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Towards biomolecule-based information processing using engineered nanopores

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ABSTRACT

In recent years, biomolecular digital information processing has received much attention. A number of logic gates and simple networks based primarily on DNA and enzymes have been demonstrated in solution. The possibilities of information processing with biomolecules can be further developed through the use of engineered nanopores. Electrochemistry at engineered nanopore membranes provides advantages in terms of mass transfer and response time, and can facilitate transduction of biochemical events into an electrical signal. We review briefly examples of biomolecule-based information processing before presenting recent developments in terms of nanopore membrane fabrication, surface functionalisation and sensing. We then present the opportunities and challenges of coupling these systems to nanopore devices.

1. Introduction

Recently, the use of molecules for digital information processing has received much attention from researchers [85]. Based on the optical, electrochemical and magnetic properties resulting from their chemical structure, a number of simple logic gates have been implemented using both naturally-occurring and synthetic biomolecules. Logic gates and computing systems can be based on recognition and sensing events using biomolecules such as enzymes [45,21], DNA molecules [63,23] and DNAzymes [95]. It is important to note that logic gates based on synthetic and biological molecules are not designed to compete with silicon technology, and instead should function as chemical transducers and actuators that can react directly in response to chemical-based environmental effects. Such logic gates could also be developed as the part of an implantable or biodegradable device.

In a biochemical logic device, if the required chemical conditions are met, the logic system would trigger an action such as the release of a drug via the activation of a pumping system or the modification of material properties. Such systems, based on an approach of "Detect – Compute – Act" (Fig. 1), could be applied in biological and biomedical devices for localised diagnostics and therapy.

Digital information is coded in the form of zeros and ones, which, in biological terms, corresponds to high and low concentrations of a chemical species. Based on the principle of a biosensor, the biomolecule specifically detects the species of interest. If the concentration of that chemical species reaches a threshold value (corresponding to the digital value of 1), the chemical information is transduced into a signal that initiates a specified action (Fig. 1). Since the development of the first biosensor by Clarke and Lyons [16] in 1962, extensive efforts have been made to take advantage of the sensitivity and selectivity of biological systems (enzymes, antibodies and DNA) to develop devices for the detection of target analytes.

Additionally, there are a vast number of strategies to immobilise biomolecules onto electrodes required for signal communication. Electrochemical or optical mechanisms can be used to convert chemical information into a quantifiable value. The drive for lower limits of detection

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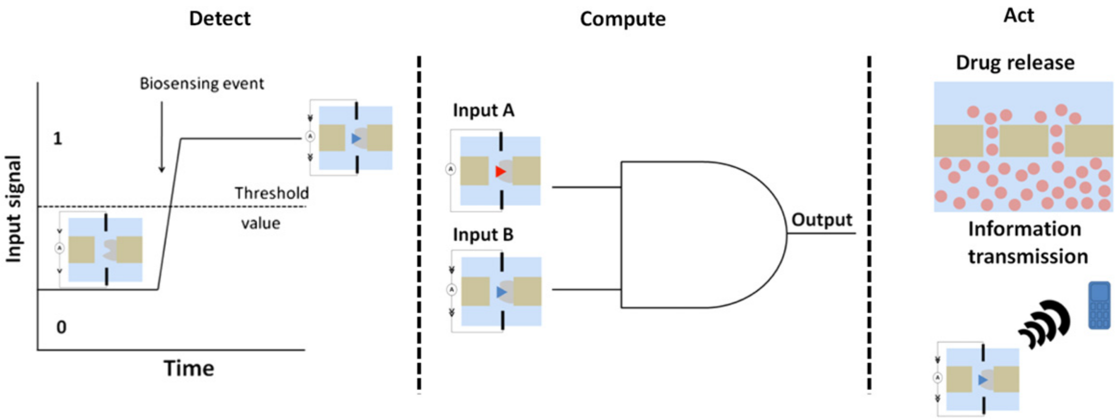

Fig. 1. Principle of operation: "Detect – Compute – Act". The input molecule is detected using a nanopore membrane. All the input signals are integrated to deliver the output signal. If required, a response is triggered (drug release, information transmission, etc …).

Table 1
Examples of biomolecule-based logic gates.

Biomolecule	Logic Gate type	Strengths	Weaknesses	References
Enzyme	AND, Identity, INHIBIT A, INHIBIT B, Inverter, NOR, OR, XOR	Highly specific recognition;	Reactions in solution; Slow response time	[45] and references therein.
DNA, DNAzymes	AND, NAND, OR, NOR, XOR, INH	Highly specific recognition;	Use of fluorescent labels; Reactions in solution; Slow response time	[63,23,95] and references therein.

and improved sensitivity has led to the examination of effects on the micro and nanoscales. Indeed, at the nanoscale, radial diffusion of species becomes prevalent, providing improvements in mass transfer and allowing faster response times. At nanoelectrodes, the ohmic drop, *iR*, is reduced, resulting in an improved signal-to-noise ratio. All these factors contribute to lower limits of detection.

Harnessing the specificity and sensitivity of biomolecules with the properties inherent to the nanoscale allows the realisation of biomimetic structures, which can be used for logic gate operations and digital computing. However, the interfacing of biology and nanotechnology to form nano-communication networks requires that a number of challenges be addressed. Firstly, issues of biomolecular activity following immobilisation on engineered nanostructures must be considered. Second, standards for the transduction of an analog biochemical event into a quantitative (digital) signal need to be established. Finally, effective harnessing of the sensing modality to the chemical actuation system needs to be developed. These problems lie at the interface between biology, chemistry and engineering, and thus require a multidisciplinary approach.

The focus of this review is not an exhaustive list of existing biomolecular logic gates found in the literature. Instead, we consider the challenges and opportunities for the use of engineered nanopores as vehicles for biomolecular information processing, and consider how such devices could be used to complement and improve on solution-based biochemical logic systems. In the following section, we present various information processing systems based on biomolecules such as enzymes, DNA and RNA. In Section 3, we describe the benefits of performing biochemical switching at the nanoscale and consider methods for the fabrication and subsequent functionalisation of nanopores. In Section 4, we discuss the various methodologies for sensing using nanopores and present some such applications. Finally, in Section 5, the challenges and opportunities of interfacing biomolecules with engineered nanopores are examined.

2. Biomolecule-based systems for information processing

A vast number of biomolecules are present in living organisms and cells, fulfilling a wide variety of functions. Indeed, the presence (or absence) of ions, small molecules, and proteins can trigger a series of biochemical reactions which can have an effect at the metabolic level. As an example, a high glucose level in blood results in the release of insulin by the pancreas, inducing cells to uptake glucose from the blood and convert it for storage. Table 1 presents examples of the biomolecule-based simple logic gates, which are found in the literature. Below, we further elaborate on these categories. In general, these examples comprise elementary logic systems common in information processing.

2.1. Enzyme-based logic systems

Boolean logic operations, AND, INHIBIT A, INHIBIT B, NOR, OR, XOR, have been achieved using chemical systems involving two or more enzymes [45]. The enzymes can be