Organising Chemical Reaction Networks in Space and Time with Microfluidics

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ABSTRACT

Information processing is essential for any lifeform to maintain its organisation despite continuous entropic disturbance. Macromolecules provide the ubiquitous underlying substrate on which nature implements information processing and have also come into focus for technical applications. There are two distinct approaches to the use of molecules for computing. Molecules can be employed to mimic the logic switches of conventional computers or they can be used in a way that exploits the complex functionality offered by a molecular computing substrate. Prerequisite to the latter is a mapping of input-output transform provided by the substrate. This paper reviews microfluidic technology as a versatile means to achieve this, show how it can be used, and provide proven recipes for its application.

Keywords: Information Processing, Logic Switches, Macromolecules, Microfluidics, Molecular Computing

INTRODUCTION

Much of the information processing within biological systems relies on the interactions of macromolecules, particular proteins, with one another and with their environment (Bray, 1995). Recognising this, enzymes have been applied in the implementation of Boolean logic gates, as demonstrated by Conrad and Zauner (2001), and by Sivan et al. (2003). Willner’s group extended the principle to networks of enzymes forming single logic gates (Baron, Lioubashevski, Katz, Niazov, & Willner, 2006c), concatenated logic gates (Niazov, Baron, Katz, Lioubashevski, & Willner, 2006) and enzymes acting in parallel as half-adders and half-subtracters (Baron, Lioubashevski, Katz, Niazov, & Willner, 2006a, 2006b). More recently, Katz and co-workers have reported many iterations of enzymatic logic gates and also interfaced them to conventional electronics (Pita et al., 2009; Zhou et al., 2009).

Given the structural complexity of proteins and their broad range of functionality in nature,
the information processing available through individual enzymes is unlikely to be limited to Boolean logic. A more sophisticated application of proteins in molecular information processing, however, faces the obstacle that there is as at present no method for designing proteins for purpose available. Instead of engineering enzymes for a particular application, through characterising the response behaviour of enzymes available from nature, arguably new modes of information processing could be supported ultimately facilitating the application of enzymatic computers (Zauner & Conrad, 2001). Fully surveying the response characteristics of an enzyme, in particular in a technical setting not limited to physiological conditions, requires sampling over high-dimensional parameter spaces. Time and materials are typically very limited compared to the large parameter space preventing a detailed investigation of behaviour. To make the best use of available resources we use autonomous experimentation based on a physical platform that minimises resource requirements per experiment with machine learning techniques to drive the experimentation platform.

Microfluidic technology provides a means of significantly reducing the resource requirements per experiment when compared to conventional laboratory hardware. Microfluidic devices may be computer-controlled through the inclusion of on-chip valves thus allowing for complex protocols to be performed. As a technology microfluidics is of more general interest for the study and implementation of molecular level information processing than in the context of our application. For the benefit of the readers not familiar with its possibilities we review key concepts of microfluidics.

For our purpose of developing a microfluidic experimentation platform particularly to characterise enzymes for information processing we have specific requirements. Ideally many different chemicals would be used to probe the behaviour of an enzyme. This necessitates a complex microfluidic device containing many channels with associated pumps and valves. Thus a low-cost implementation is strongly desired. In addressing those requirements we developed a low-cost computer interface and fabrication protocols that do not require sophisticated equipment or a cleanroom environment. For the benefit of readers who contemplate the use of microfluidic architectures we provide the details of the fabrication protocols in the Appendices. The fabrication protocols and the new interface technique should make it feasible to probe networks of enzymes with multiple chemical signals and therefore open up the potential for more complex enzymatic computing to be performed.

**MICROFLUIDICS**

Microfluidics is implemented through the patterning of micrometre-sized networks of fluidic channels on a substrate material. The fluidic channels may be designed such that multiple laboratory functions, mixing, diluting and measurement are integrated into a chip no larger than a few centimetres square—giving rise to the term lab-on-a-chip. As a technology it allows for a more fine-grained control over reaction condition than what is typically available in bulk chemistry. This is largely due to the fact that in small volumes surface effects are more prominent.

**Laminar Flow**

The behaviour of fluids flowing in microscale channels is markedly different to the familiar behaviour of fluids at the macroscale. At the macroscale, fluids tend to flow turbulently and mix readily whereas microscale flows do not. This difference arises from a shift in the competition between the inertial and viscous forces that act on a flowing fluid. This competition is represented by the dimensionless Reynolds number (Re):

\[
Re = \frac{\text{Inertial Forces}}{\text{Viscous Forces}} = \frac{\rho U D_a}{\eta} = \frac{U D_a}{\nu} = \frac{Q D_a}{\nu A v}
\]  

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