrzic, Pieter Meysman, Wout Bittremieux, Pieter Moris, Boris Cule, Bart Goethals, and Kris Laukens. Grasping frequent subgraph mining for bioinformatics applications. *BioData Min* **11**:20, 2018.
- Peng Zhang and Yuval Itan. Biological network approaches and applications in rare disease studies. *Genes* **10**: 2019.
- Hiroshi Mamitsuka. *Textbook of Machine Learning and Data Mining: with Bioinformatics Applications*. Global Data Science Publishing, 2018.
  - § 6, 7 and 8.

Graph neural networks by Alexander Gaunt



https://youtu.be/cWIeTMklzNg

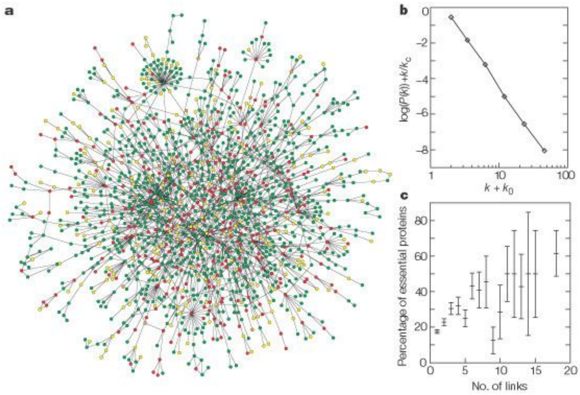
Plan

Introduction

Graphs in molecular biology

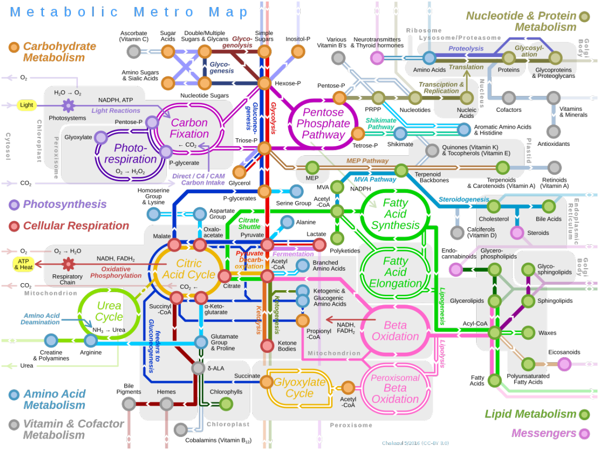
- Gene Regulatory Networks (GRN)
- Biological Pathways
- Protein-Protein Interactions (PPI)
- RNA-RNA Interaction (RRI)
- RNA secondary structure (tree, dual graph)
- Molecular graph (connectivity of molecules)
  - PubChem from NIH has 90 million entries
- Genome assembly
- Ontologies

Yeast proteome



H. Jeong, S. P. Mason, A.-L. Barabási & Z. N. Oltvai. Lethality and centrality in protein networks *Nature* **411**:4142 (2001)

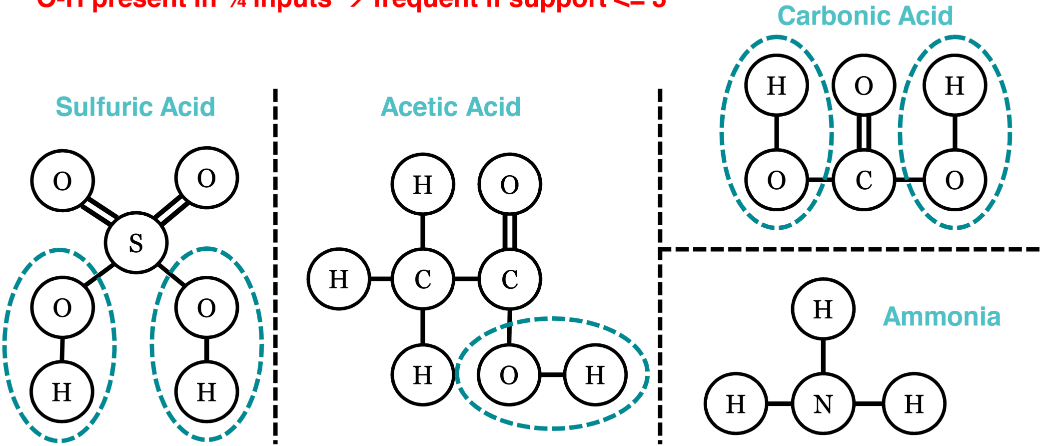
Metabolic network



Source: `https://en.wikipedia.org/wiki/File:Metabolic_Metro_Map.svg`

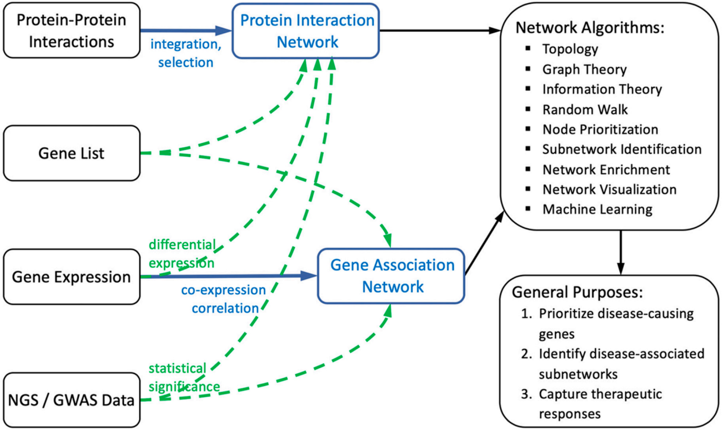
Molecular graph

O-H present in ¾ inputs → frequent if support <= 3



Source: [Samatova et al., 2013]

Biological networks and rare disease

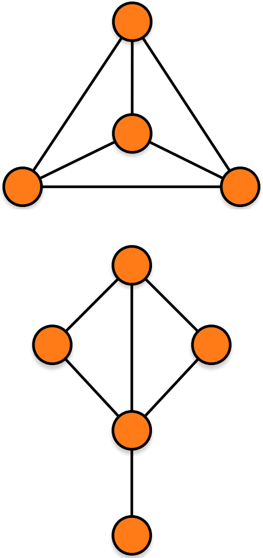


Source: [Zhang and Itan, 2019] Figure 1

Definitions

Graph

- A graph, $G = (V, E)$, consists of a set of **vertices** (V) and a set of **edges** (E) where each edge connects two nodes.



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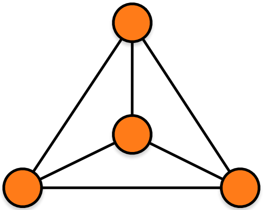

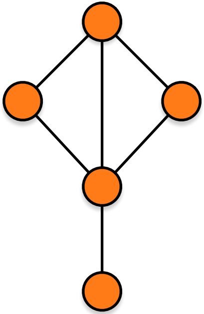

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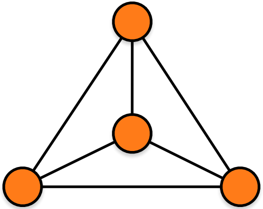

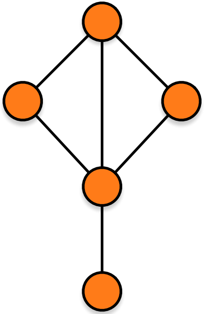

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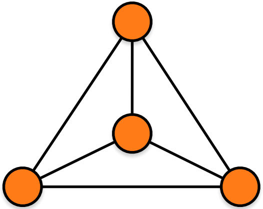
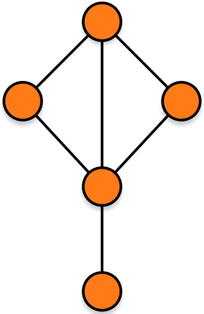
- There can be **weights** on **edges**. If so, the result is a **weighted graph**. Otherwise, the graph is **unweighted**.





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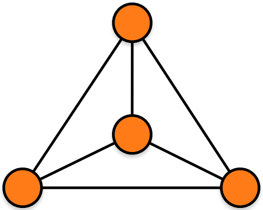

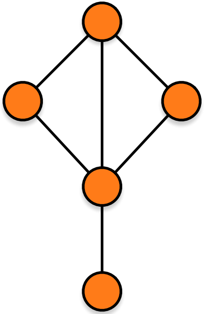

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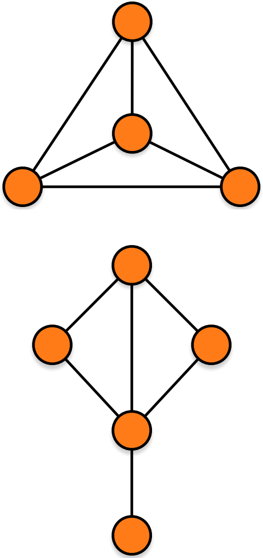

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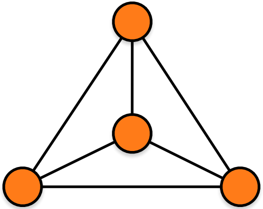
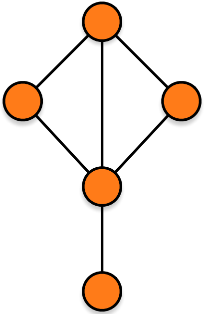
- **Weights** can be used describe a degree of **certainty** (e.g. experimental error) or **strength** of an association.





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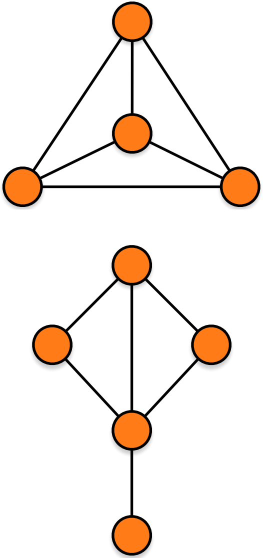

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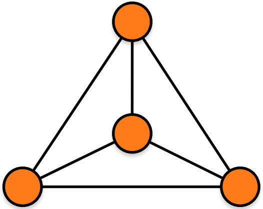

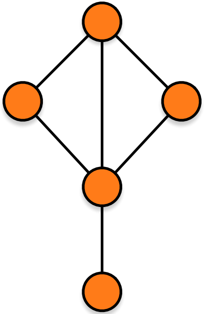

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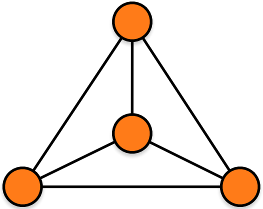

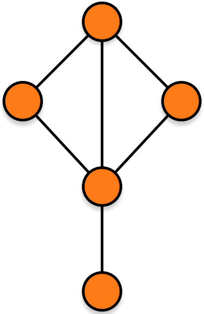

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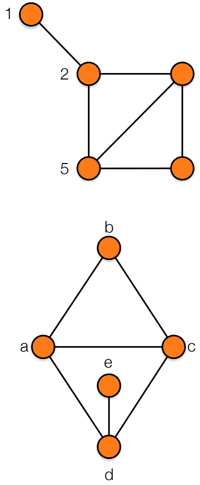

See also: `https://www.youtube.com/watch?v=Xq8o-z1DsUA`

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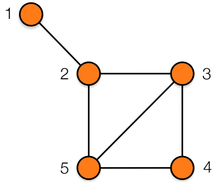
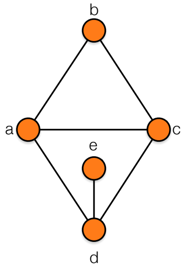
- In other words, the graphs can be seen as "**equal**".





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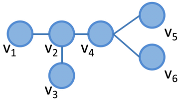
Representations

Adjacency matrix and adjacency list

a



A graph G.

$$A(G) = \begin{array}{c c} & \begin{array}{cccccc} v_1 & v_2 & v_3 & v_4 & v_5 & v_6 \end{array} \\ \begin{array}{c} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ v_6 \end{array} & \begin{pmatrix} 0 & 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 1 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \end{pmatrix} \end{array}$$

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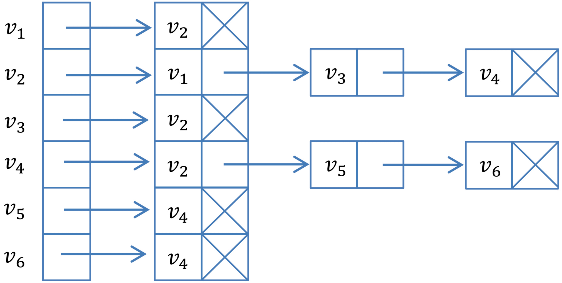

Source: [Mrzic et al., 2018] Figure 3

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- **Yikes!**

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    - **Depth-first search (DFS) code**

Problems

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  - The **output** would be one or several sugraphs, each occurring in a large proportion (good support) of the input graphs.
- The overarching theme is searching for **frequently occurring interesting subgraphs**.

Frequent subgraph mining

- **Input:** a **graph** (G) or **set of graphs** ($\mathcal{G}$).
- **Output:** **subgraphs** with good **support**.

$$\mathcal{F} = \{g | g \text{ is a subgraph of } G \text{ or } \mathcal{G}; \text{support}(g) \geq \text{minimum support}\}$$

  - Where **support** is a **problem specific** measure:
    - **Count** is larger than some threshold s.
    - **Statistical enrichment** compared to some background distribution.

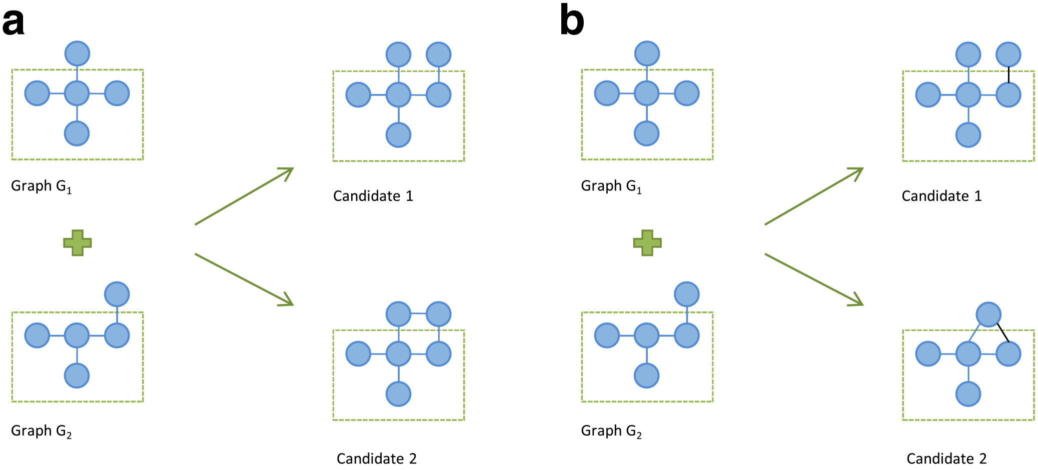
Algorithms

Frequent subgraph mining (high level)

1. **Enumerate** candidates
2. **Filter** the list
3. **Count** the number of occurrences
4. **Repeat**

Counting the number of occurrences is computationally demanding!

Join node- or edge-based enumeration



Source: [Mrzic et al., 2018] Figure 4

Pruning

- The candidate enumeration algorithms are joining subgraphs are are frequent [1].
  - The *a priori* principle says that **a graph cannot be more frequent than any of its subgraphs**.

[1] Count is higher than some threshold.

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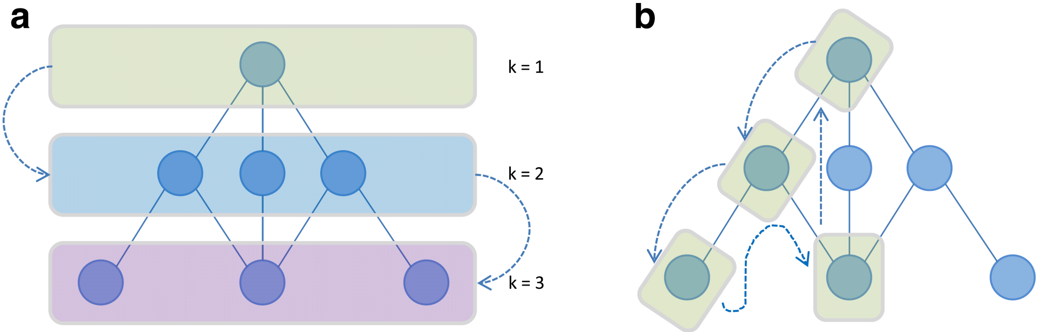
- Use **all inducible subgraphs** (graphlets) up to a given size.
  - For instance, there are 30 undirected unlabelled connected inducible subgraphs of size 2 to 5.

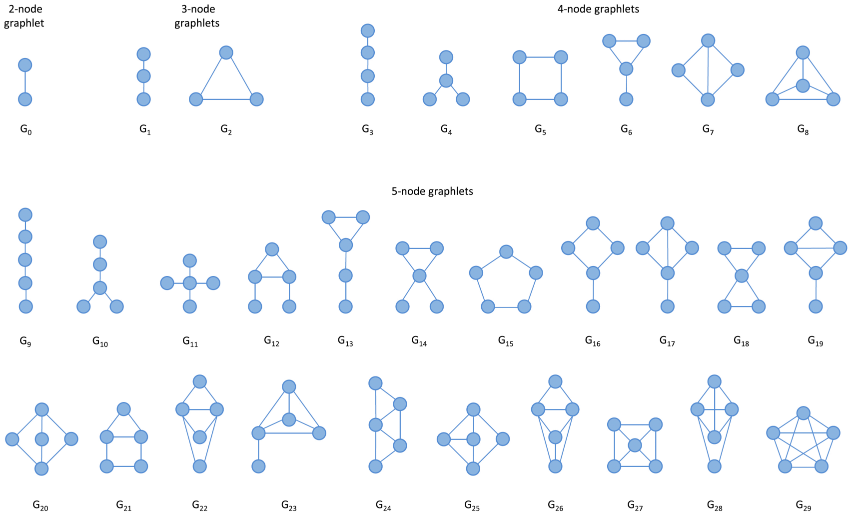
Strategies

p



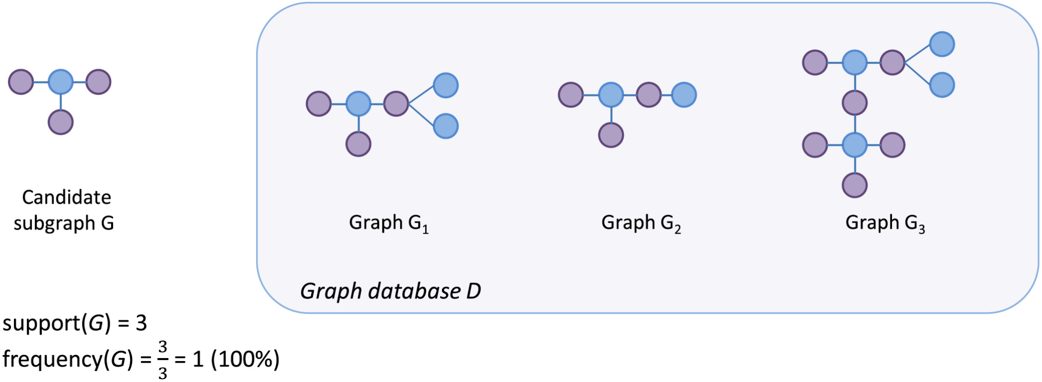
Source: [Mrzic et al., 2018] Figure 5

Strategies



Source: [Mrzic et al., 2018] Figure 6

Support (multiple graphs)



Source: [Mrzic et al., 2018] Figure 7

- When the input consists of **multiple graphs**, the support generally **ignores the number of times** a subgraph occurs in a given graph.

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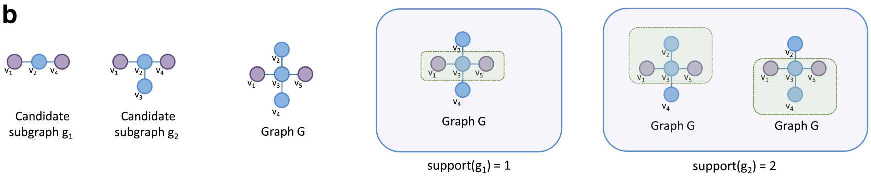
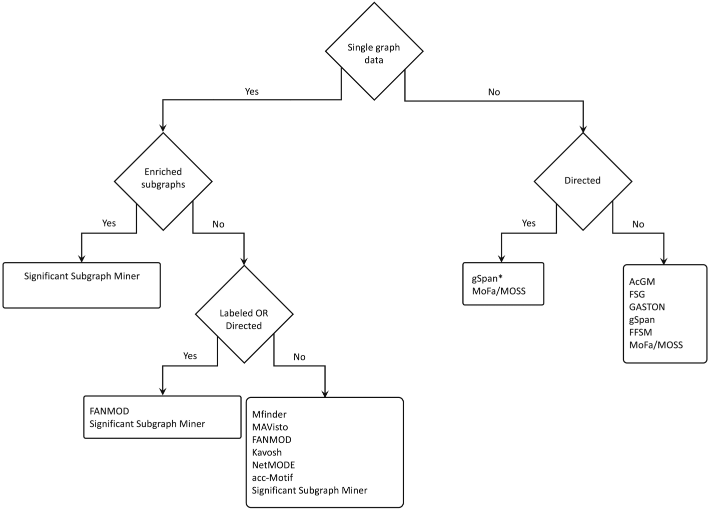
  - Counting all the occurrences, including the **overlapping** ones.
    - The *a priori* principle no longer applies as it is possible for larger subgraphs to occur more frequently than their subgraphs.



Source: [Mrzic et al., 2018] Figure 8

Existing approaches



Source: [Mrzic et al., 2018] Figure 9

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  - **Sampling** approaches are then used.
  - **See:** Alex R Gawronski and Marcel Turcotte, RiboFSM: Frequent subgraph mining for the discovery of RNA structures and interactions, *BMC bioinformatics* (2014).

Prologue

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- Frequent subgraph mining returns **all subgraphs** with **minimum support**.
- Algorithms often proceed from **small to large subgraphs**, either using **breadth-first-search** or **depth-first-search**.
- Depending on the application, the support can be the **count** or some **statistical test**.
- When the graphs are **large**, **sampling** methods are used.

Resources

- **Graph Theory FAQs: 03. Isomorphism Using Adjacency Matrix** by **Sarada Herke**
  - https://youtu.be/UCle3Smvh1s
- **Graph Theory: 10. Isomorphic and Non-Isomorphic Graphs** by **Sarada Herke**
  - https://www.youtube.com/watch?v=z-GfKbzvtBA&feature=youtu.be

Next module

- **Ensemble** Learning

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