DNAzyme Computing for Biodetection



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20 February 2015 30th TBI Winterseminar, Bled Computing using molecules in solution, via logic gates, circuits, and automata:

- Signal is concentration of particular molecules
- Combinatorial encoding of signals
- Signals can be amplified, e.g., using catalytic DNA (DNAzymes, deoxyribozymes)
- Signals can be queried, e.g., using hybridization (strand displacement)

- Why we develop silicomimetic molecular automata
- Hypothesis: specificity of DNA binding can be used to intervene at the cellular level and achieve intelligent drug delivery



Approach: develop networks of biomolecular logic gates that sense the state of a cell, perform stateful computation, and produce a diagnostic or therapeutic action

DNAzymes and molecular beacons make gates



Gate output has the same nature as the input, but...

Santoro and Joyce, PNAS, 94, 4262-4266 (1997) Stojanovic, de Prada, and Landry, ChemBioChem, 2(6), 411-415 (2001) Stojanovic, Mitchell, & Stefanovic, J.Am. Chem. Soc., 124, 3555-3561 (2002)

Making a complete set of logic gates, and more



Stojanovic, Mitchell, & Stefanovic, J.Am. Chem. Soc., 124, 3555-3561 (2002)

Demonstrations of logic gates: binary arithmetic



Stojanovic & Stefanovic, J. Am. Chem. Soc., 125, 6673-6676 (2003)

Carry

Demonstration of wide circuits: games of strategy



Stojanovic & Stefanovic, Nature Biotech., 21, 1069-1074 (2003) Macdonald et al., Nano Letters, 6, 2598-2603 (2006)

Example order of play



(i) The automaton moves first in middle well, activated by adding Mg^{2+} .



(ii) The human player adds input i4 to all wells, which only activates the YESi4 gate in well 1 to signal the automaton's response.



(iii) The human player adds input ig to all wells to block the diagonal. All wells now contain inputs i4 and i9, and thus the i4 AND i9 gate in well 3 is activated to signal the automaton's reponse.



(iv) The human player has no winning move, and adds input i7 to all wells. Since all wells now contain inputs i4, i7, and i9, the i7ANDi9ANDNOTi1 gate in well 2 is activated, which completes the top row and the automaton wins.

New logic gate design: structured substrate



Brown et al., ChemBioChem, 15, 950-954 (2014) Brown et al., Angew. Chemie Int. Ed., 53(28), 7183-7187 (2014) Lakin et al., PLoS ONE, 9(10), e110986 (2014)

Demonstration of deep circuits: 5-layer cascade



Brown et al., Angew. Chemie Int. Ed., 53(28), 7183-7187 (2014)

Demonstration of staged logic: dengue detector



Brown et al., Angew. Chemie Int. Ed., 53(28), 7183-7187 (2014)

Unified architecture for biodetection



Brown et al., ChemBioChem, 2015 (in press)

Current and future work

- Compartmentalized circuits
- Delivery to cells
- Walker circuits

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