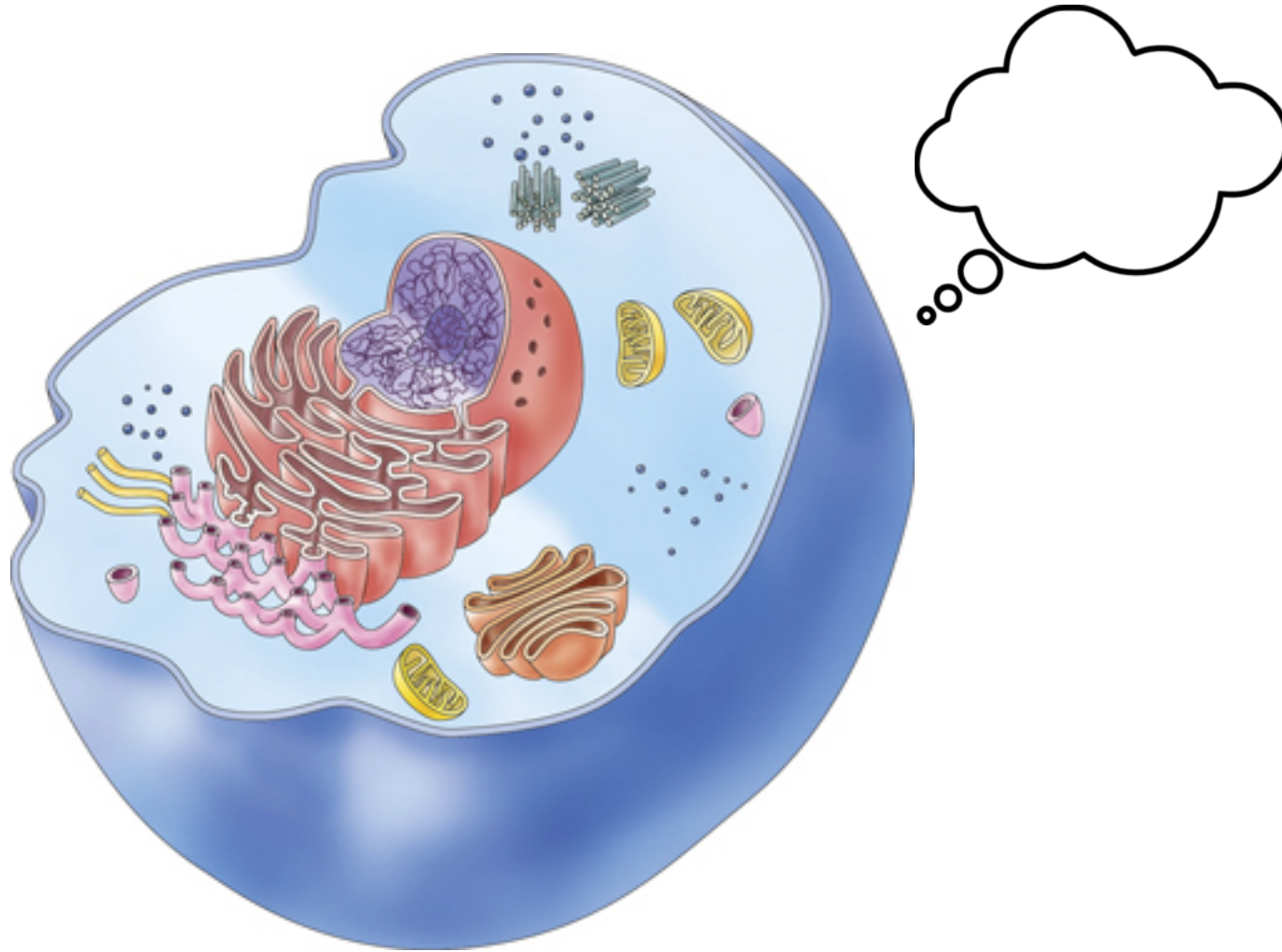


Can cells think?

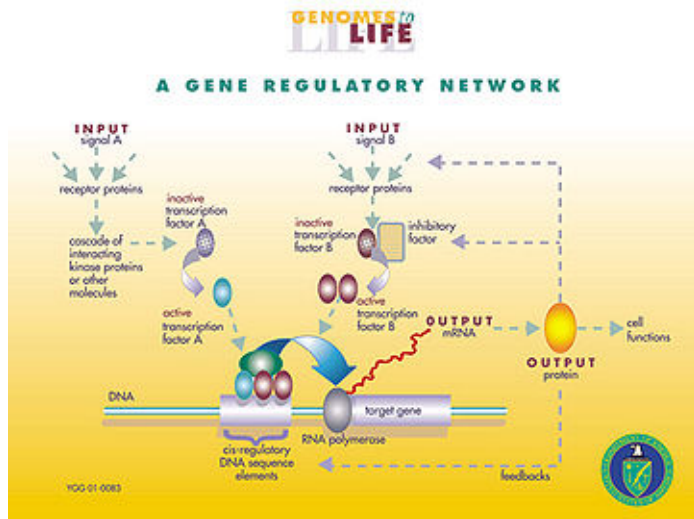


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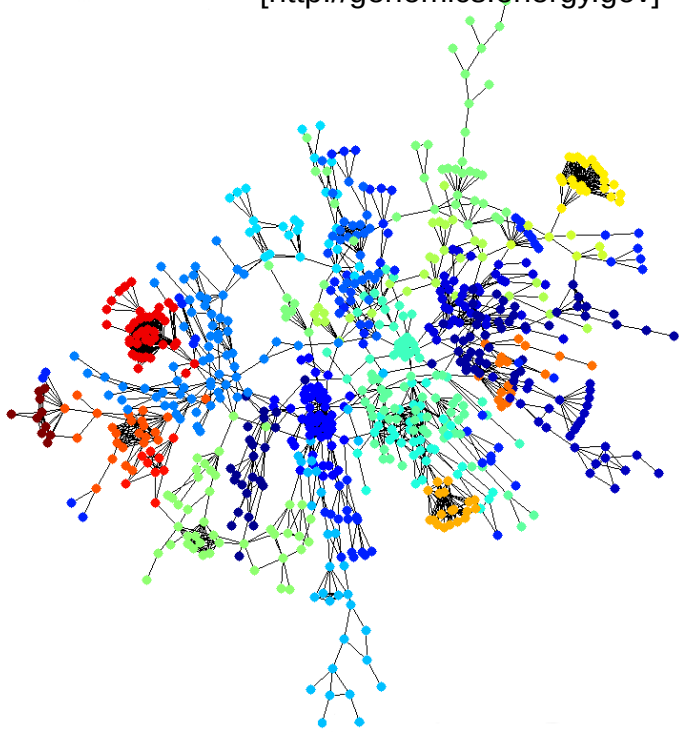
Cells as cognitive systems?

- Cells appear to have very sophisticated control mechanisms, mediated by the intracellular systems/networks of gene regulation, protein interaction, signal transduction, and metabolic pathways
- A cell can also be thought of as a decision-making system which is sensing its environment and responding/adapting in a multitude of ways
- There seem to be close analogies with the notions of *memory* and *learning* in cognitive systems
- How can we understand and model the cellular mechanisms responsible for these phenomena? Could ideas from AI / Machine Learning be relevant?

The circuitry of cells



[<http://genomics.energy.gov>]



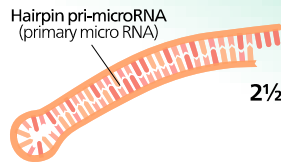
- Biological cells are essentially bags of interacting genes/proteins, which combine to carry out the various processes of life
- Given experimental data about how the concentration levels of proteins respond to various kinds of stimuli, can we try to recover the relationships of regulation and control between different genes/proteins?
- This can be thought of as learning the structure of a dynamical system, given some input/output characteristics
- We are looking at a range of approaches for mathematically modelling and learning these regulatory networks, such as Petri Nets, ODEs, and Markov Nets

Role of non-coding RNA ('junk DNA')

- Apart from transcription factors, we are now discovering that non-coding RNA (ncRNA) also appear to play a major role in regulating gene expression (e.g., gene silencing by microRNA)
- “The majority of mammalian genomic transcripts do not directly code for proteins and it is currently believed that most of these are not under evolutionary constraint.” [Deutsch 2016]
- Via inter-RNA binding (ncRNA to mRNA), and given the wide variety and abundance of ncRNA, they are potentially regulating gene expression (post-transcriptionally) in a highly distributed fashion
- This is reminiscent of artificial neural networks

nucleus

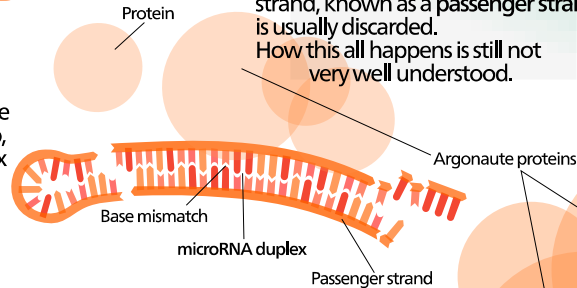
1 A protein called exportin-5 transports a hairpin primary microRNA (pri-miRNA) out of the nucleus.



Exportin-5

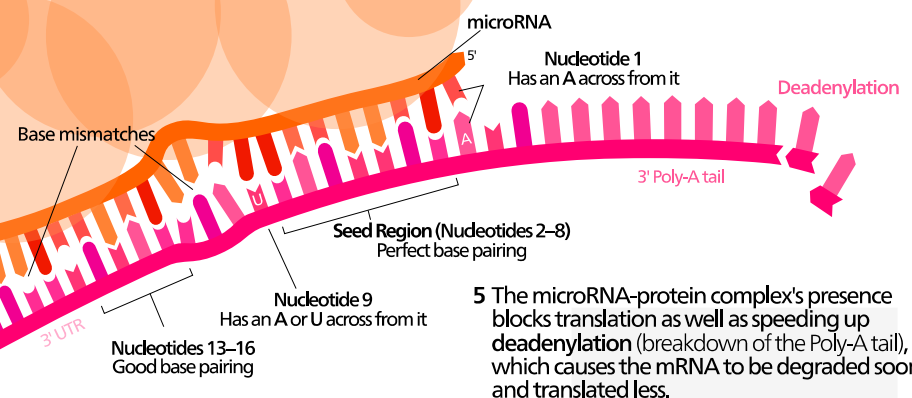
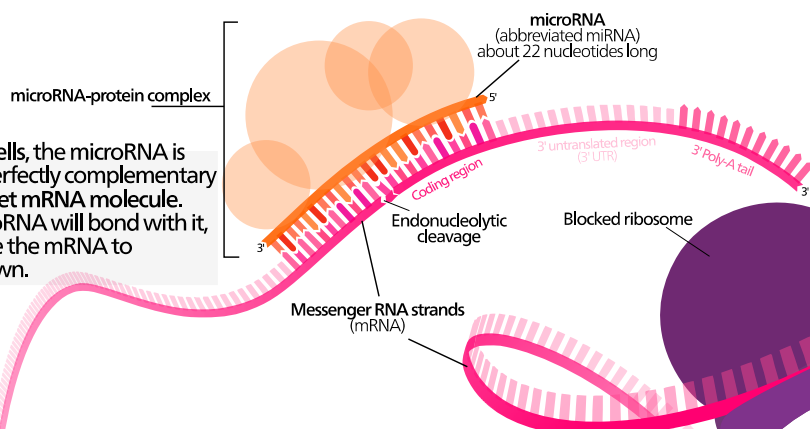
2½ Meanwhile, one of the strands joins a group of proteins, forming an microRNA-protein complex. The other strand, known as a passenger strand is usually discarded. How this all happens is still not very well understood.

2 An enzyme called dicer (not shown) trims the pri-miRNA and removes the hairpin loop, leaving a double stranded microRNA duplex molecule.



4 In animal cells, the microRNA nucleotides typically don't pair up with the mRNA nucleotides as well. Their base pairing often follows a pattern though.

3 In plant cells, the microRNA is usually perfectly complementary to its target mRNA molecule. The microRNA will bond with it, and cause the mRNA to break down.



5 The microRNA-protein complex's presence blocks translation as well as speeding up deadenylation (breakdown of the Poly-A tail), which causes the mRNA to be degraded sooner and translated less.

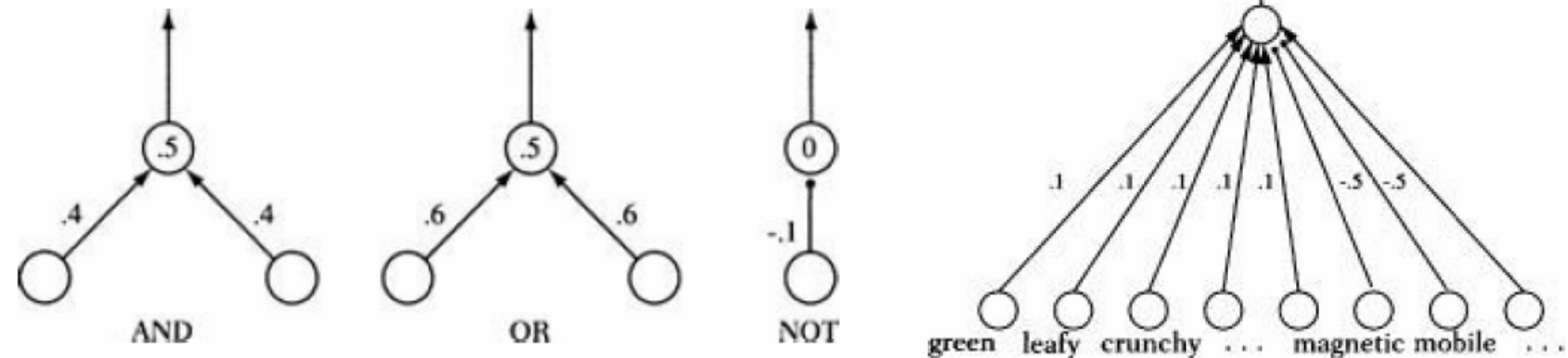
the formation and function of micro RNAs

Associative memory neural networks

- Traditional memory involves a mapping from address to content (e.g., RAM)
- But for cognitive systems, *associative memory* seems more relevant: where the full content/pattern is recoverable from the presentation of just a part of it (content addressable memory)
- *To be or not to be, that is _____*
- *I came, I saw, _____*
- Think also of associative memories triggered by specific sights/sounds/smells

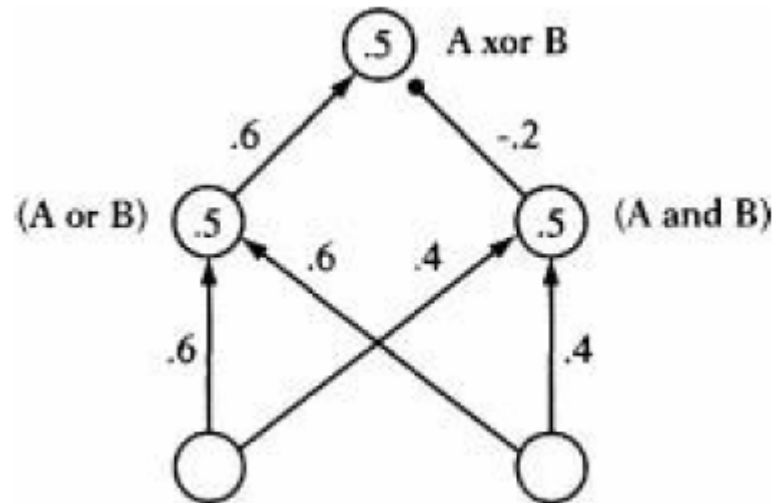
Neural networks: A very brief history

- McCulloch-Pitts model of a neuron (1943)
- Neurons: switch-like, either ON (1) or OFF (0)
- Take a weighted sum of inputs and apply a threshold to it, to decide whether to fire or not
- Can thus encode more abstract logical operations and concepts/categories



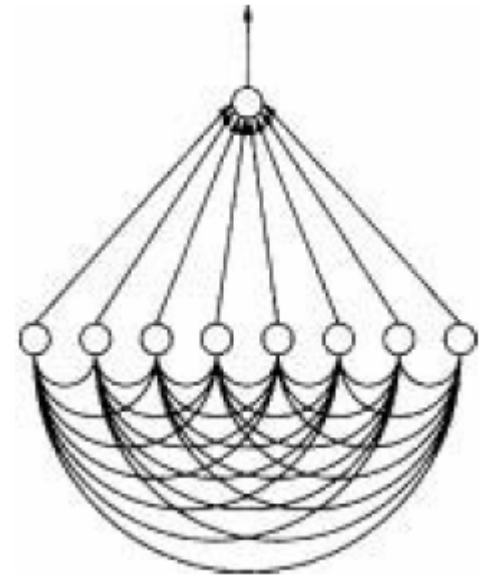
Neural networks: A very brief history

- Rosenblatt's Perceptron (1958): Learning the weights from labeled examples
- Runs into *XOR problem* (non-linearity of input-output mapping)
- Solution: have an internal representation or hidden layer
- Gave rise to *multilayer perceptrons* or *neural networks*



Auto-associative neural networks

- Connect input units amongst themselves as well
- Can learn associations between features/properties: e.g., greenness predicts leafiness, leafiness predicts crunchiness...
- Can fill in missing information via such associations learnt from frequently occurring patterns
- Also allows for some robustness to noisy inputs (relevant to thinking about ncRNA)



An associative memory model for ncRNA regulation [Deutsch 2016]

- N species of ncRNA: S_1, S_2, \dots, S_N
- Total concentrations: C_1, C_2, \dots, C_N
- Unbound concentrations: $\rho_1, \rho_2, \dots, \rho_N$
- Binding reactions and equilibrium constants:



$$K_{i,j} = \rho_{ij} / (\rho_i \rho_j)$$

- This leads to the following relation between unbound and total concentrations at equilibrium:

$$\rho_i = C_i / (1 + \sum_j \rho_j K_{i,j})$$

Dynamics

- Simple first-order kinetics:

$$\tau_\rho \, d\rho_i/dt = -\rho_i + C_i/(1+\sum_j \rho_j K_{i,j})$$

- **Regulation**: production and degradation of ncRNA (transcription rate depends on all the unbound concentrations)

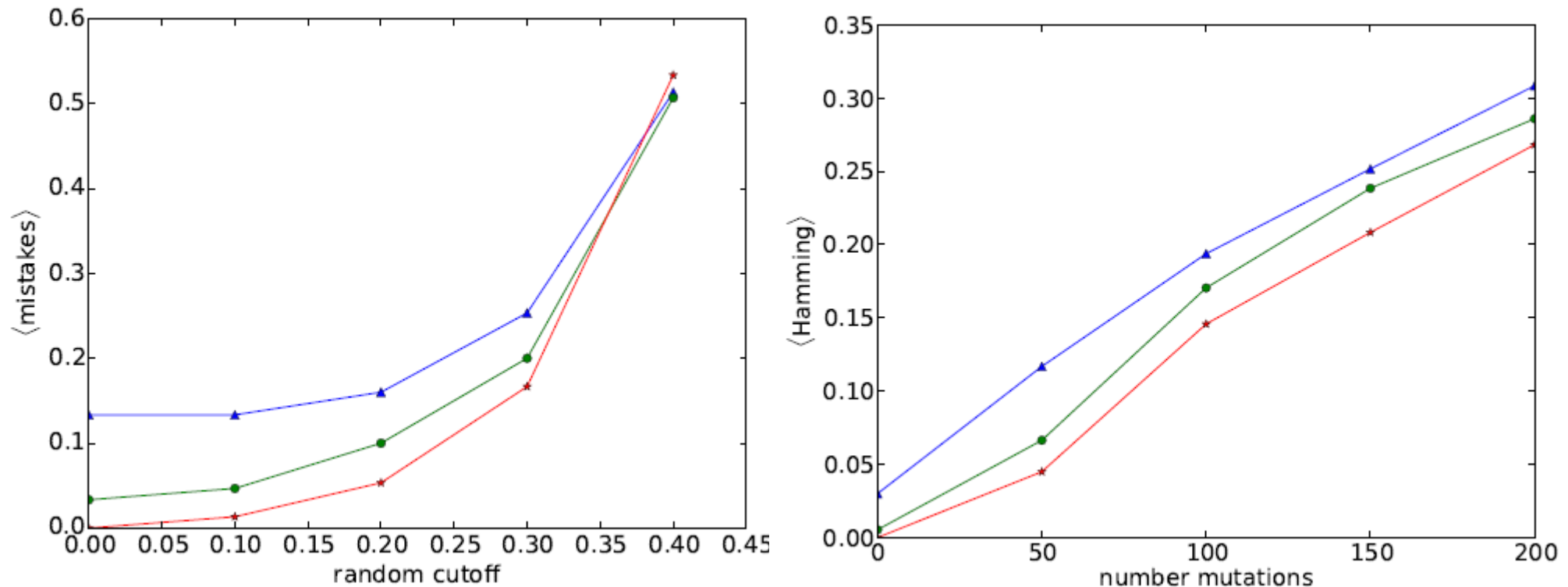
$$\tau_C \, dC_i/dt = -C_i + f(C_i, \rho_1, \dots, \rho_N)$$

- Specific form of $f()$ which leads to an associative biochemical memory:

$$f(C_i, \rho_1, \dots, \rho_N) = C_i/\rho_i \, S(4C_i/\rho_i - 2\sum_j (K_{i,j} + \rho_j) - 3N)$$

- Here $S()$ is a sigmoid function, such as a logistic or tanh

Numerical results



Patterns stored (steady-state solutions): $\{[\rho_1 \rho_2 \dots \rho_N]\}$
(corresponding to a particular setting of all $K_{i,j}$ values)
Left: initial pattern changed; Right: $K_{i,j}$ values changed

Observations/Conclusions

- The model is pretty robust to mutations in the equilibrium constants (which can be thought of as caused by mutations in the ncRNA themselves)
- Given a 'noisy' pattern with upto 20–30% altered inputs, the system tends to converge to the correct pattern
- Multiple patterns can be stored, so the network can respond appropriately to different environmental conditions
- Distributed network computation allows for robustness to mutations: so can have much higher mutation rates and hence potentially faster evolution, even though these ncRNA *are* in fact under evolutionary constraint
- Where is the learning happening? Setting of $K_{i,j}$ values by evolution: evolution as cross-generational learning? [Valiant 2009]

Observations/Conclusions

- The model presented has no intermediate representations; but what if we have a hierarchy of interactions, rather than a fully connected network?
- Neural networks with many intermediate representations or hidden layers have seen tremendous success in recent years ('deep learning'): could cells be doing something similar?
- Evolution and deep learning are currently two of the most powerful mechanisms we know for the emergence of sophisticated, adaptive, cognitive systems: could they have something in common?

“There is grandeur in this view of life, with its several powers, having been originally breathed into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved.”

References

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- Leslie G. Valiant. Evolvability. *Journal of the ACM* **56(1):3** (2009).
- Steven Pinker. *How the Mind Works*. W. W. Norton (1997).

Questions/Comments/Ideas?

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