On the menu this afternoon…
- DNA: What is it?
- DNA Tiles from DNA strands
- Self-Assembly in a DNA soup
- DNA computing
- Template DNAs
- Do we buy it or not?

DNA for nanotechnology
- Nanostructures
  - Average double helix diameter ~ 2 nm
  - Helical pitch ~ 3.4-3.6 nm
  - Pretty stiff ( persistence length ~ 50nm)
  - Perfect specimen for bottom-up approach
  - Can encode information and form complex structures
  - Proof of concept exists

What exactly is DNA?
- Nucleobase pairs are called Watson-Crick complementary pairs
- Binding process is called hybridization
  - High probability for W-C pairs
  - Temp and salinity have to be set
- Single strand DNA can be designed and made experimentally
  - Design is based on how you order the bases

Single Strand → Double Strand
- Hybridization
Double strands → Tiles

- Use the idea of combining strands to make bigger structures
- Single-strand portion of a double strand structure can link with another single-strand portion of a double strand DNA.
- This is a random process.

*What is the possible restriction with assembling DNA this way?*

Branched DNA: The Holliday Model of DNA Crossover

Two DNA strands

- [Diagram of DNA crossover](image)

Branched DNA: The Holliday Model of DNA Crossover

- [Diagram of DNA crossover](image)

Branched DNA: The Holliday Model of DNA Crossover

- [Diagram of DNA crossover](image)

Single Crossover DNA

- Can make 2-D structures using synthetic DNA
- Break point can be at fixed points that is controlled
- Has DNA properties
- BUT
- Flimsy…
Double crossover DNA

Double Crossover TILE structure

Tile Lattice Formation

- Each DNA tile can be designed to stick with a certain type of tile
- Tile formation is determined by sticky ends
- Remember: Each tile contains several short sections of unpaired, single strand DNA that extends from the tile.
- Double crossover => four pads
- Triple crossover => 6 pads

Atomic force microscopy images of DNA lattices with triple-crossover tiles that measure 3 to 4 microns on a side.

A transmission electron microscopy image of a platinum rotary-shadowed triple-crossover lattice.

Unmeditated algorithmic self-assembly

- Start with a soup of DX DNA.
- Let them self-assemble to form a lattice structure.
- Process is random and control is through ingredients
  - Programming is picking out your soup ingredients
- Lattices can be either:
  - non-computational: containing a fairly small number of distinct tile types in a repetitive, periodic pattern
  - computational: containing a larger number of tile types with more complicated association rules which perform a computation during lattice assembly
Computing with DNA Tiles

- Based on Wang tiling
  - Find a class of tiles with finite pads that would fill a certain region
- Seminal work by Leonard Adleman
  - Self-assembly computation for HPP
  - Better than brute force approach
  - Opened the door to DNA computing

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Hamiltonian Path Problem

- Given a directed edge graph
- Determine the paths beginning at START & ending at END that visits each vertex once.
- Seems simple for small number of airports
- NP-hard problem. Exponential run-time to solve the problem.
- NP-complete problem... what is the significance of this?
- Solved by DNA computing

Adleman’s approach

- Adleman assigned to each vertex, and to each link, a single DNA strand 20 bases long.
- For example:
  - Vertex 2: TATCGGATCGGTATATCCGA
  - Vertex 3: GCTATTCGAGCTTAAAGCTA
  - Vertex 4: GGCTAGGTACCAGCATGCTT
  - Link 2->3: GTATATCCGAGCTATTCGAG
  - Link 3->4: CTTAAAGCTAGGCTAGGTAC

Examples (8 bases)

<table>
<thead>
<tr>
<th>Vertices:</th>
<th>Links:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atlanta = TATCCGA</td>
<td>Atl-Dal = CCGAGCTA</td>
</tr>
<tr>
<td>Dallas = GCTAAGCT</td>
<td>Atl-Chi = CCGAGGCT</td>
</tr>
<tr>
<td>Chicago = GGCTCGTT</td>
<td>Dal-Chi = AGCTGCT</td>
</tr>
</tbody>
</table>

In the experiment, strands representing the flights are mixed in a test-tube with the complements to the strands representing the airports.

<table>
<thead>
<tr>
<th>Complement Vertices:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atlanta* = ATAGGGCT</td>
<td>Atlanta = TATCCGA</td>
</tr>
<tr>
<td>Dallas* = CGATTCGA</td>
<td>Dallas* = ATAGGGCT</td>
</tr>
<tr>
<td>Chicago* = CCGAGCAA</td>
<td>Chicago* = CCGAGCAA</td>
</tr>
</tbody>
</table>

In the test tube we have the following:

<table>
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<tr>
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More interesting reactions
Solution

- Apply separation process like Gel electrophoresis to separate out reactions we do not need:
  - All molecules which do not start with Fresno* and do not end with Boston*.
  - All molecules which do not contain exactly 7 airports (i.e. all molecules which do not have a certain exact length).
  - All molecules which contain a repeated airport.
- Gel electrophoresis uses an electric field to separate out DNA.

Adleman’s Favorite Joke

IF THERE ARE ANY PATHS LEFT, THEN THERE IS A HAMILTONIAN PATH TO THE GRAPH


DNA electrophoresis

- Direction of migration, from negative to positive electrodes, is due to the natural negative charge carried on their sugar-phosphate backbone.
- Double-stranded DNA fragments naturally behave as long rods, so their migration through the gel is relative to their radius of gyration, or, roughly, size.
- After the separation is completed, the fractions of DNA fragments of different length are often visualized using a fluorescent dye specific for DNA.

Input/Output in DNA computing

- Input via Scaffold Strands:
  - Take as input the scaffold strands which encode the data input to the assembly computation and are capable of serving as nucleation points for assembly.
  - Tiles assemble around the scaffold strand, automatically forming a chain of connected tiles which can subsequently be used as the input layer in a computational assembly.
- Output via Reporter Strands:
  - After ligation of the tiling assembly the reporter strand provides an encoding of the output of the tiling assembly computation.
  - Think of them as the last tiles to assemble.

Steps to Self-assembly computing and Parallelism

- Mix the input DNA strands to form the DNA tiles.
- Allow the tiles to self-assemble into superstructures.
- Ligation process attaches structures that have colocalized.
- Perform a separation procedure to identify the correct output.

Perks...

- Massive parallelism
  - Where is the parallelism?
    - Think of how we are computing with DNA?
  - Global parallelism
    - Each superstructure represents a different calculation
  - Local parallelism
    - Growth on each individual superstructure can occur at many locations.
And the problems…

- The speed of DNA tiling assemblies is limited by the annealing time.
  - $10^{10}$ slower than conventional computer
- Adleman’s experiment required 7 days in lab
- A reasonable assessment of the power of DNA computation must take into account both the speed of operation as well as the degree of massive parallelism.
- DNA computing may be advantageous for classes of computational problems that can be parallelized.

Arithmetic/Boolean Computations

- Model the DNA using square tiles (DX double strand DNA has four pads/sticky ends)
- Non-rotating tiles have binding sites on all 4 sides.
  - In this example, each side has binding strength (red = 2, green = 1)
  - Strength 2 needed to bond

What am I assuming in this assembly?

DNA tile computing

- Can we self-assemble the circuit for a contemporary CPU?
  - Assuming that we can create tiles that act as circuit elements what we are really asking is:
    - Can we self-assemble the layout pattern for a CPU?
- The answer, in theory, is yes, and we may do so without using any complex computation.
- The resulting program is as big as the pattern itself, with every tile in the program being used just once in the pattern.
- This is called unique addressing
- The challenge is to come up with a small number of tiles that we can repeatedly use to come up with a pattern.

Winfree Decoder

- Using the same concept as the binary counter, make an assembly that is a useful circuit.
- Making a circuit boils down to coming up with a tile system with the smallest number of tiles possible.

Errors and limitations to DNA computing

- The hybridization process is probabilistic.
  - Error in assembly are possible and extremely devastating. Error rate 1-10%
- Speed is not even remotely comparable with silicon chips
- Combinatorial problems: at best $10^{12}$ops/sec
  - Can be done faster on conventional computers.
  - Not very promising.
- Forget about computers in a test-tube!

DNA as a scaffold

- DNA as a template for arranging other molecular components into a desired pattern
- The potential of self-assembly for fabricating molecular electronic circuits is particularly intriguing.
- NAND gates, crossbars, routing elements could be chemically attached to DNA tiles at specific chemical places, and subsequent self-assembly would proceed to place the tiles (and hence circuit elements) into the appropriate locations.
- Or, DNA tiles with attachments could self-assemble into the desired pattern, and subsequent chemical processing would create functional devices at the positions specified by the DNA tiles.
- Has been demonstrated by a research team at the University of Minnesota
DNA as a scaffold

- The team patterns a select set of crystalline DNA molecules into tiles. The tiles have a unique sequence of chemical "hooks" along each edge and scaffolding on top to hold nanocomponents.
- Self-assemble the tiles with nanocomponents on top of a silicon substrate.
- Nanocomponents are gold particles that serve as single electron storage device.

What is the problem with this approach?

Conclusion

- Forget about DNA computing computers
- Nanofabrication might be a bit more realistic
  - If error rates are cut down
- Interesting, but not breathtakingly promising.
- Don’t quit your silicon yet!!

Questions??