

Inferring cell cycle phases from a temporal network of protein interactions

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10th July 2021

Networks2021

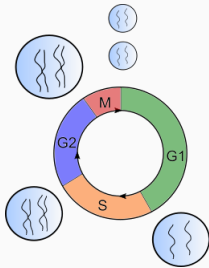
 maximelca

Aix-Marseille University

work with A. Barrat, B. Habermann, L. Tichit, A. Morris, and A. Townsend-Teague
bioRxiv:2021.03.26.437187

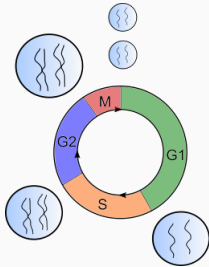
Biological systems go through different phases/states

Cell cycle phases



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Cell cycle phases

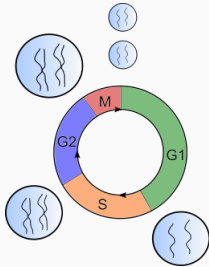


Sleep stages



Biological systems go through different phases/states

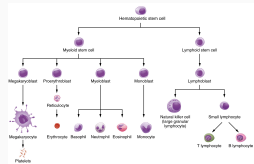
Cell cycle phases



Sleep stages

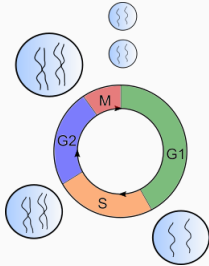


Cell differentiation



Biological systems go through different phases/states

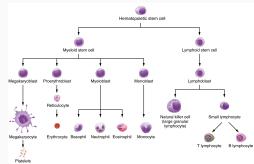
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Sleep stages



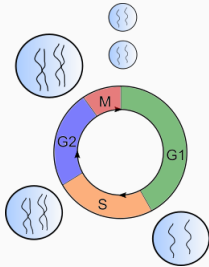
Cell differentiation



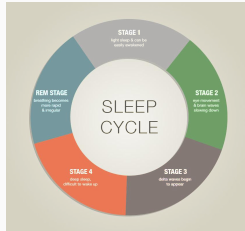
Temporal structure ↔ biological behaviour

Biological systems go through different phases/states

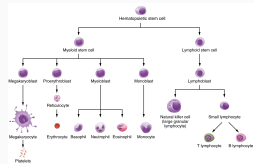
Cell cycle phases



Sleep stages



Cell differentiation



Temporal structure ↔ biological behaviour

active protein interactions

expressed genes

In this talk

A computational method, Phasik, to infer the temporal organisation of biological systems, over multiple temporal scales.

Goal : help biologist understand their system and design experiments better

In this talk

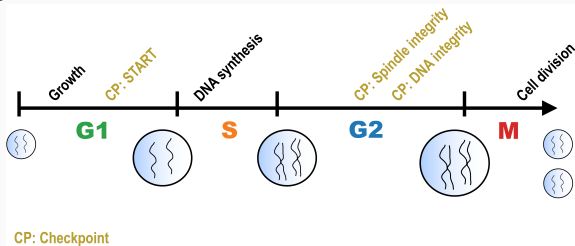
A computational method, Phasik, to infer the temporal organisation of biological systems, over multiple temporal scales.

Goal : help biologist understand their system and design experiments better

To validate our method: the **cell cycle**, because it is so well known.

Cell cycle: protein interactions that change over time

... leading to the cell division.



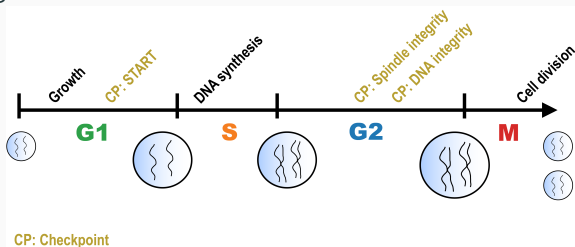
Multiple relevant timescales:

- Macro: 4 physiological phases (G1, S, G2, M)
- Meso: physiological subprocesses
- Micro: protein interactions that change over time

Time-ordering ensured by molecular **checkpoints**.

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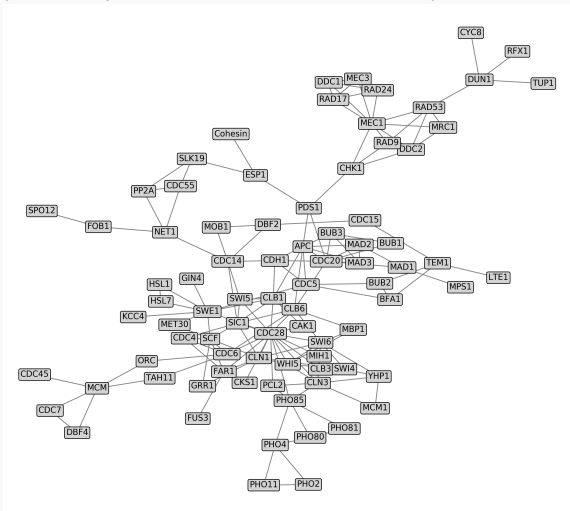
Time-ordering ensured by molecular **checkpoints**.

We focus on **budding yeast** because it is best known.

**Can we predict the phases
from the temporal protein
interactions?**

Static network of protein interactions represents the cell cycle

84 nodes (proteins) connected by 159 edges (protein interactions).



All temporal information is lost!

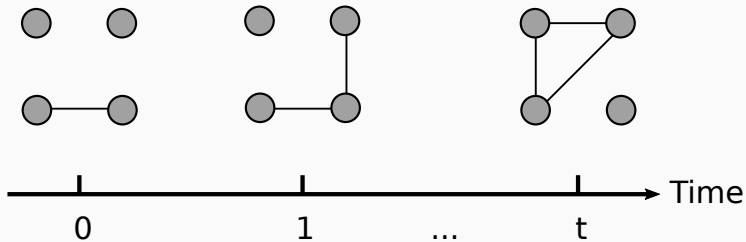
Interaction data: KEGG.

**All temporal information is lost..
we need temporal networks**

Temporal networks incorporate temporal information

The **edges** are now **time-varying**.

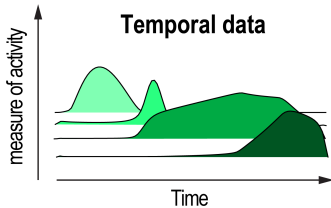
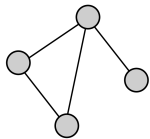
At each time corresponds a **snapshot** of the temporal network



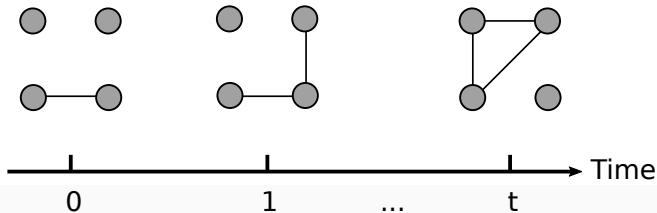
Phasik: 1. build a temporal network

Build temporal network by integrating time series

Static network



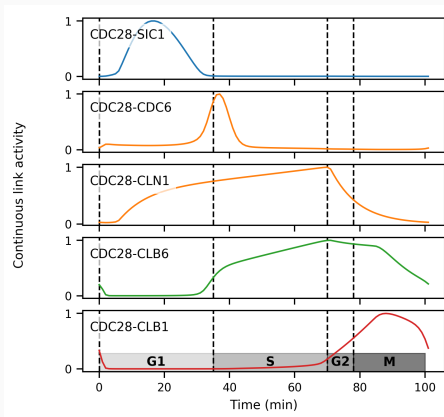
Temporal network



Inject time series data into the static network

Temporal data needed: mathematical model or RNA-seq.

Our network is **partially temporal** (34/159 edges).

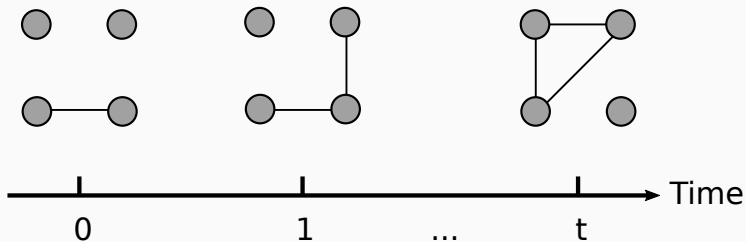


Temporal data: Chen 2014 and Kelliher 2016.

Phasik: 2. infer biological phases

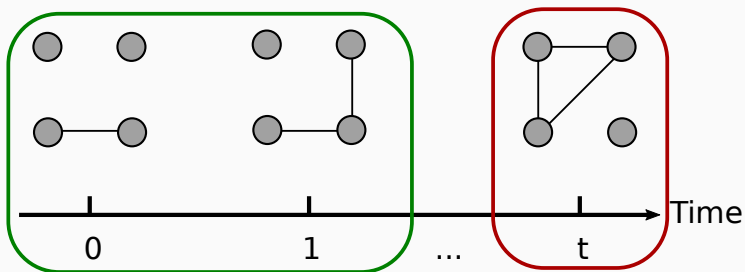
Inferring biological phases by clustering

Idea: the temporal network stays similar when it stays in the same “state” or phase, but changes a lot when it changes phase (Masuda and Holme, 2019).



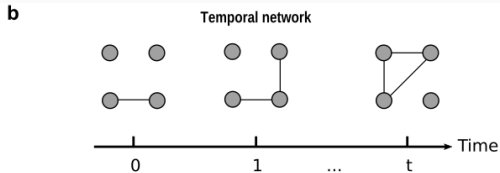
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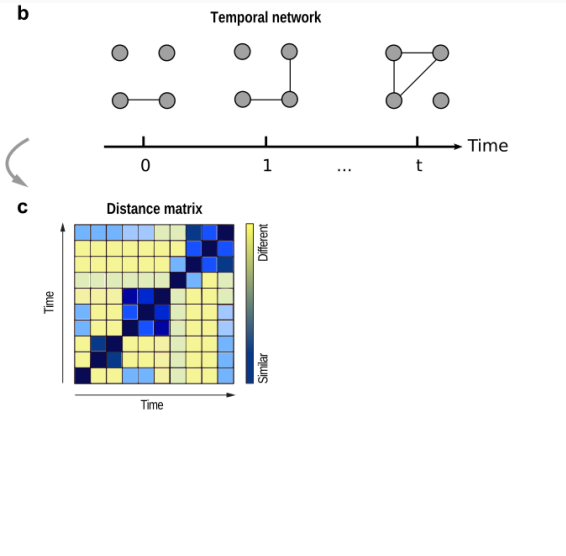
In more details

We apply hierarchical clustering to the snapshots.



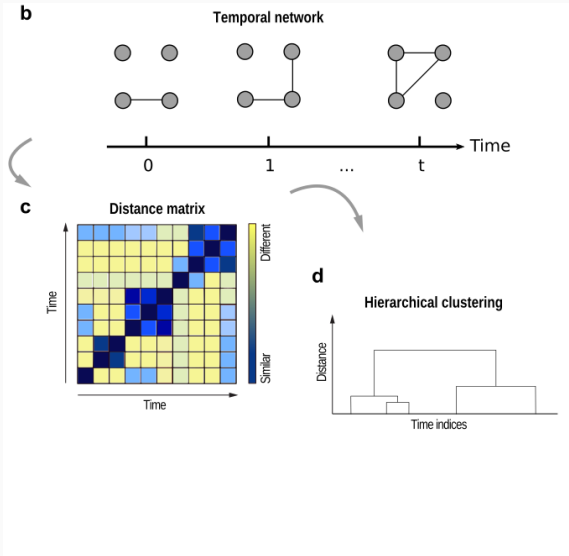
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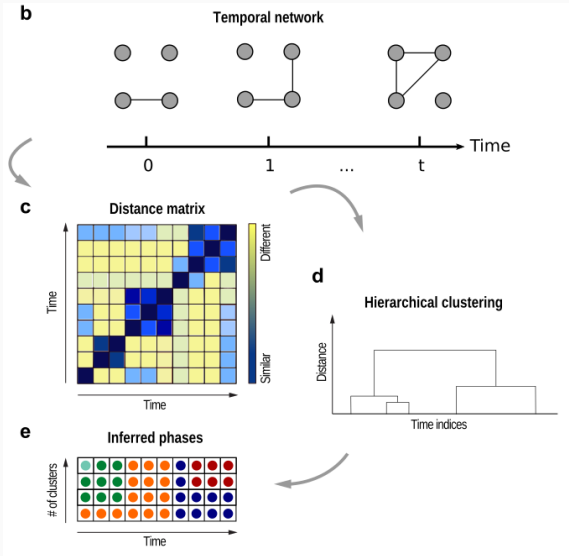
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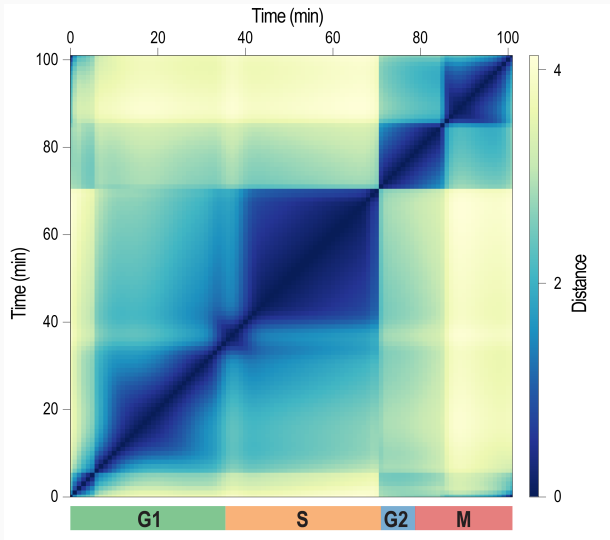
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Results

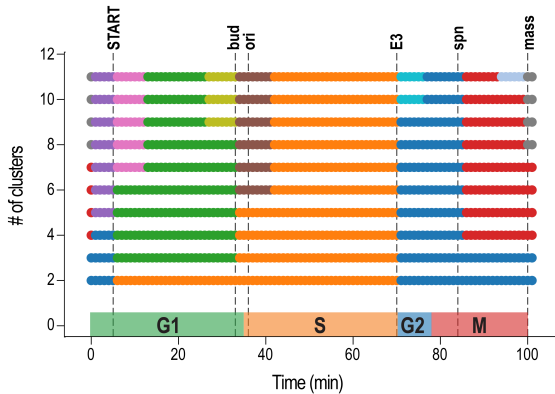
We recover known cell cycle phases

Distance matrix:



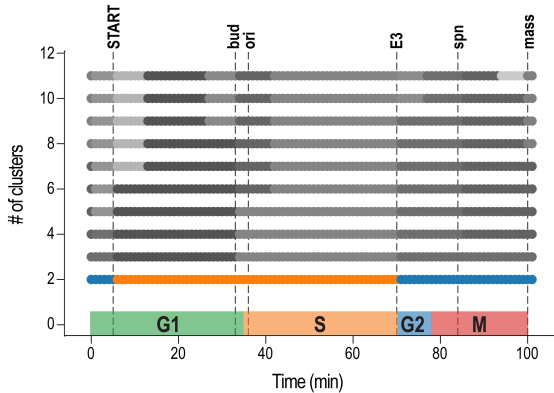
We recover known cell cycle phases

Few clusters → coarse-grained view of the cell cycle.



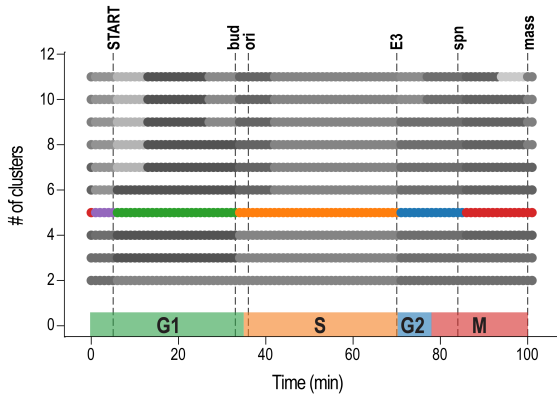
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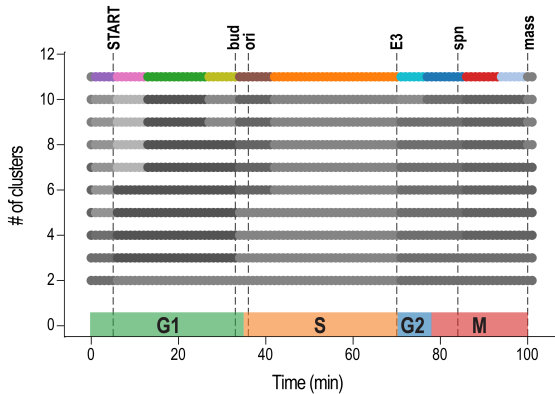
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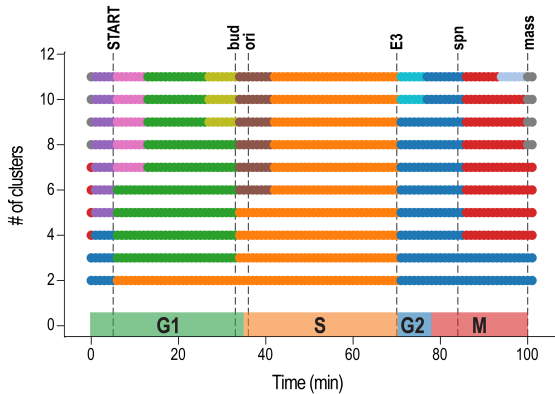
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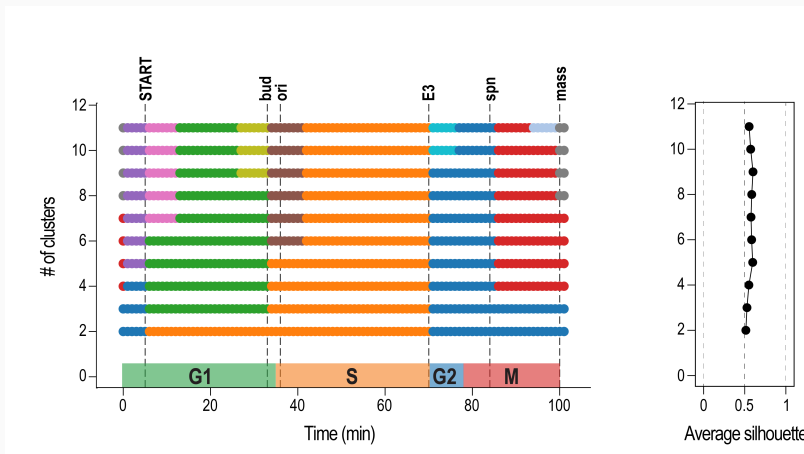
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Multiple scales are relevant

Quality of clusterings (average silhouette) is constant across scales



Is the method, Phasik, robust?

Yes, we made many robustness tests

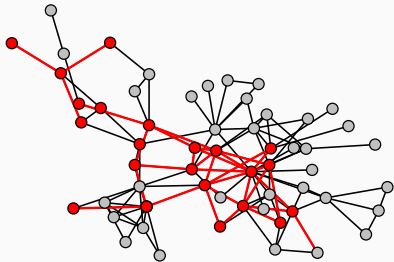
Phasik and its results are **robust against**:

- changes in clustering method
- changes in distance metric
- measurement noise in time series
- downsampling of time series

**How little temporal information do
we need?**

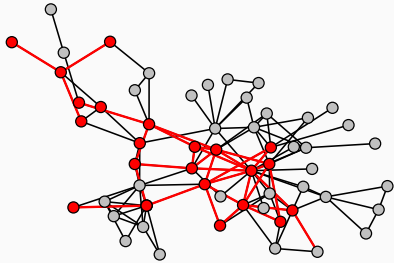
Imagine we have access to only CDC28's interactions

Original: 34 / 159 edges with
temporal information

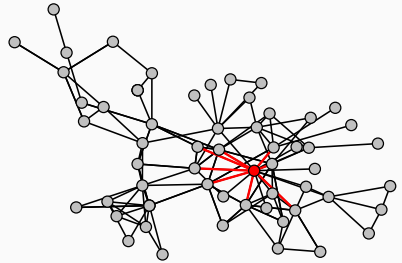


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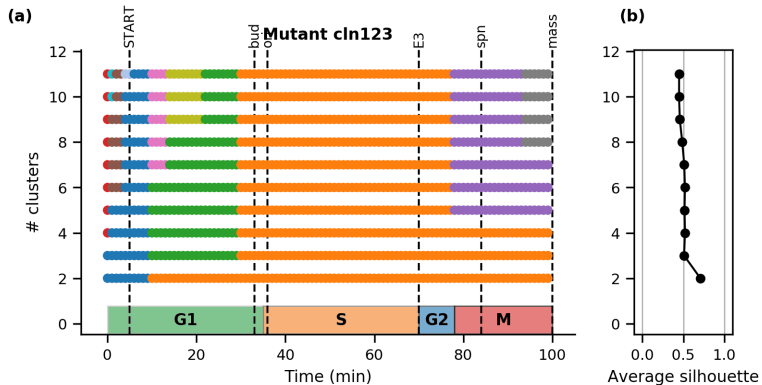
Now: 8 / 159 edges with temporal information



Edges with no temporal information are shown in grey.

**Can Phasik detect modified phases
in mutants?**

Mutant phases: G1 arrest in Δ CLN1/2/3



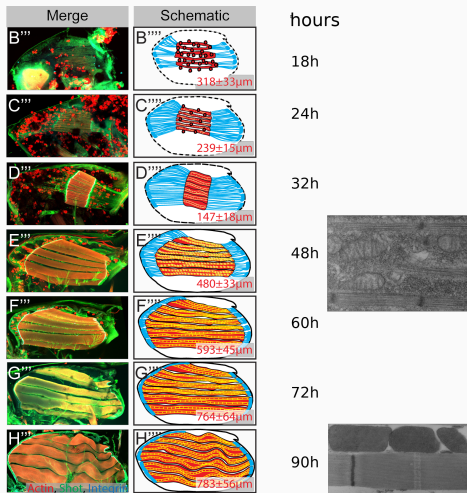
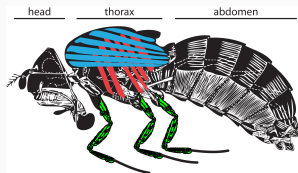
**Phasik can be used with gene
expression data too!**

**Can the method be used on other
biological systems?**

Yes!

Flight muscle development in *Drosophila*

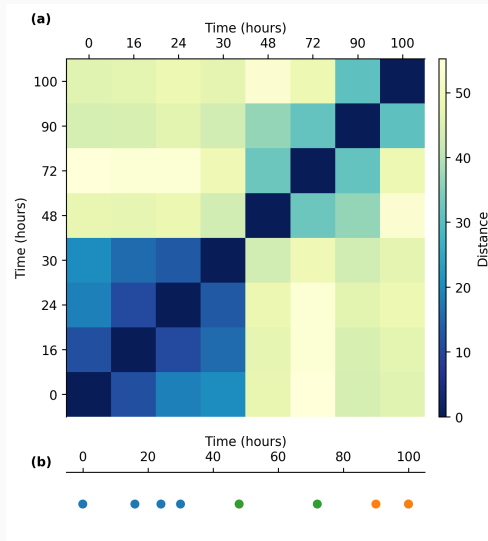
Flight muscles (blue) have densely packed, cristae-rich mitochondria



RNA-seq measurement of the genes at each time.

Flight muscle development in *Drosophila*

We have 8 time points between 0 and 100 hours.



Phasik can be used on a wide range of biological systems

All you need is:

- **time series data** about biological units (e.g. proteins/genes/..) or their interactions
- **interaction data** (e.g. static PPI network)

Use our code on your data!



- Our user-friendly **code is available online:**
`https://gitlab.com/habermann_lab/phasik`
- Functions for each step of the pipeline: temporal networks building, and phase inference.
- Online **documentation:**
`https://phasik.readthedocs.io/en/latest/`
- Available as a **Python package**. **Install it** in the terminal:
`pip install phasik`

Conclusions

- We represented the **cell cycle** as a **temporal network** of protein interactions
- From that, we **inferred biological phases** of the cell cycle by clustering snapshots
- We investigated **how much**, and what, **temporal data** is necessary.
- We applied the method to cell cycle mutants and flight muscle development in *Drosophila*

Next steps: Apply this method to other less well-known biological systems. Let us know about yours!

Thank you for your attention!

Thanks to the people I work with: Alain Barrat, Bianca Habermann, Laurent Tichit, and everyone in their teams!

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🐦 maximelca

Any questions?

