ond, we assumed that the partial monolayer of Bi in the liquid-vapor interface is supported on pure Ga. Third, from the known amplitude and penetration of the evanescent electric field in the bulk liquid we calculated the relative illumination by the x-rays of the two species in our model. To carry out these calculations we must know the densities of the several species. Nothing is known of the density of the Bi monolayer, but the form of the transverse structure function suggests that it might be in a supercooled liquid state, so we took the density to be 10.0 g/ml, which is between the solid- and normal liquid-state densities. The results of these calculations are y_{Bi} = 0.80 and y_{Ga} = 0.20. The surface concentration of the segregated Bi determined in this fashion is the same as that predicted from the Gibbs adsorption isotherm and the assumption that the binary alloy is an ideal mixture.

The raw data obtained from our grazing incidence x-ray diffraction study of the liquid-vapor interface of the 0.2%Bi:99.8%Ga alloy clearly show that the transverse structure function of the interface is different from the structure function of the bulk liquid. The qualitative character of the difference observed is consistent with a large excess concentration of Bi in the liquid-vapor interface. A simple but plausible model leads to the conclusion that the mole fraction of Bi in the liquid-vapor interface of the alloy is 0.80, in good agreement with the value predicted from the Gibbs adsorption isotherm. We do not have a good way of testing the validity of the quantitative details of the results of our analysis, but we are confident that the qualitative aspects of our observations are correct. These are (i) that Bi is strongly concentrated at the liquid-vapor interface of dilute liquid Bi:Ga and (ii) that the segregated Bi in the interface is in a liquid state. To unambiguously determine the transverse structure function of the excess Bi in the liquid-vapor interface it is necessary to carry out three experiments under conditions such that the scattering powers of the Bi and Ga atoms are different in each experiment. In principle, these conditions could be generated by taking advantage of the anomalous dispersion of x-rays near an absorption edge. We believe the necessary experiments should be attempted.

REFERENCES AND NOTES

1. J. S. Rowlinson and B. Widom, *Molecular Theory of Capillarity* (Clarendon, Oxford, 1982).
2. M. P. D'Evelyn and S. A. Rice, *J. Chem. Phys.* **78**, 5225 (1983).
3. J. G. Harris, J. Gryko, S. A. Rice, *ibid.* **87**, 3069 (1987).
4. D. Sluis and S. A. Rice, *ibid.* **79**, 5658 (1983).
5. L. Bosio and M. Oumezine, *ibid.* **80**, 959 (1984).
6. B. N. Thomas, S. W. Barton, F. Novak, S. A. Rice, *ibid.* **86**, 1036 (1987).
7. E. B. Flom *et al.*, *ibid.* **96**, 4743 (1992).
8. J. Harris and S. A. Rice, *ibid.* **86**, 5731 (1987).
9. U. Dahlborg and M. Davidovic, *Phys. Chem. Liq.* **15**, 243 (1986).
10. A. H. Narten, *J. Chem. Phys.* **56**, 1185 (1972).

11. This research was supported by a grant from the National Science Foundation (NSF) (CHE 8919570). We have also benefited from the use of facilities for materials research provided by the NSF at the University of Chicago. Our preliminary grazing incidence x-ray diffraction studies were carried out at beamline X10A and our final experiments at beamline X8C, both at the National Synchrotron Light Source (NSLS) at Brookhaven National Laboratory. We thank the NSLS for the grants of beam time that made these experiments possible.

13 November 1992; accepted 29 January 1993

Pattern Recognition in Coupled Chemical Kinetic Systems

A. Hjelmfelt, F. W. Schneider, J. Ross*

A network of open, bistable reaction systems coupled by mass transfer is simulated. The mass transfer rates are determined by a Hebb-type rule, and the programmable network can store patterns of high and low concentrations in each bistable system. In a parallel computation, the network recognizes patterns similar, but not necessarily identical, to stored patterns.

We have offered suggestions for the chemical implementation of computing machines (*1–3*): the chemical coupling of reaction mechanisms (*4*) far from equilibrium whose stationary states have properties of a McCullouch-Pitts neuron (*5*) led to the construction of logic gates, a finite state machine that generalizes to a universal Turing machine (*6*), and a parallel neural network computer. In this report, we describe a class of parallel chemical computers based on chemical kinetics systems with multiple stable stationary states coupled by mass transfer. We demonstrate the computational capacity of such a network by storing patterns in it and solving pattern recognition problems.

Consider a set of chemical reactions that occur homogeneously in an enclosure, which may be a cell compartment, a neuron, or a stirred reaction vessel. Each enclosure is an open system: reactants enter, and products, intermediates, and unreacted material exit. We use a set of chemical reactions that is bistable. There are many reaction mechanisms and physical processes in which bistability is known, including enzymatic reactions (*7*) and neuronal response (*8, 9*). For simplicity of illustration, we use an inorganic chemical reaction, the iodate–arsenous acid reaction (*10, 11*)

$$IO_3^- + 3H_3AsO_3 \rightleftharpoons I^- + 3H_3AsO_4 \quad (1)$$

for which the kinetics are adequately described by the temporal variation of a single variable, the concentration of I^- ($[I^-]$). Bistability occurs in this isothermal reaction: for a given range of input flows of reactants (given constraints), the homogeneous reaction system at steady state may have either a high or low $[I^-]$.

The systems communicate with each other by mass transfer; either diffusional, in which case it is reciprocal, or active transport, in which case we require it to be reciprocal. Although all the different chemical species are transported, the temporal evolution of the *i*th system ($i = 1, \ldots, N$) in the network is adequately described by its $[I^-]$ (*11–13*)

$$\frac{d[I^-]_i}{dt} = -k_B[I^-]_i^3 + \{k_B([I^-]_0 + [IO_3^-]_0) - k_A\}[I^-]_i^2 + \{k_A([I^-]_0 + [IO_3^-]_0) - k\}[I^-]_i + k[I^-]_0 + \lambda \sum_{j \neq i} k_{ij}([I^-]_j - [I^-]_i) \quad (2)$$

in which $[I^-]_0$ and $[IO_3^-]_0$ are, respectively, the concentrations of iodide and iodate in the reactant flows that maintain each system away from equilibrium, k_A and k_B are effective rate coefficients, and k is the reactant flow rate. The mass transfer coefficients, $k_{ji} = k_{ij} \geq 0$, are reciprocal and are chosen by a Hebbian rule (*14*), and $\lambda \geq 0$ is a scaling parameter that is chosen such that the final state of each system is influenced by the other systems but not so strongly that the network is always driven to homogeneity. There exists a Liapunov function for chemical systems described by Eq. 2 (*13*), which is an evolution criterion toward stable stationary states (analogous to the Gibbs free energy of a system approaching equilibrium). If each system has only one stable stationary state, then the only stable stationary state of *N* coupled systems

---

A. Hjelmfelt and F. W. Schneider, Institute of Physical Chemistry, University of Würzburg, Marcusstrasse 9/11, D-8700 Würzburg, Germany.
J. Ross, Department of Chemistry, Stanford University, Stanford, CA 94305.

*To whom correspondence should be addressed.

is spatially homogeneous. However, because the systems are bistable, there are 2^N possible stable stationary states of the network; the bistability of a single system is essential to the network operation. Each system represents a pixel, and thus the stable stationary states of the network are patterns of low and high [I$^-$], two of which are homogeneous.

Patterns are stored in this chemical network analogously to such storage in neural networks. Let R_i^p be the activity of the *i*th system in pattern *p*; $R_i = 1$ for the high [I$^-$] state and 0 for the low [I$^-$] state. We use a Hebbian rule (*14–18*) to determine the mass transfer coefficients. If two systems *i* and *j* are in the same state in a stored pattern, either both have high [I$^-$] or both have low [I$^-$], and the connection weight is increased; otherwise, the connection weight is decreased. The contributions to the connection weight between systems *i* and *j* is summed over each stored pattern. The Hebbian rule is

$$k_{ij} = \theta\Big[\sum_p (2R_i^p - 1)(2R_j^p - 1)\Big] \qquad (3)$$

in which $\theta[x] = x$ if $x \geq 0$ and $\theta[x] = 0$ if $x < 0$. Thus, only if two systems are in the same state in the majority of patterns will they be connected. This Hebbian rule stores both the pattern and its negative image (*16*).

A mathematical analysis (*19*) of Eq. 2 shows that, if the network is presented with a pattern with a few pixels in error relative to a stored pattern, then the network will correct the errors provided that sufficiently small numbers of patterns are stored in the network. The computational process carried out with Eq. 2 consists first of the storage of a number of patterns in the network by the Hebbian rule (Eq. 3); thus, the network is programmable. Second, the entire network is given initial conditions (that is, each system is given an initial [I$^-$] of one of the two stable stationary states of an uncoupled system). These initial conditions constitute the presented pattern (*20*). If the presented pattern is similar to a stored pattern, then the pattern recognition process consists of the temporal evolution of the network from the presented pattern to the stable stationary state corresponding to the similar stored pattern; the network corrects errors in a recognized pattern so that it more closely resembles the most similar stored pattern. If the presented pattern is not recognized, the network evolves to a homogeneous state. The number of errors in recognized patterns are not always reduced to zero; extraneous steady states develop because of the "mixing" of stored patterns (*16*). The network may correct many errors but may recall an extraneous pattern instead of a stored pattern. The number of such extraneous states increases as the number of stored patterns increases.

In Fig. 1, we show a typical temporal evolution of the numerical solution of Eq. 2 (*12*). The [I$^-$] in each system as a function of time is indicated by shading. A stored pattern is recalled perfectly at $t = 10$ from a presented pattern with 10 pixels in error relative to the recalled pattern. The total experimental time of the computer simulation is about 5 hours (the numerical solution of Eq. 2 requires only a few seconds) (*21*). If we look at system 13, we see that it is initially in the darker state, but by $t = 3$, it has been corrected to the lighter state. On the other hand, system 12 is initially in the lighter state but is corrected at $t = 7$ to the darker state.

We characterized the chemical computer by examining the percentage of presented patterns with a known number of errors relative to a stored pattern p' (*20*), which result in recall of patterns in the following classes: (i) p' or its associated extraneous patterns, (ii) other stored patterns or their associated extraneous patterns, or (iii) a homogeneous final state in the case of nonrecognition (Fig. 2). The minimum number of pixels that must be reversed to convert an extraneous pattern to a stored pattern (that is, the minimum Hamming distance) determines with which stored pattern an extraneous pattern is associated. Presented patterns with ten or fewer errors almost always result in the recall of patterns in class 1. The homogeneous state (class 3) is never found (in 100 trials) and patterns in class 2 are rarely recalled. The recall of patterns in class 1 is still the most likely result for patterns with 14 to 22 initial errors, but patterns in class 2 are occasionally recalled, and homogeneity is the second most common final state. For presented patterns with large numbers of initial errors, homogeneity is the most likely final state. Presented patterns with more than 36 initial errors are attracted to the negative image of p'. If presented patterns are chosen randomly, less than 5% will have 25 or fewer errors relative to one of the stored patterns or their negatives. Most of the other 95%, with more than 25 errors, will result in homogeneous final states. The number of basins of attraction for the stored patterns, although substantial, is small compared with the total number of possible presented patterns. The stored patterns are well separated in concentration space and surrounded by large areas of nonrecognizable patterns.

To measure the extent of the error correction in recognized patterns, we calculated the average number of errors, relative to p', from the recalled patterns in class 1 (Fig. 2). The pattern p' is almost always recalled perfectly if the presented pattern has fewer than 14 errors. For example, 99% of the presented patterns with ten initial errors result in the recall of patterns in class 1, and, of these recalled patterns, the average number of errors relative to p' is 0.17, an improvement of a factor of about 50. Only part of the presented patterns with large numbers of errors result in the recall of

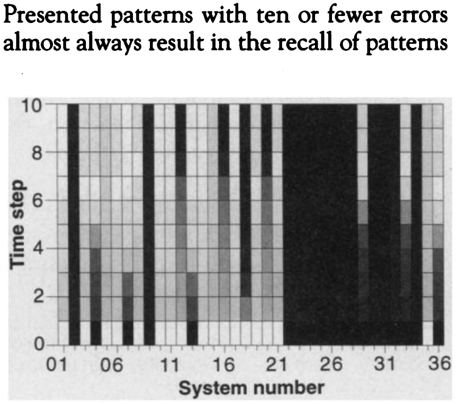

Fig. 1. Sample time series obtained from a chemical network with 36 coupled systems and three stored patterns. The shading gives the I$^-$ concentration with pure black and white representing the high and low states of an uncoupled system. Because systems in the high and the low iodide states are coupled in the network, the concentrations of I$^-$ in the recalled pattern (at $t = 10$) do not match exactly those of a collection of isolated systems, and the white and black in the recalled pattern are not as intense as in the presented pattern (at $t = 0$) in which the systems have I$^-$ concentrations set to those of uncoupled systems. The presented pattern has ten errors relative to the stored pattern, and, at $t = 10$, a stored pattern is recalled perfectly.

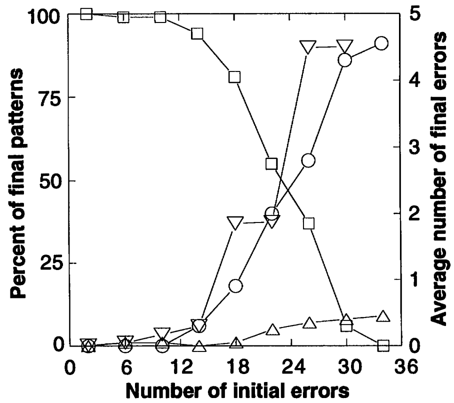

Fig. 2. Percentage of final patterns which are (○) homogeneous (class 3), (□) most closely related to p' (class 1), or (△) most closely related to the other stored patterns (class 2) against the number of errors, relative to p', in the presented pattern. Of those final patterns in class 1 the (▽) average number of errors, relative to p', is also plotted. The network has 72 systems and three stored patterns. The stored patterns are generated randomly; 100 different sets of three stored patterns and a presented pattern were simulated for each number of initial errors.

patterns in class 1, but, for those in class 1, there is a substantial reduction in the number of errors. The network typically corrects most of the errors or rejects a pattern as nonrecognizable. A network of 72 systems would be difficult to implement experimentally, but simulations of a smaller network, which could be implemented experimentally (*22*), show that this smaller network also possesses pattern recognition abilities, albeit to a lesser extent than the larger networks.

The chemical network has many similarities and some differences with a neural network of the Little (*15*) or Hopfield (*16–18*) type: patterns are stored in both the chemical and the Hopfield network by a Hebbian rule, but the connection weights (k_{ij}) may have either sign in a Hopfield network; the chemical systems must be bistable, but the neurons in a Hopfield network are typically monostable; and in both, stored patterns are stable steady states and are recalled when the network is initialized in their basins of attraction. In an electrical realization of a neural network (*17*), the neurons are amplifiers, the connections are wires, the connection weights are resistors; their analogs in the chemical computer are the bistable reaction mechanisms, mass transfer, and the mass transfer rates. The chemical network shares many of the desirable features of neural network models: both are robust in the presence of noise, both retain some computational power when damaged, and, in both, the computational abilities are not strongly dependent on model parameters. Because the connection weights can be either positive or negative in the Hopfield network, as well as in our earlier chemical networks (*1–3*), they perform better than the network presented here. The chemical implementation of parallel computers given here and in the earlier papers (*1–3*) provides a chemical basis of neural networks.

There are many biological reaction mechanisms and biological systems with multiple stationary states; mass transfer among compartments in biological systems is ubiquitous. These are the necessary components of the pattern recognition device presented here, and the components are at least available in living systems. The predictions for a small chemical network are experimentally verifiable.

REFERENCES AND NOTES

1. A. Hjelmfelt, E. D. Weinberger, J. Ross, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 10983 (1991).
2. ———, *ibid.* **89**, 383 (1992).
3. A. Hjelmfelt and J. Ross, *ibid.*, p. 388.
4. M. Okamoto, T. Sakai, K. Hayashi, *BioSystems* **21**, 1 (1987).
5. W. McCulloch and W. Pitts, *Bull. Math. Biophys.* **5**, 115 (1943).
6. M. Minsky, *Computation: Finite and Infinite Machines* (Prentice-Hall, Englewood Cliffs, NJ, 1967).
7. P. E. Rapp, *J. Exp. Biol.* **81**, 281 (1979).
8. L. Wang and J. Ross, *Proc. Natl. Acad. Sci. U.S.A.* **87**, 988 (1990), and references therein.
9. R. Guttman, S. Lewis, J. Rinzel, *J. Physiol. London* **305**, 377 (1980).
10. P. De Kepper, I. R. Epstein, K. Kustin, *J. Am. Chem. Soc.* **103**, 6121 (1981).
11. T. Pifer, N. Ganapathisubramanian, K. Showalter, *J. Chem. Phys.* **83**, 1101 (1985).
12. The necessary constants, taken from (*11*), are $k_A = 0.21\ M^{-1}\ s^{-1}$ and $k_B = 21000\ M^{-2}\ s^{-1}$. We chose $[I^-]_0 = 8 \times 10^{-5}$ M, $[IO_3^-]_0 = 0.001$ M, and $k = 0.00718\ s^{-1}$. Under these conditions, $[I^-]$ = 0.00013 M and 0.00058 M in the two possible stable steady states and 0.000357 M in the unstable steady state for each isolated system whose kinetics is described by Eq. 2. The multiplier λ is 2.3×10^{-5} for Fig. 1 and 1.6×10^{-5} for Fig. 2.
13. K. L. C. Hunt, J. Kottalam, M. D. Hatlee, J. Ross, *J. Chem. Phys.* **96**, 7019 (1992).
14. D. O. Hebb, *The Organization of Behavior* (Wiley, New York, 1949).
15. W. Little, *Math. Biosci.* **19**, 101 (1974).
16. J. J. Hopfield, *Proc. Natl. Acad. Sci. U.S.A.* **79**, 2554 (1982).
17. ———, *ibid.* **81**, 3089 (1984).
18. ——— and D. W. Tank, *Science* **233**, 625 (1986).
19. A. Hjelmfelt, F. W. Schneider, J. Ross, unpublished data.
20. Stored patterns are generated randomly, and one of them is designated *p'*. A certain number of randomly chosen pixels are reserved (a system that is in the high $[I^-]$ state is set to the low $[I^-]$ state, or vice versa) in the pattern *p'* to generate the presented pattern.
21. The average time for the emergence of a stored pattern depends on the reaction kinetics, and the iodate–arsenous acid reaction is notoriously slow.
22. As an example of what is experimentally feasible, we cite the work of J.-P. Laplante and T. Erneux [*J. Phys. Chem.* **96**, 4931 (1992)] in which they performed experiments with a system of 16 coupled bistable systems (the chlorite-iodide reaction in a continuous-flow stirred tank reactor) with the possibility of 32 connections.
23. A.H. acknowledges financial support from the Alexander von Humboldt-Stiftung. J.R. acknowledges support from the National Science Foundation.

10 November 1992; accepted 10 February 1993

Controlling Chemical Reactivity with Antibodies

Linda C. Hsieh, Shirlee Yonkovich,
Lynn Kochersperger, Peter G. Schultz*

The remarkable specificity of an antibody molecule has been used to accomplish highly selective functional group transformations not attainable by current chemical methods. An antibody raised against an amine-oxide hapten catalyzes the reduction of a diketone to a hydroxyketone with greater than 75:1 regioselectivity for one of two nearly equivalent ketone moieties. The antibody-catalyzed reaction is highly stereoselective, affording the hydroxyketone in high enantiomeric excess. Similarly, the reduction of ketones containing branched and aryl substituents, including the highly symmetrical 1-nitrophenyl-3-phenyl-2-propanone, was enantioselective. The simple strategy presented herein may find general applicability to the regio- and stereoselective reduction of a broad range of compounds.

The development of catalytic methods for the regio- and stereoselective synthesis of optically pure compounds has become an important focus in recent years (*1*). A number of chemical reagents have been designed for demanding asymmetric transformations, including titanium (IV) tartrate complexes for chiral epoxidations (*2*), rhodium and ruthenium catalysts for enantioselective hydrogenations (*3, 4*), osmium complexes for asymmetric dihydroxylations (*5*), and chiral boranes for stereoselective ketone reductions (*6*). However, while existing asymmetric catalysts have demonstrated impressive enantioselectivities, the rational design of such catalysts is still in its infancy, and high stereoselection is usually contingent upon neighboring ligands or restricted sets of substituents (*7*). Moreover, the ability to discriminate between chemically similar functional groups in the same molecule can often be achieved only by the application of extensive protecting group strategies, as in the synthesis of complex molecules such as the macrolide antibiotics, carbohydrates, and peptides (*8*).

The search for selective catalysts has also led to the increased use of enzymes in organic synthesis. Although high chemo-, regio-, and enantioselectivities have been achieved, enzymes often require expensive cofactors and are limited in number and selectivity (*9–11*). Given the extraordinary specificity of the immune system, we asked whether simple yet general strategies exist for generating antibodies that catalyze regio- and stereoselective functional group transformations. We chose the reduction of simple prochiral ketones as our initial target, specifically the regio- and stereoselective conversion of ε-diketone **5** to hydroxyketone **9** (Fig. 1). The similar chemical environments of the two carbonyl moieties

---

L. C. Hsieh and P. G. Schultz, Department of Chemistry, University of California, Berkeley, CA 94720.
S. Yonkovich and L. Kochersperger, Department of Bioorganic Chemistry, Affymax Research Institute, Palo Alto, CA 94304.

*To whom correspondence should be addressed.