MIND WITHIN THE MATTER? – HOMEOSTASIS IN COMPLEX NETWORKS

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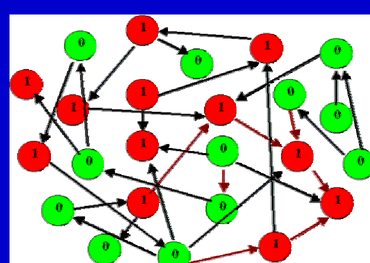
GENERAL

- Boolean networks are mathematical models for studying complex dynamical systems (biological systems on various levels of organization i.e. genetic networks, metabolic networks, neural networks, organisms, ecosystems)
- a BN consists of **N** binary elements,
- each element has randomly assigned a **Boolean function** (determines the value of the element, according to the values of its inputs)
- **Inputs** to elements are randomly determined, and the number of inputs per element varies, this is called **variable K**
- the initial values of elements are also randomly chosen



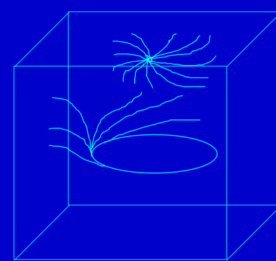
A	B	C	
0	0	0	0
0	0	1	1
0	1	0	1
0	1	1	1
1	0	0	0
1	0	1	0
1	1	0	1
1	1	1	0

- the **computation** of a network: values of elements are synchronously updated, according to the previous state of the network, so a network follows a succesion of discrete states that are represented with a curve in the state space, called a **trajectory**

-eventually all trajectories run into attractors, that are either **point attractors** (static end states) or **cyclic attractors** (periodic end states)

-all trajectories that run into the same attractor form a **basin of attraction**

-attractors define the orderliness of network´s dynamics



-point atractors and short and moderately long cyclic attractors are chracteristic for **ordered dynamics**, whereas long and extremely long cyclic attractors denote **disordered dynamics**

- the **degree of order** can be estimated from the number of attractors, their length, their similarity, the size of attractor basin, the fraction of frozen elements, ...

- a **perturbation** (switching the value of one or more elements) causes the system to leap from one trajectory to another, that can run into the same attractor or into some other attractor

-with perturbations we analyse the **homeostasis** of a network

K VARIABLE NETWORKS

-previously employed models with constant K are less appropriate for modelling real systems, because the number of inputs in real systems is not equal for all elements

-recent experimental studies of real networks (metabolic, genetic) confirmed this assumption

-independently of a similar research we introduced a variable K model and first analysed the degree of order and its origin and then the perturbations of networks

-apart from a similar Fox and Hill´s model we also allowed **no-input** and **no-output** elements

-we assumed that especially no-input elements markedly influence network´s dynamics, and confirmed this to be true, since increasing number of no-input elements **increases dynamic diversity** of the network (referring to the number and the similarity of attractors)

-we thoroughly investigated the sources of order, one being the **distribution of inputs** and **canalysing properties of Boolean functions**, and the other one the **complex dynamics** itself

-we were further interested in how much homeostasis do attractors have, so we investigated the perturbations of attractors

PERTURBATIONS OF ATTRACTORS

-a perturbation means that the value of an element is switched from 0 to 1 or vice versa

-a perturbation throws the network out from attractor on a trajectory that can run into the same or into some other attractor

-how far the perturbation throws the network depends on the number of perturbed elements

-we expected that with only one element perturbed, the network mostly returns into the same attractor and that with more element perturbed this homeostasis decreases (the network falls into other attractors more frequently)

-we also expected that perturbations of constitutive elements push the network more often into other attractors, since they have stronger influence on network´s dynamics

METHODS

-we randomly chose an attractor state and perturbed a given number of randomly chosen elements

-on each attractor we made several hundred perturbations and counted how many times the network fell into each of found attractors

-perturbations were made on all discovered attractors, and sometimes we found **new attractors**, that we further perturbed

-we varied the number of perturbed elements, the number of perturbations on one attractor, and also we peturbed only no-input elements

BIOLOGICAL INTERPRETATION

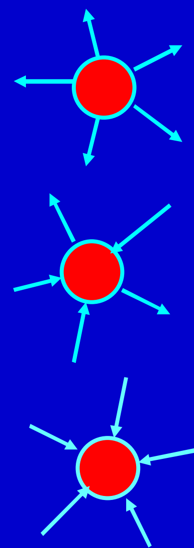
-we interpreted our model as a genetic network, but with smaller modifications it can also represent a metabolic, a neural, or an ecological network

-in this case perturbations are internal or external disturbances that influence gene expression

-no-input elements represent constitutive genes or external factors, that induce inducible genes, the network has no feedback influence on them, so their value remains constant (depending on their initial state)

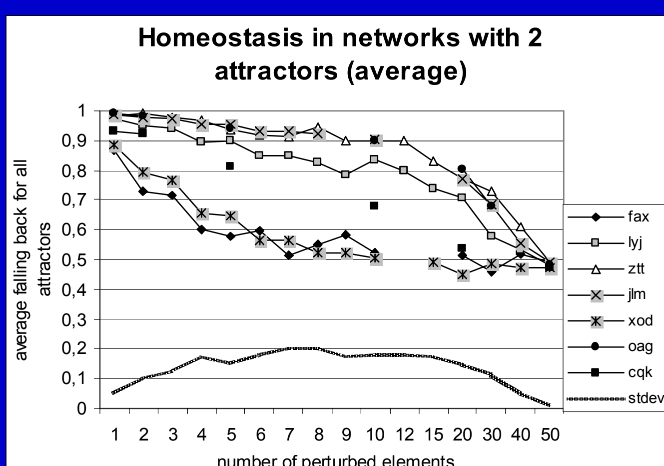
-connected elements represent inducible genes, that further induce some other genes

-no-output elements have no direct influence on the network, but they reduce the effective number of connections (increase the order), they represent inducible genes that don`t induce any other genes

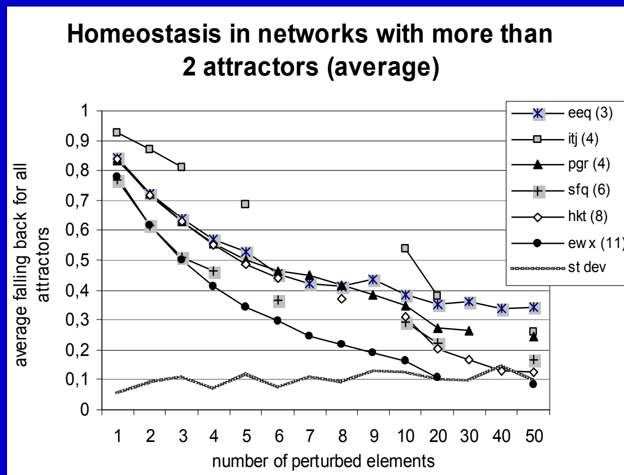


RESULTS

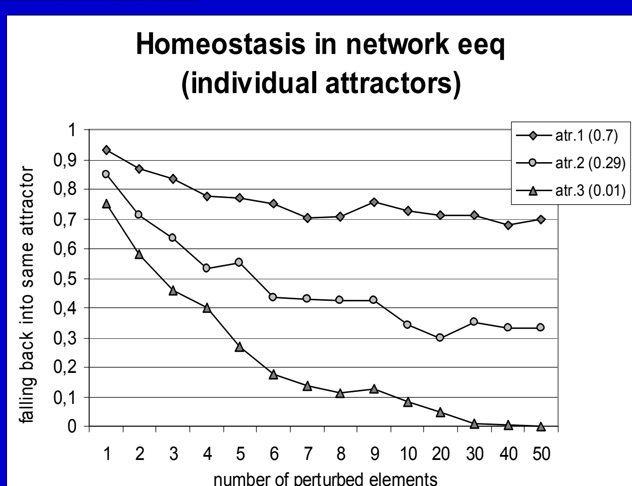
- average homeostasis in networks with 2 attractors and 0 no-input (or constitutive elements) is very diverse, depending on individual network and its attractors



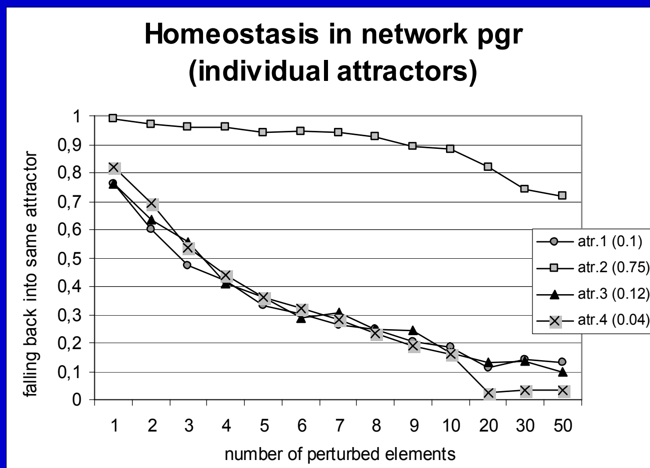
-average homeostasis in networks with more than 2 attractors is also quite diverse, though less than in networks with 2 attractors. Some attractors have higher homeostasis, than other.



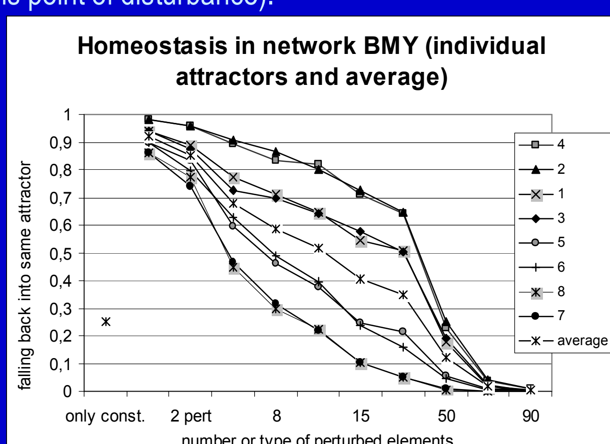
-if we perturb 50 elements this corresponds to a random initial state, so the fractions of falling back into attractor, match their relative portions, obtained with random initial state method



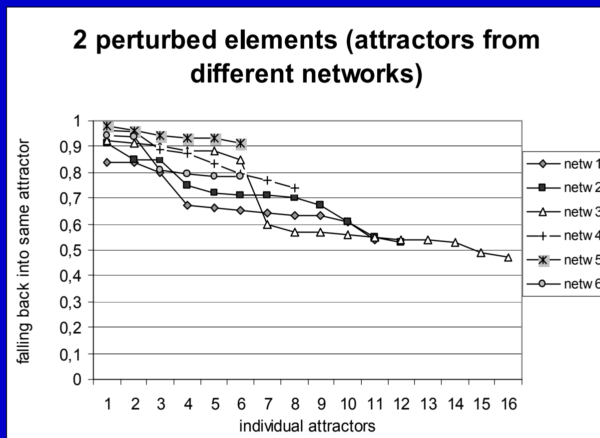
-homeostasis of attractors is very diverse, attractors with large basins (large relative portions) are very resistant to perturbations. Attractors with smaller basins have all very similar homeostasis, despite their somewhat different sizes



- homeostasis in this network is again very diverse. It is interesting that there are pairs of attractors with practically the same homeostasis. Homeostasis with only constitutive elements perturbed (2) is very low, compared to other elements perturbed (it takes 10 perturbed elements for 2 attractors with lowest homeostasis, to reach this point of disturbance).



- the graph represents different networks with 2 no-input elements, that have different numbers of attractors. Attractors were sorted in a decreasing manner, according to their homeostasis. It is interesting that within an individual network they form separated, almost discrete groups with nearly the same homeostasis



DISCUSSION

-homeostasis in networks when few elements is perturbed is on average high and decreases with increasing number of perturbed elements

-with 1 element perturbed, the network mostly returns into the same attractor, when the number of perturbed elements increases, the network falls into other attractors more frequently

-with no-input (or constitutive) elements perturbed the network mostly falls into other attractors (homeostasis is significantly lower)

-different attractors have very diverse homeostasis, that depends on its basin size (attractors with large basins have higher homeostasis, than attractors with smaller basins)

-perturbations of attractors turned out to be a very efficient method for discovering new attractors (that were not found with random initial states method)

- with further perturbations of newly found attractors, some new have been found again (we found some orders of new attractors).

-these new orders of attractors seem to be closely connected, since new attractors could be found only from previously discovered ones (they are difficult to find with random searching, probably because they have small, irregularly shaped or fragmented basins)

-in genetic interpretation of the model no-input elements represent constitutive genes or external factors that influence gene expression, and their perturbation mostly diverts the network into some other attractor, that represents a different gene expression pattern

-another way to divert the network into other attractor is to perturb more elements

-this diverting processes would happen during cell differentiation or some pathological disturbances of normal gene expression patterns (carcinogenesis)

-as all abstract models, this model is deviod of physical laws (so there is no thermodynamic fluxes, that would drive self-organization of system). The order originates solely from interactions between elements. This demonstrates that non-equilibrum thermodynamics is not the single source of order in the nature

-the matter self-organizes under favourable conditions (there are multiple organizational principles). Emergent systems have a new level of organization and new structures, that tend to maintain their organization (homeostasis). So is spontaneous organization and order a sign of some kind of mind that is innate to matter?