

Chemical Kinetics is Turing Universal

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(Received 20 February 1996; revised manuscript received 15 August 1996)

We show that digital logic can be implemented in the chemical kinetics of homogeneous solutions: We explicitly construct logic gates and show that arbitrarily large circuits can be made from them. This proves that a subset of the constructions available to life has universal (Turing) computational power. [S0031-9007(97)02332-6]

PACS numbers: 87.10.+e, 89.80.+h, 82.20.Mj

Interest in chemical computation has followed four different paths. It is one of the natural extensions of discussions about information and thermodynamics, which go back to Maxwell demon arguments and Szilard's work [1–5]. It is also a rather natural extension to the application of dynamical systems theory to chemical reactions [6–8], in particular logic networks stemming from bistable reaction systems [9]. A lot of effort has been devoted to trying to devise nonstandard computational architectures, and chemical implementations provide a distinct enough backdrop to silicon [10–12]. Finally, in recent years biology has presented us with what looks to be actual chemical computers: the enzymatic cascades of cell signaling [13–15].

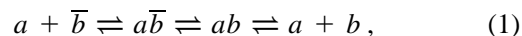
One of the first questions that can be asked in this subject is whether universal (Turing) computation can be achieved within some theoretical model of chemistry; the most immediate one is standard chemical kinetics. This question has been recently studied in some detail [16–22], and even subject to experimental tests [23]. In [18–20], Hjelmfelt *et al.* argued quite convincingly that building blocks for universal computation indeed can be constructed within ideal chemical kinetics, and that they could be interconnected to achieve computation. However, many difficulties still lie in the way. An issue not addressed by Hjelmfelt *et al.* is structural stability: the tolerance of a system to changes in parameters and functional structure. In particular, “gluing” together two groups of chemical reactions will have appreciable effects on the kinetics of both groups; the basic unit and the couplings used in [18–20] require case-by-case adjustment of individual parameters for proper functioning.

The purpose of this Letter is to provide a slightly more formal proof that chemical kinetics can be used to construct universal computers. I will concentrate on the “next” level of difficulty, which is that of the *global* behavior of a fully coupled system and its structural stability. I will do it through the simplest approach: I will show that classical digital electronics can be implemented through chemical reactions. Since my key problem in this scheme is showing *global consistency*, and the proof requires arbitrarily large circuits, I will have to show that the output of one gate can be plugged into the input of

others for arbitrarily many layers, without degrading the logic, keeping at all times full coupling.

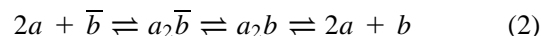
We will need a power supply. I will define mine to consist of two chemical species called *high* and *low*; their concentrations will be kept clamped strongly out of equilibrium, so an external reservoir is assumed. This approximates the power supply in cells, the two compounds ATP and ADP; the cellular “power plants” keep their concentration as constant as feasible, nearly 6 decades away from equilibrium. Thermodynamics requires the logarithm of the equilibrium constants to lie in the (left) span of the stoichiometry matrix; it is important that all reactions we use satisfy this constraint, so that there are no “hidden” power supplies.

The very first thing we need to consider is the trivial gate, the signal repeater, which copies input onto output. Any problems we encounter with it will recur for any other gate. Let's say a chemical species *a* is the input and *b* the output. We will need *b* to exist in two chemically distinct forms, *b* and \bar{b} [24]. If \bar{b} is a compound of higher energy than *b*, we can couple its production to the power supply, as in $b + \text{high} \rightleftharpoons \bar{b} + \text{low}$; in the absence of other reactions, $[b]$ goes to a small value determined by the rate of spontaneous decay in $\bar{b} \rightleftharpoons b$. This is then a sort of “capacitor,” which we charge with the power supply. If then the reaction $\bar{b} \rightleftharpoons b$ is catalyzed by *a*,



then *a* “shorts” the capacitor and discharges it, increasing the concentration of *b*. Hence when $[a]$ is low, $[b]$ is low, and when $[a]$ is high, $[b]$ becomes high, and the transitions have certain rise and decay times determined by the precise rates we use.

In Fig. 1 we see the output of simulating a chain of several such gates with $a \rightarrow b \rightarrow c \rightarrow d \dots$. The gates are all identical; the only change between them is the name of the compound. The wave forms are dying as we go down this chain: The difference between the “high” and the “low” levels is becoming smaller and smaller. So this network is not a suitable signal repeater. Figure 2 shows the output of a similar simulation using the reactions



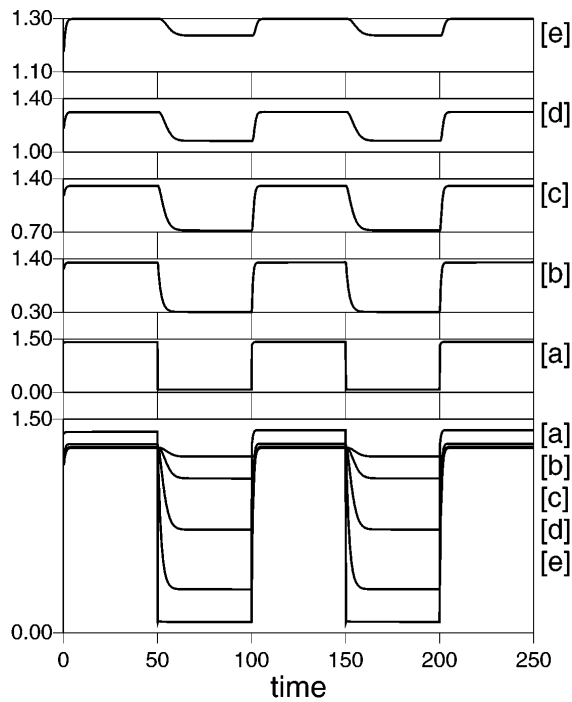


FIG. 1. A cascade of identical signal repeaters $a \rightarrow b \rightarrow c \rightarrow$, using Eq. (1). The input to [a] is a square wave. Top (small) panels show each signal individually with varying scales, bottom (large) panel shows all signals simultaneously on the same scale. The amplitude of the signal gets reduced very rapidly.

(i.e., double stoichiometry on the input). We can see that the amplitude of the pulses gets stabilized; both high and low now approach amply separate levels [25]. I will now prove that higher stoichiometry is essential.

All concentrations become stationary after some transients. If we plot these steady levels as a function of the inputs, we get the classical plots shown in Fig. 3. These diagrams represent the concentration of b as a function of a , but also of c as a function of b , and so on. If we call x_n the n th compound in the chain, then the diagram shows x_{n+1} as a function of x_n ; n here labels *position on the chain*. This is a recurrence relation, also called a *map*.

This type of map is usually studied in the theory of dynamical systems, where it represents some dynamical law, and n labels time. A large part of dynamical systems theory is devoted to the asymptotic states, i.e., what happens at arbitrarily long times. In our case this translates to “arbitrarily deep into the circuit,” which is what we want to study. Dynamical systems theory tells us that the only asymptotic states of maps which are monotonically increasing and bounded (our case) are steady states. The steady states (also called fixed points) of a map occur when $x_{n+1} = x_n$, i.e., when the curve intersects the diagonal line. They can be stable or unstable; stable (unstable) means that if some x_n is near the fixed point, then, for $m > n$, the x_m are *nearer* to (farther away from) the fixed point; this happens when

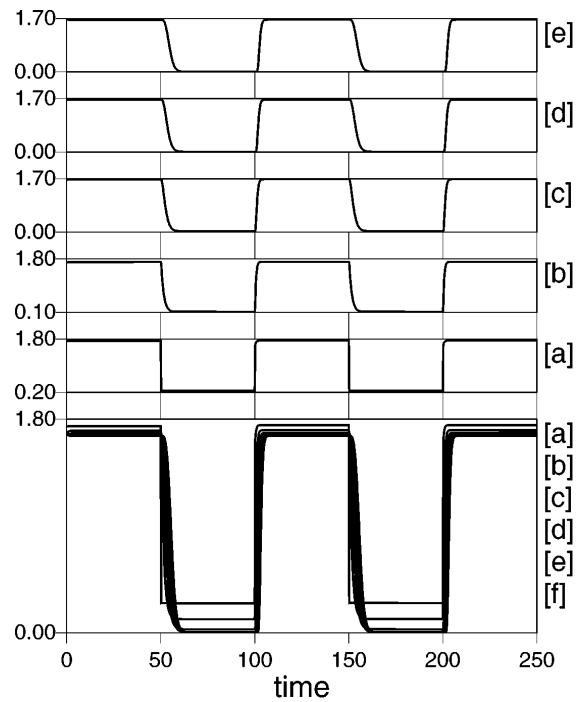


FIG. 2. A cascade of signal repeaters with double stoichiometry [Eq. (2)]. Same conventions as Fig. 1. The amplitude of the signal converges to a steady value.

the curve is shallower (steeper) than the diagonal at the intersection.

In the case of stoichiometry one ($S = 1$) there are at most two fixed points, and only one can be stable [26]. For $S > 1$ there can be three fixed points, the two outer ones being stable, the middle one unstable. We can propagate logic arbitrarily deep into the chain

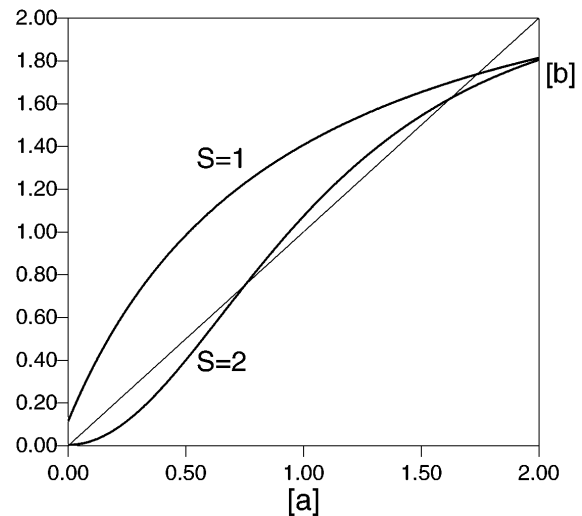


FIG. 3. The steady-state concentration of the outputs of two signal repeaters, $S = 1$ [Eq. (1)] and $S = 2$ [Eq. (2)] as a function of the steady-state level of the input a . The diagonal line is $[a]$ as a function of itself; the intersections of the two curves with this diagonal are the fixed points.

if and only if we have at least two distinct stable fixed points, with each one corresponding to a distinct logical state. But two stable fixed points are possible only for $S > 1$.

Now the main conceptual problems have been solved. The only remaining point is to construct explicitly a few different gates (Fig. 4); if all of the gates are “built” (i.e., the rates so chosen) so that their response is one of our fixed points when the inputs are at the fixed points then they will be globally compatible. Strictly speaking, one needs only NAND, since all logical functions can be constructed from it, but since each internal wire in the circuit is a chemically distinct compound, it is desirable to implement gates directly [27]. A precise definition of the gates can be found elsewhere [28].

Adding is a problem that exemplifies rather nicely the spirit of this work, because when we add, we have to shift the “carry” digits to the next column. These can accumulate to generate a cascade, so we need to be able to propagate logic across an entire network. In order to add two three-bit numbers (giving a four-bit number as the output), we need to cascade three full adders. The three-bit adder is shown in Fig. 5; it can add up to $7 + 7$.

Ephemeral memory can be implemented rather directly, but if the memory is supposed to be long-term, care must be exercised. A flip-flop can be made by having a compound in two states (c, \bar{c}), and then two inputs (a, b) which catalyze conversion to the other state by coupling to the power supply:

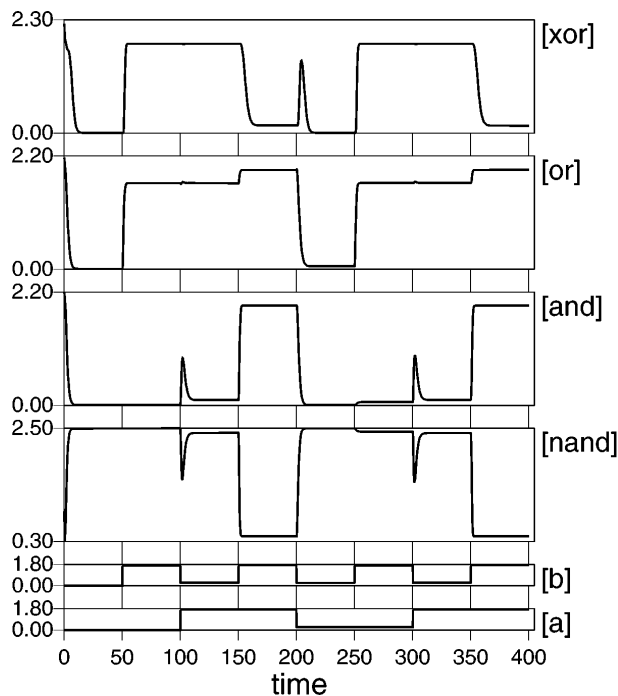
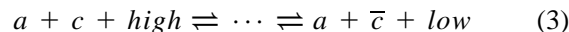
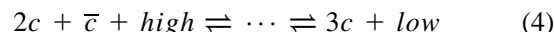


FIG. 4. The output of one implementation of the four classical gates. a and b are the inputs. While there are artifacts, the logic levels are still well separated. AND, OR, and NAND are implemented directly, XOR is implemented as AND(NAND,OR).



and similarly for b sending $\bar{c} \rightarrow c$. The lifetime of this memory would appear to be the lifetime of the uncatalyzed reaction $c \rightleftharpoons \bar{c}$. However, such a mechanism is not resistant to fluctuations in the inputs; even a minute amount of catalyst can reduce the lifetime dramatically. In order to make memory stable, we need to make the system *prefer* to be either all c or all \bar{c} . There are many ways to do this; for instance,



and vice versa [29]. The addition of these two self-catalytic reactions makes the memory strongly robust (see Fig. 6) and, in principle, infinitely long lived even in the presence of input fluctuations; however, energy is drawn from the power supply to “refresh” the flip-flop. There is some resemblance to dynamic vs static RAM, and to the self-phosphorylating enzyme CamK II [30], which might be implicated in long-term memory in neurons.

I have shown one particular explicit implementation of digital logic in chemical kinetics, and thus shown universal computation capabilities. However, many questions still remain open (which I will comment upon in some greater detail elsewhere [31]): What is the interplay between information transfer and thermodynamics? Since no catalyst

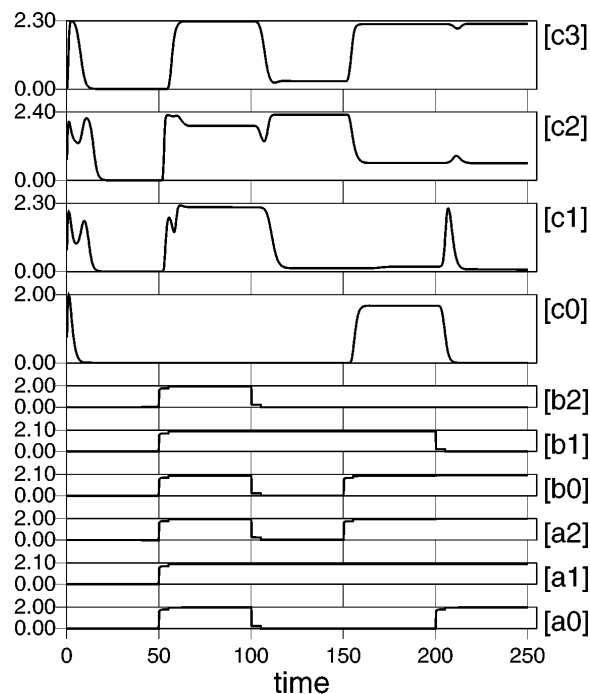


FIG. 5. Numerical simulation of the three-bit adder: $c = a + b$. The lower traces are the three bits of input a and the three bits of input b ; the four upper traces are the four bits of output c . The transients as the inputs are changed show the delays in propagating carries. The five columns of different inputs show: $0 + 0 = 0$, $7 + 7 = 14$, $2 + 2 = 4$, $6 + 3 = 9$, and $7 + 1 = 8$. The network has about 140 compounds in 290 reactions.

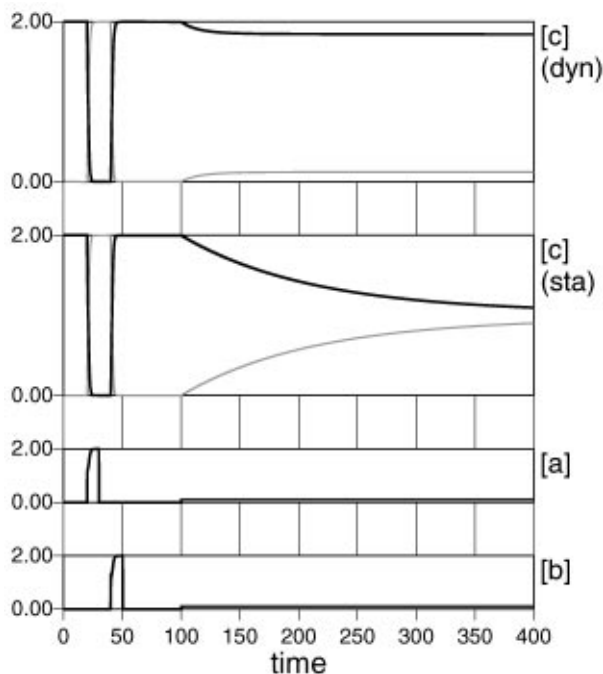


FIG. 6. Two flip-flops; sta is a “static” flip-flop [Eq. (3)], and dyn a “dynamic” one with autocatalytic stabilization [Eq. (4)]. Both can switch between states fast as the inputs a and b are pulsed. At time 100 both inputs are set to 0.1; sta forgets its state, while dyn does not.

is perfectly selective for its substrate, how robust are computations under the massive cross talk of random “unintended” reactions? Are there equivalents of the gain bandwidth and other classic theorems of electronics? And, presumably, many more.

I would like to thank A. Ajdari, G. Cecchi, D. Chate- nay, J.-P. Eckmann, A. Libchaber, G. Stolovitzky, and D. Thaler for many stimulating discussions. Completed in part at U. of Buenos Aires and Asoc. de Fisica Argentina; I want to thank G. Mindlin, S. Ponce, and J. P. Paz for their hospitality. Supported in part by the Mathers Foundation.

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- [24] Compounds which exist in two chemically distinct states can be implemented as proteins which can be phosphorylated, or as compounds which can be localized in two different places; for instance, Ca^{++} in the cytosol is “chemically distinct” from Ca^{++} in the ER, with channels and pumps playing the role of kinases and phosphatases.
- [25] These repeaters show the equivalent of input and output impedance/capacitances. If $[a]$ is changed abruptly, it bounces, due to capture and release from the bound complexes ab and $a\bar{b}$. Convergence fails on the last steps of the cascade when the last element is not “terminated.”
- [26] For $S = 1$ the curve is convex. A convex curve can be intersected by a straight line at most twice; at most one intersection can be stable.
- [27] Actual kinases from enzymatic pathways can have more than one phosphorylation site and do logic directly on the protein; so biological cascades can be more compact than the networks shown here.
- [28] Online at <http://tlon.rockefeller.edu/>
- [29] This can be done with only one autocatalytic reaction, plus a nonspecific decay like $c \rightarrow \bar{c}$ (a self-phosphorylating kinase and a phosphatase); in the absence of other interactions, either $S > 1$ or cooperativity is required. See also [9].
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- [31] A full version of this paper, including a careful description of the open problems, will appear elsewhere.