Cellular Computing

ISAT Summer Study, August 1996

Cellular Computing

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Co-chairs

Study Attendees:

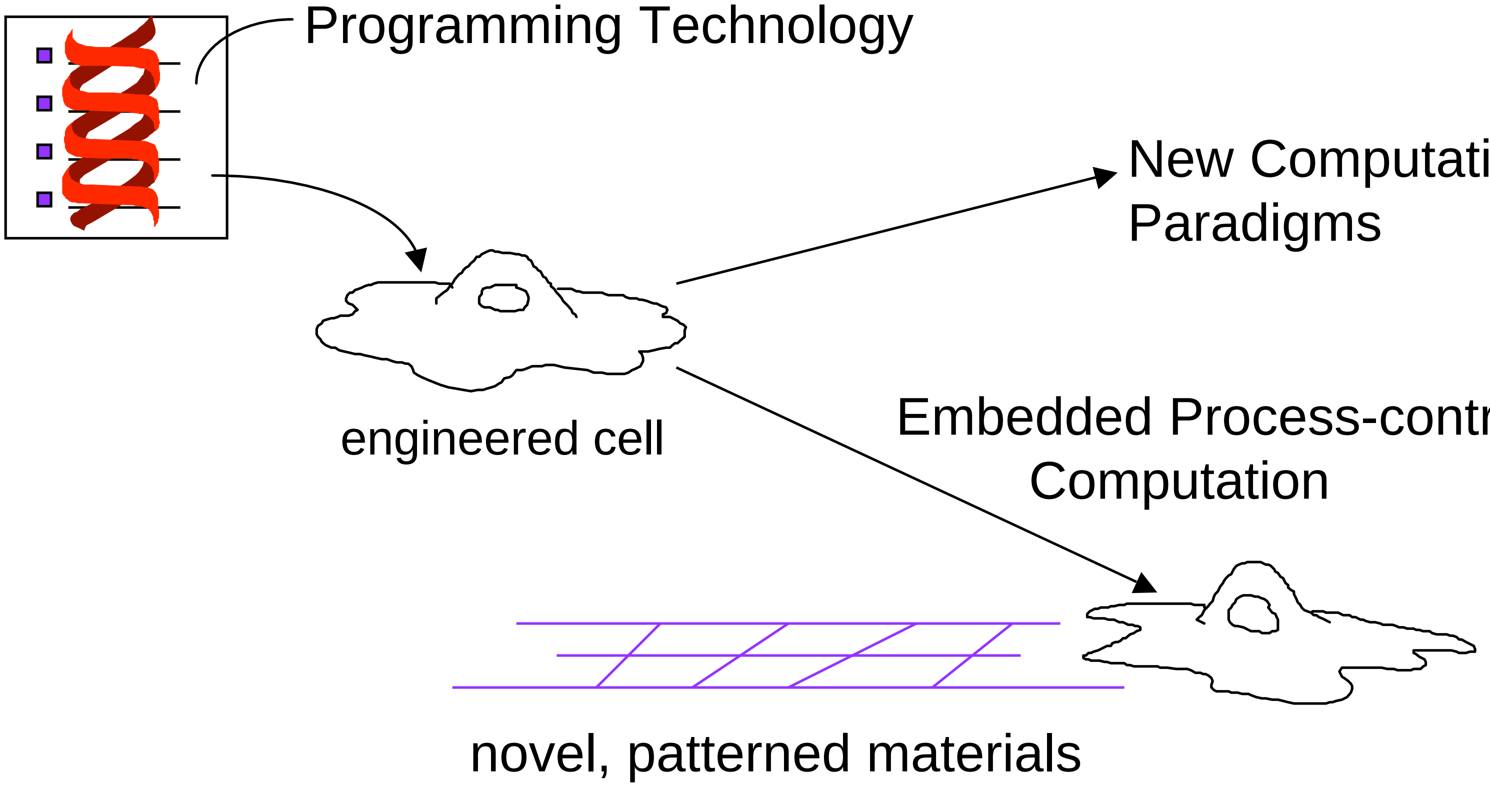
- **Jonathan Allen** (MIT)
- **Elliott Brown** (DARPA)
- **Bernie Chern** (NSF)
- **Frederica Darema** (DARPA)
- **Tony Eng** (MIT)
- **Ken Gabriel** (DARPA)
- **John Hennessey** (Stanford)
- **Mark Horowitz** (Stanford)
- **Butler Lampson** (MIT/Microsoft)
- **Bob Lucas** (DARPA)
- **Sonny Maynard** (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

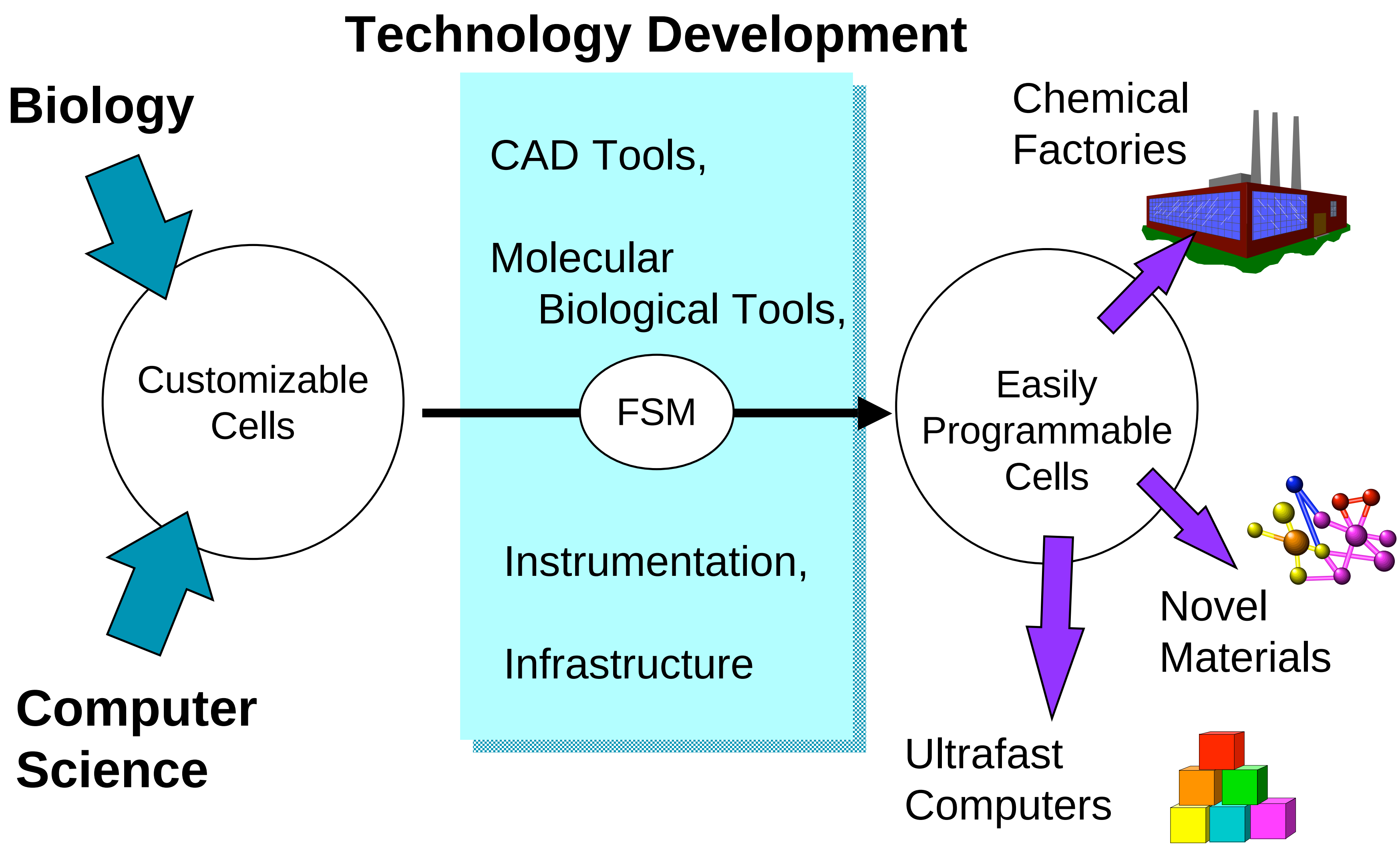
Other Participants

- **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)
- **Alan Grossman** (MIT)
- **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
Computer Science
Customizable Cells
CAD Tools,
Molecular Biological Tools,
FSM
Instrumentation,
Infrastructure
Easily Programmable Cells
Chemical Factories
Novel Materials
Ultrafast Computers

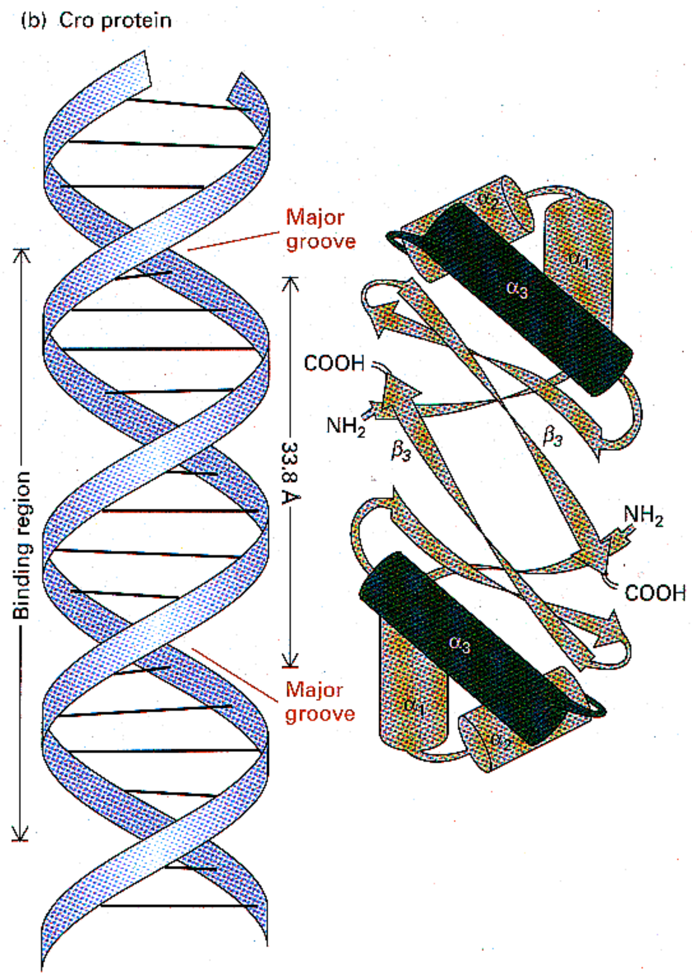
Computer Science and Biology

- **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 mutuate 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

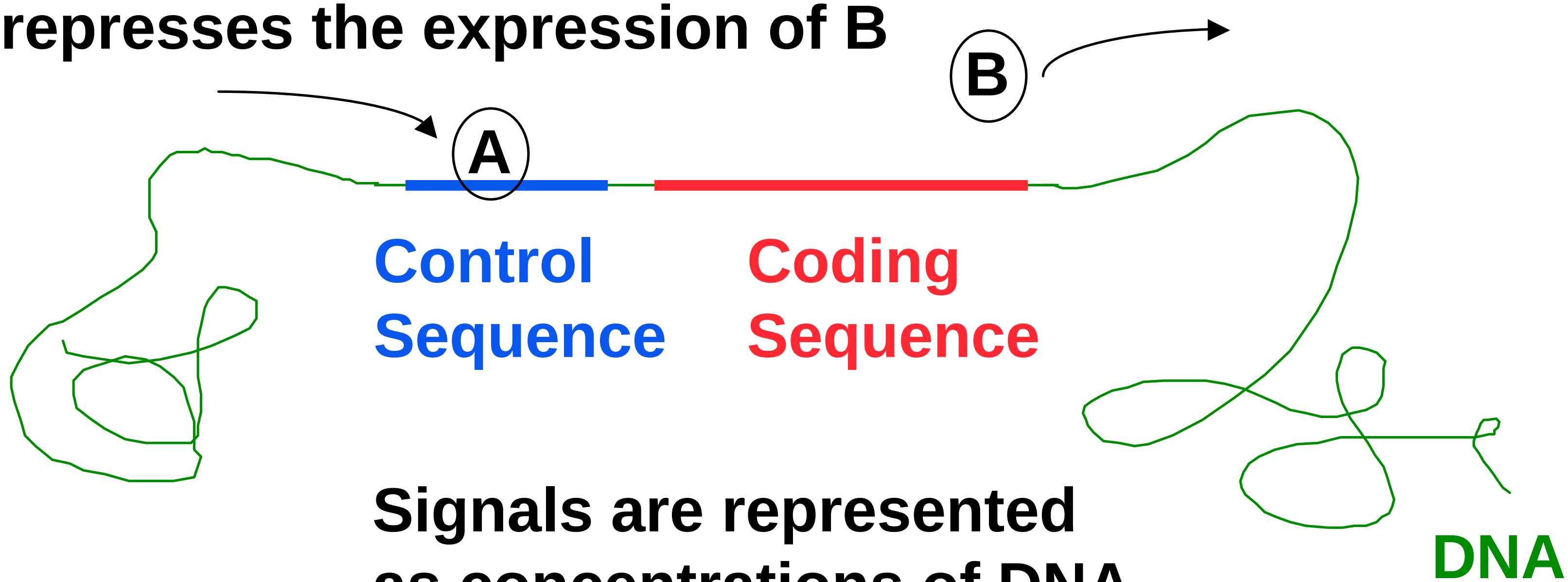


A Dimeric Protein
- Cooperative Binding

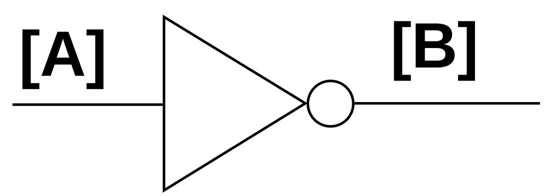
The Digital Abstraction: An Inverter

Implemented in genetic switches

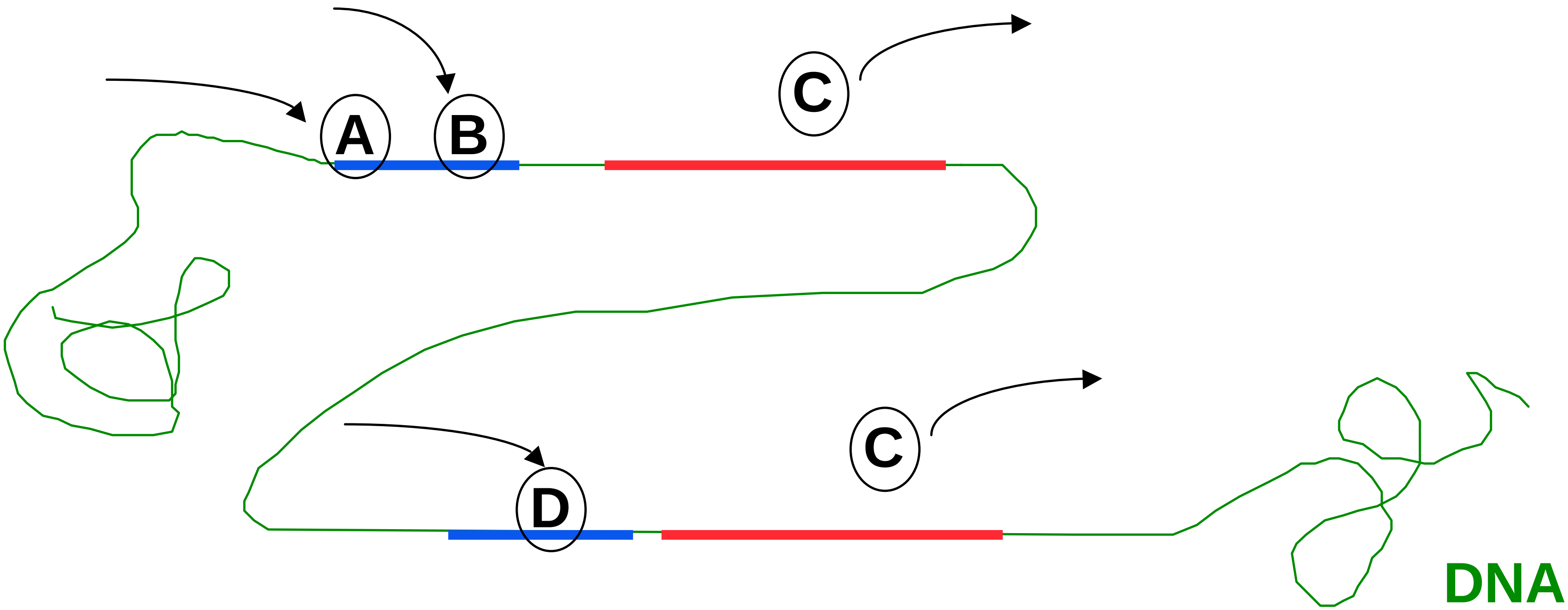
A represses the expression of B

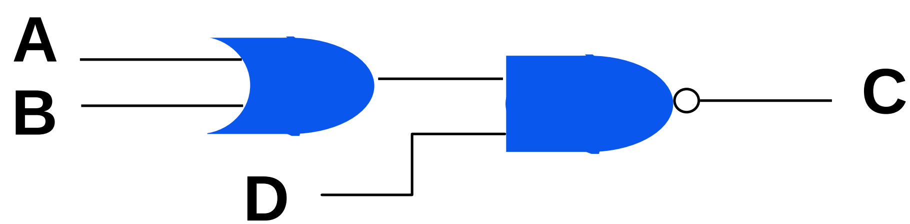


Signals are represented as concentrations of DNA binding proteins.

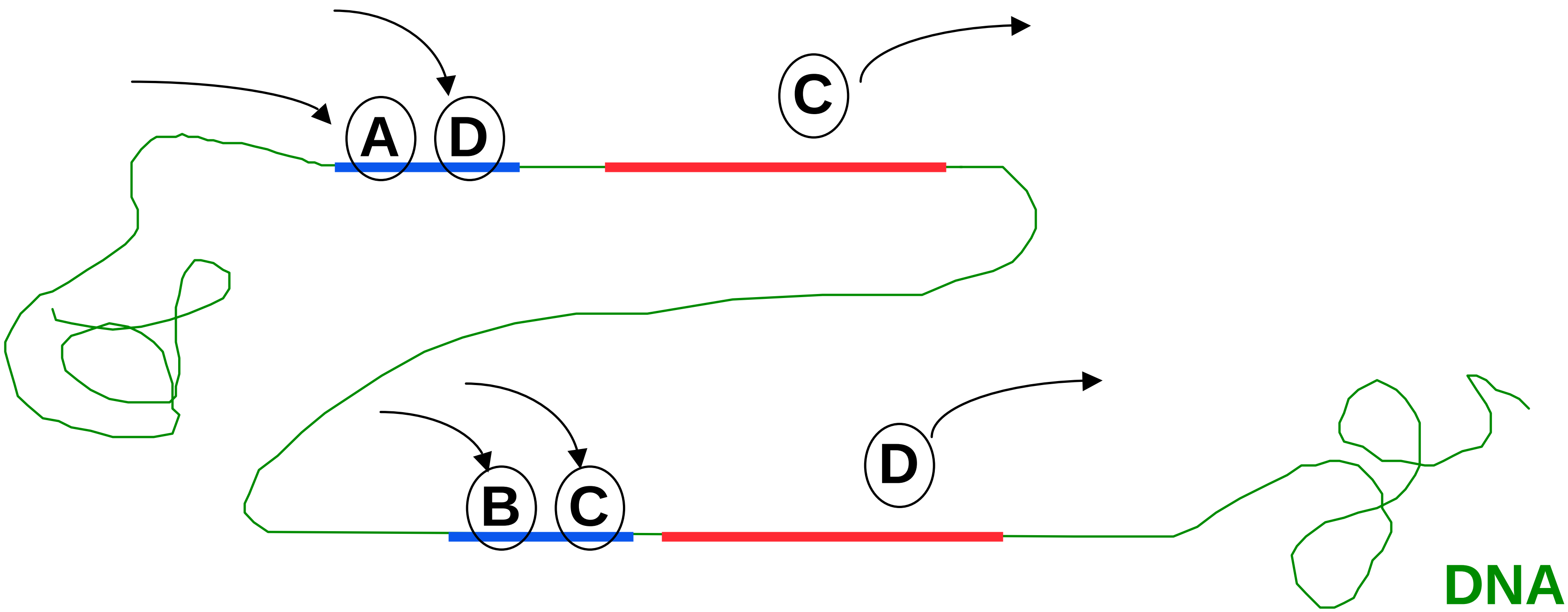


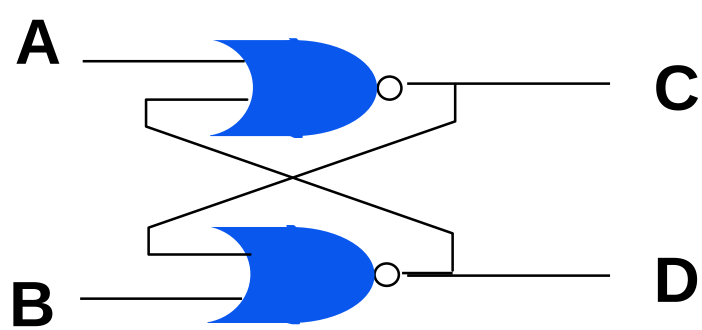
A Simple Cellular Logic Circuit





Digital Memory: A Flip Flop



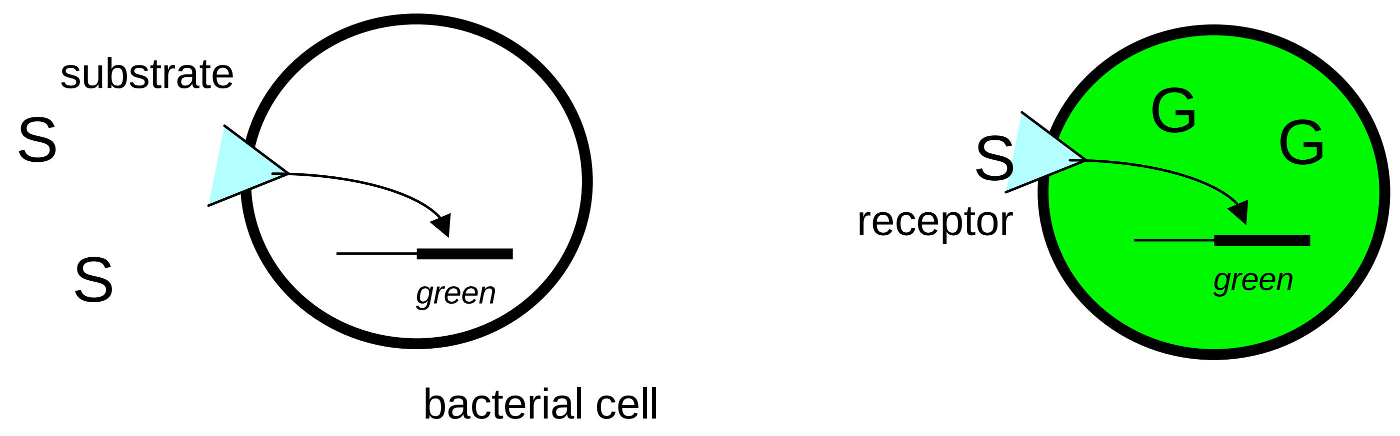


Alternative Implementations

- **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

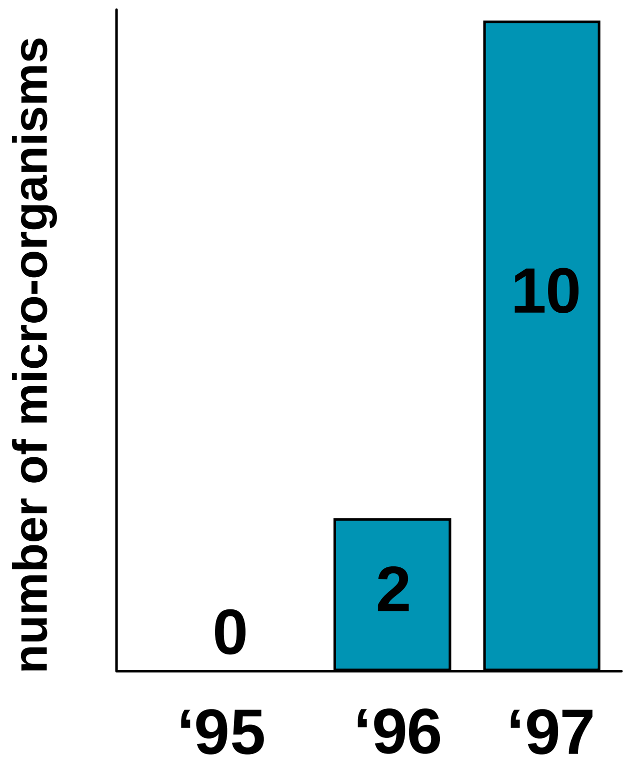
Why Now?
We can already engineer cells

- **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**

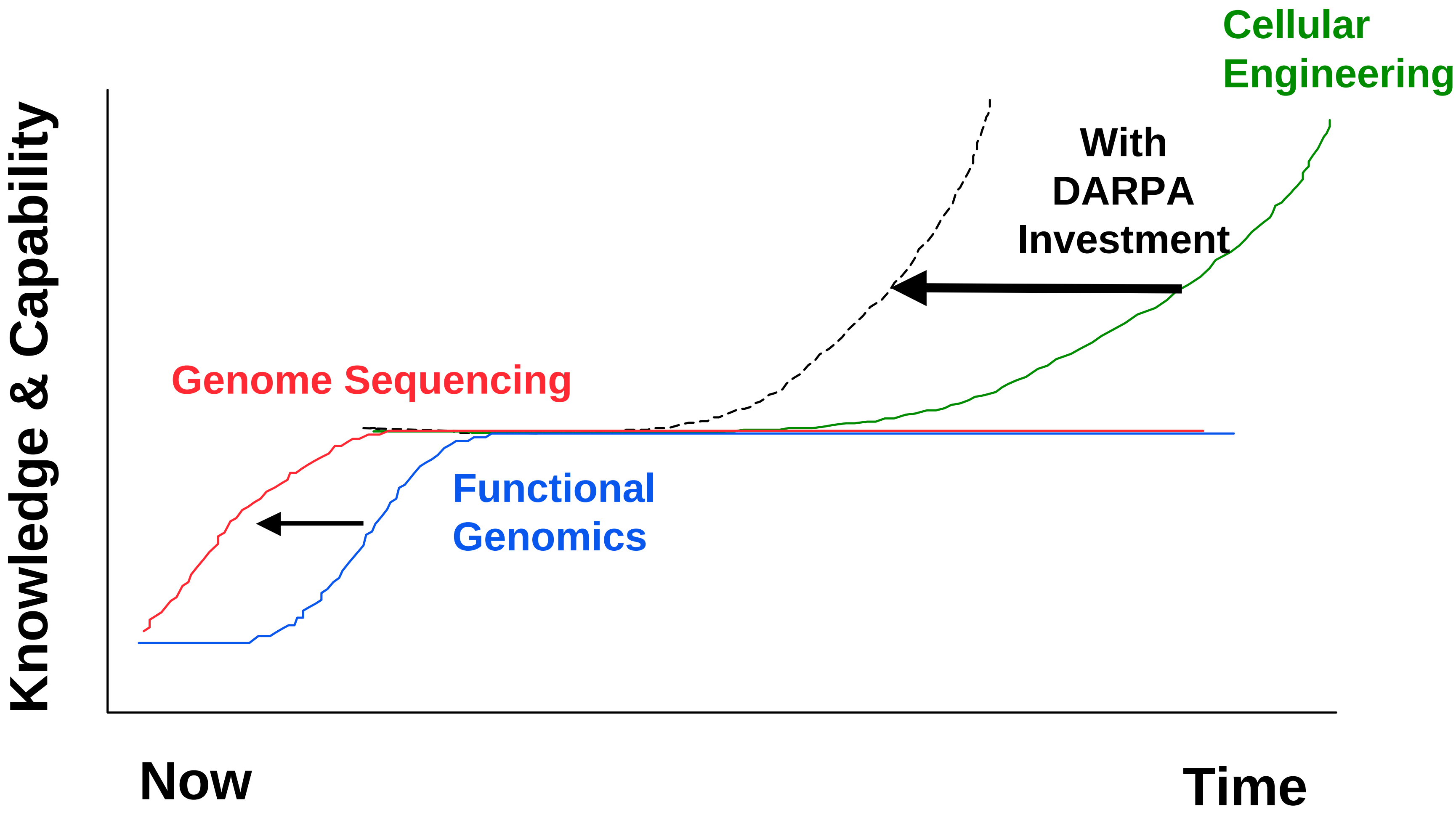


Biochemical Knowledge is Undergoing Explosive Growth

Sequenced Genomes



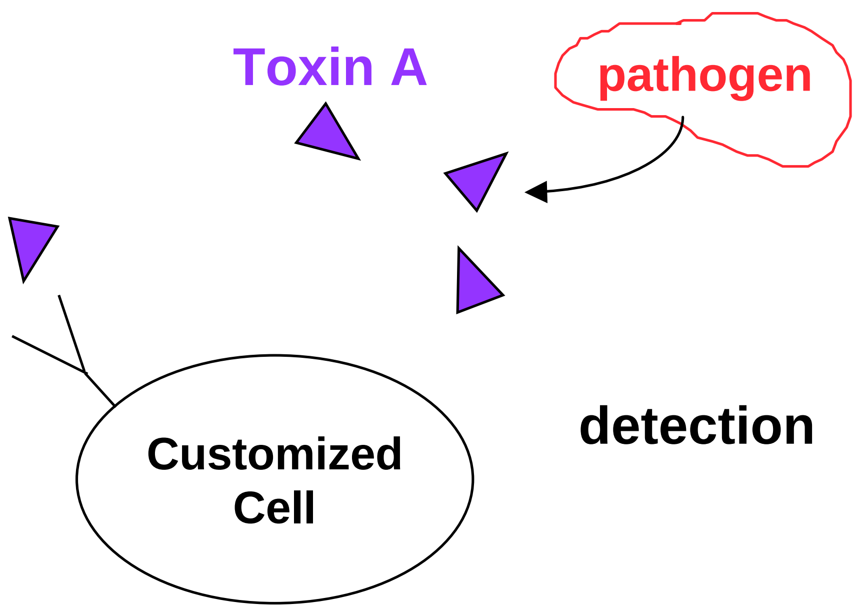
Leveraging the Ongoing Biological Investment



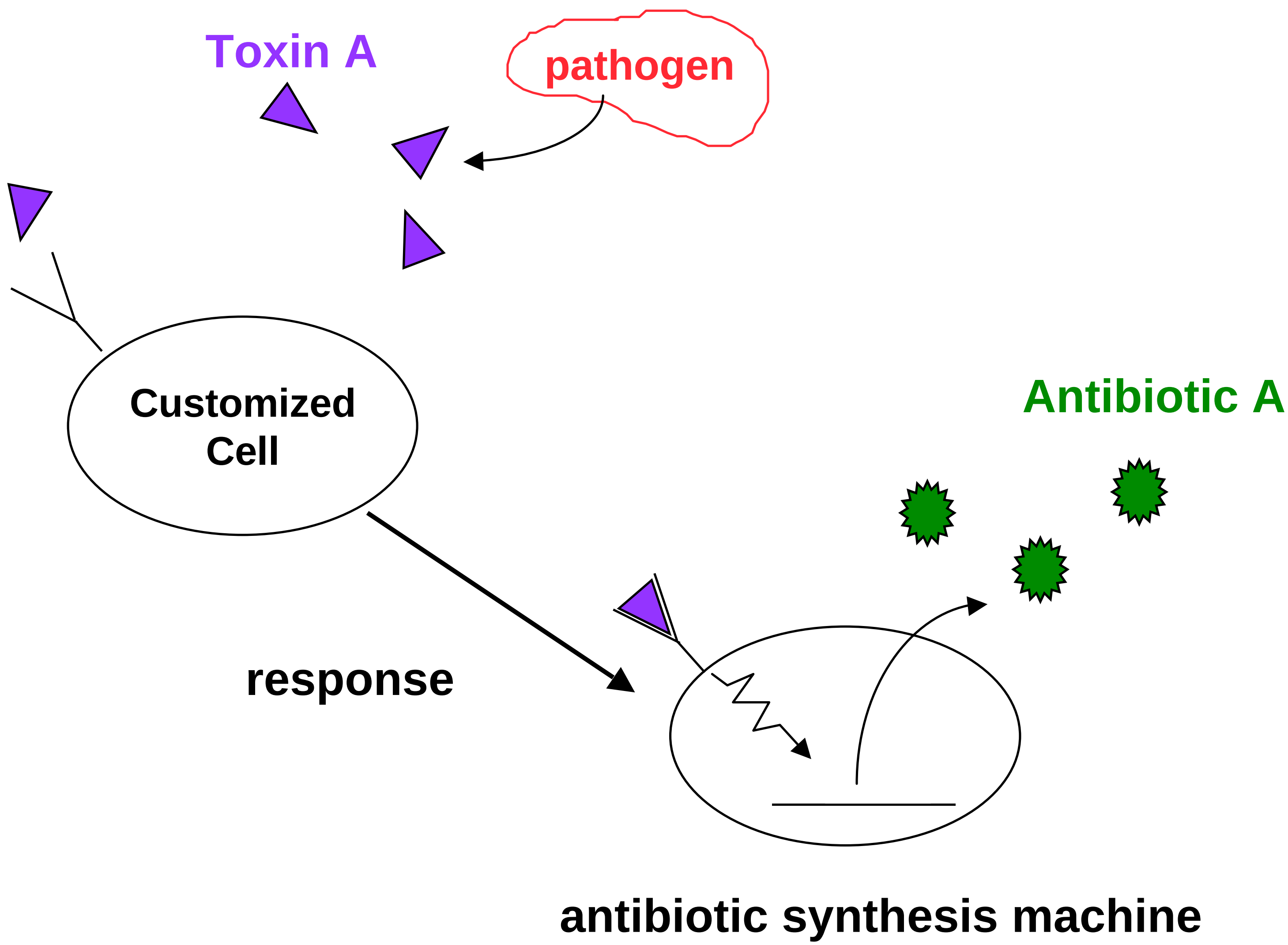
Near Term Potential (1-5 years) with DARPA investment

- **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

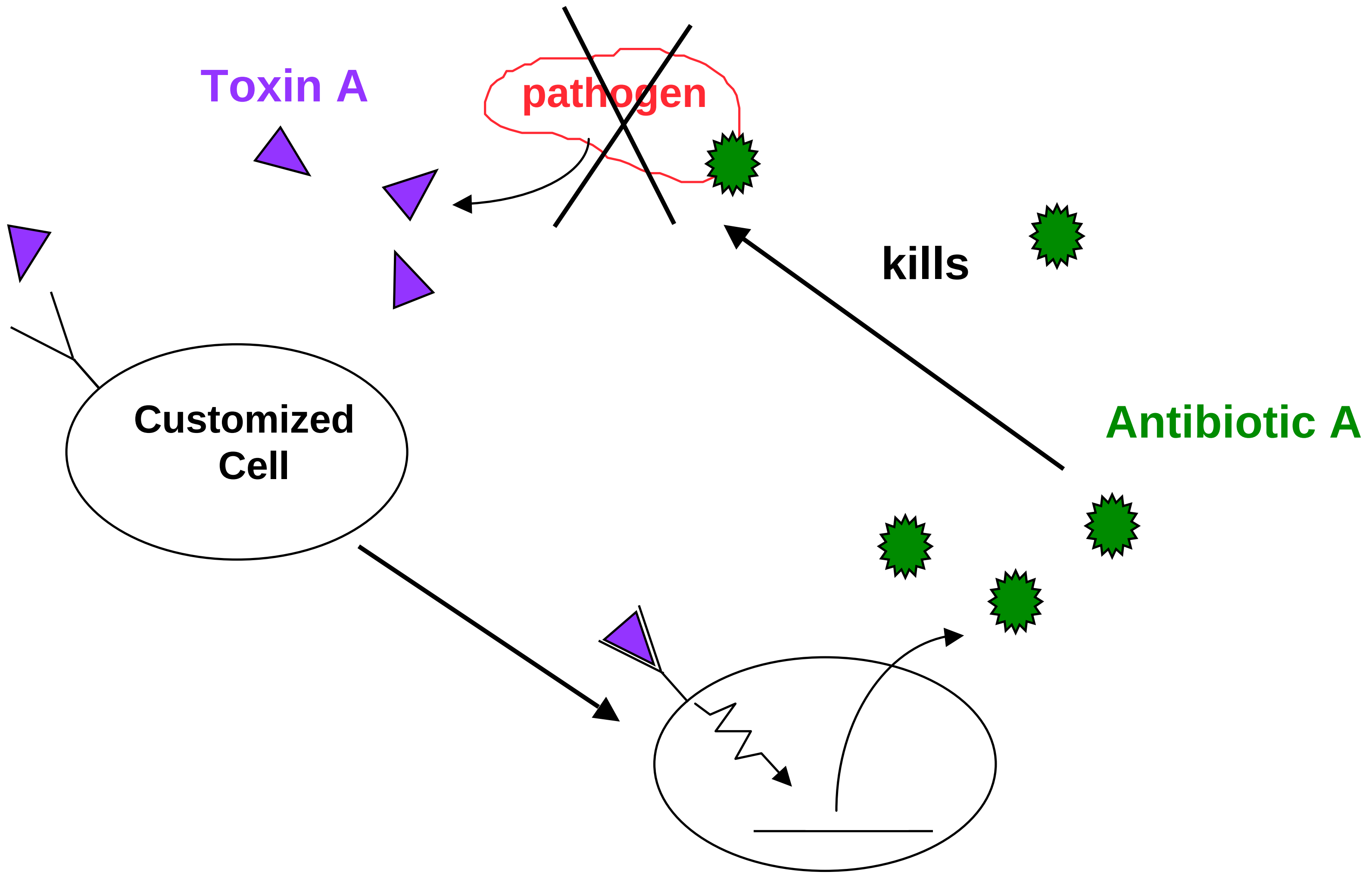
In Situ Antibiotic Delivery



In Situ Antibiotic Delivery



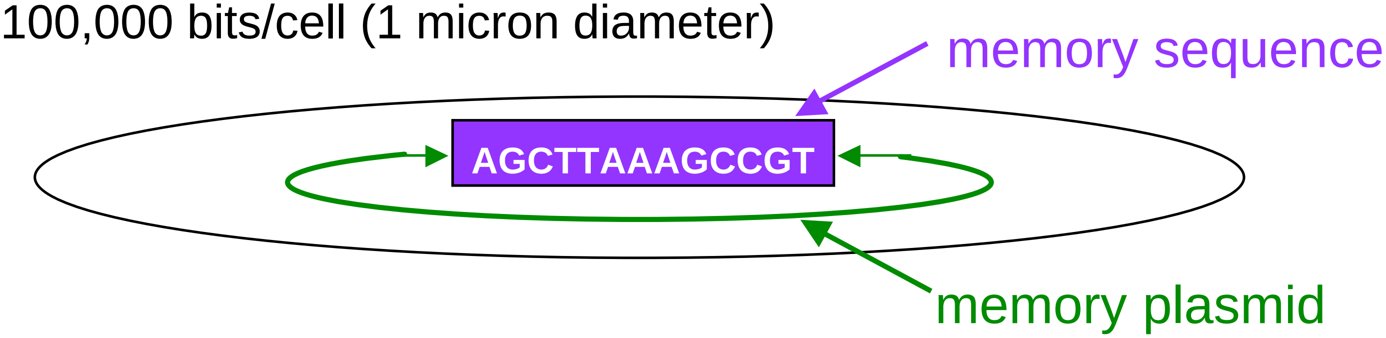
In Situ Antibiotic Delivery



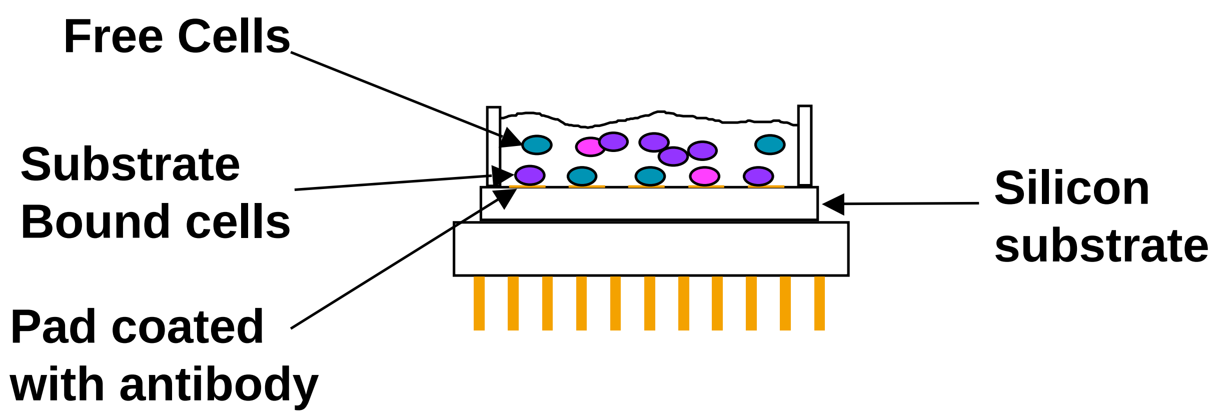
antibiotic synthesis machine

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



Long Term Potential (20+ years) with DARPA investment

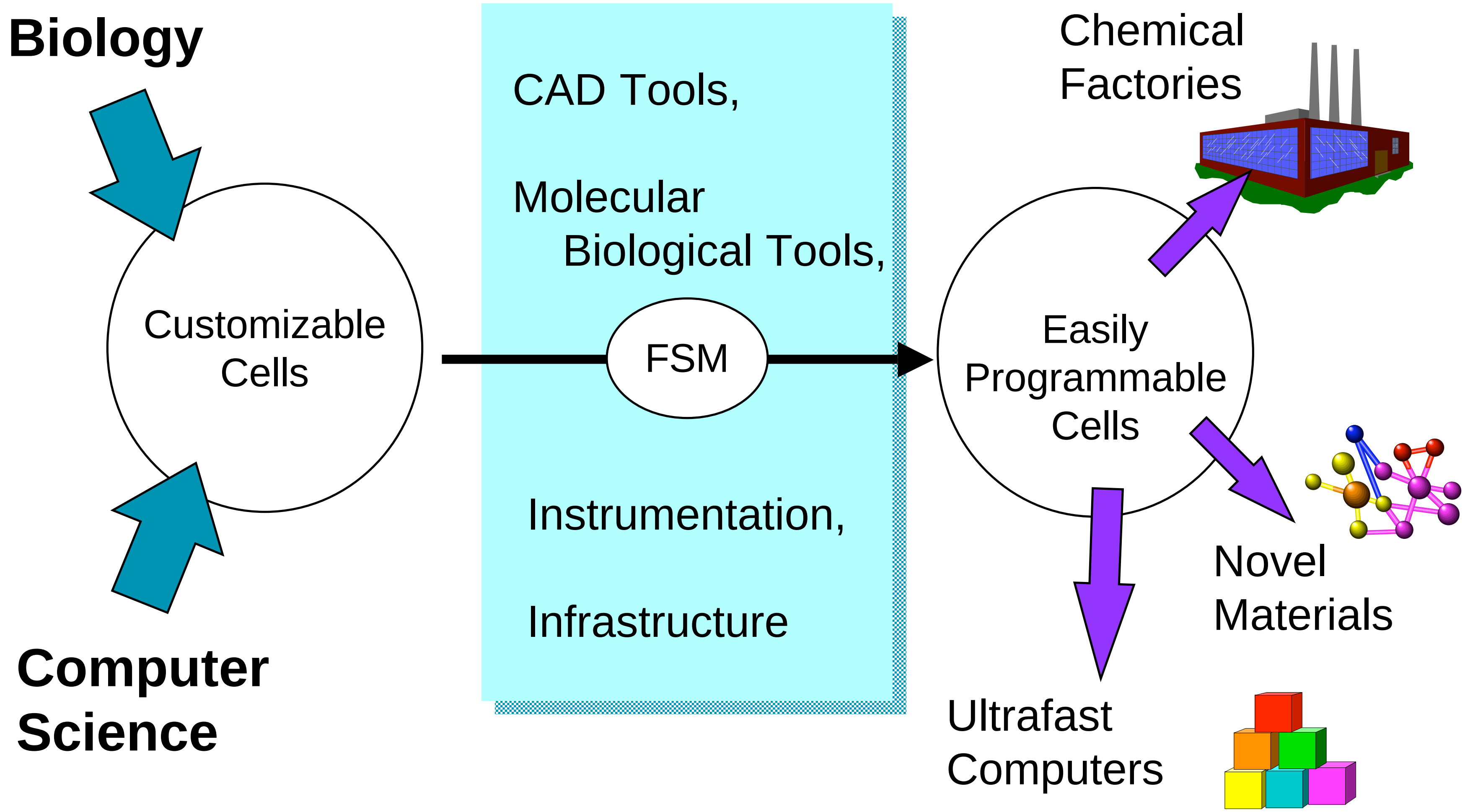
The ability to control biological processes to create patterned materials where the placement of individual molecules is under program control

- Creating molecularly perfect materials -

- **Ultrascale computing structures**
- **High strength / weight materials**
- **Nonlinear optical materials**
- **Custom organisms**
  - **Disease Blockers**
  - **Purposely engineered multicellular organisms**

Strategy

Technology Development



Naturally Occurring Sensor and Actuator Parts List

Sensors

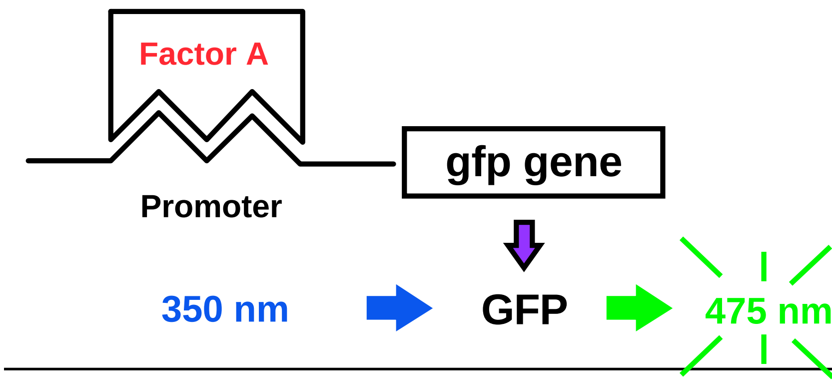
- **Light (various wavelengths)**
- **Magnetic and electric fields**
- **pH**
- **Molecules**
  - Ammonia
  - H_2S
  - maltose
  - serine
  - ribose
  - cAMP
  - NO
- **Internal State**
  - Cell Cycle
  - Heat Shock
- **Chemical and ionic membrane potentials**

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**

DARPA Gen

New Product Announcement:

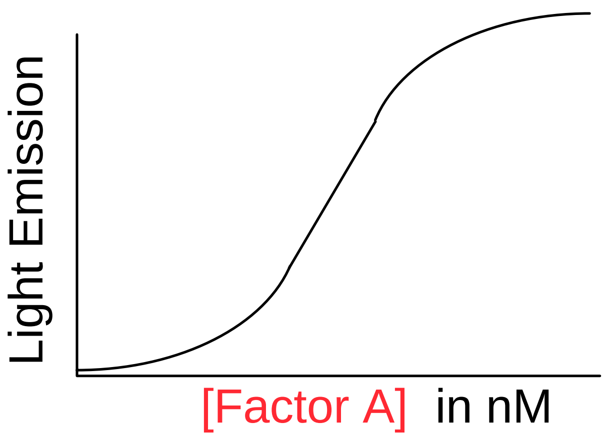


Green Fluorescent Protein Photon BioTransducer

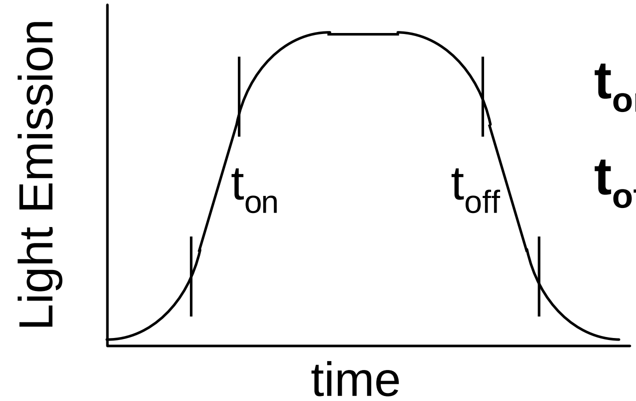
Absolute Maximum Operating Conditions: - 40 to + 80 ^{o}C

Typical Operating Conditions: + 25 to + 37^{o}C

DC Characterisitcs:



AC Characterisitcs:



t_{on} = 30 min

t_{off} = ?

Integrated Single-Cell Process-Control Systems

- Transducers
- Storage
- Control Mechanism

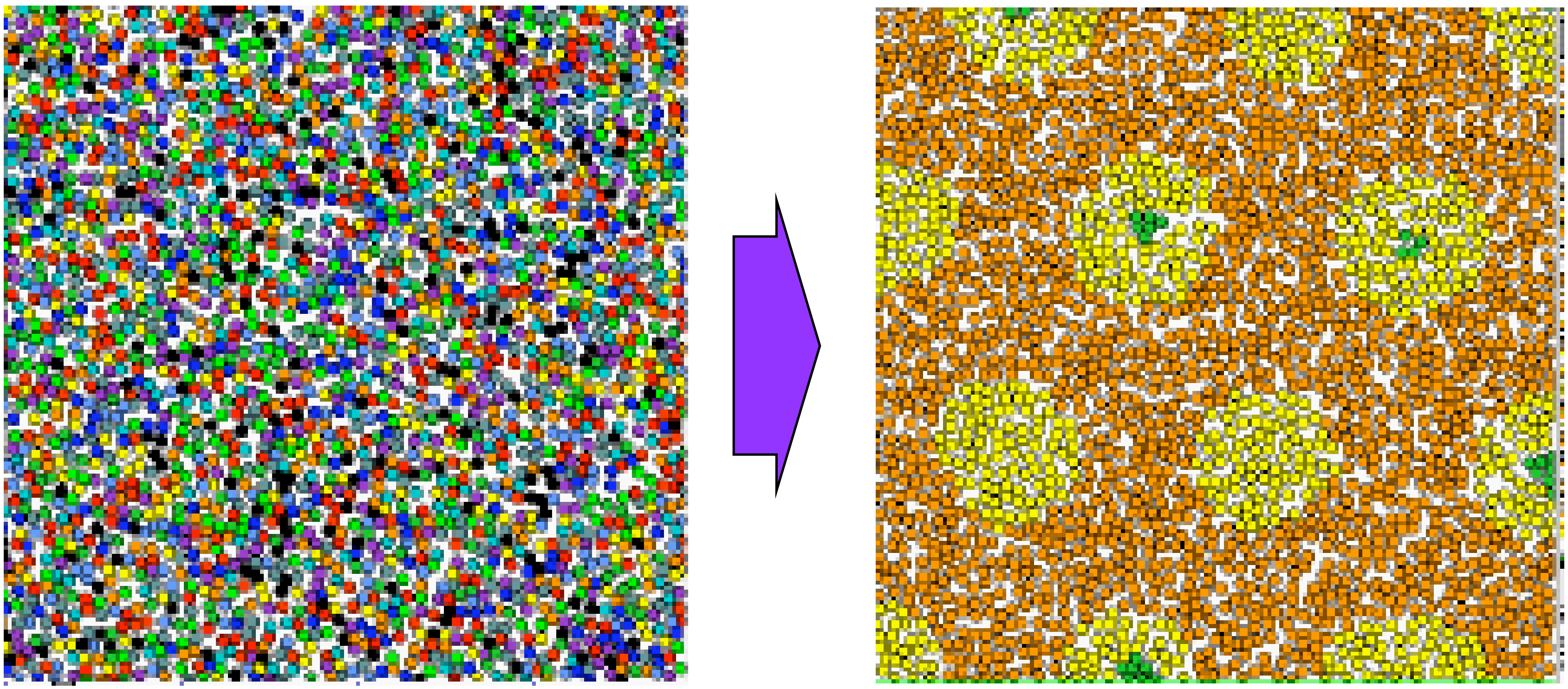
...can engineer single-celled process-control systems

Programmable Cooperative Behavior

- 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

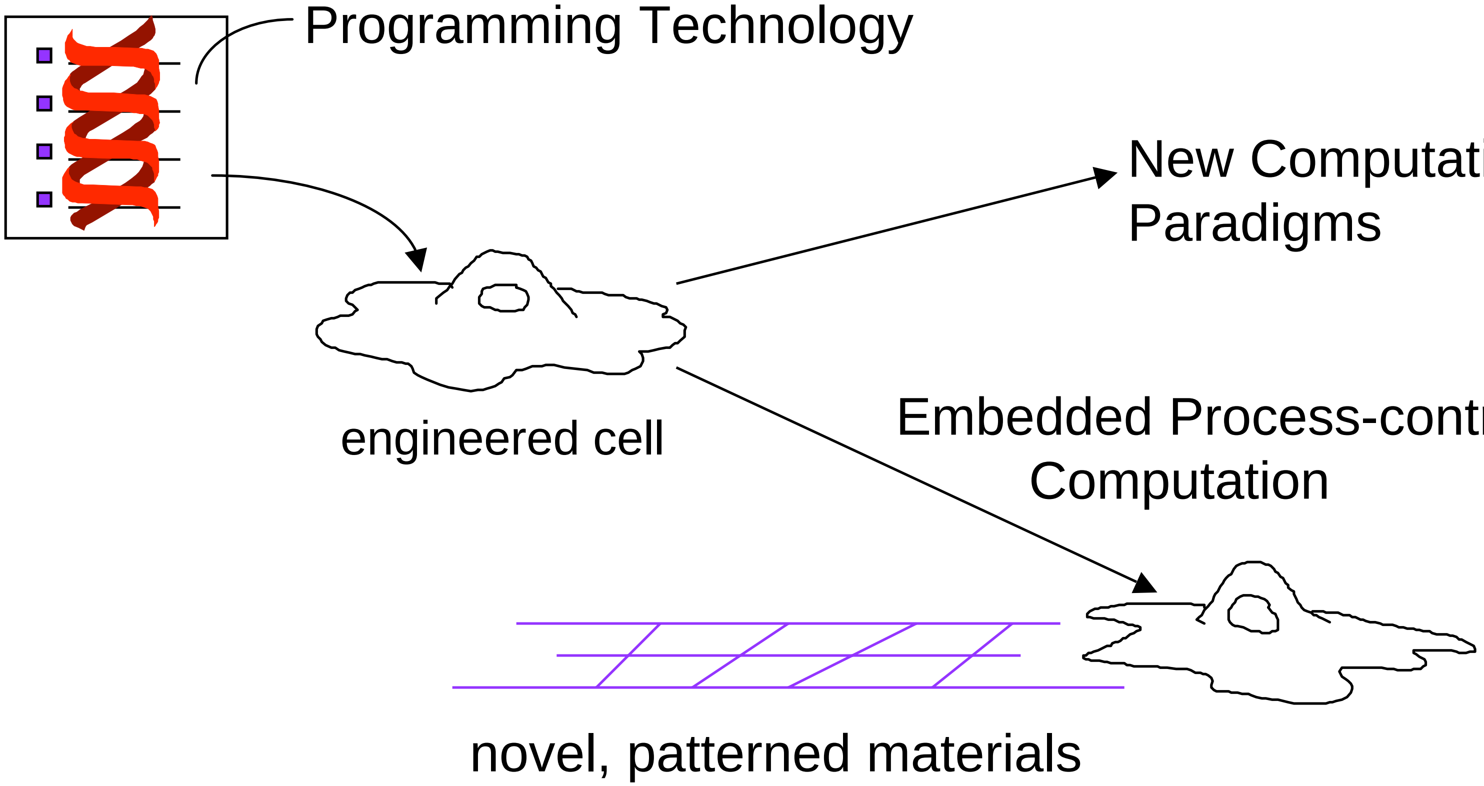
Pattern Formation with Local Rules

Initial state is random | **Final state is patterned**



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