Non Linear Dynamics and Gene Networks

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Non-linearity means that the dynamical behavior of the system cannot be viewed as a superposition of the elementary effects of its components, nor reconstructed from elementary "modes".
In simple terms, doubling the input does not necessarily double the output.

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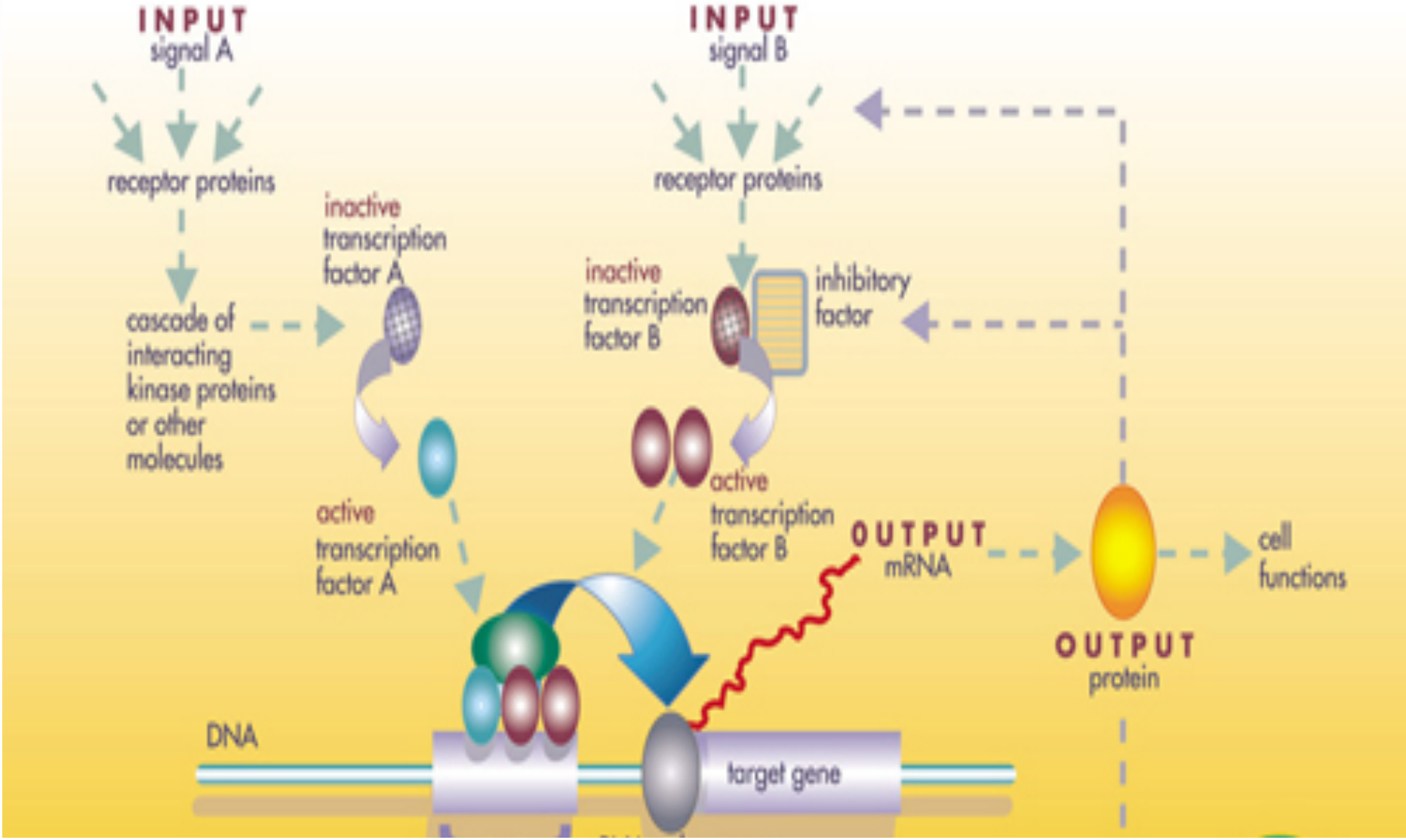
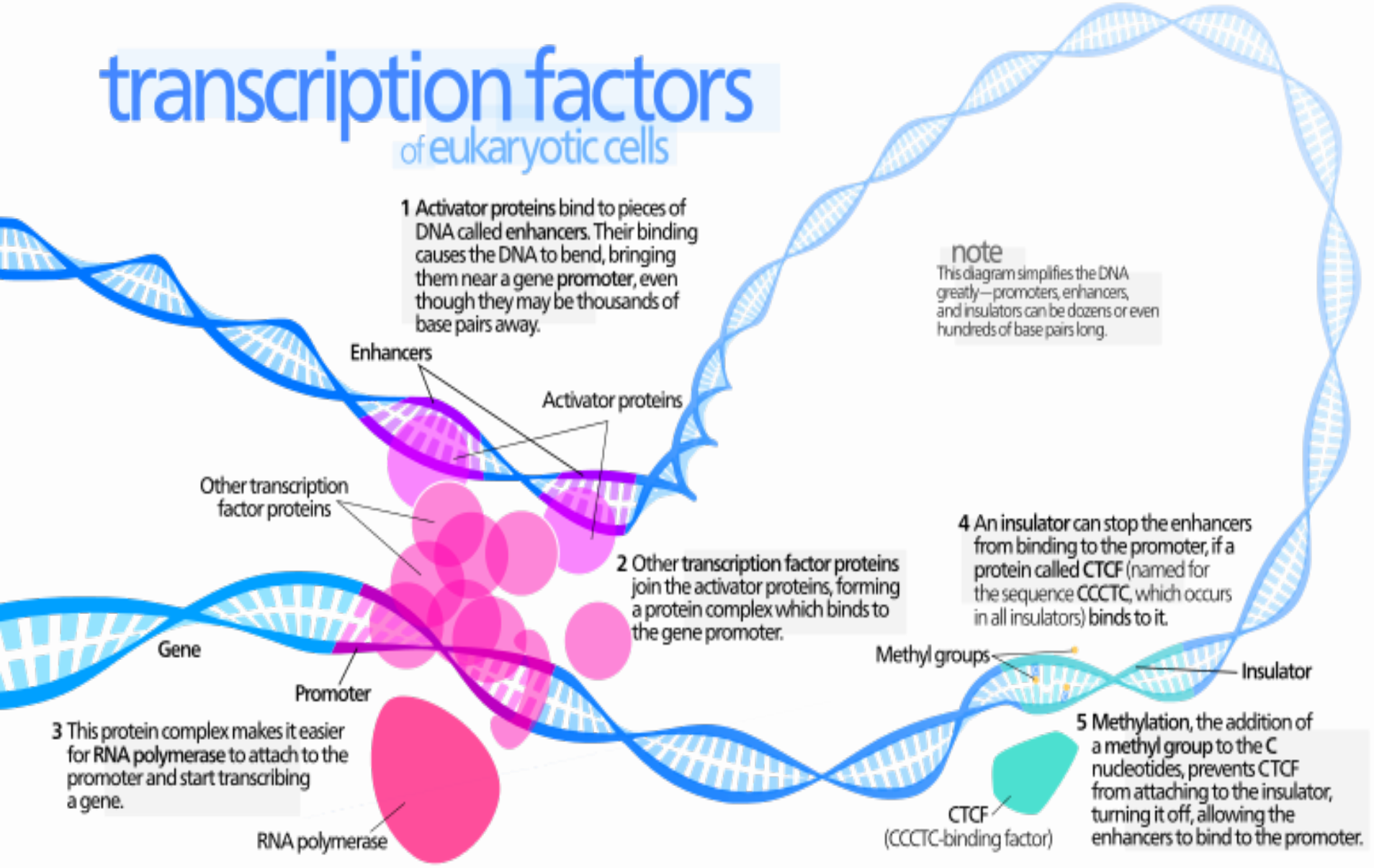
- 1. GENE NETWORK = INTERACTION GRAPH
- 2. DYNAMICS ON THE CONFIGURATION SET
- 3. EXAMPLES
- 4. SOME OPEN QUESTIONS
- 5. SUPPLEMENTARY POINTS
- 6. FINAL QUESTIONS

A GENE REGULATORY NETWORK



transcription factors
of eukaryotic cells

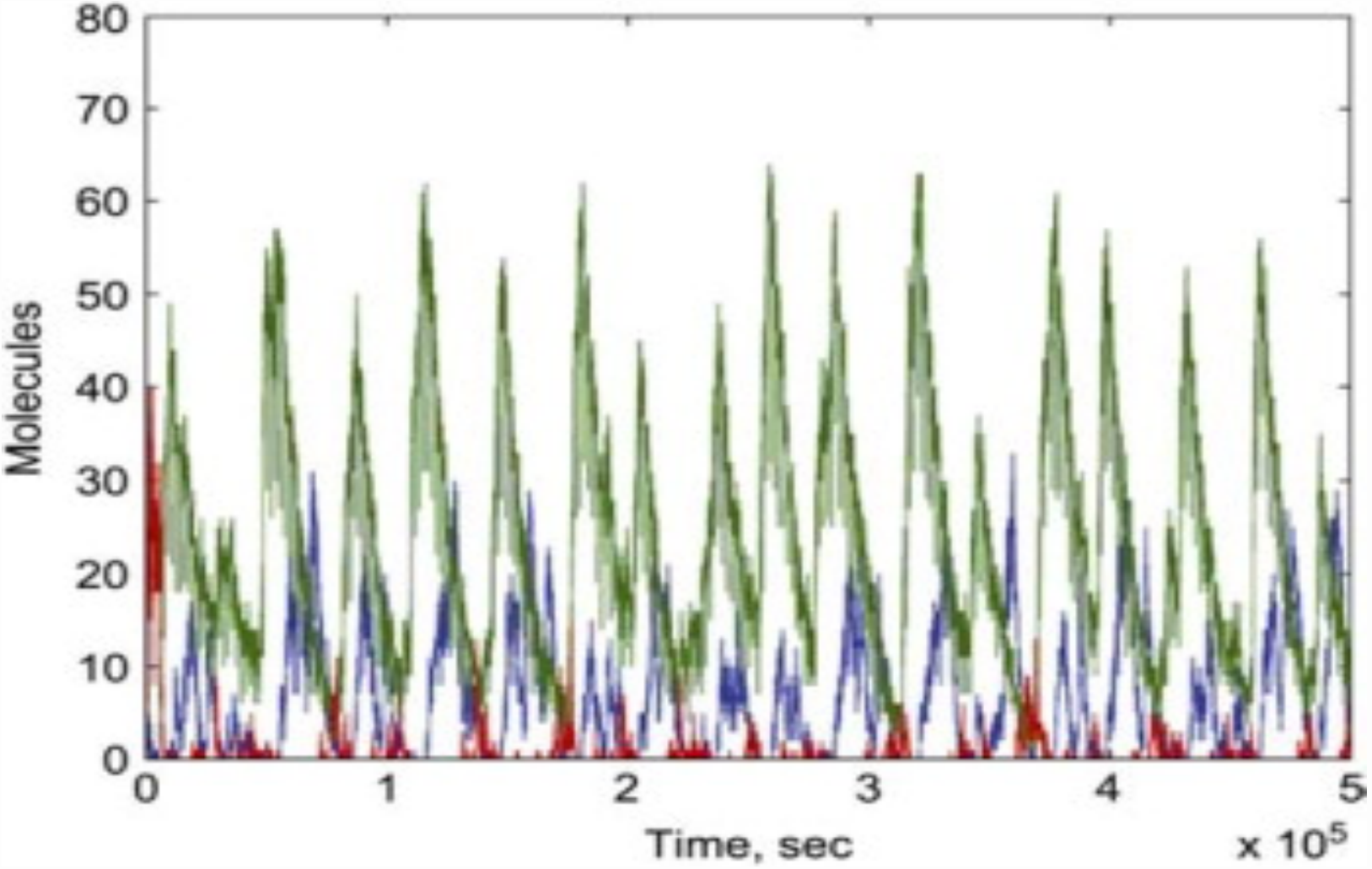


THE INTERACTION NETWORK

+ arrows →
+ interactions
activation +1
inhibition -1

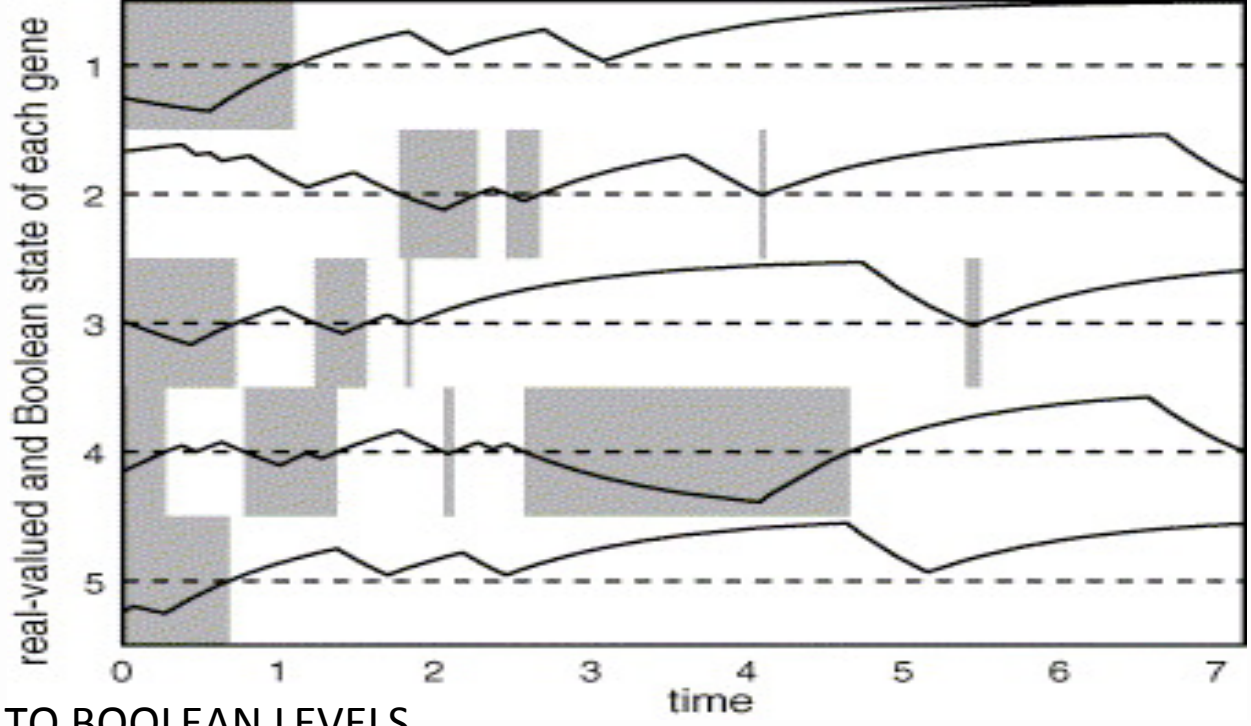
Escherichia coli

5,2 millions base pairs
~ 5 300 GENES
=> protéines

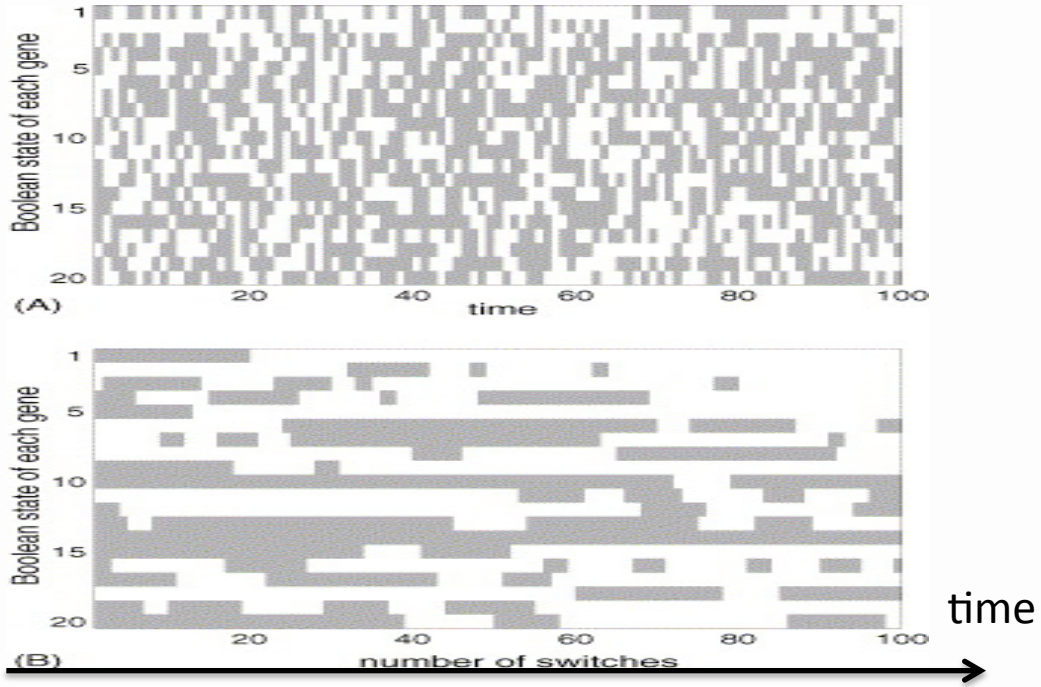


Dynamical behavior:
Dlac (red), Dtet (blue) and Dara (green) proteins.

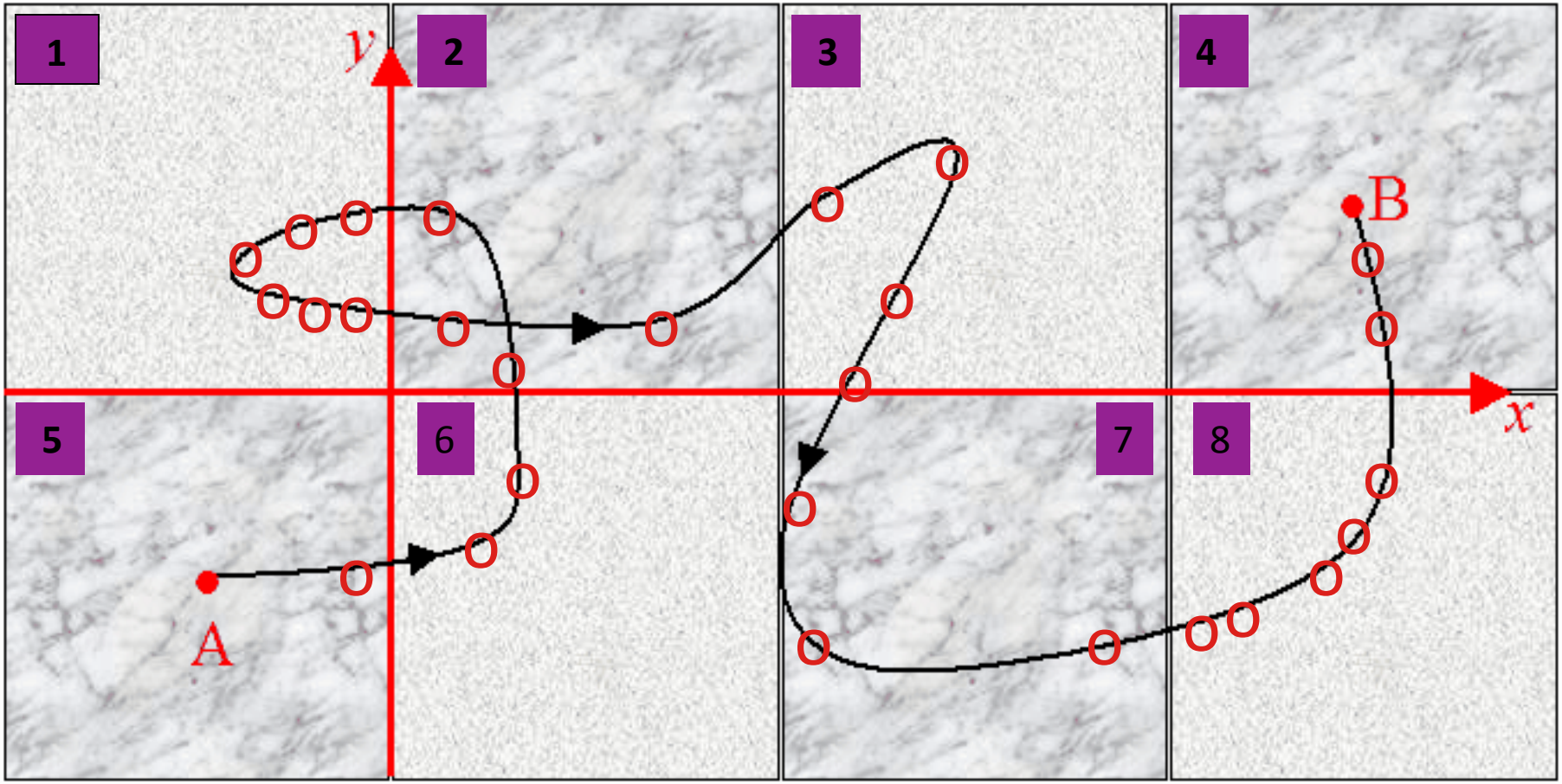
Biophysical Journal Volume 89, Issue 6 2005 3873 - 3883

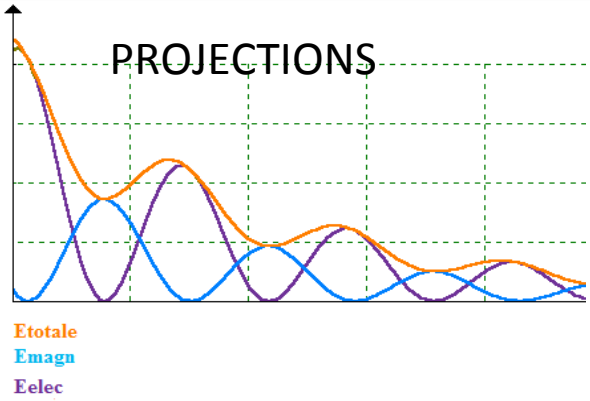


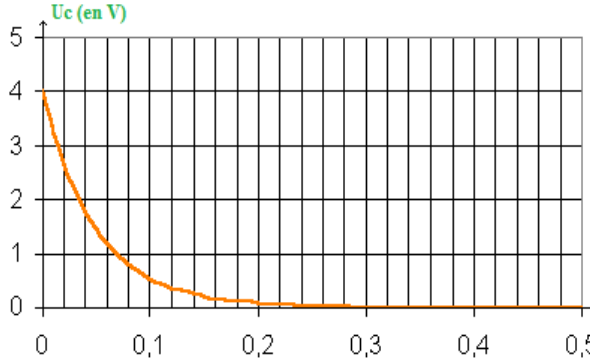
FROM REAL TO BOOLEAN LEVELS

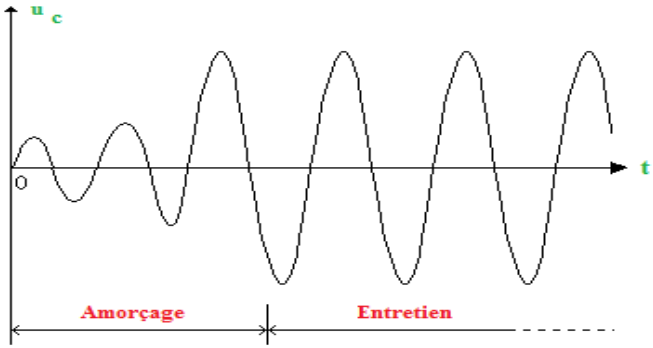


Configuration Space: DETERMINISTIC DYNAMICS

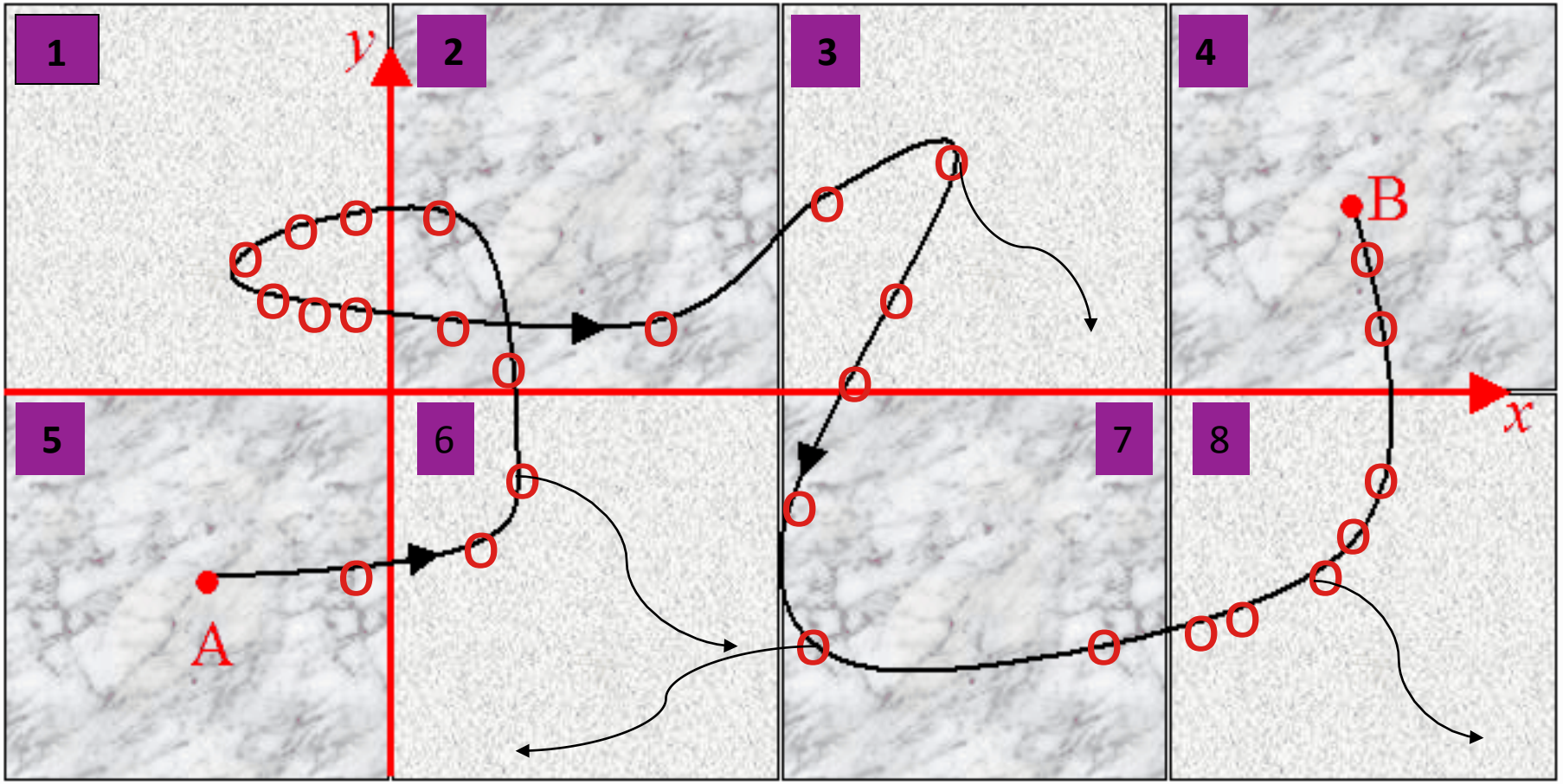


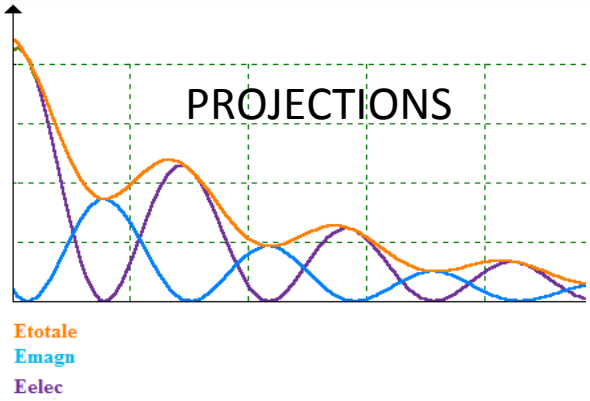


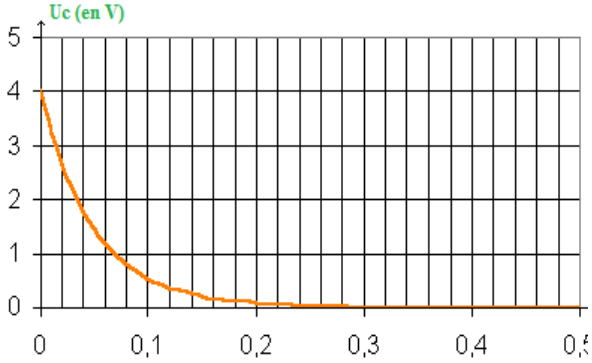


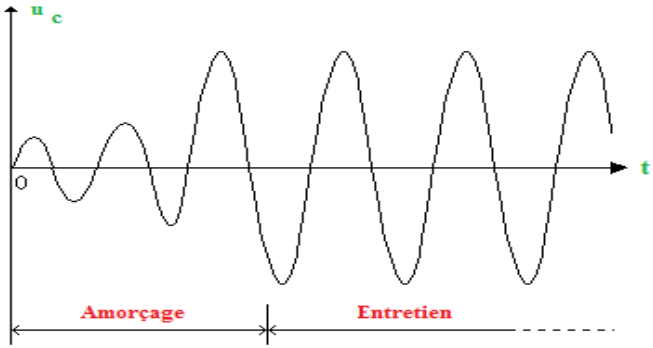


Configuration Space: MARKOV DYNAMICS



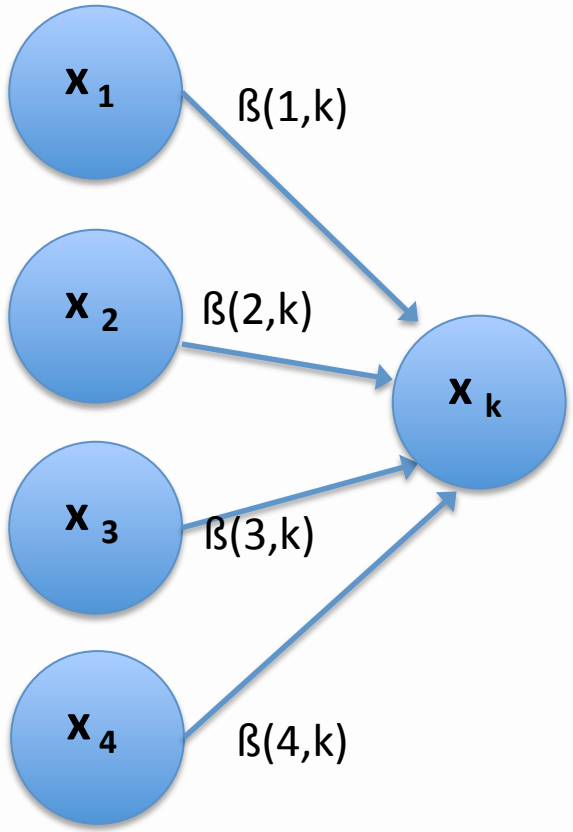







1 0 1
A
B
C
D
E
1 0 0
1 1 1
1 0 0
0 1 1

DYNAMICS ON THE CONFIGURATION SPACE



each x_n = +1 or -1

interactions ß(i,j):

activation ß = +1
inhibition ß = - 1

EX.MAJORITY RULE :

at time t: CONFIGURATION $x_1(t)$, $x_2(t)$, $x_3(t)$, $x_4(t)$, ... $x_k(t)$...

$x_k(t+1) = +1$ if $\sum = ß(1,k)\, x_1(t) + ß(2,k)\, x_2(t) + ß(3,k)\, x_3(t) + ß(4,k)\, x_4(t) > 0$

$x_k(t+1) = +1$ with probability pk or -1 with probability (1-pk) if $\sum = 0$

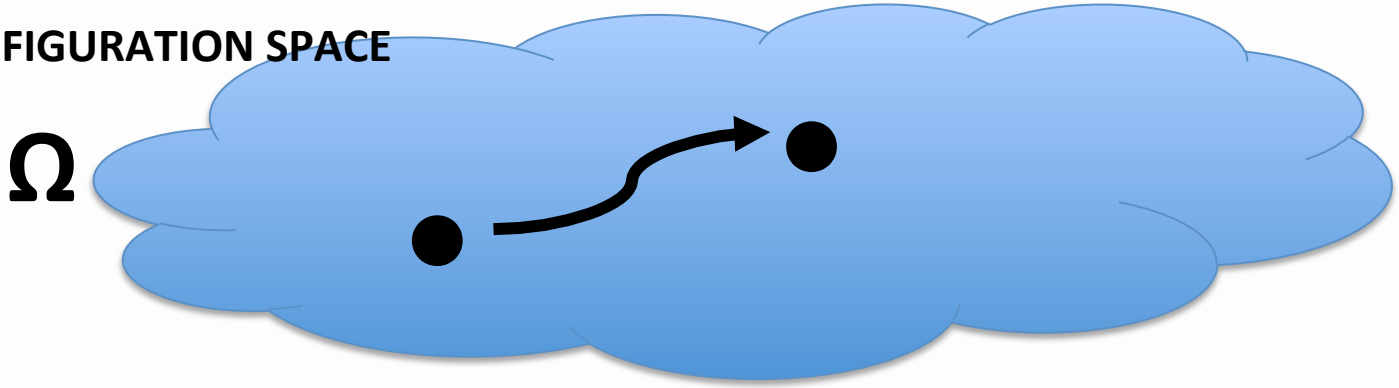
$x_k(t+1) = -1$ if $\sum = ß(1,k)\, x_1(t) + ß(2,k)\, x_2(t) + ß(3,k)\, x_3(t) + ß(4,k)\, x_4(t) < 0$

FROM THE INTERACTION NETWORK TO THE DYNAMICS

At each time step:

$\vec{x}(t) = (x_1(t), x_2(t), \ldots, x_N(t))$ ⇒ $\vec{x}(t+1) = (x_1(t+1), x_2(t+1), \ldots, x_N(t+1))$

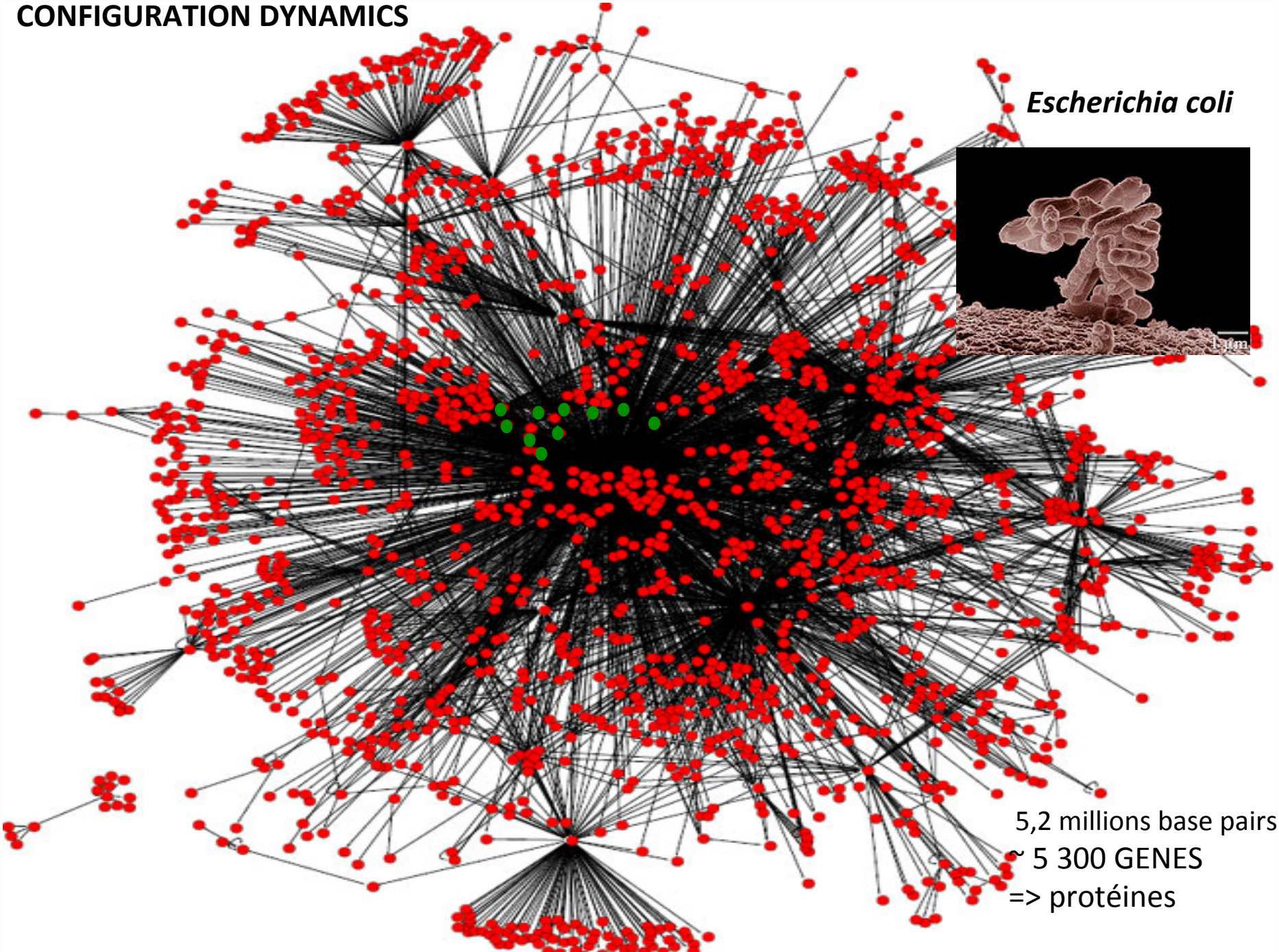
CONFIGURATION SPACE



The **INTERACTION NETWORK** defines the **DYNAMICAL RULE** on **Ω**

Determinist X Probabilist

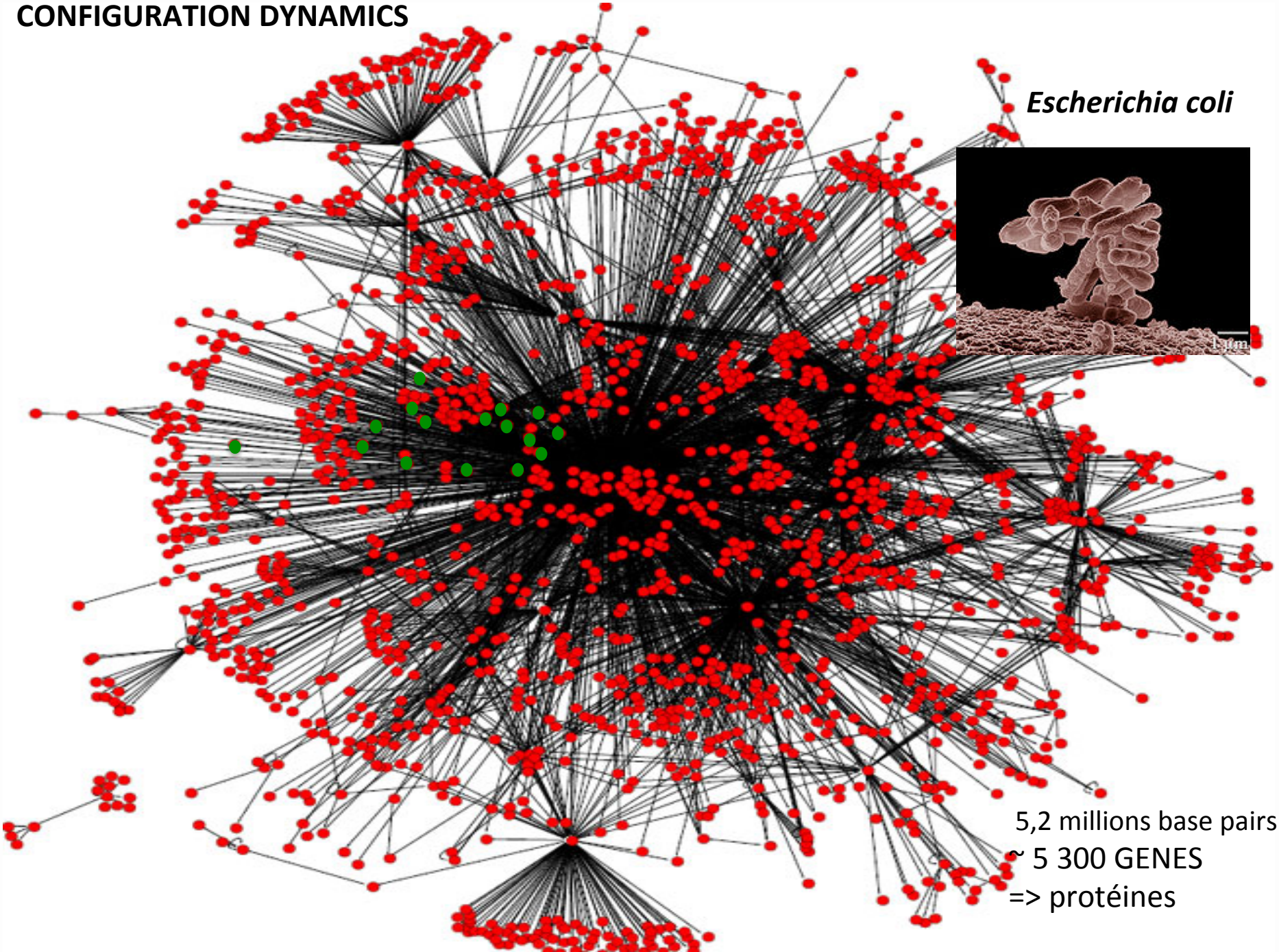
CONFIGURATION DYNAMICS



Escherichia coli

5,2 millions base pairs
~ 5 300 GENES
=> protéines

CONFIGURATION DYNAMICS



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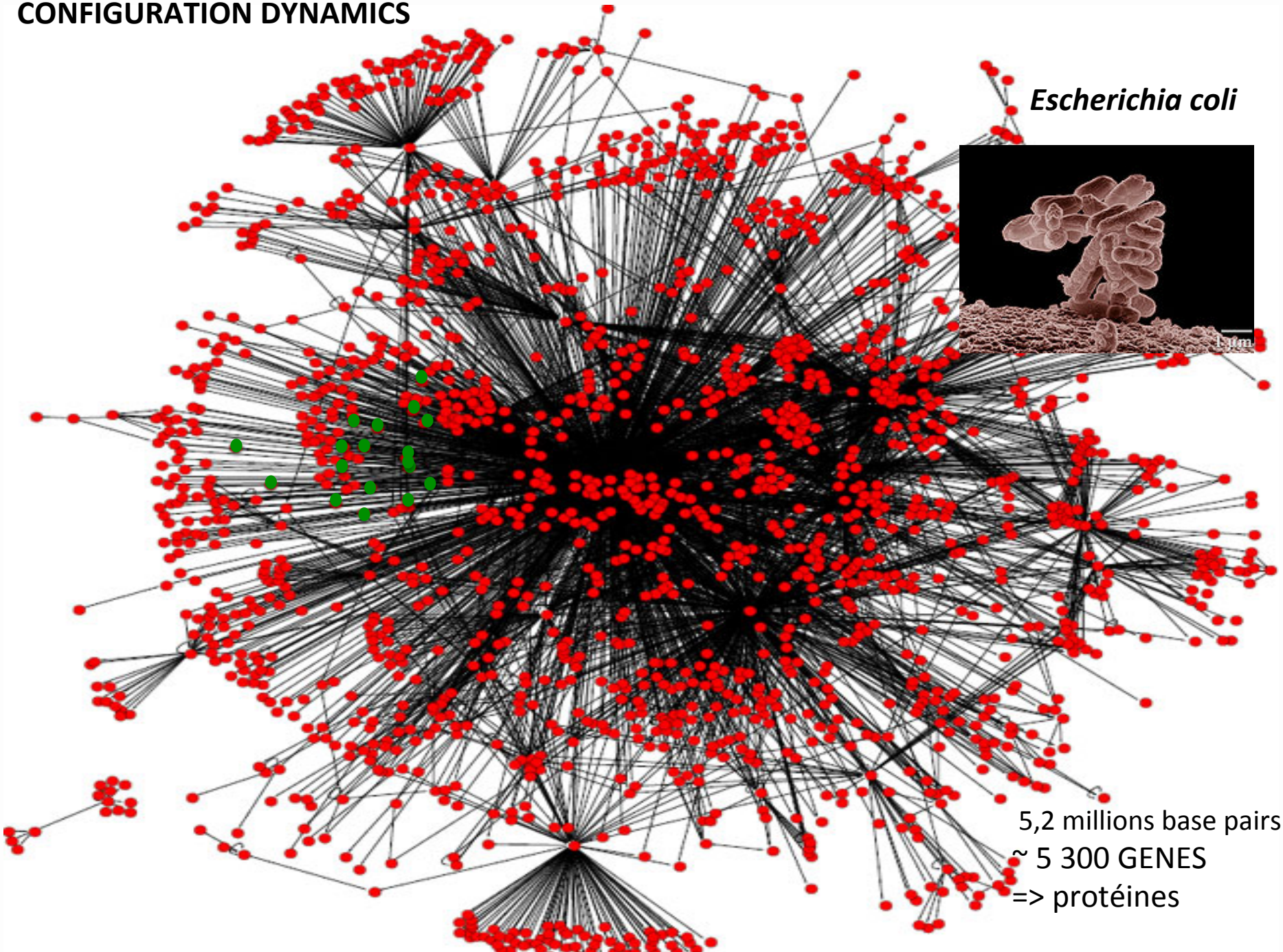

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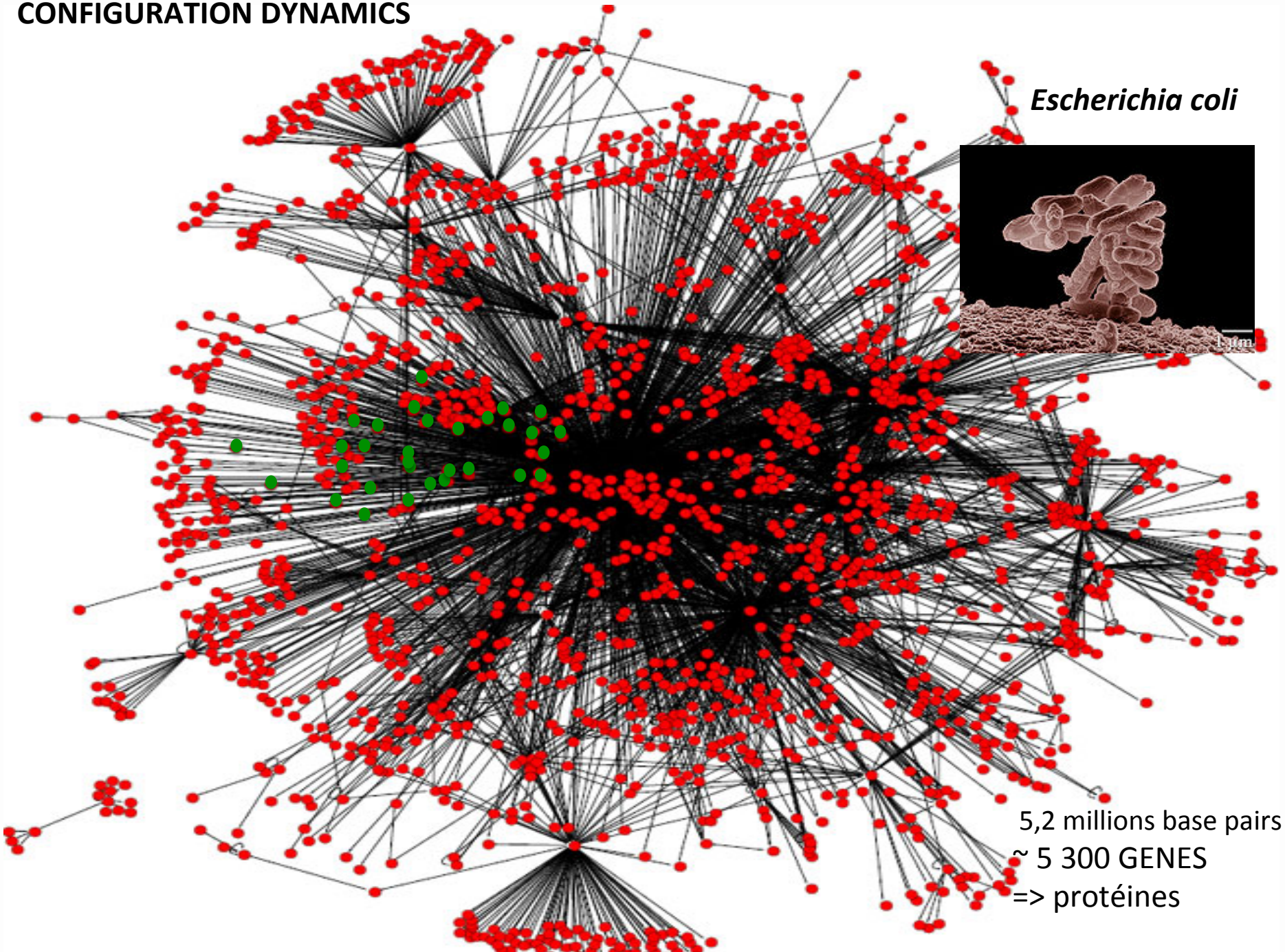

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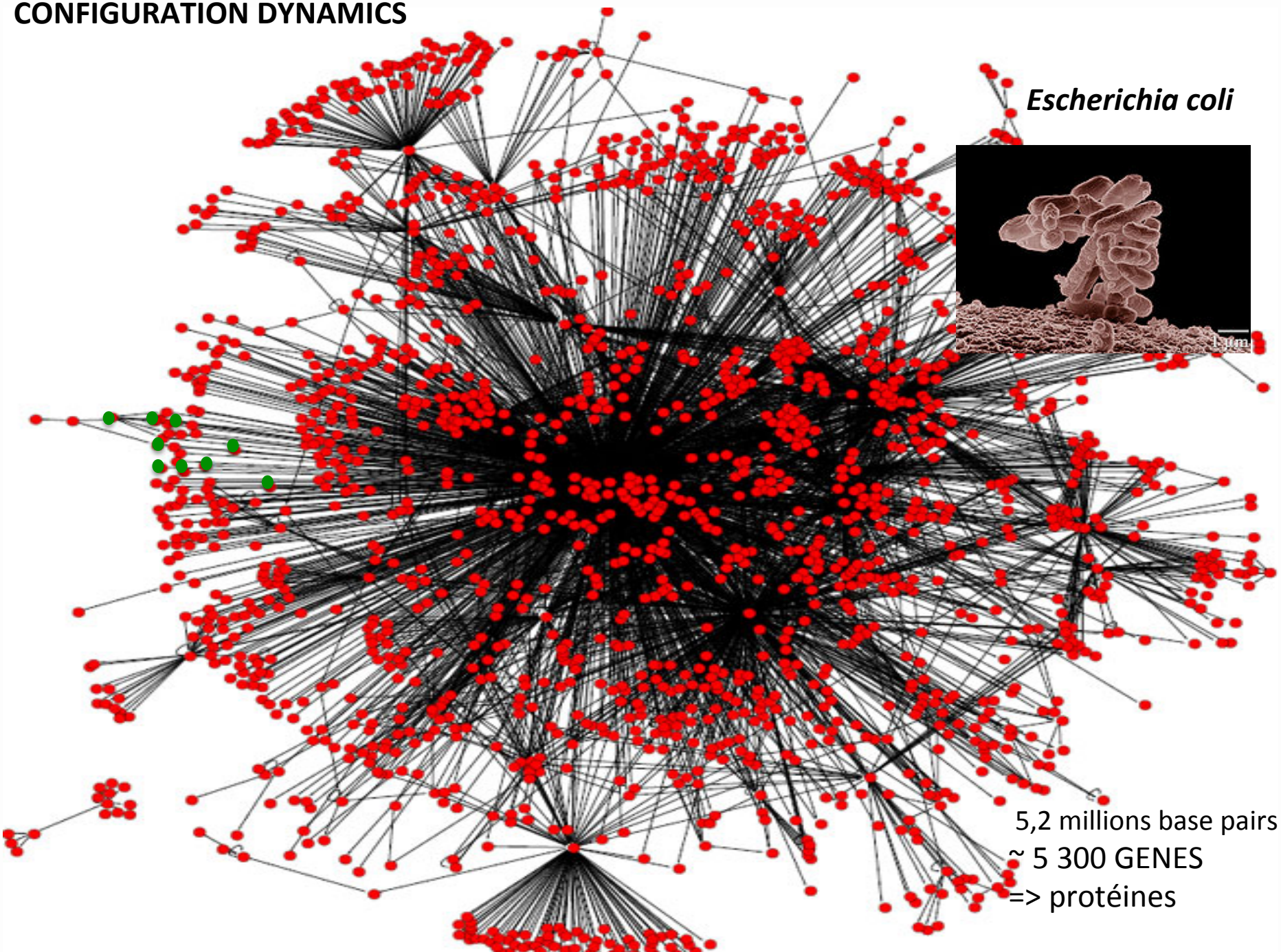

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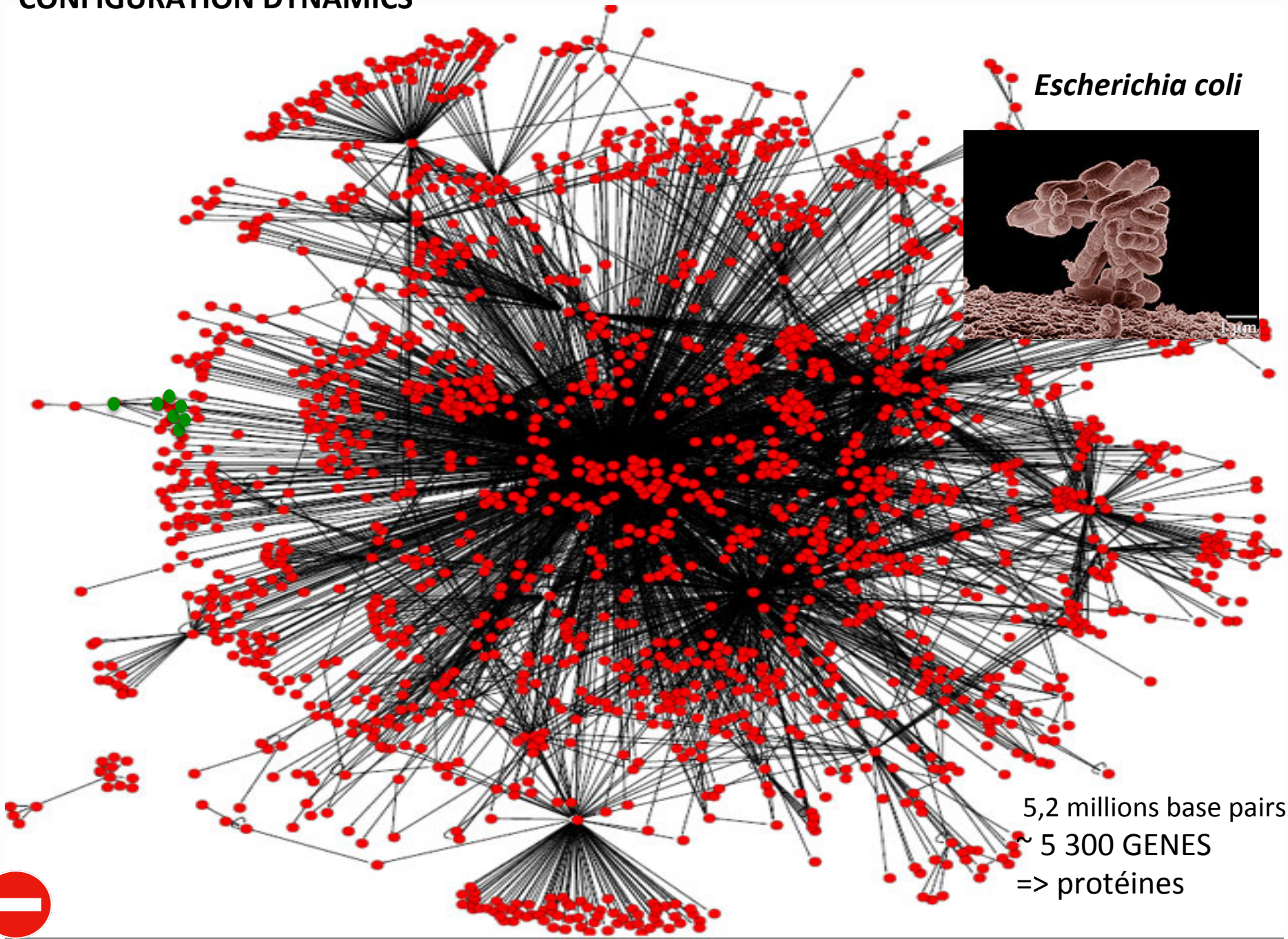
CONFIGURATION DYNAMICS



Escherichia coli

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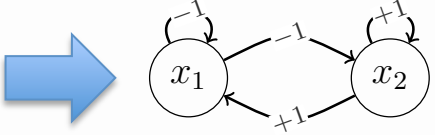
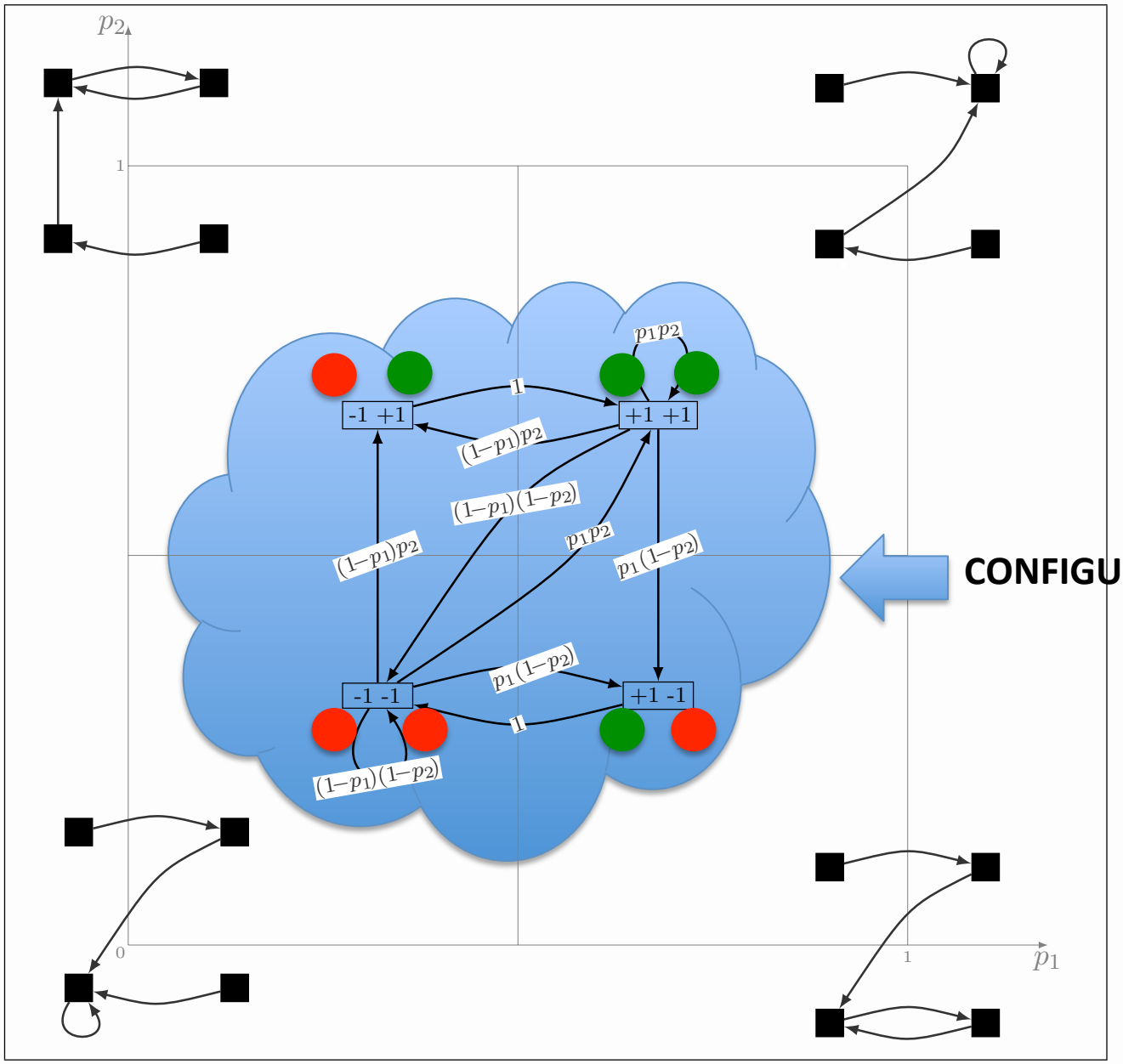
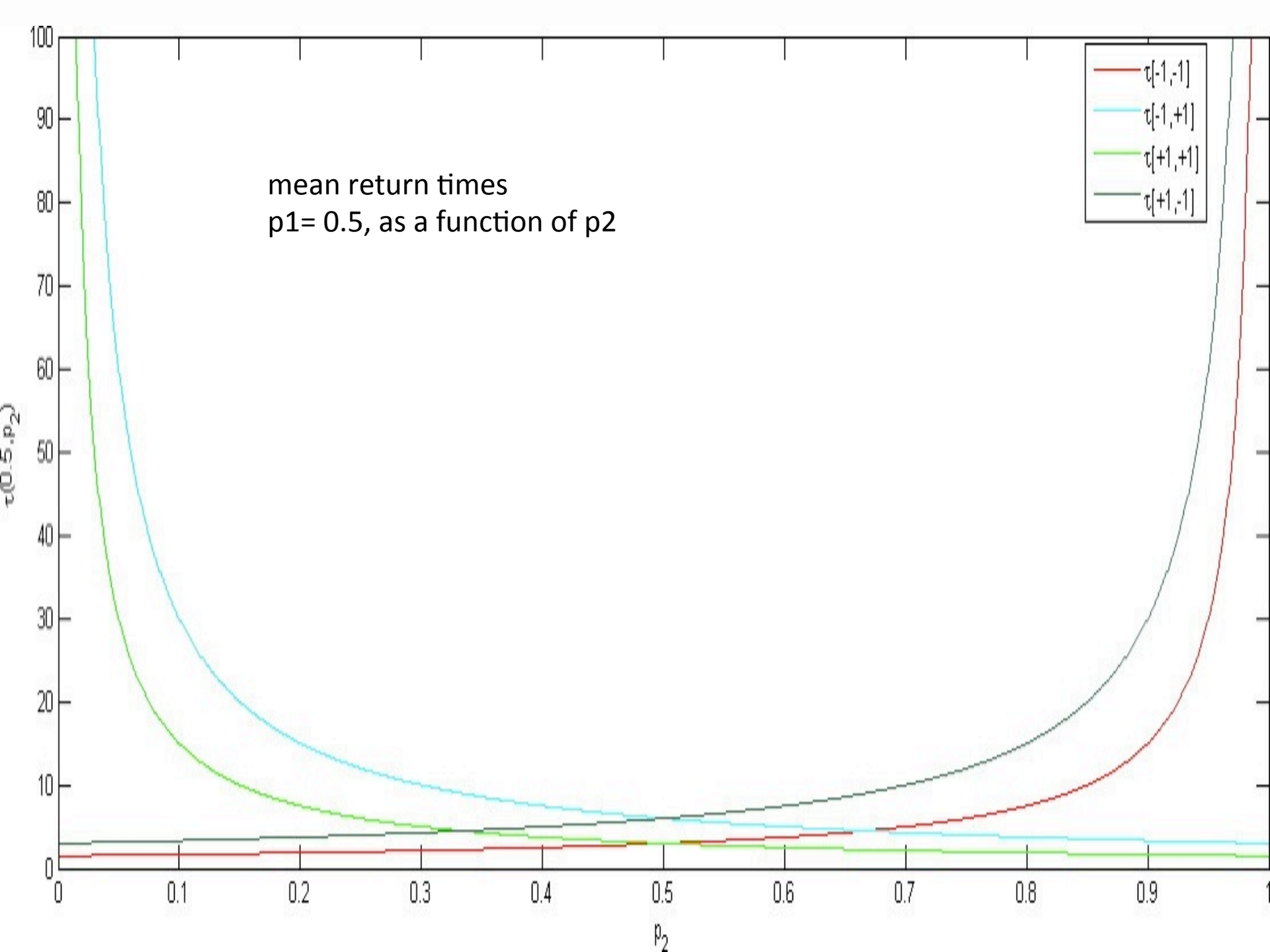
$[-1,+1\rangle \oplus [+1,-1\rangle$ (IP3)

2 GENE INTERACTION NETWORK

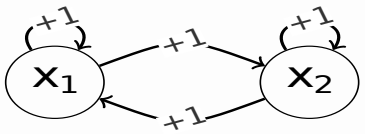


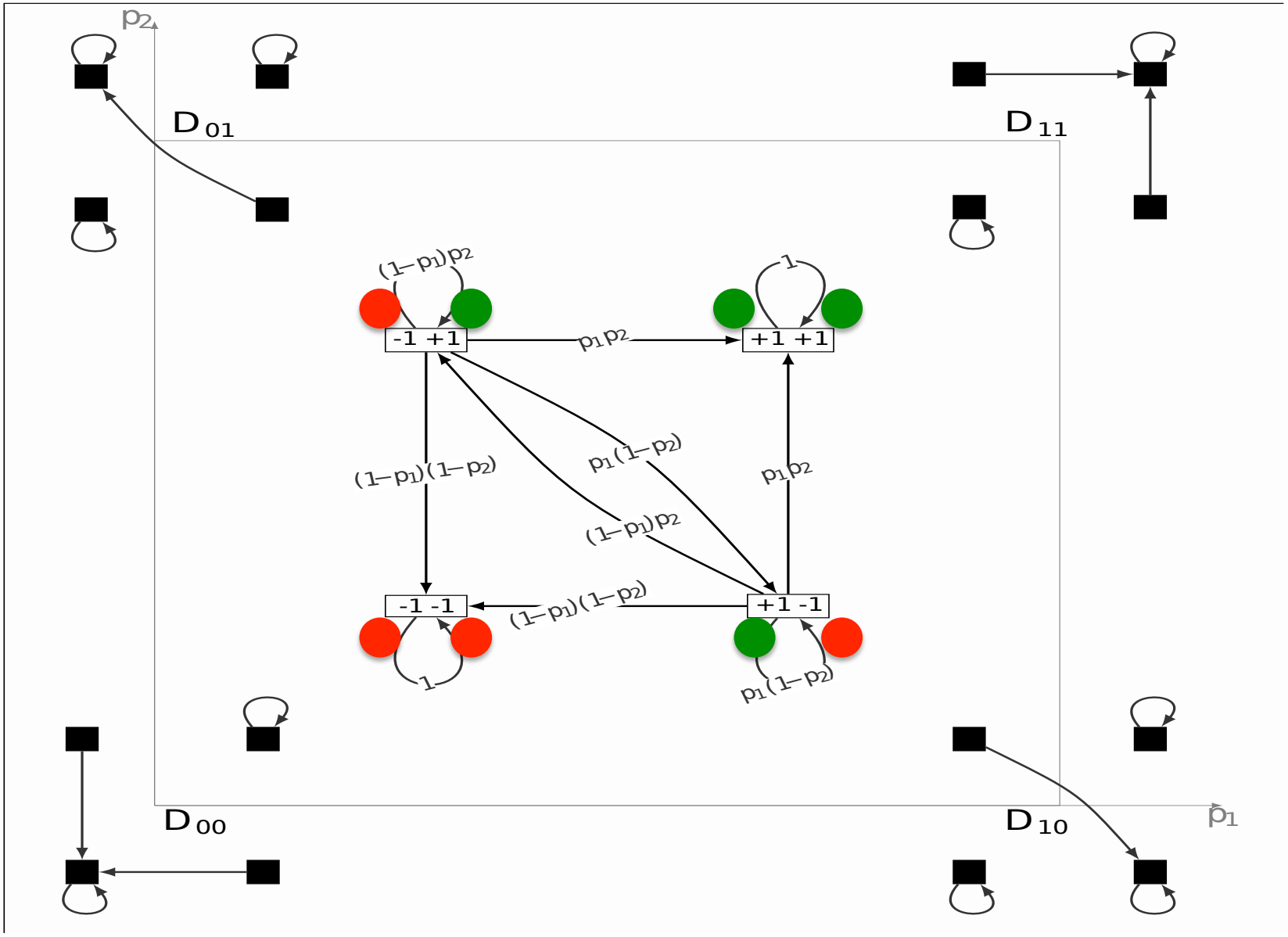


CONFIGURATION SPACE

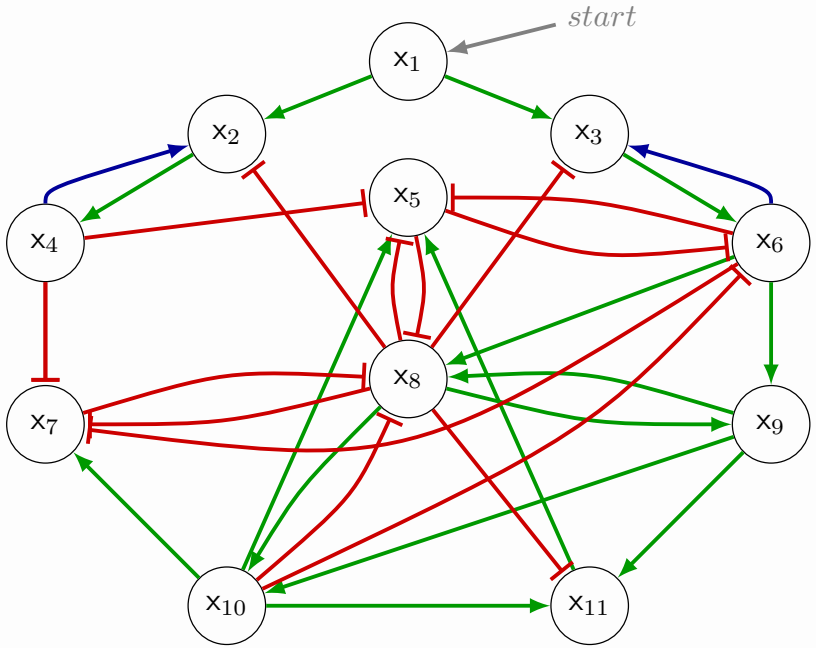

mean return times
p1= 0.5, as a function of p2
τ[-1,-1]
τ[-1,+1]
τ[+1,+1]
τ[+1,-1]
τ(0.5,p2)
p2
0
10
20
30
40
50
60
70
80
90
100
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9

[+1,+1⊕ [+1,+1 (IP1)


+1
+1
+1
+1
x1
x2


p2
D01
D11
(1−p1)p2
1
-1 +1
p1p2
+1 +1
(1−p1)(1−p2)
p1(1−p2)
p1p2
(1−p1)p2
-1 -1
(1−p1)(1−p2)
+1 -1
1
p1(1−p2)
D00
D10
p1

EUKARYOTIC CELL CYCLE GENE NETWORK



Variable	Component(s)	Value in G_1
x_1	Cln3	-1
x_2	SBF	-1
x_3	MBF	-1
x_4	Cln1 Cln2	-1
x_5	Sic1	1
x_6	Clb5 Clb6	-1
x_7	Cdh1	1
x_8	Clb1 Clb2	-1
x_9	Mcm1 SFF	-1
x_{10}	Cdc20 Cdc14	-1
x_{11}	Swi5	-1

The dynamics has a unique absorbing steady configuration: G1
(adding the 2 blue interactions)

SOME IMPORTANT OPEN QUESTIONS

1) FROM INTERACTION GRAPH TO DYNAMICAL GRAPH:
Is it possible to directly study dynamical properties by inspecting the interaction network?

2) SEARCH OF ALL ATTRACTORS (ABSORBING SETS)

3) THE DYNAMICS OF A PROJECTION

4) SYSTEMATIC STUDY OF THE DYNAMICAL PROPERTIES OF MUTANTS

5) VARIABILITY FROM CELL TO CELL, INSIDE A POPULATION, etc.

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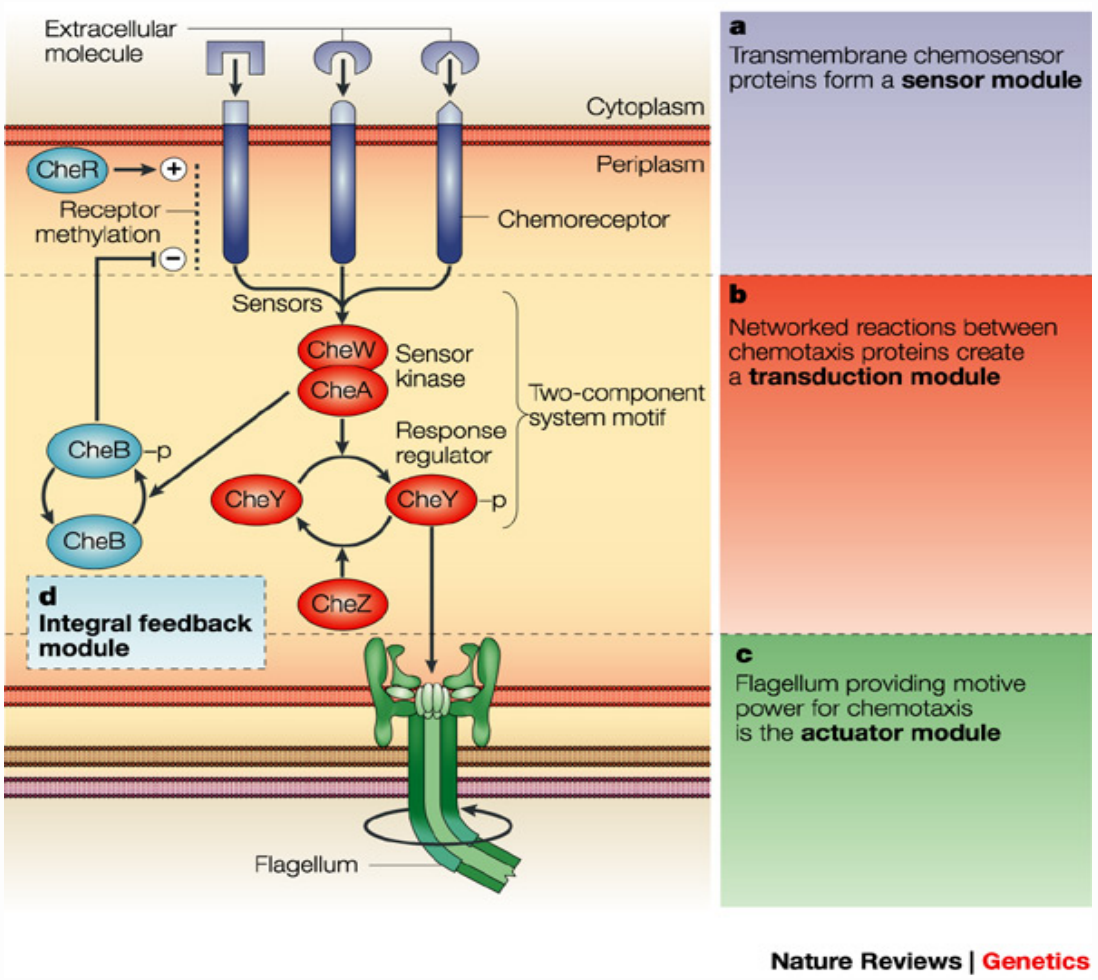
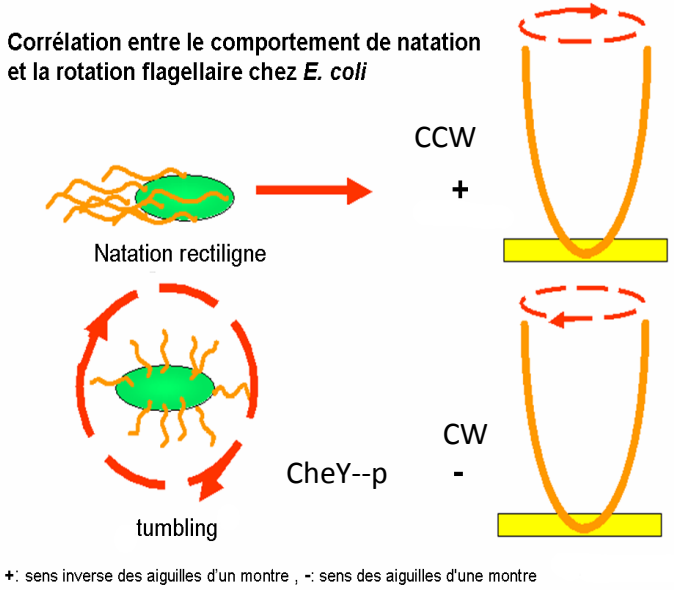
A SMALL GENE NETWORK AT WORK: BACTERIA CHEMOTAXIS(*E. coli)*

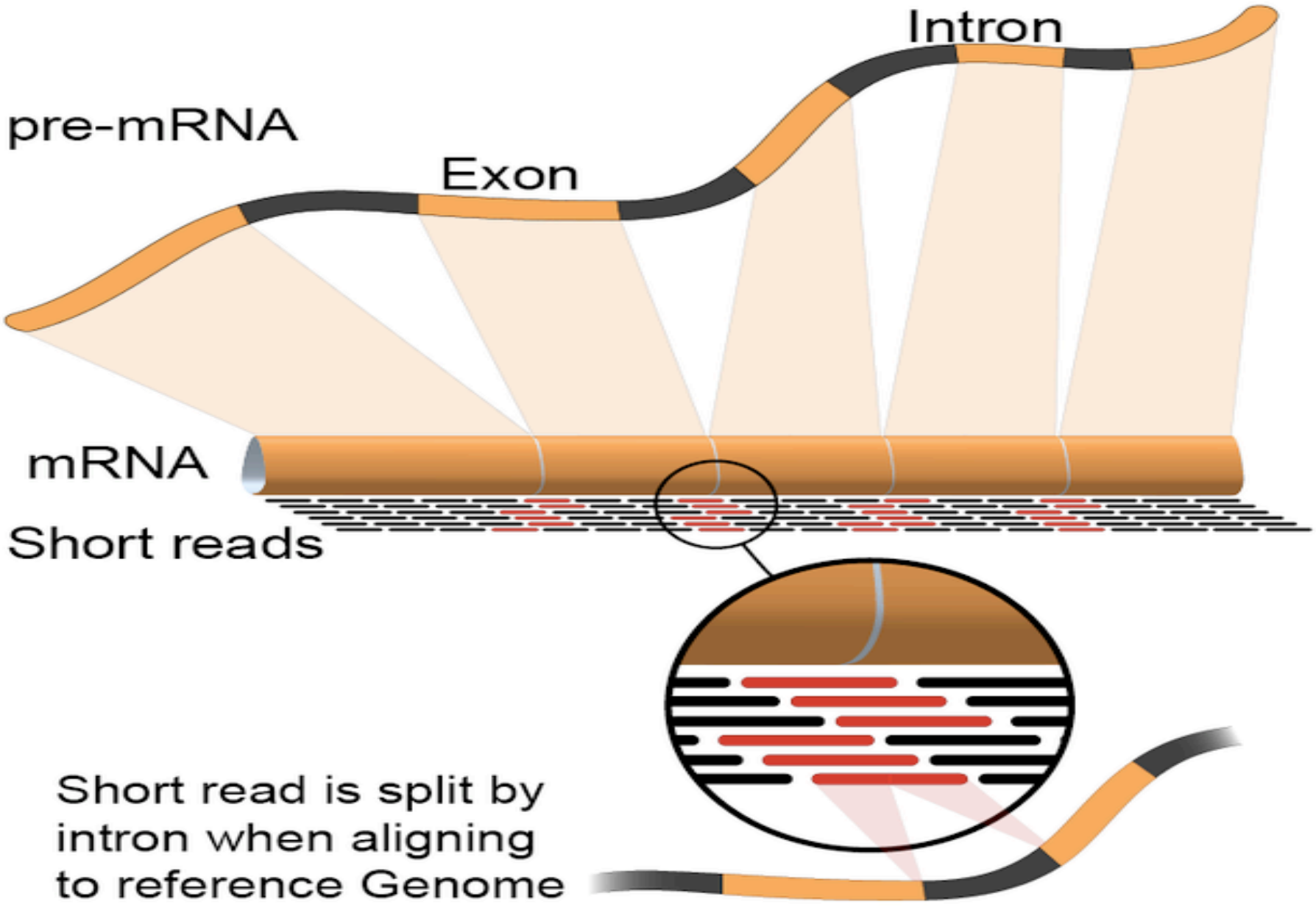




Attractants
Repellents
Flights (CCW) and Tumbles (CW)

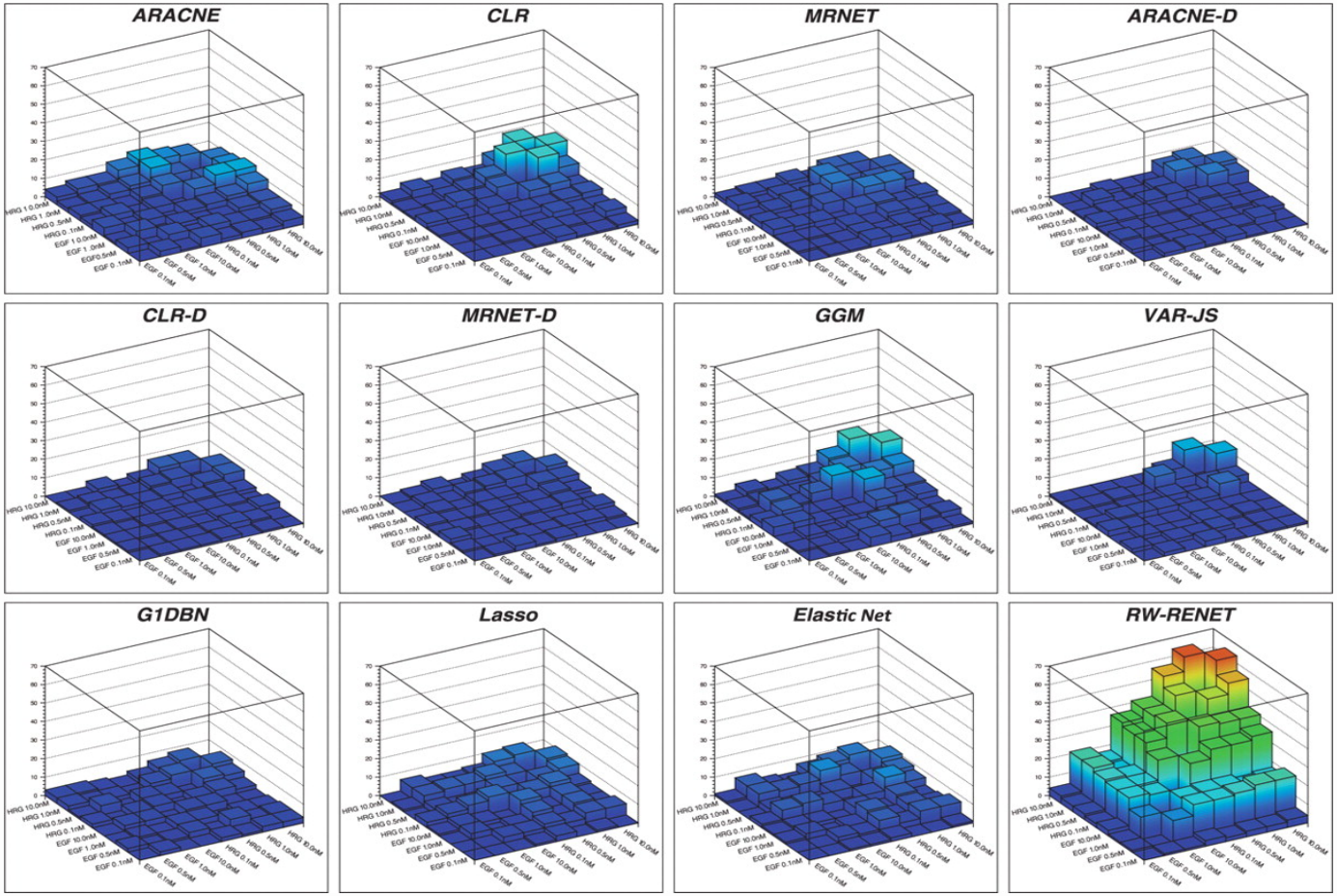
H.C. Berg, D.A. Brown, 1972, Nature 239: 500-504.

FROM READING SEQUENCES TO NETWORK INFERENCE



ON THE INCERTITUDE OF ALGORITHM INFERENCE

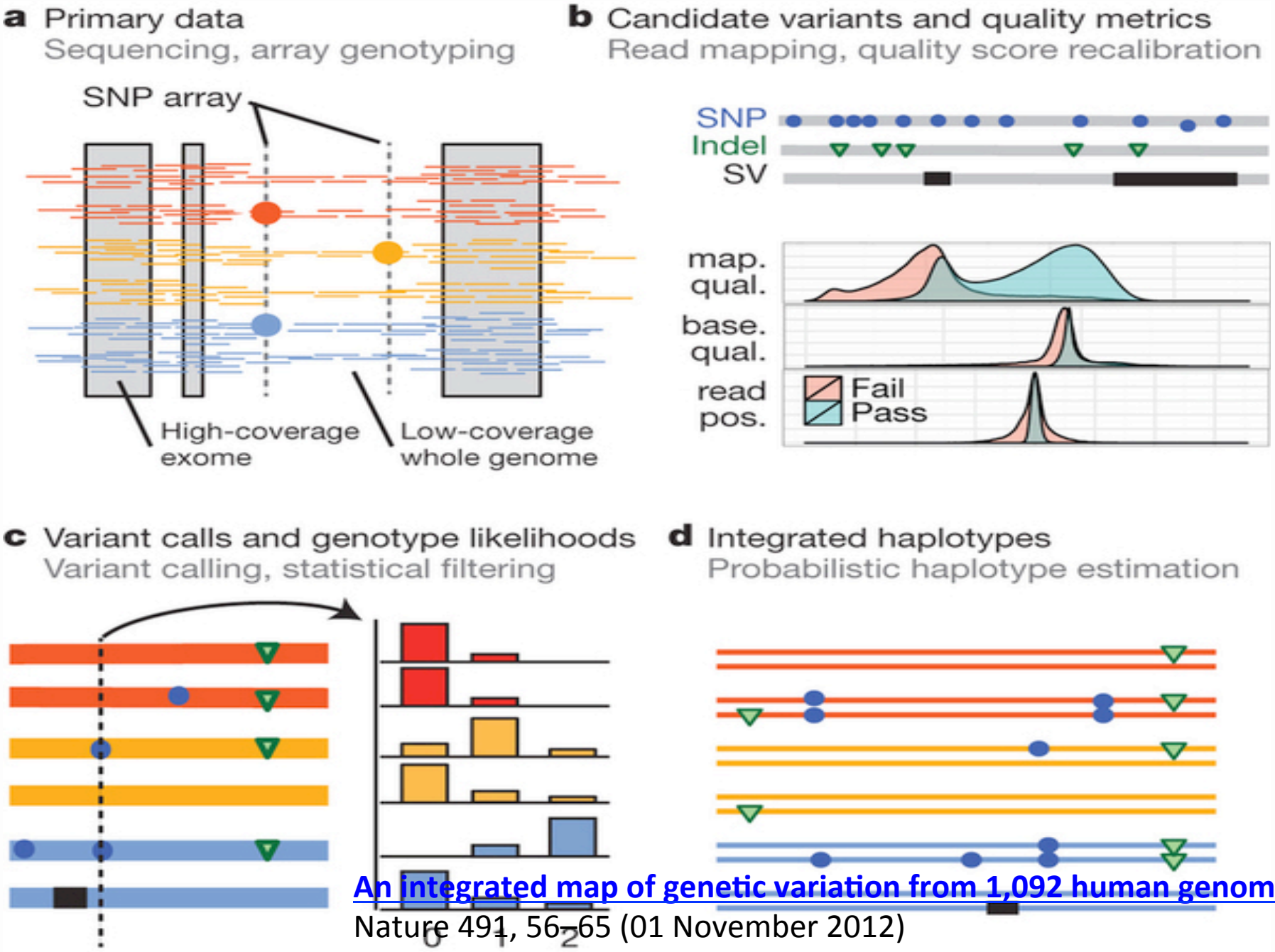
The 2D histograms showing how many edges were conserved between the inferred networks for each of the 12 inference algorithms (ARACNE, CLR, MRNET, ARACNE-D, CLR-D, MRNET-D, GGM, VAR with the James-Stein Shrinkage (VAR-JS), G1DBN, lasso, elastic net and RW-RENET).



Shimamura T et al. Bioinformatics 2010;26:1064-1072

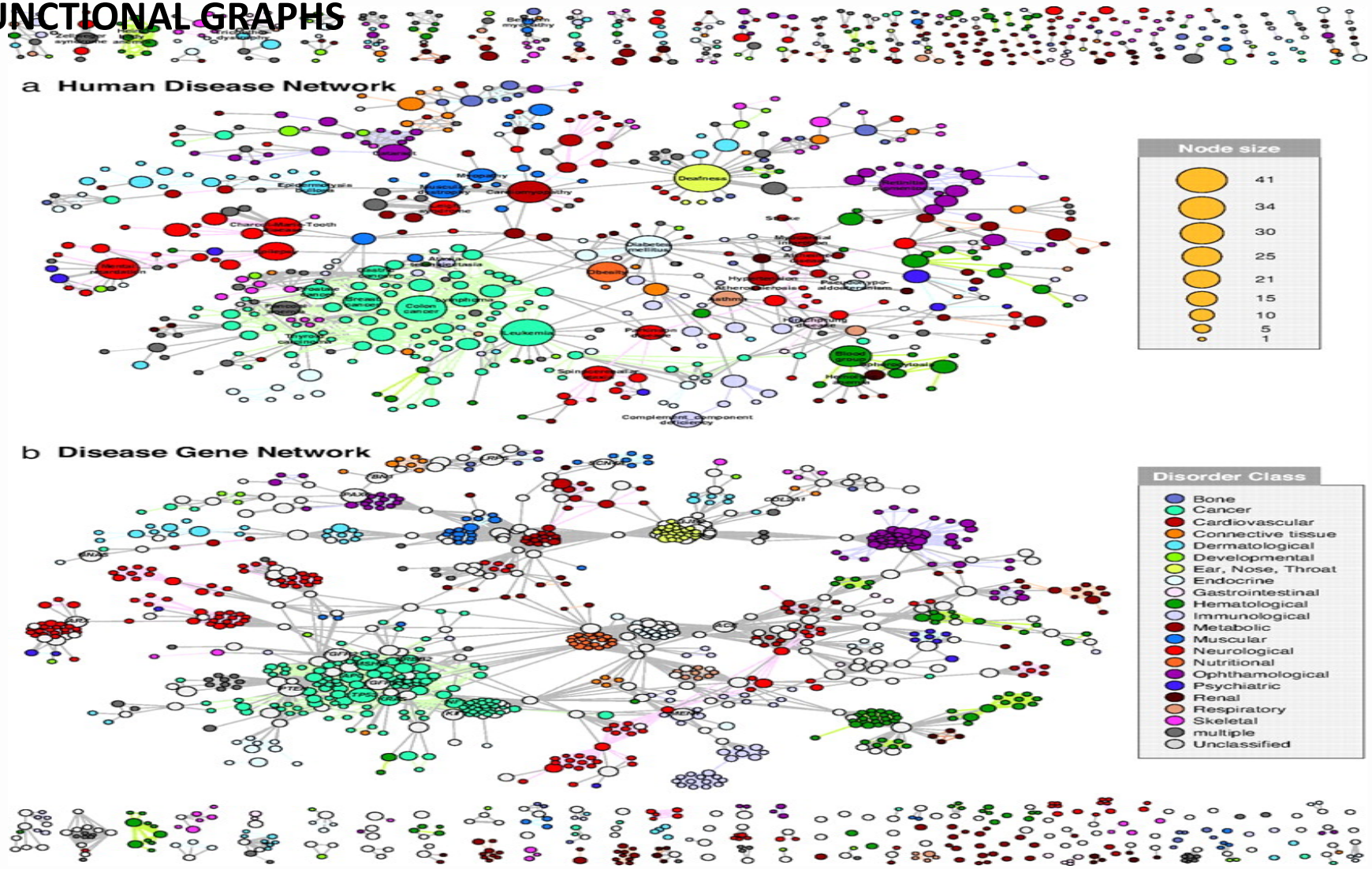
Bioinformatics

VARIABILITY



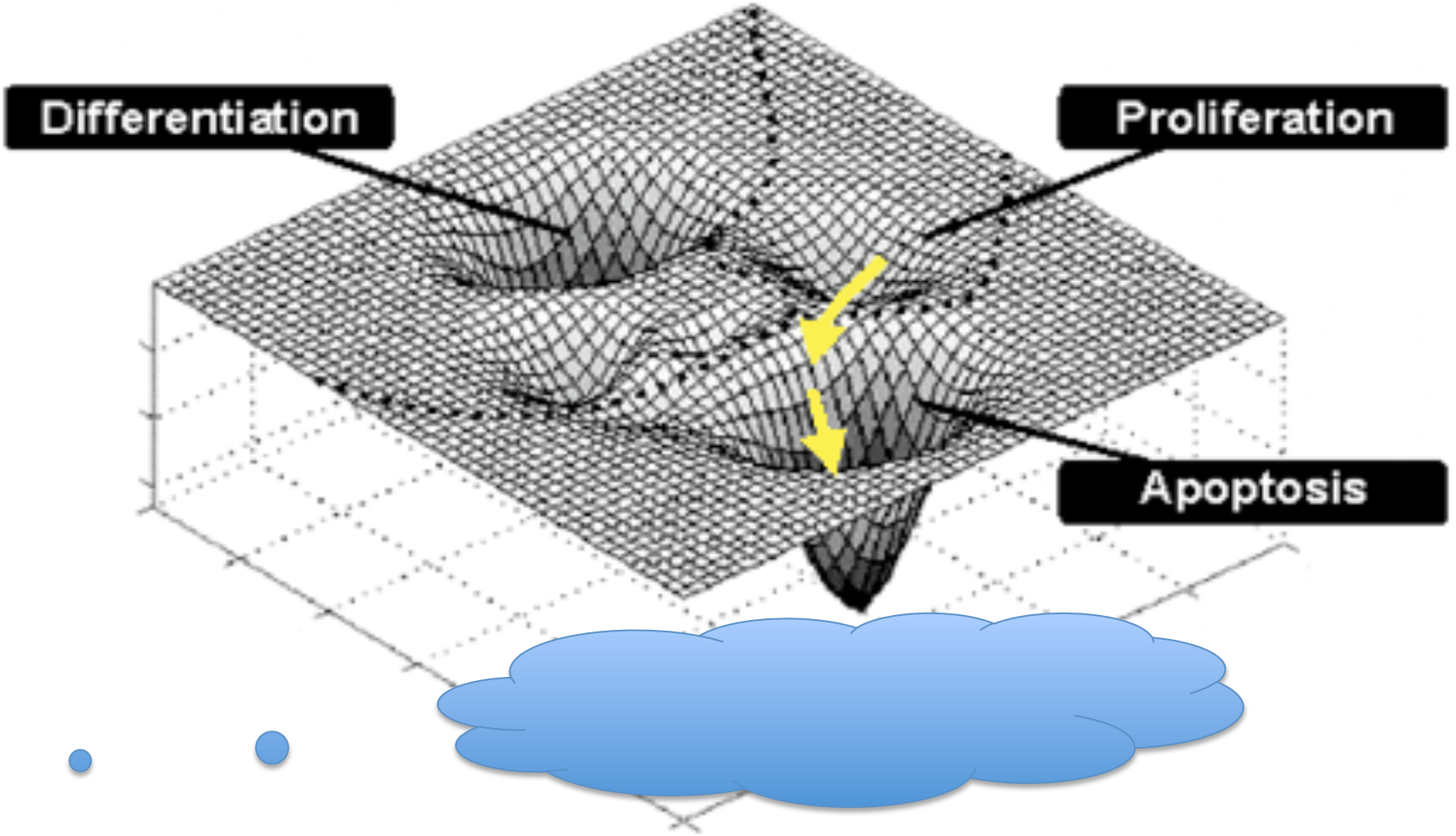
[An integrated map of genetic variation from 1,092 human genomes](#)
Nature 491, 56–65 (01 November 2012)

FUNCTIONAL GRAPHS



Goh K et al. PNAS 2007;104:8685-8690

PNAS



Attractor landscape representation of cell fate determination. A hypothetical `potential landscape' that represents the n-dimensional state space compressed into two dimensions (XY) for visualization purposes.

FINAL QUESTIONS:

1) When is gene regulation needed or benefit for a cell (or an organism)?

Under rapid changes of the environment. [E. Hartl and all, 84]. Other situations ?

2) Adaptability versus optimality [G. F. Gause , 34 …] : why modular organization of the network won [L. L. Hartwell and all , 99 …] ?

-multi needs/task and time change in the environment + slow structural change capabilities call for modularity instead of optimality. Fitness function not always exists or a good definition is not known.
-.
3) What are the known mechanisms of robustness in transcription regulation?
(against intrinsic stochasticity and extrinsic noise)

(a) Integral feedback (negative feedback proportional to time integral of the difference of the actual level to the goal. [N. Barkai, S. Leibler, 97]
(b) Kinetic proofreading (time-delay of signal, small error rate of recognition) [J. Hopfield, 74]
(c) Self-enhanced degradation (non-linear diffusion) minimize errors in pattern location [A. Eldar and all, 02]
(d) When stochasticity is a most [ex. T-cell allelic exclusion]

4) How the description of a specific level can be integrated in the next level ?
Module to network.
Single cell to cell population.