The Universal Structure of Darwinian Biopolymers

The role of synthesis in defining what alien genetics might look like

Steven Benner and the FfAME Team

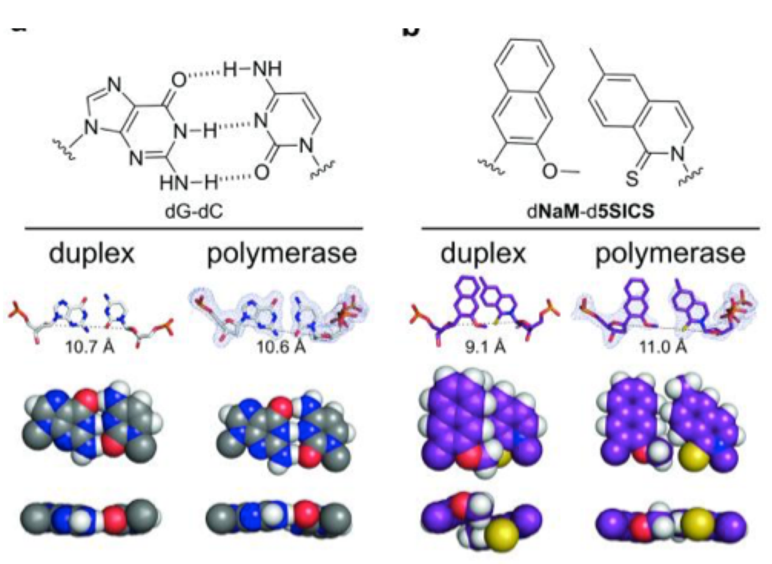
Conclusion: In water, the universal Darwinian biopolymer must have

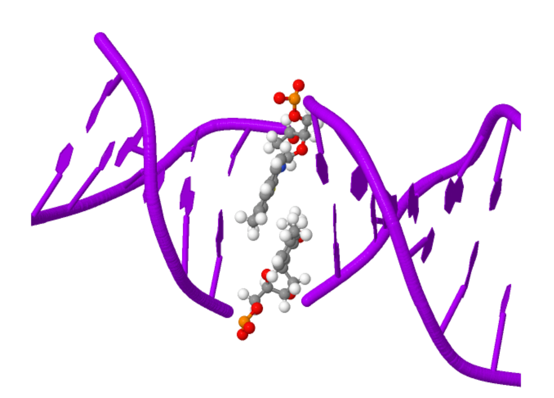
- a **polyelectrolyte** backbone
- building blocks of **uniform size/shape** that fit **Schrödinger's aperiodic crystal lattice**
- **Hydrogen bonds** to gain **directional binding**

We know this because we synthesized variants of DNA/RNA

- that *differ* from terran DNA/RNA, but *fit* these rules, ***and they work***
- that *resemble* terran DNA/RNA, but *violate* these rules, ***and they do not work***

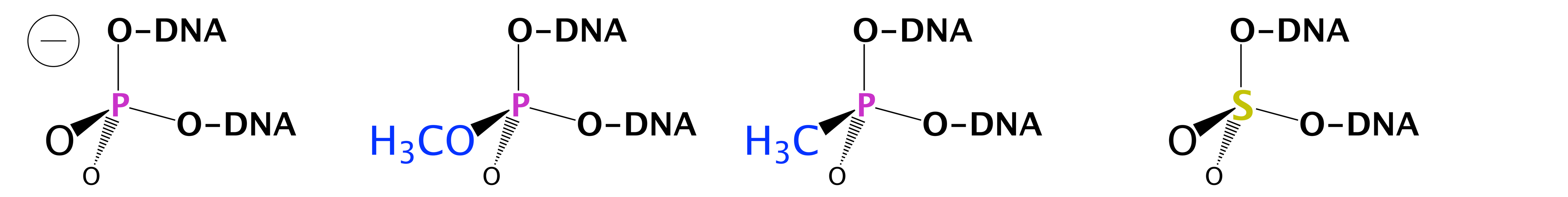
Example: A molecule resembling DNA/RNA but lacking interstrand hydrogen bonds; it fails





Schrödinger's aperiodic crystal is violated

Example: A molecule resembling DNA/RNA but lacking polyelectrolyte backbone



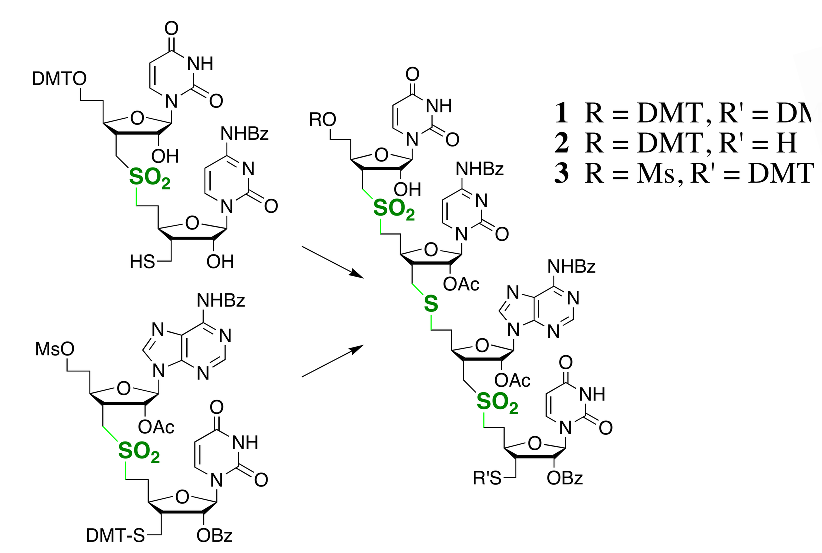
Here is phosphodiester with the charge

Put methyl on to eliminate charge

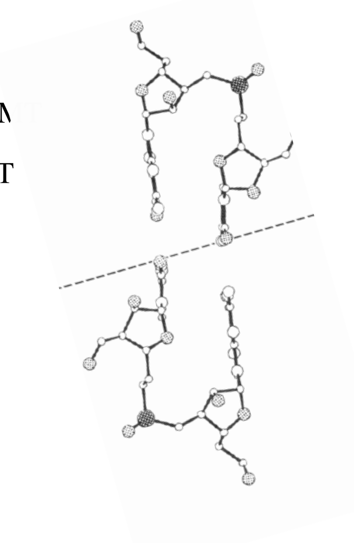
Replace O⁻ by CH_3 to eliminate charge

Make phosphorus from sulfur by adding a proton

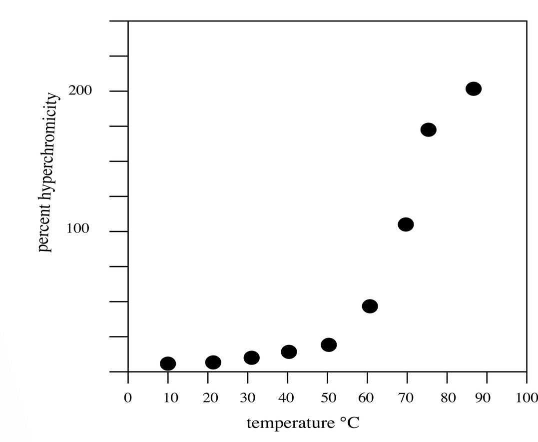
We synthesized them



Small sulfones pair

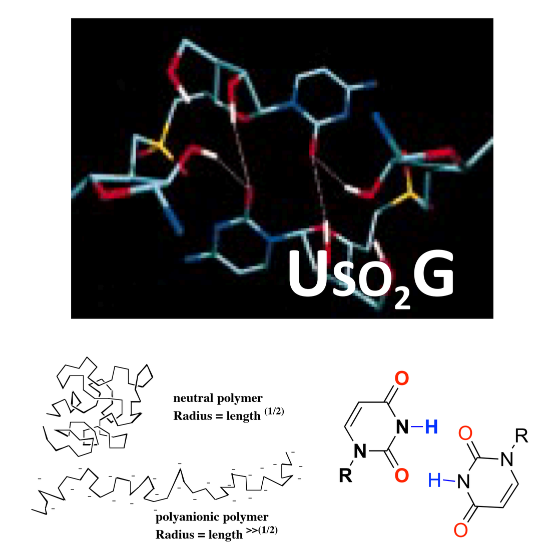


Longer sulfones fold



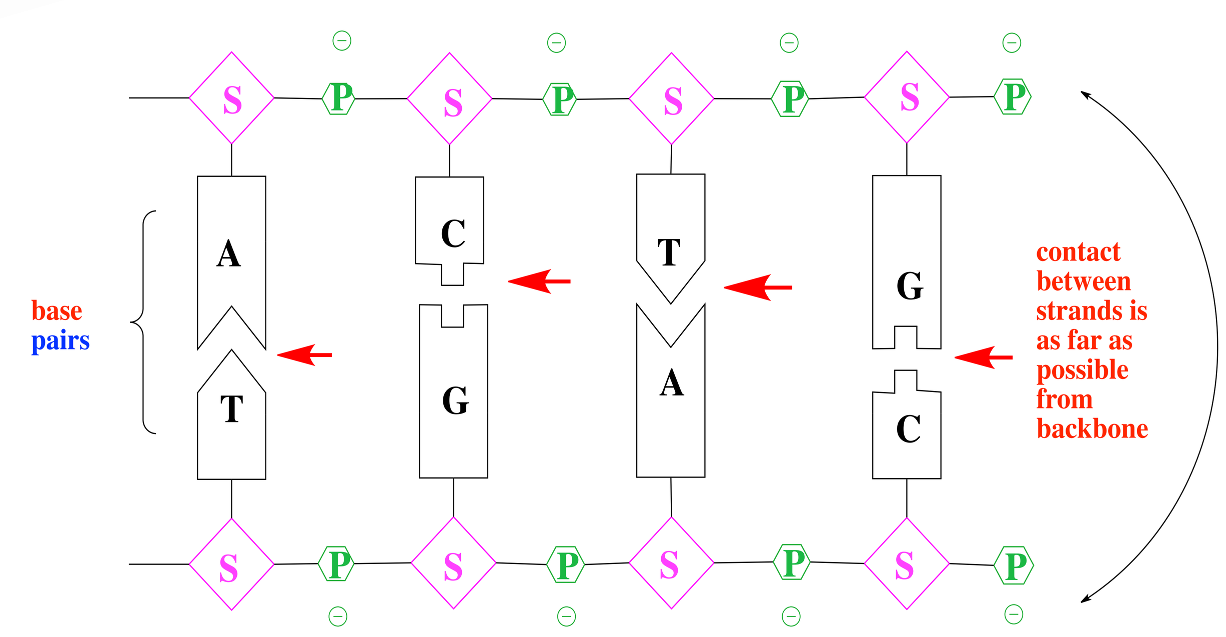
ribo-$A_{SO_2}U_{SO_2}G_{SO_2}G_{SO_2}U_{SO_2}C_{SO_2}A_{SO_2}U$

Sulfones violate rules



We learned from these syntheses that backbone charges

- keep DNA/RNA of any sequence dissolved
- determines pairing rules (A:T and G:C)
- discourages folding
- so dominates the physical properties of DNA/RNA that the sequence can change without changing physical behavior
- **This is universally necessary for Darwinism**

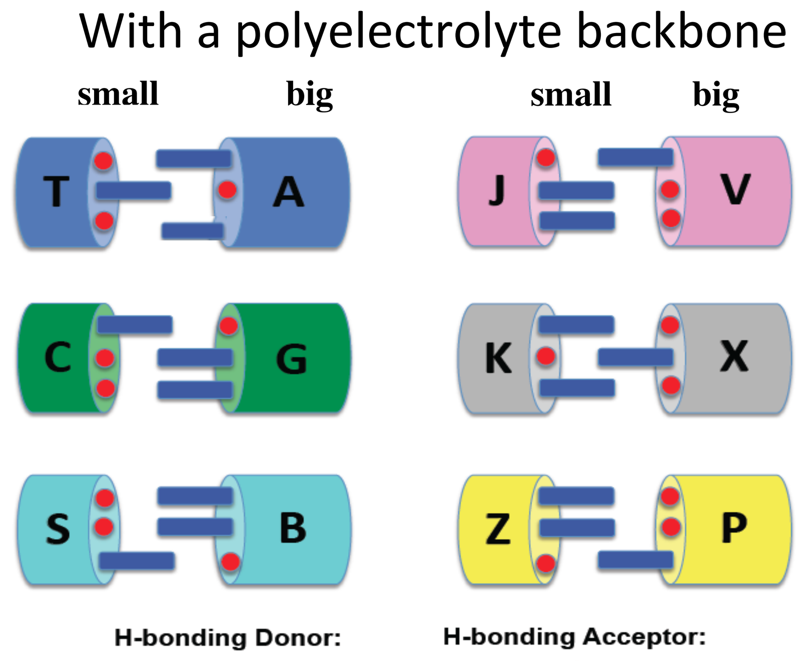


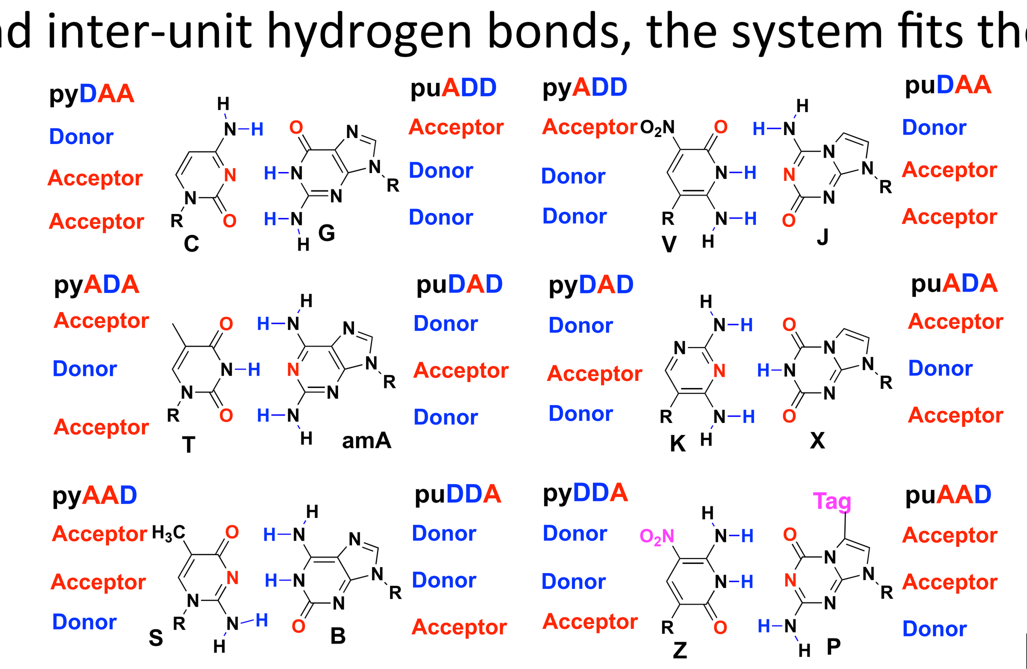
Example: Systems differing from DNA/RNA but obeying all of the rules, and they work

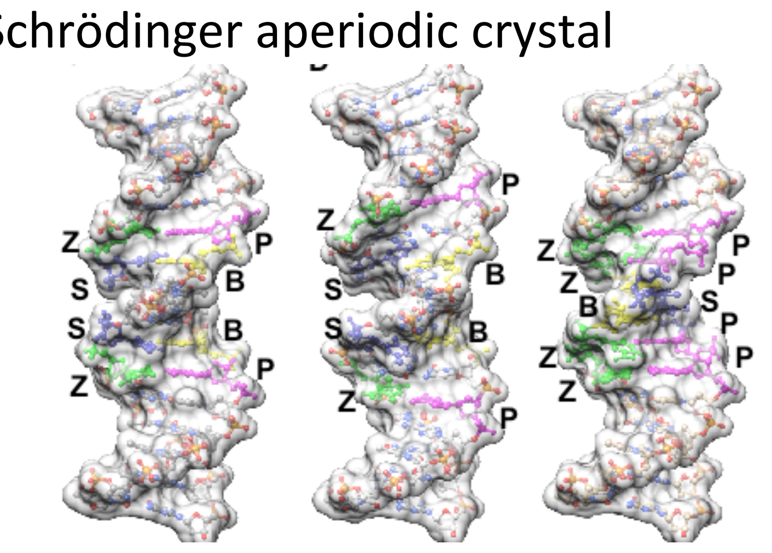
Five requirements for system to support Darwinism

- **Must be able to store information with regular rules (polyelectrolyte backbone necessary for this)**
- information must be transferrable to other, function-capable, systems
- Receiving systems must have a selectable phenotype
- The biopolymer must be able to evolve
- Must be self-sustaining, able to find its own food.

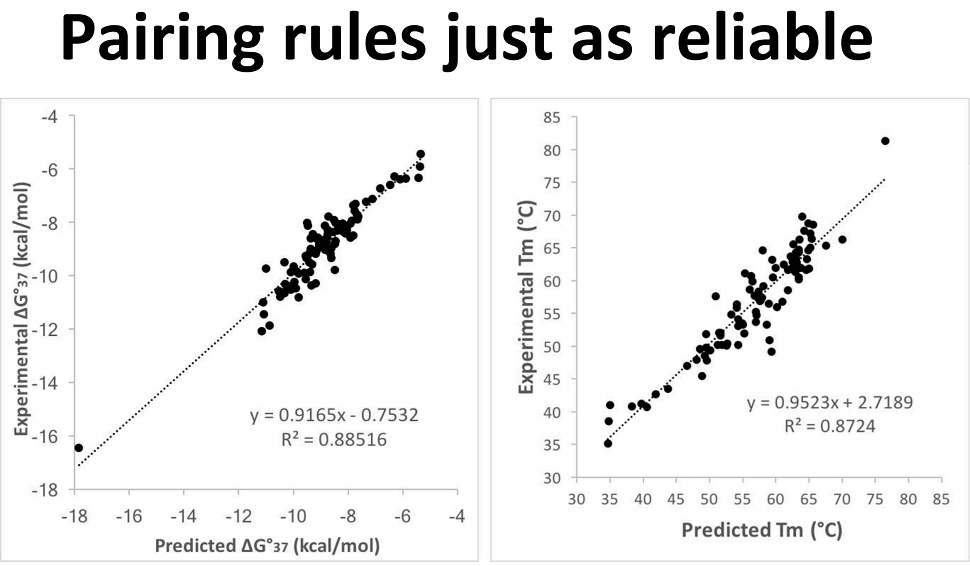
With a polyelectrolyte backbone and inter-unit hydrogen bonds, the system fits the Schrödinger aperiodic crystal



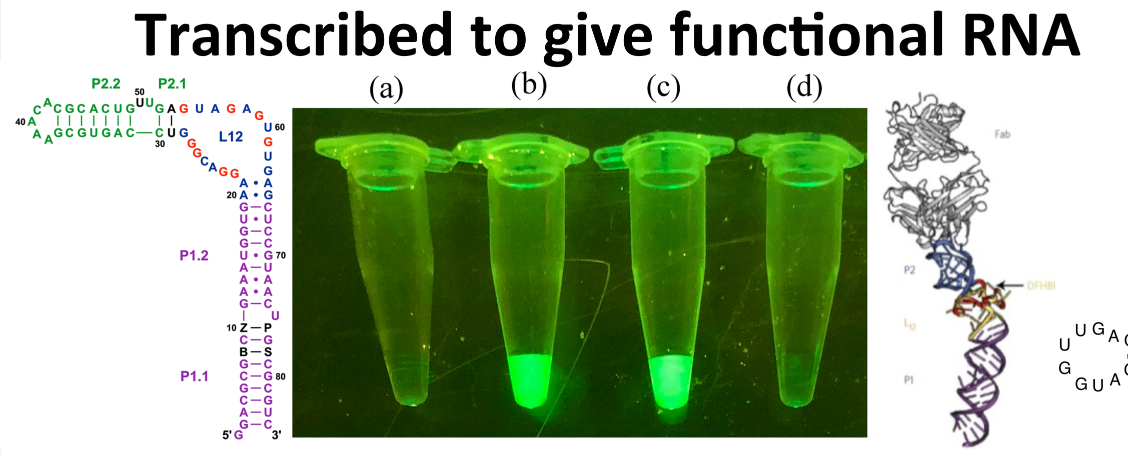




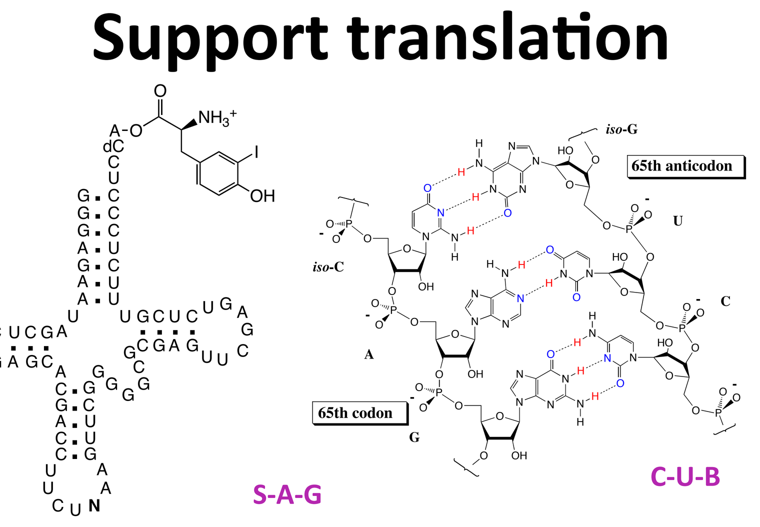
Pairing rules just as reliable



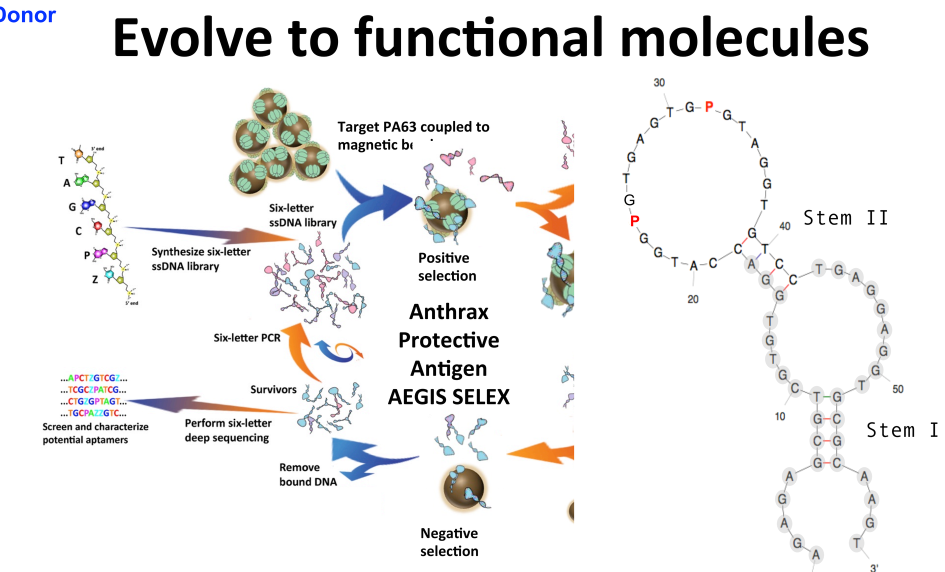
Transcribed to give functional RNA



Support translation

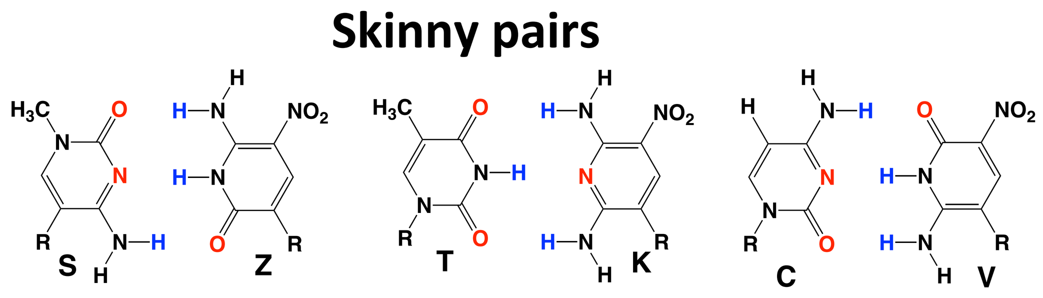


Evolve to functional molecules



Example: Systems differing *still more* from DNA/RNA but obeying all of the rules, and they work

Skinny pairs



Skinny pairs violate size complementarity, retain H-bonding complementarity. Duplexes as stable as Watson-Crick duplexes.

```
5'-KZZ TZS KTT KKS TST     5'-KZZ TZS KTT KKS TST
3'-XPP DPB XDD XXB DBD     3'-TSS KSZ TKK TTZ KZK
```

Melts at 60.0 °C — Melts at 58.3 °C

Fatty pairs

D (diaminopurine) X (7-deazaxanthosine) B (isoguanosine), as its N1 tautomer P (7-amino-imidazo-[1,2-c]pyrimidin-5[1H]one)

These are "fatty pairs", not Goodman size-compliant, but retain hydrogen bonding complementarity. Duplexes are more stable.

```
5'-KZZ TZS KTT KKS TST     5'-DBB XBP DXX DDP XPX
3'-XPP DPB XDD XXB DBD     3'-XPP DPB XDD XXB DBD
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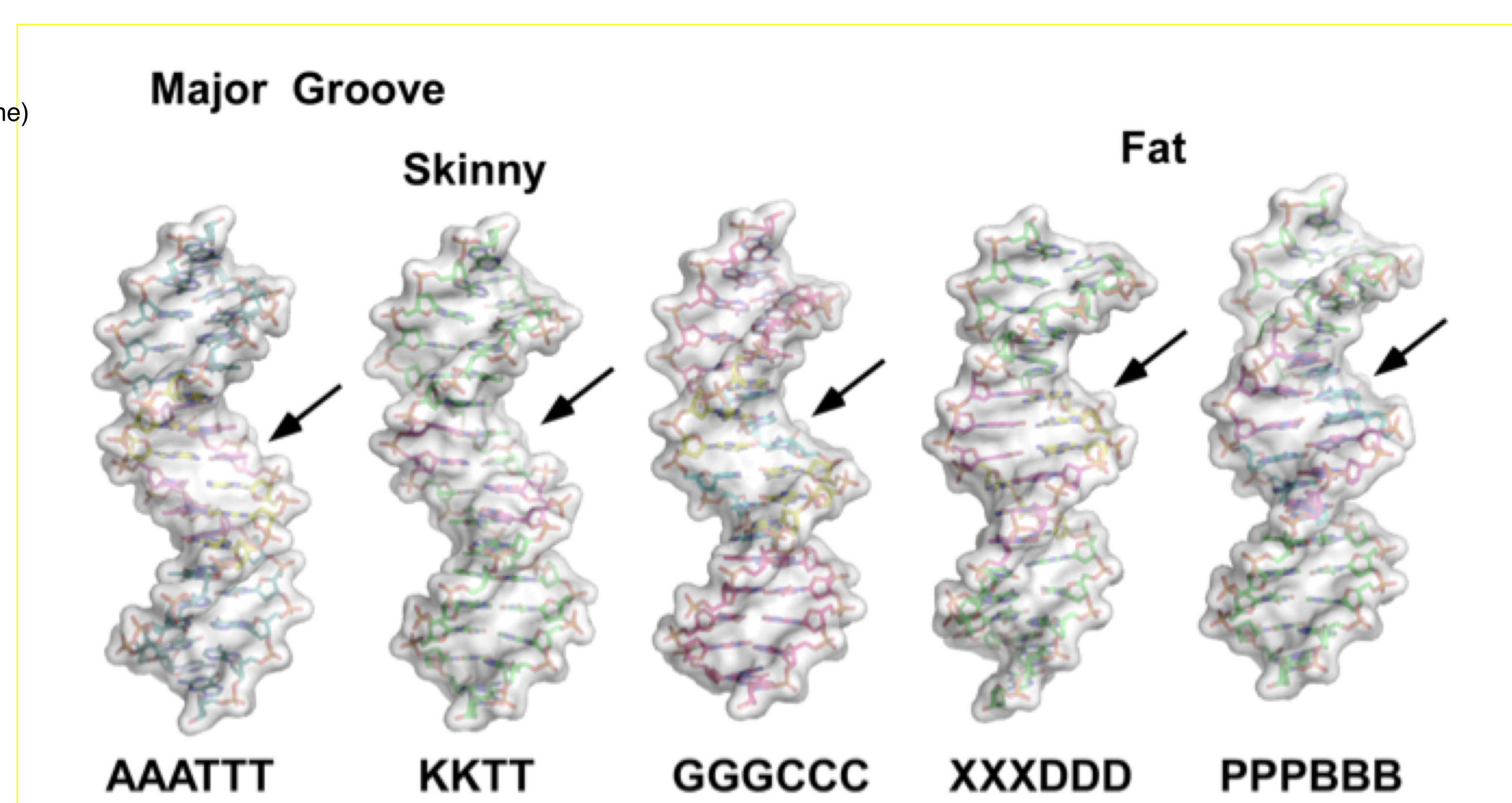
Melts at 60 °C — Melts at 77.7 °C

Skinny and fat pairs form their own Schrödinger aperiodic crystal structures, two new alien genetic systems



More reading: Hoshika, S., Singh, I., Switzer, C., Molt, R. W., Leal, N. A., Kim, M.-J., Kim, M.-S., Kim, H.-J. Georgiadis, M. M., Benner, S. A. (2018) "Skinny" and "Fat" DNA: Two new double helices. *J. Am. Chem. Soc.* **140**, 11655-11660. PMID: 30148365

Hoshika, S., Leal, N. A., Kim, M.-J., Kim, M.-S., Karalkar, N. B., Bates, A. M., Watkins Jr., N. E., SantaLucia, H. A., Meyer, A.J., DasGupta, S., Piccirilli, J. A., Ellington, A. D., SantaLucia Jr., J., Georgiadis, M. M., Benner, S. A. (2019) Hachimoji DNA and RNA. A Genetic System with Eight Building Blocks. *Science* **363**, 884–887. doi: 10.1126/science.aat0971. PMC6413494