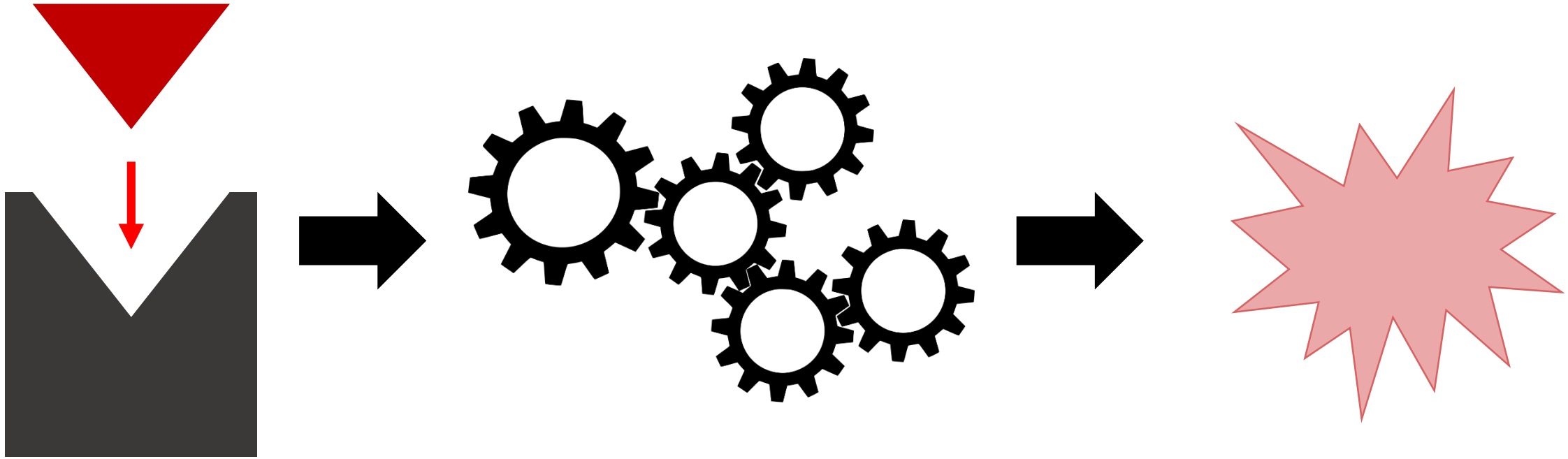
TimeNexus *identifies dynamic pathways from gene expression time-series data using temporal networks*

Michaël PIERRELÉE

Habermann's group PhD candidate

Aix Marseille Univ, CNRS, IBDM, Marseille, France

Pathways are the mechanisms behind the cellular responses



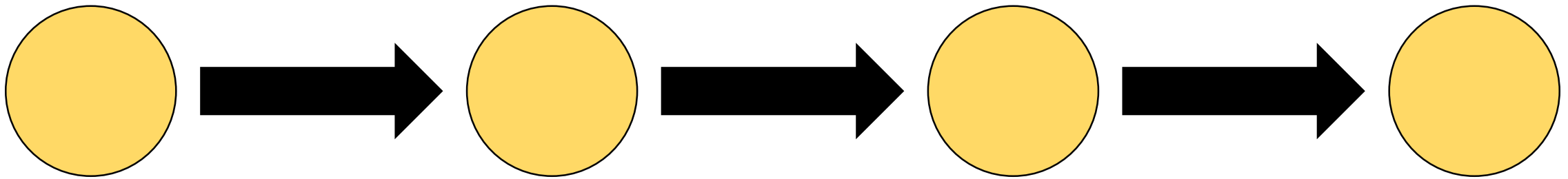
Stimulus

Pathways

Cellular responses

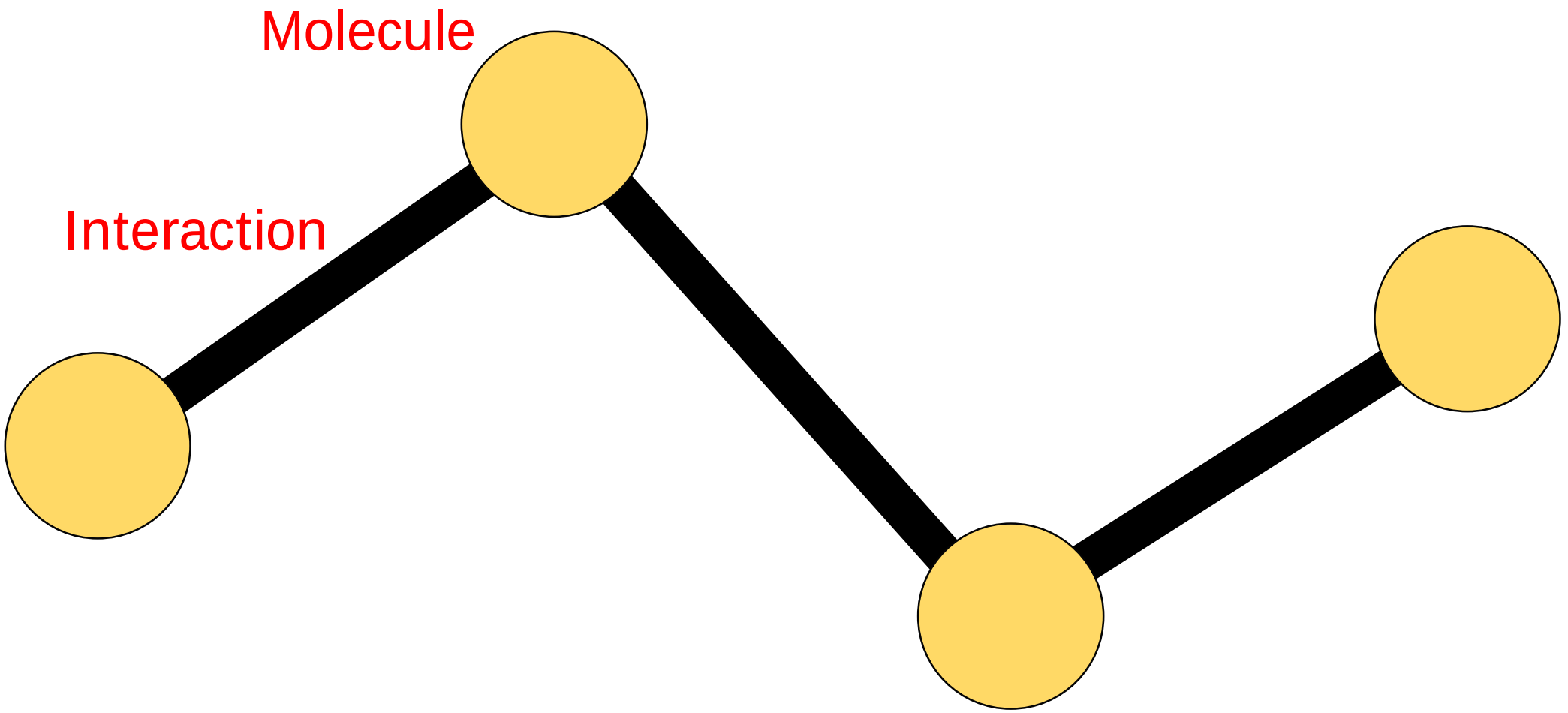
Pathways are the series of actions leading to a response

Molecule

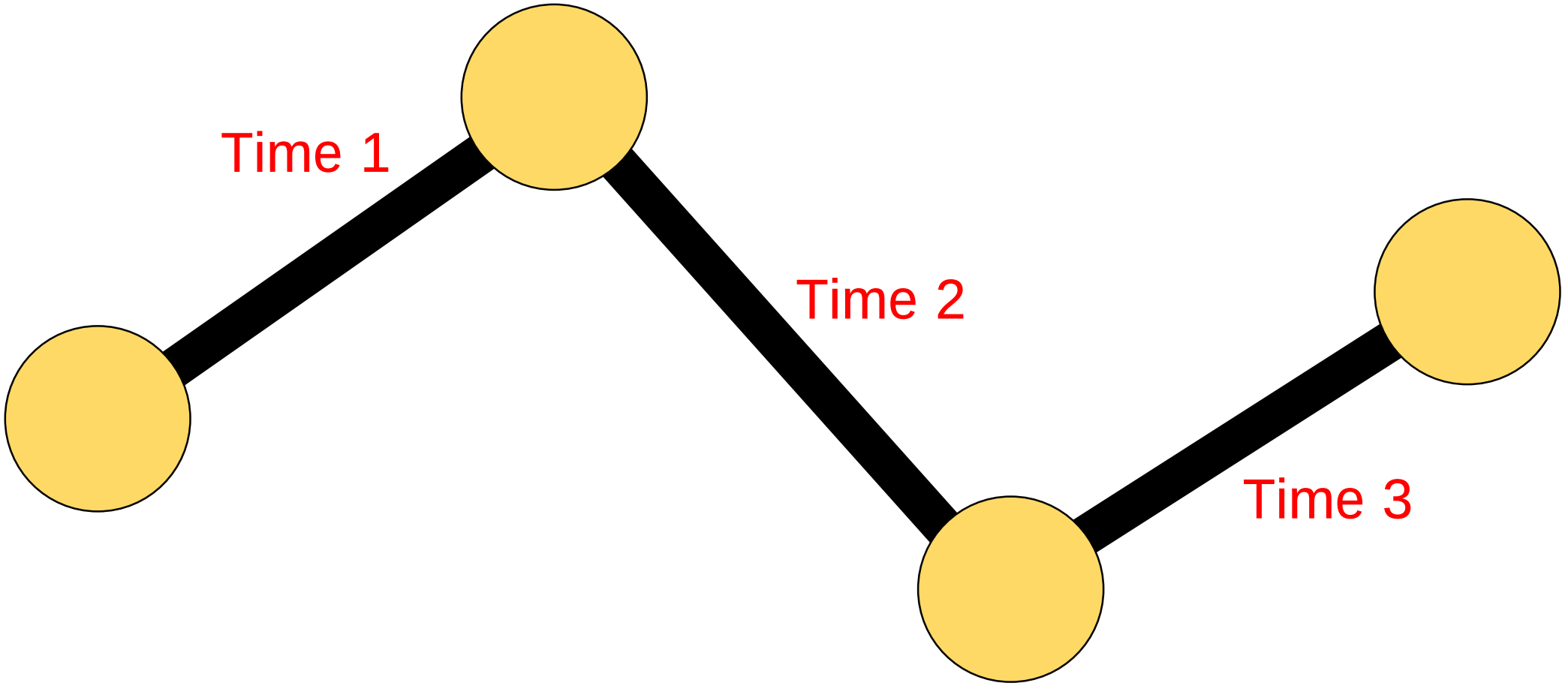


Interaction

Pathways are represented as networks

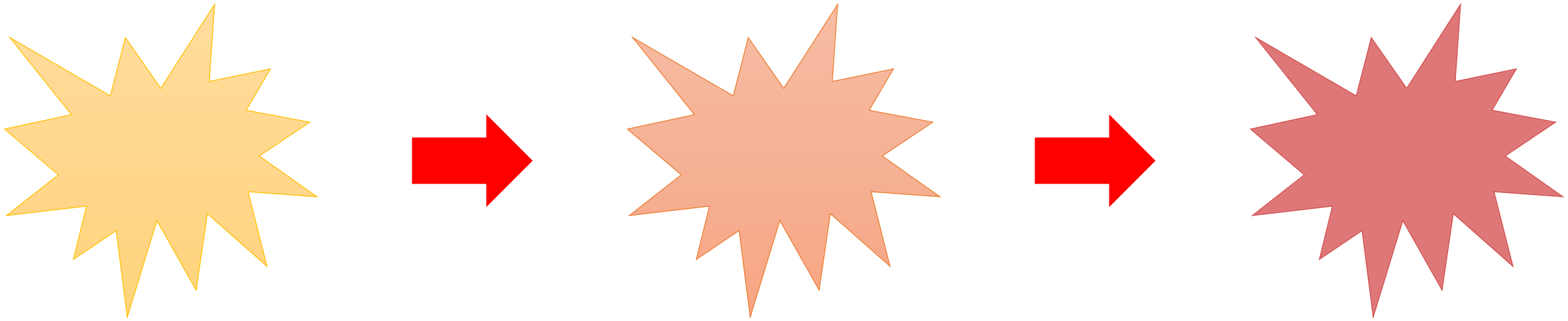


They are often represented as static mechanisms, while dynamics



We want a tool to generate dynamic pathways

Multiple cellular responses are **one** response evolving over time

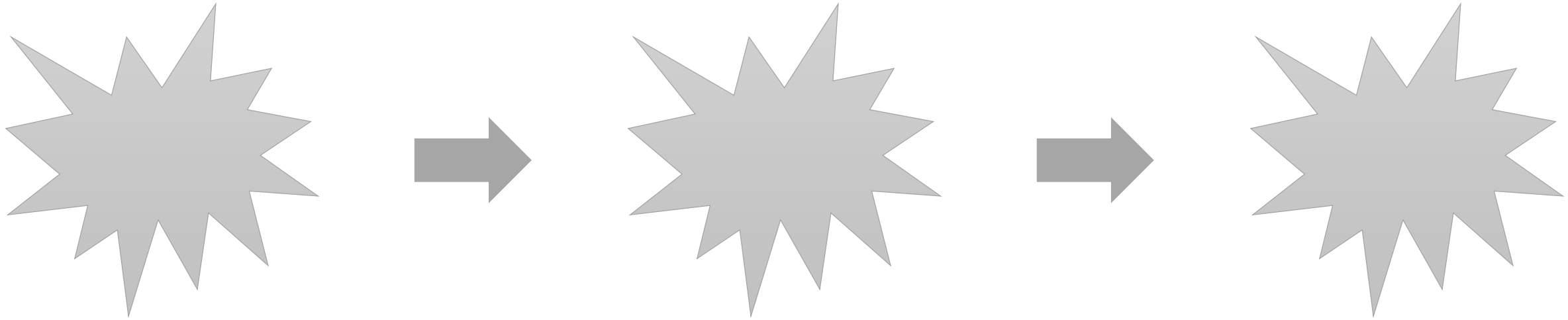


Short term

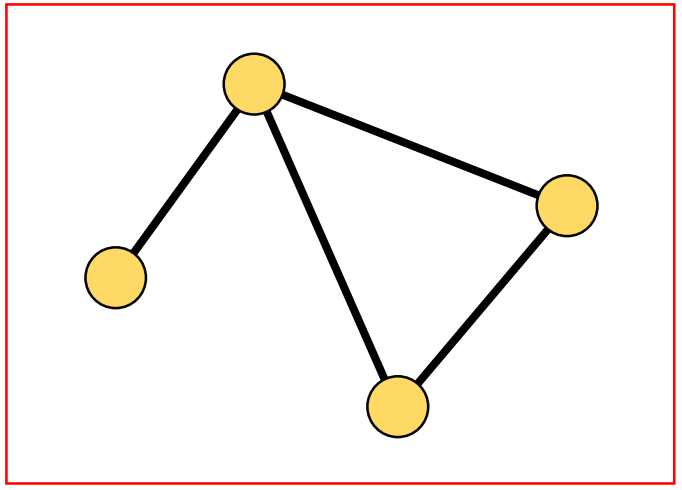
Mid term

Long term

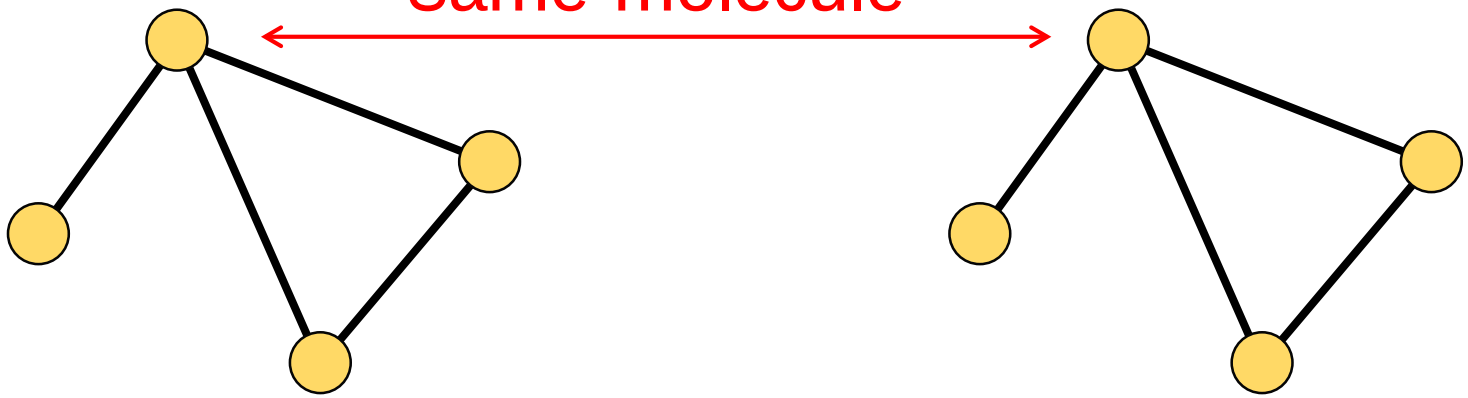
But potential interactions do not change at each time



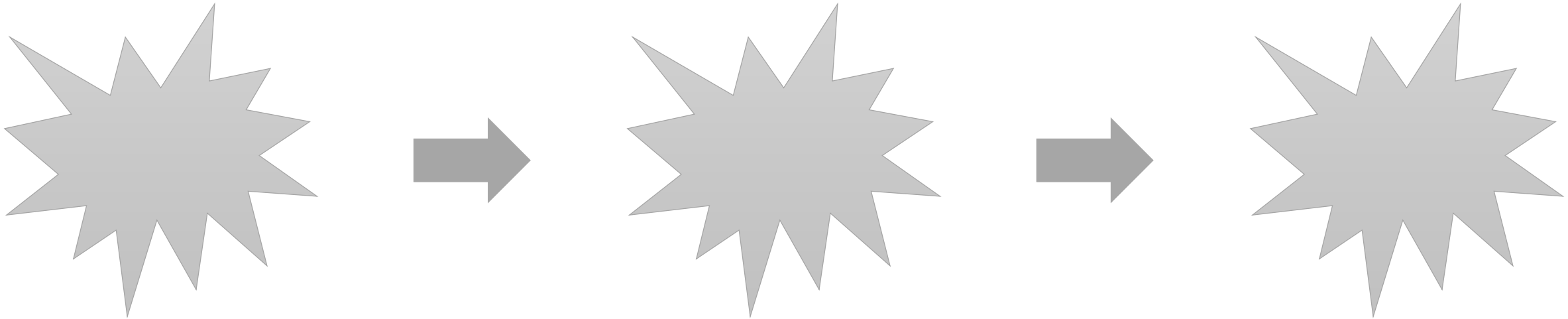
Interactome



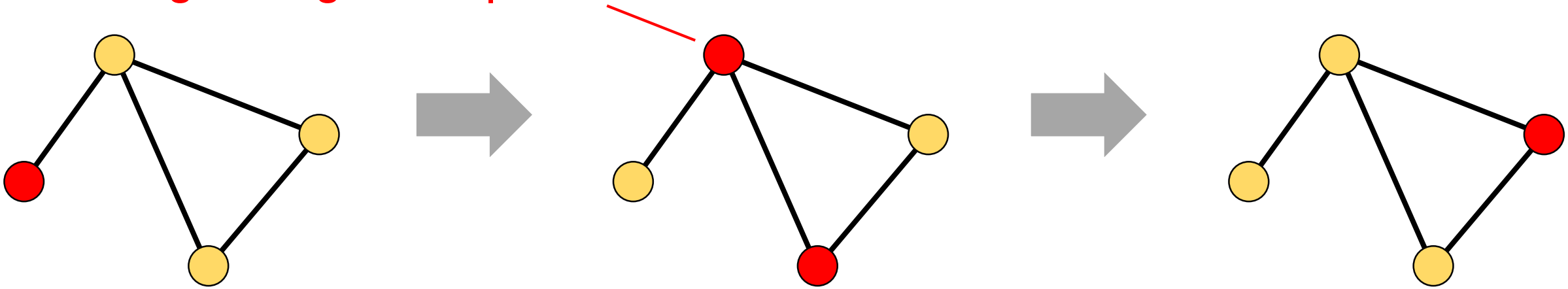
Same molecule



Then, we can map at each time the changes (= the responses)



Changes of gene expression

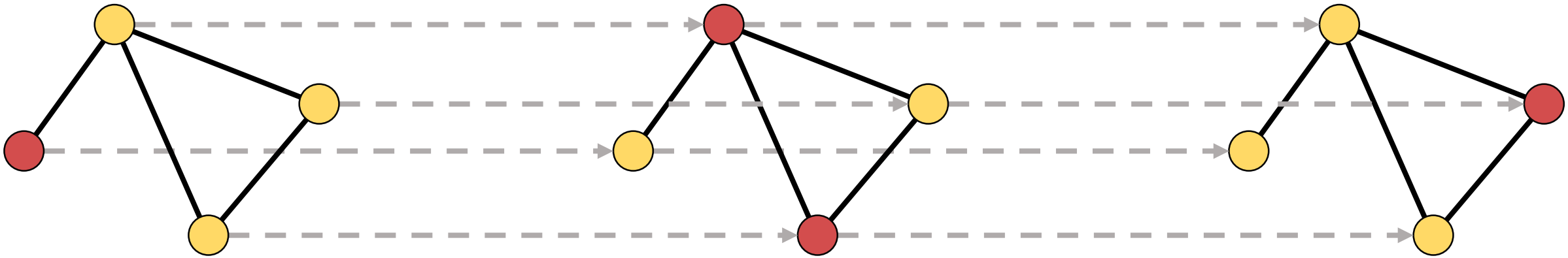


We are building a **temporal multi-layer** network

Time 1
Layer 1

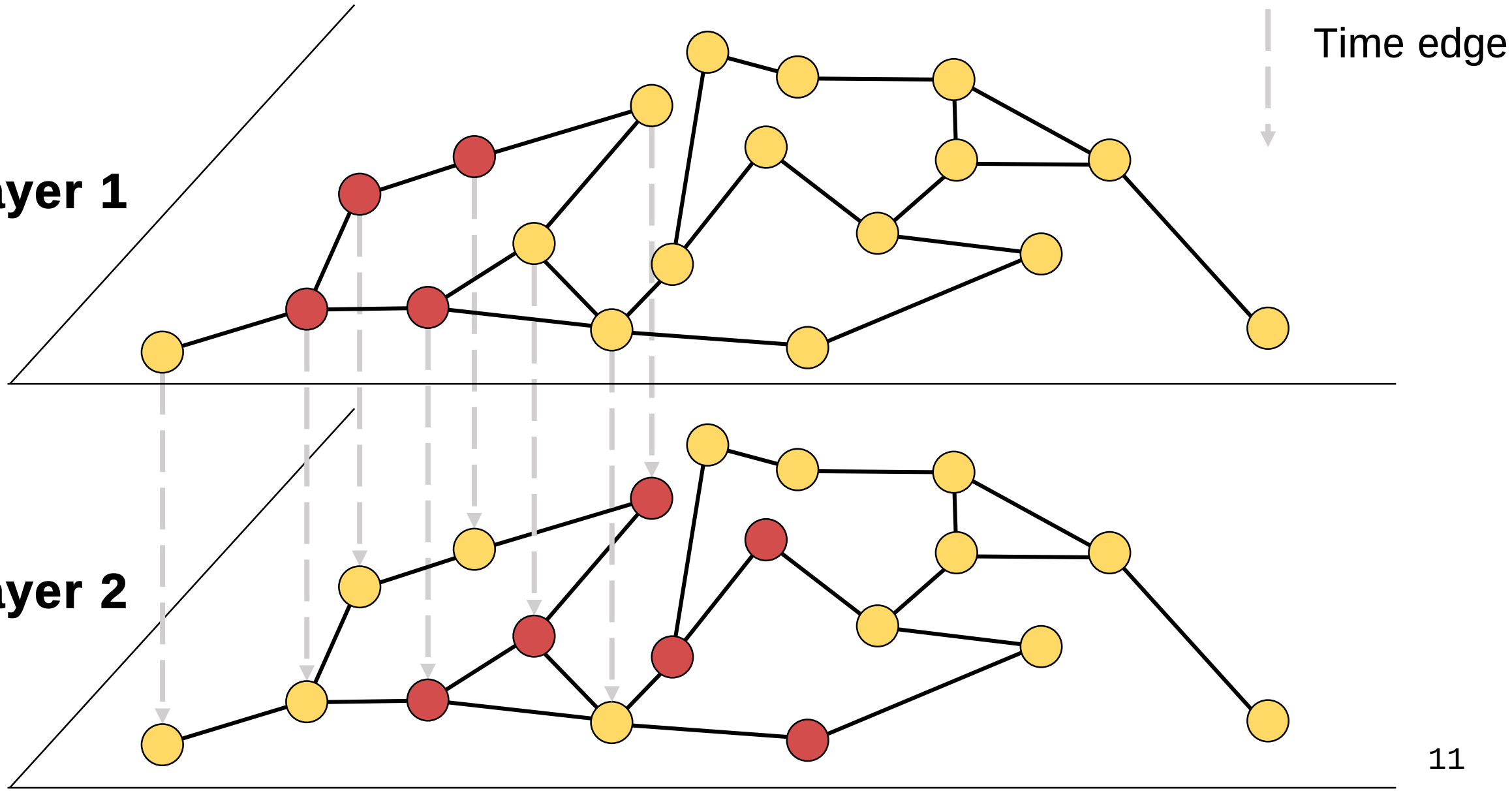
Time 2
Layer 2

Time 3
Layer 3

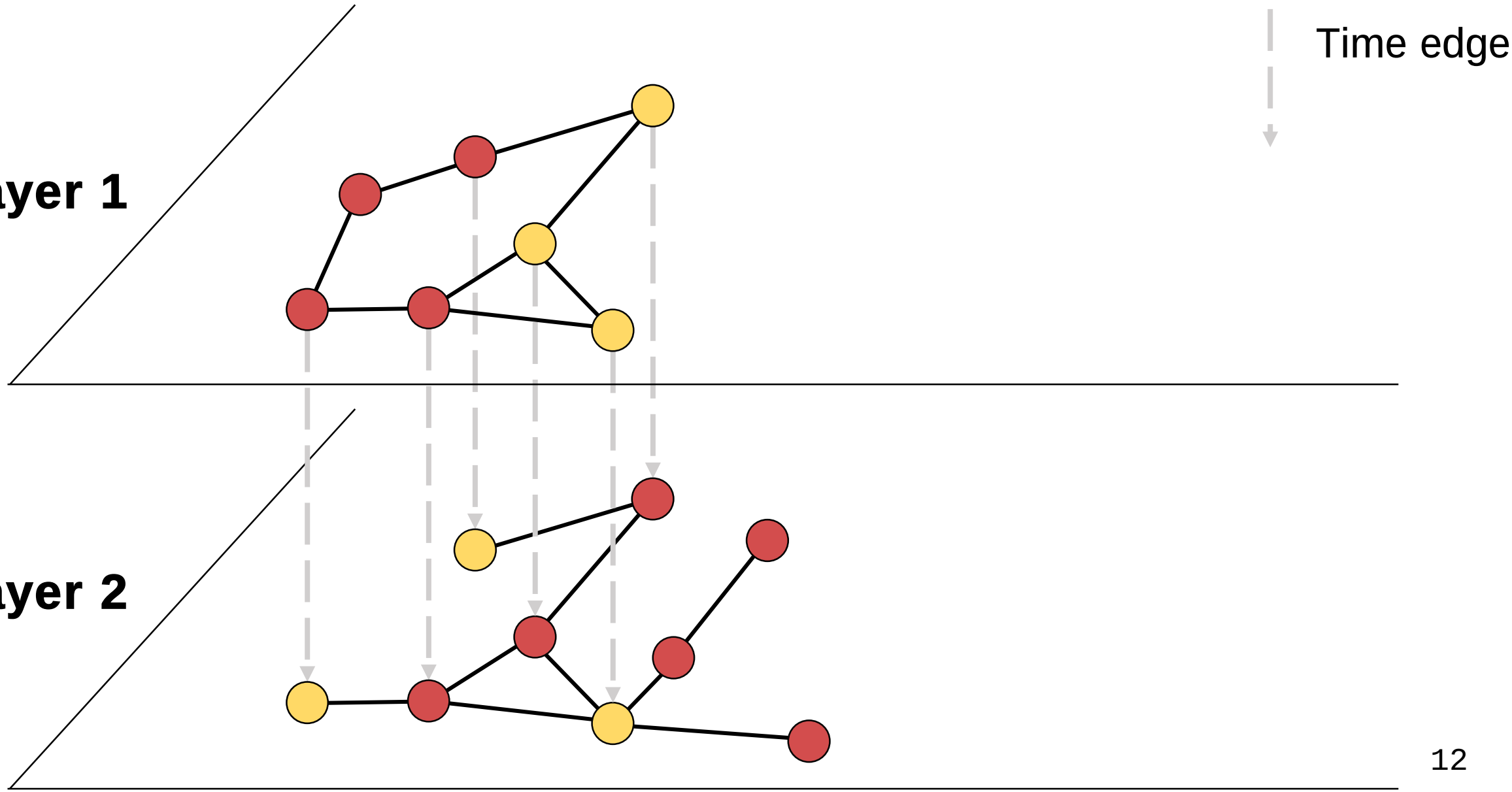


Time edges
= inter-layer edges

The pathway is the temporal subnetwork with active nodes



We assume the temporal subnetwork to be the dynamic pathway



Objectives

1. **Build** a temporal network from yeast data

   What data to use?

   What are the main features of the network?

   How to build the temporal network?

2. **Extract** temporal subnetworks

   What algorithm to use?

   How to adapt temporal network to the algorithms?

   How to use these algorithms?

3. **Get** pathways from temporal subnetworks

   How to visualize temporal subnetworks?

   How to simplify temporal subnetworks?

1. Build a temporal network from yeast data

What data to use?

Yeast interactome and core cell-cycle are well known

Interactome: protein-protein + protein-DNA interactions

Yeast: well known and “small” genome

High-time resolution RNA-seq experiments

1. Build a temporal network from yeast data

What are the main features of the network?

Nodes have a weight calculated from 3 variables

Prior weight

+

Expression weight

+

Dysregulation weight

(+) transcription factors, (–) [hub – complexes]

(+) number of counts

(+) log-fold change * -log(p-value)

⇒ Node weight

Time and interaction edges have two different weights

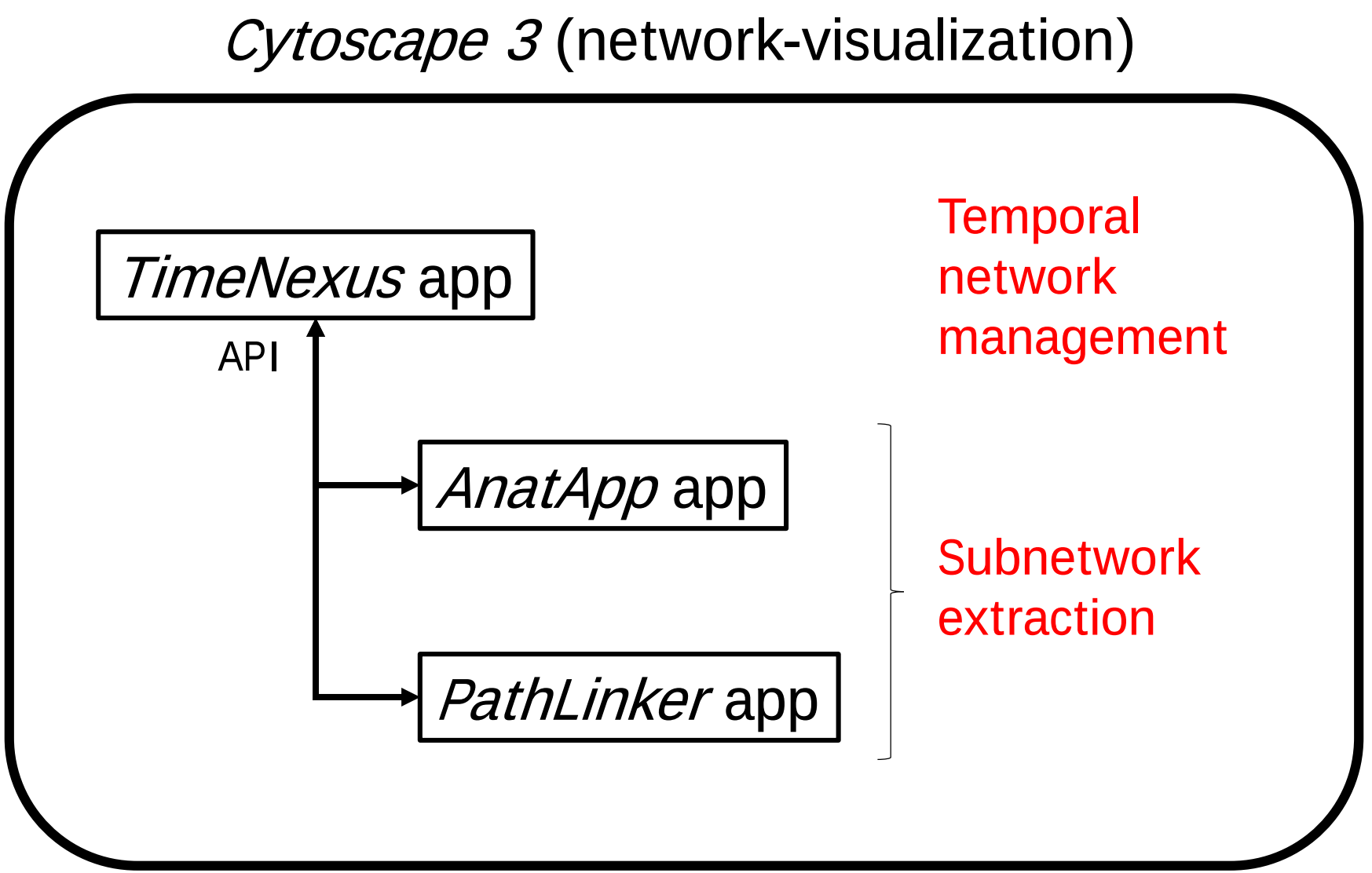
Interaction edges: confidence of the interaction

Time edges: depend on dysregulation weights of their nodes

1. Build a temporal network from yeast data

How to build the temporal network?

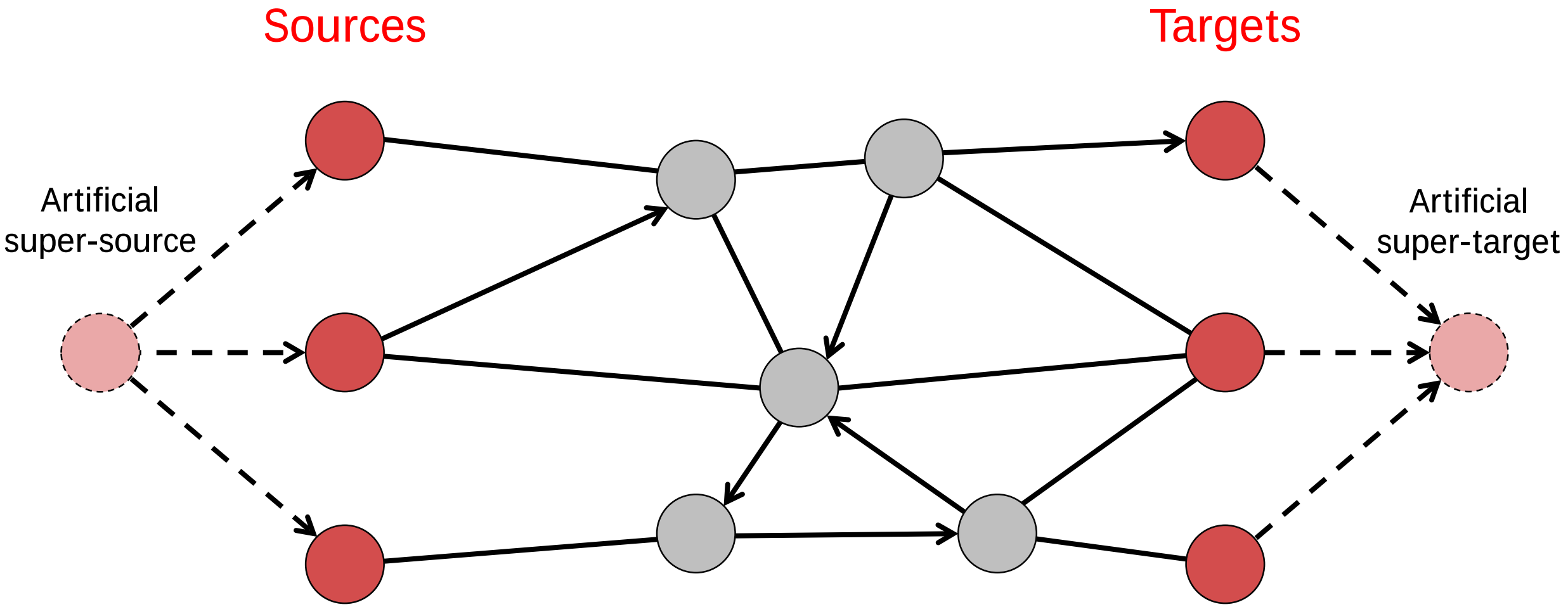
We combine our *Cytoscape* app to other apps to run computations



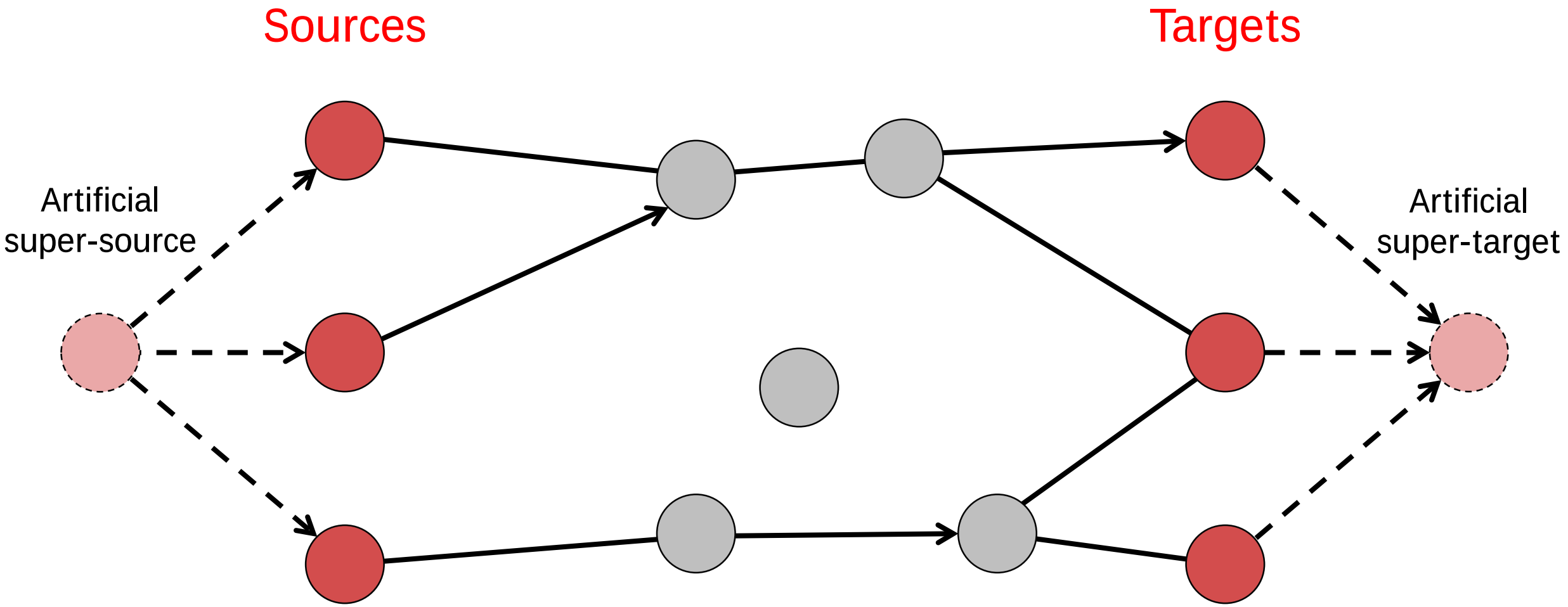
2. Extract temporal subnetworks

What algorithm to use?

Available apps allowing directed edges use shortest paths



Available apps allowing directed edges use shortest paths



2. Extract temporal subnetworks

How to adapt temporal network to the algorithms?

Available algorithms are less flexible than expected

Give paths from source to target $\Rightarrow$ layer N to layer N+1

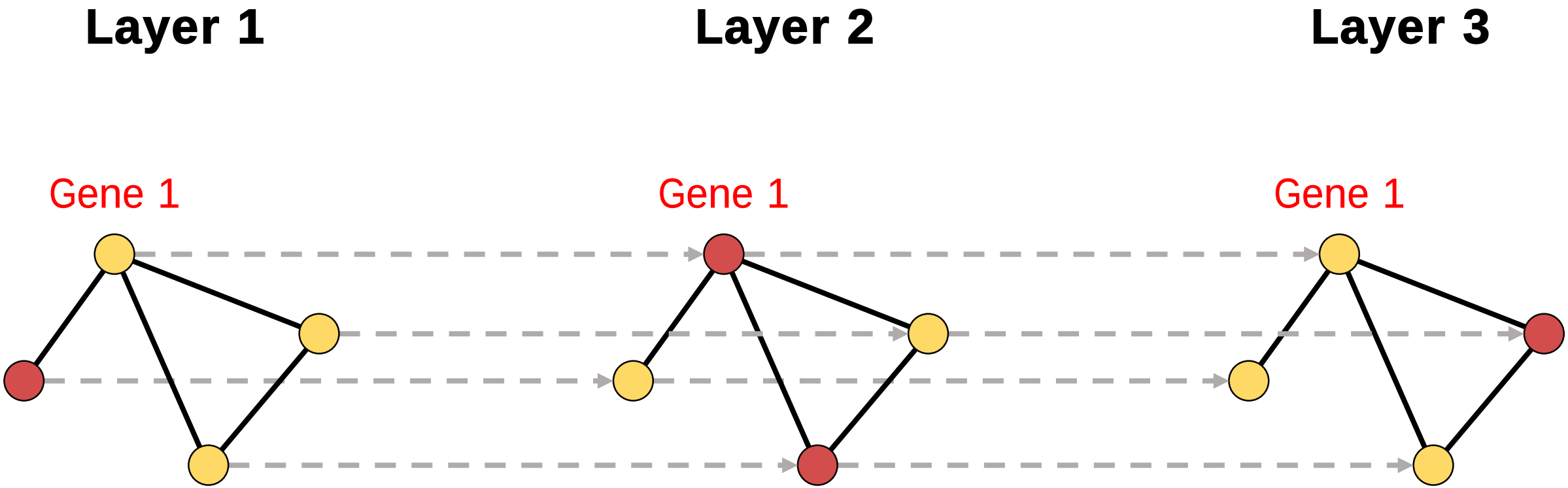
No multiple edges between nodes $\Rightarrow$ aggregate PPIs and PDIs

No node weights $\Rightarrow$ weights included by edges

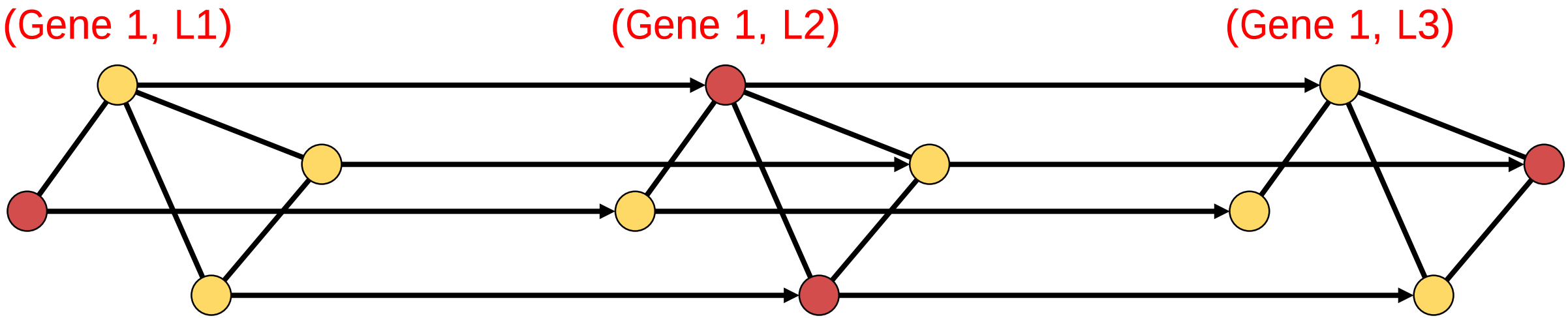
2. Extract temporal subnetworks

How to use these algorithms?

Let’s take our basic temporal network



Aggregate the **whole** network: remove the edge labels

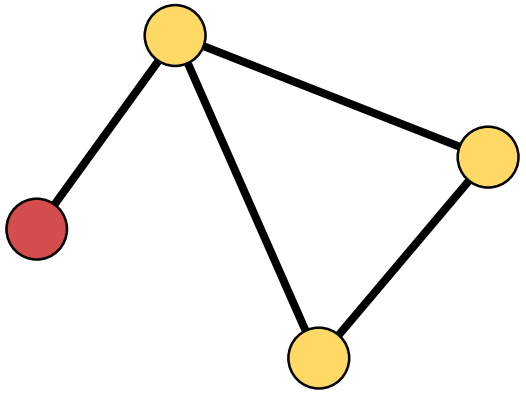


Con: need a lot of memory

Extract **independently** subnetworks from each layer

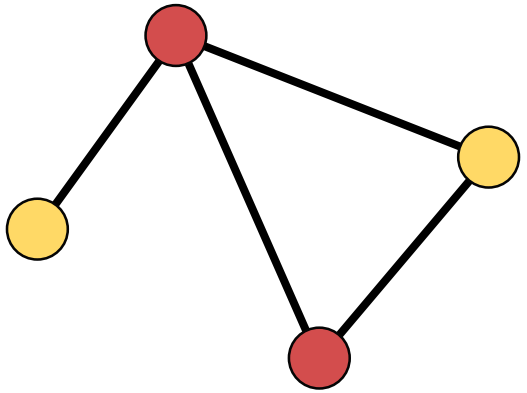
Network 1

Gene 1



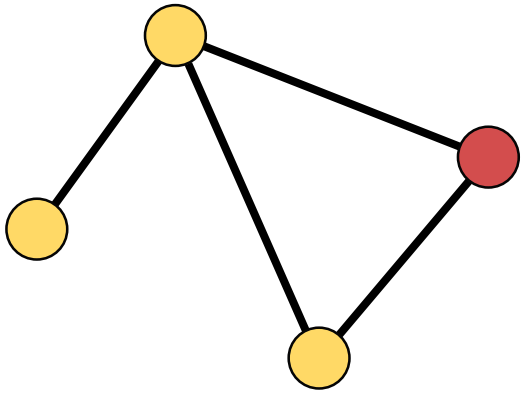
Network 2

Gene 1



Network 3

Gene 1

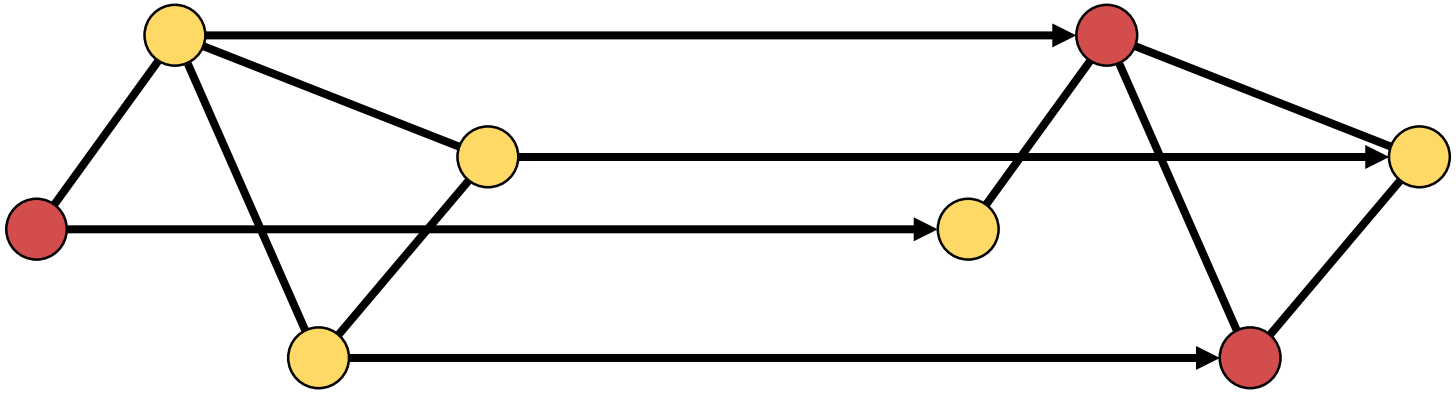


Con: how to connect back subnetworks?

Aggregate successively layers T and layers T+1

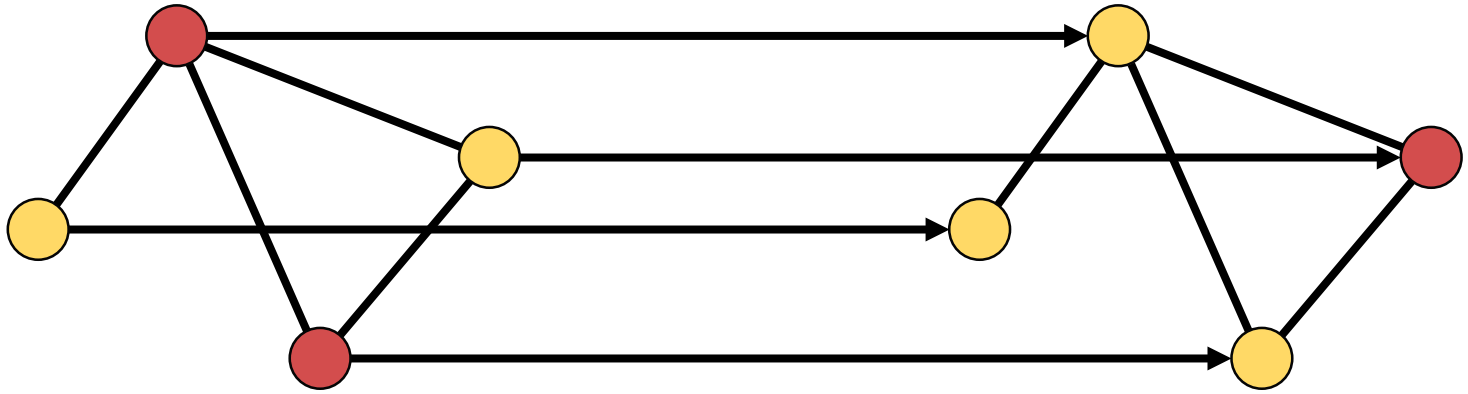
(Gene 1, L1)

(Gene 1, L2)



(Gene 1, L2)

(Gene 1, L3)



Con: how to connect back subnetworks?

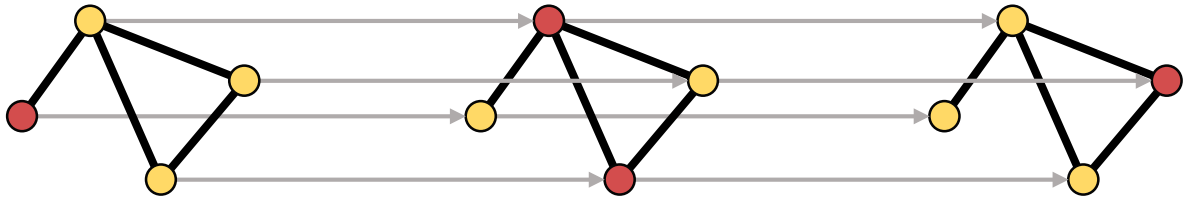
3. Get pathways from temporal subnetworks

How to visualize temporal subnetworks?

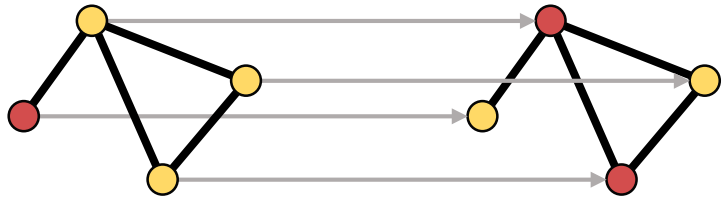
Temporal subnetworks can be fully or partially visualized

Order nodes by layers

(in 3D?)



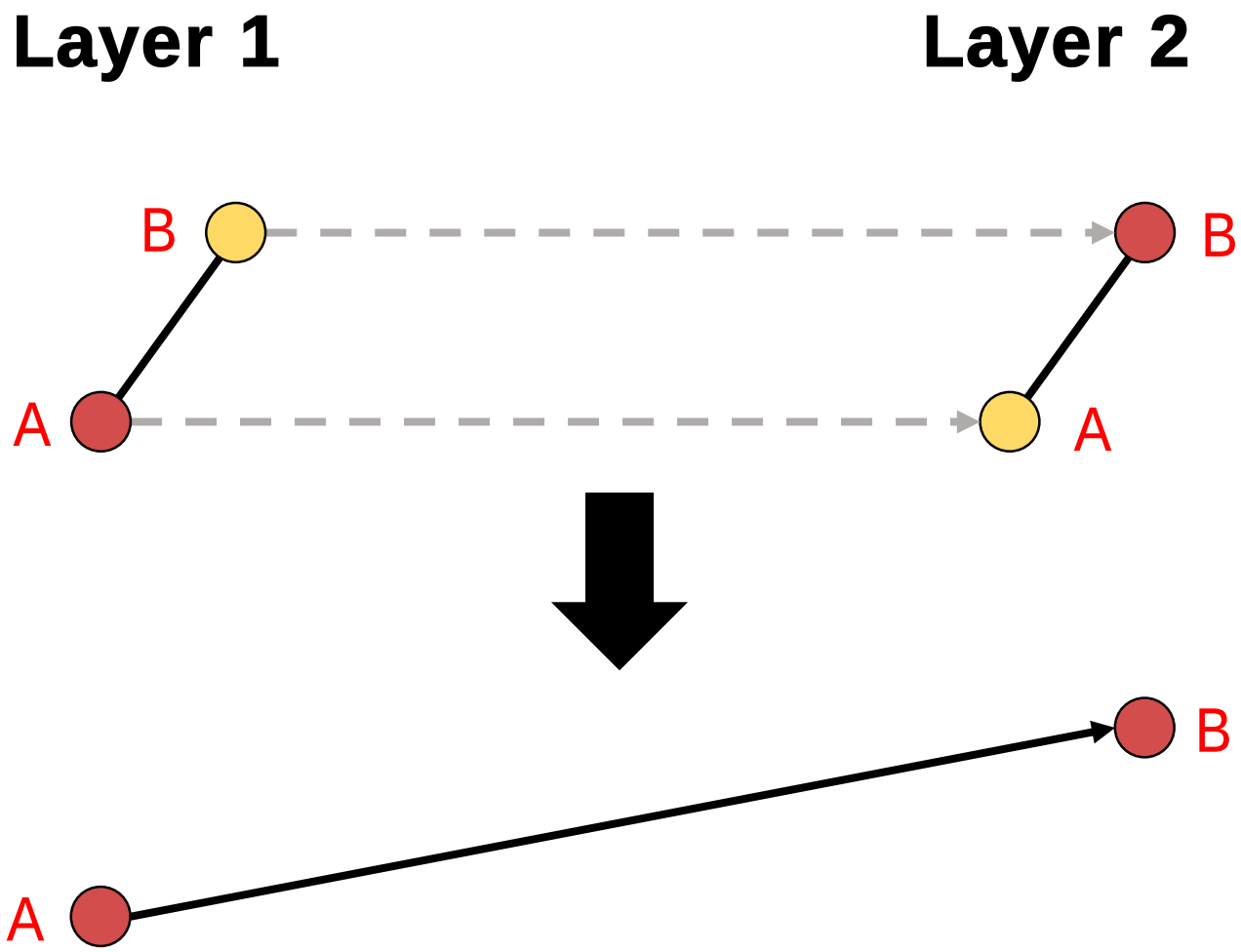
Display limited number of layers



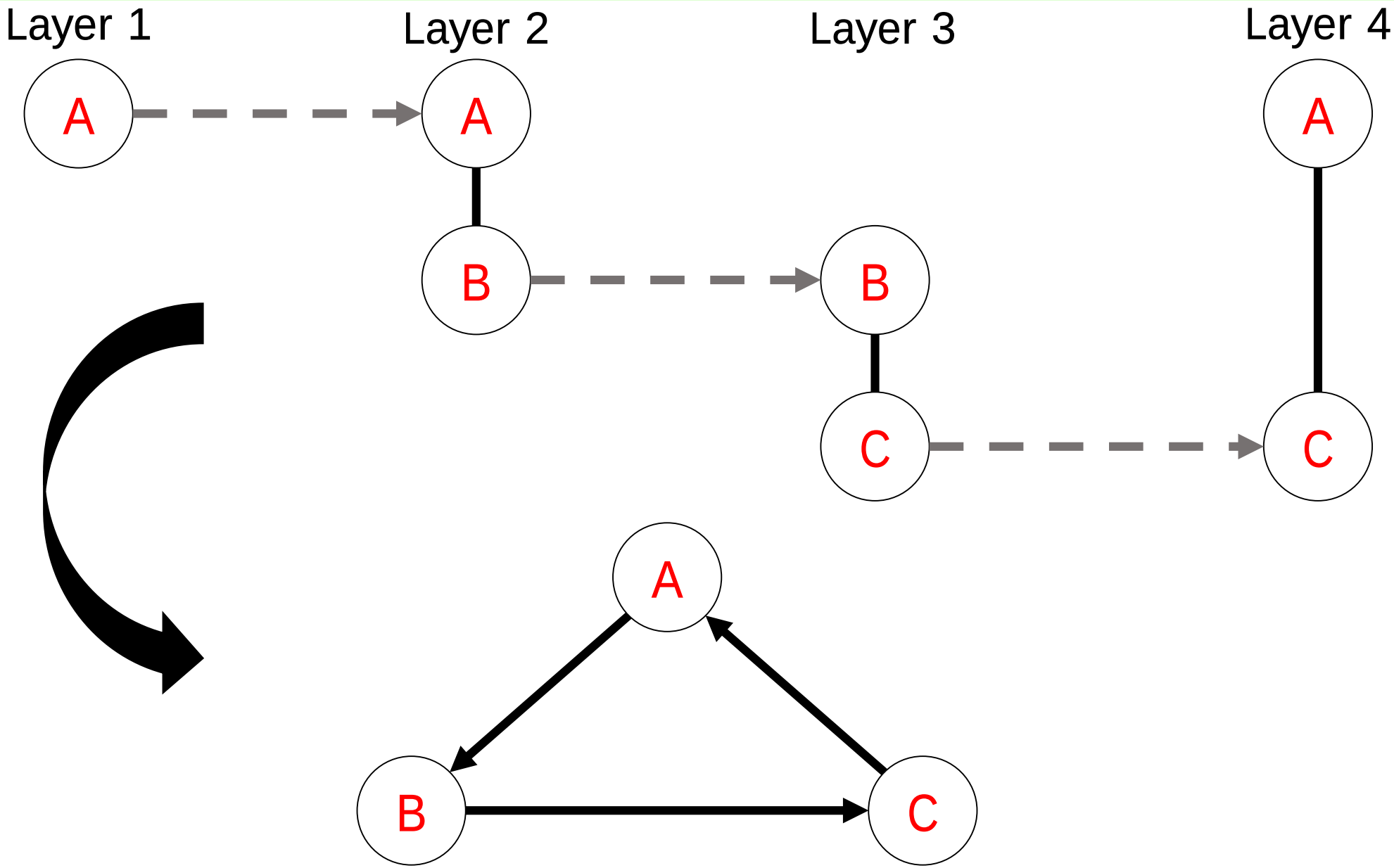
3. Get pathways from temporal subnetworks

How to simplify temporal subnetworks?

Nodes at the transitions between layers can be aggregated

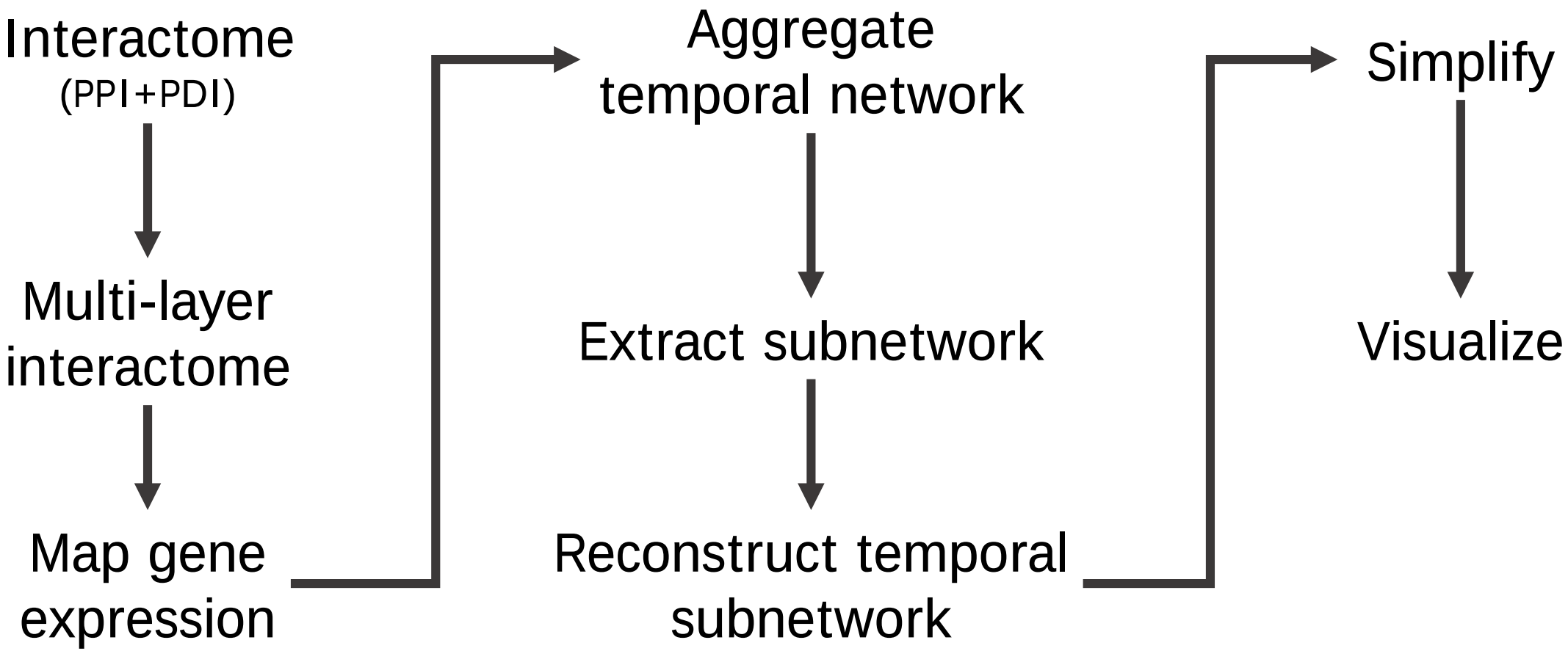


Patterns can give loops



Conclusion

The workflow extracts pathways from data-mapped interactome



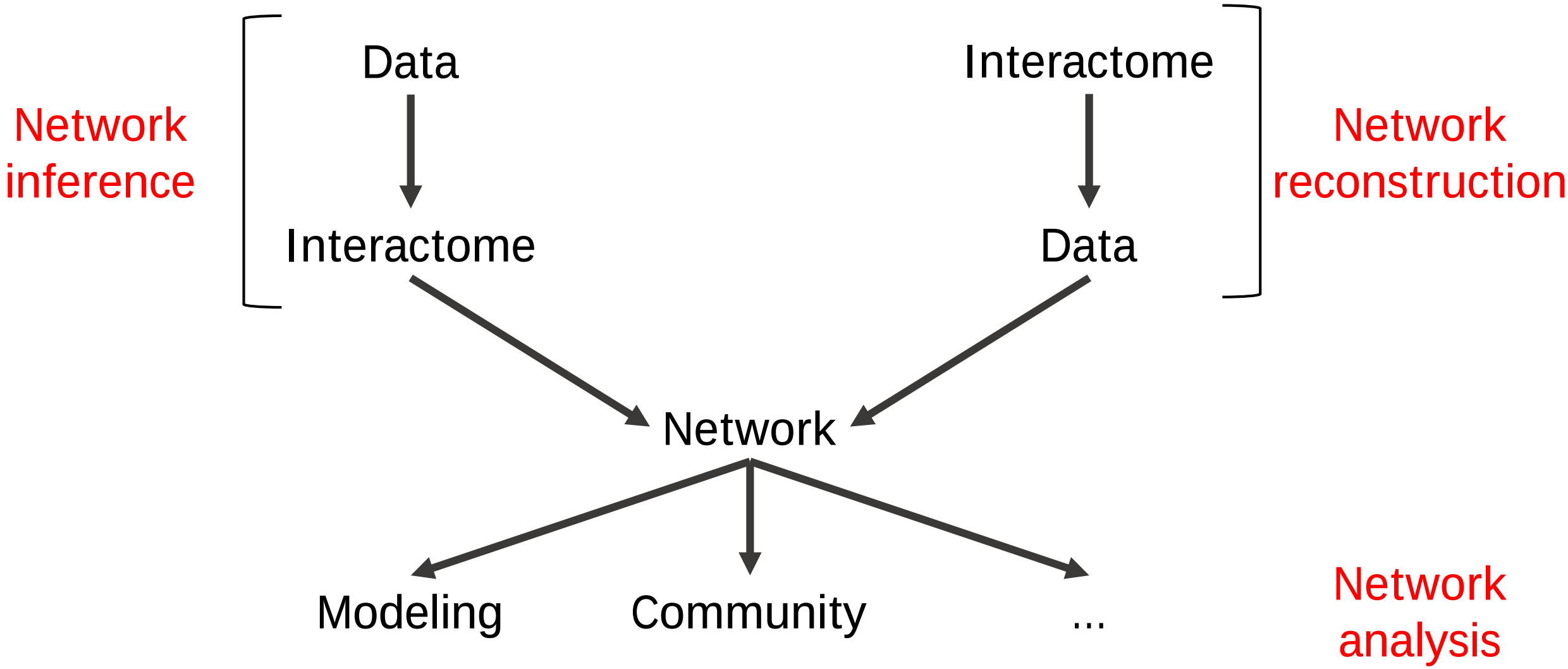
The approach brings more challenges

Computation time is expected be the major drawback

Approach limited to species with **well-known interactome**

Analyses of networks won’t be easier than currently

It’d be “network reconstruction” but it is not network inference



General conclusion

1. Temporal networks **can integrate** a lot of biological data

2. They **have to be adapted** to standard algorithms

3. Dynamic **pathway reconstruction** will be challenging

Give me your comments and suggestions!

michael.pierrelee@univ-amu.fr

Acknowledgment

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SCAN ME

Aix*Marseille université

IBDM
INSTITUT DE BIOLOGIE DU DÉVELOPPEMENT DE MARSEILLE

cnrs
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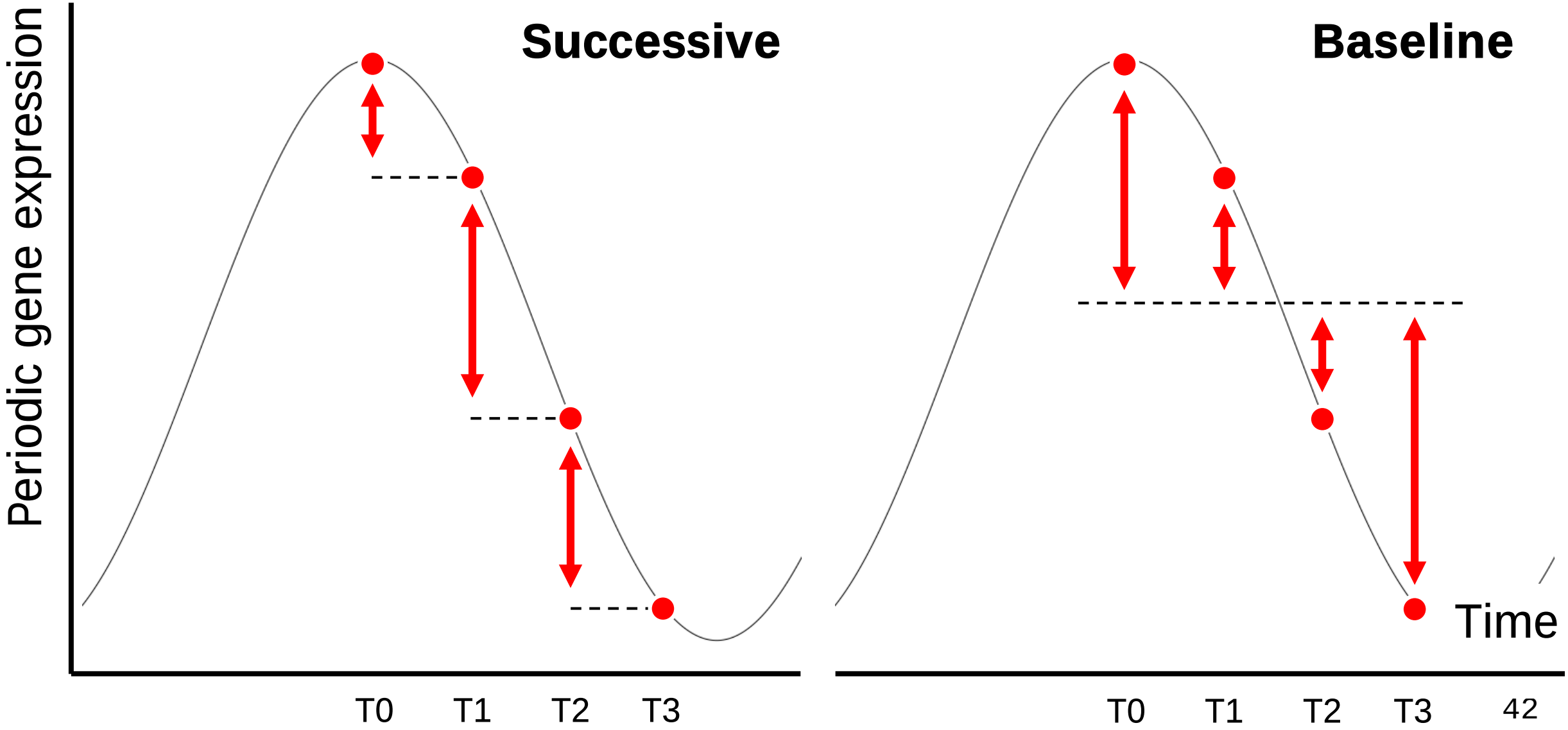
AGENCE NATIONALE DE LA RECHERCHE
ANR

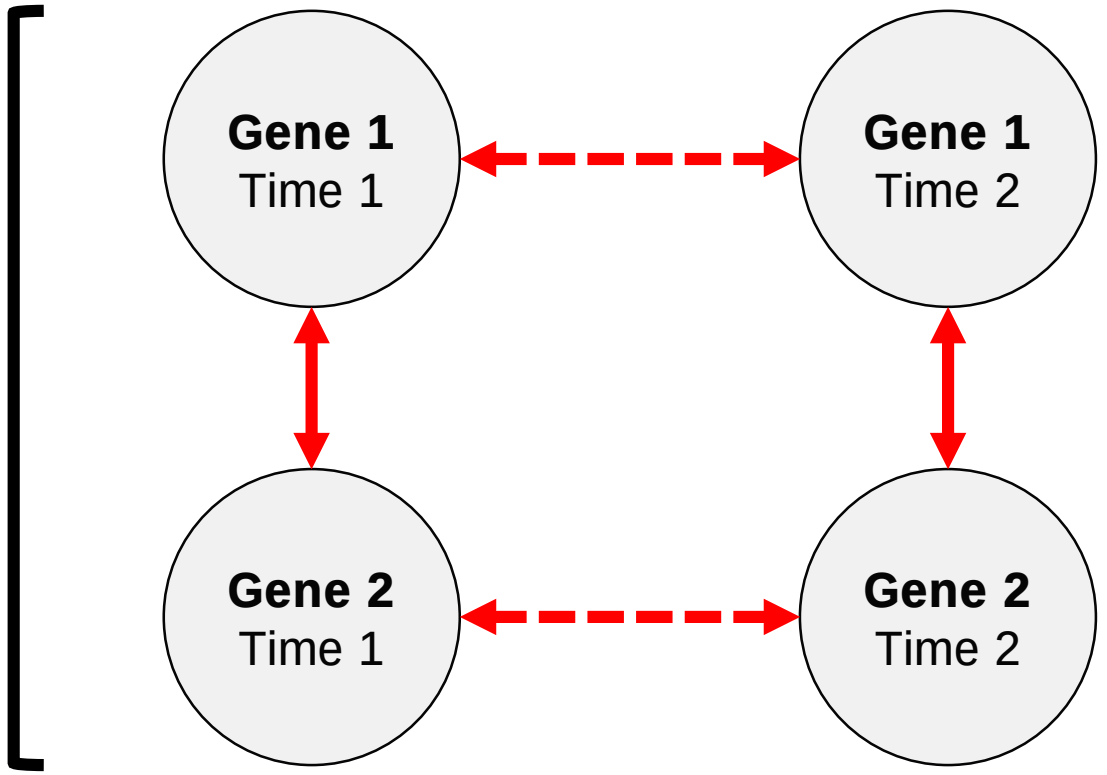
Differential expression analysis can be done in 2 manners



Expression weight should be comparable: use CQN normalization

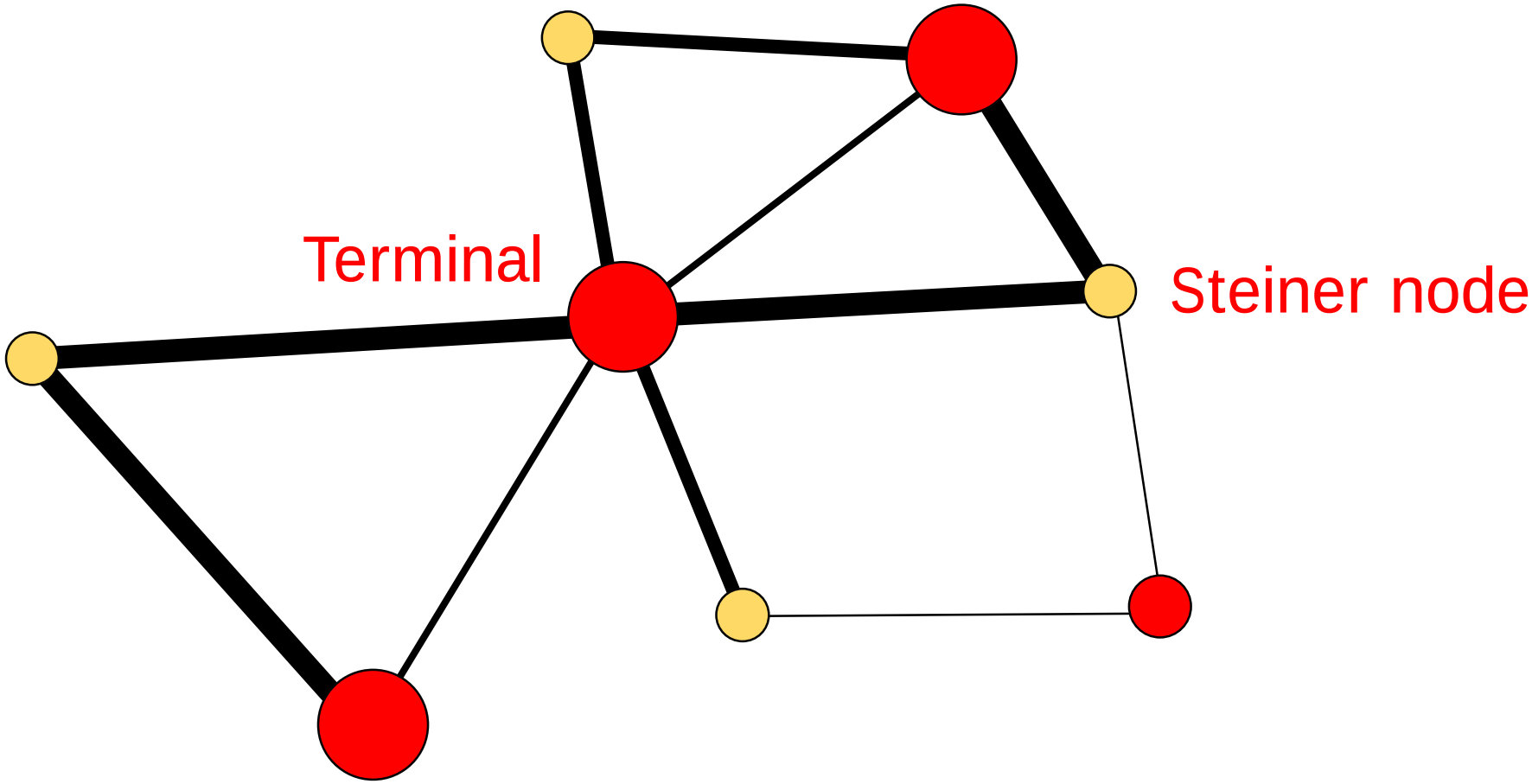
Between-sample
= library size

Within-sample
= gene length
+ GC content



Steiner tree problem seems the most adapted in our context

Between shortest path (2 terminals) and minimum spanning tree (all terminals)



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