Orthogonal pores and boolean logic

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Abstract. An orthogonal pore ('orthopore') is conceptually based on an electrolytic cell with a standard pore (the main or 'longitudinal' pore) between *cis* and *trans* compartments filled with electrolyte and augmented by a secondary or 'transverse' pore in the form of a channel that is perpendicular to and intersects the main pore. Orthopores can be designed at different scales: macro through micro to nano. With nano-sized pores an analyte (polymer) can be threaded through the main pore and exposed at the junction to electrolyte flow through the secondary pore. Polymer translocation speeds are then independent of the current measured, which can be of an arbitrary magnitude even with the polymer stationary. Orthopores have a wide range of potential applications, including polymer (DNA and protein) sequencing, DNA unzipping, logic circuitry, and protein identification. The present report shows how orthopores can be used to implement boolean logic.

Keywords: boolean logic; nanopores; logic gates; electrolytic cell; NAND gate; NOR gate

1. Orthopores and their potential applications

Orthogonal pores (or 'orthopores' for short) were introduced in [1]. An orthopore is the central component of an electrolytic structure based on the standard electrolytic cell. Conceptually it can be thought of as a standard pore (the 'main' pore) through a membrane bridging a pair of *cis* (*cis_longitudinal* or *cis_l*) and *trans* (*trans_longitudinal* or *trans_l*) compartments filled with electrolyte in an electrolytic cell and augmented by a second pore (the 'transverse' pore) in the form of a channel between a second pair of *cis* and *trans* compartments (*cis_transverse* or *cis_t* and *trans_transverse* or *trans_t*) filled with electrolyte; this second channel is perpendicular to and intersects the main pore. Such a structure lends itself to a number of applications, including polymer (DNA, protein) sequencing, DNA unzipping, boolean logic, protein identification, and biosensing in general. The first three applications were briefly considered in [1]. A similar structure, aimed at DNA and protein sequencing, has been studied theoretically in [2] and [3], where the transverse pore is referred to as a 'perpendicular channel'.

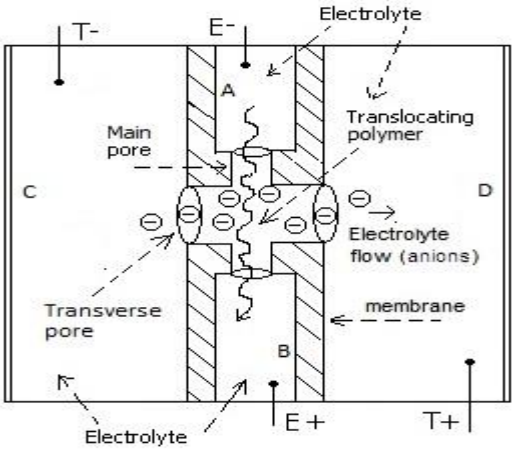

Figure 1. Schematic of an orthopore. A, B, C and D are *cis* and *trans* compartments in an electrolytic cell (A: *cis_l*; B: *trans_l*; C: *cis_t*; D: *trans_t*) bridged by a membrane and containing an electrolyte with Ag/AgCl electrodes (T^-, T^+, E^-, E^+). Membrane may be biological or synthetic.

Figure 1 shows a schematic of an orthopore structure based on electrophoresis. Structurally this is in some ways similar to transverse voltage and current methods that have been studied in the area of DNA sequencing [4,5] and protein sequencing [6-8] (including methods based on measuring tunneling currents transverse to the pore [9]). There are, however, some significant differences: a) with an orthopore there are two distinct channels intersecting each other and both have an electrical potential across them to induce electrolytic flow; and b) polymer translocation is decoupled from transverse ionic current flow. Notable advantages include no restriction on main pore length as

well as the ability to reverse electrolyte flow in the transverse channel independent of the polymer. Orthopores can be designed at different scales, from macro through nano. At all levels they may be implemented with biological and/or synthetic materials using available/emerging technology.

As noted in [1] several existing nanopore-based sequencing methods can be modified to work with orthopores in order to take advantage of the independence of polymer translocation speed from the transverse pore current. As an example, a method to sequence DNA using an orthopore via synthesis of double-stranded DNA from a single-stranded source was proposed in [1]. DNA polymerase is fixed at the pore junction to incorporate dNTPs flowing through the transverse channel for double-strand synthesis using the source as template in a succession of cycles one per source base type. This and other issues are discussed briefly in [1]. The cyclical nature of the processing more or less eliminates a rather stubborn problem in polymer sequencing, namely identification of repeat monomers (bases in DNA, residues in proteins), commonly referred to as the *homopolymer problem*.

This report looks at how binary logic can be implemented with orthopores.

2. Boolean logic with orthopores

To see how orthopore structures can be used to implement standard boolean logic with NOT, OR, and AND gates consider the following: A pair of orthogonal intersecting channels in which electrolyte flowing through the secondary channel is blockaded by a controlled obstruction introduced from the main channel can function as a NOT gate. An OR gate may be implemented using two parallel NOT-like gates with a single common secondary channel. These two gate types provide a functionally complete set so that an arbitrary boolean function can be implemented using only these types. An AND gate may be constructed similarly but has a more complicated secondary channel structure than OR as discussed below. This approach is an alternative to a model of logic gates in [10], also based in electrochemistry.

The gates may be implemented at different scales, macro through micro to nano, using channels of different sizes, different electrolytes, and charged (or uncharged) bodies of a scale-appropriate size for the blockading.

In the following paragraphs a nano-level implementation of NOT, OR, and AND functions based on orthopores is considered. In all cases the obstructor is assumed to carry a uniform charge (positive or negative) along its length.

1) NOT gate

Figure 2 shows a basic orthopore in which two alpha hemolysin (AHL) pores are separated by a horizontal channel. Electrolyte flow in the secondary channel is blockaded by a controlled obstruction introduced from the main channel that is negatively charged. To control electrolyte flow in the two orthogonal channels an electrical potential is applied between terminals T^+ and T^- in *cis_l* and *trans_l* and between E^+ and E^- in *cis_t* and *trans_t*. The following logic convention is used to define binary states based on the measured output E^+:

$$\begin{aligned} \text{Output } E^+ &= \text{ high} && \rightarrow \text{binary state value} = 1 \\ &= (\text{low, usually } 0) && \rightarrow \text{binary state value} = 0 \end{aligned} \qquad (1)$$

Assuming for simplicity that T^- and E^- are grounded, if T^+ is high then the negatively charged obstructor is retracted from the junction into *cis_l* above the top pore thereby unblocking the junction, this makes the transverse electrolytic current $I\_t = I_{out}$ go high. When T^+ is low (the potential is reversed) the obstruction translocates through the junction into *trans_l* thereby blocking the transverse channel and making I_t go low. When the current I_t is high E^+ goes low because of the voltage drop across the resistor. Similarly when I_t is low, $E^+ \approx V$.

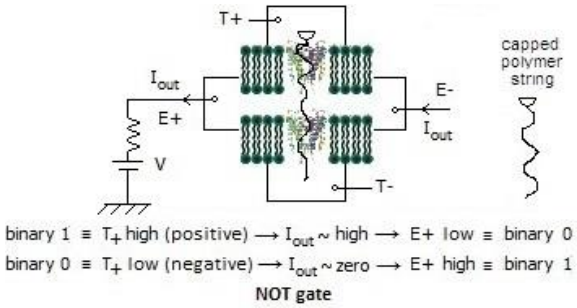

Figure 2. NOT gate with a single orthopore

Blockading bodies include polynucleotides, polypeptides, and similar polymers that carry electrical charge. Single- or double-stranded DNA (which is uniformly negatively charged along its backbone) may be considered with a biotin-streptavidin cap [6] for the controlled obstruction. The larger size of the cap (which can be bonded to the lipid layer of the AHL pore near the entrance on the *cis_l* side) prevents it from passing through the pore even while allowing the polymer to stretch out when a voltage of appropriate polarity is applied across the main pore to impede the flow of electrolyte through the secondary pore. The state can be flipped by reversing the voltage, this causes the polymer to retract and unblock the junction.

2) **OR gate**

Figure 3 shows an OR gate with orthopores. Here two parallel NOT-like gates are used with a single common secondary channel. A capped polymer string is used in each input channel as the controlled obstruction and is uniformly positively charged. (For example, npolyK or npolylysine, a homopolymer with n lysine residues, can be used with an appropriate pH value for the electrolyte.)

In the figure, T^+ is high (positive) so the obstructor on the left is fully stretched, while S^+ is low (negative) so the obstructor on the right is retracted. Since there is at least one obstructor in the transverse channel the transverse current $I\_t = I_{out}$ is low or 0. This corresponds to

$$T^+ = \text{high}, S^+ = \text{low} \rightarrow I\_t = I_{out} \approx 0 \rightarrow E^+ \text{ high} \qquad (2)$$

The other three states are similarly defined.

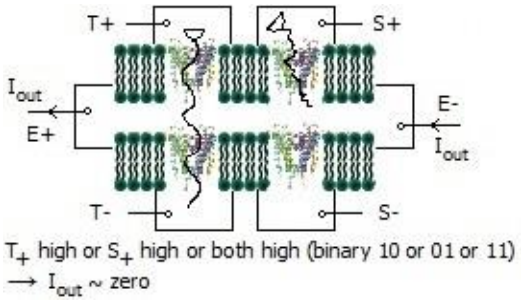

Figure 3. OR gate with two orthopores in parallel

3) **AND gate**

Figure 4 shows an AND gate with two orthopores. This is more complicated than an OR gate. Here two parallel NOT-like gates are used with the secondary channel splitting into two parallel channels. In this case too the obstructor is uniformly positively charged. As with the other gates a capped polymer string is used.

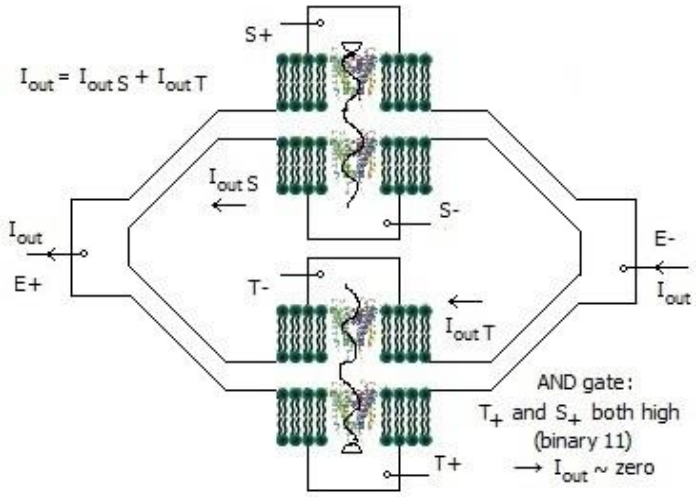

Figure 4. AND gate with two orthopores. The transverse channel is split into two parallel channels.

In the figure, T^+ and S^+ are both high (positive) so the positively charged obstructor in each channel is fully stretched. This means that the two split transverse channels are both blocked and the total tranverse current I_t = I_{out} is low. This corresponds to

$$T+ = \text{high}, S^+ = \text{high} \rightarrow I\_t = I_{out} \approx 0 \rightarrow E^+ \text{ high} \qquad (3)$$

In all the other three cases there is at least one channel that is unblocked so that I_{outt} is at least equal to $I_{out\,S}$ or $I_{out\,T}$ so the current is high and the output is correspondingly low.

4) **NOR and NAND gates**
If the positively charged obstructor is replaced with a negatively charged one, the OR and AND gates above are transformed into NAND and NOR respectively.

3. Notes

1) The proposed scheme can be extended to N-input logic in a fairly straightforward manner.
2) Two properties of nanopores that are known stumbling blocks in polymer sequencing do not pose a problem in the present case. Thus:
a) Polymer translocation speeds currently exceed available detector bandwidth required for reliable sequencing. Here, however, high speeds are a desirable feature because they mean lower switching times, or equivalently higher logic circuit bandwidth.
b) The homopolymer problem, mentioned earlier, which arises from the same base or residue occurring multiple times in succession in the polymer sequence, makes sequencing difficult and unreliable. Here, it is not an issue. In fact, obstructors that are homopolymers are more predictable in their behavior than heteropolymers and are also easier to model.
3) Translocation and retraction of the obstructor can also be done with hydraulic pressure [12] rather than with an electrical potential. In this case the obstructor does not have to be charged.

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