

February 16, 2015

Tokyo Workshop on Statistically
Sound Data Mining



Multiple Testing Correction in Graph Mining

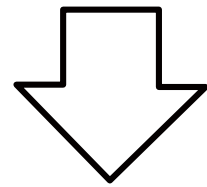
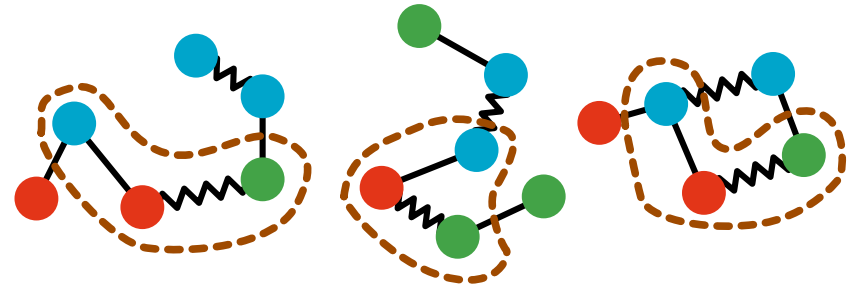
Mahito Sugiyama (Osaka University, JST PRESTO)

Joint work with Felipe Llinares López¹, Niklas Kasenburg²,
Karsten Borgwardt¹ (¹ETH Zürich, ²Univ. Copenhagen)

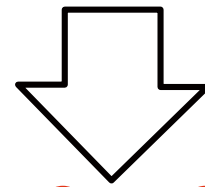
Binary data

| ID | a | b | c | d | e | f | g | h | i | j |
|----|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 |
| 2 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 0 |
| 3 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 |
| 4 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 |
| 5 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 0 |

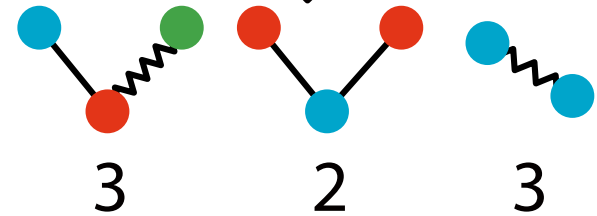
Graphs



Pattern mining



{a, b, e} {d, g, h, i}



Support:

3

4

3

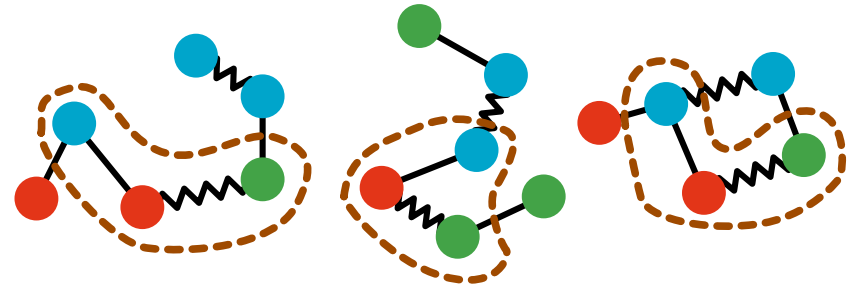
2

3

Binary data

| ID | a | b | c | d | e | f | g | h | i | j |
|----|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 |
| 2 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 0 |
| 3 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 |
| 4 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 |
| 5 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 0 |

Graphs



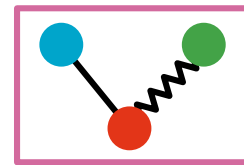
Pattern mining

{a, b, e}

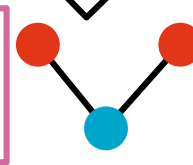
3

{d, g, h, i}

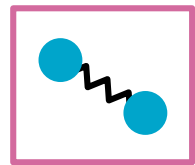
4



3



2



3

Support:



P value:

0.06

0.01

0.02

0.07

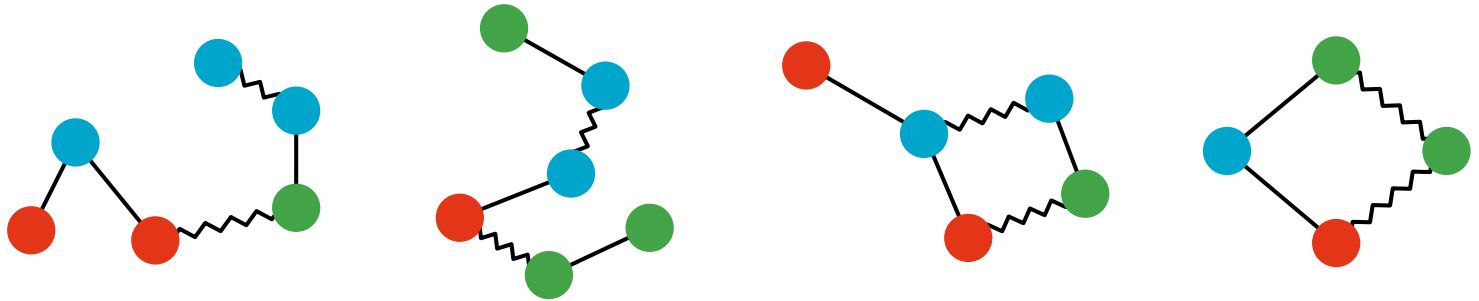
0.02

(Statistically) Significant patterns
(*P* value < 0.05)

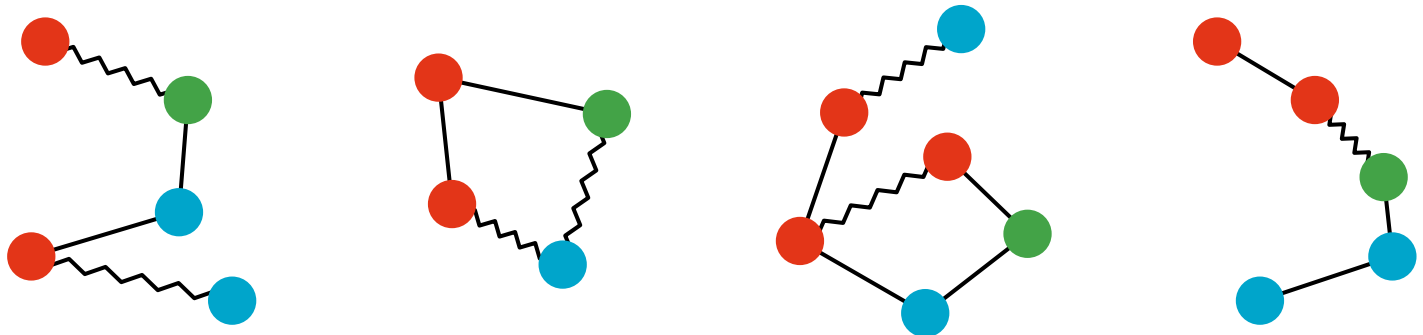
The *P* value is crucial for scientific discovery!

Find Subgraphs

Active

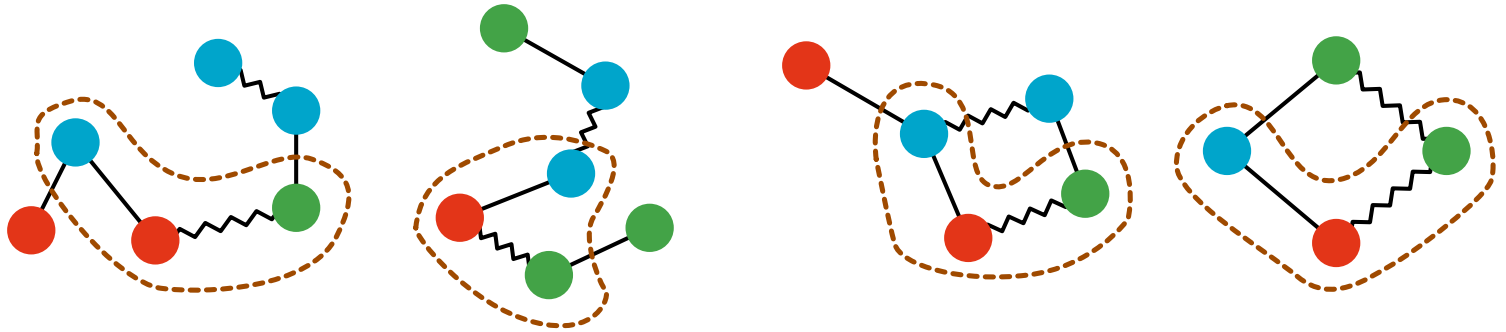


Inactive

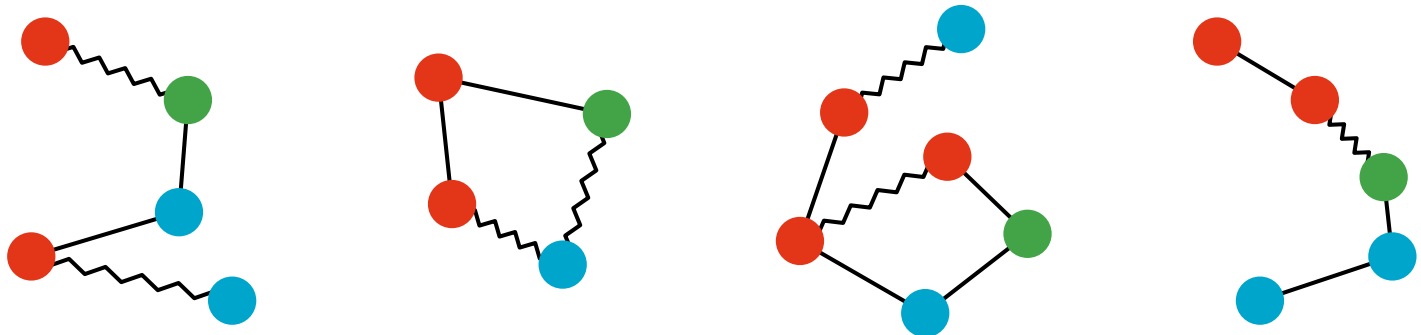


Find Subgraphs

Active

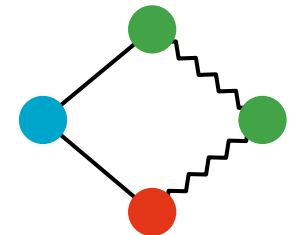
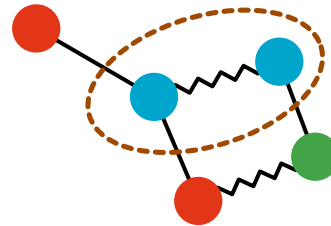
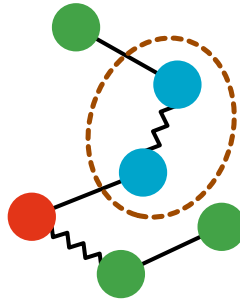
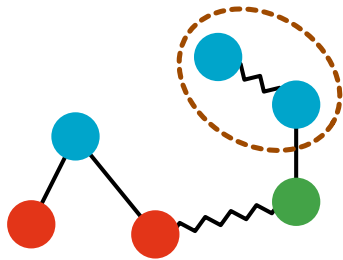


Inactive

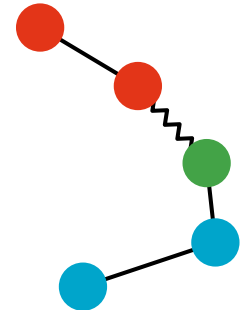
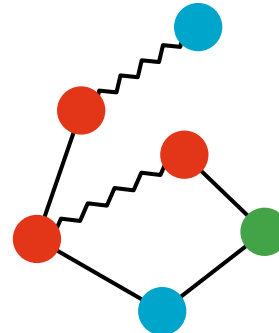
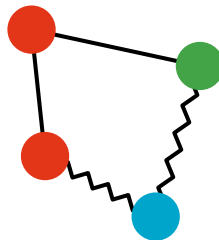
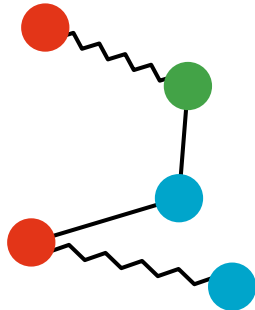


Find Subgraphs

Active

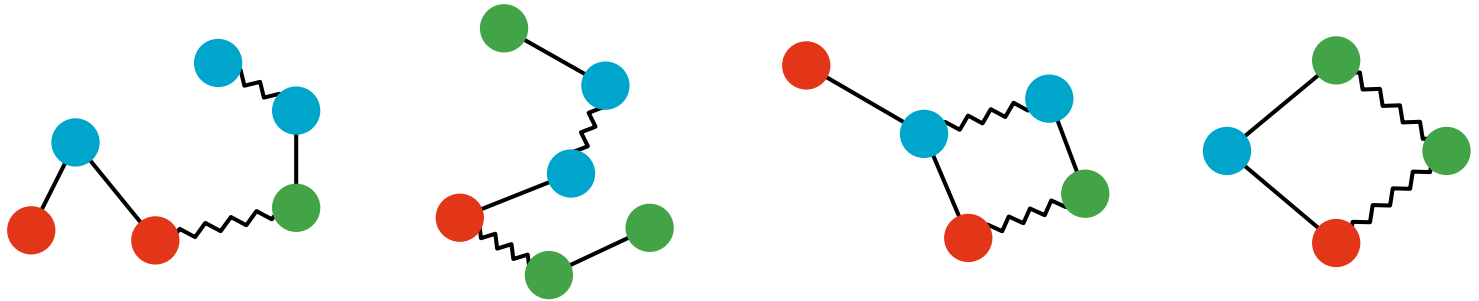


Inactive

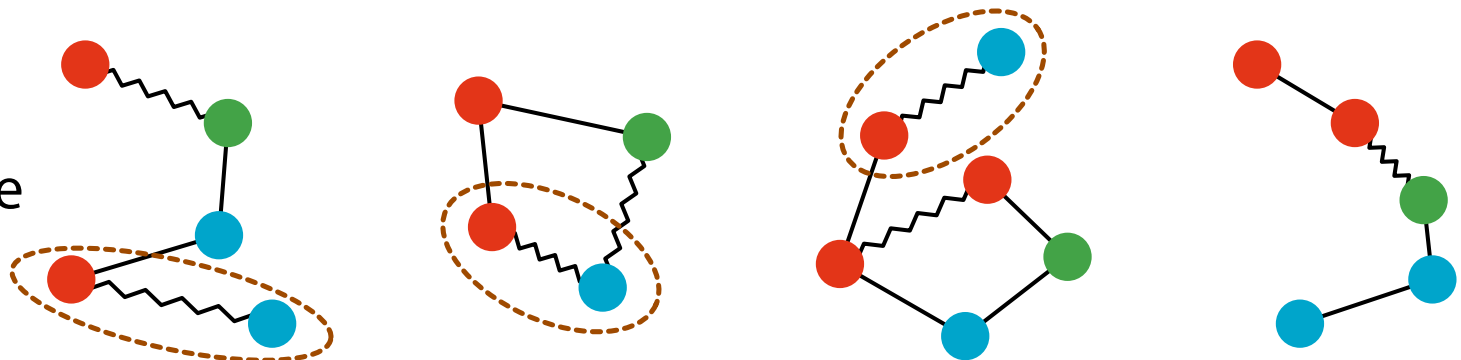


Find Subgraphs

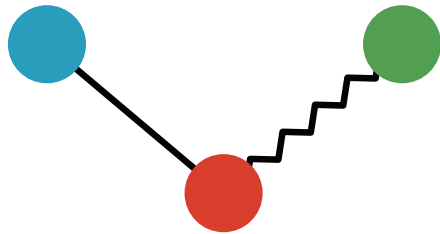
Active



Inactive



Hypothesis Test for Each Subgraph



Alternative hypothesis
is true

Null hypothesis
is true

Declared
significant

True Positive

False Positive
(Type I Error)

Declared
non-significant

False Negative
(Type II Error)

True Negative

Null hypothesis:

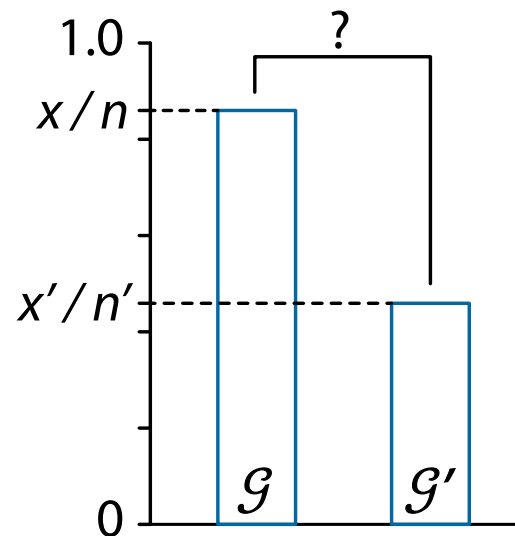
The occurrence of the subgraph is
independent from the activity

Alternative hypothesis: The occurrence of the subgraph is
associated with the activity

Testing the Independence of Subgraph

- Given two sets of graphs \mathcal{G} and \mathcal{G}'
 - $|\mathcal{G}| = n, |\mathcal{G}'| = n' (n \leq n')$
- The **P value** of each subgraph $H \sqsubseteq G$ with $G \in \mathcal{G} \cup \mathcal{G}'$ is determined by the **Fisher's exact test**

| | Occ. | Non-occ. | Total |
|----------------|----------|-----------------------|----------|
| \mathcal{G} | x | $n - x$ | n |
| \mathcal{G}' | x' | $n' - x'$ | n' |
| Total | $x + x'$ | $(n - x) + (n' - x')$ | $n + n'$ |

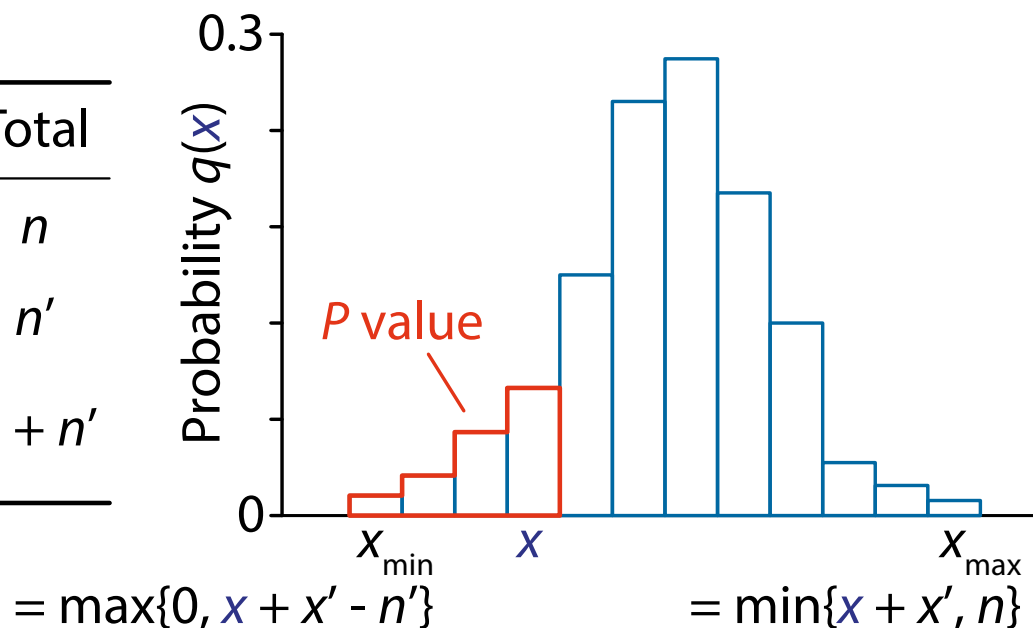


Fisher's Exact Test

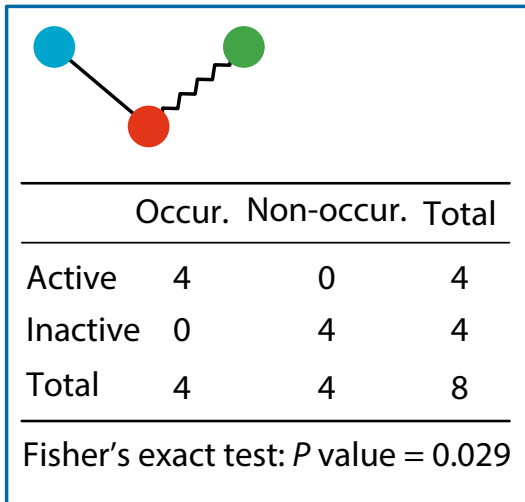
- The probability $q(x)$ of obtaining x and x' is given by the hypergeometric distribution:

$$q(x) = \frac{\binom{n}{x} \binom{n'}{x'}}{\binom{n+n'}{x+x'}}$$

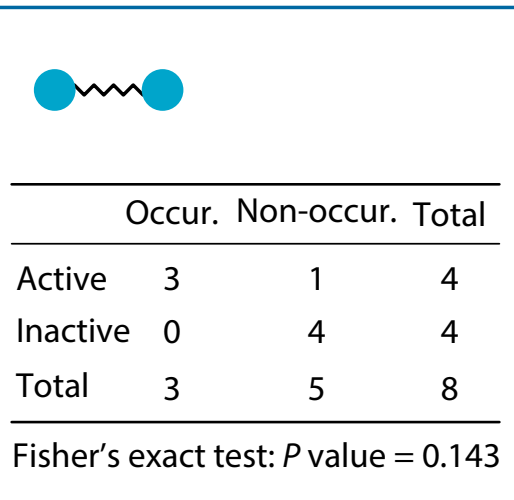

| | Occ. | Non-occ. | Total |
|----------------|----------|-----------------------|----------|
| \mathcal{G} | x | $n - x$ | n |
| \mathcal{G}' | x' | $n' - x'$ | n' |
| Total | $x + x'$ | $(n - x) + (n' - x')$ | $n + n'$ |



Multiple Testing



Multiple Testing



| | Occur. | Non-occur. | Total |
|----------|--------|------------|-------|
| Active | 3 | 1 | 4 |
| Inactive | 0 | 4 | 4 |
| Total | 3 | 5 | 8 |

Fisher's exact test: P value = 0.143

Fisher's exact test: P value = 0.029

Multiple Testing

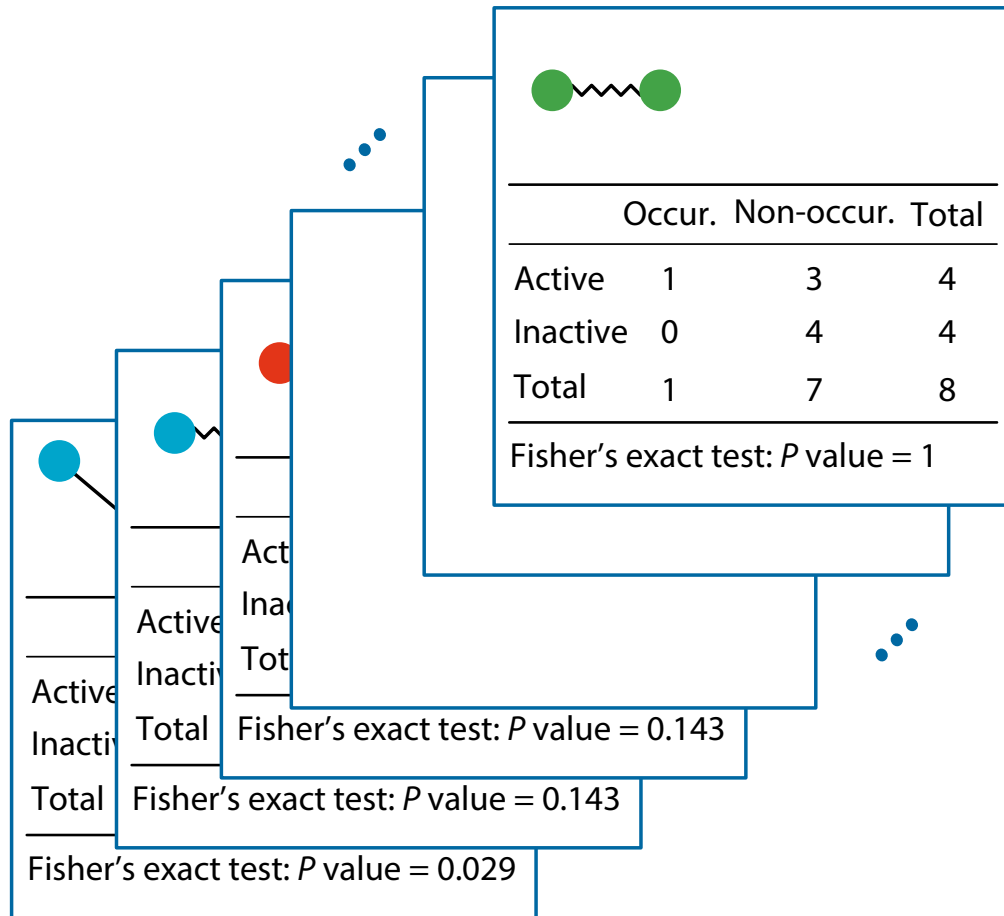
| | Occur. | Non-occur. | Total |
|----------|--------|------------|-------|
| Active | 0 | 4 | 4 |
| Inactive | 3 | 1 | 4 |
| Total | 3 | 5 | 8 |

Fisher's exact test: P value = 0.143

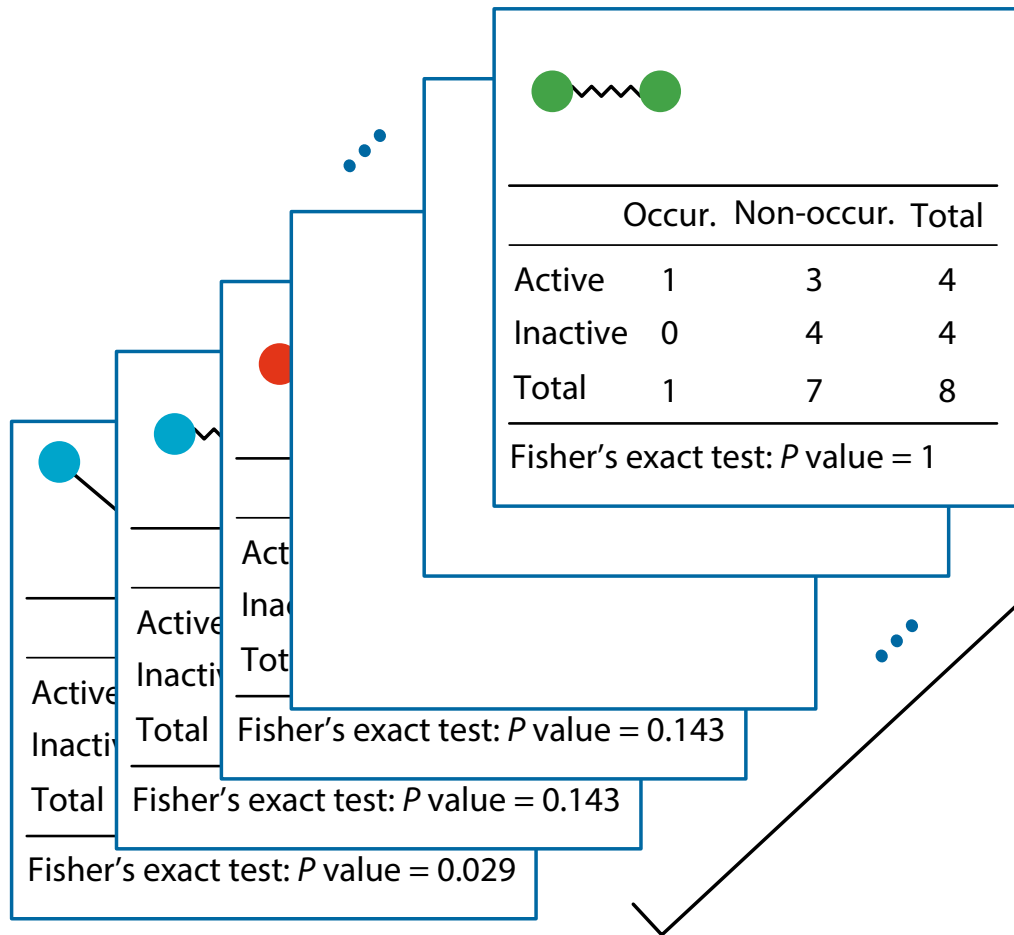
Fisher's exact test: P value = 0.143

Fisher's exact test: P value = 0.029

Multiple Testing



Multiple Testing



Task: Detect all significant subgraphs

We need multiple testing correction!

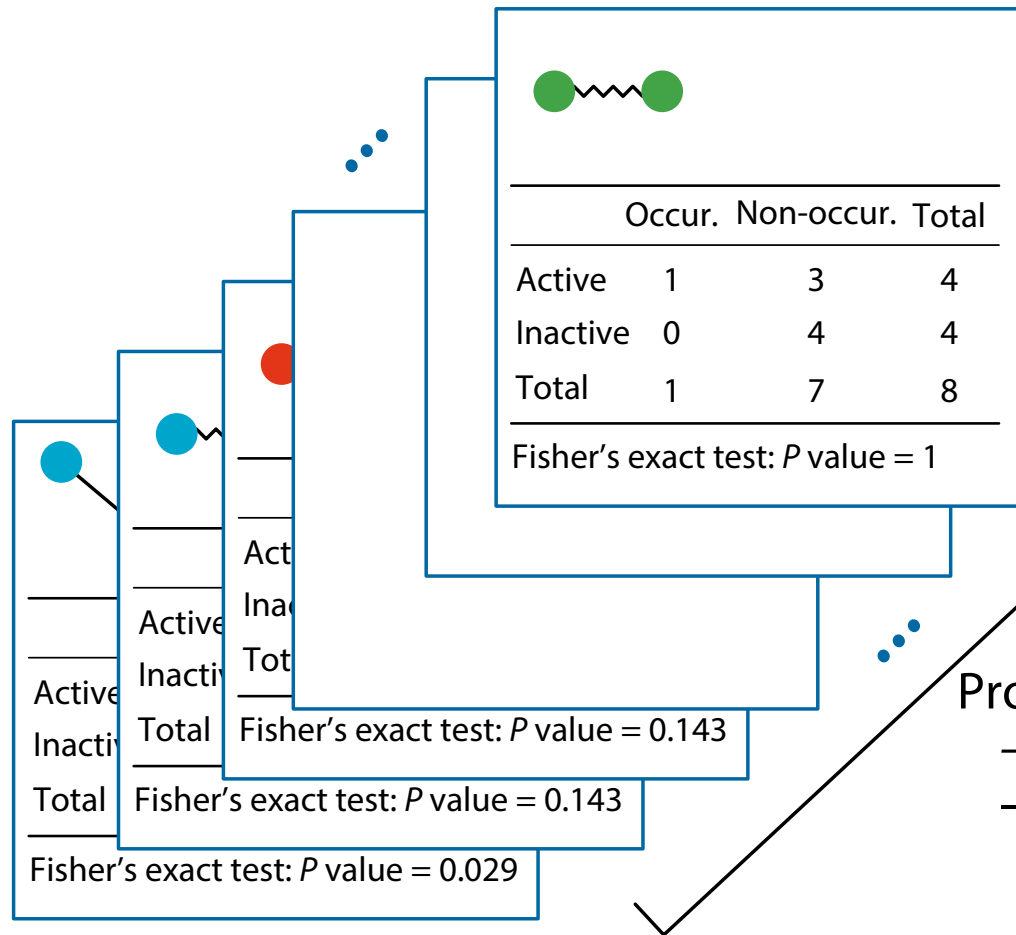
Otherwise, too many

false positives:

$$\text{FWER} = 1 - (1 - \alpha)^m$$

m subgraphs

Multiple Testing



Task: Detect all significant subgraphs

We need multiple testing correction!

Otherwise, too many

false positives:

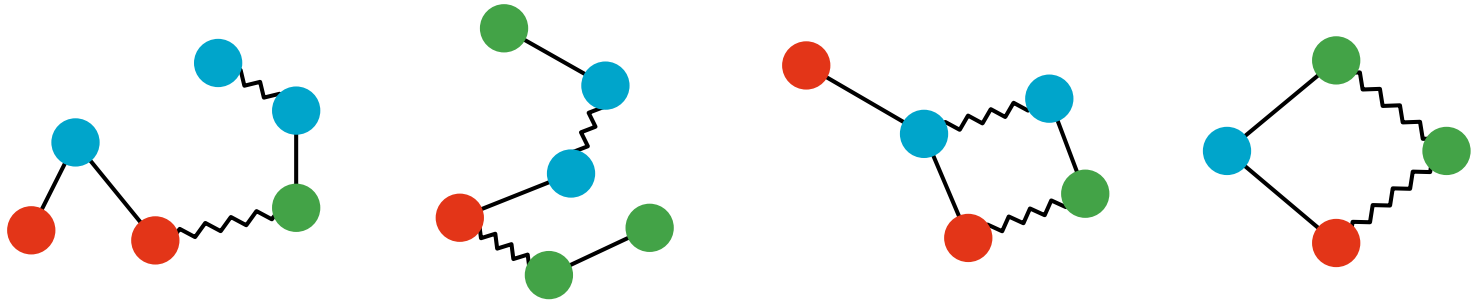
$$\text{FWER} = 1 - (1 - \alpha)^m$$

Problems:

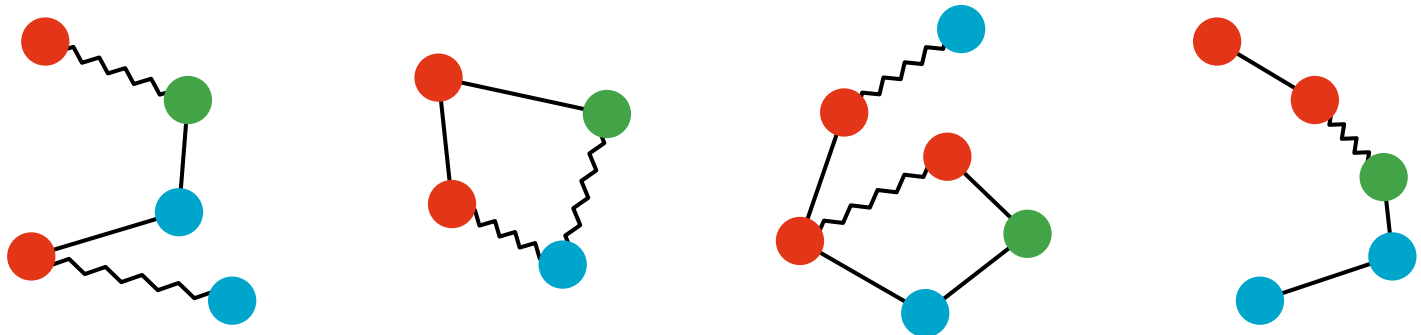
- m is massive
- The significance level α / m in Bonferroni correction becomes too conservative

Counting the Frequency of Subgraphs

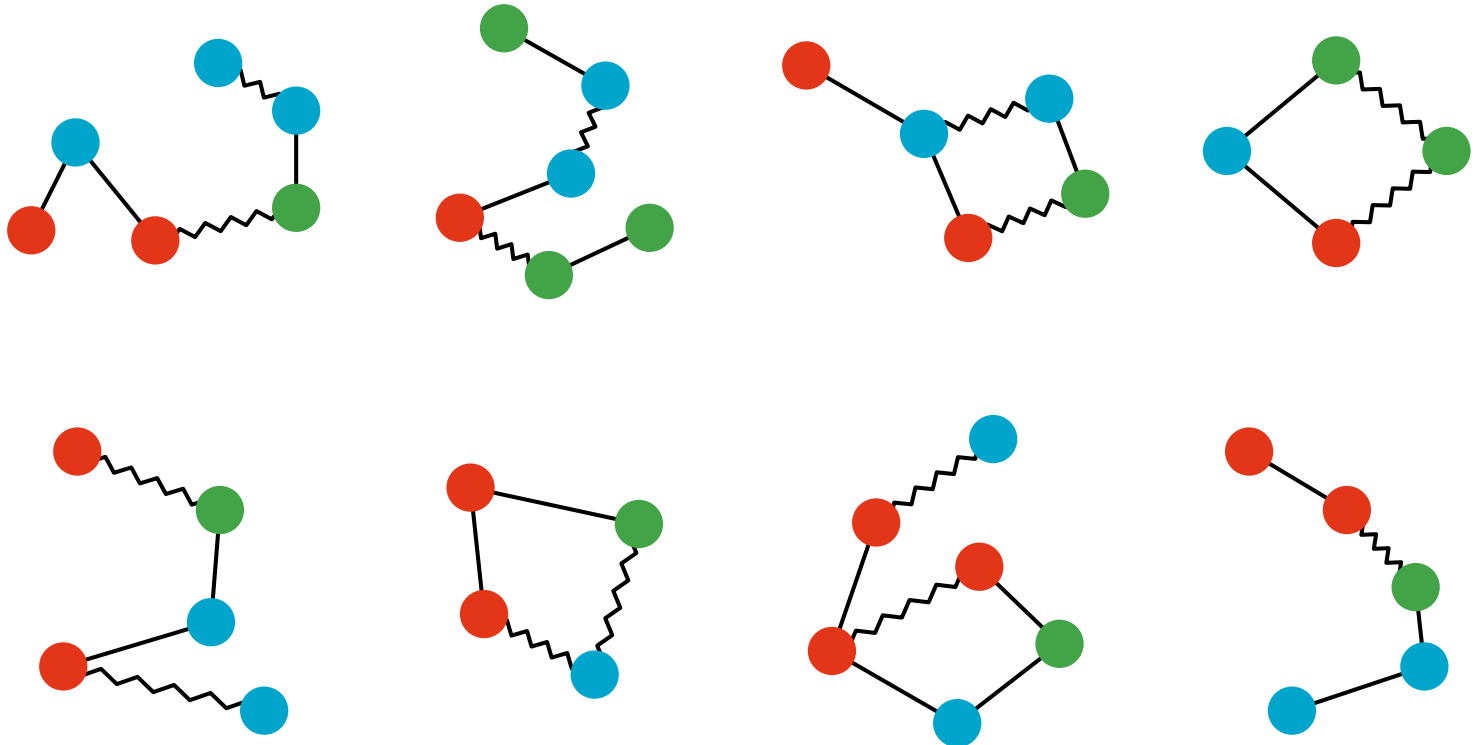
Active



Inactive



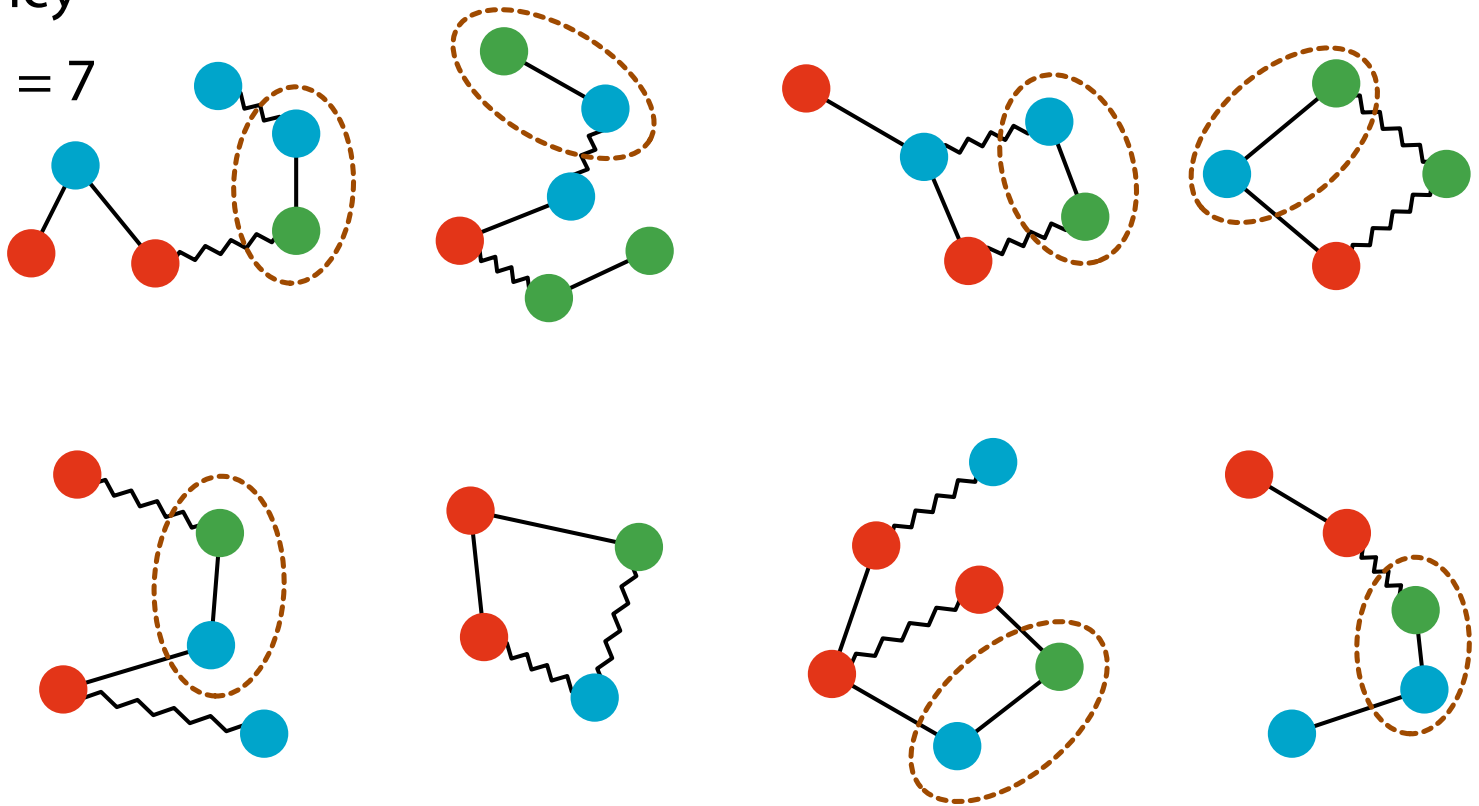
Counting the Frequency of Subgraphs



Counting the Frequency of Subgraphs

Frequency

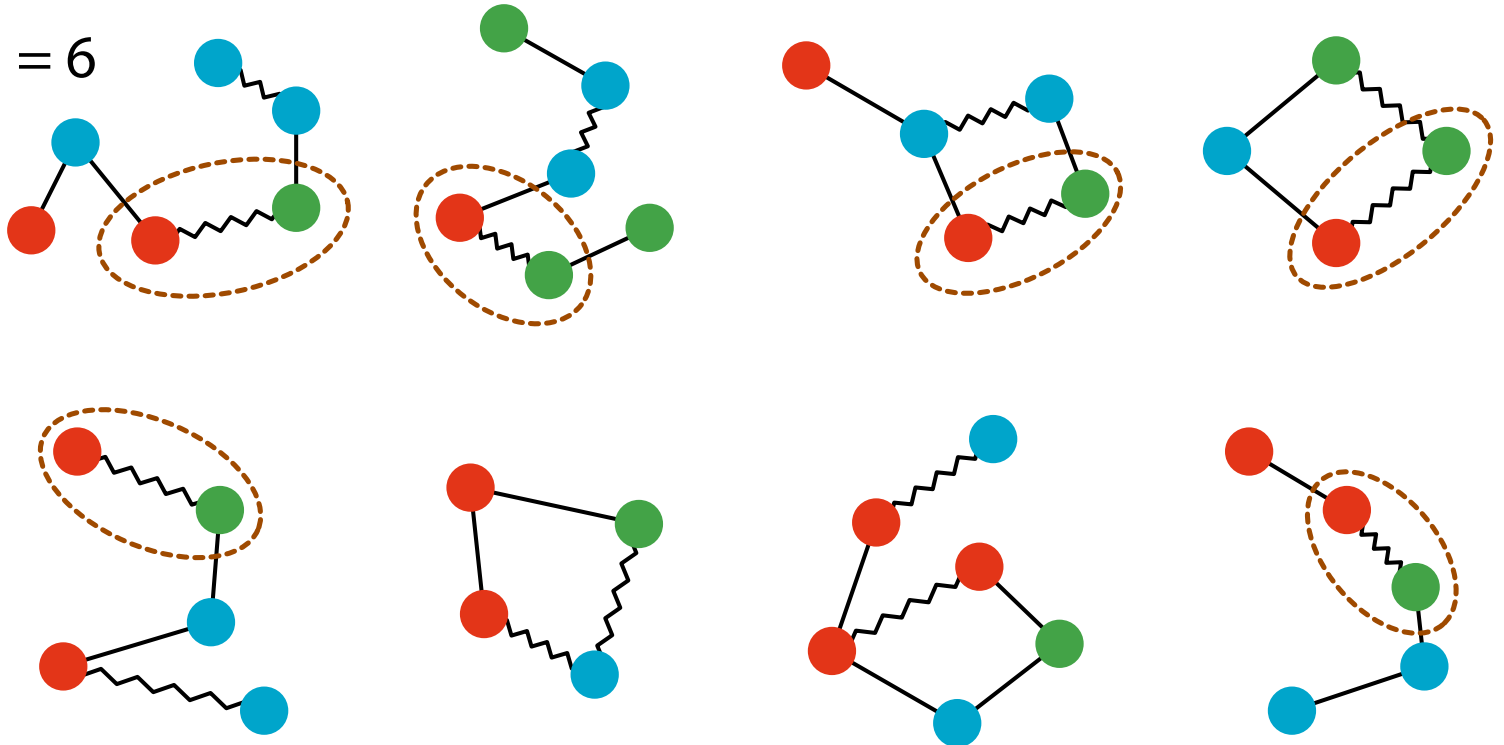
$$f(\text{subgraph}) = 7$$



Counting the Frequency of Subgraphs

Frequency

$$f\left(\begin{array}{c} \bullet \\ \text{---} \\ \bullet \end{array}\right) = 6$$



The Minimum P Value

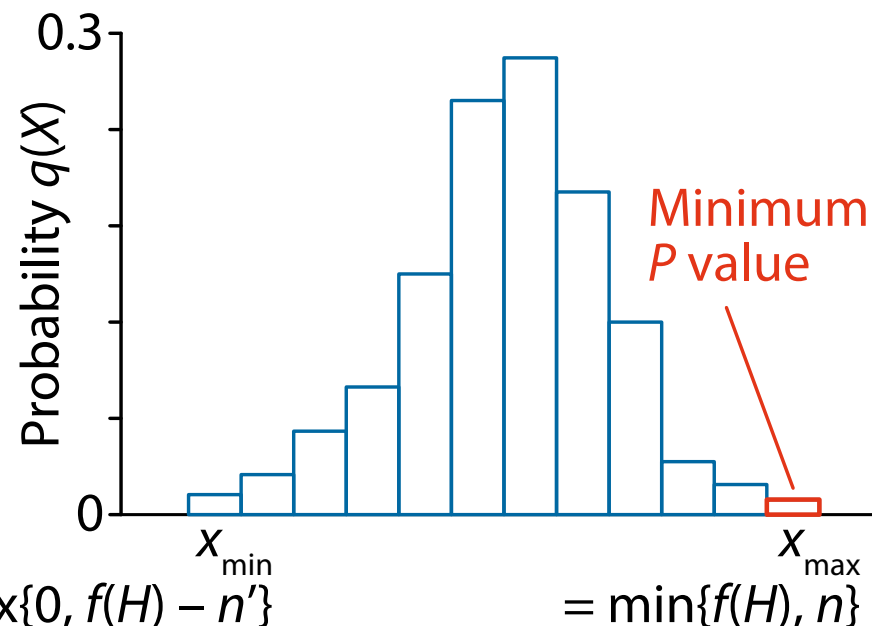
- The **minimum achievable P value** for the frequency $f(H)$ of a subgraph H is

$$P_{\min} = \binom{n}{f(H)} / \binom{n + n'}{f(H)}$$

| | Occ. | Non-occ. | Total |
|----------|--------|-------------------|----------|
| Active | $f(H)$ | $n - f(H)$ | n |
| Inactive | 0 | n' | n' |
| Total | $f(H)$ | $(n - f(H)) + n'$ | $n + n'$ |

Most biased case ($f(H) < n$)

$$= \max\{0, f(H) - n'\}$$



Testability

- The **minimum achievable P value** for the frequency $f(H)$ of a subgraph H is

$$P_{\min} = \binom{n}{f(H)} / \binom{n + n'}{f(H)}$$

- Tarone (1990) pointed out (and Terada et al. (2013) revisited):
*For a hypothesis H , if its minimum P value is smaller than the significance threshold, this is **untestable** and we can ignore it*
 - Untestable hypotheses (subgraphs) do not increase the FWER
 - The Bonferroni factor reduces to **the number of testable hypotheses**

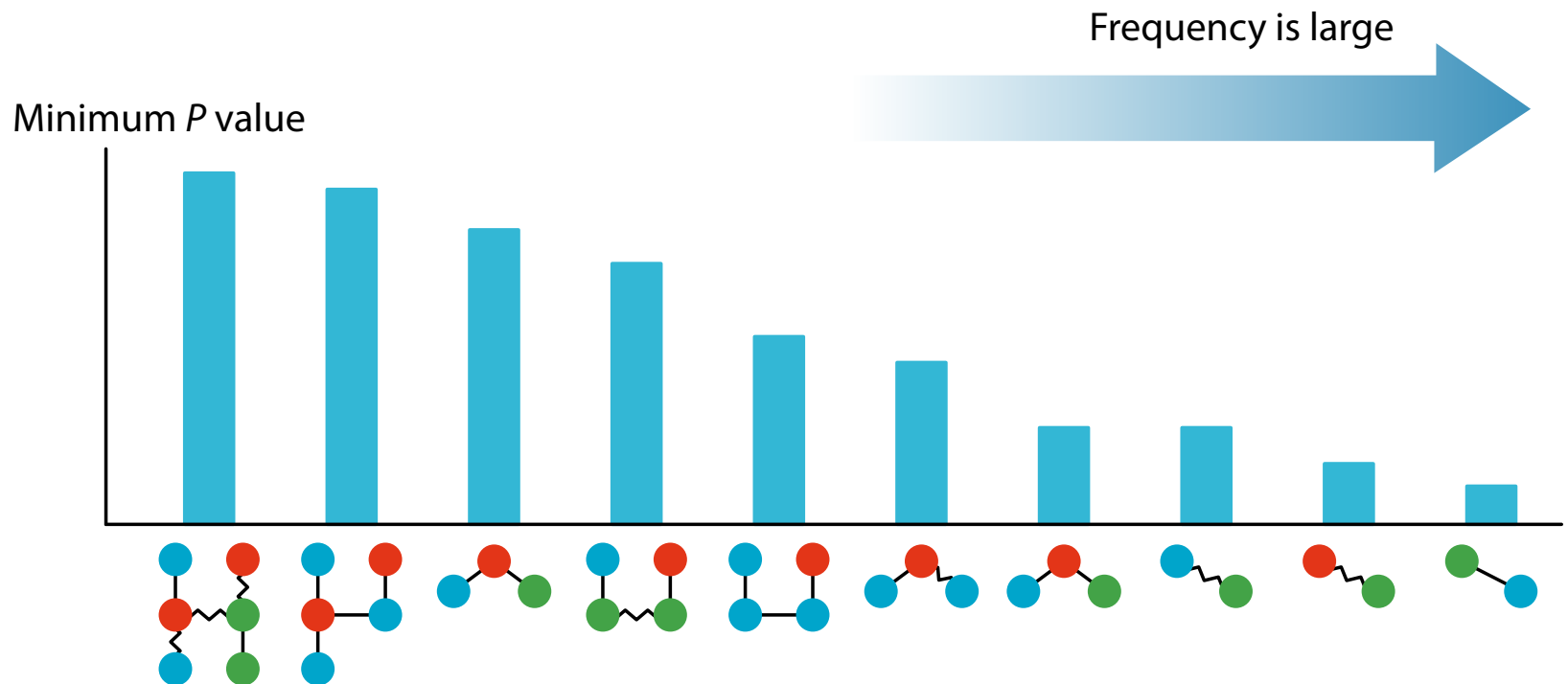
Finding the Optimal Correction Factor

- $m(k)$: # of subgraphs whose minimum P values $< \alpha/k$
 - k : the correction factor, α/k : the corrected significance level
- For each k , FWER is controlled as (Tarone 1990):

$$\text{FWER} \leq m(k) \frac{\alpha}{k} = \frac{m(k)}{k} \alpha$$

- Our task:
 - Find the **smallest** k while controlling $\text{FWER} \leq \alpha$
 - Coincides with the “**root**” k_{rt} of the function $m(k) - k$
 - $m(k) \leq k$ for all $k \geq k_{\text{rt}}$ and $m(k) > k$ for all $k < k_{\text{rt}}$
 - Enumerate **testable subgraphs** whose min. P values $< \alpha/k_{\text{rt}}$

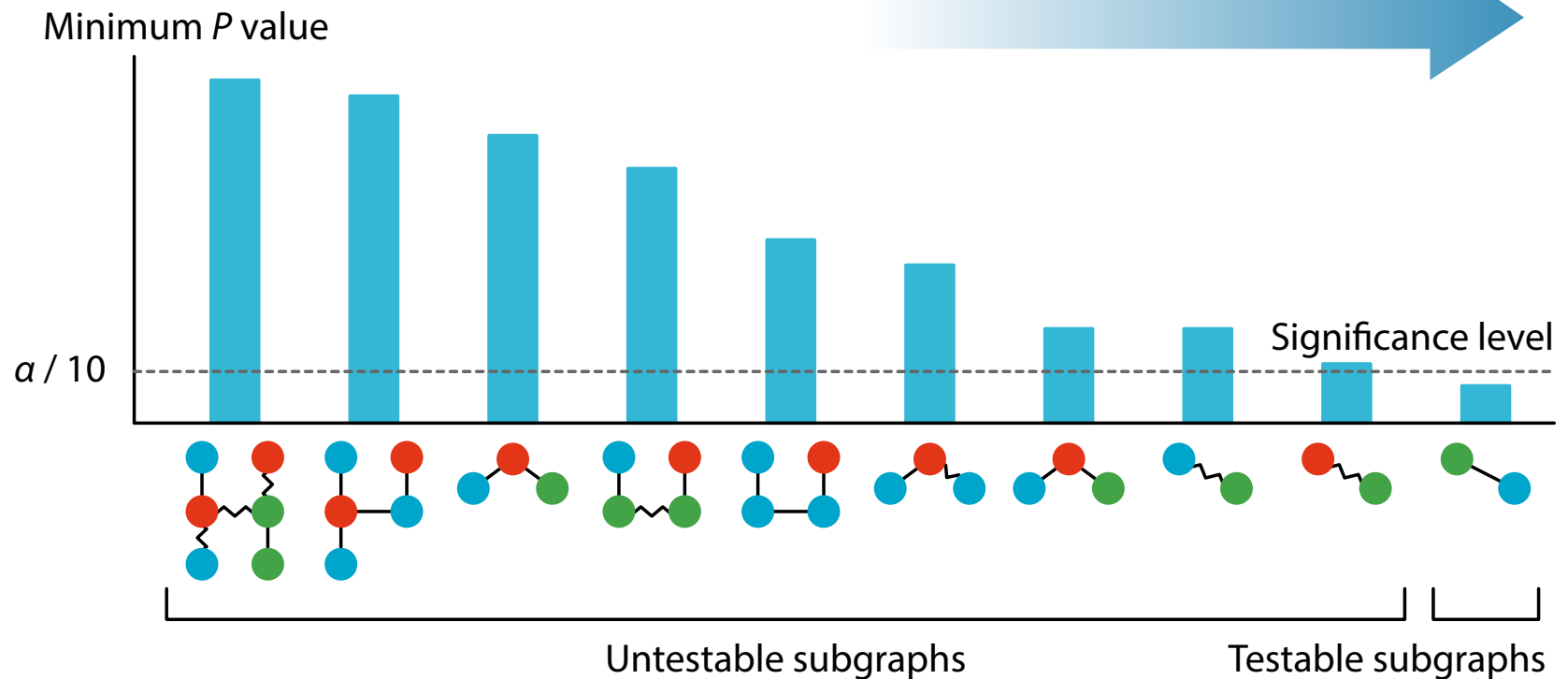
Testable Subgraphs



Testable Subgraphs

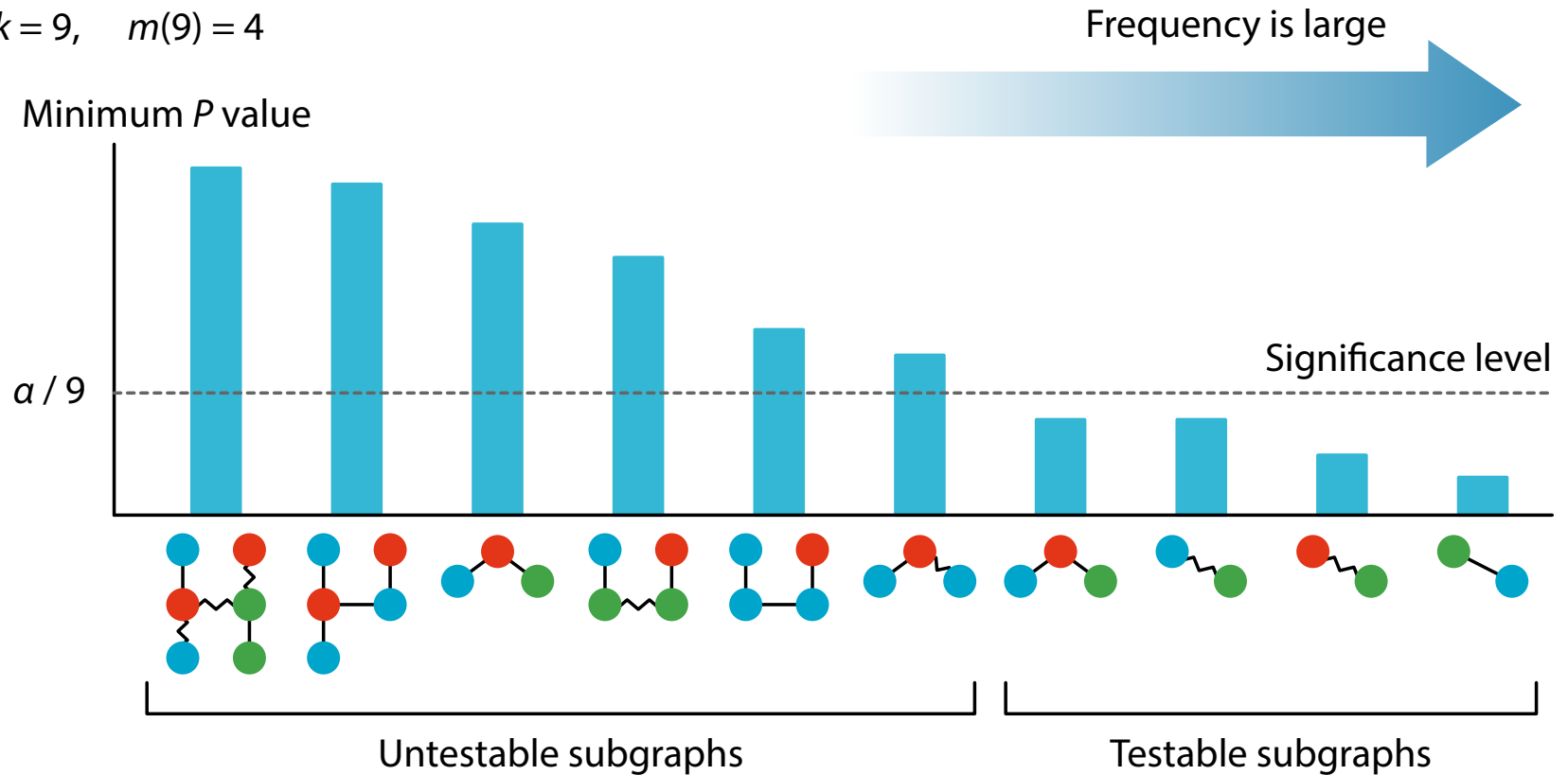
$k = 10$, $m(10) = 1$ (this k is the Bonferroni factor)

Frequency is large



Testable Subgraphs

$$k = 9, \quad m(9) = 4$$



Testable Subgraphs

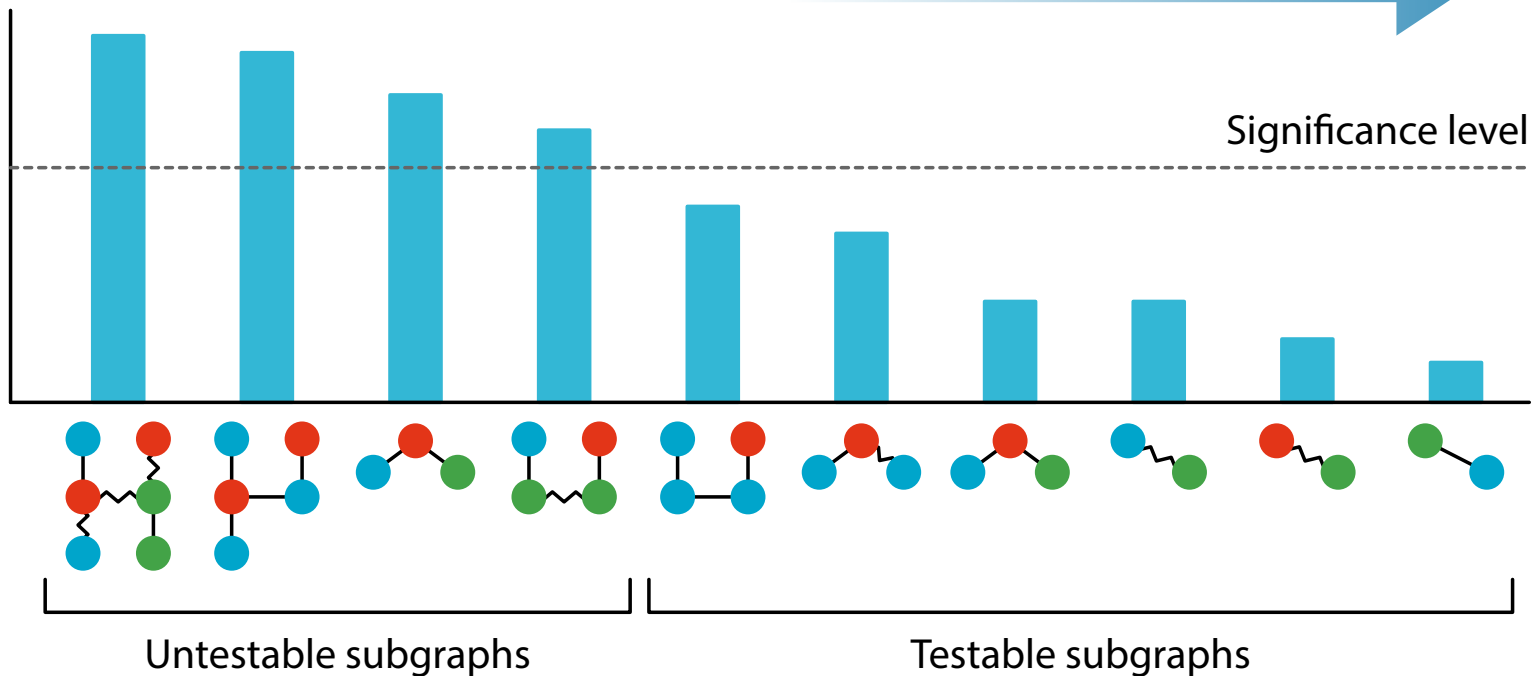
$k = 8, \quad m(8) = 6$

Minimum P value

Frequency is large

$\alpha / 8$

Significance level



Testable Subgraphs

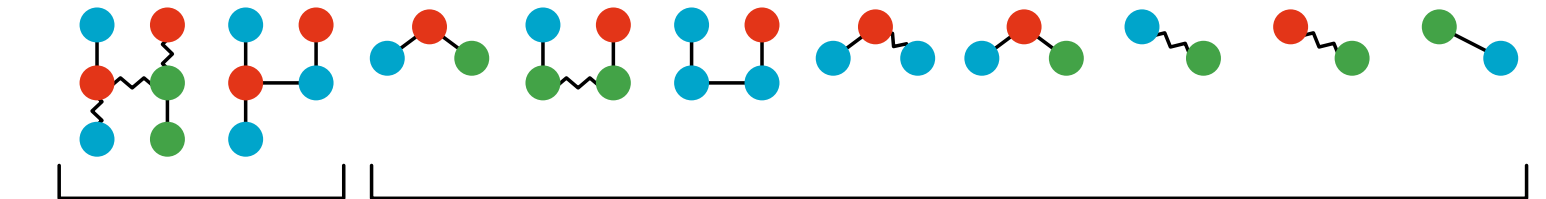
$$k = 7, \quad m(7) = 8$$

Minimum P value

$\alpha / 7$

Frequency is large

Significance level



Unstable subgraphs

Testable subgraphs

Testable Subgraphs

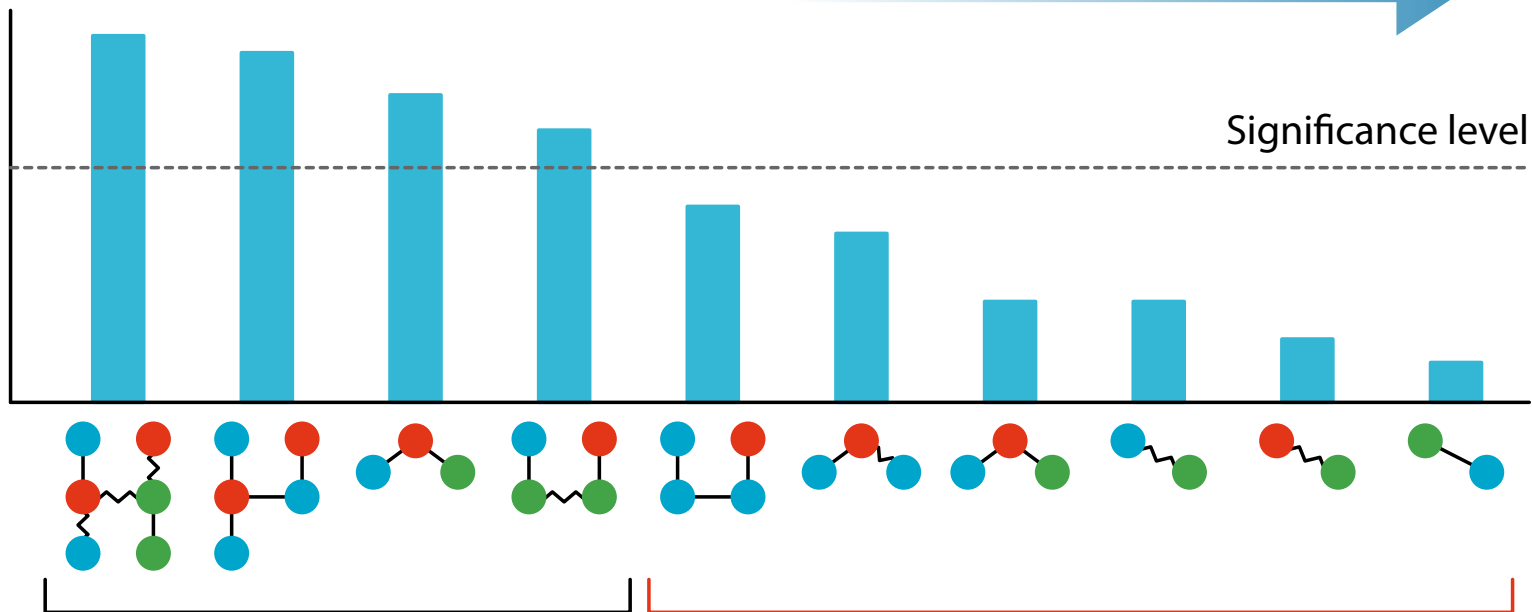
$k = 8$, $m(8) = 6$ ← The reduced Bonferroni factor

Frequency is large

Minimum P value

$\alpha / 8$

Significance level



Untestable subgraphs

Testable subgraphs

Compute the (exact) P values of these testable subgraphs

Subgraphs Are Testable Iff Frequent

- Our task:

Find k such that

(# of subgraphs whose minimum P values $< \alpha/k$) = k

Subgraphs Are Testable Iff Frequent

- Our task:

Find k such that

(# of subgraphs whose minimum P values $< \alpha/k$) = k



Find σ such that

(# of subgraphs whose supports $\geq \sigma$) = $\alpha/\psi(\sigma)$

Subgraphs Are Testable Iff Frequent

- Our task:

Find k such that

(# of subgraphs whose minimum P values $< \alpha/k$) = k



Find σ such that

(# of subgraphs whose supports $\geq \sigma$) = $\alpha/\psi(\sigma)$

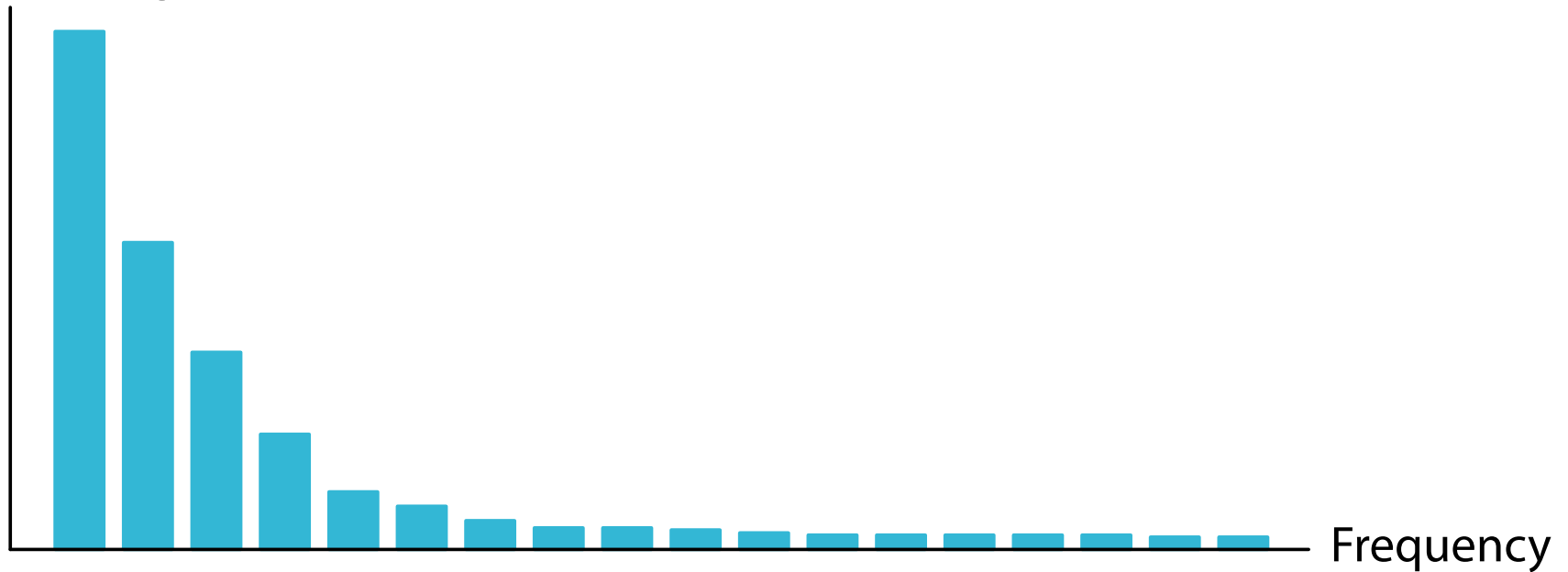
Testable subgraphs = Frequent subgraphs

Use Frequent Subgraph Mining

- Testable subgraphs can be enumerated by frequent subgraph mining algorithms
- **Proposition:**
The set of testable subgraphs $\tau(\mathcal{H})$ coincides with the set of frequent subgraphs with the threshold σ_{rt} s.t.
 - # of subgraphs with minfreq $\sigma_{rt} - 1 > \alpha / \psi(\sigma_{rt} - 1)$,
 - # of subgraphs with minfreq $\sigma_{rt} \leq \alpha / \psi(\sigma_{rt})$,
- $\alpha / \psi(\sigma)$ shows the admissible number of subgraphs at σ
 - $\psi(\sigma) = \binom{n}{\sigma} / \binom{n+n'}{\sigma}$ (Minimum P value at σ)
 - For $k_{rt} = \alpha / \psi(\sigma_{rt})$, if ψ is monotonically decreasing, $m(k_{rt}) = |\{ H \in \mathcal{H} \mid \psi(f(H)) \leq \psi(\sigma_{rt}) \}| = |\{ H \in \mathcal{H} \mid f(H) \geq \sigma_{rt} \}|$

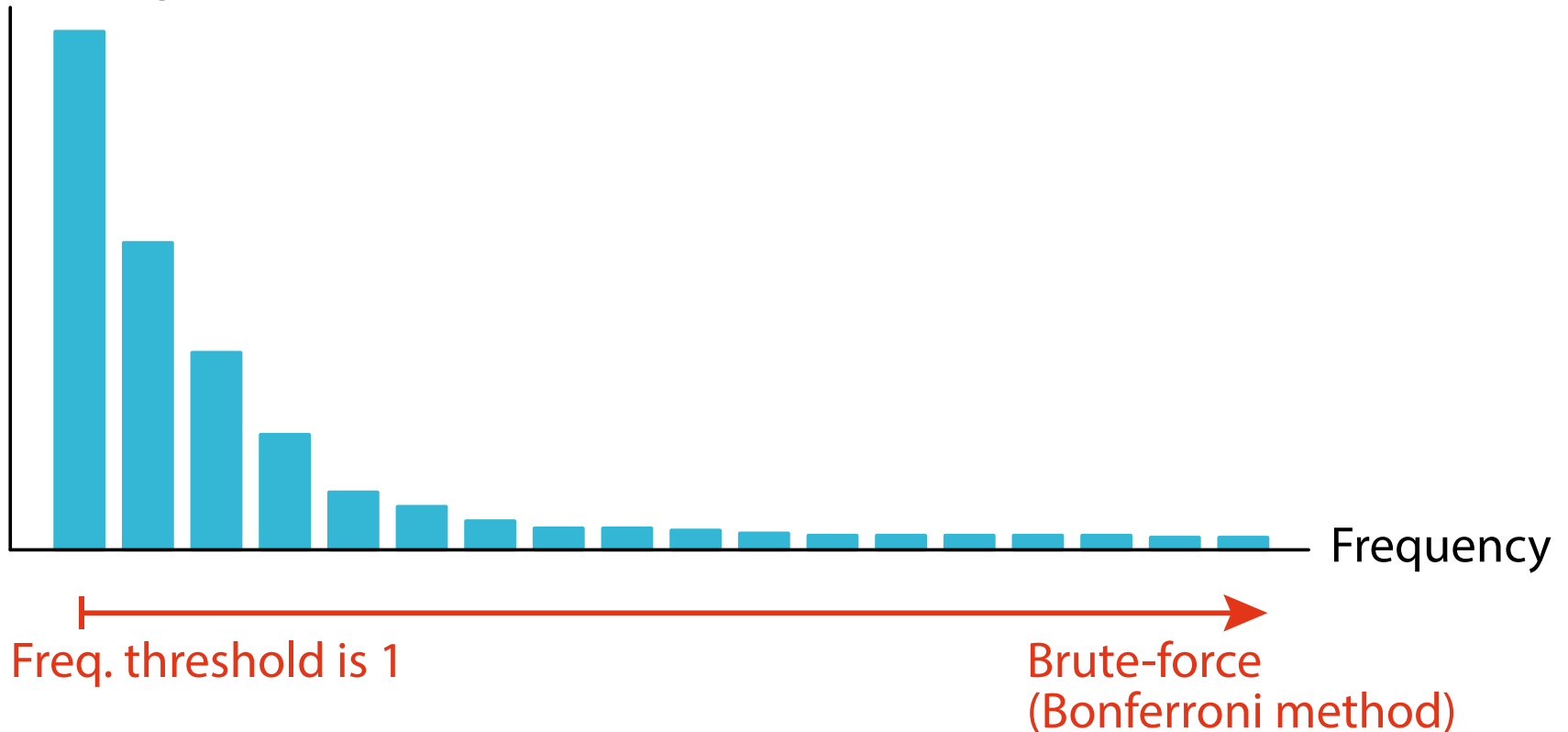
How to Use Subgraph Mining

of subgraphs



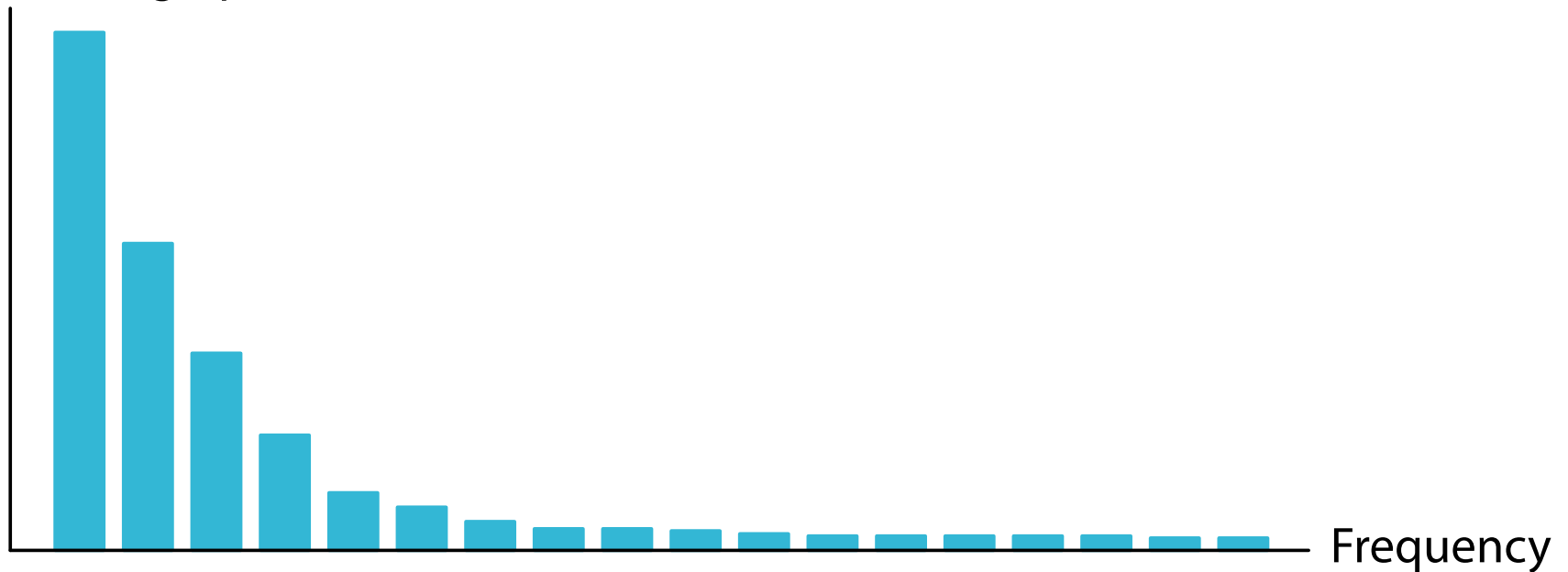
Brute-Force Search (Bonferroni)

of subgraphs



Decremental Search (LAMP)

of subgraphs



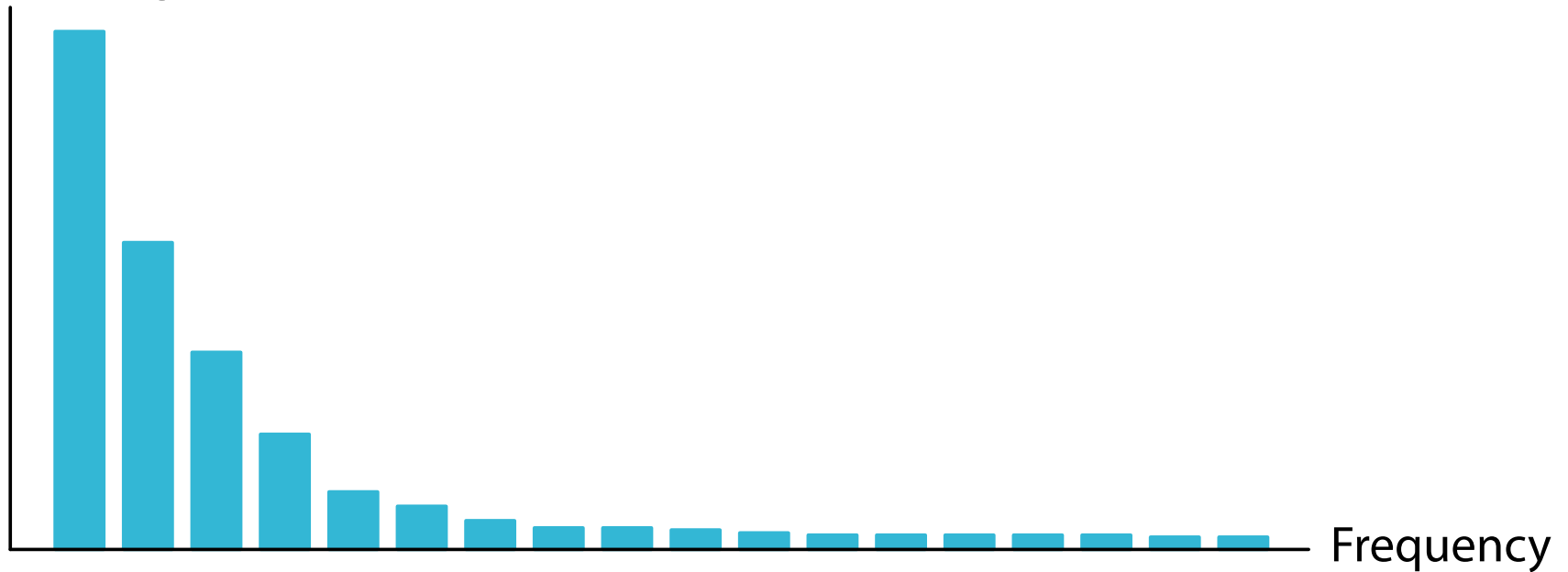
Terminate if # of subgraphs is larger than $\alpha / \psi(\sigma)$

Decremental search

⋮

Incremental Search

of subgraphs



—x Terminate if # of subgraphs detected so far exceeds $\alpha / \psi(\sigma)$

—x

—x

—x

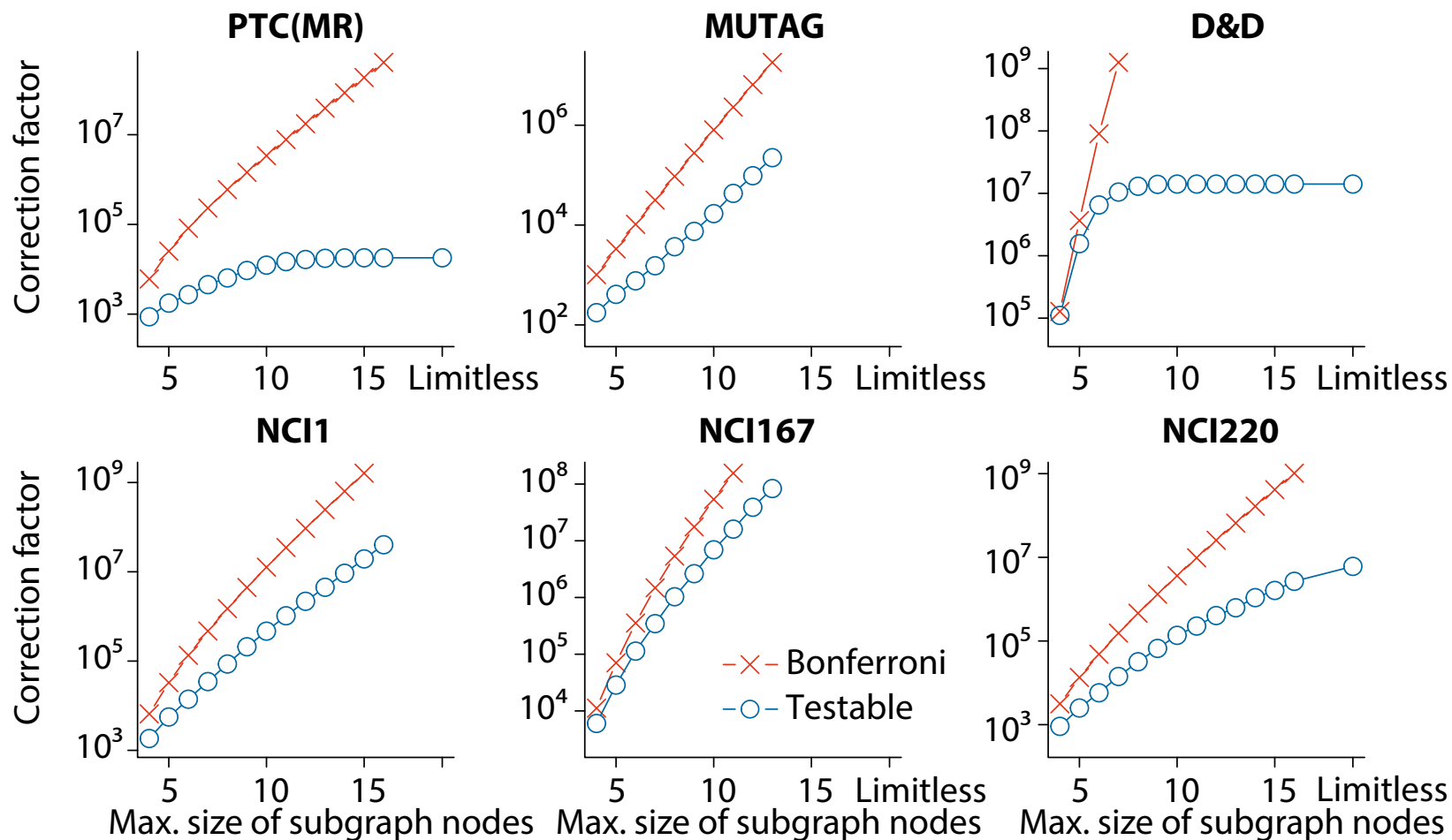
—x

Incremental
search

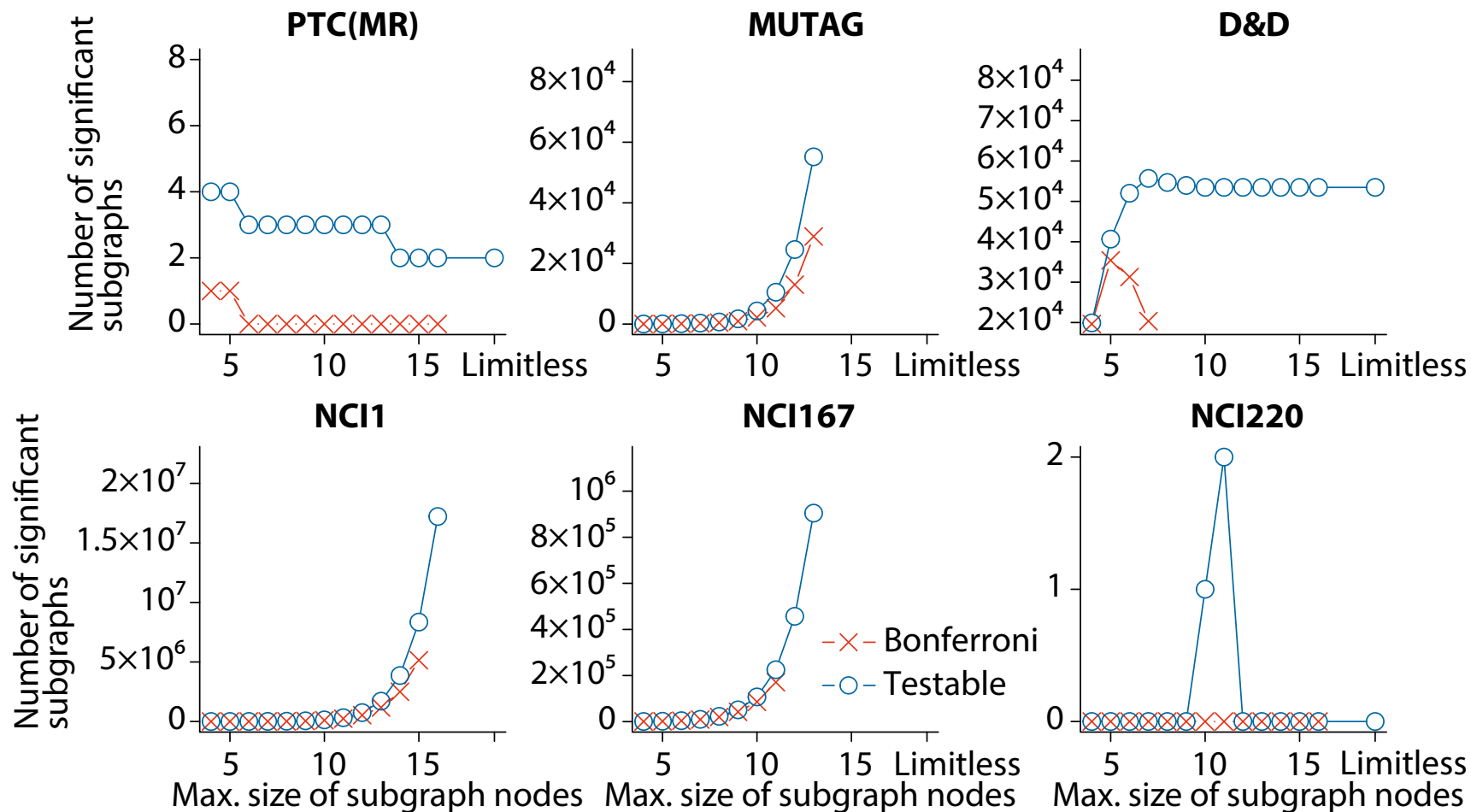
Datasets

| Dataset | Size | #positive | avg. $ V $ | avg. $ E $ | max $ V $ | max $ E $ |
|----------|-------|-----------|------------|------------|-----------|-----------|
| PTC (MR) | 584 | 181 | 31.96 | 32.71 | 181 | 181 |
| MUTAG | 188 | 125 | 17.93 | 39.59 | 28 | 66 |
| D&D | 1178 | 691 | 284.32 | 715.66 | 5748 | 14267 |
| NCI1 | 4208 | 2104 | 60.12 | 62.72 | 462 | 468 |
| NCI167 | 80581 | 9615 | 39.70 | 41.05 | 482 | 478 |
| NCI220 | 900 | 290 | 46.87 | 48.52 | 239 | 255 |

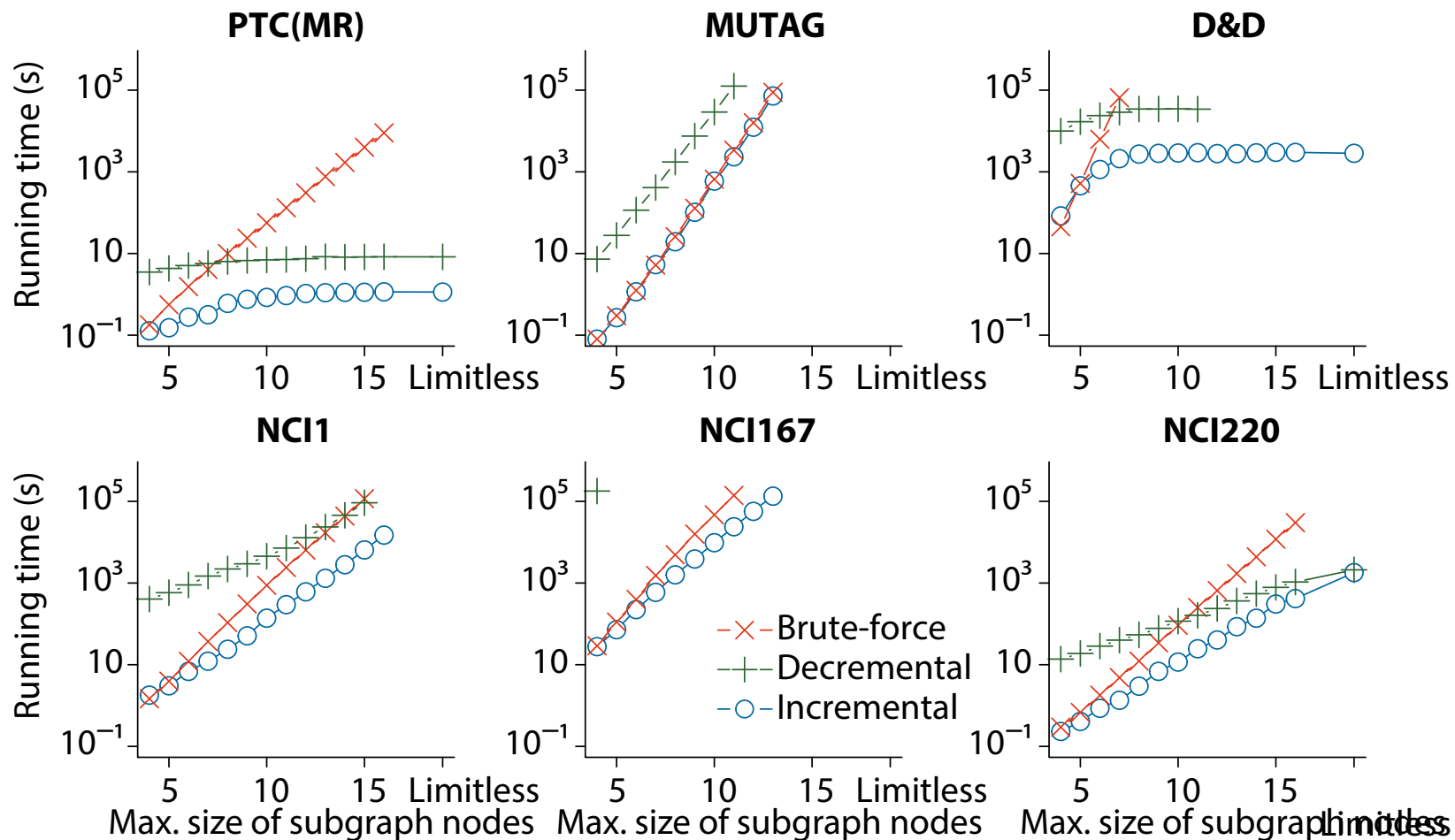
Correction Factor



Number of Significant Subgraphs



Running Time (second)



Running Time Summary

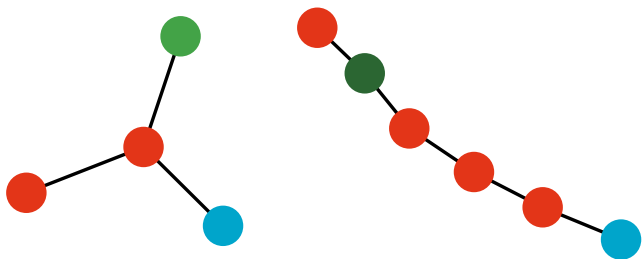
- RMSD (root mean square deviation) of running time (seconds) to the best (fastest) running time on all datasets

| Brute-force | Decremental (LAMP) | Incremental |
|---------------------|---------------------|---------------------|
| 6.994×10^4 | 2.410×10^4 | 1.230×10^2 |

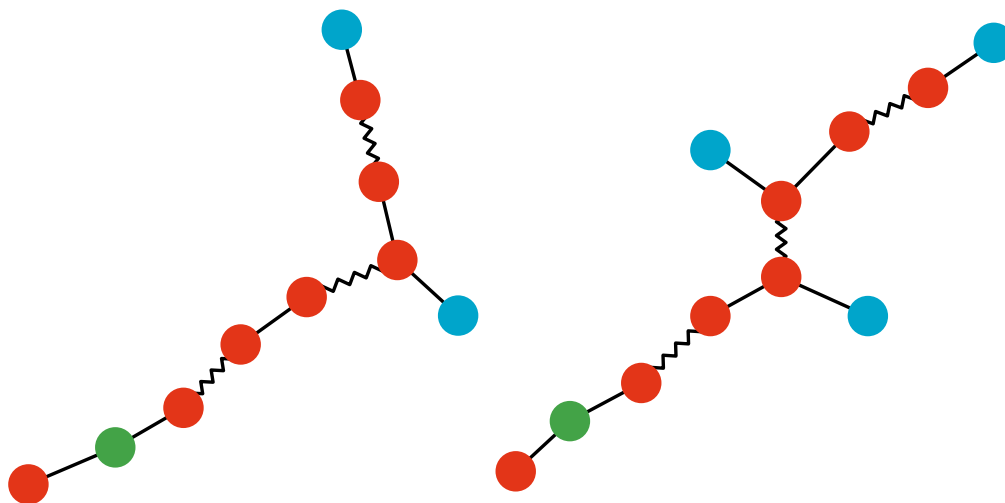
- Incremental search is the fastest
 - More than two orders of magnitude faster than brute-force
 - Much faster than decremental (LAMP) as the root frequency is usually small (~ 20)

Detected Significant Subgraphs

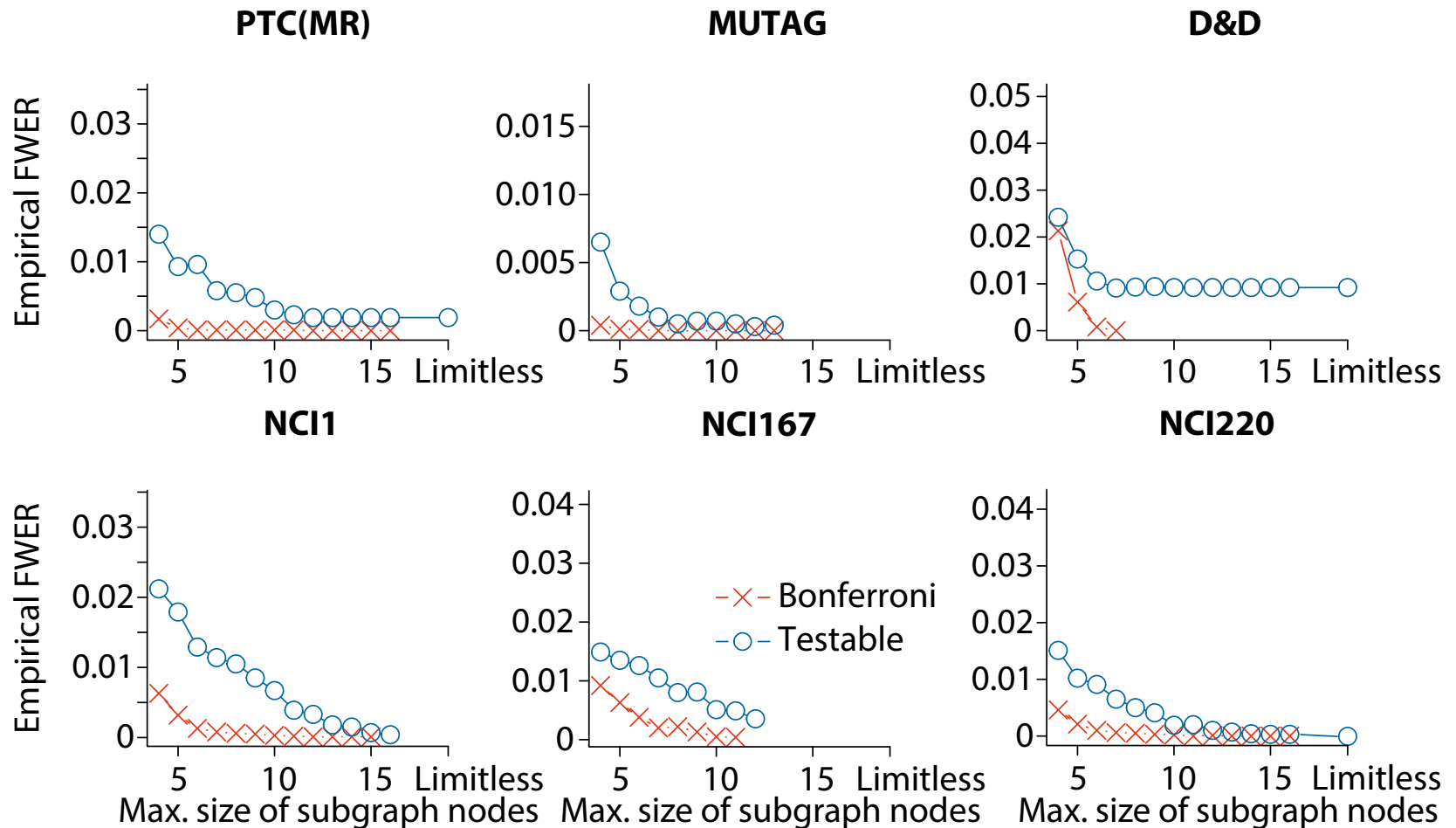
PTC (MR)
(carcinogenicity)



NCI 220
(anti-cancer activity)



FWER Is still Too Low!



Related work: LAMP version 2

- Minato et al. proposed a faster version of LAMP in itemset mining
 - Minato, S., Uno, T., Tsuda, K., Terada, A. and Sese, J.: **Fast Statistical Assessment for Combinatorial Hypotheses Based on Frequent Itemset Mining**
ECML PKDD 2014
- The idea is almost the same with our incremental search
 - Start from $\sigma = 1$, every time an item is added, the condition $|\mathcal{I}(\sigma)| \leq \alpha/\psi(\sigma)$ is checked
 - $\mathcal{I}(\sigma)$: the set of itemsets found so far with the frequency $\geq \sigma$
 - As soon as $|\mathcal{I}(\sigma)| > \alpha/\psi(\sigma)$, the current σ is too large and we decrement it

Conclusion

- Significant subgraphs mining with multiple testing correction is achieved
 - The first work that considers multiple testing correction in graph mining
- Efficient and effective (less false negatives) using **testability**
- Future work
 - Increase the FWER with keeping $\leq \alpha$
 - Currently we ignore **correlations** between subgraphs

Papers about Testability

- Tarone, R.E.:
A modified Bonferroni method for discrete data
Biometrics (1990)
- Terada, A., Okada-Hatakeyama, M., Tsuda, K., Sese, J.:
Statistical significance of combinatorial regulations,
Proc. Natl. Acad. Sci. USA (2013).
- Minato, S., Uno, T., Tsuda, K., Terada, A., Sese, J.:
**Fast Statistical Assessment for Combinatorial Hypotheses
Based on Frequent Itemset Mining**
ECML PKDD 2014
- Sugiyama, M., Llinares López, F., Kasenburg, N., Borgwardt, K.M.:
Significant Subgraph Mining with Multiple Testing Correction,
SIAM SDM 2015 (<http://arxiv.org/abs/1407.0316>)
– Code: <http://git.io/N126>