



# Introduction to Gene Regulatory Networks

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## Outline

- Gene regulation in biology
  - Introduction to gene regulation
  - Protein and genomic perspective
  - Gene regulation in developmental biology
- Artificial gene regulatory networks
  - Biological models
  - Computational models
- Applications of gene regulatory networks
  - Evo-devo
  - Agent control
  - Programming

## Gene Regulation in Biology

## Gene Regulation in Biology

A gene regulatory network is a set of DNA segments which governs gene expression in cells

The gene expression codes for levels of mRNA of e.g., structural proteins, enzymes, or other proteins (like transcription factors, etc.)

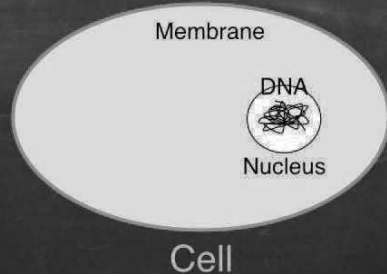
Transcription factors enhance or inhibit the production of other proteins by the cells.

Gene regulation:

- provides the behavior of the cells (reaction to environmental conditions)
- allows for specialisation in multicellular organism by turning on and off some part of the genomes

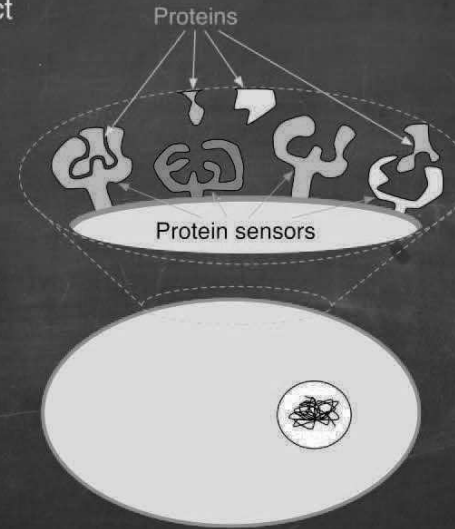
# Gene Regulation in Biology

Protein aspect



# Gene Regulation in Biology

Protein aspect



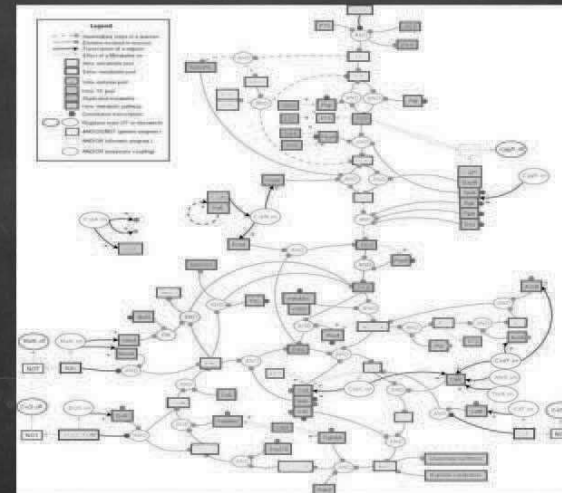
# Gene Regulation in Biology

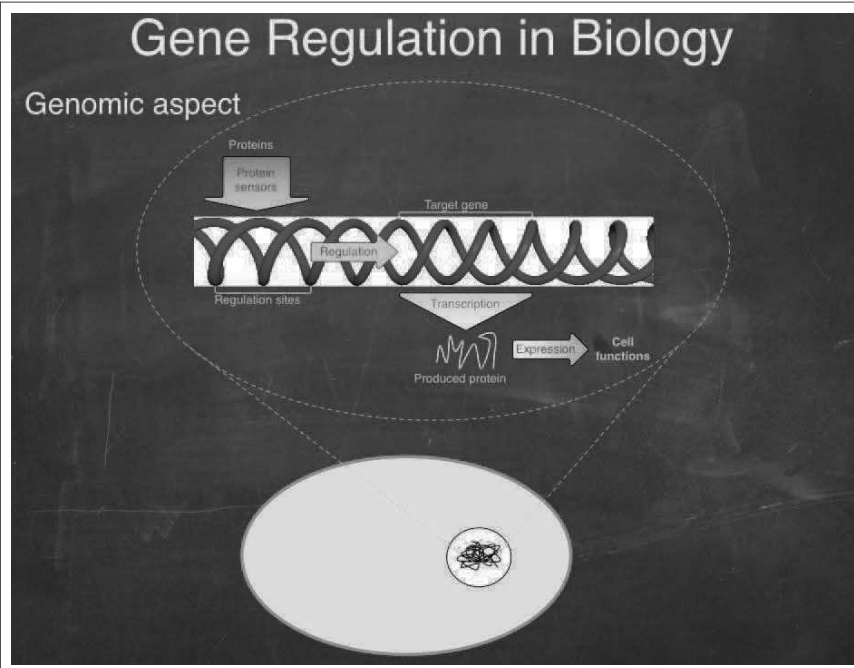
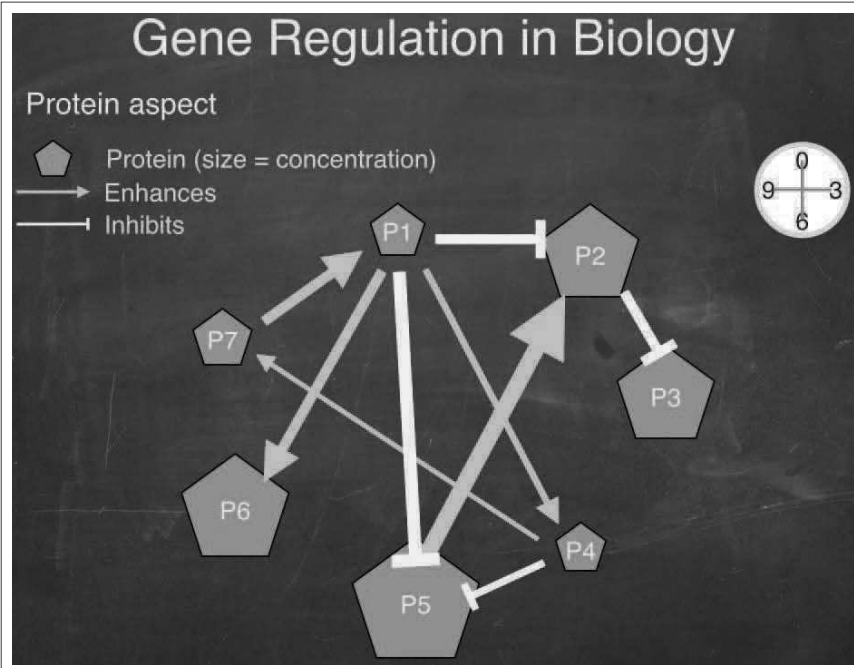
Protein aspect



# Gene Regulation in Biology

Protein aspect





## Gene Regulation in Biology

**Gene regulation in developmental biology**

- During the development of an organism, the GRN allows for:
  - the segmentation of the embryo (ex: drosophila)

(Tomer et al. 2012)

## Gene Regulation in Biology

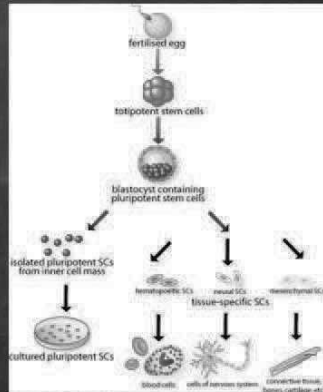
**Gene regulation in developmental biology**

- During the development of an organism, the GRN allows for:
  - the segmentation of the embryo
  - the generation of morphogen gradients
    - morphogens are signalling proteins produced by the cells
    - they are diffused in the cellular matrix for communication
    - one of the main use is the creation of a "coordinate system" in the embryo
    - example: bicoid in drosophila embryo

## Gene Regulation in Biology

Gene regulation in developmental biology

- During the development of an organism, the GRN allows for:
    - the segmentation of the embryo
    - the generation of morphogen gradients
    - the differentiation of the cells into different cell types
- => 1 DNA for multiple cell functions



Source: <http://www.sq.ubc.ca/stem-cell-bioengineering/>

## Artificial Gene Regulatory Networks

## Artificial Gene Regulatory Networks

Models of gene regulation designed for:

- biological purposes
  - simulation of real GRNs
  - interactions between the protein
  - dynamics of the network
  - implication in the developmental process
  - implication in the regulation of the cell life cycle
- computational purposes
  - inspiration from the biology
  - identical structure based on interaction between proteins
  - artificial evolution of the proteins
  - generally used to control agents (cells, robots, etc.)

## Artificial Gene Regulatory Networks

Biological models

- ODEs
  - Representation of gene regulation with ordinary differential equations, based on chemistry and enzymatic kinematics
- Boolean networks
  - Genes, inputs and outputs of the networks are Boolean nodes of the network
  - Edges are Boolean transition functions
- Stochastic gene networks
  - Gene expression in cells is not deterministic  
=> Use of probabilistic models

# Artificial Gene Regulatory Networks

## Computational models

- Models used to control agents
- Agents can be:
  - Cells in evo-devo models
  - Virtual or real robots
  - etc.
- 2 groups of models
  - Biologically plausible networks
    - Bit-string representation
  - "Object-oriented" networks
    - Networks of proteins

# Artificial Gene Regulatory Networks

## Bit-string models

### Biologically plausible model of regulation

- Encoding close to biology:
  - bit string  $\approx$  string of nucleotides
  - Use of promoters to separate genes
- Dynamics equations close to real gene regulatory networks

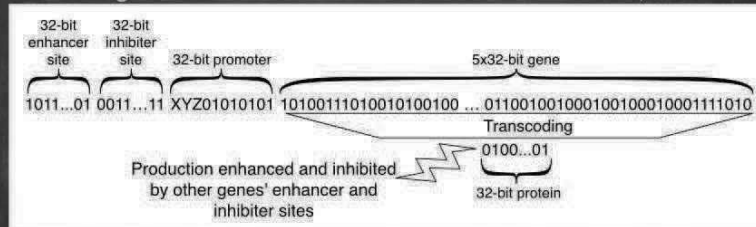
### But not efficient for computational purposes:

- Hard to evolve (junk DNA)

# Artificial Gene Regulatory Networks

## Computational models: bit-strings

- Encoding (Banzhaf 2003)



- Dynamics



$$e_i = \frac{1}{N} \sum_j c_j e^{\beta u_{ij}^+ - u_{ij}^-} \quad h_i = \frac{1}{N} \sum_j c_j e^{\beta u_{ij}^- - u_{ij}^+}$$

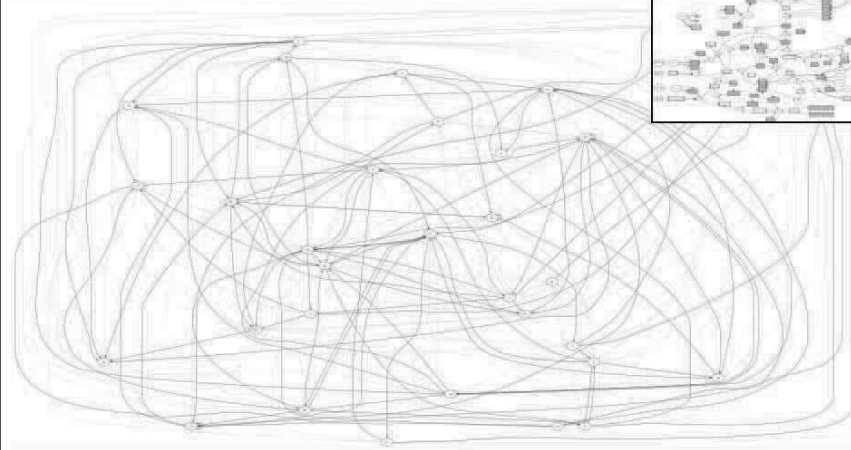
$$\frac{dc_i}{dt} = \frac{\delta(e_i - h_i)}{\Phi}$$



Matching between proteins and sensors

# Artificial Gene Regulatory Networks

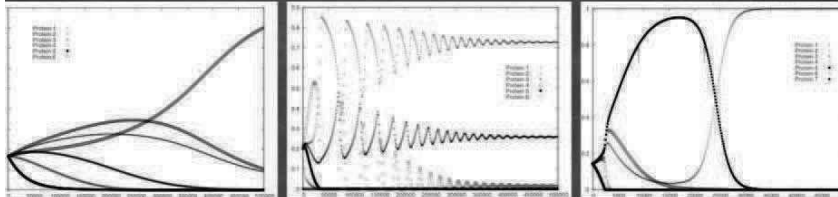
## Computational models: bit-strings



# Artificial Gene Regulatory Networks

Computational models: bit-strings

- Random DNA strings produce 3 types of behaviors (Banzhaf 2003)

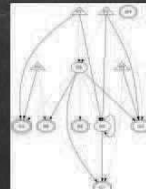
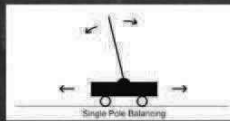


Stable

Oscillatory

Transitory

- By adding input and output proteins, possibility to control a cart pole

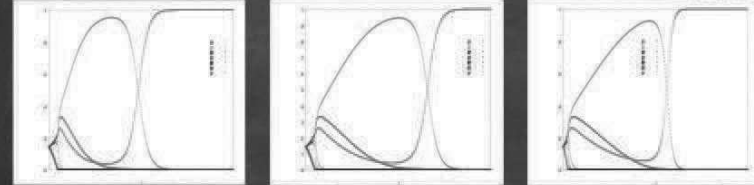


(Nicolau et al. 2010)

# Artificial Gene Regulatory Networks

Computational models: bit-strings

- Variation of dynamical behaviors is smooth (Banzhaf 2003)



Original

1-bit mutation

A further 1-bit mutation

- Both mutations were applied to the regulatory site of proteins
- Heterochrony (shift in expression timing)

# Artificial Gene Regulatory Networks

Computational models: "Object-oriented" models

- Higher level of representation
- Direct encoding of proteins and the affinities between proteins
  - No promoter
  - No junk DNA
  - Easier to evolve
- Inputs and outputs can be easily represented
  - "Plug-and-play" to any agent-based problem

# Artificial Gene Regulatory Networks

Computational models: "Object-oriented" models

GRN = network of proteins

- Nodes = Proteins ; characterized by:
  - identifier tag  $id \in [0, p]$
  - Enhancing tag  $enh \in [0, p]$
  - Protein type
  - Inhibiting tag  $inh \in [0, p]$
  - (input, output ou regulatory)
- Edges = matching between proteins

$$u_{ab}^+ = p - |id_a - enh_b| \quad u_{ab}^- = p - |inh_a - id_b|$$

Dynamics of the network

- Enhancing and inhibiting coefficients of protein i:

$$e_i = \frac{1}{N} \sum_j c_j e^{\beta u_{ij}^+ - u_{i, max}^+} \quad h_i = \frac{1}{N} \sum_j c_j e^{\beta u_{ij}^- - u_{i, max}^-}$$

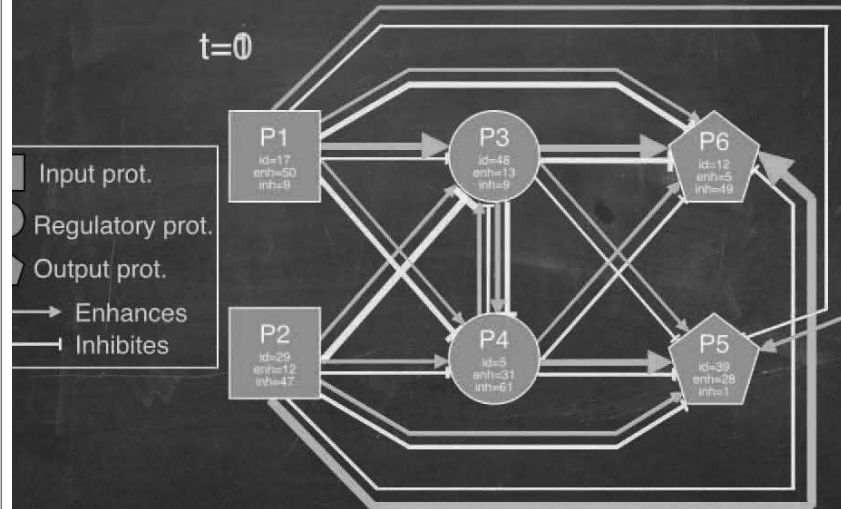
- Differential evolution of the concentration of protein i:

$$\frac{dc_i}{dt} = \frac{\delta(e_i - h_i)}{\Phi}$$



# Artificial Gene Regulatory Networks

Computational models: "Object-oriented" models

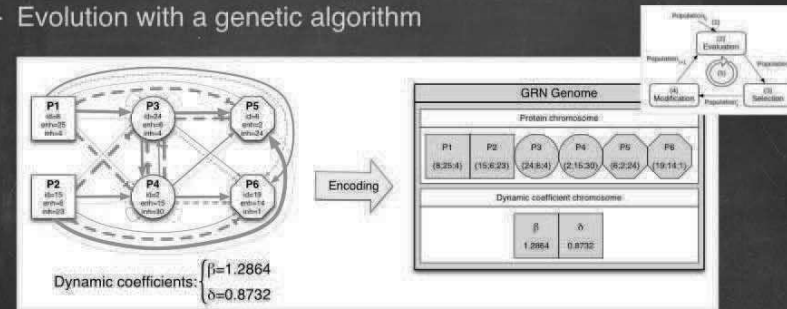


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# Artificial Gene Regulatory Networks

Computational models: "Object-oriented" models

- Evolution with a genetic algorithm



- "Neat-like" algorithm applicable to optimize GRNs more efficiently
  - ▶ Start with small networks (inputs + outputs + 1 regulatory protein)
  - ▶ Aligning crossover
  - ▶ Speciation

(Cussat-Blanco et al. 201)

# Artificial Gene Regulatory Networks

Computational models: "Object-oriented" models

- Easy to use:
  - ▶ Concentration of input proteins: sensors of the agent
  - ▶ Concentration of outputs proteins: Actuators or weight for a behavior/action



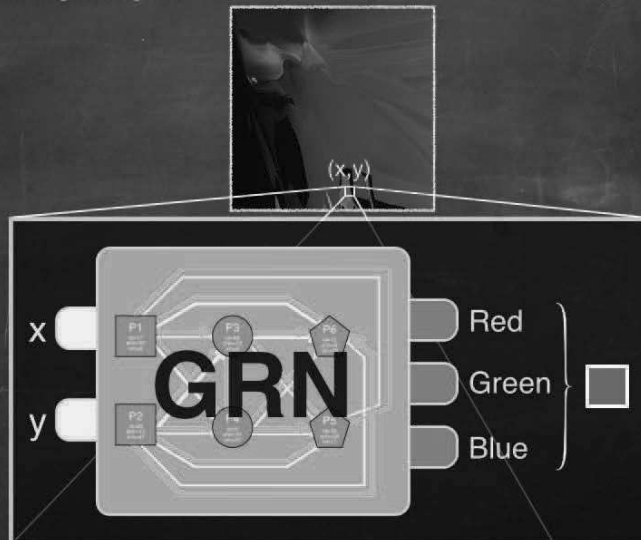
- Compact encoding in comparison to neural networks

# Application of Gene Regulatory Networks

- Viewing the dynamics
- Evo-devo
- Controlling agents' actuators
- Regulating high-level behaviors
- GRN Programming

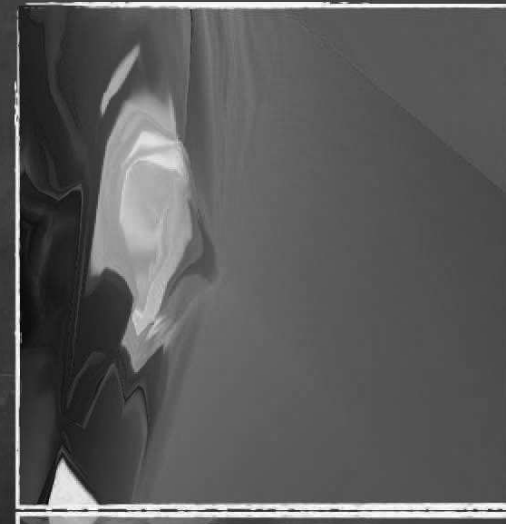
# Application of GRNs

Generating images



# Application of GRNs

Generating images



# Application of GRNs

Generating videos

**Sylvain Cussat-Blanc**  
University of Toulouse  
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**Jordan Pollack**  
Brandeis University  
Demo lab

# Application of GRNs

Evo-Devo: Evolution and Development

- Definition: grow virtual organism with evolved GRNs
- Embryogenesis: Formation Processus of multicellular organisms from the egg cell to the autonomous living being
- Artificial embryogenesis: Generation of virtual organisms by taking inspiration of the development process of living beings => based on biological concepts

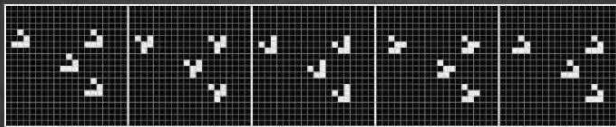




## Application of GRNs

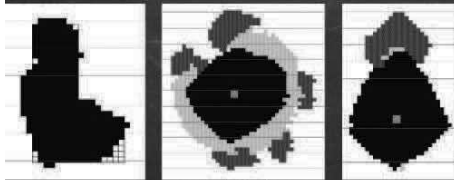
### Evo-Devo: cellular automata

- Evolution of a matrix with simple rules based on the neighborhood
- The state of the cells at time  $t$  determines their state at time  $t+1$
- Example: Conway's game of life



(Conway 1970)

- Shapes can be generated by evolving the rules



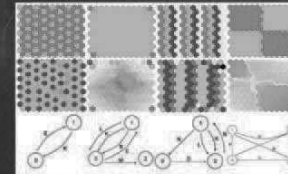
(De Garis 1999)

$$fitness = \frac{Nb_{in} - \frac{1}{2}Nb_{out}}{des}$$

## Application of GRNs

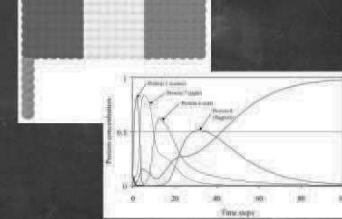
### Evo-Devo: use of GRNs

- Development of specialization patterns with a cellular automata
- French flag problem
  - Different cell specialization, depending on the position of the cells
  - Morphogen gradient pre-positioned or produced by the organisms



(Flann et al. 2005)

(Chavoya et al. 2008)

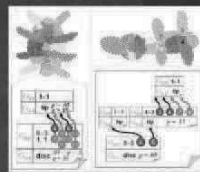


(Joachimczak et al. 2008)

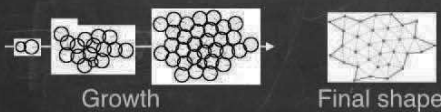
## Application of GRNs

### Evo-Devo: use of GRNs

- Complexification of the shape by introducing a developmental process
  - Probability of division for each cell
  - Intercellular adhesion (mass/spring system) to aggregate the cells
- Development and control of the morphology
  - Morphology produce by an Evo-Devo process
  - Once stable, the morphology is moved by a GRN in a fluidic environment

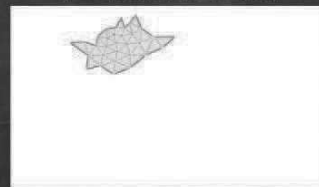


(Doursat 2009)



Growth

Final shape



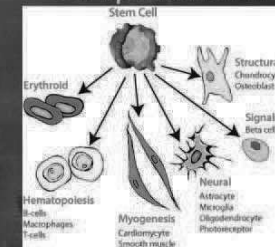
Motion

## Application of GRNs

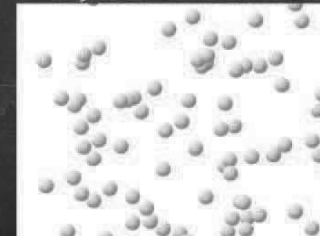
### Evo-Devo: Generating artificial creatures

- GRN used to regulate the cell's life cycle
- Optimization for the GRN to produce creatures adapted to their environment
- Functional differentiation of the cells
- Simulated physics and chemistry in the environment

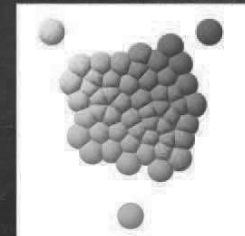
### Cell specialization



Physical environment



Chemical environment



## Application of GRNs

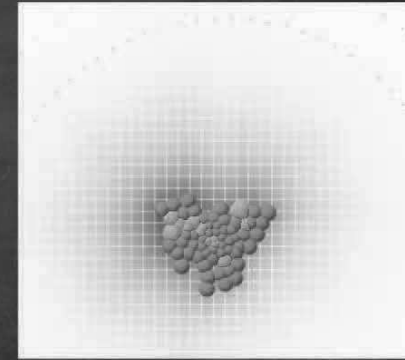
### Evo-Devo: Generating artificial creatures

- In each cell, the GRN manages:
  - High-level actions (division, apoptosis, quiescence, differentiation)
  - The chemical production of the cells (morphogens, nutrients, energy)
- For regulation, GRN uses:
  - information on the cell's internal state (energy, stock of nutrient, etc.)
  - information on its local environment local (morphogens)
- Optimization of GRN to generate complex multicellular organisms
  - Possible optimization objectives (fitness):
    - Generate colored shapes (color = differentiation state)
    - Generate user-defined functions (harvest a protein, move to a point, etc.)
    - SURVIVE
  - What does it mean to survive?
    - Have at least 1 living cell in the organism
    - => being able to adapt to environmental conditions
    - => the complexity is not in the fitness function anymore but move to the definition of the environment

## Application of GRNs

### Evo-Devo: Generating artificial creatures

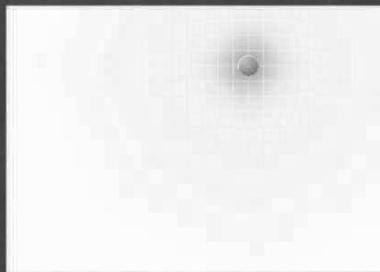
- Example:
  - 2 types of cells:
    - Nutritive => Extract energy from the environment
    - Defensive => Resist to external aggressions
- Environment :
  - Contains nutrients
  - Contains nocive particules that kills nutritive cells
- Fitness:
  - Survive == simulation duration



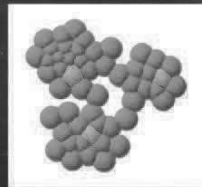
## Application of GRNs

### Evo-Devo: Generating artificial creatures

- At the beginning of the evolution, very simple strategy:



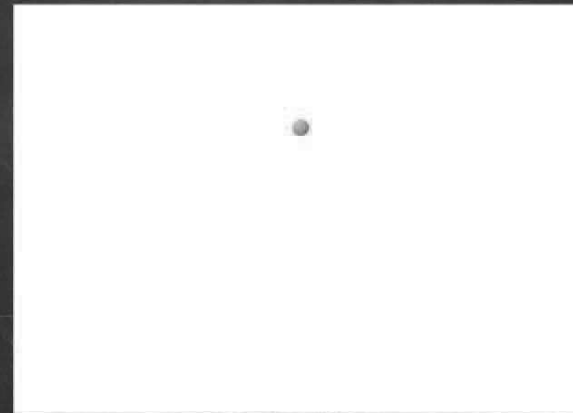
- Then, progressive complexification



## Application of GRNs

### Evo-Devo: Generating artificial creatures

- Finally, motion emerges (with no cell migration!)



(Disset et al. 2014)

## Application of GRNs

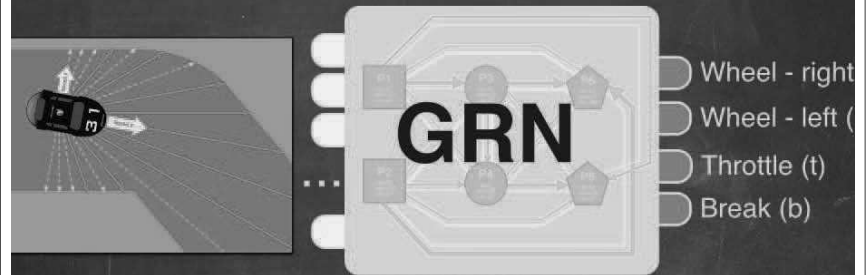
### Simulated car racing

- Direct connection of the GRN to a virtual car
- Use of TORCS for the car physics
- Available sensors:
  - 18 track sensors
  - 3 speed sensors
  - 8 state sensors (rpm, position, time, etc.)
- Available actuators:
  - Wheel angle  $\in [-1, 1]$
  - Throttle  $\in [0, 1]$
  - Break  $\in [0, 1]$
- Only keep the necessary sensors



## Application of GRNs

### Simulated car racing



Inputs must be normalized

Final actuator values given by:

- Wheel angle =  $(r-l)/(r+l)$
- Throttle =  $\max(0, (t-b)/(t+b))$
- Break =  $\max(0, (b-t)/(b+t))$

## Application of GRNs

### Simulated car racing

- How to teach the GRN to drive? What is a good fitness?
- Solution: incremental evolution
  1. Teach to drive on 1 simple track
  2. Generalize the behavior on other tracks
  3. Polish the behavior of the network



(Sanchez et al. 2014)

## Application of GRNs

### Features of system

- Easy to use
- Adaptive to the track and its surface
- Robust resistant to the noise

### Example of robustness

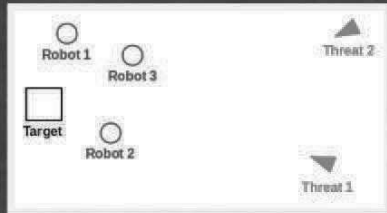
- Use of the controller trained in the game to drive a robot



## Application of GRNs

### Regulating high-level behaviors

- Example: protect a target against enemies
  - Decentralized control of a group of defenders
  - Multiple threats incoming from the environment



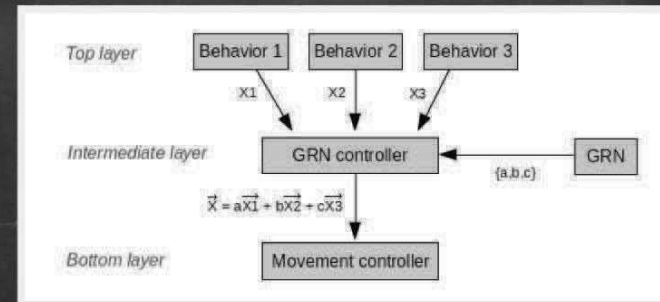
Use of a GRN to regulate high level behavior such as:

- Defence
- Attack
- Scatter
- Regroup

## Application of GRNs

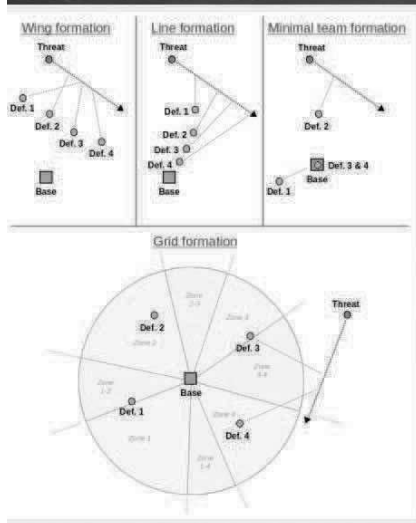
### Regulating high-level behaviors

- Hybrid and modular architecture
- Behaviors generate direction vector
- The GRN aggregate the vectors to produce the final move

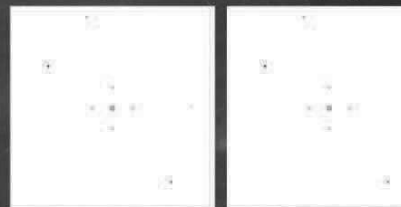


## Application of GRNs

4 strategies emerge:



Line Wing



Minimal Grid

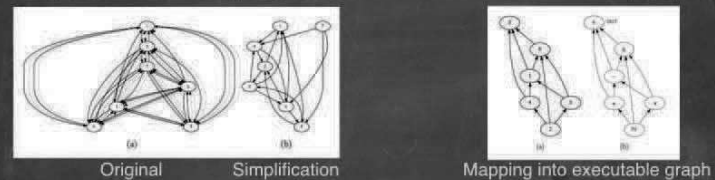


## Application of GRNs

### GRN programming

- Map network into program

(Lopes and Costa 201)

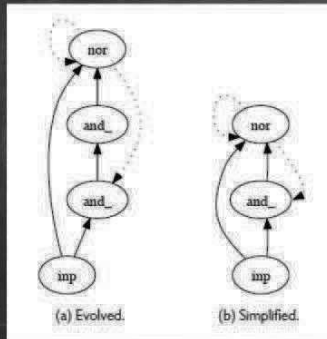


- Here, the static network connectivity is used to determine program structure, including feedback connections
- Input and output nodes are fixed
- Input data stream is applied and output data stream read off.

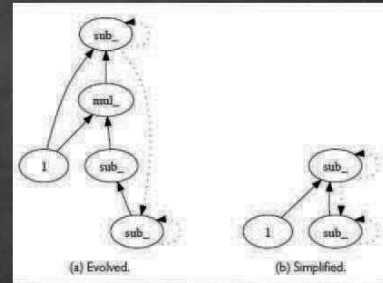
# Application of GRNs

## GRN programming

- Output at top node



Even n-bit Parity



Fibonacci Series

(Lopes 2015)

# Gene Regulation - Pros and Cons

## Pros:

- Plug-and-play
- Temporal aspect: Many tasks are dynamic
- Natively continuous
- Many different behaviors possible
- Close to natural systems

## Cons:

- Can be difficult to evolve
- Black-box system

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