Artificial Gene Regulatory Networks

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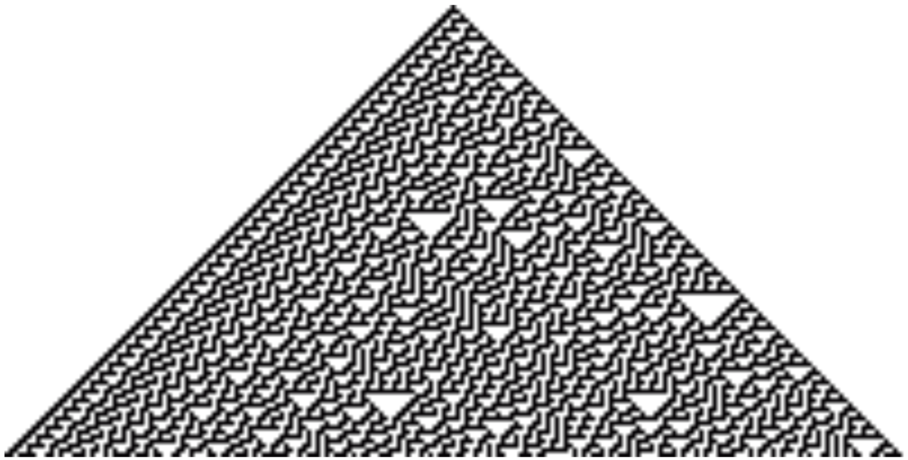
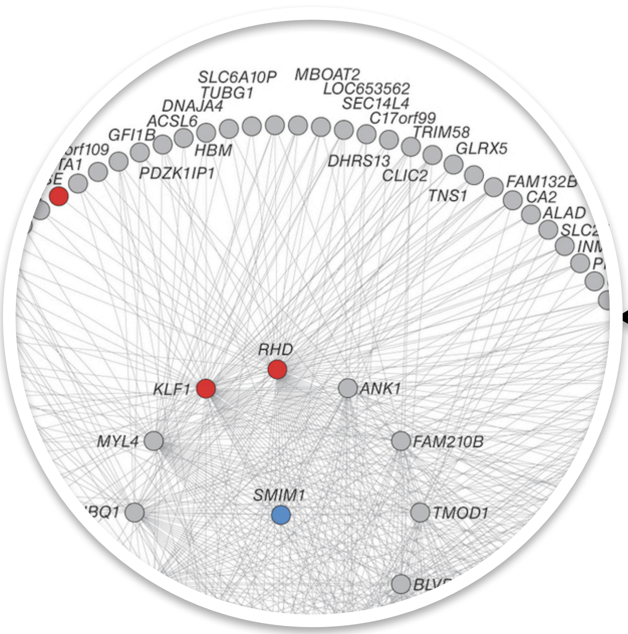
Previous Lecture

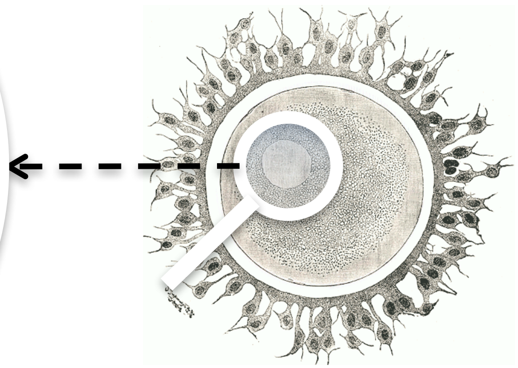
- Cellular automata
  - Distributed, bottom-up, emergent behaviour
  - Used to model natural systems
  - Complexity from simple systems
  - Can be used to compute

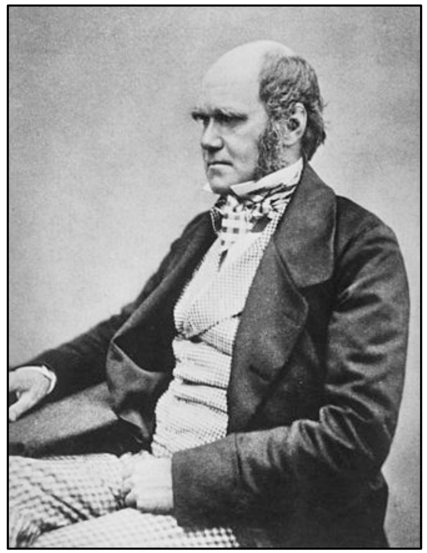


Today's Lecture

- How biological cells actually "compute"
  - Gene regulatory networks (GRNs)
  - Computational models of GRNs (Artificial GRNs)
  - Theoretical properties and examples of use

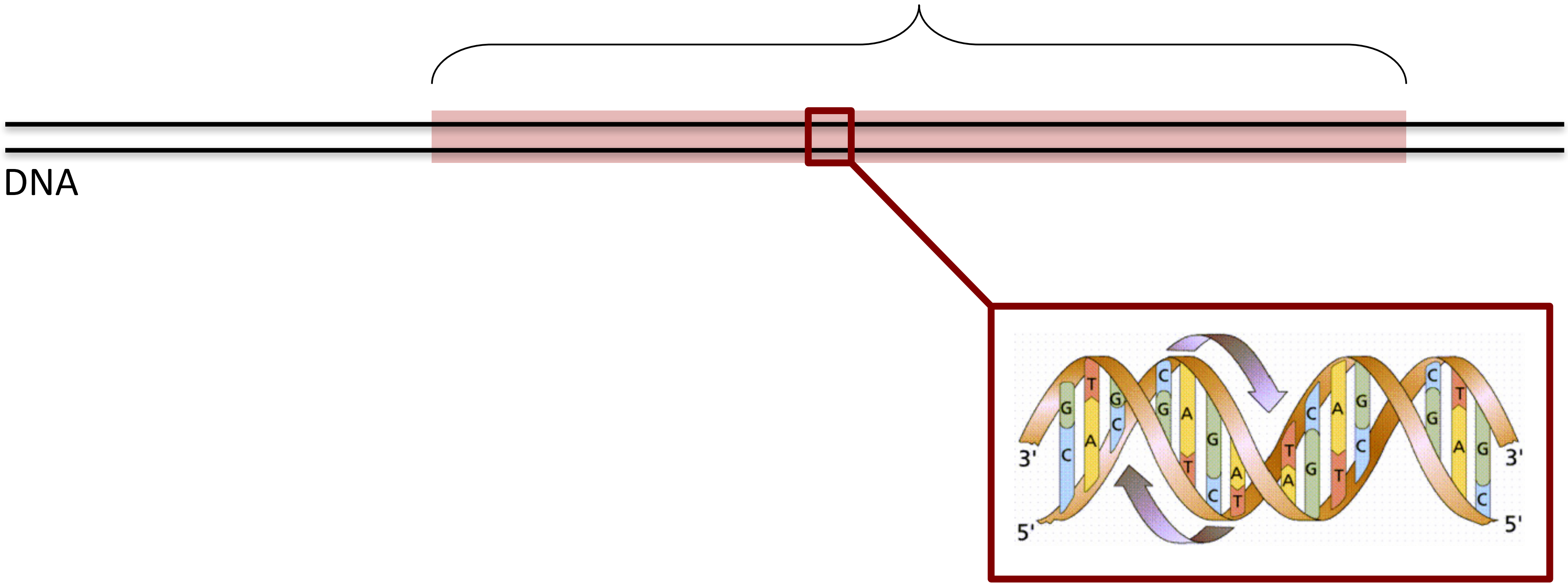






Gene Regulation in Biology

A **gene** is a contiguous region of DNA



http://c2.plzcdn.com

Gene Regulation in Biology

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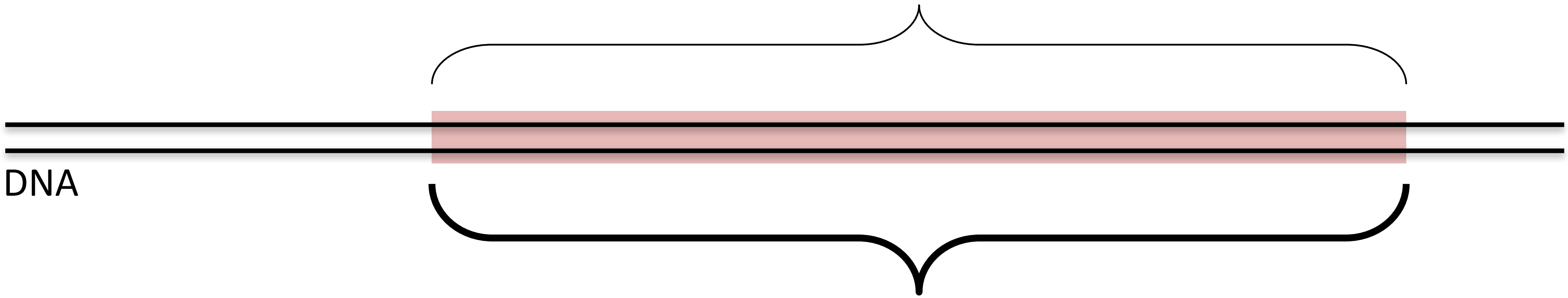
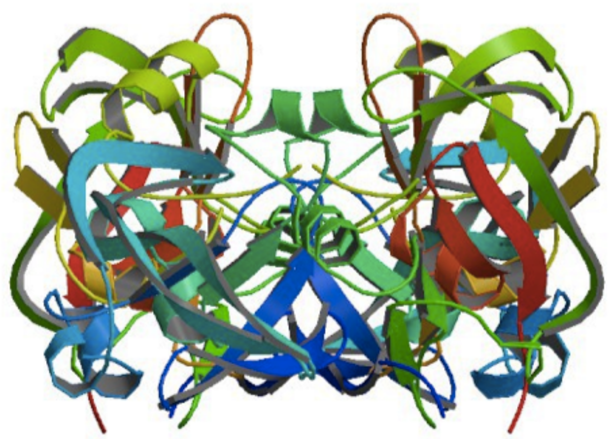


Each gene describes how to make a **protein**, which is a molecular machine

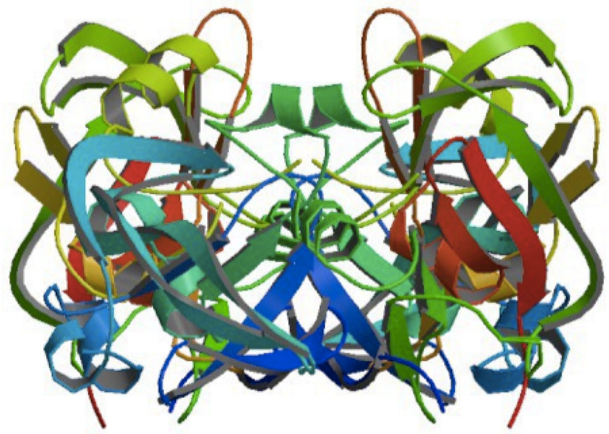


Gene Regulation in Biology

Genes are expressed when a **transcription complex** forms – this is a bit like a photocopier

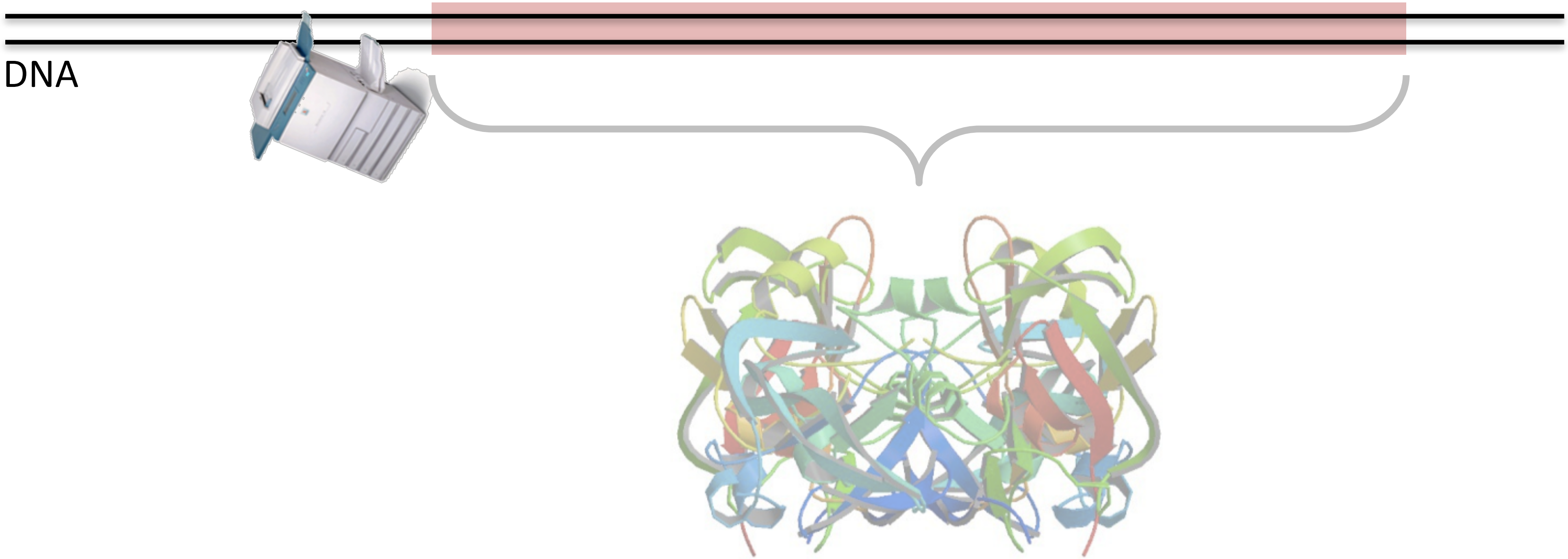
DNA

The transcription complex binds to conserved patterns that mark the start of genes, e.g. TATA



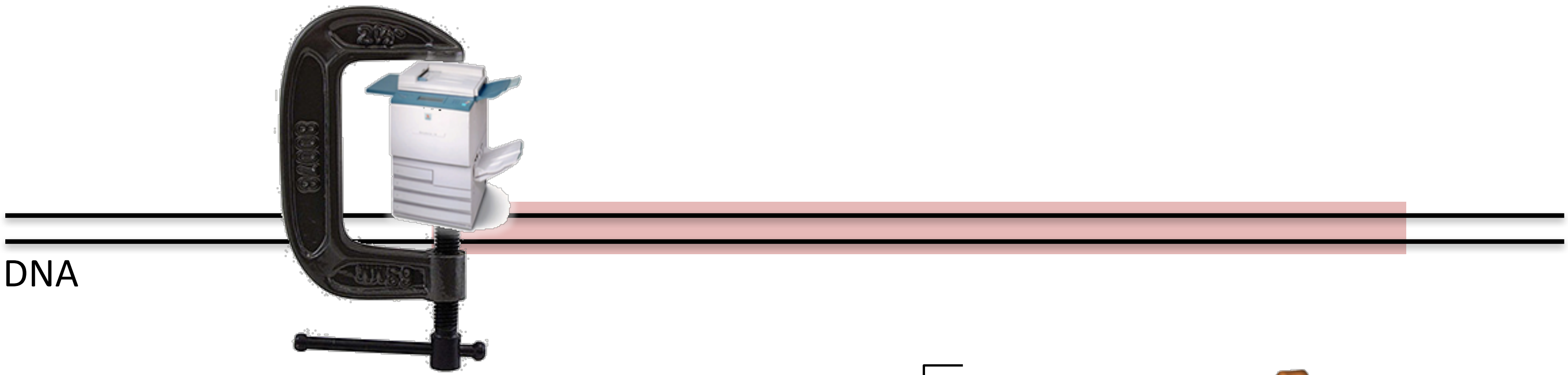
Gene Regulation in Biology

However, the transcription complex is unstable, and rarely copies genes by itself

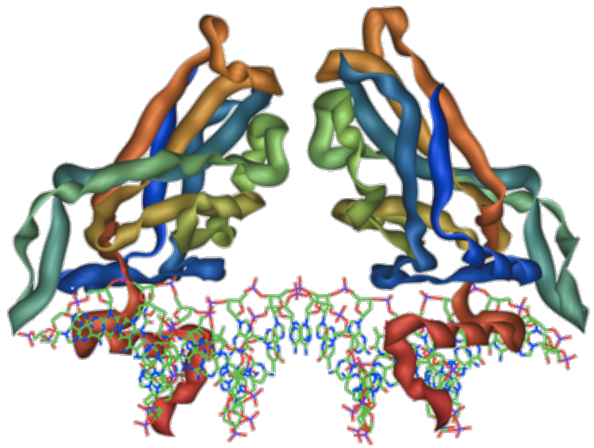


Gene Regulation in Biology

Instead, it must be helped out by <u>proteins</u> called **transcription factors (TFs)**

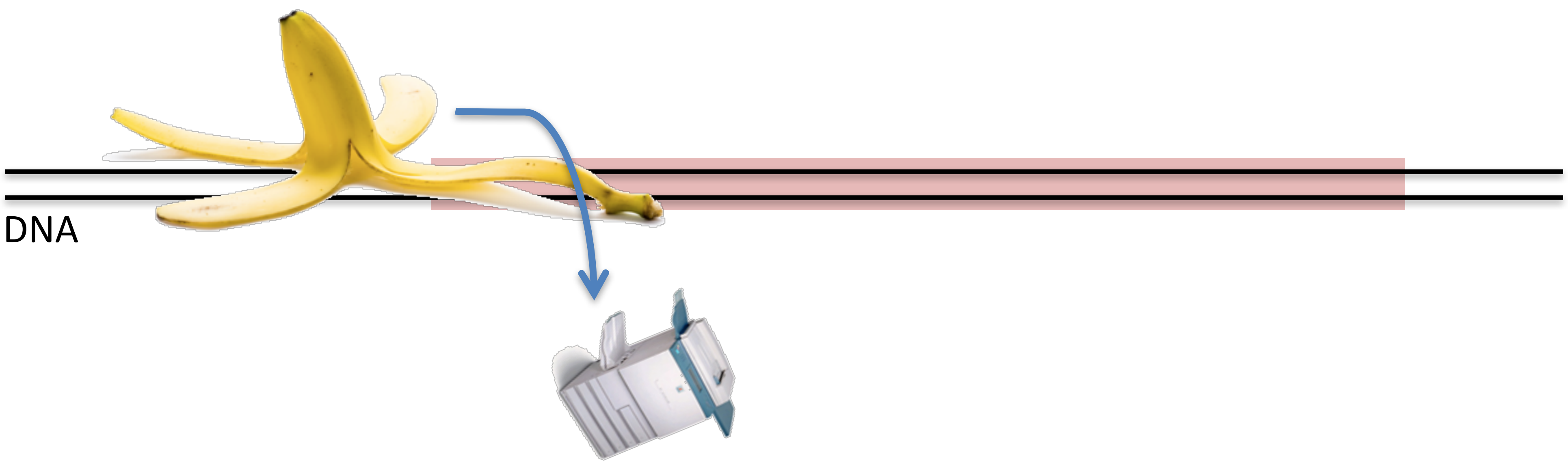


These bind to both the DNA and the transcription complex, holding everything in place – a bit like a clamp



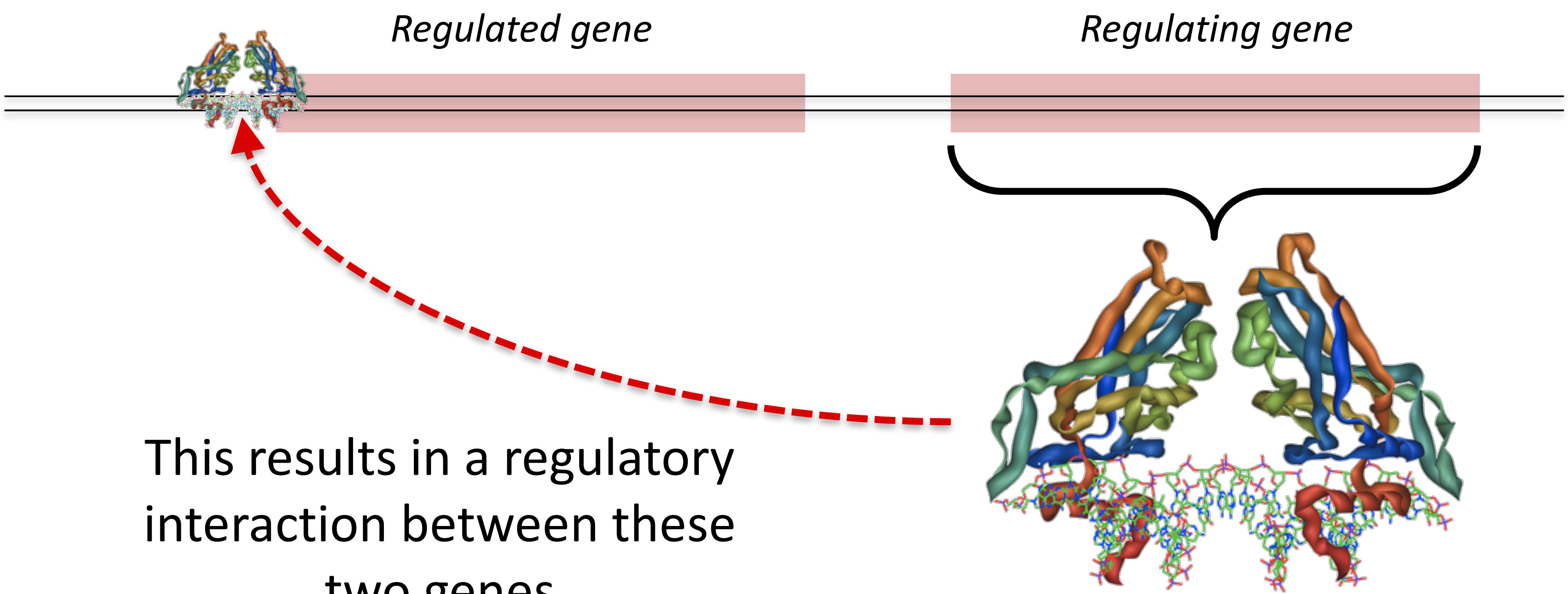
Gene Regulation in Biology

Some TFs are inhibitory and act to destabilise the transcription complex



Gene Regulation in Biology

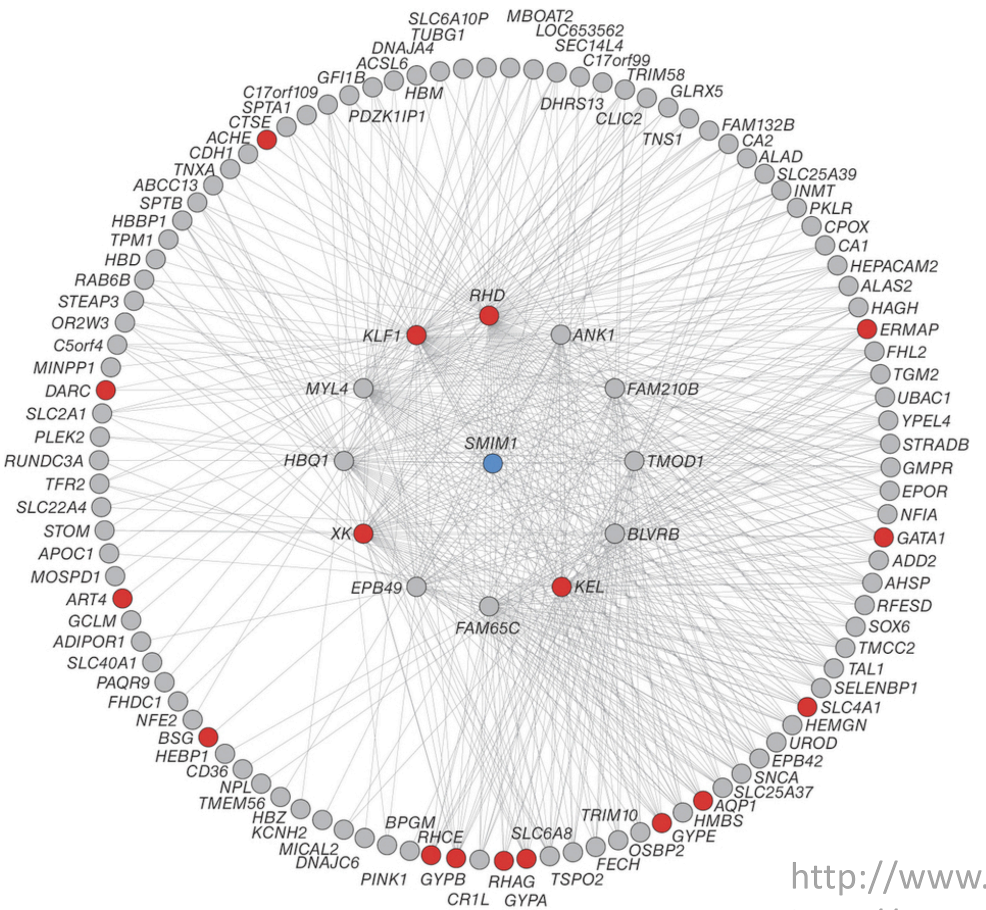
Since transcription factors are proteins, they must be produced by other genes …

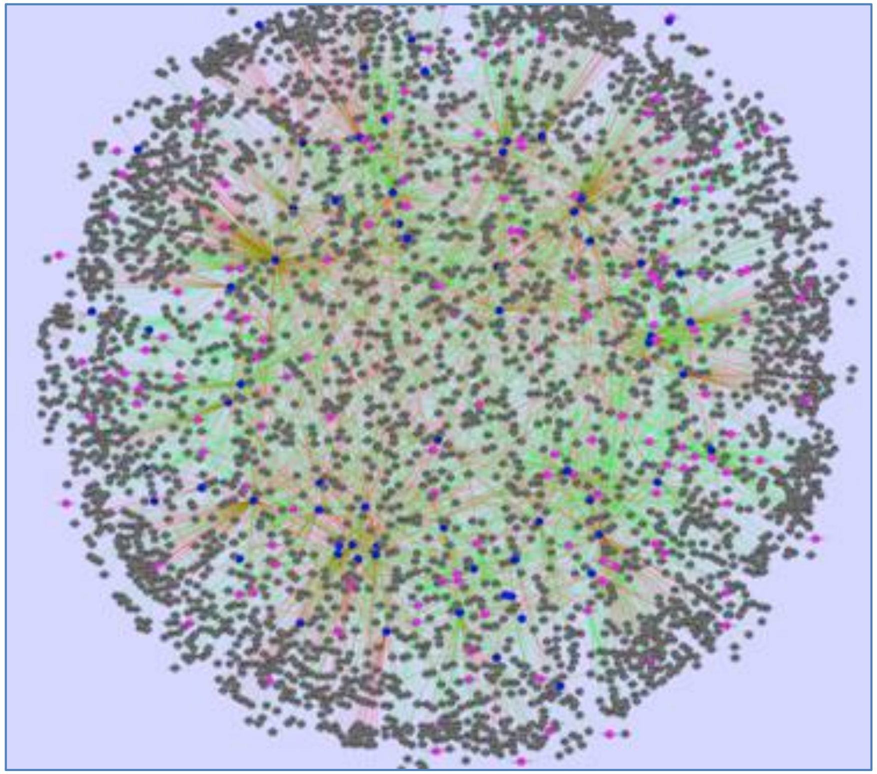


This results in a regulatory interaction between these two genes

Gene Regulation in Biology

- The pattern of interactions between all genes is known as the gene regulatory network (or GRN)

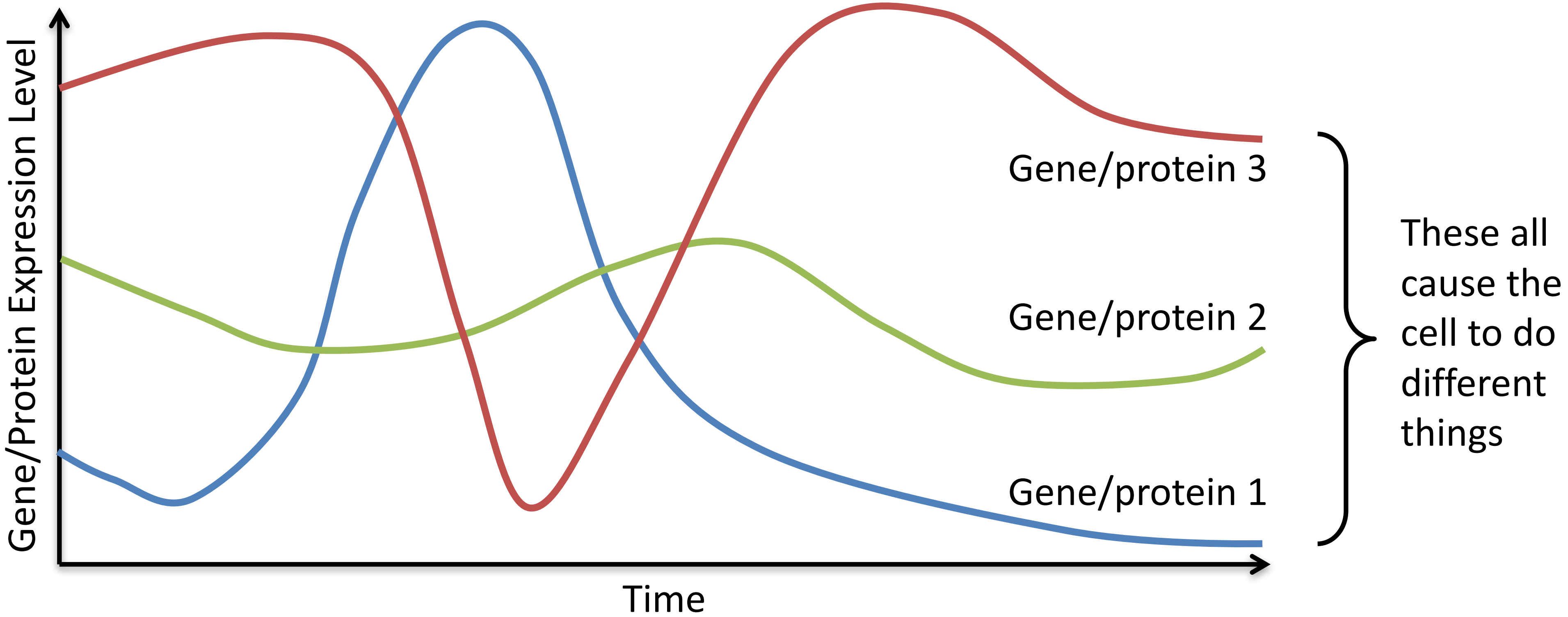




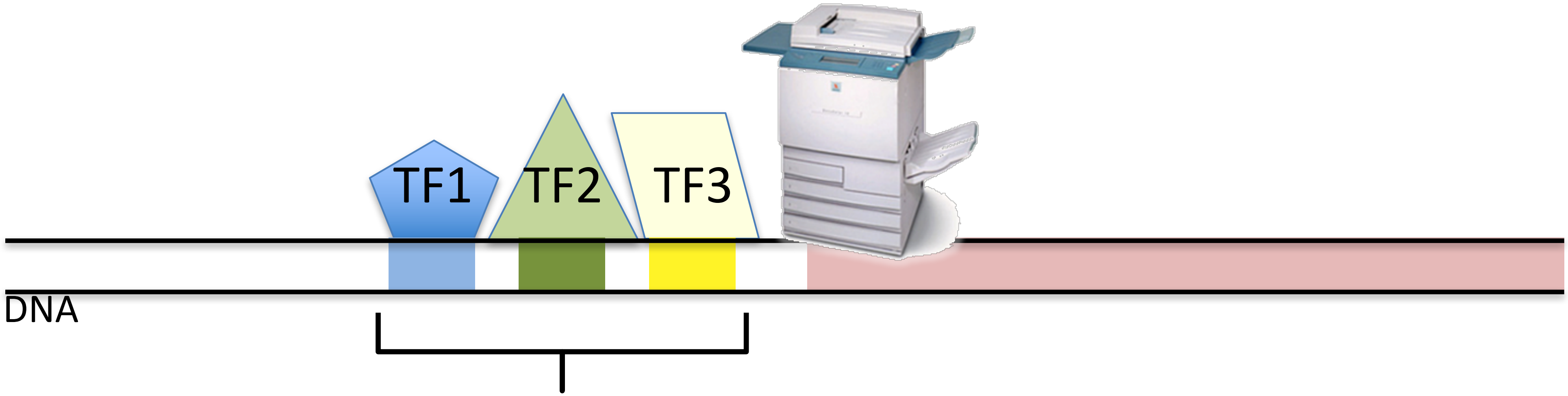
http://www.nature.com/ng/journal/v45/n5/fig_tab/ng.2600_F2.html
http://www.scbit.org/cgrnb/faq.htm

Gene Regulation in Biology

- The GRN controls the expression of proteins, and hence the behaviour of the cell, over time
  - Proteins are the molecular machines of the cell
  - The GRN is, basically, the cell's computer



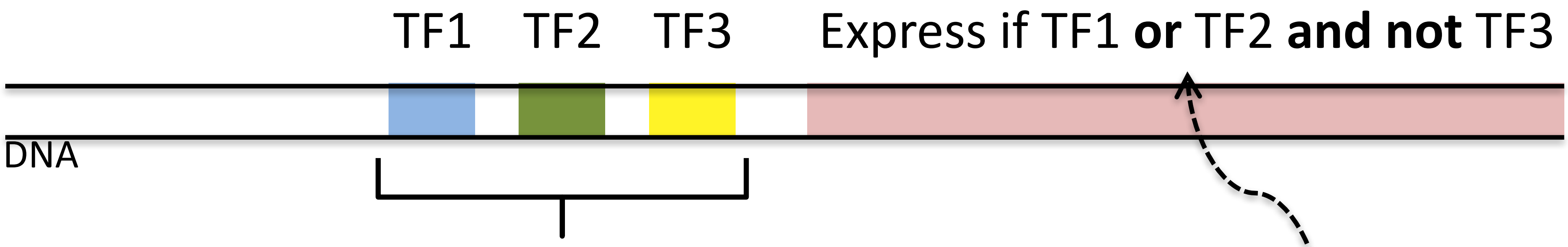
Gene Regulation in Biology



A number of different TFs are often involved in regulation, binding to different patterns in the **regulatory region** upstream of the gene

This pattern is different for every gene

Gene Regulation in Biology

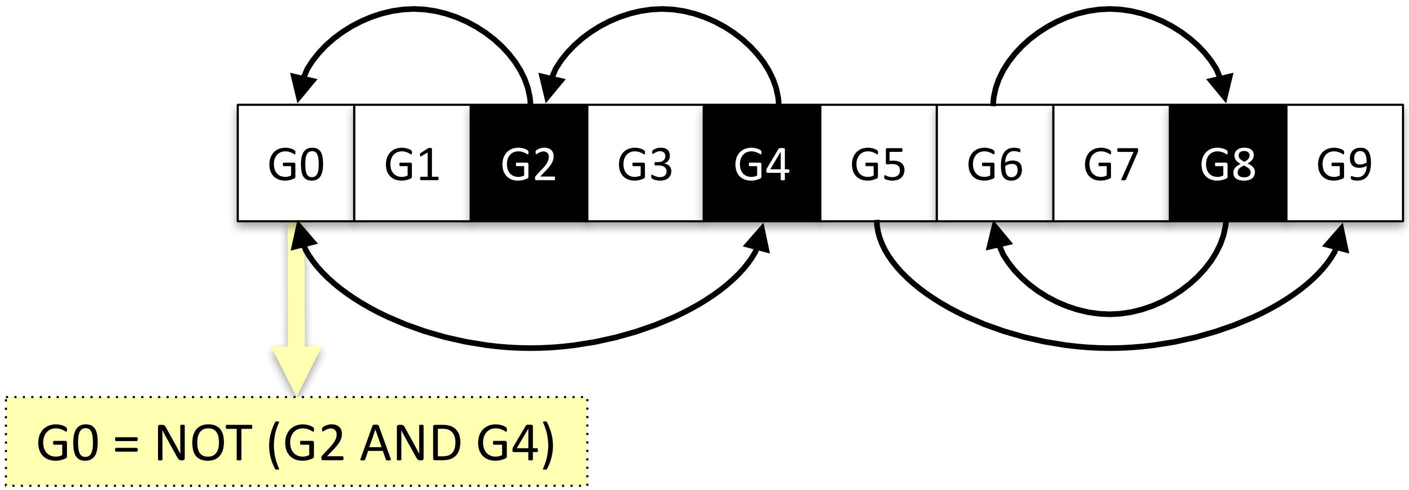


So, whether a gene is expressed depends on whether some other genes are expressed and whether some other genes are not expressed – this is the gene's **regulatory function**

Often this can be captured by a Boolean function

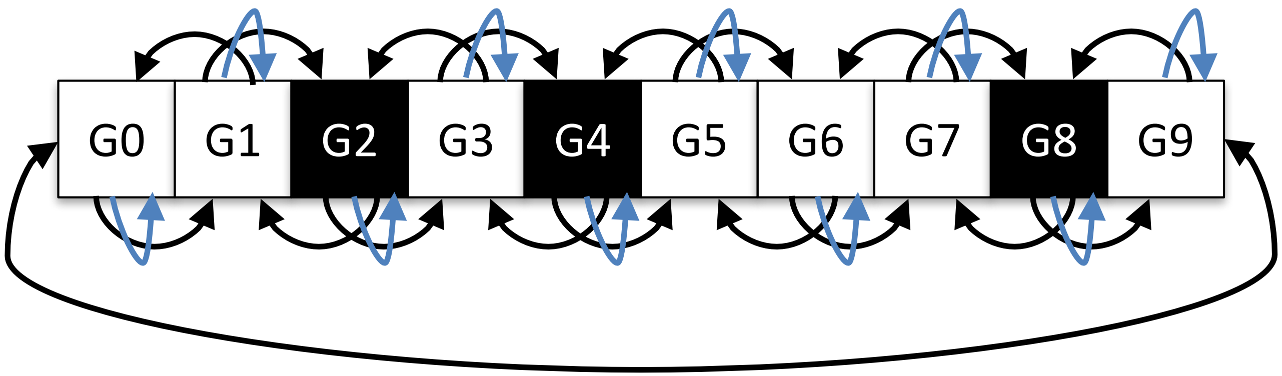
Boolean Network (BN)

- This idea can be modelled as a Boolean Network
  - A set of nodes (representing genes)
    - each with a binary state (expressed or not expressed),
    - a set of input nodes (their regulating genes),
    - and a Boolean function (their regulatory function).
  - These are executed synchronously at each time step



Boolean Network (BN)

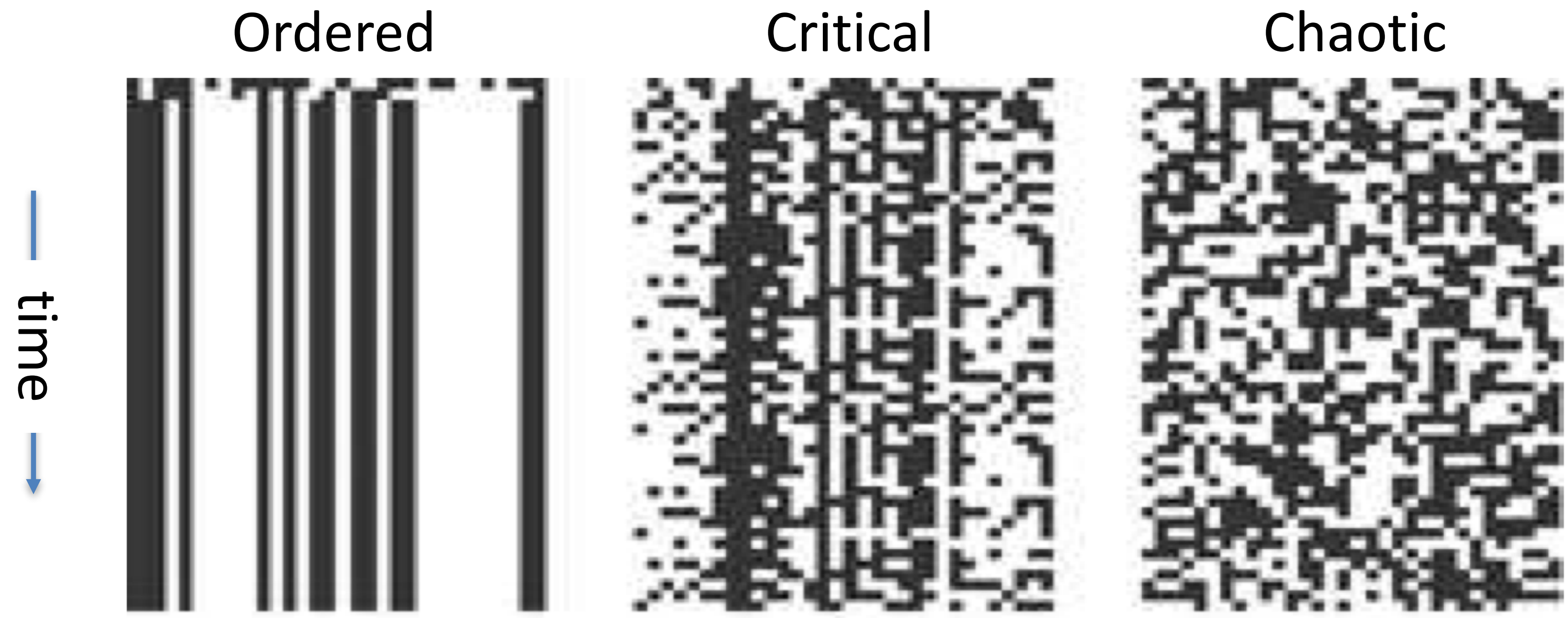
- It looks a bit like an elementary cellular automata
  - But without a fixed neighbourhood and with a different update rule in each cell
  - In fact, a Boolean network is a generalisation of a CA (i.e. a Boolean network can implement a CA 🡻)
  - Therefore must be capable of universal computation



Some Important Theoretical Properties

Dynamical Regimes

- The behaviour of an BN falls into 3 categories:

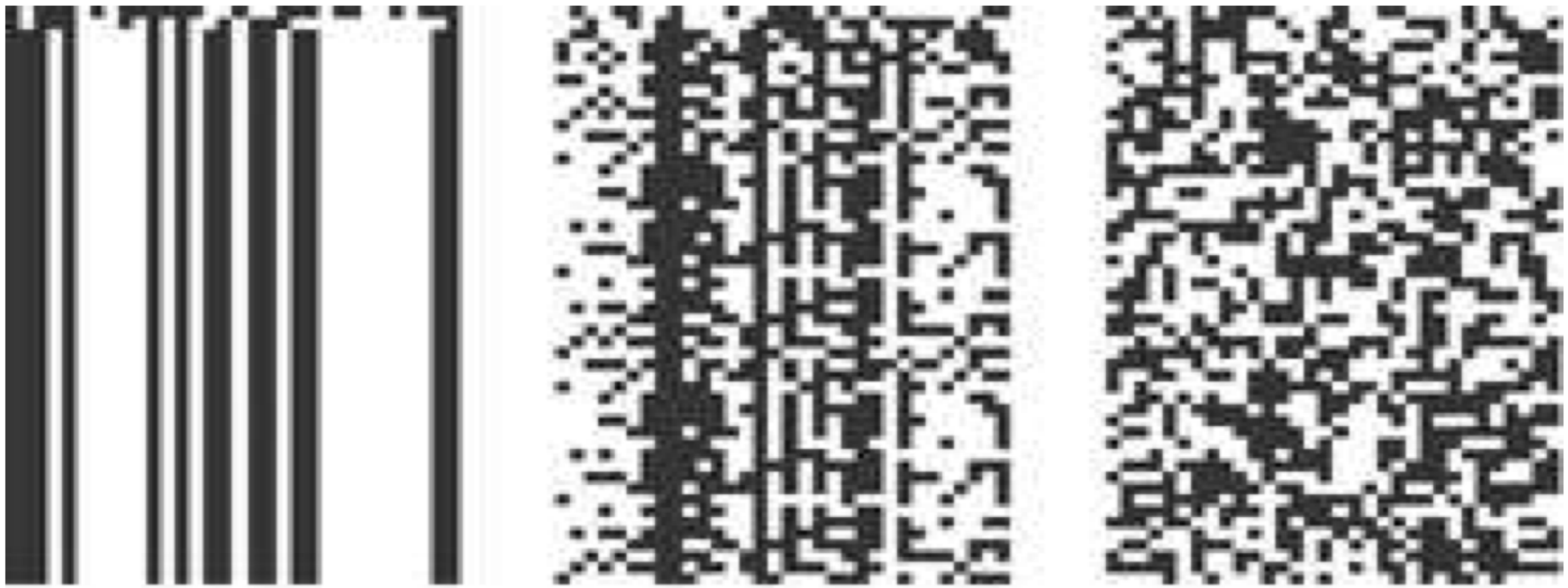


From [Gershenson, 2004] Introduction to Random Boolean Networks
http://uk.arxiv.org/abs/nlin.AO/0408006

Dynamical Regimes

- On average*, the behaviour of a BN is related to the number of connections between genes (K)

Ordered when K<2 | Critical when K=2 | Chaotic when K>2

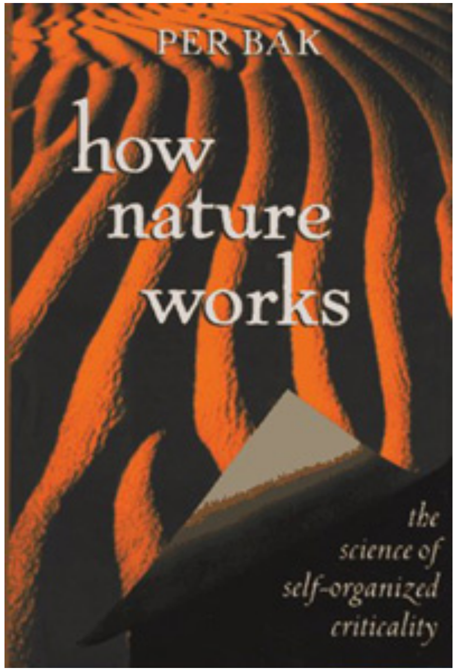


*But note this doesn't mean that **all** K=2 networks are critical, or that critical networks can't be found for K>2

The Edge of Chaos

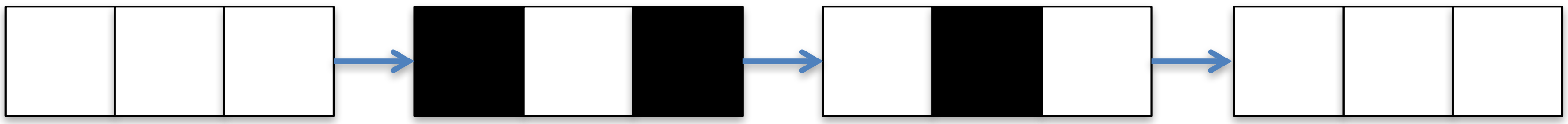
- Criticality is also known as the 'edge of chaos'
  - Dynamics are neither ordered nor chaotic, but complex
  - Hypothesised to be the sweet spot for computation
  - This is also where CA Rule 110 (universality) is found

- Appears frequently in natural systems
  - Genes, brains, proteins, flocks …
  - Evolution may select for criticality
  - Per Bak, "How Nature Works" ➔
  - "Are biological systems poised at criticality?" [Mora and Bialek, 2010] http://arxiv.org/pdf/1012.2242v1.pdf



Attractors

- Attractors are an important concept for BNs
  - A finite number of nodes means that states must repeat
  - An attractor of length *L* repeats every *L* steps
  - e.g. *L*=3:

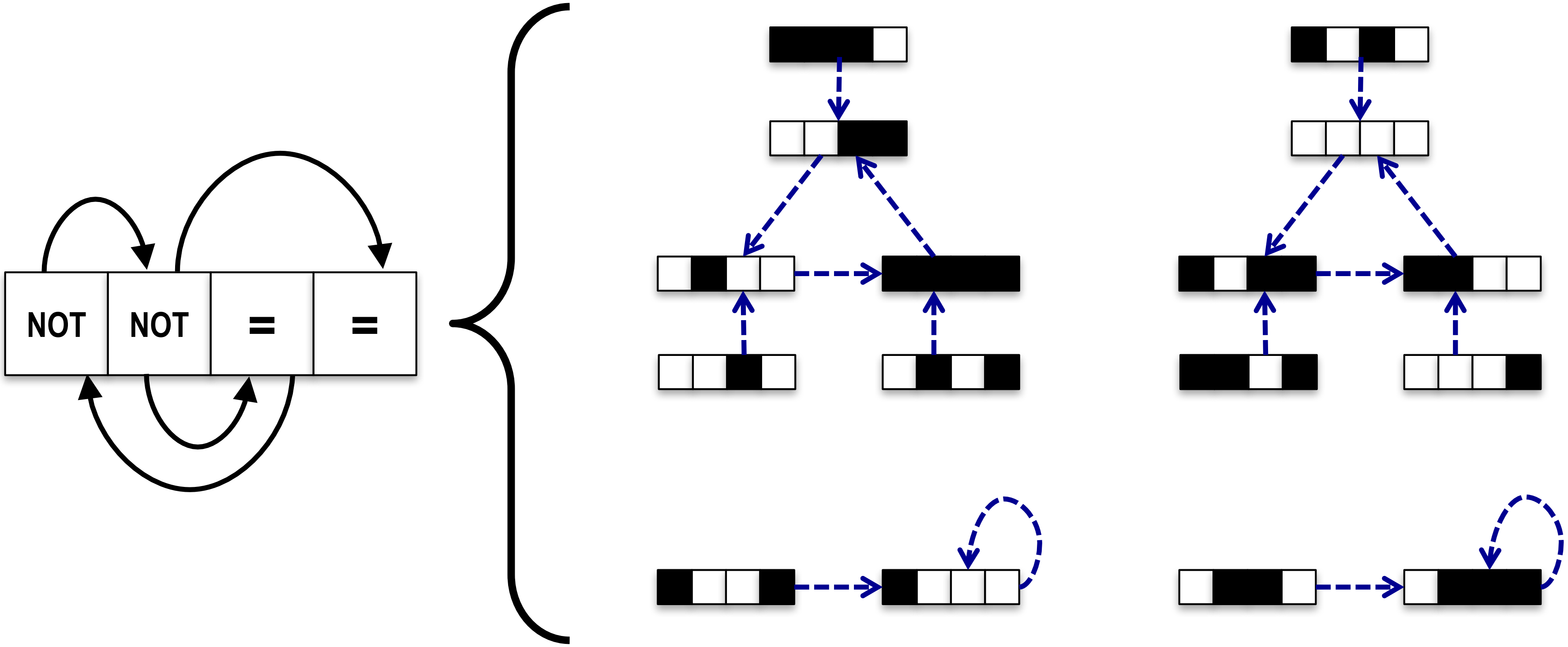


  - An attractor of length 1 is termed a point attractor

- Transients occur before an attractor is reached
  - e.g. “Acorn” is a transient leading to a stable attractor

Attractors

- Complete attractor map for a small network



  - 2 attractors of length 3, and 2 point attractors

Attractors

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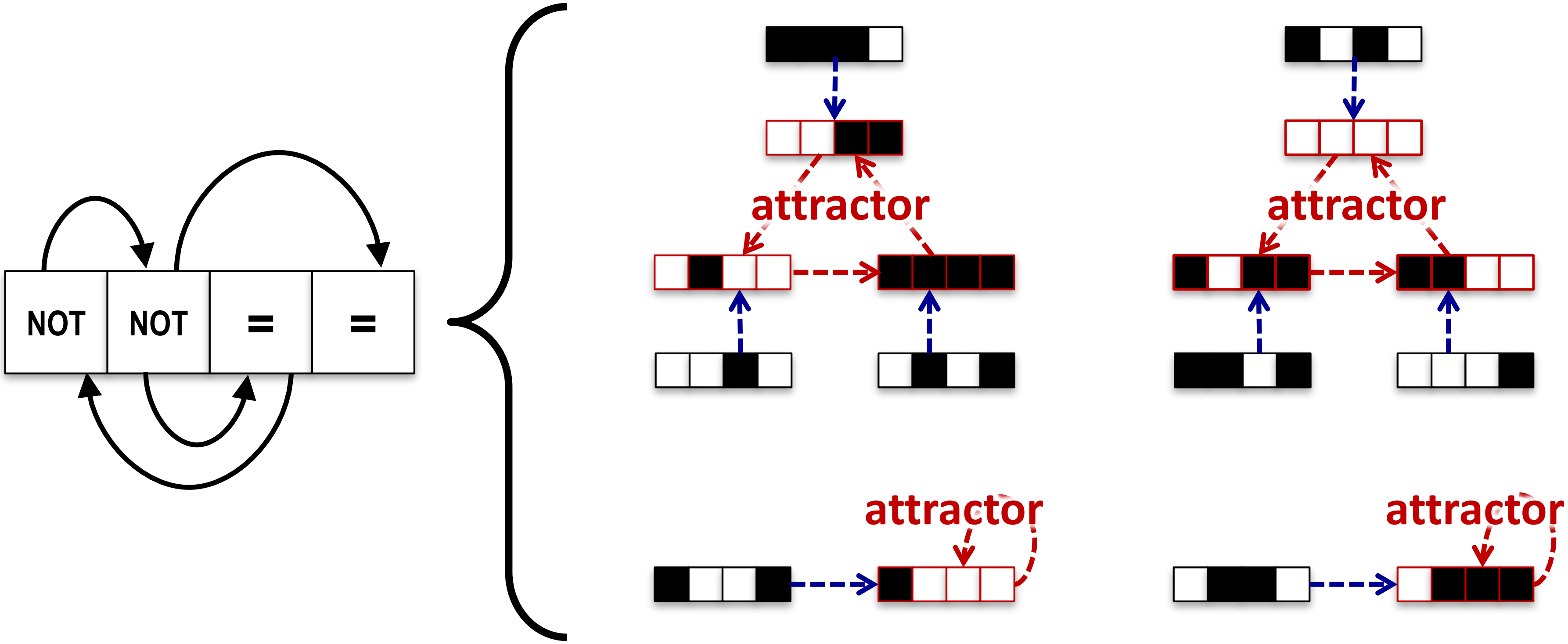

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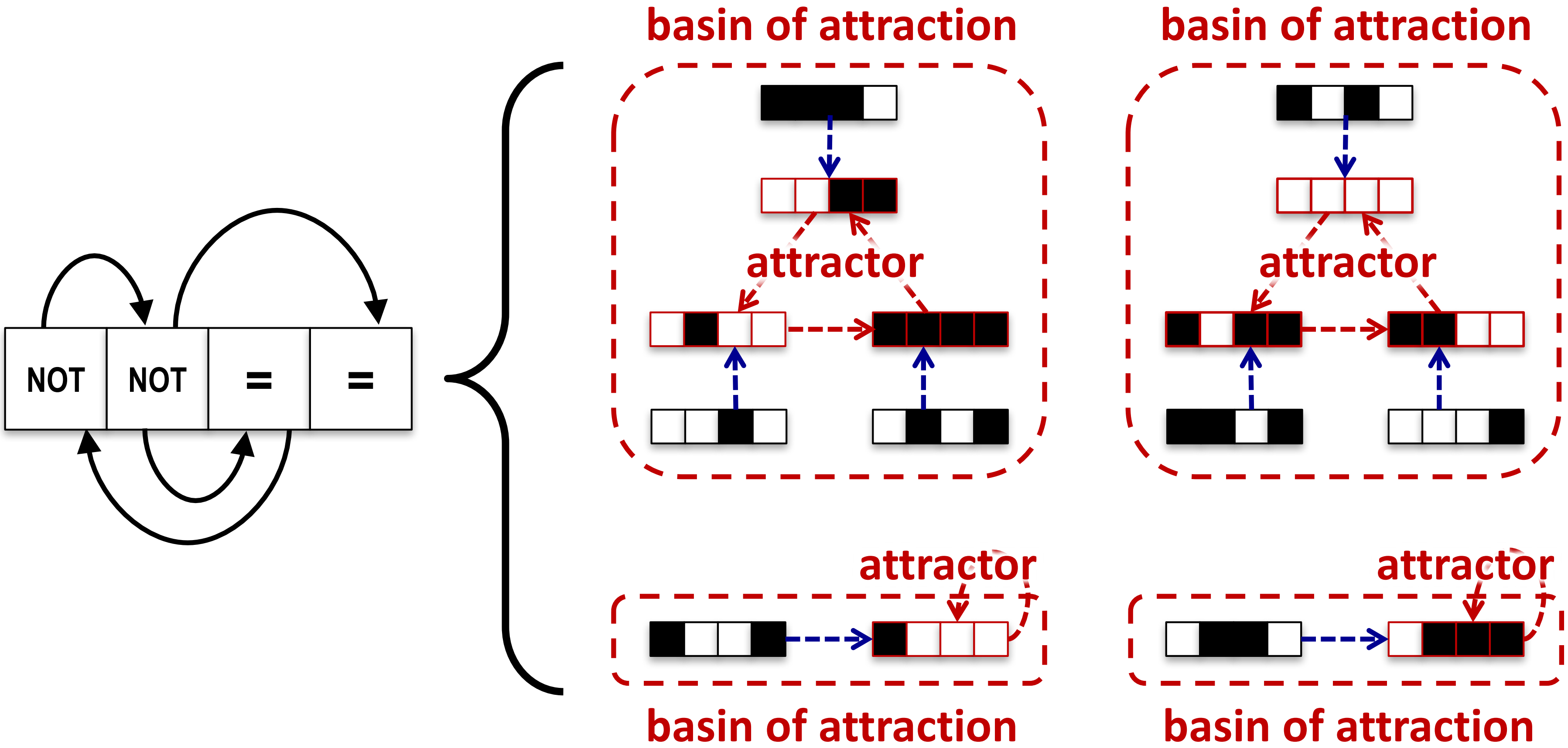
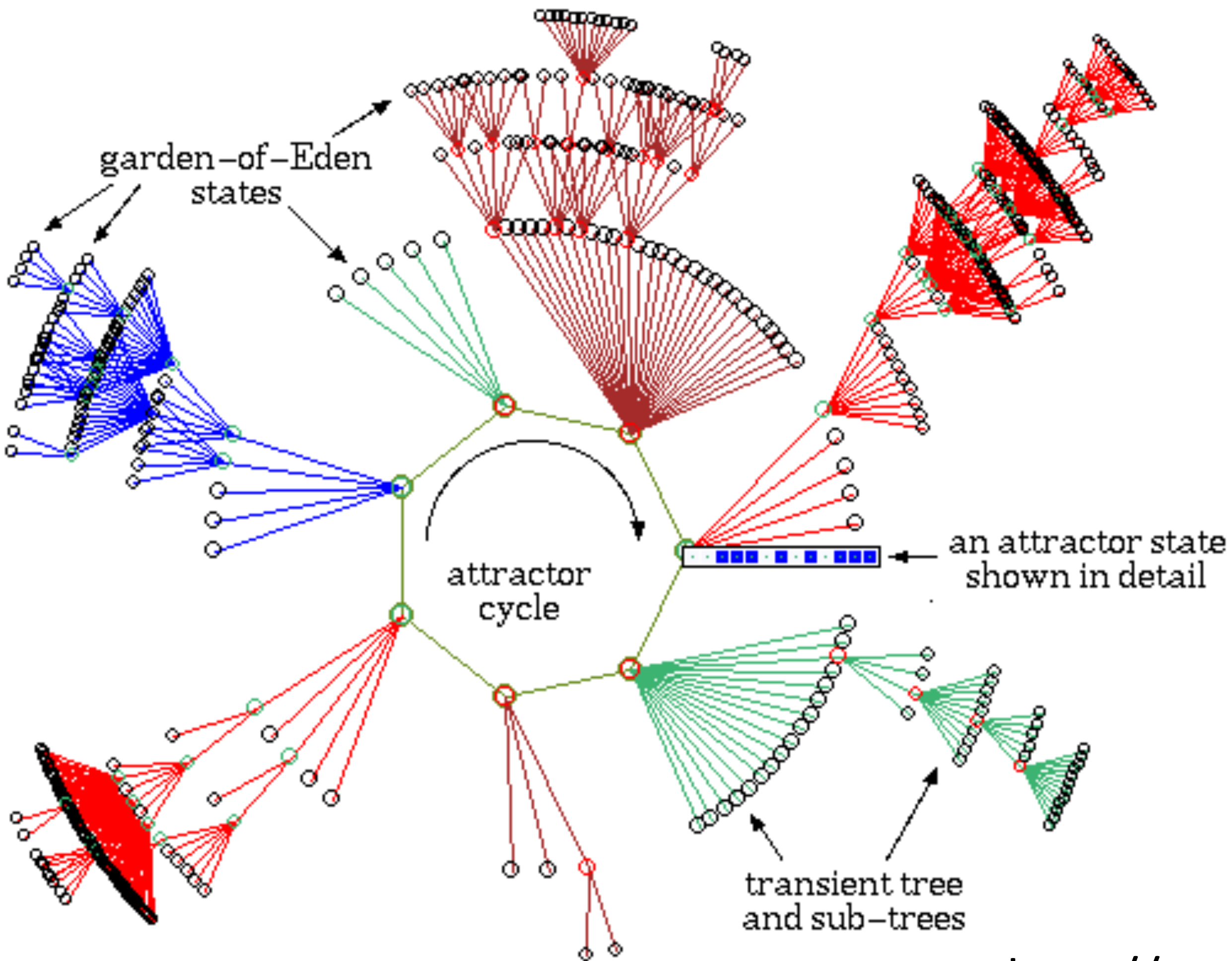


  - 2 attractors of length 3, and 2 point attractors

Attractors

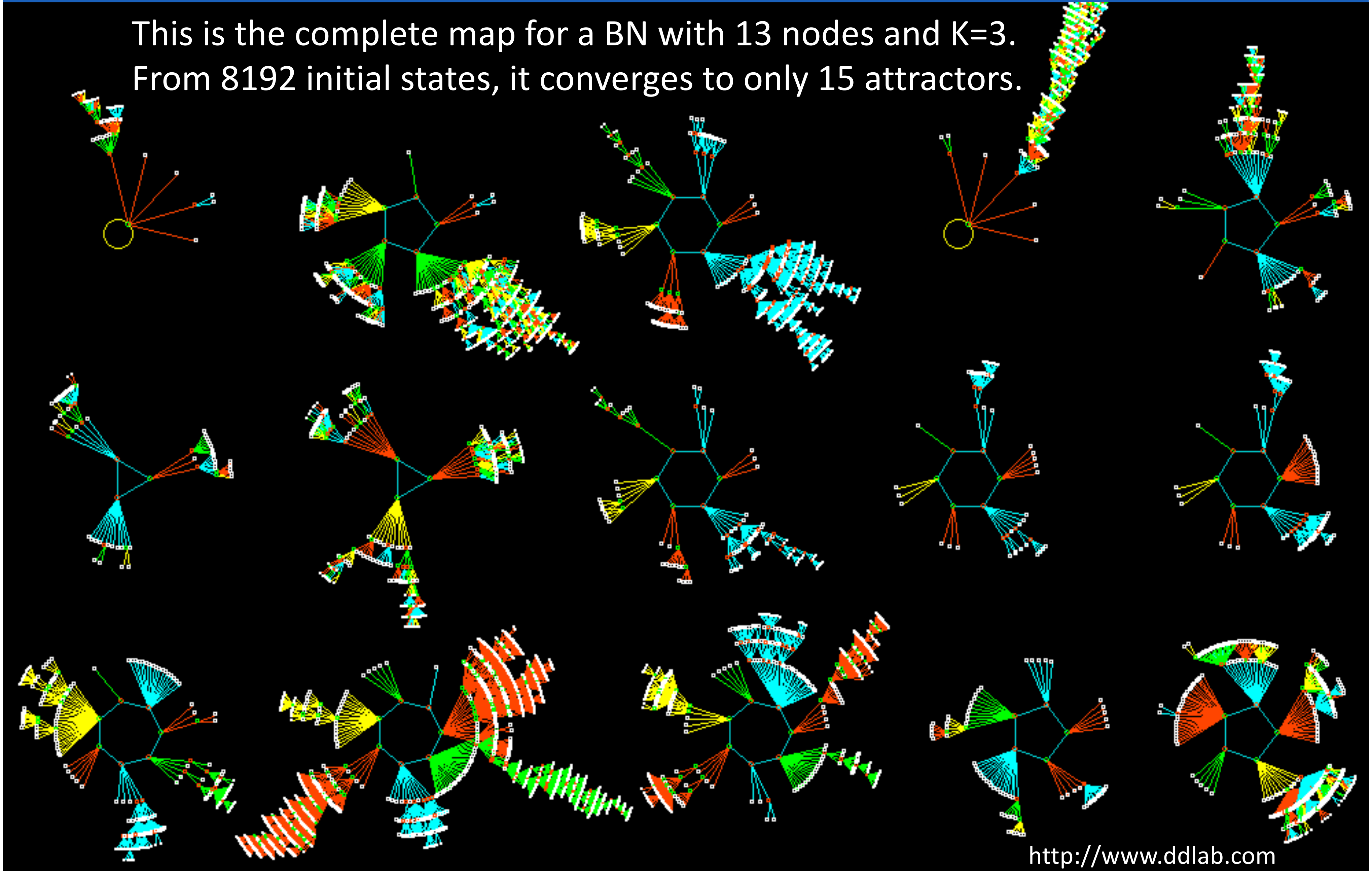
- Attractors often have large **basins of attraction**



http://www.ddlab.com

Attractors

This is the complete map for a BN with 13 nodes and K=3.
From 8192 initial states, it converges to only 15 attractors.

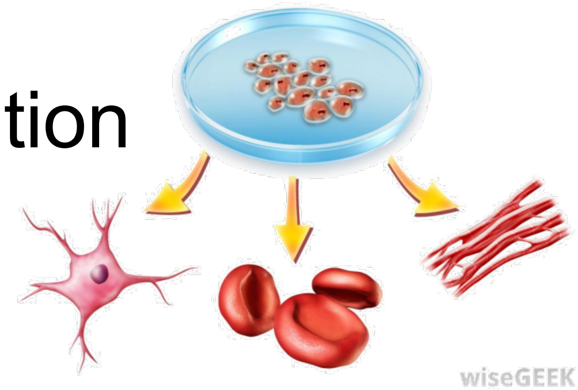


http://www.ddlab.com

Attractors

- The presence of attractors makes BNs (and GRNs) naturally robust
  - It takes a large perturbation to escape a basin of attraction
  - This limits the impact of noise and mutations

- Attractors have a biological interpretation



  - Stable states for a cell
    e.g. cell types: neuron, liver, skin, …
  - Cancer can also be seen as an attractor
  - Boolean networks are often used to model and study biological GRNs. See [Saadatpour & Albert 2013]

Computing with Boolean Networks

Computing with BNs

- These theoretical properties mean that BNs are interesting from a computational perspective:
  - We know that they can in principle generate **any computational behaviour** (i.e. CA equivalence)
  - We know that they can readily generate **complex behaviour** (i.e. edge of chaos when k=2)
  - We know that they are **naturally robust** (i.e. attractors)
  - We also know that relatively small BNs (and GRNs) can generate relatively complex behaviours, which is not generally the case with conventional programs

Computing with BNs

- EAs can be used to find useful Boolean networks
  - Unlike for elementary CAs, exhaustive search is not an option: the search space is much larger
  - e.g. for K=3, N=10, there are ~6x10^{15} possible BNs

Computing with BNs

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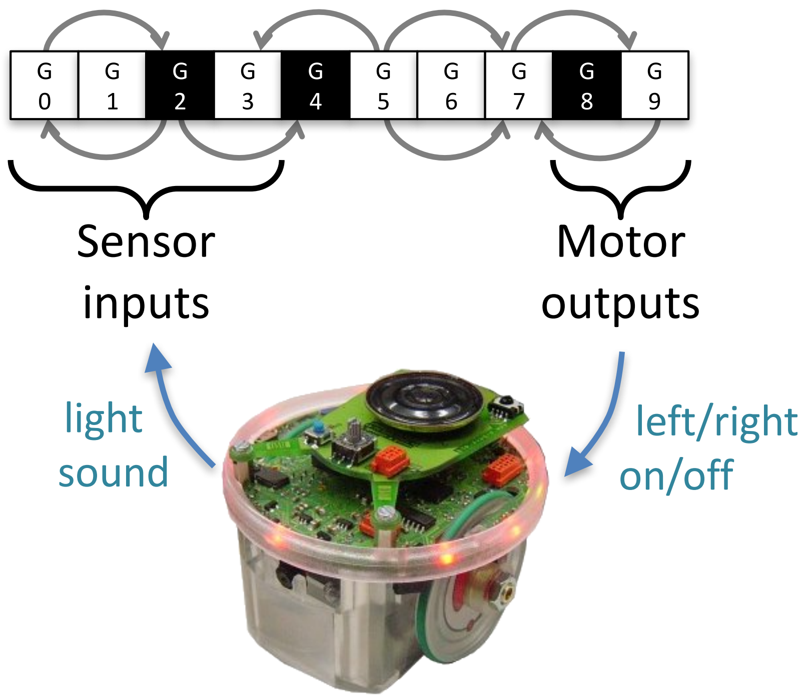
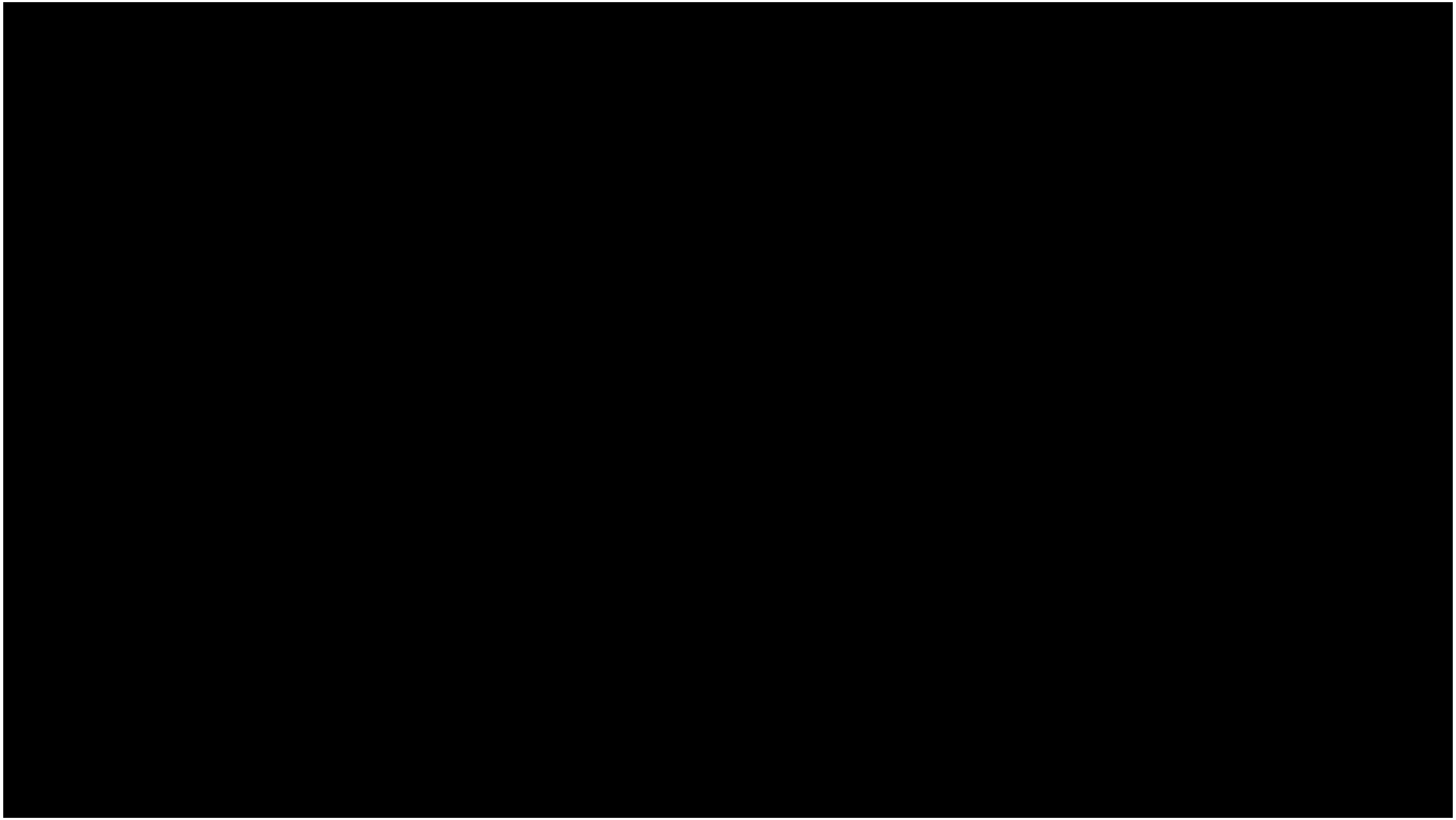
- Robot controllers [Roli, 2011]
  - Searched for BNs which responded to light and sound
  - Controlled a real ePuck
  - Evolved BNs were found to be robust to sensor noise



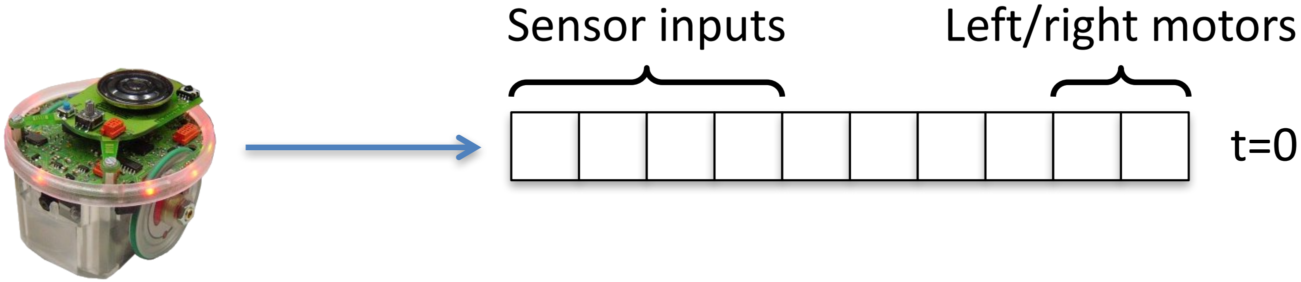
Example



https://www.youtube.com/watch?v=6ZF9Ijpwkd8

Example

Initial State
No sensor signals
Not moving



Note: This is a simplified example. See paper for full details of how this works.

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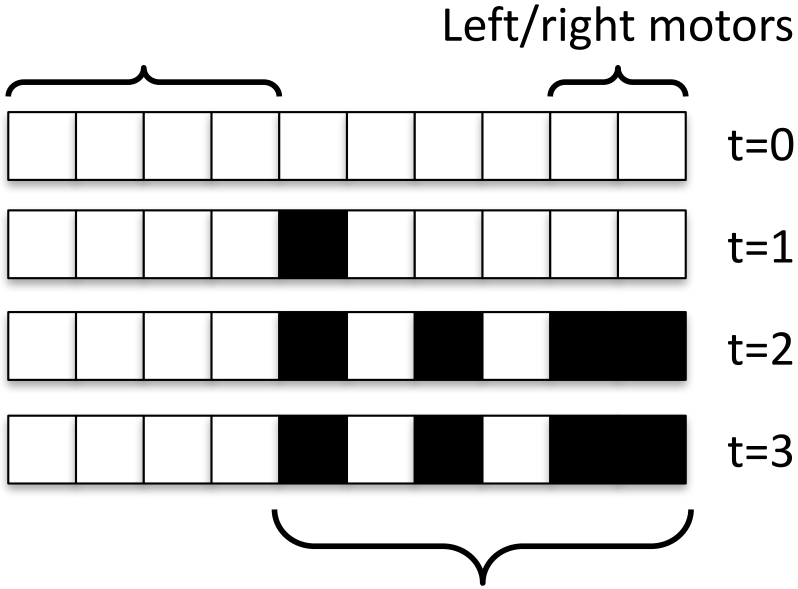

Note: at this point the BN has entered a point attractor

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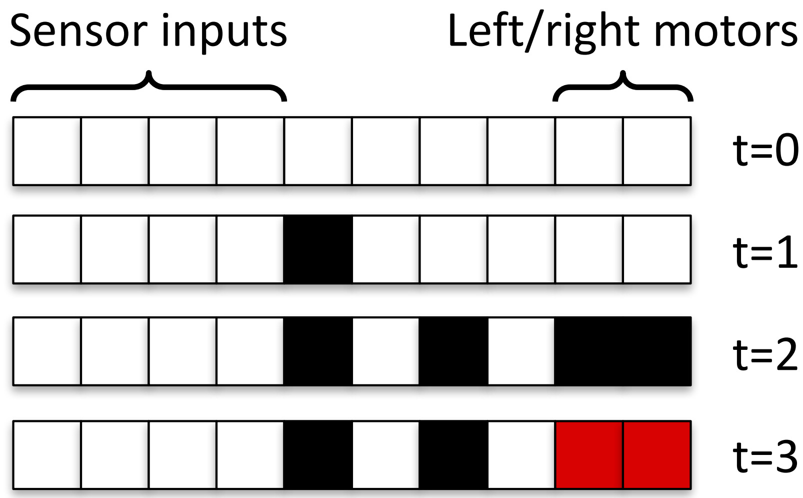


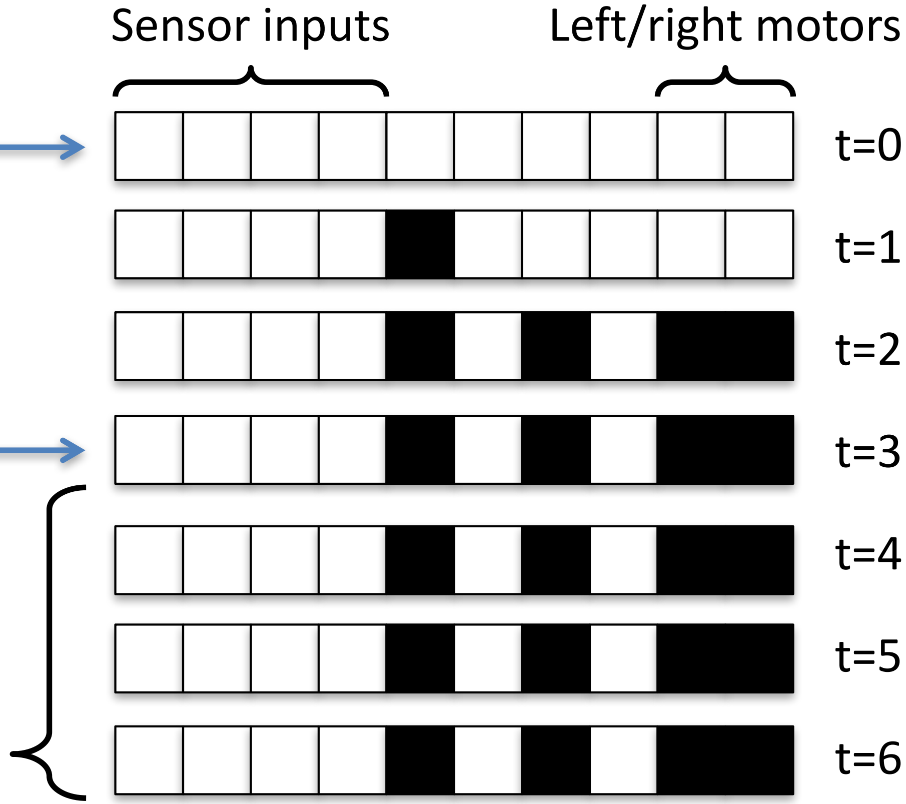
First Update
No sensor signals
Moving forward
(since left and right motors are turned on by the BN)

Note: This is a simplified example. See paper for full details of how this works.

Example

Initial State
No sensor signals
Not moving

First Update
No sensor signals
Moving forward



Note: the inputs didn't change, so the BN remains in the same attractor.

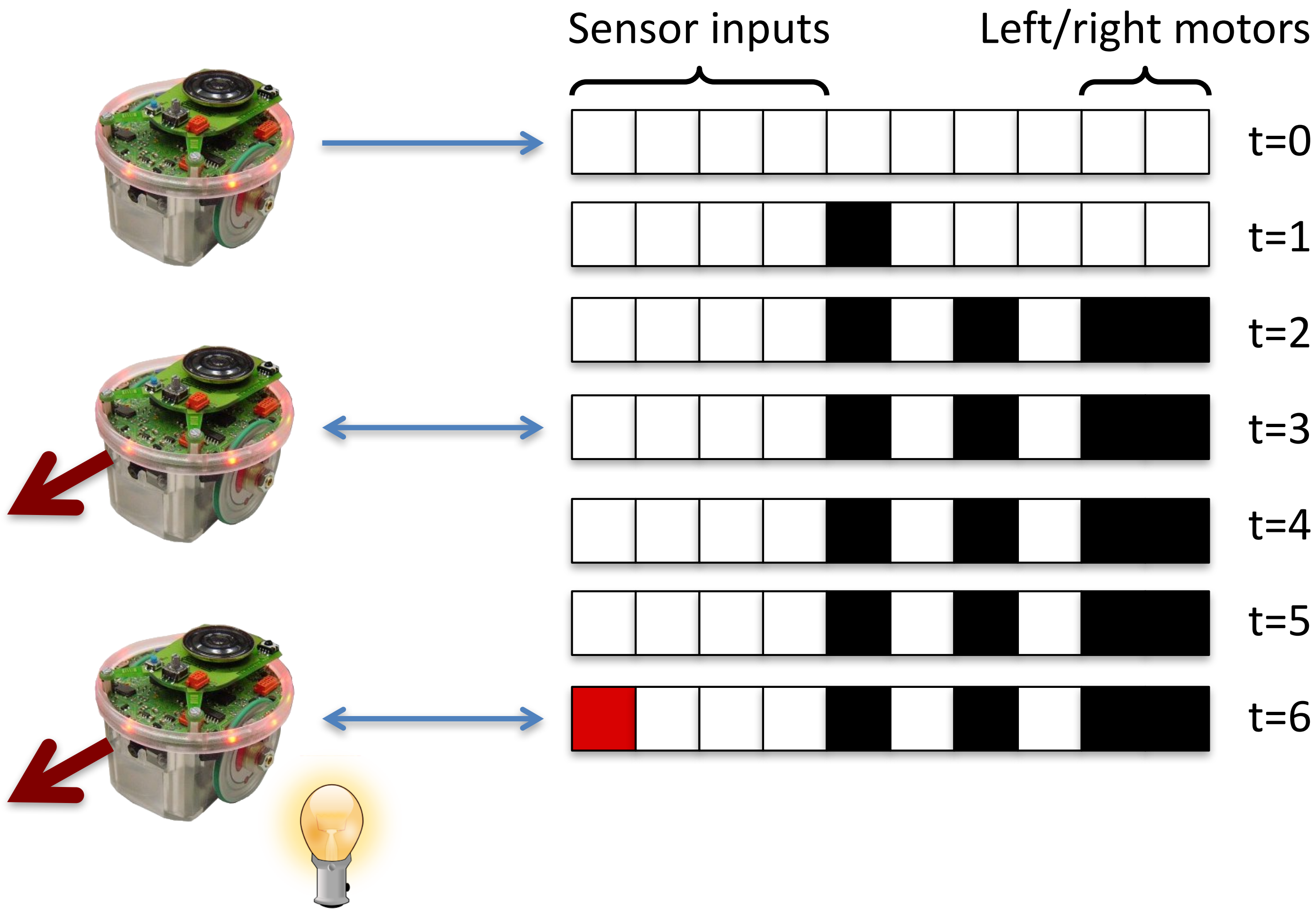
Note: This is a simplified example. See paper for full details of how this works.

Example

Initial State
No sensor signals
Not moving

First Update
No sensor signals
Moving forward

Second Update
Light on left
Moving forward



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Moving forward

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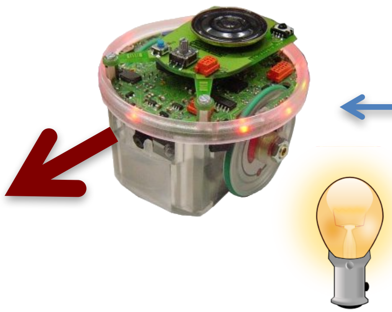
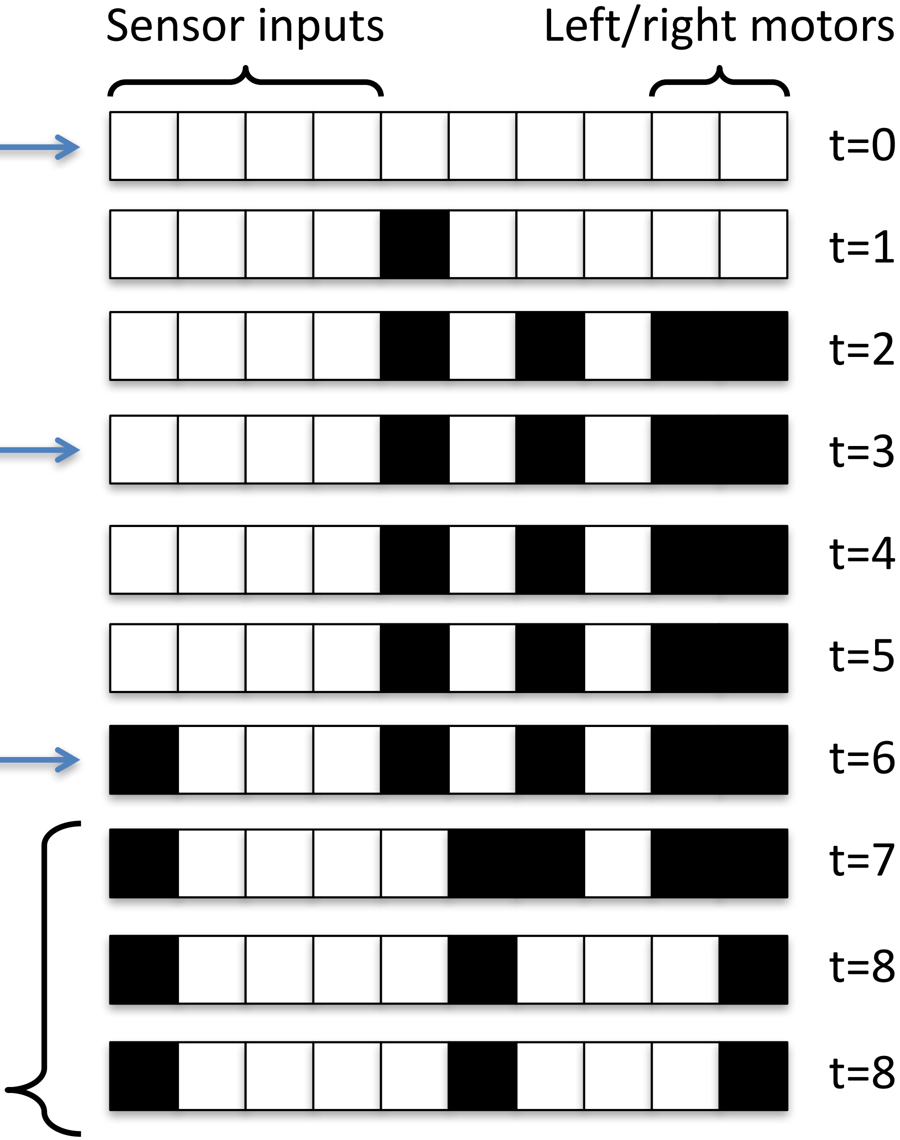




Note: the inputs did change, causing the BN to move to a different attractor.

Note: This is a simplified example. See paper for full details of how this works.

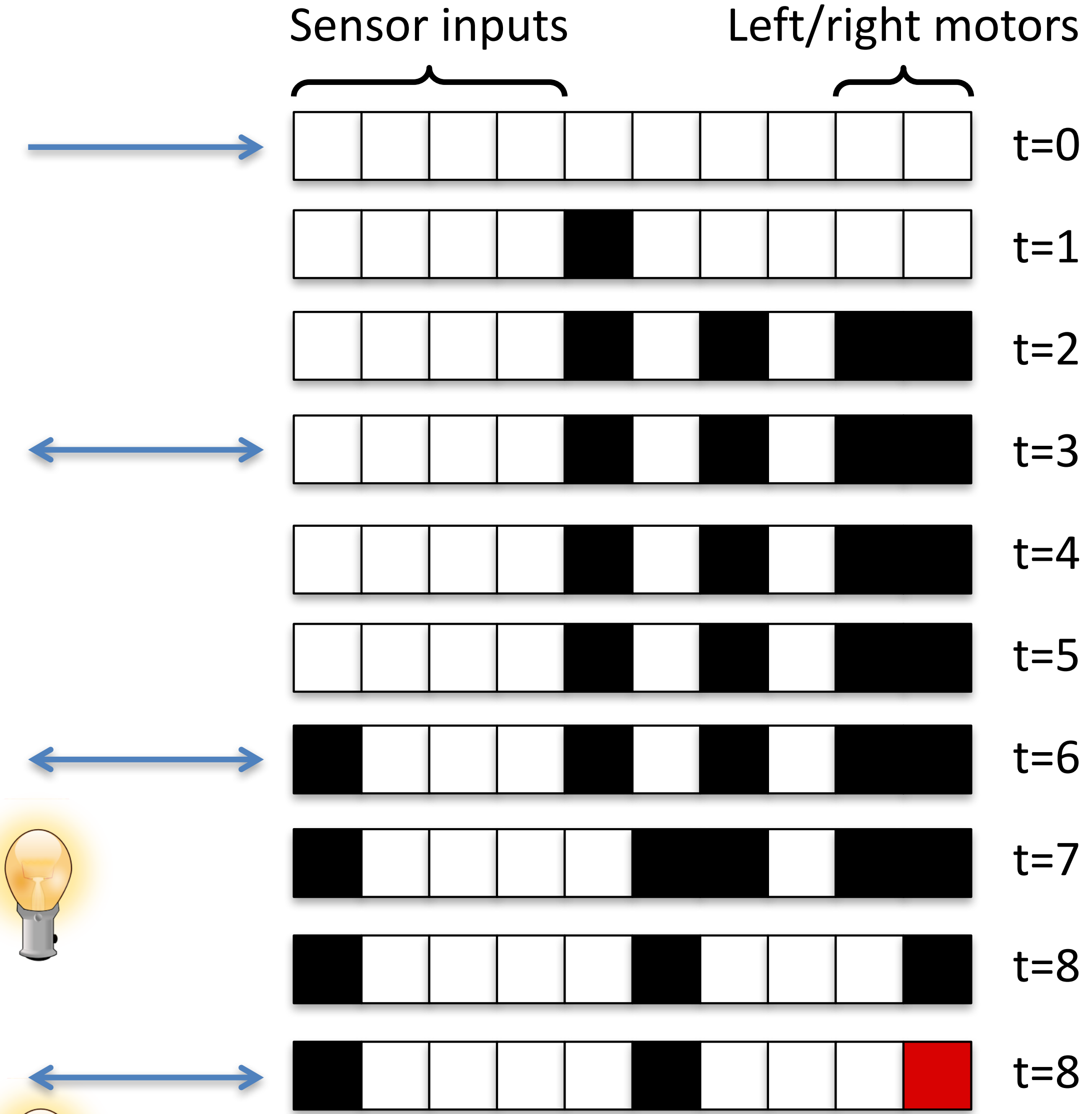
Example

Initial State
No sensor signals
Not moving

First Update
No sensor signals
Moving forward

Second Update
Light on left
Moving forward

Third Update
Light on left
Turning left (since only the right motor is on)



Note: This is a simplified example. See paper for full details of how this works.

Some More Advanced Models

Artificial Genome

- This is at the other end of the GRN model spectrum
  - Captures genome organisation and gene products
  - More expressive, but also a lot more complex

This is how a GRN is encoded in a typical artificial genome

TAAGCTACTATAGAAACTGCGCGTATAAGCAAATGCGCGTATAAGCA

- Note: This is an advanced topic; I don't expect you to know about the details, just the general idea.

Artificial Genome

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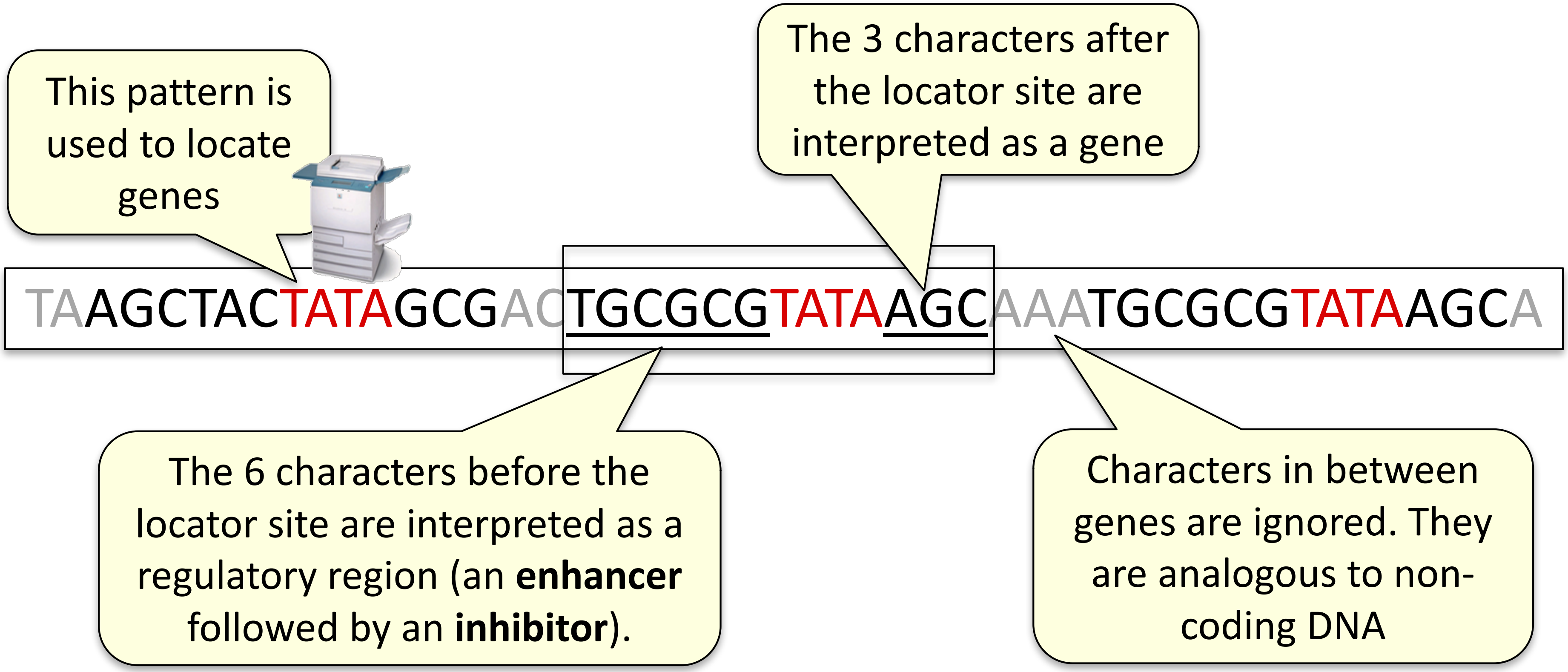

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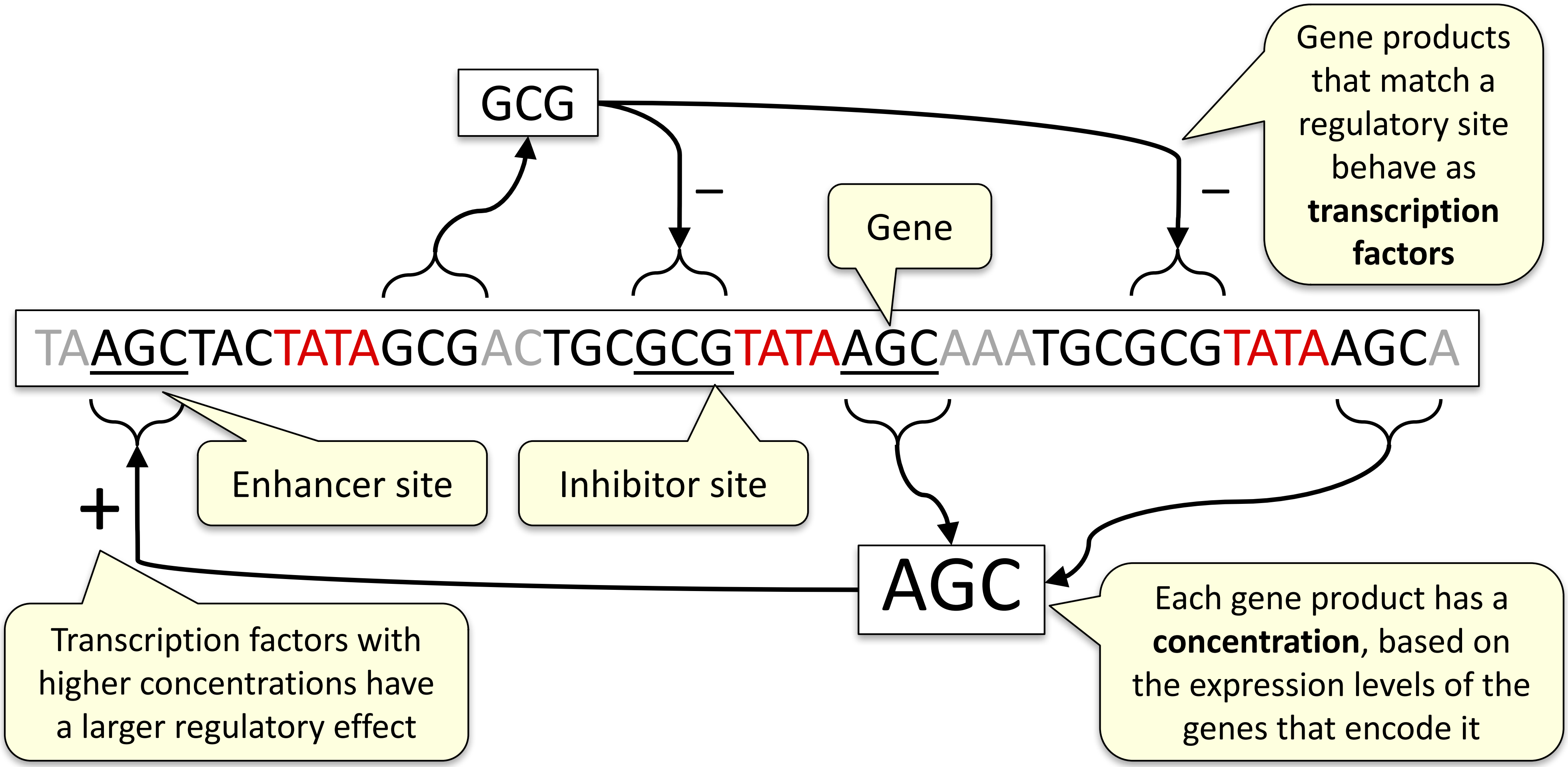

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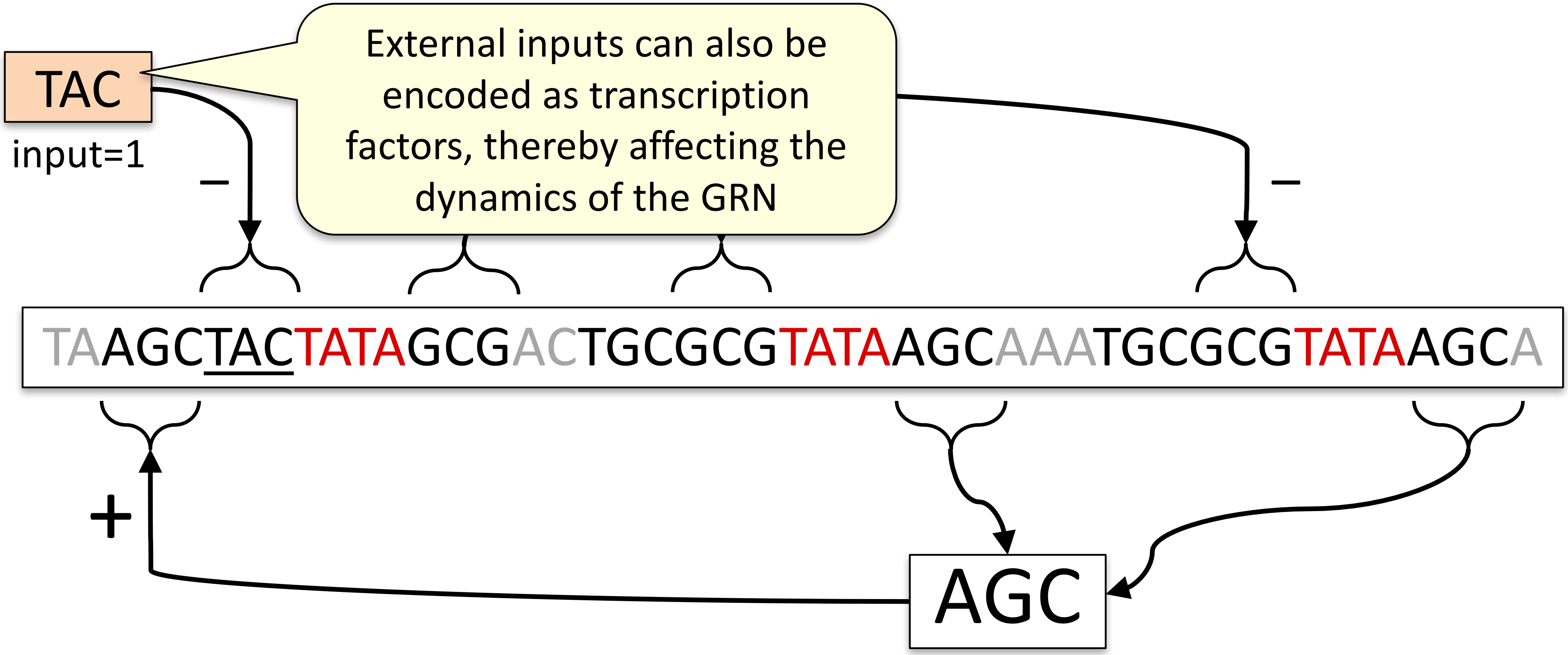

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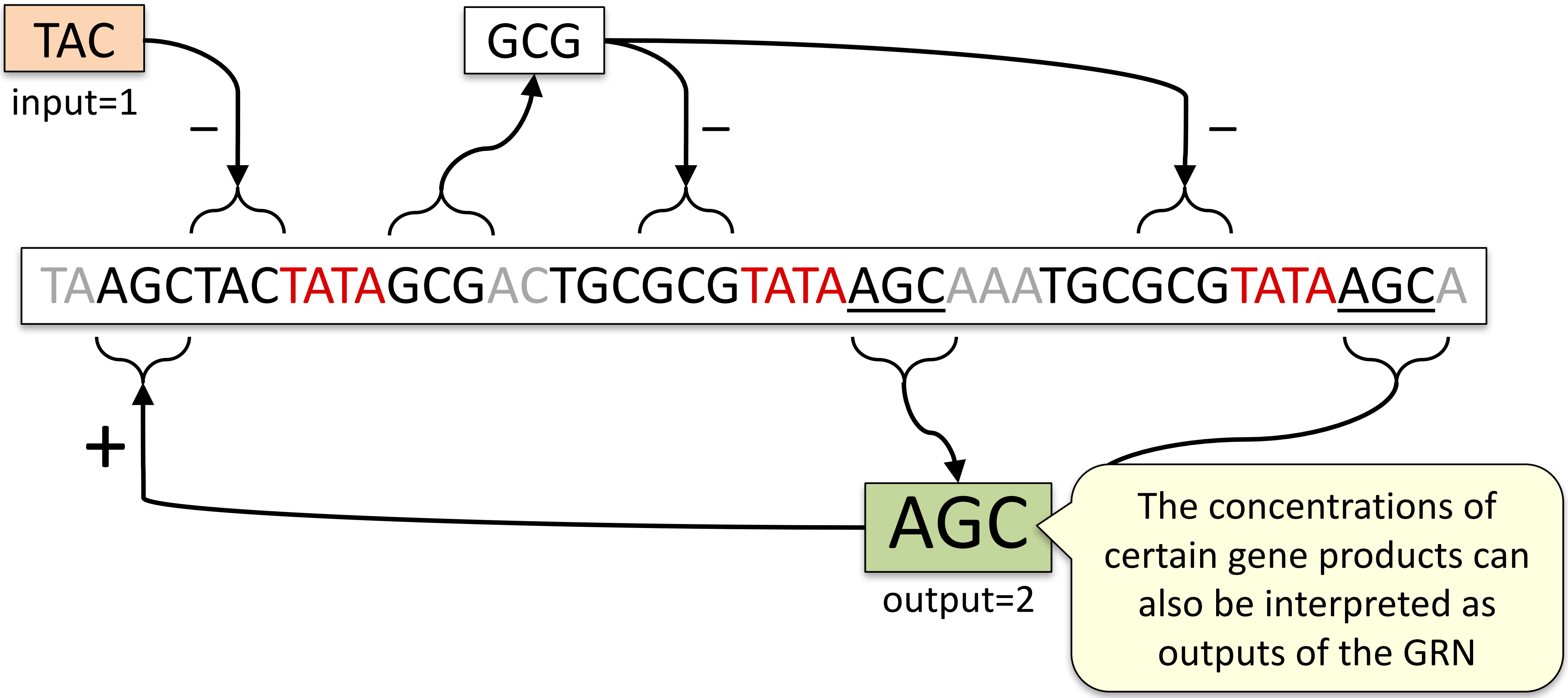
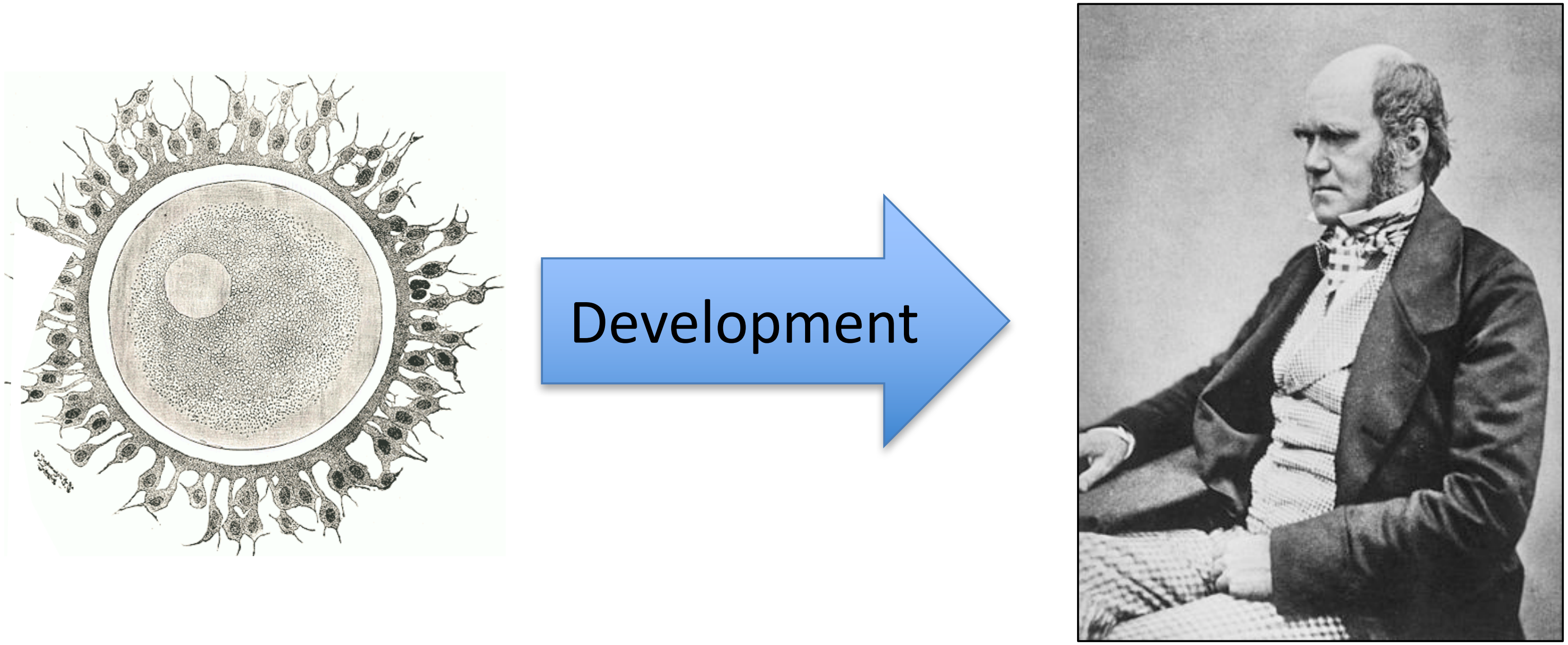


Robustness

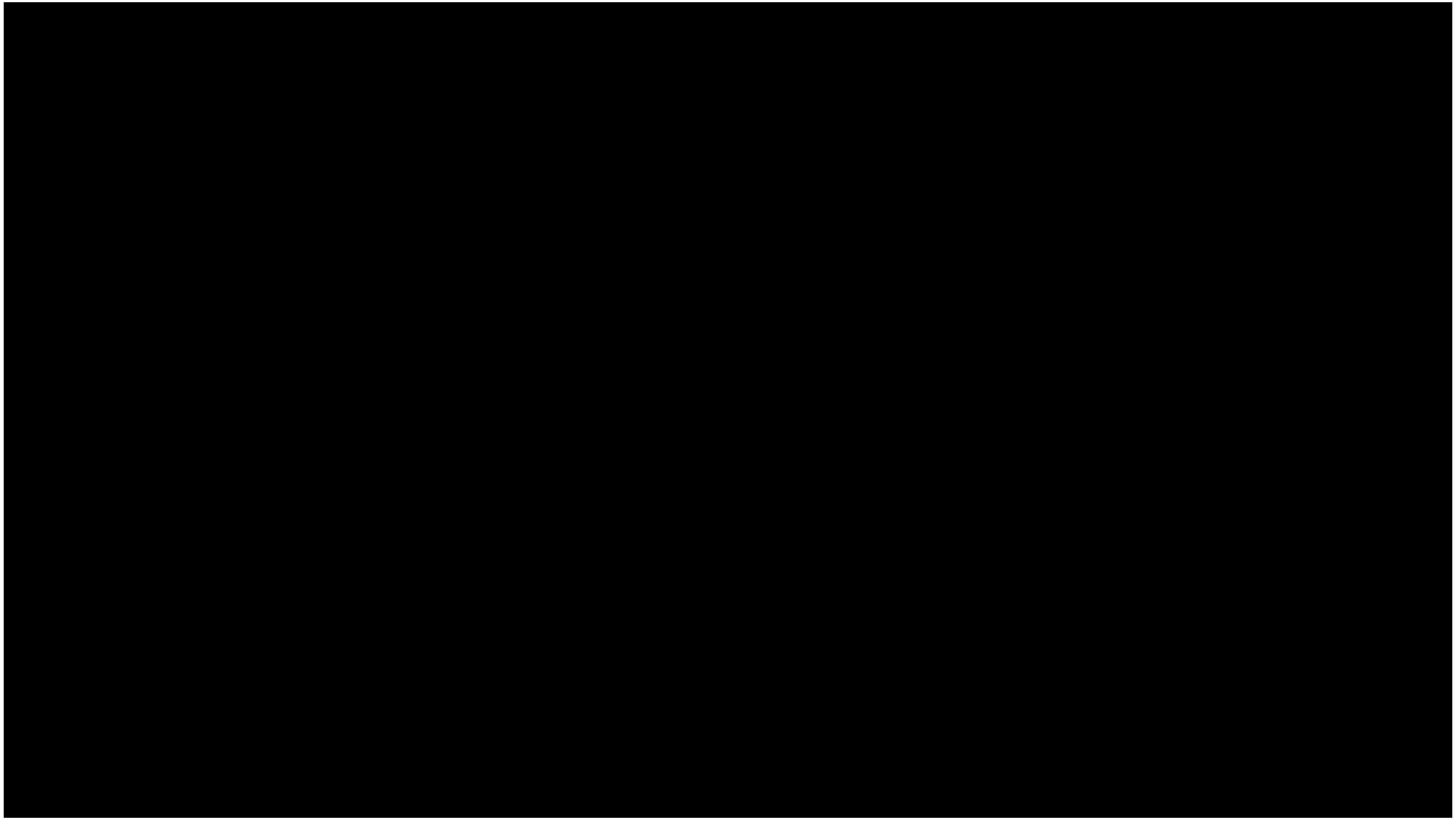
Stéphane Sanchez and Sylvain Cussat-Blanc
http://www.irit.fr/~Sylvain.Cussat-Blanc/GRNDriver/index_en.php

Development

- In biology, the GRN also determines when cells divide and the kind of cells they will become
  - i.e. an organism's developmental process



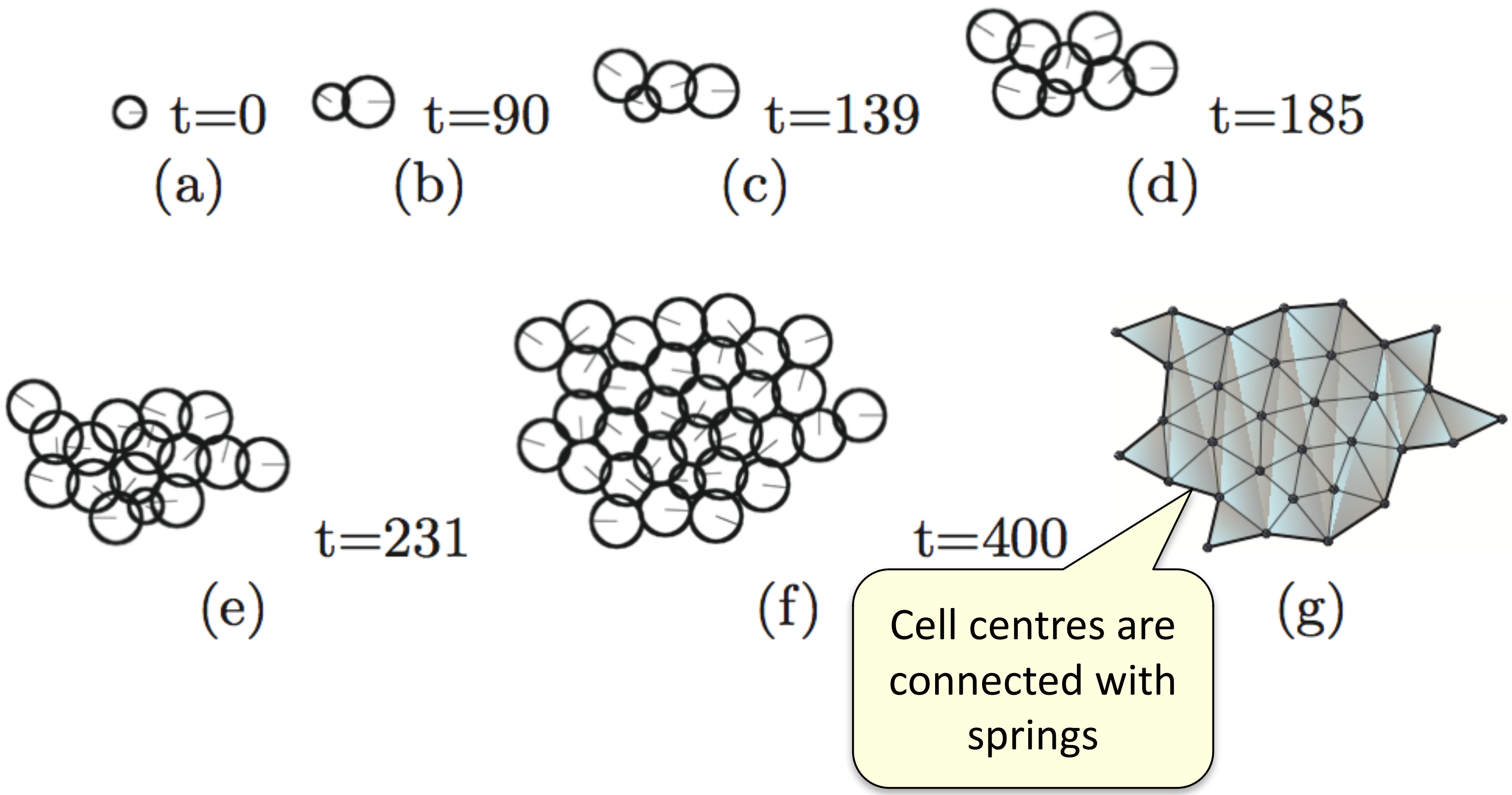
Artificial Development



Joachimczak et al. 2012, https://www.youtube.com/watch?v=JJYpHfccnwA

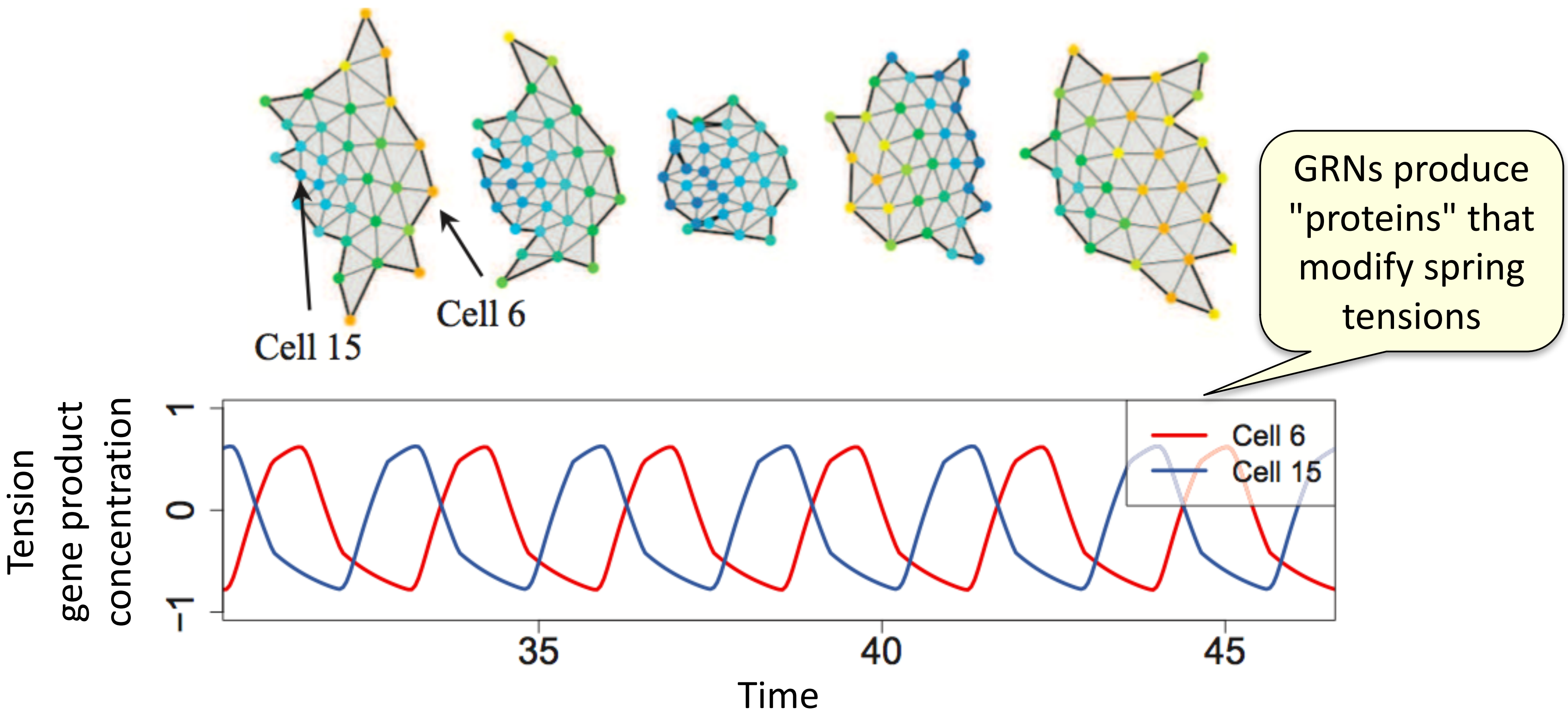
Artificial Development

- The artificial GRN describes how to grow a structure
  - See [Joachimczak et al. 2012]

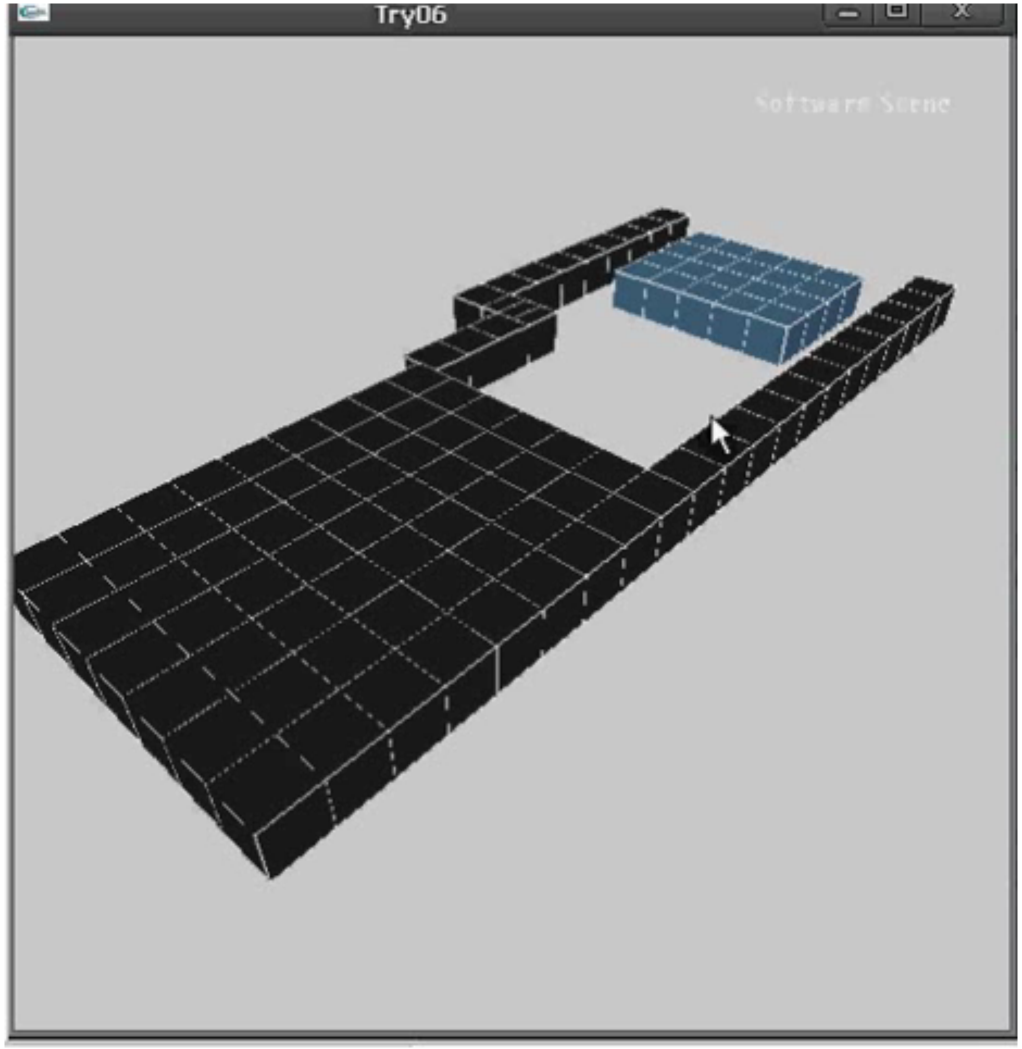


Artificial Development

- The same GRN then controls its movement
  - See [Joachimczak et al. 2012]



Artificial Development



Jin et al., 2012, https://www.youtube.com/watch?v=09TirOH8OIM

Summary

- Computational models of gene regulatory networks
  - Boolean networks and artificial genomes
- Main applications
  - Control, especially in robotics
  - Generating complex structures
  - Understanding biological systems
- Suggested reading
  - Introduction to Boolean networks [Gershenson 2004]
  - Applications [Joachimczak 2012, Sanchez 2014]
  - Review of artificial GRNs [Lones 2016 – on Vision]

Things you should know

- Boolean networks
  - What are they? How are they different to a CA?
  - Awareness of dynamical regimes and their significance
  - Awareness of attractors and their significance
  - How can you compute with them?

- Artificial genomes
  - A very basic understanding of how they work
  - That they can be used for artificial development
  - Ability to give examples of applications

Next Week

- Swarm Intelligence
  - What we can learn from the collective swarming behaviours of ants/birds etc.
  - Examples of optimisation algorithms motivated by the foraging behaviours of biological organisms

Bibliography

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