Feed-forward loops: Linking Function, Plasticity, Evolvability and Abundance

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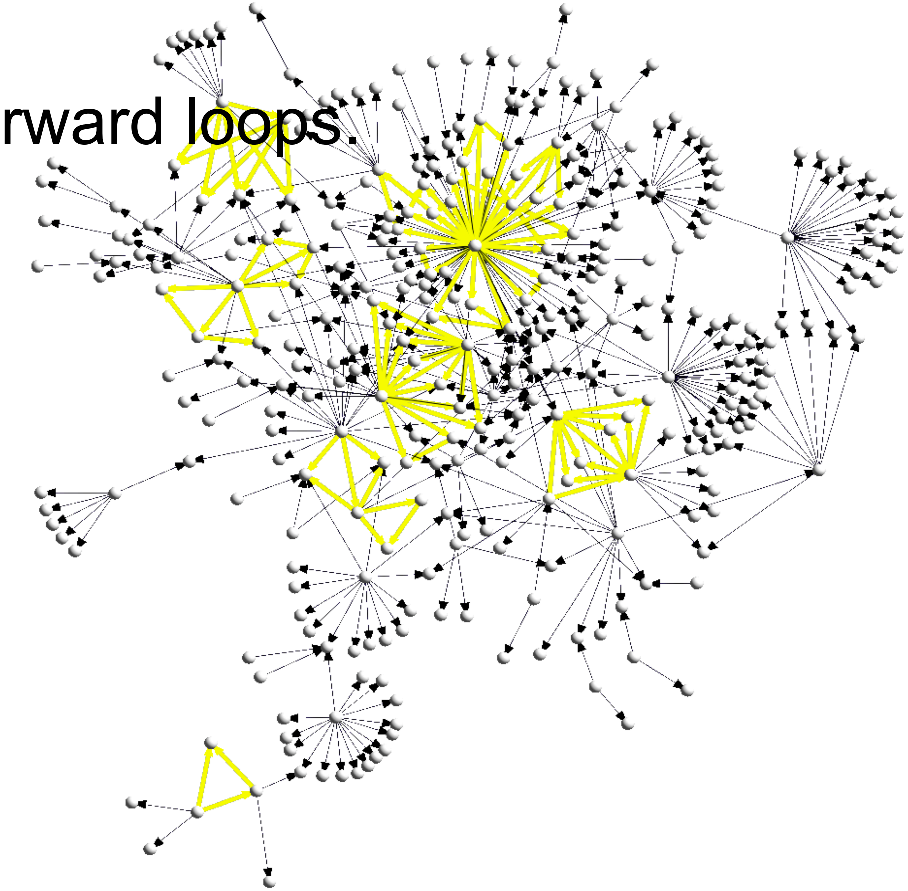
Outline

1.Why networks?

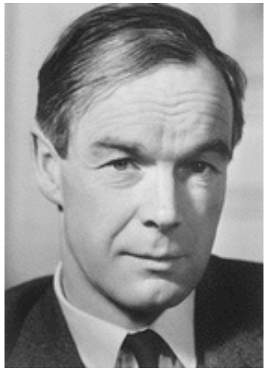
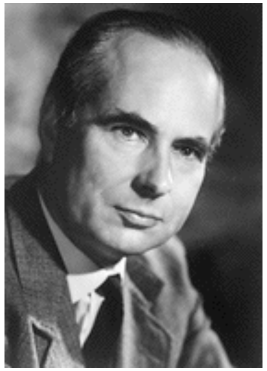
Systems biology and interaction webs.

2. Who put all the motifs?

The evolvability of feed-forward loops.



Early Pioneers

Alan Hodkin Andrew Huxley

Modelization of the nerves action potential (giant squid neuron) 1952
Noble Prize in 1963

Alan Turing

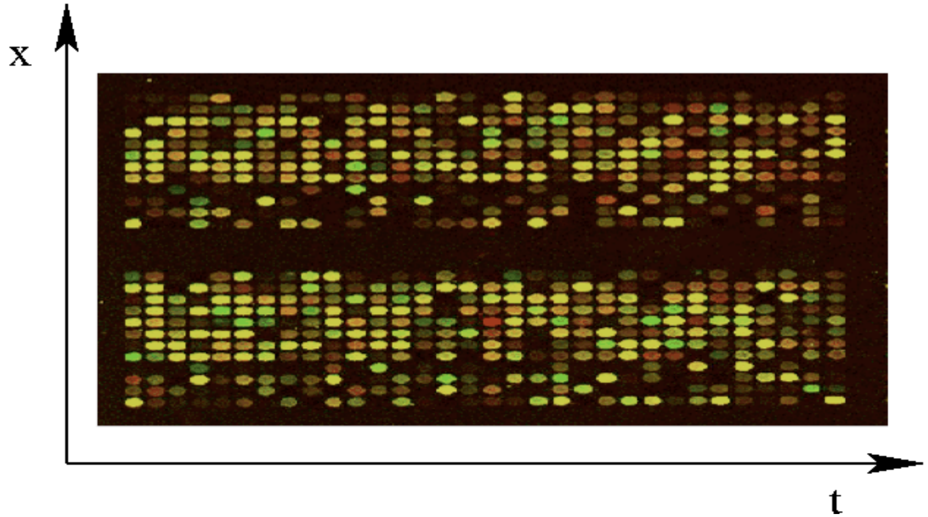
(Biological) pattern formation as result of simple physical constraints (reaction-diffusion).

Denis Noble

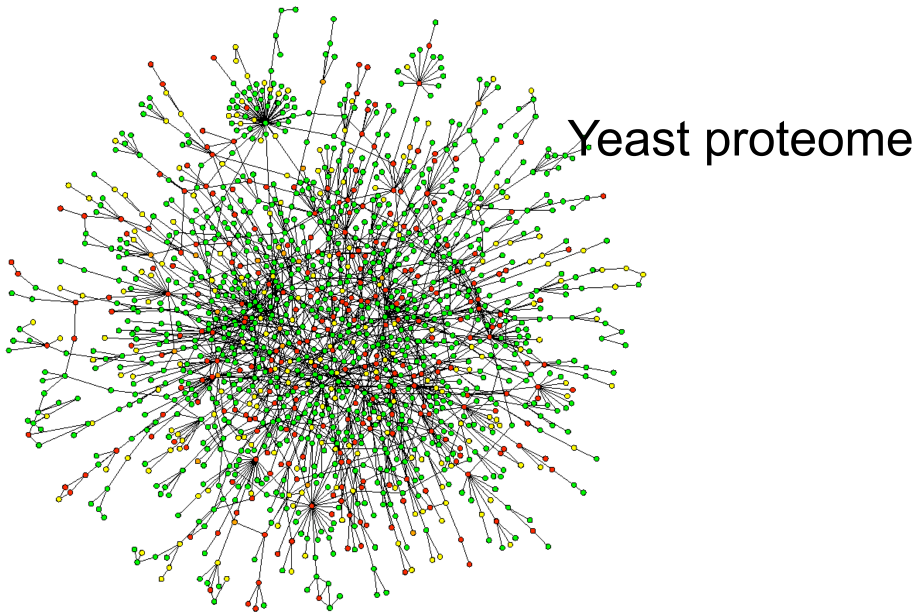
Modelization of a working heart in 1960 and development of the virtual heart using supercomputers.

Why NWs? A wealth of data

interactions
in space and time

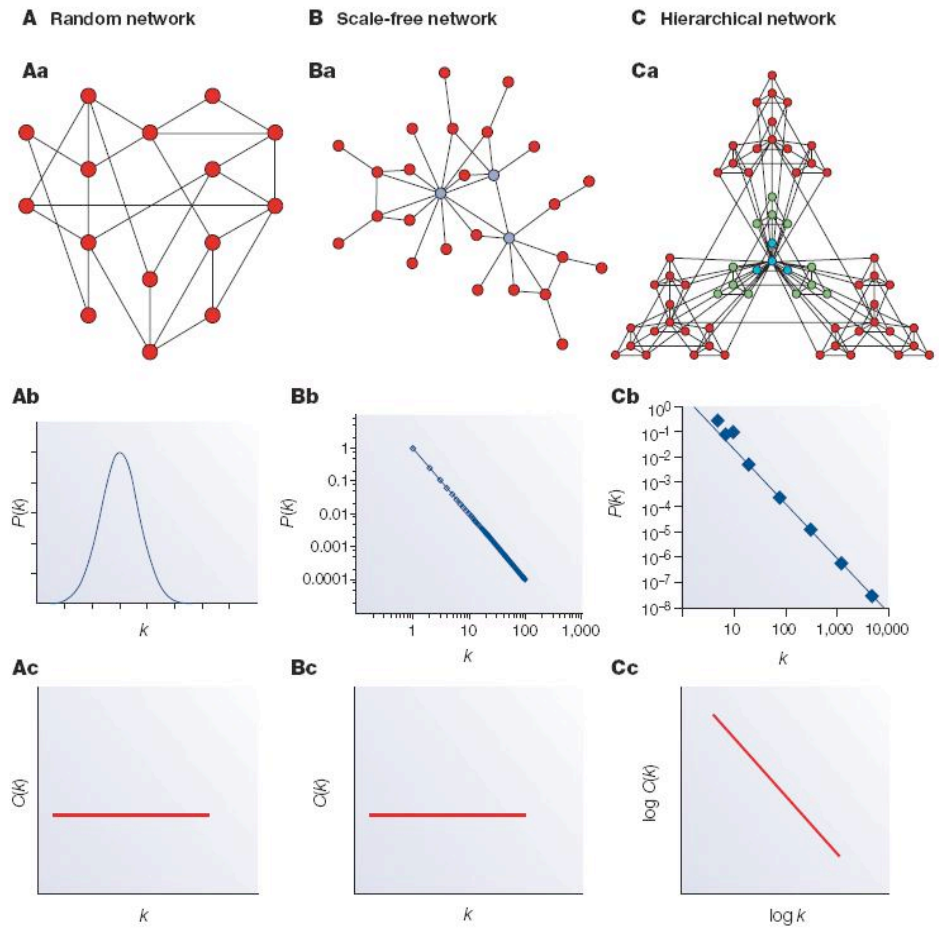


networks as representation
for maximal physical interactions



Large NWs

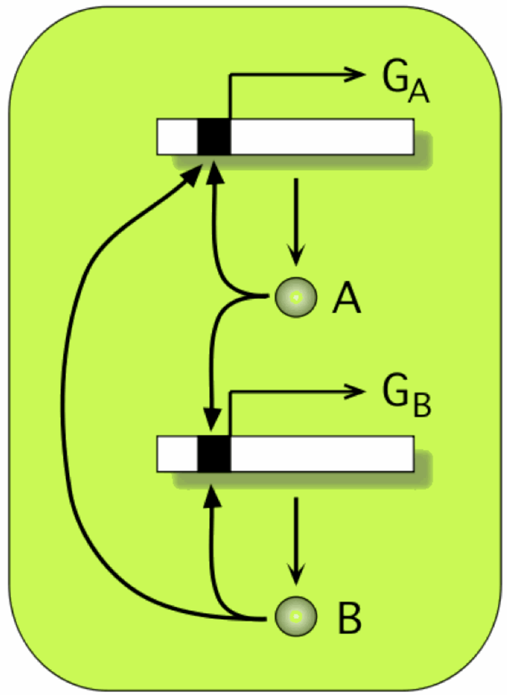
metabolic
protein interaction
transcriptional
ecological
functional: apoptosis
cancer
signaling



Barabasi et al. 2004

graph theory and statistical measures (eg. k, p(k), <l>, C(k))

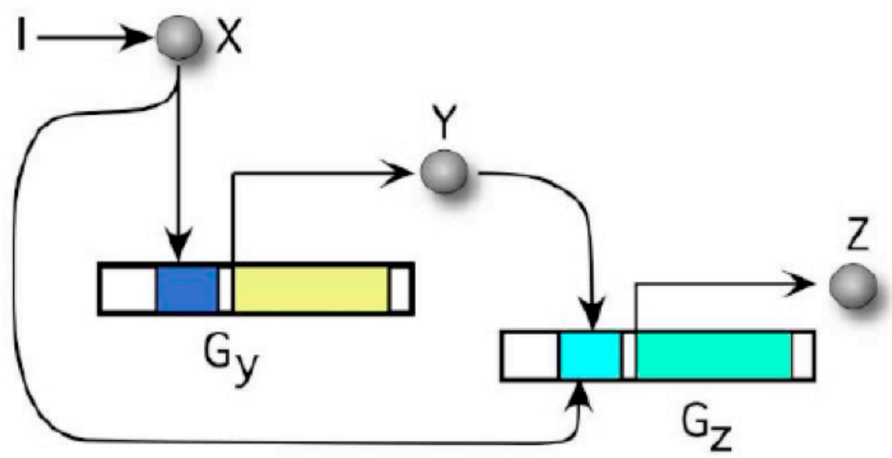
Small NWs



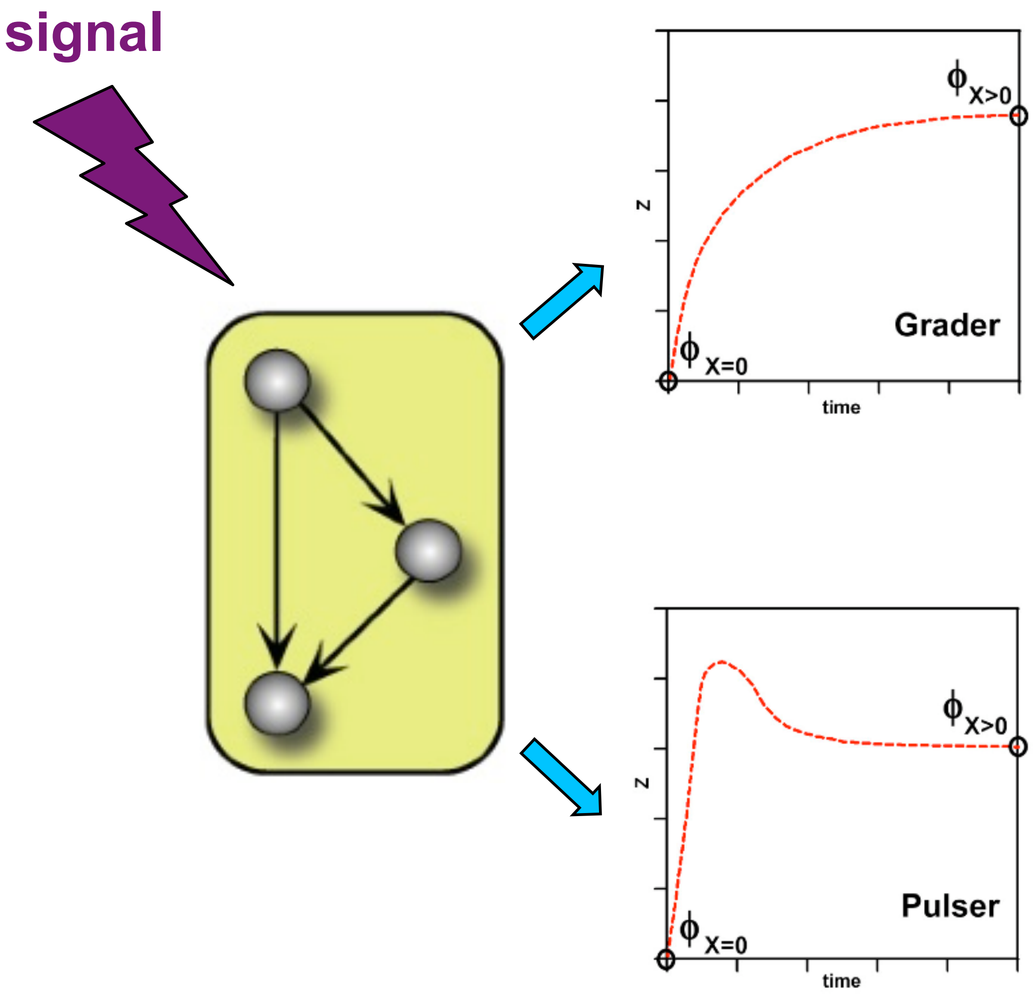
.. subsections of large NWs

- analytically calculable in their entirety for their *local* qualities
- supersection crucially important for understanding their plasticity
- questions on the emergence of the *status quo*

The feed-forward loop motif (FFL)



Response to external signals



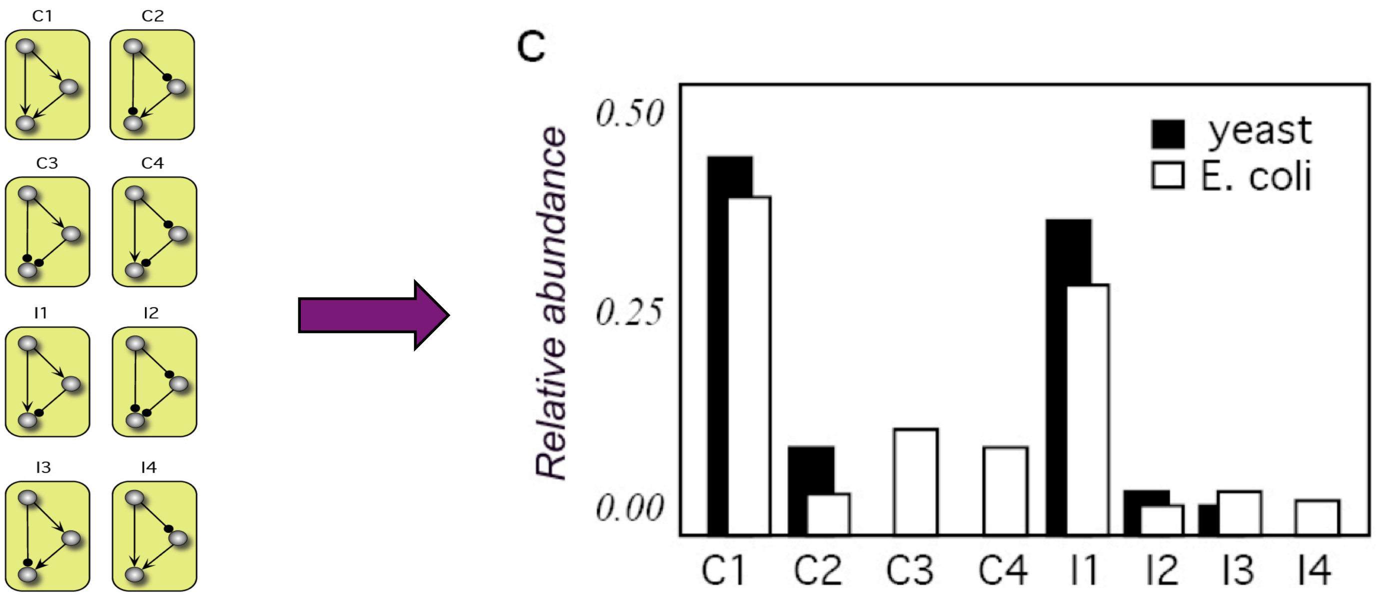
delayed/filtering response to signal

accelerated response to signal

FFLs and their natural abundance

	X-Y	X-Z	Y-Z
C1	+	+	+
C2	-	-	+
C3	+	-	-
C4	-	+	-

	X-Y	X-Z	Y-Z
I1	+	+	-
I2	-	-	-
I3	+	-	+
I4	-	+	+

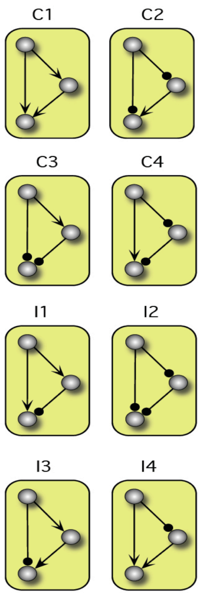


Mangan et al. 2006

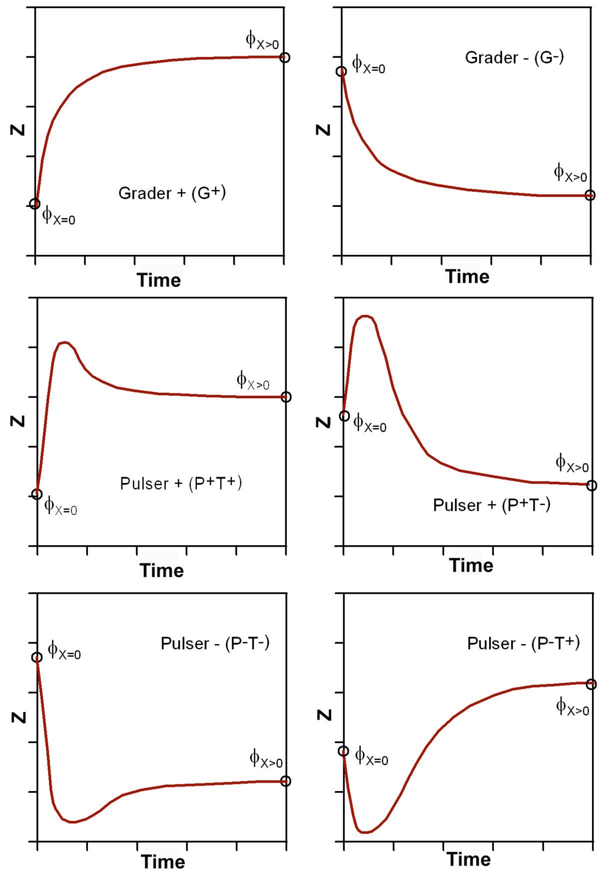
The pattern of abundance cannot be explained in a satisfactory manner by functionalist (single topology -> single function) nor by neutralist (by-product of growth rules) arguments.

FFLs and their Trajectory

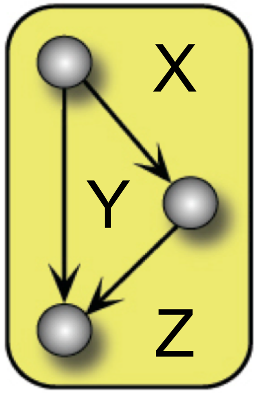
set of all FFLs



set of all functionalities



FFL model



$$\dot{Y} = \gamma_Y \left(\frac{1+\alpha^X \omega_Y^X X^n}{1+\omega_Y^X X^n} \right) - d_Y Y$$

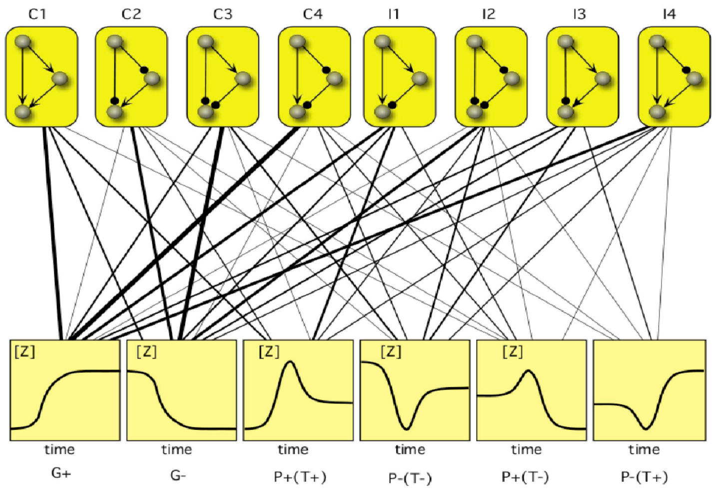
$$\dot{Z} = \gamma_Z \left(\frac{1+\beta^X \omega_z^X X^n + \beta^Y \omega_Z^Y Y^m + \beta^{XY} \omega_Z^{XY} X^n Y^m}{1+\omega_z^X X^n + \omega_Z^Y Y^m + \omega_Z^{XY} X^n Y^m} \right) - d_Z Z.$$

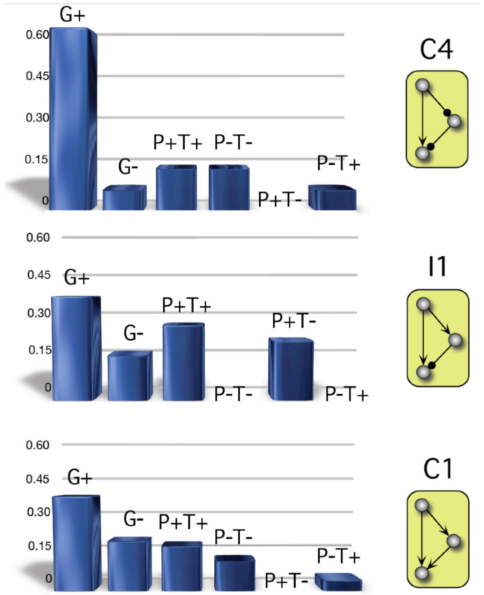
- Which functionality can be expected?

- Intrinsic properties of the system allow to deduce the probability for a given function, independent from the numeric values of the parameters.

  - Key parameter define the characteristic shape of the nullcline (BR)
  - Nullclines‘ shape confines the trajectory
  - A separatrix defines the limit of two distinct qualit. behavior of the trajectory

Probability of Function





$$P_{ij} = \Omega_k \sum_{i=1}^{T_{jk}} p_{ik} \Psi_{ijk}$$

p_{ik} prob for a certain set of parameters to implement seq. *i* for motif *k*

P_{ij} prob for motif *k* to implement functionality *j* described by seq. *i*

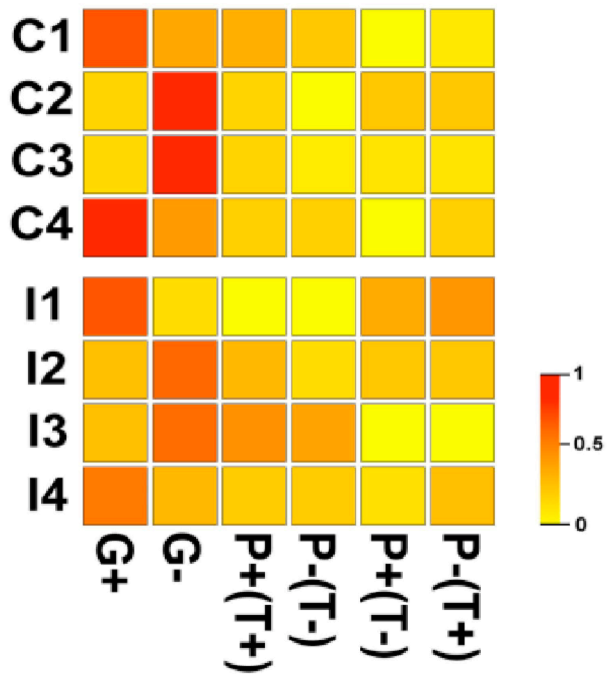
Ψ_{ijk} number of equal dynamical outcomes j

T_{jk} total number of backbone seq. *i* implementing dynamic *j*

Ω_k normalization constant

Macía, Widder and Solé 2009

Plasticity of FFLs



Quantitative description of the FFLs‘ underlying plasticity independent of parameters.

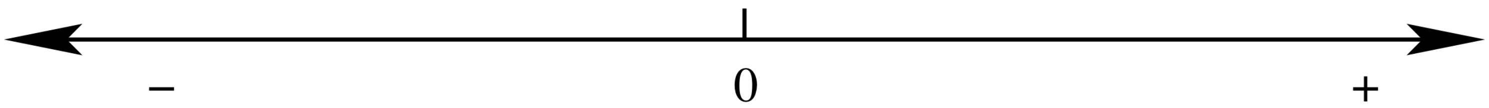
Kurtosis

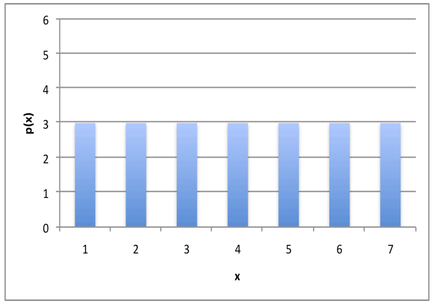
$$K = \frac{\mu_4}{\sigma^2} - K_0$$

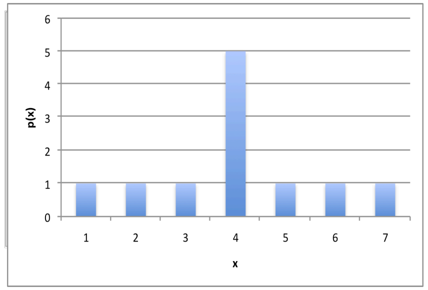
μ_4 4th moment around the mean

σ standard deviation

K_0 reference value (normal dist. 3)





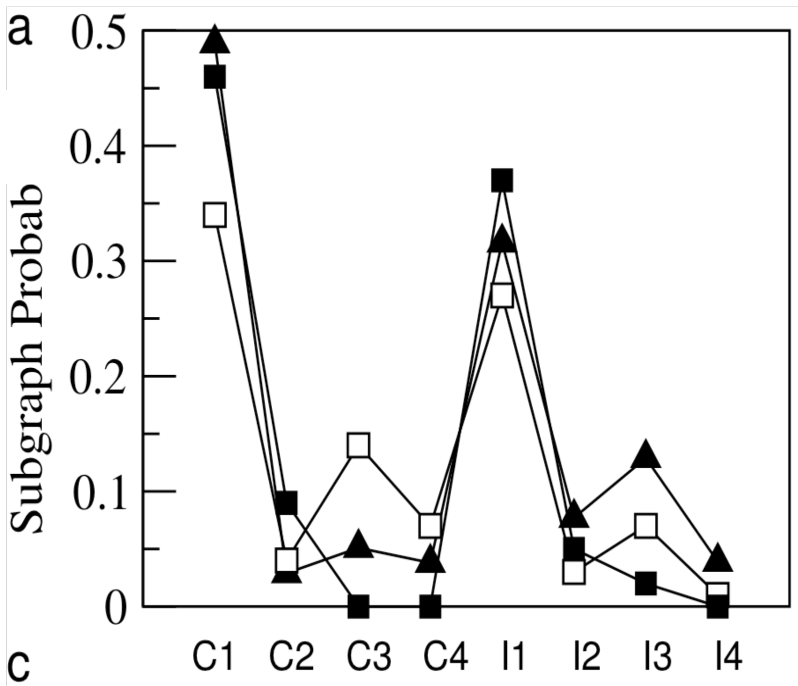


..the peakedness of a probability distribution

Breaking the abundance pattern

$$\psi(\Gamma_i) = \mid K(\Gamma_i) \mid - K_0$$

$$\boxed{\begin{aligned} \rho(\Gamma_i) &= \frac{1}{\alpha}\psi(\Gamma_i)^{-1} \\ \alpha &= \textstyle\sum_{j=1}^{8} \psi(\Gamma_j)^{-1} \end{aligned}}$$



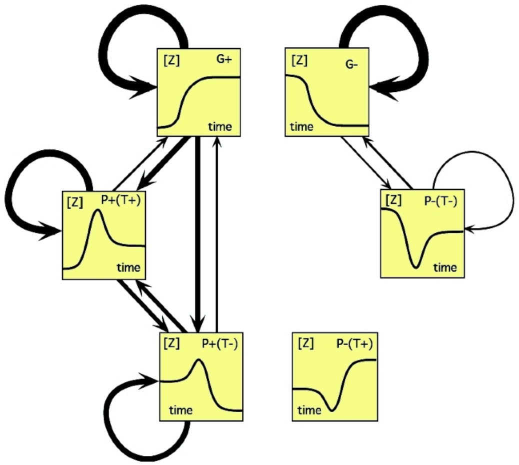
$\rho(\Gamma_i)$ prob of appearance for subgraph Γ_i

$\psi(\Gamma_i)$ degree of plasticity of subgraph Γ_i

black boxes.......natural abundance yeast
white boxes.......natural abundance E.coli
black triangles...predicted probabilities

Linking plasticity and evolvability

C1



transition probabilities between different functions for a given subgraph upon mutation (of parameters)

Table 1: Transition probabilities for single mutations, C1

	G^+	G^-	P^+T^+	P^-T^-	P^+T^-	P^-T^+
G^+	0.251	0	0.027	0	0	0
G^-	0	0.329	0	0	0.008	0
P^+T^+	0	0	0.180	0	0	0
P^-T^-	0	0	0	0.157	0	0
P^+T^-	0	0.016	0	0	0.031	0
P^-T^+	0	0	0	0	0	0

robustness against mutation

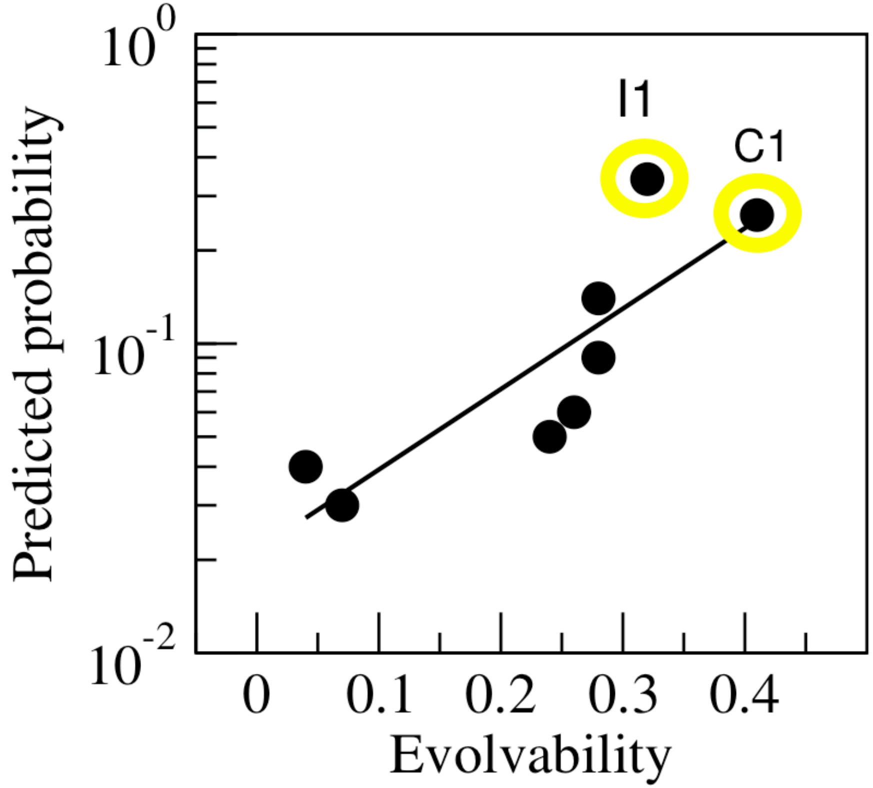
Linking evolvability and abundance

$$\mathcal{E}(\Gamma_i) = 1 - \frac{Tr(\mathbf{\Omega}_m(k))}{Tr(\mathbf{\Omega}_1(k))}$$

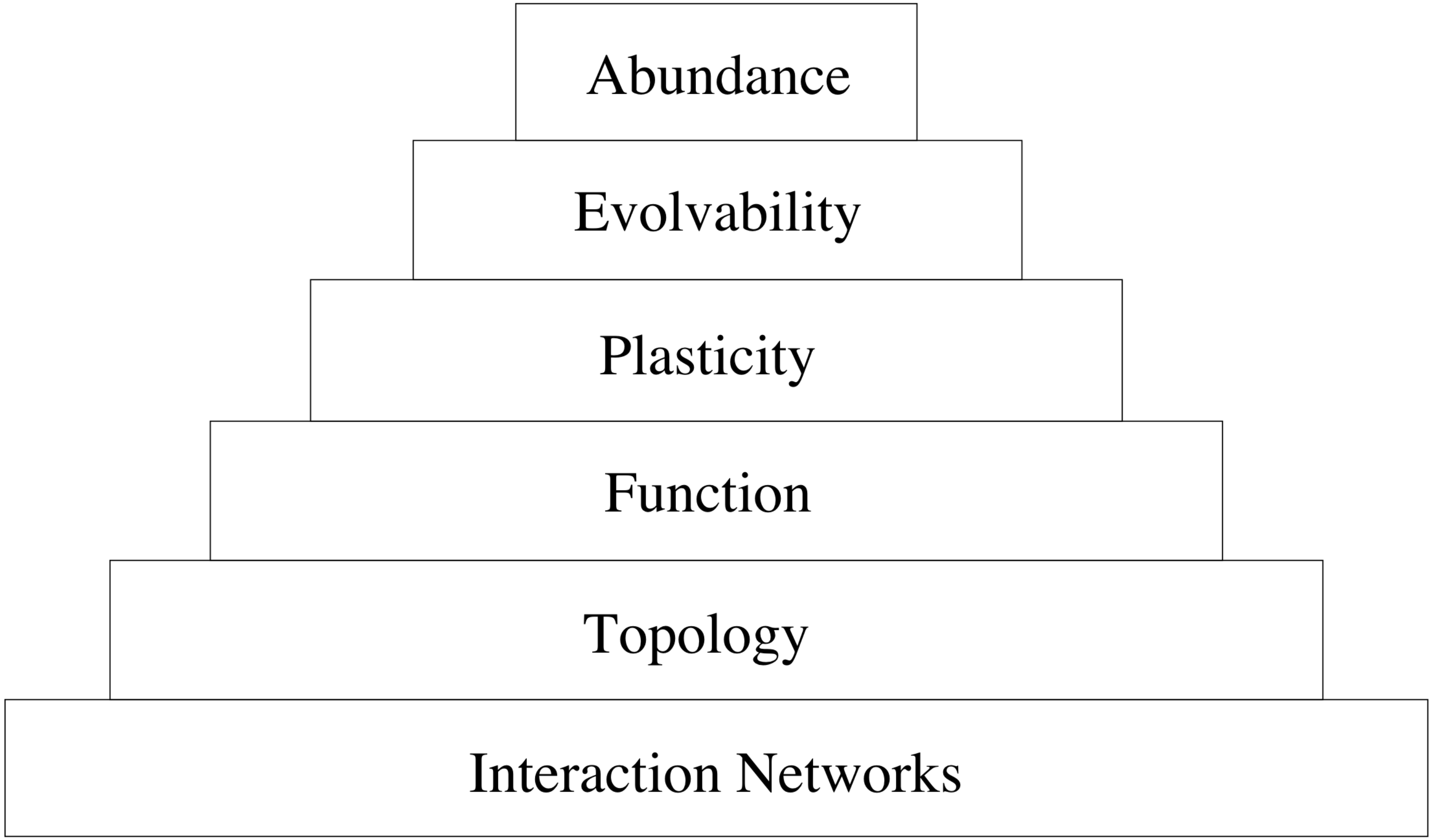
$\mathcal{E}(\Gamma_i)$ evolvability of subgraph Γ_i

$Tr(\Omega_n(k))$ trace of the transition matrix between functions with n mutations applied

comparing robustness against single and multiple mutations



Conclusions



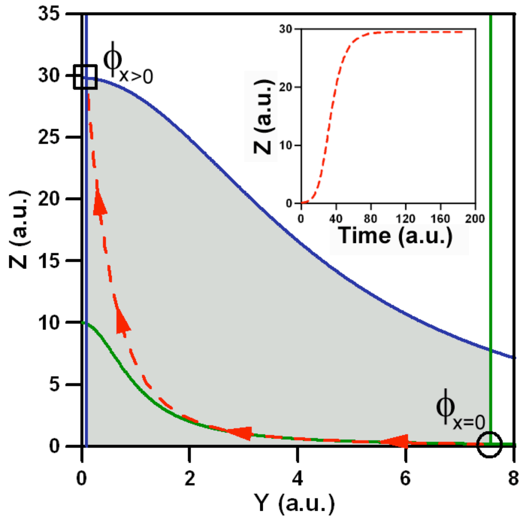
Thanks!

Part 3 – FFL and its Nullclines

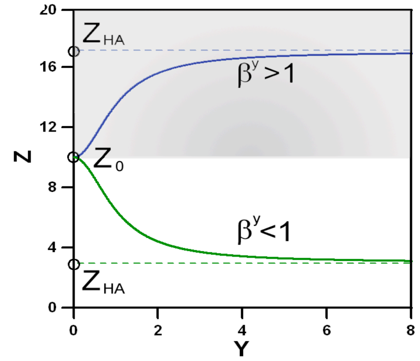
$$(Y)_{\dot{Y}=0} = \frac{\gamma_Y}{d_Y}\left(\frac{1+\alpha^X\omega_Y^X X^n}{1+\omega_Y X^n}\right)$$

$$(Z)_{\dot{Z}=0} = \frac{\gamma_Z}{d_Z}\left(\frac{1+\beta^X\omega_z^X X^n+\beta^Y\omega_Z^Y Y^m+\beta^{XY}\omega_Z^{XY}X^nY^m}{1+\omega_z^x X^n+\omega_Z^Y Y^m+\omega_Z^{XY}X^nY^m}\right)$$

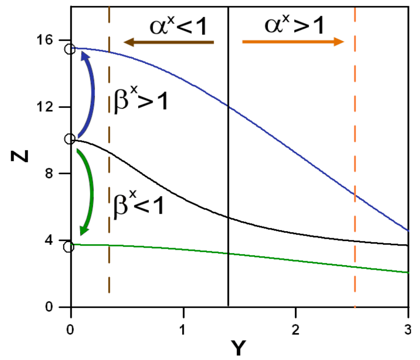
change of the nullcline's shape
upon input confine the trajectory



certain parameters account for
characteristic shapes



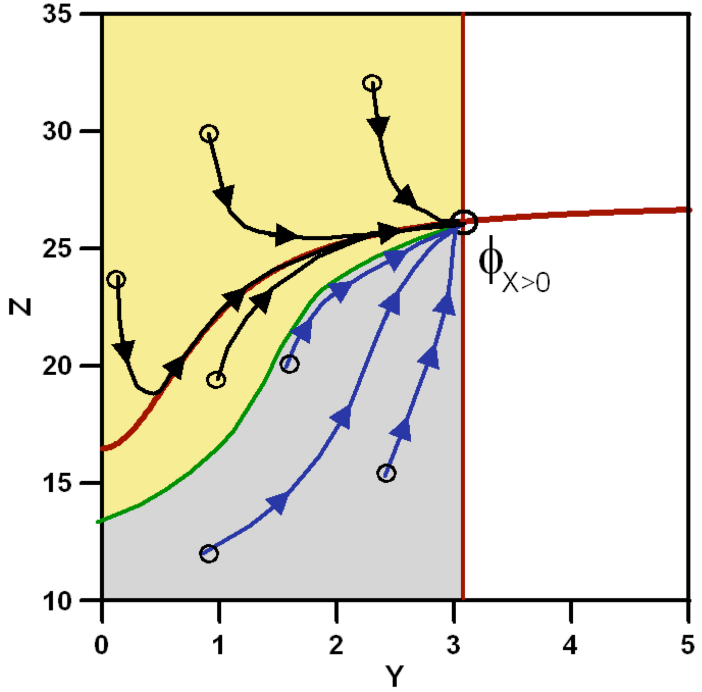
w/o input



with input

Part 3 – The Separatrix

Starting from different ICs in phase space, two distinct qualitative behaviours are encountered: joining of the nullcline before the FP or joining at the FP. The regions are separated by Z(Y).



Using condition $\frac{Y_f - Y}{Z_f - Z} = \frac{\dot{Y}}{\dot{Z}}$

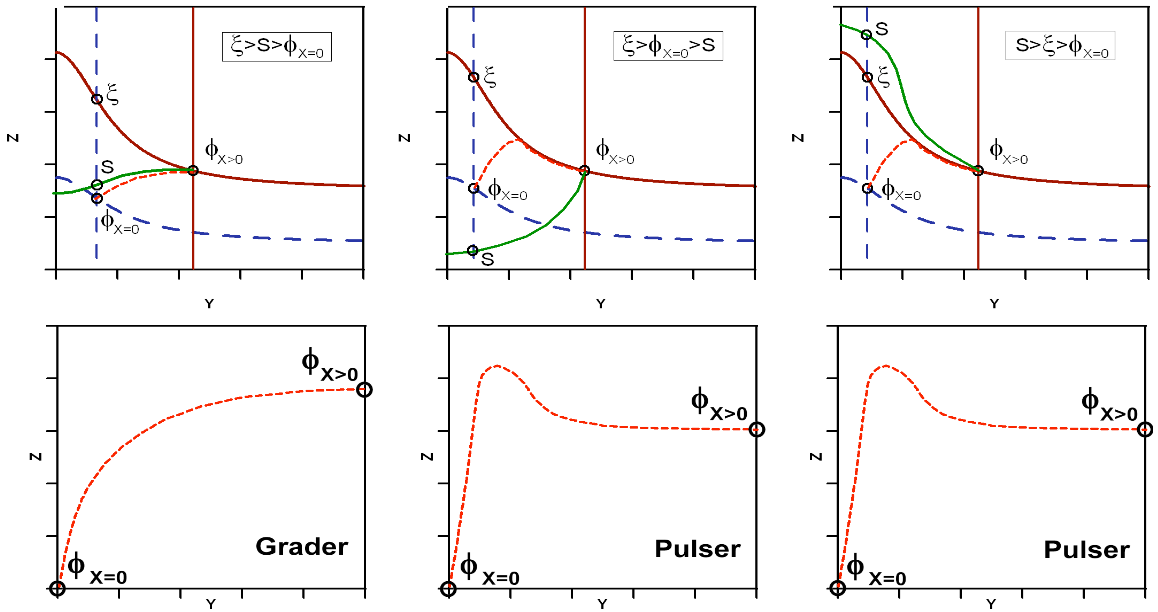
we find the analytical expression of the separatrix

$$Z(Y) = \left(\frac{1}{1 - \frac{dY}{dz}} \right) \left[\frac{\gamma Z}{dz} \left(\frac{1 + \beta^X \omega_Z^X X^n + \beta^Y \omega_Z^Y Y^m + \beta^{XY} \omega_Z^{XY} X^n Y^m}{1 + \omega_Z^X X^n + \omega_Z^Y Y^m + \omega_Z^{XY} X^n Y^m} \right) - \frac{dY}{dZ} Z_f \right]$$

Part 3 – Which functionality?

The relative position of 3 points at the crossing with $Yo|_{x=0}$ determines the functionality of the trajectory for a given nullcline:

Separatrix, $Zo|_{x=0}$ and $Zo|_{x>0}$



$\beta^{xy}, 1$	β^{xy}, β^{y}	$Zo\vert_{x=0}, Z_{HA}\vert_{x>0}$	$Zo\vert_{x>0}, Z_{HA}\vert_{x=0}$	Slope	$\phi_{x=0}, \phi_{x>0}$	$\phi_{x=0}, \xi$
Ø	>	>	*	*	<	*

The parametric backbone sequence determines the shape of the nullcline.