SimSoup

Molecules Designed for Chemical Network Memory and Non-Genetic Inheritance

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Background, Motivation and Objectives

Background, Motivation and Objectives

Inheritance at the Origin of Life

- Contemporary organisms and viruses use DNA or RNA template molecules for inheritance
- These molecules are too complex to be plausible in the pre-biotic world. So how did evolution get started?
- Some Origin of Life theories envisage *metabolism based inheritance* in which proto-organisms without template molecules reproduced by growth and division
- Variations in metabolism would have led to differences in fitness that would drive evolution
- Successful variations in metabolism would have to be ‘remembered’ and inherited
- Questions:
  - Can a metabolic network provide the memory needed to ‘remember’ new solutions to the problem of ‘how to survive and reproduce’
  - *How many variations are possible?* Will there be sufficient diversity to enable evolution to ‘get a foothold’?

Background, Motivation and Objectives

Biological and Chemical Computing

- A key challenge for the newer field of biological and chemical computing is the development of memory systems using components that can be readily constructed
- Such systems may be used for various purposes, including an inheritance mechanism for artificial evolution
- The simple memory mechanism being investigated here is relevant to this

Background, Motivation and Objectives

Conceptual Background

- Metabolism based Origin of Life theories including those of Aleksandr Oparin, Stuart Kauffman, Freeman Dyson, and the Lipid World theory and GARD model of Doron Lancet's group
- Günter Wächtershäuser's chemo-autotrophic Iron-Sulphur World
- Walter Fontana's Algorithmic Chemistry
- Graham Cairns-Smith's clay crystal and genetic takeover theory
- Tibor Gánti's principles of life and chemoton theory
- Network theory, particularly the work of Sanjay Jain and Sandeep Krishna
- The Chemical Organisation Theory of Peter Dittrich and Pietro Speroni di Fenizio
- Nathaniel Virgo's 'Spots' model
- Linus Pauling's chemical bond theory

Background, Motivation and Objectives

Objectives for this Work

- Proof of principle to show that a metabolic inheritance (memory) mechanism can support ‘substantial’ variability
- Make the system *switchable*:
  - Previous work had shown a non-switchable memory system
  - This may limit ability to adapt to a changing environment
  - Switchability is also required for IT uses

SimSoup Model

Molecular Structure

- *Molecules* are two dimensional rigid structures built from *Atoms* bonded together such that they occupy fixed positions on a square 'board'
- Each square contains at most one Atom
- Each Atom Type has a defined maximum number of bonds
- Bond angles are always either 90° or 180°, and bond lengths are all equal
- Bonding is broadly consistent with valence theory
- Bond strengths are usually fixed according to the Atom Types, but some are *Perturbable*; they can be weakened or strengthened by other nearby Atoms

Molecular Interactions

- Molecules can Join or Split to form Molecules of different types
  - A join (eg $A + B \rightarrow C$), is a *Construction Interaction*
  - A split (eg $D \rightarrow E + F$) is called a *Fission Interaction*
- Join/Split rules are analogous real chemistry, but simpler:
  - Joining: According to valence rules. Maximize total bond energy. Atoms cannot overlap
  - Split: Break bonds with least total energy
- This allows open-ended exploration of chemical space. New Molecule Types and Interaction Types are *discovered* as the simulation runs

Interaction Kinetics

- Constructions and Fissions occur in a well-stirred *Reactor*
- Interaction Rates
  - Bimolecular Interaction Types: Rate $= k[R1][R2]$
  - Unimolecular Interaction Types: Rate $= k[R1]$
- Rate constants are thermodynamically realistic, using the Arrenhius equation $k = Ae^{-\frac{E_a}{RT}}$
  - E_a is the activation energy for an Interaction
  - T is temperature
  - R is the gas constant
  - A and E_a are known as the Arrenhius Parameters

The SimSoup Guide

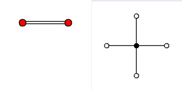
- For full documentation of SimSoup (Conceptual Model, Logical Model, and User Manual) see the SimSoup Guide at: http://www.simsoup.info/Publications.html

Scenario Setup for the Example

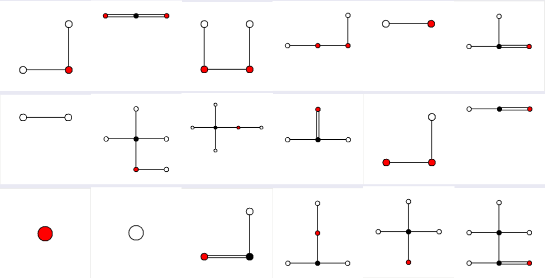
- Define Atom Types (elements) for Carbon, Oxygen and Hydrogen
- Define Bond Strengths as for ‘real’ chemistry
- Add 20000 Molecules of molecular Oxygen (O2) to the Reactor
- Add 10000 Molecules of Methane (CH4) to the Reactor
- Add nothing else, but give names to some Molecule Types that may appear
- Limit the mass of Molecule Types that can be created to 44.1 to avoid combinatorial ‘explosion’

SimSoup Model
Methane Combustion Example

Input Molecules

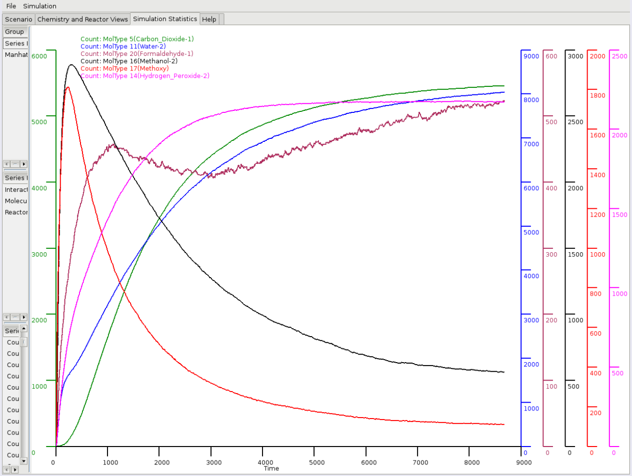


Examples of Molecule and Interaction Types Produced



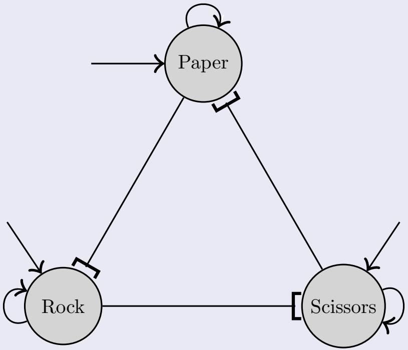
By time 8601, over 250 Molecule Types had been discovered.

Molecule Count Time Series Plots



Memory Unit

Concept: Rock-Paper-Scissors



- A memory unit has three possible active states; ‘Rock’, ‘Paper’ and ‘Scissors’
- ‘Loopback’ arrows indicate autocatalytic feedback
- Straight arrows indicate external activating stimuli
- Lines terminated with ‘[’ signify that activity for one state inhibits another
- Switching occurs when an external stimulus activates a new state, and simultaneously inhibits the old state
- Multiple units can co-exist in the same physical environment

Physical Chemistry: Atom Types

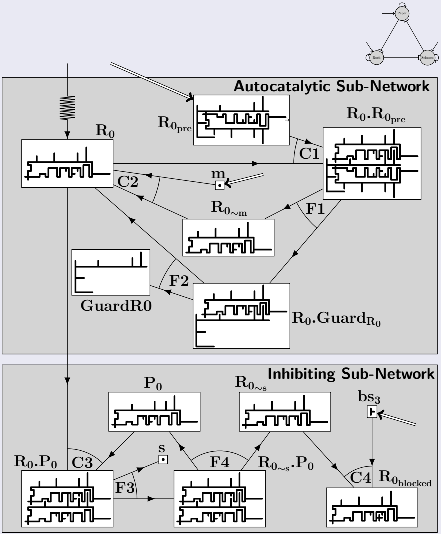
Name/Symbol	Bonds	Usage / Capability
Assemblite ●	2	Used to build framework of molecular structures
Blockite (b)	4	Used to build bs_3 'Blocker'
Hookite (h)	4	Used to provide a 'hook' bonding site
Junctium (j)	3	Used to provide a 3 way junction in a structure
Loosium-1 (w)	2	Provides a weak (loose) bonding site for Loosium-2
Loosium-2 (x)	2	Provides a weak (loose) bonding site for Loosium-1
Metal (m)	1	Can perturb nearby Perturbium bonds, even though not bonded to Perturbium
Perturbium (p)	3	Produces bonds that can be weakened or strengthened by nearby Metal atoms
Stoppite (s)	1	Stops further growth of the Molecule at a site

Physical Chemistry: Bond Types

	a	h	j	b	m	p	s	w	x
a	x								
h	x								
j	x	x	x						
b									
m	x	x	x						
p	x	p	x	x					
s	x	x	x	x		p	x		
w	x		x						
x	x		x					w	

- Blank: Atoms of these types do not bond
- x: Atoms bond with Enthalpy (strength) 100
- w: Atoms bond weakly, with Enthalpy 10
- p: Perturbable Bond

Maintenance and Inhibition of Rock State of Memory Unit 0



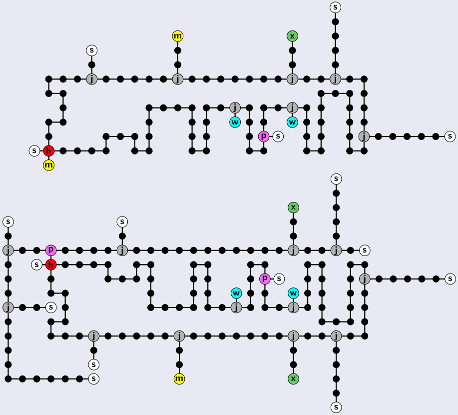
- $R_{0_{pre}}$, m and bs_3 are 'food'
- The $Rock_0$ Autocatalytic Sub-Network is activated by a short stimulus of R_0, which enables Construction C1
- After F1, F2 and C2, an excess of R_0 is produced. The process is self maintaining. Overall reaction:

$$R_{0_{pre}} + m \xrightarrow{R_0} R_0 + Guard_{R_0}$$

- A later stimulus of P_0 activates the $Paper_0$ Autocatalytic Sub-Network (not shown here)
- C3 is enabled, producing $R_0.P_0$ in the Inhibiting Sub-Network
- Subsequent Interactions F3, F4 and C4 disable R_0 by converting it to $R_{0_{blocked}}$. This 'kills' the $Rock_0$ Autocatalytic Sub-Network
- Overall reaction for Inhibiting Sub-Network is:

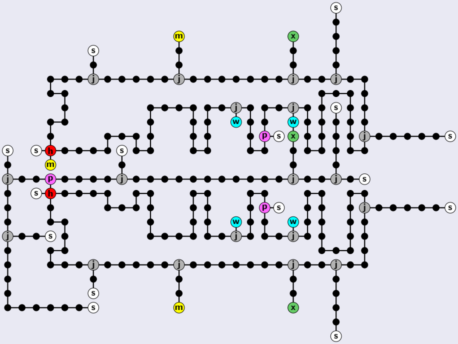
$$R_0 + bs_3 \xrightarrow{P_0} R_{0_{blocked}} + s$$

R_0 and $R_{0_{pre}}$: The Rock$_0$ Core Molecule Type and its Precursor



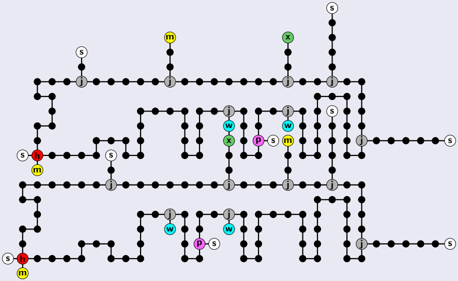
- R_0 (above) has three central recesses
- These are key to the operation of the 'Rock-Paper-Scissors' mechanism
- $R_{0_{pre}}$ (below) comprises $R_{0_{\sim m}}$ with a 'guard' that protects the recesses
- R_0 and $R_{0_{pre}}$ can join by forming a w-x (Loosium-1 / Loosium-2) bond

$R_0.R_{0_{pre}}$: The $Rock_0$ Precursor Splitter Complex



- The yellow metal (m) Atom on the left is close to the perturbable p-h Bond
- Bond is weakened and breaks, releasing $R_{0_{\sim m}}$
- $R_{0_{\sim m}}$ soon encounters a Metal (m) Atom, producing a new R_0 Molecule
- The loose w-x Bond also breaks, releasing the original R_0 Molecule
- Summary: An R_0 has split an $R_{0_{pre}}$ to release another R_0

$R_0.P_0$: Core-Core Complex for the $Rock_0$ Inhibiting Sub-Network

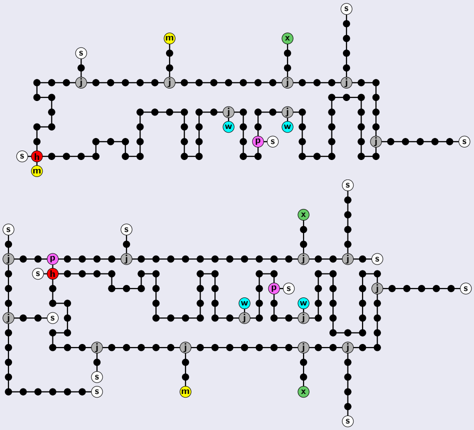


- P_0 (below) bonds with R_0 by forming a loose w-x Bond in the central recess of R_0
- A Metal (m) Atom is placed close to the perturbable p-s Bond in R_0. The Bond is weakened and breaks
- This leaves a bonding site that will soon be occupied by a bs_3 'Blocker'
- Summary: A P_0 has converted an R_0 to a 'blocked' form that cannot split $R_{0_{pre}}$

Memory Unit

Avoiding Interference Between Memory Units

Variations in Molecular Structure Prevent Interference Between Co-Existing Memory Units

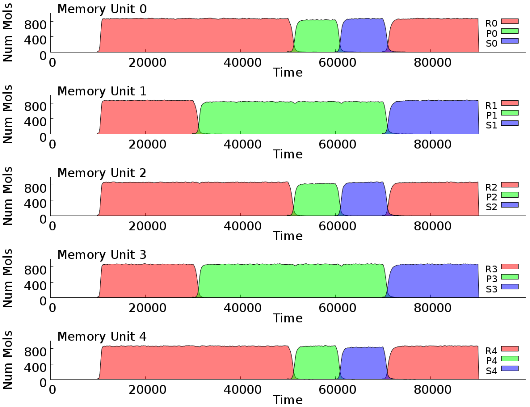


- R_1 above, $R_{0_{pre}}$ below
- If these two Molecules joined, an ‘incorrect’ Precursor Splitter complex would be formed. Memory units 0 and 1 would interfere
- Joining is prevented due to variations in structure

Memory System Operation

Memory System Operation

Operation of a 5 Unit Memory System

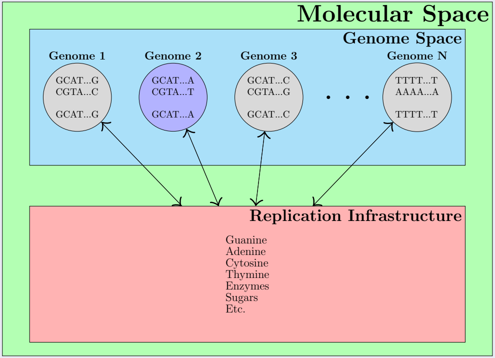


- A system of five co-existing memory units is switched between different states
- Stimuli for P1 and P3 at time 30000 switch the system to state R0P1R2P3R4
- Other stimuli cause subsequent switches at times 50000, 60000 and 70000
- Note: These are ‘stop press’ results based on modified versions of the Molecule Types shown in earlier slides

Taking Stock

A Short Review of Network Architectures for Chemical Memory

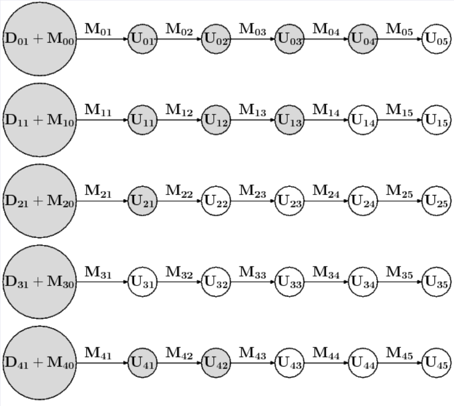
DNA: A Genome is a Single Autocatalytic Unit



- Circles represent autocatalytic units
- Each autocatalytic unit has single strand and double strand DNA. Ie the unit has two Molecule Types, each of which can be produced from the other
- Each organism has a genome consisting of single autocatalytic unit (‘Genome 2’ in the example)
- (Example is for single chomosome organisms - Eg prokaryotes)

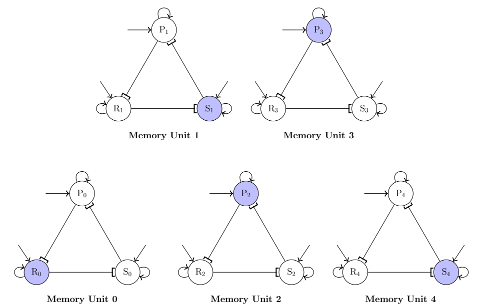
Network Architectures for Chemical Memory

SimSoup - 1: Parallel series of Autocatalytic Units



- Figure is from ECAL 2011 paper (based on diagram from Life and Mind presentation in June 2010)
- Five ‘rows’ of five autocatalyic units (small circles) connected in series
- Large circles are ‘food’
- Each row can have between one and five active units
- Output of one unit is required as a prerequisite for activation of the next unit
- Shaded units are active. Figure shows ‘genome’ 43102
- Each row can be in 6 alternative states
- Network as a whole can have 6^5 = 7776 different states
- Drawback: Memory units are not switchable

SimSoup - 2: Independent Groups of Autocatalytic Units



- A 'genome' is defined by the state of multiple independent switcable memory units
- Each memory unit has three autocatalytic (sub) units
- Each memory unit has only one active autocatalytic (sub) unit (except during switching)
- Figure shows 'genome' $R_0 S_1 P_2 P_3 S_4$

Multiple Autocatalytic Cores

Figure omitted from the Web version of this presentation for copyright reasons.

The paper is available at:
http://www.biologydirect.com/content/pdf/1745-6150-7-1.pdf
Refer to Figure 2 in the paper.

- Figure is from 'Evolution Without Genes': Vasas, Fernando, Santos, Kauffman and Szathmáry, 2012
- There are two separate autocatalytic 'cores'
- The first consists of two loops: A $\rightarrow$ A and A $\rightarrow$ B $\rightarrow$ A
- The second consists of the two loops C $\rightarrow$ C and C $\rightarrow$ D $\rightarrow$ E $\rightarrow$ C
- Each of these two cores is a (non-switchable) autocatalytic memory unit
- The paper concludes that autocatalytic cores can be seen as (one bit) units of evolution

SimSoup

Conclusions

- Results suggest that chemical memory is possible. A five unit switchable system with 243 alternative states has been designed and simulated
- The design supports systems with more units. A ten unit system would have $3^{10} = 59049$ states
- The system is simpler than RNA/DNA based systems (complexity measure: number of slides needed to describe)
- It is nonetheless highly non-random and modularised
- The following questions can be asked:
  - What network and molecular architectures would be prebiotically plausible and also lead to substantial variability?
  - Can low specificity molecules support substantial variability?

Questions?