

# Using higher-order networks to represent time-dependent binding events in the budding yeast cell cycle

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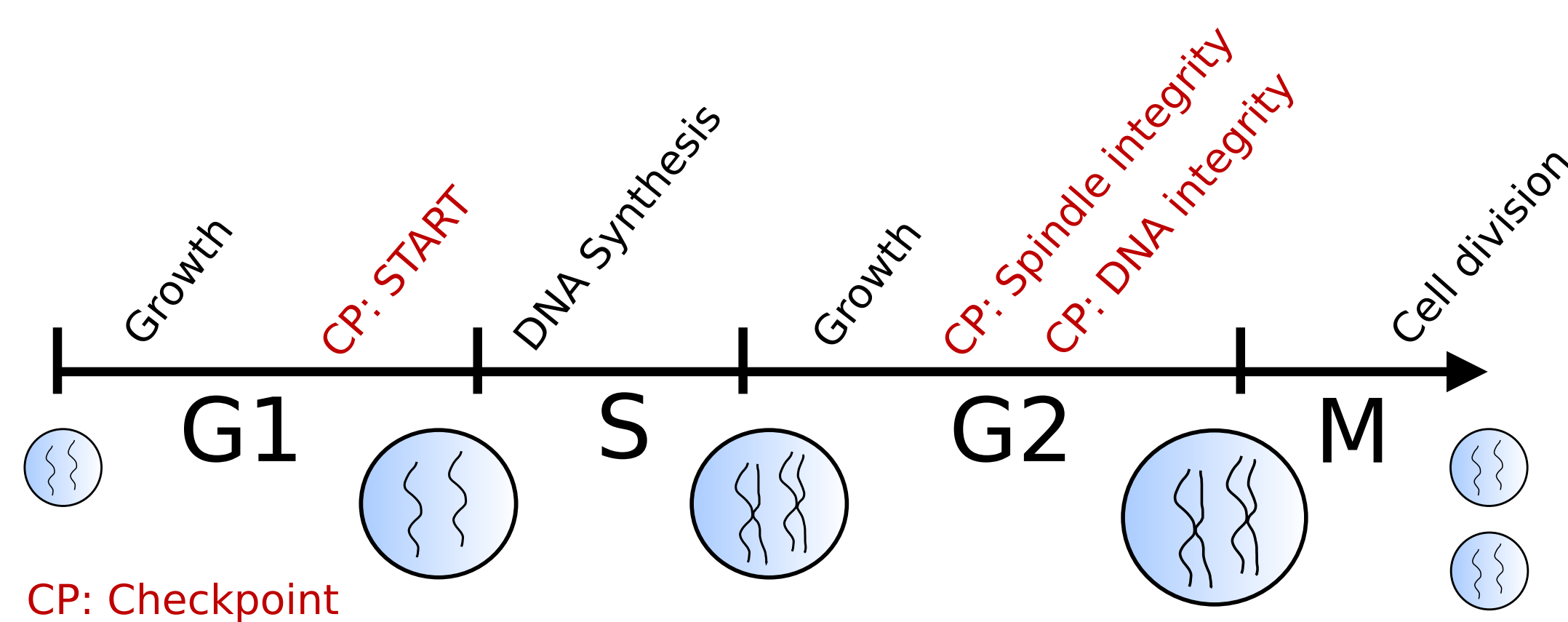
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## Biological introduction

### 1. Cell cycle: biological basis

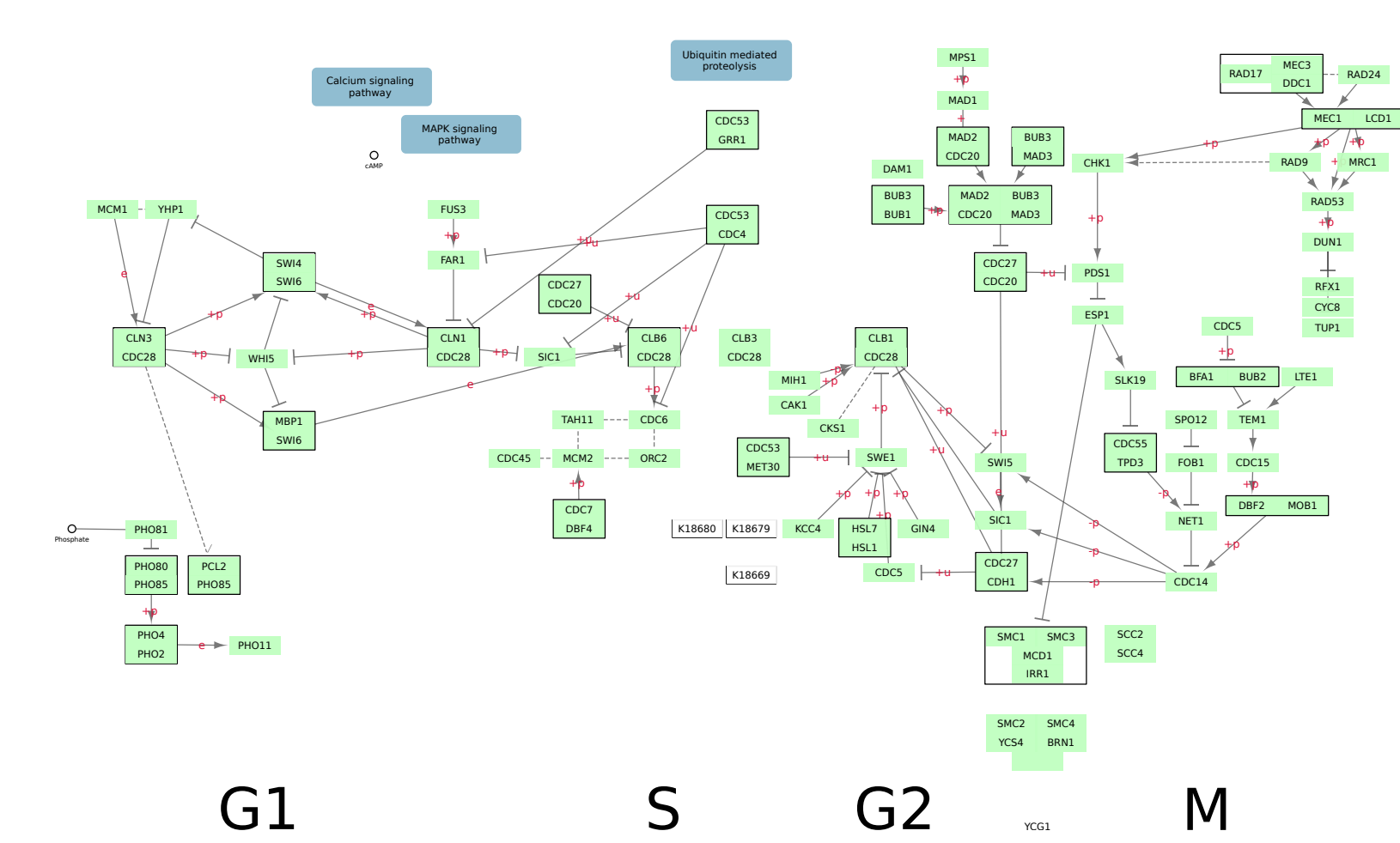
The **cell cycle** consists in a succession of biochemical processes leading to the **division of the cell**. It is crucial to life.

The cycle is divided into **four main phases**. Moreover, progression from one phase to the next is controlled by **checkpoints**.



### 2. Cell cycle: temporally ordered and pathway interactions

The protein-protein **interactions** in the cell cycle are **temporally ordered**. Some **pathways** are activated at overlapping times and some proteins are part of multiple pathways (e.g. master regulator CDC28). Network from [1]:



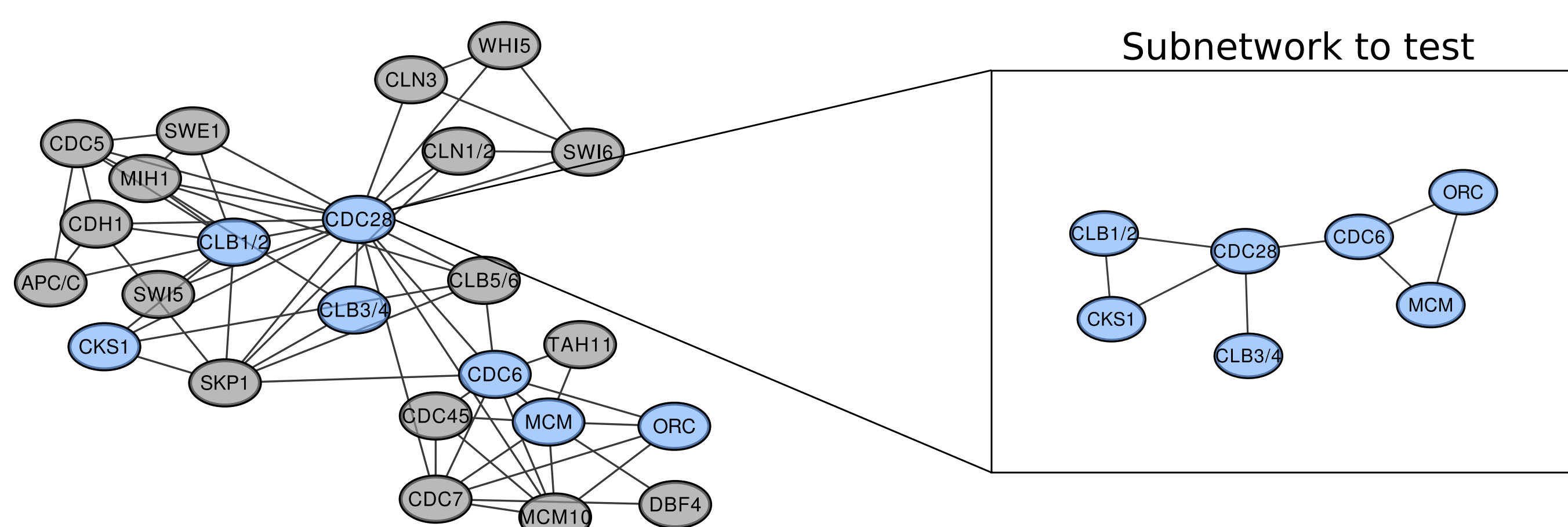
## From first- to higher-order networks

### 3. Typical protein-protein interaction network

Protein-protein interaction networks are **typically represented by static memoryless graphs**.

Example: cell cycle from String database [2] (centered on CDC28, with max. 20 of its 1st neighbours, and max. 20 of its 2nd neighbours).

Input data:  $(A, B)$ .



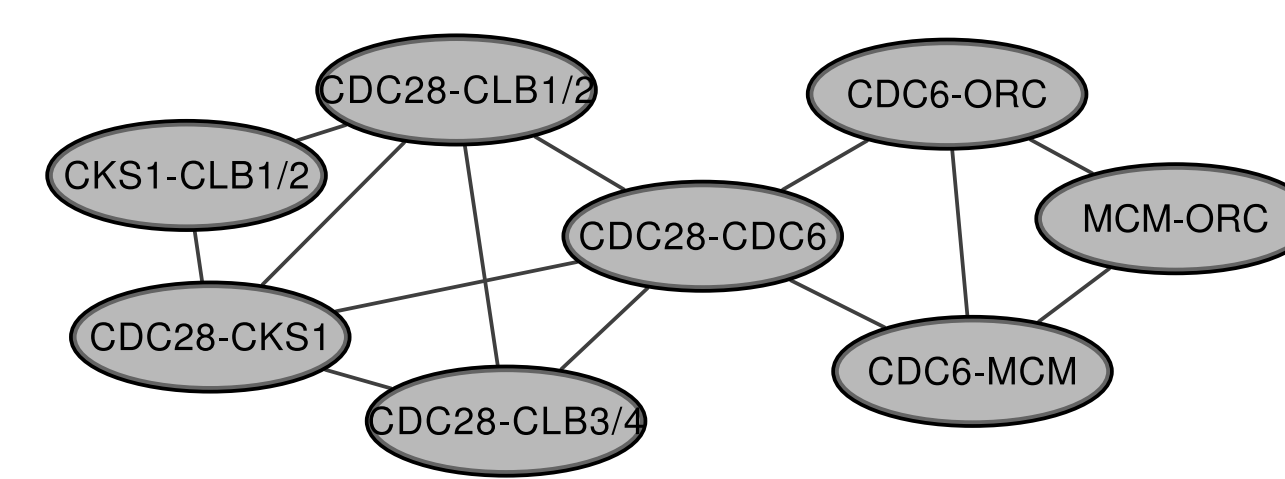
Left: full network. Right: smaller subnetwork we use in the next boxes.

On such a traditional first-order network, all the networks science tools and measures can be applied, such as centrality measures or community detection.

### 4. Naive line graph

Input data:  $(A, B)$

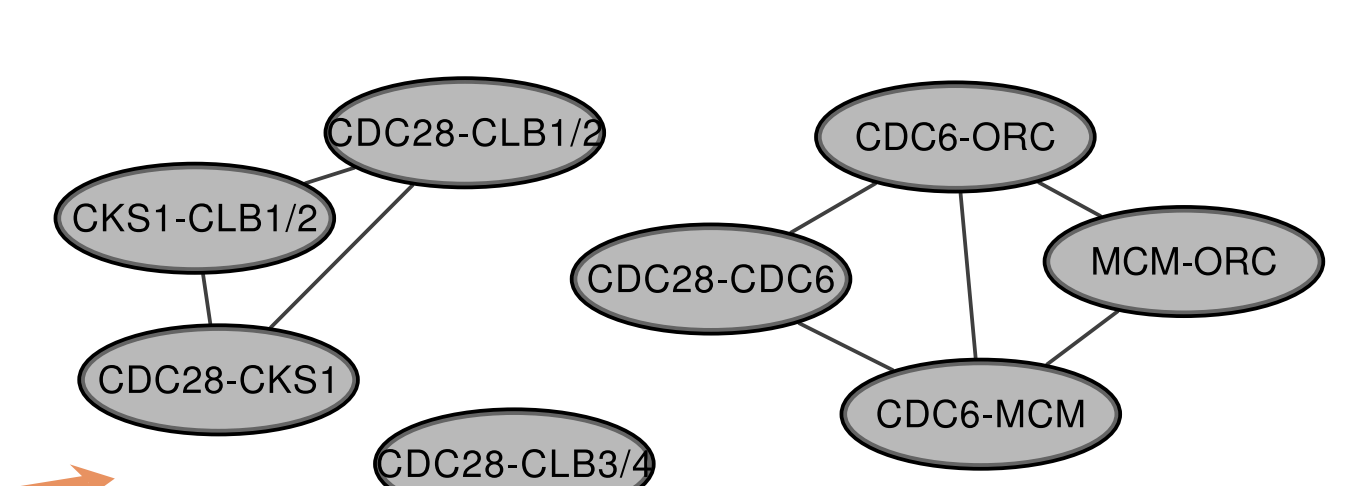
Result: no information gained



### 5. Plus pathway

Input data:  $(A, B, C)$

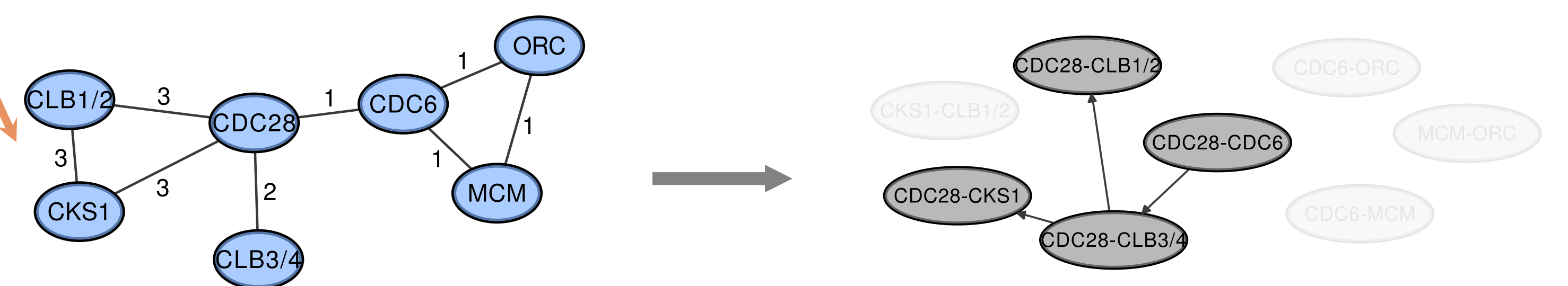
Result: structural separation of "phases" (3 disconnected components)



### 6. 2-nd order aggregated temporal network

Input data:  $(A, B; t)$

Build 2nd-order aggregated network [4]



## Conclusions

### 7. Discussion

**Disclaimer:** this project is still in its **exploratory phase**.

Higher-order networks start to get attention in the physics community, but have not been applied to biological networks where they are much needed.

**Questions to explore:**

What biological insight can we gain from **including temporality** in our description? How to construct the higher-order network in an automated and reliable way?

How to deal with the **nonlinear**, rather event-driven, **time** of the cycle? This is unlike most temporal networks.

## References

- [1] KEGG database
- [2] String database
- [3] Lambiotte R., Rosvall M. and Scholtes I., Nat. Phys. 15, 313-320 (2019).
- [4] Scholtes, I., Wider, N. and Garas, A., Euro. Phys. J. B, 89, 61 (2016)

## Acknowledgements

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