Molecular Computing: An Overview

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Outline

- What Is Molecular Computing?
- DNA Computing Operators
- Examples
  - Solving a Combinatorial Problem
  - Theorem Proving Using DNA
- The Difficulties of DNA Computer
- DNA Computing Applications
- Conclusion
- Information Sources
Biocomputing vs. Bioinformatics

Biocomputing

Bioinformatics

IT

BT

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What Is Molecular Computing?

The use of biological molecules, primarily DNA, DNA analogs, and RNA, for computation purpose.
DNA Computing
DNA Computing
DNA Computing
DNA Computing
DNA Computing

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DNA Computing

011001101010001

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DNA Computing

011001101010001
ATGCTCGAAGCT

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A Different Approach

- **What DNA computing is:**
  - a completely new method among a few others (e.g., quantum computing) of general computation alternative to electronic-semiconductor technology
  - uses biochemical processes based on DNA

- **What DNA computing isn’t:**
  - not to confuse with bio-computing which applies biological laws (evolution, selection) to computer algorithm design.

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Why Try New Stuff?

- Will need a dramatically new technology to overcome some CMOS limitations and offer new opportunity.
- Certain types of problems (learning, pattern recognition, fault-tolerant system, large set search algorithms) are intrinsically very difficult to solve even with fast evolution of CMOS.
- Hope of achieving massive parallelism.
Why Try DNA Computing?

- $6.022 \times 10^{23}$ molecules / mole
- Massively Parallel Search of All Possibilities
  - Desktop: $10^9$ operations / sec
  - Supercomputer: $10^{12}$ operations / sec
  - 1 µmol of DNA: $10^{26}$ reactions
- Favorable Energetics: Gibb’s Free Energy
  \[ \Delta G = -8 \text{ kcal mol}^{-1} \]
  - 1 J for $2 \times 10^{19}$ operations
- Storage Capacity: 1 bit per cubic nanometer
Why Try DNA Computing?

- The fastest supercomputer vs. DNA computer
  - $10^6$ op/sec vs. $10^{14}$ op/sec
  - $10^9$ op/J vs. $10^{19}$ op/J (in ligation step)
  - 1 bit per $10^{12}$ nm$^3$ vs. 1 bit per 1 nm$^3$
    (video tape vs. molecules)
Known CMOS limitations

Source: Texas Instruments and ITRS IC Design Technology Working Group
Future Technology Enablers

- Bio-electric computers
- True neural computing
- 1e6-1e7 x lower power for lifetime batteries
- Quantum computer, molecular electronics
- Vertical/3D CMOS, Micro-wireless nets, integrated optics
- Smart lab-on-chip, plastic/printed ICs, self-assembly
- Metal gates, Hi-k/metal oxides, Lo-k with Cu, SOI
- Wearable communications, wireless remote medicine, ‘hardware over internet’!
- Pervasive voice recognition, “smart” transportation
- Wearable voice recognition, “smart” transportation
- Vertical/3D CMOS, Micro-wireless nets, integrated optics
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- Wearable communications, wireless remote medicine, ‘hardware over internet’!
- Pervasive voice recognition, “smart” transportation
- Smart lab-on-chip, plastic/printed ICs, self-assembly
- Quantum computer, molecular electronics
- True neural computing
- Bio-electric computers

This talk

- Now +2
- +4 +6 +8 +10 +12
- +4 +6 +8 +10 +12

Source: Motorola, Inc, 2000

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Historical Timeline

Research

1950’s …

R.Feynman’s paper on submicroscopic computers

1994

L.Adleman solves Hamiltonian path problem using DNA.
Field started

1995

D.Boneh paper on breaking DES with DNA

2000

Lucent builds DNA “motor”

2005

DNA computer architecture?

Commercial

1970’s …

DNA used in bio application

1996

Affymetrix sells GeneChip DNA analyzer

2000

Human Genome Sequenced

2015

Commercial computer?
What’s Up to Date

Research still in very early stages but promise is big

First groundbreaking work by Adleman at USC only 6 years ago

No commercialization in sight within ~10 years

Main work on settling for a logic abstraction model, ways of using DNA to compute

Research sponsored by universities (Princeton, MIT, USC, Rutgers, etc) and NEC, Lucent Bell Labs, Telcordia, IBM

One way or another, DNA computing will have a significant impact
## DNA Computers vs. Conventional Computers

<table>
<thead>
<tr>
<th>DNA-based computers</th>
<th>Microchip-based computers</th>
</tr>
</thead>
<tbody>
<tr>
<td>slow at individual operations</td>
<td>fast at individual operations</td>
</tr>
<tr>
<td>can do billions of operations simultaneously</td>
<td>can do substantially fewer operations simultaneously</td>
</tr>
<tr>
<td>can provide huge memory in small space</td>
<td>smaller memory</td>
</tr>
<tr>
<td>setting up a problem may involve considerable preparations</td>
<td>setting up only requires keyboard input</td>
</tr>
<tr>
<td>DNA is sensitive to chemical deterioration</td>
<td>electronic data are vulnerable but can be backed up easily</td>
</tr>
</tbody>
</table>
DNA Computing Takes Advantage of

- Our ability to produce massive numbers of DNA molecules with specific properties (size, sequence)
- The natural proclivity of specific DNA molecules to chemically interact according to defined rules to produce new molecules
- Laboratory techniques that allow the isolation/identification of product molecules with specific properties
  - PCR, Ligation, Gel Electrophoresis, etc.
DNA Computing Operators
Basic Building Blocks

- Found in every cell’s nucleus, genes consist of tight coils of DNA’s double helix
- Number of genes/length of DNA depends on species
DNA Structure

Deoxyribonucleic Acid (DNA)

Nitrogenous Bases

- **G** Guanine
- **C** Cytosine
- **A** Adenine
- **T** Thymine
- **U** Uracil

Hydrogen bonds

Base pair

Sugar-phosphate backbone

Nucleotide
DNA Memory

A string composed of a series of four types of units (nucleotides), DNA may be viewed as logic memory or gate.

Number System (Base 4):

Two strings of DNA are bonded by paired nucleotides A-C and C-G which may be considered as complements. Example: Number \textbf{TTACAG} has a complement \textbf{AATGTC}
DNA Memory

Writing: make DNA sequences

Reading: hybridization and readout

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DNA Operators

- The bio-lab technology.
- Hybridization
- Ligation
- Polymerase Chain Reaction (PCR)
- Gel electrophoresis
- Affinity separation (Bead)
- Enzymes: restriction enzyme…
Hybridization & Ligation

- **Hybridization**
  - base-pairing between two complementary single-strand molecules to form a double stranded DNA molecule

- **Ligation**
  - Joining DNA molecules together

- **Solution generation step!**
PCR

- Polymerase Chain Reaction
- Amplifies (produces identical copies of) selected dsDNA molecules.
- Make $2^n$ copies ($n$: number of iteration)
- Solution filtering or amplification step!
PCR
(Polymerase Chain Reaction)

Region to be amplified

5’ 3’
3’ 5’

Target DNA

Add excess primers 1 and 2, dNTPs,
and Taq polymerase

Heat to 95° to melt strands
Cool to 60° to anneal primers

Primer 1

5’ 3’
3’ 5’

Primer 2

Primers extended by Taq polymerase at 60°

5’ 3’
3’ 5’

Heat to 95° to melt strands
Cool to 60° to anneal primers

3’ 5’
5’ 3’

Primers extended by Taq polymerase at 60°

5’ 3’
3’ 5’

Heat to 95° to melt strands
Cool to 60° to anneal primers

5’ 3’
3’ 5’

Primers extended by Taq polymerase at 60°

And so on
Gel Electrophoresis

- Molecular size fraction technique

Bead Separation

- Detect the specific DNA

Solution detection or filtering step!
Gel Electrophoresis

(A) Standard agarose gel electrophoresis

Wells for samples

Agarose gel
UV transparent plastic support

Soak in 0.5 μg ml⁻¹ ethidium bromide solution for 15 min

Bands of DNA fluoresce

UV UV UV

Poor separation of DNA molecules > 50 kb

Gel image
Bead Separation

Magnetic Beads

Magnet

Complementary

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Restriction Enzymes

- Cut the specific DNA site.
- Solution detection or filtering step!

EcoRI

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The First Special DNA Computer

- Special problem: given N points, find a path visiting each and every point only once, and starting and ending at a given locations. (Hamiltonian path problem)
- Solved with a DNA computer by Leonard Adleman in 1994 for N=6
- Basic approach: code each point as an 8 unit DNA string, code each possible path, allow DNA bonding, suppress DNA with incorrect start/end points.
The Hamiltonian path problem: as the number of cities grows, even supercomputers have difficulty finding the path.
Adleman’s Molecular Computer: A Brute Force Method

Each city (vertex) is represented by a different sequence of nucleotides (6 here, but Adleman used 20).

A DNA linker (edge) joining two city (vertex) strands.
Encoding (Basic Concept)

AGCT | TAGG
P_{1A} | P_{1B}

ATCC | TACC
\frac{P_{1B}}{} | \frac{P_{2A}}{}

ATGG | CATG
\frac{P_{2A}}{} | \frac{P_{2B}}{}

CGAT | CGAA
\frac{P_{3A}}{} | \frac{P_{3B}}{}}
| Procedure                  | Generate random paths through the graph | Keep only those paths that begin with \(v_\text{in}\) and end with \(v_\text{out}\) | If the graph has \(n\) vertices, then keep only those paths that enter exactly \(n\) vertices | Keep only those paths that enter all of the vertices of the graph at least once. | If any paths remain, say “Yes”;
otherwise, say “No.” |
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<tr>
<td>Hybridization &amp; Ligation</td>
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<td>PCR with (v_\text{in}) and (v_\text{out})</td>
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<td>Gel electrophoresis</td>
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<td>Antibody bead separation</td>
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<td>Sequecing</td>
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</table>
Step 1: Hybridization

Step 2: Ligation

Step 3: PCR

Step 4: Gel Electrophoresis

Step 5: Magnetic Bead Affinity Separation
Node 0: ACG
Node 1: CGA
Node 2: GCA
Node 3: TAA
Node 4: ATG
Node 5: TGC
Node 6: CGT

ACGCGAGCATAAATGTGCCGT
ACGCGAGCATAAATGTGCCGT
ACGCGAGCATAAATGTGCCGT

ACGCGAGCATAAATGTGCCGT
ACGCGAGCATAAATGTGCCGT
ACGCGAGCATAAATGTGCCGT

ACGCGAGCATAAATGTGCCGT
ACGCGAGCATAAATGTGCCGT
ACGCGAGCATAAATGTGCCGT

Gel Electrophoresis
PCR (Polymerase Chain Reaction)
Affinity Column
Ligation
Decoding
Encoding

HPP

Solution

ACGCGT
ACGCGT
ACGCGT
DNA Finds a Solution!

A Hamiltonian path with all vertices included is isolated and recovered
Another Practical Example: Molecular Theorem Proving
Molecular Theorem Prover

Resolution refutation method

Problem under consideration:

\[ P \land Q \implies R, S \land T \implies Q, S, T, P \]

Turn into: add \( R \) as

\[ \neg A \lor B \]

\[ \neg R \]

\[ \neg P \lor \neg Q \lor R, \neg S \lor \neg T \lor Q \]

\[ S, T, P, \neg R \]

\[ R = \text{true} \]

\[ \text{nil} \]

R is true!
Molecular Theorem Prover
(Abstract Implementation)
Experimental Procedure

Step 1. DNA Sequence Design
Step 2. DNA Synthesis
Step 3. Chemical Reaction in a Test Tube
  ◦ Hybridization
  ◦ Ligation
Step 4. Detection of Solutions
  ◦ PCR
  ◦ Gel Electrophoresis
Sequence Design

\[ \neg Q \lor \neg P \lor R : \]

5' \quad CGT ACG TAC GCT GAA CTG CCT TGC GTT GAC TGC GTT CAT TGT ATG

3'

\[ Q \lor \neg T \lor \neg S : \]

3' \quad TTC AGC GTA CGT ACG TCA ATT TGC GTC AAT TGG TCG CTA CTG CTT

5'

\[ S : \]

5' \quad AAG CAG TAG CGA CCA

3'

\[ T : \]

3' \quad GTC AAC GCA AGG CAG

5'

\[ P : \]

5' \quad TGC GTT CAT TGT A

3'

\[ R : \]

5' \quad CAT ACA ATG AAC GCA

3'

\[ \neg R : \]

3' \quad 5'
Reaction in a Test Tube

\[ R \lor \neg P \lor \neg Q \]

\[ T \lor \neg S \]

\[ R \lor \neg P \lor \neg Q \]

\[ \neg R \]
Reaction in a Test Tube

Q \lor \neg T \lor \neg S

T

P

R \lor \neg P \lor \neg Q

S

\neg R
Reaction in a Test Tube

\[
\begin{align*}
R &\lor \neg P \\
\neg Q &\lor \neg T \lor \neg S
\end{align*}
\]
Reaction in a Test Tube

Q ∨ ¬T ∨ ¬S

T

P

R ∨ ¬P ∨ ¬Q

¬R

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Reaction in a Test Tube

\[ Q \lor \neg T \lor \neg S \]

\[ T \]

\[ P \]

\[ R \lor \neg P \lor \neg Q \]

Reaction in a Test Tube

\[ R \lor \neg P \lor \neg Q \]

\[ Q \lor \neg T \lor \neg S \]

\[ T \]

\[ P \]

\[ \neg R \]

\[ S \]

\[ \neg Q \lor \neg T \lor \neg S \]

\[ \neg P \lor \neg Q \]

\[ \neg R \]
Hybridization and Ligation
Hybridization and Ligation

Q ∨ ¬T ∨ ¬S

TTC AGC GTA CGT ACG TCA ATT TGC GTC AAT TGG TCG CTA CTG CTT

AGT TAA ACG CAG TTA

T

GTC AAC GCA AGG CAG

S

ACC AGC GAT GAC GAA

P

CAT ACA ATG AAC GCA

T

GTA TGT TAC TTG CGT CAG TG CGT TCC GTC AAG TCG CAT GCA TGC

R ∨ ¬P ∨ ¬Q

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Hybridization and Ligation

\[ Q \lor T \lor S \]

\[ \neg R \]

\[ P \]

\[ Q \lor T \lor S \]

\[ Q \lor T \lor S \]

\[ \neg P \lor \neg Q \]

\[ \neg R \]

\[ P \]

\[ Q \lor T \lor S \]

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\[ \neg R \]

\[ P \]

\[ Q \lor T \lor S \]

\[ Q \lor T \lor S \]

\[ \neg P \lor \neg Q \]

\[ \neg R \]

\[ P \]

\[ Q \lor T \lor S \]

\[ Q \lor T \lor S \]

\[ \neg P \lor \neg Q \]
Molecular Theorem Prover

Experimental Steps

I. MIX
100pmol/each \(\rightarrow\) Total 20 ul

II. Denaturation
(95°C 10 min)

III. Annealing
95°C 1 min \(\rightarrow\) 15°C : 1°C down/min

IV. Polyacrylamide gel Electrophoresis(20%)
(PAGE)

V. Detection of solution
: 75bp ds DNA

Results

20 bp DMA marker (Talara)

Mixture Reaction

20 bp DNA marker

bp

20 bp

2 3 4 5 6
The Difficulties of DNA Computer
The Reality of DNA Based Computation

- Symmetry makes control difficult.
- Importance of Non-Watson-Crick Pairing.
- Importance of hybridization protocols.
- Importance of concentration and environment.
- Fidelity of ligation is high, but **NOT** perfect.
- DNA molecules breath.
The Reality of DNA Based Computation

- Affinity binding is a filtration process.
- Complex ligation produces complex products.
- Restriction enzymes produces partial digestion products.
- Base stacking is often determining interaction.
- DNA is a physical chemical system.
Encoding Problems

- Encoding Problems
  - encoding problem is mapping the problem instance onto a set of DNA molecules and molecular biology protocols so that the resulting products contain an answer to instance of the problem
  - prevent errors
  - enable extraction
Operational Problems

- It takes TOO long times
  - hybridization/ligation operation over 4 hours
  - In Adleman’s experiments : 7 days!
Operational Problems

- Not Perfect Operation
  - Hybridization Mismatches
  - Extraction Errors
  - Volume and Mass to solve a problem

- False Negatives
- False Positives
Hybridization Mismatches

- Reliability: False Positives and Negatives
- Efficiency

Mismatched Hybridization

\begin{align*}
\text{AGGCTTAGCT} \\
\text{TCCAGATCGA}
\end{align*}

Hairpin Hybridization

\begin{align*}
\text{AGGC}^T \text{A}_C \\
\text{TCC}_{T} \text{T} \text{G}
\end{align*}

Shifted Hybridization

\begin{align*}
\text{AGGCTTAGCT} \\
\text{CGAATCGAGC}
\end{align*}
Detection Problems

- NOT exact detection
- Gel electrophoresis is widely used detection technique.
  - We can not separate the exact solution!
Sources of Errors

a) Common operation in handling DNA is filtering:

- Heterogenous mix
- DNA filter
  - 5% error rate
- Single DNA solution

Leads to high output error rate

b) Chain Reaction for DNA amplification.

- ATTGA..
- ATGGA..

Rare type of error, but does present a problem

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Sources of Errors

c) Binding error. Expect binding between complements

Formation of double helix

Error causes bulges, missed bonds -- translates into output errors

- Error resilient computation techniques required:
  - classic error correction with redundant representation
  - careful data encoding - trade off density for resiliency
  - varying environment conditions may improve performance

- Question: are errors always bad? In this case, an occasional mutation may lead to improved learning
DNA Computing Applications
Applications of Biomolecular Computing

- Massively parallel problem solving
- Combinatorial optimization
- Molecular nano-memory with fast associative search
- AI problem solving
- Medical diagnosis, drug discovery
- Cryptography
- Biocomputer
- Further impact in biology and medicine:
  - Wet biological data bases
  - Processing of DNA labeled with digital data
  - Sequence comparison
  - Fingerprinting
DNA Adder

- [UC Berkely, USA]

The Addition Reaction: Primer Extension

5’ Primer Extension 5’ Primer DNA (= 2^{nd} digit)

3’ Template DNA

Polymerase
Massively Parallel Theorem Proving

- [Warsaw Univ. of Technology, Poland]

IF Premise THEN Conclusion

Premise

Conclusion
Breaking DES

[Princeton, USA]

A path in the graph
Future Applications
a) Self-replication: Two for one
   Based on DNA self-replication

b) Self-repair:
   Based on regeneration

c) DNA computer
   mutation/evolution

or

(d) New meaning of a computer virus?

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Sequence programmable and evolvable molecular systems have been constructed as cell-free chemical systems using biomolecules such as DNA and proteins.
Molecular Storage for Massively Parallel Information Retrieval

Trillions of DNA

<table>
<thead>
<tr>
<th>Name</th>
<th>Tel.</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>James</td>
<td>419-1332</td>
<td>Washington DC</td>
</tr>
<tr>
<td>David</td>
<td>352-4730</td>
<td>La Jolla, CA.</td>
</tr>
<tr>
<td>Paul</td>
<td>648-7921</td>
<td>Honolulu, HI</td>
</tr>
</tbody>
</table>

| Julia | 418-9362 | Palo Alto CA |

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Molecular Computer on a Chip

DNA computing algorithm + MEMS (Microfluidics)

Microreactor  PCR  Gel Electrophoresis

Real DNA computer

Detection  Bead
BioMEMS: The Next Transistors
Integrates sample handling, separation and detection and data analysis for: DNA, RNA and protein solutions using **LabChip technology**.
Conclusion

- DNA computing uses DNA molecules for computing or as storage materials.
- DNA computing technology has many interesting properties, including
  - Massively parallel, solution-based, biochemical
  - Miniaturized, nano-scale, biocompatible
  - High energy efficiency
  - High memory storage density
- DNA computing is in a very early stage of development.
Research Projects/Groups

- **MIT**, Caltech, Princeton University, Bell Labs
- **EMCC** (European Molecular Computing Consortium) is composed of national groups from 11 European countries
- **BioMIP Institute** (BioMolecular Information Processing) at the German National Research Center for Information Technology (GMD)
- Molecular Computer Project (**MCP**) in Japan
- Leiden Center for Natural Computation (**LCNC**)
- Molecular Evolutionary Computing (**MEC**) Project in Korea, Seoul National Univ.
Web Resources

- European Molecular Computing Consortium (EMCC): http://www.csc.liv.ac.uk/~emcc/
- BioMolecular Information Processing (BioMip): http://www.gmd.de/BIOMIP
- Leiden Center for Natural Computation (LCNC): http://www.wi.leidenuniv.nl/~lcnc/
- Biomolecular Computation (BMC): http://bmc.cs.duke.edu/
- DNA Computing and Informatics at Surfaces: http://www.corninfo.chem.wisc.edu/writings/DNAcomputing.html
- SNU Molecular Evolutionary Computing (MEC) Project: http://bi.snu.ac.kr/Research/
Books