A fast, robust and reconfigurable molecular circuit breadboard using leakless DNA strand displacement cascades

Chris Thachuk & Erik Winfree, California Institute of Technology
{thachuk,winfree}@caltech.edu

The promise of molecular programming lies in its ability to not only process information autonomously, but to do so in a biochemical context in order to sense and actuate matter. The most sophisticated molecular computing systems have been built upon the DNA strand displacement (DSD) primitive, where a soup of rationally designed nucleotide sequences interact, react, and recombine over time in order to carry out sophisticated computation. Existing systems are often slow, error-prone, require bespoke design and weeks of effort to realize experimentally. Building upon the leakless DSD architecture [1, 2] we have developed a reconfigurable molecular breadboard. Its purpose is to "scale-up" what is possible with this technology and to "scale-out" its adoption to new contexts. The power of this approach is found in its simplicity and the high quality of the rationally designed components. In order to facilitate the rapid design of new circuits from a common molecular broth, we have developed a compiler that takes as input a logic description and provides as output the optimized set of breadboard components necessary to activate the desired logic behavior. By mixing these pre-existing components as prescribed, it is possible to achieve fast, leakless and robust molecular circuits, from conception to implementation, within the time frame of an afternoon as confirmed by undergraduate students at Caltech. We expect our molecular breadboard approach will enable the implementation of circuits $2\times$–$10\times$ larger than have been previously demonstrated. Due to the large separation of time scales between designed and spurious computation, we expect the breadboard architecture will open new research directions in molecular sensing, actuation and interfacing with self-assembly systems.

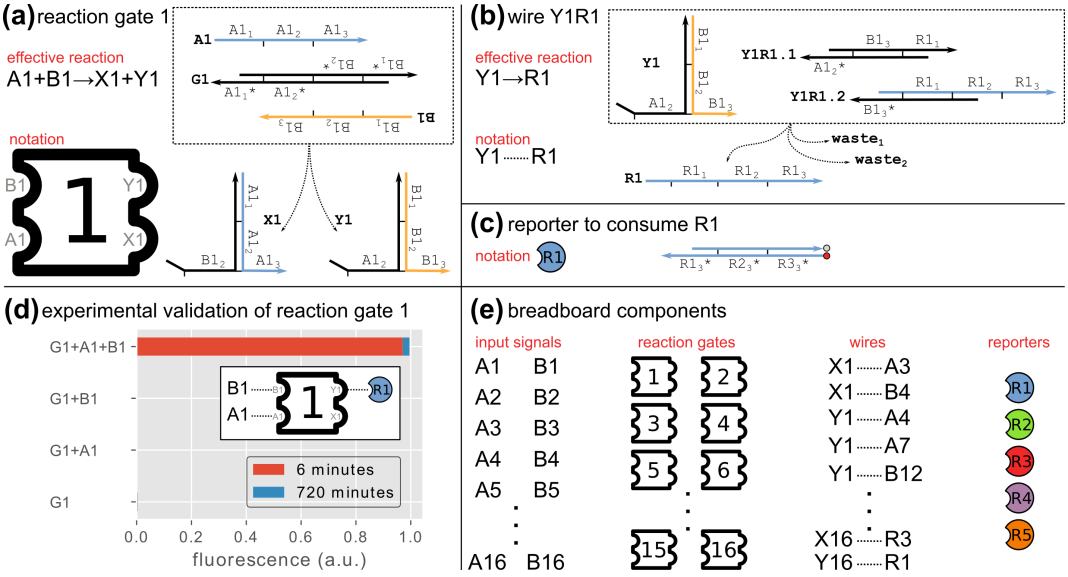

Figure 1: (a), (b) and (c) give cartoon representations of notation and molecule design for the reaction gates, wires and reporters used in the breadboard. Some sequence and domain level modifications omitted for clarity. (d) Experimental validation of reaction gate 1 wired to reporter R1. [gates]=[input]=2048nM, [reporter]=2457nM. First observed data point at $t = 6$ minutes. (e) Breadboard components can be wired together arbitrarily to implement molecular circuits.

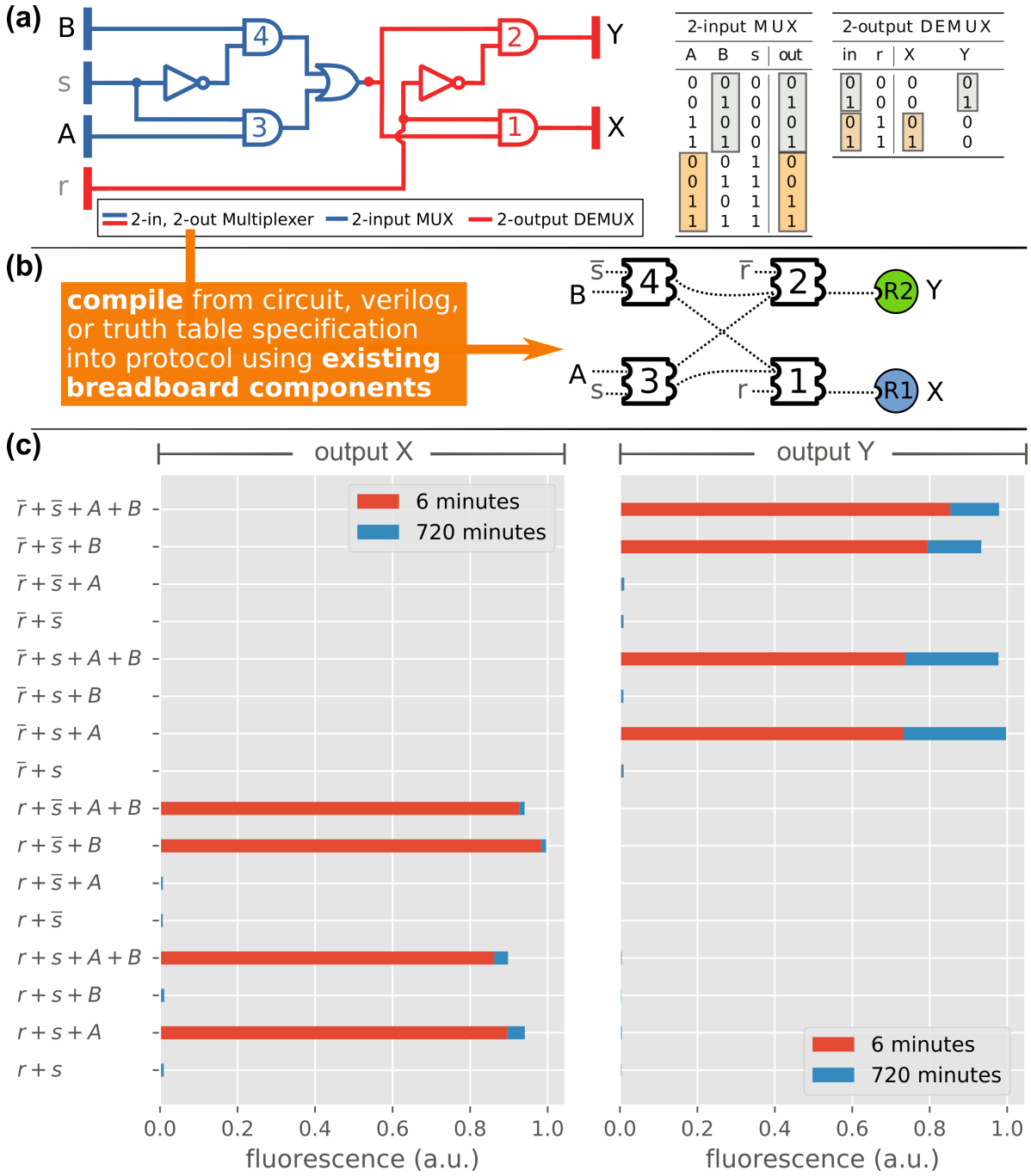

Figure 2: (a) A two-input, two-output multiplexer circuit maps the value of either input (selected by setting s) to either output (selected by setting r). (b) The breadboard compiler produces a protocol to mix existing components into a logically equivalent molecular circuit, consisting of 24 complexes composed from 42 distinct DNA strands. (c) Experimental validation of the molecular multiplexer circuit over the 16 possible input combinations. [gates]=[input]=2048nM, [reporters]=1024nM. First observed data point at $t = 6$ minutes. Fluorescence signal is normalized per reporter, where 0.0 and 1.0 are the minimum and maximum signals observed over 12 hours.

Related Work

[1] Thachuk, C., Winfree, E., & Soloveichik, D. (2015). *Leakless DNA strand displacement systems*. In International Conference on DNA Computing and Molecular Programming (pp. 133-153).

[2] Wang, B., Thachuk, C., Winfree, E., & Soloveichik, D. (2018). *Effective Design Principles for Leakless Strand Displacement Systems*. In Preparation.