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pH Oscillating System for Molecular Computation as a Chemical Turing Machine

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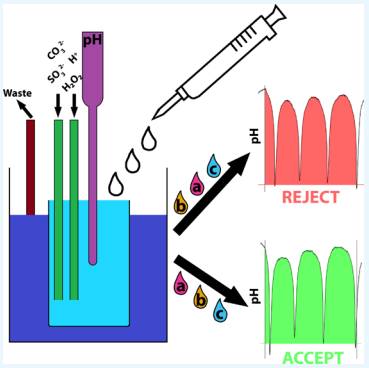
ABSTRACT: It has previously been demonstrated that native chemical Turing machines can be constructed by exploiting the nonlinear dynamics of the homogeneous oscillating Belousov−Zhabotinsky reaction. These Turing machines can perform word recognition of a Chomsky type 1 context sensitive language (CSL), demonstrating their high computing power. Here, we report on a chemical Turing machine that has been developed using the H_2O_2−H_2SO_4−SO_3^{2-}−CO_3^{2-} pH oscillating system. pH oscillators are different to bromate oscillators in two key ways: the proton is the autocatalytic agent, and at least one of the reductants is always fully consumed in each turnover—meaning the system has to be operated as a flow reactor. Through careful design, we establish a system that can also perform Chomsky type 1 CSL word recognition and demonstrate its power through the testing of a series of in-language and out-of-language words.



INTRODUCTION

The field of molecular computing exploits the deterministic reactions of molecules in order to perform computations using chemical architecture. A simple realization of this is a precipitation reaction that only occurs once both components are present.[1] Such a reaction can be considered as an AND gate, providing an output only when both necessary conditions are met. More generally, it can also be considered as the acceptance/rejection of a Chomsky type 3 language,[2,3] with the form L_1: ab. In this form, acceptance is portrayed via physical precipitation when the "word" *ab* is presented to the system, with the letters in any order and quantity. (For further information on the Chomsky hierarchy, we direct the interested reader to Chomsky[2] and Brookshear.[3]) This, of course, scales with Avogadro's number, potentially allowing for high processing parallelism.

Chemistry is, however, not limited to either simple reactions or simple computations. Use of the out-of-equilibrium, nonlinear, dynamic, oscillating Belousov−Zhabotinsky (BZ) reaction has previously enabled the construction of a native chemical Turing machine.[1,4−7] This chemical Turing machine was programmed to recognize words in the Chomsky type 1 Context Sensitive Language L_3: $a^nb^nc^n$, where n is a natural number representing the count of each letter. An example word that is in-language (IL) for L_3 could be *abc* or *aabbcc*, while an out-of-language (OoL) word could be *bac* or *abbc*. In this system, the start of the computation is indicated with a start−stop symbol (#); each letter is then added sequentially to the BZ reaction (with a specified time interval between each addition[7]) before the start−stop symbol is added again to indicate the end of the word. Each symbol and letter are specific aliquots of a known chemical identity, concentration, and volume. These aliquots therefore contain a combination of both analog (chemical concentration and volume) and digital (chemical identity) information. The output of the system is determined by observing the Area[1,8] of the oscillations after the final addition: if the Area falls within a prespecified range, it indicates acceptance of the inputted word, else the word has been rejected. In this way, the system operates as a Linear Bounded Automaton (LBA), which is the highest level of automaton that does not require an infinite tape or energy for its operation. The output of chemical Turing machines of this type has a dual thermodynamic-chemical nature, as the Area metric can be linked to the Gibbs energy via the Nernst equation, and additionally has the properties of the Action in physics. A fuller description of the Area (and its importance) can be obtained from our prior publications.[1,5,8] Other authors have also reported on utilizing the power of BZ for computation, with a variety of different approaches.[9−13]

Such a chemical Turing machine has implications in the computational understanding of life.[14,15] It has been demonstrated that chemical reactions can be interpreted as computations, and biological life is the result of a series of complex reactions, often held out of equilibrium.[16] It therefore follows that any system that enables life should also support

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computations,[17−22] and it is possible that the reverse is also true. However, all previous native chemical Turing machines have used non-naturally occurring chemicals and very harsh conditions to support oscillations.

Here, we demonstrate the first native chemical Turing machine that operates as a pH oscillator. We use a continuous-flow stirred tank reactor (CSTR) to generate a dynamic oscillating system using only chemicals plausibly found on the early Earth. Life and computations are intrinsically linked, and so it is important to demonstrate computability using life-plausible systems: pH is critical to all known life, pH is controlled by life (e.g., proton pumps), and pH is used by life (e.g., ATP synthesis). Additionally, it has been previously shown that cell-like encapsulation, a fundamental attribute of "simple" life, can be driven by pH oscillations.[23−26]

RESULTS AND DISCUSSION

The pH oscillating system that we chose to employ was the H_2O_2−H_2SO_4−SO_3^{2-}−CO_3^{2-} system, reported separately by Rábai[27] and Frerichs and Thompson.[28] This system was selected because it permits rapid oscillations with a suitable period−residence time ratio. The choice was not straightforward, and several other systems were first attempted unsuccessfully. Other pH oscillators tested proved to have periods that were too long or were too stable. This pH oscillating chemical system is known to be delicate,[29] which has a few advantages for our use. First, all reported pH oscillators consume at least one of the present reductants in each turnover, which means that the consumed reductant cannot be used as a letter to write words in a language because it would affect only a single turnover (unlike in BZ-based chemical systems). (This also means that all pH oscillators are required to run in either CSTR or semi-batch, as this reductant must be continuously replaced.[30]) However, most other pH oscillating systems also have the oxidant in large excess, which is not the case in this system, meaning that the oxidant can be used as a symbol. Second, the system's responses to aliquot additions are significant, which means that the reaction pathway can be easily altered through symbol additions, making it suitable for our purposes.

As shown in Table 1, the pH oscillator operates through the autocatalytic generation of protons, accompanied by a delayed negative feedback that consumes protons. H_2O_2 oxidizes hydrogen sulfite to sulfate in reaction (3), which is autocatalytic with respect to protons. Additionally, the sulfite anion is directly oxidized to sulfate (reaction (1)), which depletes the concentration of sulfite anions, causing more hydrogen sulfite to dissociate (reaction (4)), and further increases the proton concentration. Once the sulfite is consumed and a certain proton concentration is reached, the negative feedback has a stronger effect. The carbonic acid is dehydrated slowly to $CO_{2(aq)}$ in reaction (7), decreasing its concentration. This in turn promotes reaction (−6) (i.e., the reverse of reaction (6)), which consumes protons through the generation of carbonic acid.

In many CSTR systems, the continuous in and out flow of material results in the entire system being regularly refreshed (or reset) every ∼3 residence times (τ_{res}).[8,31] The delicate nature of this pH oscillating system means that the reaction pathway invoked by aliquot additions does not revert to the original conditions after $3\tau_{res}$. However, in order to ensure that this does not cause any issues, the time interval (τ) for aliquot additions was chosen to be 130 s ($\tau \approx 0.7\tau_{res}$).[7]

As this chemical Turing machine operates using a completely different chemical system than all previous versions (i.e., a pH oscillator instead of the BZ reaction), new aliquots were required to represent the symbol and letter additions. These are listed in Table 2. The start−stop symbol (#) was selected to be H_2O_2, the primary oxidizer of this system and one of the primary reagents required for oscillations, because it is capable of marking the end of the computation, without completely "resetting" the system. Letter "a", a Cu^{2+} catalyst that also affects the SO_4^{2-} salt balance, causes a reduction in amplitude and an increase in frequency, suggesting that it affects both feedback loops. Letter "b" is iodine, whose redox potential sits between that of H_2O_2 and sulfite[32] and will therefore interact with multiple components; there is also a known chemistry between I_2, H_2O_2, and sulfite. Letter "c" is represented by carbonate, which is also a primary reagent of the system. The carbonate anion is involved in multiple steps of the reaction both directly and indirectly (by reducing the total available proton concentration, which correlates positively with oscillation frequency in this pH range). The concentration of each aliquot was designed such that it would minimize the volume of the said aliquot and thereby keep dilution effects to a minimum. Additionally, it was important to have each aliquot's effect sufficient to perturb the system while ensuring that it would not become dominant or push the system out of the oscillatory regime.

In the original chemical Turing machine, the Area was determined using eq 1,[1] which essentially encapsulates the region above the oscillation profile (V_{osc}) and below the peak redox potential, V_{max}, for a time period τ. A CSTR system never reaches the peak redox potential during a computation because it is already oscillating when the computation starts;

Table 1. Reaction Mechanism for the pH Oscillator Reaction[a]

number	reaction
(1)	$H_2O_2 + SO_3^{2-} \rightarrow SO_4^{2-} + H_2O$
(2)	$H_2O_2 + HSO_3^- \rightarrow H^+ + SO_4^{2-} + H_2O$
(3)	$H_2O_2 + HSO_3^- + H^+ \rightarrow 2H^+ + SO_4^{2-} + H_2O$
(4)	$HSO_3^- \rightleftharpoons H^+ + SO_3^{2-}$
(5)	$HCO_3^- \rightleftharpoons CO_3^{2-} + H^+$
(6)	$H_2CO_3 \rightleftharpoons HCO_3^- + H^+$
(7)	$H_2CO_3 \rightleftharpoons CO_{2(aq)} + H_2O$

[a]Proposed by Frerichs and Thompson.[28] The reverse reaction can be indicated using the negative of the reaction number. The autocatalytic generation of protons occurs during reaction (3), while the negative feedback primarily occurs through reaction (−6).

Table 2. New Aliquots Used as Symbols to Influence the Reaction Pathway of the pH Oscillating Chemical Turing Machine[a]

symbol	chemical	concentration (mM)	volume (μL)
#	H_2O_2	585	300
a	$CuSO_4$	1.25	20
b	I_2	50.0	8
c	Na_2CO_3	6.0	80

[a]Two of the symbols (# and c) are part of the primary oscillating reagents, while the other two (a and b) are introduced as external influencers.

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consequently, it was not possible to use this definition of Area. Instead, the modified eq 2 was developed (cf. alternative formulation previously reported[8]), which maintained the significance and interpretation of the interpeak area and also accounted for the waveform of the H_2O_2–H_2SO_4–SO_3^{2-}–CO_3^{2-} oscillating system being inverted (with respect to the original BZ system originally used to introduce the Area metric). pH_{min} is the arithmetic mean of the minima pH reached in the specified region (excluding the first 20 s, to allow for transients to dissipate). A typical pH trace of an example test word is shown in Figure 1, wherein the word *abc*

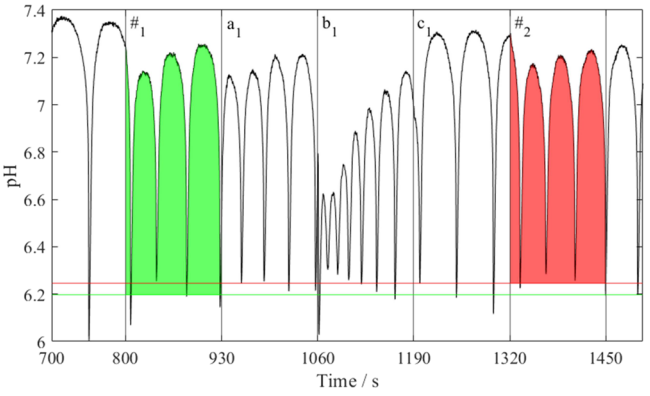

Figure 1. A pH trace of an example test word being run using the pH oscillator chemical Turing machine in CSTR. The input sequence is #abc#, with appropriate aliquot additions at the marked timepoints. Note that the oscillations are established before addition of $\#_1$. The output Area is derived by subtracting the green shaded region from the red shaded region.

has been inputted along with the required start–stop symbol #. The output Area, as defined in eq 2, is essentially the difference between the regions shaded red and green in Figure 1.

$$A_{batch} = [V_{max} \times (t_{\#_2+\tau} - t_{\#_2+30})] - \int_{t_{\#_2+30}}^{t_{\#_2+\tau}} V_{(osc)}(t)\,dt \quad (1)$$

$$A_{CSTR} = \left(\int_{t_{\#_2}}^{t_{\#_2+\tau}} pH_{(osc)}(t)\,dt - pH'_{min} \times \tau\right) - \left(\int_{t_{\#_1}}^{t_{\#_1+\tau}} pH_{(osc)}(t)\,dt - pH_{min} \times \tau\right) \quad (2)$$

For our pH oscillator-based chemical Turing machine, we demonstrate computability through the acceptance or rejection of inputs according to the Chomsky type 1 Context Sensitive Language L_3: $a^nb^nc^n$, as with the previous BZ-based chemical Turing machines.[1] Addition of aliquots causes a systematic and reproducible change in both the period and amplitude of the oscillations, as seen in Figure 2. The specific experimental methods and materials as well as a photo and schematic of the setup can be seen in the Supporting Information. We tested several IL and OoL words with the system, calculated their output Area, and plotted the area difference between the final and initial #-symbol (i.e., area difference between the start and end of sequence) against their string length, which is shown in Figure 3. The Area difference is proportional to the free-energy change in the automaton during the course of the computation.

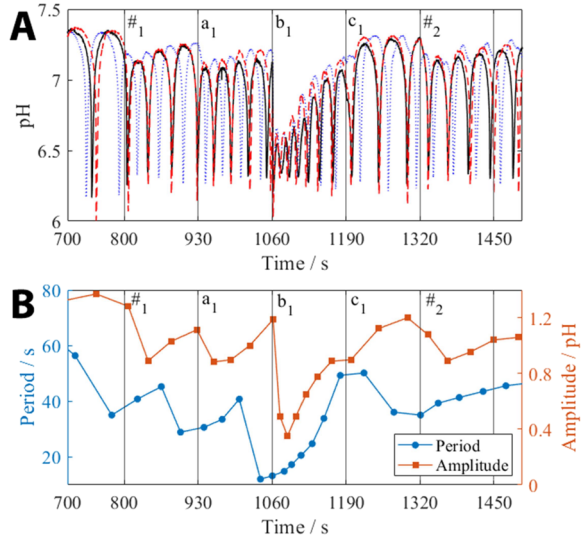

Figure 2. (a) Overlay of three experimental runs showing the progression of the pH oscillations as the aliquots for the word *abc* are sequentially added to the system, indicating high reproducibility. The black solid, red dashed, and blue dotted lines each portray a different experimental run. (b) Ongoing change in both oscillation periodicity (blue circles) and amplitude (orange squares) as the aliquots for word *abc* are sequentially added. It is the progression of the reaction pathway, as influenced by these additions, that permits use as a chemical Turing machine.

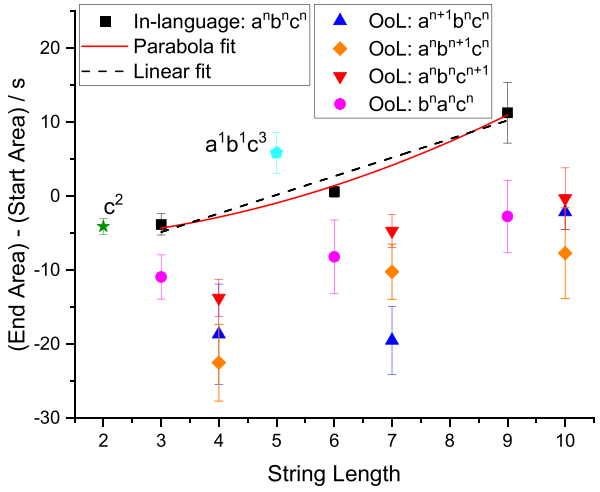

Figure 3. Plot of the output Area differences for multiple tested words in the pH oscillator chemical Turing machine. Points are the arithmetic means of three experiments, and error bars are the standard deviation. The red curved line is a parabola fit of the IL words with the equation $f(x) : (2.12 \pm 0.194) \times 10^{-1}x^2 - (6.22 \pm 0.998)$ and an R^2 of 0.9917. The black dotted line is a linear fit of the IL words, with the equation $f(x) : (2.52 \pm 0.601)x - (12.4 \pm 3.89)$ and an R^2 of 0.9461.

Figure 3 shows that our pH oscillator-based chemical Turing machine provides a clear distinction between words based on whether or not they fit the parabola $f(x) : (2.12 \pm 0.194) \times 10^{-1}x^2 - (6.22 \pm 0.998)$—if they do, they are accepted and considered IL, and if they do not, they are rejected and considered OoL. As well as testing IL words, a large variety of chemically and algebraically similar but still OoL words were also tested (e.g., *bac* and *abbc*) and found to be distinct, illustrating the language-discerning power of our chemical

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system. This demonstrates, and relies on, the reaction pathway of the pH oscillating system being dependent on the sequence and count of each aliquot addition, despite the "continuous soft resetting" nature of a CSTR system. We note that the Area[8] has properties that make it akin to the action in physics, and we can see that the dependence of the Area difference on sequence details parallels the extremum of the action principle in physics when the physical system executes a physically viable trajectory corresponding to a minimum of the action. This has profound ramifications for the understanding and interpretation of native chemical automata and their computations.[1,8,33,34] Additionally, while the Area-related metric that we are using here corresponds to the difference between the initial and final Area, we note that an alternative metric involving the ratio of the two Areas (instead of their difference) is similarly effectual (see the Supporting Information). Furthermore, we also discover experimentally (cf. Figure S2) that the Area-difference and the Area-ratio metrics for IL words are universally proportional to each other. (We have reason to believe that this is not a coincidence, and we are currently investigating the significance of this finding in the context of theoretical statistical mechanics.)

Repeatability is obviously important in any chemical system, specially so in the context of chemical computation, including the native Turing machine. As has been alluded to by others,[28,29] the pH oscillating system that we employed can be delicate, and so several provisions were made in order to provide and ensure the reproducibility of results (see Figure 2a). Care was made not to unnecessarily expose reaction solutions to air, which involved the use of degassed water, sonicating to dissolve solids, and purging headspaces. Though the reaction itself was open to air, the system was operated inside a cabinet to prevent unwanted airflow from affecting the system.[29] Syringe pumps were used to control the inflow of the reactants into the reactor, as the regular pulsing of a peristaltic pump introduced unwanted spurious perturbations into the system.[35] All solutions were made daily and stored in syringes at 4 °C for 20 h before use. The reaction cap was designed and 3D printed to hold all required tubing in place, without restricting the diffusion of gases to/from the reactor. The CSTR inlet tube depths were maintained at a set height throughout. A constant volume of the reactor was achieved using the "overflow technique", whereby the reactor is allowed to overflow and the waste is collected from the outside, because use of a peristaltic pump caused excessive variance in the residence time. Due to use of the "overflow technique", the outside of the glass vessel was hydrophobized using dichlorodimethylsilane in order to prevent unwanted droplets connecting between the reactor and the outside waste, which would affect the pH measurements. The system was sensitive to the stirring rate and temperature, and so it was run at 870 rpm and (20.0 ± 0.1) °C throughout. Finally, a pH meter with a liquid, as opposed to a gel, internal electrolyte was selected for response speed, which was operated at a fixed height and calibrated daily.

The development of this pH oscillator-based chemical Turing machine bridges the gap between the biologically plausible reagents and computation. This also enables the power of chemical computation to be brought to bear on scenarios associated with the geochemical origins of life in, for example, the context of alkaline/acidic pools at Yellowstone.[36−38] Additionally, the experimental work presented here proves that it is the general concept of oscillatory chemistry that applies to computation at this high level and that it is not an isolated power of a specific class (redox oscillators) of chemical reactions.

CONCLUSIONS

In summary, we have demonstrated that if some early-Earth inorganic small molecules come together as plausible reagents in such a way so as to produce a nonlinear dynamic chemical system, capable of supporting pH oscillations, it is also potentially capable of supporting nontrivial computations at the Turing machine level. Therefore, native chemical Turing machines are not limited to the BZ reaction or the class of oscillatory redox reactions, or even to heavy metal catalyzed systems. The pH-oscillator chemistry allows computing automata to operate under much milder and greener conditions using milli- and micromolar concentrations of hydrogen peroxide and sulfuric acid, respectively. Finally, we note that such a system in a geophysical setting could also be combined with polymerization-induced self-assembly to facilitate the simultaneous self-encapsulation[24−26] of (at least) the elementary components for computation needed for life—when information is still conformational or compositional, but not yet genetic.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c06505.

Description and comparison of an alternative Area definition; extended methods and materials; example pH traces for multiple words; and a photograph and cartoon schematic of the experimental setup (PDF)

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Notes

The authors declare no competing financial interest.

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