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# Structure, dynamics and evolution of complex systems

## (The parts and the whole: Some examples of their relationship)

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### **Sanjay Jain**

Department of Physics and Astrophysics, University of Delhi, India

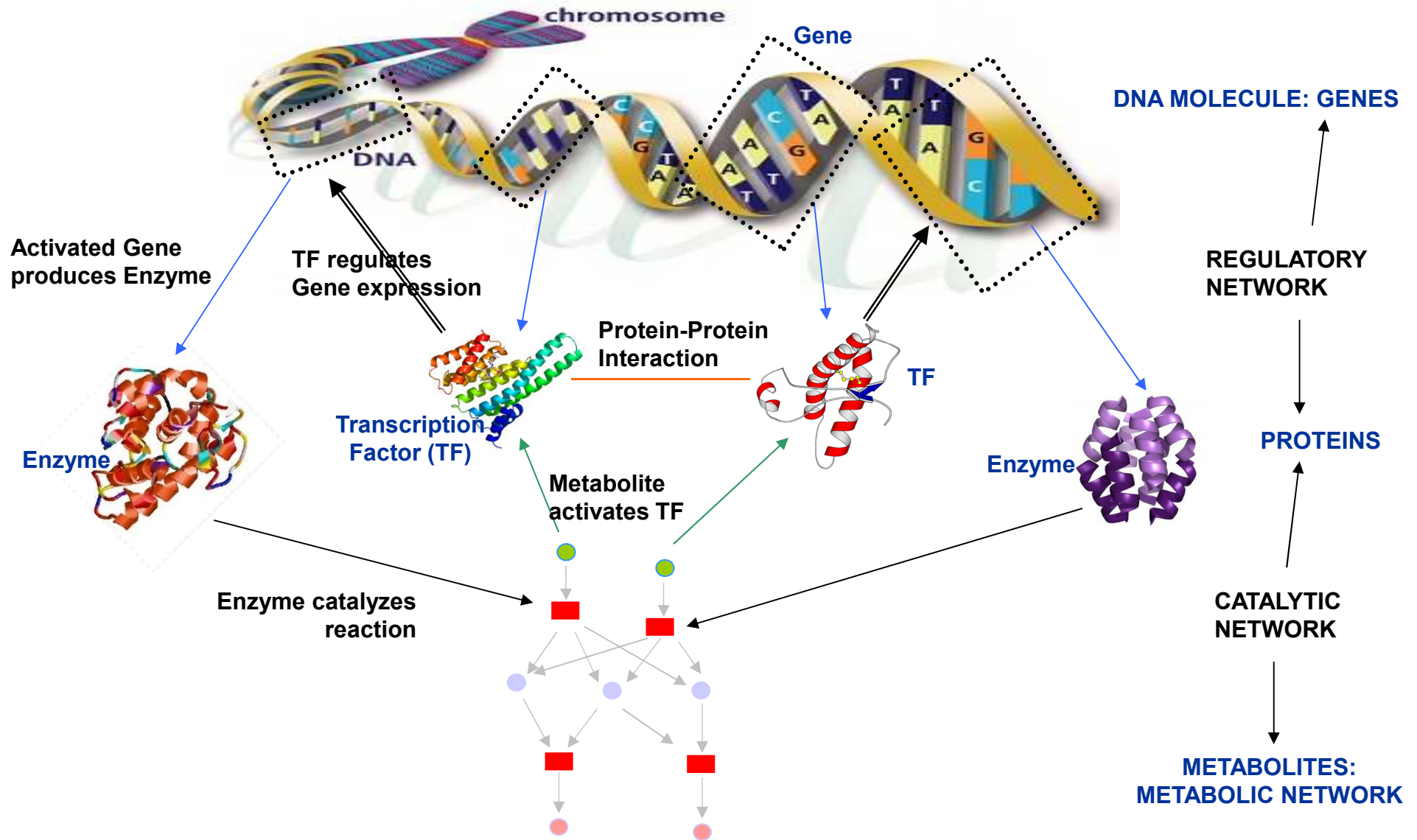
Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore

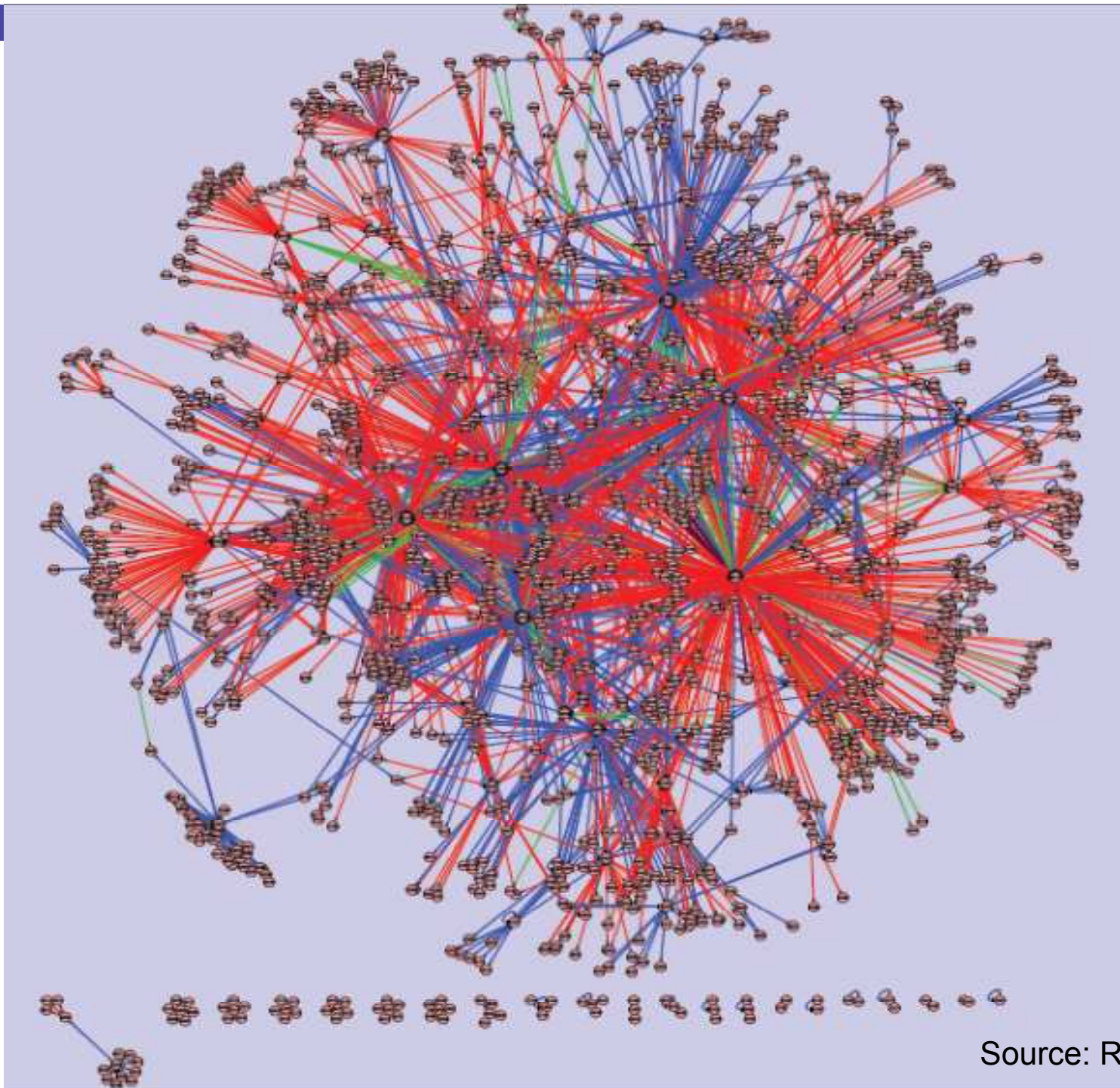
Santa Fe Institute, Santa Fe, NM, USA

Email: [jain@physics.du.ac.in](mailto:jain@physics.du.ac.in)

Homepage: <http://people.du.ac.in/~jain/>

# Mutually Interacting Networks inside a cell





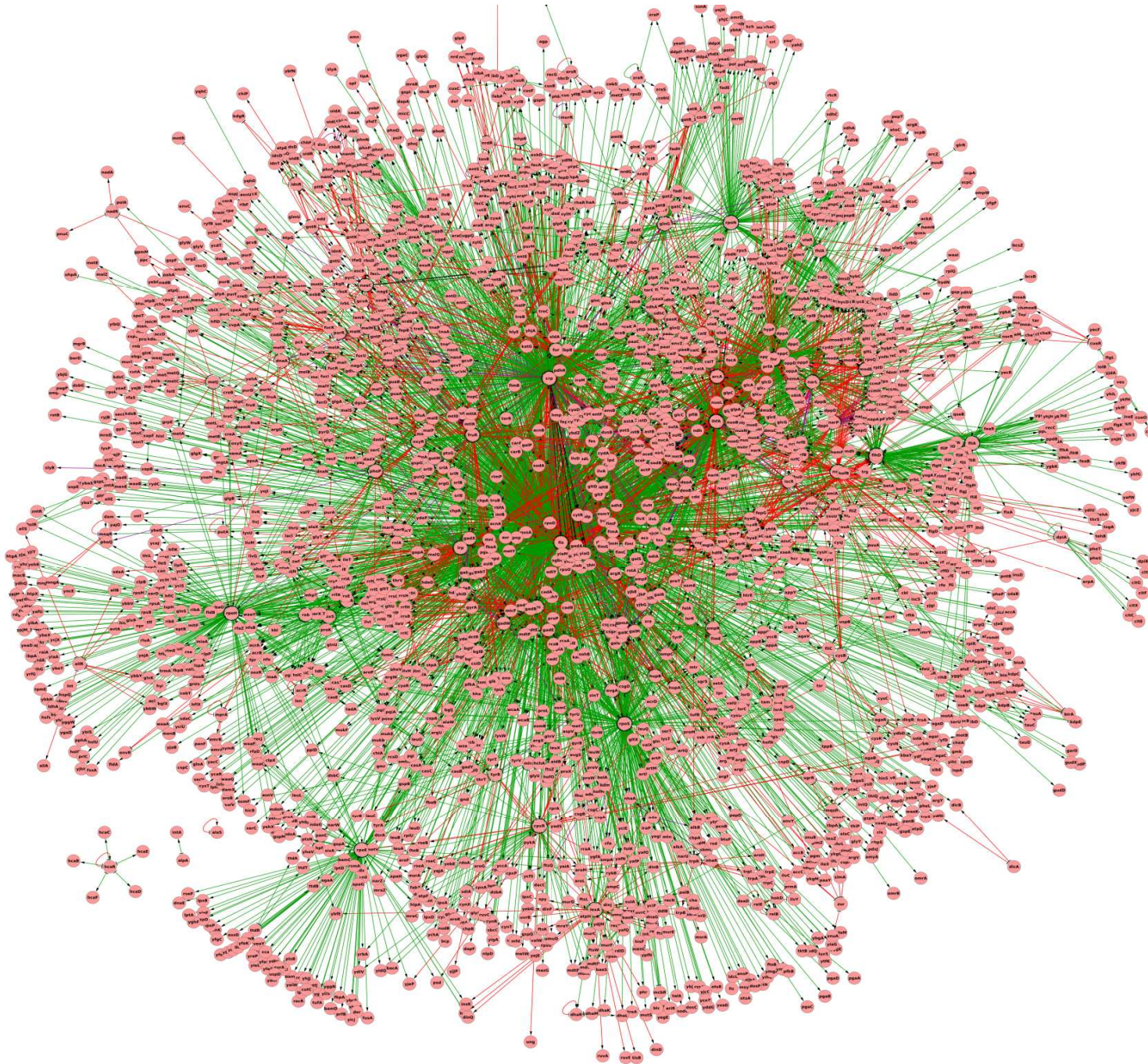
Source: Regulon DB



## The parts and the whole: Some examples of their relationship

1. Return to the 'whole', now with a strong understanding of the parts. New design principles at the level of the whole.
2. Interplay between multiple scales: the whole is robust to large perturbations of many of its parts but extremely sensitive to perturbations of some parts.

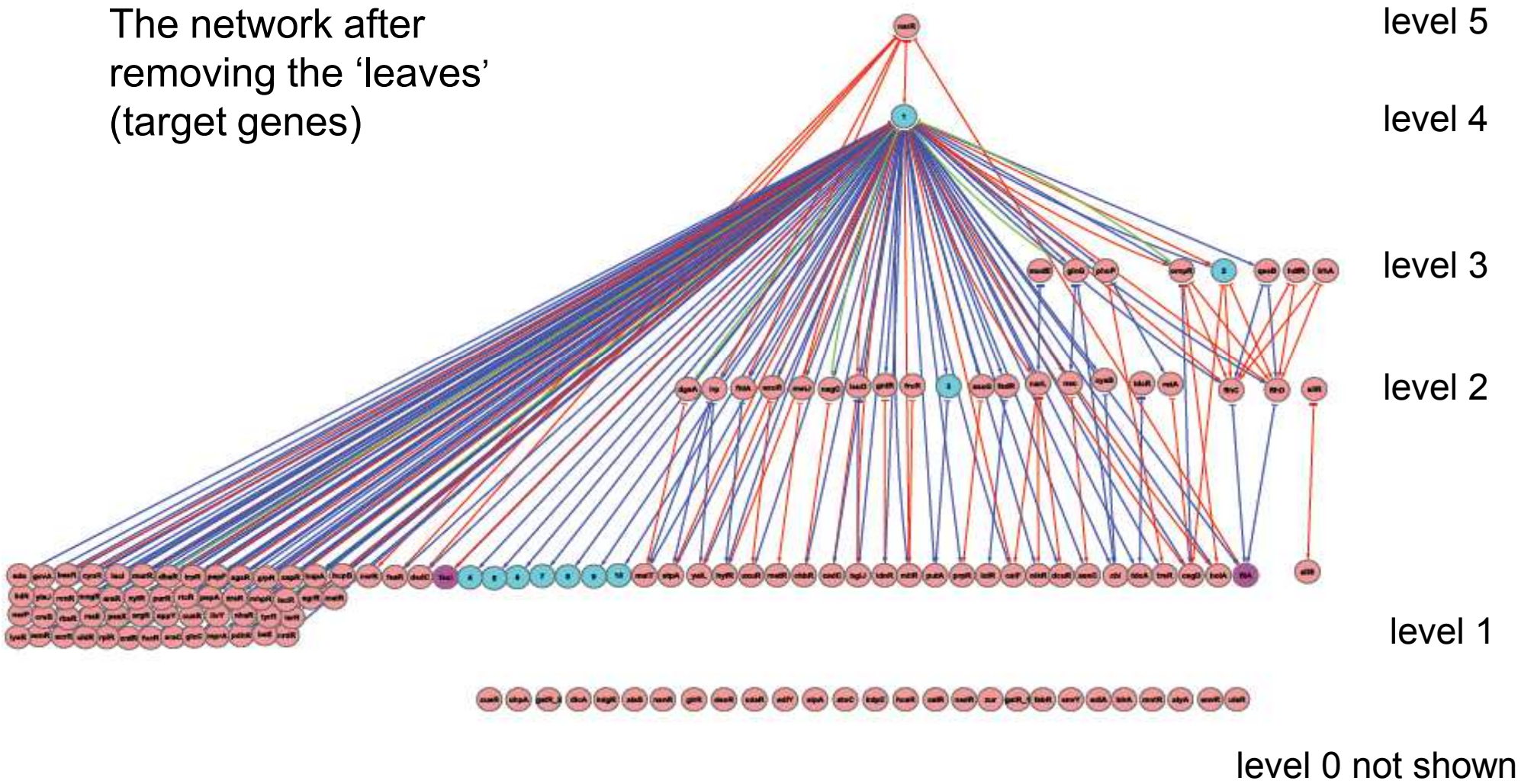
# Structure of the genetic regulatory network of *E. coli*



**Node:** gene  
**Link:** regulatory interaction

Data from Regulon database

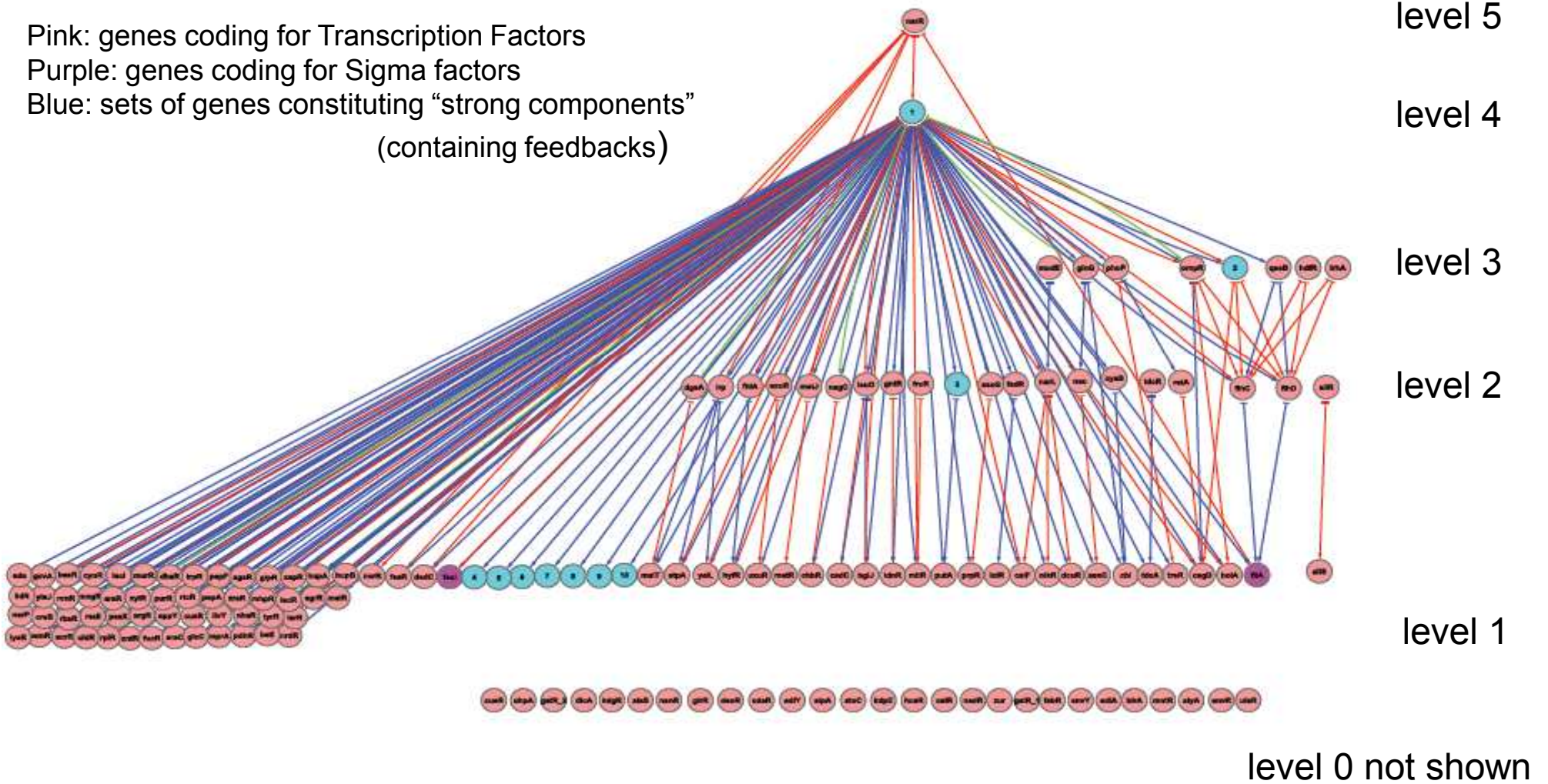
The network after removing the 'leaves' (target genes)



Pink: genes coding for Transcription Factors  
 Blue: sets of genes constituting "strong components"  
 (containing feedbacks)

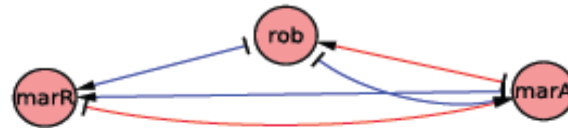
# Structure of the genetic regulatory network of *E. coli*

Pink: genes coding for Transcription Factors  
 Purple: genes coding for Sigma factors  
 Blue: sets of genes constituting “strong components”  
 (containing feedbacks)



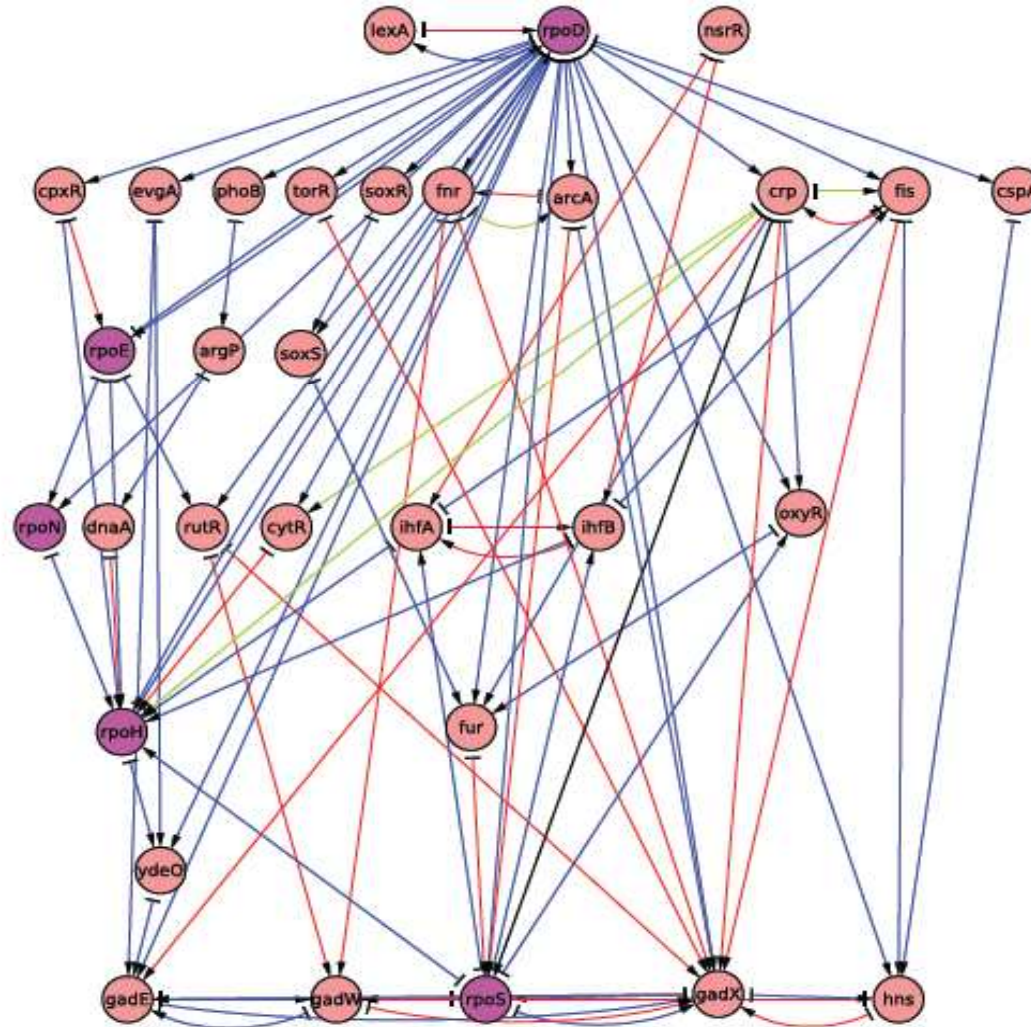
Other refs: Uri Alon group, Barabasi group, Ma and Zeng, Collado-Vides group, Madan Babu group

# The strong components at level 1,2 and 3



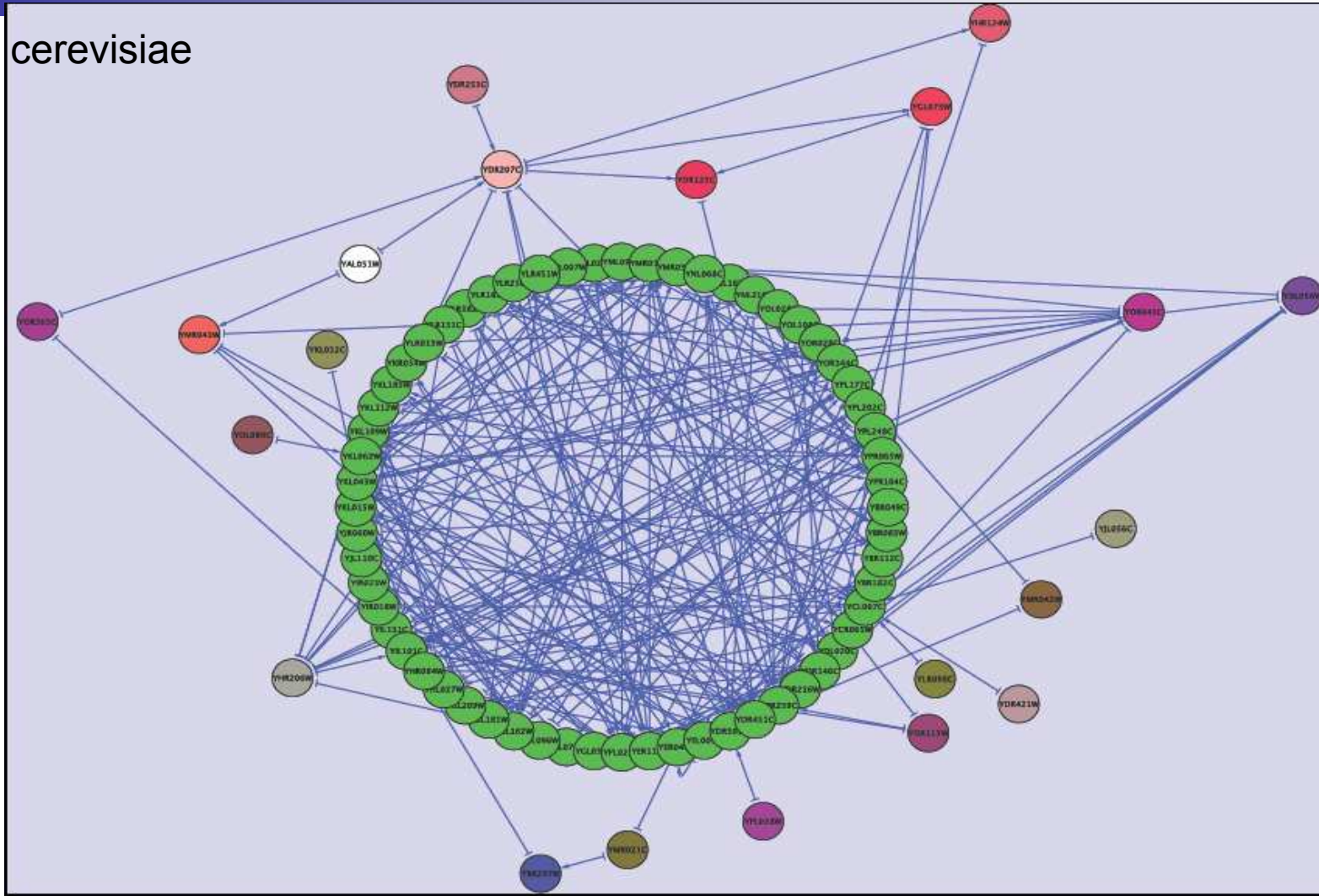


# The strong component at level 4 ("core")



“genetic feedbacks”

For *S. cerevisiae*



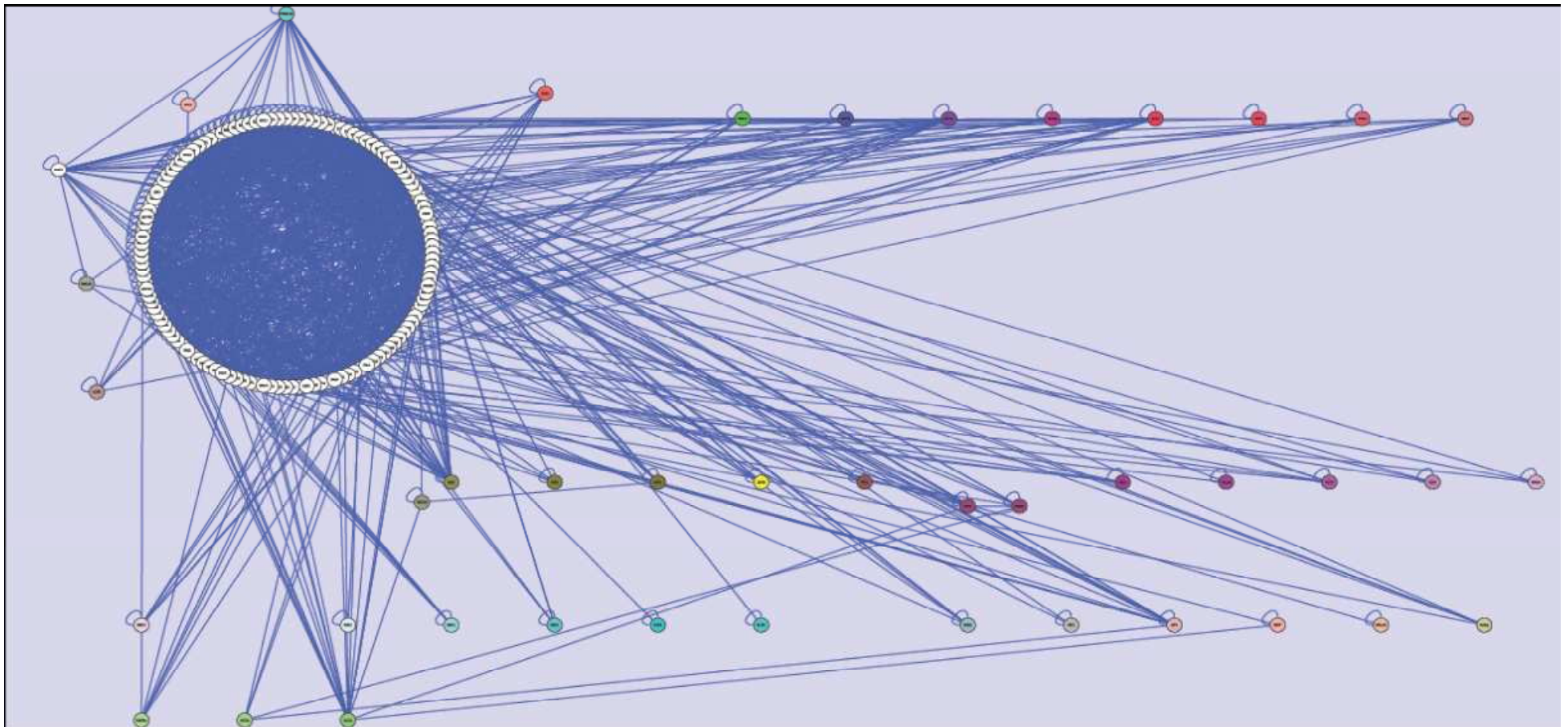
**Tnet Database:** 4410 Genes, 12873 Links, 157 TFs

Balaji, Madan Babu, Iyer, Luscombe, and Aravind, J. Mol. Bio. (2006) 360(1): 213-27.

22 Irreducible components

136 Nodes in the largest irreducible component

Hannes Beushausen, Areejit Samal, S.J.



**Yeastract Database:** 5784 Genes, 31880 Links, 169 TFs

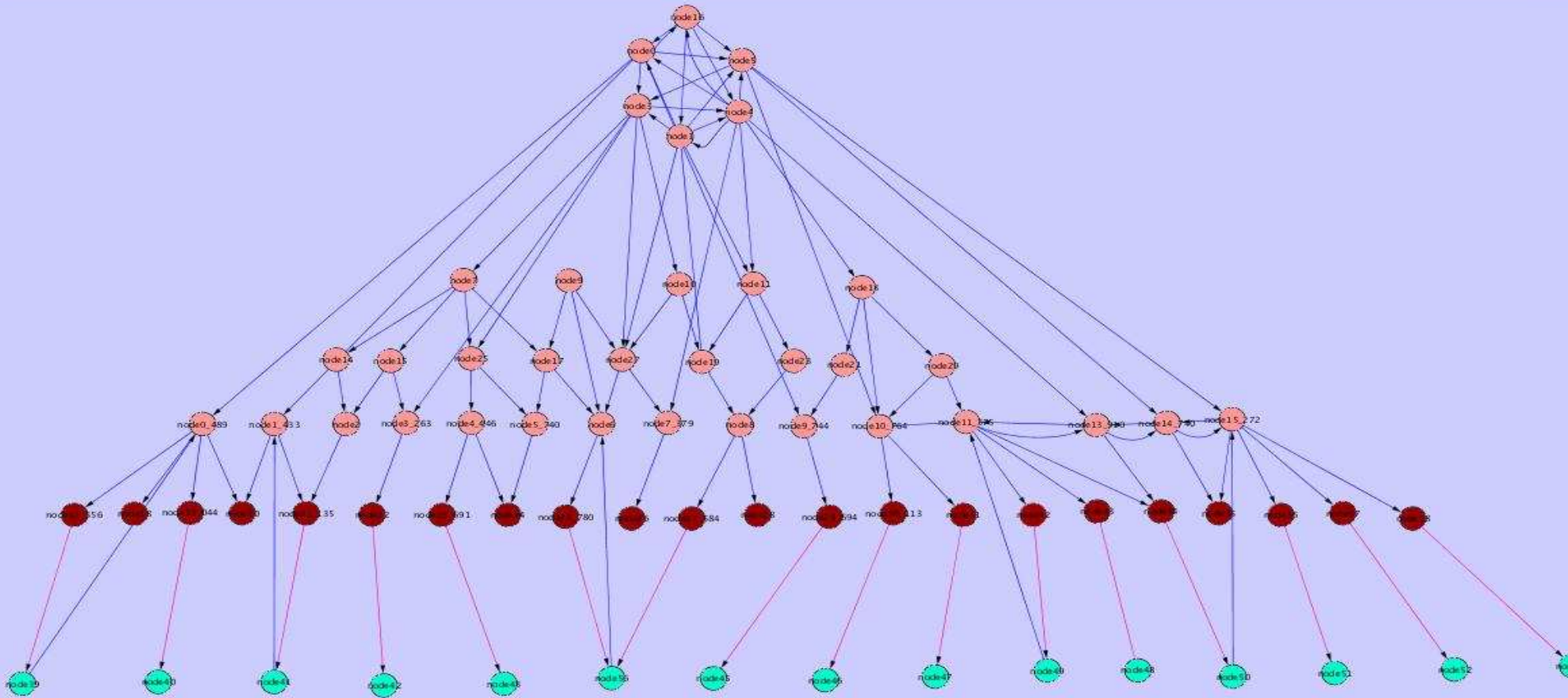
Ref: Teixeira, et. al., Nucl. Acids Res. (2006) and Monteiro, et. al. Nucl. Acids Res. (2008)

42 Irreducible components

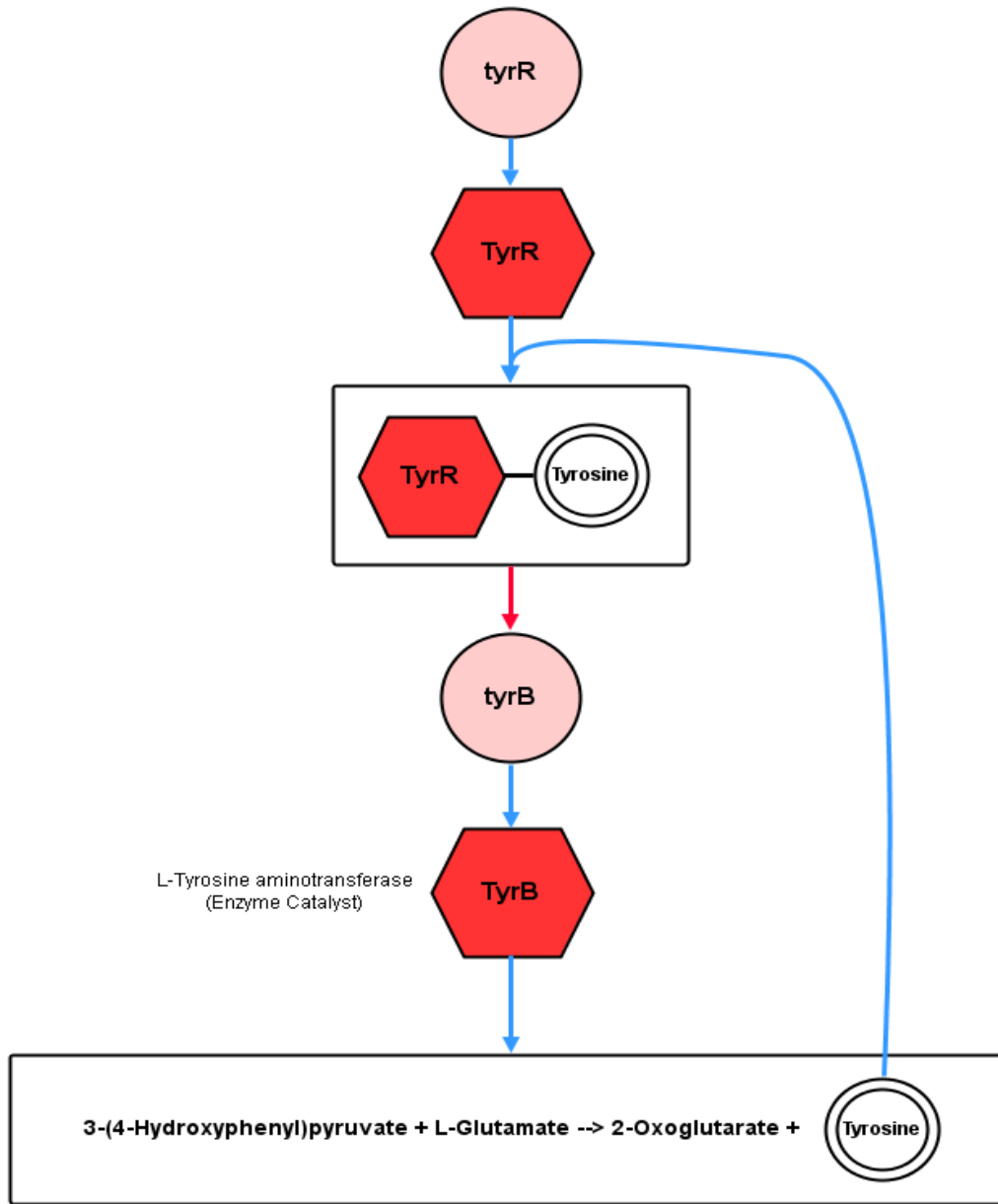
128 Nodes in the largest irreducible component

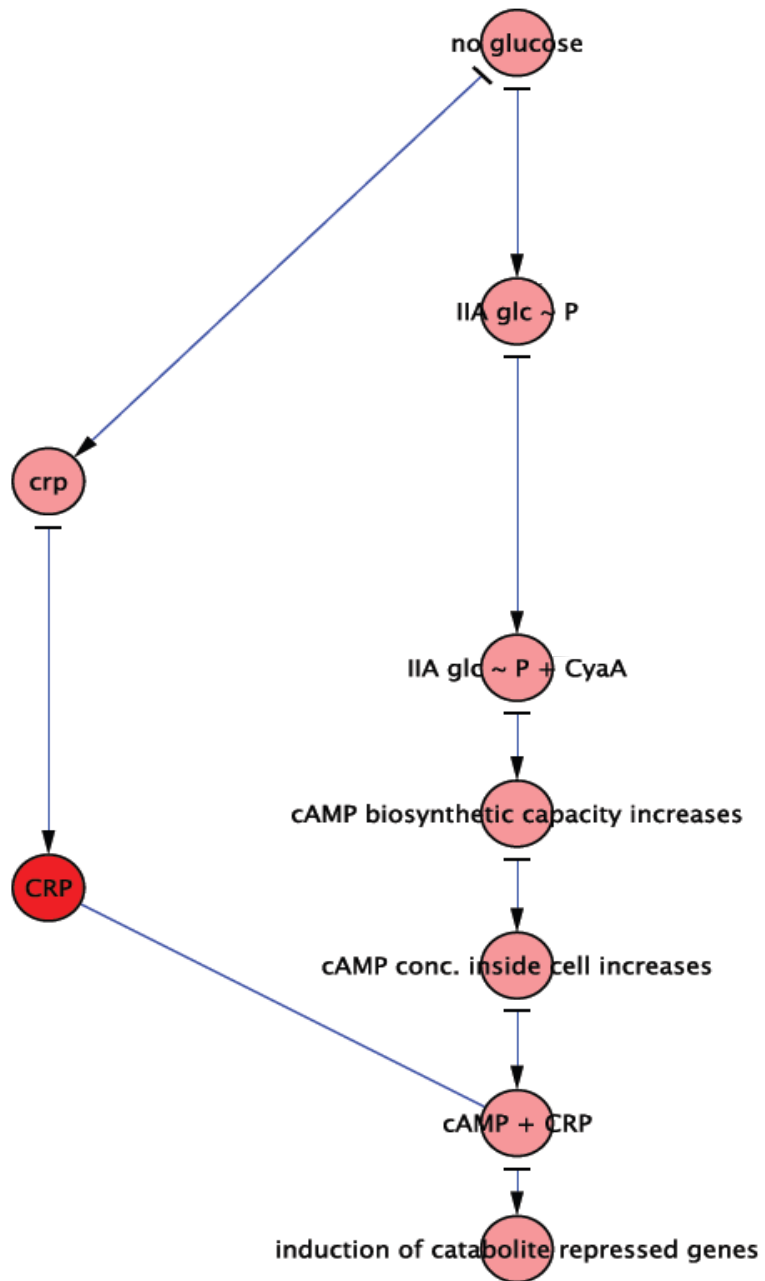
Hannes Beushausen, Areejit Samal, S.J.

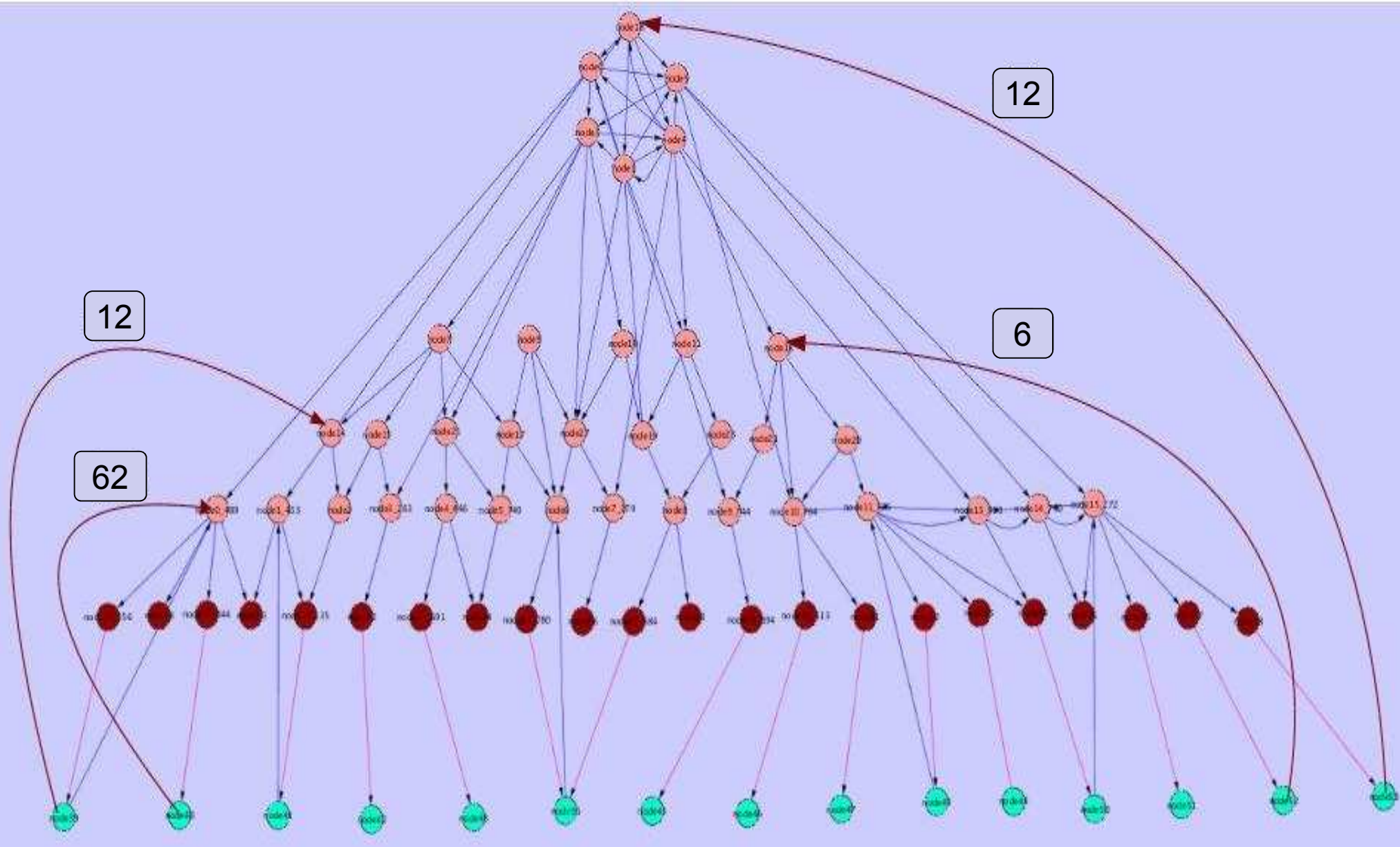
# Schematic picture



“metabolic feedbacks”

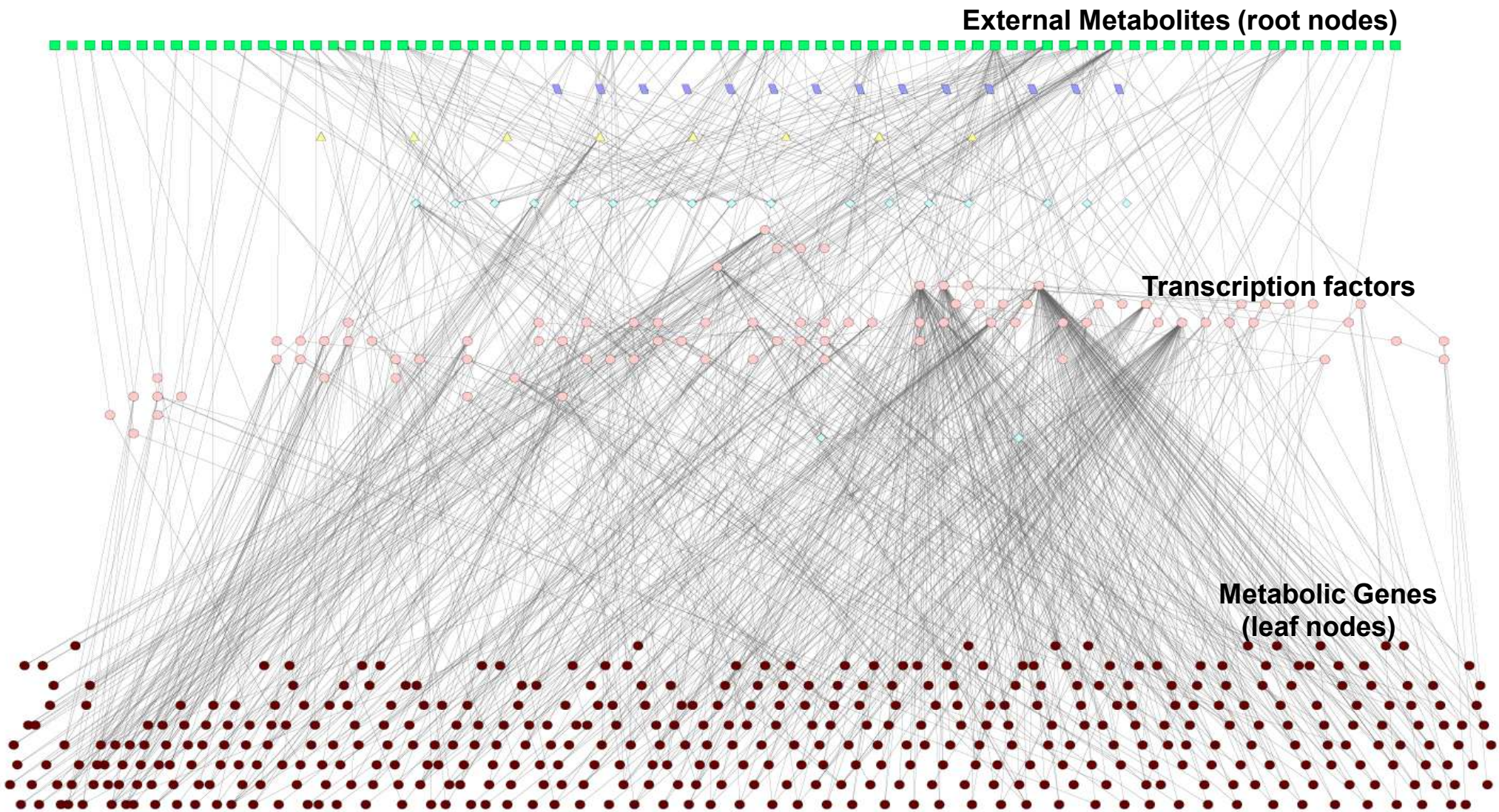




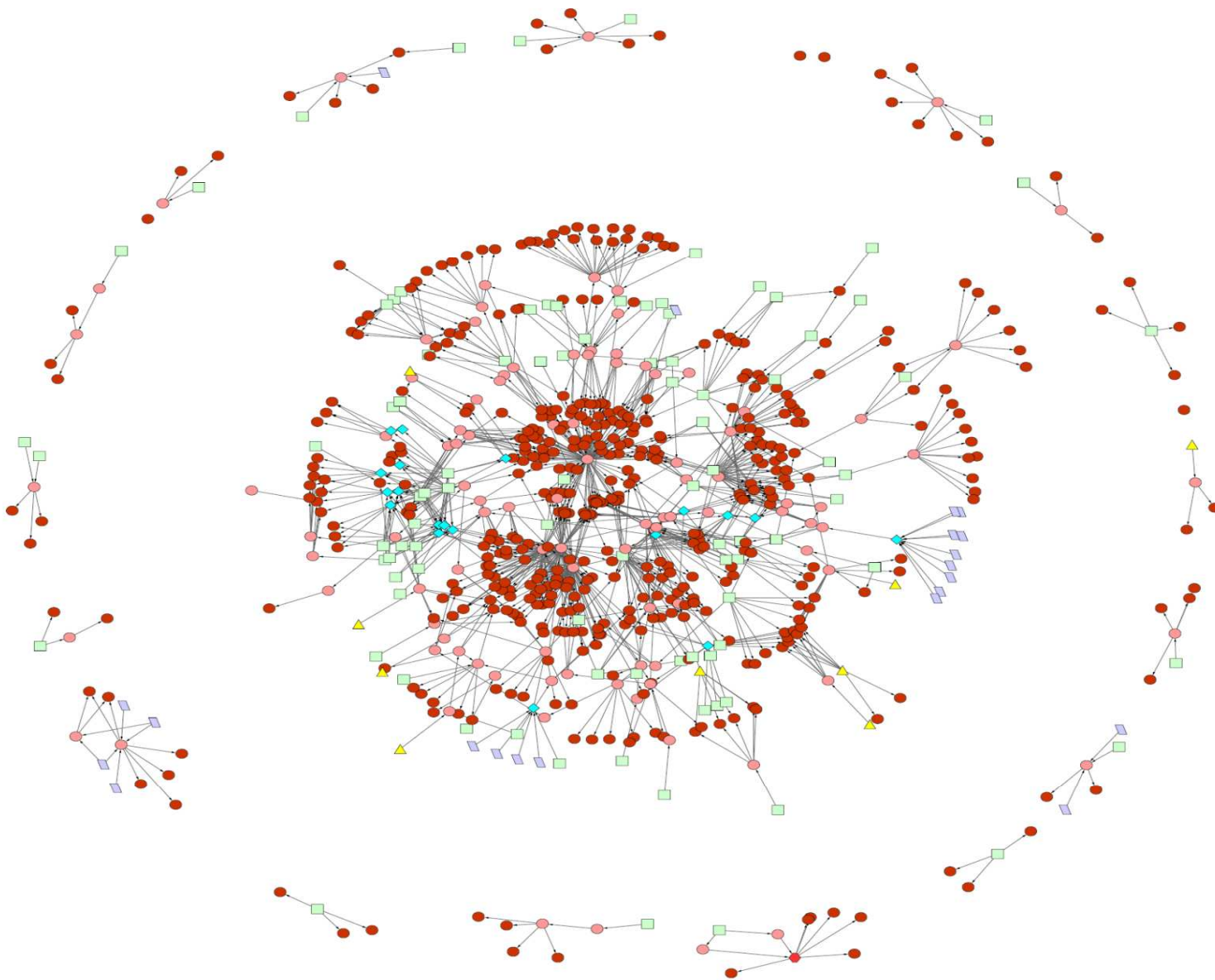


Metabolic feedbacks compiled from Ecocyc data base (Karp et al) and Regulon database

# Structure of the network



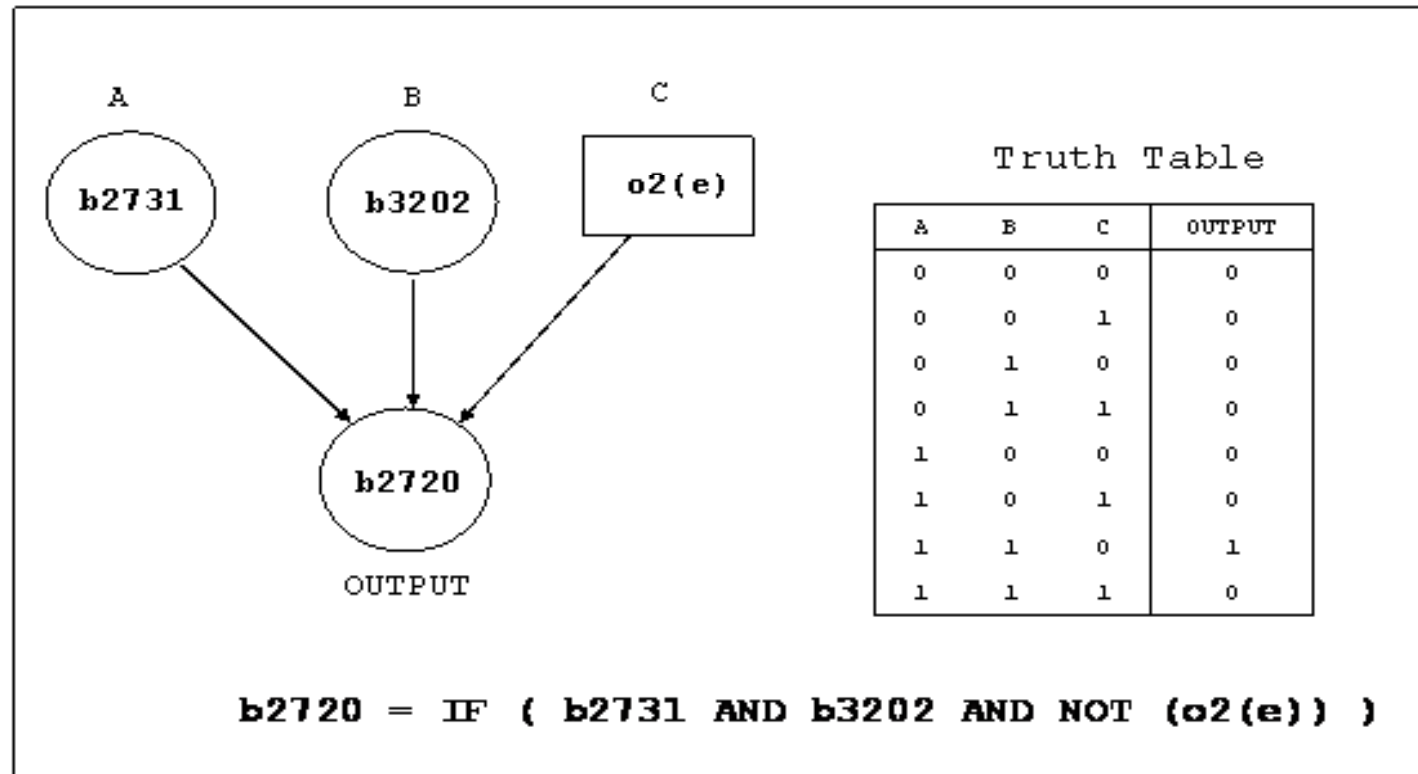


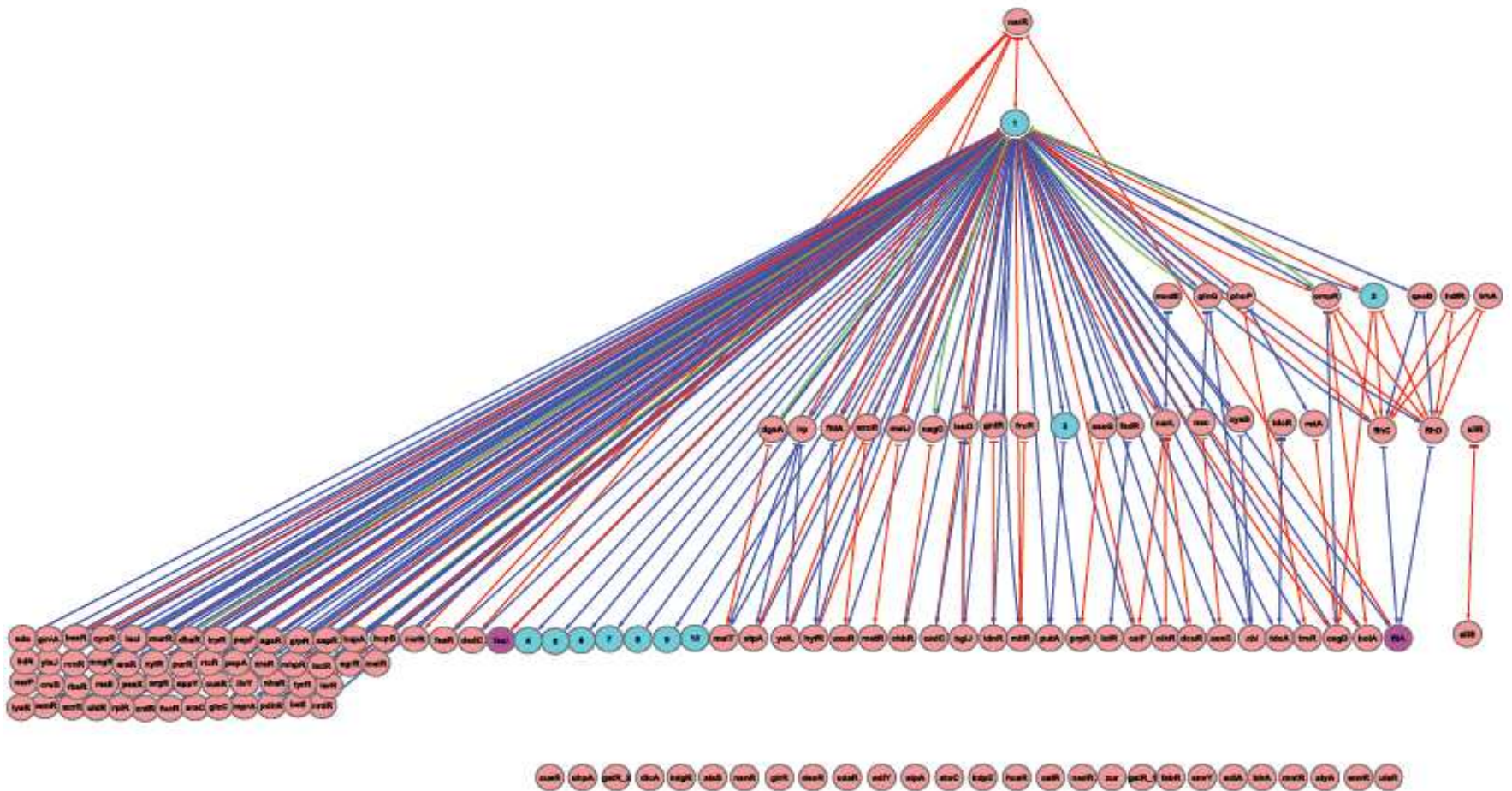


**The graph shows the Genetic network controlling metabolism in *Escherichia coli*. The pink nodes represent genes coding for transcription factors, brown nodes represent genes that code for enzymes and the green nodes represent external metabolites.**

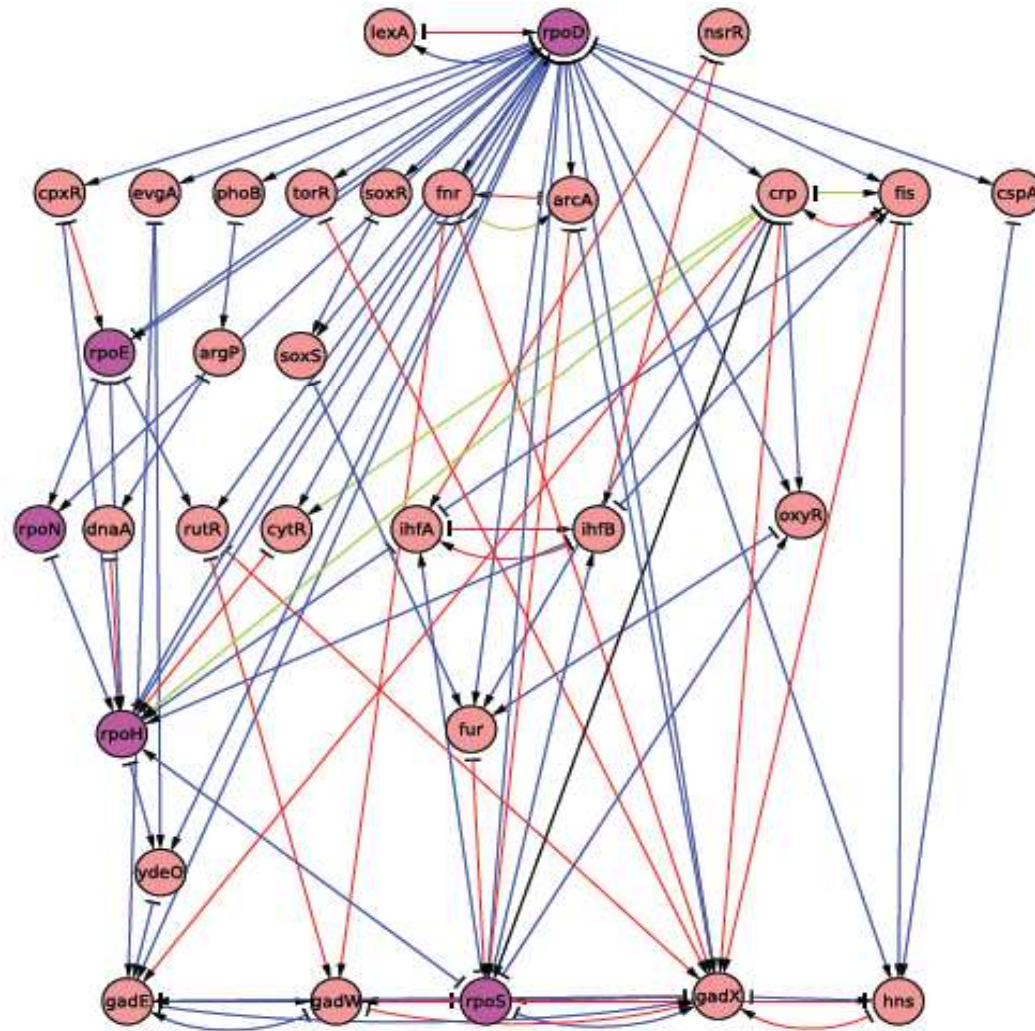
The database also gives the regulatory logic of every gene as a function of its input nodes' configuration, i.e., given the on-off status of all its input nodes, whether the gene will be turned on or off.

## Example of an input function in the form of a boolean rule

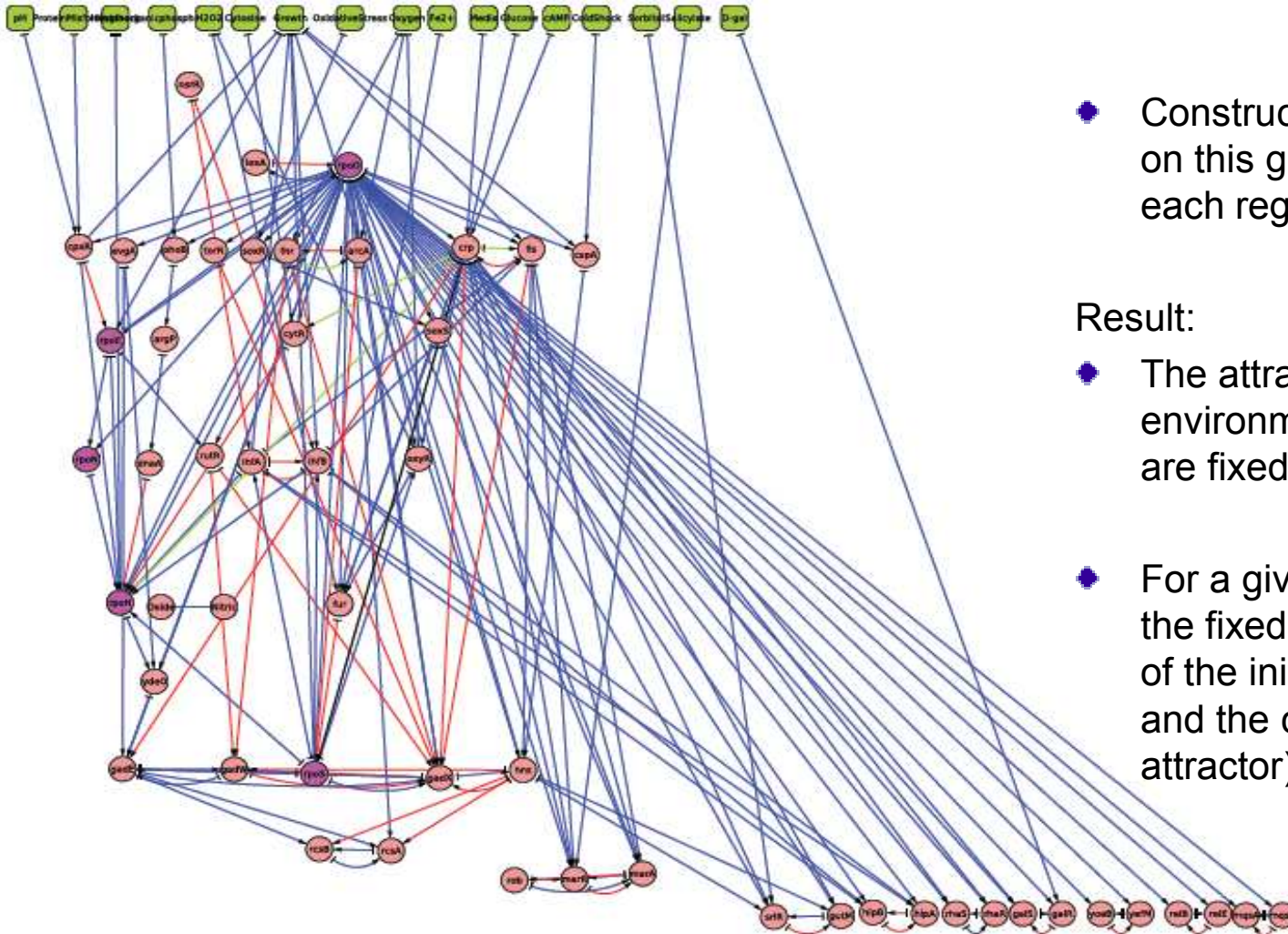








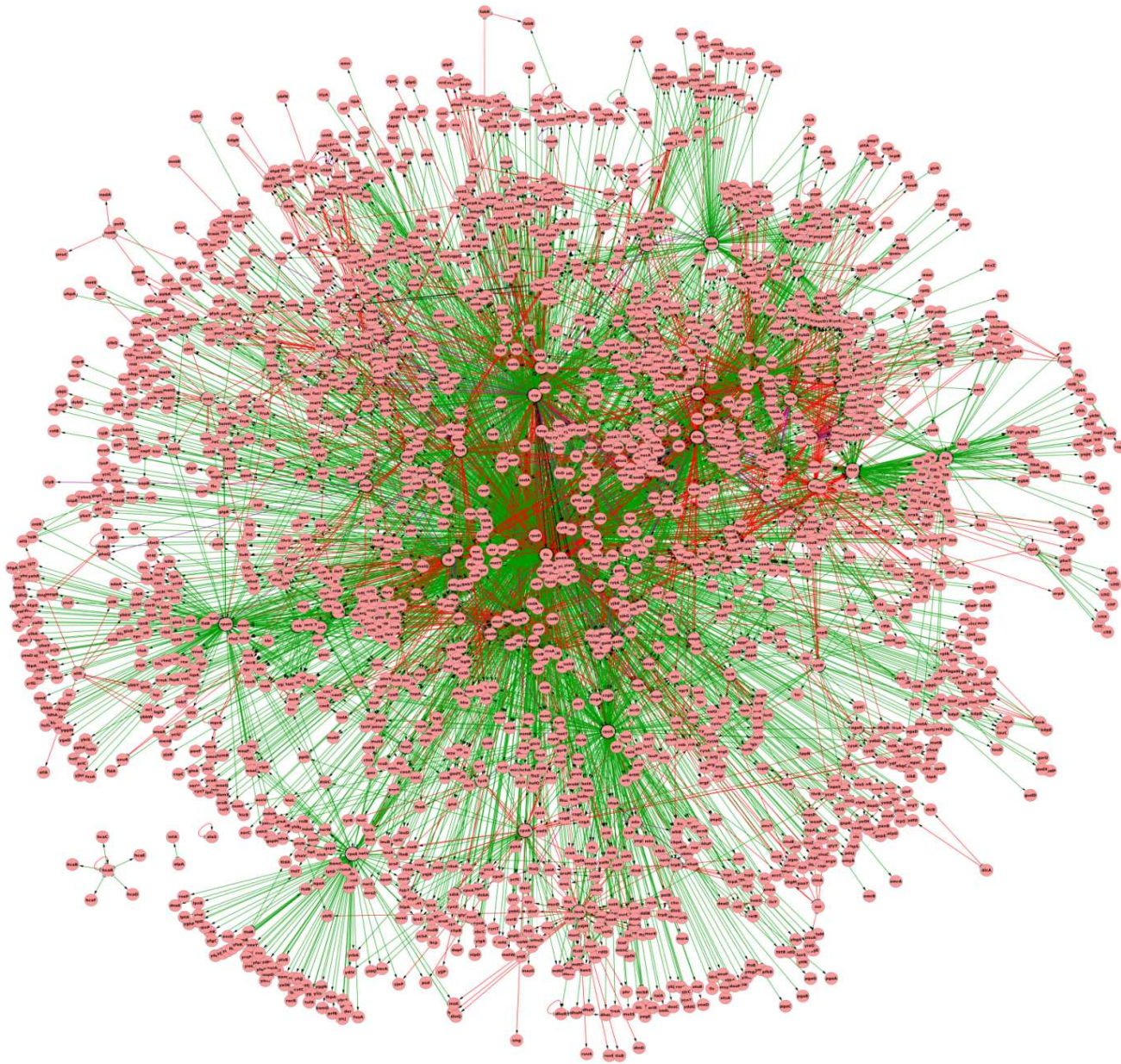
# The dynamical system with (genetic) feedback loops



- Construct a discrete dynamical system on this graph using logical rules for each regulated node

Result:

- The attractors of this system for all environmental conditions considered are fixed points.
- For a given environmental condition, the fixed point attractor is independent of the initial conditions of the genes and the corresponding proteins (global attractor)



The 'whole' seems to have design principles of its own that are not visible by studying the parts themselves or even modules consisting of a few parts, but are only apparent upon integrating the subsystems into a sufficiently large system

# An illustration of the rules

fnr =

2: RpoD > 0 AND Fnr = 0;

1: RpoD > 0 AND Fnr > 0;

0

IF RpoD is active AND Fnr transcription factor is not active, the level of activation will be 2;

ELSEIF RpoD is active, AND Fnr transcription factor is active, it will be 1;

ELSE it will be 0.

FNR =

2: fnr = 2 AND Oxygen = 0;

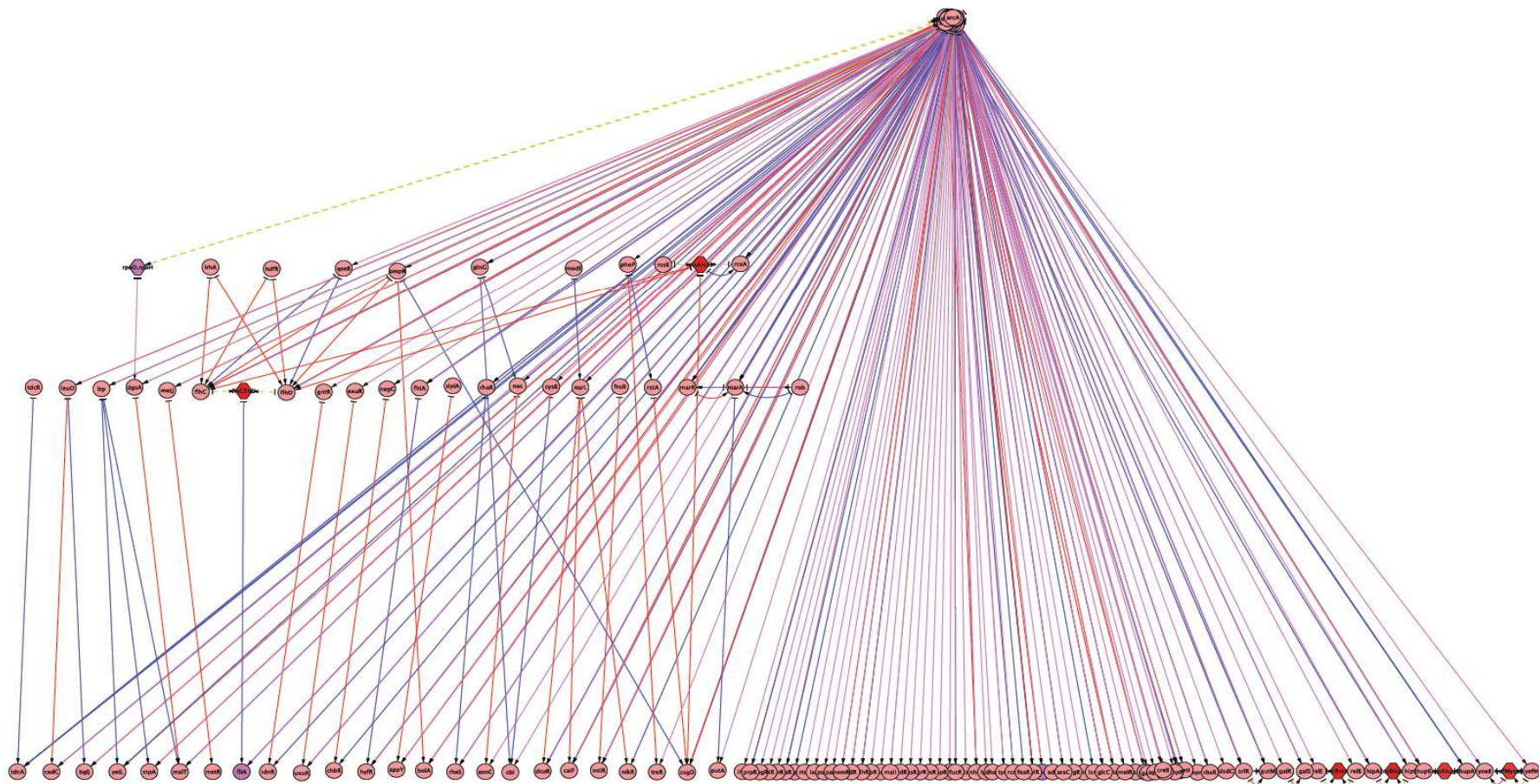
1: fnr = 1 AND Oxygen = 0;

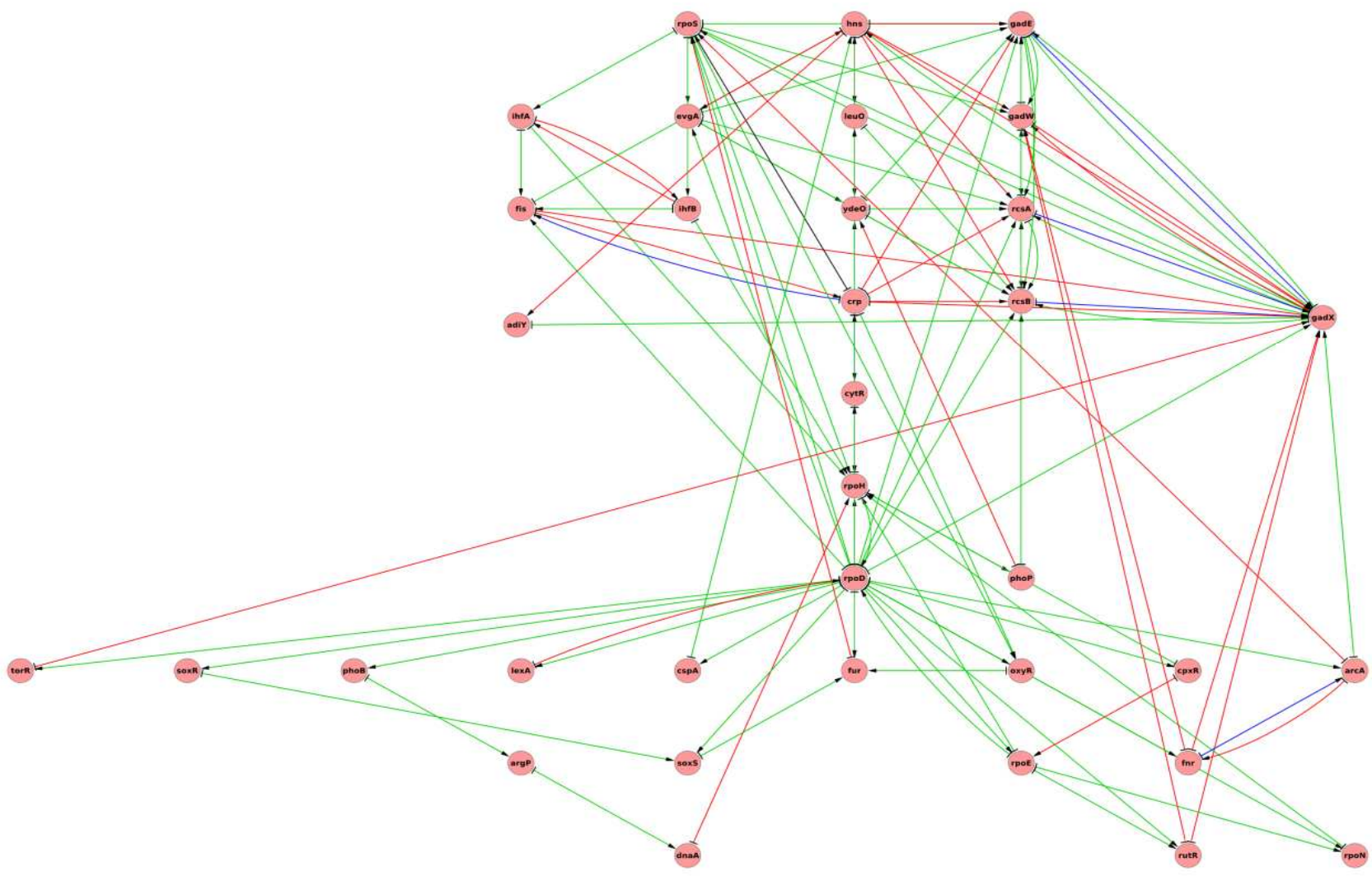
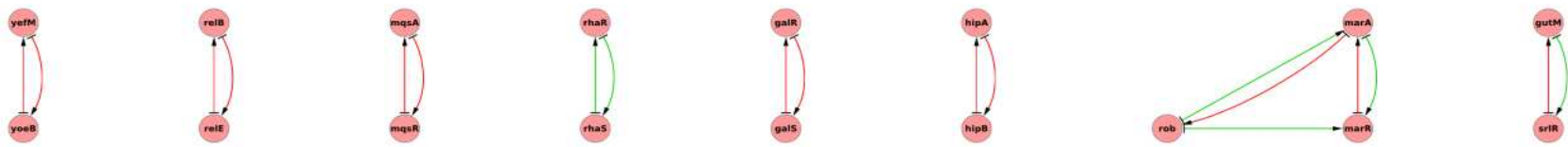
0

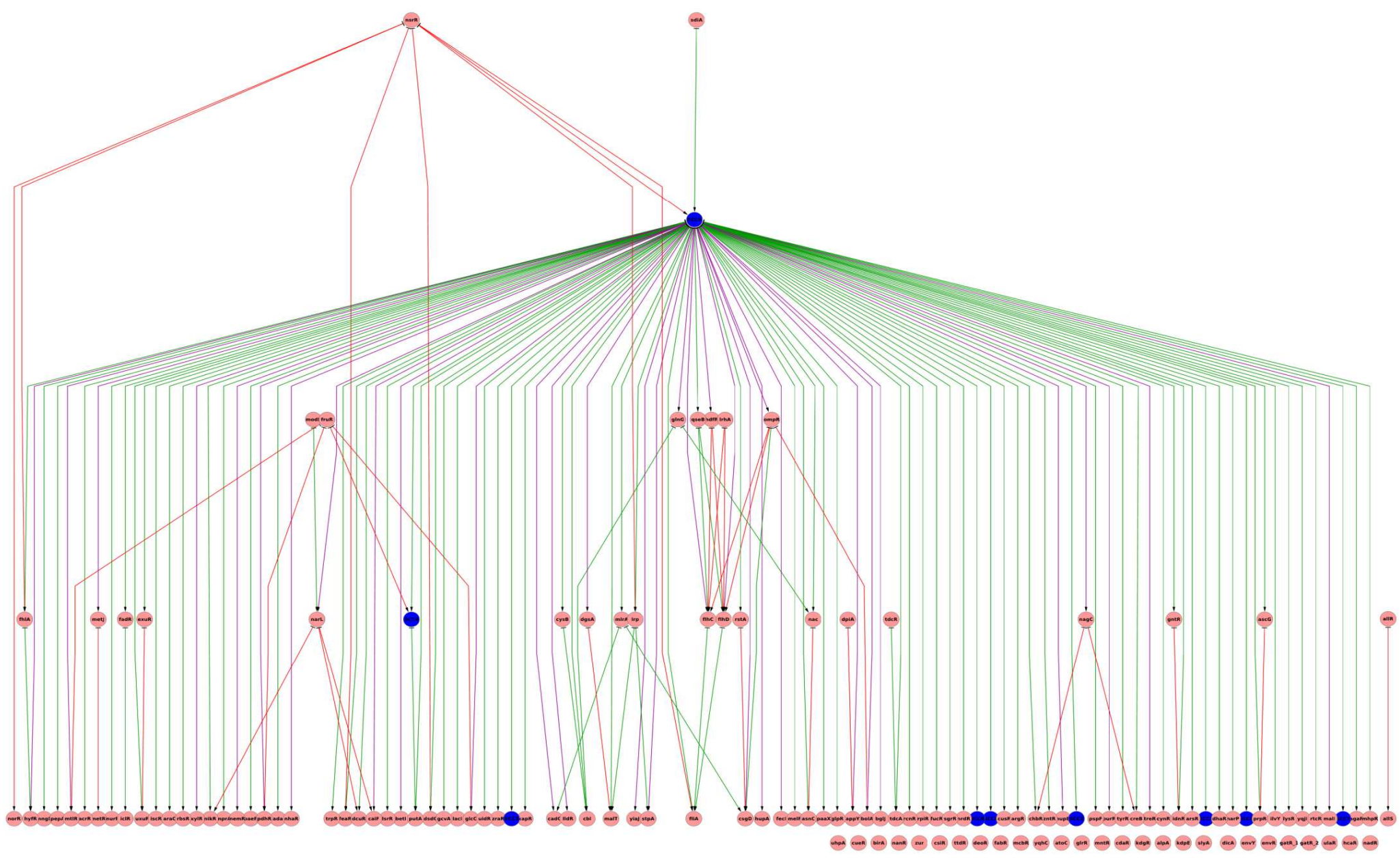


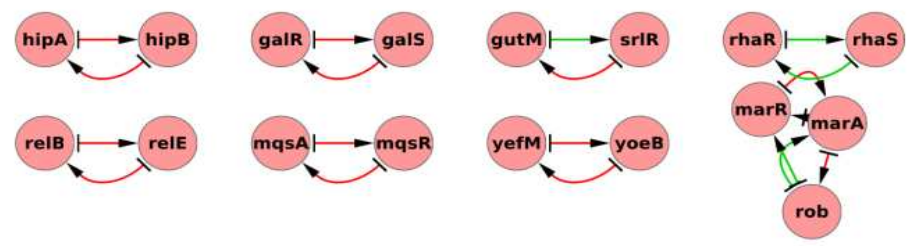
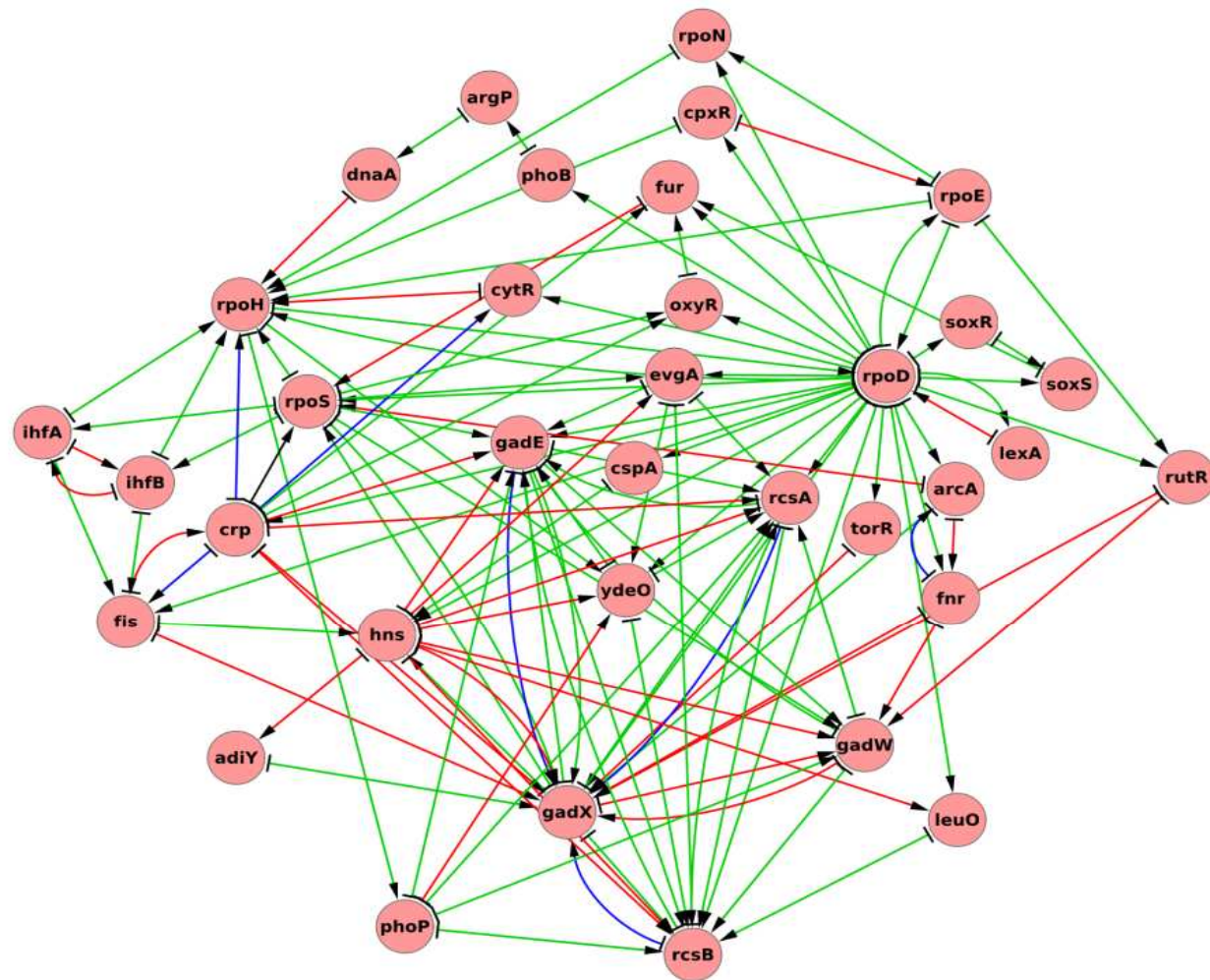
# Results

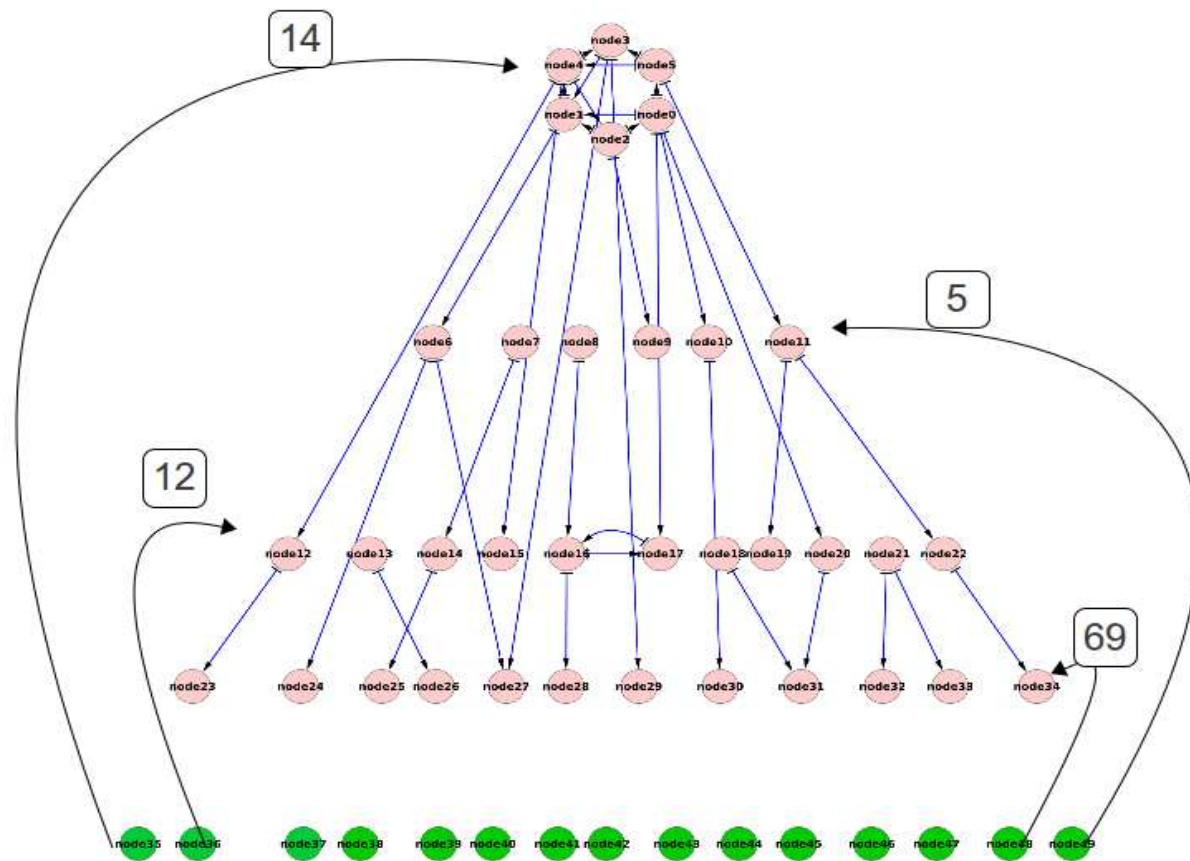
- ◆ The attractors of this system for all environmental conditions considered are again fixed points.
- ◆ For a given environmental condition, the fixed point attractor is independent of the initial conditions of the genes and the corresponding proteins.











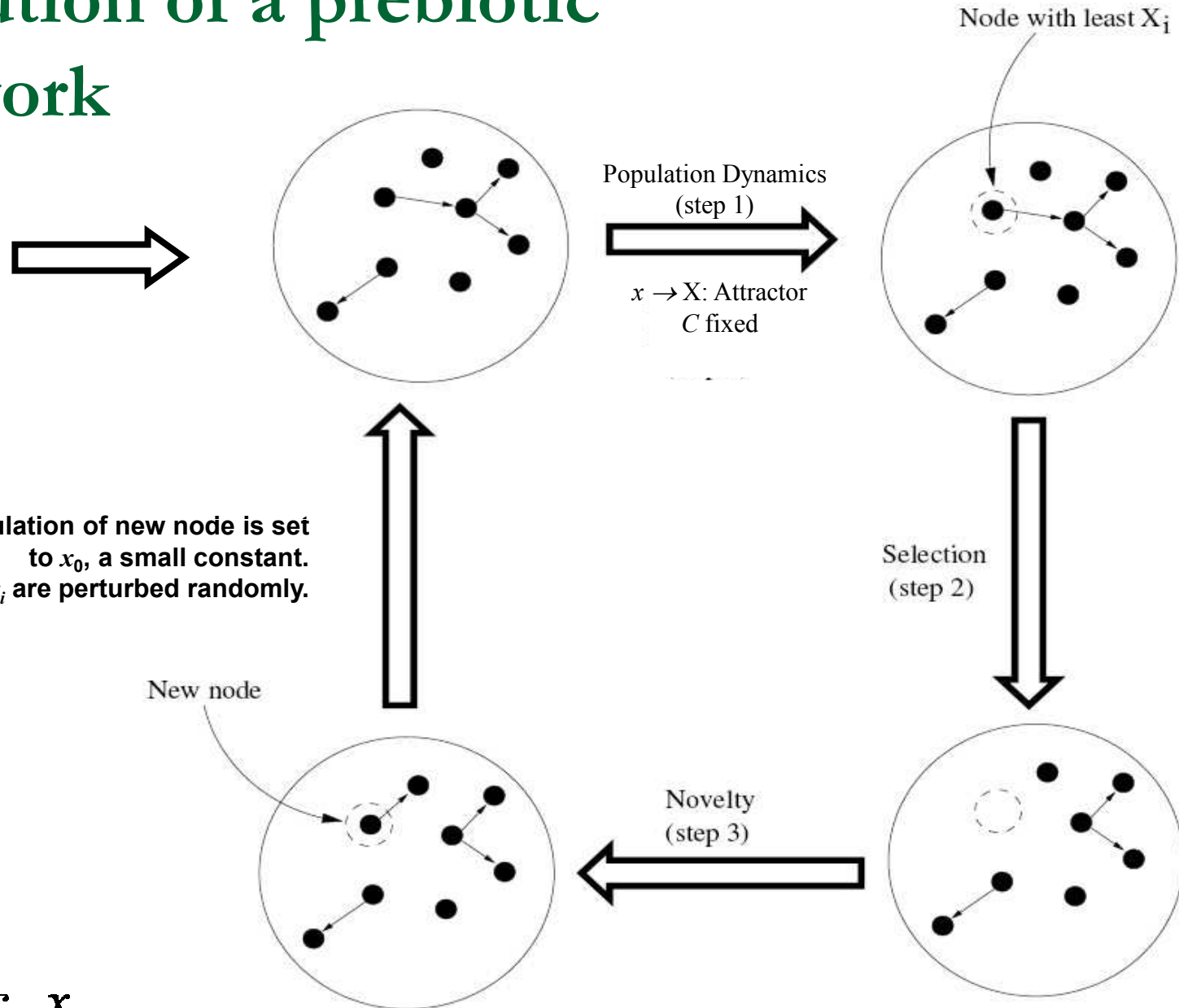
# Model of evolution of a prebiotic chemical network

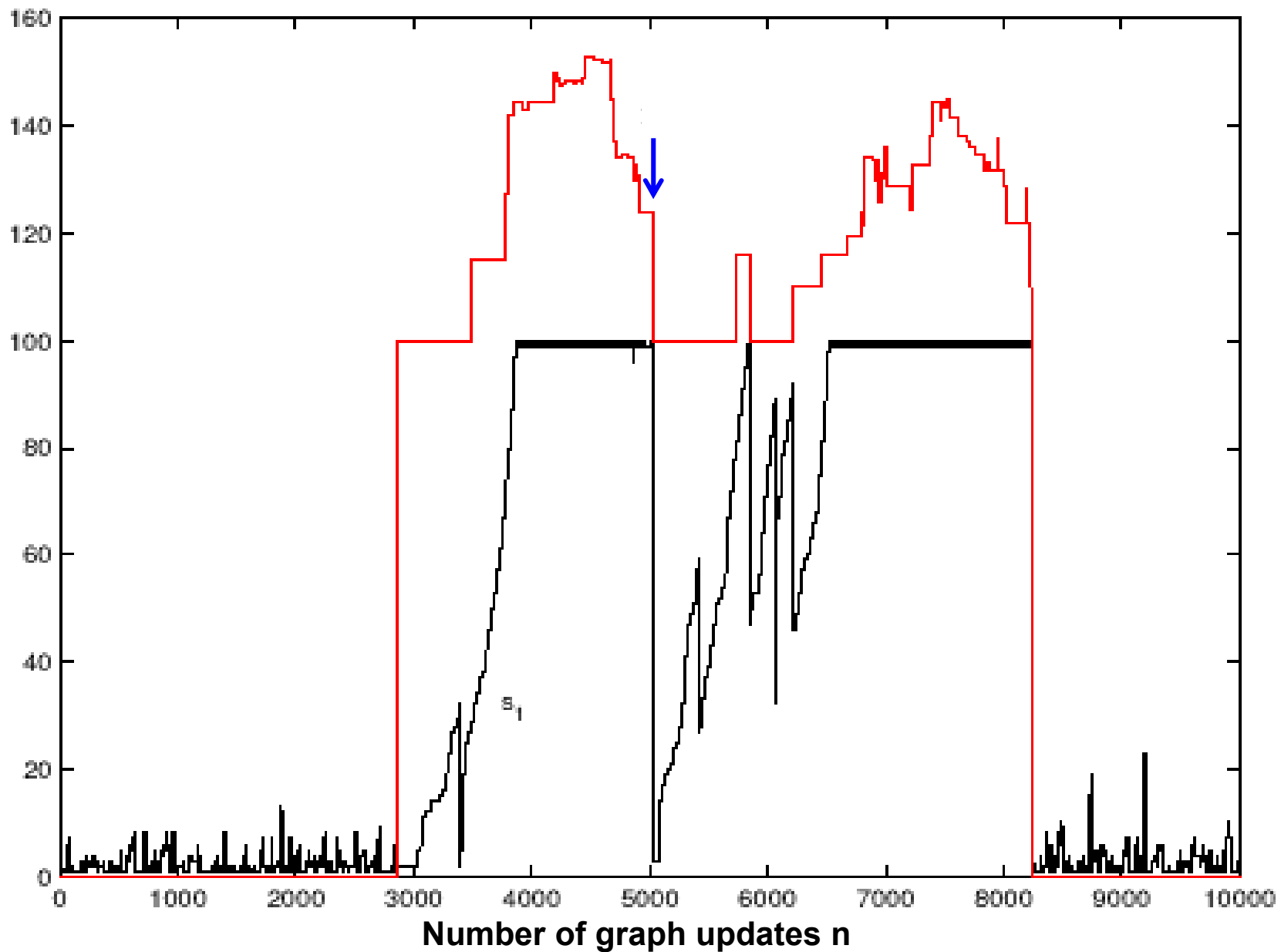
## Initialization:

$C_{ij} = 1$  with probability  $p$ ,  
 $C_{ij} = 0$  with probability  $1-p$   
 $p$  is the “catalytic probability”.  
 $x_i$  are chosen randomly.

Relative population of new node is set  
 to  $x_0$ , a small constant.  
 All other  $x_i$  are perturbed randomly.

$$\frac{dx_i}{dt} = \sum_{j=1}^s c_{ij} x_j - x_i \sum_{j,k=1}^s c_{jk} x_k$$

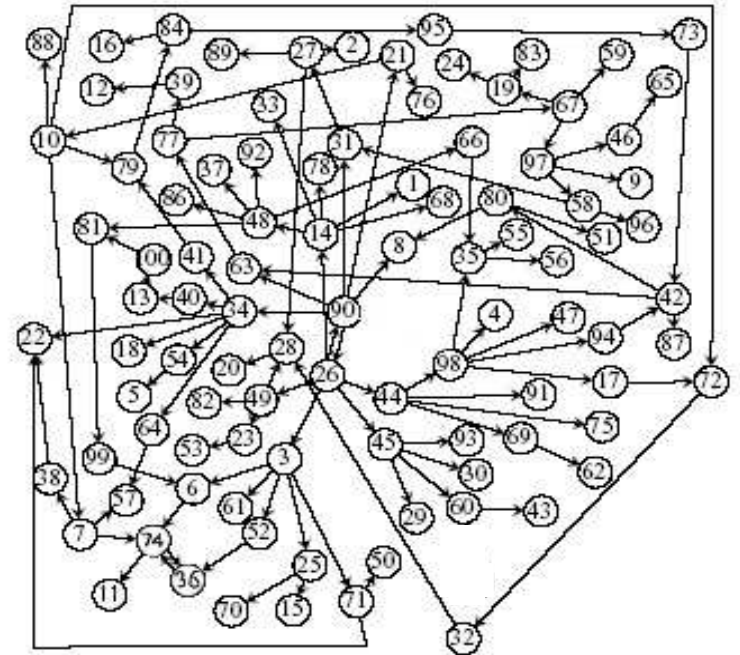
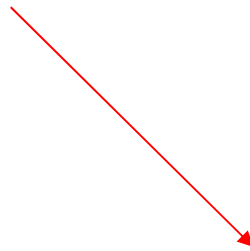
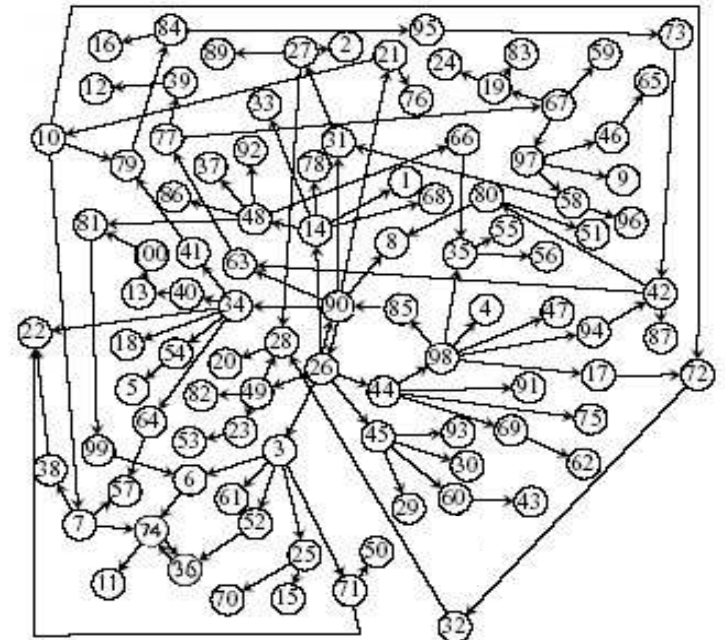
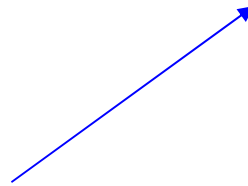
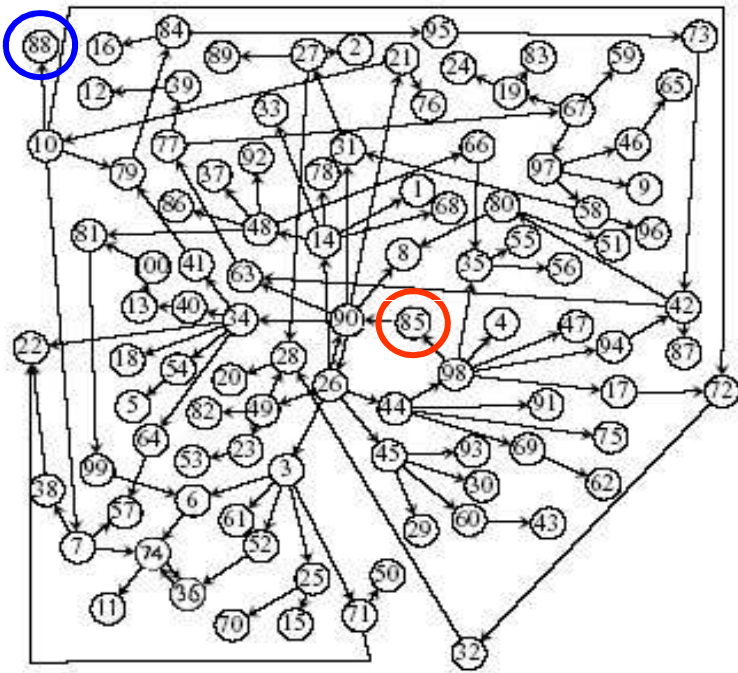




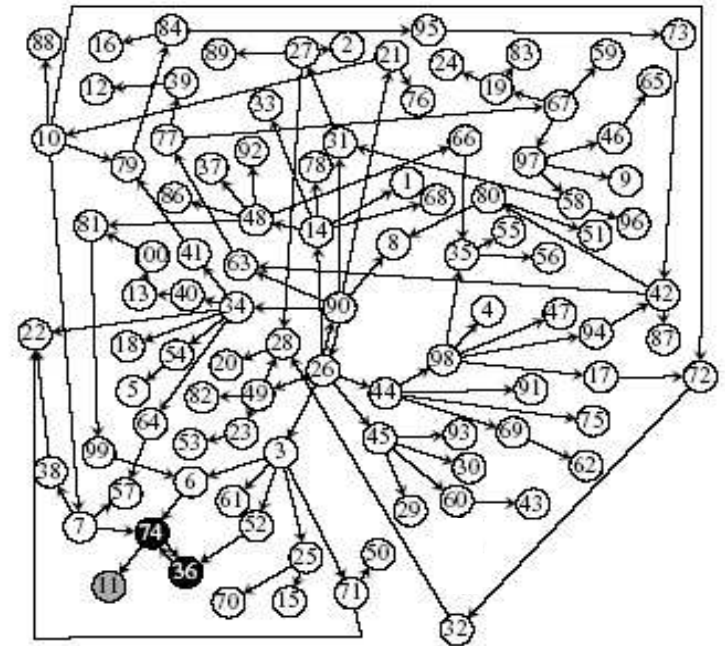
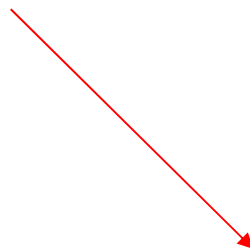
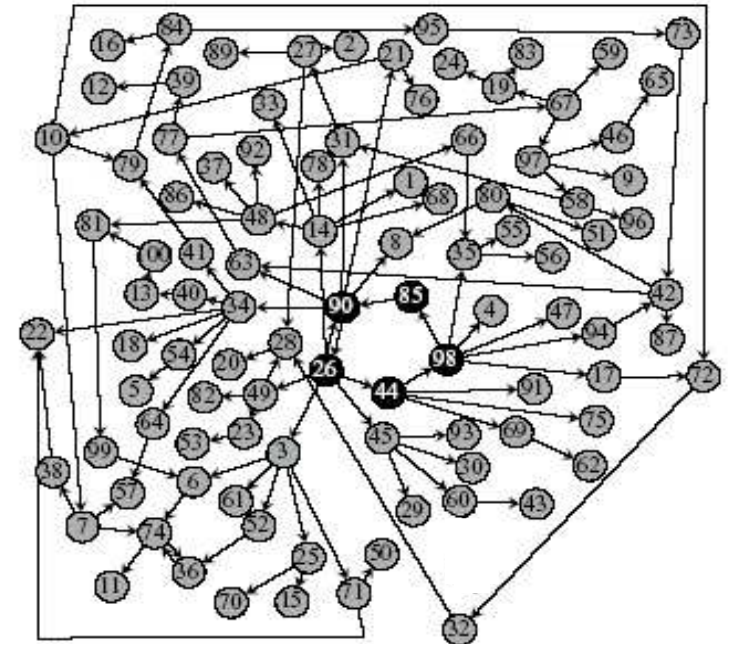
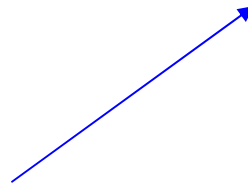
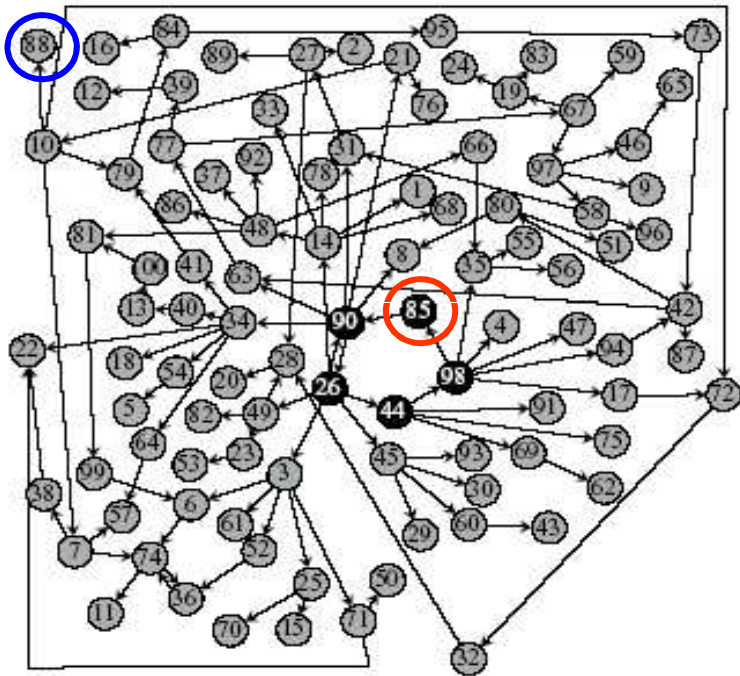
Black curve: Number of nodes with relative populations  $> 0$   
Red curve: Perron-Frobenius eigenvalue of the graph



# Comparing two small changes in a graph



# Comparing two small changes in a graph



**Fragility and Crash**

# Dynamical rules

1. Keeping  $C$  fixed, let the relative populations  $\mathbf{x}$  change with time according to

$$\frac{dx_i}{dt} = \sum_{j=1}^s c_{ij} x_j - x_i \sum_{j,k=1}^s c_{jk} x_k \quad (\text{catalytic dynamics})$$

$c_{ij} = 1$  if molecule  $j$  is a catalyst for the production of molecule  $i$   
 $= 0$  otherwise

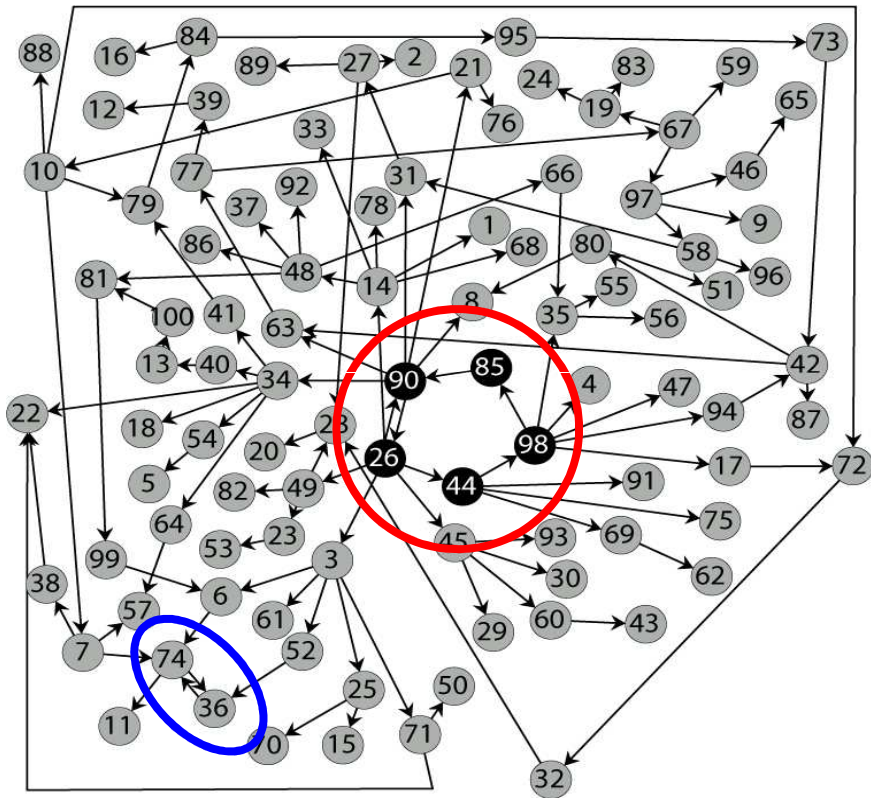
Let the populations reach a steady state (attractor is a fixed point, and is an eigenvector of  $C$  corresponding to its largest eigenvalue – Perron Frobenius eigenvalue)

2. Now change  $C$

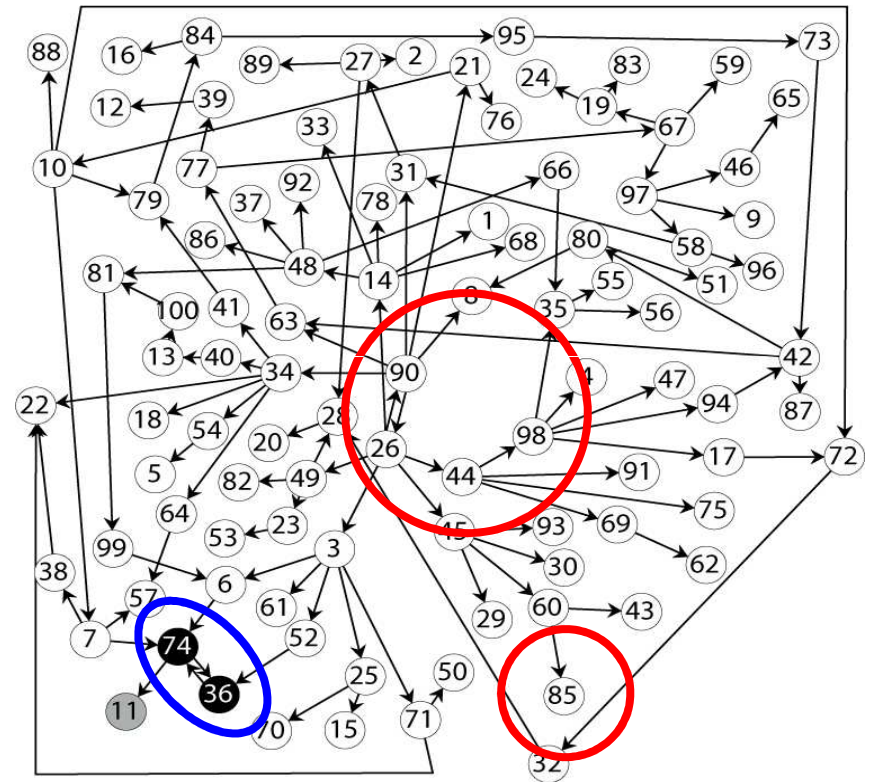
- (a) Remove the node with the least population along with all its links (selection; tide washes out the least populated molecular species)
- (b) Introduce a new node whose connections to the existing nodes are made randomly with prob  $p$  (introduction of novelty; tide brings in a new molecule)

3. Iterate steps 1 and 2

n = 5041

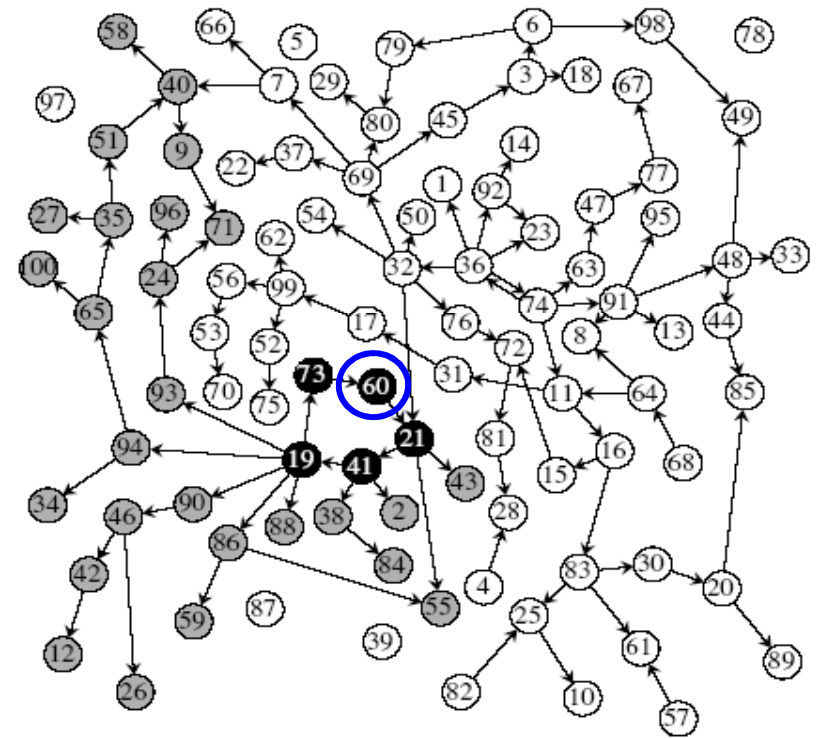
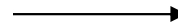
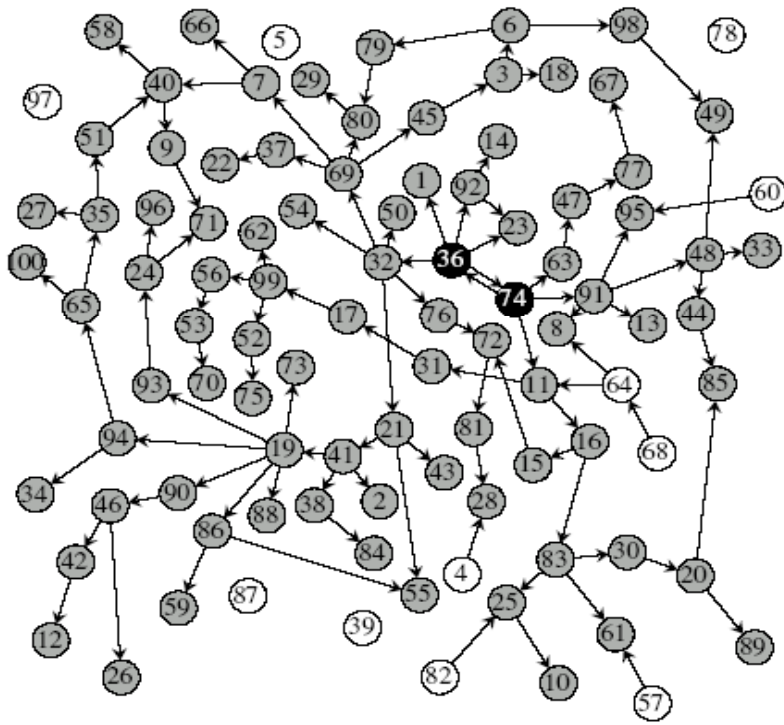


n = 5042



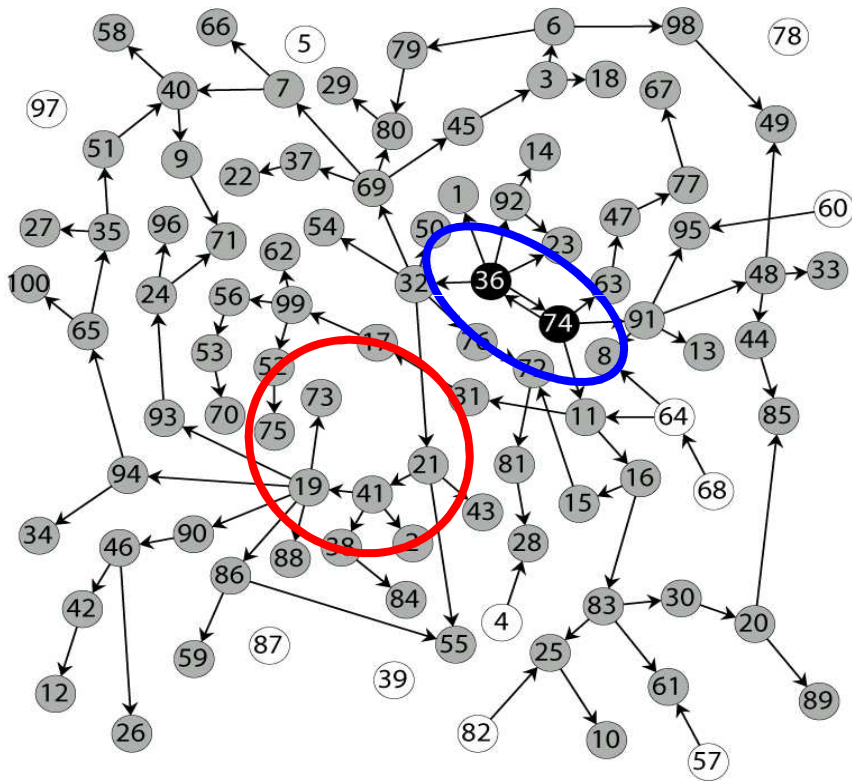
Core shift: Takeover by a dormant innovation (Creative Destruction Type 2)  
The flourishing of dormant phyla after the Permian extinction.

# Effect of a single new node

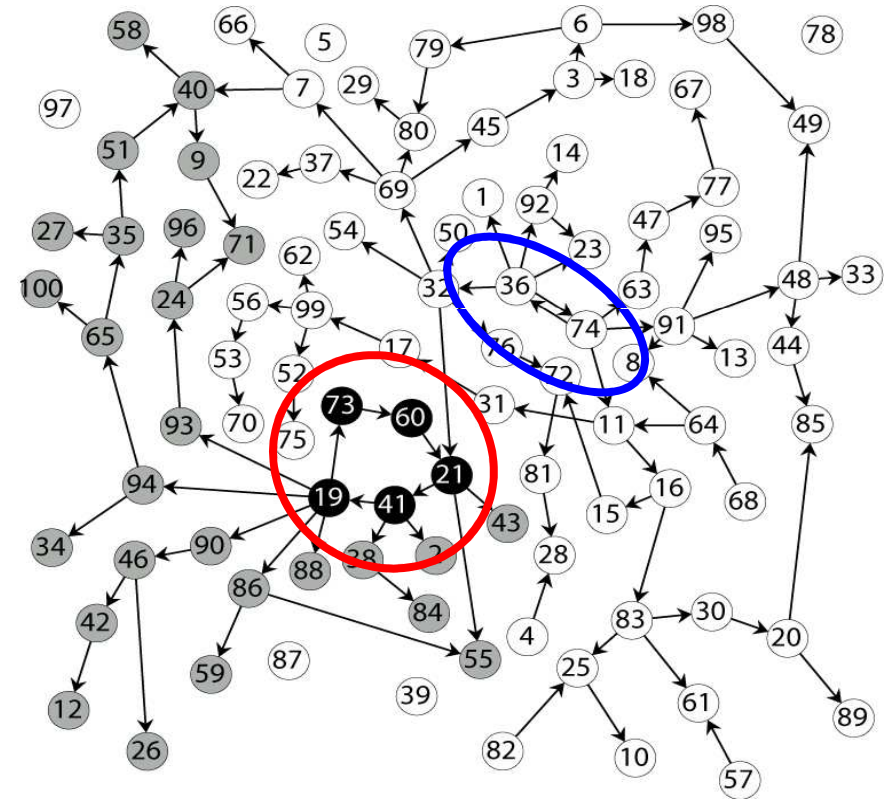


Innovation

n = 6061



n = 6062



Another example of a core shifting innovation (Creative Destruction Type 1)  
The automobile causes the demise of the horse drawn carriage industry

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# Main points

- Thinking about the whole in biology, starting from the parts, can reveal new design principles.
- A manageable theory of the whole will require coarse-graining. Otherwise there are too many degrees of freedom.
- The coarse graining must be such that the sensitivity to some of the microscopic parts is retained at the level of the whole. This is necessary to capture the most interesting aspects of evolution.
- A methodology: starting from the study of network structure and dynamics, and connecting it with evolution.