

Introduction to Gene Regulatory Networks

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GECCO '17 Companion, July 15–19, 2017, Berlin, Germany.
ACM 978-1-4503-4979-0/17/07. http://dx.doi.org/10.1145/3067695.3067728

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

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Gene Regulation in Biology

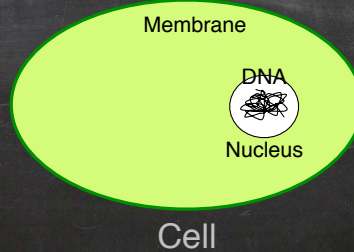
Gene Regulation in Biology

- 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

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Gene Regulation in Biology

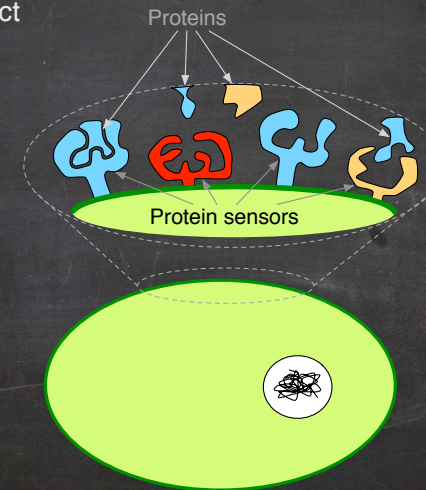
- Protein aspect



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Gene Regulation in Biology

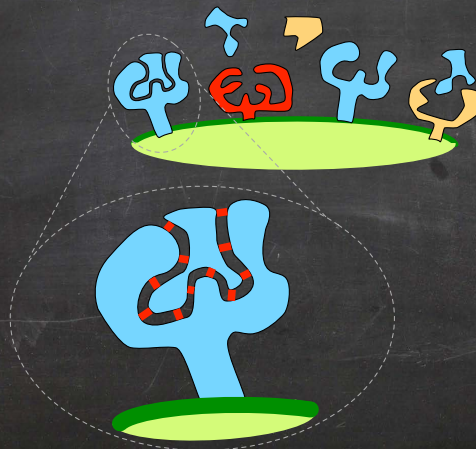
- Protein aspect



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Gene Regulation in Biology

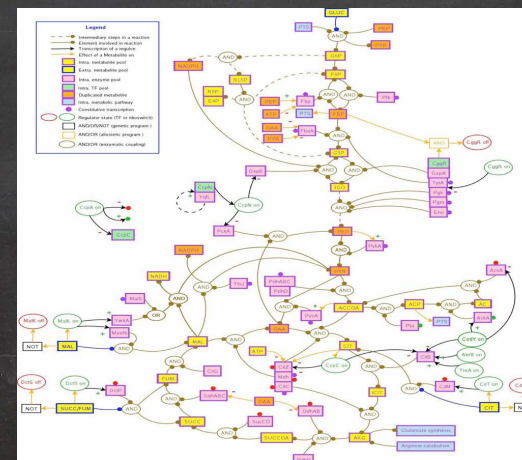
- Protein aspect



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Gene Regulation in Biology

- Protein aspect

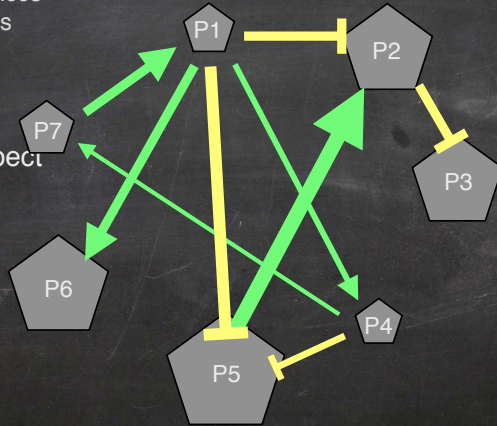


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Gene Regulation in Biology

- Protein (size = concentration)
- Enhances
- Inhibits

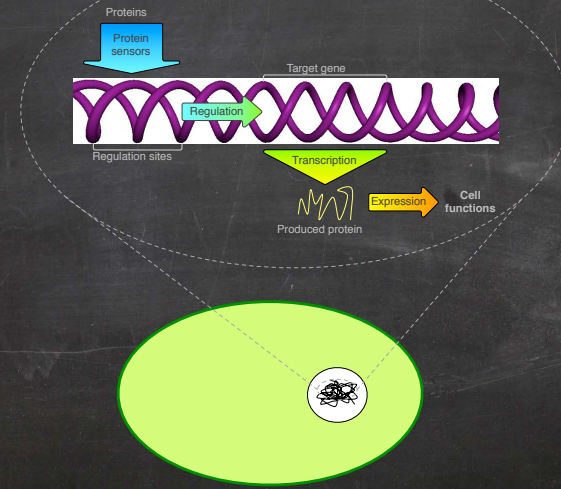
Protein aspect



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Gene Regulation in Biology

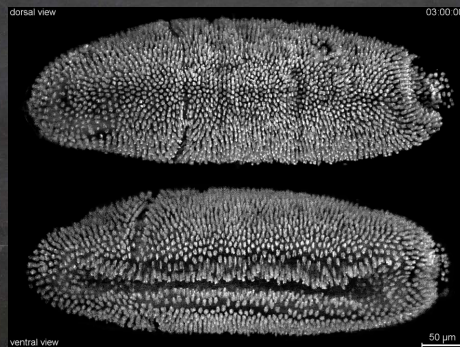
Genomic aspect



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Gene Regulation in Biology

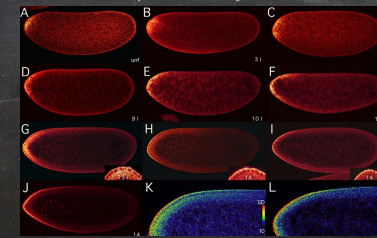
- Gene regulation in developmental biology
 - During the development of an organism, the GRN allows for:
 - the segmentation of the embryo (ex: drosophila)



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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

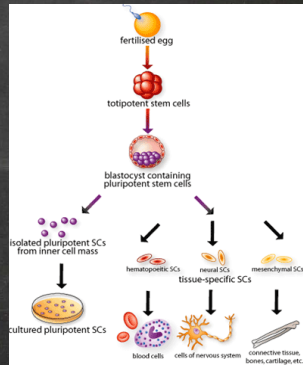


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Gene Regulation in Biology

- 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.scripps.edu/cell-bioengineering/>

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Artificial Gene Regulatory Networks

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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.)

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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

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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

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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)

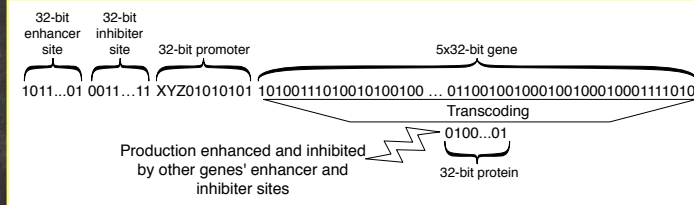
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Artificial Gene Regulatory Networks

- Computational models: bit strings

- Encoding

(Banzhaf 2003)



- Dynamics



$$e_i = \frac{1}{N} \sum_j c_j e^{\beta(u_j^+ - \bar{u}_{max}^+)} \quad in_i = \frac{1}{N} \sum_j c_j e^{\beta(u_j^- - \bar{u}_{max}^-)}$$

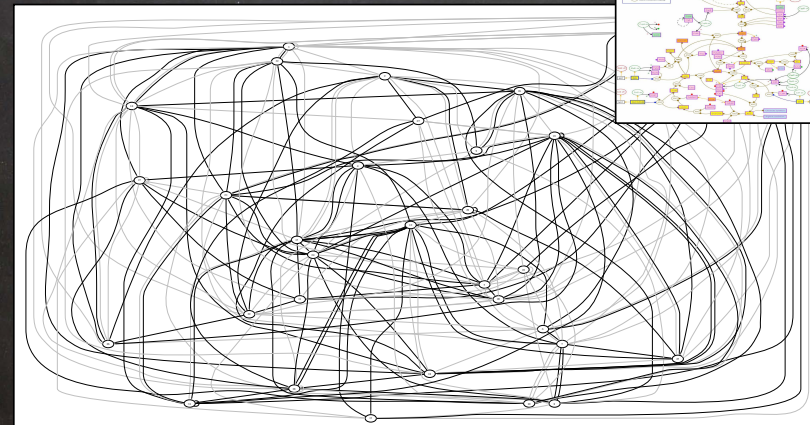
$$\frac{dc_i}{dt} = \delta(e_i - in_i)c_i - \Phi$$

Matching between proteins and sensors

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Artificial Gene Regulatory Networks

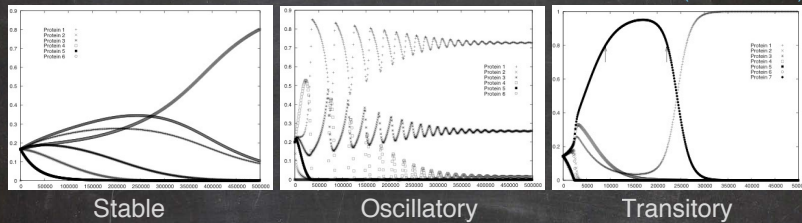
- Computational models: bit-strings



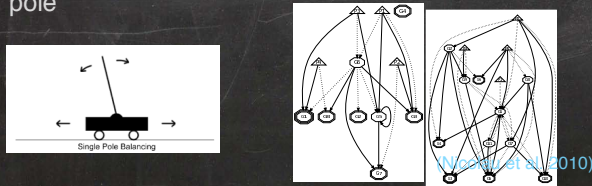
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Artificial Gene Regulatory Networks

- Computational models: bit-strings
 - Random DNA strings produce 3 types of behaviors (Banzhaf 2003)



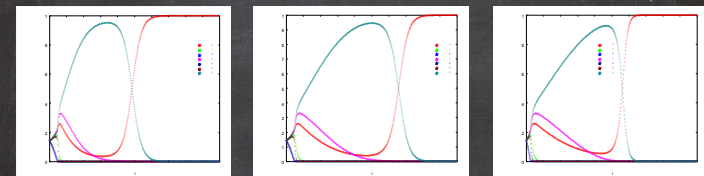
- By adding input and output proteins, possibility to control a cart pole



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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)

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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

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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:

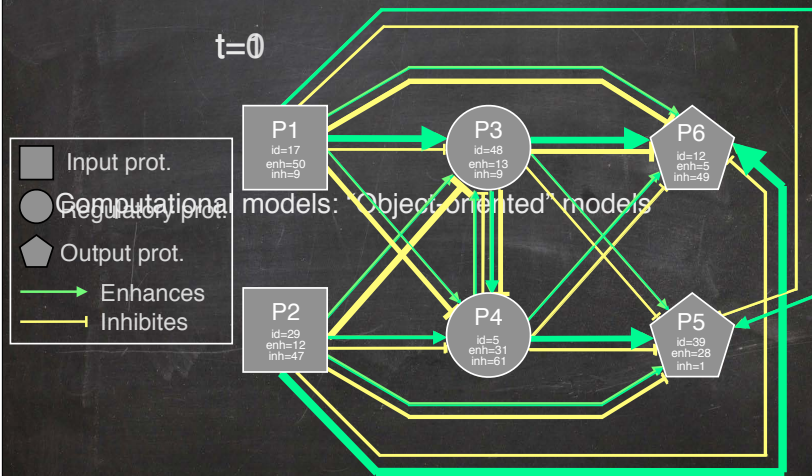
$$e_i = \frac{1}{N} \sum_j c_j e^{\beta u_{ij}^+ - u_{max}^+} \quad h_i = \frac{1}{N} \sum_j c_j e^{\beta u_{ij}^- - u_{max}^-}$$

- Differential evolution of the concentration of protein i:

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

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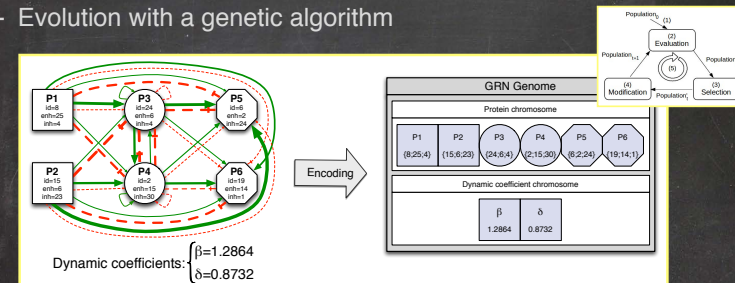
Artificial Gene Regulatory Networks



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Artificial Gene Regulatory Networks

- Computational models: “Object-oriented” models
 - Evolution with a genetic algorithm



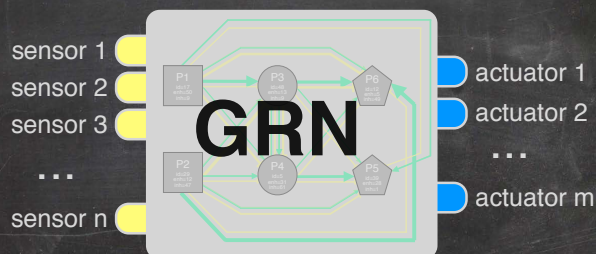
- “Neat-like” algorithm applicable to optimize GRNs more efficiently
 - Start with small networks (inputs + outputs + 1 regulatory protein)
 - Aligning crossover
 - Speciation

(Cussat-Blanc et al. 2015)

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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

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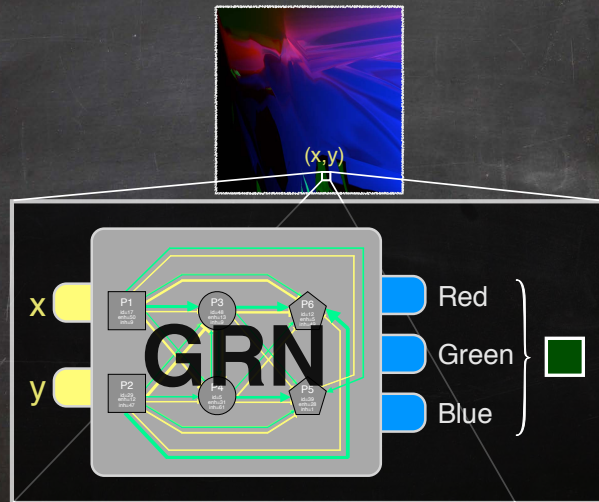
Application of Gene Regulatory Networks

- Viewing the dynamics
- Evo-devo
- Controlling agents' actuators
- Regulating high-level behaviors
- ANN & GP with GRNs

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Application of GRNs

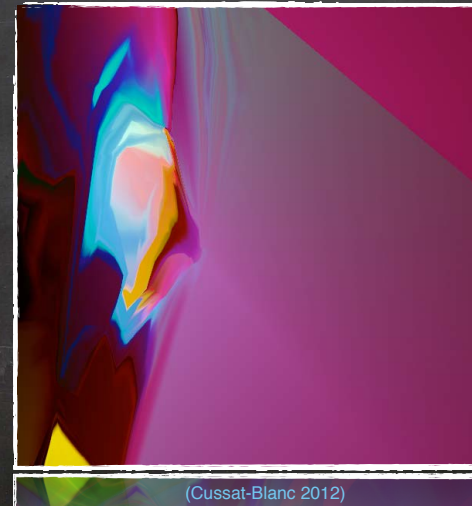
- Generating images



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Application of GRNs

- Generating images



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Application of GRNs

- Generating videos





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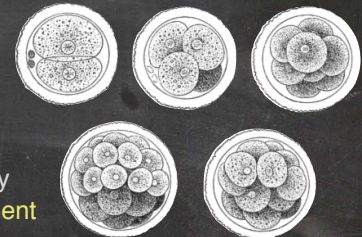
Jordan Pollack
Brandeis University
Demo lab




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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



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Application of GRNs

Policy	Stability	Efficiency	Reliability	Flexibility
Policy A	High	Medium	Low	High
Policy B	Medium	High	Medium	Medium
Policy C	Low	Low	High	Low
Policy D	High	High	High	High
Policy E	Medium	Medium	Medium	Medium

(Conway 1970)

(De Garis 1999)

[illegible]

Application of GRNs

-
- Figure 1 illustrates the two-step process of the algorithm. The left panel shows the initial state, where a complex, multi-colored structure is represented by a table of parameters. The right panel shows the final state, where the structure is simplified to a single color, and the parameters are updated accordingly.
- Left Panel (Initial State):**
- Table 1:

C_{top}	1-1
C_{bot}	1p
 - Table 2:

C_{top}	9-3
C_{bot}	1-1
 - Table 3:

C_{top}	disc
C_{bot}	disc
- Right Panel (Final State):**
- Table 4:

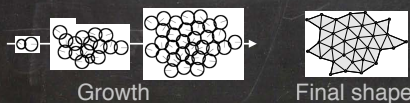
C_{top}	1-1
C_{bot}	1p
 - Table 5:

C_{top}	1-1
C_{bot}	4-2
 - Table 6:

C_{top}	3-3
C_{bot}	disc

(Doursat 2009)

(Joachimczak et al. 2012)

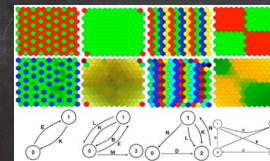


Motion

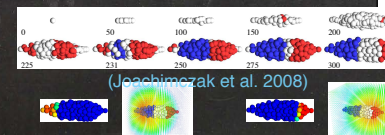
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Application of GRNs

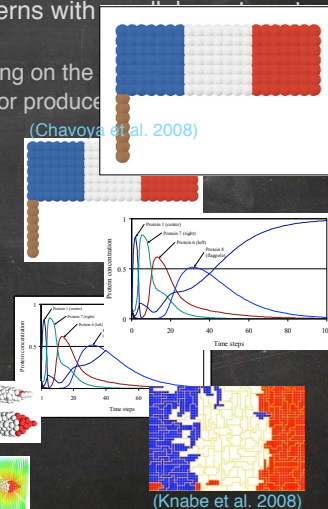
- (Chavoya et al. 2008)



(Flann et al. 2005)



(Joachimczak et al. 2008)

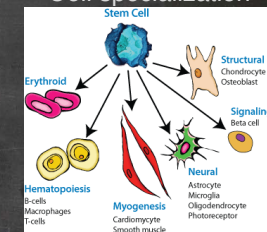


(Knabe et al. 2008)

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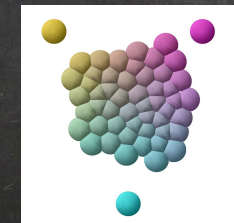
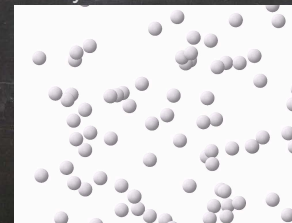
Application of GRNs

- ## Cell specialization



Physical environment

Chemical environment



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CON 1

RESULTS

s used for the above experiments were as follows :-

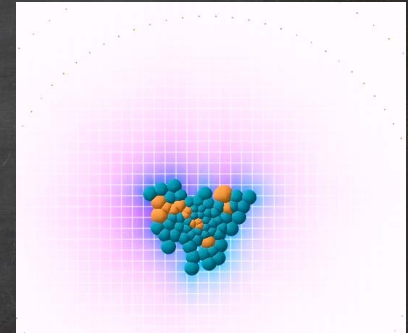
Application of GRNs

- 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

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Application of GRNs

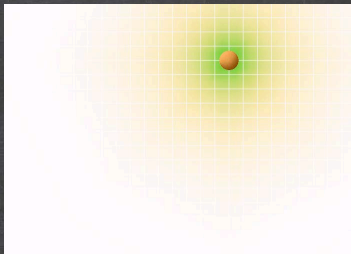
- Evo-Devo: Generating artificial creatures
 - Example:
 - 2 types of cells:
 - Nutritive => Extract energy from the environment
 - Defensive => Resist to external aggressions
 - Environment :
 - Contains nutrients
 - Contains nocive particules that kills nutritive cells
 - Fitness:
 - Survive == simulation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



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Application of GRNs

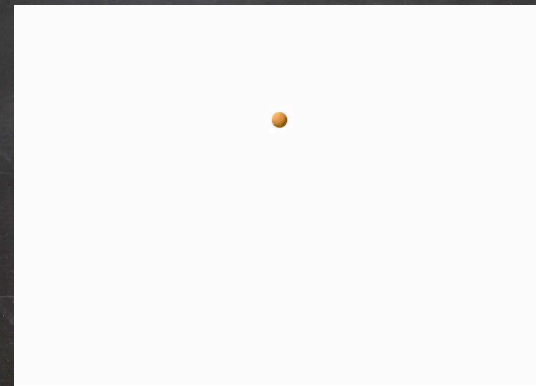
- Evo-Devo: Generating artificial creatures
 - At the beginning of the evolution, very simple strategy:
 - A single cell in the center of the environment
- Then, progressive complexification
 - A cluster of cells forming a simple shape



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Application of GRNs

- Evo-Devo: Generating artificial creatures
 - Finally, motion emerges (with no cell migration!)



(Disset et al. 2014)

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Application of GRNs

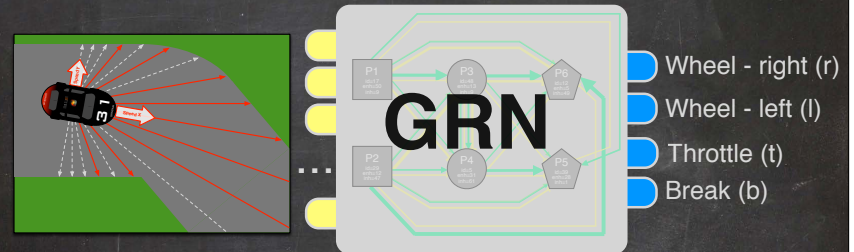
- Simulated car racing
 - Direct connection of the GRN to a virtual car
 - Use of TORCS for the car physics
 - Available sensors:
 - 18 track sensors
 - 3 speed sensors
 - 8 state sensors (rpm, position, time, etc.)
 - Available actuators:
 - Wheel angle $\in [-1, 1]$
 - Throttle $\in [0, 1]$
 - Break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



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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 = $\max(0, (b-t)/(b+t))$

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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)

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Application of GRNs

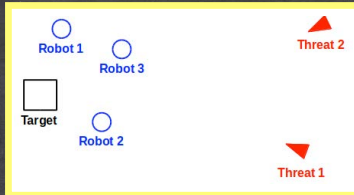
- Features of system
 - Easy to use
 - **Adaptative** to the track and its surface
 - **Robust** resistant to the noise
- Example of robustness
 - Use of the controller trained in the game to drive a robot



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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

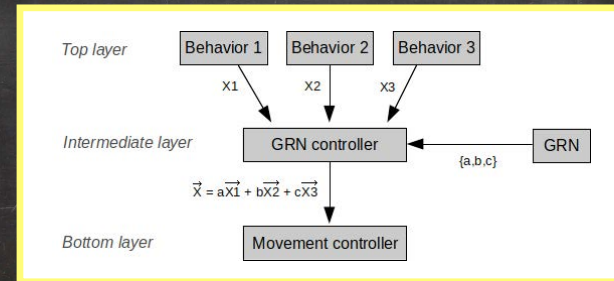


- Use of a GRN to regulate high level behavior such as:
 - Defence
 - Attack
 - Scatter
 - Regroup

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Application of GRNs

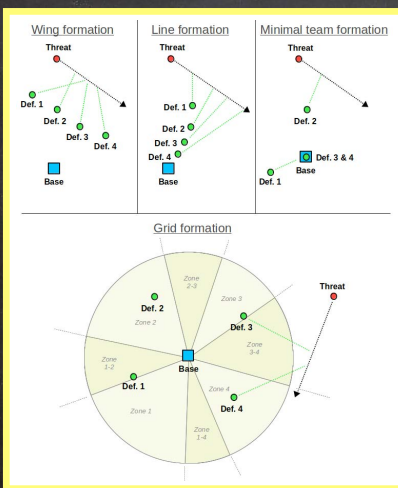
- Regulating high-level behaviors
 - Hybrid and modular architecture
 - Behaviors generate direction vector
 - The GRN aggregate the vectors to produce the final move



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Application of GRNs

- 4 strategies emerge:

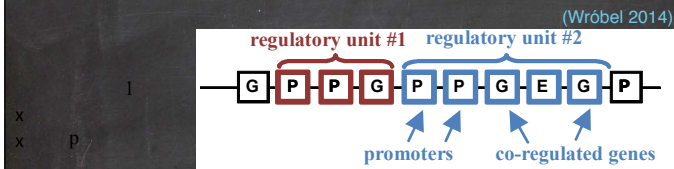


(Delecluse 2013)

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Application of GRNs

- Producing ANN with GRNs



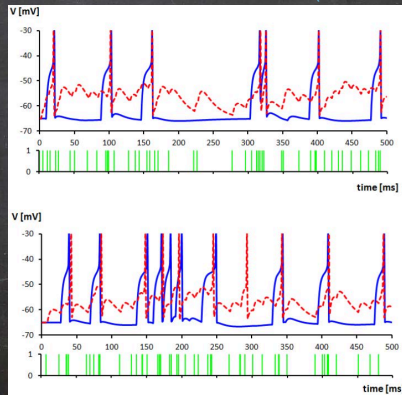
- Transform a GRN into a Spiking Neural Network
 - 1 regulatory unit = 1 neuron
 - protein concentration = neuron membran potential
 - regulatory unit connections = synapses

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Application of GRNs

- Producing ANN with GRNs
 - Usage example: reproducing spikes

(Wróbel 2012)

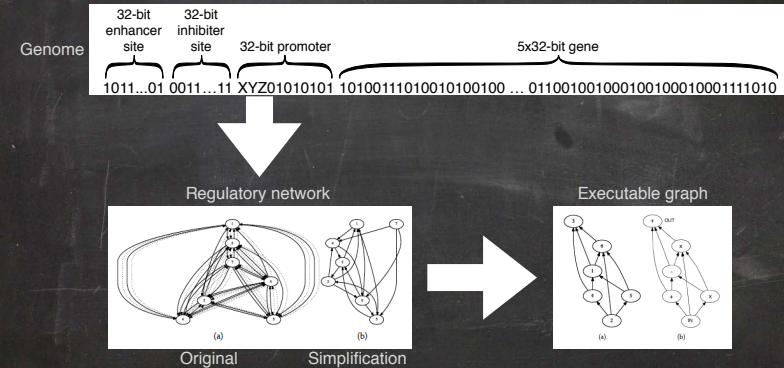


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Application of GRNs

- GRN programming
 - Map network into program

(Lopes and Costa 2012)



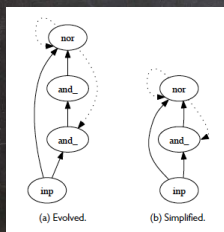
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Application of GRNs

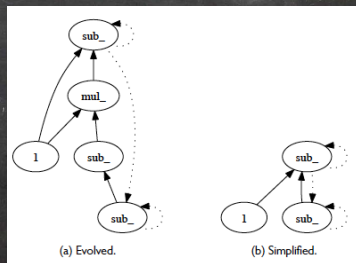
- GRN programming

(Lopes 2015)

Problem	S.R. (%)	AvgEval	StdDev	MinEval	AvgFun	MinFun	G.R. (%)
<i>nbitparitv</i>	100	10871	34290	100	5.4	4	91
<i>squares</i>	100	16478	45725	100	4.8	4	99
<i>Fibonacci</i>	100	37009	65622	100	5.4	4	100
<i>modfactorial-42x1</i>	100	3087	3890	100	5.3	4	78
<i>modfactorial-42x2</i>	100	22065	34791	100	5.1	4	100
<i>modfactorial-42x3</i>	5	567500	274475	220600	7.4	7	100



Even n-bit Parity



Fibonacci Series

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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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