Making a computer out of junk DNA

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UCSC

Funded by the Foundational Questions Institute
http://fqxi.org.

Outline

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- Overview of development

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  - Cell signaling

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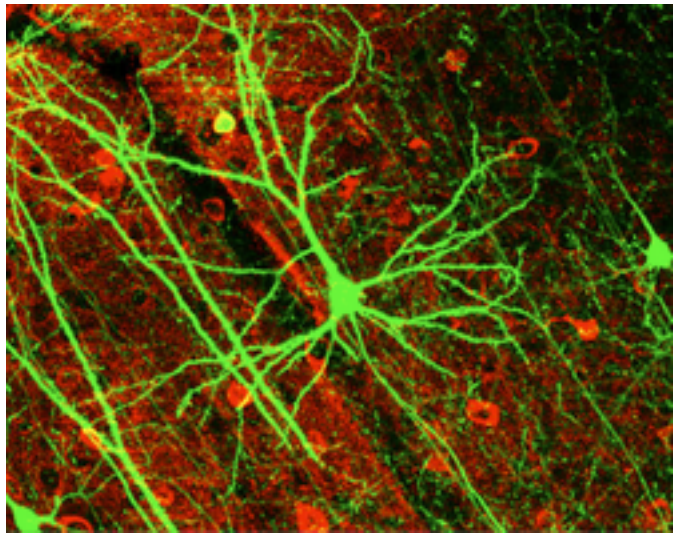
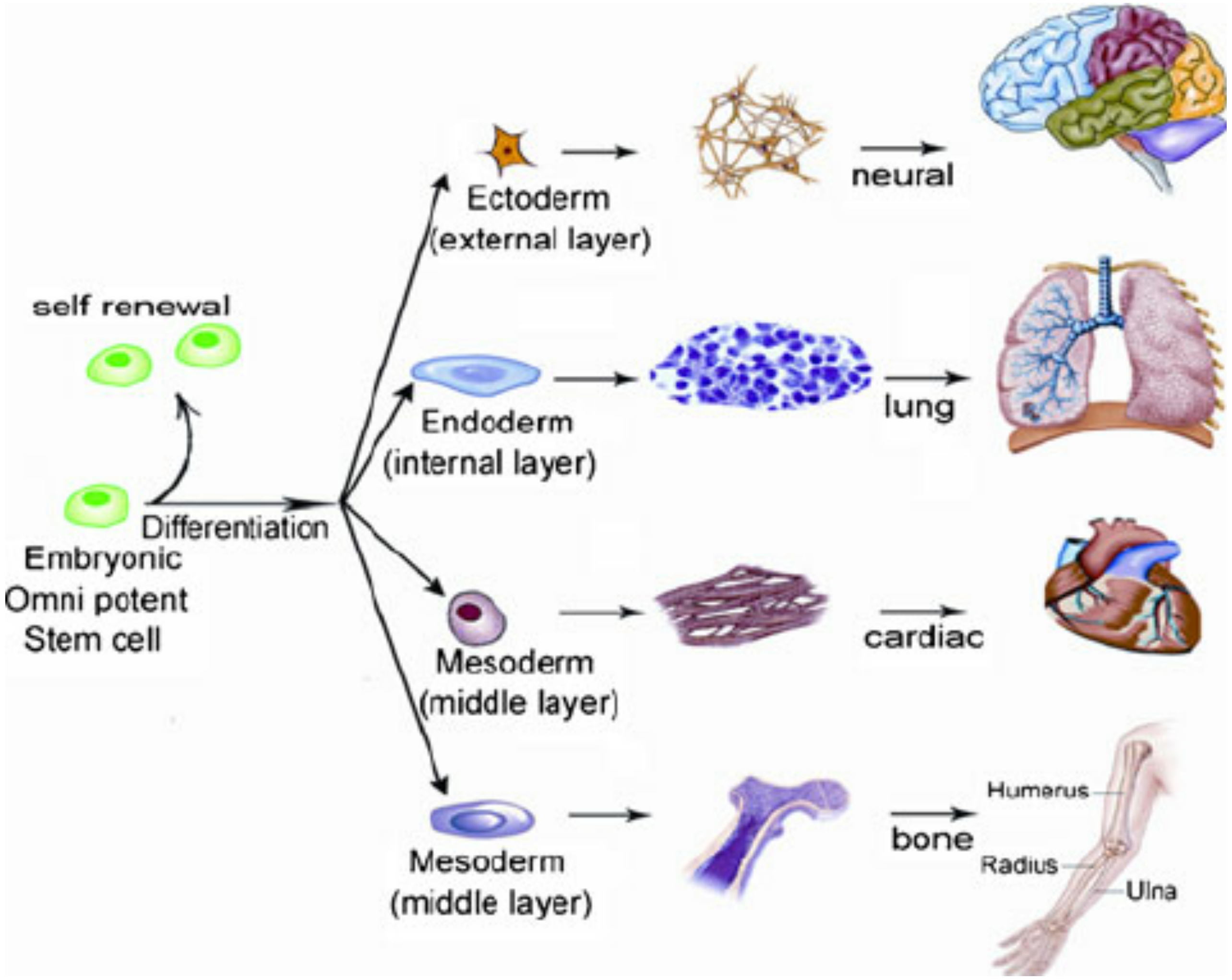
Development

How does an organism develop from a single cell?

How does a brain develop?



Cells receive signals from neighboring cells and their environment, causing them to differentiate.



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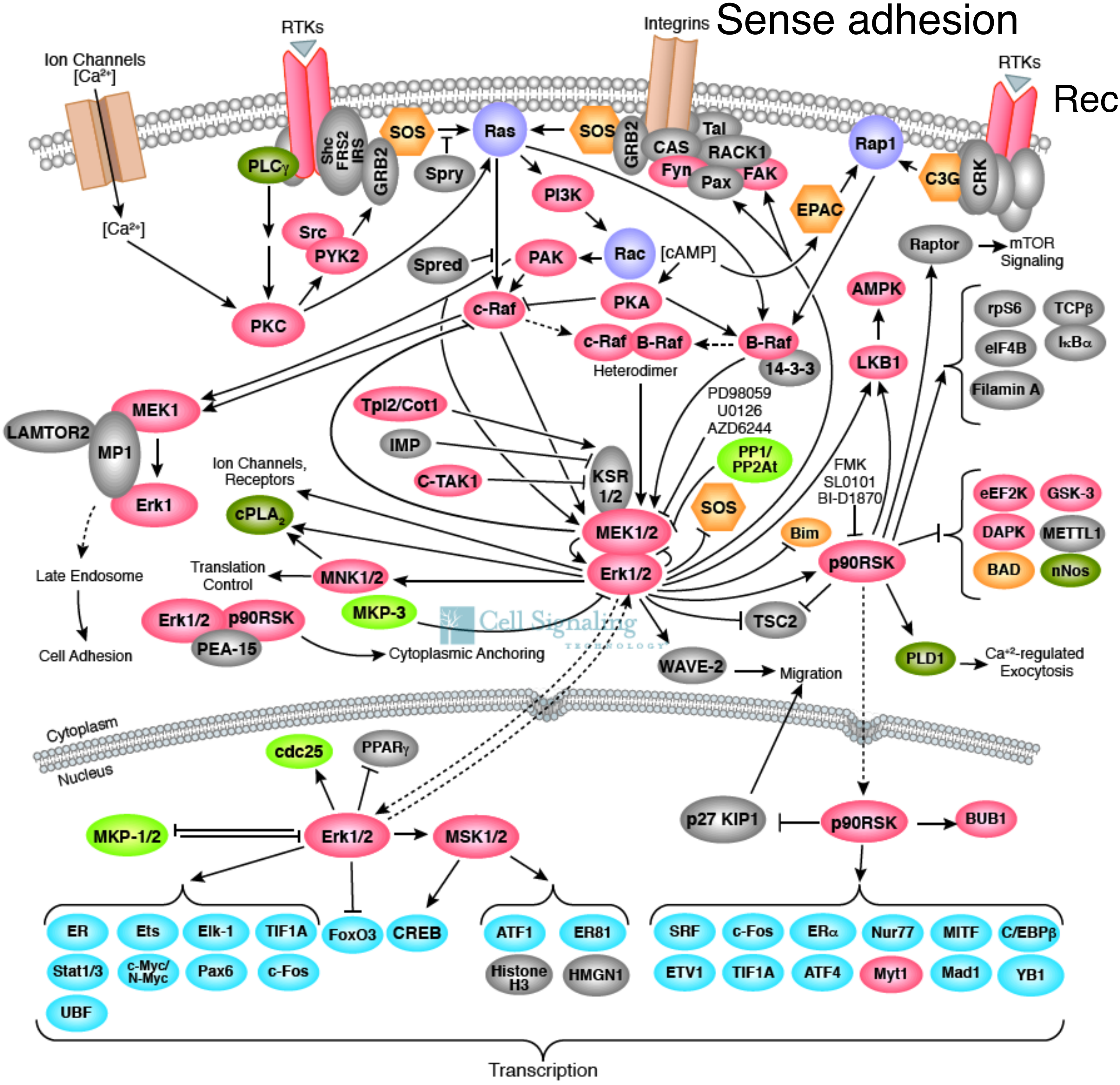
- This changes what the cell does, like what proteins it will produce.

- It can tell it for example, to stop growing or form a synapse with another cell.



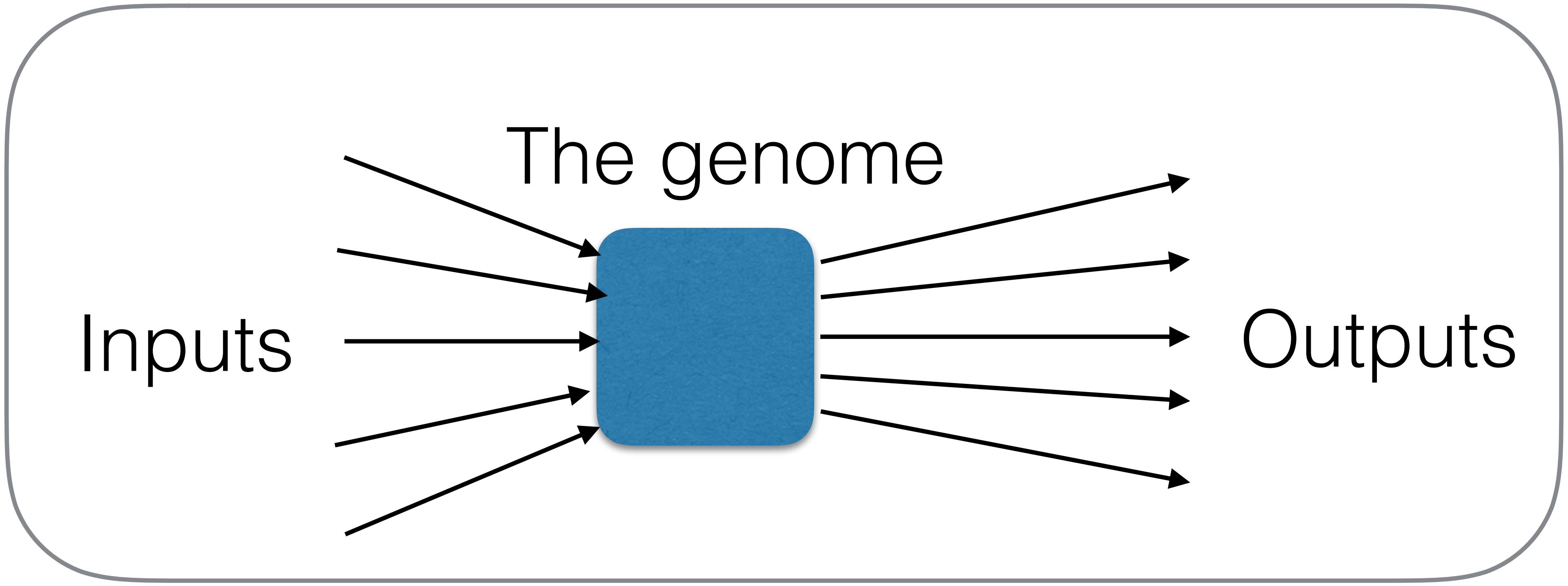
Sense adhesion

Receptor Tyrosine Kinase

Proteins involved in the MAPK/Erk pathway

Communicates surface receptors with DNA

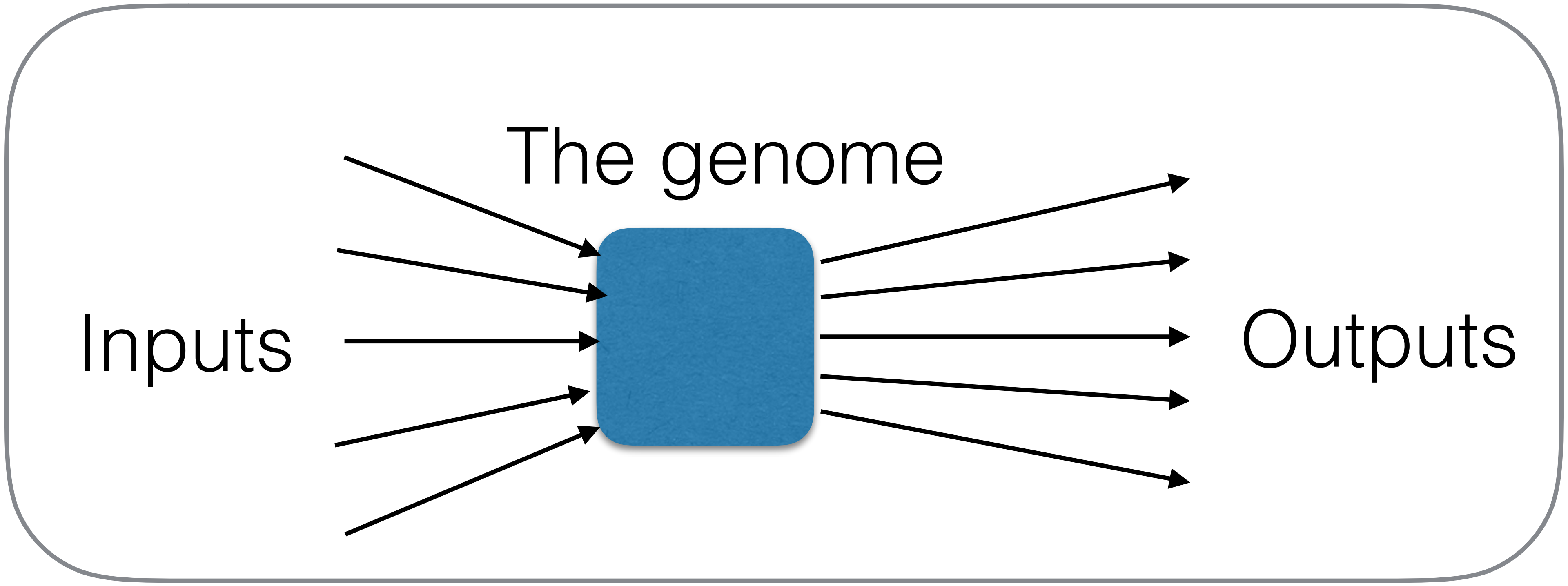
Gene regulation



A cell

Gene regulation

- The input proteins modify the state of the genome to produce output proteins.



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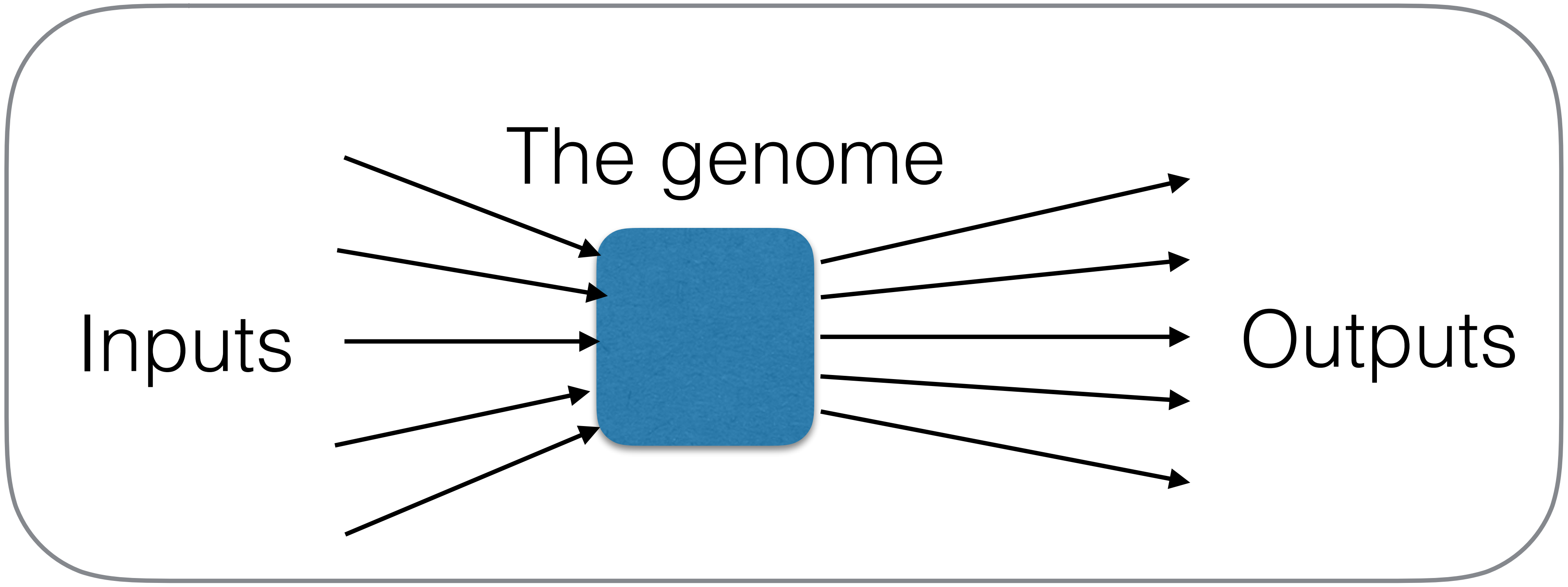

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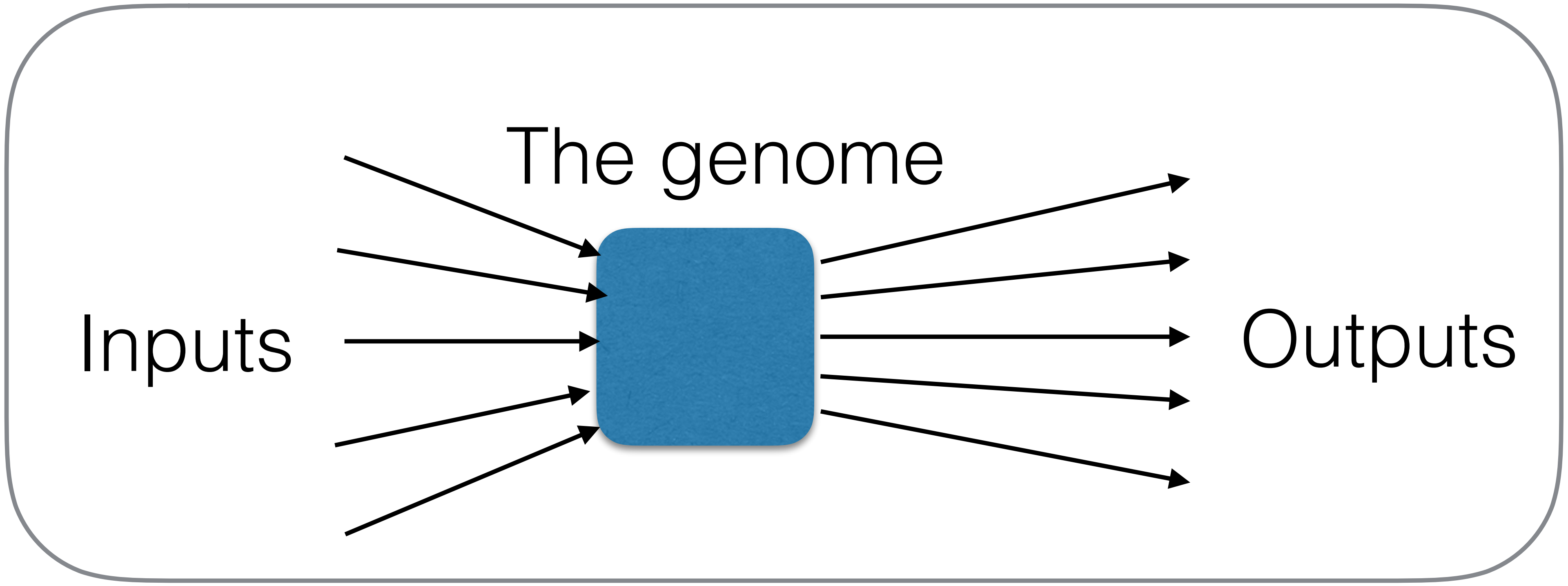
- It is intimately involved with neural development.



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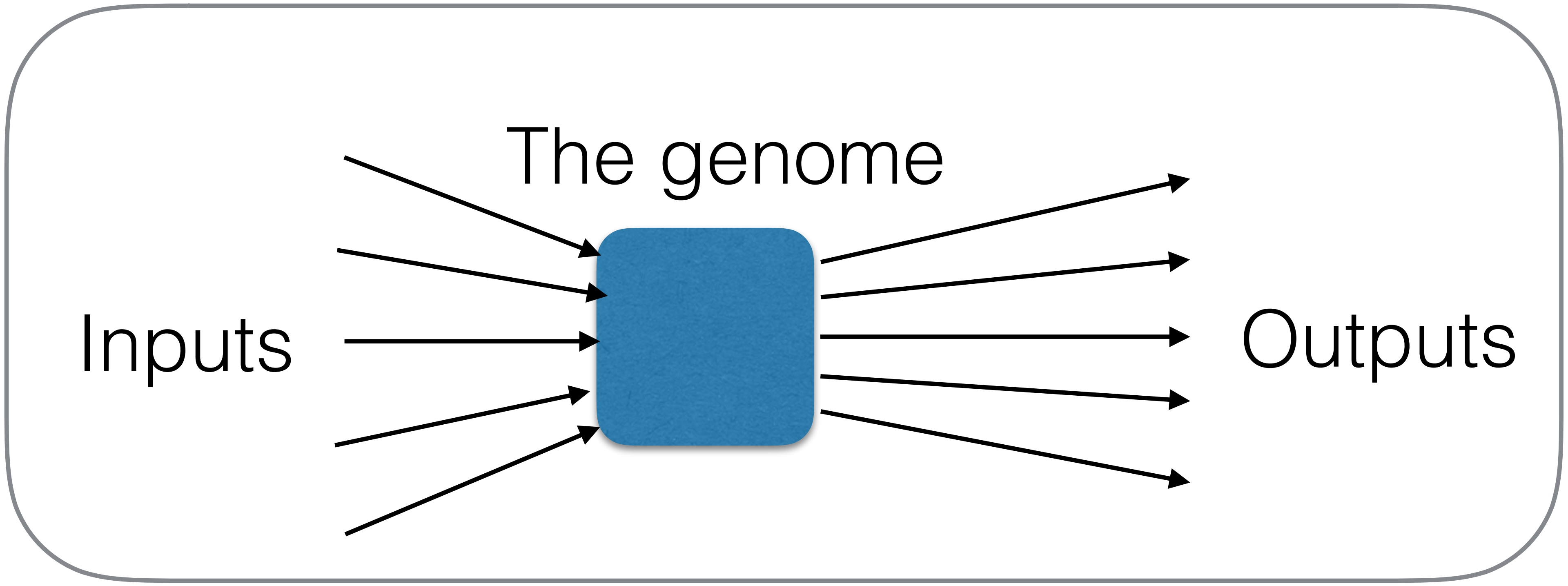
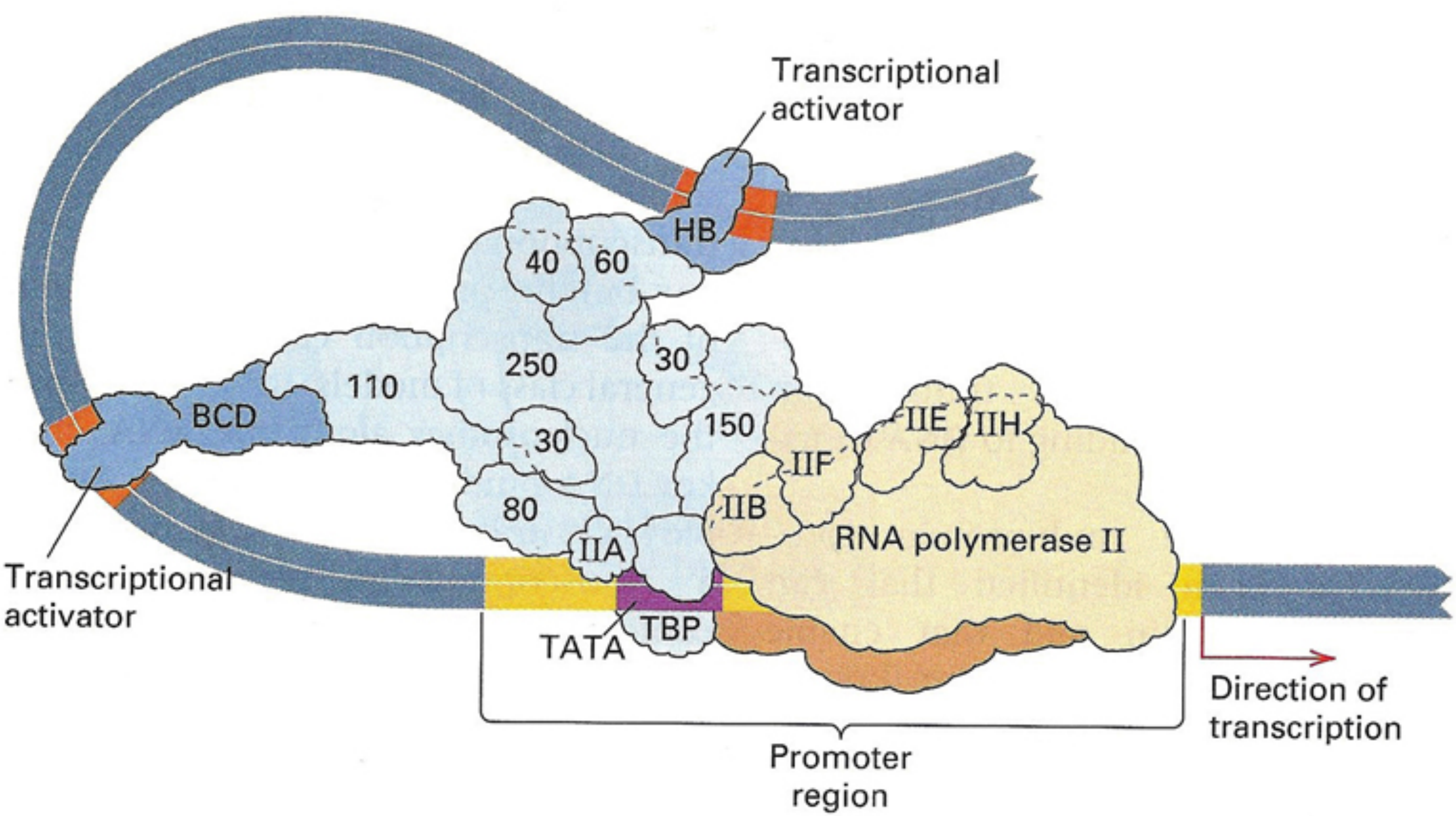


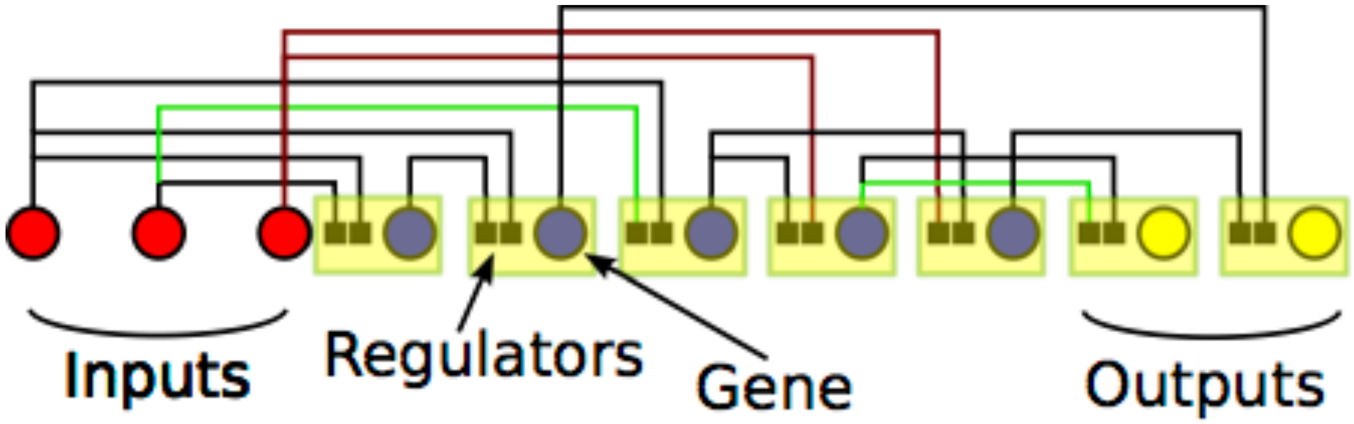
A cell

Activation of eukaryotic transcription



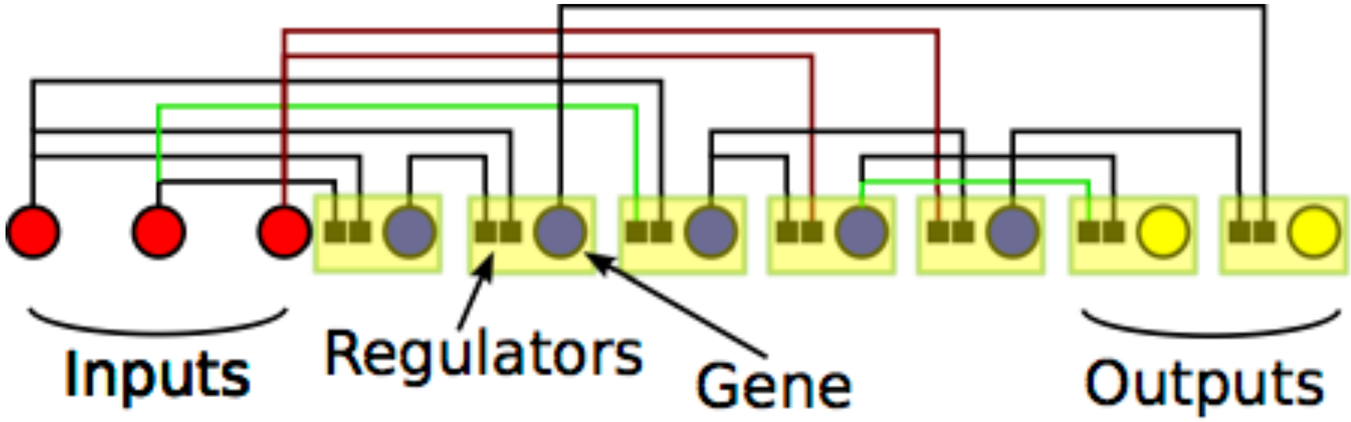
Biological Science, 4th edition, Freeman, 2010

Gene networks



Gene networks

- Gene expression is controlled by a highly complex mechanism, including other genes.



Gene networks

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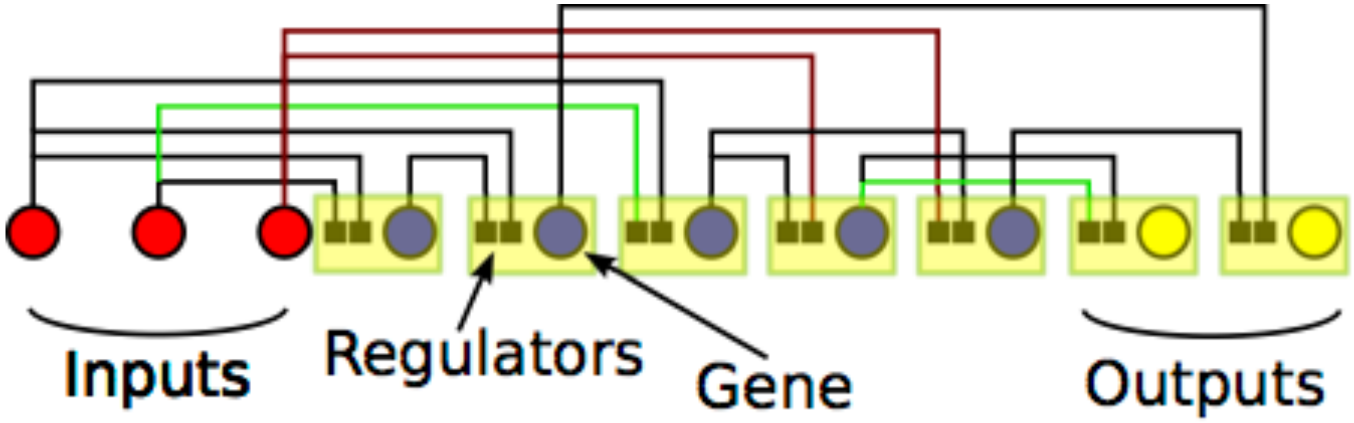
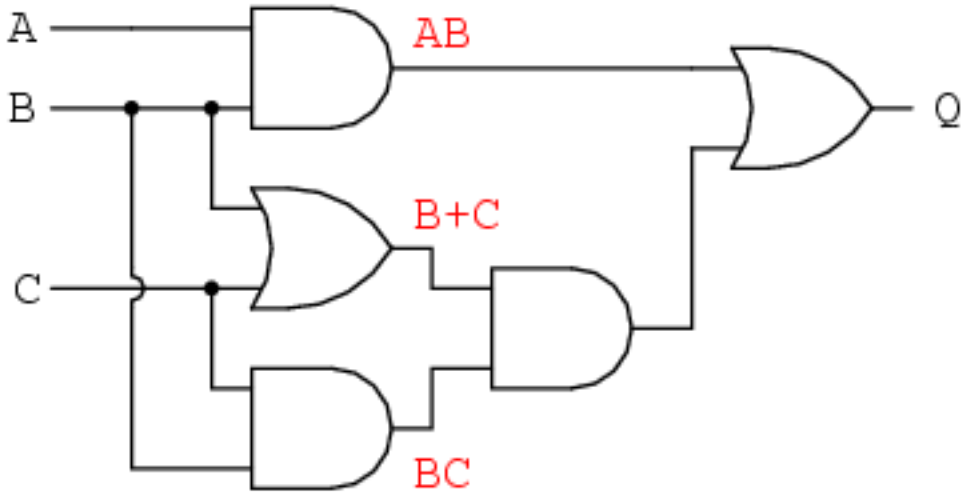
- Some regulatory proteins enhance and others repress transcription, by binding to regulatory elements.



Analogous to digital logic



Relatively small number of inputs and outputs

Complication:
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The salamander as 10 times our DNA

A pine tree has 7 times

Yet the bladder wort has only 3% noncoding DNA

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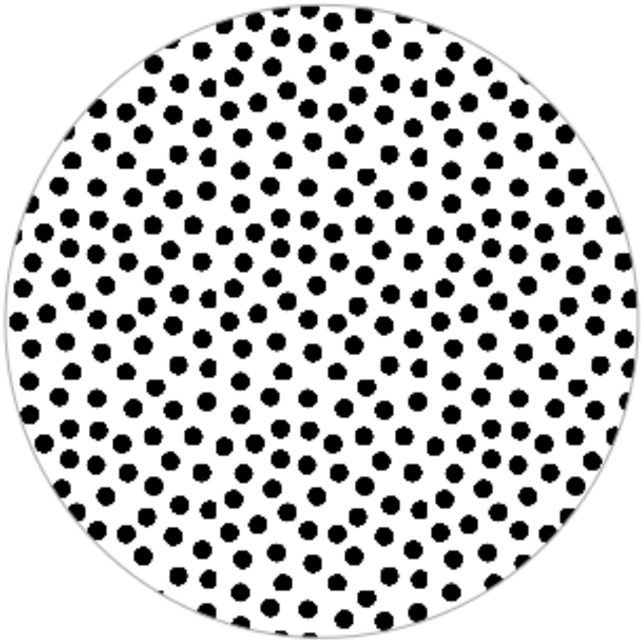
- It is pervasively transcribed.
- However it is largely not evolutionarily conserved.
- Is most of doing anything “useful”?
- There appear to be quite a few examples, but most of the function of it is still unknown.

Does it “get in the way”?

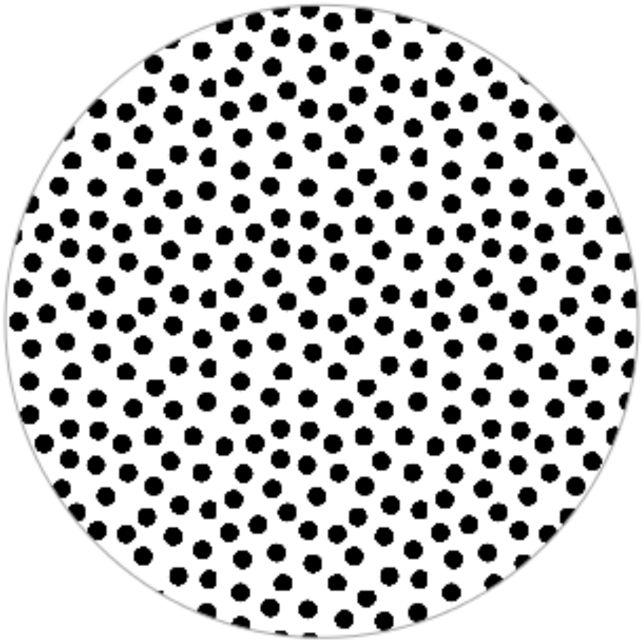
Back of the envelope



Does it “get in the way”?

Back of the envelope

The number of mRNA in human cells ~ 500,000



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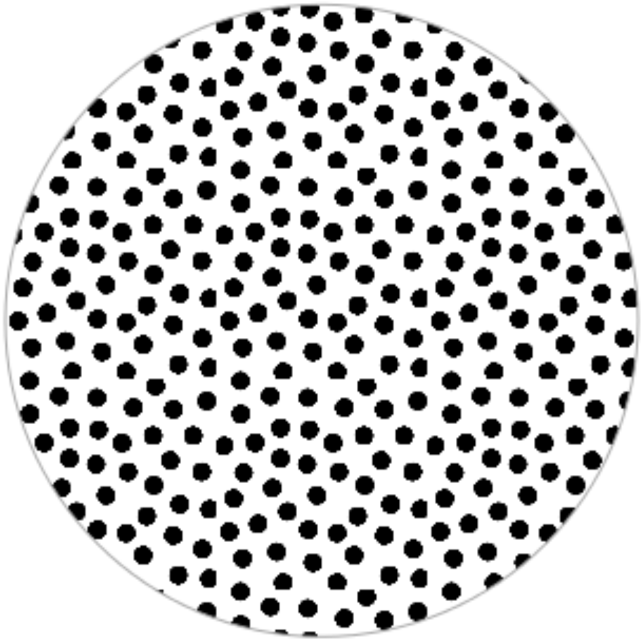

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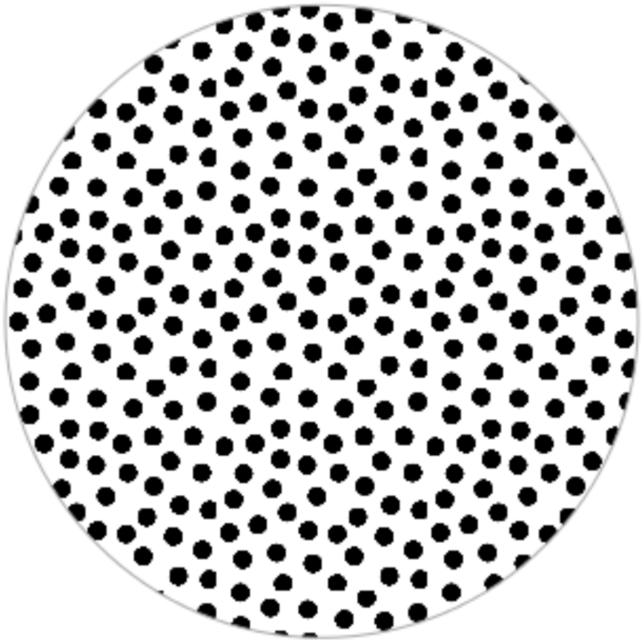

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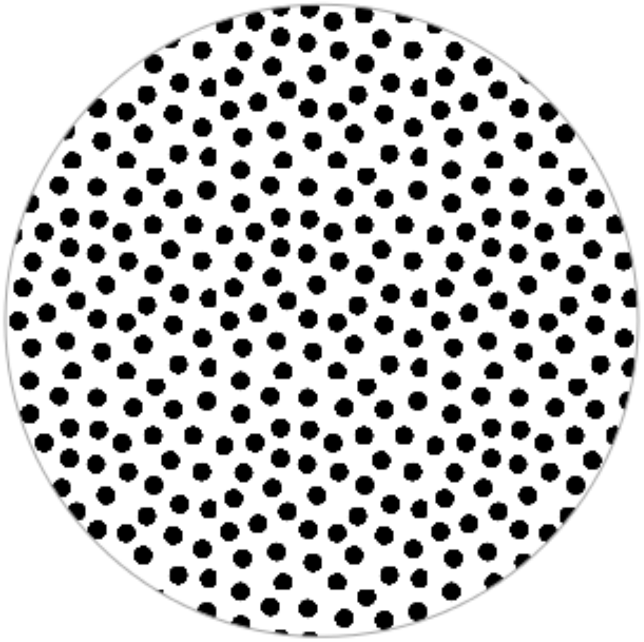

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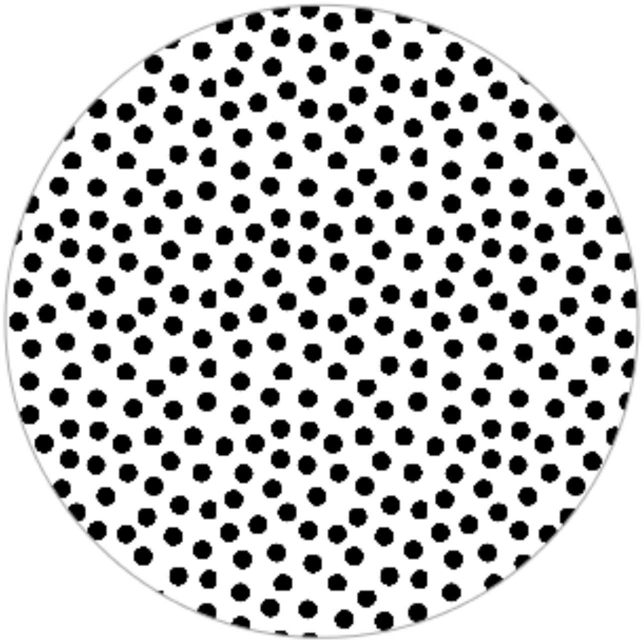

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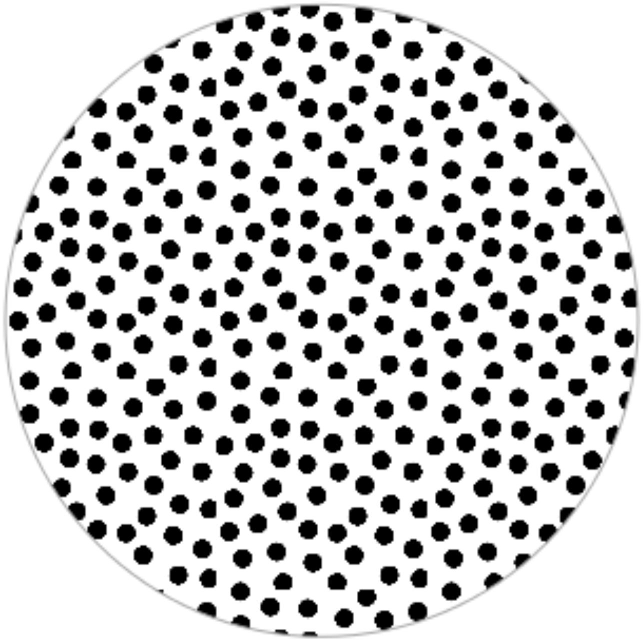

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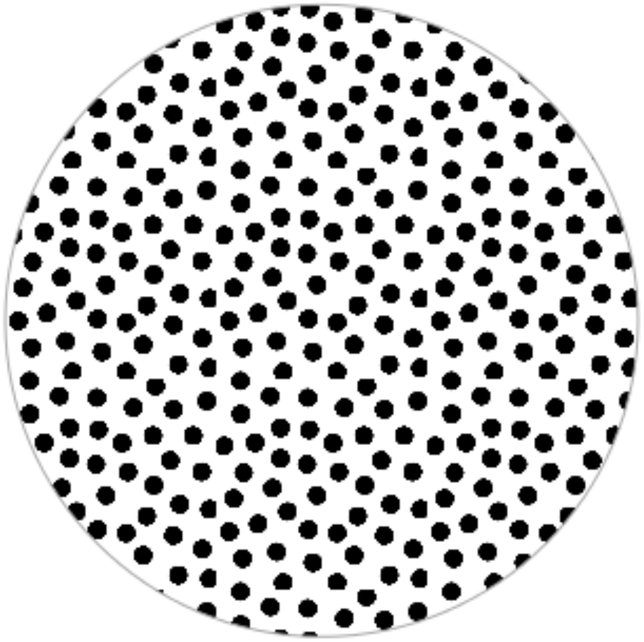

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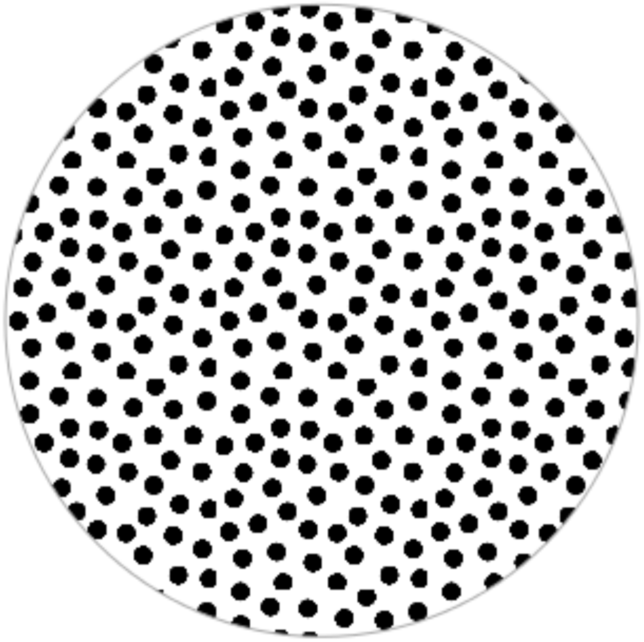

D = 0.1 $\mu m^2/s$

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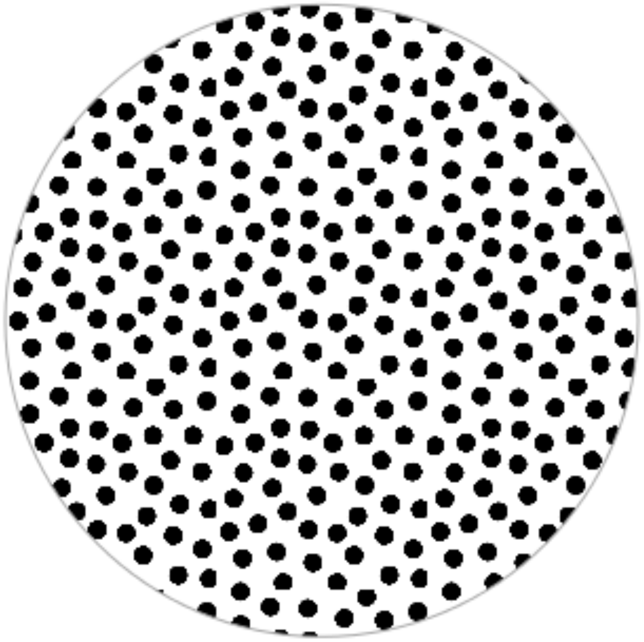

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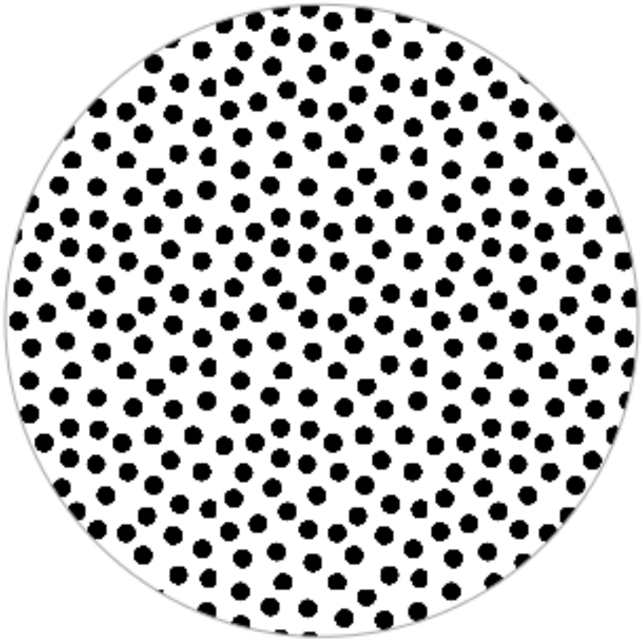

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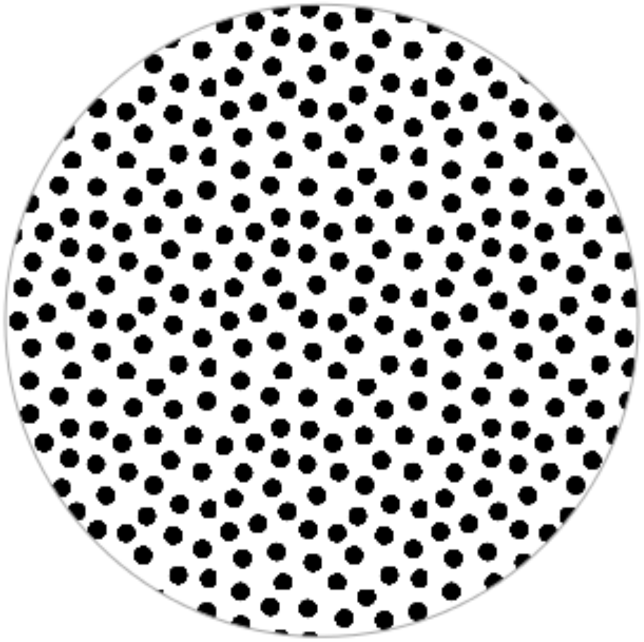

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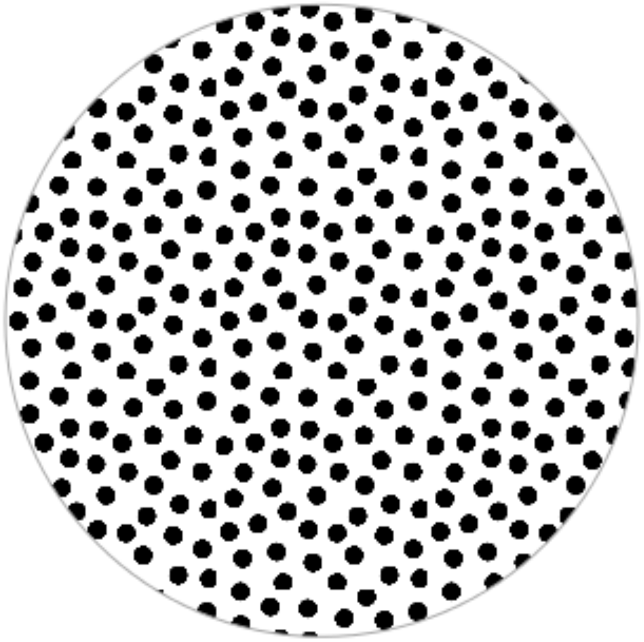

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=> Timescale for interaction ~ 0.25 s

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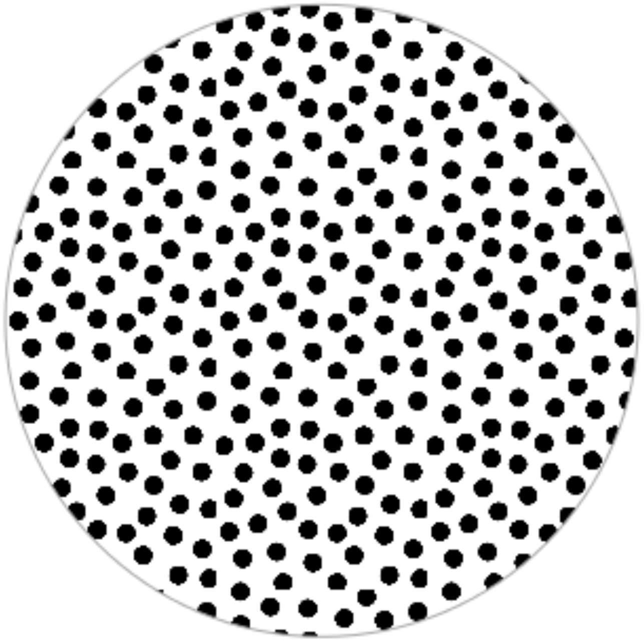

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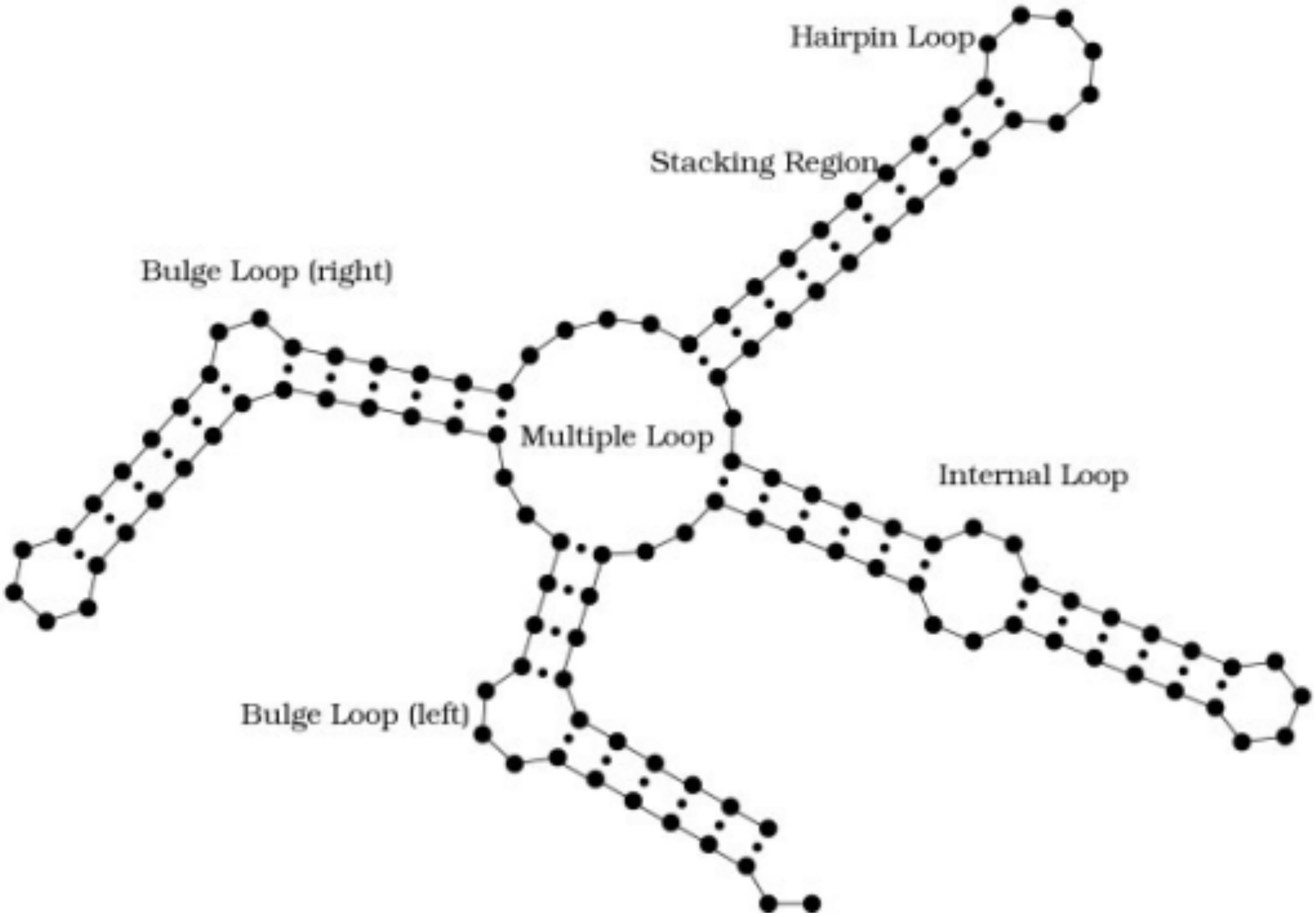
RNA is “sticky”. e.g. It has a lot of secondary structure



Non-coding RNA takes about 30 - 60 minutes to degrade!

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It’s certainly interacting with itself and lots of other stuff in the nucleus!

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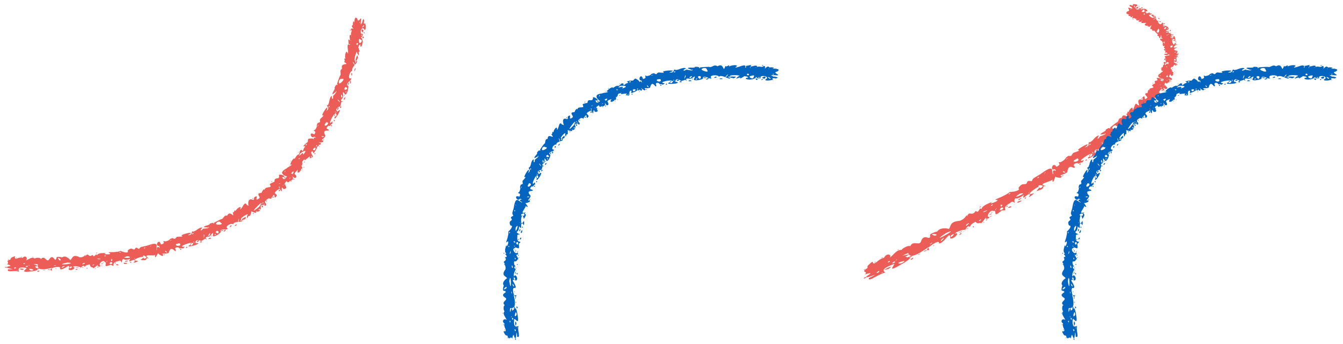
On physical grounds, it is doing something!

RNA Chemical equilibration

$$i + j \rightleftharpoons ij$$



Total concentration

$$\rho_i = \frac{C_i}{1 + \sum_j \rho_j K_{ij}}$$

$$K_{ij} = \rho_{ij} / \rho_i \rho_j$$

unbound concentration

Equilibrium constant

Relaxation

$$\tau_\rho \frac{d\rho_i}{dt} = -\rho_i + \frac{C_i}{1 + \sum_j \rho_j K_{ij}}$$

Equilibration time, of order 1s

RNA creation

RNA is both degraded and created. For species i

$$\tau_C \frac{dC_i}{dt} = -C_i + f(C_i, \{\rho_k\})$$

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Creation rate, f, is regulated by the total concentration of i and the concentration of unbound molecules.

Assumption:

All this “junk” will evolve to do something useful

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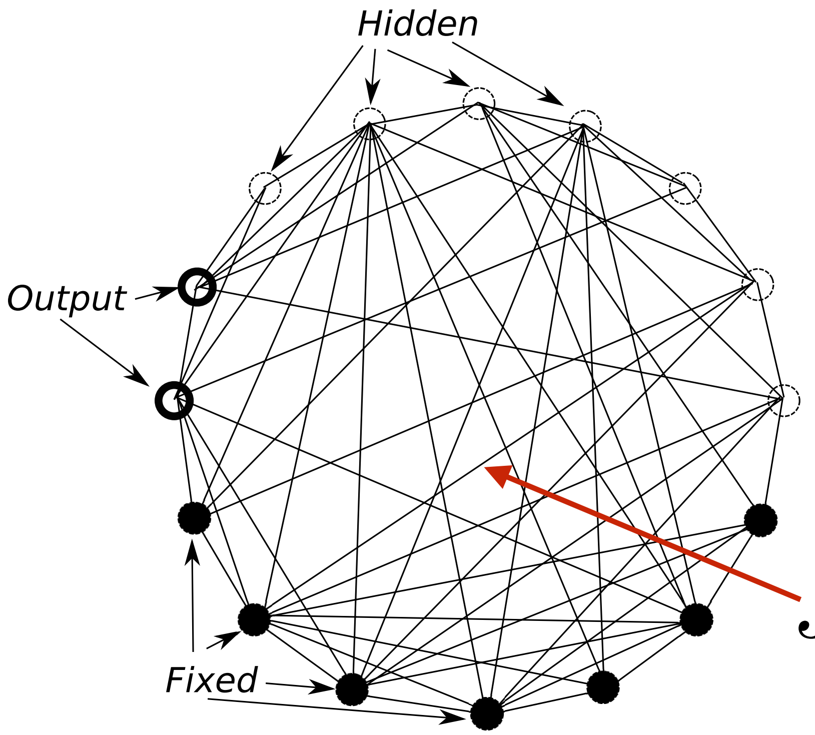
i.e. Inputs to the genome will give sensible outputs

Boltzmann Machine & Hopfield Model

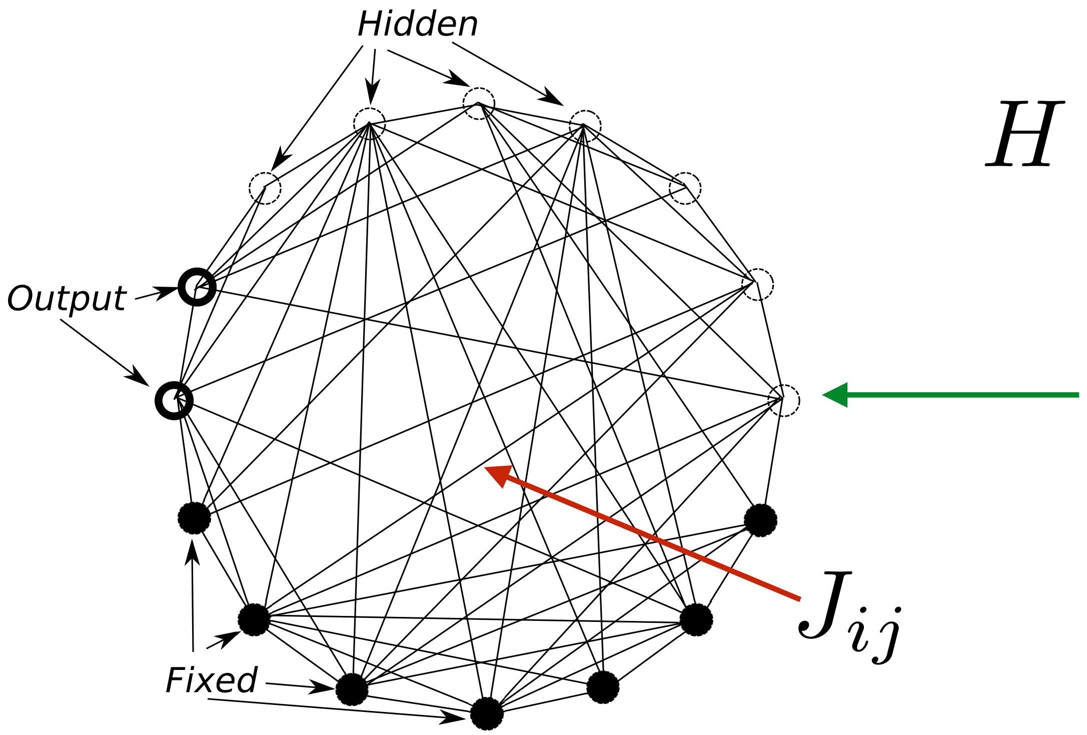


$$H = - \sum_{i=1,j=1}^{N} J_{ij} s_i s_j$$

$$s_i = \pm 1$$

J_{ij}

Boltzmann Machine & Hopfield Model



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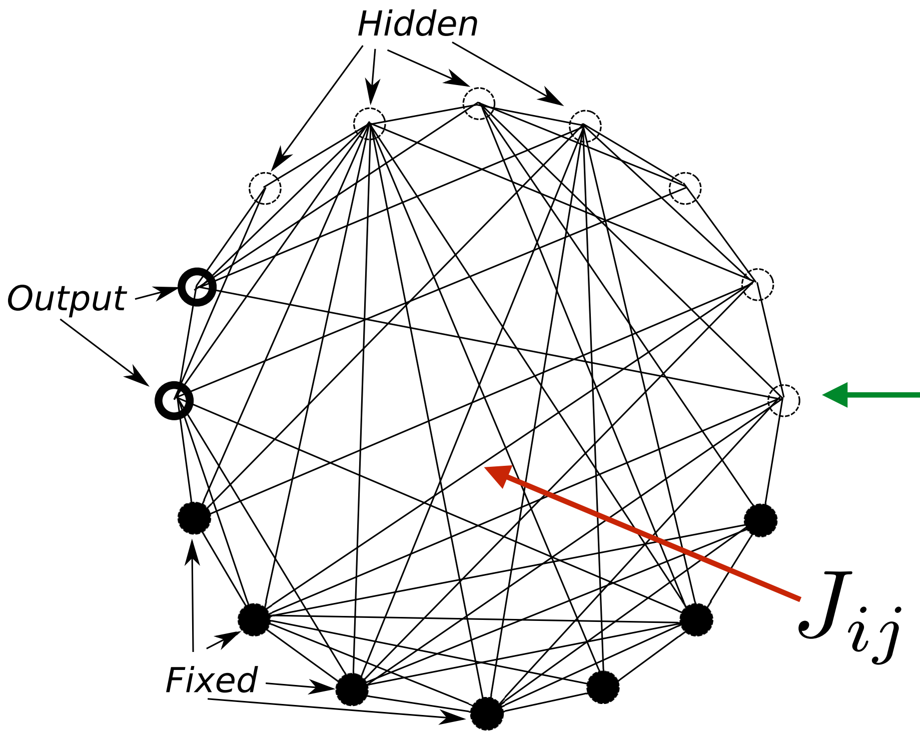

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J_{ij}'s chosen to give optimal outputs given inputs

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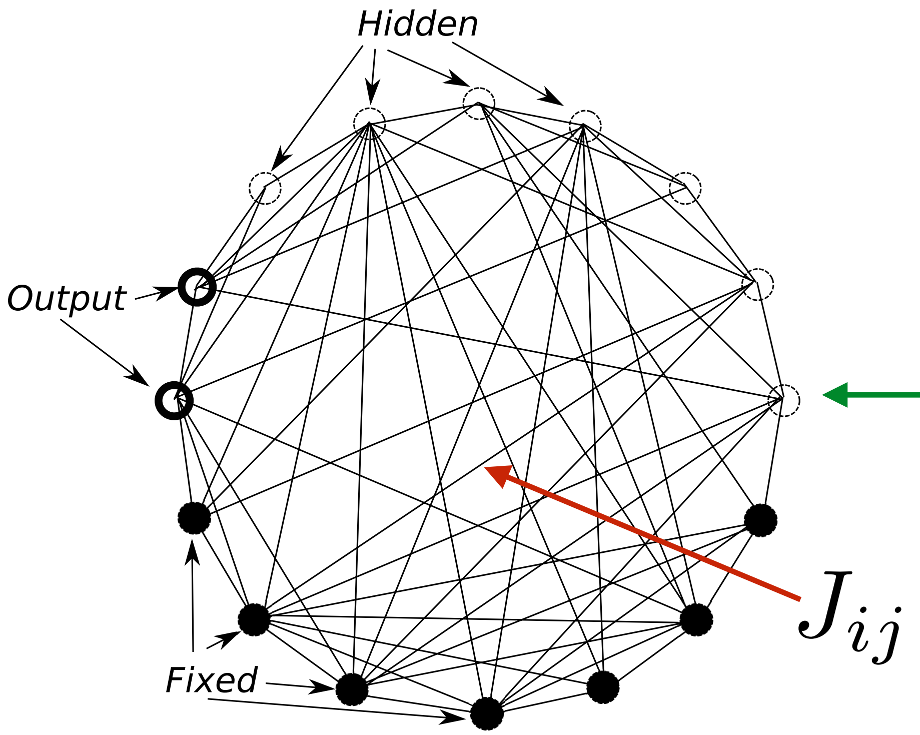

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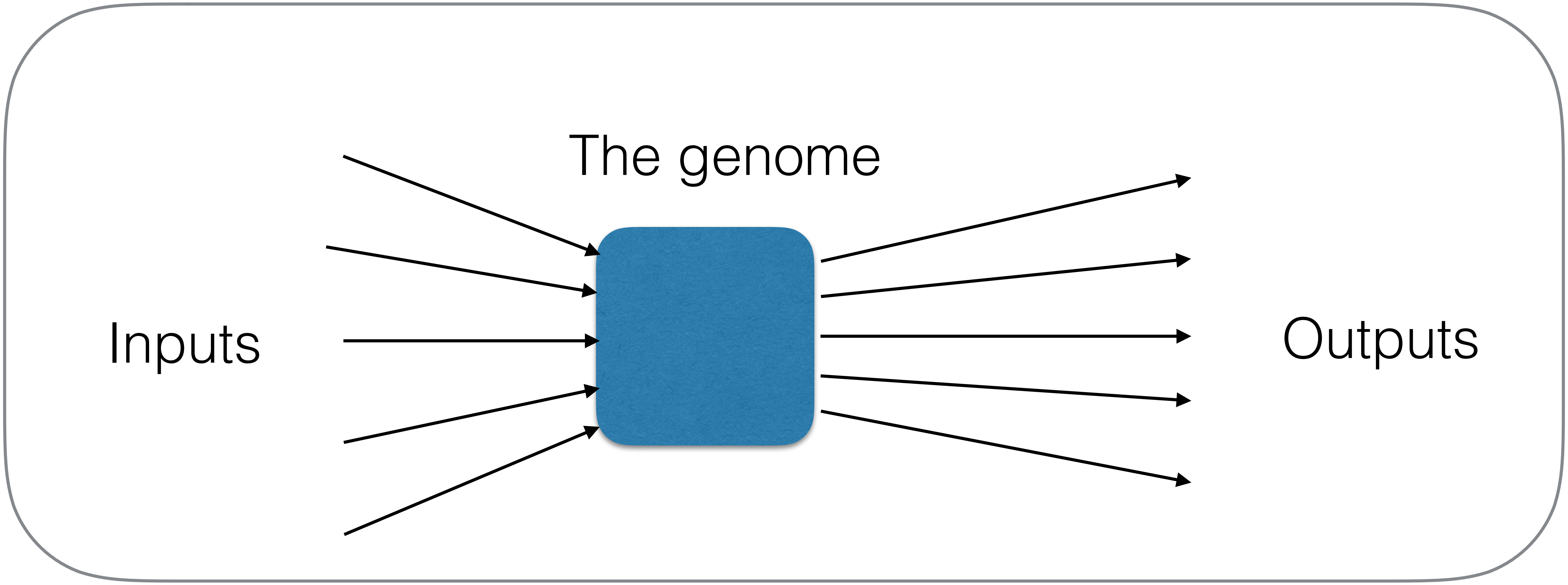
$$s_i = \tanh(\frac{\beta}{N}\sum_j J_{ij} s_j)$$



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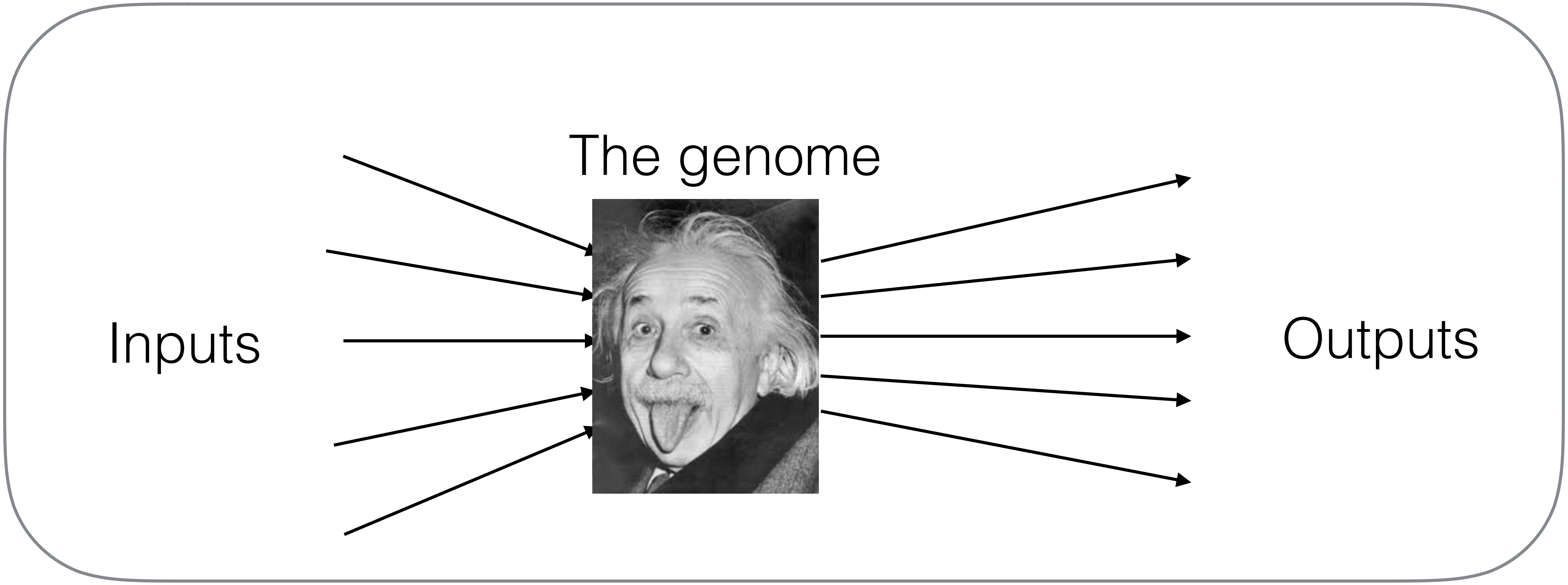

The genome

Inputs

Outputs

A smart cell

Neural net / RNA mapping

spin $\longrightarrow$ $s_i \Longleftrightarrow \rho_i$ $\longleftarrow$ Unbound concentration

spin coupling $\longrightarrow$ $J_{ij} \Longleftrightarrow K_{ij}$ $\longleftarrow$ Equilibrium Constant

$$\rho_i = \delta \frac{1 + s_i}{2} + b$$

$$K_{ij} = \epsilon \frac{1 + J_{ij}}{2} + a$$

$t \to \infty$: Want RNA’s to give neural net behavior

Choose creation rate

Choose creation rate

$$f(C_i, \{\rho_k\}) = \frac{C_i}{\rho_i} S[\frac{4}{\epsilon}(\frac{C_i}{\rho_i} - 1) - 2(1 + 2\frac{a}{\epsilon}) \sum_{j=1}^{N} \rho_j \frac{2(\delta + 2b)}{\epsilon} \sum_j K_{ij} + (\frac{2a}{\epsilon} + 1)(\delta + 2b)N]$$

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Minimum spin states for Boltzmann machine/ Hopfield

More universal creation

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An ugly mess!

More universal creation

$$f(C_i, \{\rho_k\}) = \frac{C_i}{\rho_i} S(\frac{4}{\epsilon}(\frac{C_i}{\rho_i} - 1) - 2(1 + 2\frac{a}{\epsilon}) \sum_{j=1}^{N} \rho_j - \frac{2(\delta + 2b)}{\epsilon} \sum_j K_{ij} + (\frac{2a}{\epsilon} + 1)(\delta + 2b)N)$$

An ugly mess!

More universal creation

$$f(C_i, \{\rho_k\}) = \frac{C_i}{\rho_i} S(\frac{4}{\epsilon}(\frac{C_i}{\rho_i} - 1) \underbrace{- 2(1 + 2\frac{a}{\epsilon}) \sum_{j=1}^{N} \rho_j - \frac{2(\delta + 2b)}{\epsilon} \sum_j K_{ij} + (\frac{2a}{\epsilon} + 1)(\delta + 2b)N)}$$

An ugly mess!

$$f(C_i, \{\rho_k\}) = \frac{C_i}{\rho_i} S(\frac{4}{\epsilon}(\frac{C_i}{\rho_i} - 1) - A)$$

$\sum_j \rho_j$'s chosen to be target value

More universal creation

$$f(C_i, \{\rho_k\}) = \frac{C_i}{\rho_i} S(\frac{4}{\epsilon}(\frac{C_i}{\rho_i} - 1) - \underbrace{2(1 + 2\frac{a}{\epsilon})\sum_{j=1}^{N} \rho_j - \frac{2(\delta + 2b)}{\epsilon} \sum_j K_{ij} + (\frac{2a}{\epsilon} + 1)(\delta + 2b)N}_{})$$

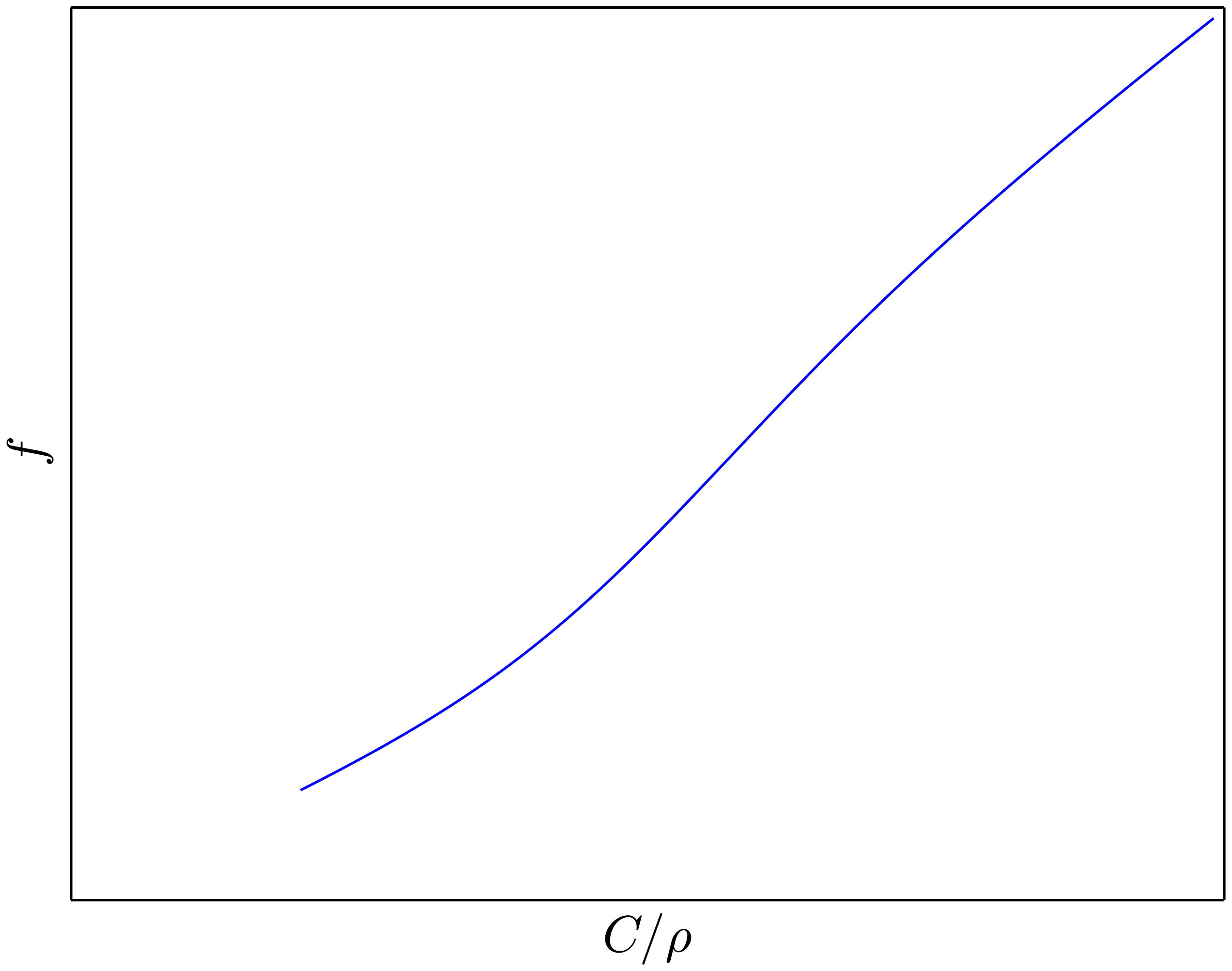
An ugly mess!

$$f(C_i, \{\rho_k\}) = \frac{C_i}{\rho_i} S(\frac{4}{\epsilon}(\frac{C_i}{\rho_i} - 1) - A)$$

$\sum_j \rho_j$'s chosen to be target value

A is a constant

Creation function



Creation rate

Total/unbound RNA

This system gives rise to “Collective Regulation”

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Each interaction has a minute effect but together
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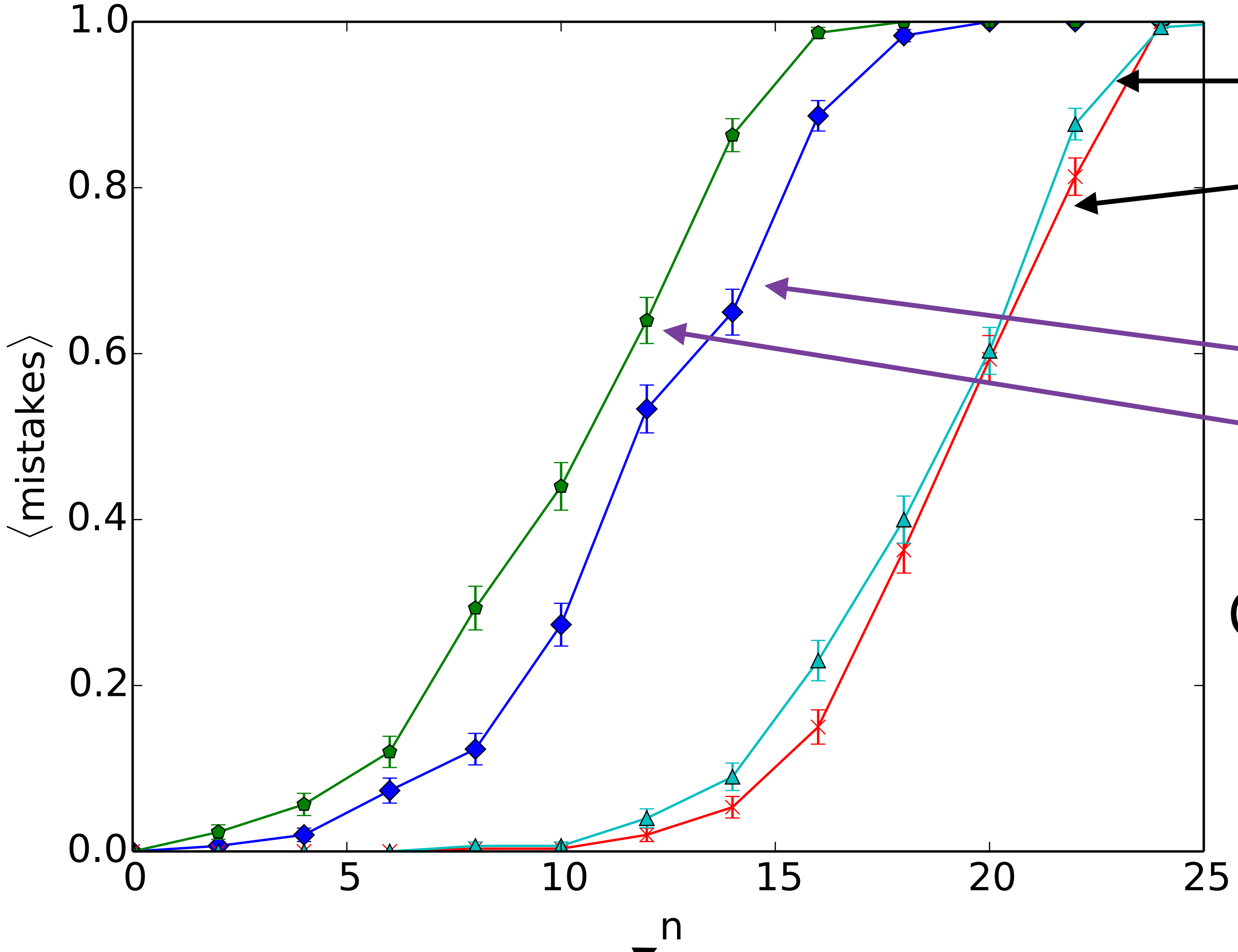
Equivalent to a neural network

Tests



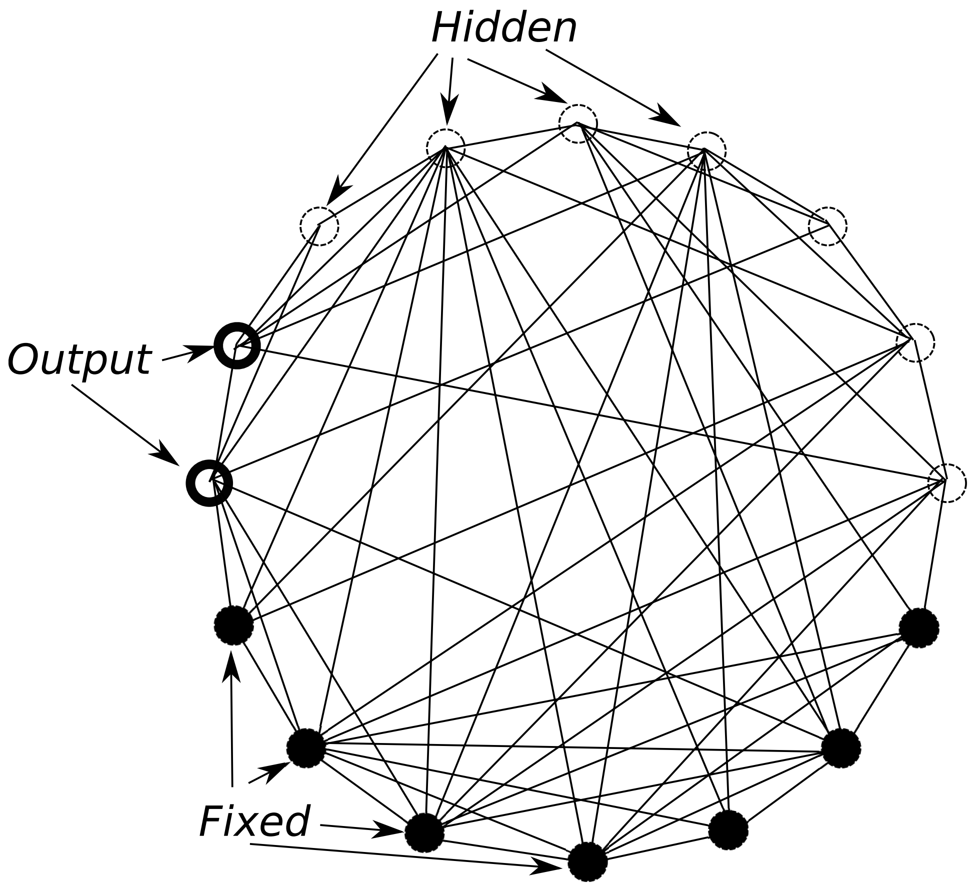
Different $\beta's$

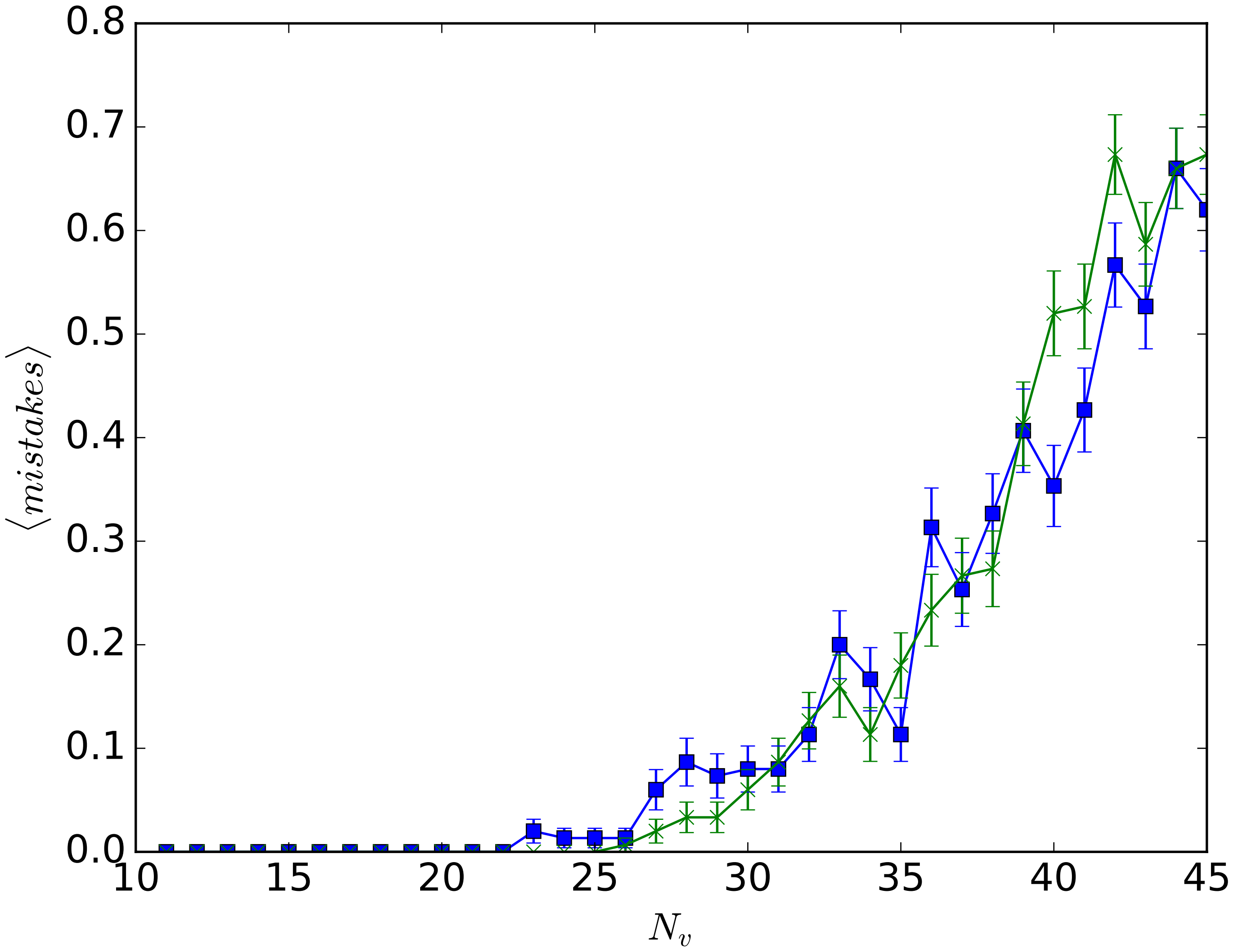
Different initial RNA concentration

Initial Hamming distance

N=50 species

M=3 patterns



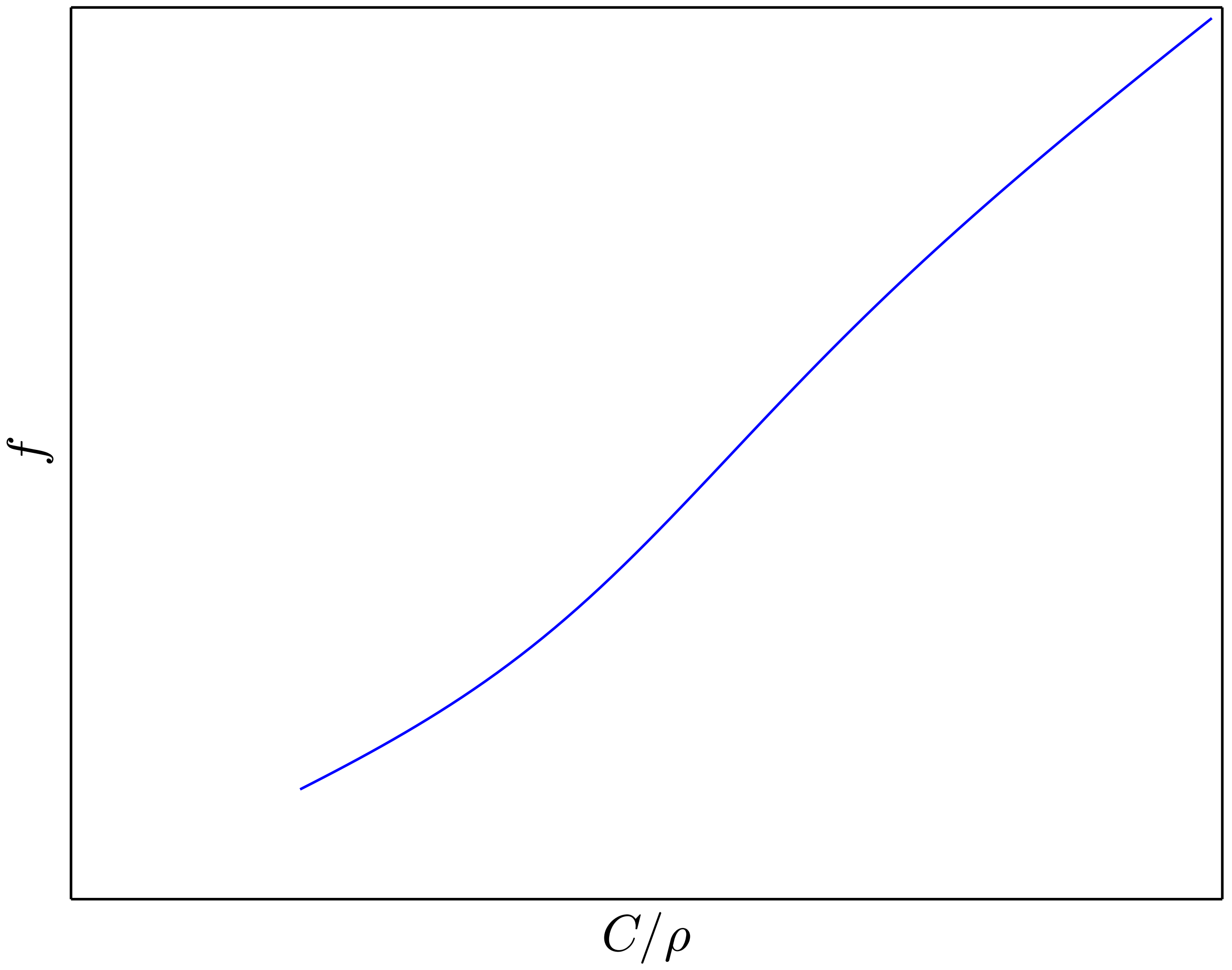


Fraction of mistakes as a function of number of hidden units.

Hidden units are initially scrambled.

50 neurons, 3 patterns. 2 output units.

Is this plausible?



Creation rate

Total/unbound noncoding RNA

Use a known mechanism

Presence of RNA increases its own transcription

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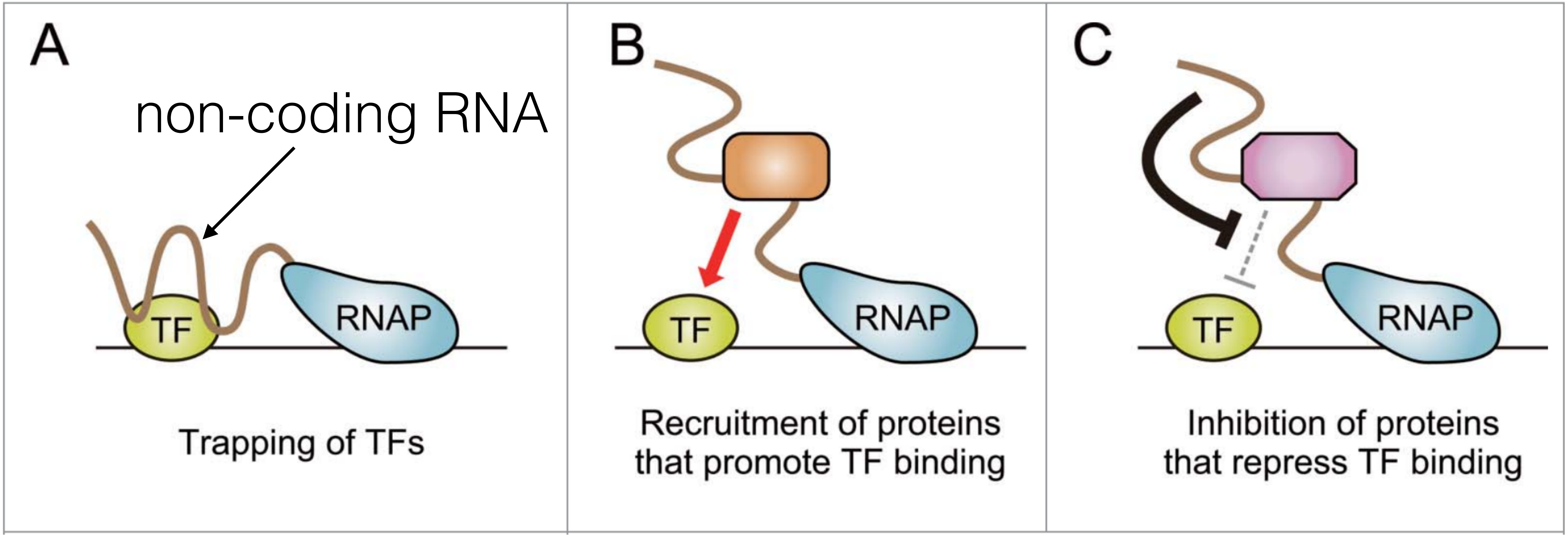
Presence of RNA increases its own transcription

Possible models for how this happens:



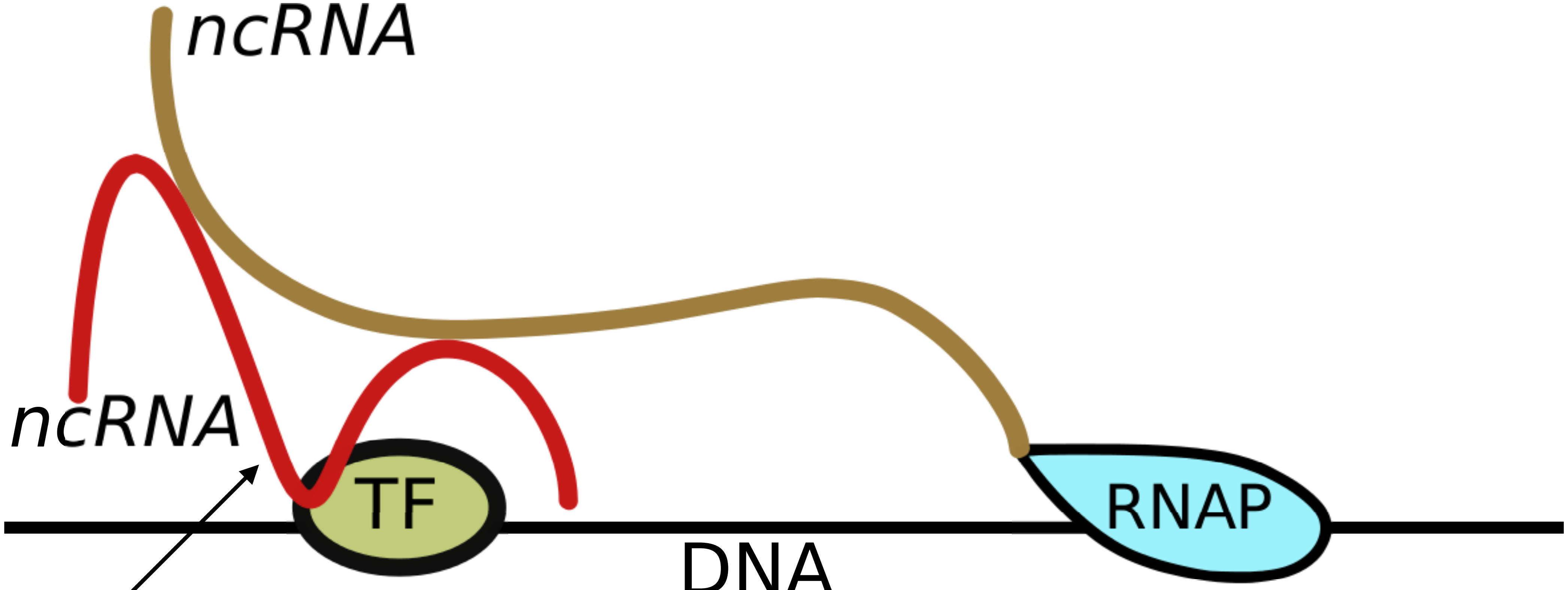
Trapping of TFs

Recruitment of proteins that promote TF binding

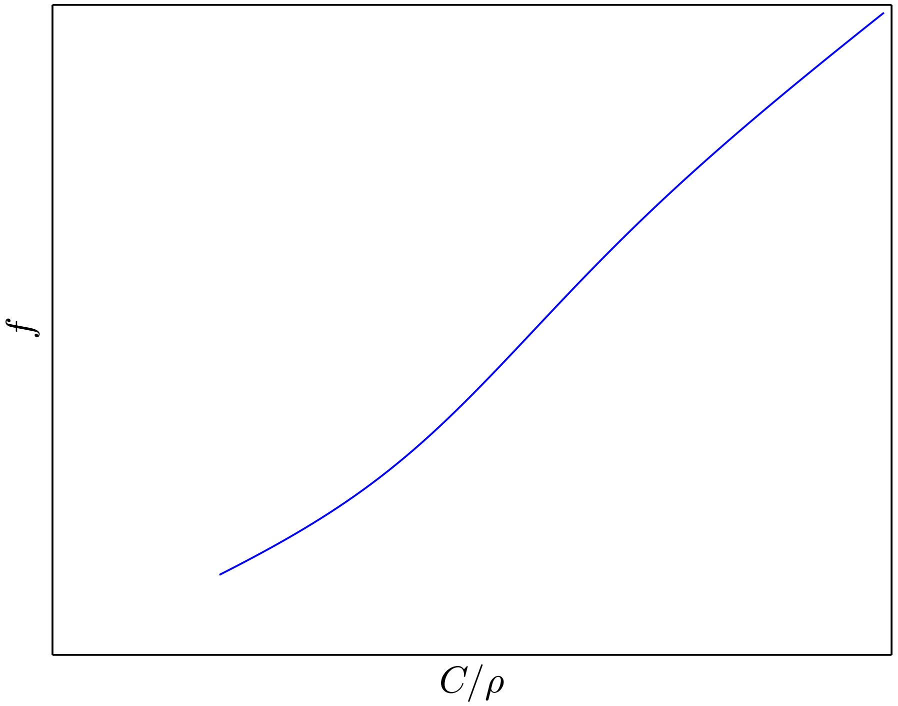
Inhibition of proteins that repress TF binding

“Role of non-coding RNA transcription around gene regulatory elements in transcription factor recruitment”
Naomichi Takemata and Kunihiro Ohta RNA BIOLOGY 2017

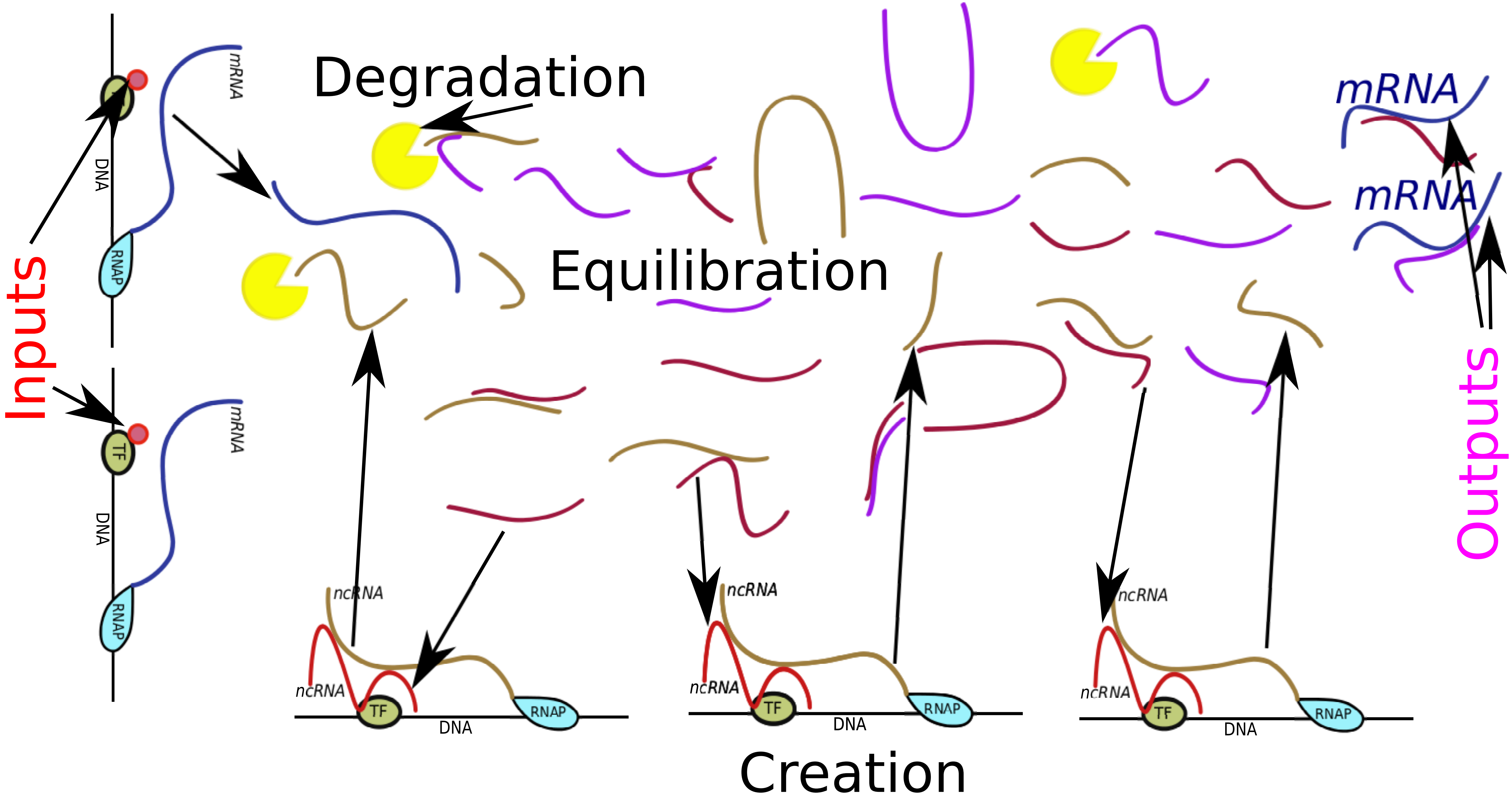
What happens with bound RNA?



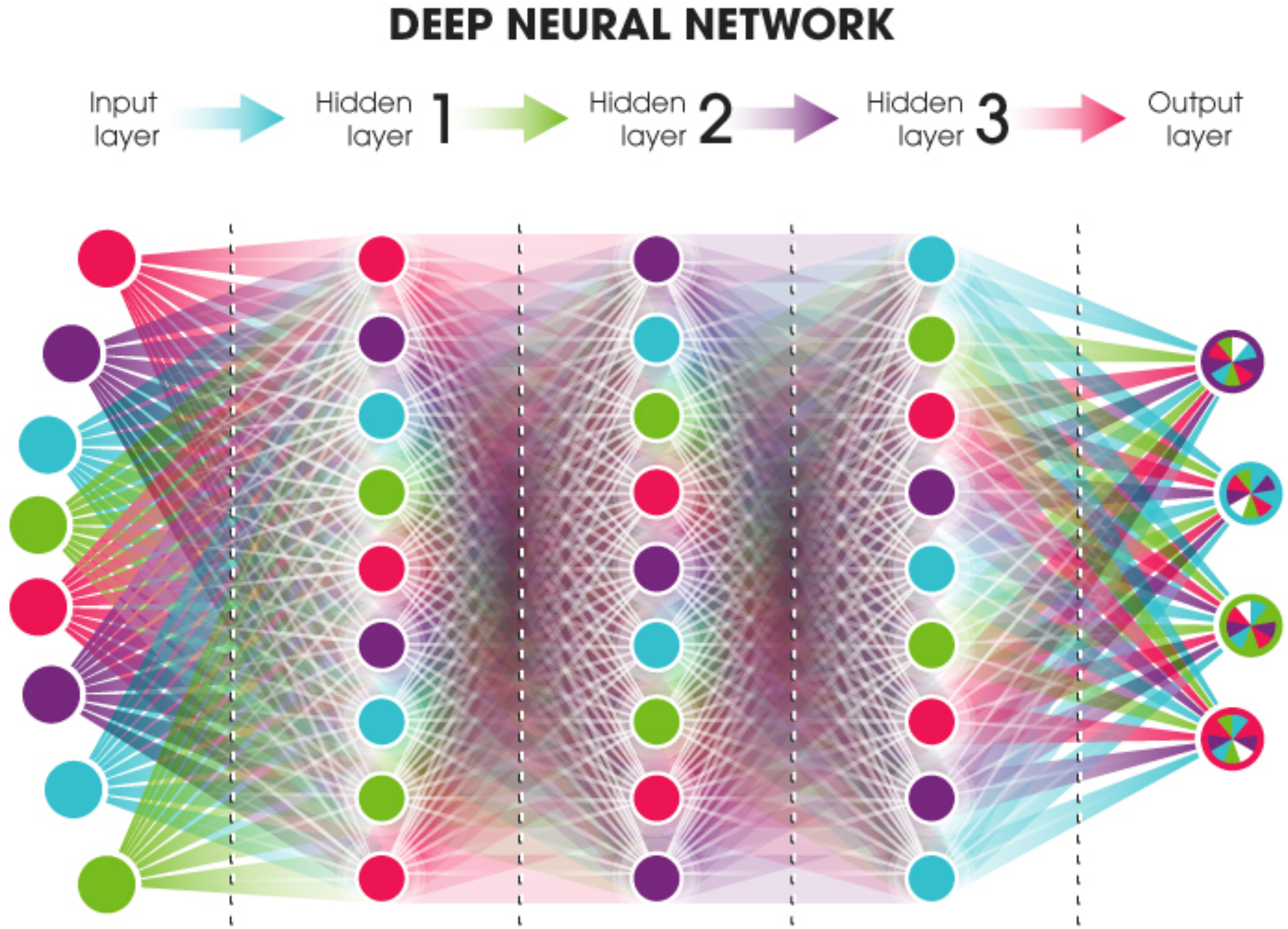
Additional bound noncoding RNA increases rate further



Making a computer out of junk



Equivalent to:



neuralnetworksanddeeplearning.com - Michael Nielsen, Yoshua Bengio, Ian Goodfellow, and Aaron Courville, 2016.

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