Systems Biology Across Scales: A Personal View

I. Introduction

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What is Systems Biology ?

Wikipdeia:
"Systems Biology is the computational and mathematical modeling of complex biological systems."

"…focuses on complex interaction within biological systems, using a holistic approach"

"…to model and discover emergent properties of cells, tissues and organisms…"

"A series of operational protocols … composed of theory, analytic or computational modelling to propose specific testable hypotheses about a biological system, experimental validation, and then using the newly acquired quantitative description of cells or cell processes to refine the computational model or theory."

"Experimental techniques that most suit systems biology are those that are system-wide … transcriptomics, metabolomics, proteomics and high-throughput techniques are used to collect quantitative data for the construction and validation of models"

Sydney Brenner's Critique

Brenner in Salk Institute talk (2009):
"What is missing in all of biology is a theoretical framework"
In order to make sense of the large quantities of data that high-throughput biology is producing we need a theoretical framework

2002

Sydney Brenner
(1927-)

Brenner's program (1974):
"Behavior is the result of a complex and ill-understood set of computations performed by nervous systems and it seems essential to decompose the problem into two:

- one concerned with the question of the genetic specification of the nervous system, and,
- the other with the way nervous systems work to produce behavior."

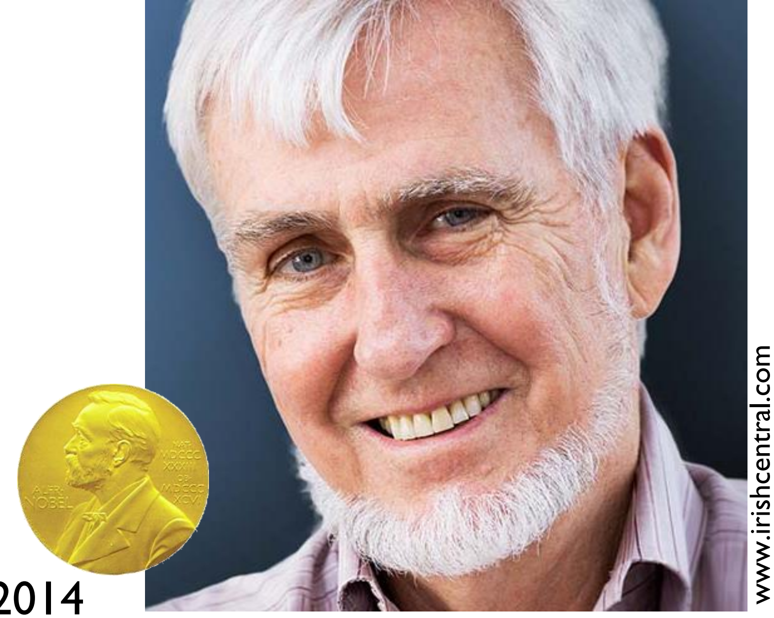
Systems biology ≡ solving inverse problems

"An inverse problem maps the data space, the observation space on to the model parameter space" (Brenner, Salk Institute lecture 2009)

Solving an inverse problem

What is the function of the hippocamus ?

Without knowing what problem the hippocampal cells are solving, can one just do single cell recordings of the activity of these cells and figure out what they are coding ?



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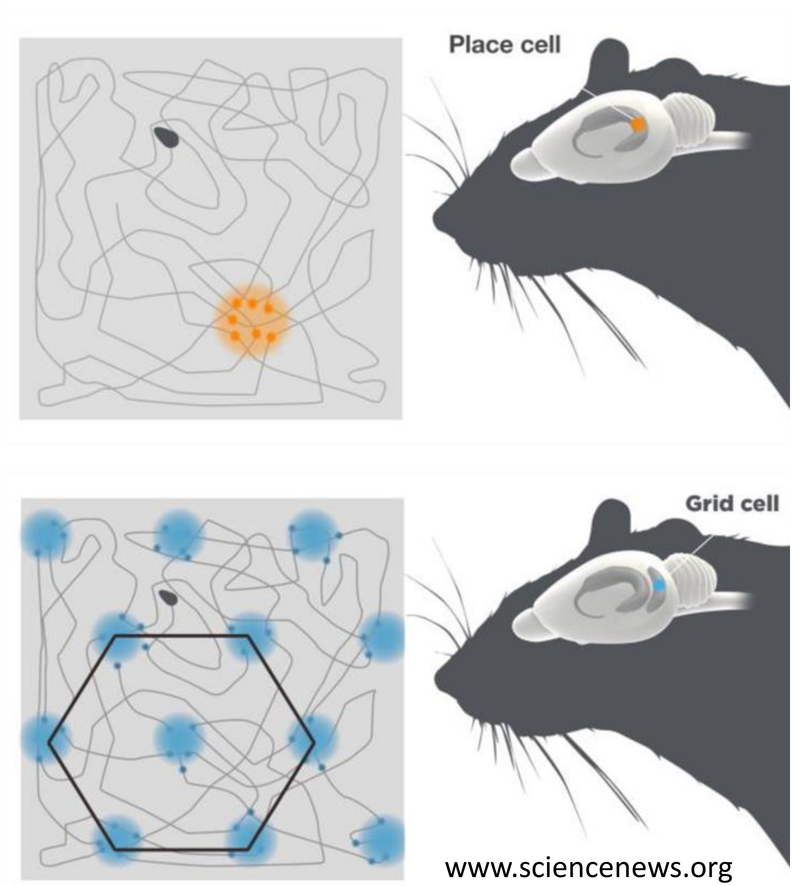
John O'Keefe (1939 -)



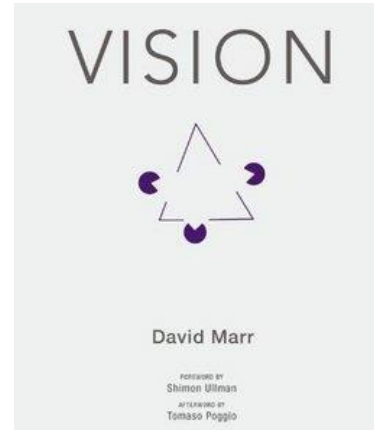
Coding for a "sense of space":

How does the brain of an organism work out where its body is located in relation to the surrounding objects (i.e., its environment) ?

John O'Keefe discovered "place cells" in the hippocampus.: different cells were activated when a rat – allowed to move freely in a bounded area – reached different locations in the environment ("place field"). Together the cells form an internal representation (map) of the external environment.

Marr’s Three Levels of Analysis

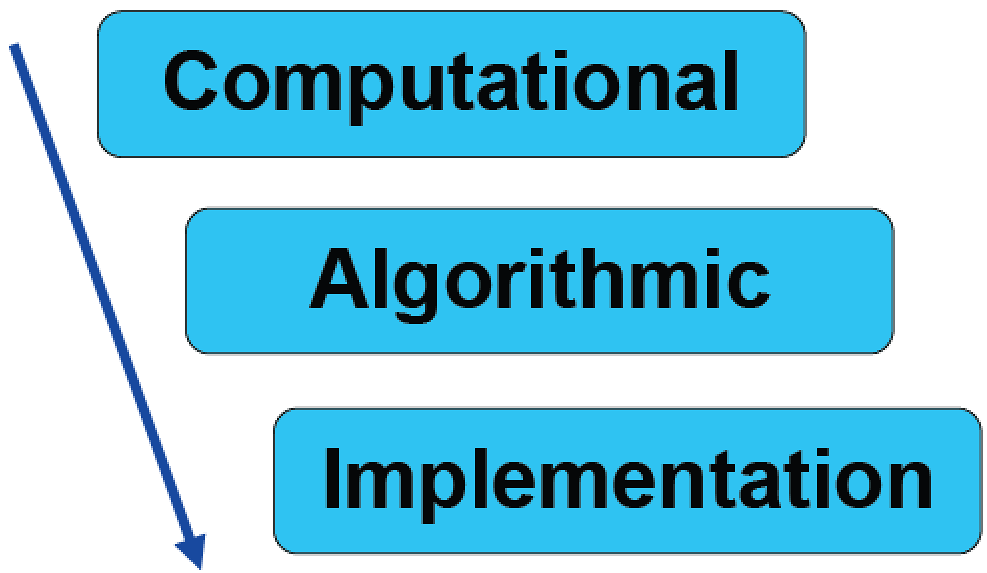
David Marr, *Vision: A Computational Investigation into the Human Representation and Processing of Visual Information* (1982)



David Marr
(1945-1980)

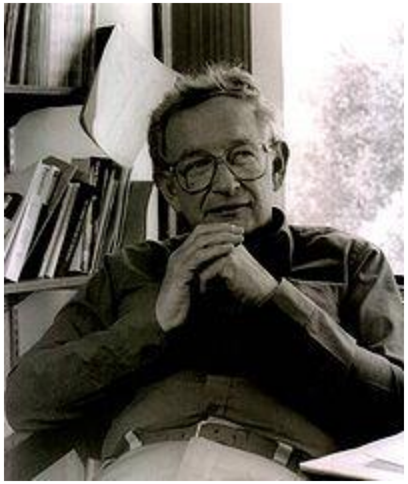
A complex system (e.g., the nervous system) can be understood at multiple levels of abstraction/generality

- **Computational level:** Defining the process being performed or computed – what the system does and why ?
- **Algorithmic level:** a representation for the input and output of the system and the procedure by which transformations are performed – how the computation is performed ?
- **Implementation level:** the physical hardware or substrate in which the algorithm is embodied – how are the representations & computations realized ?



http://blog.shakirm.com/

Emergence: "More is Different"



Philip W Anderson

P W Anderson, *Science* 1972

The elementary entities of science X obey the laws of science Y.

X	Y
solid state or many-body physics	elementary particle physics
chemistry	many-body physics
molecular biology	chemistry
cell biology	molecular biology
.	.
.	.
.	.
psychology	physiology
social sciences	psychology

But this hierarchy does not imply that science X is "just applied Y."

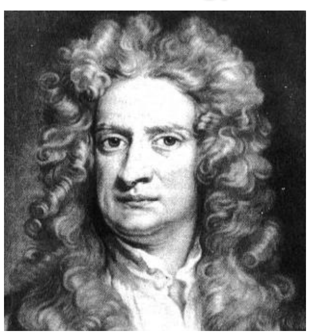
At each stage entirely new laws, concepts, and generalizations are necessary, requiring inspiration and creativity to just as great a degree as the previous one. Psychology is not applied biology, nor is biology applied chemistry.

Example: Why statistical mechanics ?

Classical Mechanics
N = 1 particle

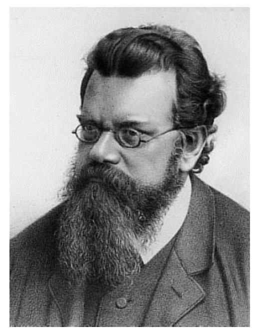
Relevant variables:
x, p

Phenomenology: Kepler’s laws



Foundation: Newton’s laws

Statistical Mechanics

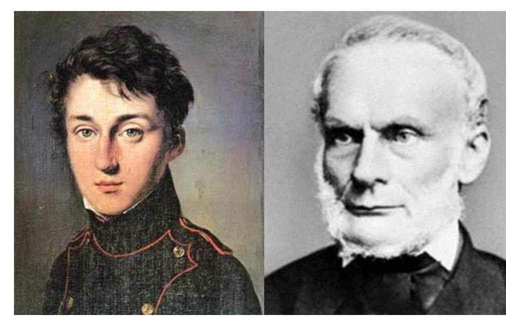


Ludwig Botzmann

Thermodynamics
N = 10^{23} particles

Relevant variables:
P,V,T

Phenomenology: Boyle’s law etc



Foundation: The laws of thermodynamics (Carnot, Clausisus)

Problem:

The components of complex biological systems are much more complicated than the simple particles of conventional statistical mechanics

Also, in general we are dealing with systems far from equilibrium

The Quest:

Are there universal organizing principles for biological phenomena & systems in different domains and scales ?

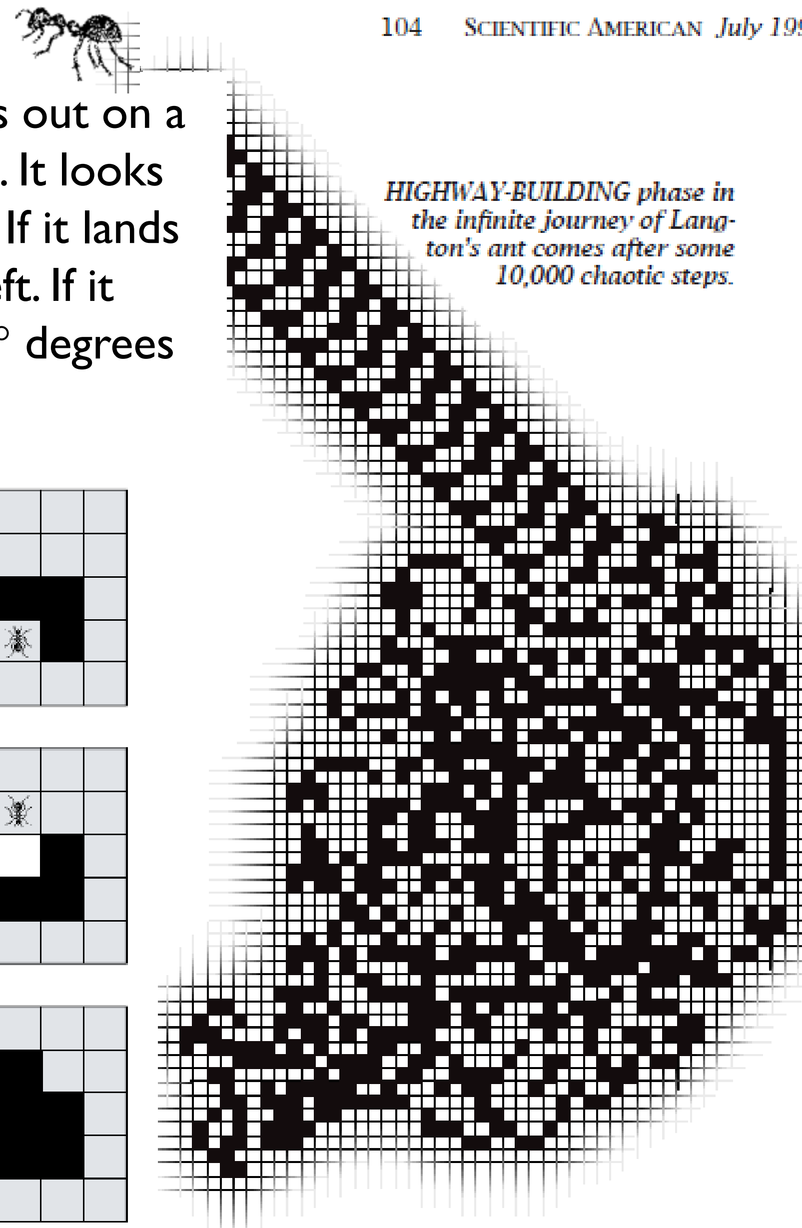
For example,

• can similar principles be at work behind the design of signaling machinery inside the cell and the design of networks of neurons in the brain ? Why networks rather than pathways ?

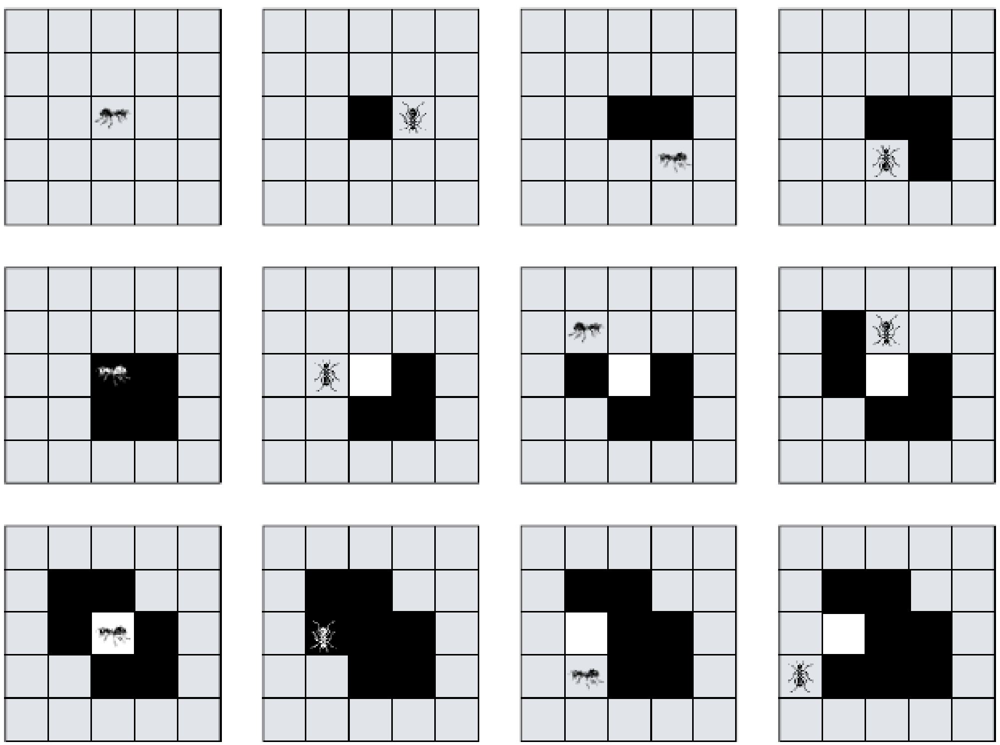
The Ultimate in Anty-Particles

104 SCIENTIFIC AMERICAN July 1994

Chris Langton's cellular automata: An "ant" starts out on a central square and moves one square in any direction . It looks at the color of the square it lands on - black or white. If it lands on a black square, it paints it white and turns 90° to left. If it lands on a white square, it paints it black and turns 90° degrees to right. It keeps on following these rules forever.



HIGHWAY-BUILDING phase in the infinite journey of Langton's ant comes after some 10,000 chaotic steps.



FIRST 12 STEPS followed by Langton's ant are indicated. (For clarity, squares not yet visited are shown as gray: these should be treated as white when applying the rules.)

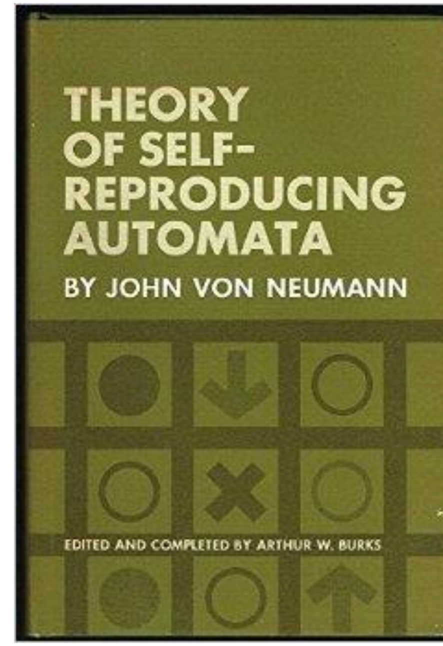
Example of emergence in agent-based systems

The concept of cellular automata was pioneered by

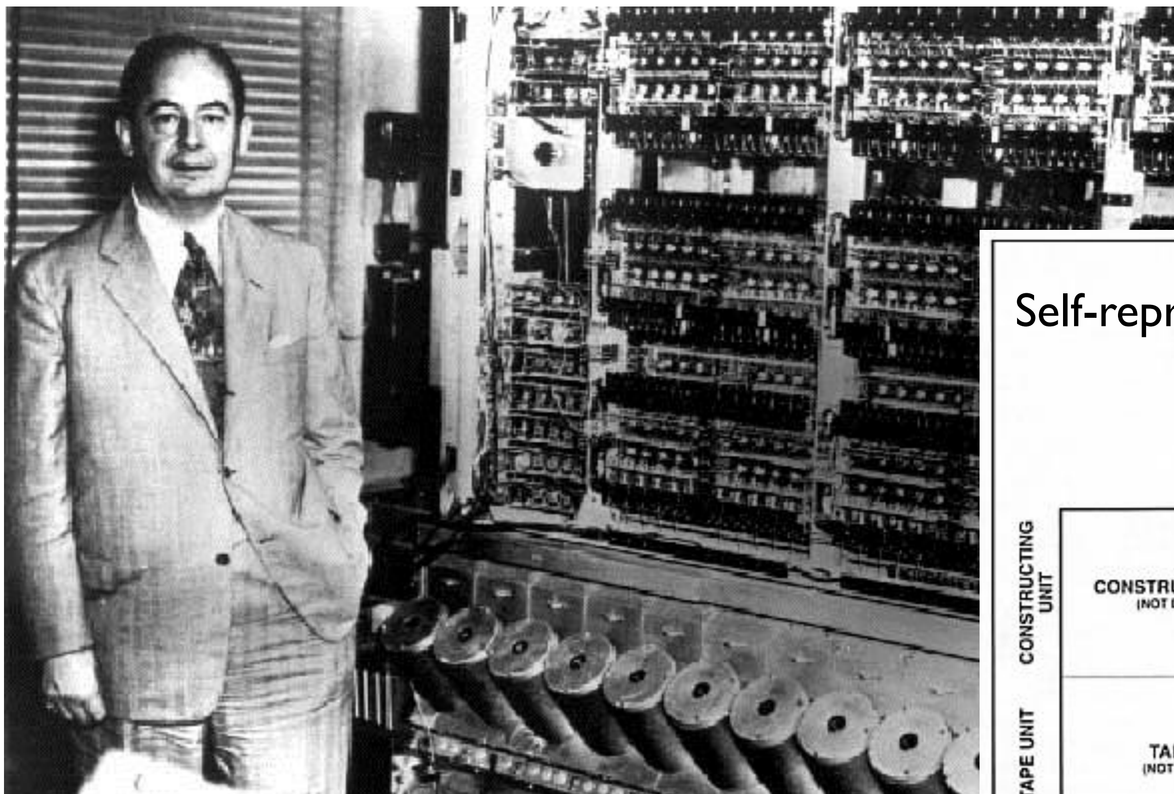
John von Neuman (1903-1957)

while proposing the “universal constructor”, a self-replicating machine that could in principle be “programmed” (through a tape on which a specific program is written that was read by the machine)

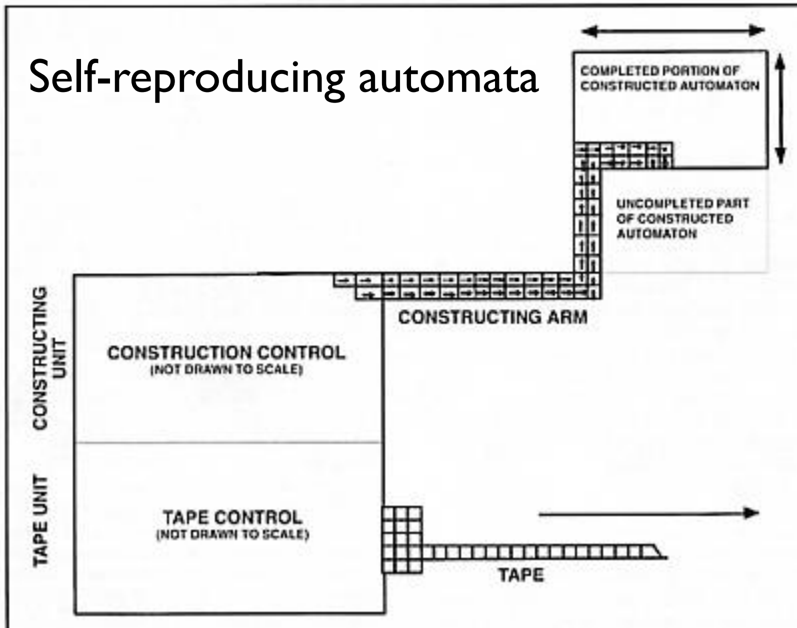
Von Neumann specified such a machine using 29 states



1966



Self-reproducing automata



A crucible of complexity: The Game of Life

A cellular automata defined on a 2-D square lattice with each cell having 8 nearest neighbors – invented by Conway in 1970

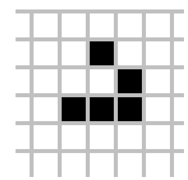
The "Theory of Everything" of Life

- **Any live cell with < 2 live neighbours dies ("out of loneliness").**
- **Any live cell with 2 or 3 live neighbours lives on to the next generation.**
- **Any live cell with > 3 live neighbours dies ("due to overcrowding").**
- **Any dead cell with exactly 3 live neighbours comes alive ("reproduction").**

These simple rules can give rise to unexpectedly rich patterns, such as, the "glider" and the "glider gun" which creates a "glider" every few iterations.

In fact, Conway has created AND, OR and NOT logic gates in Life and it has been shown to have same computational power as a **universal Turing machine**.

John H Conway (1937-)



Glider

Image:wikipedia

Glider Gun

Image:wikipedia