An evolutionary and functional assessment of regulatory network motifs

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Research

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Abstract

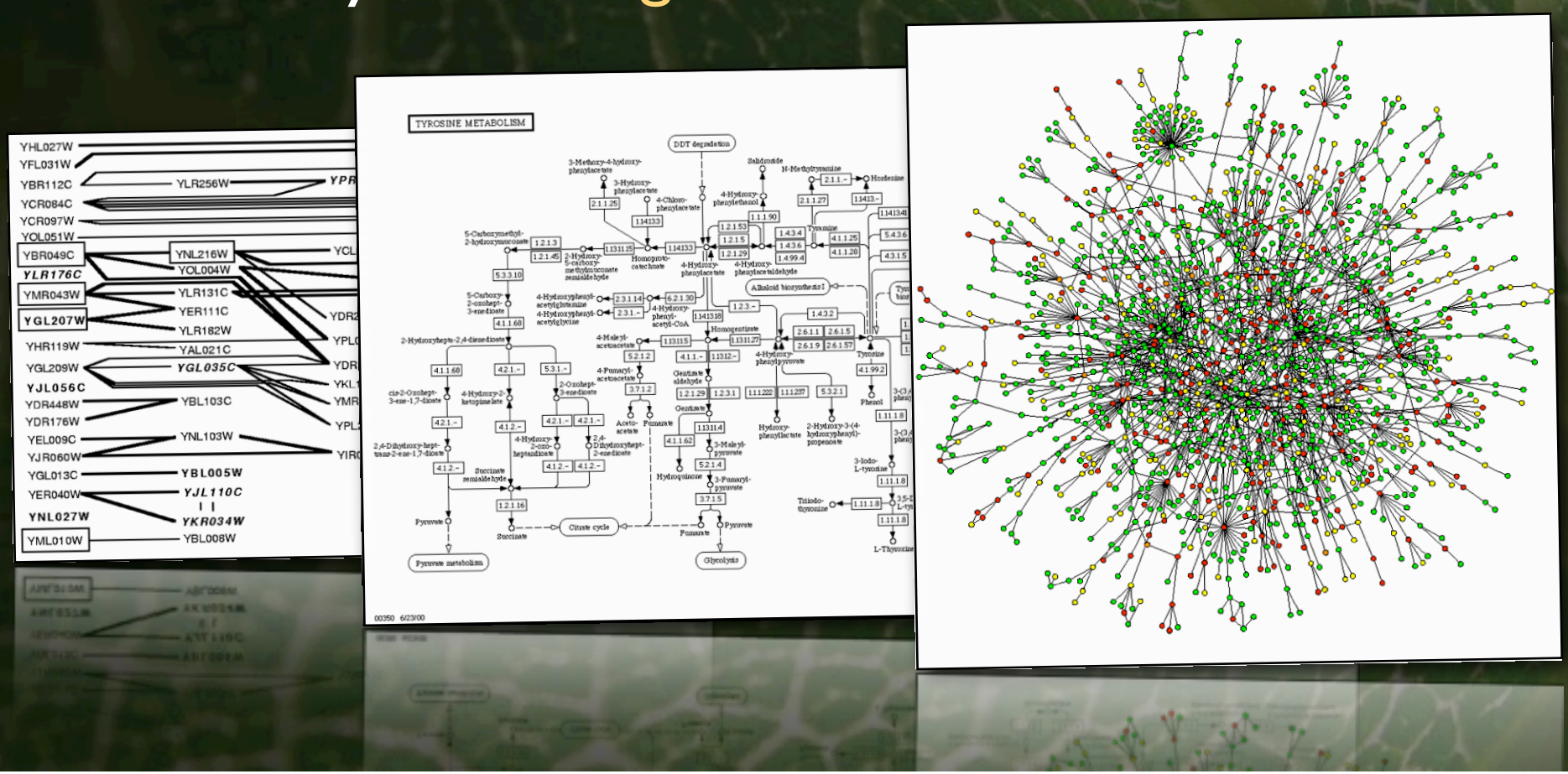
Background

Cellular functions are regulated by complex webs of interactions that might be schematically represented as networks. Two major examples are transcriptional regulatory networks, describing the interactions among transcription factors and their targets, and protein-protein interaction networks. Some patterns, dubbed motifs, have been found to be statistically over-represented when biological networks are compared to randomized versions thereof. Their function *in vitro* has been analyzed both experimentally and theoretically, but their functional role *in vivo*, that is, within the full network, and the resulting evolutionary pressures remain largely to be examined.

http://oenone.net/papers

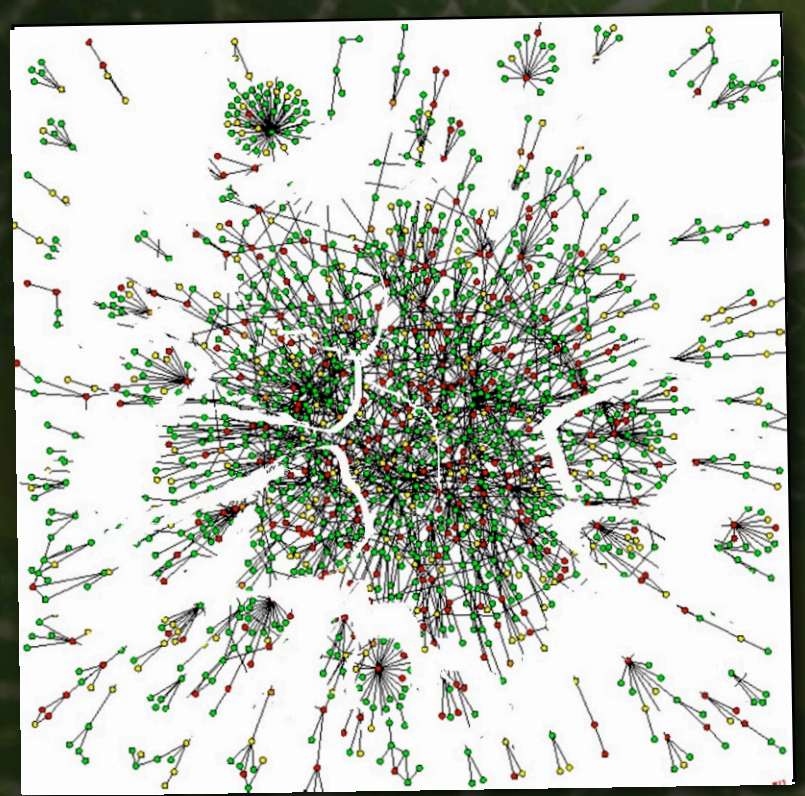
Biological Network are Complex

They have a non-random topology.
They are resistant to random damages.
They are resistant to noise.
They are ... huge.



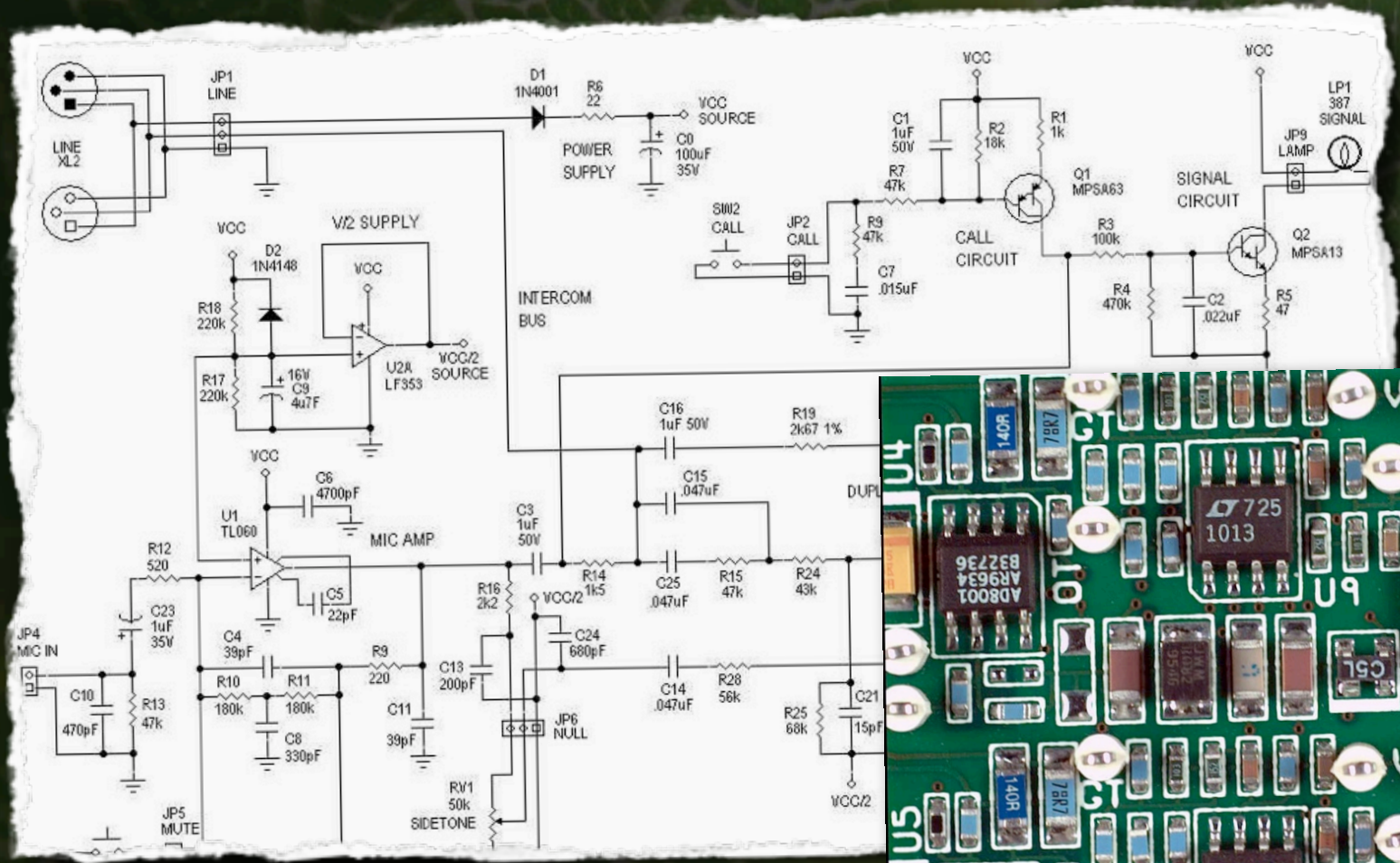
How to deal with them?

Reductionist approach: let's decompose them into tractable smaller elements.



Two approaches: motifs and modules.

Network Motifs

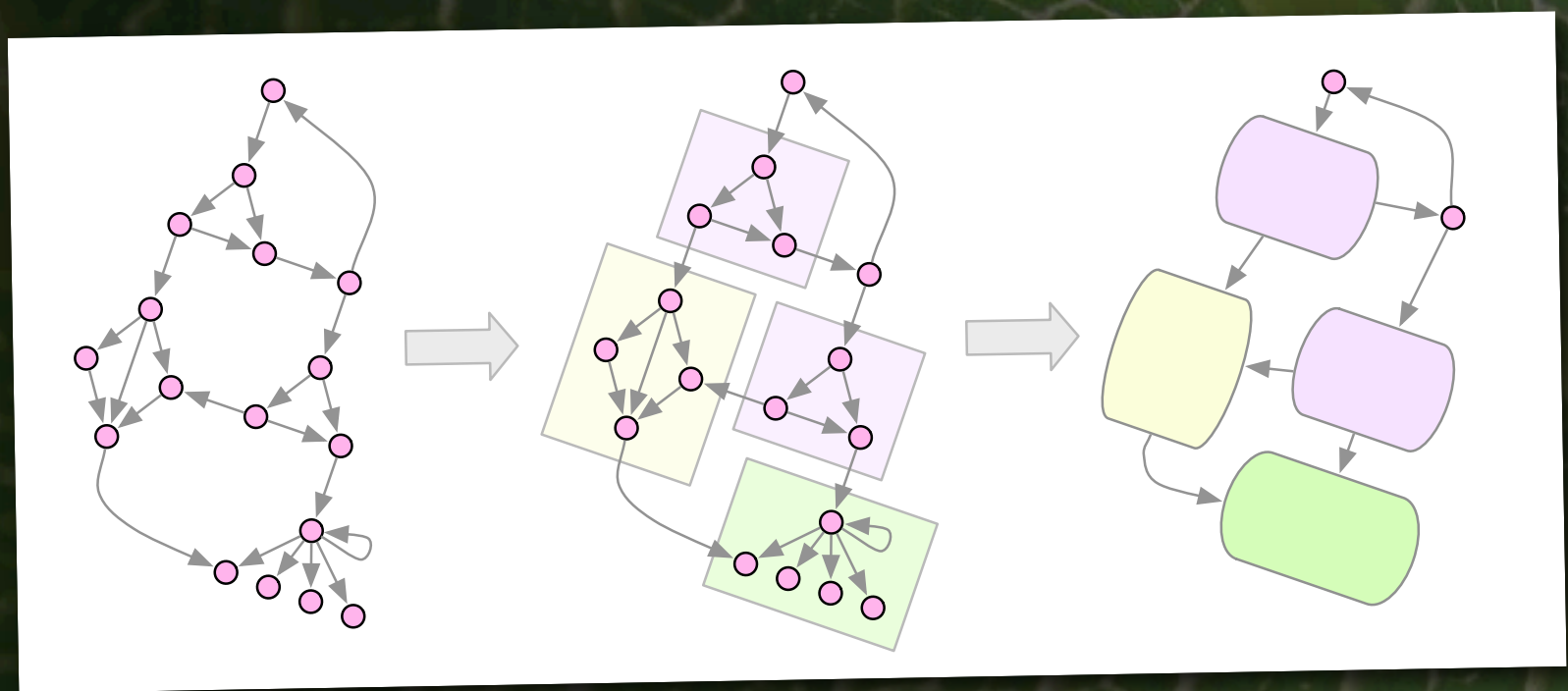


Engineering

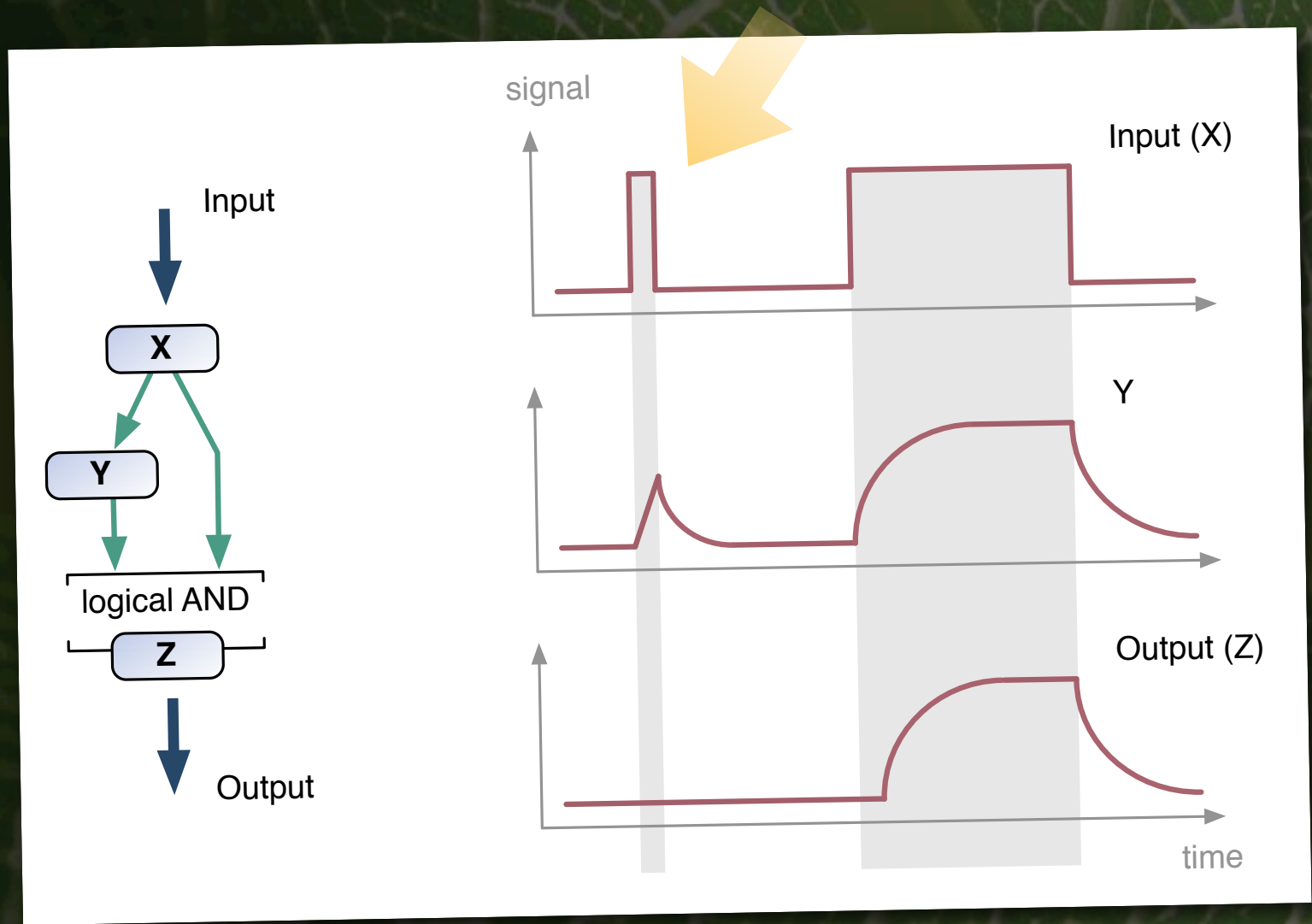
Repetitive structure = Given task of signal processing

What about biological networks?

- 'Signal' could be gene activity level
- 'Circuits' could be gene regulatory networks

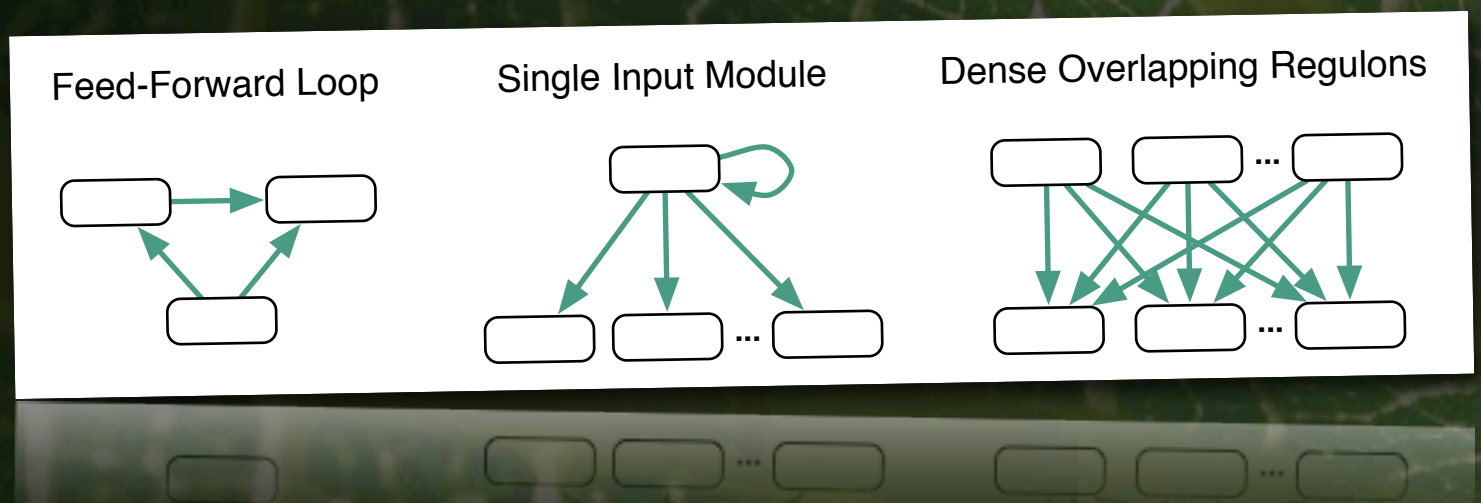


Candidate: the feed-forward loop

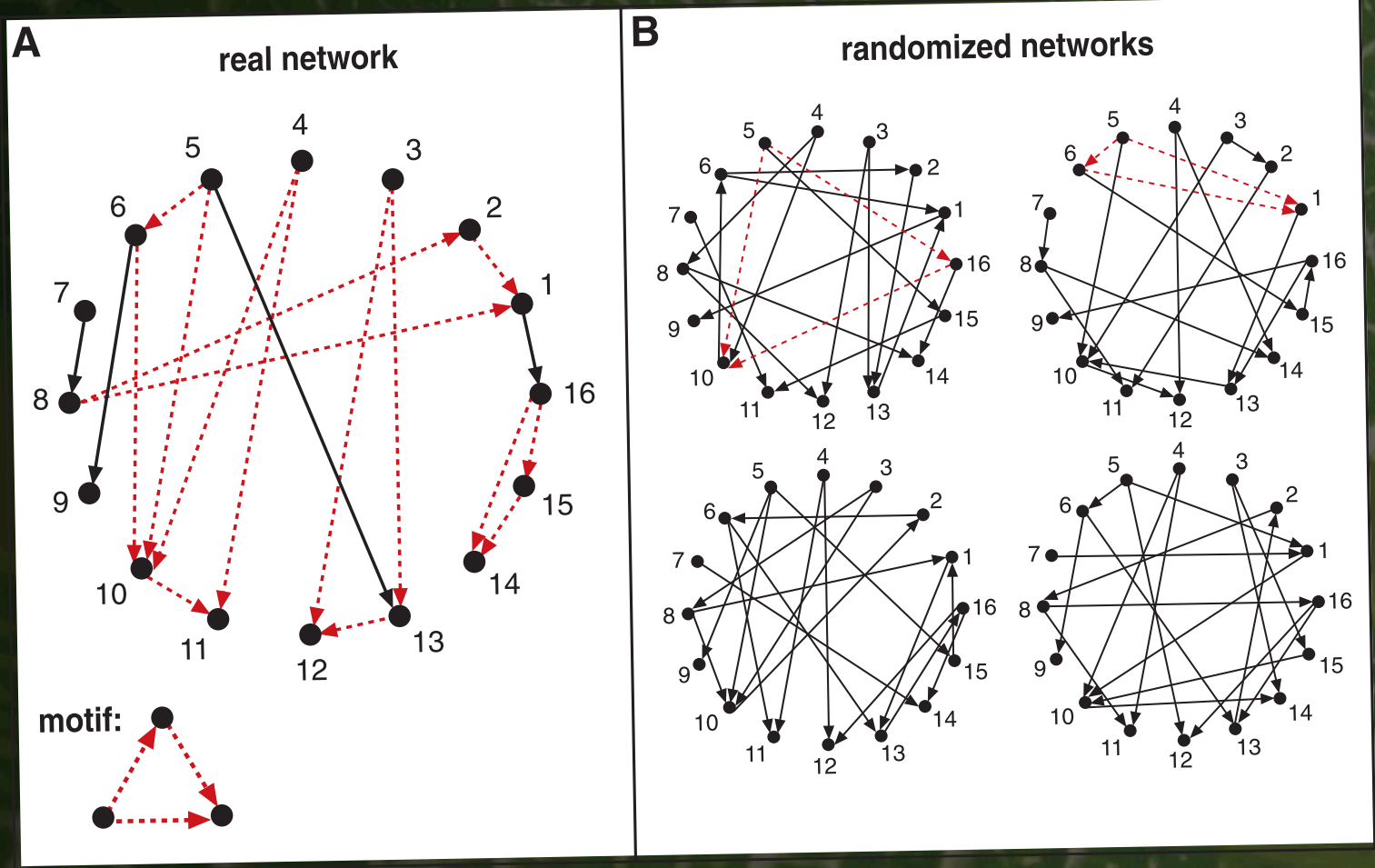


Repeated subgraphs have been found

- In gene regulatory networks
- In protein interaction networks



They are over-represented when compared to randomized networks.


A
real network
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
motif:
B
randomized networks

Simple and intuitive hypothesis of how biological networks are structured to process information.

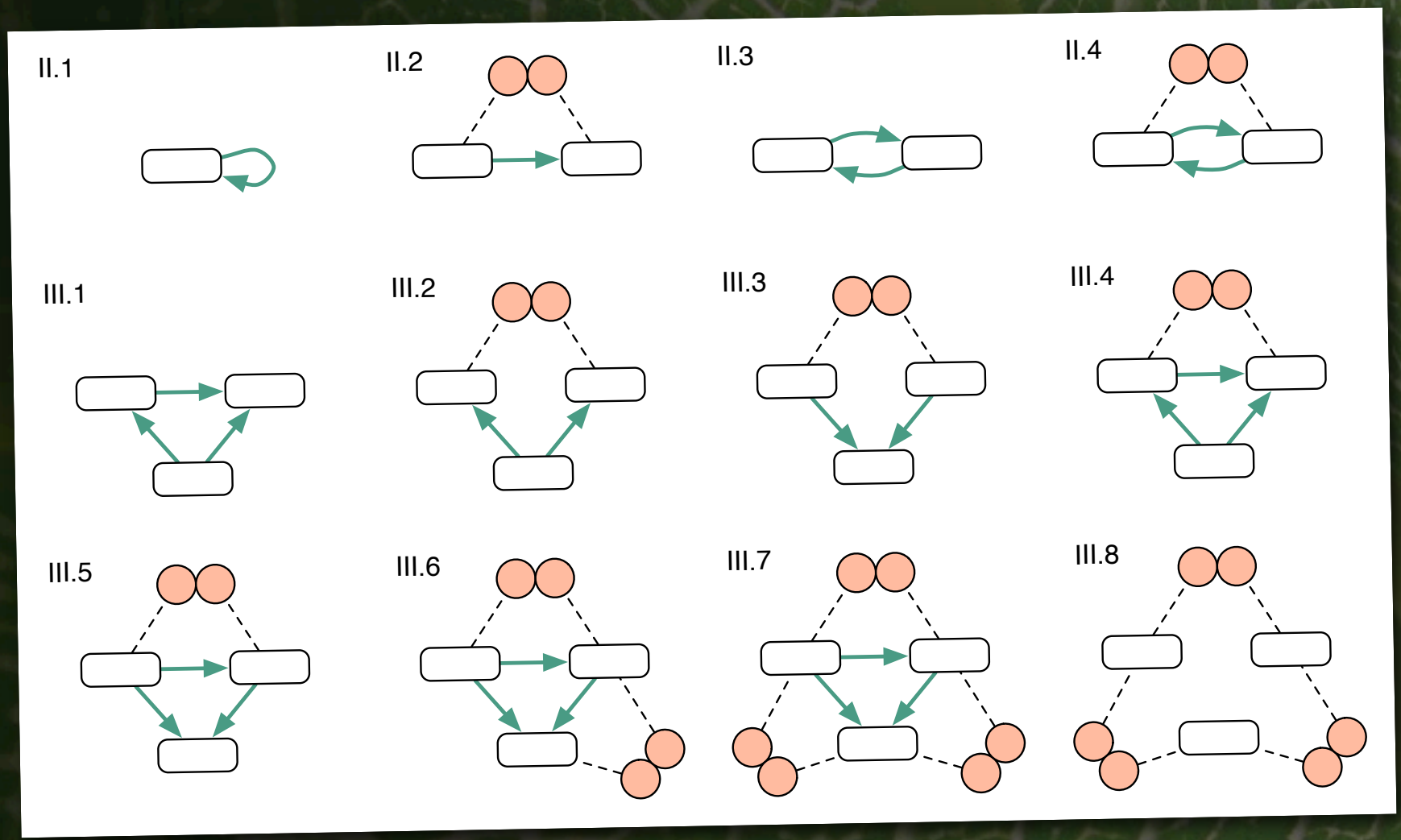
Detailed dynamic models of motifs have been proposed *in silico* (mainly FFLs).

Numerous algorithms have been proposed to efficiently search for motifs in any network.

But ...

Are they real building blocks of biological systems? Are motifs biologically relevant?

Step 1: Identification of 'rich' network motifs

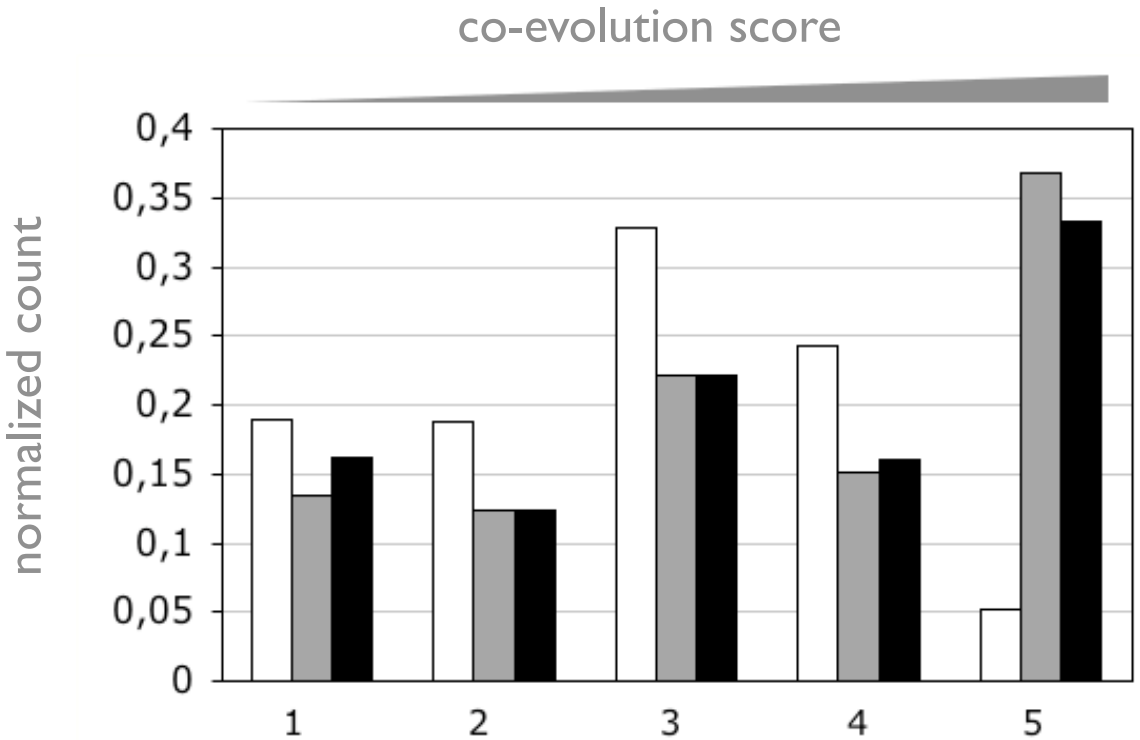


Step 2. Phylogenetic study

Biologist's claim:

Functional interactions between genes should correspond to a selective pressure that preserves this interaction.

Evaluation in five yeast species.



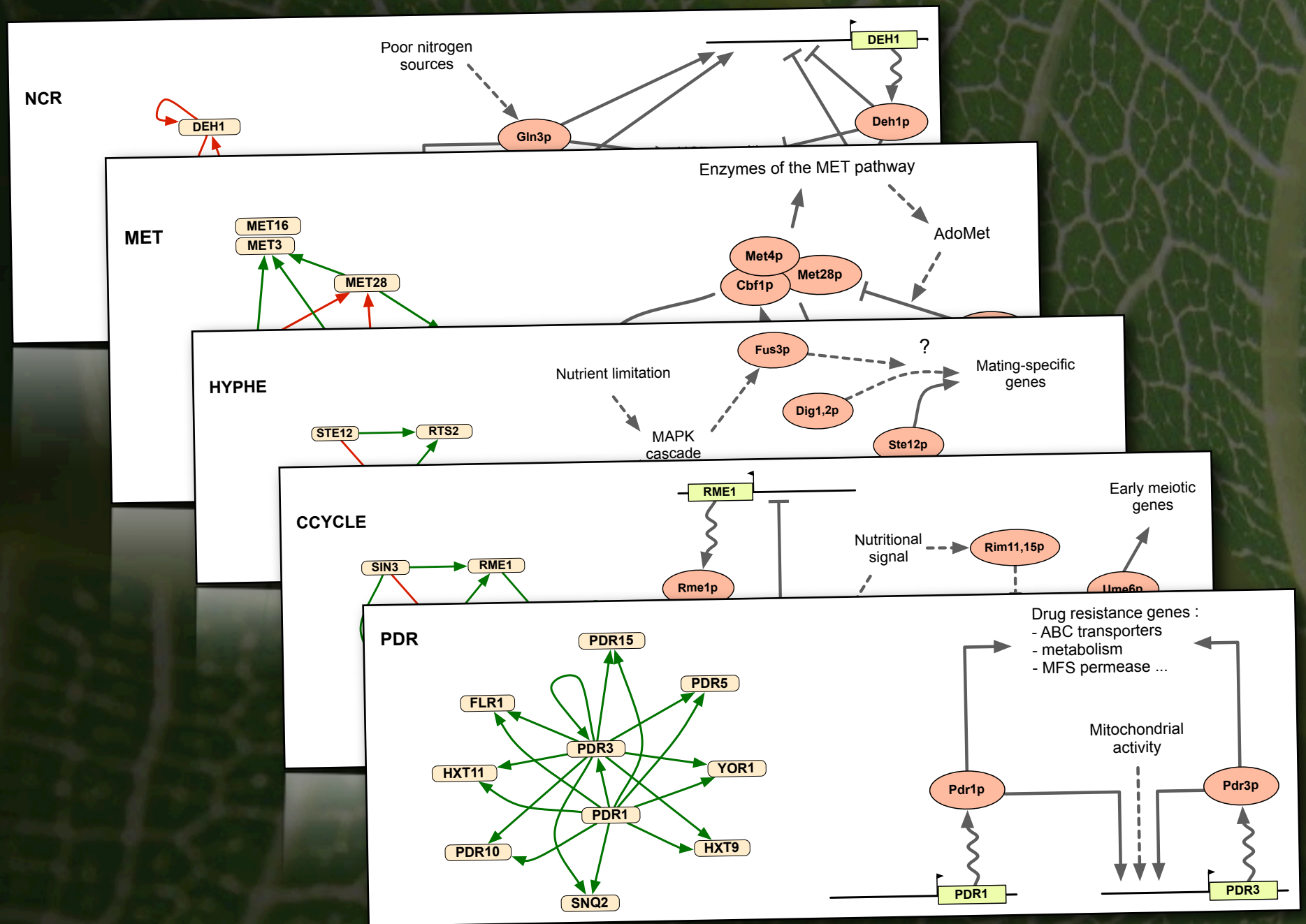
	1	2	3	4	5
random triples	1888	1884	3280	2428	521
linked genes triples	1337	1229	2212	1513	3669
motifs	78	59	106	77	160

Step 3. Functional study

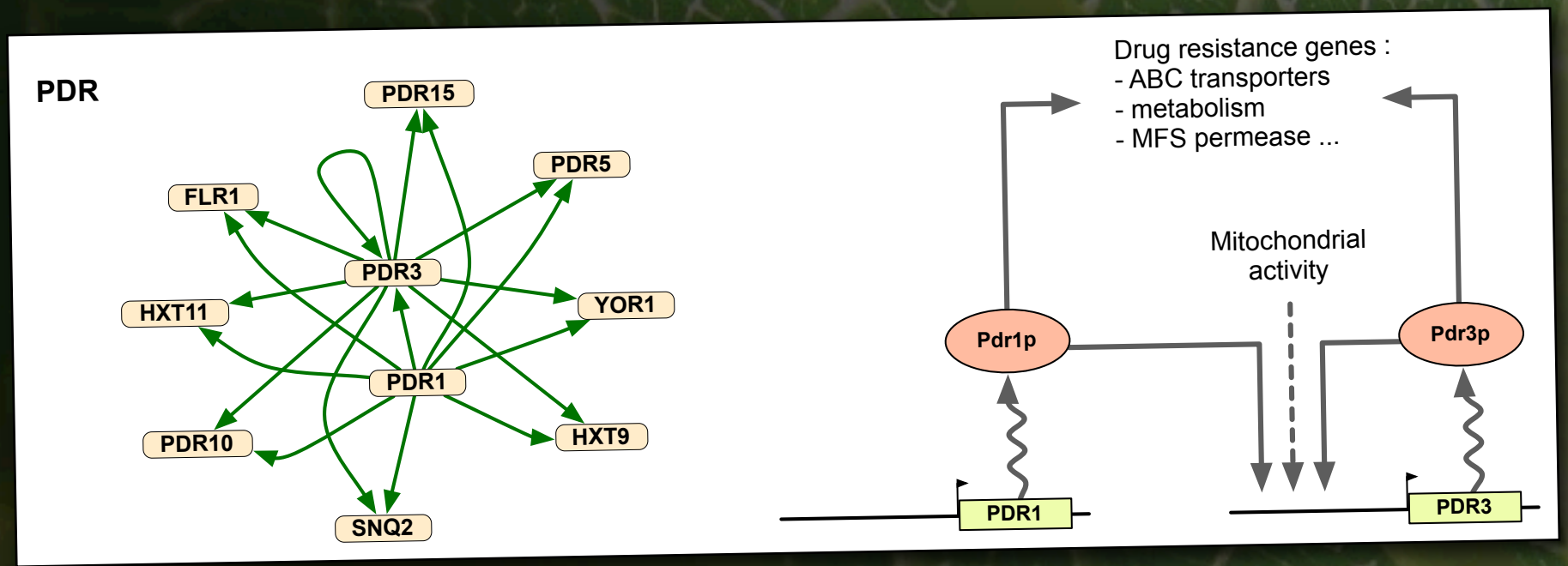
Biologist's claim:

Identified motifs instances must play a key role in the regulation of biological processes.

Evaluation in five well known systems.


NCR
Poor nitrogen sources
DEH1
Gln3p
DEH1
Deh1p
MET
MET16
MET3
MET28
Enzymes of the MET pathway
AdoMet
Met4p
Cbf1p
Met28p
HYPHE
Nutrient limitation
Fus3p
?
Mating-specific genes
Dig1,2p
Ste12p
MAPK cascade
STE12
RTS2
CCYCLE
RME1
Early meiotic genes
Nutritional signal
Rim11,15p
SIN3
RME1
Rme1p
PDR
PDR15
PDR5
FLR1
PDR3
YOR1
HXT11
PDR1
PDR10
HXT9
SNQ2
Drug resistance genes :
- ABC transporters
- metabolism
- MFS permease ...
Mitochondrial activity
Pdr1p
Pdr3p
PDR1
PDR3

Pleiotropic drug resistance system



- Pdr1 and Pdr3 respond to different signals
- They're never active at the same time
- No evidence of cooperativity on the targets

> These motifs do not exist in practice.

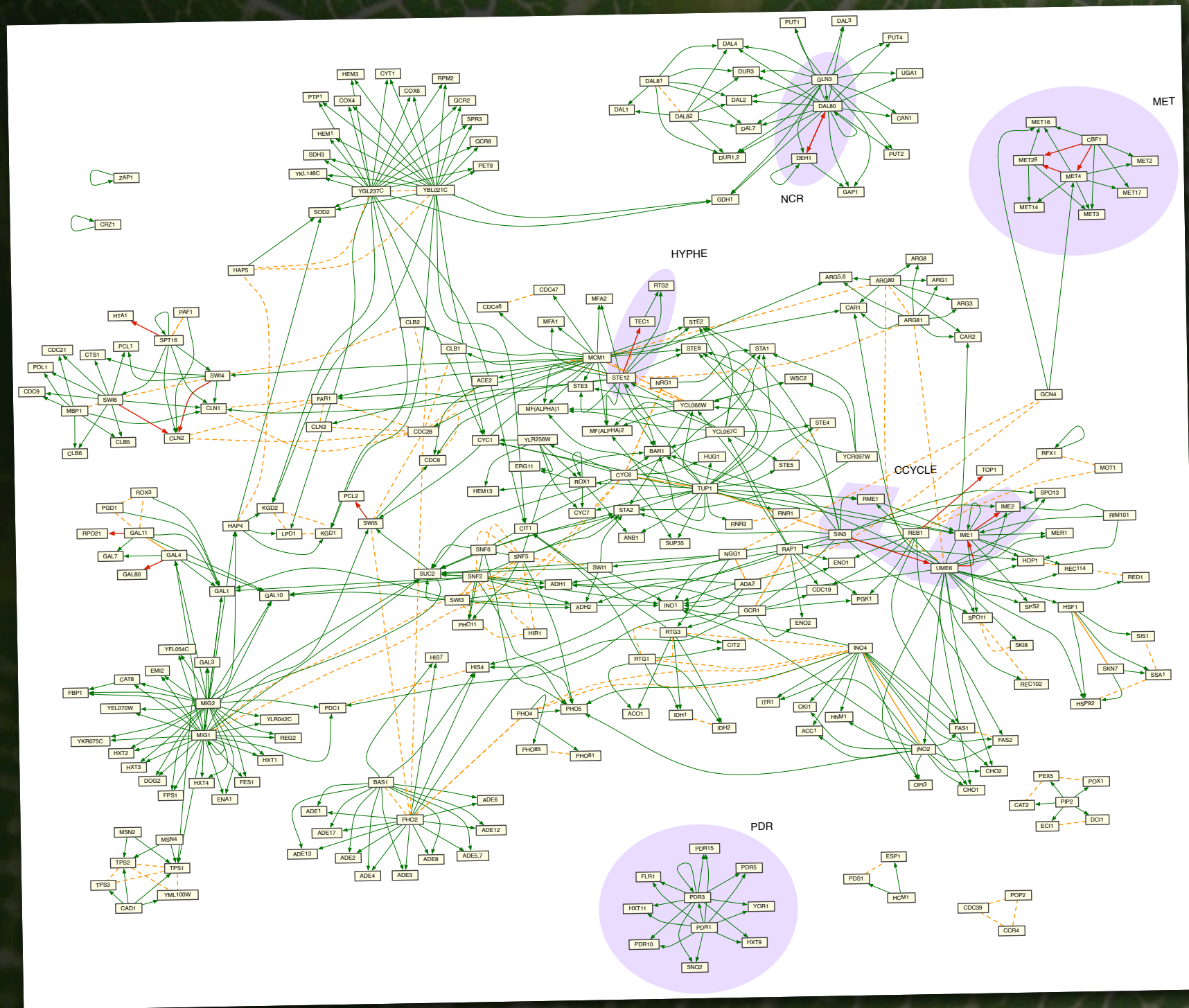
Biases 1 & 2

Most network representations don't distinguish linear from non-linear interactions

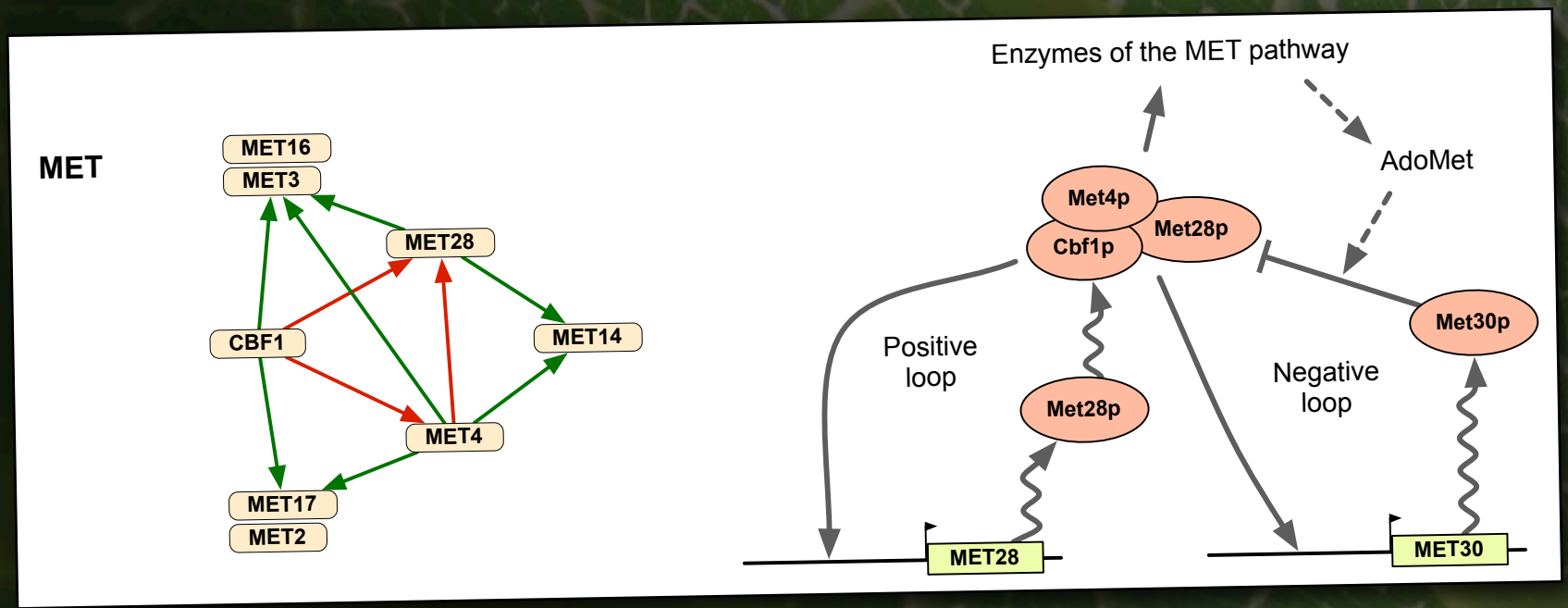
- *pdr1 and pdr3 don't cooperate on their targets*

Network motifs do not exist in isolation

- *pdr3 have its own regulation schedule, which destroy any property these FFL could have*


NCR
HYPHE
MET
CCYCLE
PDR
GLN3
DAL80
YGL237C
YBL021C
MCM1
STE12
TUP1
SIN3
REB1
IME1
UME6
INO4
INO2
PHO2
BAS1
MIG1
MIG2
SWI6
SWI4
SWI5
SWI3
SWI1
SUC2
SNF2
SNF6
SNF5
GAL1
GAL4
GAL10
GAL11
GAL3
GAL7
GAL80
PHO5
PHO4
PHO81
PHO85
PHO11
ADH1
ADH2
ADA2
ACO1
IDH1
IDH2
ITR1
CKI1
HNM1
ACC1
FAS1
FAS2
CHO1
CHO2
OPI3
CIT1
CIT2
RTG1
RTG3
RTG2
RTS2
TEC1
MFA1
MFA2
CDC46
CDC47
CLB1
CLB2
CLB5
CLB6
CLN1
CLN2
CLN3
CDC28
CDC6
CYC1
CYC7
CYC8
ERG11
HEM13
ROX1
BAR1
HUG1
STE2
STE3
STE4
STE5
STE6
STA1
STA2
ANB1
SUP35
NRG1
WSC2
YCL066W
YCL067C
YCR097W
YLR256W
MF(ALPHA)1
MF(ALPHA)2
ACE2
FAR1
SPT16
HTA1
PAF1
CDC21
CTS1
PCL1
POL1
CDC9
MBP1
ZAP1
CRZ1
HAP5
HEM3
CYT1
RPM2
PTP1
COX4
COX6
QCR2
SPR3
HEM1
QCR8
SDH3
PET9
YKL148C
SOD2
GDH1
DAL1
DAL2
DAL3
DAL4
DAL7
DAL81
DAL82
DUR3
DUR1,2
DEH1
GAP1
PUT1
PUT2
PUT4
UGA1
CAN1
ARG1
ARG3
ARG5,6
ARG8
ARG80
ARG81
CAR1
CAR2
GCN4
RFX1
MOT1
TOP1
SPO13
IME2
RIM101
MER1
HOP1
REC114
RED1
SPS2
HSF1
SPO11
SKI8
SIS1
SKN7
SSA1
REC102
HSP82
RME1
RNR1
RNR3
RAP1
NGG1
ENO1
ENO2
CDC19
PGK1
GCR1
PCL2
KGD2
KGD1
LPD1
HAP4
ROX3
PGD1
RPO21
YFL054C
EMI2
CAT8
FBP1
YEL070W
YKR075C
YLR042C
REG2
HXT1
HXT2
HXT3
HXT4
FES1
FPS1
ENA1
DOG2
MSN2
MSN4
TPS1
TPS2
TPS3
YML100W
CAD1
PDC1
HIS7
HIS4
ADE1
ADE2
ADE3
ADE4
ADE5,7
ADE6
ADE8
ADE12
ADE13
ADE17
PDR15
PDR5
PDR3
PDR1
FLR1
HXT11
YOR1
PDR10
HXT9
SNQ2
ESP1
PDS1
HCM1
CDC39
POP2
CCR4
PEX5
POX1
CAT2
PIP2
ECI1
DCI1
MET16
CBF1
MET28
MET2
MET4
MET17
MET14
MET3

The methionine pathway



- Cbf1 and Met28 have no regulatory activity
- The key regulatory mechanisms (loops) are not captured by the motifs found

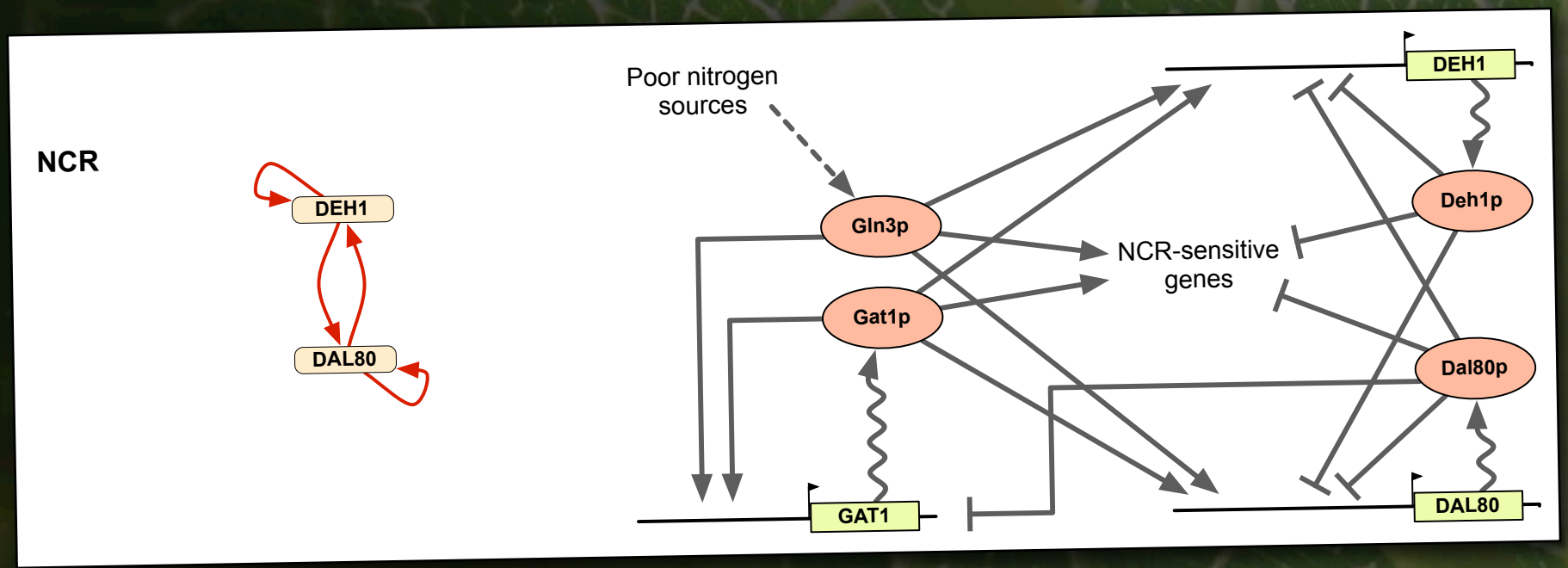
> These motifs do not exist in practice.

Bias 3

Most network representations don't deal with transient objects, like protein complexes.

- *cbf1, met4 and met28, while in complex, spuriously inherited the regulatory activity of met4, artificially creating motifs*

The nitrogen catabolite repression system



- The key regulatory mechanisms (oscillation between Gln3p/Gat1p and Deh1p/Dal80p) are not captured by the motifs found

> This motif exists but have no role in practice.

Bias 4

Not all over-represented motifs are significant.

- *deh1p and dal80p are paralogs of an ancestor protein with homo-dimerization capability*
- *The duplication is too recent for the function of these two proteins to have diverged*

Conclusion

Motifs do not seems to be biologically relevant.
They either do not exist or have no role.

But motifs are statistically significant ... aren't they?

Counter argument

The existence of over-represented subgraphs is a consequence of the network growth, without need of any hypothesis of selection along evolution.

- Artzy-Randrup Y, Fleishman SJ, Ben-Tal N, Stone L *Comment on "Network motifs: simple building blocks of complex networks" and "Superfamilies of evolved and designed networks"* Science 2004, 305:1107
- Banzhaf W and Kuo P D, *Network motifs in natural and artificial transcriptional regulatory networks* Journal of Biological Physics and Chemistry, 4 (2004) pp. 85 - 92

Take-home messages

Beware of artifacts from network representation!

- Networks are static, i.e. they superpose all existing (and not necessarily co-occurring) interactions
- Networks are not rich enough to represent non-linearities and transient objects. Examples of gene regulation logic and protein complexes

Don't rely too much on the topology of networks.

Beware of statistical significance!

- Biological systems are not designed, they're the result of trial-and-errors over billions of years. They contains lot of structures, that are not necessarily (or no more) of use.

Don't rely too much on the abundance of an object to judge of its relevance. Ask the question of the biological relevance.

Alternative to motifs?

The idea of small structures performing signal-processing tasks is actually good.

We biologists expect such tasks to be performed: signal conversion, memorization, amplification, extinction, discretization, integration, etc.

Idea

To make a clear separation between structure and function: distinguish tasks from implementations.

Implementations: the particular molecular mechanisms used to perform these tasks.

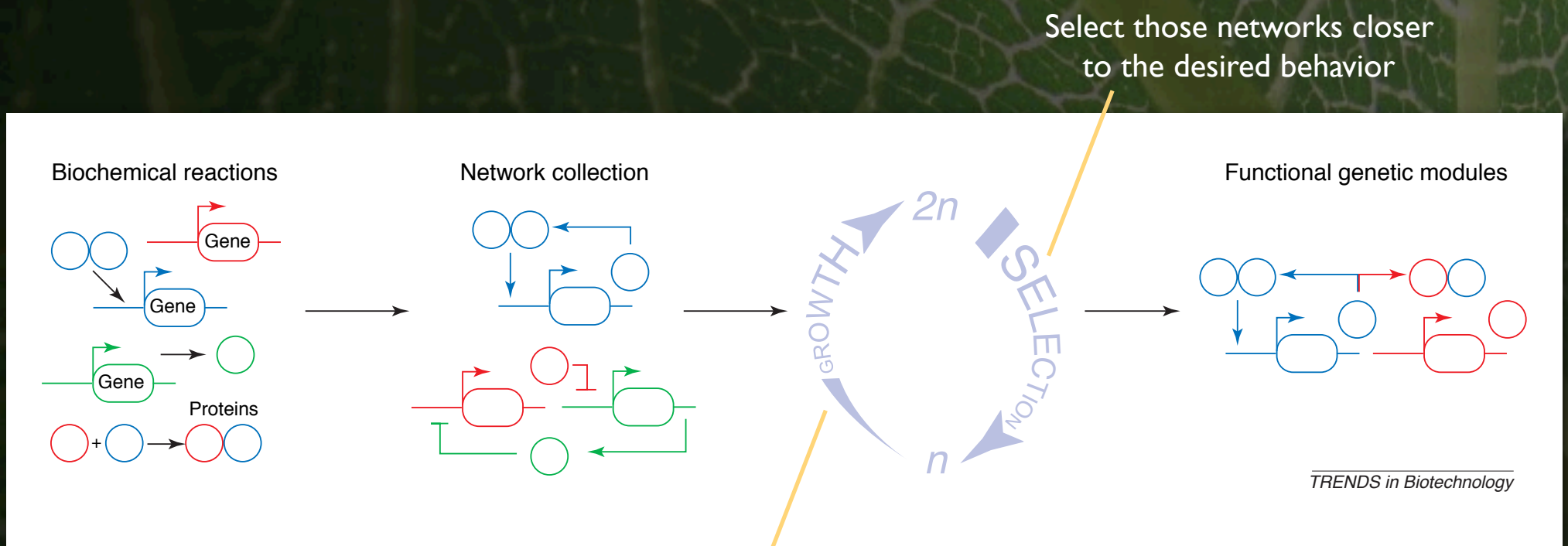
New approach

We must look for tasks, not implementations.

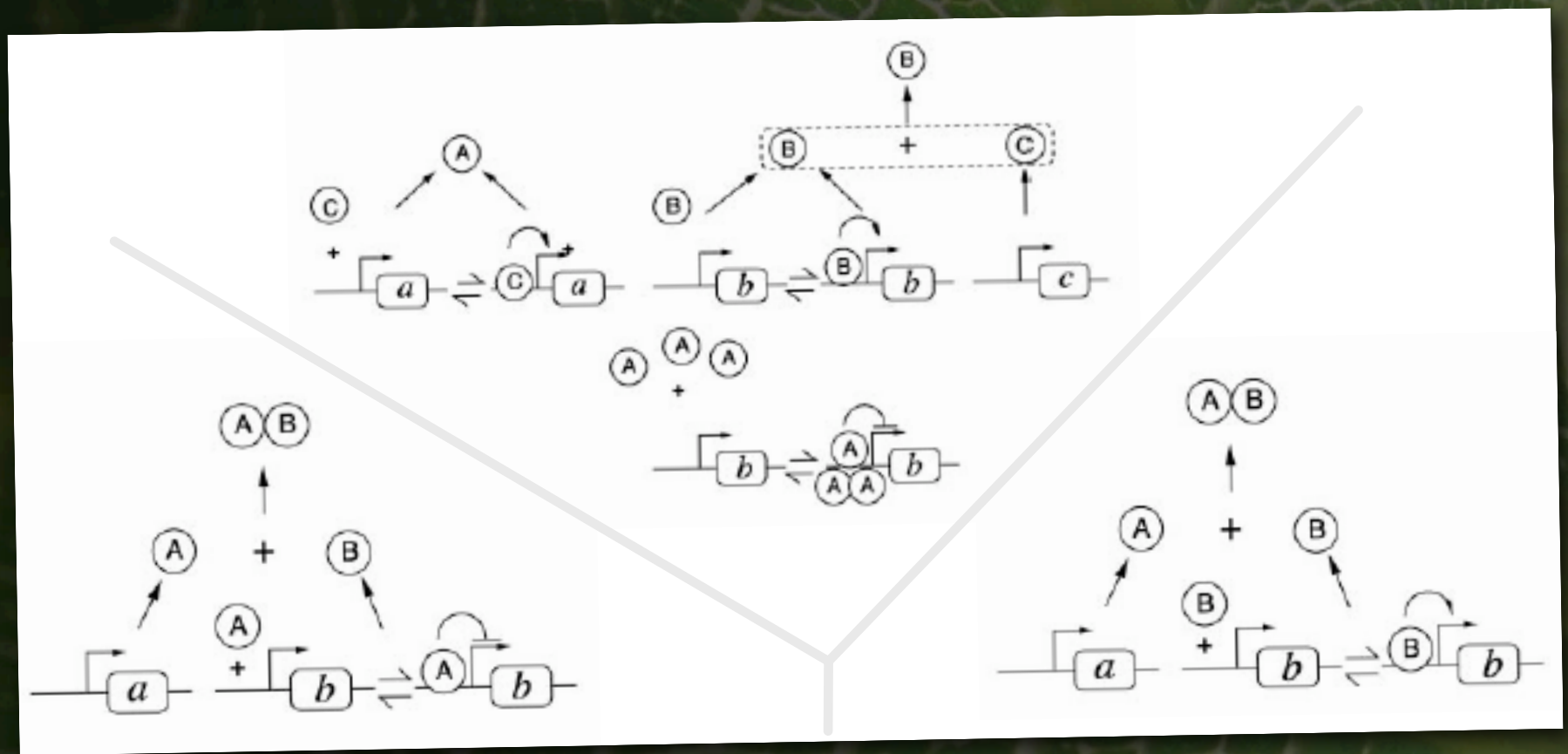
Rationale

It have been shown that a single task can be implemented with many different mechanisms with distinct topologies.

François P, Hakim V *Design of genetic networks with specified functions by evolution in silico* PNAS 2004 vol. 101, 580–585



Implementation of a toggle switch



Acknowledgments

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