Université de Toulouse

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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

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Gene Regulation in Biology

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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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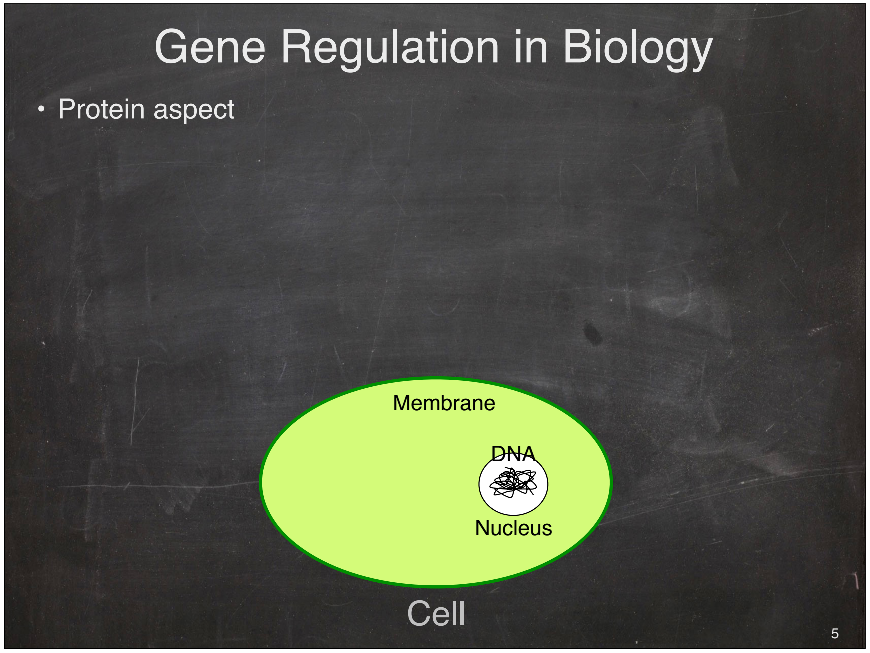
Gene Regulation in Biology
• Protein aspect
Membrane
DNA
Nucleus
Cell
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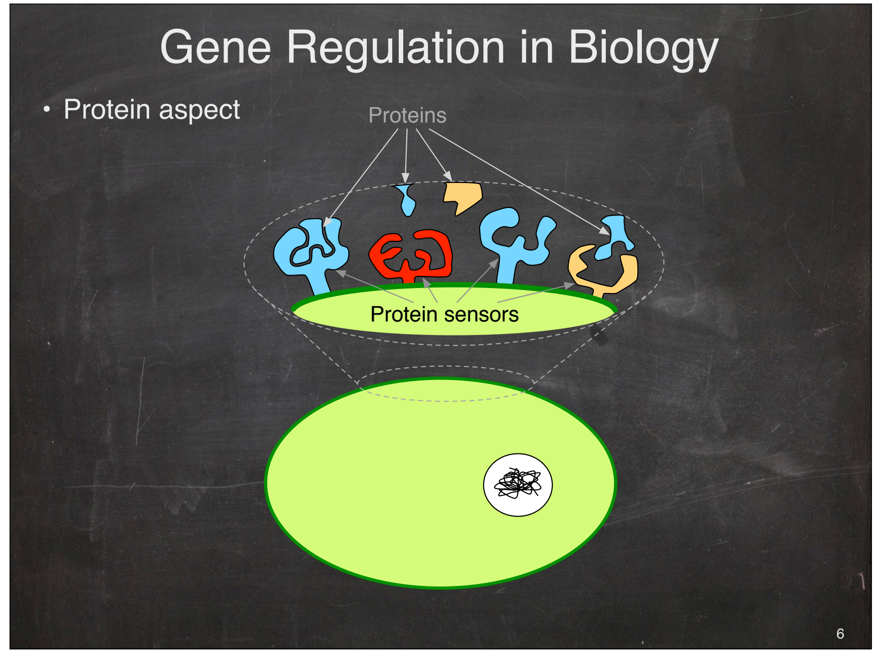
Gene Regulation in Biology
• Protein aspect
Proteins
Protein sensors
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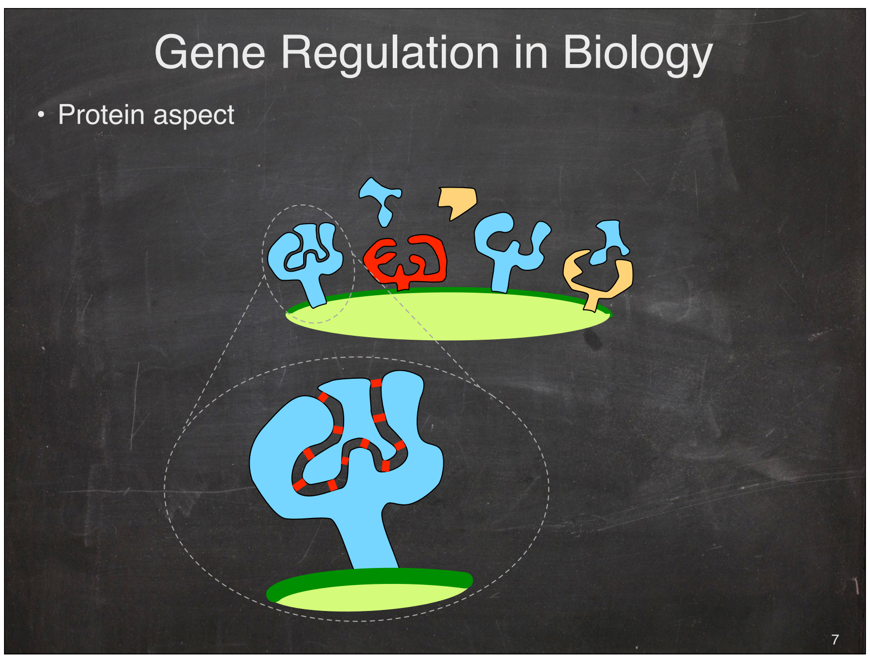
Gene Regulation in Biology
• Protein aspect
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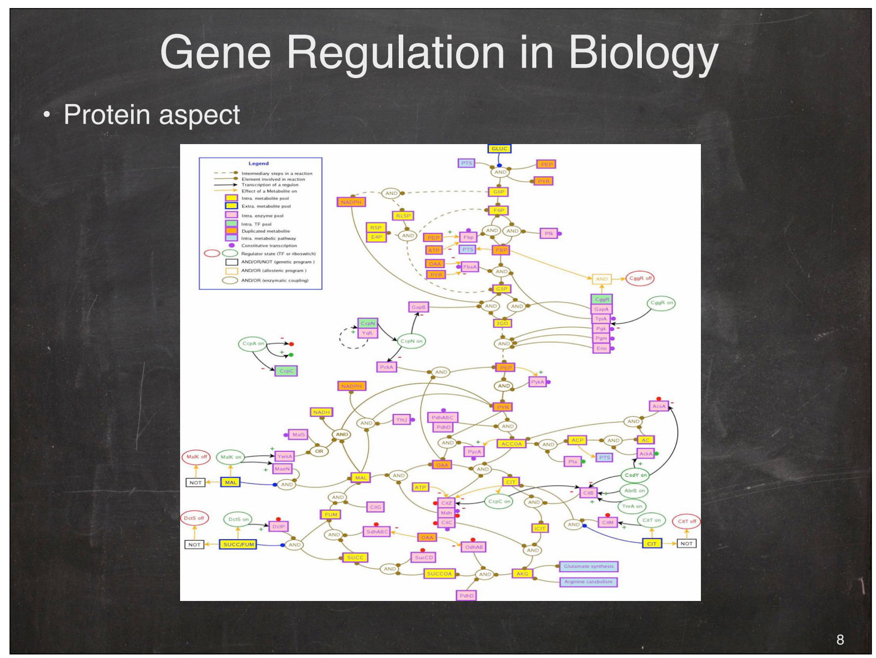
Gene Regulation in Biology
• Protein aspect
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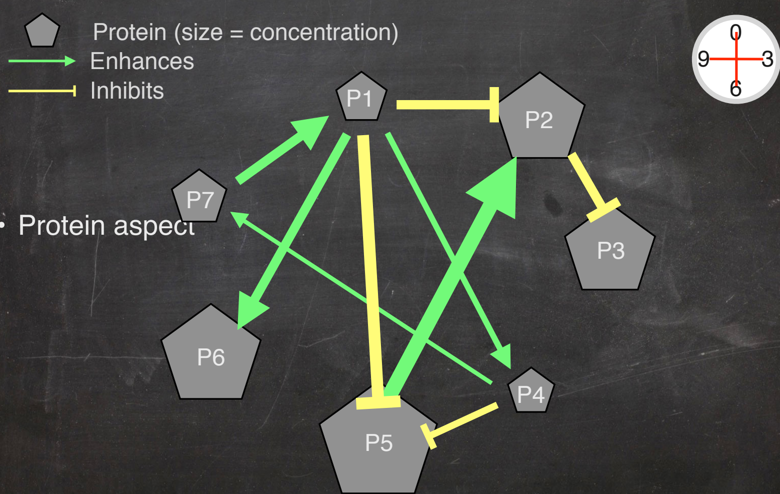
Gene Regulation in Biology

- Protein aspect



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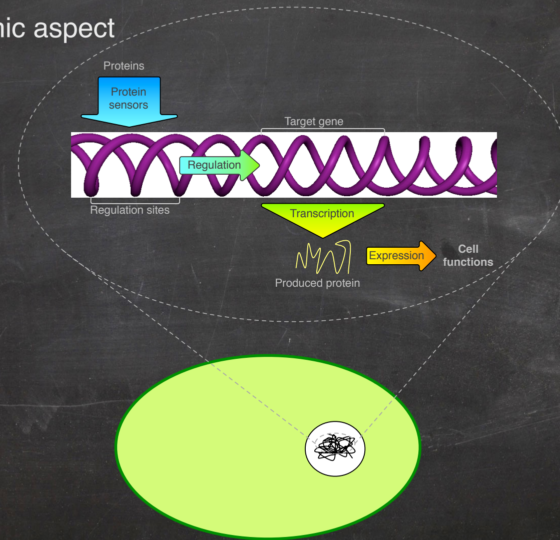
Gene Regulation in Biology

- Genomic aspect



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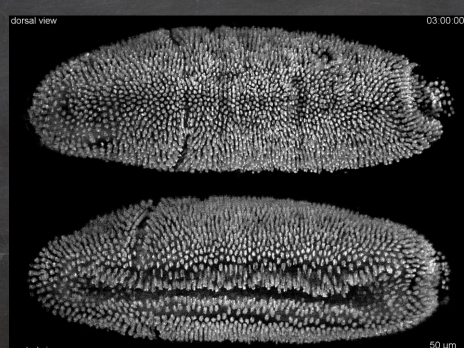
Gene Regulation in Biology

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



(Tomer et al. 2012)

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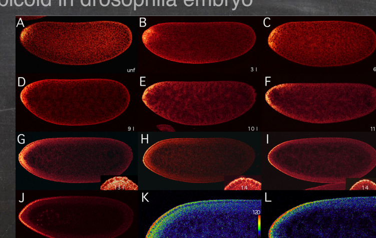
Gene Regulation in Biology

- 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



(Spirov et al. 2009)

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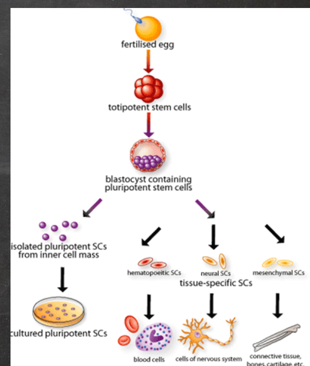
Gene Regulation in Biology

- 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.scq.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

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Artificial Gene Regulatory Networks

- Bit-string models
- Biologically plausible model of regulation
  - Encoding close to biology:
    - bit string ≈ 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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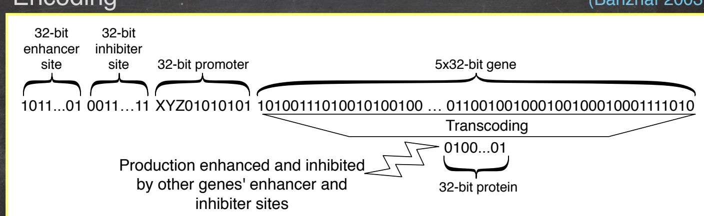
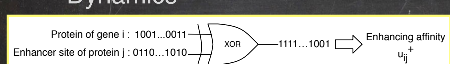
Artificial Gene Regulatory Networks

- Computational models: bit-strings
  - Encoding

(Banzhaf 2003)

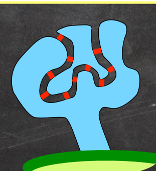


  - Dynamics



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

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



Matching between proteins and sensors

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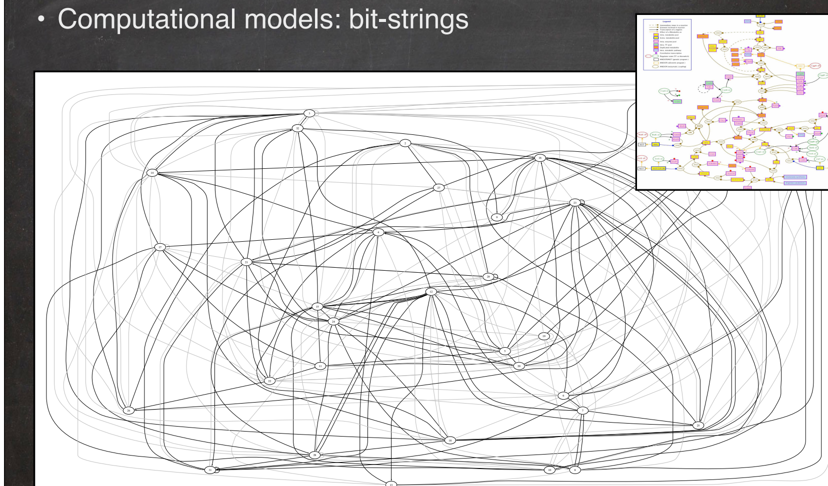
Artificial Gene Regulatory Networks

- Computational models: bit-strings



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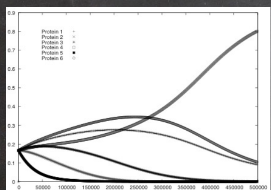
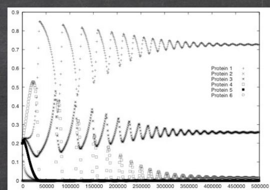
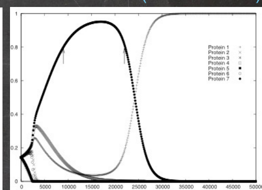
Artificial Gene Regulatory Networks

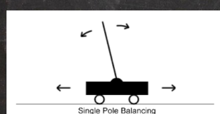
- Computational models: bit-strings
  - Random DNA strings produce 3 types of behaviors (Banzhaf 2003)

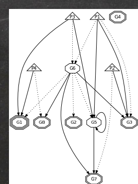

Stable


Oscillatory


Transitory

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

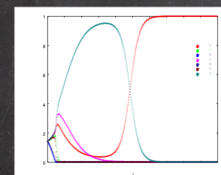


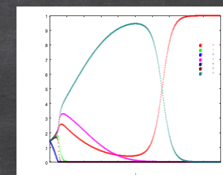


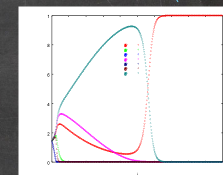
(Nicolau et al. 2010)

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* ∈ [0, p]
    - Protein type (input, output ou regulatory)
    - Enhancing tag *enh* ∈ [0, p]
    - Inhibiting tag *inh* ∈ [0, p]
  - Edges = matching between proteins

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

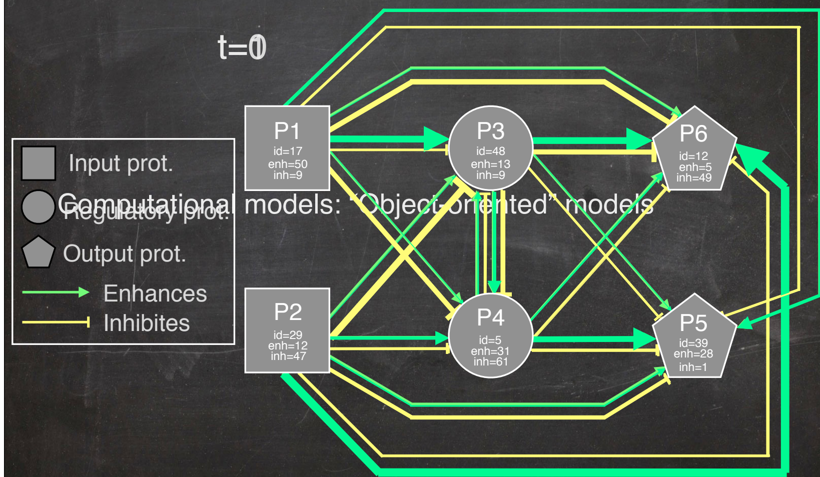
- Dynamics of the network
  - Enhancing and inhibiting coefficients of protein i:

$$e_i = \frac{1}{N}\sum_{j}^{N} c_j e^{\beta u_{ij}^{+} - u_{max}^{+}} \qquad h_i = \frac{1}{N}\sum_{j}^{N} c_j e^{\beta u_{ij}^{-} - u_{max}^{-}}$$

  - Differential evolution of the concentration of protein i:

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

Artificial Gene Regulatory Networks



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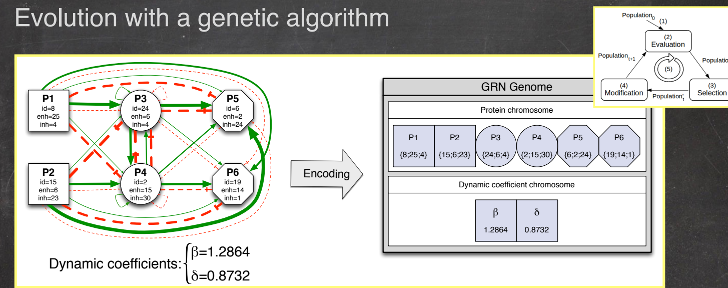
Artificial Gene Regulatory Networks

- Computational models: "Object-oriented" models
  - Evolution with a genetic algorithm

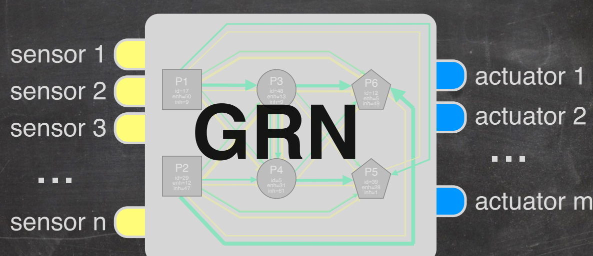


  - "Neat-like" algorithm applicable to optimize GRNs more efficiently
    - Start with small networks (inputs + outputs + 1 regulatory protein)
    - Aligning crossover
    - Speciation

(Cussat-Blanc et al. 2015)

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



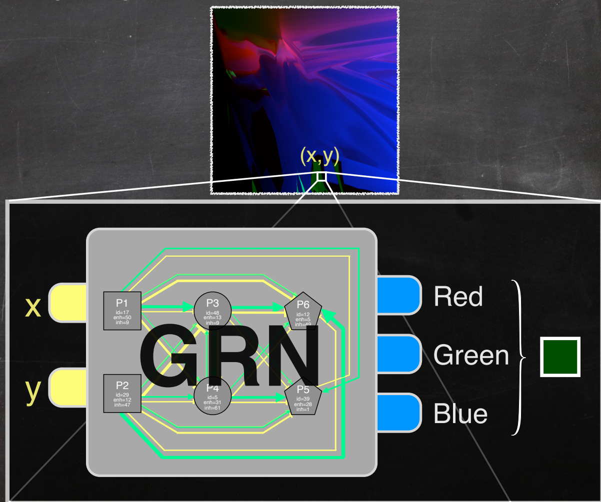
  - Compact encoding in comparison to neural networks

Application of Gene Regulatory Networks

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

Application of GRNs

- Generating images



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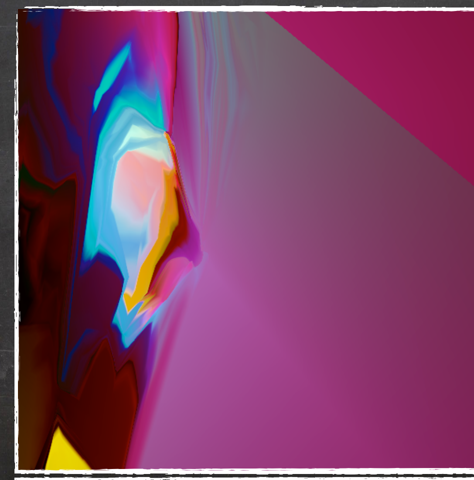
Application of GRNs

- Generating images



(Cussat-Blanc 2012)

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Application of GRNs

- Generating videos

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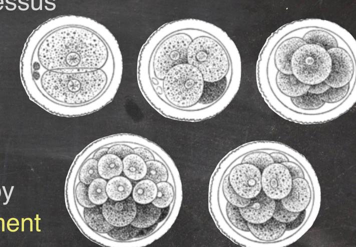
Application of GRNs

- 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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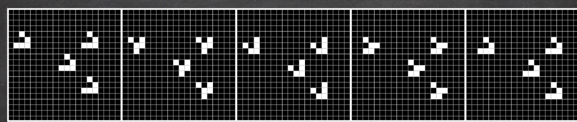
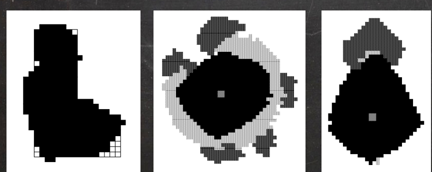
Application of GRNs

- 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



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

(De Garis 1999)

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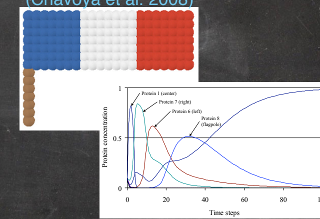
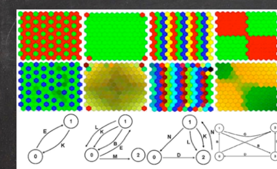
Application of GRNs

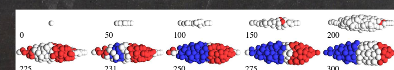
- Evo-Devo: use of GRNs
  - Development of specialization patterns with a cellular automata
  - French flag problem
    - Different cell specialization, depending on the position of the cells
    - Morphogen gradient pre-positioned or produced by the organisms

(Chavoya et al. 2008)

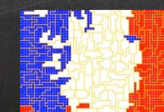




(Flann et al. 2005)



(Joachimczak et al. 2008)



(Knabe et al. 2008)

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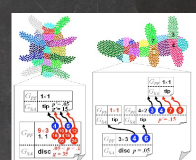
Application of GRNs

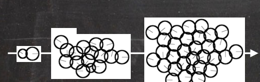
- Evo-Devo: use of GRNs
  - Complexification of the shape by introducing a developmental process
    - Probability of division for each cell
    - Intercellular adhesion (mass/spring system) to aggregate the cells



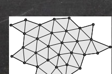
(Doursat 2009)

  - 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

(Joachimczak et al. 2012)



Growth



Final shape

Motion

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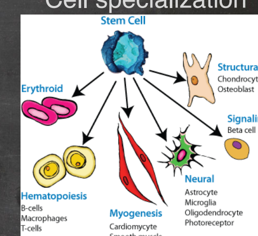
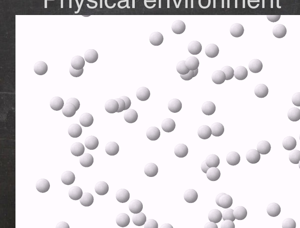
Application of GRNs

- Evo-Devo: Generating artificial creatures
  - GRN used to regulate the cell's life cycle
  - Optimization fo the GRN to produce creatures adapted to their environment
  - Functional differentiation of the cells
  - Simulated physics and chemistry in the environment

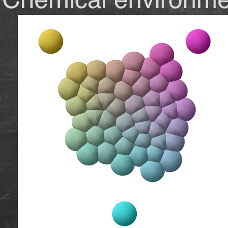
Cell specialization



Physical environment



Chemical environment



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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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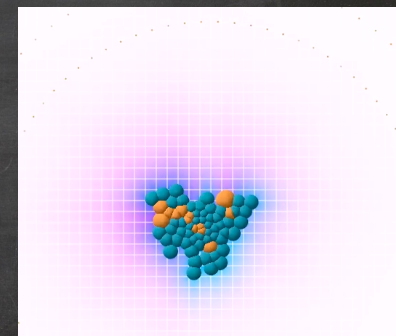
Application of GRNs

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



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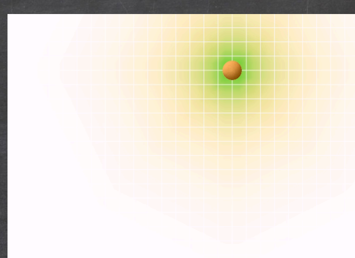
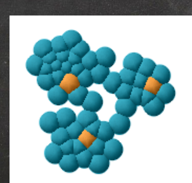
Application of GRNs

- Evo-Devo: Generating artificial creatures
  - At the beginning of the evolution, very simple strategy:



  - Then, progressive complexification



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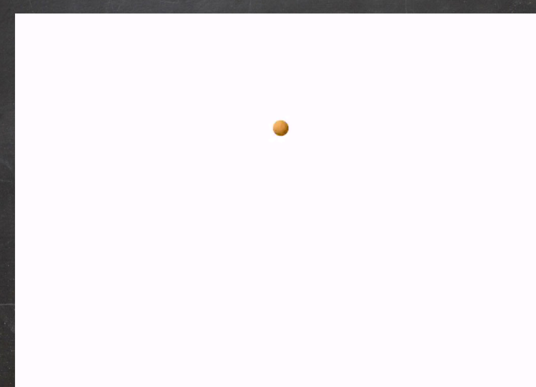
Application of GRNs

- 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 ∊ [-1, 1]
    - Throttle ∊ [0, 1]
    - Break ∊ [0, 1]
  - Only keep the necessary sensors

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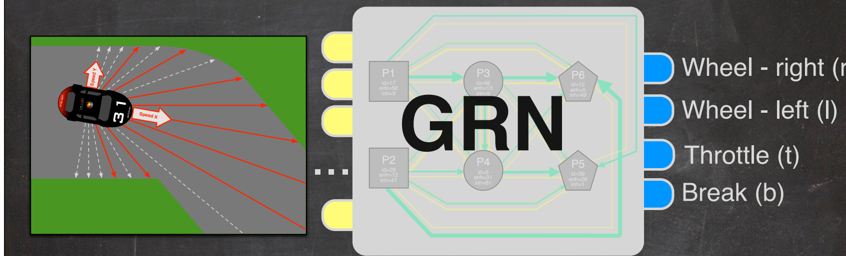
Application of GRNs

- 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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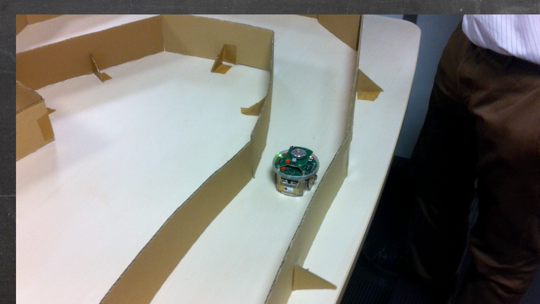
Application of GRNs

- 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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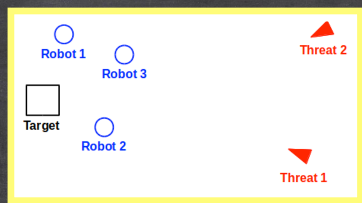
Application of GRNs

- 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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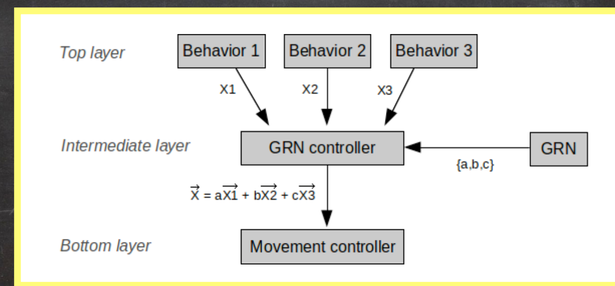
Application of GRNs

- 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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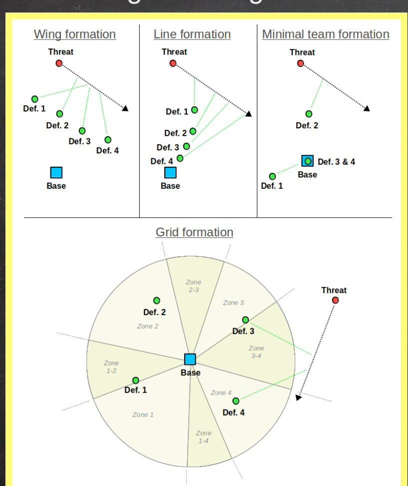
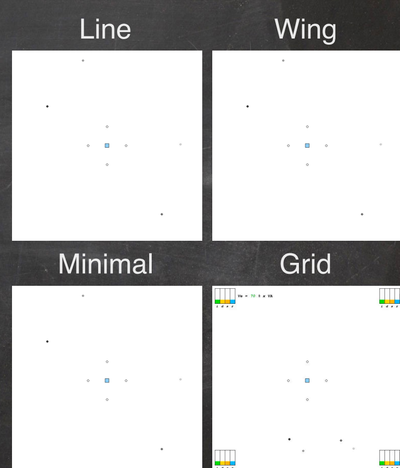
Application of GRNs

- 4 strategies emerge:



(Delecluse 2013)



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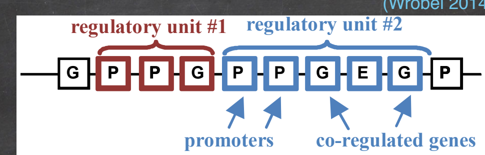
Application of GRNs

- Producing ANN with GRNs

(Wróbel 2014)



  - 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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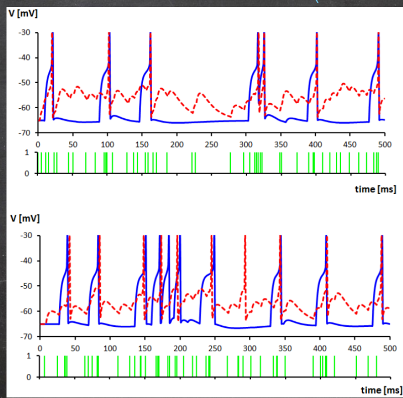
Application of GRNs

- Producing ANN with GRNs
  - Usage example: reproducing spikes

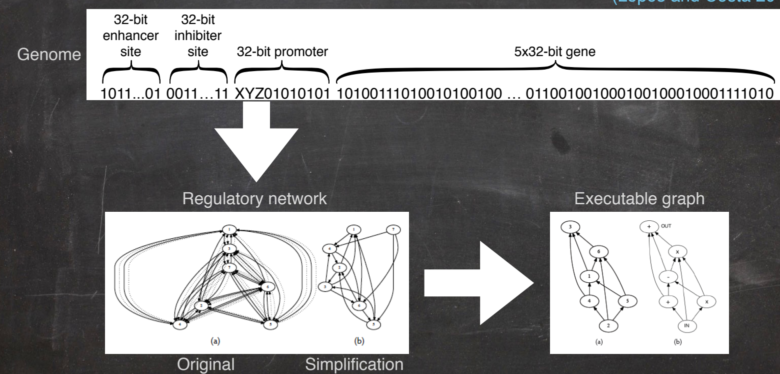
(Wróbel 2012)



Application of GRNs

- GRN programming
  - Map network into program

(Lopes and Costa 2012)

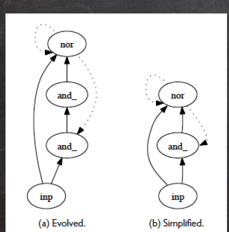


Application of GRNs

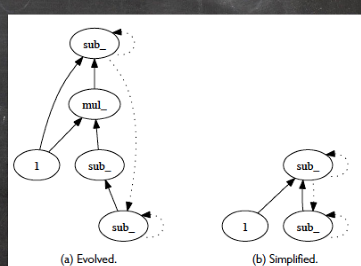
- GRN programming

(Lopes 2015)

Problem	*S.R. (%)*	*AvgEval*	*StdDev*	*MinEval*	*AvgFun*	*MinFun*	*G.R. (%)*
nbitparity	100	10871	34290	100	5.4	4	91
squares	100	16478	45725	100	4.8	4	99
Fibonacci	100	37009	65622	100	5.4	4	100
modfactorial-k2s1	100	3087	3890	100	5.3	4	78
modfactorial-k2s2	100	22065	34791	100	5.1	4	100
modfactorial-k2s3	5	567500	274475	220600	7.4	7	100



Even n-bit Parity



Fibonacci Series

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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