The Brave New World of Synthetic Biology

+ a few MSc-level projects

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A real-life Mighty Mouse: Rodent with double the normal muscle strength created in lab

By TAMARA COHEN

Last updated at 2:02 AM on 11th November 2011

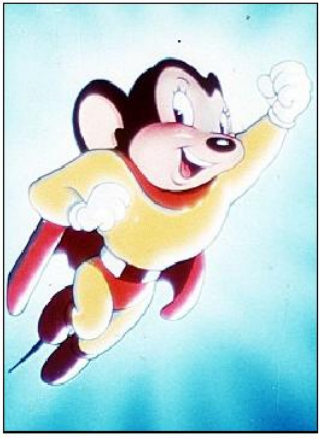
A 'mighty mouse' with double the normal muscle strength has been created by scientists looking for ways to treat age-related diseases.

It not only has bigger muscles but, in tests, could run for twice as long on the treadmill.

Swiss scientists created the 'super strong marathon mice' by tweaking a gene and found without it the rodents' muscles bulked up and they had more energy.

If the effects could be replicated in humans, they believe it could lead to therapies against muscle-wasting in the elderly which can lead to falls and broken bones, as well as incurable diseases such as muscular dystrophy.

However, there are also ethical concerns that such therapies could be used to give athletes an unfair advantage.



Swiss scientists created the 'super strong mice' by tweaking a gene and found without it the rodents' muscles bulked up and they had more energy

Researchers at the Ecole Polytechnique Federale in Lausanne found that a tiny inhibitor – called NCoR1 – may be responsible for how strong and powerful our muscles are.

Move towards Synthetic Biology

- genetic engineering on steroids
- building programs from genetic parts
- funding agencies like this term
- brings together sciences + ELS Issues

The BioBricks project

BioBrick standard biological parts are DNA sequences of defined structure and function;

they share a common interface and are designed to be composed and incorporated into living cells such as E. coli to construct new biological systems.

One of the goals of the BioBricks project is to provide a workable approach to nanotechnology employing biological organisms. Another, more long-term goal is to produce a synthetic living organism from standard parts that are completely understood.

from Wikipedia

Registry of Standard Biological Parts

Catalog

< Back to Registry

- **Browse parts by type • devices by type**
- **Browse parts and devices by function • by chassis • by standard • or by contributor**
- **Browse chassis**
- **Browse user-supplied catalog pages** - these pages have not undergone curation by the Registry but have been made by the Registry user community. Please feel free to add new catalog pages to this section.

Browse parts by type

Catalog	List	
	(http://partsregistry.org/cgi/partsdb/pgroup.cgi?pgroup=Regulatory)	**Promoters (?)**: A promoter is a DNA sequence that tends to recruit transcriptional machinery and lead to transcription of the downstream DNA sequence.
	(http://partsregistry.org/cgi/partsdb/pgroup.cgi?pgroup=RBS)	**Ribosome Binding Sites (?)**: A ribosome binding site (RBS) is an RNA sequence found in mRNA to which ribosomes can bind and initiate translation.
	(http://partsregistry.org/cgi/partsdb/pgroup.cgi?pgroup=Tag)	**Protein domains (?)**: Protein domains are portions of proteins cloned in frame with other proteins domains to make up a protein coding sequence. Some protein domains might change the protein's location, alter its degradation rate, target the protein for cleavage, or enable it to be readily purified.
	(http://partsregistry.org/cgi/partsdb/pgroup.cgi?pgroup=Coding)	**Protein coding sequences (?)**: Protein coding sequences encode the amino acid sequence of a particular protein. Note that some protein coding sequences only encode a protein domain or half a protein. Others encode a full-length protein from start codon to stop codon. Coding sequences for gene expression reporters such as LacZ and GFP are also included here.
		Translational units (?): Translational units are composed of a ribosome binding site and a protein coding sequence. They begin at the site of translational initiation, the RBS, and end at the site of translational termination, the stop codon.
	(http://partsregistry.org/cgi/partsdb/pgroup.cgi?pgroup=terminator)	**Terminators (?)**: A terminator is an RNA sequence that usually occurs at the end of a gene or operon mRNA and causes transcription to stop.

Browse parts and devices by function

*This section replaces the previous **Featured parts** pages.*


Biosynthesis: Parts involved in the production or degradation of chemicals and metabolites are listed here.


Cell-cell signaling and quorum sensing: Parts involved in intercellular signaling and quorum sensing between bacteria.


Cell death: Parts involved in killing cells.


Coliroid: Parts involved in taking a bacterial photograph.


Conjugation: Parts involved in DNA conjugation between bacteria.


Motility and chemotaxis: Parts involved in motility or chemotaxis of cells.


Odor production and sensing: Parts the produce or sense odorants.


DNA recombination: Parts involved in DNA recombination.


Viral vectors: Parts involved in the production and modification of Viral vectors.

Browse parts and devices by chassis

Unless otherwise specified, most parts in the Registry work in Escherichia coli.

Catalog	List	
		**Escherichia coli (?)**: Most parts in the Registry function in *E. coli*.
	 (http://partsregistry.org/cgi/partsdb/pgroup.cgi?pgroup=Yeast)	**Yeast (?)**: Yeast are simple eukaryotes.
	 (http://partsregistry.org/cgi/partsdb/pgroup.cgi?pgroup=T7)	**Bacteriophage T7 (?)**: Bacteriophage T7 is an obligate lytic phage of *E. coli*.
		**Bacillus subtilis (?)**: Bacillus subtilis is a model gram-positive bacterium.
		**MammoBlocks (?)**: MammoBlocks are a new category of BioBrick introduced by the MIT iGEM team in 2010 and continued in 2011. There are now dozens of MammoBlocks suitable for rapid expression in mammalian cells.

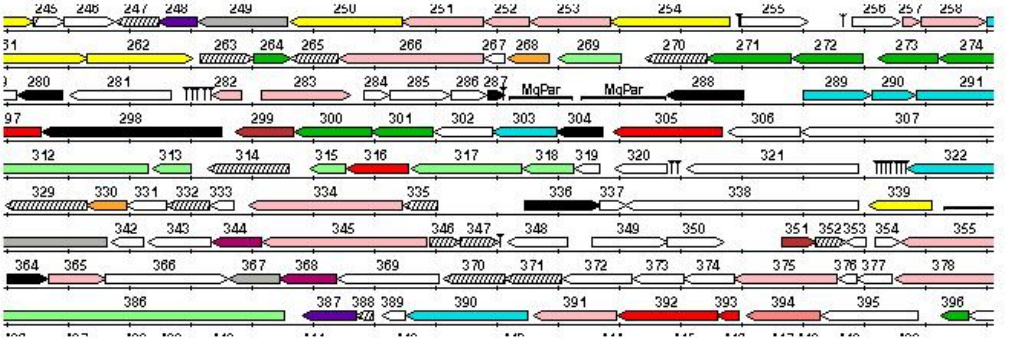
Browse parts and devices by standard

Unless otherwise specified, most parts in the Registry comply with the original BioBrick assembly standard (also known as Assembly standard 10).

WIRED SCIENCE
NEWS FOR YOUR NEURONS

From Artificial Genome to Artificial Life: Hold Your (Synthetic) Horses

By Brandon Keim | January 24, 2008 | 12:51 pm | Categories: Biotech



The creation of an entirely artificial genome by J. Craig Venter Institute researchers has set the science world abuzz, and with good reason: it's a landmark step on the road to synthetic organisms that could someday produce everything from clean fuel to better medicines.

But scientists caution that the step, though large, is still just a beginning. Much more remains to be learned before the first artificial organisms are up and running, much less running our cars.

Venter, best-known for his work with the Human Genome Project but just as pioneering in the world of synthetic biology, is quite open about this. "We have this complete synthetic chromosome that's been sequenced and validated. Next we want to boot that up in a cell. There are multiple barriers for this. It's not just a slam dunk, or we'd announce it today," he said.

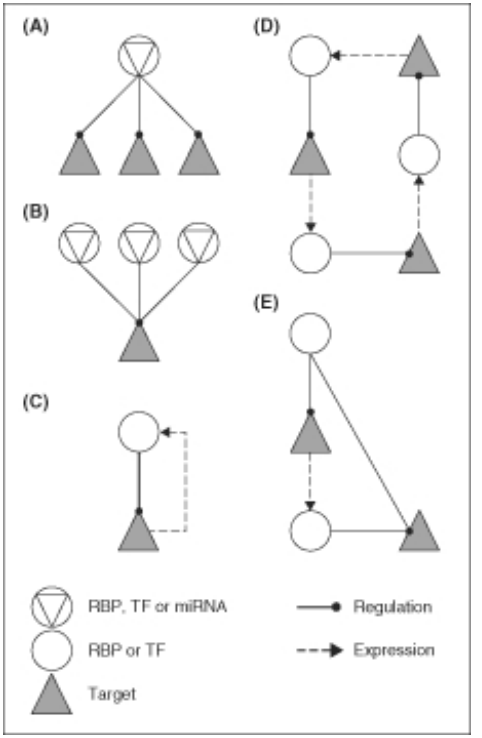
Computational Challenges

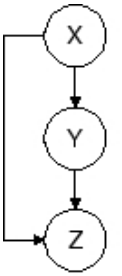
While it is possible to specify a DNA sequence and have it produced, it is much more difficult to make sure the circuit will work.

Suppose we design gene G to produce a protein P:

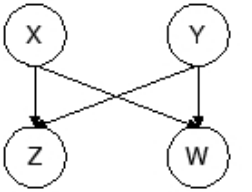
- How can we ensure gene G will be "taken" into a cell?
- How can we ensure gene G will be activated?
- How can we ensure other genes will not inactivate gene G?
- How can we ensure protein P is actually produced?
- How can we ensure the cell survives long enough?

Representing Genetic Circuits

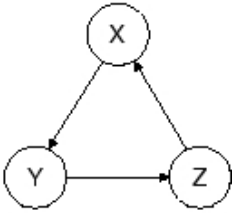




Feed-forward loop



Bi-fan

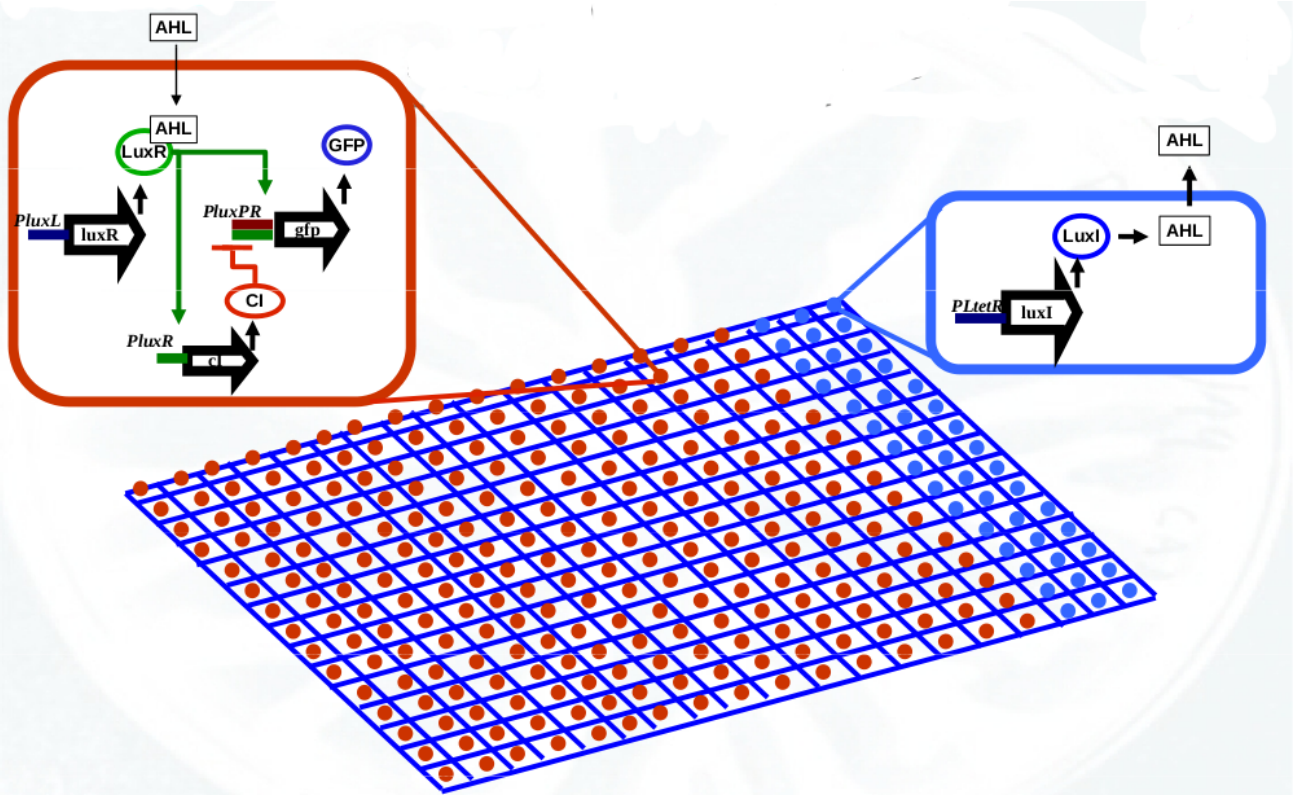


Three-node feedback loop

(but now imagine hundreds or even thousands of nodes . . .)

Simulating Cells and Circuits

We may need to look at interaction between populations:



The Infobiotics Workbench

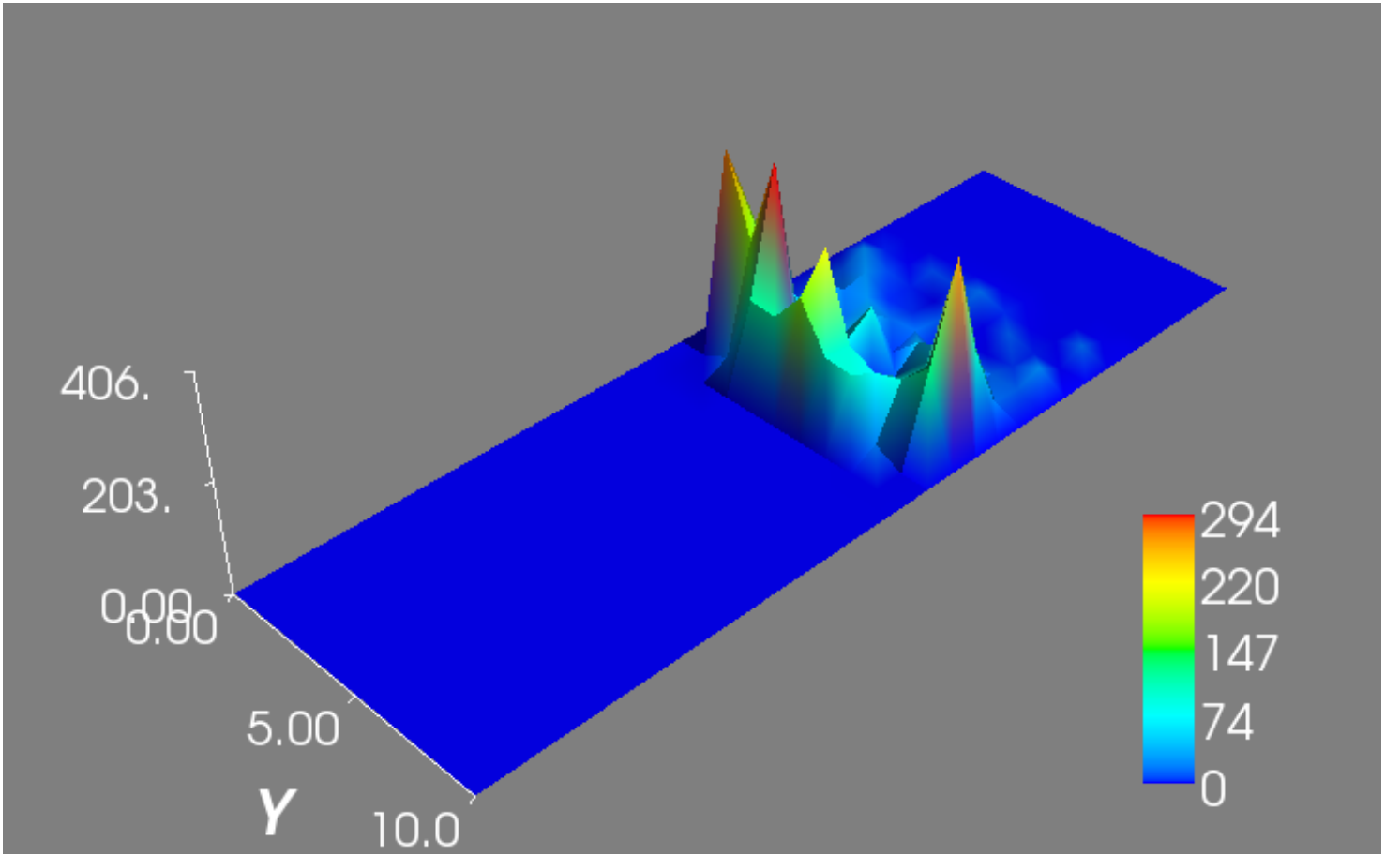
Formalising genes and interactions:

```
PluxPR({X},{c_1,c_2,c_3,c_4,c_5,c_6,c_7,c_8,c_9},{l}) =
   {
      # This module represents a promoter #
      type: promoter

      # DNA sequence corresponding to biobrick BBa_I1051 from the Registry of S
      sequence: ACCTGTAGGATCGTACAGGTTTACGCAAGAAAATGGTTTGTTATAGTCGAATACCTCTGGCGG

 rules:
    r1: [ LuxR2 + PluxPR_geneX ]_l -c_1-> [ PluxPR_LuxR2_geneX ]_l
    r2: [ PluxPR_LuxR2_geneX ]_l -c_2-> [ LuxR2 + PluxPR_geneX ]_l
    r3: [ LuxR2 + PluxPR_CI2_geneX ]_l -c_3-> [ PluxPR_LuxR2_CI2_geneX ]_l
    r4: [ PluxPR_LuxR2_CI2_geneX ]_l -c_4-> [ LuxR2 + PluxPR_CI2_geneX ]_l
    r5: [ CI2 + PluxPR_geneX ]_l -c_5-> [ PluxPR_CI2_geneX ]_l
    r6: [ PluxPR_CI2_geneX ]_l -c_6-> [ CI2 + PluxPR_geneX ]_l
    r7: [ CI2 + PluxPR_LuxR2_geneX ]_l -c_7-> [ PluxPR_LuxR2_CI2_geneX ]_l
    r8: [ PluxPR_LuxR2_CI2_geneX ]_l -c_8-> [ CI2 + PluxPR_LuxR2_geneX ]_l
    r9: [ PluxPR_LuxR2_geneX ]_l -c_9-> [ PluxPR_LuxR2_geneX + rnaX_RNAP ]_l
   }
```

A model like the above can be simulated:



The ROADBLOCK Project

Funded by EPSRC, starting in February:

> "This project will investigate synthetic biology routes for creating artificial coatings and skins, based on modified bacteria, that could act as a bio-programmable shield against infection.
>
> We anticipate that, as a result of this project, an integrated software suit (i.e. an in silico workbench for synthetic biology) that permits for rapid model prototyping and specification, simulation, verification, analysis, and optimisation, as well as ROADBLOCK parts, devices, systems and, ultimately, strains will be made available."

Modelling the Morphology of Platelet Aggregation

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Abstract

Platelet aggregation is an important tool for maintaining the integrity of blood vessels after damage, but it is also associated with many health risks, such as strokes and myocardial infarctions. It is thus important to understand and characterize the process of aggregation, and relate the bio-molecular processes within each platelet to the behaviour between the thousands of platelets that normally take part in the process. There are difficulties in studying the natural system, due to the need to capture the continuous flow of blood in a vessel, so a computational model can be very useful. In this research we explore the macro-level interactions within blood vessels through simulations that are built on the well-known concepts of diffusion-limited aggregation and Eden growth models.

Keywords: Simulation; Platelet; Blood; Diffusion Limited Aggregation; Eden Model

1. Introduction

Animal physiology relies on the maintenance of blood circulation throughout the body at all times, and many organisms have specialized circulatory systems for this purpose. Humans and other vertebrates have a closed circulatory system, which means under normal circumstances, blood stays inside the blood vessels at all times. However, when blood vessels are damaged, blood can escape into the interstitial tissues or even outside the body. Loss of blood is technically known as hemorrhage and it might have serious and even fatal consequences if a large amount of blood tissue is lost. Naturally, organisms have developed mechanisms to reduce and stop blood loss.

Hemostasis is a vital mechanism in animals, which acts to stop bleeding, repair damaged blood vessels and maintain a healthy circulatory system. The first response of the body to a ruptured or damaged blood vessel is the constriction of blood vessels near the damaged area to reduce blood flow and thus blood loss. The next action involves generation of a temporary plug formed by platelets to block the hole on the interior surface of the blood vessel. Platelets are small blood cells (or more precisely cell fragments) that are normally in an inactive state. However, when they come into contact with the damaged layer of cells on the interior wall of a vessel (called the *endothelium*) they become activated, change shape and adhere to the surface of the vessel. They then release chemicals that promote the activation and adhesion of other platelets. As more platelets are activated, they become part of an aggregate that grows continuously until the whole damaged endothelium is covered. The platelet aggregate seals the hole on the wall of the blood vessel until new endothelial tissue is generated and the blood vessel is repaired. The process is illustrated in Figure 1, though in reality an aggregate consists of thousands of platelets.

Platelet activation, adhesion and aggregation are complex phenomena, which are influenced by many different chemicals and physical characteristics of the blood, blood cells and blood vessels. Many different biochemical substances and body cells play a part during the process and it is affected by physical properties of the blood and the blood vessel. It is a process still not fully

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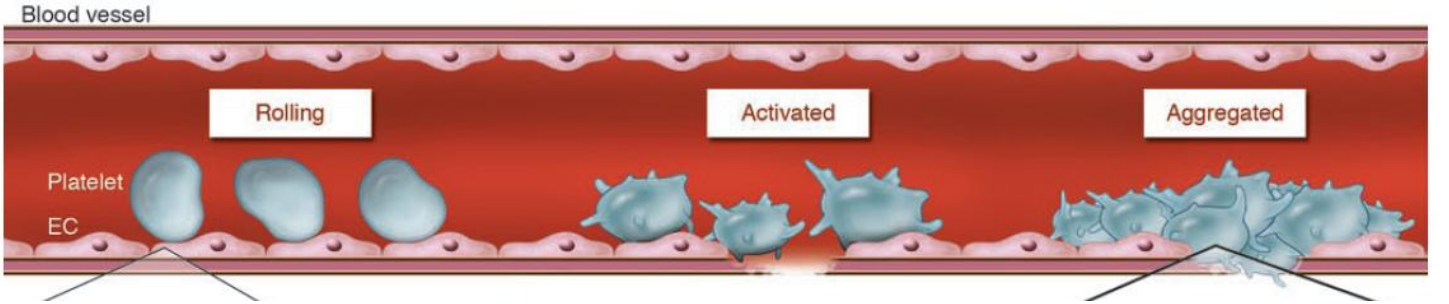
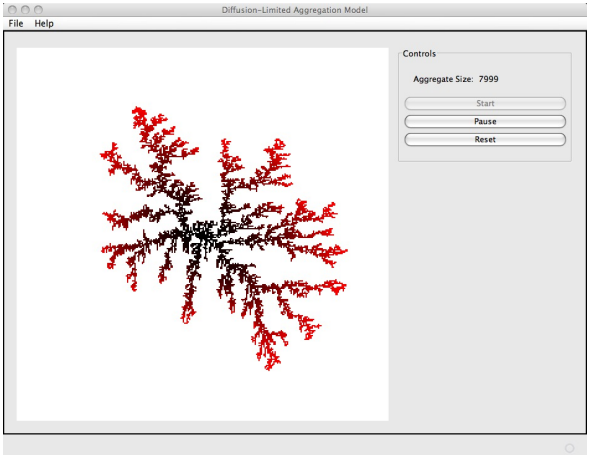
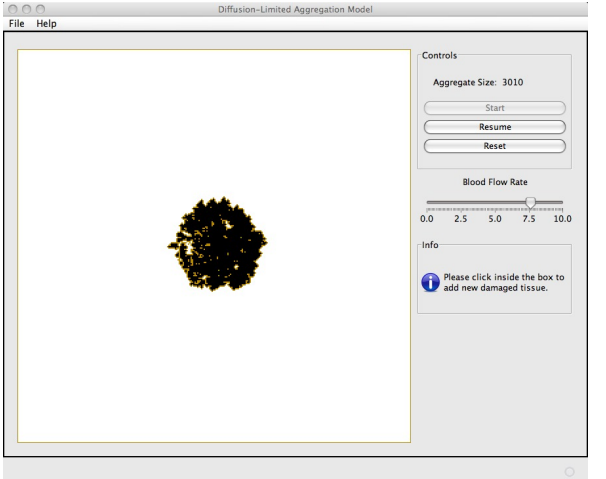
URL: http://go.warwick.ac.uk/kalvala (Sara Kalvala)


Blood vessel
Rolling
Activated
Aggregated
Platelet
EC


Diffusion-Limited Aggregation Model
File Help
Controls
Aggregate Size: 7999
Start
Pause
Reset


Diffusion-Limited Aggregation Model
File Help
Controls
Aggregate Size: 3010
Start
Resume
Reset
Blood Flow Rate
0.0 2.5 5.0 7.5 10.0
Info
Please click inside the box to add new damaged tissue.

A Model of Spatial Predator-Prey Dynamics in a Myxobacteria Colony

Anthony Nash[1], Sara Kalvala[2]
1. MOAC, University of Warwick 2. Computer Science, University of Warwick

Introduction: We investigate pattern formation of a myxobacteria colony under predation of *E. coli* cells using P Systems. P System rewrite rules were used to model the bacterial behaviour and were implemented as a generic Java software suite. Simulations were run for a straight edge colony and a circular colony. Our results demonstrate that P Systems can model swarming and aggregation of myxobacteria.

Myxobacteria

- Gram-negative soil dwelling social bacteria.
- Best known for ripple and fruiting body stages under starvation.
- Driven by two models of transport: adventurous and social.
- Contact-signal (C-signal) transduction through head-head collision, causes reversal in intracellular motors.

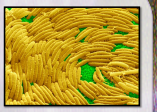


Fig 1: A swarm of myxobacteria, showing distinct structural alignment [1].

P Systems

- Distributed parallel computability models based on cellular membrane structures and diffusing chemical signals.
- Each membrane has a cellular region which can hold a multiset of objects.
- Assigned to each membrane region is a set of rules which allow the multiset to evolve typically through the use of rewrite rules.

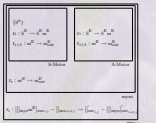


Fig 2: A Venn diagram representation of a basic P System.

Multi-Environment P System

- A P System containing thousands of regions joined by communication links, similar to a Cellular Automaton.
- Each region is capable of holding bacterial P Systems and myxobacteria slime.

Bacterial P System

- Myxobacteria and *E. coli* cells are represented by P Systems with an empty rule set.
- Multi-environment rules can modify the state of any bacterial P System within its region.

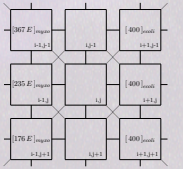


Fig 3: Example of the multi-environment structure.

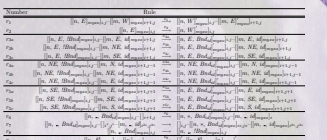


Fig 4: A sample of stochastic P System rewrite rules for each multi-environment region.

Circular Colony Results

- Population behaviour of the P System model showed close resemblance to *in vitro* behaviour.
- Colony structure is maintained through C-signal interactions.

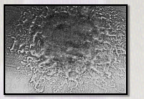
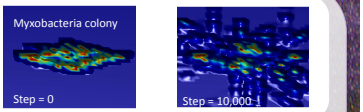


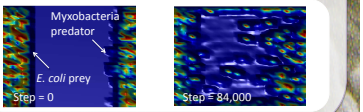
Fig 5: Circular Colony [2]



Colony Edge with Prey

- A straight edge of myxobacteria maintains a tight structure through C-signal interaction.
- Migrating myxobacteria form structures similar to those observed *in vitro*.
- Interaction with prey causes myxobacteria to reverse direction.

Fig 6: Colony edge with peninsula formations [2].



Conclusion

- Using a multi-environment P System design embedded in a Java software suite we managed to model myxobacteria movement.
- Even though myxobacteria began to interact with the *E. coli* cells, further study into the rules is required to recreate the predation ripple phase.

References

[1] G Velicer and M Vos. Sociobiology of the myxobacteria. *Annual Reviews*, Jan 2009.

[2] D Kaiser and C Crosby. Cell movement and its coordination in the swarms of myxococcus xanthus. *Cell Motility and the Cytoskeleton*, Jan 2005.

µCell - Interdisciplinary Research in Modelling and Simulation of Cell Spatial Behaviour

by Dominic Orchard, Jonathan Gover, Lee Lewis Herrington, James Lohr, Duncan Stead, Cathy Young and Sara Kalvala,[1] Department of Computer Science, University of Warwick

Abstract

A central aim of systems biology is the strengthening of quantitative and qualitative knowledge of biological systems by studying the interactions between components and processes that lead to emerging properties and behaviours. Systems biology proliferated over the latter half of the twentieth century with the aid of technological advances and subsequent interdisciplinary research between natural scientists, computer scientists, and mathematicians. In this paper we present µCell, an interdisciplinary research project undertaken by undergraduates at the University of Warwick, seeking to aid systems biology intuition. The project's main contribution is a modelling and simulation tool for multi-cellular environments aimed at simulating higher-level cellular behaviours based on the interoperation of biochemical signalling pathway models and procedural models of cell components and structures, such as flagella. Based on these interoperated models, µCell is able to simulate spatial properties and behaviours of cells, such as chemotaxis. This paper introduces µCell, gives a case study model and simulation of flagella-based chemotaxis in *E. coli*, and discusses the pedagogical outcomes of the project for the students.

Keywords: µCell, systems biology, biological modelling, simulation, model interoperation, chemotaxis.

Introduction

Technological and scientific progress has yielded successively higher resolution techniques for the observation and manipulation of cells, aiding biological research. However, there is still much to be understood. The interaction of cells with their environment and with each other, via processes such as adhesion, movement, and quorum sensing, induces behaviour such as cell migration, aggregation of cells into tissues, precision growth across relatively large distances, and group behaviour such as fruiting body formation (Hynes and Lander, 1992). A thorough understanding of the cause and control of such behaviours is difficult due to the complexity of cells and their interactions.

Studying the components and processes of a cell independently from other components and processes often fails to expose the full spectrum of a cell's properties and behaviour. The study of emergent behaviours and properties at the cellular and organismal level requires an understanding of the dynamic interactions and causal relationships between individual lower-level processes within a cell, and between cells. Such study is the focus of the burgeoning field of systems biology (Kitano, 2002). In the last decade, interdisciplinary research between natural scientists, computer scientists, and mathematicians has greatly improved understanding through computational analyses, modelling, and simulation.

parameters regarding the environment or simulation. For statistical analysis and data logging, time-series can be defined in terms of formulae associated with the simulation to be calculated at user-defined time intervals (Figure 5).

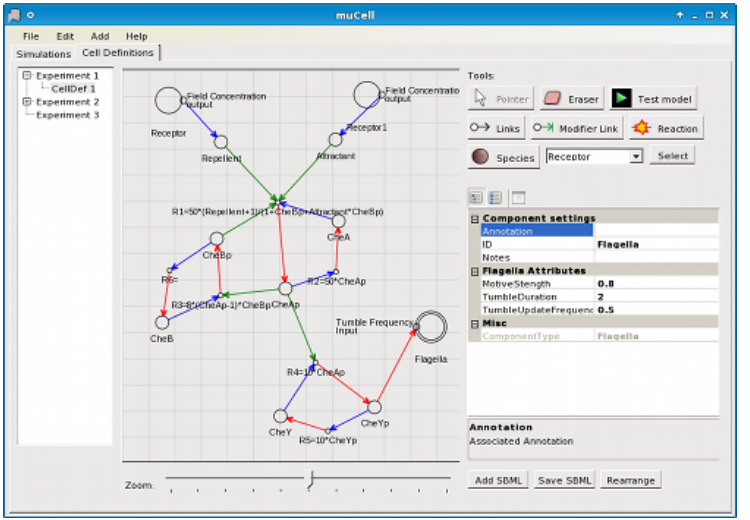


Figure 1. µCell cell model editor - Editing an imported SBML model.

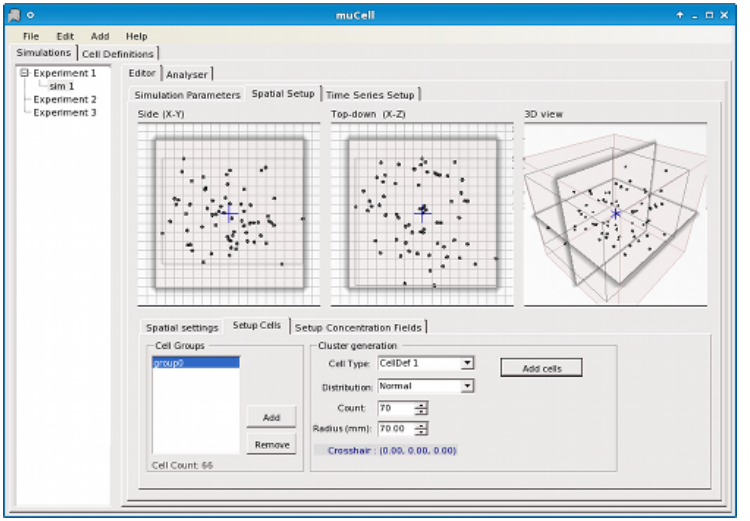


Figure 3. µCell spatial editor for cells - Defining initial cell placement.

as opposed to quantising locations into a grid as in cellular automata. In the current simulator, cells reaching a boundary are simply deflected without loss of energy. By default the cells are represented as points in the space but can be given a size and mass via the "cell body" component for simulating collisions.

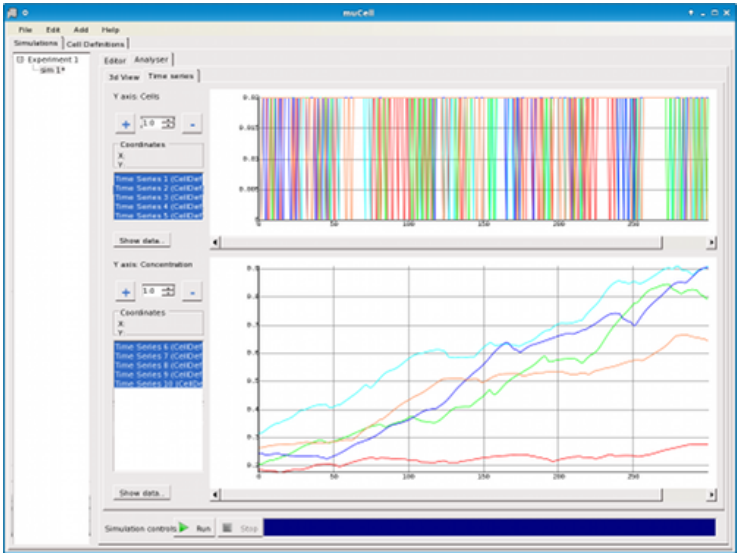


Figure 7. µCell Analyser - Plots showing concentration of attractant during chemotaxis and run lengths for 5 sampled cells.

Analyser

The analyser provides an interface for viewing data collected during and after a simulation, and provides feedback on simulation progress. The analyser provides a 3D representation of the spatial environment and the cells within it (Figure 6). Concentration gradients are shown via a 2D planar slice that moves through the environment showing a coloured representation of the concentration in that plane where a lighter colouring corresponds to a low molar concentration and a darker colouring corresponds to a high concentration.

The analyser also provides access to time-series data generated during simulation in the form of plots (Figure 7). The raw numerical data for the plots can be viewed

A System for the Graphical Development of New Synthetic Biological Parts

Author: James Clark (0716158)

Supervisor: Sara Kalvala

Year: 2010/2011

Abstract

This paper presents a software solution for the graphical construction of synthetic biological parts. The software performs validation on constructed synthetic models via the use of a context-free grammar used to capture valid biological structure. The system also provides a repository of simple biological parts with which new synthetic parts can be created and which can be expanded with new part information.

The software was found to be an effective method for the creation of new synthetic biological parts and an interesting framework with which to continue the investigation of modelling biological structure via the use of context-free grammars.

Keywords

Synthetic Biology

Modelling

Parser

DNA

GUI

FASTA

P-Systems

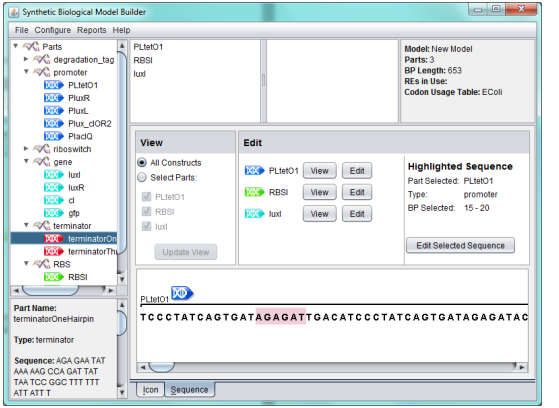


Figure 4: Model Sequence Editing

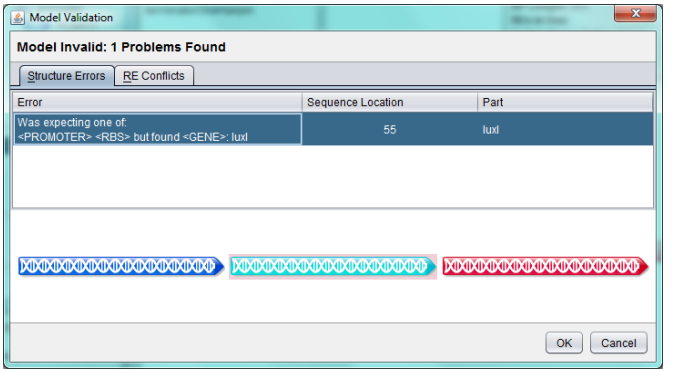


Figure 5: Model Validation

Further screenshots of the system can be found in Appendix A.

From Computation to Biology

Opportunities:

- hot subject, industrial need, funding
- source of new practical problems, and solutions
- interdisciplinary knowledge

Challenges:

- steep learning curve
- low level of abstraction
- hard to make impact

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