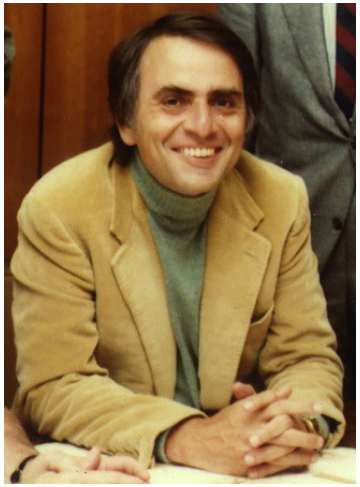
Theory-definition of life

A self-sustaining chemical system capable of Darwinian evolution

Carol Cleland



Carl Sagan

Our adopting this theory-definition tells you that *we* think that the only way to generate matter having the properties that we value in life is through a process of: (a) replication, (b) where replicates have non-anticipatory imperfections, that (c) are themselves replicable.

Natural selection does the rest.

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What does Darwinism need for an informational polymer?

Building blocks must fit Schrödinger's aperiodic crystal
Must keep *structure constant with changing information*

Needs a repeating backbone charge (negative or positive)
Must keep *properties constant with changing information*

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What does Darwinism need for an informational polymer?

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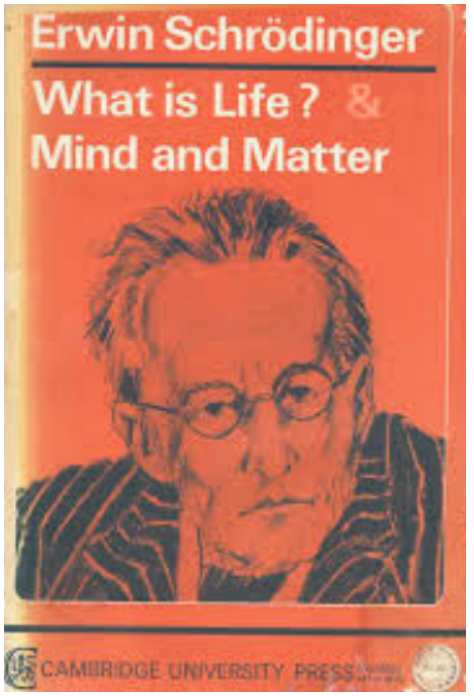
Must keep *properties constant with changing information*

Schrödinger in 1943 knew nothing about DNA.
But he knew that simple binding cannot guarantee fidelity of information transfer needed for biology. For that, Schrödinger needed the **physics of phase transitions**. For *that*, exchangeable informational building blocks must all have the same size/shape. They must all fit in an **aperiodic crystal structure**.



This eliminates some polymer "concepts"

For example, many suggest that inter-base hydrogen bonding is not important

Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 10493–10495, September 1997

Myron Goodman
USC

Commentary

Hydrogen bonding revisited: Geometric selection as a principal determinant of DNA replication fidelity

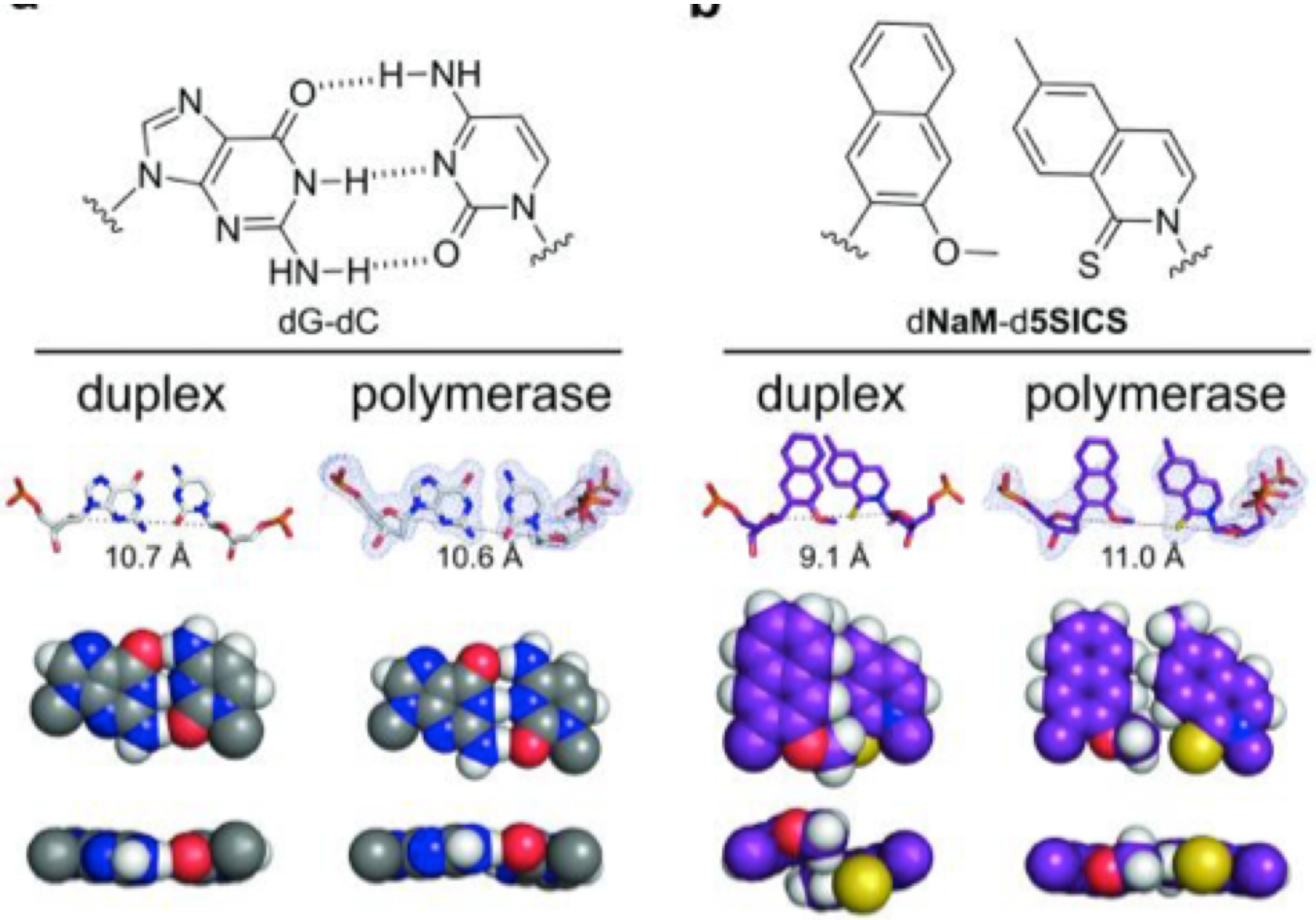
Myron F. Goodman

Not an incoherent view

- Hydrophilic part of the DNA is the phosphates, on outside.
- The nucleobases are the hydrophobic parts.
- Bases move into stacked Schrödinger aperiodic “crystal”.
- This requires uniform size/shape (= geometry).
- Hydrophobic interactions drive duplex formation energy.
- Hydrogen bonds incidental; can be dispensed with.

Goodman's view influenced modern synthetic biology

Hydrophobic size complementary added base pairs



Eric Kool
Ichiro Hirao
Floyd Romesberg

Hydrophobic pairs replicated by DNA polymerases

Floyd got *E. coli* to replicate a plasmid with a hydrophobic pair.

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But when not constrained by a polymerase active site...

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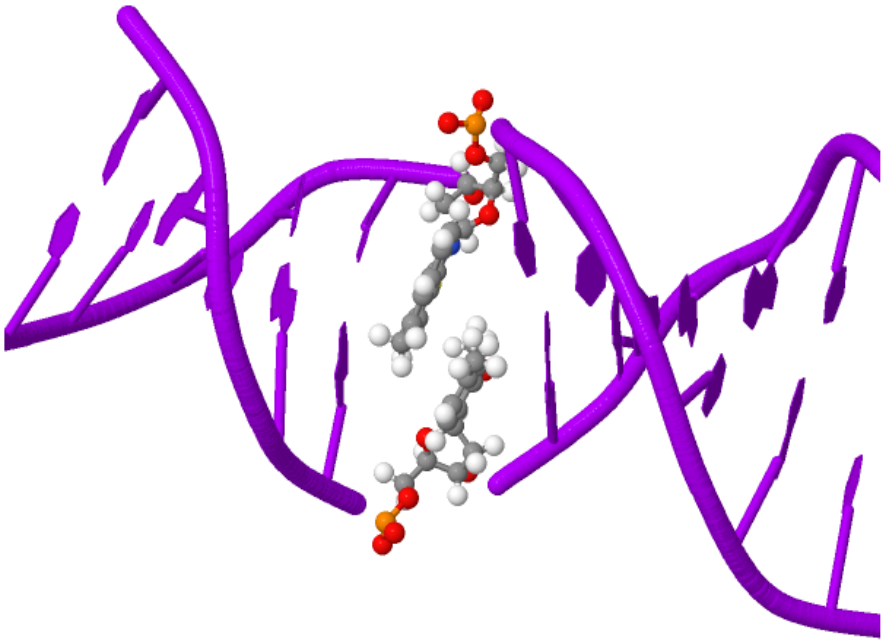

… the double helix is distorted when size-complementary hydrophobic bases are not joined by hydrogen bonds.

Oily structures intercalate, distort DNA.

This defeats the Schrödinger aperiodic crystal structure.

The universal informational genetic polymer will not exclusively rely on hydrophobic forces for self-assembly

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Synthesis lest us test this with genetic systems that completely exploits H-bonds

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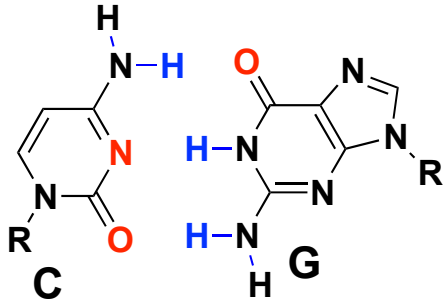
pyDAA

Donor

Acceptor

Acceptor



puADD

Acceptor

Donor

Donor

pyADD

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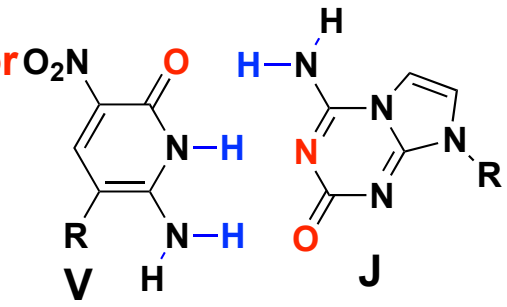


puDAA

Donor

Acceptor

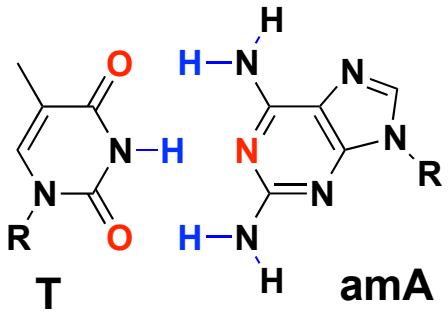
Acceptor

pyADA

Acceptor

Donor

Acceptor



puDAD

Donor

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pyDAD

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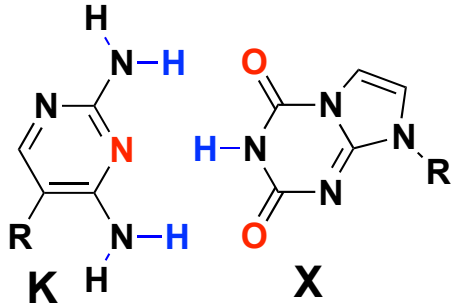


puADA

Acceptor

Donor

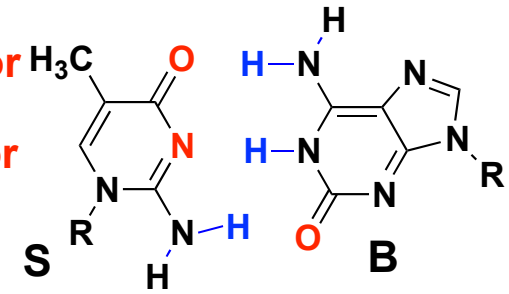
Acceptor

pyAAD

Acceptor

Acceptor

Donor



puDDA

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Acceptor

pyDDA

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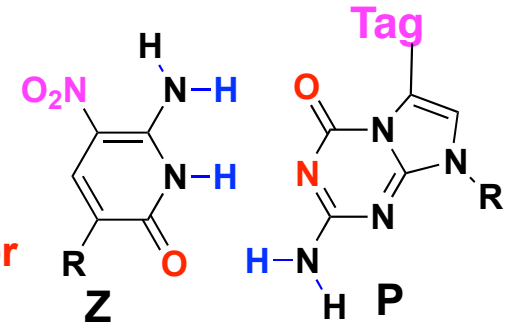

puAAD

Acceptor

Acceptor

Donor

Artificially Expanded Genetic Information System (AEGIS)

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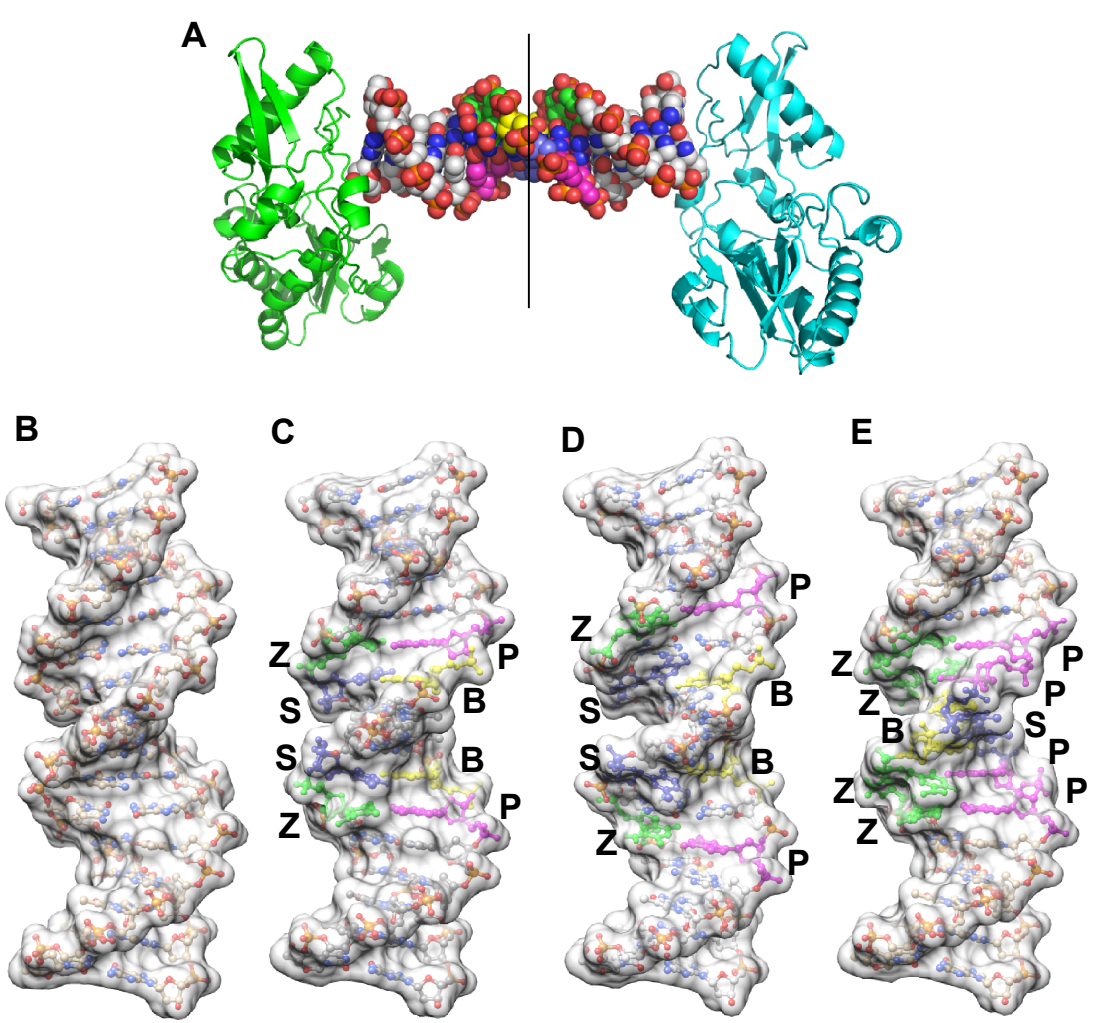
These building blocks are interchangeable in size and shape



(**A**) Georgiadis host-guest with reverse transcriptase (cyan/green) bound 16mer hachimoji DNA.
(**B**) Hachimoji DNA **PB** (green), **P**C (red), **PP** (blue) atop GC DNA.
(**C**) Self-complementary CTTAT**PB**TA**SZ**ATAAG
(**D**) Self-complementary CTTA**P**C**B**TA**S**G**Z**TAAG.
(**E**) Self-complementary CTTAT**PPSBZZ**ATAAG

Aperiodic crystal violated most by A:T, not hachimoji pair

What does Darwinism need?

A genetic system able to change encoded information without changing its regular structure (= Schrödinger)

Homochirality is a derivative of this

A genetic system able to change its encoded information content without changing its physical chemical behavior

Such as: its solubility, its molecular recognition, reactivity

Lessons from terran biochemistry

In proteins, polysaccharides, most every other class of molecules, including abiological polymers, physical behavior and reactivity change dramatically even with small structure changes.

Sickle cell, 1 amino acid change

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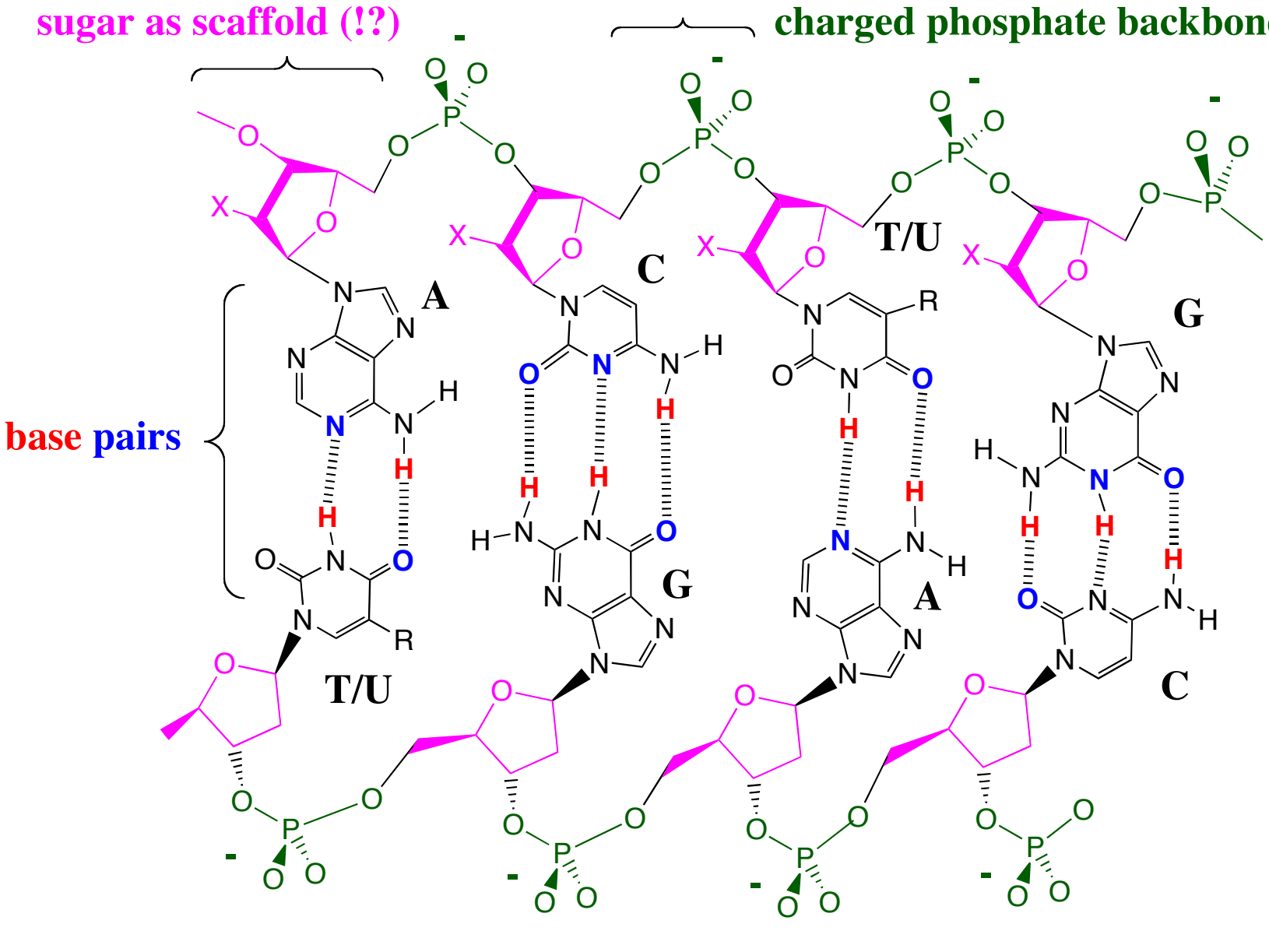
Polyelectrolyte allows DNA to be Darwinian

Can change its information without changing its behavior



NASA

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Synthesis again supports this. Made DNA without repeating charges

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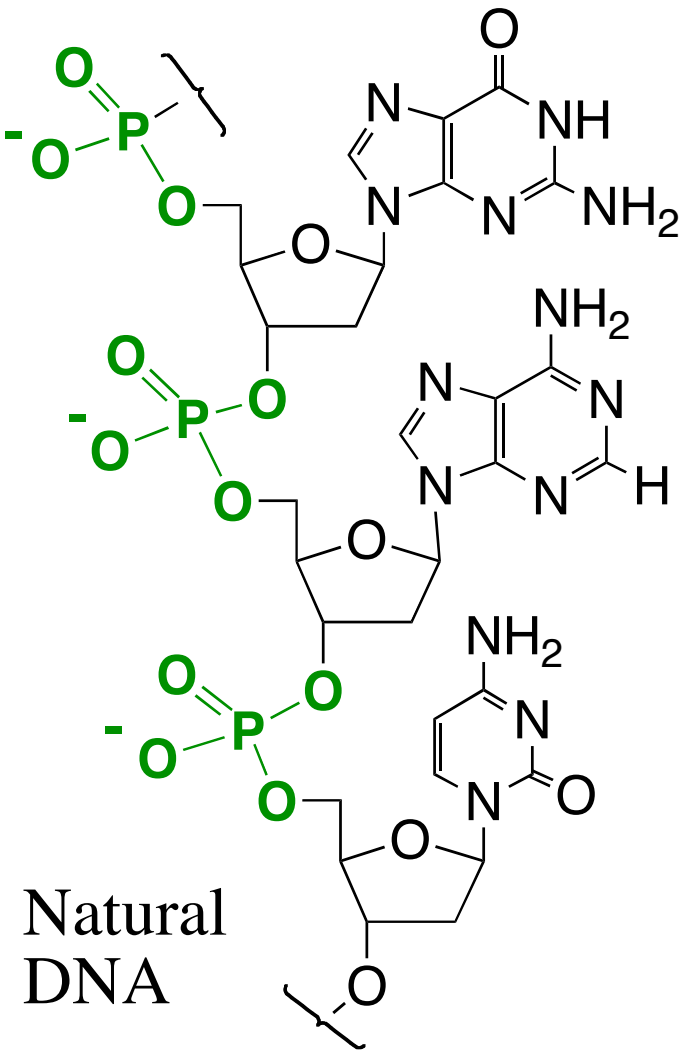
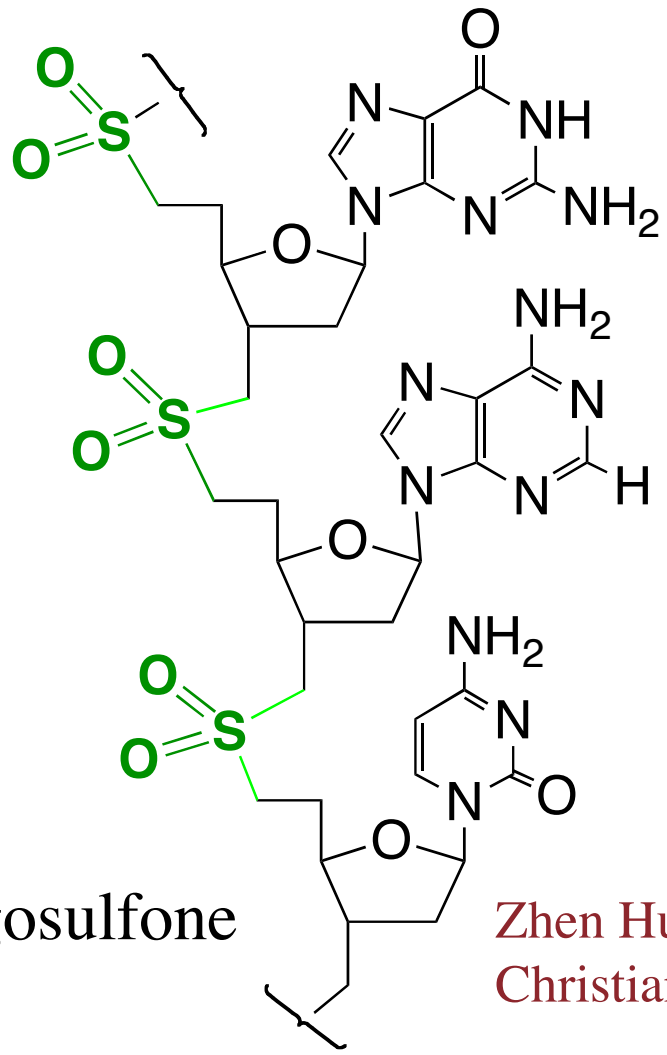


Natural DNA

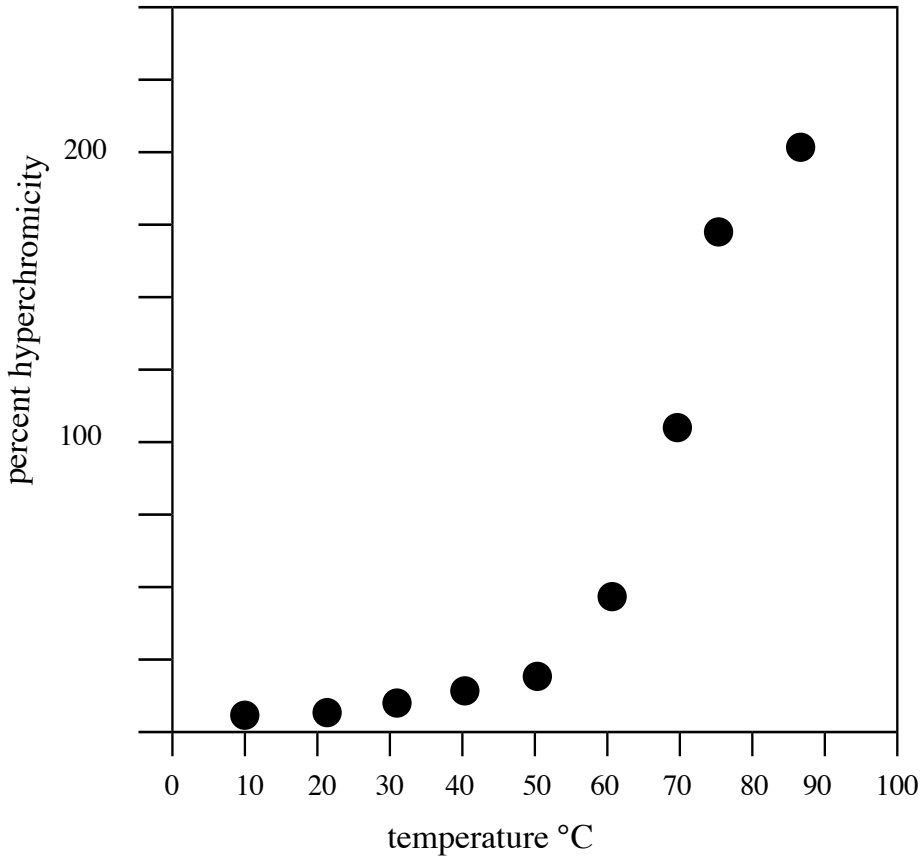


Oligosulfone

Zhen Huang
Christian Schneider

Rule-based molecular evolution fails n > 6

Richert, C., Roughton, A. L., Benner, S. A. (1996) Nonionic analogs of RNA with dimethylene sulfone bridges. *J. Am. Chem. Soc.* 118, 4518

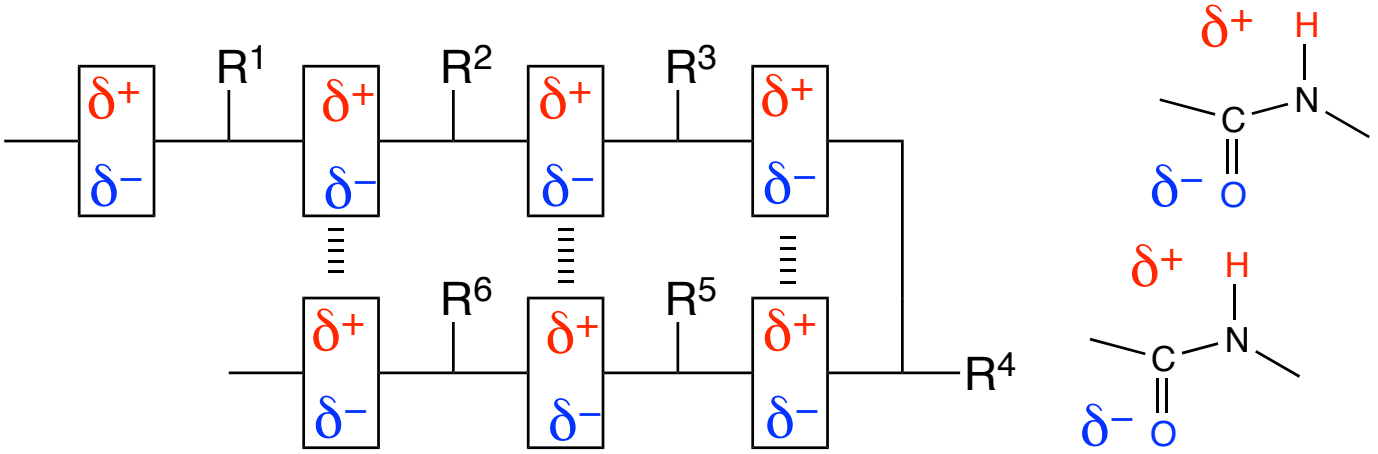


Zhen Huang
Clemens Richert

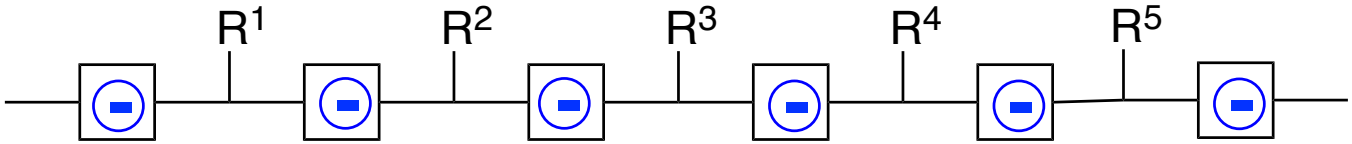
ribo-ASO_2USO_2GSO_2GSO_2USO_2CSO_2ASO_2U

Longer oligosulfones fold (like proteins); Different oligosulfone sequences have very different properties (like proteins).

Compare peptides, with repeating dipole

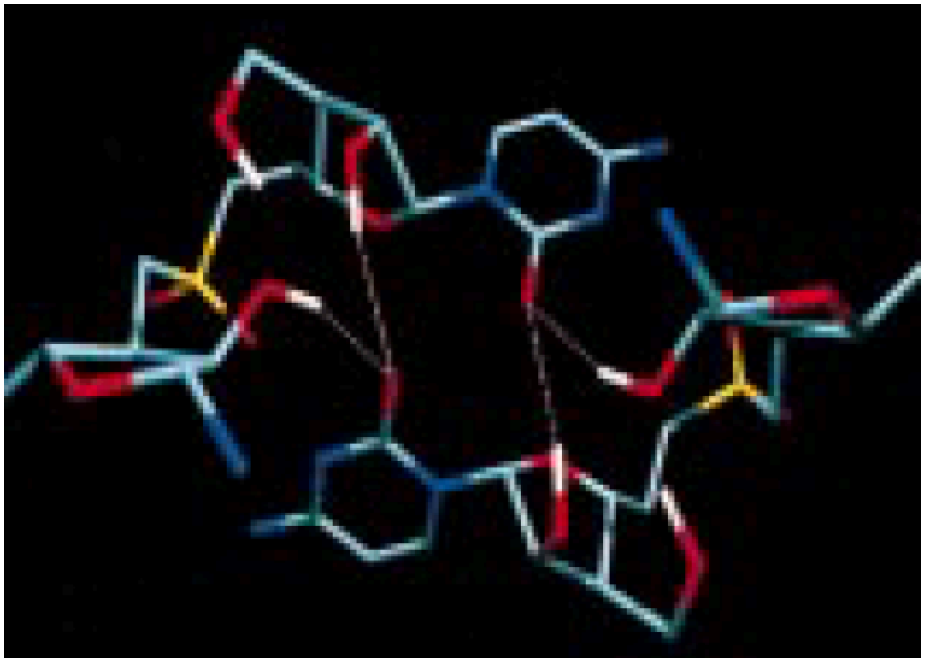


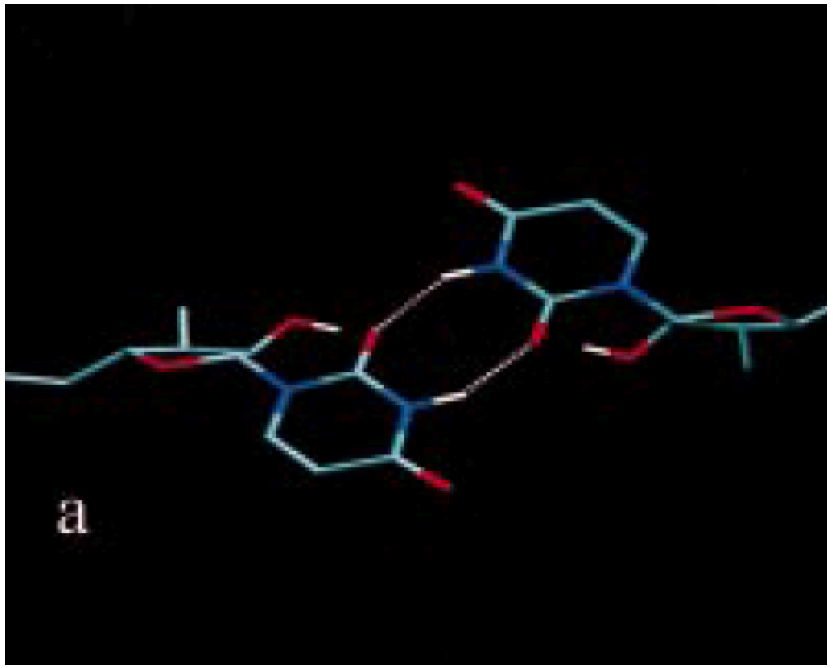
(above) A backbone with a repeating dipole easily folds
(below) A backbone with a repeating charge extends to template

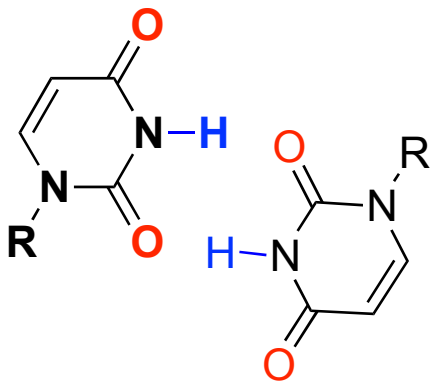


Polyelectrolyte backbone slows folding, allows templating.
= polyelectrolytes are soluble in water.

Sulfones fold, no Watson Crick rules

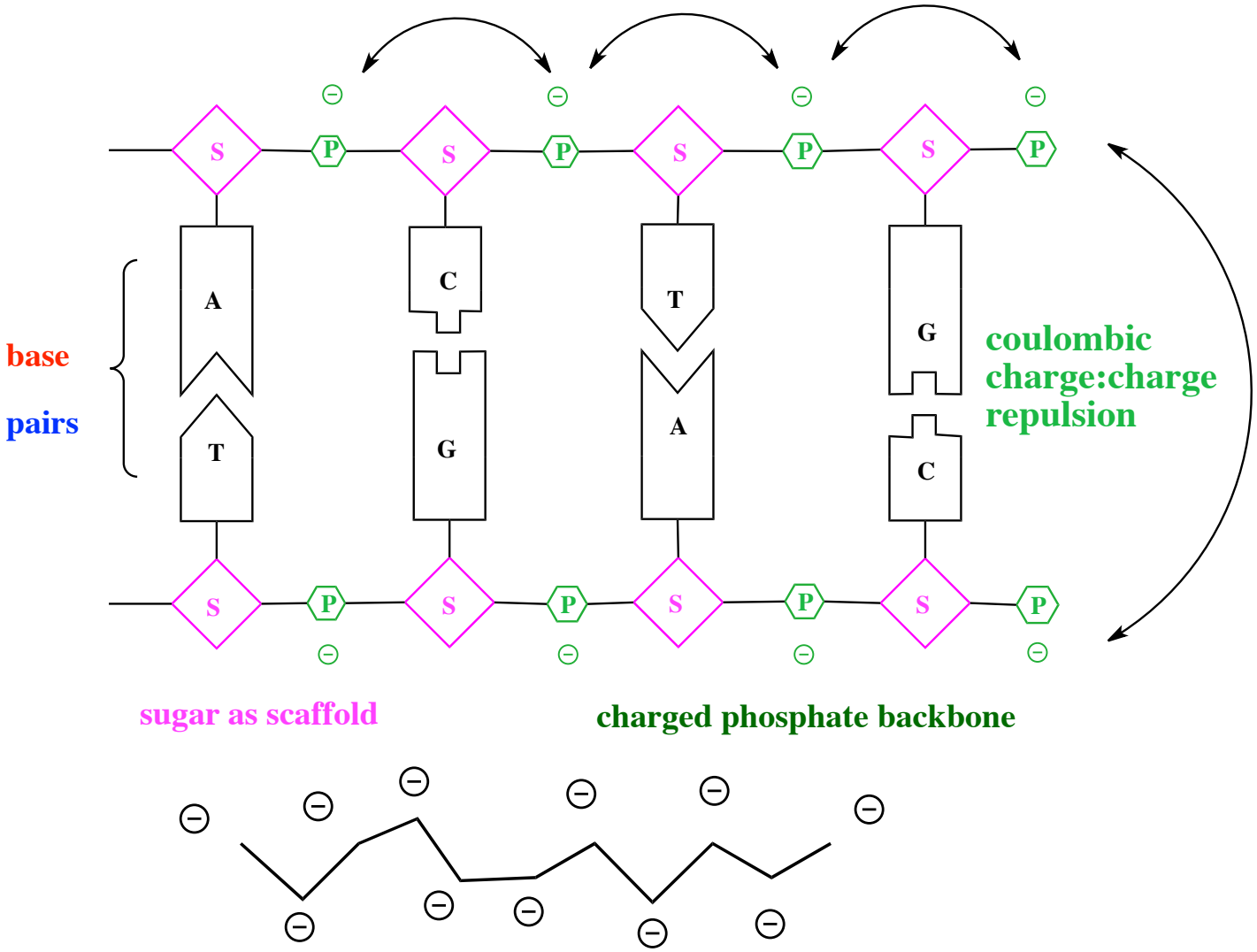






USO_2G

Do not overlook interstrand repulsion



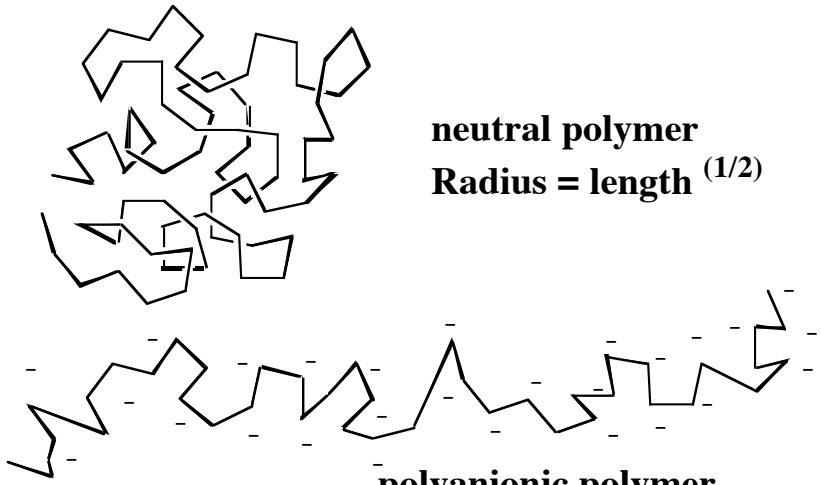
Coulomb's law predicts that the backbones repel. ***Duplex is more stable in high salt.***

Drives strand-strand inter-actions as far from backbone as possible.

This is what gives Watson-Crick rules

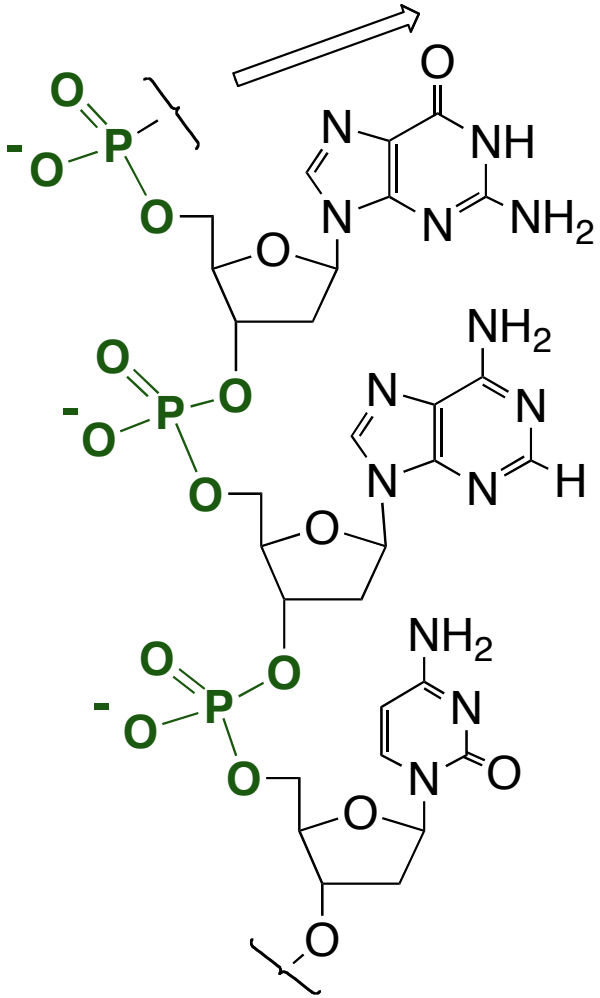
Darwinian informational biopolymers molecules *must* be charged

1. Keeps the biopolymer dissolved (in water).
2. Backbone-backbone coulombic repulsions force strand-strand contacts to Watson-Crick edges of nucleobases (**= rules**).
3. Polyanion discourages folding.



neutral polymer
Radius = length $^{(1/2)}$

polyanionic polymer
Radius = length $^{>>(1/2)}$



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Synthesis lets us test this with genetic systems that completely exploits H-bonds

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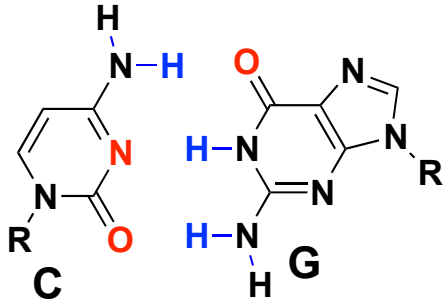
FAME

pyDAA

Donor

Acceptor

Acceptor



puADD

Acceptor

Donor

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pyADD

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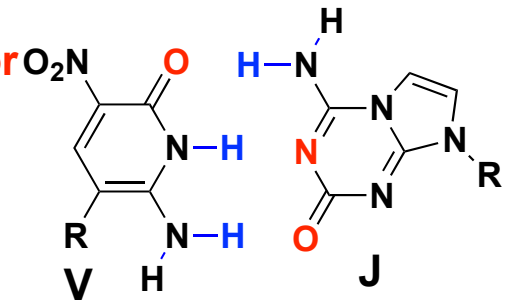

puDAA

Donor

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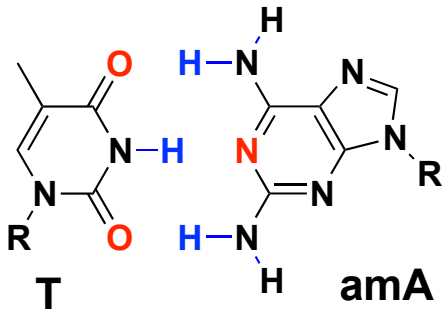

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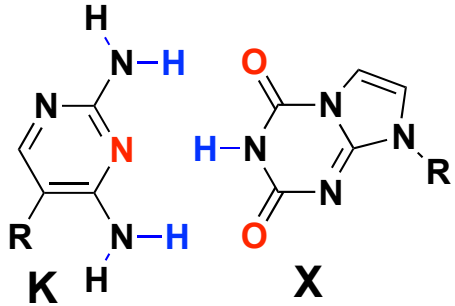

puADA

Acceptor

Donor

Acceptor

pyAAD

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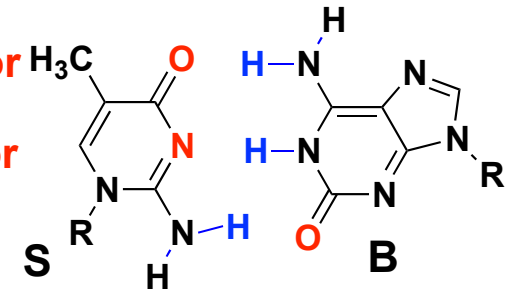

puDDA

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Acceptor

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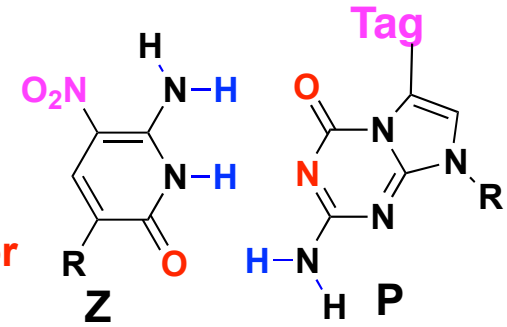


puAAD

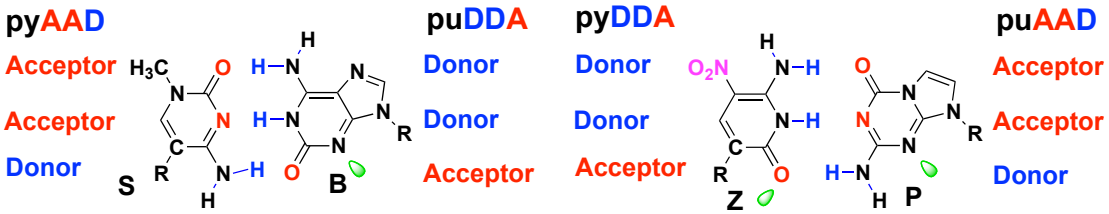
Acceptor

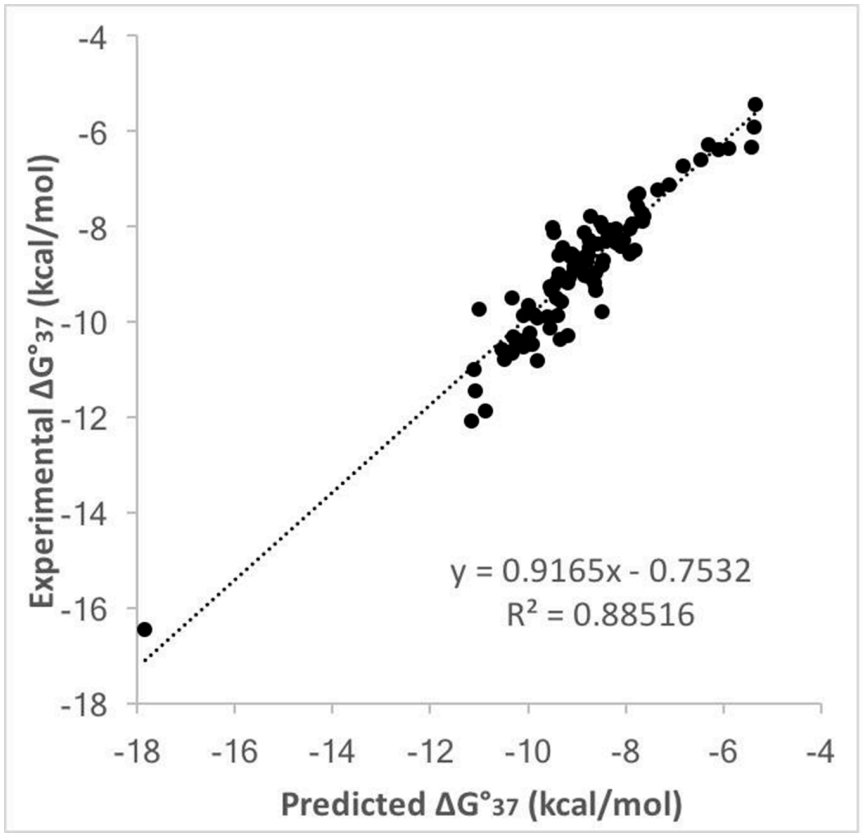
Acceptor

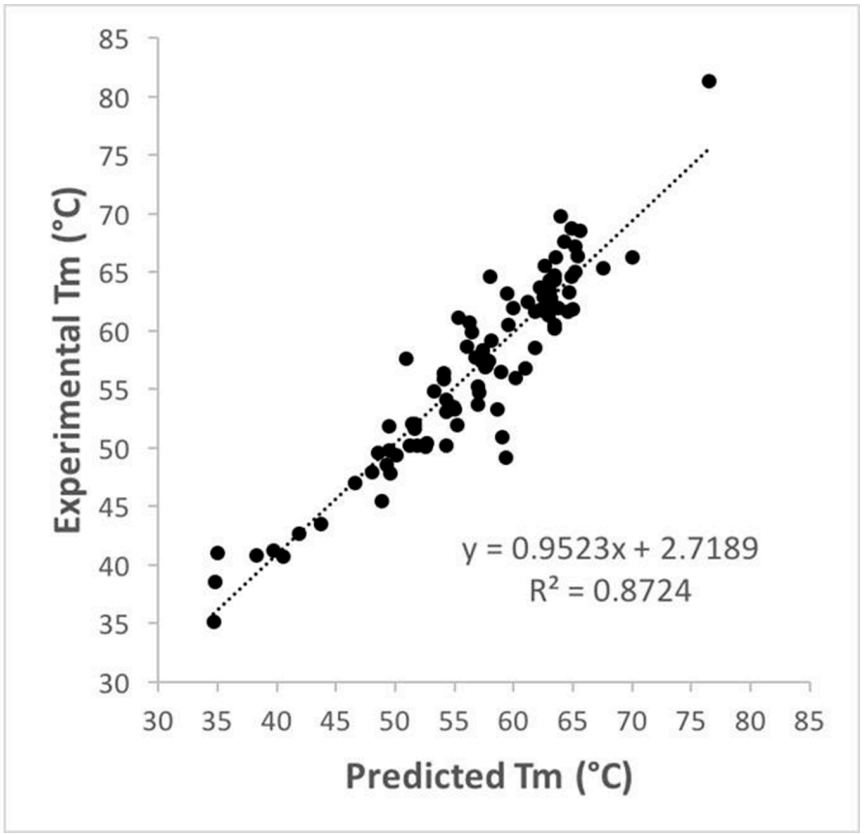
Donor

Artificially Expanded Genetic Information System (AEGIS)

Thermodynamic parameters for 8-letter hachimoji DNA s predict pairing as well as in 4-letter GACT DNA







In fact, the outlier is A:T, with just 2 hydrogen bonds

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Why genetic systems in water must have a polyelectrolyte backbone

the foundation for applied molecular evolution

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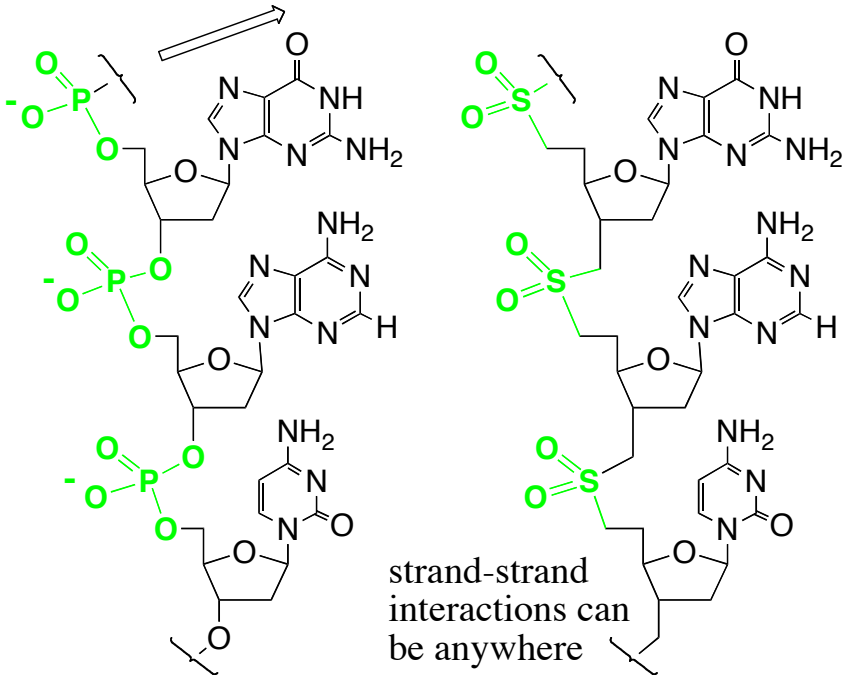
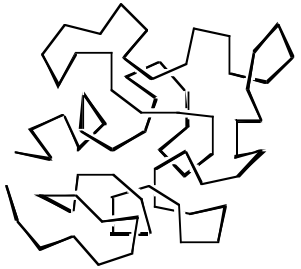
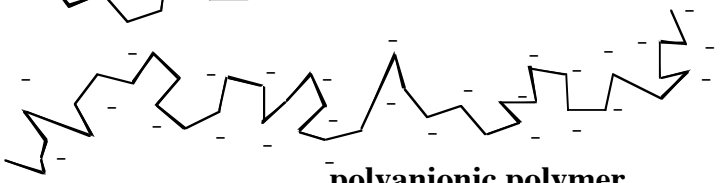
1. Keeps DNA soluble in water
2. Backbone-backbone coulombic interactions force strand-strand contacts to Watson-Crick edges of the nucleobases (= rules)
3. Repeating charges discourages folding; "excluded volume" effect
4. Repeating charge dominates the molecule's properties, allowing mutation to occur without changing properties of molecule (= evolution)



strand-strand interactions can be anywhere



neutral polymer
Radius = length $^{(1/2)}$



polyanionic polymer
Radius = length $^{>>(1/2)}$

Benner, S. A., Hutter, D. (2002) Phosphates, DNA, and the search for nonterrean life. A second generation model for genetic molecules. *Bioorg. Chem.* **30**, 62-80

Polyelectrolyte Theory of the Gene

NASA

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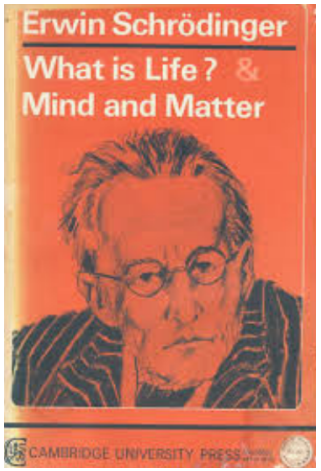
FAME

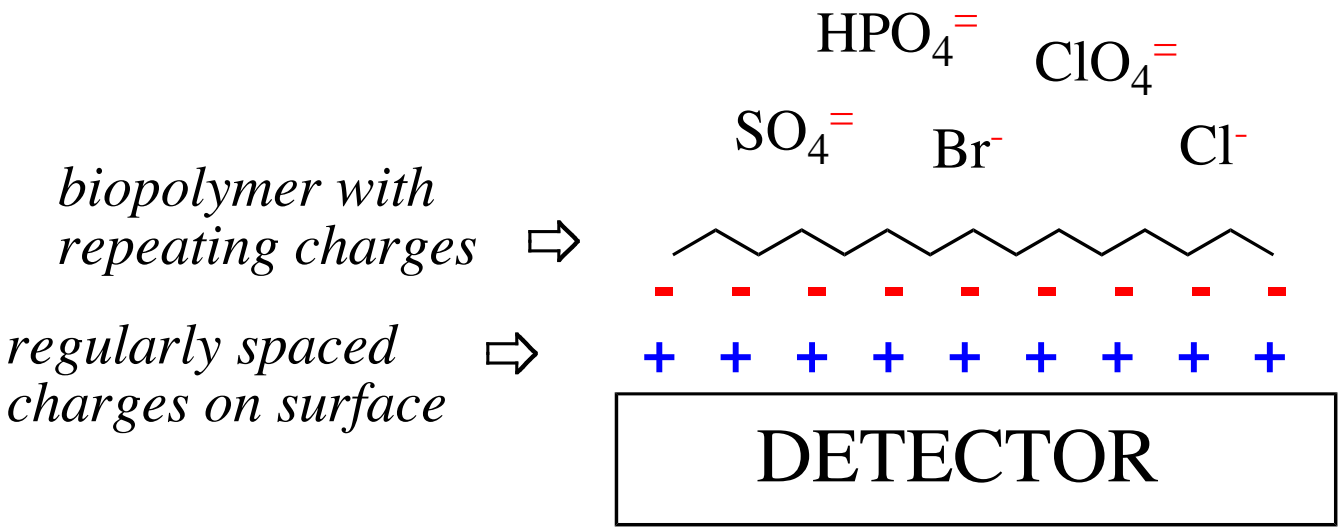
Using these features necessary for Darwinism and inaccessible without Darwinism to search for life?

Building blocks must fit Schrödinger's aperiodic crystal
Must keep *structure constant with changing information*

Needs a repeating backbone charge (negative or positive)
Must keep *properties constant with changing information*

Polyelectrolytes easy to concentrate from dilute solution, even in presence of anions containing single charges.



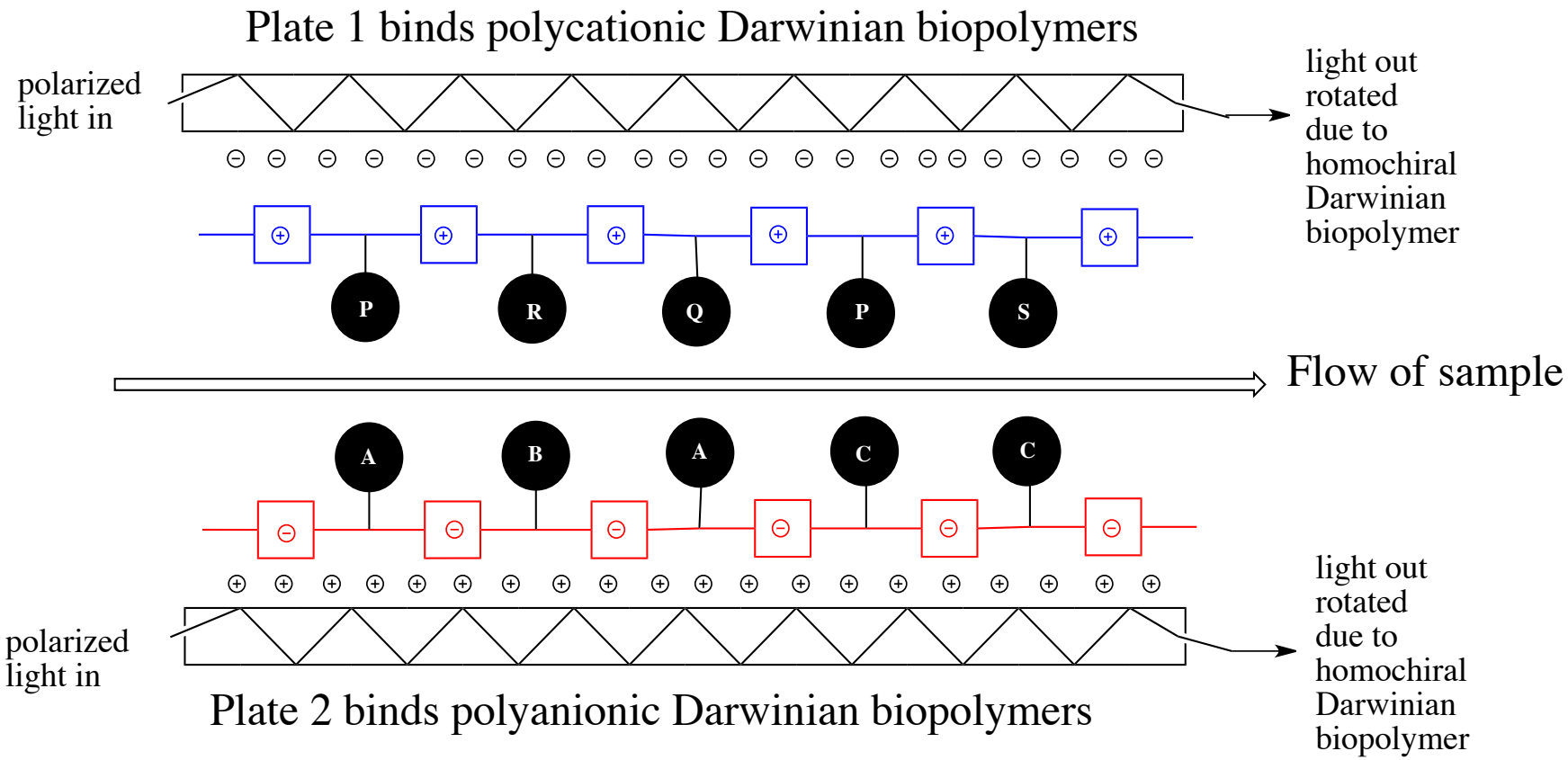


Universal life detection in water

Regardless of origins, Darwinism requires a genetic polymer with a repeating backbone charge and regular building blocks.

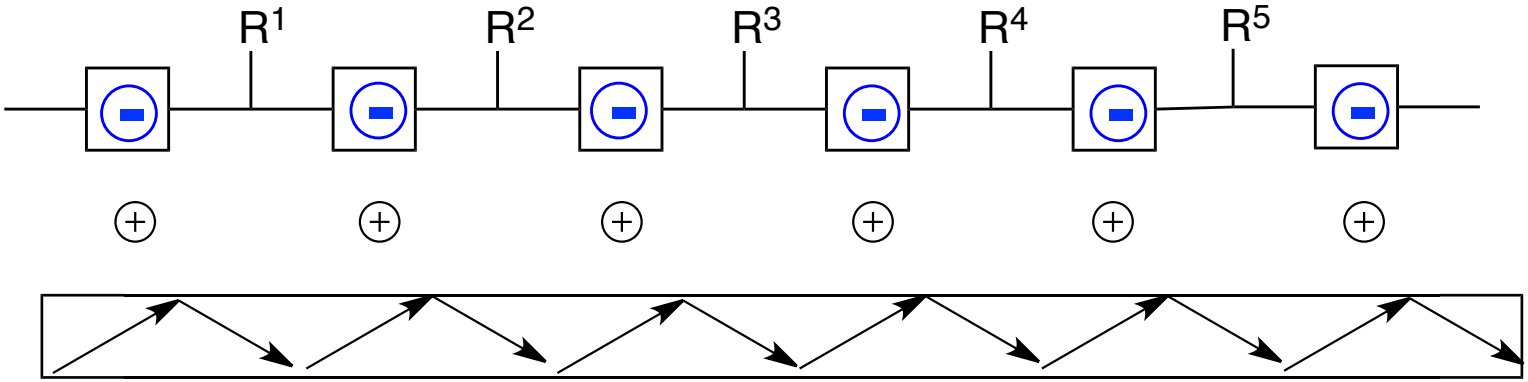
Benner, S. A. (2017) Detecting Darwinism from molecules in the Enceladus plumes, Jupiter's moons, and other planetary water lagoons. *Astrobiology* **17**, 840

Polyelectrolytes concentrated coulombically from dilute solution



How to detect concentrated polyelectrolytes

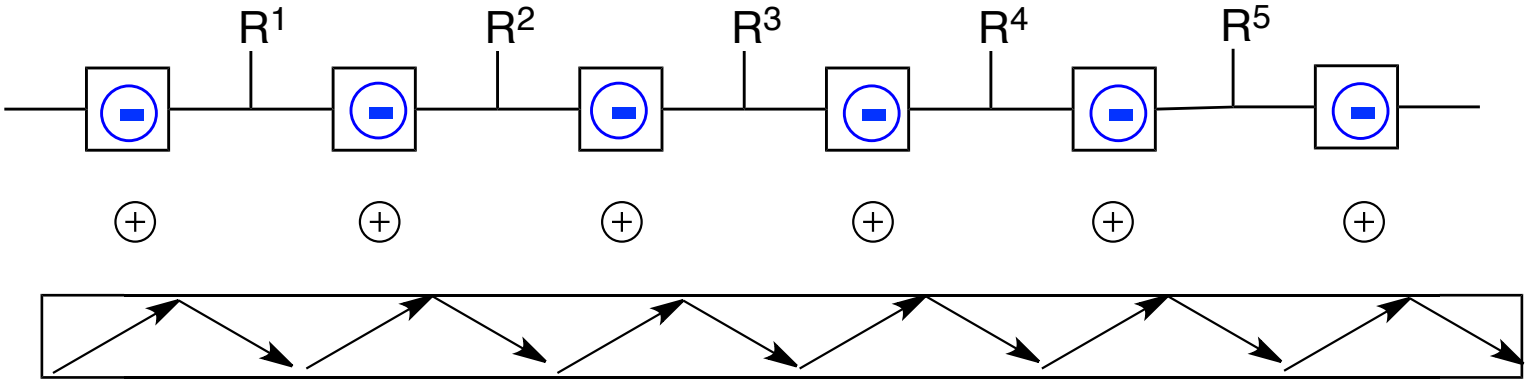
Refractive index change in total internal reflection system (Biacore)



Sensitivity is low, long path length, differential refractive index is uncertain with unknown ions being displaced

What detection architecture is most sensitive?

Ultraviolet absorption of the side chains

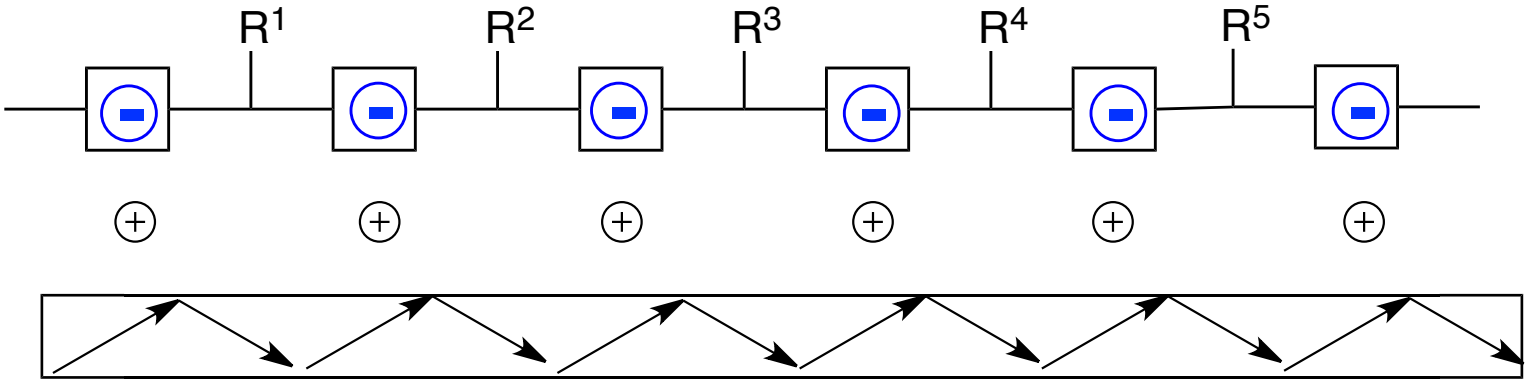


Detector

Sensitivity better, long path length, UV spectra of side chains unknown; spectral measurements would be informative?

What detection architecture is most sensitive?

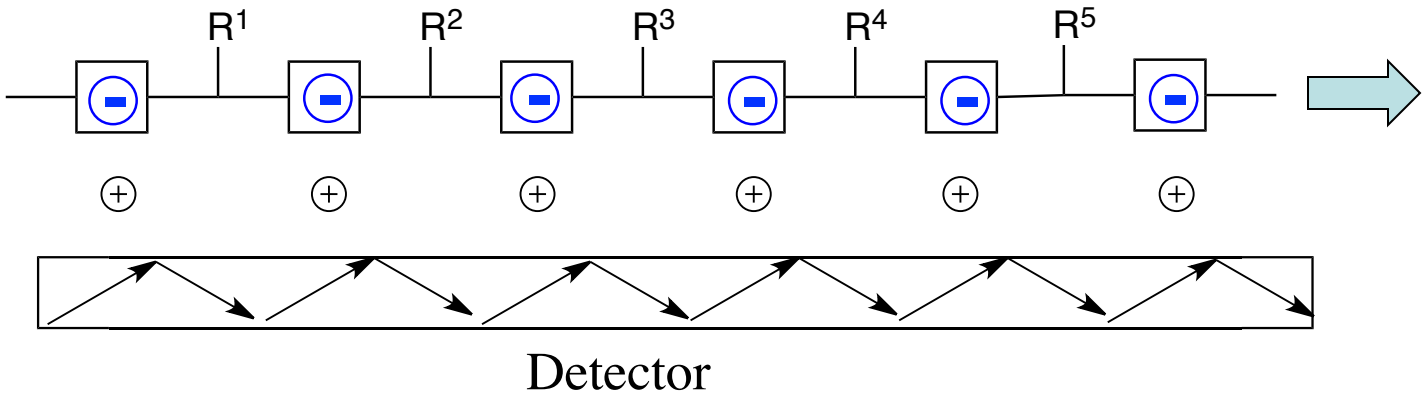
Macrochirality. Rotation of polarized light greater for a polymer of homochiral building blocks than rotation of the monomers collectively



Applying the Schrödinger criterion to material isolated by exploiting the polyelectrolyte theory of the gene.

This does not preclude downstream analysis

Displacement of adsorbed polyelectrolyte → Mass spec



ESI MS
MALDI MS

We could get some information about the detailed structure of the polyelectrolyte

A complete architecture

- Must find the sample

Mars ice caps survey accessible surface
No caching, correct guesses about locales

- Must thaw the sample

Energy from all steps does this "for free"

- Must disrupt cell compartments

Abrasive dust in Mars ice does this "for free"

- Must separate minerals

Sharpless centrifuge ruptures cells and removes chiral minerals that might interfere

- Pass liquid through capture zone

Polylelectrolyte capture

- Complete Mars analysis package

Can inspect sample microscopically
Mineralogical sample of planet (borate …)
Can seek metabolites in evaporated waste
Downstream analysis of polyelectrolytes

- No possibility of false positives