

# Bridging multi-omic time series data and dynamic modelling

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# Top down approach to build dynamic models from big data

Multi-omic time series data



Computational  
Method

Dynamic Modelling

# Time series chondrogenesis data

Time points (days):  
0, 1, 3, 6, 10, 14.

mRNA + microRNA



STEM CELL TECHNOLOGY: EPIGENETICS,  
GENOMICS, PROTEOMICS AND  
METABONOMICS

## Genome-Wide MicroRNA and Gene Analysis of Mesenchymal Stem Cell Chondrogenesis Identifies an Essential Role and Multiple Targets for miR-140-5p

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**Key Words.** Mesenchymal stem cells • miRNA • Chondrogenesis • Gene expression •  
Differentiation • Epigenetics

siCon



siDICER1



Defects in 3 day old chondrocyte disks when DICER is removed. DICER is involved in the maturation of microRNAs. MicroRNAs are important chondrogenesis.

# Layers of complexity in the data

Big data

Time Series

Multi-omic (mRNAs and microRNAs)

# Big data bioinformatics and dynamic modelling

Generic bioinformatic approaches

- Differential expression
- Gene ontology analysis

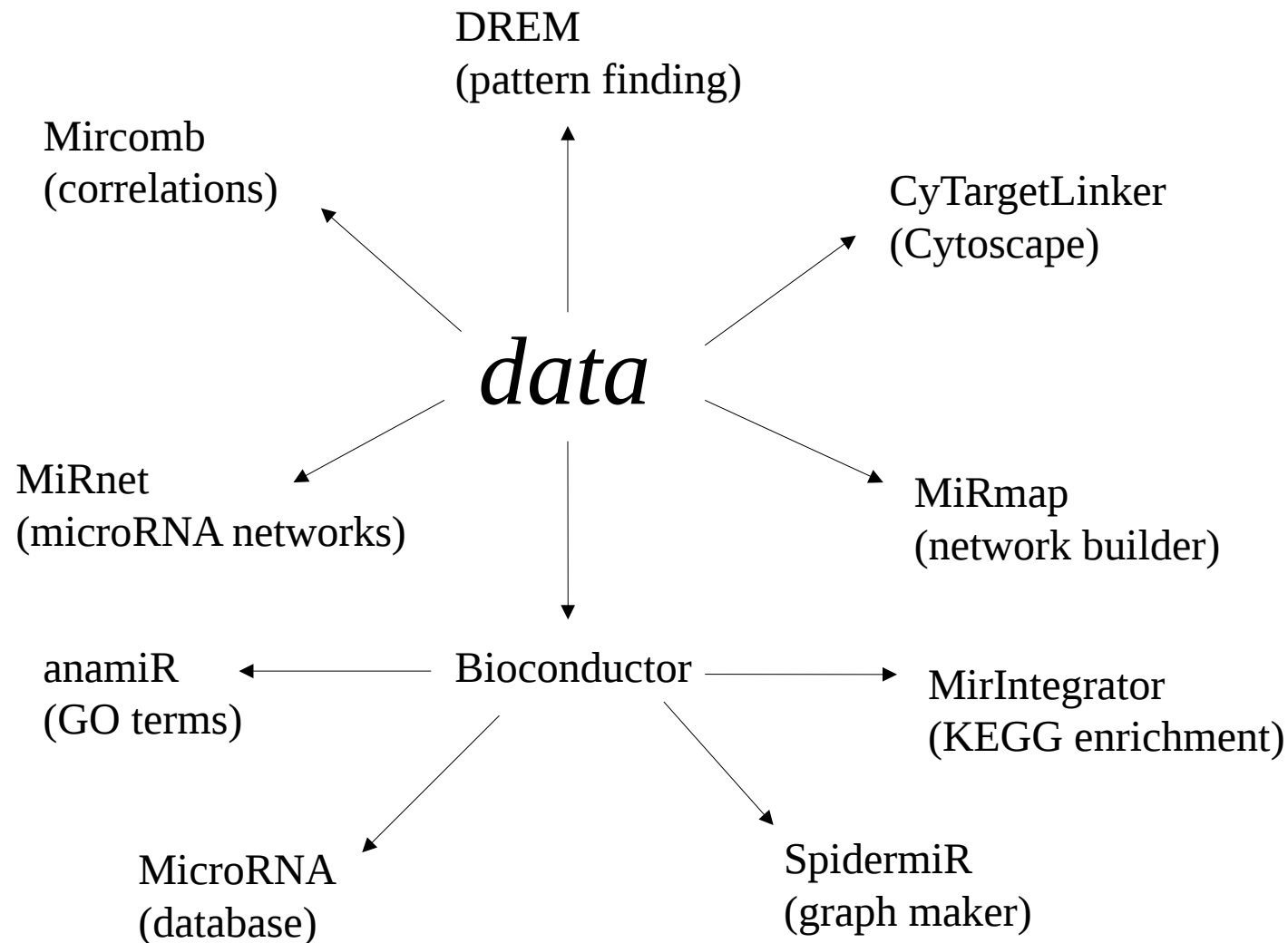
Tell us what is occurring on a global scale.

Dynamic modelling is an approach to investigate interactions between biological processes.

Is there a method to link these disciplines which lacks bias?

- **Handle multi-omic time series data**
- Reduce complexity
- Does not reduce the biology
- Empirical data

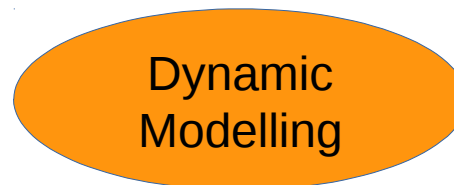
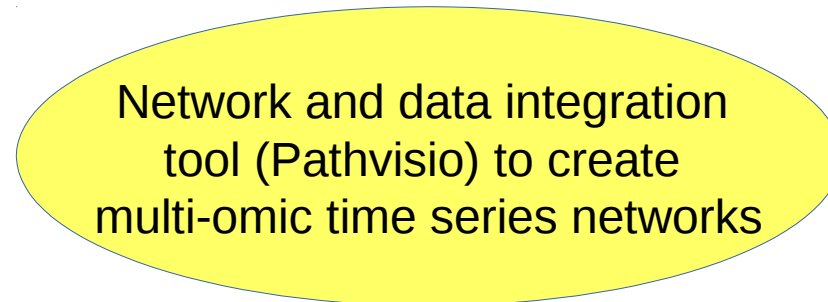
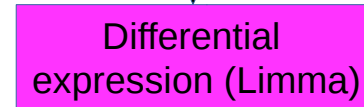
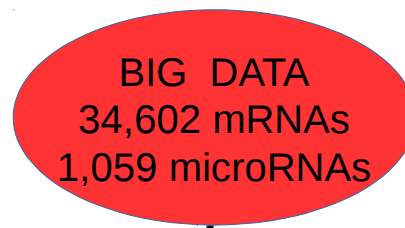
# What can deal with large multi-omic time series data?



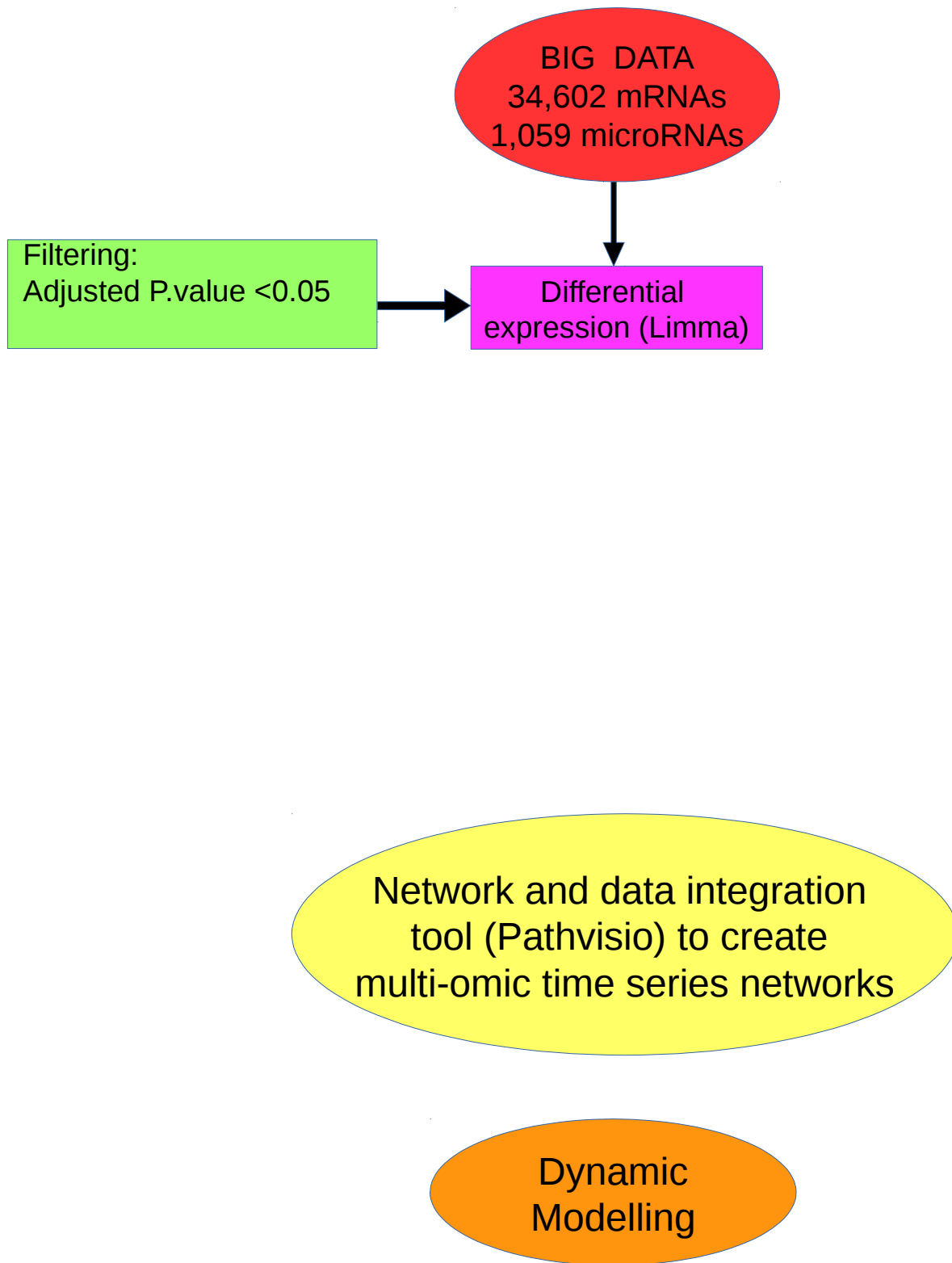
BIG DATA  
34,602 mRNAs  
1,059 microRNAs

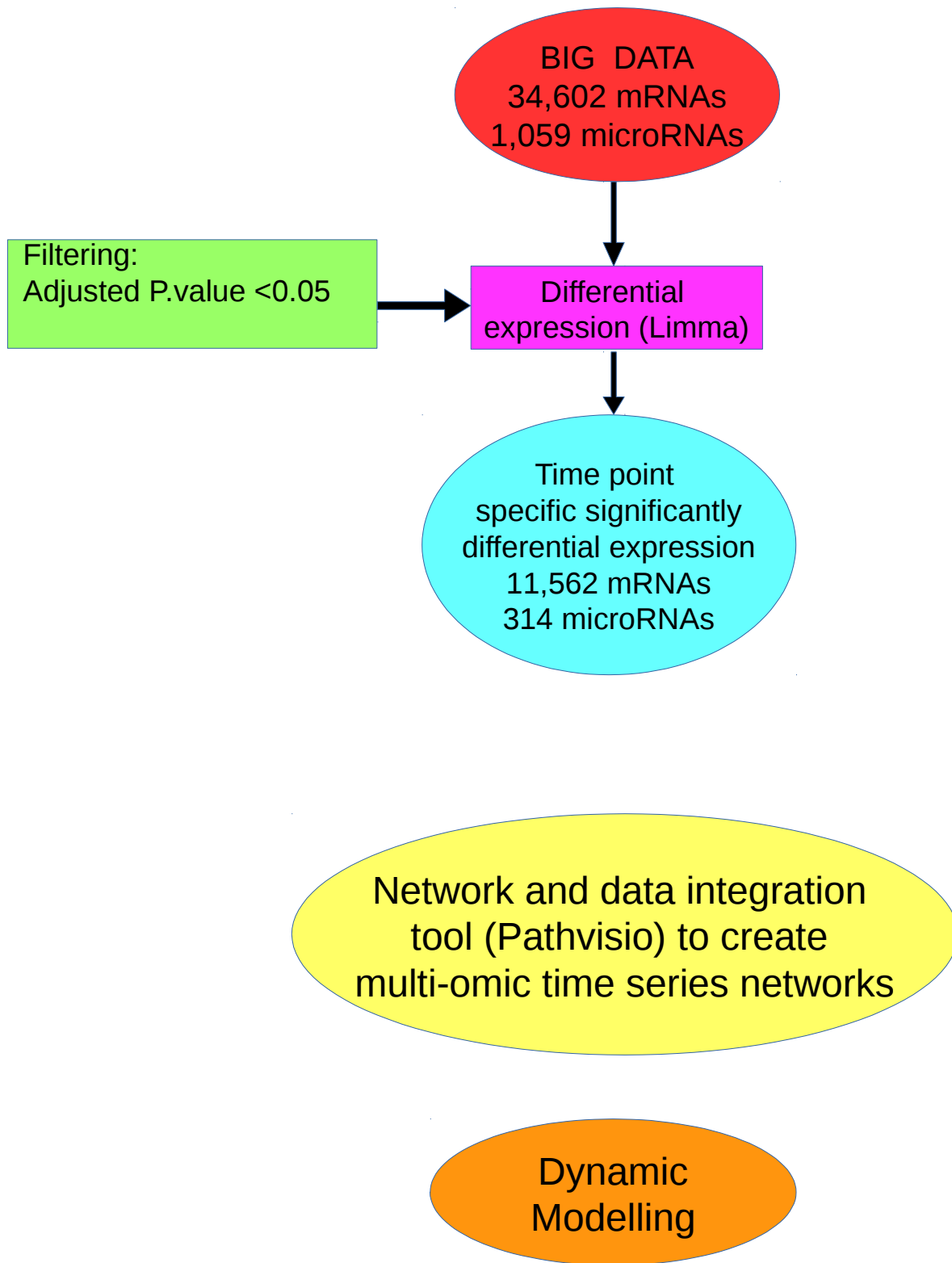
Network and data integration  
tool (Pathvisio) to create  
multi-omic time series networks

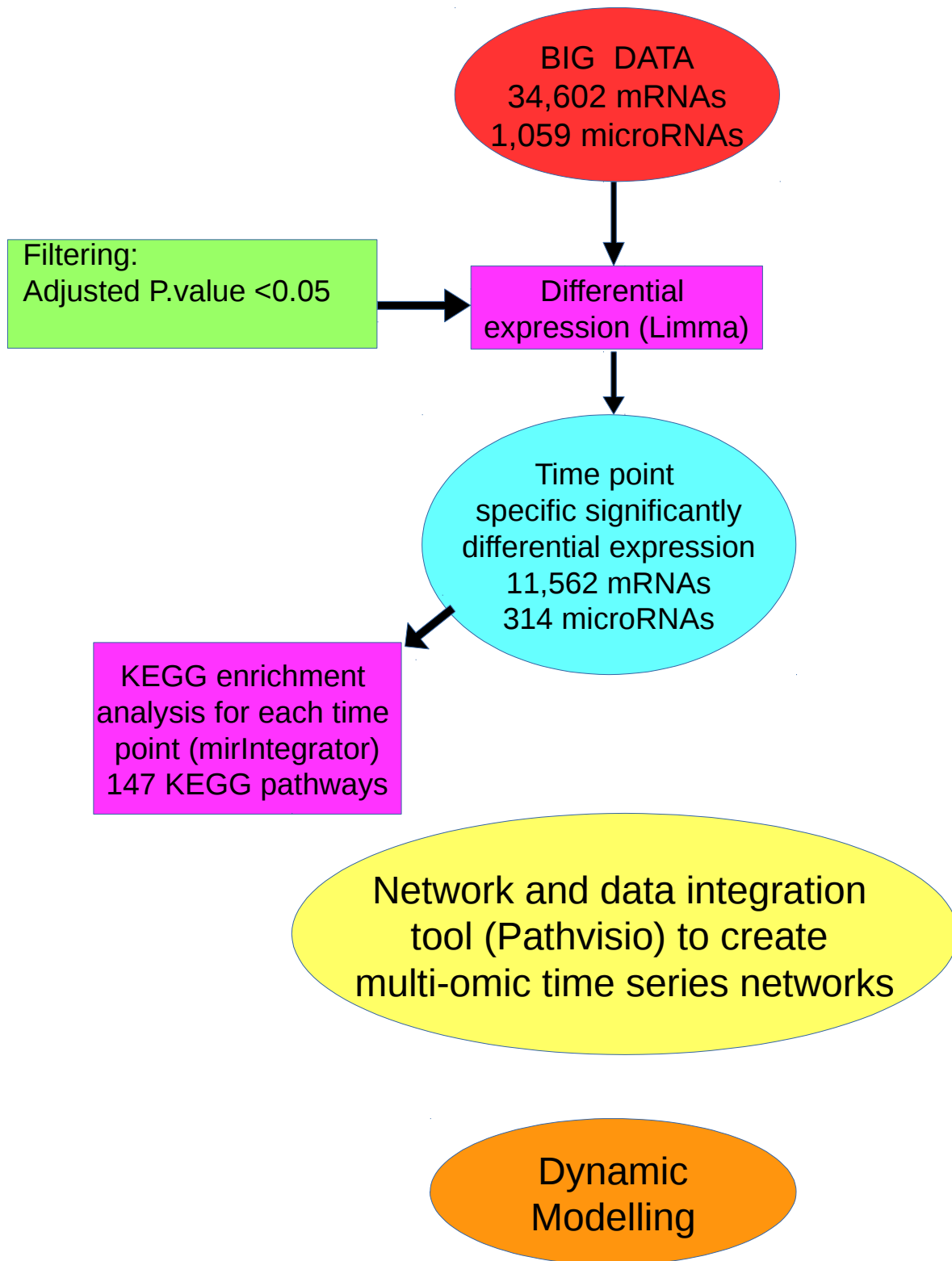
Dynamic  
Modelling

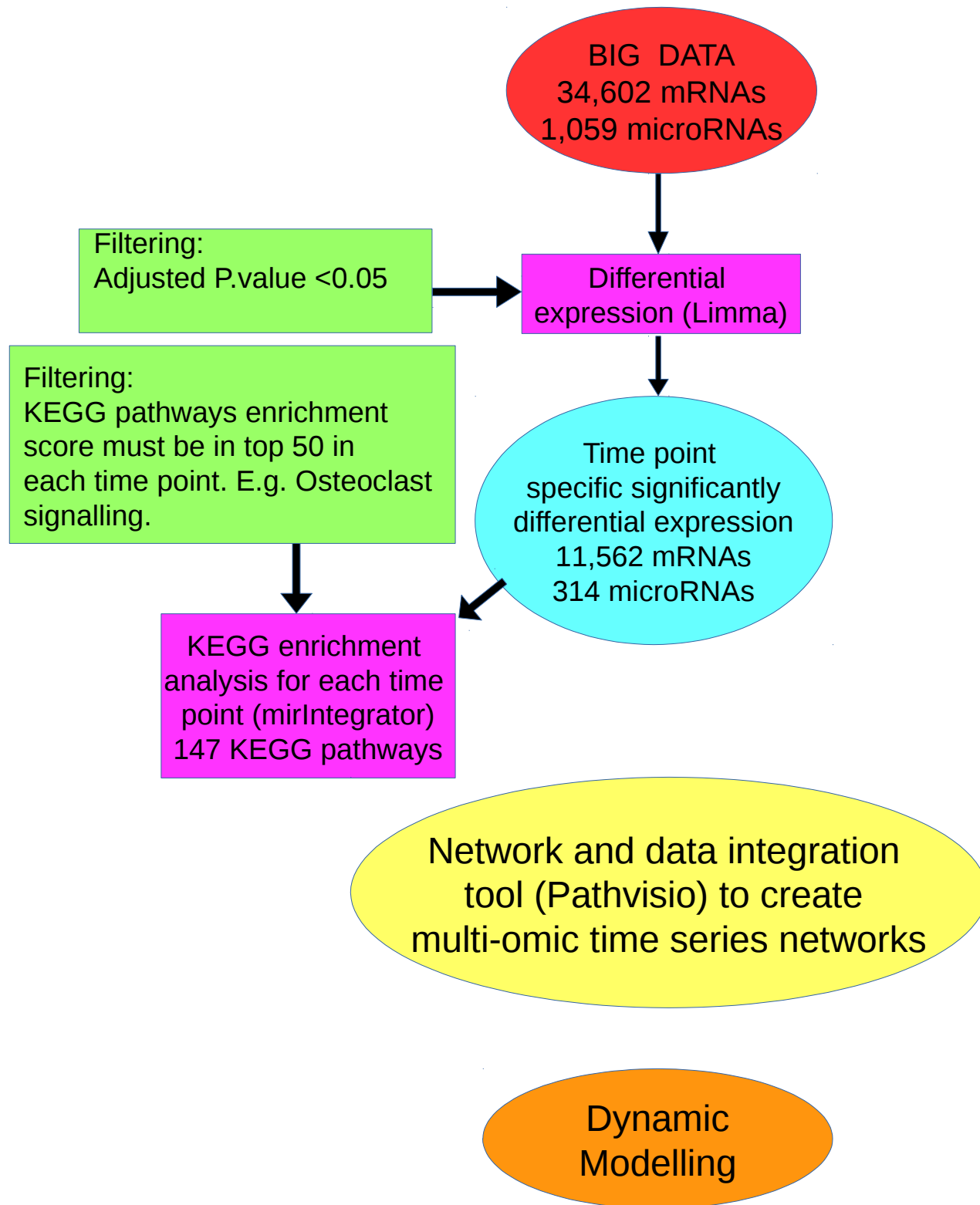


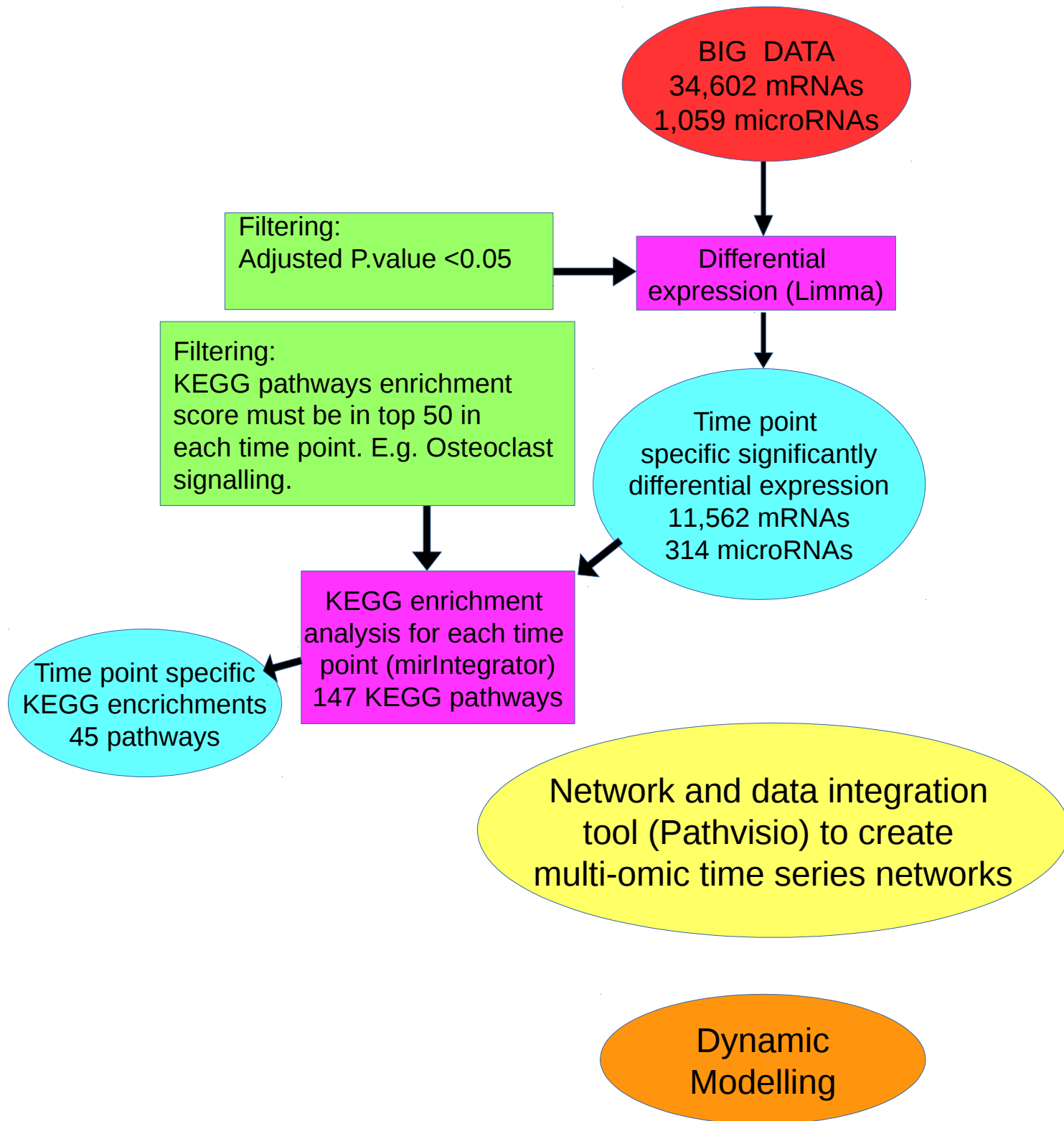


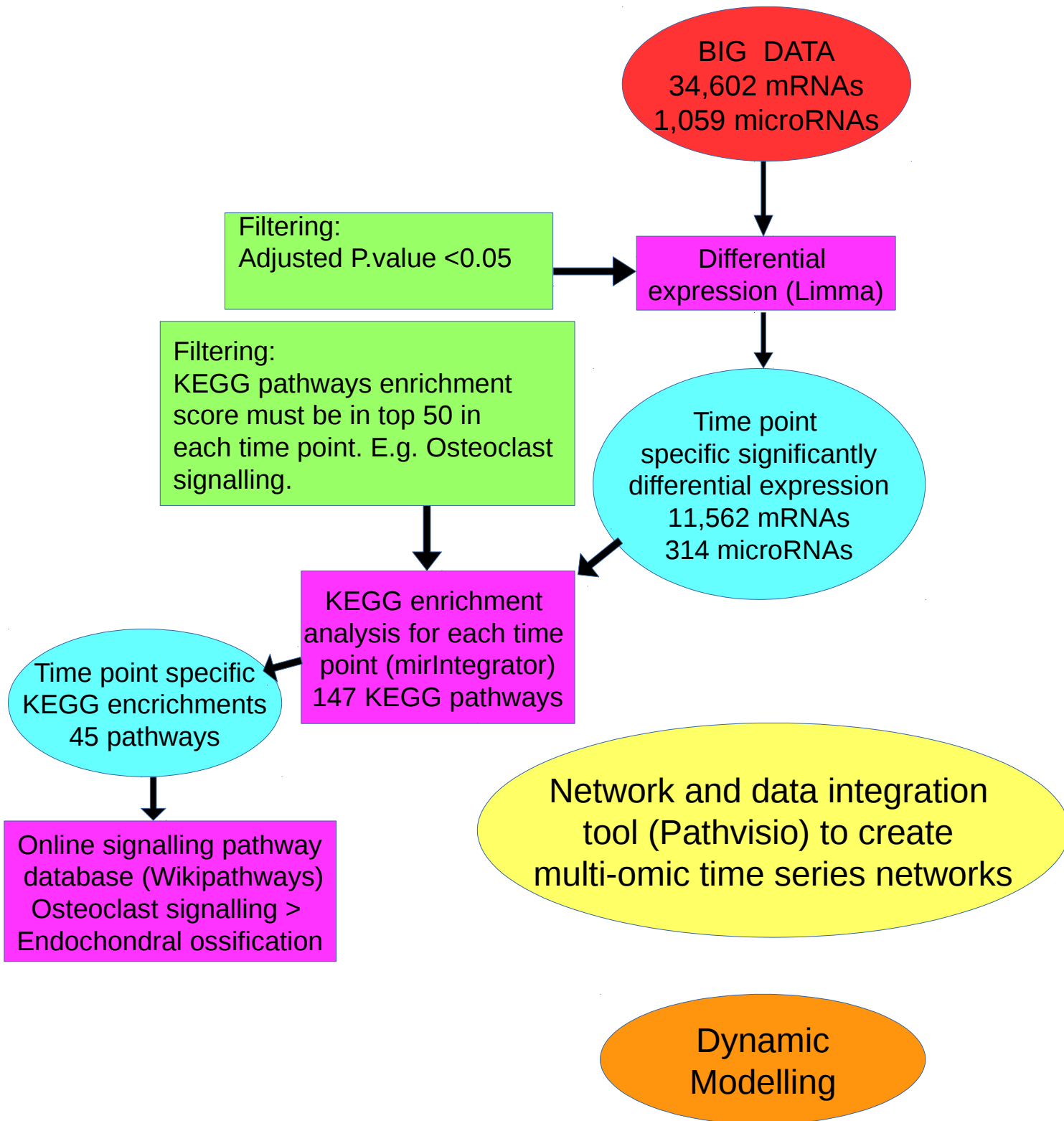




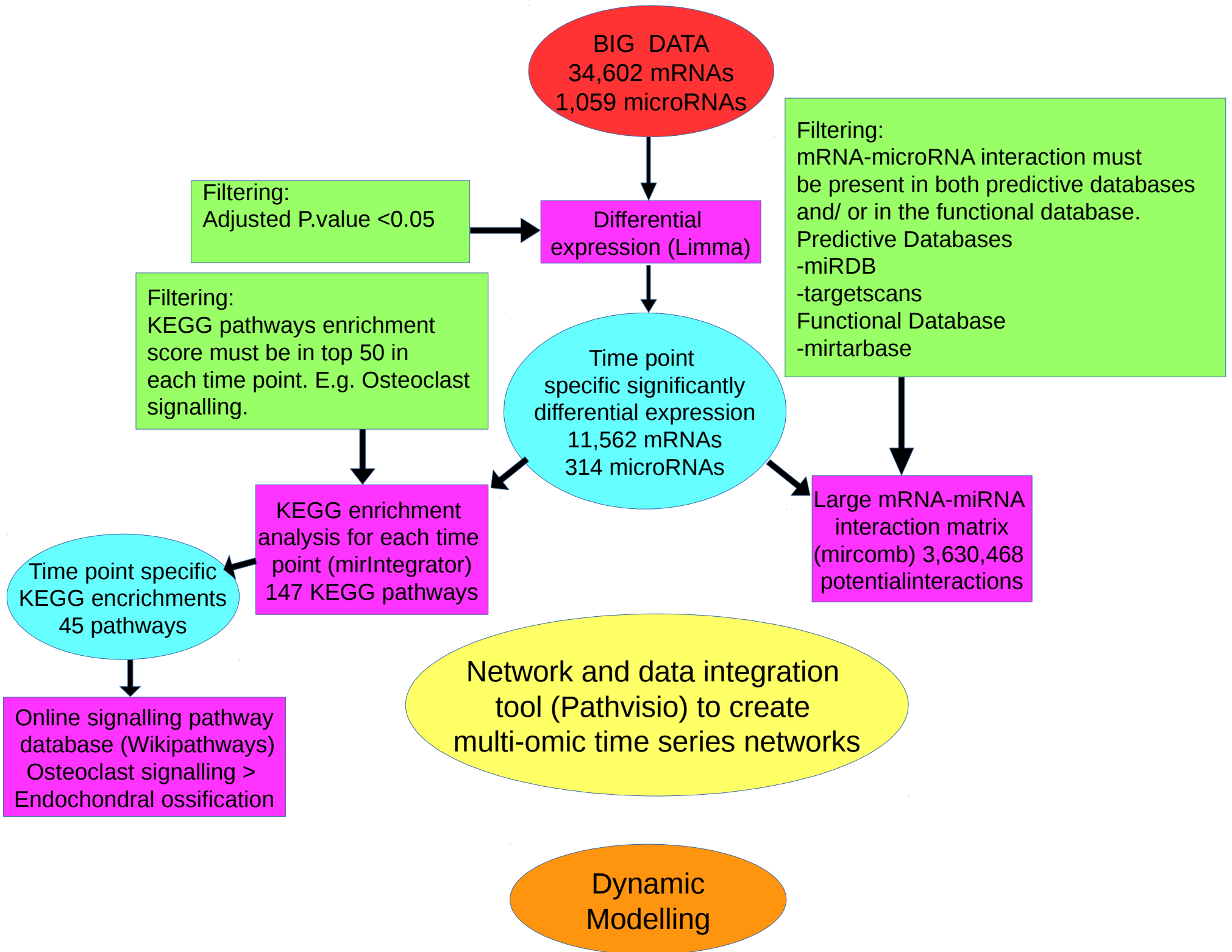






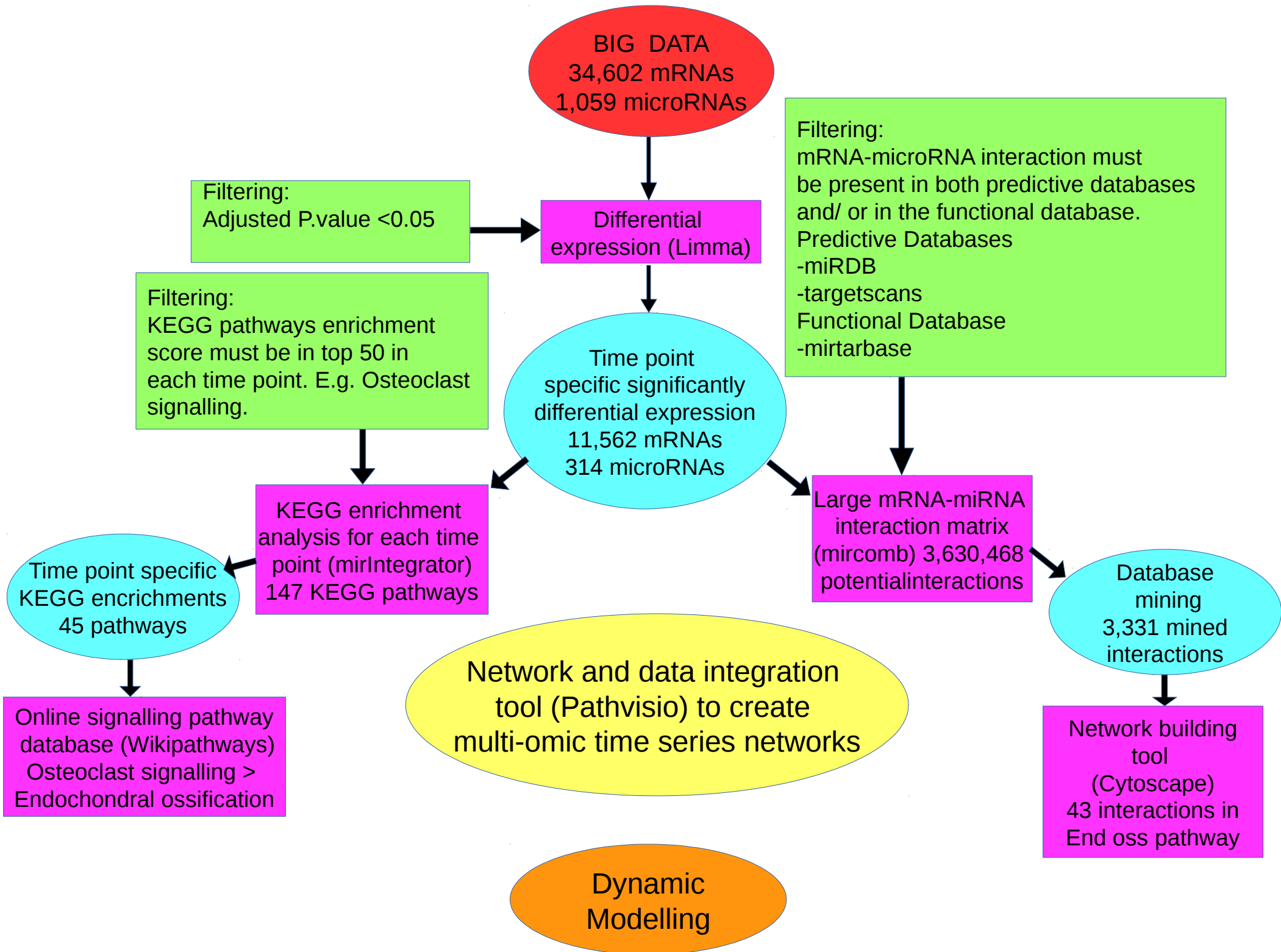


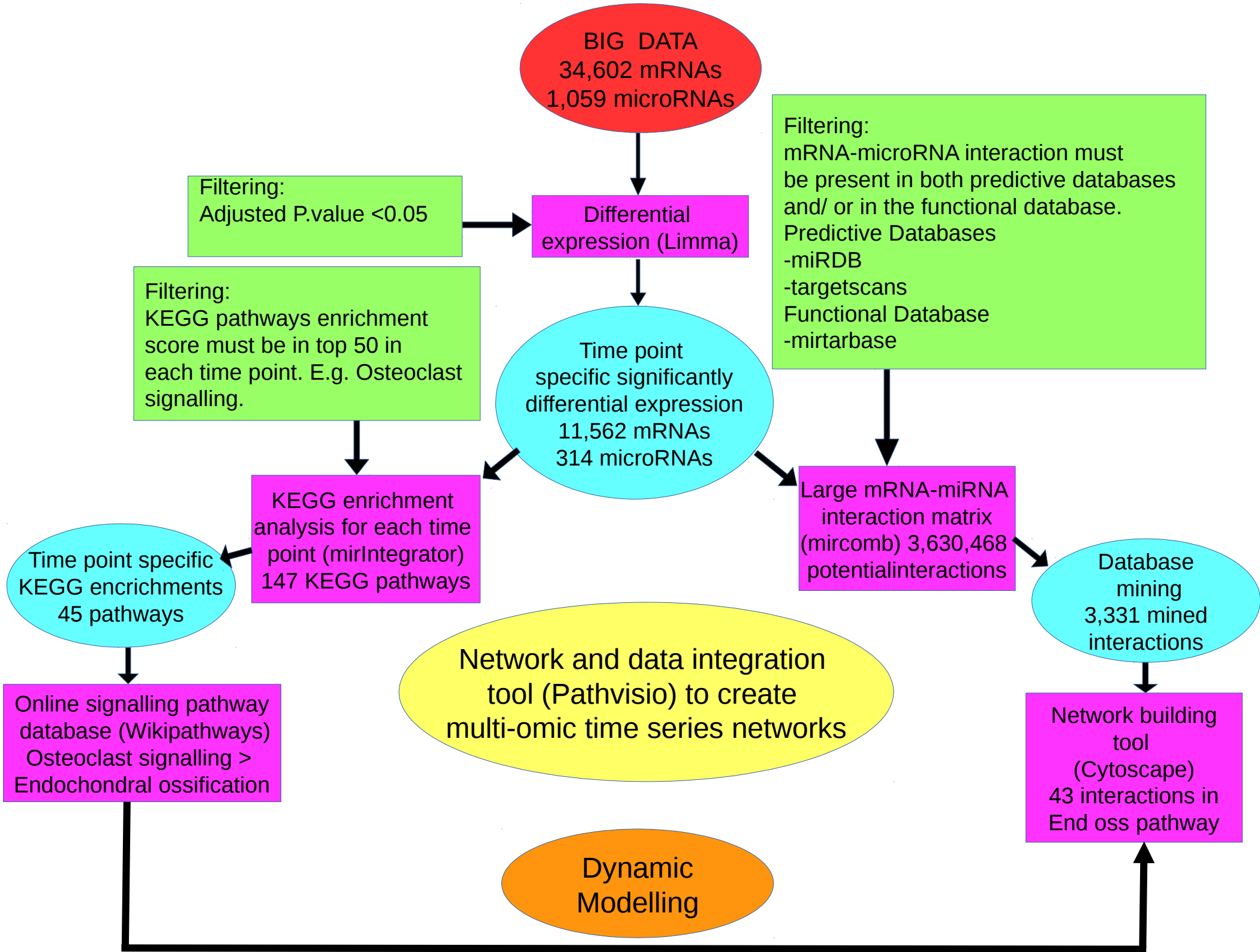


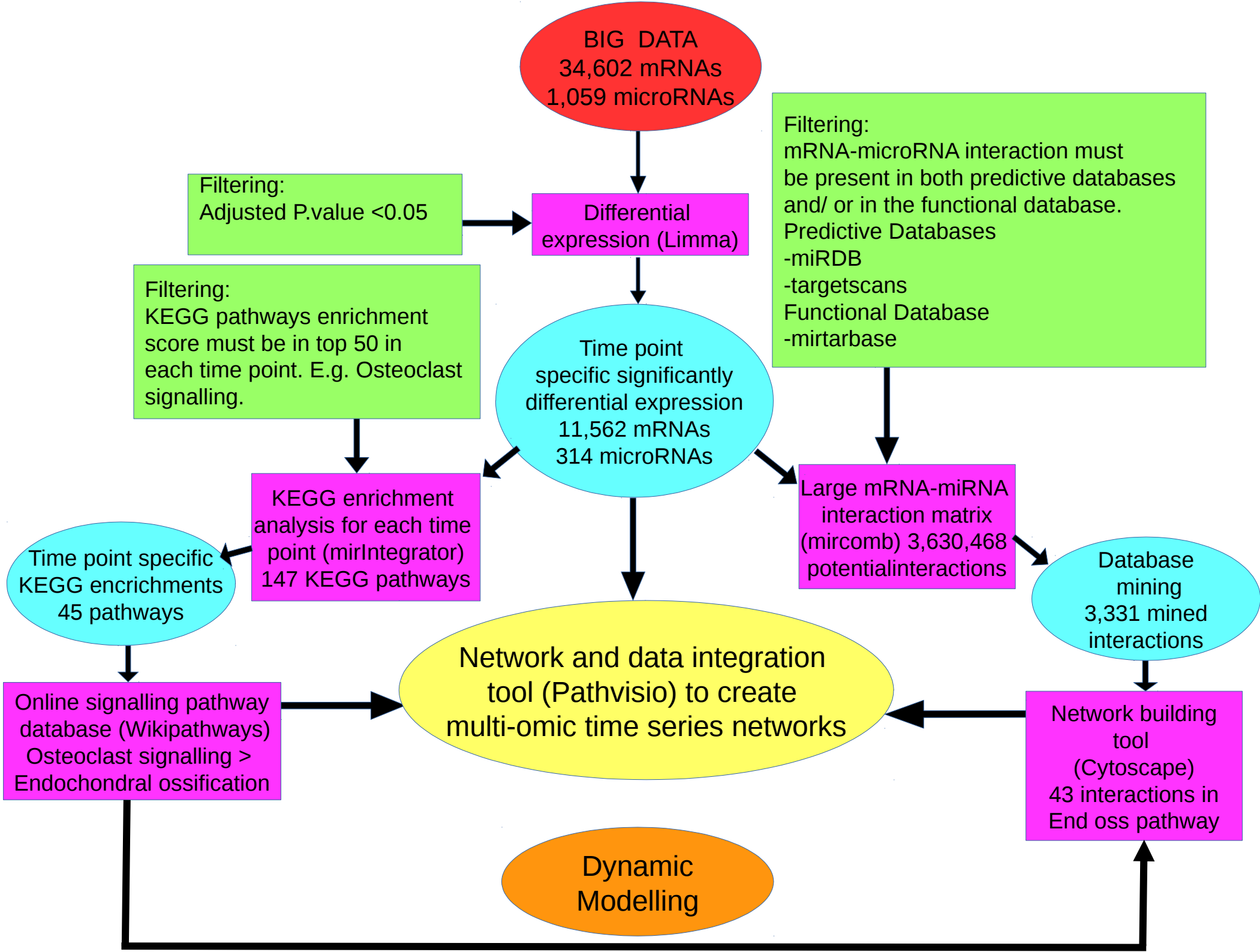












# Multi-omic time series network for Endochondral Ossification

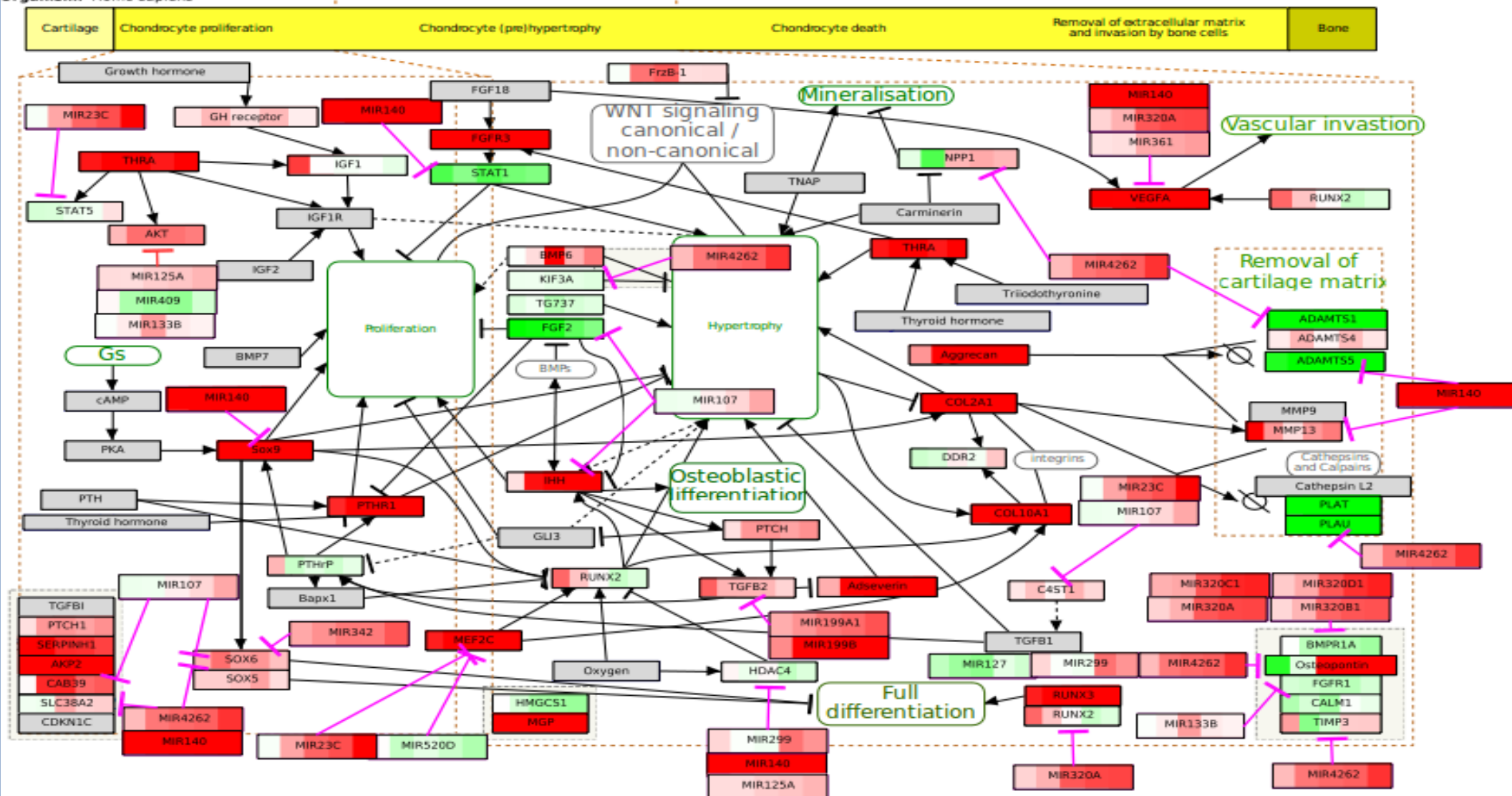
Log2FC

-2                      0                      +2

1D/0D | 3D/0D | 6D/0D | 10D/0D | 14D/0D

**Title:** Endochondral Ossification<sup>1,3</sup>

**Organism:** Homo sapiens



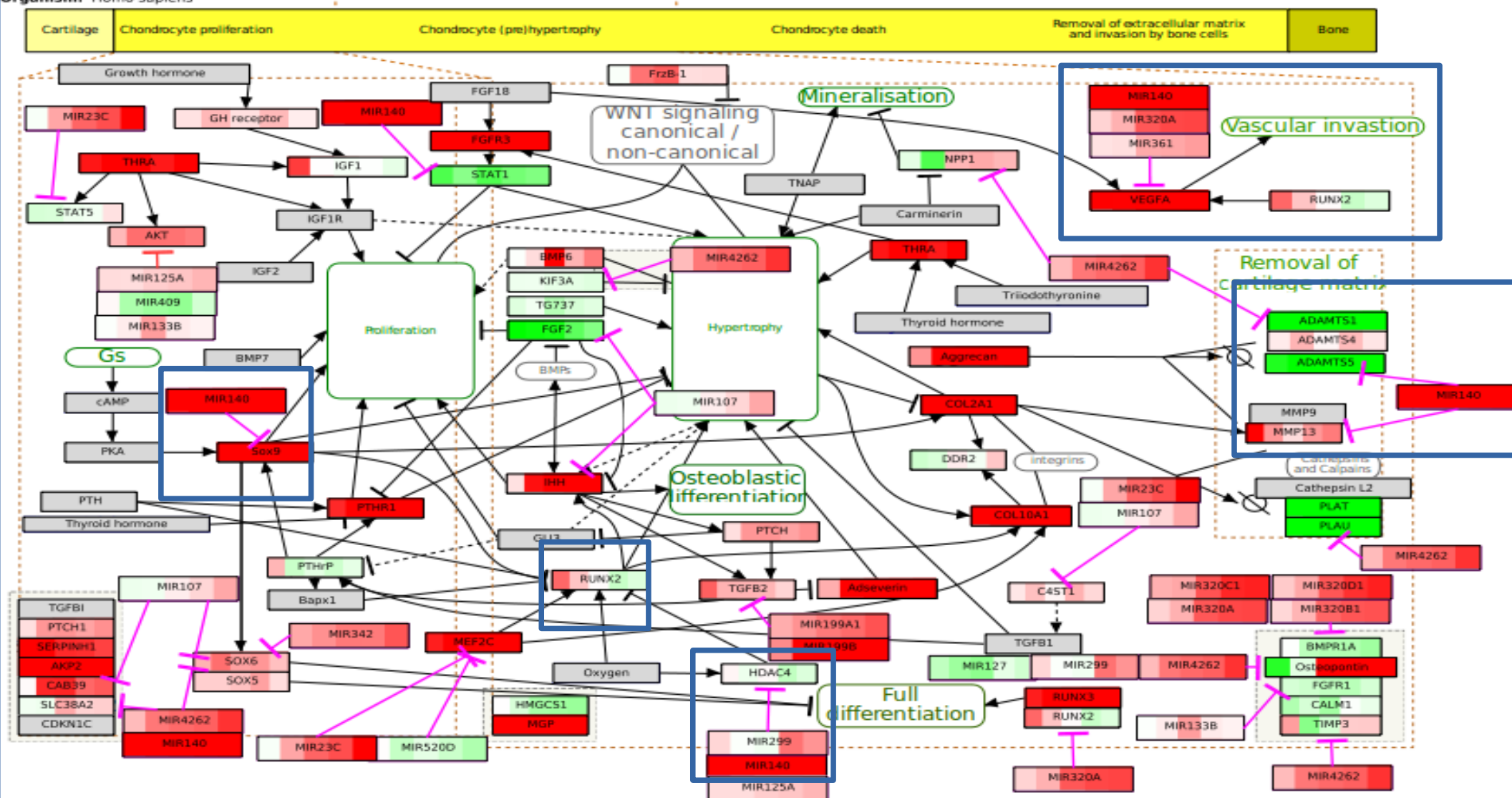
# Multi-omic time series network for Endochondral Ossification

Log2FC

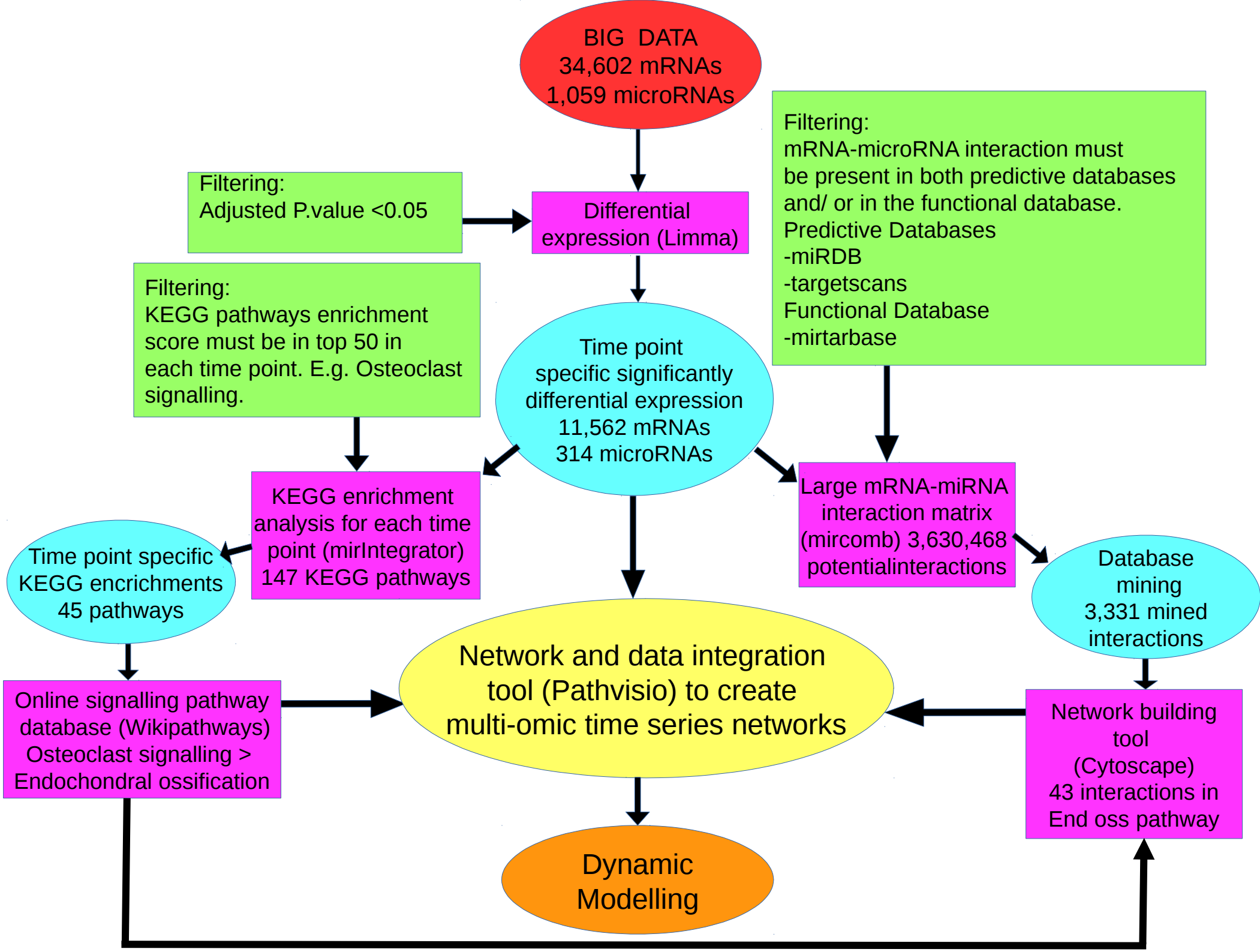
-2 0 +2

1D/0D | 3D/0D | 6D/0D | 10D/0D | 14D/0D

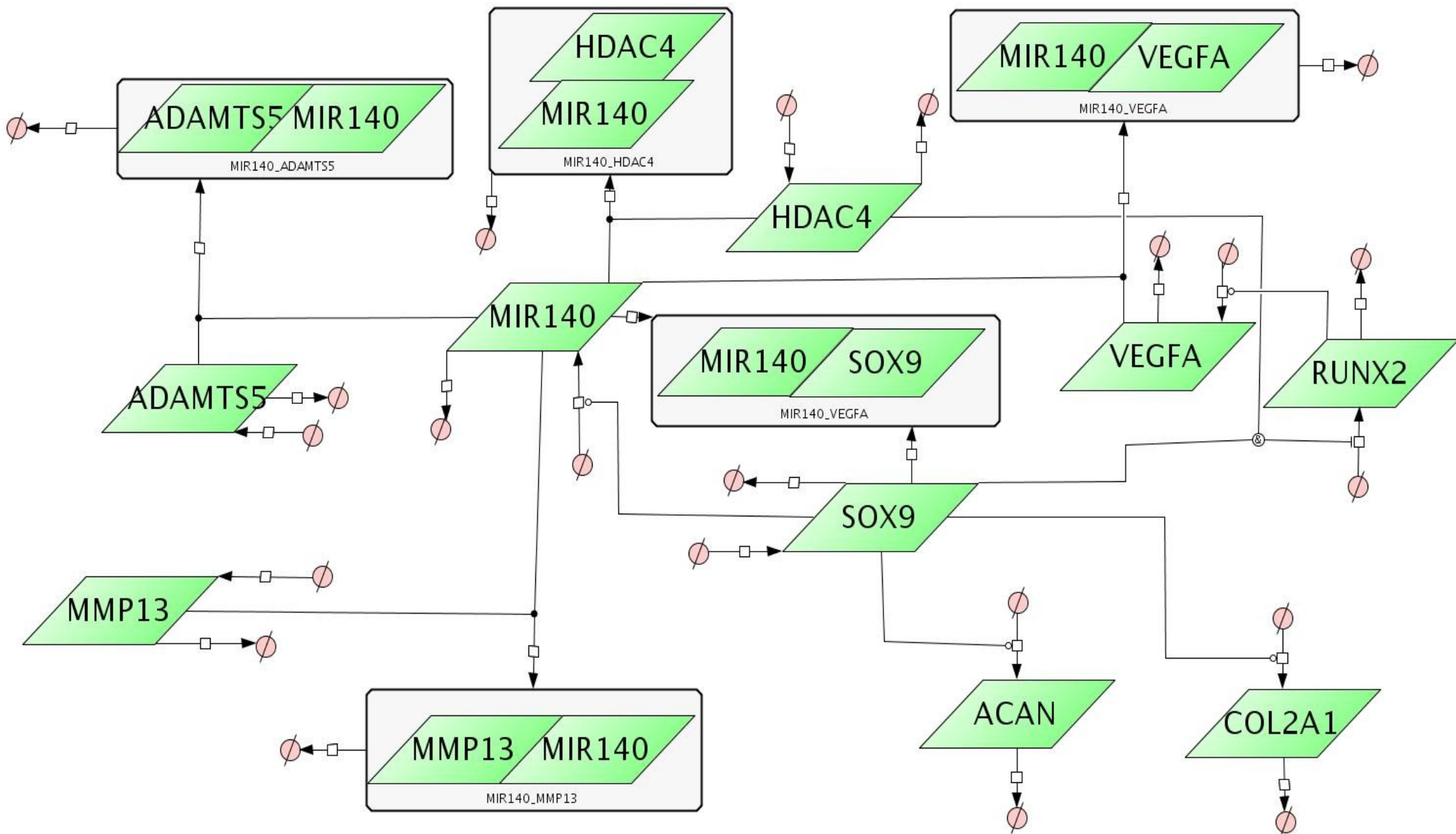
Title: Endochondral Ossification<sub>1-3</sub>  
Organism: Homo sapiens







# MIR140 RNA based Gene Regulatory Network

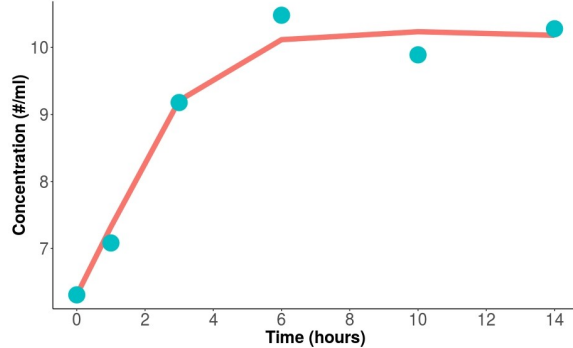




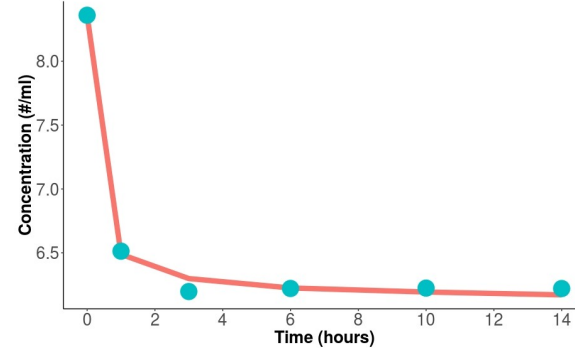
# The model fits well

— = Fitted  
● = Measured

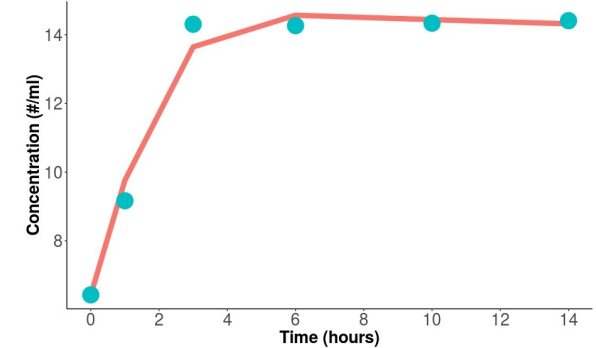
Parameter estimations for ACAN



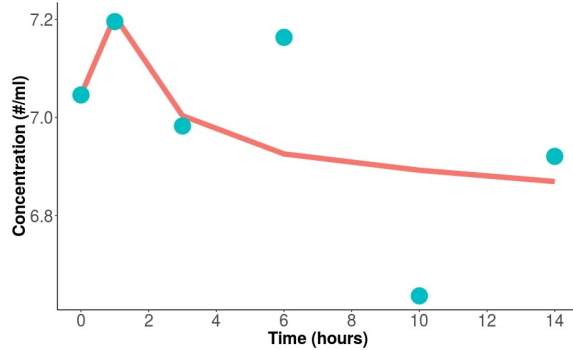
Parameter estimations for ADAMTS5



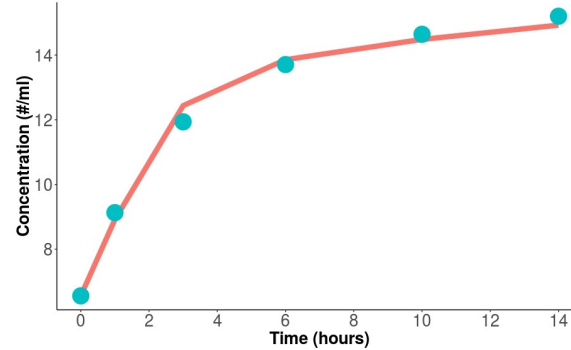
Parameter estimations for COL2A1



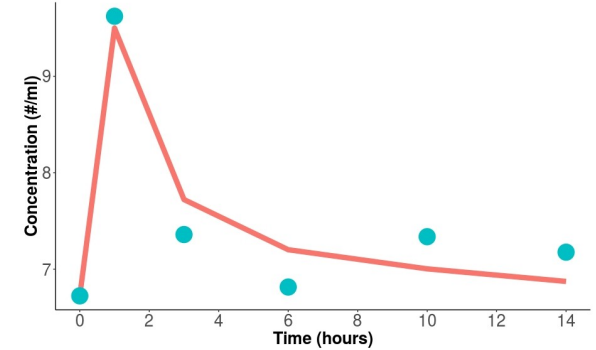
Parameter estimations for HDAC4



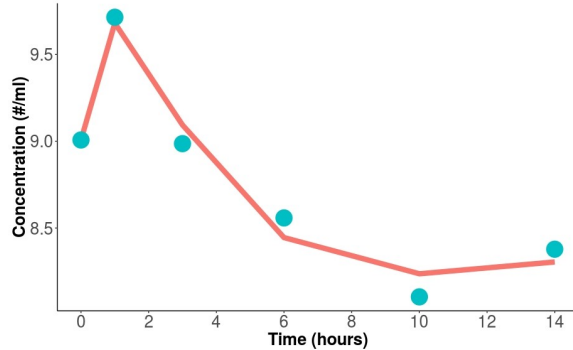
Parameter estimations for MIR140



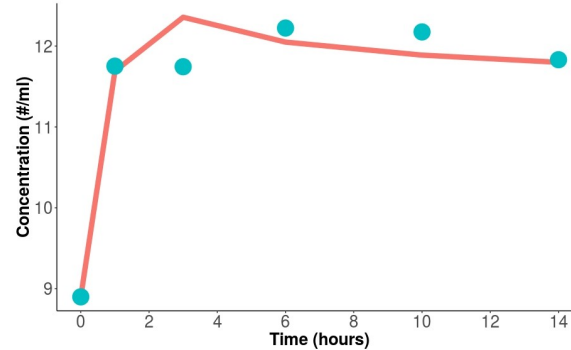
Parameter estimations for MMP13



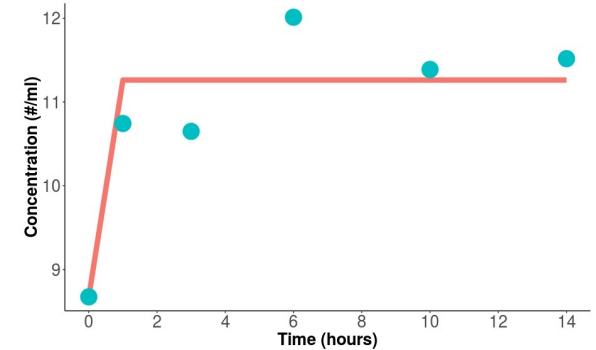
Parameter estimations for RUNX2



Parameter estimations for SOX9



Parameter estimations for VEGFA

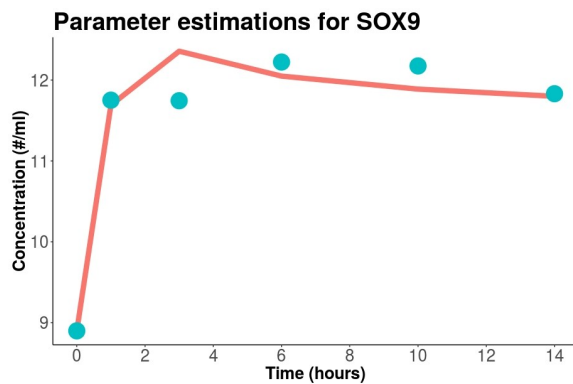


# Modelling allows for the exploration of different topologies

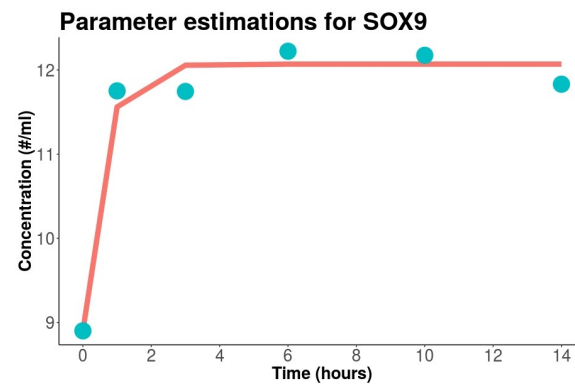
— = Fitted  
● = Measured

## Better fit

### Original

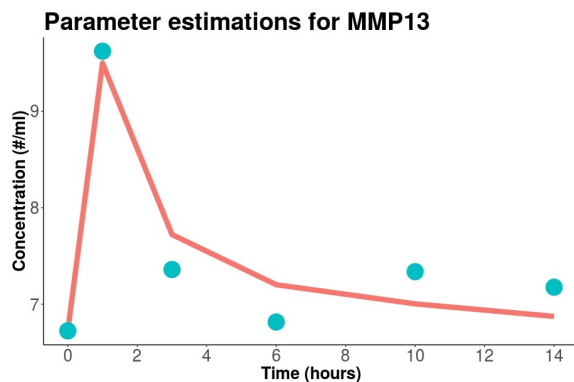


### No MIR140\_SOX9 interaction

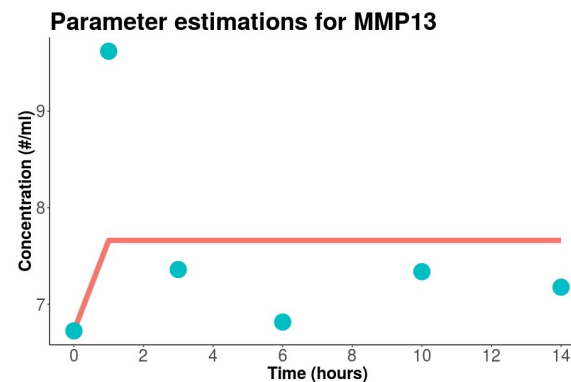


## Worse fit

### Original

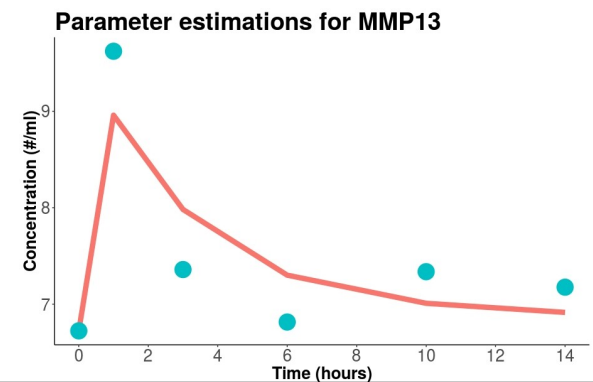


### No MIR140\_MMP13 interaction



## Indirect worse fit

### No MIR140\_ADAMTS5 interaction



# Conclusions

The mutli-omic time series network generation pipeline reduced the complexity of big data to start building dynamic models.

Modelling allows for the exploration of different topologies to investigate how a small signalling network functions.

- Genes fit better if they do not interact with MIR140.
- Genes fit worse if they do not interact with MIR140.
- MIR140 targets may require other MIR140 targets to be present to indirectly be beneficial to one anothers fits.

# Thanks

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Adrian Falconer  
David Wilkinson  
Hua Lin  
Julia Falk  
Marjolein Burgers



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