# Compositional Basis of Biological Design

# *(the interaction of modules)*

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Freiburg, Germany

2009-2012

# Outline

- Complexity
- Recognition of modules
  - modularity in engineering
  - modularity in nature
- Origin of modularity
  - nature of mutations
  - generalization of copy, cut and paste mechanisms
- Modularity of genetic networks in pi-calculus
  - elements of networks
  - genetic motifs
- Scalable design
  - emergent behavior
  - compositional evolution

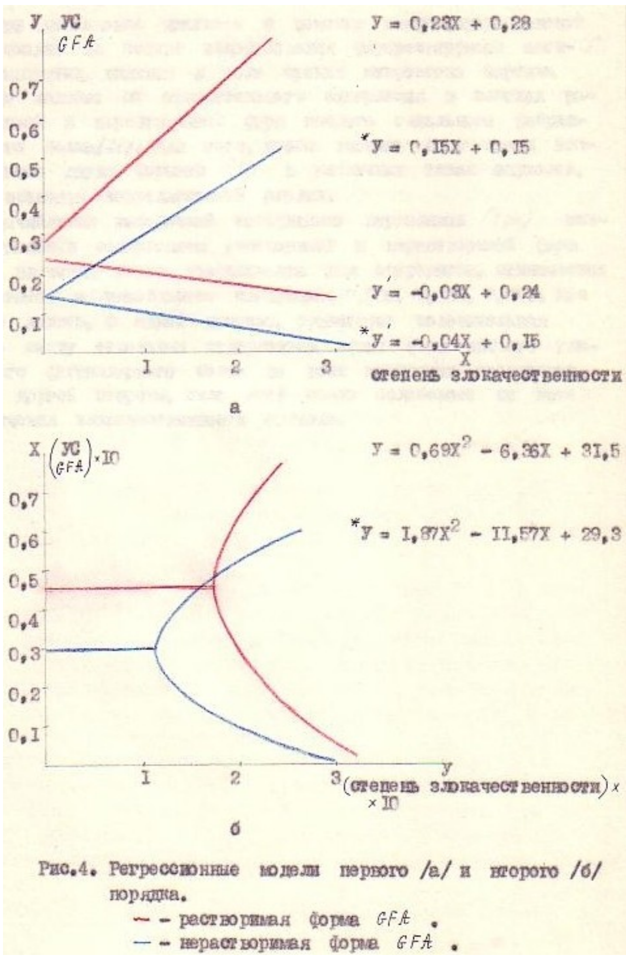

Kuznetsov, IGI Global. 2009

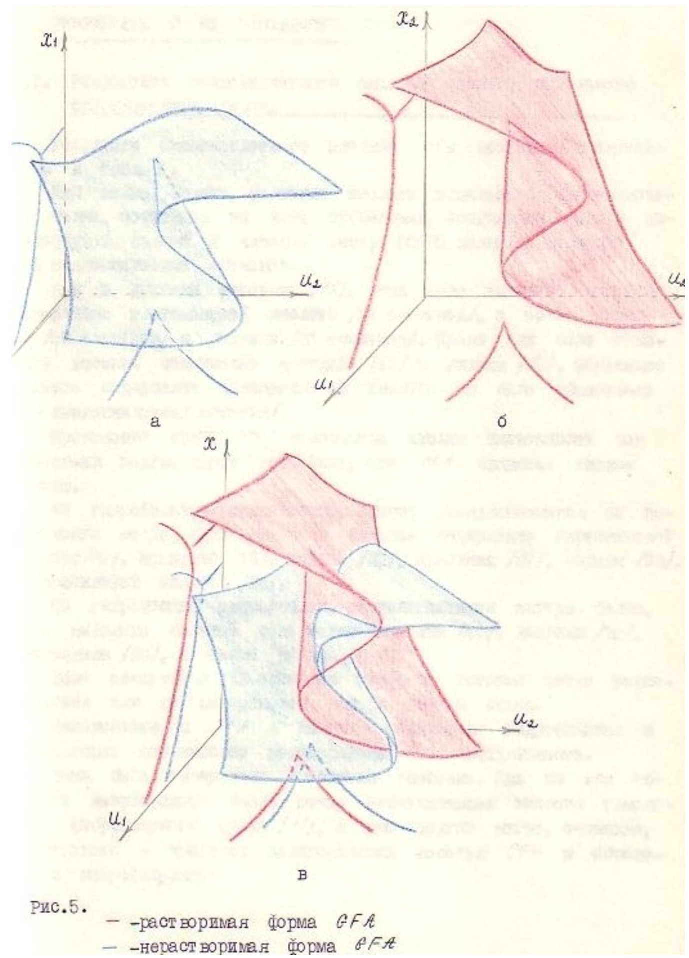
# Complexity

- a fundamental problem of science, why does matter growth in complexity?

- “**Complexity** arises then … components interact with each other in ways ... more than uniform, frequent elastic collisions. Interactions among components can lead to all kinds of nonlinear behavior.” [Herbert A. Simon, 2005]

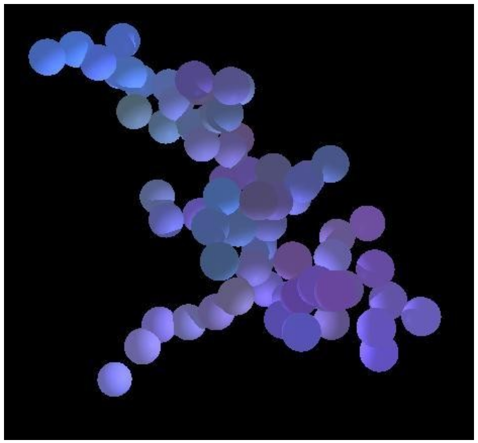
# Divergence of astrocytes for GFA content depending on malignation

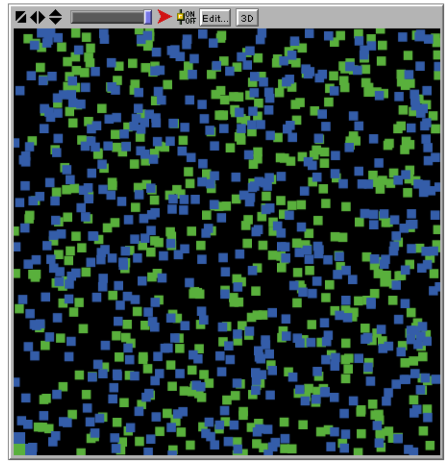


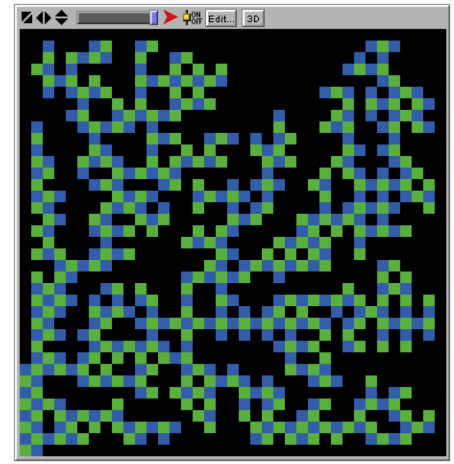




Кузнецова, 1984; Березин и др, Нейрохимия. 1984

# Assembling by adhesion rules (DLA)







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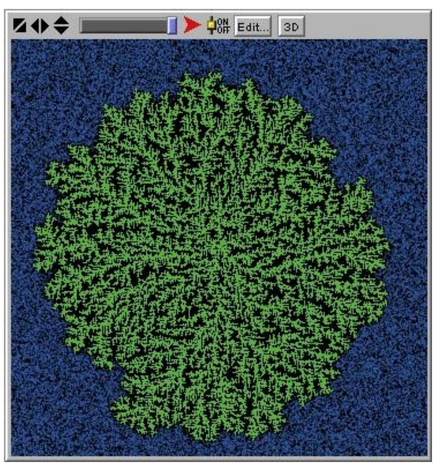

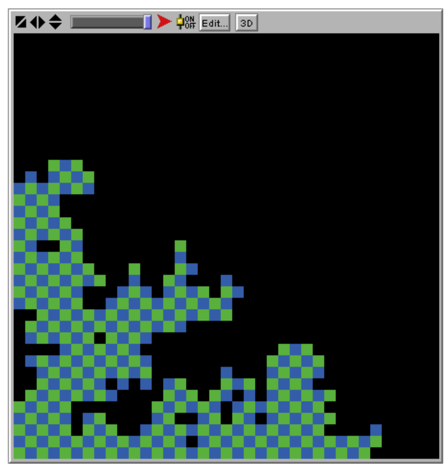

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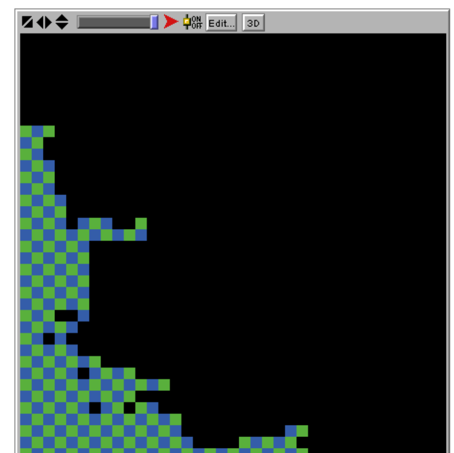


<=10

Chessboard pattern formation

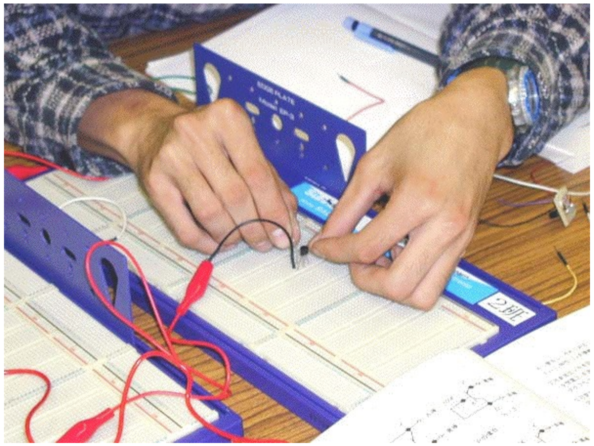
Kuznetsov, DECOI 2007

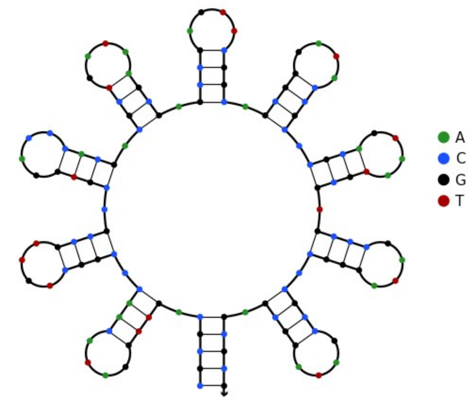
# Nearly decomposable and modular systems

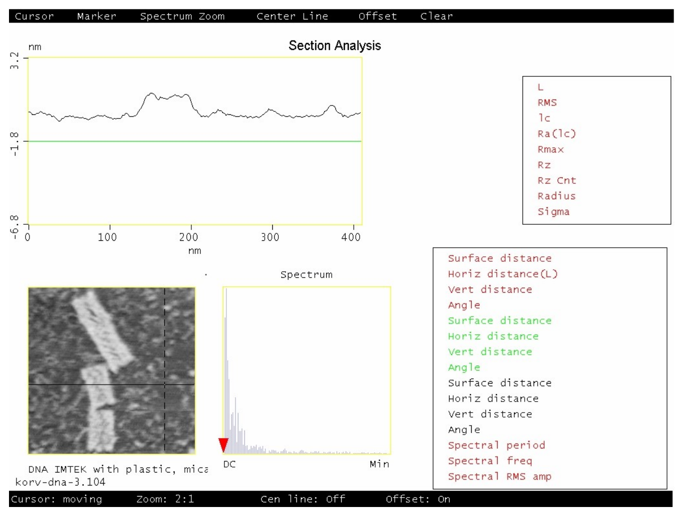
- "… the frequencies of interaction among elements in any particular subsystem of a system are an order of magnitude or two greater than the frequencies of interaction between the subsystems. We call this … **nearly decomposable** (ND) system." [Simon and Ando, 1961]

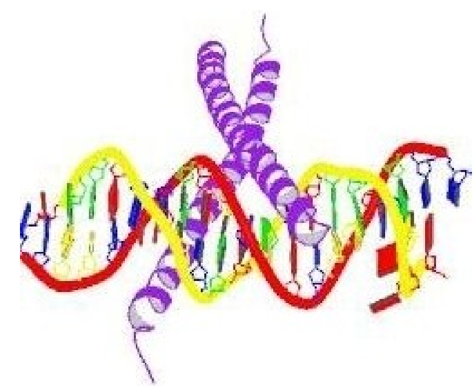
- "A system may be characterized as **modular** to the extent that of its components operates primary according to its own, intrinsically determined principles. Modules within a system or process are tightly integrated but relatively independent." [Herbert A. Simon, 2005]

# Modularity in electronics, optics and DNA-nanotechnology





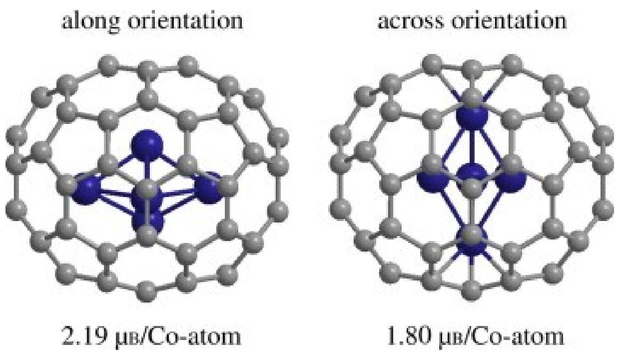



GCN4 bZIP + DNA

Kuznetsov, IET Synthetic Biology. 2007

# Endohedral metallofullerenes

$Co_5@C_{70}$




*ab initio* calculations:

**Method**: DFT - density functional theory
GGA-PBE - generalized gradient approximation
[Perdew, Burke, Ernzerhof, 1996]
**Calculation**: the total spin magnetic moment, $\mu$B
**Software**: OpenMX v.3.5 [Ozaki, 2003]

- $\boldsymbol{M \sim \langle L \rangle / N}$,
- where ***M*** is the magnetic moment per Me-atom of given complex ($\mu$B), **<*L*>** is the average Me–C bond length in Å, and ***N*** is the total number of Me–C bonds in the complex

Kuznetsov, Comp. Mat. Sci. 2012
Kuznetsov, Am. J. Biomed. Eng. 2012

# What is a module? (1)

- "... we define a **module** as an assembly of biological structures that fulfill a function in an integrated and context insensitive manner. Function as defined here is not merely the interaction of molecules but an interaction that yields a biological output which is characteristic of the module. Furthermore, the application of the module is flexible. To be recognized as a module, it has to be used either in different processes in the same organism or in different organisms, exploiting its invariant functional properties in the same or different processes. A **module** is therefore characterized by its reiterated use."

Uwe Strähle, Patrick Blader
The Basic Helix-Loop-Helix Proteins in Vertebrate and Invertebrate Neurogenesis. in Modularity and Evolution

- **Modularity** is defined through a process that starts by recognizing patterns, shapes, or events that repeat at some scale of observation
- **Modularity** is a hallmark of biological organization and an important source of evolutionary novelty
- **Modularity** is a sign of the universal principle of economy in nature

# What is a module? (2)

**Module** is a set of genes that act together to carry out a specific function

The recognition of modularity came as a surprise:

- Try to find modules, relations between modules, the origin of modules
- Try to understand the hierarchy of a modular system and a reason of the entanglement within modules and between modules

The answer following questions could have given a key to control an evolution process:

  - How does a system evolve and fall?
  - What is a limit of evolvability?

**Evolvability** is the ability to respond to a selective challenge by producing the right kind of variation

# Researches in modularity

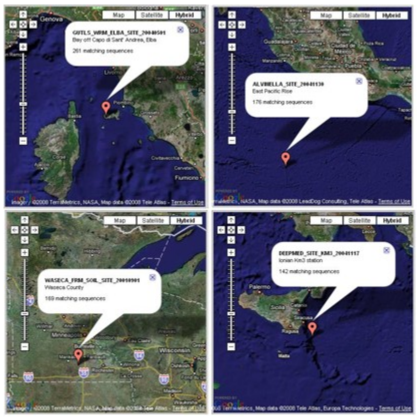
**Modularity is an old concept in the biological science:**

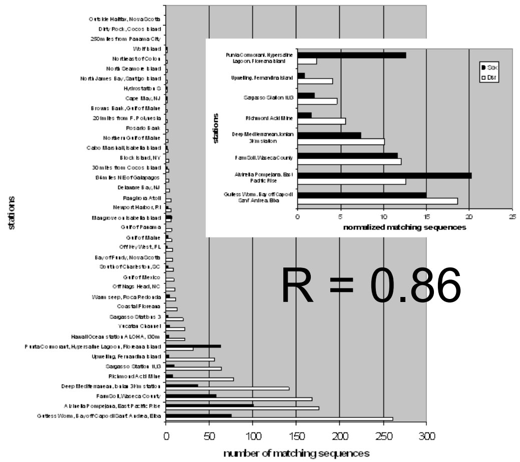
- Cuvier and Saint-Hilaire (18th century) – structural modules representing parts of organisms
- Joseph Needham (1930s) – development consists of distinct processes that are operating in coordination

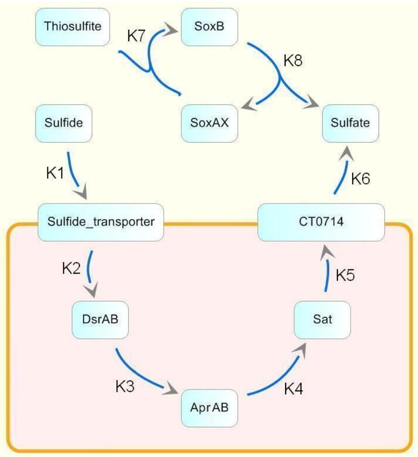
**In a modern time** (W. Fontana, G.P. Wagner, U. Alon and many others):

- A constant environment (that does not change over time) leads to non-modular structures
- The modular structure can spontaneously emerge if environment changes over time
- Variability in the natural habitat of an organism promotes modularity
- Modularity can also dramatically speed up evolution
- Adaptation of bacteria to new or changing environments is often associated with uptake of foreign genes through horizontal gene transfer (HGT)
- HGT is an important force that contributes significantly to modularity

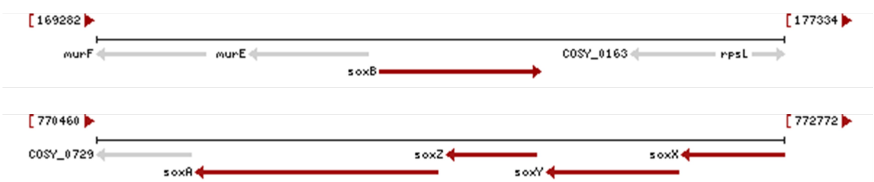
# Natural modularity
# (*dsr* and *sox* gene clusters)



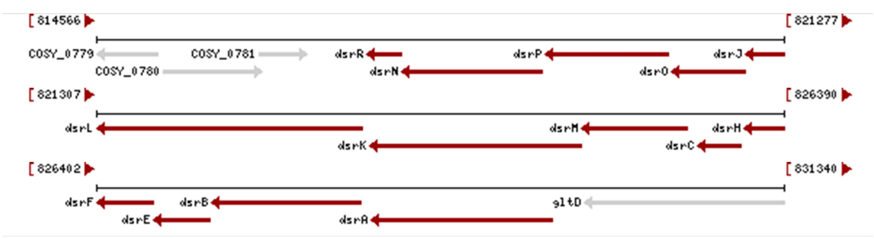


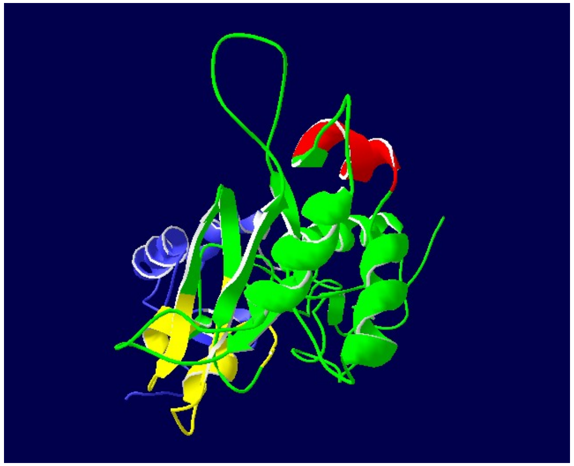




*sox* locus




*dsr* locus



Kuznetsov, JCSB. 2010

# Nature of mutations

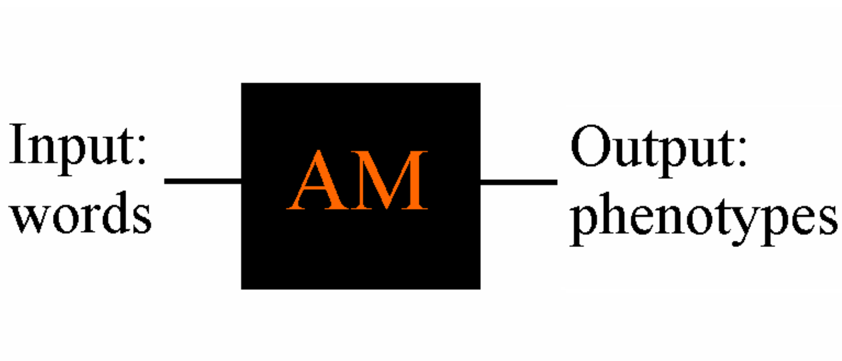
- change of topology of genetic networks and
- change of parameters

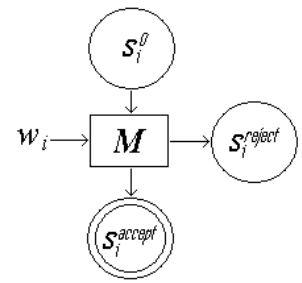
are induced in DNA sequences

```
      AprA  298 GQHLSHKPIPTCLR-NHAFISEVNAGRGPIHMVTMEA----------FKDPHLEEVGWENFLGMTVGQAVLWAATDVDPKYENPELTTSEPYVMGSHATG
1432856135  107 ASHLTHRPIPTCLR-NHALINEINAGRGPIHMVTMEA----------FQDPHLEEIGWHNFLGMTVGQAVLWAATDVNPKYENPELTTSEPYVMGSHATG
1433546210  217 ASHLTHRPIPTCLR-NHALINEINAGRGPIHMVTMEA----------FQDPHLEEIGWHNFLGMTVGQAVLWAATDVNPKYEXPELTTSEPYVMGSHATG
1433688352  154 APYGTAAITPTCLR-NHLMLFEMKEGRGPIIMDTVSALAALGETMDKKELKHLESEAWEDFLDMTCGQANLWCATNTEPEKKNSEVMPTEPYLLGSHSGC
1433766319   99 ASHLTHRPIPTCLR-NHALINEINAGRGPIHMVTMEA----------FQDPHLEEIGWHNFLGMTVGQAVLWAATDVNPKYENPELTTSEPYVMGSHATG
1433547459    1 --HLTHXPIRTCLGIRHXSMSQCPSRSDP--YVTRKL----------FRSA-SGEIGWHTFLGMTVGQAVLWAAXDVNPKYENPELTTSEPYVMGSHATG
1434025767   17 ASHXTHRPIPTCLR-NHALINEINAGRGPIHMVTMEA----------XQDPHLEEIGWHNFLGMTVGQAVLWAATDVNPKYENPELTTSEPYVMGSHATG
```

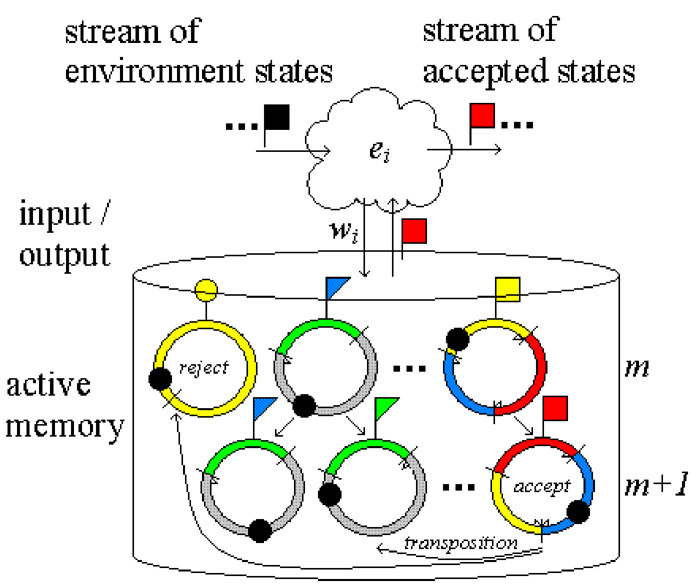
Kuznetsov, JCSB. 2010

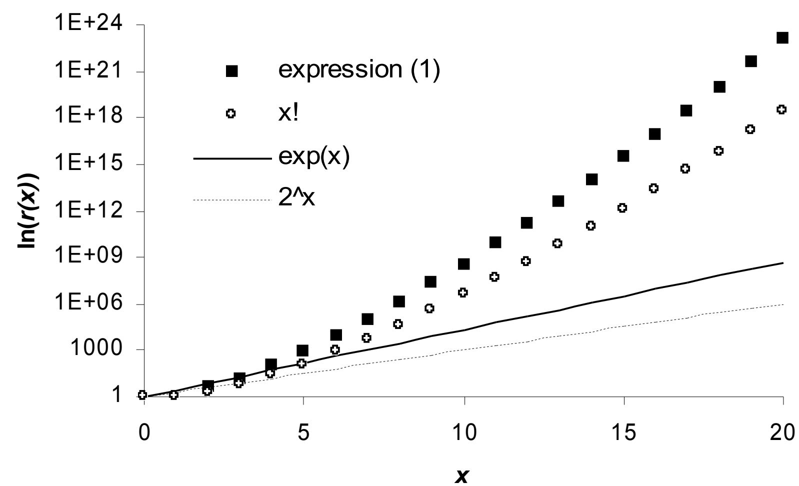
# Modularity as a set of construction rules, the cut and paste Argo-machine




$$\begin{cases} r_0 = r_1 = 0, \\ r_x = 2^x * (x-1)!,\ x \geq 2 \end{cases} \qquad (1)$$




Kuznetsov et al, GWAL. 2006.

# Modularity of genetic networks in pi-calculus, a modular 'table of elements'

*Elements of genetic networks*:

decay (degradation of a transcription factor ***tr*(*b*)**)

$\boldsymbol{\tau_\delta}$,

null gate ***null*(*b*)** (constitutive transcription)

$\boldsymbol{\tau_\varepsilon.\ (tr(b)\ |\ null(b))}$,

gene product ***tr*(*b*)** (protein transcription factor)

$\boldsymbol{!b.\ tr(b) + \tau_\delta}$,

neg gate ***neg*(*a*,*b*)** (negative regulation)

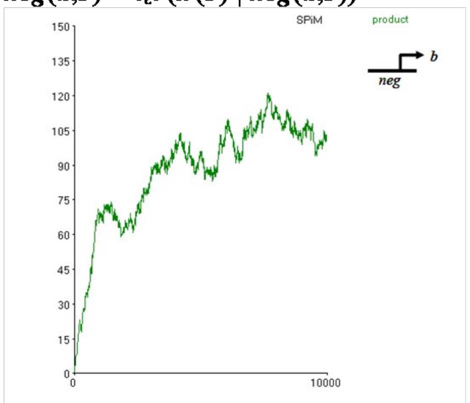
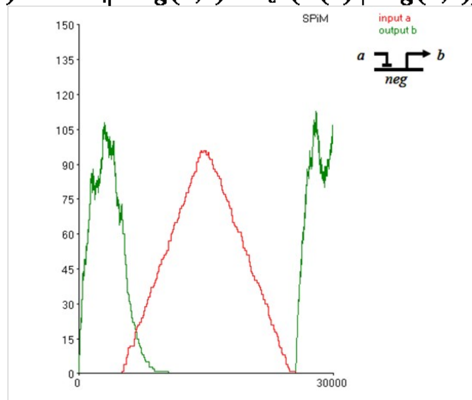
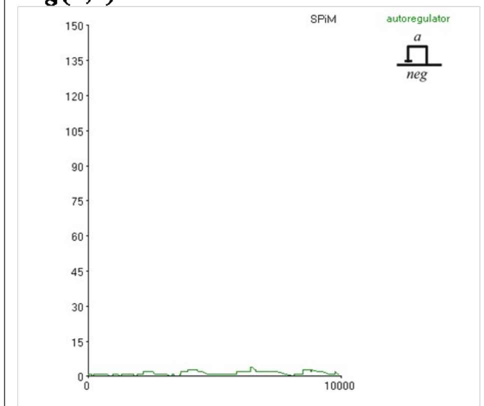
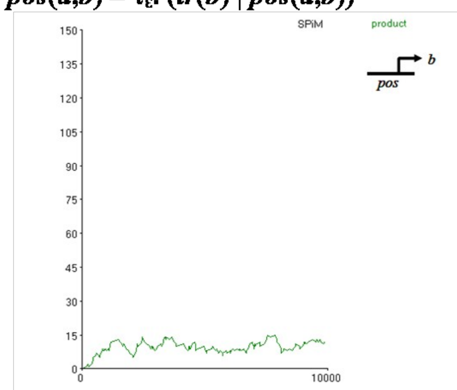
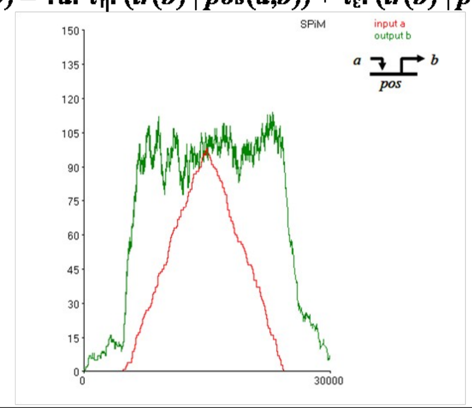
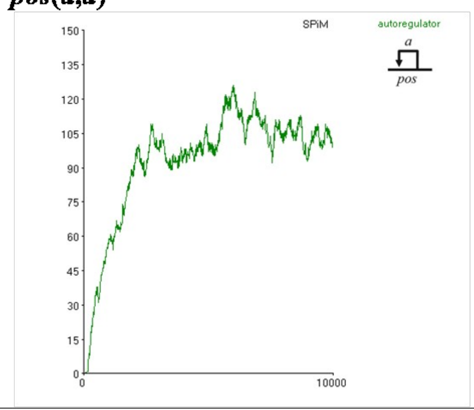
$\boldsymbol{?a.\ \tau_\eta.\ neg(a,b) + \tau_\varepsilon.\ (tr(b)\ |\ neg(a,b))}$,

pos gate ***pos*(*a*,*b*)** (positive regulation)

$\boldsymbol{?a.\ \tau_\eta.\ (tr(b)\ |\ pos(a,b)) + \tau_\varepsilon.\ (tr(b)\ |\ pos(a,b))}$.

Kuznetsov, JCSB. 2009

# Basic genetic gates

<table>
<tr><th></th><th>without input</th><th>regulated input</th><th>autoregulation</th></tr>
<tr><td>negative regulation</td>
<td>$neg(a,b) \equiv \tau_\varepsilon.\ (tr(b) \mid neg(a,b))$<br><br></td>
<td>$neg(a,b) \equiv ?a.\ \tau_\eta.\ neg(a,b) + \tau_\varepsilon.\ (tr(b) \mid neg(a,b))$<br><br></td>
<td>$neg(a,a)$<br><br></td></tr>
<tr><td>positive regulation</td>
<td>$pos(a,b) \equiv \tau_\varepsilon.\ (tr(b) \mid pos(a,b))$<br><br></td>
<td>$pos(a,b) \equiv ?a.\ \tau_\eta.\ (tr(b) \mid pos(a,b)) + \tau_\varepsilon.\ (tr(b) \mid pos(a,b))$<br><br></td>
<td>$pos(a,a)$<br><br></td></tr>
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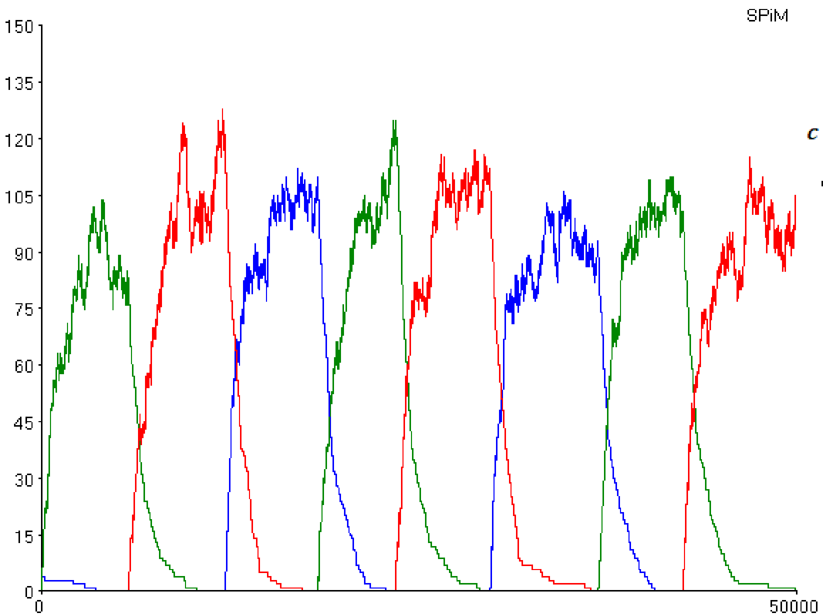
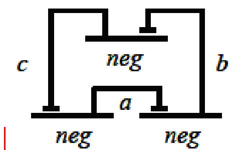
# Repressilator

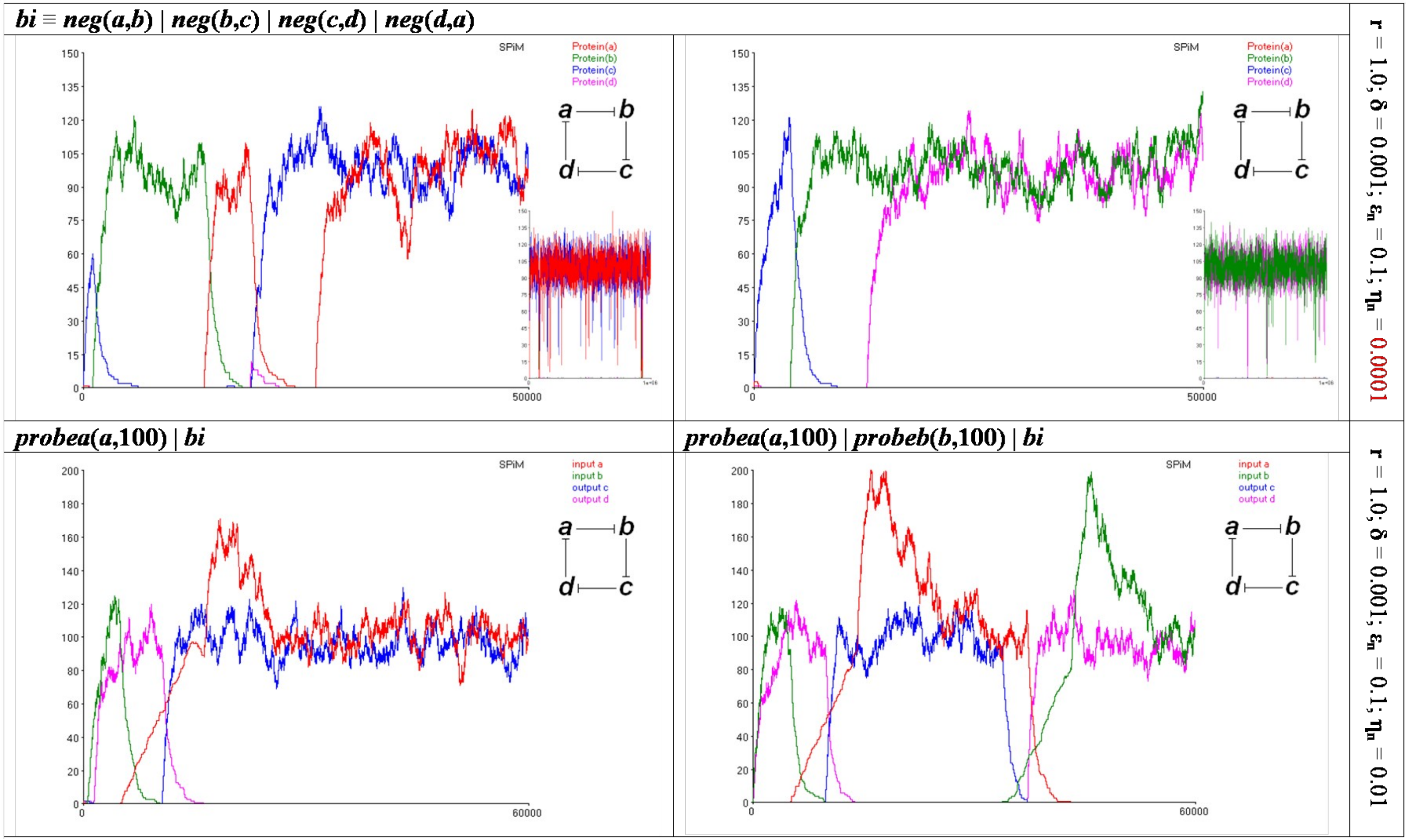


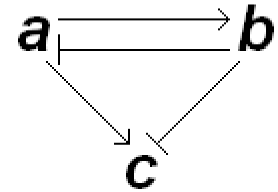

$r = 10.0$; $\varepsilon_n = 0.1$; $\eta_n = 0.001$; $\delta = 0.001$

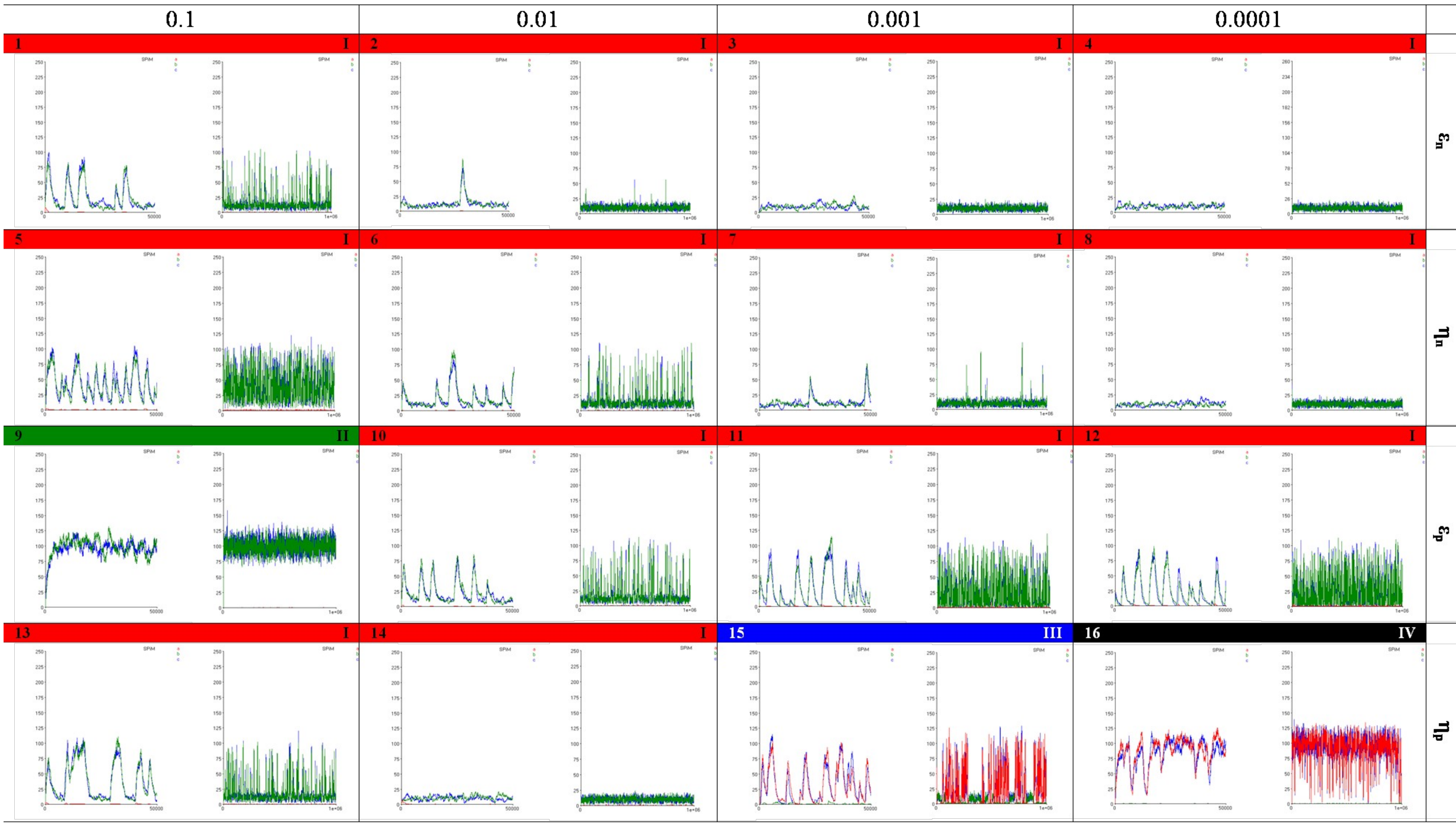
```
(* Repressilator *)

directive sample 50000.0
directive plot !a as "a"; !b as "b"; !c as "c"
directive graph

val bind = 10.0       (* protein binding - r *)
val transcribe = 0.1  (* constitutive expression - epsilon
*)
val unblock = 0.001   (* repression delay - eta *)
val degrade = 0.001   (* protein decay - delta *)

(* transcription factor *)
let tr(p:chan()) =
  do !p; tr(p)
  or delay@degrade

(* neg gate *)
let neg(a:chan(), b:chan()) =
  do ?a; delay@unblock; neg(a,b)
  or delay@transcribe; (tr(b) | neg(a,b))

(* circuit *)
new a@bind:chan()
new b@bind:chan()
new c@bind:chan()

run (neg(a,b) | neg(b,c) | neg(c,a))
```

# Bi-stability and memory

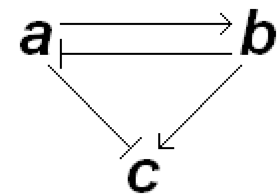


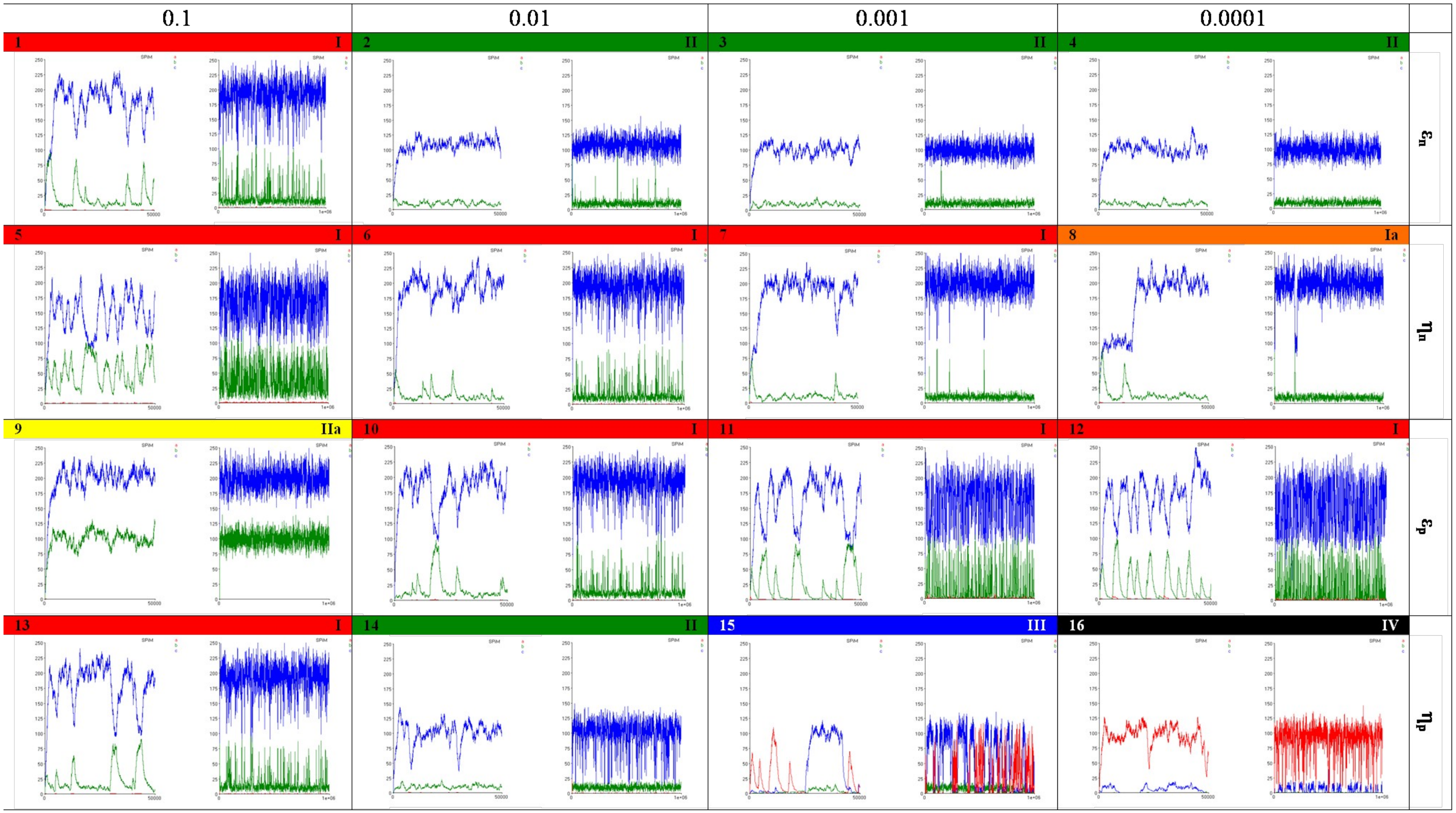
# Synchronous FFBL



# Asynchronous FFBL



# Compositional mechanisms of modularity; interaction, communication

- recombination
- hybridization
- symbiotic encapsulation
- horizontal gene transfer (HGT)
- ‘hopeful monster’ [Goldschmidt, 1940]

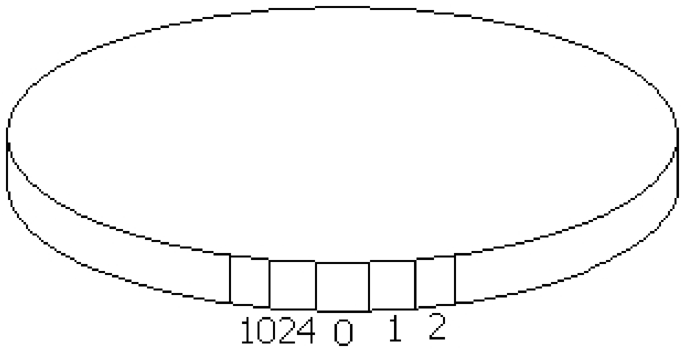
Sperm Mediated Gene Transfer (SMGT)
Control loach fry – mock analysis
Experimental β-gal-positive fry 72 h after the eggs fertilization by sperm cells transfected with pcDNA3-*lacZ*

Andreeva et al, Russian Journal of Genetics. 2003

# Design of complex systems: make parts, repeat them, and change them

Recursive functions

- Fractals
- Agents



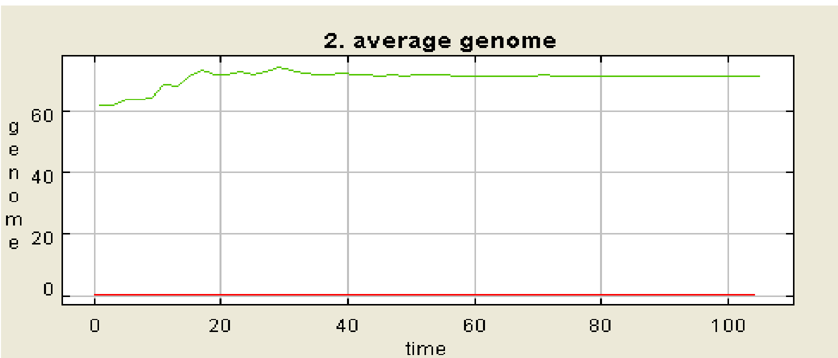

**T(i+1) = |[T(i) + P(i)] / 2 * R|mod(**1024)
**P(i+1) = T(i+1),**
where **T(i)** is the color code of the individual Spermatozoon and **P(i)** is the color code of the individual Ovum at the time **i** of breeding. **R** is the mutation parameter on the interval ]0, 4]

Each creature has a circular genome consisting of 1024 'genes', only one of them is active and coded by color with mod(1024)

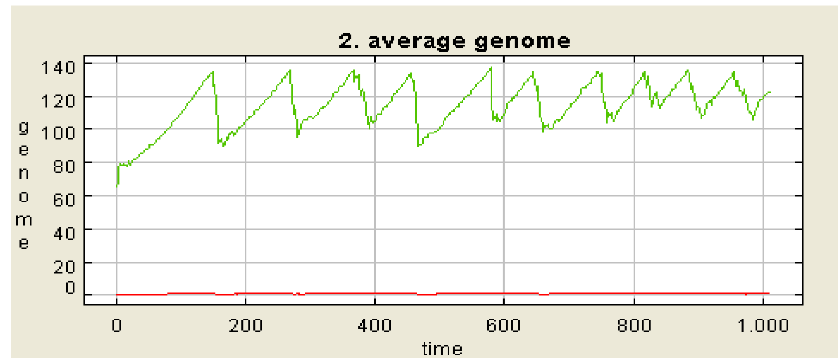
Kouznetsov, AMHSO. 2004

# Emergent behavior depending on mutation parameter

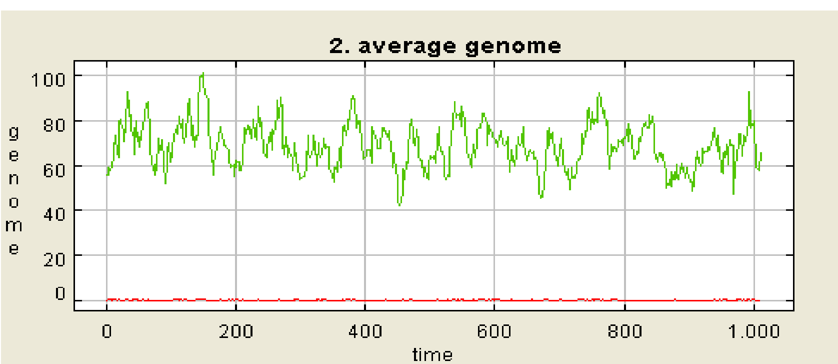
The system demonstrated ordered (R<=1) and complex (R>1) regimes



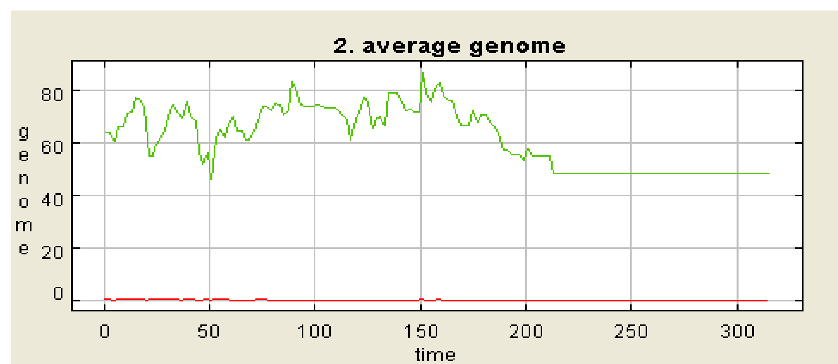

stable focus, R=1




periodic, R=1.01

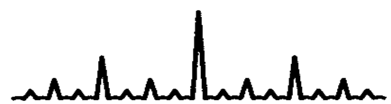



chaotic, R=3



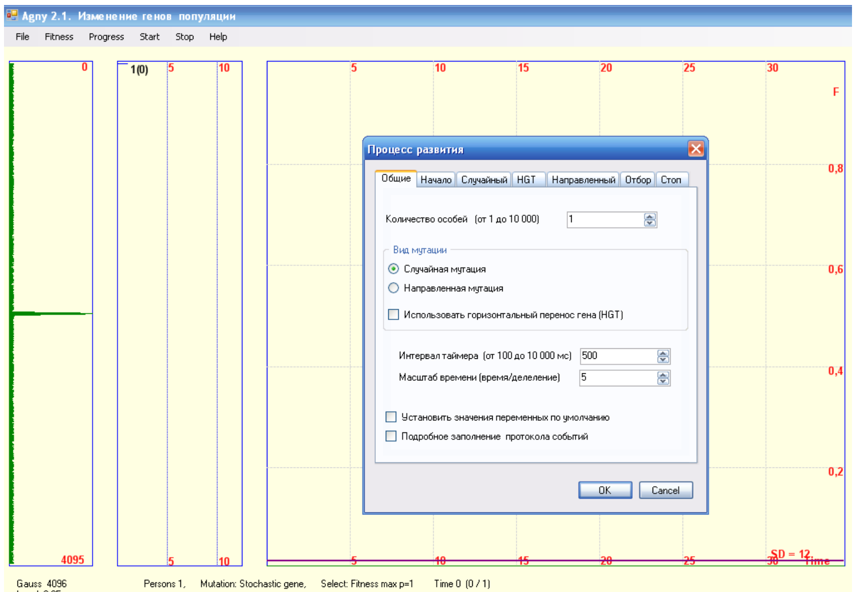

strange attractor, R=4

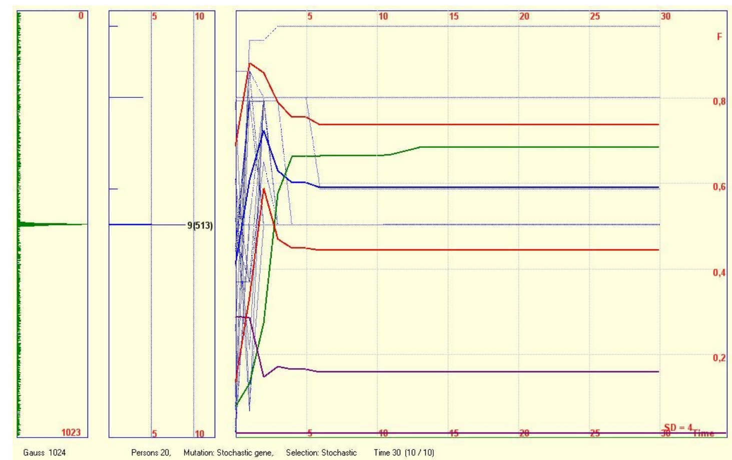
# Compositional evolution by Richard Watson, 2006

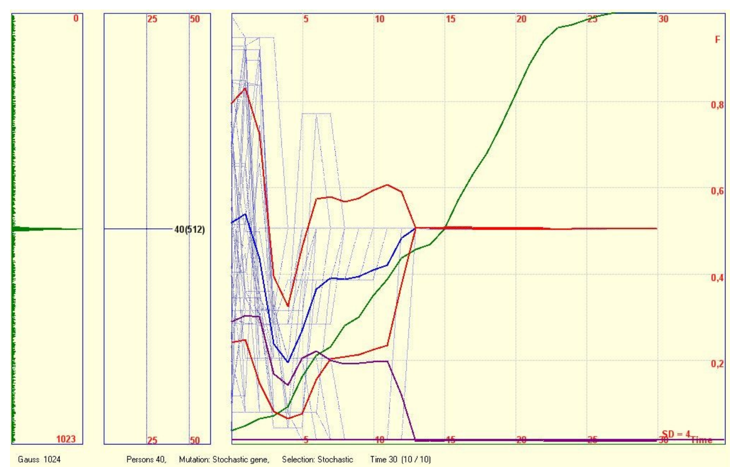
| | | | |
|---|---|---|---|
| **Dependency of variables** | Few / weak interdependencies | Modular interdependencies | Arbitrary interdependencies |
| **Landscape** |  |  |  |
| **Algorithmic paradigm** | hill-climbing – accumulation of small variations | divide-and-conquer problem decomposition | exhaustive search, random search |
| **Complexity** | $KN$ | $N^K$ | $K^N$ |
| **Evolutionary analogy** | gradual evolution | compositional evolution | “impossible” / ”intelligent design” |

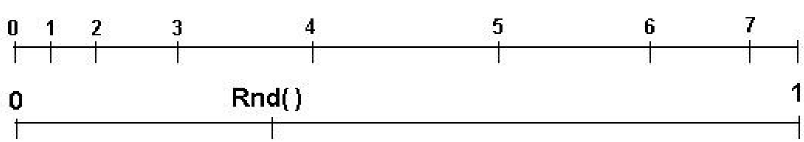
N – # of variables, K – # of values for each variable

# Agny simulator, S. Golutvin



# Conclusion

- A module is the component which operates independent of other components of the system
- A functional modularity is the independence in space and time
- Modularity is driven by interaction and communication of components
- A set of modules can be combined in different ways when the environment changes (HGT)
- Origin of modularity is in the compositional evolution
- Modularity expands parallel development and enhances evolvability
- Specific interaction between modules is a subject of compositional design of complex systems
- Modularity is the relationships between the whole and the parts

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