Cellular Computing

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Cellular Computing

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Co-chairs

Study Attendees:

- Jonathan Allen (MIT)
- Elliott Brown (DARPA)
- Bernie Chern (NSF)
- Frederica Darema (DARPA)
- Tony Eng (MIT)
- Ken Gabriel (DARPA)
- John Hennessey (Stanford)
- Mark Horowitz (Stanford)
- Butler Lampson (MIT/Microsoft)
- Bob Lucas (DARPA)
- Sonny Maynard (DARPA)
- Harley McAdams (Consultant)
- Gary Minden (DARPA)
- Jose Munoz (DARPA)
- Hilarie Orman (DARPA)
- Bob Parker (DARPA)
- Rose Ritts (DARPA)
- Lucy Shapiro (Stanford)
- Gerry Sussman (MIT)
- Anna Tsao (DARPA)
Cellular Computing

Other Participants

- Bonnie Berger (MIT)
- Roger Brent (Mass General)
- George Church (Harvard Medical)
- Millie Donlon (DARPA)
- Paul Dunlap (WHOI)
- Eric Eisenstadt (ONR)
- Denny Freeman (MIT)
- Terri Gaasterland (U. Chicago)
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- Shaun Jones (DARPA)
- Peter Karp (SRI)
- Eric Lander (Whitehead)
- Mark Reed (Yale)
- Dave Stenger (NRL)
- Bruce Tidor (MIT)
- George Whitesides (Harvard)
Create and exploit a novel technology for information processing and manufacturing by controlling processes in living cells.
Strategy

Technology Development

Biology
Customizable Cells

CAD Tools,
Molecular Biological Tools,
Instrumentation,
Infrastructure

FSM

Easily Programmable Cells

Chemical Factories

Computer Science

Novel Materials

Ultrafast Computers
Life is an information process
  - DNA is a storage medium for programs
  - There is evidence for abstract structure in the genetic program
    ✦ A hierarchy of structure in complex organisms
    ✦ An ability to mutate one structure at a time
    ✦ Divergent implementations of the same structure
  - Gene expression is the means of execution

A cell contains a complex software system
  - Haemophilus influenzae Rd has 1,830,137 base pairs = 457,534 bytes
  - Homo Sapiens has about a 1 GByte fabrication and operational program

Study of computational processes is synergistic with biological science
  - Computational science is the study of management of complexity
Implementing the Digital Abstraction with DNA Binding Proteins

- Represent signals as the concentration of specific DNA binding proteins
- Implement the nonlinearity by dimerization of proteins and with cooperative binding at DNA binding sites
- Control the maximum concentration by negative self regulation of concentration
- Turning signals off is handled by normal protein degradation mechanisms
- Lambda Phage Switch is a good model
  - Mark Ptashne “A Genetic Switch” is highly recommended
The Cro Repressor in Lambda Phage

A Dimeric Protein - Cooperative Binding
The Digital Abstraction: An Inverter

Implemented in genetic switches

A represses the expression of B

Signals are represented as concentrations of DNA binding proteins.
A Simple Cellular Logic Circuit
Digital Memory: A Flip Flop

A DNA

B

C

D

A

B

C

D

A

B

C

D
DNA binding protein logic is very slow
  - millihertz gate speeds
  - Even with $10^{12}$ cells, this is still slow

Biology can compute more quickly
  - Allosteric modification of protein behavior
  - Covalent modification of proteins to affect activity
    - phosphorylation
    - GDP/GTP binding proteins
    - Cyclic AMP binding proteins
  - These techniques will be much more difficult to engineer at least until we understand protein structure and function better
  - Potentially 10 - 100 hertz response rates
Why Now?
We can already engineer cells

- **Example: a Sucrose sensor**
  - Bacteria fluoresces green in the presence of sucrose

- **Are there parts available?**
  - Surface receptors for sucrose exist
  - Genes exist for Green Fluorescent Protein (GFP)

- **If no parts found, engineer parts from scratch (difficult!)**

- **How do we connect the receptor to the GFP gene**
  - Determine internal response to the receptor
  - Identify site to introduce GFP activation into the sucrose response chain

- **Create the Sucrose Sensor cell and test**

![Diagram of a bacterial cell with a sucrose sensor](image)
Biochemical Knowledge is Undergoing Explosive Growth

Sequenced Genomes

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<th>Year</th>
<th>Number of Micro-organisms</th>
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<td>10</td>
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Leveraging the Ongoing Biological Investment

- Genome Sequencing
- Functional Genomics
- Cellular Engineering

Knowledge & Capability

Now

Time

With DARPA Investment
Near Term Potential (1-5 years) with DARPA investment

- **Applications of programmable cells**
  - Integration of sensors, actuators and control systems
    - e.g. sucrose sensor turns cell blue
  - *in vivo* delivery of pharmaceuticals
    - e.g. selective delivery of antibodies

- **Technology Spinouts**
  - Bio Spice
  - Improve infrastructure for biotechnology
    - Reduce GSY/ fact
  - Better understanding of organizational principles
  - Improved readiness for biological threats
In Situ Antibiotic Delivery

Customized Cell

Toxin A

pathogen

detection
In Situ Antibiotic Delivery

Customized Cell

Toxin A

pathogen

response

antibiotic synthesis machine

Antibiotic A
In Situ Antibiotic Delivery

Customized Cell

Toxin A

pathogen

Antibiotic A

kills

antibiotic synthesis machine
Medium Term Potential with DARPA investment

- **Dense Molecular Memory**
  - 100,000 bits/cell (1 micron diameter)

- **Hybrid Silicon / Cell Structures**
  - silicon computation
  - biological interfaces
    - natural connection to the chemical world

```
AGCTAAAGCCGT
```

Free Cells

Substrate
Bound cells

Pad coated with antibody

Silicon substrate

memory sequence

memory plasmid
The ability to control biological processes to create patterned materials where the placement of individual molecules is under program control
- Creating molecularly perfect materials -

- Ultrascale computing structures
- High strength / weight materials
- Nonlinear optical materials
- Custom organisms
  - Disease Blockers
  - Purposely engineered multicellular organisms
# Naturally Occurring Sensor and Actuator Parts List

## Sensors
- Light (various wavelengths)
- Magnetic and electric fields
- pH
- Molecules
  - Ammonia
  - H₂S
  - maltose
  - serine
  - ribose
  - cAMP
  - NO
- Internal State
  - Cell Cycle
  - Heat Shock
- Chemical and ionic membrane potentials

## Actuators
- Motors
  - Flagellar
  - Gliding motion
- Light (various wavelengths)
- Fluorescence
- Autoinducers (intracellular communications)
- Sporulation
- Cell Cycle control
- Membrane transport
- Exported protein product (enzymes)
- Exported small molecules
- Cell pressure / osmolarity
- Cell death
New Product Announcement:

Green Fluorescent Protein Photon BioTransducer

Absolute Maximum Operating Conditions: - 40 to + 80 °C

Typical Operating Conditions: + 25 to + 37 °C

DC Characteristics:

AC Characteristics:

\[ t_{on} = 30 \text{ min} \]

\[ t_{off} = ? \]
Integrated Single-Cell Process-Control Systems

- Transducers
- Storage
- Control Mechanism

...can engineer single-celled process-control systems
Multicellular systems display cooperative behavior

Establishing cooperative behavior is a computational problem

Biologically, it requires cell to cell communications

Control results in
  - Patterned biological behavior
  - Patterned material fabrication
Even simple, locally-controlled systems can produce predictable patterns, with only local communication.
Create and exploit a novel technology for information processing and manufacturing by controlling processes in living cells.
Current Challenges

- Engineer the first digital control system into a living cell
- Engineer the system support for experimental cellular engineering into living cells
- Engineer component interfaces
- Develop instrumentation and modelling tools -- BioSpice
  - Obtain missing data in spec sheet fields
  - Discover unknown fields in the spec sheet
- Create computational organizing principles
  - Invent languages to describe phenomena
  - Build models for organizing cooperative behavior