CSCI 2570 Introduction to Nanocomputing

Synthetic Biology

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What is Synthetic Biology?

- Biology re-engineered to implement novel biological functions and systems.

- Examples:
  - Replace expensive, time-consuming chemical processes by processes at the molecular level.
  - Design molecular systems (“circuits”) that respond to special conditions in the environment.

Genome Design and Construction

- Genomes can now be synthesized efficiently.
- Mycoplasma genitalium, smallest known reproducible bacterial genome being redesigned by J. Craig Venter as a flexible platform.
- Venter wants to his cells to produce hydrogen and ethanol.
- He seeks a controversial patent.

Applied Protein Design

- Efficient enzymes (catalytic proteins)
  - Improved laundry detergents
- Protein-based drugs designed to resist rapid degradation in the body.
  - Produce slow-acting drugs

Product Synthesis

- Microbes re-designed to produce drugs
  - Insulin, a protein, can now be inexpensively produced
  - Artemisinin, an anti-malarial produced by the sweet wormwood tree, is now expensive. Work is underway to produce it inexpensively in a re-engineered cell.

- Synthetic organisms programmed to
  - Scan the environment for toxic pollutants and break them down before they cause harm.
  - Shut down gene activity when pathogens detected in blood.

Natural Product Synthesis

- Microbes re-designed to produce drugs.
- Insulin, a protein, is now inexpensively produced.
- Artemisinin, an anti-malarial produced by the sweet wormwood tree, native to China and Vietnam, is now expensive.
  - Work is underway to produce it inexpensively in a re-engineered cell.

Standard Biological Parts

- Used to make programmable circuits.
- Brings engineering principles to biology.
- BioBricks – short pieces of DNA encoding functional elements that when assembled and placed in a cell perform computations.

Synthetic Biology Goes Commercial

- Synthetic Genomics – Rockville, MD
  - Founded by Venter and others
  - Goal: energy production
- Codon Devices – Cambridge, MA
  - Founded by Endy and Keasling
  - Goal: synthetic biology tools
- Cellicon – Boston, MA
  - Founded by Collins
  - Goal: synthetic drug development

BioBricks

- Composable set of genetic building blocks (genes, short pieces of DNA).
  - They interact in a cell.
  - More than 1,000 in 2006.
- Consist of sensors, actuators, input and output devices, and regulatory elements.
- Students are enthusiastic about BioBricks.
  - iGEM 2007: more than 600 students at 60+ universities competed using BioBricks.

Types of BioBrick Parts

- Promoters – initiates transcription DNA $\rightarrow$ RNA
- Terminators – halts RNA transcription
- Repressors – encodes protein that blocks transcription of another gene
- Ribosome-binding sites – initiate protein synthesis
- Reporters – encode fluorescent proteins

- Each BioBrick can send and receive standard biochemical signals and be cut and pasted into a linear sequence of other BioBricks.

Examples of BioBrick Applications

- Re-programmed E.coli that blinks.
- A biofilm sensitive to light – captures images
- Logic gates – inputs and outputs are proteins
  - AND, OR, NOT, NAND, etc. built
  - Gates communicate by controlling concentrations of proteins.
  - Goal is to build small programmable computer

Issues with Synthetic Biology

- Systems are noisy and unpredictable
- Genetic circuits mutate & become unusable
- Biologists need to understand molecular processes better to increase reliability.
- Standardized components and environments increase reliability.

A FAB for Biology

- Oligonucleotide production is error-prone
  - Commercial methods use solid phase phosphoramidite chemistry.
    - Oligos assembled one base at at time
    - Error rate is one base in 100.
- Polymerase can repair DNA in living systems with error rate of one base in a billion.

A FAB for Biology (cont.)

- Two microarray used to produce oligos.
  - Oligos on one, their complements on another.
    - They may have errors
  - Oligos are designed to overlap & form long strings
  - Oligos on one array are cut and bind with those another.
  - Unmatched or mismatched oligos are discarded.
- This proofreading method error rate = $1{,}300^{-1}$
- When perfected, error rate = 10^{-4}.

Risks of Synthetic Biology

- Synthetic biology differs from chemistry.
  - Genetically engineered microorganisms (GEMs) are self-replicating.
  - They can evolve.
- Concerns
  - GEMS might escape the lab.
  - GEMs might proliferate out of control.
  - GEMs might threaten public health.
  - GEMs might be used maliciously.
    - Polio virus has been genetically engineered.
    - Same may be possible for smallpox and flu viruses.

Risk Containment
The Precautionary Principle

- Classify all GEMs as probably dangerous.

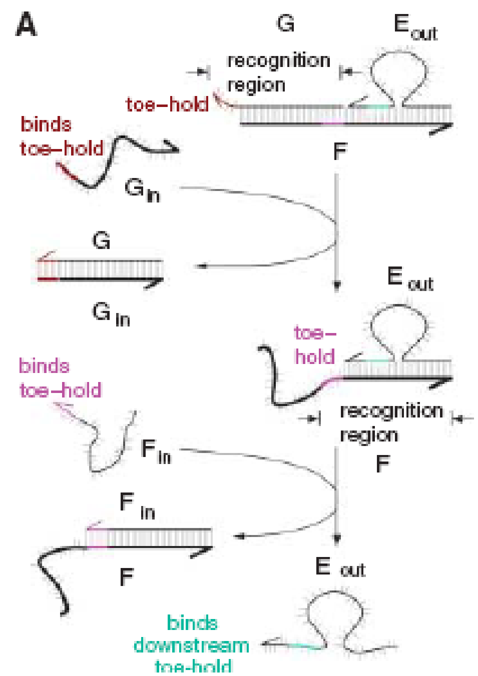
- Do studies under high level of biocontainment
- Avoid open testing
  - E.g. cleanup of toxic wastes
- Conduct research in isolated environments.
- Screen all oligonucleotide orders at supply houses.

Enzyme-Free Nucleic Acid Logic Circuits

- AND, OR, NOT gates, signal restoration, and fan-out provided in vitro.
- Doesn't release proteins into the environment.
  - Decreases the risks
- Gates are double helices of bases with dangling "toe-holds" of single base strands.
- Input and output are single strands of DNA.

AND Gate

- Gate has 3 DNA strands, E_{out} (57 nt), F (60 nt) and G (36nt).
- The 3′ ends are marked by arrows.
- Toeholds and binding regions (all six nucleotides) are in color.
- Input strands F_{in} and G_{in} (36 nt) are complementary to recognition regions within the corresponding gate strands F and G.
- E_{out} released only when F_{in} and G_{in} are present.



Other gates

- NOT
  - Design an AND gate with one fixed input that releases the complement of a string associated with a variable.
- Translator gates
  - Same as above.

Building Circuits

- Need unique DNA strings for each variable, and output to a gate.

Issues

- “The circuit without signal restoration take s2 hours to reach half-activation.”
- “The circuit with singal restoration … takes 10 hours to achieve half-activation.”

Conclusions

- Synthetic biology is generating lots of interest
- It has promise to produce new drugs and chemicals.
- Synthetic biology has important risks.
- Computation may be done more safely with enzyme-free DNA logic gates.