Nucleic Acids
Why do I care?

Proteins do everything, right?

revolutions at the turn of the century
opportunities for the 21st century
In the beginning...

DNA $\rightarrow$ mRNA $\rightarrow$ Protein

Archival information storage

Transient information storage

Catalysis, structure, regulation, et al.
Chicken & Egg?

DNA

↓

mRNA

↓

Protein

Archival information storage

Transient information storage

Catalysis, structure, regulation, et al.
RNA can do everything

DNA → RNA → Protein

Archival information storage

Transient information storage

Catalysis! 1980-2000

Catalysis, structure, regulation, et al.
Project Encode (2007)

(More) rewriting of textbooks

June 2007, published in Nature

- Some regions of DNA far from protein-coding genes (extreme “junk?”) are nevertheless highly conserved
- Most of both strands of the DNA is transcribed (far beyond that required for protein-coding genes)
21st Century Opportunities

DNA → pre-mRNA → mRNA → Protein

- DNA
- late '80s

- pre-mRNA
  - early '80s, but...
  - Alternative splicing
  - RNA Editing
    - late '80s
  - Riboswitches
    - early '00s

- mRNA
  - Riboswitches
  - micro RNA
    - late '90s
  - RNAi
    - late '90s

- Protein
  - To be discovered...
  - 2010

- "so 20th century"

Tuesday, November 6, 12
DNA(RNA) Nanotechnology

Folding DNA to create nanoscale shapes & patterns


Start with long single stranded DNA (black line)

Then add a large number of carefully designed short, complementary oligos (staples) to “stitch” the DNA into a more compact (and well-defined) structure
DNA(RNA) Nanotechnology

Start with long single stranded DNA (black line)

Then add a large number of carefully designed short, complementary oligos (staples) to “stitch” the DNA into a more compact (and well-defined) structure

Pay careful attention to the DNA helical phasing

Tuesday, November 6, 12
DNA(RNA) Nanotechnology
Reconfigurable DNA Origami to Generate Quasifractal Patterns

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†Department of Chemistry and Biochemistry and ‡The Biodesign Institute, Arizona State University, Tempe, Arizona 85287, United States

Supporting Information

ABSTRACT: The specificity of Watson–Crick base pairing, unique mechanical properties of DNA, and intrinsic stability of DNA double helices makes DNA an ideal material for the construction of dynamic nanodevices. Rationally designed strand displacement reactions can be used to produce dynamic reconfiguration of DNA nanostructures postassembly. Here we describe a ‘fold–release–fold’ strategy of multiple strand displacement and hybridization reactions to reconfigure a simple DNA origami structure into a complex, quasifractal pattern, demonstrating a complex transformation of DNA nanoarchitectures.

KEYWORDS: Dynamic DNA nanotechnology, strand displacement, reconfiguration, fractal
DNA(RNA) Nanotechnology

LETTER

DNA-based self-assembly of chiral plasmonic nanostructures with tailored optical response


Tuesday, November 6, 12
Molecular robots guided by prescriptive landscapes

Kyle Lund1,2, Anthony J. Manzo3, Nadine Dabby4, Nicole Michelotti3,5, Alexander Johnson-Buck3, Jeanette Nangreave1,2, Steven Taylor6, Renjun Pei6, Milan N. Stojanovic6,7, Nils G. Walter3, Erik Winfree4,8,9 & Hao Yan1,2

Figure 1 | Deoxyribozyme-based molecular walker and origami prescriptive landscape. a, The NICK3.4A_{+1} spider consists of a substrate track, turns and continues to a STOP site (red). d, Schematic of the DNA origami landscape with positions A–E labelled; track EABD is shown.
DNA(RNA) Nanobiotechnology

Ribosome
An RNA machine with protein cofactors
What stabilizes protein structures?

What *directs* protein structures?
The DNA Duplex

What stabilizes the duplex?

What *directs* duplex structure?
Which is most stable?

5’-ACCGCCGACGT-3’
3’-TGGCGGCTGCA-5’

5’-ACCGCCGACGT-3’
3’-AGGCGGCTGCC-5’
DNA
A look at the Chemistry
DNA
A look at the Chemistry
DNA
A look at the Chemistry
DNA
A look at the Chemistry
DNA
A look at the Chemistry
DNA
A look at the Chemistry

Tuesday, November 6, 12
DNA
A look at the Chemistry
DNA
A look at the Chemistry
DNA
A look at the Chemistry
DNA
A look at the Chemistry

Tuesday, November 6, 12
What forces are important?

Electrostatics

Hydrogen Bonding

Burial of Hydrophobic Surface & Stacking

Tuesday, November 6, 12
Base Pairing
(Donors matched to Acceptors)
Base Pairing
(Donors matched to Acceptors)

Major Groove

Minor Groove
Base Pairing
(Donors matched to Acceptors)
Base Pairing
(Donors matched to Acceptors)

Good base pairing
Watson-Crick facing
but *Anti-Watson-Crick* orientation
Base Pairing
(Donors matched to Acceptors)

Good base pairing
WC-Hoogsteen facing
Bad Base Pairing
(Donors *not* matched to Acceptors)
Bad Base Pairing
(Donors to Acceptors with terrible angles)
Wild (but good) Base Pairing

G-quartet (Telomeres)
AT Base Pair

Ten H-Bonds

Tuesday, November 6, 12
How important are H-bonds in DNA?

Table 1. Free Energies and Melting Temperatures for Dodecamer Duplexes Containing a Variable T-X, F-X, B-X, or D-X Base Pair (X = A, T, C, G)

<table>
<thead>
<tr>
<th>duplex</th>
<th>Tm (°C)</th>
<th>(\Delta G^\circ) (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5'-CTTTCGTTTCTT-3'</td>
<td>39.4</td>
<td>12.3</td>
</tr>
<tr>
<td>5'-GAAAAAGAAAAA-3'</td>
<td>26.4</td>
<td>8.7</td>
</tr>
<tr>
<td>5'-CTTTCGTTTCTT-3'</td>
<td>30.7</td>
<td>9.3</td>
</tr>
<tr>
<td>5'-GAAAAAGAAAAA-3'</td>
<td>27.1</td>
<td>8.9</td>
</tr>
<tr>
<td>5'-CTTTCGTTTCTT-3'</td>
<td>21.4</td>
<td>7.4</td>
</tr>
<tr>
<td>5'-GAAAAAGAAAAA-3'</td>
<td>25.0</td>
<td>8.2</td>
</tr>
<tr>
<td>5'-CTTTCGTTTCTT-3'</td>
<td>23.0</td>
<td>8.0</td>
</tr>
<tr>
<td>5'-GAAAAAGAAAAA-3'</td>
<td>20.2</td>
<td>7.3</td>
</tr>
<tr>
<td>5'-CTTTCGTTTCTT-3'</td>
<td>21.0</td>
<td>7.5</td>
</tr>
<tr>
<td>5'-GAAAAAGAAAAA-3'</td>
<td>22.9</td>
<td>7.8</td>
</tr>
<tr>
<td>5'-CTTTCGTTTCTT-3'</td>
<td>20.1</td>
<td>7.6</td>
</tr>
<tr>
<td>5'-GAAAAAGAAAAA-3'</td>
<td>20.3</td>
<td>6.7</td>
</tr>
<tr>
<td>5'-CTTTCGTTTCTT-3'</td>
<td>20.8</td>
<td>7.4</td>
</tr>
<tr>
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<td>7.6</td>
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<tr>
<td>5'-CTTTCGTTTCTT-3'</td>
<td>19.7</td>
<td>7.4</td>
</tr>
<tr>
<td>5'-GAAAAAGAAAAA-3'</td>
<td>17.6</td>
<td>6.9</td>
</tr>
</tbody>
</table>

*Conditions: 100 mM NaCl, 10 mM MgCl₂, 10 mM Na·PIPES, pH 7.0, 1.6 μM each strand.
Burial of hydrophobic surface drives helix formation (hydrophobic core / stacking interactions)

Flat faces are nonpolar
Edges are very polar (can H-bond)
Furanose Sugar Ring
Furanose Sugar Ring

C3' exo

C2' exo

Unpuckered

C2' endo

C3' endo

C2' endo - C3' exo

C2' exo - C3' endo

Staggered Puckered

Eclipsed Planar
Why is Watson-Crick so good?

All four WC base pairs are *isosteric*.
Why is Watson-Crick so good?

All four WC base pairs are *isosteric*. 

Tuesday, November 6, 12
Why is Watson-Crick so good?

All four WC base pairs are *isosteric*.
Why is Watson-Crick so good?

All four WC base pairs are isosteric.
Why a helix?
Why *major* and *minor* grooves?
Why is the major groove so good?

Major Groove

Minor Groove
Why is the major groove so good?

Major Groove

Minor Groove
Why is the major groove so good?

Major Groove

Minor Groove
Why is the major groove so good?

**Major Groove**

**Minor Groove**
Nucleic Acid “Triples / Platforms”

Major Groove Interactions
Protein - Nucleic Acid Interactions

Gln

Asn

Arg

Major Groove Interactions
B-form DNA

B-form

Residues per turn =10
Twist per base pair = 36°
Rise per pair = 3.4Å
c2’-endo

Minor groove width = 5.7Å
Major groove width = 11.7Å

Minor groove depth = 7.5Å
Major groove depth = 8.8Å
B-form DNA

Residues per turn = 10
Twist per base pair = 36°

Rise per pair = 3.4Å
c2'-endo

Minor groove width = 5.7Å
Major groove width = 11.7Å

Minor groove depth = 7.5Å
Major groove depth = 8.8Å

A-form

Residues per turn = 11
Twist per base pair = 33°

Rise per pair = 2.9Å

Minor groove width = 11Å
Major groove width = 2.7Å

Minor groove depth = 2.8Å
Major groove depth = 13.5Å

Tuesday, November 6, 12
A-form RNA

Residues per turn = 11
Twist per base pair = 33°
Rise per pair = 2.9Å
c3'-endo

Minor groove width = 11Å
Major groove width = 2.7Å

Minor groove depth = 2.8Å
Major groove depth = 13.5Å
A-form RNA

- Residues per turn = 11
- Twist per base pair = 33°
- Rise per pair = 2.9 Å
- c3'-endo
- Minor groove width = 11 Å
- Major groove width = 2.7 Å
- Minor groove depth = 2.8 Å
- Major groove depth = 13.5 Å
Compare

A-form (RNA)

- Minor groove width = 11Å
- Major groove width = 2.7Å

- Minor groove depth = 2.8Å
- Major groove depth = 13.5Å

B-form (DNA)

- Minor groove width = 5.7Å
- Major groove width = 11.7Å

- Minor groove depth = 7.5Å
- Major groove depth = 8.8Å
Z-DNA

- Residues per turn = 12
- Twist per base pair = -9 / -51°
- Rise per pair = 3.7Å
- "c3'-endo(syn) / c2'-endo"
- Minor groove width = 2.0Å
- Major groove width = 8.8Å
- Minor groove depth = 13.8Å
- Major groove depth = 3.7Å

Tuesday, November 6, 12
Ends of DNA duplexes

“Blunt” ends
Ends of DNA duplexes

“Blunt” ends
Simple Structure - Hairpin
Classic Structure - Pseudoknot
Hammerhead Ribozyme
Ribosome
An RNA machine with protein cofactors
Winged Helix DNA Binding Domain
Classic helix-turn-helix
Winged Helix DNA Binding Domain

Classic helix-turn-helix

Hrfx1 bound to its X-box binding site

Arg58

Hrfx1 bound to its X-box binding site